Australian Government
Department of Health
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: buprenorphine extended release injection, 100 & 300mg

Product name: SUBLOCADE 100mg & 300 mg

Sponsor: Indivior

Submission number: PM-2018-01872-1

eSubmission number: 003260

File number: E18-284729

Date of first round report: 14 August 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

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Abbreviation	Meaning
BUP	buprenorphine
COWS	Clinical Opiate Withdrawal Scale. The COWS is an 11-item, instrument used to assess symptoms of opiate withdrawal. The score on the assessment is the sum of the response for each of the 11 items. A score of 5 to 12 is considered mild withdrawal, 13 to 24 is considered moderate, 25 to 36 is considered moderately severe, and a score exceeding 36 is considered severe withdrawal.
Nor-BUP	norbuprenorphine
Opioid Craving VAS	The Opioid Craving Visual Analog Scale - the VAS was a 100 mm scale
OUD	opioid use disorder
PCC	Percentage Clean Urines
PLGH	50:50 poly(lactide-co-glycolide) with a carboxylic acid end group
RBP-6000	Sublocade
SOWS	The Subjective Opiate Withdrawal Scale is a 16-item scale completed by the subject and used to assess the subject's perception of opiate withdrawal symptoms.
Timeline Follow back Interview	The Timeline Follow back Interview assessed recent drug use. Subjects were asked to estimate, retrospectively, their drug use during the 30 days preceding each visit to the clinical site. Only the frequency of use was captured (i.e., used or did not use).
TEC	Treatment Effectiveness Percentage
μO-RO	mu-opioid receptor occupancy

4. Submission details

4.1. Identifying information

Submission number	PM-2018-01872-1
eSubmission number	003260
Sponsor	Indivior
Trade name	Sublocade 100mg & 300 mg
Active substance	buprenorphine extended release injection, 100 & 300mg

4.2. Submission type

This is a PopPK study based Category 1, type F submission to register a new dosage form of buprenorphine – an extended release injection in two strengths.

4.3. Drug class and therapeutic indication

The approved indication for Subutex Sublingual Tablets is:

> Treatment of opioid dependence, within a framework of medical, social and psychological treatment.

4.4. Dosage forms and strengths

There are multiple buprenorphine preparations registered some with the same Indication as proposed others with different indications e.g. Temgesic Injection and Temgesic Sublingual Tablets indications are:

> Strong analgesic for the short-term (not more than one week) relief of moderate to severe pain, including post-operative and terminal pain. Temgesic Injection should be employed when sublingual administration is not practical e.g. pre- or peri-operatively. It is not recommended for use in children.
>
> Temgesic does not have an approved role in opioid dependence rehabilitation programmes.

The submission proposes registration of the following dosage forms and strengths:

> Buprenorphine extended release injection, 100 & 300mg in pre-filled syringes for single use with an already registered 19G 16mm hypodermic needle for subcutaneous administration.

4.5. Dosage and administration

The proposed section is extensive. It can be found at 22.1. It includes:

> Patients appropriate for Sublocade are adults who have undergone induction on a buprenorphine-containing product. Withdrawal signs and symptoms should be suppressed (COWS ≤ 12) before transitioning to Sublocade.
>
> Dosing and induction of buprenorphine-containing products should be based on instructions in their Product Information.

FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. DO NOT ADMINISTER Sublocade INTRAVENOUSLY OR INTRAMUSCULARLY (see section 4.4 Special Warnings and Precautions for use).

•Only healthcare providers should prepare and administer Sublocade.

•Administer Sublocade monthly with a minimum of 26 days between doses.

• Initiating treatment with Sublocade as the first buprenorphine product has not been studied. Initiate Sublocade treatment only following induction and dose adjustment with a transmucosal buprenorphine containing product.

• Administer each injection only using the syringe and safety needle included with the product.

• Do not administer part of a dose

Recommended dosing

Patients appropriate for Sublocade are adults who have initiated treatment on a transmucosal buprenorphine-containing product. The patient may only be transitioned to Sublocade after stabilisation on transmucosal buprenorphine (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

The recommended dose of Sublocade is 300mg monthly for the first two months. The recommended maintenance dose is 100mg monthly. However patients who do not show a satisfactory clinical response following the second dose can receive a maintenance dose of 300mg monthly.

Buprenorphine plasma levels in the month following the second 300mg dose are maintained with 100mg maintenance dosing. The 300mg maintenance dose achieves higher levels and reaches steady state after the fourth monthly injection (see section 5.2 pharmacokinetic properties).

A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Clinical supervision

Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot.

Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment. For some patients, treatment may continue indefinitely. If considering stopping treatment, the clinical status of the patient should be considered.

If Sublocade is discontinued, its extended-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal or buprenorphine effects and treated appropriately. After steady-state has been achieved (4-6 months), patients discontinuing Sublocade may have detectable plasma levels of buprenorphine for twelve months or longer. The correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

4.6. Proposed changes to the product documentation

Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION and Section 3 PHARMACEUTICAL FORM will of necessity be new.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The addition of a section Risk of serious harm or death with intravenous administration.

Considerable amendments were made including to the Misuse, abuse and diversion section, the Risk of Respiratory and Central Nervous System (CNS) Depression sections, the Managing Risks From Concomitant Use of Benzodiazepines Or Other CNS Depressants With Buprenorphine section, the Opioid Withdrawal Effects section, the Neonatal Abstinence Syndrome section, the Use in hepatic impairment section and the Use in renal impairment section.

New sections: Risks associated with Treatment of Emergent Acute Pain and Use in Patients at Risk for Arrhythmia.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Has been replaced by a Tabular section.

4.6 FERTILITY, PREGNANCY AND LACTATION

The Effects on fertility section is replaced.

The Use in Pregnancy (Category C) and the Use in lactation sections while the subject of a separate current submission, have been modified.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) is of necessity amended.

5.1 PHARMACODYNAMIC PROPERTIES

The Mechanism of action section is modified.

New sections: Plasma concentration and Clinical Response, Clinical trials.

5.2 PHARMACOKINETIC PROPERTIES is mostly new.

5. Background

5.1. Information on the condition being treated

In Australia, death from opioid overdose is increasing, and opioid use in 2012 was estimated to have increased to 15 times that reported in 1992. In 2013 the Australian Bureau of Statistics reported that 668 Australians died (including all ages) from overdose of opioids. Additionally, it was determined that 597 Australians between the ages of 15 and 54 died from accidental overdose of opioids, with 70% of deaths including strong prescription painkillers. Accidental death related to opioid overdose is more likely to affect older Australians. Deaths among 45- to 54-year-olds are now higher than at the peak of the heroin epidemic in 2001. Moreover, according the Australian Bureau of Statistics, heroin was present in 1 in 5 drug-induced deaths in 2016, and has the second lowest median age at death at 41.2 years. Therefore, heroin, heroin-related overdoses and heroin overdoses leading to death still remain a major public health issue in Australia.

According to the Australian National Drug & Alcohol Research Centre, the major cause of opioid deaths has changed over time from heroin to prescription opioids such as oxycodone and fentanyl, and overdose deaths occur in all age groups.

5.2. Current treatment options

Medication-assisted treatment includes methadone (an opioid agonist) or buprenorphine (a partial agonist).

5.3. Clinical rationale

Opioid withdrawal suppression (the prevention of withdrawal symptoms and craving) appears to require ≥ 50% brain mu-opioid receptor occupancy, associated with buprenorphine plasma concentrations ≥ 1ng/mL.

To block the full subjective agonist induced effects (opioid blockade) at least 70% brain mu-opioid receptor occupancy by buprenorphine is required - this being provided by buprenorphine plasma concentrations ≥ 2-3ng/mL.

This level 2ng/mL cannot be maintained over 24h by sublingual buprenorphine, hence the proposed delayed release injection to provide 24h cover.

5.4. Formulation

5.4.1. Formulation development

This application relies not only nonclinical pharmacology information from the approved labelling for buprenorphine products, but also studies from the scientific literature that provide relevant or supporting nonclinical pharmacological data for buprenorphine or the Atrigel Delivery System components (i.e., NMP and PLGH). Indivior has not conducted any new pharmacology studies to support this application.[1]

The Atrigel Delivery System is a non-aqueous solution consisting of a biodegradable polymer, 50:50 poly(DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH) and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP).[2]

The Atrigel Delivery System is on the ARTG e.g. in Bi Eligard cp.

5.4.2. Excipients

The proposed formulation contains the following excipients:

Atrigel Delivery System contains: 50:50 Poly(DL-lactide-co-glycolide) polymer, *N*-methyl-2-pyrrolidone.

5.5. Regulatory history

5.5.1. Australian regulatory history

Temgesic buprenorphine was first placed on the ARTG 30 September 1991.

Subutex sublingual tablets were first placed on the ARTG 2 November 2000.

5.5.2. Related submissions

Submission 2017-02665 to amend the Dosage and Administration section and remove the contraindication for pregnancy and lactation currently being reviewed.

[1] 2.6.2 Pharmacology Written Summary page 4
[2] 2.2 Introduction

5.5.3. Overseas regulatory history

Registration approved US 30/11/17 for 'Treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days. Sublocade should be used as part of a complete treatment plan that includes counselling and psychosocial support.' FDA Cross-Discipline Team Leader Review And Summary Basis for Approval is in the submission.[3]

Applied for in Canada.

5.6. Guidance

- EMA/CHMP/EWP/280/96 Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1).
- CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Guideline on the Investigation of Bioequivalence.
- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a Clinical Investigation of Medicinal Products for Long-Term Use.

6. Contents of the clinical dossier

6.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5

  Clinical pharmacology studies, including:

  - RB-US-10- 0011 An open-label, single-centre, first-in-human study, designed to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of a single SC injection of Sublocade containing 20mg buprenorphine in opioid dependent subjects.
  - RB-US-11-0020 A multicentre, open-label, single ascending-dose study to evaluate the safety, tolerability, and pharmacokinetics of depot buprenorphine in opioid-dependent subjects.
  - RB-US-12-0005 An open-label, multicentre, multiple dose study of the safety, tolerability, pharmacokinetics, efficacy markers, and opioid receptor availability of subcutaneous injections of depot buprenorphine in treatment seeking opioid-dependent subjects.
  - RB-US-13-0006 A single-centre, randomized, open-label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of depot buprenorphine (Sublocade) using poly (dl-lactide-co-glycolide) polymer of two different molecular weights (low and high molecular weights as test treatments) in comparison to intermediate molecular weight (reference treatment) in treatment-seeking subjects with opioid use disorder.
  - CR87/027 A comparative assessment of the bioavailability of buprenorphine administered by the intravenous and sublingual routes.

[3] Module 1/ 111-foreign/ 1114-eval-reports

  - CR96-008 Relative bioavailability study of buprenorphine sublingual liquid and sublingual tablet formulations.
  - P01242 Single centre, Phase 1, open-label, fixed sequence drug interaction' study of ketoconazole in opiate dependent subjects effects of ketoconazole on the pharmacokinetics of sublingual buprenorphine.

- Population pharmacokinetic and/or pharmacodynamic analyses including:
  - INDV-6000-M01 Population PK modelling & simulation report of RB-US-11-0020 A single ascending-dose study of Sublocade in opioid-dependent subjects.
  - INDV-6000-M03 Population pharmacokinetic analysis of buprenorphine after repeated subcutaneous injections of Sublocade in treatment-seeking opioid-dependent subjects in study RB-US-12-0005.
  - NDV-6000-M05 Population pharmacokinetics of Sublocade in treatment-seeking subjects with opioid use disorder combined analysis of studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003.
  - INDV-6000-M07 Modelling & Simulation Report *in vitro-in vivo* Correlation evaluation for Sublocade using a population pharmacokinetic modelling approach.
  - INDV-6000-M04 Population pharmacokinetic and exposure-response analyses for buprenorphine after repeated subcutaneous injections of Sublocade in treatment-seeking subjects with opioid use disorder.
  - INDV-6000-M02 Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy in the brain.
  - INDV-6000-M06 Drug-drug interaction modelling & simulation for Subutex and Sublocade with ketoconazole.
  - INDV-6000-Q01 Concentration-QT analysis for Sublocade using plasma concentration and ECG data pooled from studies RB-US-10-0011, RB-US-11-0020, RB-US-12-0005, RB-US-13-0001, and RB-US-13-0006.
- Pivotal efficacy/safety studies.
  - RB-US-13-0001 A randomized, double-blind, placebo-controlled, multicentre study to assess the efficacy, safety, and tolerability of multiple subcutaneous injections of depot buprenorphine (Sublocade 100mg and 300mg) over 24 weeks in treatment-seeking subjects with opioid use disorder.
- Other efficacy/safety studies including:
  - B-US-13-0002 A multiple-dose study of blockade of subjective opioid effects, plasma levels, and safety of subcutaneous injections of depot buprenorphine in subjects with opioid use disorder.
  - INDV-6000-301 An open-label, depot buprenorphine treatment extension study in subjects with opioid use disorder.
  - RB-US-13-0003 an open-label, long-term safety and tolerability study of depot buprenorphine in treatment-seeking subjects with opioid use disorder.
  - RB-US-13-0003 HEOR Health economics and outcomes research (HEOR) report for the RB-US-13-0003 clinical trial.
  - INDV-6000-h01 Health economics and outcomes research endpoints report: a randomized, double-blind, placebo-controlled, multicentre study to assess the

efficacy, safety, and tolerability of multiple subcutaneous injections of depot buprenorphine (Sublocade 100mg and 300mg) over 24 weeks in treatment-seeking subjects with opioid use disorder.

- Other
    - *Integrated Summary of Efficacy*.
    - *Integrated Summary of Safety*.
    - IND-2015-Vail-FTl-503 Rev A a "pre-summative" usability test.
    - Summary of all abuse-related animal and human data, discussion of these data, and conclusions about the drug's abuse potential.
    - FC-FDV-0141R A simulated intravenous *in vitro* study to evaluate local tolerance of intravenous or intra-arterial injection of Sublocade.
    - Expert summary report The risk of QT prolongation associated with the use of buprenorphine containing products.

- Module 1
    - Application letter, application form, draft Australian PI and CMI, FDA-approved product label and FDA Cross-Discipline Team Leader Review and Summary Basis for Approval, RMP.
- Module 2.
    - Introduction, Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Clinical Pharmacology and literature references.

Comment: Almost all the relevant data is there, but oddly study reports are often dated years after publications.

References were not all in the submission and one at least did not appear to exist. The PI annotations often did not reflect the source with much accuracy, or could not be found. All this delays evaluation.

The submission is based on 2 different approaches:

- Based on 2 articles by Grenwald in 2003 & 2007 that measured plasma buprenorphine levels after doses of buprenorphine and the resulting μ-opioid receptor occupancy in the brain using ^{11}C carfentanil PET scans.
  These were then modelled (see 21.1.3.1).
  Based on this model, a buprenorphine plasma concentration of 2 to 3ng/mL was predicted to achieve sufficient μ-opioid receptor occupancy —approximately 70%—to suppress opioid withdrawal signs and symptoms and to block the response to a μ-opioid receptor agonist e.g. hydromorphone.
  The sponsor then undertook to show that this level was consistently achieved (see Figure 1).
- The sponsor also undertook 2 efficacy studies using different endpoints, comparing to placebo (13-0001 and 13-0002).

There are multiple PopPK and PK/PD studies. Mostly the modelling only is found in the CSRs with the results of simulations found in the Clinical Summaries.

6.2. Sponsor's Justification for not providing biopharmaceutic and/or absolute bioavailability data

The sponsor admits a justification is required:

Sublocade is therefore being submitted to the TGA as a major variation to Subutex, type F, for which a head-to-head biopharmaceutical study would be required under strict interpretation of ARGPM Guidance 15.4: Medicines that require biopharmaceutic data – complex intravenous solutions for injection and new dosage form.[4]

The PPF summarises the sponsor's approach to justification:

Although Sublocade is submitted for registration as an alternative to Subutex sublingual tablets as both medicines share the same active ingredient and indication, a head-to-head biopharmaceutic comparison is not relevant due to the difference in the buprenorphine plasma level patterns through time. The efficacy and safety of the products in their common indication is compared in detail on a clinical level in modules 2.5 and 2.7 and conclude to therapeutic comparability, with Sublocade being designed to bring improved adherence to treatment and convenience for patients.[5]

The sponsor argues for bioequivalence based on efficacy:

Efficacy (as measured by urine drug screen and self-reports of illicit opioid use as well as withdrawal symptoms and craving) was maintained when subjects were transitioned from sublingual buprenorphine treatment to Sublocade during the clinical development programme.[6]

Comment: The Clinical Overview has Buprenorphine plasma concentrations required to provide opioid blockade are ≥ 2-3ng/mL. Although SL buprenorphine achieves the 2ng/mL threshold, it is not maintained over the 24-hour dosing interval. For daily doses of 16mg SL buprenorphine, brain mu-opioid receptor occupancy was reported to be 70% at 4 hours post-dose but only 46% at 28 hours post-dose.

6.3. Paediatric data

The submission did not include paediatric data.

6.4. Good clinical practice

While not specifically stated as complying with Good clinical practice in Study CR87-027 the protocol required:[7]

The investigator will submit the study protocol, subject consent form and any other documents as may be requested to an appropriate Ethics or Institutional Review Committee for review and approval.

The articles by Grunwald complied with the Declaration of Helsinki and were Institutional Review Boards of Wayne State University and University of Michigan approved.

[4] Module 1 1.9.2
[5] PPF page 23
[6] Module 1 1.9.2
[7] Page 93 CSR

7. Pharmacokinetics

7.1. Studies providing pharmacokinetic information

Summaries of the pharmacokinetic studies are presented in Section 21.1 of this report. Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1 Submitted PK studies- all studies (except CR87/027) were in Opioid-dependent treatment-seeking subjects.

PK topic	Subtopic	Study ID	*	Synopsis
Single dose	First-in-human	10-0011	*	21.1.1.1
	Single ascending dose	11-0020	*	21.1.1.2
	To assess the relative bioavailability with different MWs of PLGH polymer s†	13-0006	*	21.1.1.4
	Comparative bioavailability of intravenous and sublingual routes†	CR87/027	*	Previous submission
Multi-dose	Multiple ascending dose	12-0005	*	21.1.1.3
	Opioid blockade study	13-0002		21.1.1.4
	Double-blind, placebo-controlled, 24-week, efficacy, safety and tolerability study	13-0001		Only 80 page table in study. Analysis combined at 21.1.3.4 21.1.3.5
	Long-term open label safety and tolerability study (extension of Study RB-US-13-0001)	13-0003		Only listing in study. Analysis combined at 21.1.3.4
	Relative bioavailability of sublingual liquid and sublingual tablet†	CR96-008	*	Previous submission
PK drug interactions	Ketoconazole vs. sublingual	P01242	*	Previous submission
	Modelling & simulation for Subutex and Sublocade with ketoconazole	M06		21.1.3.6
Population PK analyses	Modelling & Simulation Report *in vitro-in vivo* Correlation evaluation	M07	*	21.1.3.7
	Modelling & simulation report single ascending dose study 11-0020	M01	*	21.1.3.1
	Analysis of buprenorphine multiple	M03	*	21.1.3.3

	ascending dose study 12-0005			
	Combined analysis of studies 12-0005, 13-0001 and 13-0003	M05	*	21.1.3.4

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations.

None of the PK studies had deficiencies that excluded their results from consideration; some were related to a previous submission.

7.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

7.2.1. Physicochemical characteristics of the active substance

The following information is derived from the Sponsor's summaries in Module 2.

Sublocade contains 18% buprenorphine base in solution with the Atrigel Delivery System. The Atrigel Delivery System is a non-aqueous solution consisting of a biodegradable polymer with a carboxylic acid end group, 50:50 poly(D,L-lactide-co-glycolide) with a carboxylic acid end group (PLGH), and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). Sublocade forms a solid depot when injected subcutaneously and releases buprenorphine over a month by diffusion as the polymer is hydrolysed and degrades.

7.2.2. Pharmacokinetics in opioid-dependent subjects

7.2.2.1. Absorption

Following SC administration of Sublocade, buprenorphine was rapidly absorbed and peaked at approximately 24 hours post-dose, then declined to a plateau throughout the dosing interval consistent with the slow release of buprenorphine from the Atrigel Delivery System (Studies 11-0020 and 12-0005).

7.2.2.2. Bioavailability

The absolute bioavailability of Sublocade has not been determined in a dedicated clinical study.

However, based on buprenorphine clearance estimates from the literature (Yassen 2007[8]: 93 L/hr; Huestis 2013:[9] 50 - 60 L/hr), the absolute bioavailability of Sublocade is expected to be high, given buprenorphine CL/F values of 63 to 103L/hr following single and repeated SC injections.

7.2.2.3. Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Once absorbed, buprenorphine distributes extensively into the body, as evidenced by a large apparent volume of distribution (V_d/F) with mean values ranging from 96,120 to 154,369L over the dose range of 50 to 200mg (Study 11-0020).[10] The extensively large Vd/F is also because Sublocade is administered as a depot injection, resulting in a large amount of drug being available at the injection site.

[8] Mechanism-Based Pharmacokinetic-Pharmacodynamic Modelling of the Reversal of Buprenorphine-Induced Respiratory Depression by Naloxone Yassen et al Clln Pharmacokinet 2007: 46(!1): 965-980
[9] Intravenous buprenorphine and norbuprenorphine pharmacokinetics in humans M.A. Huestisa et al Drug and Alcohol Dependence 131 (2013) 258– 262
[10] Page 124 Table 11

7.2.2.4. Metabolism

From the Suboxone PI:

> In animals and man buprenorphine is metabolised by Phase 1 (oxidative) and Phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP 3A4. The reported K_m for buprenorphine for CYP 3A4 in human liver microsomes was 89mM, and addition of specific inhibitors of CYP 3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine. There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4 (reported mean K_i in human liver microsomes was 10.3μM and 40.2 μM respectively). Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity and is considered to be an inactive metabolite.

In vitro studies have shown some pharmacological activity associated with norbuprenorphine; however, norbuprenorphine steady-state plasma concentrations in humans after SC injection of Sublocade are low (AUC norbuprenorphine/buprenorphine ratio of 0.23-0.39, based on Study 12-0005).[11] Furthermore, norbuprenorphine is expected to have negligible contribution to brain mu-opioid receptor occupancy given its limited ability to cross the blood-brain barrier.

7.2.2.5. Excretion

The apparent plasma terminal half-life of buprenorphine (mean $t_{½}$) increased slightly with the increase in dose from 50mg to 200mg (1078 hours at 50mg, 1376 hours at 100mg, and 1573 hours at 200mg) (Study 11-0020 page 124). In this study, the CL/F of buprenorphine remained fairly constant over the investigated dose range of 50 to 200mg (64 - 68L/hr).[12] After multiple doses (Study 12-0005), CL/F was also fairly constant over the dose range of 50 to 300mg (81 - 105 L/hr).[13]

7.2.2.6. Intra and inter individual variability of pharmacokinetics

BMI was found to affect the SC absorption of buprenorphine, with higher peak levels of buprenorphine in subjects with a lower BMI. However, these effects were not of sufficient magnitude to suggest that dose adjustments might be necessary.

7.2.3. Population pharmacokinetics

There were multiple models developed. (See 21.1.3).

7.2.4. Pharmacokinetic interactions

7.2.4.1. ketoconazole

A drug-drug interaction population PK model was developed to account for this first-pass effect and to predict the effect of ketoconazole on the PK of Sublocade which bypasses first-pass metabolism. The model predicted a comparatively modest increase (60%) in buprenorphine AUC with concomitant administration of ketoconazole. See 21.1.3.6

7.2.5. Clinical implications of *in vitro* findings

A report on *in vitro-in vivo* Correlation evaluation for Sublocade using a population pharmacokinetic modelling approach found that comparison of *in-vitro* and *in-vivo* data showed a more rapid initial release of drug *in vitro* that was not reflected on the *in-vivo* absorption-time profile. Simple Level A correlation could not be established. (See 21.1.3.7).

[11] Page 153
[12] Page 122
[13] Page 185

7.3. Evaluator's overall conclusions on pharmacokinetics

Some proposed insertions in the PI are not supported in the submission. See 15.1.

8. Pharmacodynamics

8.1. Studies providing pharmacodynamic information

Summaries of the pharmacodynamic studies are presented in Section 21.1 of this report. Table 2 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 2 Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*	Synopsis
Primary Pharmacology	Opioid blockade study	13-0002	*	21.1.2.1
	PET substudy	12-005		21.1.2.3
Secondary Pharmacology	Multiple PD parameters	11-0020		21.1.2.1
	Multiple PD parameters	13-002		21.1.2.1
Population PD and PK-PD analyses	PopPK & Exposure-response analyses after repeated subcutaneous injection Studies 12-005 & 13-0001	MO4	*	21.1.3.4
	Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy	MO2	*	21.1.3.1
	Concentration-QT analysis	NDV-6000-Q01	*	21.1.3.8

* Indicates the primary PD aim of the study.

8.2. Summary of pharmacodynamics

8.2.1. Mechanism of action

From the Suboxone PI:

> Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.
>
> During clinical pharmacology studies in opioid-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, "good effect", and respiratory depression.

8.2.2. Pharmacodynamic effects

8.2.2.1. Primary pharmacodynamic effects

The sponsor submitted Study INDV-6000-M02 (see 21.1.3.1) Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy in the brain.

Based on this model, a buprenorphine plasma concentration of 2 to 3ng/mL was predicted to achieve sufficient μ-opioid receptor occupancy — approximately 70% — to suppress opioid withdrawal signs and symptoms and to block the response to a μ-opioid receptor agonist.

8.2.2.2. Secondary pharmacodynamic effects

Study 13-0002 (see 21.1.2.1). This complex study set out to show that after Sublocade was given hydromorphone, previously shown to be subject desirable in the absence of buprenorphine, was now no more desirable that saline. This was demonstrated with visual analog scales for “Drug Liking" "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High".

Secondary Objectives included:

- To evaluate the correlation between the opioid blockade subjective effects (VAS of "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High") and the reinforcing effects of hydromorphone and simulated mu opioid receptor occupancy (using the maximal effect [E_{max}] model).
- To determine the relationship between plasma concentration and predicted mu opioid receptor occupancy of buprenorphine and both the blockade of the subjective effects of hydromorphone post injection of buprenorphine 300mg (Sublocade).

8.2.3. Pharmacodynamic interactions - QT interval

PopPK analysis INDV-6000-Q01 Concentration-QT analysis (see 21.1.3.8) found no effect of buprenorphine on QT after accounting for the covariates that may influence HR and QT in subjects with opioid use disorder.

The sponsor also submitted a 15 page Expert summary report on The risk of QT prolongation associated with the use of buprenorphine containing Products that found:

The presently published literature does not suggest that buprenorphine is causally associated with QT prolongation and TdP-type ventricular arrhythmias.

and:

There was no strong evidence to demonstrate the extent to which buprenorphine may have contributed to the development of QT prolongation, given the fact that some patients concomitantly received drugs known to prolong the QT interval, as well as had a history of abnormal thyroid function, structural heart disease, bradycardia, hypokalaemia and polysubstance abuse, which confound any interpretation.

8.3. Evaluator’s overall conclusions on pharmacodynamics

Among the proposed PI insertions were:

1.

Following sublingual administration, a dose response relationship has been observed for buprenorphine plasma levels and brain mu-opioid receptor occupancy by buprenorphine at 4 hours after dosing. A relationship has also been observed between buprenorphine plasma levels and blockade of subjective opioid agonist symptoms produced by co-administered opioids at 4 hours after dosing. Plasma concentrations of buprenorphine and mu-opioid receptor occupancy decrease between 4 hours and 28 hours post dose correlating with a return of subjective agonist symptoms produced by co-administered opioids, together with opioid withdrawal symptoms and opioid craving.

These statements are from the sponsor’s review derived from the two Grunwald Studies. Which are only available in the submission in their published form.

However Study RB-US-13-0002 CSR[14] found 'Scatter plots of the buprenorphine plasma concentration versus the VAS scores for the subjective measures (Drug Liking, Any Drug Effect, Good Drug Effect, Bad Drug Effect, Sedation, and High,) are presented in Figure 37, Figure 38, Figure 39, and Figure 14.2.2.5. Overall, these plots indicate there was a reduction in VAS scores with increased buprenorphine plasma concentration' (see 15.1 for further discussion).
Comment: The proposed insertion relates to the use of sublingual tablets and is not found in the Subutex PI.

2.

In a Positron Emission Tomography (PET) study with Sublocade in 2 subjects (one subject receiving 200mg SC injections and one subject receiving 300mg SC injections) with opioid use disorder, 75 to 92% occupancy of the mu-opioid receptors in the brain was maintained for 28 days following the last dose under steady-state conditions.

This statement is misleading.

The subject who received 200mg showed 79% and 75% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively. The subject who received 300mg showed 92% and 81% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively.[15]

3.

The *(Sublocade opioid blockade)* study evaluated the blockade of subjective opioid effects, pharmacokinetics (PK) and safety of SC injections of Sublocade. Stabilisation doses of SL buprenorphine prior to injection of Sublocade failed to provide full blockade of subjective effects of hydromorphone 18mg IM After Sublocade injections at weeks 0 and 4, on average, subjective effects of both 6 and 18mg doses of hydromorphone were blocked; however wide variability was seen across subjects. Complete blockade continued throughout the 8 weeks of observation that followed the 2nd Sublocade injection.

The primary endpoint was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade). The study failed to meet that endpoint.

For the 18mg hydromorphone to placebo treatment comparison, opioid blockade was observed from Week 1 to Week 3, while at Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade. After the first injection of SC Sublocade, during week 4, a decrease in mean buprenorphine plasma concentration (from 1.9 to 1.8ng/mL) correlated with a 65% μ-opioid receptor occupancy, which corresponded to the increase in VAS scores.

9. Dosage selection for the pivotal studies

Simulations used the population PK model developed from study 11-0020 data (doses of 50 to 300mg) along with the PK/brain mu-opioid receptor occupancy model. Multiple SC injections of Sublocade were simulated for doses ranging from 50 to 300mg. The 300mg dose was the highest dose tested in the clinical development program. The results of these simulations indicated that the C_{max} achieved at an Sublocade dose of 300mg enabled the target of 70% brain mu-opioid receptor occupancy to be reached after the first SC injection. Mean predicted

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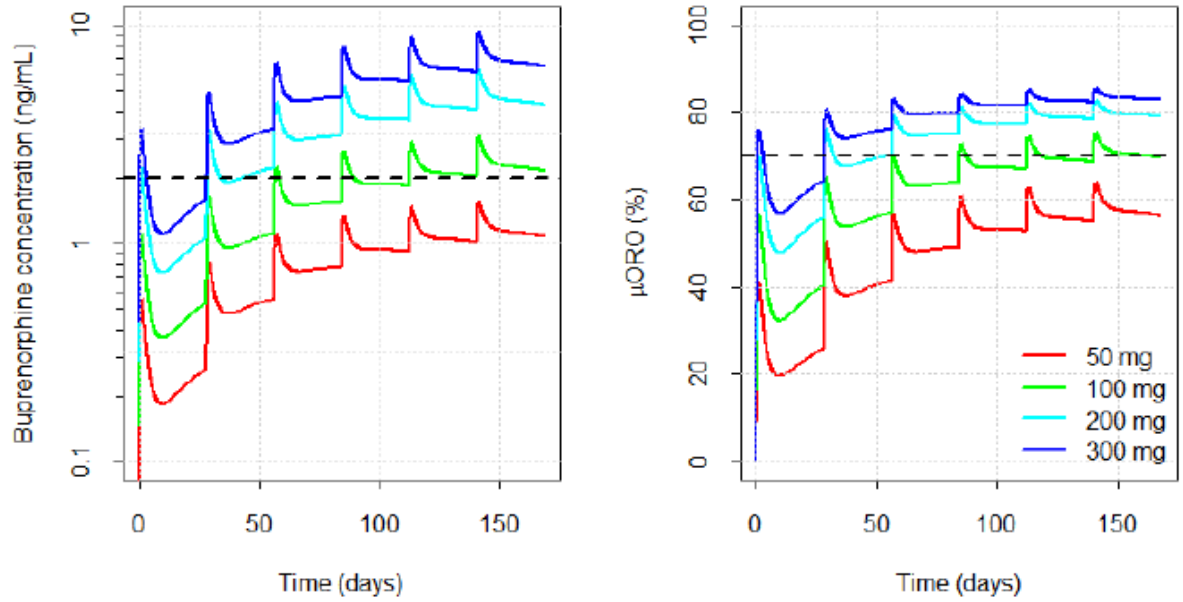
receptor occupancy levels were consistently higher than 70% after the second and subsequent injections. The target brain mu-opioid receptor occupancy level could also be reached with the dose of 200mg. However, at this dose, the expected mu-opioid receptor occupancy did not reach the effective level during the first month of treatment. Altogether, these findings supported the choice of 300mg as a starting dose for the treatment of opioid use disorder. The selection of the 300mg dose as an opioid blocking dose was supported by the results from the opioid blockade study.

Simulations also indicated that repeated doses of 100mg of Sublocade provided effective levels of brain mu-opioid receptor occupancy under steady-state conditions. However, given the low predicted levels of brain mu-opioid receptor occupancy after the first and second SC injections at 100mg, the model supported the use of 2 monthly loading doses of 300mg each.[16]

Figure 1 Mean Predicted Buprenorphine Plasma Concentrations and Brain Mu-Opioid Receptor Occupancies After Repeated SC Injections of Sublocade at Various Doses



Left panel = buprenorphine plasma concentrations; Dashed line=2ng/mL
Right panel = mu-opioid receptor occupancy (μ-opioid receptor occupancy); Dashed line=70% μ-opioid receptor occupancy
A total of 6 SC injections given 28 days apart were simulated
Models used for simulation: INDV-6000-M03 Table 10 and INDV-6000-M02 Table 2 Source: Figure 41

[16] Summary of Clinical Pharmacology Studies page 99

11. Clinical efficacy

11.1. Studies providing evaluable efficacy data

Table 3 Efficacy Studies

Study	Description	Synopsis
RB-US-13-0001	A double-blind, placebo-controlled efficacy, safety and tolerability study	11.2.1
RB-US-13-0002	An open-label multiple-dose opioid blockade (OB) study	11.2.2
RB-US-13-0003	A long-term open-label safety and tolerability study	11.2.3
INDV-6000-301	An open-label extension study providing up to 6 months of additional treatment for subjects who completed Study 13-0003 and for whom a new treatment venue had not been identified or arranged	11.2.4

All studies were in opioid dependent subjects

11.2. Pivotal or main efficacy studies

11.2.1. Study 13-0001

A randomized, double-blind, placebo-controlled, multicentre[17] study to assess the efficacy, safety, and tolerability of multiple subcutaneous injections of depot buprenorphine (Sublocade [100mg and 300mg]) over 24 weeks in treatment-seeking subjects with Opioid Use Disorder.

11.2.1.1. Study design, objectives, locations and dates

Carried out from 28 January 2015 to 29 April 2016 in 33 US sites.

Male and female subjects ≥ 18 and ≤ 65 years of age, who were seeking medication-assisted treatment for the treatment of moderate or severe opioid use disorder. 470 subjects planned, 505 randomised, one in error.

The **primary objective** was to assess the efficacy of Sublocade (regimens of SC injections containing either 300mg buprenorphine or 300mg and 100mg buprenorphine) compared with placebo in treatment-seeking subjects with opioid use.

The **secondary objective** of this study was to continue evaluating the safety and tolerability of Sublocade compared with placebo in treatment-seeking subjects with opioid use disorder.

Endpoints

The **primary efficacy endpoint** for this study was the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use (from the TLFB interview) collected from Week 5 through Week 24 in the FAS.

There were 6 subgroup analyses.

There were 11 **secondary efficacy endpoints,** 3 exploratory efficacy endpoints and 11 Supplemental Presentations of efficacy data.

[17] Site 20 was excluded from primary and key secondary efficacy analyses due to compliance issues, but was included in all safety analyses

The **key secondary efficacy endpoint** was changed mid trial on FDA advice:

~~Two key secondary efficacy endpoints for this study will be evaluated to assess clinically relevant differences between treatment and placebo groups. These endpoints are:~~

~~1. Treatment success, which is defined as any subject with ≥75% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 17 and Week 24.~~

~~2. Duration of treatment success, which is defined as the longest sequence of consecutive weeks of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 17 and Week 24.~~

~~Both key secondary efficacy endpoints will be measured during the final 8 weeks of the double-blind phase of the study (Weeks 17 through 24) to allow subjects the greatest amount of time to engage in treatment and attain abstinence, which will be defined as having urine samples negative for opioids as well as self-reports negative for illicit opioid use. This strategy is supported by results from a multiple ascending dose study of RBP- 6000 (RB-US-12-0005), in which self-reported opioid drug use and actual opioid drug use as assessed by urine negative samples decreased following treatment with repeated SC injections of Sublocade. Reductions were the highest at the end of the study, approaching 90% or more by Day 65 (Week 9) following a dose of 300mg Sublocade.~~

<u>The key secondary endpoint in this study is treatment success. A responder is defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24.</u>

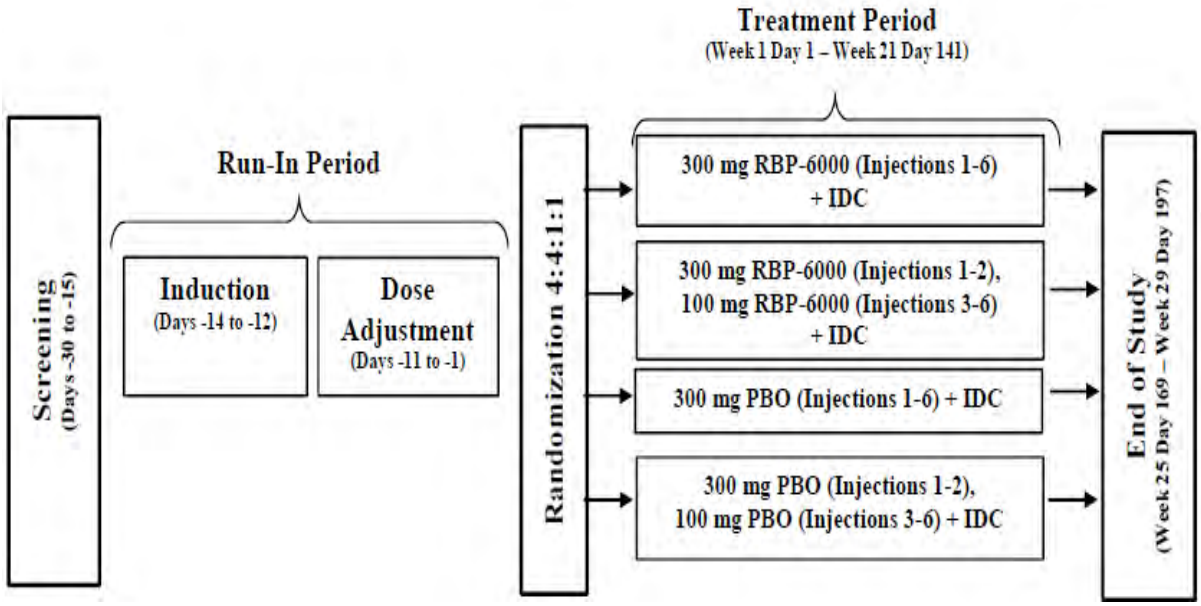
The study comprised:

- Up to 2-week screening period,
- Open-Label Run-in induction Phase with Suboxone sublingual film for 3 days followed by a 4-day to 11-day Suboxone sublingual film open-label run-in dose-adjustment period to achieve buprenorphine doses ranging from 8 to 24mg.
- Double-Blind Treatment Phase with randomisation on Day 1 to 1 of 2 dose regimens of Sublocade or equivalent volume of placebo for 6 SC injections separated by 28 days (± 2). Subjects also received manual-guided behaviour counselling (IDC) at least once per week starting at Day 1 and continuing through the end of the study. Eligible subjects were to be randomised to study treatment in a 4:4:1:1 ratio as follows:
    - Regimen 1: Sublocade 300mg SC every 28 days (± 2) × 6 doses + IDC
    - Regimen 2: Sublocade 300mg SC every 28 days (± 2) × 2 doses + IDC followed by Sublocade 100mg SC every 28 days (± 2) × 4 doses + IDC
    - Placebo Regimen 1: Volume-matched to Regimen #1 + IDC
    - Placebo Regimen 2: Volume-matched to Regimen #2 + IDC.

The design of the trial was also changed mid trial (21 August 2015) on FDA advice:

All randomised subjects who received an injection of study treatment began a 5-day Suboxone sublingual film taper on Day 1. This taper was intended to preserve the blind of the study and to mitigate potential withdrawal signs and symptoms in placebo-treated subjects. A total of 163 randomised subjects received a 5-day Suboxone sublingual film taper.

Figure 2 Study Design



IDC=individual drug counselling: Subjects received IDC during the double-blind treatment period. A total of 163 of the 504 subjects enrolled (32.3%) received a 5-day Suboxone taper as follows: Day 1 (6 mg), Day 2 (4 mg), Day 3 (4 mg), Day 4 (2 mg) and Day 5 (2 mg), according to Amendment 2. Source: Figure 1

11.2.1.2. Analysis populations

Included **Full Analysis Set**:

The Full Analysis Set (FAS) was comprised of all randomised subjects. A randomised subject was defined as any subject that was randomised and allocated study treatment in the IXRS system. This population was used for all efficacy analyses.

11.2.1.3. Sample size

Although there is no true consensus on what constitutes a clinically meaningful difference between placebo and an active treatment in a subject population with opioid use disorder, recent studies suggested that 20% is a clinically meaningful difference.[18] For the purpose of sample size estimation for this study, a slightly smaller treatment difference was assumed to avoid under powering the study. Assuming a placebo response of 15%, a difference of 15% between Sublocade (100mg) and placebo, and a common SD of 30%, the minimum required sample size to achieve at least 90% power using a 2-sided Wilcoxon rank sum test with $\alpha = 5\%$, is 92 subjects per group.

In order to obtain at least 150 completed subjects per active treatment group for inclusion in a long-term safety study (13-0003), and assuming that approximately 20% of the subjects randomised to the active treatment would drop out, the minimum planned sample size was increased to 188 subjects in each active treatment group and 94 subjects in the placebo group.

Hence, a total of 470 subjects were to be randomised in a 4:4:1:1 ratio to Sublocade (300/300mg), Sublocade (300/100mg) or volume-matched placebo (188:188:47:47). Assuming that 20% of the enrolled subjects were to drop out during the Suboxone sublingual film run in phase, approximately 588 subjects were to be enrolled.

11.2.1.4. Statistical methods

The **primary** null (H_0) and research hypotheses (H_a) were as follows:

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H_0: Neither of the 2 dose regimens of Sublocade (dose Regimen 1: 6 × 300mg or dose Regimen 2: 2 × 300mg + 4 × 100 mg) is superior to placebo at Week 24 with respect to the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24, examined as a cumulative distribution function.

H_a: At least 1 of the 2 dose regimens of Sublocade (dose Regimen 1: 6 × 300mg + or dose Regimen 2: 2 × 300mg + 4 × 100 mg) is superior to placebo at Week 24 with respect to the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24, examined as a cumulative distribution function.

Since the primary endpoint was not normally distributed, a nonparametric test procedure, the Wilcoxon rank-sum test, was used to compare the treatment groups. To test the 2 primary hypotheses, a truncated Hochberg procedure was used with a truncation parameter of 0, which reduces to Bonferroni. Therefore, the 2 primary hypotheses were tested at $\alpha = 0.025$ level.

The null (H_{10}) and research hypotheses (H_{1a}) for the **key secondary** efficacy endpoint of treatment success were:

- H_{10}: Neither of the 2 dose regimens of Sublocade is superior to placebo with respect to treatment success.
- H_{1a}: At least 1 of the 2 dose regimens of Sublocade is superior to placebo with respect to treatment success.

The Cochran-Mantel-Haenszel (CMH) test was used to test the difference in treatment success rates.

The primary hypotheses were tested. In order to enable a flexible α propagation, a truncated Hochberg procedure was used with a truncation parameter of 0, which reduces to Bonferroni.

If at least 1 of the primary hypotheses was significant, the key secondary hypotheses were to be tested.

Only the 4 comparisons of the 2 primary efficacy and 2 key secondary efficacy endpoints had adjustments for multiplicity.

11.2.1.5. Participant flow

Table 4 Subject Disposition - All Screened Subjects

Category	Total	RBP-6000 300mg/100mg+IDC (N = 203) n (%)	RBP-6000 300mg/300mg+IDC (N = 201) n (%)	Placebo+IDC (N = 100) n (%)
Screened Subjects	1187			
Screen Failures	682			
Screen Failures and entered the Run-in Phase[1]	160			
Screen Failures and not in Run-in Phase	522			
Entered the Run-in Phase[2]	665			
Run-in Failures[3]	161			
Death during Run-in Phase	0			
Randomised	504	203 (100.0)	201 (100.0)	100 (100.0)
Randomised but not treated[4]	0	0 (0.0)	0 (0.0)	0 (0.0)
Randomised and treated	504	203 (100.0)	201 (100.0)	100 (100.0)
Completed	288	125 (61.6)	129 (64.2)	34 (34.0)
Discontinued	216	78 (38.4)	72 (35.8)	66 (66.0)
Reasons for discontinuation				
Lost to follow-up	61	26 (12.8)	23 (11.4)	12 (12.0)
Subject withdrew consent to participate	59	20 (9.9)	21 (10.4)	18 (18.0)
Other[5]	30	17 (8.4)	6 (3.0)	7 (7.0)
Lack of efficacy	26	3 (1.5)	5 (2.5)	18 (18.0)
Adverse event	18	6 (3.0)	10 (5.0)	2 (2.0)
Protocol deviation	7	2 (1.0)	5 (2.5)	0 (0.0)
Withdrawal symptoms	5	1 (0.5)	1 (0.5)	3 (3.0)
Noncompliance with study drug	4	2 (1.0)	0 (0.0)	2 (2.0)
Subject was withdrawn by the investigator	4	1 (0.5)	0 (0.0)	3 (3.0)
Physician decision	2	0 (0.0)	1 (0.5)	1 (1.0)
Death[6]	0	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0	0 (0.0)	0 (0.0)	0 (0.0)

IDC = individual drug counselling

[1] These subjects were in the clinical database as screen failures; however, they also received at least 1 dose of Suboxone SL film.

[2] Includes subjects who received at least 1 dose of Suboxone sublingual film during the run-in phase.

[3] An additional 34 subjects were identified as run-in failures in the datasets but didn't enter the run-in phase. These 34 subjects are not included in the count of run-in failures, as they did not take any run-in medication and are therefore included in the 522 subjects who were "Screen failures and not in run-in phase".

[4] one subject was randomised, but did not receive any study treatment during the double-blind phase, including the Suboxone sublingual film taper.

[5] Discontinuation due to "other" includes site closed by sponsor (n = 9), incarceration (n = 7), relocation (n = 4), noncompliance with study visits/lost to follow-up type reasons (4)

[6] one subject in Sublocade 300 mg/300mg group discontinued due to adverse event that led to death.

Note:2 subjects were run-in failures due to the primary reason of adverse event. The action taken was reported as not applicable as the case report form was intended to capture action taken only with randomised study treatment. Source: Table 13

11.2.1.6. Major protocol violations/deviations

41 subjects had important protocol deviations pertaining to violation of inclusion/exclusion criteria (14 subjects received 300mg/100mg, 17 subjects received 300mg/300mg and 10 subjects received placebo) and 1 subject had a protocol deviation pertaining to receipt of incorrect study treatment (placebo group).

11.2.1.7. Baseline data

Table 5 Demographic and Baseline Characteristics - Full Analysis Set

Subject Characteristics	Sublocade 300mg/100mg+IDC (N = 194)	Sublocade 300mg/300mg+IDC (N = 196)	Placebo+IDC (N = 99)
Age (years)			
n	194	196	99
Mean (SD)	40.4 (11.23)	39.3 (10.96)	39.2 (10.96)
Median	39.0	38.0	38.0
Min, Max	20, 64	19, 64	20, 63
Age (years) by categories (%)			
≥ 18 to < 30	39 (20.1)	43 (21.9)	23 (23.2)
≥ 30 to < 45	84 (43.3)	93 (47.4)	44 (44.4)
≥ 45 to < 60	64 (33.0)	52 (26.5)	30 (30.3)
≥ 60	7 (3.6)	8 (4.1)	2 (2.0)
Sex (%)			
Male	128 (66.0)	132 (67.3)	64 (64.6)
Female	66 (34.0)	64 (32.7)	35 (35.4)
Baseline Weight (kg)			
n	194	196	99
Mean (SD)	76.68 (15.932)	79.65 (16.233)	75.48 (16.143)
Median	74.95	78.05	72.90
Min, Max	45.5, 123.4	47.6, 128.0	48.2, 132.0
Baseline BMI (kg/m^2)			
n	194	196	99
Mean (SD)	25.32 (4.206)	26.35 (4.395)	25.30 (4.266)
Median	24.70	25.50	25.00
Min, Max	18.0, 34.9	18.0, 35.0	17.9, 35.0
Opioid Users at Screening (%)			
Non-injectable Opioid Users	138 (71.1)	136 (69.4)	57 (57.6)
Injectable Opioid Users	84 (43.3)	80 (40.8)	50 (50.5)
Subjects used illicit opioids in addition to run-in medication as indicated by positive UDS on Day 1 (%)	91 (46.9)	104 (53.1)	45 (45.5)
Subjects did not use illicit opioids in addition to run-in medication as indicated by negative UDS on Day 1 (%)	103 (53.1)	92 (46.9)	54 (54.5)

IDC = individual drug counselling Subjects from Site 20 were excluded from the analysis. Source: Table 15 & 16

Results

11.2.1.1. Results for the primary efficacy Endpoint

The primary efficacy endpoint was the Cumulative Distribution Function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24. Both the 300mg/100mg and 300mg/300mg groups were statistically significantly superior to placebo (both $P < 0.0001$); mean (median) percentages were 42.7% (32.5%), 41.3% (30%) and 5% (0%), respectively.

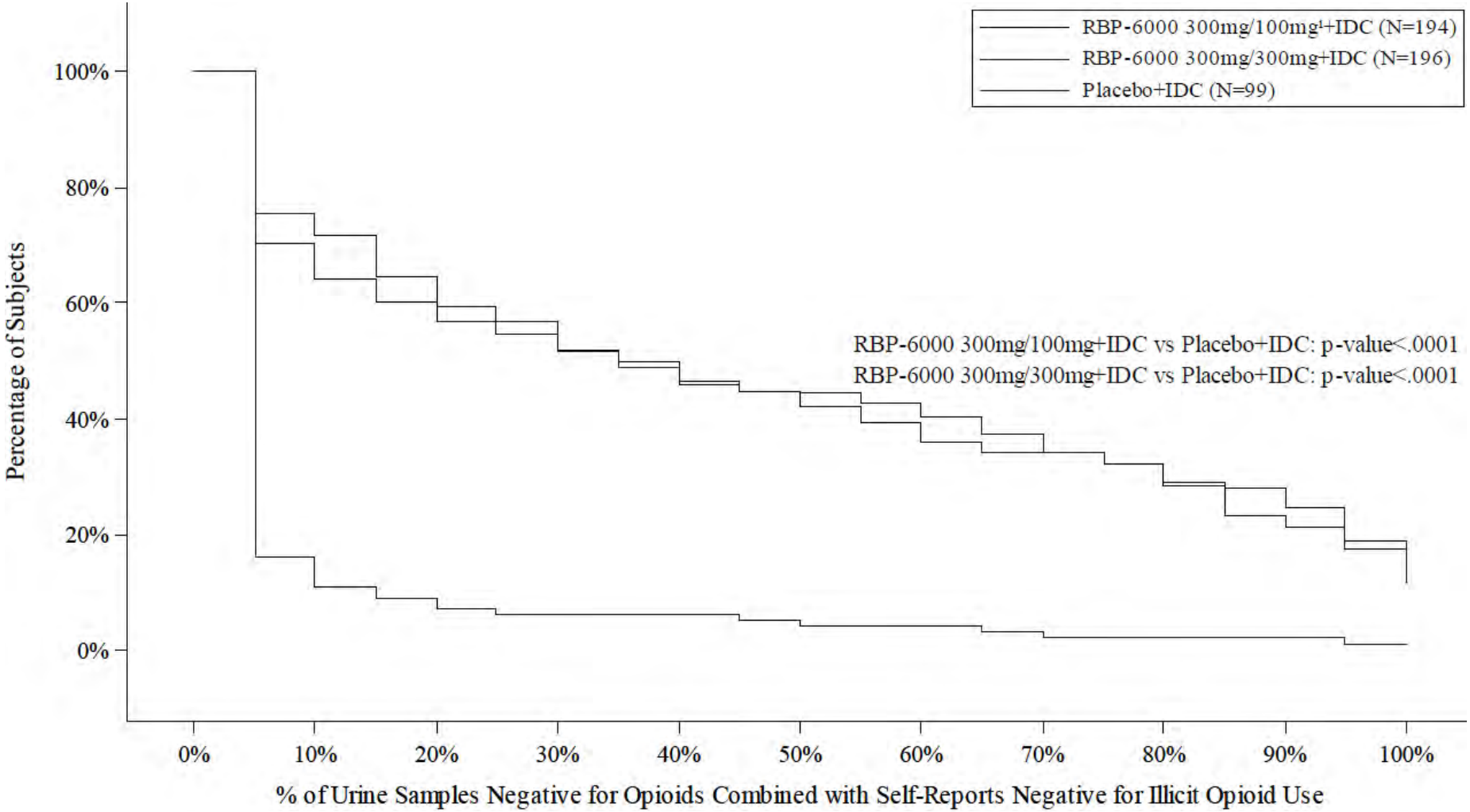
Table 6 Primary Efficacy Endpoint: Cumulative Distribution Function of the Percentage Abstinence From Week 5 Through Week 24 - Full Analysis Set

	Number (%) of Subjects		
Percentage Abstinence	RBP-6000 300mg/100mg+IDC (N = 194)	RBP-6000 300mg/300mg+IDC (N = 196)	Placebo+IDC (N = 99)
≥ 0%	194 (100.0)	196 (100.0)	99 (100.0)
≥ 10%	139 (71.6)	126 (64.3)	11 (11.1)
≥ 20%	115 (59.3)	111 (56.6)	7 (7.1)
≥ 30%	101 (52.1)	101 (51.5)	6 (6.1)
≥ 40%	90 (46.4)	90 (45.9)	6 (6.1)
≥ 50%	86 (44.3)	82 (41.8)	4 (4.0)
≥ 60%	78 (40.2)	70 (35.7)	4 (4.0)
≥ 70%	66 (34.0)	67 (34.2)	2 (2.0)
≥ 80%	55 (28.4)	57 (29.1)	2 (2.0)
≥ 90%	41 (21.1)	48 (24.5)	2 (2.0)
P-value[1] (comparison with Placebo+IDC)	< 0.0001	< 0.0001	
n	194	196	99
Mean (SD)	42.7% (38.50%)	41.3% (39.66%)	5.0% (16.98%)
Median	32.5%	30.0%	0.0%
Min, Max	0%, 100%	0%, 100%	0%, 100%

IDC = individual drug counselling; The primary endpoint, percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use, is "percentage abstinence". Subjects from Site 20 were excluded from the analysis. All missing results for opioids were considered non-negative.

[1] Wilcoxon rank-sum test was used to compare the treatment groups. Each dosing regimen was compared to placebo with respect to the composite primary efficacy endpoint at a significance level of $\alpha = 0.025$. Source: Table 23

Figure 3 Primary Efficacy Endpoint: Cumulative Distribution Function of the Percentage of Subjects Abstinent From Week 5 Through Week 24 – Full Analysis Set



IDC = individual drug counselling Subjects from Site 20 were excluded from the analysis.
All missing results for opioids were considered nonnegative. Depicted data are inverse-cumulative distribution function.
[1] Subjects received Sublocade containing 300mg buprenorphine for the first 2 injections, followed by 4 injections of Sublocade containing 100mg buprenorphine. Source: Figure 3

11.2.1.2. Results for the key secondary efficacy endpoint

The key secondary endpoint in this study was treatment success. A responder was defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24.

Both the 300mg/100mg and300 mg/300mg groups were statistically significantly superior to placebo (both P < 0.0001); percentages were 28.4% and 29.1% vs. 2.0% respectively.

Table 7 Treatment Success - Full Analysis Set

	Number (%) of Subjects				
Key Secondary Efficacy Endpoint	RBP-6000 300mg/100mg+IDC (N = 194)	RBP-6000 300mg/300mg+IDC (N = 196)	Placebo+IDC (N = 99)	*P*-Value[2] (300mg/100 mg+IDC vs Placebo+IDC)	*P*-Value[2] (300mg/300 mg+IDC vs Placebo+IDC)
Treatment Success[1]	55 (28.4)	57 (29.1)	2 (2.0)	< 0.0001	< 0.0001

IDC = individual drug counselling
Subjects from Site 20 were excluded from the analysis.
[1] Treatment success was defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24.
[2] The Cochran-Mantel-Haenszel test was used to compare the treatment groups. Source: Table 29

11.2.2. Study 13-0002

A US single centre multiple-dose study of blockade of subjective opioid effects, plasma levels, and safety of subcutaneous injections of depot buprenorphine in subjects with opioid use disorder.

The study was from 19 November 2013 – 29 July 2014, publication[19] was February 2016, but this report is dated 27 February 2017. 39 enrolled, 38 in ITT population.

From the Protocols:

"Based on a review of the protocol by Reckitt Benckiser Pharmaceuticals, Inc. and Vince and Associates Clinical Research, Inc., and feedback from the U.S. Food and Drug Administration (FDA)" the primary objective was modified twice mid trial and all the secondary objectives were modified once.

Comment: These changes were not described in the CSR.

The **primary objective** of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade).

Secondary Objectives:

- To evaluate the reinforcing effects (using Choice Sessions) of the daily randomized hydromorphone challenge dose (relative to money) at weekly time points post injection of buprenorphine 300mg (Sublocade).
- To evaluate the correlation between the opioid blockade subjective effects (VAS of "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and

[19] Nasser et al Sustained-release Buprenorphine (RBP-6000) Blocks the Effects of Opioid Challenge with Hydromorphone in Subjects with Opioid Use Disorder. J Clin Psychopharmacol. 2016 Feb 1;36(1):18-26.

"High") and the reinforcing effects of hydromorphone and simulated mu opioid receptor occupancy (using the maximal effect [E_{max}] model). (See also 21.1.2.1).

- To determine the relationship between plasma concentration and predicted mu opioid receptor occupancy of buprenorphine and both the blockade of the subjective effects of hydromorphone post injection of buprenorphine 300mg (Sublocade). (See also 21.1.2.1).
- To continue evaluating the safety of Sublocade when administered once per month for 2 months as a depot injection of 300mg in individuals who have been inducted and dose stabilized on sublingual (SL) buprenorphine (Suboxone Film) on a dose between 8 and 24 mg/day and in the presence of 6 and 18mg of hydromorphone.

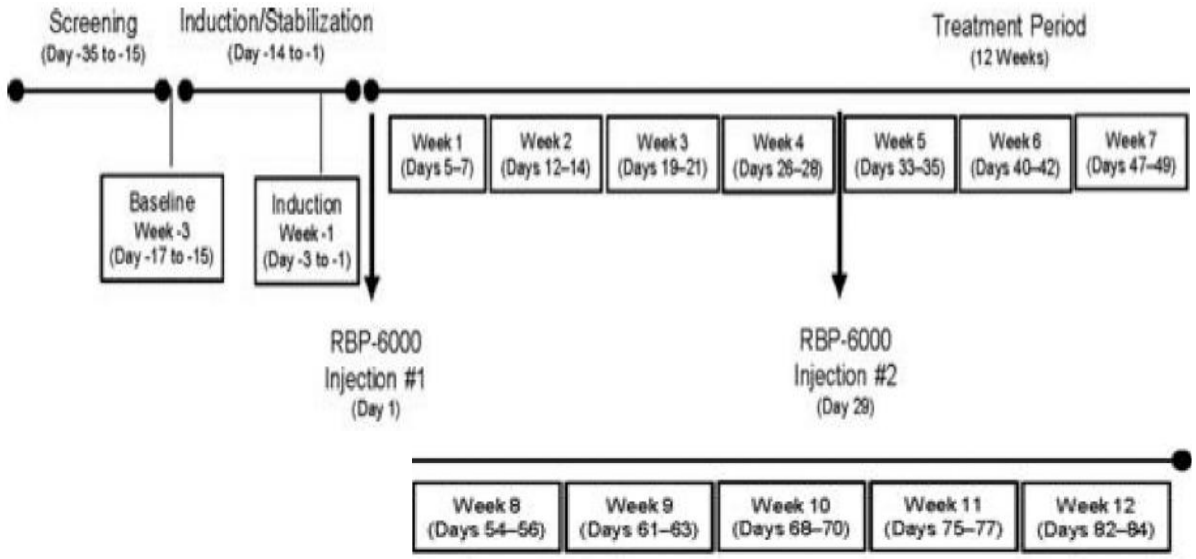
For PKs see 21.1.1.5.

A *post-hoc* analysis was conducted[20] to assess whether the peak (E_{max}) of "Drug Liking" VAS score measured after challenge with IM injections of 6mg and 18mg hydromorphone was not inferior compared to the E_{max} of "Drug Liking" VAS score measured after challenge with placebo at Weeks 1 through 12.

To enter the trial subjects had establish their opiate liking by undertaking a **hydromorphone challenge** of 18mg. [21]

The study comprised an initial 2 weeks on SL Suboxone (buprenorphine and naloxone) followed by 2 injections of Sublocade (depot buprenorphine) 4 weeks apart associated with 12 weeks of observation.

Figure 4 Study design



The boxes represent days of hydromorphone challenge tests they go on out to 12weeks Source: Figure 1 article

Subjects were initially stabilised over 3 days on a dose of 8mg to 24mg of Suboxone sublingual film daily which was continued for the rest of 2 weeks.

On day 1, subjects were administered a single SC injection of Sublocade (300mg) into the abdominal area. A second injection of Sublocade was administered on day 29. The final study visit was 9 weeks after the second injection of Sublocade or after early study termination.

[20] at the request of the US FDA

[21] an acceptable response was defined as having a "Drug Liking" VAS score of at least 40 mm [out of 100 mm on a scale anchored by "none" or "not at all" and "extreme" or "extremely" CSR page 29

Testing for efficacy was done on blocks of 3 consecutive days:

- The last 3 days of Suboxone exposure.
- At the end of every successive week after Sublocade injection.

Following administration of a varying dose of hydromorphone (hydromorphone challenges), subjective effects were measured and Reinforcing Effects Tasks undertaken in order to evaluate opioid blockade.

Hydromorphone challenges

Subjects received one intramuscular injection of placebo (0mg hydromorphone; 0.45% sodium chloride) or 6 or 18mg of hydromorphone (constant 1.8mL volume) in 1 of 6 randomized sequences[22] and 6 VAS assessments and the drug vs. money choice task were conducted.

Reinforcing Effects Tasks were described in the protocol,[23] they are better described in the journal article as Drug Versus Money Choice Task:

At least 5 hours after the baseline and treatment period, randomized hydromorphone challenges subjects completed a 12-trial drug/money choice task. On each trial, the subject could choose to earn 1 of the 12 total hydromorphone (or placebo) unit doses (i.e. 0mg, 0.5mg or 1.5mg per trial) they had received that morning or US $2. To earn each choice, subjects had to click either the "drug" or "money" box displayed on the computer screen. The number of mouse clicks required to receive each reward (drug or money) increased exponentially across trials (5, 40, 70, 120, 180, 260, 395, 555, 775, 1110, 1558, 2160 mouse clicks), according to a progressive ratio schedule of reinforcement. The response requirement for both drug and money increased (independently from one another) until responding ceased, all 12 ratios were completed or the participant chose to work for the alternative option. The "breakpoint" was defined as the highest number of mouse clicks completed to receive the hydromorphone unit dose.

In the initial Suboxone period on the last 3 days of Suboxone treatment, hydromorphone challenges were given 8h prior to Suboxone.

Table 8 Relative and Absolute Treatment Times for Hydromorphone and Suboxone

Drug/Activity	Time to Start Prior to SUBOXONE Sublingual Film	Time to Start Prior to Earned Hydromorphone	Suggested Time
Randomised Hydromorphone Challenge	-8 hours	-6 hours	9 AM
Start of Reinforcing Effects Tasks	-3 hours	-1 hour	2 PM
Hydromorphone earned from Reinforcing Effects Tasks	-2 hours	NA	3 PM
SUBOXONE sublingual film administration	NA	NA	5 PM

Source: Table 1

After the initial Sublocade injection, hydromorphone challenges (in randomized study drug sequences) and 6 VAS assessments and the drug vs. money choice task were conducted on 3 consecutive residential days at the end of each week for a total of 12 weeks. During each 3-day hydromorphone challenge, the clinical staff and subjects remained blinded to the sequence.

[22] Sequence 1: 0 mg (placebo), 6 mg, 18 mg Sequence 2: 6 mg, 18 mg, 0 mg (placebo) Sequence 3: 18 mg, 0 mg (placebo), 6 mg Sequence 4: 0 mg (placebo), 18 mg, 6 mg Sequence 5: 6 mg, 0 mg (placebo), 18 mg Sequence 6: 18 mg, 6 mg, 0 mg (placebo)
[23] E.g. page 426

Statistical analysis

Opioid Blockade Subjective Effects Analysis ("Drug Liking" Visual Analog Scale)

For each hydromorphone challenge week, a mixed-effects model with period (where period is day), hydromorphone sequence, and hydromorphone dose as fixed effects and subject nested within hydromorphone sequence as a random effect were used for analysis. The difference in mean outcome between hydromorphone doses was compared using SAS™ estimate statements.

Opioid blockade was achieved at dose 1 of the hydromorphone challenge if:

the null hypothesis (H_0:M_1-M_0 > d)

was rejected in favour of

the alternative hypothesis (HA: M_1-M_0 ≤ d)

Where

M_0 = the mean response to placebo (0mg hydromorphone)

M_1 = the mean response to hydromorphone challenge dose 1 (6mg hydromorphone)

M_2 = the mean response to hydromorphone challenge dose 2 (18mg hydromorphone),

d is the non-inferiority margin = 11.

Complete hydromorphone blockade was claimed for Sublocade if blockade was achieved for both hydromorphone doses (6mg and 18mg) during each week of testing for the 4 weeks after the first dose of Sublocade.

Each of the above tests was performed at a 2-sided α = 0.05. Since this was an intersection union test, there was no need to adjust for multiple testing, and the overall test was a size-α test

If a significant departure from normality was found in the data, descriptive statistics were provided to assess whether there were sequence, period, or first-order-carryover effects. Chen's t-test for the mean of a skewed distribution was used to test the individual differences between responses to dose 1 and placebo and dose 2 and placebo.

Reinforcing Effects

The ability of Sublocade to attenuate the reinforcing effects of hydromorphone was analysed using the hydromorphone breakpoint value. For each subject, the hydromorphone breakpoint value was determined at each hydromorphone challenge based on the hydromorphone units earned values on the electronic case report form after the completion of each session.

Hydromorphone breakpoint values for all subjects were then analysed by week using a repeated measures mixed-effects model with period, hydromorphone sequence, and hydromorphone dose as fixed effects and subject nested within hydromorphone sequence as a random effect. Difference in mean outcome between hydromorphone doses was compared using SAS™ estimate statements. The purpose of this analysis was to show that there was no difference in breakpoint value between placebo, 6mg hydromorphone and 18mg hydromorphone at each week.

Determination of Sample Size

The sample size calculation formula for testing a non-inferiority hypothesis in a Williams' square design was used, the resulting sample size needed per sequence was n = 4 (with 4 subjects assigned to each sequences of a Williams' 6 x 3 design a minimum of 24 subjects).

For this study, a non-inferiority margin of 11 (δ = 11) was proposed according to Chen (2011).[24]

[24] Analysis of Data from Human Abuse Potential Studies. CPDD 73rd Annual Meeting (presentation). 2011.

Comment: The CSR reference was not provided in the submission nor found in the meeting abstract book on line. A different reference for this in the Summary of Clinical Pharmacology Studies was also not in the submission but the abstract existed online.[25]

There were a total of 27 **major deviations** reported; 3 involved hydromorphone dosing irregularities and there were 24 incidences in which the subjective effects VAS assessments were administered with 95mm scales instead of 100mm scales on Day-17.

Table 9 Summary of Subject Disposition (Population: Safety)

	Overall N = 39 n (%)
Safety Population	39 (100.0)
Completed	30 (76.9)
Withdrew	9 (23.1)
Reason for Withdrawal	
Lost to follow-up	3 (7.7)
Physician decision	3 (7.7)
Withdrawal by subject	3 (7.7)

Source: Table 7

Table 10 Summary of Demographics (Population: Safety)

	Category or Statistic	Overall N=39
Gender - n (%)	Male	35 (89.7)
	Female	4 (10.3)
Age (yr)	N	39
	Mean	34.6
	SD	8.93
	Median	34.0
	Min, Max	20, 55
Weight (kg)	N	39
	Mean	79.55
	SD	11.178
	Median	78.40
	Min, Max	60.9, 102.5
BMI (kg/m^2)	N	39
	Mean	25.35
	SD	3.017
	Median	25.20
	Min, Max	20.7, 31.5

N = number of subjects; n = number of subjects in a subset in a given category
The safety population included all subjects who received at least one dose of Sublocade, Suboxone sublingual film, or hydromorphone (starting with the baseline hydromorphone challenge). Source: Table 8

[25] Chen L, Bonson KR. An equivalence test for the comparison between a test drug and placebo in human abuse potential studies. J Biopharm Stat. 2013 Mar 11;23(2):294-306.

Results

Primary endpoint "Drug Liking" VAS score Weeks 1-4

The study failed to achieve the primary endpoint failing to meet the non-inferiority margin at one time point during the first 4 weeks (18mg hydromorphone at 4 weeks).
During the hydromorphone challenge qualification period (screening, referred here as Week -1), no opioid blockade was observed. After treatment with Suboxone SL film, a decrease in "Drug Liking" VAS scores was observed, but not opioid blockade.
Following SC injection of Sublocade, the "Drug Liking" VAS analysis demonstrated opioid blockade for the 6mg hydromorphone to placebo treatment comparison from Week 1 to Week 4 (Sublocade injection 1 period). For the 18mg hydromorphone to placebo treatment comparison, opioid blockade was observed from Week 1 to Week 3, while at Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade. After the first injection of SC Sublocade, during week 4, a decrease in mean buprenorphine plasma concentration (from 1.9 to 1.8ng/mL) correlated with a 65% μ-opioid receptor occupancy , which corresponded to the slight increase in VAS scores.[26]
Following the second SC injection of Sublocade, opioid blockade was achieved for both the 6mg and 18mg hydromorphone to placebo treatment comparison over the full dosing interval (from Week 5 to Week 8) and was maintained for an additional 4 weeks (from Week 9 to Week 12), despite no further injections of Sublocade.

Secondary Endpoints

Reinforcing effects

For the Reinforcing Effects Tasks analysis, no diminished reinforcing effect of hydromorphone was observed during the hydromorphone qualification challenge period.
The Reinforcing Effects Tasks analysis showed that the reinforcing effects of hydromorphone compared to placebo diminished over the course of the study. Specifically, whereas the LSMeans of the $\log_{10}$ transformed values of the Reinforcing Effects Tasks scores remained for the most part consistent for the placebo (mean = 1.937, SD = 0.2221), the corresponding values for the 6mg and 18mg doses of hydromorphone decreased from baseline through Week 12. For the 6mg dosage, the observed reduction was from approximately 3.093 at baseline to 2.008 at the end of Week 12. For the 18mg dosage, the corresponding range was from 3.058 at baseline to 2.438 at the end of Week 12.
If the 95% CI for the difference in the LSMeans of the $\log_{10}$ transformations of the breakpoint values for the Reinforcing Effects Task scores for either of the active hydromorphone doses (6mg and 18mg) compared to placebo enclosed 0, then there was considered to be no difference between the active dose and placebo. The results indicated that there was no difference between the 6mg dose of hydromorphone and placebo at Weeks 1, 2, and 5 through 12; and no difference between the 18mg dose and placebo at Weeks 5, 6, 8, 9, 10, and 11

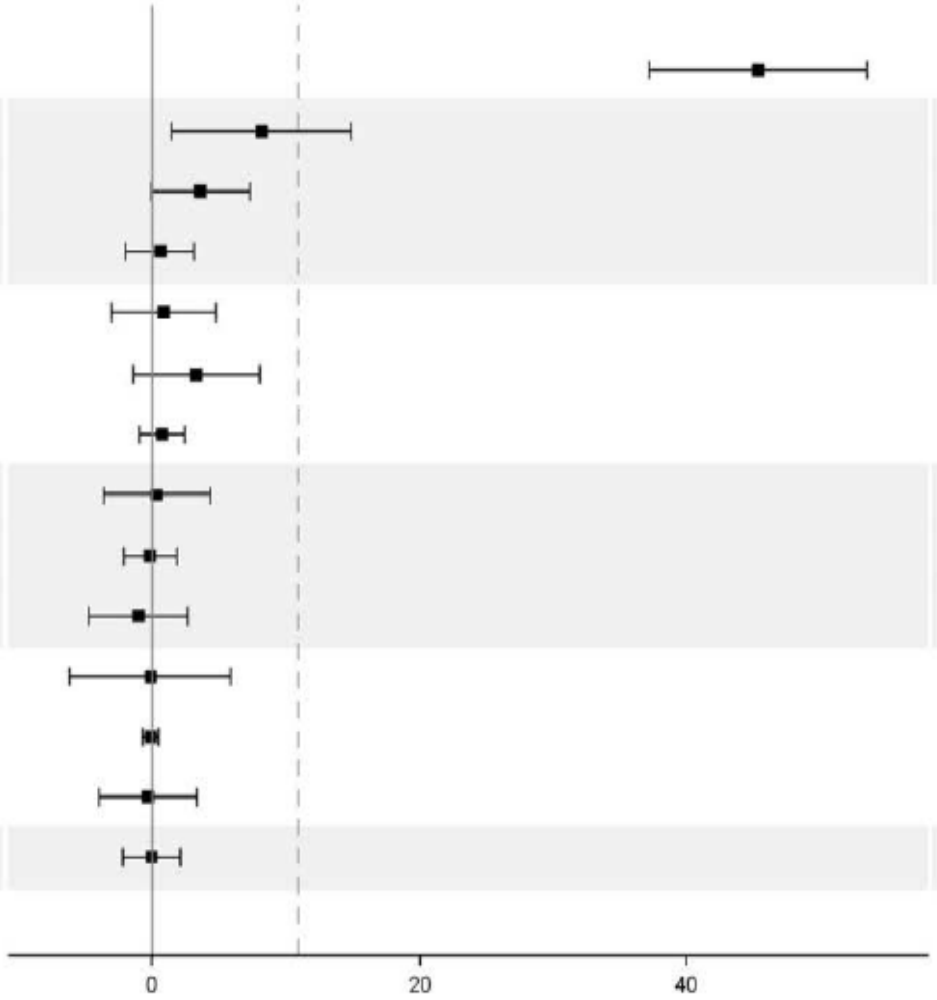
Opioid Blockade Subjective Effects (VAS of "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High")

For the 5 additional VAS analyses, full opioid blockade was observed from Week 1 to Week 12 after Sublocade treatment for both the 6mg and 18mg hydromorphone to placebo treatment comparisons, except for the following 18mg to placebo comparisons: Week 3, Good Drug Effect (upper 95% CI = 11.238); Week 4, High (12.009), Week 4, Any Drug Effect (12.743), and Week 4, Good Drug Effect (12.502).

[26] Publication

Table 11 Plot of Mean Difference and 95% CI for VAS Score: Drug Liking Comparison: 6mg Hydromorphone vs. Placebo

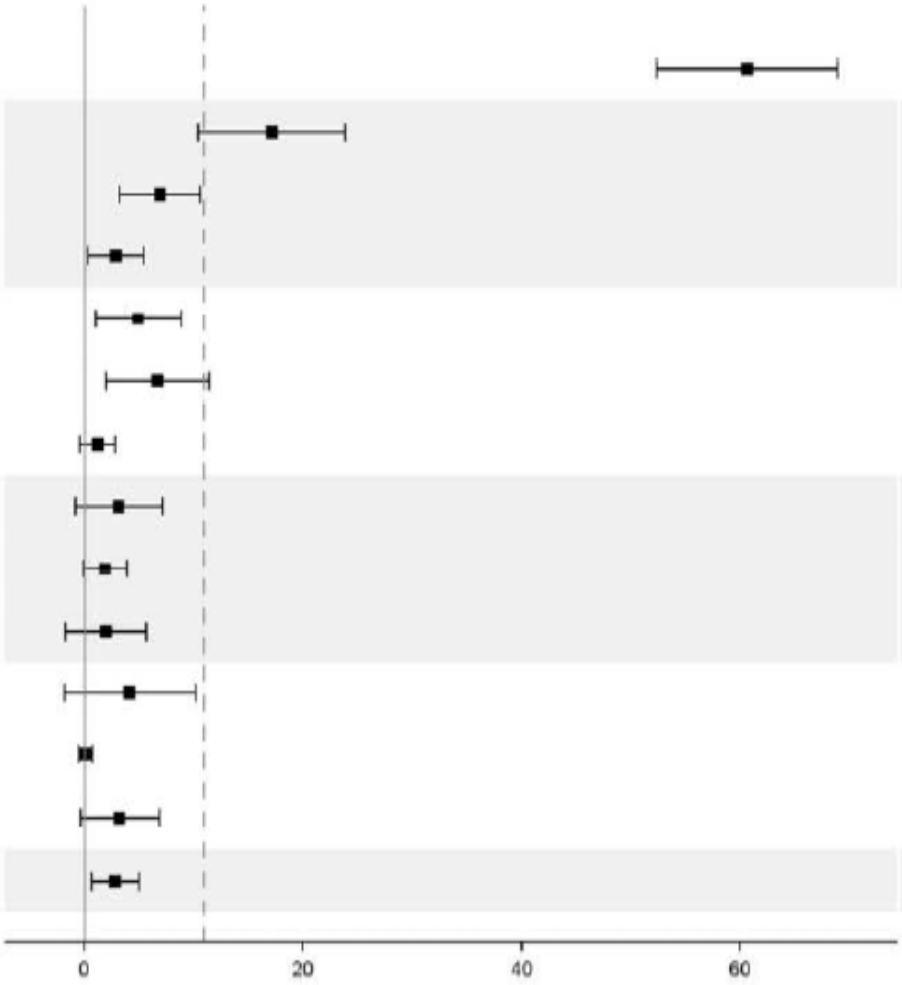
Weeks in Study	LS Means[1]	STDERR[2]	Lower 95% CI	Upper 95% CI
Baseline (Week -1)	45.36	4.11	37.16	53.56
Week 0	8.2	3.38	1.47	14.94
Week 1	3.66	1.85	-0.03	7.34
Week 2	0.59	1.28	-1.98	3.15
Week 3	0.86	1.96	-3.05	4.78
Week 4	3.32	2.37	-1.42	8.06
Week 5	0.74	0.84	-0.94	2.42
Week 6	0.35	1.98	-3.62	4.32
Week 7	-0.15	1	-2.16	1.86
Week 8	-1.04	1.85	-4.77	2.68
Week 9	-0.12	3.01	-6.2	5.95
Week 10	-0.09	0.3	-0.69	0.51
Week 11	-0.32	1.81	-3.97	3.34
Week 12	-0.03	1.07	-2.19	2.12



STDERR = Standard Error of LSMeans difference Dashed line is non-inferiority bound (11). Blockade was achieved for weeks on study if the plot wholly lied left of the non-inferiority bound.
Baseline (pre-buprenorphine treatment phase) was defined as Day -17, Day -16, and Day -15 Week 0 (Suboxone sublingual phase) was defined as Day -3, Day -2, and Day -1
[1] Estimate of Least Squares (LS) Means difference between active drug and placebo (Intent-to-treat population: 38 subjects).
[2] Standard Error of the LSMeans difference between active drug and placebo. Source: Figure 26

Table 12 Plot of Mean Difference and 95% CI - VAS Score: Drug Liking - Comparison: 6mg Hydromorphone vs Placebo (Population: ITT)

Weeks in Study	LS Means[1]	STDERR[2]	Lower 95% CI	Upper 95% CI
Baseline (Week -1)	60.61	4.16	52.32	68.9
Week 0	17.17	3.38	10.43	23.9
Week 1	6.93	1.85	3.24	10.61
Week 2	2.9	1.28	0.33	5.46
Week 3	4.93	1.96	1.02	8.84
Week 4	6.68	2.37	1.94	11.42
Week 5	1.21	0.82	-0.43	2.85
Week 6	3.16	1.99	-0.83	7.15
Week 7	1.88	0.99	0.11	3.87
Week 8	1.93	1.85	-1.79	5.66
Week 9	4.16	2.97	-1.84	10.17
Week 10	0.13	0.31	-0.5	0.76
Week 11	3.24	1.78	-0.35	6.83
Week 12	2.78	1.08	0.61	4.96



STDERR = Standard Error of LSMeans difference Dashed line is non-inferiority bound (11). Blockade was achieved for weeks on study if the plot wholly lied left of the non-inferiority bound.
Baseline (pre-buprenorphine treatment phase) was defined as Day -17, Day -16, and Day -15 Week 0 (Suboxone sublingual phase) was defined as Day -3, Day -2, and Day -1
[1] Estimate of Least Squares (LS) Means difference between active drug and placebo (Intent-to-treat population: 38 subjects).
[2] Standard Error of the LSMeans difference between active drug and placebo. Source: Figure 27

11.2.3. Study 13-0003

An open-label, long-term safety and tolerability study of depot buprenorphine in treatment-seeking subjects with opioid use disorder. Conducted at 39 US sites from 27 July 2015 to 31 January 2017.

The **primary** objective of this study was to assess the long-term safety and tolerability of SC administration of Sublocade in subjects with opioid use disorder

The **secondary** objective of this study was to collect clinical outcome data after SC administration of Sublocade in subjects with opioid use disorder.

Run-in Period

After 14 days of Suboxone SL Subjects who had no significant opioid craving (Opioid Craving VAS of ≤ 20 mm) and no significant withdrawal (COWS score of ≤ 12) were continued into the treatment period.

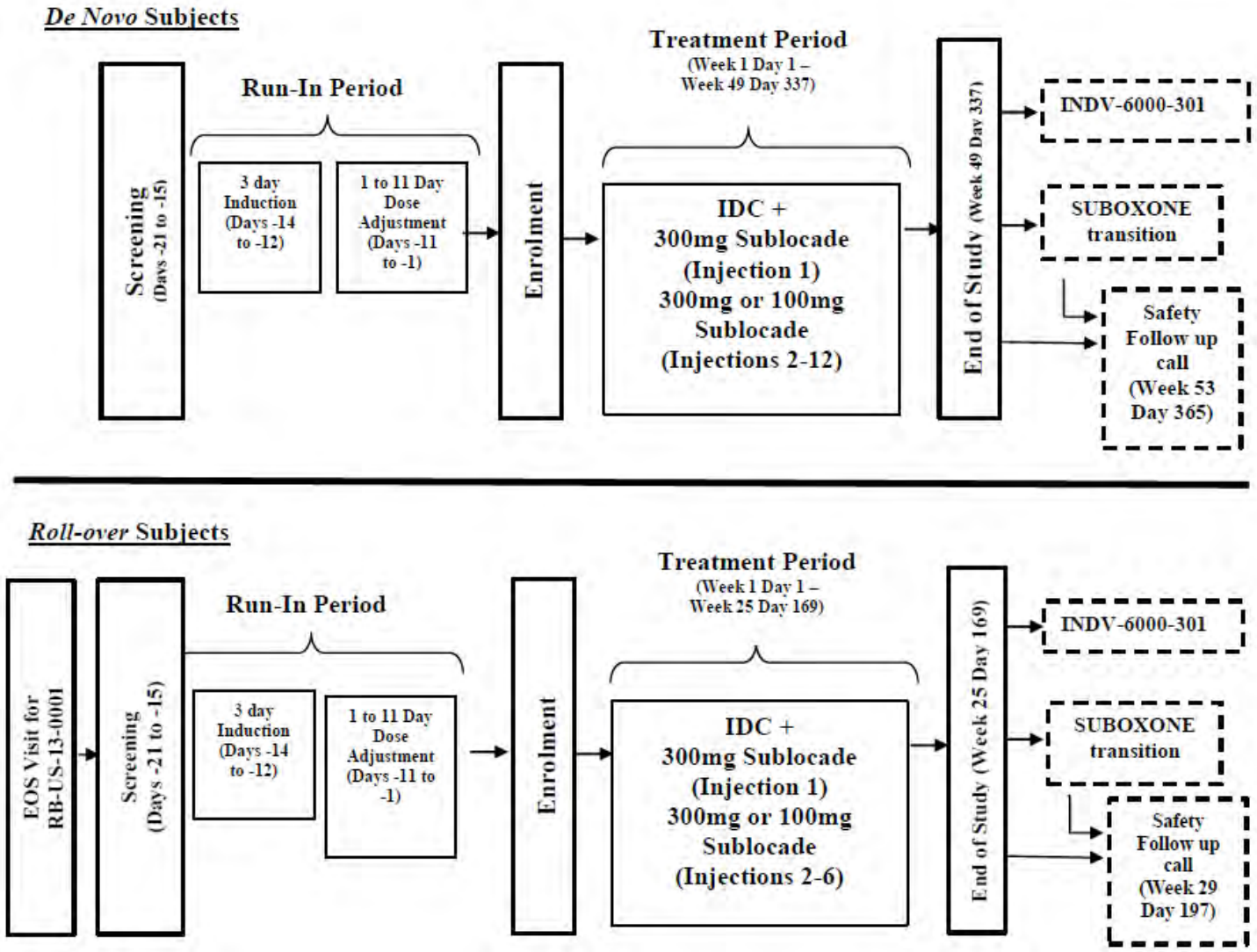
Treatment Period

After an initial 300mg SC injection of Sublocade subsequent 28 day doses of Sublocade could be adjusted down to 100mg with the possibility of adjusting back up to 300 mg.

The *de novo* subjects' maximum duration was up to a 48-week open-label treatment period.

The roll-over subjects' maximum duration was up to a 24-week open-label treatment period.

Figure 5 Study Overview – *de novo* Subjects and Roll-over Subjects



Source: Figure 1

Table 13 Subject Disposition Sublocade treatment

Category	*De novo* Subjects n (%)	Roll-over Subjects n (%)	Total n (%)
Entered Sublocade treatment period[4]	412 (81.1)	257 (96.3)	669 (86.3)
Completed[5,7]	206 (50.0)	200 (77.8)	406 (60.7)
Discontinued[5,7]	206 (50.0)	57 (22.2)	263 (39.3)
Reasons for discontinuation[6]			
Adverse event[8]	11 (2.7)	4 (1.6)	15 (2.2)
Death	0	0	0
Withdrawal symptoms[8]	3 (0.7)	0	3 (0.4)
Lost to follow-up	80 (19.4)	19 (7.4)	99 (14.8)
Non-compliance with study treatment[5]	0	0	0
Physician decision	5 (1.2)	0	5 (0.7)
Subject withdrew consent to participate	67 (16.3)	24 (9.3)	91 (13.6)
Subject was withdrawn from participation by the investigator	7 (1.7)	1 (0.4)	8 (1.2)
Lack of efficacy	0	0	0
Protocol violation	4 (1.0)	4 (1.6)	8 (1.2)
Study terminated by sponsor	0	0	0
Other[9]	28 (6.8)	5 (1.9)	33 (4.9)

[4] The denominator is the number of subjects who entered the run-in period in each subject group Source: Table 11
[5] Non-compliance with study treatment is listed as a protocol violation.
[6] The denominator is the number of subjects who entered the treatment period in each subject group
[7] A Subject missed injection 4 and was not considered to have completed the study, however had an EOS/ET visit listed as Day 337. This subject does not have a reason for discontinuation listed.
A Subject walked out in the middle of the EOS visit and was considered to have discontinued the study, however, the subject received all 12 injections and has an EOS date
[8] Withdrawal symptoms are listed separately from AEs leading to discontinuation. Three subjects had AEs of withdrawal symptoms reported under withdrawal symptoms (not AEs) in this table.
[9] "Other" reasons included incarceration (n = 19), pregnancy (n = 13), and subject unable to continue study due to new job (n = 1)

Table 14 Demographic and Baseline Characteristics – Safety Analysis Set

Subject Characteristics	*De novo* Subjects (N=412)	Roll-over Subjects (N=257)	Total (N=669)
Age (years)[1]			
N	412	257	669
Mean (SD)	38.4 (12.10)	41.6 (11.07)	39.6 (11.81)
Median	36.0	40.0	38.0
Min, Max	19, 65	21, 64	19, 65
Age (years) by categories [n (%)][1]			
≥18 to <30	122 (29.6)	40 (15.6)	162 (24.2)
≥30 to <45	157 (38.1)	114 (44.4)	271 (40.5)
≥45 to <60	107 (26.0)	89 (34.6)	196 (29.3)
≥60	26 (6.3)	14 (5.4)	40 (6.0)
≥65	1 (0.2)	0	1 (0.1)
Sex [n (%)]			
Male	263 (63.8)	169 (65.8)	432 (64.6)
Female	149 (36.2)	88 (34.2)	237 (35.4)
Baseline weight (kg)			
n	412	257	669
Mean (SD)	75.49 (14.658)	78.43 (18.097)	76.62 (16.117)
Median	74.60	74.70	74.70
Min, Max	42.4, 125.0	44.5, 140.2	42.4, 140.2
Baseline BMI (kg/m^2)[2]			
n	412	257	669
Mean (SD)	25.38 (4.286)	26.14 (5.067)	25.67 (4.613)
Median	24.70	25.40	25.00
Min, Max	17.9, 35.8	16.7, 42.3	16.7, 42.3

[1] Age is derived at the time of informed consent using subject date of birth. Source: Table 13
Percentages are based on the number of subjects in the Safety Analysis Set in each subject group.

Results

This study was not powered for efficacy comparisons, and no statistical testing was performed.

Table 15 Cumulative Distribution Function for Percentage Abstinence – Safety Analysis Set

Percentage Abstinent	*De novo* Subjects (N=412) n (%)	Roll-over Subjects (N=257) n (%)
≥ 0%	412 (100)	257 (100)
≥ 10%	315 (76.5)	206 (80.2)
≥ 20%	278 (67.5)	200 (77.8)
≥ 30%	239 (58.0)	189 (73.5)
≥ 40%	217 (52.7)	159 (61.9)
≥ 50%	187 (45.4)	150 (58.4)
≥ 60%	166 (40.3)	137 (53.3)
≥ 70%	132 (32.0)	110 (42.8)
≥ 80%	98 (23.8)	96 (37.4)
≥ 90%	62 (15.0)	74 (28.8)
= 100%	32 (7.8)	47 (18.3)

TLFB = Timeline follow back; UDS = urine drug screen
The percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use, is "percentage abstinence." All missing results for opioids were considered non-negative for opioids. Opioids non-negative indicates detection of codeine, hydrocodone, hydromorphone, methadone, morphine, opiates, oxycodone, and oxymorphone in the UDS and amphetamine/methadone, buprenorphine, methadone, and opioids in the TLFB. Due to an error in the TLFB question, all amphetamine/methadone responses of Use on the TLFB were assumed to be non-negative. Percentages are based on the number of subjects in the Safety Analysis Set in each subject group.
Subjects in the roll-over group participated in this study for 6 months. Subjects in the de novo group participated in this study for 12 months. Source: Table 18

11.2.4. Study INDV-6000-301

An open-label, depot buprenorphine treatment extension study in subjects with opioid use disorder.

There was no primary efficacy endpoint for this study, only exploratory efficacy endpoints.

11.3. Analyses performed across trials: pooled and meta analyses

Study treatment doses and durations and other study parameters precluded pooling of the data.[27]

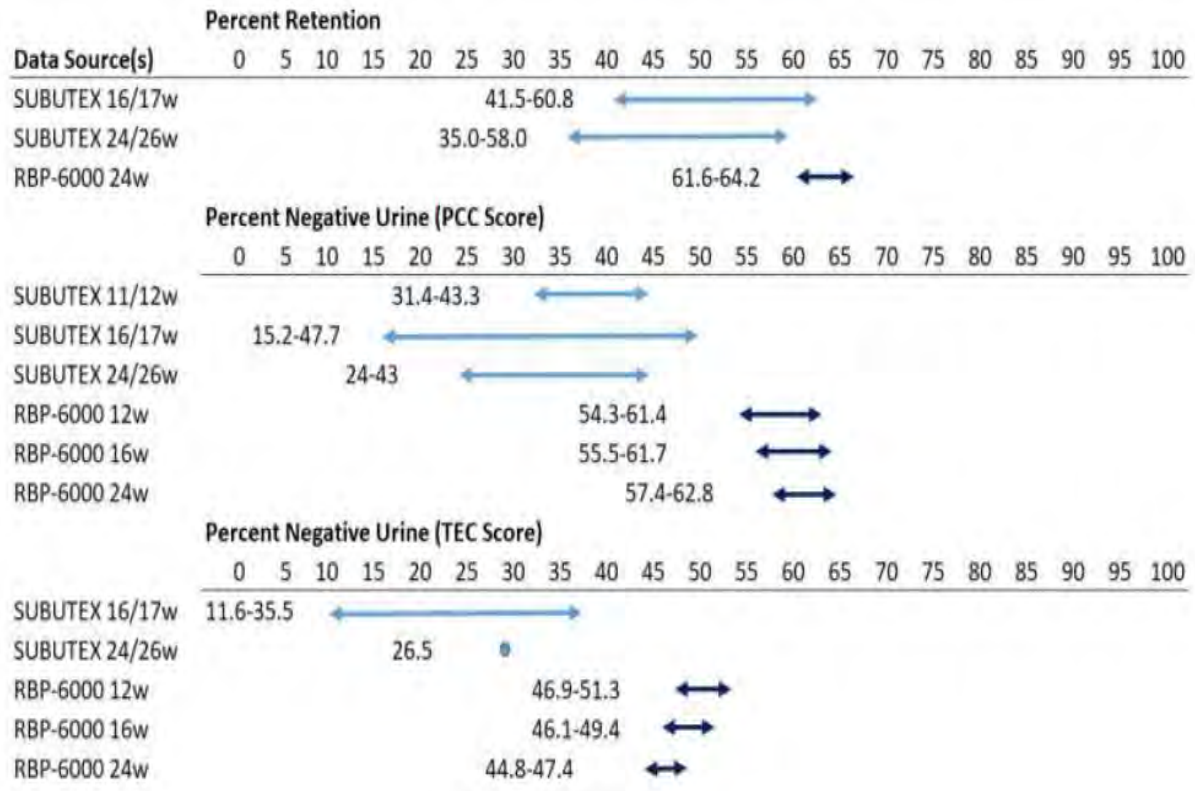
The sponsor compared the results for 13-0001 with those from historical Subutex studies using Percentage Clean Urines (PCC)[28] , Treatment Effectiveness Percentage (TEC)[29] and Retention.[30]

[27] 2.7.3 Summary of Clinical Efficacy page 16
[28] the number of negative ("clean") urine samples for each subject expressed as a percentage of the total number of samples that should have been provided during the time the subject remained in the "maintenance phase" (post induction)
[29] the number of negative ("clean") urine samples for each subject expressed as a percentage of the total number of samples that should have been provided during the full "maintenance phase" (post induction)
[30] the number of subjects remaining in treatment over a given study period expressed as a percentage of the total number of treated subjects

In the Subutex studies the highest mean PCC score was in Study CR88/130 47.7%[31] the highest mean TEC score was 34.5% (same study), the greatest retention rate was Study CR92/099 60.8%.[32]

The PCC and TEC scores for Sublocade calculated for both earlier (Week 6, Week 12) and later (Week 24) timepoints were higher.

Figure 6 Comparison of Percent Retention in Treatment and Opioid-Negative Urine Results (Expressed as PCC and TEC Scores) Between Sublocade (Study 13-0001) and Historical Subutex Studies



PCC = the number of negative ("clean") urine samples for each subject expressed as a percentage of the total number of samples that should have been provided during the time that the subject remained in the "maintenance phase" (post induction);
Retention = the number of subjects remaining in treatment over a given study period expressed as a percentage of the total number of treated subjects;
TEC = the number of negative ("clean") urine samples for each subject expressed as a percentage of the total number of samples that should have been provided during the full "maintenance phase" (post induction); w = weeks
Source: Figure 44 Summary of Clinical Efficacy

11.4. Evaluator's conclusions on clinical efficacy

The study13-0001 was statistically significantly superior to placebo in both the primary efficacy endpoint[33] and the key secondary efficacy endpoint.[34] The study had of the 300mg/100mg

[31] achieved at the end of a 17-week treatment with 8 mg SL buprenorphine
[32] SL buprenorphine d over a 16-weeks at a daily dose of 16 mg
[33] the Cumulative Distribution Function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24
[34] Treatment success. A responder is defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24.

group 125/203 completed, for 300mg/300mg 129/201 completed and for placebo 34/100 completed.

Of those randomised 62% on 300mg/100mg, 64.2% on 300mg/300mg and 34% on placebo completed (~12% of each group were lost to follow up).

30/39 completed the study13-0002 which failed to achieve the primary endpoint - failing to meet the non-inferiority margin at one time point during the first 4 weeks (18mg hydromorphone at 4 weeks). After the second injection all such endpoints were met for the following 4 weeks – this is consistent with the time (4 injections) to reach steady state for Sublocade. There appeared to be no precedent trials to 13-0002 with the non-inferiority margin based on an un-submitted article and no p-vales were submitted in support of the results.

Study 13-0003 was not powered for efficacy comparisons, and no statistical testing was performed.

12. Clinical safety

12.1. Studies providing evaluable safety data

12.1.1.1. Pooled Efficacy studies

- Study 13-0001 - a completed efficacy, safety and tolerability study (see 11.2.1).
- Study 13-0003 – a completed long-term safety and tolerability study (see 11.2.3).

These studies were pooled in the Summary of Clinical Safety.

12.1.1.2. Efficacy studies

- Study-13-0002 - a completed multiple-dose efficacy and opioid blockade study (see 11.2.2).

12.1.1.3. Extension Studies

- Study INDV-6000-301 - a completed extension of Study 13-0003, providing up to 6 months of additional treatment for subjects (see 12.2.1).

12.1.1.4. Studies with evaluable safety data: dose finding and pharmacology

- Study 12-0005 - a completed multiple ascending dose safety and tolerability study (see 21.1.1.3).
- Study 11-0020 - a completed single ascending dose safety and tolerability study (see 21.1.1.2).
- Study 13-0006 - a completed single-dose study to assess the relative bioavailability of Sublocade formulated with different MWs of polymer (see 21.1.1.4).
- Study 10-0011 - a completed single-dose first-time-in-human safety and tolerability study (see 21.1.1.1).

12.2. Studies that assessed safety as the sole primary outcome

12.2.1. Study INDV-6000-301

12.2.1.1. Study design, objectives, locations and dates

Conducted from 17 August 2016 to 23 August 2017 in 25 centres.

An open-label, multicentre, depot buprenorphine treatment extension study in subjects with opioid use disorder.

Only subjects who completed the End of Study (EOS) procedures for Study RB-US-13-0003, could be considered for inclusion in this study.

Subjects may have received monthly either an injection dose of 100mg Sublocade or 300mg Sublocade for a total of up to 6 injections.

After enrolment, subjects also received counselling (manual-guided individual behavioural therapy) at each scheduled study visit.

The objective was: To provide ongoing treatment with Sublocade and safety monitoring for subjects who completed the RB-US-13-0003 study and for whom a new treatment venue had not been identified or arranged.

12.2.1.2. Safety variables and outcomes

The injection site was assessed for pain, tenderness, warmth, itching, erythema, inflammation or swelling, and bruising using a 5-point severity scale (Injection Site Grading Scale). In addition, subjects assessed injection site pain using a visual analogue scale (VAS) (referred to as the Injection Site Pain VAS). Subjects were also assessed for adverse events (AEs) and use of concomitant medications. Vital signs were assessed.

12.2.1.3. Participant flow

In the original protocol 600 subjects were to be enrolled, this was modified to 300. Only 208 were screened.

208 subjects entered the treatment period and received at least 1 dose of Sublocade. A total of 166 subjects (79.8%) completed the treatment period by completing the end of study visit. The most common reasons for discontinuation were subject lost to follow-up (45.2% of subjects who discontinued), withdrawal of consent (23.8%), and "other" (21.4%). One subject (2.4%) was withdrawn because of an AE. There were 138 male subjects (66.3%) and 70 female subjects (33.7%). The mean age was 42.1 years (range: 21 to 66 years).

12.2.1.4. Results for Injection Site Reactions and Tolerability Assessments

A customised MedDRA query was utilised to search for TEAEs potentially related to injection site reactions. Injection site reaction TEAEs were reported for 3 subjects (1.4%) overall. All 3 events were mild in severity. No TEAEs pertaining to an injection site reaction were reported as an SAE or led to discontinuation of study treatment.

Injection site tolerability assessments were also performed after each injection. Of the tolerability assessments, mild tenderness at the injection site was the most common reaction, reported in 73 subjects (35.1%). The most common severities of injection site tolerability assessments were none or mild; there were no severe injection site tolerability assessments reported.

Overall, 34 of 208 subjects (16.3%) reported local injection site burning/stinging at least once during the trial. There was a trend for the proportion of subjects reporting burning/stinging to decrease over time with increasing number of injections.

Injection site reactions, whether as TEAEs or as observed by the investigators during tolerability assessments, were not treatment limiting.

12.2.1.5. Results for Withdrawal Symptoms

Overall, 11.5% of subjects had TEAEs potentially pertaining to drug withdrawal symptoms. No terms included in the search were reported in at least 5% of subjects. None of the TEAEs potentially pertaining to drug withdrawal symptoms were reported as an SAE or led to discontinuation of study treatment.

12.2.1.6. Pancreatitis

There were no reports of TEAEs of pancreatitis. There were no TEAEs potentially pertaining to pancreatitis. One subject had simultaneous elevations in lipase and amylase at the end of study/end of treatment visit that were not reported as TEAEs by the investigator.

12.2.1.7. Overall Safety

< 5% of subjects had an AE, mostly mild or moderate in severity. Treatment-emergent AEs were reported in 71 of 208 subjects (34.1%). Most common AEs were in the infections and infestations SOC (13.9% overall), gastrointestinal disorders SOC (6.7% overall), general disorders and administrative site conditions SOC (6.3% overall), and psychiatric disorders SOC (6.3% overall).

23 subjects (11.1%) had ≥ 1 treatment related AE.

There was 1 discontinuation (0.5%) due to an AE (lethargy).

There were 5 subjects (2.4%) with SAEs, none treatment relate. 3 subjects, (1.4%) had pneumonia, the remaining SAEs occurred in 1 subject (0.5%) each.

3 subjects (1.4%) were reported to have TEAEs pertaining to hepatic disorders. TEAEs potentially pertaining to hepatic disorders included ALT increased, AST increased, hepatic enzyme increased and liver function test increased (all reported for 1 subject; 0.5% each).

There were no cases of Hy's Law. 4 subjects (2.2% overall) who had both ALT and AST > 3 x ULN to < 5 x ULN during the study. These 4 subjects had co-existing factors for hepatic enzyme elevation such as an ongoing medical history of hepatitis C, elevated LFTs at screening, alcohol use or concomitant use of hepatotoxic drugs. For all 4 subjects, the hepatic enzymes were elevated at the Screening Visit and remained elevated at the end of study/end of treatment visit.

There were no TEAEs of orthostatic hypotension reported.

There were no TEAEs potentially pertaining to respiratory depression and failure.

TEAEs potentially related to central nervous system depression were reported for 1.9% of subjects.

12.3. Patient exposure

1083 subjects received at least 1 injection of Sublocade.

In Studies 13-0001 and 13-0003 overall, a total of 542 subjects received Sublocade for at least 24 weeks and 291 subjects received Sublocade for at least 48 weeks. The mean (median) duration of exposure to Sublocade was 32.1 (40.0) weeks.

In Study INDV-6000-301 of the 208 subjects who completed study 13-0001 and 13-0003 in which they had already received 12 Sublocade injections, a total of 171 subjects (82.2%) received 6 additional Sublocade injections (a combined total of 18 injections received).

In Study 12-0005 46 subjects received 4 injections of 100 to 300mg, 5 others received > 4.

In Study 13-0002 39 subjects received a single Sublocade 300mg dose and 30 subjects received 2 Sublocade 300mg doses.

In Study 11-0020 24 received a single 100mg dose and 12 a 200mg dose.

In Study 13-0006 subjects received single SC injections of Sublocade 300mg.

Table 16 Individual and Pooled Studies 13-0001 and 13-0003: Study Treatment Exposure by Injection Number

	13-0001			13-0003				Total Sublocade
				Roll–over [a]			De novo [c]	
Injection #	Sublocade 300/100 mg (N = 203) n (%)	Sublocade 300/300 mg (N = 201) n (%)	PBO (N = 100) n (%)	Sublocade 100 →Sublocade 300/Flex [b] (N=112) n (%)	Sublocade 300 →Sublocade 300/Flex [b] (N=113) n (%)	PBO → Sublocade 300/Flex [b] (N=32) n (%)	Sublocade 300/Flex (N=412) n (%)	(N=848) n (%
1	27 (13.3)	26 (12.9)	40 (40.0)	1 (0.9)	5 (4.4)	2 (6.3)	46 (11.2)	101 (11.9)
2	15 (7.4)	15 (7.5)	10 (10.0)	4 (3.6)	7 (6.2)	2 (6.3)	24 (5.8)	56 (6.6)
3	11 (5.4)	12 (6.0)	7 (7.0)	6 (5.4)	7 (6.2)	2 (6.3)	27 (6.6)	52 (6.1)
4	9 (4.4)	14 (7.0)	4 (4.0)	5 (4.5)	6 (5.3)	0	21 (5.1)	44 (5.2)
5	13 (6.4)	5 (2.5)	4 (4.0)	1 (0.9)	6 (5.3)	0	14 (3.4)	30 (3.5)
6	128 (63.1)	129 (64.2)	35 (35.0)	95 (84.8)	82 (72.6)	26 (81.3)	15 (3.6)	75 (8.8)
7	-	-	-	-	-	-	13 (3.2)	20 (2.4)
8	-	-	-	-	-	-	10 (2.4)	20 (2.4)
9	-	-	-	-	-	-	9 (2.2)	22 (2.6)
10	-	-	-	-	-	-	5 (1.2)	16 (1.9)
11	-	-	-	-	-	-	10 (2.4)	18 (2.1)
12	-	-	-	-	-	-	218 (52.9)	394 (46.5)

placebo=placebo Percentage is computed based on the N as a denominator from the respective columns. Source: Tables 14 & 15

Study 13-0001: All subjects in the Sublocade treatment groups were scheduled to receive 2 injections of Sublocade 300 mg. Subjects in the 300/100mg and 300/300mg treatment groups were scheduled to then receive up to 4 injections of Sublocade 100mg or up to 4 injections of Sublocade 300 mg, respectively.

Study 13-0003:

[a]. Roll-over subjects: The treatment groups represent the treatment received in the Ph3DB study and subsequent treatment in Ph3OL study. Subjects received 6 injections in the Ph3DB study; Injection 1 in the Ph3OL study corresponds to their 7th injection

[b]. Sublocade 300/Flex: Represents treatment with an initial injection of Sublocade 300mg followed by up to 5 additional injections using flexible dosing with either Sublocade 300mg or Sublocade 100mg as deemed appropriate by the investigator.

[c]. All de novo subjects received an initial injection of Sublocade 300mg followed by up to 11 additional injections using flexible dosing with either Sublocade 300mg or Sublocade 100mg as deemed appropriate by the investigator.

Total Sublocade includes injections received in 13-0001 plus those in rollover 13-0003 as well as those given *de novo*

12.4. Adverse events

12.4.1.1. Study 13-0001

Treatment-emergent AEs were reported in 76.4% of subjects in the 300/100mg group and 66.7% in the 300/300mg group and in 56.0% the placebo group.

Treatment related AEs to study treatment were in 33.0% of subjects in the 300/100mg and 34.8% in the 300/300mg and in 3.0% of the placebo groups (vs. 2, respectively). Study drug related AEs for ≥ 5% of subjects in any treatment group were injection site pruritus, constipation and injection site pain, reported for 7.4%, 6.4% and 5.4% of subjects in the active total treatment group compared with 4.0%, 0% and 3.0% of subjects in the placebo group, respectively.

Severe AEs were reported in a 7.4%, 6.5% and 4.0% of subjects in the 300/100mg group, 300/300mg group and placebo group, respectively.

SAEs were reported in 2.0%, 3.5% and 5.0% of subjects in the 300/100mg group, 300/300mg group and placebo group, respectively.

On death (gunshot wound) was reported for 1 subject (0.2%) in the 300/300mg group.

AEs leading to study treatment discontinuation were reported in 3.4%, 5.0% and 2.0% of subjects in the 300/100mg group, 300/300mg group and placebo group, respectively. 2 subjects in the 300/100mg group had Drug withdrawal syndrome; 2 subjects in the 300/300mg group had Aspartate aminotransferase increased.

12.4.1.2. Study 13-0003

The overall incidence of TEAEs was 73.3% and 56.4%, respectively, in the *de novo* and roll-over groups.

The only treatment related AEs for ≥ 5% of subjects in either subject group were constipation and injection site pain, reported for 7.2% and 6.7% of subjects overall.

Severe AEs were reported for 8.7% of subjects in the *de novo* subject group and 2.7% of subjects in the roll-over group.

Overall, SAEs were reported for 3.7% of subjects;16 subjects (3.9%) in the *de novo* subject group and 9 subjects (3.5%) in the roll-over subject group. There were 3 SAEs of cellulitis overall and in the *de novo* group 2 accidental overdoses.

AEs led to drug discontinuation for 2.5% of subjects; 13 subjects (3.2%) in the *de novo* group and 4 subjects (1.6%) in the roll-over group.

Table 17 Study 13-0003: TEAEs Leading to Sublocade Dose Reduction

Preferred Term	Sublocade 300/Flex		
	De novo Subjects (N=412) n (%)	Roll-over Subjects (N=257) n (%)	Total (N=669) n (%)
Any TEAE leading to dose reduction	29 (7.0)	17 (6.6)	46 (6.9)
Sedation	2 (0.5)	5 (1.9)	7 (1.0)
Alanine aminotransferase increased	5 (1.2)	1 (0.4)	6 (0.9)
Constipation	4 (1.0)	1 (0.4)	5 (0.7)
Nausea	3 (0.7)	1 (0.4)	4 (0.6)
Fatigue	2 (0.5)	2 (0.8)	4 (0.6)
Aspartate aminotransferase increased	3 (0.7)	1 (0.4)	4 (0.6)
Headache	3 (0.7)	0	3 (0.4)
Lethargy	2 (0.5)	1 (0.4)	3 (0.4)
Somnolence	3 (0.7)	0	3 (0.4)
Injection site pain	1 (0.2)	1 (0.4)	2 (0.3)
Hepatic function abnormal	2 (0.5)	0	2 (0.3)
Gamma-glutamyltransferase increased	2 (0.5)	1 (0.4)	3 (0.4)
Hepatic enzyme increased	1 (0.2)	1 (0.4)	2 (0.3)
Insomnia	2 (0.5)	0	2 (0.3)
Decreased appetite	0	1 (0.4)	1 (0.1)
Muscle twitching	0	1 (0.4)	1 (0.1)
Dizziness	0	1 (0.4)	1 (0.1)
Hypersomnia	1 (0.2)	0	1 (0.1)
Migraine	1 (0.2)	0	1 (0.1)
Euphoric mood	1 (0.2)	0	1 (0.1)
Erectile dysfunction	0	1 (0.4)	1 (0.1)
Flushing	0	1 (0.4)	1 (0.1)

Source: Table 66

12.4.1.3. Study INDV-6000-301

AEs were reported in 71 of 208 subjects (34.1%), most were mild or moderate in severity. One subject had a TEAE (lethargy) leading to treatment discontinuation.

SAEs were reported in 5 subjects (2.4%), 3 subjects, (1.4%) subjects had an SAE of pneumonia.

12.4.1.4. Study 12-0005

89 subjects (100%) receiving Sublocade had an AE. 48 (53.9%) were considered treatment related. 1 AE was severe, 6 (6.7%) were SAEs. 8(9%) led to withdrawal.

12.4.1.1. Study 13-0002

34/39 (87%) subjects had an AE, 25(64%) were treatment related.

12.4.1.2. Study 11-0020

46/48 (95.8%) had AEs, 30 (62.5%) were treatment related, 2 (4.2%) were severe, 7 (14.6%) were SAEs.

12.4.1.3. Study 13-0006

42/47 (89.4%) had AEs, 37 (78.7%) were treatment related, none were severe, 3 (6.4%) were SAEs, 1 led to withdrawal.

12.4.2. Overall AEs

In study 13-0001, No individual TEAEs were reported in > 10% of subjects in the active total, 300/100mg or 300/300mg groups; insomnia was reported in 11.0% of subjects in the placebo group. The most common (reported in ≥ 5% of subjects) TEAEs reported in the active total group were headache, constipation, nausea, injection site pruritus, vomiting, insomnia and upper respiratory tract infection. The percentage of subjects with the most common TEAEs was generally similar across treatment groups, although constipation was reported in only the active treatment groups and upper respiratory tract infection was reported more frequently in the active treatment groups compared with the placebo group. The maximum severity of TEAEs was reported as mild or moderate for most subjects with TEAEs.

In study 13-0003, no individual TEAE was reported in at least 5% of subjects in the roll-over group. TEAEs reported in at least 5% of subjects in the *de novo* subject group included constipation, nausea, injection site pain, insomnia, headache, nasopharyngitis and injection site erythema.

In study INDV-6000-301, no individual TEAE was reported in at least 5% of subjects. The most common TEAEs were similar to those reported in the *de novo* group of study 13-0003 and included constipation, headache, pneumonia and upper respiratory tract infection.

Additional exposure with Sublocade (up to 18 monthly injections of 100mg or 300mg) in study INDV-6000-301 did not reveal any new safety signals.

Frequently reported TEAEs in the Phase 2 and Phase 1 studies did not raise any new safety concerns.

Table 18 Study 13-0001: TEAEs Reported in ≥ 5% of Subjects in Any Treatment Group During the Double-blind Phase

Preferred Term	Active Total (N=404) n (%)	RBP-6000 300mg/100mg (N=203) n (%)	RBP-6000 300mg/300mg (N=201) n (%)	PBO (N=100) n (%)
Any TEAE	289 (71.5)	155 (76.4)	134 (66.7)	56 (56.0)
Headache	36 (8.9)	19 (9.4)	17 (8.5)	6 (6.0)
Constipation	35 (8.7)	19 (9.4)	16 (8.0)	0 (0.0)
Nausea	34 (8.4)	18 (8.9)	16 (8.0)	5 (5.0)
Injection site pruritus	32 (7.9)	13 (6.4)	19 (9.5)	4 (4.0)
Vomiting	30 (7.4)	19 (9.4)	11 (5.5)	4 (4.0)
Insomnia	30 (7.4)	13 (6.4)	17 (8.5)	11 (11.0)
Upper respiratory tract infection	27 (6.7)	15 (7.4)	12 (6.0)	1 (1.0)
Injection site pain	22 (5.4)	10 (4.9)	12 (6.0)	3 (3.0)
Nasopharyngitis	21 (5.2)	11 (5.4)	10 (5.0)	1 (1.0)
Fatigue	20 (5.0)	8 (3.9)	12 (6.0)	3 (3.0)
Anxiety	18 (4.5)	10 (4.9)	8 (4.0)	5 (5.0)
Drug withdrawal syndrome	16 (4.0)	9 (4.4)	7 (3.5)	6 (6.0)
Blood creatine phosphokinase increased	16 (4.0)	11 (5.4)	5 (2.5)	1 (1.0)
Diarrhoea	10 (2.5)	5 (2.5)	5 (2.5)	5 (5.0)

placebo=placebo Source: Table 41

Table 19 Study 13-0003: TEAEs Reported in ≥ 5% of Subjects in Either Subject Group during the Treatment Phase

Preferred Term	RBP-6000 300/Flex		
	De novo Subjects (N=412) n (%)	Roll-over Subjects (N=257) n (%)	Total (N=669) n (%)
Any TEAE	302 (73.3)	145 (56.4)	447 (66.8)
Constipation	47 (11.4)	9 (3.5)	56 (8.4)
Nausea	37 (9.0)	10 (3.9)	47 (7.0)
Injection site pain	39 (9.5)	7 (2.7)	46 (6.9)
Insomnia	27 (6.6)	10 (3.9)	37 (5.5)
Headache	31 (7.5)	5 (1.9)	36 (5.4)
Nasopharyngitis	24 (5.8)	6 (2.3)	30 (4.5)
Injection site erythema	22 (5.3)	5 (1.9)	27 (4.0)

Source: Table 42

12.5. Evaluation of issues with possible regulatory impact

12.5.1. Injection site reaction

AEs

In 13-0001 and 13-0003, 17.2% of Sublocade subjects had at least 1 injection site reaction TAE. Including: injection site pain (7.8%), injection site pruritus (6.6%), injection site erythema (4.8%) and injection site induration (1.4%). No injection site reaction AE was reported as serious. Injection site reaction AEs led to study treatment discontinuation for < 1% of subjects in either.

In study 13-0001, 13.8% of 300/100mg and 18.9% of 300/300mg subjects reported ≥ 1 injection site reaction AE compared with 9.0% in those who received placebo.

Injection site tolerability assessments (grading)

In study 13-0001 and 13-0003, local injection site grading was performed by an observer.[35] Less than 1% of subjects had reports of injection site erythema/redness, induration, pain, or swelling with a maximum intensity of severe. Injection site tenderness with a maximum intensity of severe was reported for < 5% of subjects.

In study INDV-6000-301, mild tenderness at the injection site was the most common reaction, reported in 73 subjects (35.1%). There were no severe injection site tolerability assessments reported.

Subject-reported injection site pain – Visual Analogue Scale (VAS)

Across 13-0001 and 13-0003 Sublocade subjects, the worst mean VAS pain scores (on a 100-mm scale) at any post-injection time point decreased over time; at the 1-minute, 5-minute, 10-minute, 15-minute, 30-minute, 1-hour and 2-hour post-injection time points the worst mean VAS pain scores were 63.0, 29.2, 16.3, 11.2, 8.3, 6.0 and 4.5, respectively.

[35] Injection sites were assessed erythema/redness, induration, pain, swelling and tenderness and each symptom was assigned a severity grade of none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3) or potentially life-threatening (grade 4).

In study INDV-6000-301, the overall mean worst injection site pain at 1 hour post injection ranged from 0.9 following Injection 5, to 2.5 following Injection 3 using the 100mm VAS scale.

Injection site burning or stinging

Across 13-0001 and 13-0003 Sublocade subjects, nearly all subjects who received Sublocade (95.4%) reported local injection site burning or stinging at one or more 1 minute post-injection assessments when all injections were considered. The percentages of subjects reporting local injection site burning or stinging decreased over time through the 2 hour post-injection assessment. At the 2 hour assessment, 16.2% of subjects reported burning or stinging when all injections were considered.

In study INDV-6000-301, 34 of 208 subjects (16.3%) reported local injection site burning/stinging at least once during the trial. There was a trend for the proportion of subjects reporting burning/stinging to decrease over time with increasing injections.

12.5.2. Liver function and liver toxicity

Treatment-emergent AEs potentially associated with hepatic disorders were reported in 9.3% of subjects exposed to Sublocade in the pooled 13-0001 and 13-0003 studies. In the 13-0001 study, the frequency of TEAEs potentially associated with hepatic disorders was 6.9% in the 300/100mg and 7.5% in the 300/300mg Sublocade treatment groups compared with 1.0% in the placebo group.

In study INDV-6000-301, TEAEs potentially associated with hepatic disorders were reported in 1.4% of subjects exposed to Sublocade for up to 18 months.

12.5.3. Opioid Withdrawal

AEs potentially associated with opioid withdrawal signs and symptoms were commonly reported in subjects exposed to Sublocade in the pooled 13-0001 and 13-0003 studies: 33.4% of subjects reported TEAEs. In study 13-0001, these were observed for similar percentages of subjects across treatment groups (300/100mg 35.0% and 300/300mg 29.9% vs. placebo 36.0%). In study INDV-6000-301, 11.5% of subjects reported TEAEs potentially pertaining to drug withdrawal symptoms.

12.5.4. CNS depression

AEs potentially associated with CNS depression were reported in 10.8% of subjects exposed to Sublocade in the pooled 13-0001 and 13-0003 studies. In the 13-0001 study, these AEs were observed for a greater percentage of subjects in the 300/100mg group (11.8%) than in the 300/300mg group (7.0%) or placebo group (4.0%). All PTs in this special interest topic were reported in < 4% of subjects overall. In study INDV-6000-301, TEAEs potentially related to CNS depression were reported for 1.9% of subjects during the treatment period.

12.5.5. Respiratory Depression

No AEs potentially associated with respiratory depression were reported in any of the Phase 3 studies.

12.5.6. Orthostatic Hypotension

AEs potentially associated with orthostatic hypotension were reported for a small percentage of subjects exposed to Sublocade during the pooled 13-0001 and 13-0003 studies (2.8%). In study 13-0001, these AEs were marginally higher in the 300/100mg group (3.4%) compared with the 300/300mg group (2.5%) and placebo group (2.0%).

A treatment-emergent AE potentially related to orthostatic hypotension (mild dizziness) was reported for 1 subject (0.5%) in study INDV-6000-301.

12.5.7. Acute Pancreatitis

AEs potentially associated with acute pancreatitis were reported for a small percentage of subjects exposed to Sublocade (2.5%) in the pooled 13-0001 and 13-0003 studies. In study 13-0001, these were reported for 2.0% of subjects who received 300/100mg or placebo and at 1.0% in the 300/300mg group. One subject had an event reported as elevated lipase that was coded as pancreatitis.

In study INDV-6000-301, no TEAEs potentially associated with acute pancreatitis were reported.

12.5.8. Clinical Chemistry

While the percentages of subjects with transaminase elevations > 3 x ULN were higher in the Sublocade arms compared with the placebo arm in study 13-0001, the large majority of these cases had coexisting factors for hepatic enzyme elevation such as hepatitis C, chronic alcohol use or history of alcoholic hepatitis/pancreatitis, or elevated LFTs at screening and/or baseline. There were no SAEs potentially pertaining to liver dysfunction in any subject in the study. Findings from the 13-0003 and INDV-6000-301 studies were similar; no signal indicative of hepatic injury was observed during long-term use of Sublocade.

No clinically important effects on adrenocorticotropic hormone (ACTH), FSH or testosterone (total and free) were observed following treatment with Sublocade in either the 13-0001 and 13-0003 studies.

Evaluation of mean values, shifts and TEAEs related to other clinical laboratory parameters across all studies in the Sublocade development program did not reveal any new safety concerns for Sublocade compared with the known safety profile for buprenorphine.

In Study INDV-6000-301 in general, mean values for all haematology parameters remained within the normal range throughout the study. Evaluation of the patterns in shift data for haematology parameters were generally considered not clinically important.

12.5.9. Haematology and haematological toxicity

In study 13-0001 and 13-0003 mean values for haematology parameters predominantly remained within the central laboratory reference range at each time point in all 3 treatment groups with a few minor exceptions that were not considered clinically important.

12.5.10. Electrocardiograph findings and cardiovascular safety

PopPK analysis INDV-6000-Q01 Concentration-QT analysis (see 21.1.3.8) found no effect of Buprenorphine on QT after accounting for the covariates that may influence HR and QT in subjects with opioid use disorder.

The sponsor also submitted a 15 page Expert summary report on The risk of QT prolongation associated with the use of buprenorphine containing Products that found:

The presently published literature does not suggest that buprenorphine is causally associated with QT prolongation and TdP-type ventricular arrhythmias.

and:

there was no strong evidence to demonstrate the extent to which buprenorphine may have contributed to the development of QT prolongation, given the fact that some patients concomitantly received drugs known to prolong the QT interval, as well as had a history of abnormal thyroid function, structural heart disease, bradycardia, hypokalaemia and polysubstance abuse, which confound any interpretation.

12.5.1. Renal Impairment

Based on relevant scientific data, renal impairment is expected to have a limited effect on buprenorphine PK following SC administration of Sublocade. Therefore, a dedicated PK study in subjects with renal impairment with Sublocade was not conducted.

12.6. Other safety issues

12.6.1. Withdrawal and Rebound

No formal evaluation of withdrawal and rebound was included in the Sublocade clinical development program beyond the month following discontinuation of Sublocade. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 or 300mg, respectively).

12.6.2. Safety related to drug-drug interactions and other interactions

In study 13-0001, the percentage of subjects taking at least 1 concomitant CNS depressant medication was similar for the 300/300 mg, 300/100mg and placebo groups, respectively, as follows: 33.0%, 33.8% vs 29.0%. TEAEs potentially associated with CNS depression were reported in similar percentages of subjects across treatment groups for the subset of subjects taking concomitant CNS depressant medications compared with the overall safety population.

Co-administration of CYP3A4 inducers may induce the metabolism of buprenorphine and therefore, may cause an increase in the clearance of the drug, potentially leading to a decrease in buprenorphine plasma concentrations. The effects of CYP3A4 inducers may be dependent on the route of administration of buprenorphine. Buprenorphine is a high extraction ratio drug (hepatic extraction ratio, 0.6 - 0.9). Hence, elimination is expected to be hepatic blood flow-dependent and relatively insensitive to changes in intrinsic clearance (i.e., hepatic metabolism). Since Sublocade is injected SC, the induction of CYP3A4 enzymes is expected to result in minimal decrease in buprenorphine exposure.

12.7. Post marketing experience

Not applicable.

12.8. Evaluator's overall conclusions on clinical safety

Although generally similar to SL buprenorphine, the following points are made:

The safety concerns relate principally to injection reactions. While the polymer is already on the ARTG, it is not so combined with buprenorphine. According to the buprenorphine PI Injection site reaction is rare. The incidence is approximately double that seen with placebo and led to discontinuation in < 1%. The C_{max} seen in PK studies was similar to that seen with SL buprenorphine which carries the warning that it may cause drowsiness, particularly when used together with alcohol or central nervous system depressants, however in Study 13-0001 CNS depression was approximately double that seen with placebo.

The lack of an effect of buprenorphine on QTc in the present analysis is consistent with some reports of buprenorphine from the literature, but not with others including results from a healthy volunteer study and from a study of buprenorphine transdermal system. The discrepancy may be due to differences between subject populations, where healthy volunteers

are more likely to have larger changes in blood pressure and their resulting changes in HR than opioid use disorder subjects.[36]

13. First round benefit-risk assessment

13.1. First round assessment of benefits

The benefits of Sublocade in the proposed usage are:

Indication	
Benefits	Strengths and Uncertainties
A single monthly injection.	There is the possibility of sub-therapeutic dosing in the first months as shown by the failure to meet the noninferiority margin in Study 13-0002. Removal requires surgery. There is a possibility of injection site reactions.
It could be administered only by a health care professional to avoid diversion.	The existing SL buprenorphine treatment is self-administered and could be diverted.

13.2. First round assessment of risks

The risks of Sublocade in the proposed usage are:

Risks	Strengths and Uncertainties
2 cases of accidental overdose occurred.	Once given, prolonged activity would necessitate surgical removal. BMI was found to affect the SC absorption of buprenorphine, resulting in higher peak levels of buprenorphine in subjects with a lower BMI dose adjustments were not considered necessary.
There is the possibility of intravenous or even intra-arterial injection.	The sponsor studied this and found if the Atrigel Delivery System is injected IV or IA, blockage of a blood vessel or vascular occlusion would likely result.

[36] Concentration QT Report page 40

Risks	Strengths and Uncertainties
No direct efficacy comparison with existing SL buprenorphine was made.	
There is an increased exposure.	This does not appear to affect the safety profile, patients are likely to be opioid tolerant

13.3. First round assessment of benefit-risk balance

The benefit-risk balance of Sublocade, given the proposed usage, is favourable.

14. First round recommendation regarding authorisation

Based on clinical evaluation, it is recommended that, subject to an approved PI and the separate statistical evaluation of the PopPK and PK/PD studies, Sublocade be approved for registration for Treatment of opioid dependence, within a framework of medical, social and psychological treatment.

15. First round comments on product documentation

15.1. First round comments on draft PI (clinical aspects)

The clinical aspects of the draft Product Information are not entirely satisfactory and should be revised, having regard to the comments below:

Precautions

Managing Risks From Concomitant Use of Benzodiazepines Or Other CNS Depressants With Buprenorphine

1. The sponsor proposes to insert this section

   ~~Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose, respiratory depression, and death. Medication-assisted treatment of opioid use disorder, however, should not be categorically denied to patients taking these drugs. Prohibiting or creating barriers to treatment can pose an even greater risk of morbidity and mortality due to the opioid use disorder alone.~~

   ~~As a routine part of orientation to buprenorphine treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics and alcohol.~~

   ~~Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at initiation of buprenorphine treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required. There is no evidence to support dose limitations or arbitrary caps of buprenorphine as a strategy to address benzodiazepine use in buprenorphine-treated patients. However, if a patient is sedated at the time of buprenorphine dosing, delay or omit the buprenorphine dose if appropriate.~~

   ~~Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use with buprenorphine. In some cases, monitoring in a higher level~~

~~of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.~~

~~For patients in buprenorphine treatment before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use~~

The justification provided was Information from Subutex + Sublocade US PI. It is not in the Australian Subutex PI.

It is **not** recommended that the proposed insertion be approved.

Neonatal Abstinence Syndrome

2. The sponsor proposes to amend this section:

   Chronic use of buprenorphine by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth. (See Use in Pregnancy). Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

   ~~Advise pregnant women receiving opioid addiction treatment with Sublocade of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. This risk should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance of management of opioid addiction throughout pregnancy.~~

Justification given for the first sentence inserted was 'Same information as for Subutex' and for the added paragraph 'Information from Sublocade US PI' the first statement is correct. The second is not in the Subutex recently reviewed PI.

It is recommended that the proposed insertion as modified by deletion be approved.

Use in Opioid Naïve Patients

3. The sponsor proposes to amend this section:

   There have been reported deaths of opioid naive individuals who received doses as low as 2mg of buprenorphine sublingual tablet for analgesia. Sublocade is not appropriate <u>as an analgesic</u> ~~for use in opioid-naïve patients~~.

The justification provided was Same Information as for Subutex. It is not in the Australian Subutex PI.

It is **not** recommended that the proposed insertion be approved.

Use in hepatic impairment

4. The sponsor proposes to replace this section:

Buprenorphine is extensively metabolised by the liver. The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study, in which a Suboxone 2.0/0.5mg (buprenorphine/naloxone) sublingual tablet was administered to healthy subjects and subjects with varying degrees of hepatic impairment. Plasma levels were found to be elevated for buprenorphine in patients with moderate to severe hepatic impairment (Table 2). Buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function.

Table 2: Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following buprenorphine/naloxone administration (change relative to healthy subjects)

PK parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
BUPRENORPHINE			
Cmax	1.2 fold increase	1.1 fold increase	1.7 fold increase
AUC_{last}	Similar to control	1.6 fold increase	2.8 fold increase

In the same study, changes in C_{max} and AUC_{last} in subjects with HCV infection without hepatic impairment were not clinically significant in comparison to the healthy subjects.

~~In a pharmacokinetic study with transmucosal buprenorphine, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment.~~

This study was not submitted Justification given was 'Information consistent with Subutex PI' it is not.

The existing statement following is not appropriate and should be replaced by the proposed statement:

~~Buprenorphine should be used with caution in patients with moderate to severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Lower initial doses and cautious titration of dosage may be required in patients with severe hepatic impairment~~

Proposed replacement

The effect of hepatic impairment on the pharmacokinetics of SUBLOCADE has not been studied.

Because of the long-acting nature of the product, adjustments to dosages of SUBLOCADE are not rapidly reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing severe hepatic impairment are not candidates for treatment with SUBLOCADE.

Patients who develop moderate to severe hepatic impairment while being treated with SUBLOCADE should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

These latter proposed insertions are supported by the submission.

1. It is recommended that the existing Subutex PI statement be retained except for that relating to use with caution.

2. It is recommended that this usage statement be replaced with that proposed.

Use in renal impairment

5. The sponsor proposes to replace the existing section:

   Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine ~~Subutex~~. Therefore no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min), which may require dose adjustment.

With

> Clinical studies of SUBLOCADE did not include subjects with renal impairment. ~~No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3mg buprenorphine.~~

The reference (Summary of Clinical Pharmacology Studies page 111) in relation to that study also says 'mean buprenorphine-3-glucuronide and norbuprenorphine plasma concentrations were higher in individuals with renal impairment compared to normal healthy subjects.' Thus the proposed statement adds nothing to the existing statement and is incorrect in that there was a difference.

1. It is recommended that the existing Subutex statement be retained with the additional statement on the lack of renal impairment studies.

Use in Patients at Risk for Arrhythmia

6. The sponsor proposes to add this new section:

   Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of Sublocade on the QT interval in five clinical studies including the Phase 3 study. In a Phase 3 study, seven patients had an increase from baseline QTc greater than 60 msec at any time [2/203 patients (1.0%) in the 300 mg/100mg group and 5/201 patients (2.0%) in the 300 mg/300mg group] and one patient in the 300 mg/300mg group was found to have a QTc greater than 500 msec. These QTc findings were all sporadic and transient and none led to aberrant ventricular rhythm. Review of ECG and adverse event data provided no evidence for syncope, seizure, or ventricular tachycardia or fibrillation.

   Consider these observations in clinical decisions when prescribing buprenorphine to patients with hypokalaemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval.

The first proposed paragraph is supported by the submission.

It is recommended that the proposed insertion be approved.

Risks associated with Treatment of Emergent Acute Pain

7. The sponsor proposes to add this new section:

   While on Sublocade, situations may arise where patients need acute pain management, or may require anaesthesia. Treat patients receiving Sublocade with a non-opioid analgesic whenever possible. Patients requiring opioid therapy for analgesia may be treated with a high-affinity full opioid analgesic under the supervision of a physician, with particular attention to respiratory function. Higher doses may be required for analgesic effect. Therefore, a higher potential for toxicity exists with opioid administration.

   If sedation or opioid therapy is required e.g. as part of anaesthesia, patients should be continuously monitored in an anaesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The sedation or opioid therapy should be provided by individuals specifically trained in the use of anaesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.

   Advise patients of the importance of instructing their family members, in the event of emergency, to inform the treating healthcare provider or emergency room staff that the patient is being treated with Sublocade.

   The above guidance should also be considered for any patient who has been treated with Sublocade within the last 6 months.

Only justification offered was 'Information consistent with Sublocade US PI'. It is however consistent with good clinical practice. The reference to sedation is to comply with a multi Australian (& NZ) Colleges document.

It is recommended that the propose insertion as modified by insertions be approved.

Paediatric use

8. The sponsor proposes to amend this section:

   SUBLOCADE is not recommended for use in children. The safety and effectiveness of SUBLOCADE in subjects below the age of 18 has not been established.

   ~~Due to lack of data, patients below the age of 18 should be closely monitored during treatment~~

The last statement is related to off label use.

It is recommended that the propose insertion as modified by deletion be approved.

4.5 Interactions with Other Medicines and Other Forms of Interactions

9. The sponsor proposes to amend this section:

Table 1 - Clinically Significant Drug Interactions

Benzodiazepines and other Central Nervous System depressants	
Examples	Alcohol, Benzodiazepines, Non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, antipsychotics and other opioids (e.g. methadone, analgesics, and antitussives), sedative H1-receptor antagonists, clonidine

Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments. This combination with benzodiazepines may result in death due to respiratory depression of central origin; therefore, patients must be closely monitored when prescribed this combination, and this combination should be avoided in cases where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed Use caution with medicines containing alcohol.
Other Opioid Analgesics	
Clinical Impact:	The analgesic properties of other opioids may be reduced in patients receiving treatment with buprenorphine for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.
Intervention	Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see Section 4.4 Special Warnings and Precautions).
Naltrexone and other opioid antagonists	
Clinical Impact:	Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of SUBLOCADE. Patients maintained on buprenorphine may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations.
CYP3A4 inhibitors	
Examples	Protease inhibitors (like ritonavir, ~~nelfinavir~~, saquinavir or indinavir), azole antifungals like ketoconazole or itraconazole, calcium channel antagonists, and macrolide antibiotics like erythromycin.

Clinical Impact:	The effects of co-administered CYP3A4 inhibitors on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied and the effects may be dependent on the route of administration; however, such interactions have been established in studies using transmucosal buprenorphine. Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4, therefore potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. The concomitant use of sublingual buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects
Intervention	Patients who transfer to SUBLOCADE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate. If patients already on SUBLOCADE require newly-initiated treatment with CYP3A4 inhibitors, patients should be monitored for signs and symptoms of over- medication. Within 2 weeks of SUBLOCADE administration, if signs and symptoms of buprenorphine toxicity or overdose occur but the concomitant medication cannot be reduced or discontinued, it may be necessary to remove the depot and treat the patient with a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilised on SUBLOCADE in the setting of concomitant medication that is a CYP3A4 inhibitor, and the concomitant medication is discontinued, the patient should be monitored for withdrawal. If the dose of SUBLOCADE is not adequate in the absence of the concomitant medication, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments.
CYP3A4 inducers	
Examples	Rifampicin, phenobarbital, carbamazepine, phenytoin.
Clinical Impact:	The effects of co-administered CYP3A4 inducers on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied. Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4; therefore, potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause increased clearance of the drug which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome.
Intervention:	Patients who transfer to SUBLOCADE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inducers should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate. If patients already on SUBLOCADE require newly-initiated treatment with CYP3A4 inducers, the patients should be monitored for withdrawal. If the dose of SUBLOCADE is not adequate and the concomitant medication cannot be reduced or discontinued, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilised on SUBLOCADE in the setting of concomitant medication that is a CYP3A4

	inducer, and the concomitant medication is discontinued, the patient should be monitored for signs and symptoms of over-medication. Within 2 weeks of SUBLOCADE administration, if the dose provided by SUBLOCADE is excessive in the absence of the concomitant inducer, it may be necessary to remove SUBLOCADE and treat the patient with a formulation of buprenorphine that permits dose adjustments
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Examples	Efavirenz, nevirapine, etravirine, delavirdine
Clinical Impact:	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and sublingual buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.
Intervention:	Patients who are on chronic treatment with SUBLOCADE should be monitored for increase or decrease in therapeutic effects if NNRTIs are added to their treatment regimen.
Antiretrovirals: Protease inhibitors (PIs)	
Examples	Atazanavir, ritonavir
Clinical Impact:	Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (~~nelfinavir,~~ lopinavir/ritonavir, ritonavir) have little effect on sublingual buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine after sublingual administration, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving sublingual buprenorphine and atazanavir with and without ritonavir concomitantly.
Intervention:	If treatment with atazanavir with and without ritonavir must be initiated in a patient already treated with SUBLOCADE, the patient should be monitored for signs and symptoms of over-medication. It may be necessary to remove the depot and treat the patient with a sublingual buprenorphine product that permits rapid dose adjustments.
~~Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs)~~	
~~Clinical Impact:~~	~~Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.~~
~~Intervention:~~	~~None~~

The recommended insertions are for consistency with the Subutex PI.

Of the recommended deletions:

- Nelfinavir, delavirdine not on ARTG. Nelfinavir subsequent proposed insertion says it has little effect on SL buprenorphine.
- The proposes insertion on NRTIs is not an interaction.

The sponsor has proposed additional insertions based on the US PI that are considered acceptable.

It is recommended that the proposed insertions as modified by deletion and insertion be approved.

Changes to remove the contraindication for pregnancy and lactation are in Submission 2017-02665, were initially currently being reviewed and have now been approved 30 August 2018.

4.7 Effects on Ability to Drive and Use Machines

10. The sponsor proposes to amend this section:

    Buprenorphine may influence the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness or impaired thinking, especially during the first few days following treatment and dose adjustment. If used with alcohol or central nervous system depressants the effect is likely to be more pronounced (See section 4.4 Special warnings and precautions for use). Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that SUBLOCADE does not adversely affect their ability to engage in such activities.

    There is an increased level of buprenorphine for 3 days after each injection, buprenorphine levels accumulate during the first two months and are maintained with the 100mg dose; further accumulation occurs with the 300mg maintenance dose, which achieves steady-state after the fourth monthly injection.

It is recommended that the proposed insertion as modified by rearrangement and insertion of a further warning be approved.

4.8 Adverse Effects (Undesirable Effects)

Post-marketing experience with buprenorphine

11. The sponsors propose to include under this section:

    ~~In cases of intravenous or intentional misuse, local reactions, such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections have been reported.~~

This has no relevance to Sublocade (see 13.2).

It is **not** recommended that the proposed insertion be approved.

4.9 Overdose

12. The sponsor proposes to include under this section:

    ~~Clinicians should consider the potential role and contribution of buprenorphine, other opioids, and other CNS depressant drugs in a patient's clinical presentation.~~ Clinical data are limited with regards to the possible surgical removal of the depot as only two cases of surgical removal were reported in premarketing clinical studies.

The first statement is redundant.

It is recommended that the proposed insertion as modified by deletion be approved.

5.1 PHARMACODYNAMIC PROPERTIES

Plasma concentration and Clinical Response

13. The sponsor proposes to insert:

    The Sublocade opioid blockade study evaluated the blockade of subjective opioid effects, pharmacokinetics (PK) and safety of SC injections of Sublocade. Stabilisation doses of SL buprenorphine prior to injection of Sublocade failed to provide full blockade of subjective effects of hydromorphone 18mg I.M. ~~After Sublocade injections at weeks 0 and 4, on average, subjective effects of both 6 and 18mg doses of hydromorphone were blocked; however wide variability was seen across subjects. Complete blockade continued throughout the 8 weeks of observation that followed the 2nd Sublocade injection~~.

The **primary objective** of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior to the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade).

At Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade.

These deletions are secondary end points, the study failed to achieve its primary objective.

It is recommended that the proposed insertion as modified by deletion be approved.

14. The sponsor proposes to insert:

    ~~Figure 11 illustrates the relationship between buprenorphine plasma level and drug liking after 18mg hydromorphone I.M.~~

This was the result of a *post hoc* analysis.[37]

It is **not** recommended that the proposed insertion be approved.

Clinical trials

15. The sponsor proposes to insert:

    Opioid blockade study (13-0002)

    The study evaluated the blockade of subjective opioid effects, PK and safety of SC injections of SUBLOCADE in 39 subjects with opioid use disorder (not treatment-seeking).

    The primary objective of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior to the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade).

[37] Figure 11 was page 134 Summary of Clinical Efficacy

At Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade. In the 4 weeks following the second injection all such endpoints were met. This is consistent with the time (4 injections) to reach steady state for Sublocade.

~~The peak (E_{max}) effect of "Drug Liking" Visual Analogue Scale (VAS) measurement after challenge with I.M. injections of 6mg and 18mg hydromorphone (HM) was not inferior (i.e., shown to be not substantially more likeable) compared to the E_{max} of "Drug Liking" VAS, measured after challenge with placebo (at weeks 1 through 4 following the first injection of 300mg Sublocade). The noninferiority (NI) margin, the largest difference allowed for the 6 or 18mg HM VAS to exceed the placebo VAS (the maximum VAS recorded following IM injection of 0mg HM) before being considered significant, was set at 20. Based on comparison to the historical response to opioid agonists in unblocked subjects, a difference of less than 20 points (on a unipolar scale) between the mean maximum response to hydromorphone and the mean maximum placebo response for the same challenge was considered to indicate near-complete blockade.~~

The deleted paragraph was the result of a *post hoc* analysis.[38]

It is recommended that the proposed insertion as modified by insertion and deletion be approved.

16. The sponsor proposes to insert:

    ~~All 12 weeks of the treatment period demonstrated blockade for both 6mg and 18mg following SUBLOCADE injections. However, wide variation can be seen in isolated measurements from individual subjects, described in section "Plasma concentration and clinical response".~~ For comparison, stabilisation doses of SL buprenorphine in Week 0 failed to provide full blockade to 18mg of HM. ~~Complete blockade continued throughout the 8 weeks of observation that followed the 2nd SUBLOCADE injection.~~

The **primary objective** of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior to the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade).

At Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade.

The deletions relate to secondary end points.

It is recommended that the proposed insertion as modified by deletions be approved.

17. Proposed Figure 10 is based on Figure 5 Summary of Clinical Pharmacology Studies page 49.
18. Proposed Figure 11. Median (95% Confidence Interval) of Placebo-Corrected Drug Liking VAS Scores by Hydromorphone Dose and by Week is based on Figure 33 page 135 Summary of Clinical Efficacy and is the result of a *post hoc* analysis.

It is **not** recommended that the proposed insertion be approved.

[38] page 134 Summary of Clinical Efficacy

Efficacy study (13-0001)

19. The sponsor proposes to insert:

> Efficacy was evaluated over Weeks 5 to 24 based on weekly urine drug screens combined with self-reported use of illicit opioid use. A "grace period" was applied for Weeks 1 through 4 to allow patients to stabilise in treatment. During this period, opioid use, if it occurred, was not considered in the analysis. Missing urine drug screen samples and/or self-reports during weeks 5-24 were counted as positive for illicit opioids. The key secondary endpoint was treatment success (responder), defined as any subject with ≥80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use (opioid-free weeks) from Week 5 through Week 24. ~~Weekly assessments of other markers of efficacy were also collected: Opioid Craving VAS, Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), Clinical Global Impression – Severity (CGI-S) Scale, Clinical Global Impression – Improvement (CGI-I) Scale.~~

As well as 2 key secondary endpoints there were a further 10 secondary endpoints these latter had no allowances for multiplicity.

It is recommended that the proposed insertion as modified by deletion be approved.

20. The sponsor proposes to insert:

> Based on the cumulative distribution function (CDF) of the percentage of urine samples negative for illicit opioids combined with self-reports of negative for illicit opioid is collected from week 5 through week 24 (Table 3), regardless of dose, SUBLOCADE was superior to the placebo group with statistical significance.
>
> The proportion of patients achieving treatment success (defined as patients with ≥ 80% opioid-free weeks) was <u>statistically significantly</u> higher in both groups receiving SUBLOCADE compared to the placebo group.
>
> ~~Secondary endpoints included the Opioid Craving VAS, COWS and SOWS, CGI-S, CGI-I. These consistently reached statistical significance compared to placebo for the 300/300mg group; however, statistical significance compared to placebo was not seen in the 300/100mg group for the Opioid Craving VAS, COWS, and SOWS.~~

As well as 2 key secondary endpoints there were a further 10 secondary endpoints with no allowances for multiplicity.

It is recommended that the proposed insertion as modified by deletion be approved.

21. The sponsor proposes to insert:

> Analysis of the dropout pattern in Study 13-0001 indicated that opioid craving was a major predictor of dropout. An opioid craving score > 20 was associated with an increase in dropout rate of up to 3.0 and 3.6-fold in active treatment arms and placebo arm, respectively, compared to craving ≤ 5.

This is supported by the submission.[39]

Dropout of subjects from the study was modelled using survival (time-to-event) analysis. Treatment effect was modelled to account for a 2 times lower dropout rates in Sublocade

[39] Summary of Clinical Pharmacology Studies page 84

treatment arms (300mg/300mg: 36%; 300mg/100mg: 38%) compared to placebo (66%). Covariate analysis identified opioid craving as a significant predictor of dropout: an opioid craving VAS score > 20 was associated with an increase in dropout rate of up to 3.0 to 3.6 - fold in active treatment arms and placebo arm, respectively, compared to craving VAS scores ≤ 5.

It is recommended that the proposed insertion be approved.

22. The sponsor proposes to insert Figure 12. This is supported by the submission.
23. The sponsor proposes to insert Table 3:

Most of this is supported by Table 23 in the CSR (see Table 1 Table 6 above).

However the final line

= 100%	25 (13)	23 (12)	1 (1.0)

Is not in that Table.

Please supply the source for the final line in Table 3.

24. The sponsor proposes to insert Table 4. This is supported by the submission.
25. The sponsor proposes to insert Table 5:

This table gives the results for 5 of the 10 secondary endpoints with no provision for multiplicity.

It is **not** recommended the proposed Table 5 insertion be approved.

26. The sponsor proposes to insert:

~~In addition, the effect of SUBLOCADE on the following health economics and outcomes research endpoints (HEOR) was prospectively assessed as part of the initial study design; health status, (EQ-5D-5L), health related quality of life (SF-36®-v2), medication satisfaction questionnaire (MSQ), health care resource utilization (HCRU) and employment status and health insurance (ESHI).~~

~~At the end of the study (Week 25), mean scores in the general health, vitality, social functioning, role, emotional and mental health domains as assessed by the SF-36 scale were significantly higher in each of the active treatment groups compared to placebo. At Week 25, significantly fewer subjects in the active treatment groups reported problems on EQ-5D-5L mobility for 300 mg/300mg (10.0%; P = 0.010) and 300 mg/100mg (12.7%; P = 0.048) versus placebo (17.9%). In addition, significantly fewer subjects reported problems with anxiety/depression at Week 25 in the 300 mg/300mg (23.1%) versus placebo (43.6%) group (P = 0.010).~~

~~Subjects in both active treatment groups had a statistically significantly higher mean medication satisfaction score compared to subjects in the placebo group at all time points. When analysed by level of medication satisfaction, more subjects in the active treatment groups were satisfied, very satisfied, or extremely satisfied compared to the placebo group at Week 25 (87.7% versus 46.2%, P < 0.001, SUBLOCADE 300 mg/300mg versus placebo; 88.1% versus 46.2%, P < 0.001, 300 mg/100mg versus placebo).~~

As well as 2 key secondary endpoints there were a further 10 secondary endpoints with no allowances for multiplicity.

It is **not** recommended that the proposed insertion be approved.

5.1 Pharmacodynamic Properties - Plasma concentration and Clinical Response

27. The sponsor proposes to insert:

~~Following sublingual administration, a dose response relationship has been observed for buprenorphine plasma levels and brain mu-opioid receptor occupancy by buprenorphine at 4 hours after dosing. A relationship has also been observed between buprenorphine plasma levels and blockade of subjective opioid agonist symptoms produced by co-administered opioids at 4 hours after dosing. Plasma concentrations of buprenorphine and mu-opioid receptor occupancy decrease between 4 hours and 28 hours post dose correlating with a return of subjective agonist symptoms produced by co-administered opioids, together with opioid withdrawal symptoms and opioid craving~~.

These statements are from the sponsor's review derived from the two Grunwald Studies. Which are only available in the submission in their published form.

However Study 13-0002 CSR[40] found 'Scatter plots of the buprenorphine plasma concentration versus the VAS scores for the subjective measures (Drug Liking, Any Drug Effect, Good Drug Effect, Bad Drug Effect, Sedation, and High,) are presented in Figure 37, Figure 38, Figure 39, and Figure 14.2.2.5. Overall, these plots indicate there was a reduction in VAS scores with increased buprenorphine plasma concentration.'

Comment: The proposed insertion relates to the use of sublingual tablets and is not found in the Subutex PI. An appropriate statement that relates to the use of Sublocade would be:

> In Opioid blockade study (13-0002) overall, scatter plots of the buprenorphine plasma concentration versus the VAS scores for the subjective measures (Drug Liking, Any Drug Effect, Good Drug Effect, Bad Drug Effect, Sedation, and High,) indicate there was a reduction in VAS scores with increased buprenorphine plasma concentration.

1. It is **not** recommended that the proposed insertion be approved.
2. It is recommended that the above insertion be made.

28. The sponsor proposes to insert:

> In a Positron Emission Tomography (PET) study with Sublocade in 2 subjects (one subject receiving 200mg SC injections and one subject receiving 300mg SC injections) with opioid use disorder, ~~75 to 92%~~ 79% & 92% occupancy of the mu-opioid receptors in the brain at day 7 ~~was maintained for 28 days to~~ following the last dose under steady-state conditions was maintained for 28 days to 75 & 81%.

This statement is misleading.

The subject who received 200mg showed 79% and 75% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively. The subject who received 300mg showed 92% and 81% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively.[41]

It is recommended that the proposed insertion as modified by deletion and insertion be approved.

[40] Page 130

[41] CSR Page 239

5.2 Pharmacokinetic Properties - Absorption

29. The sponsor proposes to insert Table 6:

Table 6 Comparison of Buprenorphine Mean Pharmacokinetic parameters between SUBUTEX and SUBLOCADE.

Pharmacokinetic parameters	SUBUTEX daily stabilisation		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg# (1st injection)	100 mg* (steady-state)	300 mg* (steady-state)
$C_{avg,ss}$ (ng/ml)	1.71	2.91	2.19	3.21	6.54
$C_{max,ss}$ (ng/ml)	5.35	8.27	5.37	4.88	10.12
$C_{min,ss}$ (ng/ml)	0.81	1.54	1.25	2.48	5.01

#Exposure after 1 injection of 300mg SUBLOCADE following 24mg SUBUTEX stabilisation.

*Steady-state exposure after 4 injections of 100mg or 300mg SUBLOCADE, following 2 injections of 300mg SUBLOCADE.

$$C_{avg,ss} = \frac{AUC_{0-T,ss}}{T}$$

Proposed Table 6 is sourced from Study 13-0001 based on the description *Steady-state exposure after 4 injections of 100mg or 300mg Sublocade, following 2 injections of 300mg Sublocade.

CSR for 13-0001[42] says only Raw PK and PGx data are briefly summarised in this CSR.

The 2.7.2 Summary of Clinical Pharmacology Studies[43] says Summary statistics of buprenorphine and norbuprenorphine plasma concentrations are provided per Sublocade treatment arm in CSR 13-0001 Table S14.2.22. Buprenorphine plasma concentrations from that study were analysed using a population PK modelling approach (Section 2.7.2.3.2.3).

Table S14.2.22 Plasma Concentration Summary – Sublocade 300mg/300mg+IDC Subjects Full Analysis Set is a *post hoc* analysis as its caption says only of plasma concentrations not PK parameters, nor are these parameters found in the PK model report INDV-6000-M04.

Table 16[44] has some of these parameters.

The following comparisons at steady state show a C_{max} with 100mg Sublocade similar to Subutex but with 300mg it is almost double, C_{min} with 100mg Sublocade is in the range of 2-3ng/mL for 70% μ-opioid receptor occupancy, while for 300mg it is well above it.

Table 20 Comparison steady state Subutex SL Tablet vs. Sublocade C_{max} and C_{min}

Formulation	Study	Dose (mg)	Cohort	N	C_{max} (ng/mL)	C_{min} (ng/mL)
Subutex SL Tablet	12-0005	8	1	15	3.52	0.52
		8	4	15	3.96	0.57

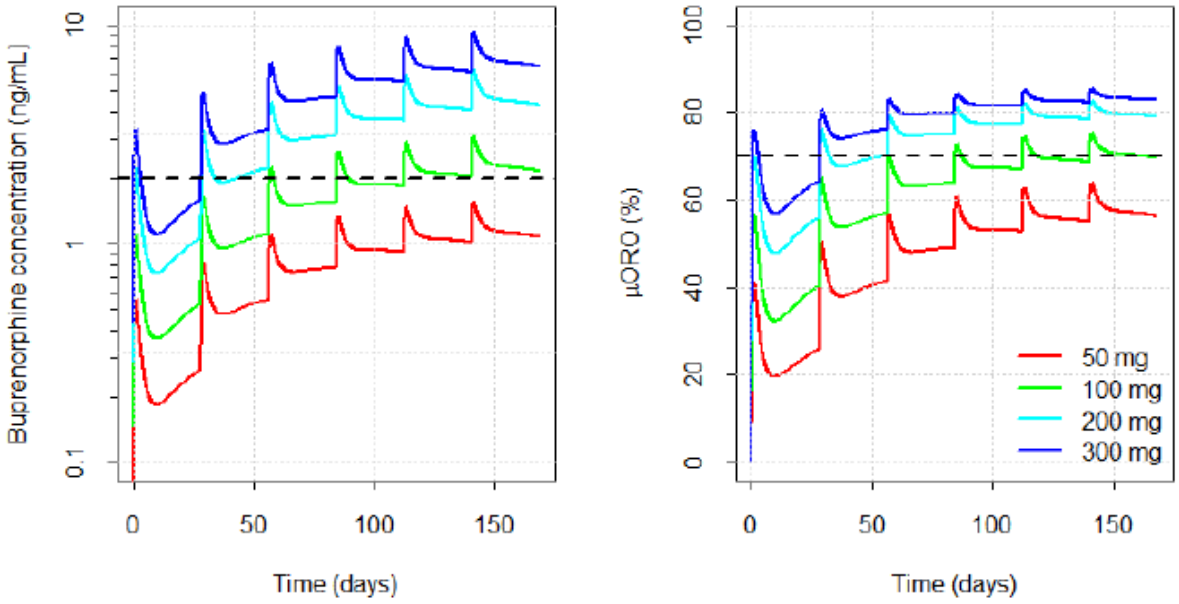
[42] Page 144
[43] Page 57
[44] Page 109 Summary of Clinical Pharmacology Studies

		12	2	15	5.35	0.81
		14	5	15	5.26	0.92
Sublocade	13-0001	100	6 SC injections (observed)	102	4.88	2.48
			6 SC injections (model)	194	4.11	2.74
		300	6 SC injections (observed)	102	10.12	5.01
			6 SC injections (model)	196	8.68	5.11

Source: Table 16 Summary of Clinical Pharmacology Studies

In Study 13-0001 on Day 29 after the first injection (see Table 41) mean C_{min} was 1.82ng/mL, below the range of 2-3ng/mL for 70% μ-opioid receptor occupancy, but the range was 0.98 to 3.93ng/mL. This is reflected in the modelling.

Figure 7 Mean Predicted Buprenorphine Plasma Concentrations and Brain Mu-Opioid Receptor Occupancies After Repeated SC Injections of Sublocade at Various Doses



Left panel = buprenorphine plasma concentrations; Dashed line=2ng/mL
Right panel = mu-opioid receptor occupancy (μ-opioid receptor occupancy); Dashed line=70% μ-opioid receptor occupancy
A total of 6 SC injections given 28 days apart were simulated
Models used for simulation: INDV-6000-M03 Table 10 and INDV-6000-M02 Table 2 Source: Figure 41

1. It is recommended that the sponsor clearly identify the source of the Table 6.
2. It is recommended that an explanatory note on the derivation of C_{avg} be added.

Excretion

30. The sponsor proposes to insert:

Buprenorphine is metabolised and eliminated in urine and faeces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of SUBLOCADE ranged from ~~43 to 60~~ 45 to 66 days as a result of the slow release of buprenorphine from the subcutaneous depot.

Study 11-0020 page 124.

It is recommended that the proposed insertion as modified by deletion and insertion be approved.

15.2. First round comments on draft CMI (clinical aspects)

The clinical aspects of the draft Consumer Medicine Information are not entirely satisfactory and should be revised, having regard to the comments below:

When you must not use it

1. The sponsor proposes to delete:

If you have serious problems with your liver, or if your doctor detects the development of such a problem during treatment.

The existing PI has:

Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing severe hepatic impairment are not candidates for treatment with SUBLOCADE.

It is **not** recommended that the proposed deletion be approved.

Taking Other Medicines

2. Please add to the list

- Medicines containing alcohol

How much to use

3. The sponsor proposes to insert:

SUBLOCADE is only for adults ~~and children over the age of 16 years~~.

This is not consistent with the PI.

It is recommended that the proposed insertion as modified by deletion be approved.

Side effects

4. The sponsor proposes to delete:

- fatigue, ~~weakness, numbness~~

Fatigue is in the PI.

It is **not** recommended that all the proposed deletion be approved.

15.3. First round comments on draft RMP (Summary of Safety Concerns)

The Clinical aspects of the draft Risk Management Plan are satisfactory.

16. Clinical questions

16.1. Clinical questions

16.1.1. PI and CMI

1. Please supply the source for the final line in Table 3.
2. Please clearly identify the source of the Table 6.

20. References

Not applicable.

21. Supporting information, tables and figures

21.1. Clinical pharmacology study synopses

21.1.1. Synopses of pharmacokinetic studies

21.1.1.1. PK study RB-US-10-0011

An open-label, single-centre, first-in-human study, designed to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of a single SC injection of Sublocade containing 20mg buprenorphine in opioid dependent subjects.

The 20mg dose was investigated to evaluate the safety and tolerability of buprenorphine in the ATRIGEL delivery system and not necessarily to evaluate any therapeutic dose.[45]

Conducted from 30 November 2010 to 31 May 2011 in the US. 12 subjects were enrolled with 6 completing (6 withdrawn at subjects request). Subjects were generally healthy aged 18 to 60 years inclusive, opioid dependent.

Primary Objectives :

- To assess the safety and tolerability of a single subcutaneous (SC) injection of Sublocade containing 20mg buprenorphine in opioid-dependent subjects.
- To characterize the PK profile of a single SC injection of Sublocade containing 20mg of buprenorphine in opioid-dependent subjects.
- To facilitate the determination of an appropriate dose of Sublocade for subsequent studies.

On Study Day 1, subjects received a single SC injection of Sublocade containing 20mg buprenorphine after a 2 hour fast, blood samples for determination of buprenorphine and norbuprenorphine levels were collected 15 minutes prior to and then at 0.5, 1, 2, 4, 6, 8 and 12h after injection.

Blood for PK was collected once per day during Days 2 to 32 Subjects were administered oral methadone during Days 25 to 30 of residential treatment.

During the inpatient portion of the study (Days -2 to 30), subjects who displayed clinically significant signs of opioid withdrawal were treated with oral hydromorphone.

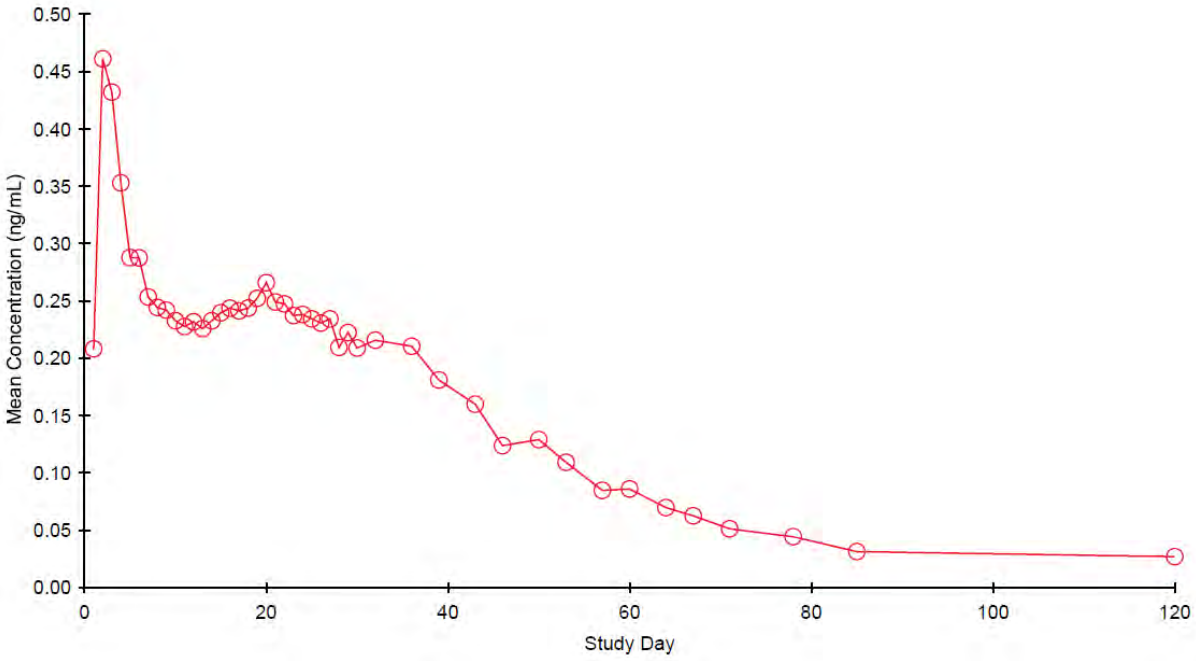
[45] Page 161 CSR

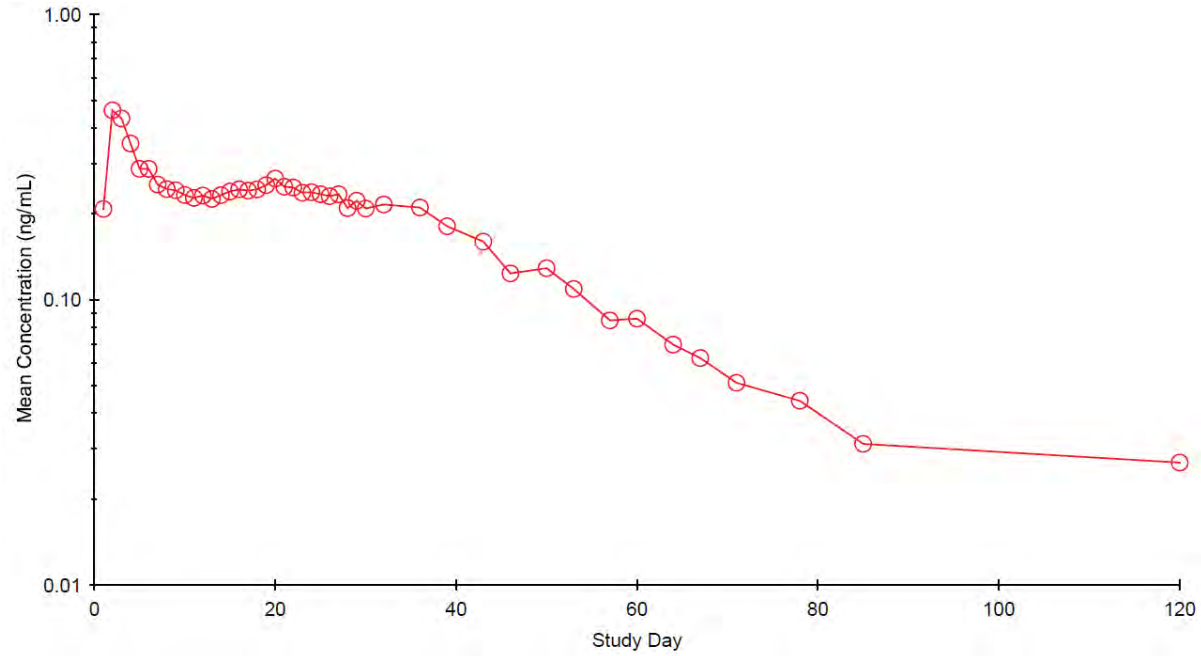
From Study Day 30 subjects were treated as outpatients and blood collected for PKs on Study Days 32, 36, 39, 43, 46, 50, 53, 57, 60, 64, 67, 71, 78, and 85 for and monitored for safety, withdrawal and illicit drug use. Subjects whose buprenorphine plasma concentrations were not below 100pg/mL by Day 85, continued to come to the CU weekly (Day 92, 99, 106, 113), until buprenorphine plasma levels were below 100pg/mL up to Day 120.

Buprenorphine peaked on Day 2 (0.461 ± 0.134ng/mL), and all subjects had buprenorphine concentrations below 100pg/mL by Day 85. There was substantial intrasubject and intersubject variability in norbuprenorphine plasma concentrations throughout the sampling period. Quantifiable norbuprenorphine concentrations were observed at 0.5h.

Analysis used a liquid chromatograph tandem mass spectroscopy (LC-MS-MS) procedure validated for a range of 0.025 to 10.0ng/mL for buprenorphine and 0.020 to 8.00ng/mL for norbuprenorphine.

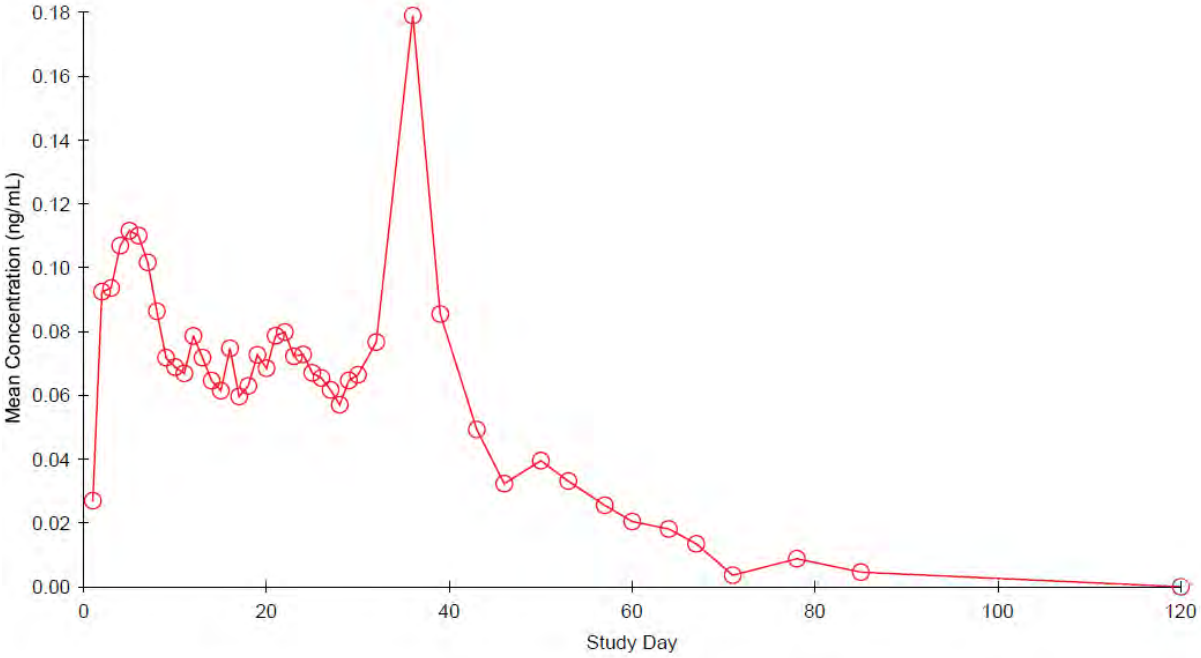
Figure 8 Mean Buprenorphine Concentration-Time Profiles after Administration of a Single Subcutaneous (SC) Injection of Sublocade Containing 20mg Buprenorphine

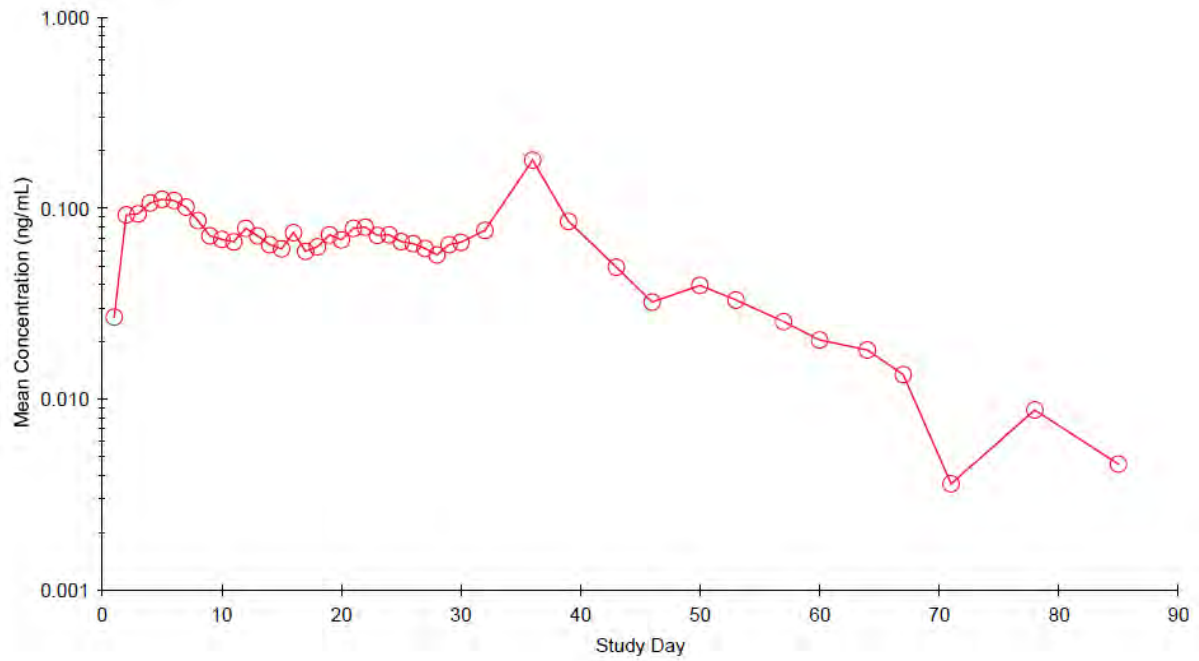




Source: Figure 3

Figure 9 Mean Norbuprenorphine Concentration-Time Profiles after Administration of a Single SC Injection of Sublocade Containing 20mg Buprenorphine





Source: Figure 4

As can be seen from the above figures there was an initial burst of absorption followed by a secondary more sustained peak plasma concentration.

Table 21 Initial Burst Pharmacokinetic Parameters of Buprenorphine

Parameter	n	Mean	SD	CV%
T_{max} (day)	6	1.04	0.78	75.00
C_{max} (ng/mL)	6	0.550	0.166	30.16
$AUC_{0\text{-}30}$ (day*ng/mL)	6	7.516	1.892	25.17

Source: Table 19

Table 22 Overall PK Parameters of Buprenorphine

Parameter	n	Mean	SD	CV%
T_{max} (day)	6	1.04	0.78	75.00
C_{max} (ng/mL)	6	0.550	0.166	30.16
$AUC_{0\text{-}85days}$ (day*ng/mL)	6	13.29	3.547	26.68
AUC_{last} (day*ng/mL)	6	14.20	4.149	29.21
AUC_{inf} (day*ng/mL)	2	15.78	2.799	17.74
AUC_{Extrap} (%)	2	4.52	0.87	19.33
λ_z (day^{-1})	2	0.0445	0.0240	54.03
$T_{1/2}$ (day)	2	18.24	9.86	54.03
T_{last} (day)	6	95.00	28.36	29.85
C_{last} (ng/mL)	6	0.0431	0.0200	46.52

Source: Table 20

Table 23 Initial Burst PK Parameters of Norbuprenorphine

Parameter	n	Mean	SD	CV%
T_{max} (day)	6	6.67	9.14	137.04
C_{max} (ng/mL)	6	0.144	0.0566	39.23
$AUC_{0\text{-}30}$ (day*ng/mL)	6	2.184	1.153	52.79

Source: Table 21

Table 24 Overall PK Parameters of Norbuprenorphine

Parameter	n	Mean	SD	CV%
T_{max} (day)	6	19.17	17.39	90.75
C_{max} (ng/mL)	6	0.231	0.127	54.90
$AUC_{0\text{-}85days}$ (day*ng/mL)	6	4.339	1.885	43.45
AUC_{last} (day*ng/mL)	6	4.224	1.932	45.74
AUC_{inf} (day*ng/mL)	1	4.981	NC	NC
AUC_{Extrap} (%)	1	6.75	NC	NC
λ_z (day^{-1})	1	0.0642	NC	NC
$T_{1/2}$ (day)	1	10.79	NC	NC
T_{last} (day)	6	63.33	17.01	26.86
C_{last} (ng/mL)	6	0.0556	0.0708	127.39

Source: Table 22

Urine drug screening results showed that buprenorphine was detectable in the urine of all subjects starting on Day 2 and continued to be positive in 5 subjects at Day 85, when plasma levels were all below 100pg/mL.

Safety:

12 subjects experienced drug withdrawal syndrome.

10 subjects experienced injection site pain, 5 experienced rebound hypertension, 4 experienced constipation, 3 experienced headache and 2 experienced injection site warmth, increased respiratory rate, and upper respiratory tract infection.

In the completers all AEs were felt not treatment related except injection site pain (6 mild), Rebound hypertension (2 mild), Respiratory rate increased (2 mild), Hepatic enzyme increased (1 moderate), constipation (1 mild) and Tinnitus (1 mild).

The one SAE, psychosocial stress leading to prolonged hospitalization that occurred in this study was not considered to be related to the study drug.

Increases above the ULN for all haematology or coagulation parameters except WBC were less than 1.5-fold the ULN. In one subject, WBCs were elevated 2.2- fold above the ULN. Decreases in haematology parameters were generally within 10% of the LLN. No changes in haematology parameters or coagulation parameters were considered clinically significant.

Alkaline phosphatase increases ranged from 1.1 to 1.7 x ULN. ALT increases ranged from 1.1 to 7.4 x ULN. AST increases ranged from 1.1 to 8.0 x ULN.

These elevated liver function tests were primarily due to one Subject and were considered a grade 2 moderate severity TEAE. They started on Study Day 27 and resolved on Day 56. This subject had alkaline phosphatase, AST and ALT within normal laboratory limits at baseline.

Another Subject had 3.7 x ULN ALT and another Subject had 3.1 x ULN ALT, but these elevations were not considered clinically significant.

Increased liver function tests in Subject ID 132 that were reported as a TEAE.

BUN was slightly decreased in two subjects 0.9 x LLN. Glucose levels were decreased in all subjects as much as 0.62 x LLN; however, glucose levels were below the LLN for all subjects at baseline.

Five of the twelve subjects who received study drug injections had blood pressure increases after study drug injection considered to be clinically significant that were reported as mild rebound hypertension.

21.1.1.2. PK study RB-US-11-0020

A Phase 1, single-centre,[46] open-label, single ascending-dose study, designed to evaluate the safety, tolerability, and PK profile of a single SC injection of Sublocade containing 50mg, 100mg, or 200mg of buprenorphine.

Conducted from 10 July 2012 to 16 February 2013 in the US. 51 subjects were Included and Dosed and 35 completed.

Primary objectives:

- To assess the safety and tolerability of single subcutaneous (SC) injections of Sublocade (50mg, 100mg, and 200mg), administered as buprenorphine, in opioid-dependent subjects.
- To characterize the pharmacokinetics (PK) of single SC injections of Sublocade.
- To evaluate the safety and PK of Sublocade when administered as a single SC injection of 100mg of buprenorphine after up to 12mg daily dosing of Suboxone (buprenorphine/naloxone) sublingual (SL) tablets (Suboxone SL) for 7 days in opioid-dependent subjects.

Secondary objective was to explore pharmacodynamic (PD) markers using the Columbia Suicide Severity Rating Scale (C-SSRS), Clinical Opiate Withdrawal Scale (COWS), and Opioid Craving Visual Analog Scale (VAS) total scores.

Cohorts 1-3 were admitted on Day -2 and were confined for 23 days. Upon admission, non-opioid rescue medications to treat the signs and symptoms of withdrawal were initiated, as clinically appropriate. In these 3 cohorts, 12 subjects per cohort received Sublocade containing 50mg, 100mg, or 200mg buprenorphine, with safety, tolerability, and available PK data reviewed prior to dose escalation.

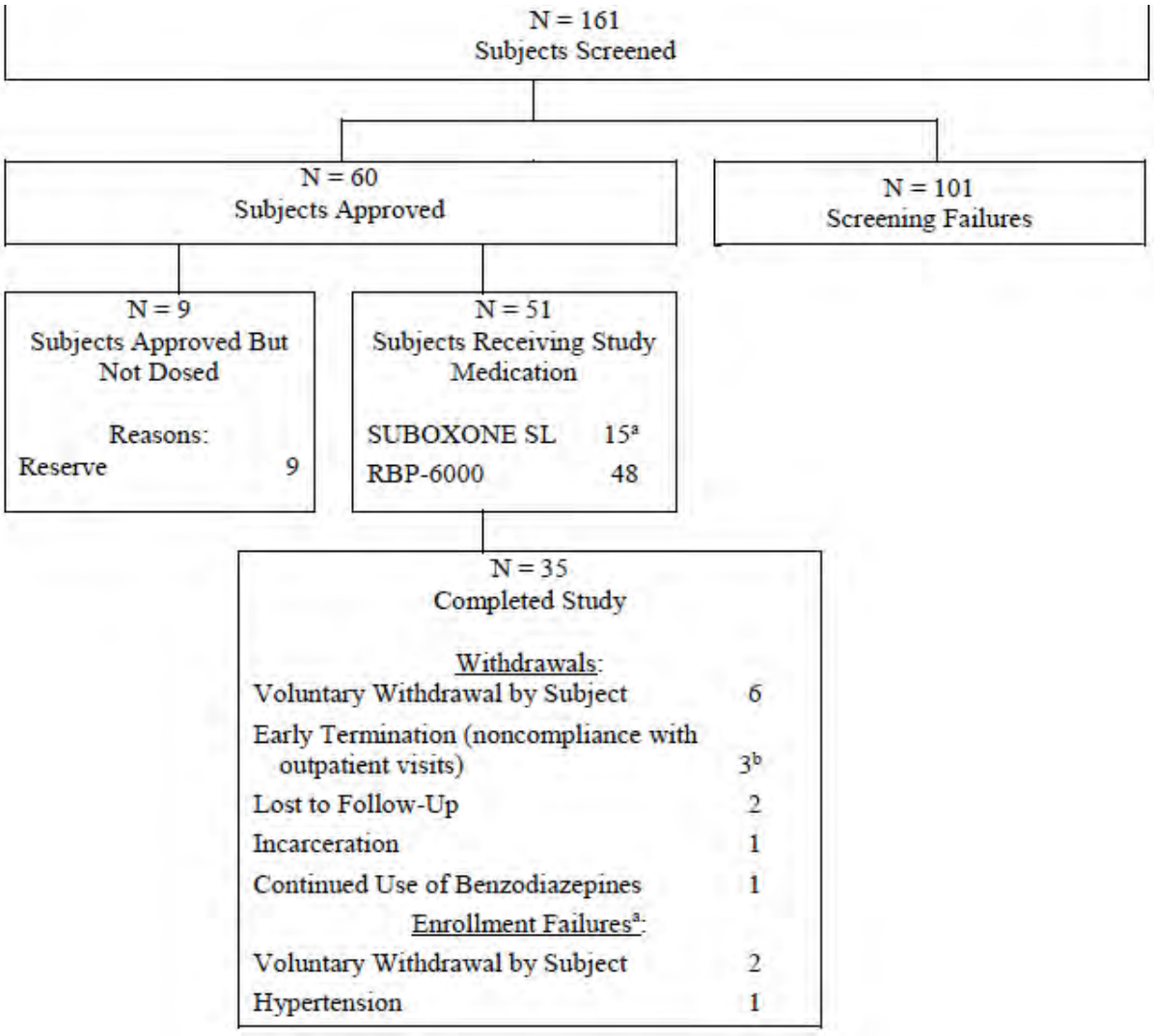
Cohort 4 were admitted on Day -9 and were confined for 30 days. 15 subjects enrolled in cohort 4 and after 7 consecutive days of up to 12mg daily dosing of Suboxone SL Tablets, 3 enrolment failures meant 12 subjects then received a single SC injection of 100mg buprenorphine Sublocade.

Subjects were discharged from the study following the end of study visit as early as 1 week after plasma buprenorphine concentration fell below 100pg/mL. If plasma buprenorphine concentrations were above 100pg/mL on Day 140, subjects were discharged from the study after the end of study visit on Day 150.

[46] The study CSR and protocol are labelled as multicentre, however the Design section (page 43) describe it as single centre and 16.1.4 List and Description of Investigators and Other Important Participants in the Study shows all subjects enrolled in a single site.

During the inpatient portion of the study (from Day 11 post injection), subjects who displayed clinically significant signs of opioid withdrawal were treated with oral hydromorphone. Methadone was allowed, beginning on Day 16 only if hydromorphone was not being used concurrently on that day to aid the ability of individual subjects to abstain from illicit drug use.

Figure 10 Summary of Subject Disposition



N = number of subjects Source: Figure 3

[a] Three subjects received Suboxone SL only and were not administered Sublocade.

[b] Includes Subject 001330 who lived out of area and was unable to comply with visit schedule.

There were problems with the concentration analyses. It was planned to undertake the analysis using a validated procedure for samples using K_2EDTA as the anticoagulant. By error all samples were collected using K_3EDTA as the anticoagulant. Once the error was discovered, a method for the quantitation of samples collected in K_3EDTA tubes was partially validated.

Results

Buprenorphine

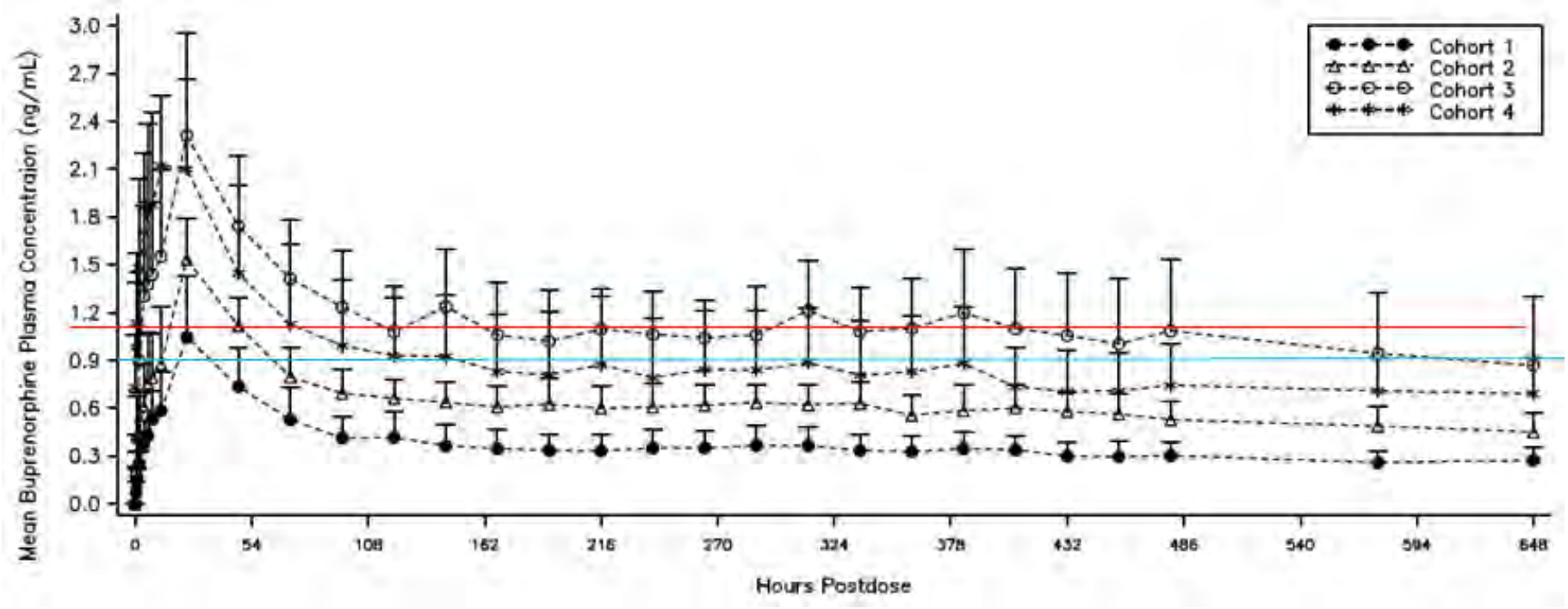
Buprenorphine exposure (AUC_{0-48} and C_{max}) during Day 1 to Day 3 (initial burst period) increased with increasing dose of Sublocade, from 50mg to 200mg in Cohorts 1-3.
Cohort 4, which received Suboxone SL for 7 days prior to dosing with 100mg Sublocade, showed a similar AUC_{0-48} and C_{max} as Cohort 3 (200mg Sublocade). Median t_{max} for the initial burst period was 24h in Cohorts 1-3, and 18h in Cohort 4.

In the secondary peak and overall periods, $AUC_{Day3-28}$, $AUC_{Day1-29}$, AUC_{0-inf}, and C_{max}, increased with the increasing dose of Sublocade in Cohorts 1-3, while Cohort 4 results were between those of Cohorts 2 and 3.
The secondary peak median t_{max} was 144h, 228h, and 264h at 50 mg, 100 mg, and 200 mg, respectively. Median t_{max} was 180h in Cohort 4.
In the overall profile, median t_{max} was 24h for Cohorts 1-3 and 18h for Cohort 4.
Apparent clearance (CL/F) was fairly constant at the 50 mg, 100 mg, and 200mg doses.
Apparent volume of distribution (V_d/F) increased with the increase in Sublocade dose (96120L, 127235L and 154369L for 50mg, 100mg, and 200mg doses respectively).
For buprenorphine, mean t½ increased slightly with the increase in dose (1078h at 50mg, 1376h at 100mg, and 1573h at 200mg).
Overall, the degree of fluctuation of buprenorphine plasma concentrations was similar between all cohorts. Swing increased with the dose between Cohorts 1-3, while the lowest swing value was observed in Cohort 4.

Norbuprenorphine

Norbuprenorphine AUCs, and $C_{max,}$ in the initial burst, secondary peak period, and the overall profile increased with increasing dose of Sublocade, with Cohort 4 showed much greater AUC_{last} compared to Cohort 2 and 3.
Median t_{max} for the initial burst period was 48h in Cohorts 1-3, and 5h in Cohort 4
Median t_{max} in the secondary peak period was 144h in Cohort 4, and 300h for Cohorts 1 and 2 and 264h in Cohort 3.
Overall, geometric mean $AUC_{Day1-29}$ of norbuprenorphine for Cohort 4 was greater by 3.1 fold and 1.7 fold compared to Cohort 2 and Cohort 3, respectively.
Geometric mean C_{max} for Cohort 4 was 7.5-fold and 4-fold greater compared to Cohort 2 and Cohort 3, respectively.
Mean t½ was 1510h, 980h, 1156h, and 847h for Cohorts 1-4, respectively.
Fluctuation was similar between Cohorts 1-3 in the overall profile. Swing was lowest in Cohort 1, but comparable between Cohorts 2 and 3. Cohort 4 norbuprenorphine had the highest percent fluctuation and swing compared to other cohorts.

Figure 11 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 28

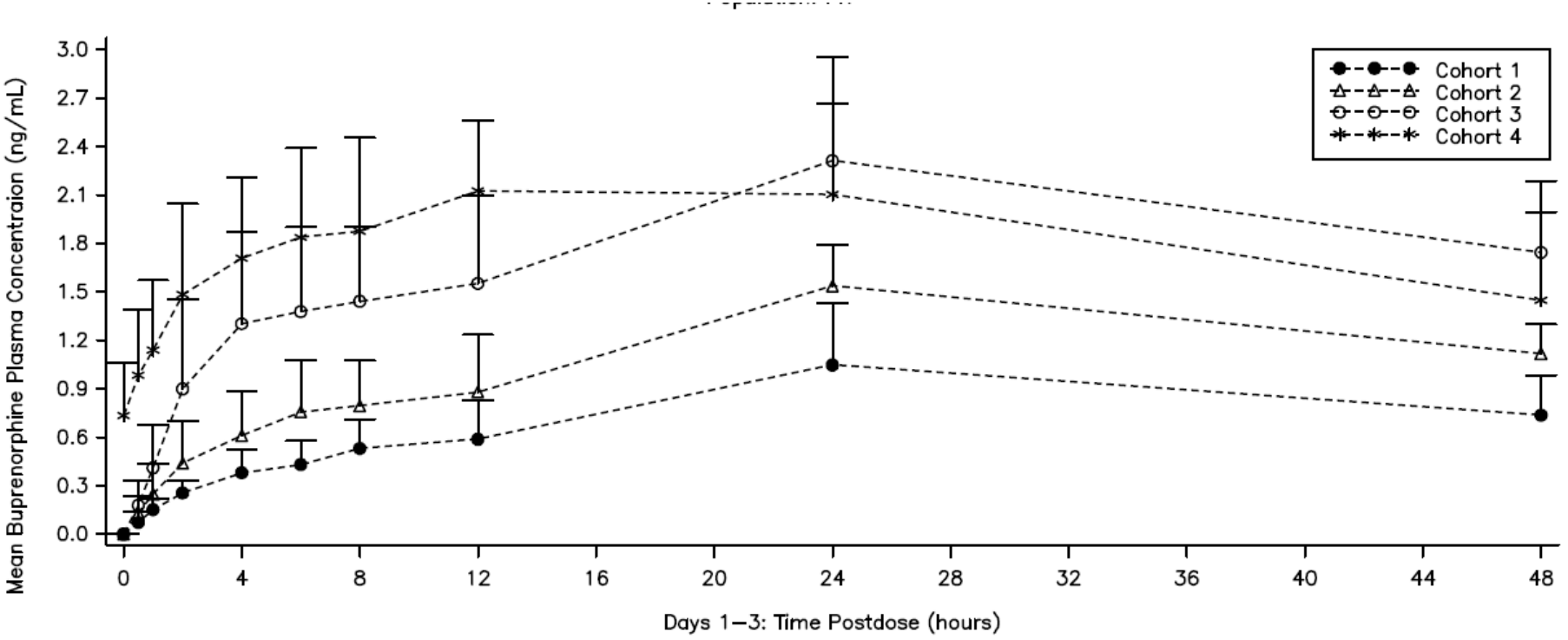


Cohort 1: Sublocade containing 50mg Buprenorphine Source: Figure 14.2.2. 1 .4
Cohort 2: Sublocade containing 100mg Buprenorphine
Cohort 3: Sublocade containing 200mg Buprenorphine The red line is at ~1.1ng/mL i.e. mean C_{avg}
Cohort 4: 7 days of SL Suboxone dosing (6 days at 12mg daily) followed by Sublocade containing 100mg Buprenorphine the blue line is at ~0.95ng/mL i.e. . mean C_{avg}

Comment: The concentration of 2-3ng/mL for 70% μ-opioid receptor occupancy is not achieved except in the early days. The sponsor defined both C_{avg} and $C_{avg\ Day\ 3\text{-}28}$ in the Statistical Analysis Plan[47] but in the CER only referred to C_{avg}. As can be seen for Cohorts 3 & 4 neither result particularly reflect plasma concentrations, at times either being well above or below the observed results. C_{avg} is a mathematical concept, not a measurement, which for comparative purposes only serves to diminish absolute values of differences in AUCs.

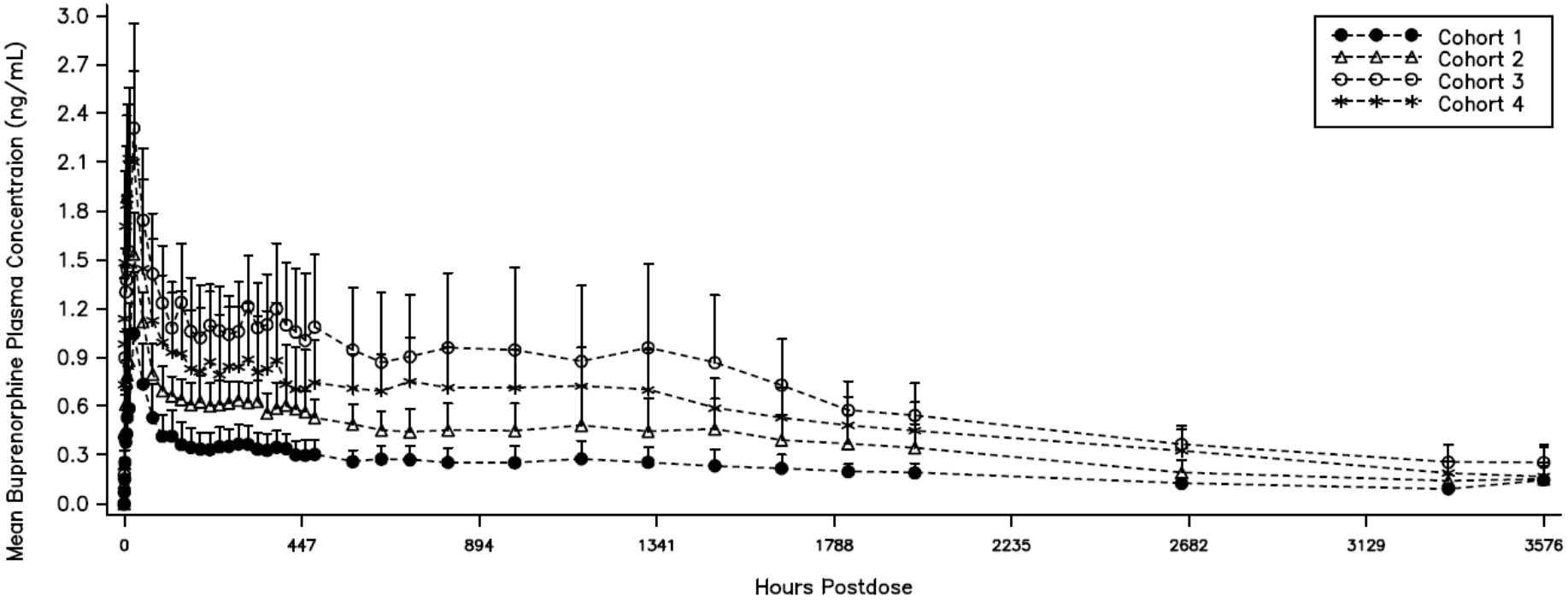
[47] Page 9 C_{avg} = The average of plasma concentrations calculated as $AUC_{Day\ 1\text{-}29}$/28 days and $C_{avg\ Day\ 3\text{-}28}$ = The average of plasma concentrations in the plateau (day 3 to day 28),calculated as $AUC_{Day\ 3\text{-}28}$/time Mean results were found in Table 11 CER

Figure 12 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 3



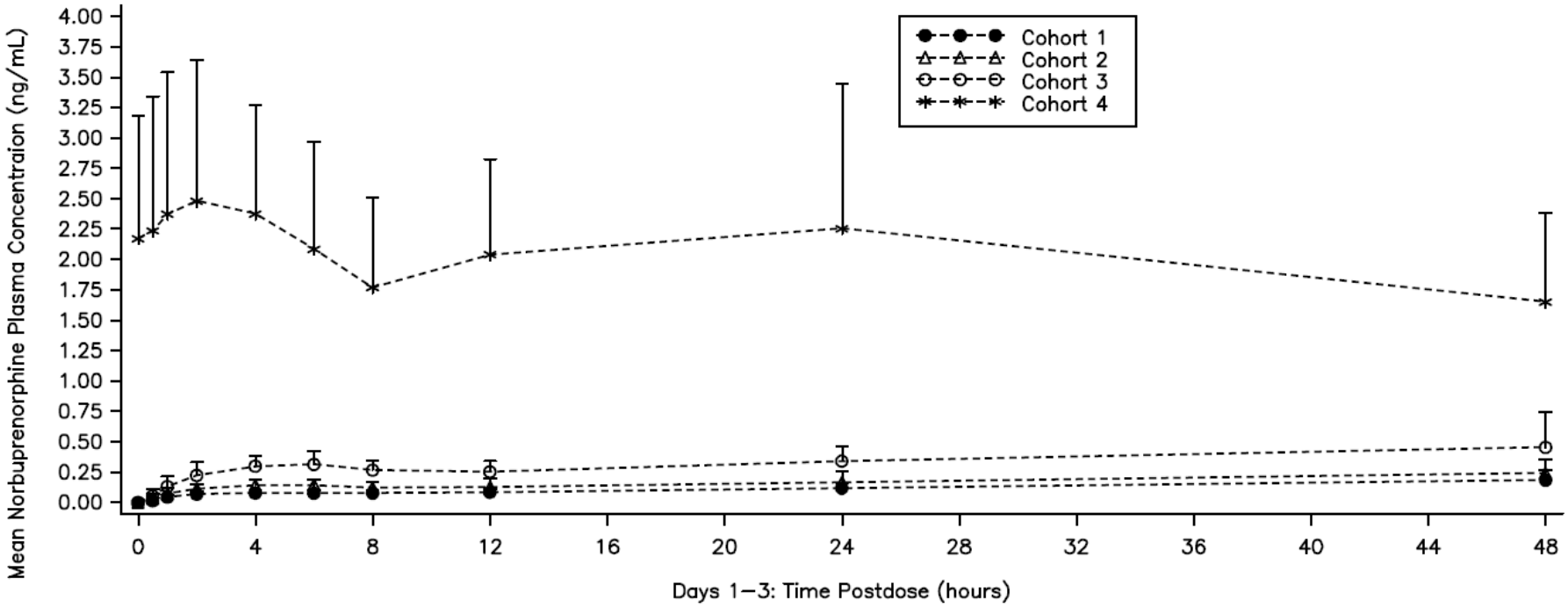
Cohort 1: Sublocade containing 50mg Buprenorphine
Cohort 2: Sublocade containing 100mg Buprenorphine
Cohort 3: Sublocade containing 200mg Buprenorphine
Cohort 4: 7 days of SL Suboxone dosing (6 days at 12mg daily) followed by Sublocade containing 100mg Buprenorphine Source: Figure 14.2.2. 1 .2

Figure 13 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 150



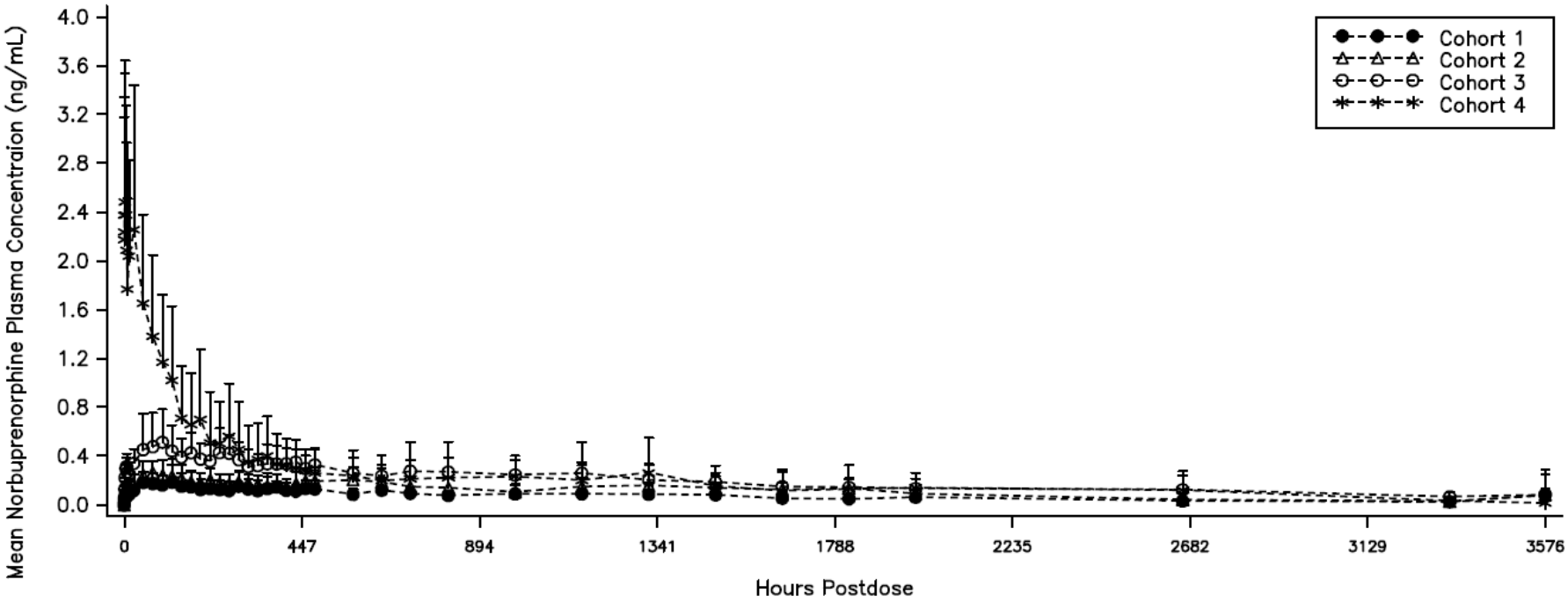
Cohort 1: Sublocade containing 50mg Buprenorphine
Cohort 2: Sublocade containing 100mg Buprenorphine
Cohort 3: Sublocade containing 200mg Buprenorphine
Cohort 4: 7 days of SL Suboxone dosing (6 days at 12mg daily) followed by Sublocade containing 100mg Buprenorphine Source: Figure 14.2.2. 1 .3

Figure 14 Plot of Mean (+ SD) Norbuprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to 3



Cohort 1 = a single SC injection of Sublocade containing 50mg buprenorphine.
Cohort 2 = a single SC injection of Sublocade containing 100mg buprenorphine.
Cohort 3 = a single SC injection of Sublocade containing 200mg buprenorphine.
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day -7 and 12mg on Days -6 through -1. Source: Figure 14.2.2.3.2

Figure 15 Plot of Mean (+ SD) Norbuprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to 150



Cohort 1 = a single SC injection of Sublocade containing 50mg buprenorphine.
Cohort 2 = a single SC injection of Sublocade containing 100mg buprenorphine.
Cohort 3 = a single SC injection of Sublocade containing 200mg buprenorphine.
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day -7 and 12mg on Days -6 through -1. Source: Figure 14.2.2.3.3

Table 25 Summary Statistics of Buprenorphine Plasma PK Parameters (Study 11-0020)

Parameter	Statistic	RBP-6000			SUBOXONE + RBP-6000
		Cohort 1 50 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 100 mg
AUC_{0-inf} (ng*hr/mL)	N	8	9	8	8
	Geometric Mean	846.78	1528.74	2919.43	2117.26
	%CV	22.9	19.3	25.7	29.4
CL/F (L/hr)	N	10	11	10	NC
	Geometric Mean	62.90	64.38	66.57	
	%CV	24.4	21.5	25.8	
C_{avg} (ng/mL)	N	12	12	12	10
	Geometric Mean	0.36	0.62	1.11	0.91
	%CV	27.4	16.6	25.7	32.5
C_{max} (ng/mL)	N	12	12	12	12
	Geometric Mean	1.00	1.52	2.38	2.23
	%CV	35.6	16.4	20.9	23.2
C_{min} (ng/mL)	N	12	12	12	12
	Geometric Mean	0.05	0.08	0.11	0.23
	%CV	56.1	44.3	67.8	64.3
T_{max} (hr)	N	12	12	12	12
	Median	24.00	24.00	24.00	18.00
	Min, Max	4.00, 24.03	24.00, 48.00	4.00, 144.00	4.00, 24.00
$t_{½}$ (hr)	N	10	11	10	10
	Geometric Mean	1036.76	1234.43	1429.41	1140.51
	%CV	27.2	47.3	49.6	16.7

NC=not calculated Source: Table 4Summary of Clinical Pharmacology Studies
Cohort 1=single SC injection of Sublocade containing 50mg buprenorphine
Cohort 2=single SC injection of Sublocade containing 100mg buprenorphine
Cohort 3=single SC injection of Sublocade containing 200mg buprenorphine
Cohort 4=once daily dosing with SL Suboxone, 8mg (2-, 4-mg doses approximately 3 hours apart) on Day -7 and 12mg on Day -6 through Day -1 followed by single SC injection of Sublocade containing 100mg Buprenorphine

Table 26 Summary Statistics of Norbuprenorphine Plasma PK Parameters (Study 11-0020)

Parameter	Statistic	RBP-6000			SUBOXONE + RBP-6000
		Cohort 1 50 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 100 mg
AUC_{0-inf} (ng*hr/mL)	N	3	7	5	7
	Geometric Mean	327.07	476.34	733.15	686.90
	%CV	33.5	51.6	34.4	36.2
AUC_{last} (ng*hr/mL)	N	12	12	12	12
	Geometric Mean	194.69	348.42	583.84	589.54
	%CV	72.2	62.2	45.0	60.2
C_{max} (ng/mL)	N	12	12	12	12
	Geometric Mean	0.22	0.34	0.64	2.53
	%CV	60.3	50.4	40.2	42.5
T_{max} (hr)	N	12	12	12	12
	Median	204.00	468.09	264.03	5.00
	Min, Max	48.00, 3581.02	48.00, 1825.80	4.00, 1130.60	2.00, 48.00
$t_{½}$ (hr)	N	4	7	6	7
	Geometric Mean	1383.80	856.74	1146.28	603.36
	%CV	49.3	52.6	14.1	68.7
M:P Ratio $RAUC_{last}$	N	12	12	12	12
	Geometric Mean	0.27	0.24	0.23	0.41
	%CV	48.0	54.1	36.6	97.6
M:P Ratio RC_{max}	N	12	12	12	12
	Geometric Mean	0.20	0.20	0.24	1.00
	%CV	50.3	54.8	42.3	43.4

M:P Ratio RC_{max} = Metabolite-to-parent ratio on C_{max} Source: Table 5 Summary of Clinical Pharmacology Studies
M:P Ratio $RAUC_{last}$ = Metabolite-to-parent ratio on AUC_{last}
Cohort 1=single SC injection of Sublocade containing 50mg buprenorphine
Cohort 2=single SC injection of Sublocade containing 100mg buprenorphine
Cohort 3=single SC injection of Sublocade containing 200mg buprenorphine
Cohort 4=once daily dosing with SL Suboxone, 8mg (2-, 4-mg doses approximately 3 hours apart) on Day -7 and 12mg on Day -6 through Day -1 followed by single SC injection of Sublocade containing 100mg buprenorphine

Pre-treatment with Suboxone SL slightly increased the exposure to buprenorphine and considerably increased exposure to norbuprenorphine (geometric mean $AUC_{Day1-29}$ and C_{max} were greater than Cohort 2 by 3 fold and 7.5 fold, respectively) after administration of Sublocade. Metabolite to parent (norbuprenorphine/buprenorphine) ratios of AUC_{last} and C_{max} were also considerably higher in Cohort 4 compared to Cohorts 1-3. Metabolite to parent C_{max} and C_{avg} ratios were lower after administration of Sublocade than following administration of Suboxone SL. The metabolite to parent C_{max} (geometric mean) ratio was ~0.2 for all the 3 doses in Cohorts 1-3 following administration of Sublocade compared to 0.87 following administration of Suboxone SL and 1.0 in Cohort 4 (Suboxone SL and Sublocade). The ratio of C_{avg} (R_{Cavg}) for buprenorphine and norbuprenorphine were 1.5251 and 4.1959, respectively,

which further explains the greater exposure to norbuprenorphine compared to buprenorphine after pre-treatment with Suboxone SL in Cohort 4.

Table 27 Summary Statistics of Buprenorphine and Norbuprenorphine Plasma PK Parameters for Cohort 4 During Treatment with Suboxone SL

Parameter	Statistic	Buprenorphine	Norbuprenorphine
$C_{max,ss}$ (ng/mL)	n	13	13
	Mean	4.3223	4.5115
	%CV	44.0	61.4
	Median	3.6000	3.6000
	Min,Max	1.980, 7.930	2.010, 11.600
	Geometric Mean	3.9670	3.9163
$T_{max,ss}$ (hr)	n	13	13
	Median	1.0000	1.0000
	Min,Max	0.500, 2.000	1.000, 12.067
AUC_{0-24} (hr*ng/mL)	n	13	13
	Mean	34.417	66.435
	%CV	34.9	51.3
	Median	31.956	61.698
	Min,Max	13.19, 60.49	26.10, 136.89
	Geometric Mean	32.410	58.885
C_{avg} (SL) (ng/mL)	n	13	13
	Mean	1.4340	2.7681
	%CV	34.9	51.3
	Median	1.3315	2.5708
	Min,Max	0.550, 2.520	1.087, 5.704
	Geometric Mean	1.3504	2.4536
R_{Cavg} (SL)	n	10	11
	Mean	1.6398	4.5992
	%CV	44.9	47.0
	Median	1.3902	3.8391
	Min,Max	0.987, 3.417	2.406, 8.589
	Geometric Mean	1.5251	4.1959
RCmax,ss	n		13
	Mean		1.0218
	%CV		54.3
	Median		1.0228
	Min, Max		0.302, 2.182
	Geometric Mean		0.8730

R_{Cavg} Ratio of Suboxone C_{avg}/Sublocade C_{avg} Source: Table 13
$R_{Cmax,ss}$ Ratio of C_{max} norbuprenorphine/C_{max} buprenorphine (C_{max} was converted to molar concentration; buprenorphine MW: 467.64, norbuprenorphine MW: 413.55)
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day-7 and 12mg on Days -6 to -1.

With the increase in dose of Sublocade from 50mg to 200mg, mean buprenorphine exposure parameters in the initial period (C_{max} and AUC_{0-48}), secondary period ($AUCD_{ay3-28}$ and Cm_{ax}), and entire profile (C_{max}, C_{avg}, $AUC_{Day1-29}$, AUC_{last}, and AUC_{0-inf}), increased less than proportionally to dose, where the difference of the slope from unity was statistically significant for all the above exposure parameters except for AUC_{last} and AUC_{0-inf} in the overall profile. Mean norbuprenorphine exposure parameters in the initial burst period (C_{max} and AUC_{0-48}), secondary

peak period ($AUC_{Day3-28}$ and C_{max}), and entire profile (C_{max}, C_{avg}, $AUC_{Day1-29}$, AUC_{last}, and AUC_{0-inf}) increased less than proportionally to dose, but the difference of slope from unity was statistically significant only for initial burst parameters.

Table 28 Statistical Analysis of Dose Proportionality for Buprenorphine

Phase	PK Parameter	Estimate (beta1)	p-value	90% CI of Slope
Initial Burst	C_{max} (ng/mL)	0.620	<.001	(0.501, 0.739)
	AUC_{0-48} (hr*ng/mL)	0.641	<.001	(0.525, 0.756)
Secondary Peak	C_{max} (ng/mL)	0.828	0.044	(0.688, 0.967)
	$AUC_{Day\ 3-28}$ (hr*ng/mL)	0.846	0.043	(0.721, 0.970)
Overall	C_{max} (ng/mL)	0.626	<.001	(0.509, 0.744)
	C_{avg} (ng/mL)	0.819	0.014	(0.700, 0.937)
	$AUC_{Day\ 1-29}$ (hr*ng/mL)	0.819	0.014	(0.700, 0.937)
	AUC_{last} (hr*ng/mL)	0.889	0.171	(0.754, 1.023)
	AUC_{0-inf} (hr*ng/mL)	0.893	0.208	(0.751, 1.035)

Source: Table 14

Table 29 Statistical Analysis of Dose Proportionality for Norbuprenorphine

Phase	PK Parameter	Estimate (beta1)	p-value	90% CI of Slope
Initial Burst	C_{max} (ng/mL)	0.673	0.016	(0.455, 0.891)
	AUC_{0-48} (hr*ng/mL)	0.741	0.025	(0.555, 0.927)
Secondary Peak	C_{max} (ng/mL)	0.804	0.183	(0.561, 1.048)
	$AUC_{Day\ 3-28}$ (hr*ng/mL)	0.775	0.089	(0.558, 0.992)
Overall	C_{max} (ng/mL)	0.764	0.124	(0.511, 1.017)
	C_{avg} (ng/mL)	0.768	0.075	(0.555, 0.981)
	$AUC_{Day\ 1-29}$ (hr*ng/mL)	0.768	0.075	(0.555, 0.981)
	AUC_{last} (hr*ng/mL)	0.792	0.178	(0.537, 1.047)
	AUC_{0-inf} (hr*ng/mL)	0.587	0.068	(0.220, 0.954)

Source: Table 15

Confounding

Although the use of *cannabis sativa* was prohibited during the study, multiple subjects continued to use cannabis throughout the study. Throughout the entire duration of the study, cannabis use ranged from 17-75%, 0-42%, 8-83%, and 7-33% (8 to 33% by *post hoc* analysis) of subjects in Cohorts 1-4, respectively. The impact of continued cannabis use on study integrity could not be determined, because buprenorphine and cannabinoids are both metabolized by CYP3A4, and cannabinoids are known to induce and inhibit CYP3A4.13.

21.1.1.3. PK study RB-US-12-0005

An open-label multiple dose study of the safety, tolerability, pharmacokinetics, efficacy markers, and opioid receptor availability of subcutaneous injections of depot buprenorphine (Sublocade) in treatment seeking opioid-dependent subjects.

This was described as multicentred (e.g. on title page) but Appendix 16.1.4.1 List of Investigators gives only a single centre in the US. Conducted from 05 October 2012 to 05 May 2014. Cohort 6 was added by amendment 4 (18 June 2013).

90 subjects were planned to be enrolled with at least 6 subjects per cohort completing the study. A total of 89 subjects received both Subutex SL tablet and Sublocade and were included in the PK, pharmacodynamic (PD) and safety evaluations.

The primary objectives of this study were:

- To assess the safety and tolerability of multiple subcutaneous (SC) injections of 50mg, 100mg, 200mg and 300mg doses of buprenorphine in Sublocade in treatment seeking opioid-dependent subjects who were inducted and then stabilised on a Subutex sublingual (SL) tablet dose of 8mg, 12mg, 14mg, 24mg or 8-24mg[48] prior to transfer.
- To evaluate the multiple dose pharmacokinetics (PK) of buprenorphine and norbuprenorphine after SC injections of 50mg, 100mg, 200mg and 300mg doses of buprenorphine in Sublocade in treatment seeking opioid-dependent subjects who were inducted and then stabilised on a Subutex SL tablet dose of 8mg, 12mg, 14mg, 24mg or 8-24mg.
- To compare the steady-state PK of buprenorphine and norbuprenorphine after SC doses of Sublocade relative to the corresponding Subutex SL tablet doses.

The secondary objectives of this study were to evaluate the overall clinical response to Subutex SL tablet and to Sublocade with respect to the following:

- The Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), Opioid Craving Visual Analog Scale (VAS), Clinical Global Impression - Severity scale (CGI-S), and Clinical Global Impression - Improvement scale (CGI-I) total scores.
- Illicit opioid and non-opioid drug use as measured by urine drug screen results.
- The Columbia-Suicide Severity Rating Scale (C-SSRS).

The study population consisted of male and female subjects aged ≥ 18 to ≤ 65 years who met DSM-IV-TR criteria for opioid-dependence at screening and were seeking opioid-dependence treatment.

Subjects entered an open-label Subutex SL tablet induction and stabilisation period to achieve stable[49] daily doses.

For Cohorts 1-5 they were 8mg, 12mg, 14mg, or 24mg during a 13-day inpatient (Day -14 to Day -1) period. They then received 4 SC injections of Sublocade separated by 28 days.

For Cohort 6 the stable doses were 8 - 24mg (variable) followed by 6 SC injections of Sublocade separated by 28 days

- Cohort 1: 50mg Sublocade (8mg Subutex SL tablet)
- Cohort 2: 100mg Sublocade (12mg Subutex SL tablet)
- Cohort 3: 200mg Sublocade (24mg Subutex SL tablet)
- Cohort 4: 100mg Sublocade (8mg Subutex SL tablet)
- Cohort 5: 200mg Sublocade (14mg Subutex SL tablet)
- Cohort 6: 300mg Sublocade (8 to 24mg Subutex SL tablet)

Any subject who reached a total daily dose of 24mg of Subutex SL tablet during the stabilisation period, was receiving Sublocade injections and required rescue medication for opioid

[48] The "8-24mg" Subutex designator refers to the range of doses of Subutex SL tablet allowed for Cohort 6 subjects. These subjects were on 1 of the following doses of Subutex SL tablet at the time of transfer to Sublocade: 8mg, 12mg, 16mg, 20mg or 24mg

[49] subjects were considered stable if they had a COWS score of < 12 and an Opioid Craving VAS score of < 20 mm from Day -5 through Day 1 predose

withdrawal symptoms (e.g., Subutex SL tablet or methadone) was discontinued from the study for a lack of efficacy.

Plasma concentrations of buprenorphine and norbuprenorphine were quantified using validated LC-MS/MS methods validated for a range of 0.0500 to 25.0ng/mL for buprenorphine and 0.0400 to 20.0ng/mL for norbuprenorphine.

Results

Buprenorphine

Following the first dose of Sublocade, buprenorphine plasma concentrations rose to a peak at a median time of 20h post-dose and declined to a plateau throughout Day 1 to Day 29. Similar results were seen for subsequent doses of Sublocade.

Mean plasma concentrations of buprenorphine showed an apparent increase with the dose from 50mg to 300mg following all injections of Sublocade. Within each dose level, mean concentrations of buprenorphine increased with every injection from Injections 1 to 4.

The mean pre-dose concentrations (C_{trough}) also increased from Injection 1 to 4 for buprenorphine.

Nor-buprenorphine

After Injection 1 of Sublocade, norbuprenorphine concentrations showed peak concentrations 6 to 12h post dose. There was a secondary peak that was at 24 to 48h post dose.

Following Injection 2, 3 and 4, norbuprenorphine concentrations peaked at 48h, with a secondary peak from Day 42 to Day 48, on Day 65, and on Day 93 to Day 101 after the SC Injections 2, 3 and 4, respectively. Following the secondary peaks concentrations declined to a plateau throughout the dosing interval.

Mean plasma concentrations of the metabolite, norbuprenorphine, showed an apparent increase with the dose from 50mg to 300mg following all injections of Sublocade. For each dose level, mean concentrations of norbuprenorphine increased with every injection, from Injections 1 to 4.

For norbuprenorphine, the pre-dose concentrations (C_{trough}) following Sublocade SC injections were much lower when compared with the pre-dose concentrations prior to the first SC injection, i.e., following Subutex SL tablet administration during the stabilisation phase.

Table 30 Summary of Subject Disposition: Subjects Who Received Both Subutex Sublingual Tablet and Sublocade (Population: Safety)

	Subutex SL; Sublocade							
	Cohort 1 8 mg; 50 mg (N = 15) n (%)	Cohort 2 12 mg; 100 mg (N = 15) n (%)	Cohort 3 24 mg; 200 mg (N = 15) n (%)	Cohort 4 8 mg; 100 mg (N = 15) n (%)	Cohort 5[b,c] 14 mg; 200 mg (N = 15) n (%)	Cohort 6[d] 8-24 mg; 300 mg (N = 14) n (%)	Overall (N = 89) n (%)	PET Imaging Sub-study[e] (N = 2) n (%)
Safety Population	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	14 (100.00)	89 (100.00)	2 (100.00)
PK Population	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	14 (100.00)	89 (100.00)	2 (100.00)
PD Population	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	14 (100.00)	89 (100.00)	2 (100.00)
Completed to Day 113[a]	10 (66.67)	10 (66.67)	9 (60.00)	7 (46.67)	9 (60.00)	6 (42.86)	51 (57.30)	2 (100.00)
Withdrew from Main Study	5 (33.33)	5 (33.33)	6 (40.00)	8 (53.33)	6 (40.00)	8 (57.14)	38 (42.70)	0 (0.0)
Reason for Withdrawal								
Adverse Event	1 (6.67)	0 (0.0)	1 (6.67)	2 (13.33)	2 (13.33)	2 (14.29)	8 (8.99)	0 (0.0)
Lost To Follow-Up	0 (0.0)	3 (20.00)	4 (26.67)	1 (6.67)	1 (6.67)	5 (35.71)	14 (15.73)	0 (0.0)
Physician Decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Subject	1 (6.67)	0 (0.0)	1 (6.67)	1 (6.67)	1 (6.67)	1 (7.14)	5 (5.62)	0 (0.0)
Noncompliance with Study Drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Violation	3 (20.00)	1 (6.67)	0 (0.0)	4 (26.67)	2 (13.33)	0 (0.0)	10 (11.24)	0 (0.0)
Other	0 (0.0)	1 (6.67)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.12)	0 (0.0)

[a] A completed subject in the main study was defined in the Statistical Analysis Plan (SAP) as anyone who completed study treatment through Day 113. Cohort 6 was added by protocol amendment; initially, subjects could receive up to 4 injections (Day 113 completion) and subsequent to an additional amendment could receive up to 6 injections (study treatment through Day 141). Subjects in Cohorts 3, 5 and 6 who completed the main study were eligible to enrol in the PET imaging sub-study (see footnote e).

[b] Four subjects in Cohort 5 consented to receive additional doses of Sublocade to be eligible for participation in the PET imaging sub-study. PET imaging was completed for 1 of the 4 subjects. This subject received 12 injections of Sublocade.

[c] One subject in Cohort 5 (001789) completed the main study, enrolled in the PET imaging sub-study and received 7 injections of Sublocade. The subject subsequently experienced an SAE of thyroid cancer and was discontinued from the PET imaging sub-study but was counted as having completed the main study.

[d] Two subjects in Cohort 6 consented to receive additional doses of Sublocade to be eligible for participation in the PET imaging sub-study. Both subjects received 6 doses of Sublocade. PET imaging was completed for 1 of the 2 subjects.

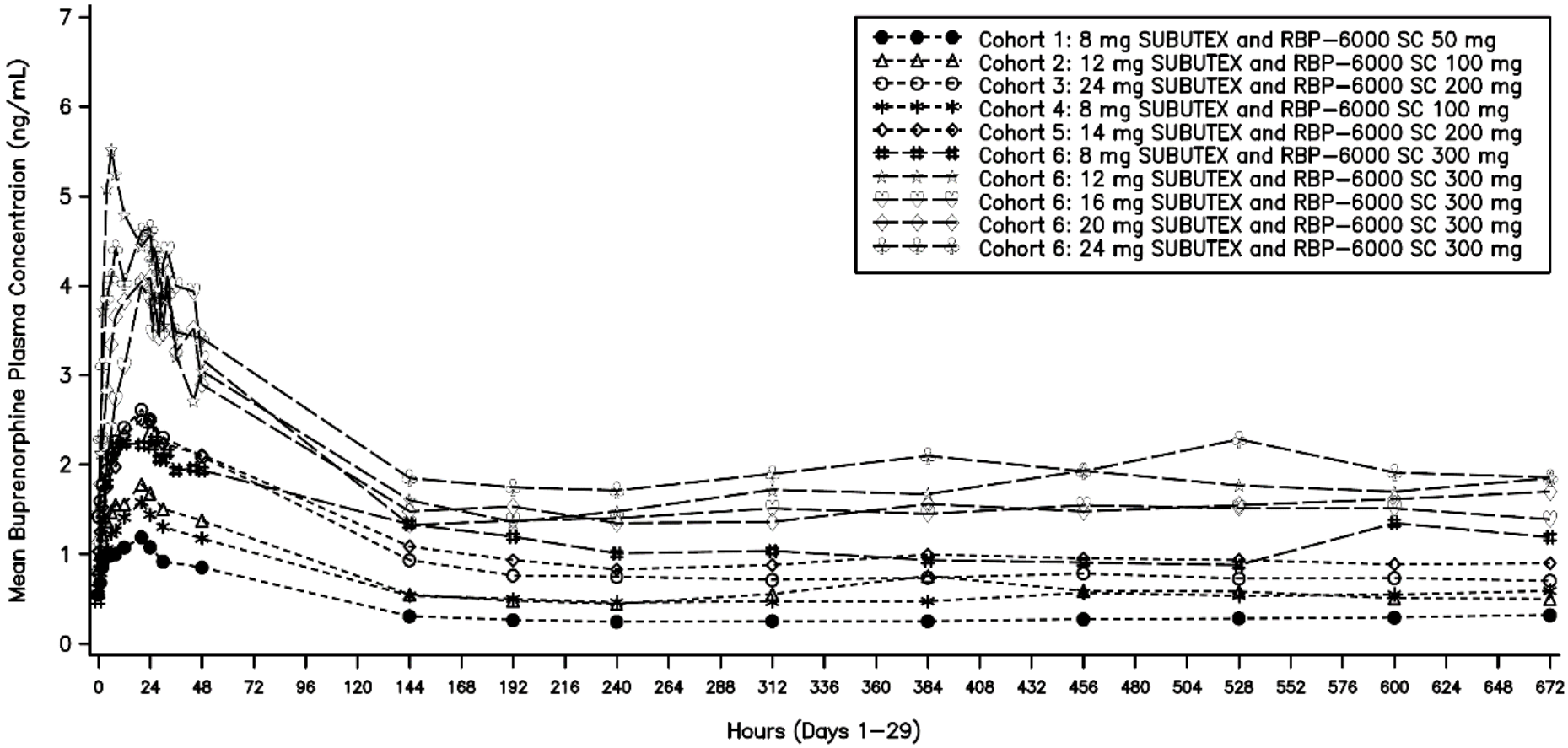
[e] Subjects who received Sublocade containing 200mg or 300mg buprenorphine (Cohorts 3, 5 or 6) and reached Day 112 (and had received all 4 or 6 planned SC injections) had the option to consent to participate in the PET imaging sub-study in which they remained on their assigned Sublocade dose SC injections at 28-day intervals until they completed an MRI, PET scan and PK samples at Week 1 and Week 4 post injection. It was anticipated that subjects could receive up to 12 injections of Sublocade to complete the PET imaging sub-study, depending on the availability of the PET imaging facilities. A total of 6 subjects who completed the main study consented to participate in the PET imaging sub-study; 2 subjects completed the sub-study. Source: Table 11

Table 31 Summary of Demographics for Subjects Who Received Both Subutex Sublingual Tablet and Sublocade (Population: Safety)

		SUBUTEX SL: Sublocade						
	Category or Statistic	Cohort 1 8 mg; 50 mg (N = 15) n (%)	Cohort 2 12 mg; 100 mg (N = 15) n (%)	Cohort 3 24 mg; 200 mg (N = 15) n (%)	Cohort 4 8 mg; 100 mg (N = 15) n (%)	Cohort 5 14 mg; 200 mg (N = 15) n (%)	Cohort 6 8-24 mg; 300 mg (N = 14) n (%)	Overall (N = 89) n (%)
Gender - n (%)	Male	12 (80.0)	10 (66.7)	10 (66.7)	9 (60.0)	9 (60.0)	10 (71.4)	60 (67.4)
	Female	3 (20.0)	5 (33.3)	5 (33.3)	6 (40.0)	6 (40.0)	4 (28.6)	29 (32.6)
Age (yr)	n	15	15	15	15	15	14	89
	Mean	36.5	31.1	30.1	36.1	36.2	32.9	33.8
	SD	11.36	11.14	11.21	14.87	12.85	11.00	12.10
	Median	34.0	30.0	24.0	32.0	31.0	28.0	30.0
	Min, Max	24, 60	20, 55	19, 54	20, 59	19, 56	22, 56	19, 60
Weight (kg)	n	15	15	15	15	15	14	89
	Mean	71.12	73.71	68.08	74.43	73.16	74.64	72.50
	SD	12.929	10.411	9.900	15.995	12.753	16.825	13.159
	Median	71.40	72.30	67.70	73.00	73.60	73.60	71.60
	Min, Max	56.4, 100.9	56.3, 97.7	51.6, 87.3	52.3, 109.1	50.0, 94.1	48.1, 107.0	48.1, 109.1
	Median	22.50	23.80	24.10	23.90	26.50	25.25	24.20
	Min, Max	19.4, 29.5	20.9, 31.3	19.8, 27.2	19.7, 32.2	19.1, 31.6	18.4, 30.9	18.4, 32.2
Other Opioid Use (yr)	n	12	11	12	11	11	10	67
	Mean	6.75	6.18	4.17	5.27	8.36	6.30	6.15
	SD	5.545	4.191	2.887	3.927	9.770	8.693	6.165
	Median	5.00	6.00	4.50	6.00	5.00	3.50	5.00
	Min, Max	1.0, 17.0	2.0, 15.0	1.0, 11.0	1.0, 13.0	1.0, 36.0	1.0, 30.0	1.0, 36.0
Heroin Use (yr)	n	12	9	11	14	10	9	65
	Mean	11.25	9.78	5.00	11.64	10.70	8.56	9.62
	SD	10.463	11.454	5.604	12.549	7.987	12.471	10.292
	Median	9.50	4.00	3.00	7.50	11.50	2.00	6.00
	Min, Max	1.0, 36.0	1.0, 30.0	1.0, 20.0	1.0, 43.0	1.0, 26.0	1.0, 40.0	1.0, 43.0

Source: Table 12

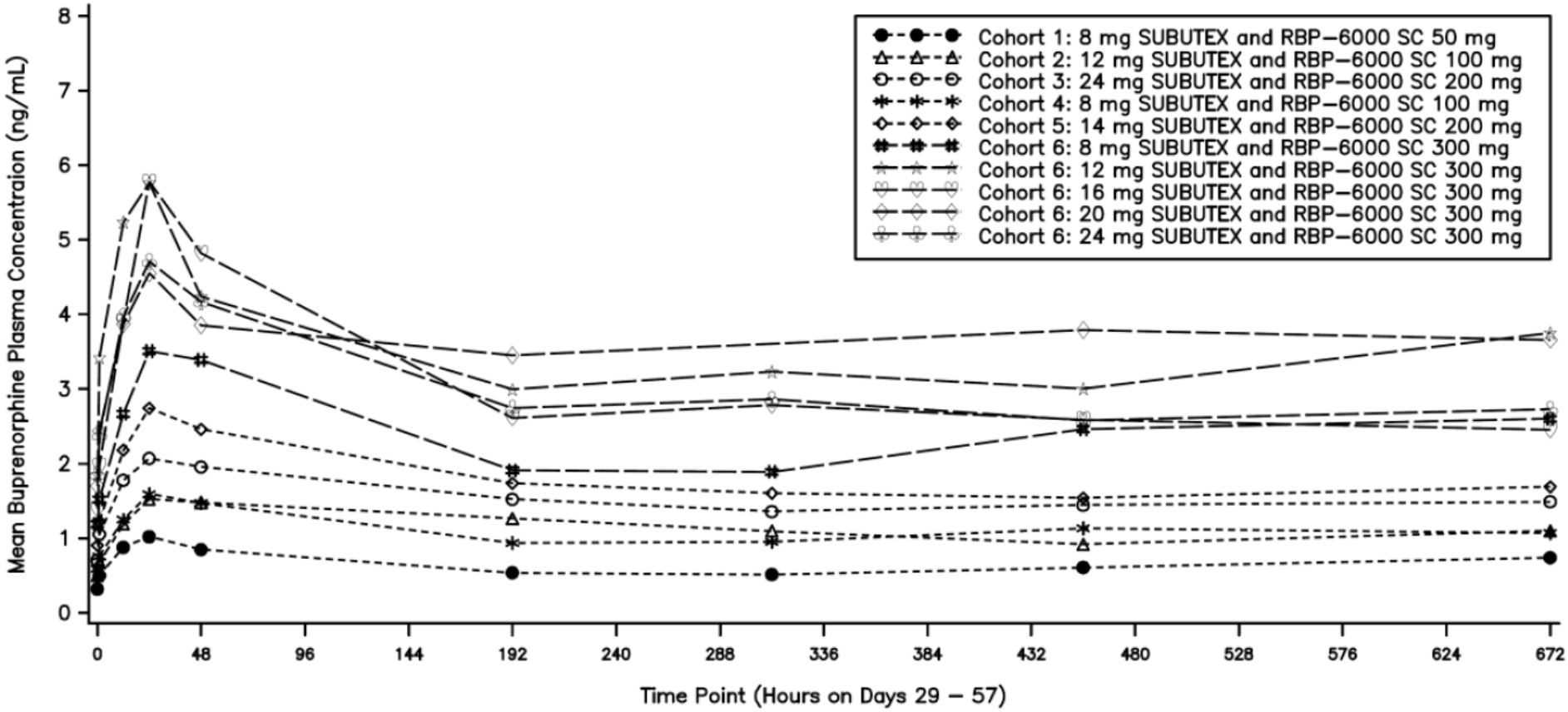
Figure 16 Mean Buprenorphine Plasma Concentrations vs. Time on a Linear Scale Post Sublocade SC Injection 1 from Study Day 1 to Day 29 (672h) (Pop: PK)



Source: Figure 6

Comment: The sponsor uses both **D**ays and hours for description of time. They are not concurrent, thus two days or48h (from time of injection will) occur on **D**ay 3. Reinjection at 28 days will occur on **D**ay 29.

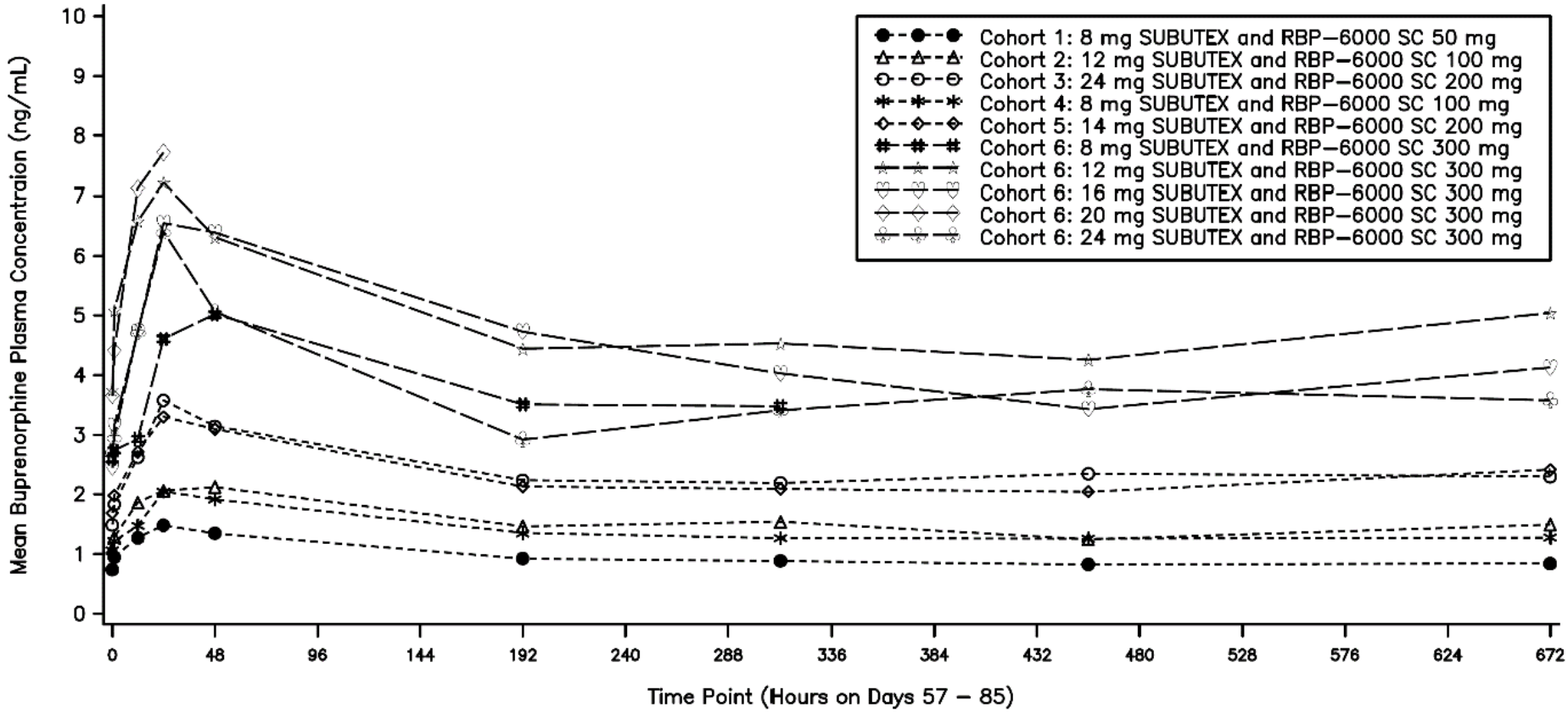
Figure 17 Mean Buprenorphine Plasma Concentrations vs. Time on a Linear Scale Post Sublocade SC Injection 2 from Study Day 29 to Day 57 (672h) (Pop: PK)



Source: Figure 8

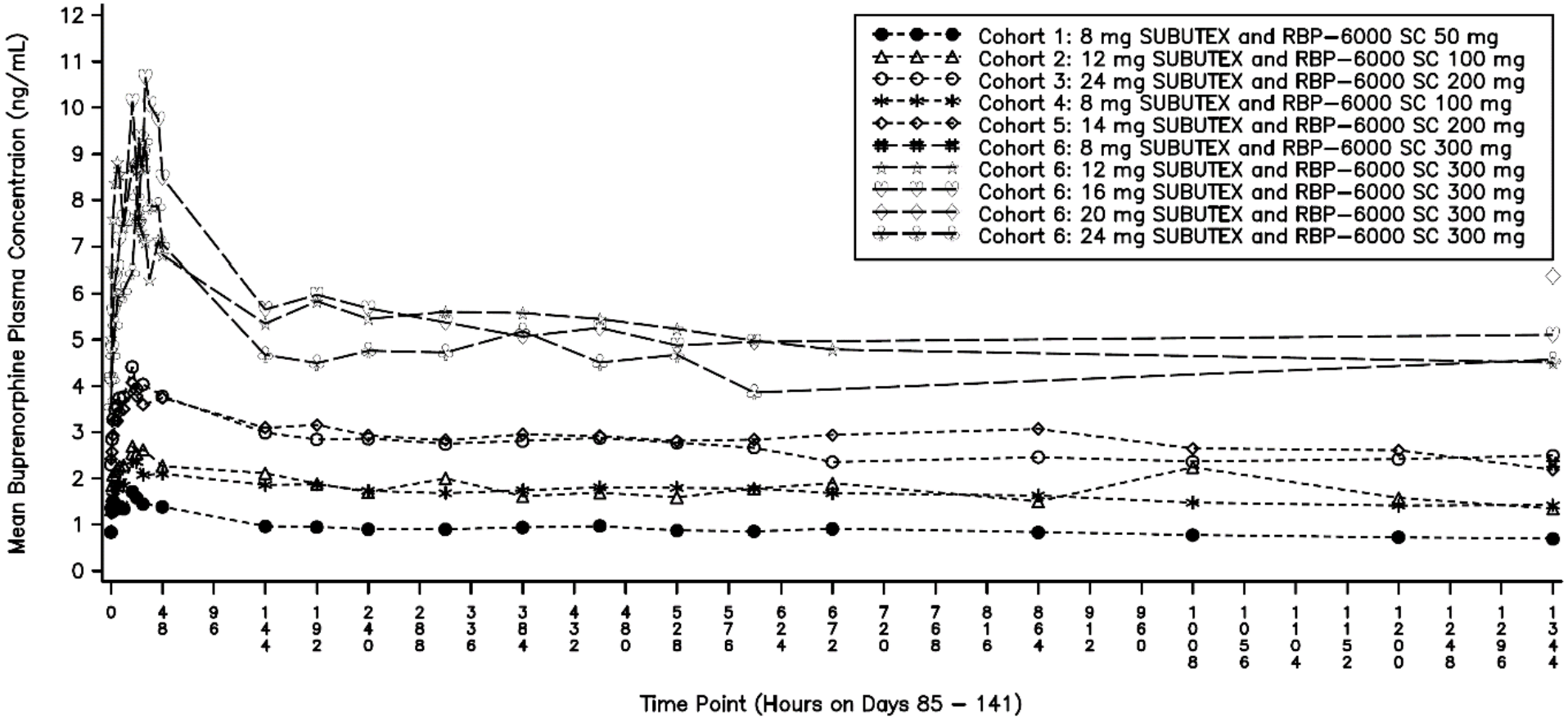
Mean Buprenorphine Plasma Concentrations versus Time on a Linear Scale

Figure 18 Post Sublocade SC Injection 3 from Study Day 57 to Day 85 (672h) (Pop: PK)



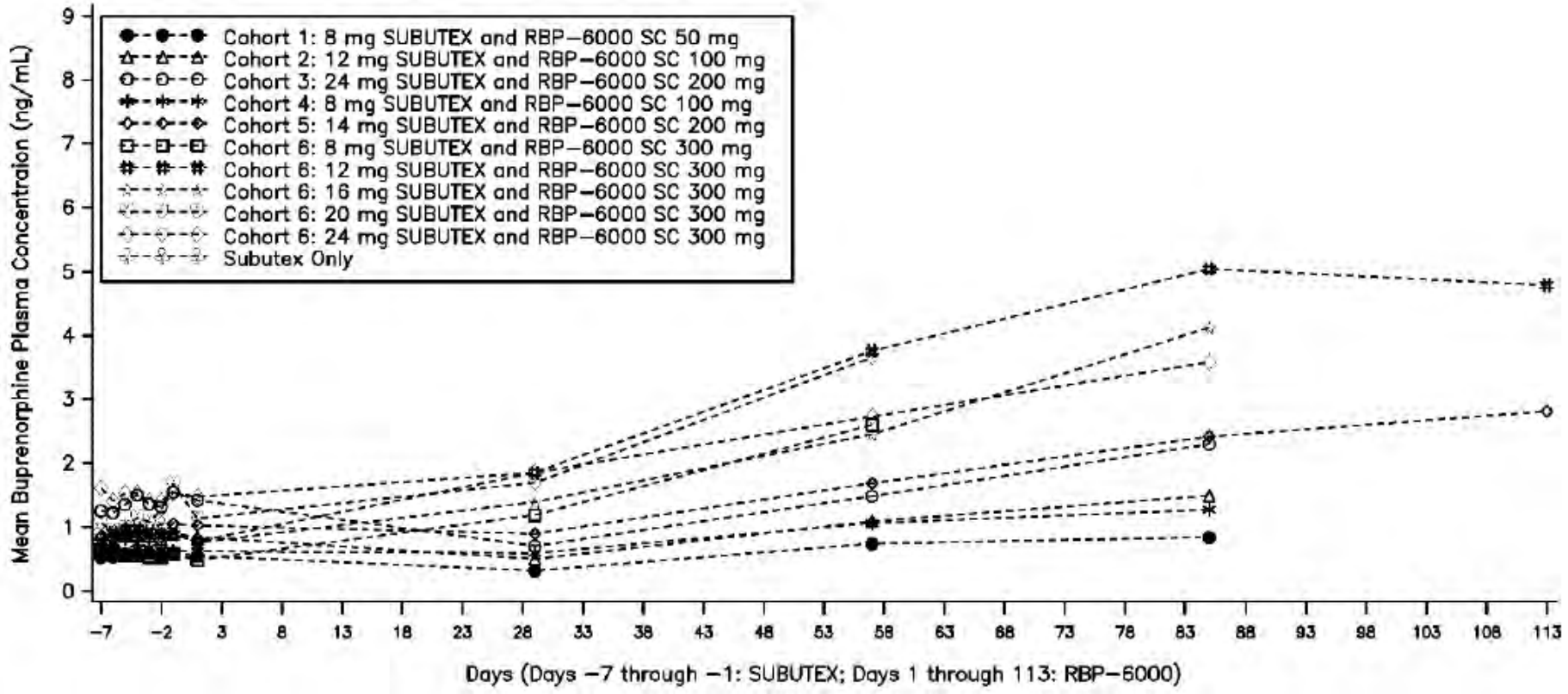
Source: Figure 10

Figure 19 Mean Buprenorphine Plasma Concentrations vs. Time on a Linear Scale Post Sublocade SC Injection 4 from Study Day 85 to Day 141 (Pop: PK)



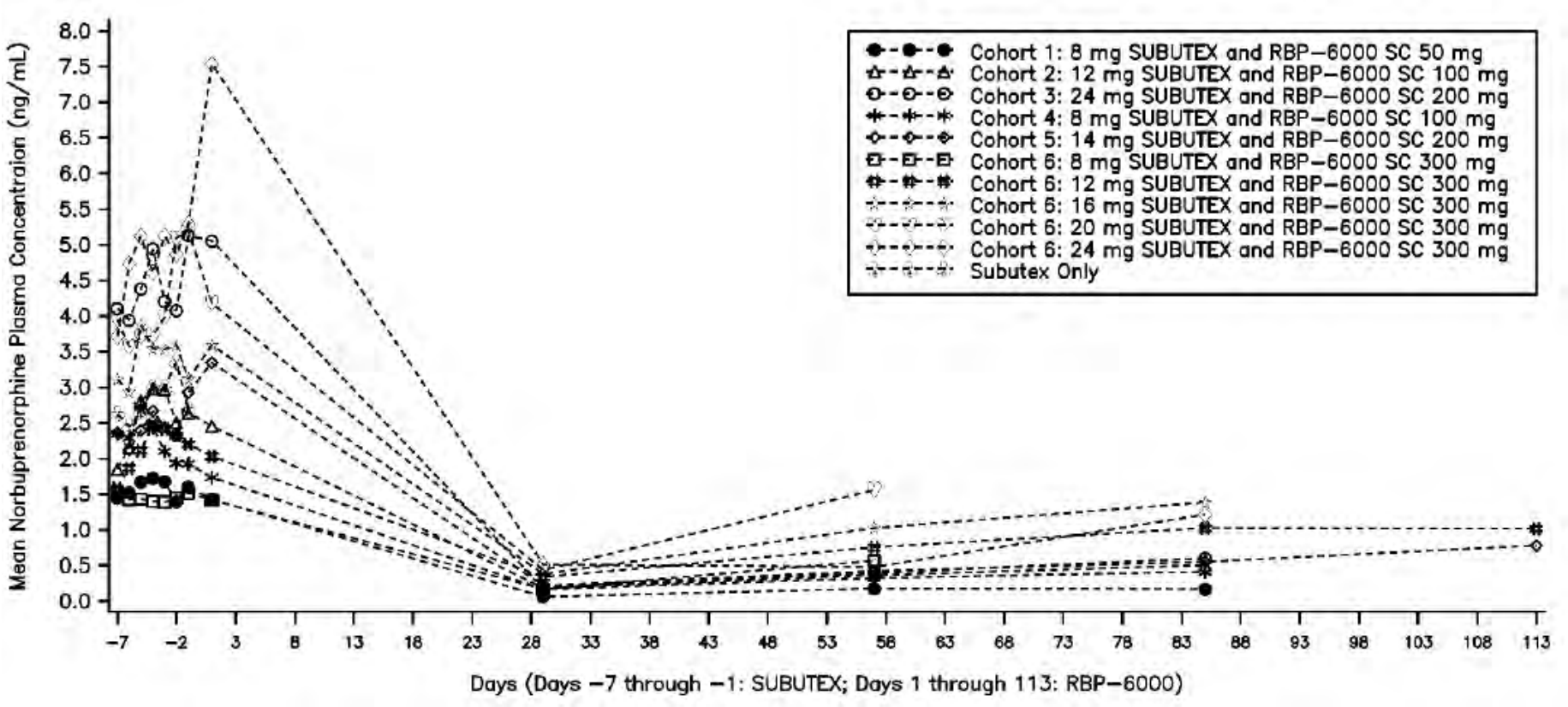
Source: Figure 12

Figure 20 Mean Predose (C_{trough}) Buprenorphine Plasma Concentrations vs. Time on a Linear Scale Following Subutex SL and Sublocade SC Injection Administration (Study Days -7 to -1, 1, 29, 57, 85, and 113) (Pop: PK)



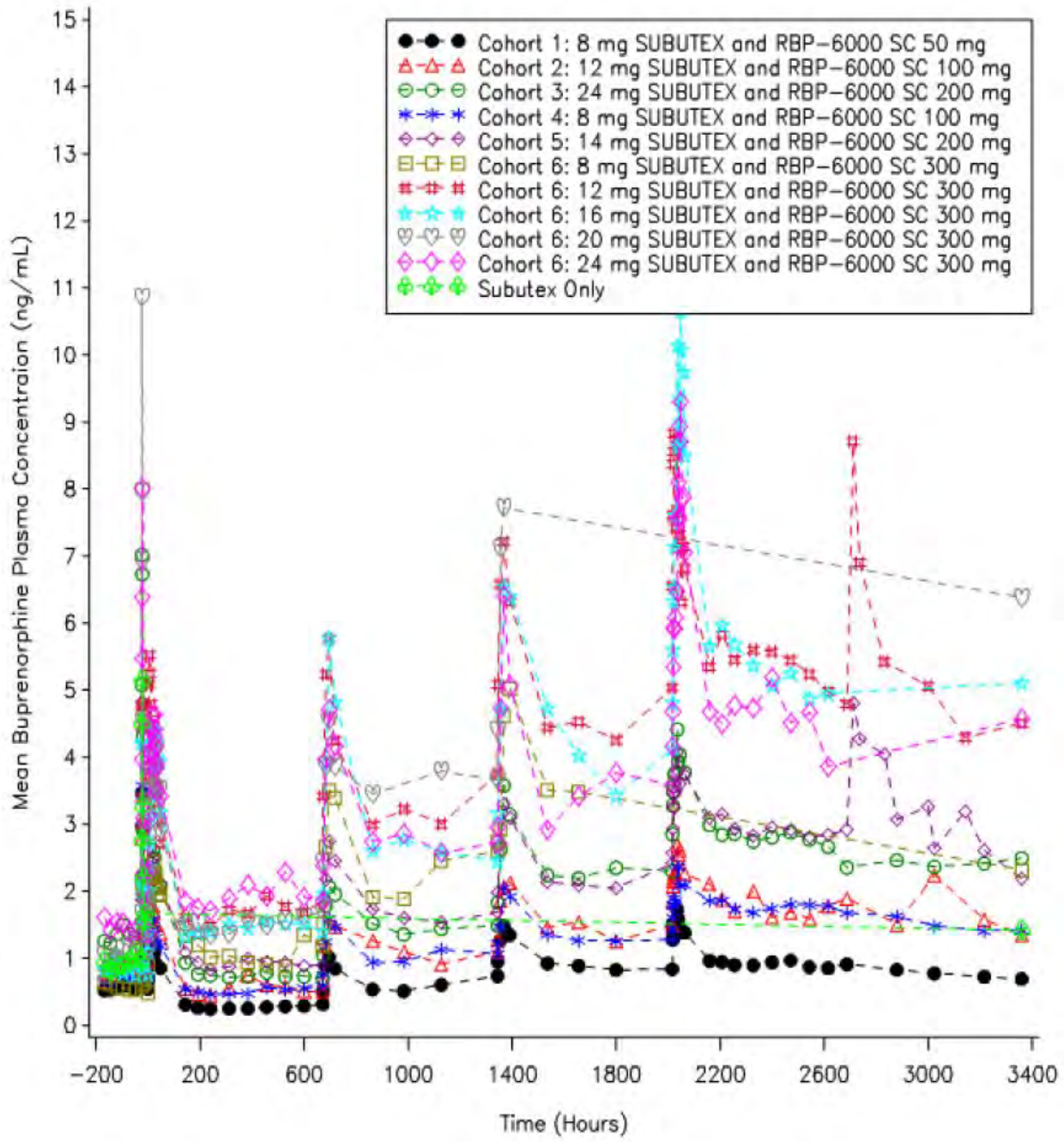
Source: Figure 16

Figure 21 Mean Predose (C_{trough}) Norbuprenorphine Plasma Concentrations vs. Time on a Linear Scale Following Subutex SL and Sublocade SC Injection Administration (Study Days -7 to -1, 1, 29, 57, 85, and 113) (Pop: PK)



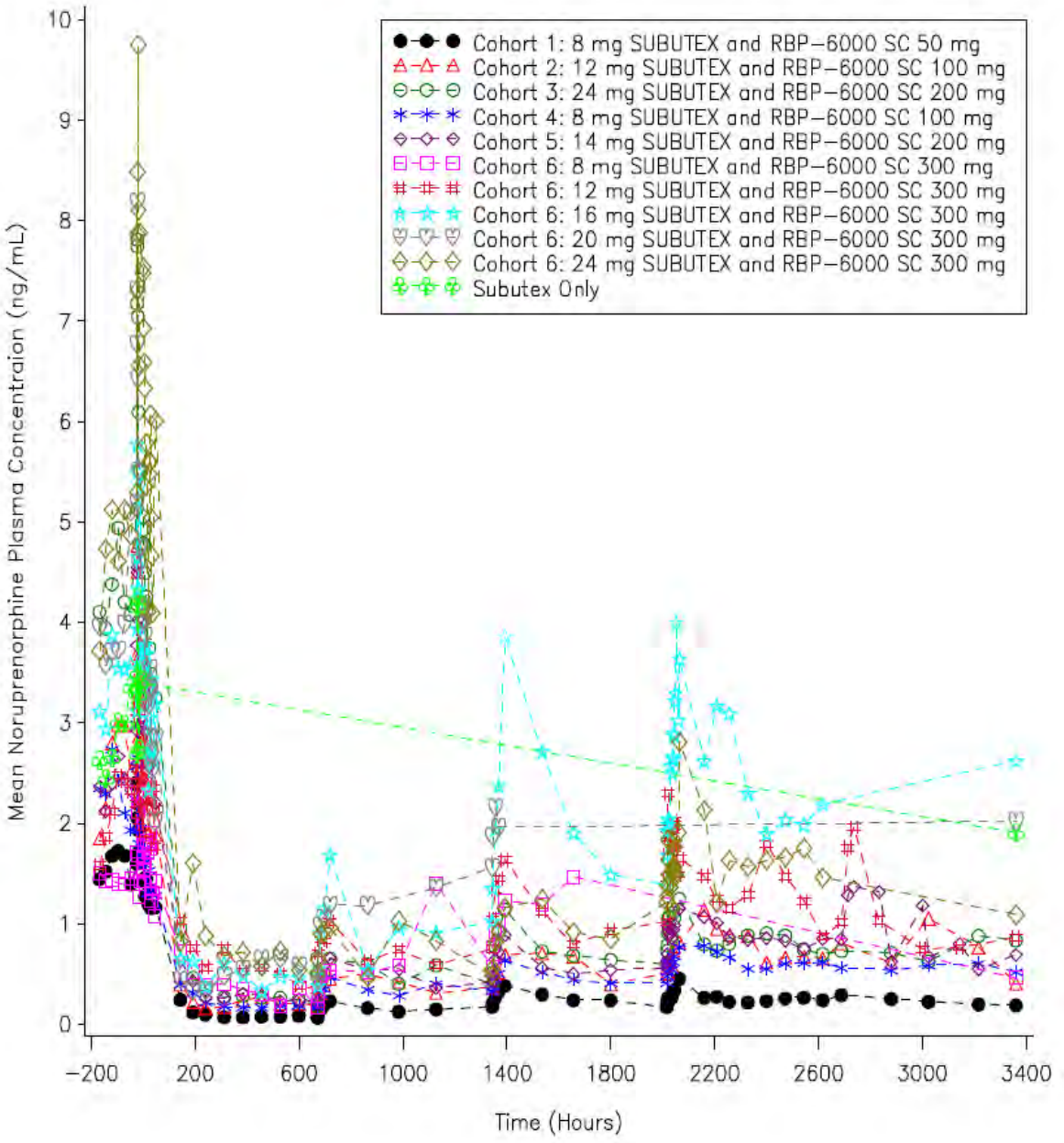
Source: Figure 27

Figure 22 Mean Buprenorphine Plasma Concentrations by Scheduled Sampling Time for All Cohorts Study Days -7 to 141 on a Linear Scale (Pop: PK)



Source: Figure 14

Figure 23 Mean Norbuprenorphine Plasma Concentrations by Scheduled Sampling Time for All Cohorts Study Days -7 to 141 on a Linear Scale (Pop: PK)



Source: Figure 25

PK Parameters

Comment: The CSR provided extensive tabular summary results. Briefer summaries of those tables are provided in the Summary of Clinical Pharmacology Studies and are reproduced below.

Of concern in those tables is the use of C_{avg} for comparison. As can be seen from the following definitions, when for comparison $AUC_{0-\tau}$ is used, using C_{avg} also achieves nothing except to divide any difference by 28x24.

The sponsor defined 3 different C_{avg} rather than using AUCs for comparison:

- $C_{avg, ss}$ = Average plasma concentration on Study Day -1, calculated as AUC_{0-24}/ 24h
- $C_{avg, Day\ 2-28}$ = The average of plasma concentrations in the plateau, calculated as $AUC_{Day2-28}$/ time, where time was 624h.

- C_{avg} = The average of plasma concentrations calculated as AUC_{tau}/ tau (assuming tau = 28 days) for Injections 1, 4, and 6 (for Cohort 6, as applicable).

Table 32 Summary Statistics of Buprenorphine Plasma PK Parameters (Study 12-0005)

			Subutex; Sublocade					
Parameter	Day	Statistic	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
			8 mg; 50 mg	12 mg; 100 mg	24 mg; 200 mg	8 mg; 100 mg	14 mg; 200 mg	8-24 mg; 300 mg
AUC_{0-24hr} (ng*hr/mL)	Day 1	N	15	15	14	15	12	14
		Geo Mean	24.09	34.33	53.08	29.50	48.90	79.89
		CV%	25.9	38.8	30.8	41.6	23.0	33.7
	Day 85	N	11	12	11	10	8	7
		Geo Mean	33.13	54.06	87.70	46.77	79.67	173.78
		CV%	41.2	27.8	30.0	20.2	22.6	24.3
AUC_{0-48hr} (ng*hr/mL)	Day 1	N	15	15	15	15	15	14
		Geo Mean	45.43	68.19	105.48	59.51	102.63	157.50
		CV%	24.7	35.1	27.8	32.5	21.6	29.1
	Day 85	N	11	11	11	10	11	6
		Geo Mean	66.41	109.70	180.06	97.19	170.14	374.10
		CV%	35.1	26.3	26.0	18.1	17.0	21.3
AUC_{tau} (ng*hr/mL)	Day 1	N	15	14	13	14	14	11
		Geo Mean	240.62	442.11	610.63	394.19	726.67	1218.90
		CV%	22.3	30.8	35.5	32.2	29.6	30.7
	Day 85	N	10	11	9	8	7	2
		Geo Mean	622.70	1217.72	1887.78	1249.05	2013.34	3216.49
		CV%	38.1	34.1	23.6	19.8	22.7	13.3
C_{avg} (ng/mL)	Day 1	N	15	14	13	14	14	11
		Geo Mean	0.36	0.66	0.91	0.59	1.08	1.81
		CV%	22.3	30.8	35.5	32.2	29.6	30.7
	Day 85	N	10	11	9	8	7	2
		Geo Mean	0.93	1.81	2.81	1.86	3.00	4.79
		CV%	38.1	34.1	23.6	19.8	22.7	13.3
C_{max} (ng/mL)	Day 1	N	15	15	14	15	15	14
		Geo Mean	1.29	1.87	2.64	1.59	2.78	4.60
		CV%	34.3	40.8	28.8	36.8	24.9	29.8
	Day 85	N	11	12	11	10	11	7
		Geo Mean	1.84	2.96	4.36	2.52	4.32	9.38
		CV%	69.0	28.2	28.9	18.7	21.0	24.3

C_{min} (ng/mL)	Day 1	N	15	15	14	15	15	14
		Geo Mean	0.20	0.36	0.55	0.38	0.67	0.76
		CV%	27.0	26.7	42.8	47.6	31.4	44.9
	Day 85	N	11	12	11	10	11	7
		Geo Mean	0.54	1.22	2.07	1.15	2.17	3.99
		CV%	28.0	28.3	22.1	23.8	28.7	17.2
T_{max} (hr)	Day 1	N	15	15	14	15	11	7
		Median	20.00	20.00	20.00	20.00	20.00	20.00
		Min, Max	4.00, 20.05	4.00, 414.17	6.00, 30.00	4.00, 48.00	6.00, 48.00	4.00, 32.00
	Day 85	N	11	12	11	10	11	7
		Median	20.00	20.00	20.08	24.00	24.00	24.00
		Min, Max	2.00, 24.00	12.00, 315.95	8.00, 30.08	4.00, 529.83	4.00, 48.00	4.00, 36.00
CL/F (L/hr)	Day 85	N	11	12	11	10	8	5
		Geo Mean	79.95	82.21	102.72	85.34	101.88	79.62
		CV%	40.5	25.8	22.3	24.1	27.9	19.6
Rac(AUC)	Day 85	N	10	11	9	8	7	2
		Geo Mean	2.40	2.69	3.34	3.28	2.72	3.55
		CV%	37.5	18.6	26.9	27.2	30.5	15.8

Rac(AUC)=accumulation index in terms of AUC calculated as ratio of AUCtau Injection 4/ AUCtau Injection 1
Cohort 1=8mg Subutex and Sublocade 50 mg.
Cohort 2=12mg Subutex and Sublocade 100 mg.
Cohort 3=24mg Subutex and Sublocade 200 mg.
Cohort 4=8mg Subutex and Sublocade 100 mg
Cohort 5=14mg Subutex and Sublocade 200 mg
Cohort 6=8mg Subutex and Sublocade 300 mg Source: Table 7 Summary of Clinical Pharmacology Studies

Table 33 Summary Statistics of Norbuprenorphine Plasma PK Parameters (Study 12-0005)

			Subutex; Sublocade					
Parameter	Day	Statistic	Cohort 1 8 mg; 50 mg	Cohort 2 12 mg; 100 mg	Cohort 3 24 mg; 200 mg	Cohort 4 8 mg; 100 mg	Cohort 5 14 mg; 200 mg	Cohort 6 8-24 mg; 300 mg
AUC_{tau} (ng*hr/mL)	Day 1	N	11	12	13	14	14	11
		Geo Mean	163.72	312.68	516.15	248.86	361.55	618.79
		CV%	44.9	43.8	32.6	31.1	52.6	62.4
	Day 85	N	10	11	9	8	7	2
		Geo Mean	166.94	417.39	521.66	424.24	654.28	648.84
		CV%	50.2	84.5	44.6	33.7	24.8	24.3
C_{max} (ng/mL)	Day 1	N	15	15	14	15	15	14
		Geo Mean	1.51	2.38	5.28	1.84	3.39	3.84
		CV%	45.6	51.0	34.6	39.8	58.1	68.1
	Day 85	N	11	12	11	10	11	7
		Geo Mean	0.43	1.09	1.39	0.88	1.38	2.51
		CV%	60.2	81.4	31.4	32.9	41.6	45.3
T_{max} (hr)	Day 1	N	15	15	14	15	15	14
		Median	8.00	6.00	2.53	6.00	4.00	4.00
		Min, Max	0.00, 48.00	0.00, 457.15	0.00, 30.00	0.00, 30.00	0.00, 30.00	0.00, 36.00
	Day 85	N	11	12	11	10	11	7
		Median	48.00	48.00	48.00	182.81	30.07	12.00
		Min, Max	1.00, 408.52	4.00, 604.77	6.00, 456.80	8.00, 629.07	4.00, 459.00	6.00, 48.00

Cohort 1=8mg Subutex and Sublocade 50 mg.
Cohort 2=12mg Subutex and Sublocade 100 mg.
Cohort 3=24mg Subutex and Sublocade 200 mg.
Cohort 4=8mg Subutex and Sublocade 100 mg
Cohort 5=14mg Subutex and Sublocade 200 mg
Cohort 6=8mg Subutex and Sublocade 300 mg

Source: Table 8 Summary of Clinical Pharmacology Studies

Dose Proportionality

Overall, the results show that buprenorphine plasma exposure increased slightly less than dose proportionally. A 6-fold increase in dose resulted in approximately a 5.1-fold and 5.2-fold increase in buprenorphine C_{max} and AUC_{tau}, respectively. For norbuprenorphine, plasma exposure increased with the increase in dose from 50 to 300mg, at a rate that was less than dose-proportional.

Table 34 Statistical Analysis of Dose Proportionality (Study 12-0005)

RBP-6000 Dose Range	Analyte	Parameter (unit)	Injection Number	Slope Estimate (beta1)	P-value[a]	90% CI of Slope	Critical Region
50 - 300 mg	Buprenorphine	C_{max} (ng/mL)	1	0.675	<0.001	(0.573, 0.776)	(0.875, 1.125)
			4	0.779	0.003	(0.659, 0.898)	(0.875, 1.125)
			6	0.891	0.874	(-2.542, 4.325)	(0.875, 1.125)
		AUC_{tau} (ng*hr/mL)	1	0.826	0.003	(0.731, 0.922)	(0.875, 1.125)
			4	0.823	0.023	(0.697, 0.950)	(0.875, 1.125)
	Norbuprenorphine	C_{max} (ng/mL)	1	0.645	<0.001	(0.482, 0.808)	(0.875, 1.125)
			4	0.857	0.213	(0.666, 1.047)	(0.875, 1.125)
			6	0.880	0.924	(-5.459, 7.218)	(0.875, 1.125)
		AUC_{tau} (ng*hr/mL)	1	0.711	0.003	(0.553, 0.869)	(0.875, 1.125)
			4	0.804	0.171	(0.568, 1.041)	(0.875, 1.125)

[a] Dose proportionality was to be declared if the 90% CI was contained entirely within the critical region
Subjects were dosed with Subutex SL tablets followed by SC injections of Sublocade.
Power Model: ln(PK) = ln(beta0) + beta1*ln(Dose) + C, where PK is the pharmacokinetic parameter tested, ln(beta0) is the y intercept, beta1 is the slope and C is an error term Source: Table 9 Summary of Clinical Pharmacology Studies

Comparison with SL Subutex

After 4 SC injections of Sublocade, buprenorphine average plasma concentrations (C_{avg}) for the 100mg and 200mg doses were similar to the steady-state C_{avg} concentrations observed following daily Subutex administration at 12mg and 24mg, respectively. The C_{max} following Sublocade administration was lower than the C_{max} observed following Subutex administration.

Table 35 Buprenorphine Plasma C_{max}, C_{min}, AUC Subutex SL & Sublocade

Parameter	Time point	Statistic	Cohort 1 8 mg; 50 mg	Cohort 2 12 mg; 100 mg	Cohort 3 24 mg; 200 mg	Cohort 4 8 mg; 100 mg	Cohort 5 14 mg; 200 mg	Cohort 6 Total; 300 m
Sublingual Buprenorphine (Subutex) at steady state								
Cmax,ss (ng/mL)	DAY -1 DOSE	n	15	15	15	15	15	14
		Mean	3.521	5.350	7.571	3.964	5.260	5.813
		SD	1.0407	1.7340	3.0928	1.9131	1.5595	3.4264
		%CV	29.6	32.4	40.9	48.3	29.6	58.9
		Median	3.520	4.690	6.530	3.240	5.280	5.585
		Min,Max	1.09, 5.90	3.05, 9.45	4.48, 16.30	1.44, 7.94	1.87, 7.61	1.51, 14.10
		Geometric Mean	3.341	5.112	7.084	3.551	4.996	4.920
Cmin,ss (ng/mL)	DAY -1 DOSE	n	15	15	15	15	15	14
		Mean	0.524	0.806	1.385	0.568	0.920	0.927
		SD	0.2212	0.3638	0.4806	0.2367	0.2800	0.4667
		%CV	42.2	45.1	34.7	41.7	30.4	50.4
		Median	0.473	0.821	1.230	0.473	0.925	0.907
		Min,Max	0.20, 0.83	0.27, 1.45	0.73, 2.30	0.22, 0.94	0.39, 1.34	0.40, 1.76
		Geometric Mean	0.477	0.721	1.308	0.519	0.875	0.815
AUCtau,ss (hr*ng/mL)	DAY -1 DOSE	n	15	15	15	15	15	14
		Mean	28.452	40.971	63.019	30.029	46.681	46.628
		SD	7.9415	12.6823	16.4068	12.8676	11.8403	23.2554
		%CV	27.9	31.0	26.0	42.9	25.4	49.9
		Median	28.571	37.086	60.138	28.778	48.952	43.632
		Min,Max	12.48, 42.69	20.29, 60.93	43.52, 94.00	11.17, 55.51	18.84, 64.77	14.83, 86.26
		Geometric Mean	27.273	39.039	61.142	27.484	44.875	40.830
Sublocade								
AUC 0-48 (hr*ng/mL)	DAY 1 DOSE	n	15	15	15	15	15	14
		Mean	46.855	72.453	109.029	62.395	104.868	164.511
		SD	11.5533	25.4451	30.2598	20.3054	22.6943	47.8237
		%CV	24.7	35.1	27.8	32.5	21.6	29.1
		Median	49.568	70.786	104.765	59.319	98.468	159.227
		Min,Max	24.55, 71.16	34.71, 119.57	71.48, 176.90	35.21, 108.75	70.37, 147.60	83.26, 235.95
		Geometric Mean	45.425	68.190	105.476	59.514	102.630	157.500
Cmax (INT) (ng/mL)	DAY 1 DOSE	n	15	15	15	15	15	14
		Mean	1.352	1.916	2.755	1.686	2.861	4.817
		SD	0.4641	0.6773	0.7630	0.6200	0.7136	1.4337
		%CV	34.3	35.4	27.7	36.8	24.9	29.8
		Median	1.280	1.850	2.620	1.530	2.670	4.750
		Min,Max	0.66, 2.61	0.94, 3.12	1.71, 4.61	0.87, 3.14	1.80, 4.11	2.41, 6.74
		Geometric Mean	1.287	1.801	2.665	1.588	2.781	4.604
Cmax (INT) (ng/mL)	DAY 85 DOSE	n	11	12	11	10	11	7
		Mean	2.085	2.958	4.526	2.549	4.404	9.637
		SD	1.4381	0.9624	1.3078	0.4797	0.9231	2.3409
		%CV	69.0	32.5	28.9	18.8	21.0	24.3
		Median	1.650	2.885	4.230	2.380	4.040	9.840
		Min,Max	1.10, 6.26	1.58, 5.05	2.88, 6.64	2.10, 3.43	3.02, 6.16	6.46, 12.60
		Geometric Mean	1.835	2.820	4.360	2.511	4.317	9.383
Cmin (ng/mL)	DAY 1 DOSE	n	15	15	14	14	15	13
		Mean	0.206	0.388	0.600	0.388	0.714	1.244
		SD	0.0556	0.1145	0.2623	0.1554	0.2315	0.4455
		%CV	27.0	29.5	43.7	40.1	32.4	35.8
		Median	0.207	0.381	0.497	0.345	0.626	1.130
		Min,Max	0.09, 0.30	0.23, 0.74	0.30, 1.29	0.17, 0.71	0.42, 1.12	0.66, 2.27
		Geometric Mean	0.198	0.375	0.555	0.362	0.683	1.177

$AUC_{0-\tau}$ for Subutex was not defined but is probably 0-24h Source Tables 13,15 & 17 CSR

The total exposure within the first 24h ($AUC_{0\text{-}24hr}$) observed after the first SC injection of Sublocade was similar to the corresponding steady-state $AUC_{0\text{-}24hr}$ estimates following Subutex administration on Day -1 within the same cohort. The $AUC_{24\text{-}48hr}$ following the first SC injection of Sublocade were also similar.

Table 36 Statistical Analysis of Plasma PK Parameters: Subutex versus Sublocade (Study 12-0005)

Cohort, SUBUTEX, RBP-6000	PK Parameter	Injection Number	Geometric LSMean		Geometric LSMean Ratio Test/Ref (%)
			SUBUTEX (Reference)	RBP-6000 (Test)	
Cohort 1 8 mg, 50 mg	C_{avg} (ng/mL)	1	1.14	0.36	31.5
		4	1.14	0.89	78.5
	C_{max} (ng/mL)	1	3.34	1.29	38.5
		4	3.34	1.73	51.7
Cohort 2 12 mg, 100 mg	C_{avg} (ng/mL)	1	1.63	0.66	40.3
		4	1.63	1.78	109.7
	C_{max} (ng/mL)	1	5.11	1.87	36.6
		4	5.11	2.85	55.7
Cohort 3 24 mg, 200 mg	C_{avg} (ng/mL)	1	2.55	0.91	35.6
		4	2.55	2.89	113.6
	C_{max} (ng/mL)	1	7.08	2.65	37.4
		4	7.08	4.39	62.0
Cohort 4 8 mg, 100 mg	C_{avg} (ng/mL)	1	1.15	0.59	51.9
		4	1.15	1.94	169.7
	C_{max} (ng/mL)	1	3.55	1.59	44.7
		4	3.55	2.59	72.8
Cohort 5 14 mg, 200 mg	C_{avg} (ng/mL)	1	1.87	1.08	58.0
		4	1.87	2.93	156.6
		6	1.87	3.99	213.6
	C_{max} (ng/mL)	1	5.00	2.78	55.7
		4	5.00	4.26	85.3
		6	5.00	4.77	95.4
Cohort 6 12 mg, 300 mg	C_{avg} (ng/mL)	1	1.68	1.75	104.3
		4	1.68	4.79	284.5
	C_{max} (ng/mL)	1	4.68	6.01	128.6
		4	4.68	9.51	203.3
		6	4.68	7.58	162.0

Source: Table 10 Summary of Clinical Pharmacology Studies

Table 37 Statistical Analysis of C_{min} (ng/mL) Injection No. 1 Subutex Sublingual Tablet vs. Sublocade

	Geometric LSMean		Geometric LSMean Ratio Test/Reference (%)	90% CI of Geometric Mean Ratio Test/Reference (%)
	Subutex SL (Reference)	Sublocade (Test)		
Cohort 1, 8 mg, 50 mg	0.48	0.20	41.5	(33.3, 51.7)
Cohort 2, 12 mg, 100 mg	0.72	0.36	50.5	(43.2, 59.0)
Cohort 3, 24 mg, 200 mg	1.31	0.55	41.7	(35.8, 48.5)
Cohort 4, 8 mg, 100 mg	0.52	0.37	72.2	(61.7, 84.5)
Cohort 5, 14 mg, 200 mg	0.87	0.67	76.6	(66.7, 87.9)
Cohort 6, 12 mg, 300 mg	0.71	0.70	98.8	(60.4, 161.4)

Source: Table 23 CSR

Achieving Steady state

For Subutex SL tablet, buprenorphine achieved steady state by Day -7 in all dose groups except for the 12mg dose for which steady-state was achieved on Day -6.

Steady-state for buprenorphine following multiple SC injections was achieved by Day 57 (Injection 3) in the 50mg dose group, by Day 85 (Injection 4) in the 300mg dose group, and by Day 141 (Injection 6) for the 200mg dose group. Steady-state was not achieved for the 100mg dose group but data were only available for 4 SC injections.

Table 38 Assessment of Steady-State of Sublocade (Study 12-0005)

RBP-6000	Day	N	Geometric LS Mean	% Ratio of Geometric LS Means	P-value
50 mg RBP-6000	Day 29	15	0.30	39.2	<0.001
	Day 57	12	0.68	82.8	0.200[a]
	Day 85	11	0.80	96.0	0.815
	Day 113	10	0.83		
100 mg RBP-6000	Day 29	27	0.52	39.2	<0.001
	Day 57	24	1.05	69.8	<0.001
	Day 85	22	1.35	81.3	0.033
	Day 113	19	1.66		
200 mg RBP-6000	Day 29	27	0.76	30.7	<0.001
	Day 57	24	1.53	54.8	<0.001
	Day 85	22	2.28	76.3	0.013
	Day 113	16	2.53	78.1	0.088
	Day 141	3	3.00	85.9	0.537[a]
	Day 169	3	3.49		
300 mg RBP-6000	Day 29	11	1.55	36.0	<0.001
	Day 57	10	2.92	61.5	0.007
	Day 85	7	4.23	86.0	0.472[a]
	Day 113	2	4.70	93.5	0.834
	Day 141	2	5.41	115.7	0.730
	Day 169	1	4.68		

[a] This was the first non-significant comparison at the 0.1 level; steady-state was attained.
Source: Table 11 Summary of Clinical Pharmacology Studies

Evaluator Comment on Study PKs: The PKs show that the subjects received every 28 days a substantial rapid rise in plasma buprenorphine lasting >3days followed by a steady level for the rest of the 28 days.

Safety

Of 35 that received only Subutex SL tablets, 24 subjects (68.6%) had AEs. Those for > 2 subjects were: drug withdrawal syndrome (12 subjects, 34.3%), headache (8 subjects, 22.9%), constipation (6 subjects, 17.1%) and vomiting (3 subjects, 8.6%). The majority of TEAEs were moderate in severity (18 subjects, 51.4%). 1 severe AE (limb abscess) occurred in the 24mg group. There were no study drug related AEs to, no deaths , no SAEs and no withdrawals due to AEs.

All of the 89 that received both Subutex SL tablet and Sublocade reported AEs.

The most common were: drug withdrawal syndrome (67 subjects, 75.3%), headache (45 subjects, 50.6%), constipation (41 subjects, 46.1%), musculoskeletal pain (35 subjects, 39.3%), and anxiety (34 subjects, 38.2%).

The majority of TEAEs were moderate in severity (88 subjects, 98.9%). 1 AE was considered severe (deep vein thrombosis), which occurred in Cohort 5 (200mg).

There was 1 report of suicidal ideation in Cohort 3 (200mg), which was considered moderate in severity and not related to study drug.

There were 9 SAEs reported in 6 subjects; none of which were considered to be related to study drug. There were no deaths and 8 (9.0%) subjects were withdrawn from the study due to AEs. The number of subjects with at least 1 TEAE decreased as a function of the number of injections received from Injection 1 (89.9%) through Injection 7 (33.3%; n = 3; n ≤ 2 for subsequent injections).

Injection Site reactions overall appeared to increase in frequency with increased dose but the numbers are small.

Injection site reactions were reported in 88 (98.9%) subjects. The majority of injection site reactions were of moderate severity with a total of 5 (5.6%) injection site reactions (all for injection site pain) being severe. The number of subjects with at least 1 injection site reaction remained relatively constant as a function of the number of injections. The plots of injection site pain on the VAS demonstrated that by about 10 to 15 minutes after an injection, the pain had generally resolved.

Table 39 Overall Summary of Injection Site Reactions by System Organ Class and Preferred Term: Subjects Who Received Both Subutex Sublingual Tablet and Sublocade (Population: Safety)

	SUBUTEX SL; RBP-6000						All Subjects All Cohorts (N = 89) n (%)
System Organ Class Preferred Term[a] Severity	Cohort 1 50 mg (N = 15) n (%)	Cohort 2 100 mg (N = 15) n (%)	Cohort 3 200 mg (N = 15) n (%)	Cohort 4 100 mg (N = 15) n (%)	Cohort 5 200 mg (N = 15) n (%)	Cohort 6 300 mg (N = 14) n (%)	
Overall							
Total Subjects with at Least one Injection Site Reaction	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	13 (92.9)	88 (98.9)
Mild	4 (26.7)	1 (6.7)	6 (40.0)	4 (26.7)	2 (13.3)	2 (14.3)	19 (21.3)
Moderate	10 (66.7)	14 (93.3)	9 (60.0)	9 (60.0)	11 (73.3)	11 (78.6)	64 (71.9)
Severe	1 (6.7) (Injection Site Pain)	0 (0.0)	0 (0.0)	2 (13.3) (Injection Site Pain)	2 (13.3) (Injection Site Pain)	0 (0.0)	5 (5.6)
General Disorders and Administration Site Conditions	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	13 (92.9)	88 (98.9)
Injection Site Pain	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	13 (92.9)	88 (98.9)
Injection Site Erythema	7 (46.7)	13 (86.7)	12 (80.0)	9 (60.0)	14 (93.3)	11 (78.6)	66 (74.2)
Injection Site Swelling	1 (6.7)	9 (60.0)	6 (40.0)	5 (33.3)	9 (60.0)	10 (71.4)	40 (44.9)
Injection Site Warm	2 (13.3)	4 (26.7)	4 (26.7)	3 (20.0)	7 (46.7)	4 (28.6)	24 (27.0)
Injection Site Haematoma	4 (26.7)	8 (53.3)	6 (40.0)	6 (40.0)	10 (66.7)	6 (42.9)	40 (44.9)
Injection Site Pruritus	6 (40.0)	11 (73.3)	7 (46.7)	6 (40.0)	11 (73.3)	6 (42.9)	47 (52.8)

N = total number of subjects exposed per cohort; n = number of subjects in a subset in a given category; Source: Table 40
Subjects were dosed with Subutex SL tablet followed by SC injections of Sublocade containing buprenorphine.

In contrast to the above Table the following Table was extracted from a listing Table 6 of Overall Treatment-Emergent Adverse Events by System Organ Class and Preferred Term that Occurred in 2 or more Subjects: Subjects Who Received Both SUBUTEX Sublingual Tablet and RBP-6000 (Population: Safety)

Table 40 Injection Site reactions extracted from Table 6 of Overall TEAs ≥ 2 subjects

	SUBUTEX SL; RBP-6000						All Subjects All Cohorts (N=89) n (%)
System Organ Class Preferred Term[a]	Cohort 1 50 mg (N=15) n (%)	Cohort 2 100 mg (N=15) n (%)	Cohort 3 200 mg (N=15) n (%)	Cohort 4 100 mg (N=15) n (%)	Cohort 5 200 mg (N=15) n (%)	Cohort 6 300 mg (N=14) n (%)	
Injection Site Dermatitis	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)	2 (2.2)
Injection Site Pruritus	1 (6.7)	2 (13.3)	2 (13.3)	0 (0.0)	0 (0.0)	3 (21.4)	8 (9.0)
Injection Site Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (7.1)	2 (2.2)
Injection Site Pain	0 (0.0)	0 (0.0)	1 (6.7)	1 (6.7)	0 (0.0)	1 (7.1)	3 (3.4)

N = total number of subjects exposed per cohort; n = number of subjects in a subset in a given category;
Subjects were dosed with Subutex SL tablet followed by SC injections of Sublocade containing buprenorphine.
A treatment-emergent adverse event was any event not present prior to exposure to study drug or any event already present that worsened in either intensity or frequency following exposure to study drug.
'n' is the number of subjects with at least 1 treatment-emergent adverse event in a given category. Source: Table 36

21.1.1.4. Study RB-US-13-0001

The Plasma Concentration Summary[50] is some 80 pages. There was no other summary.

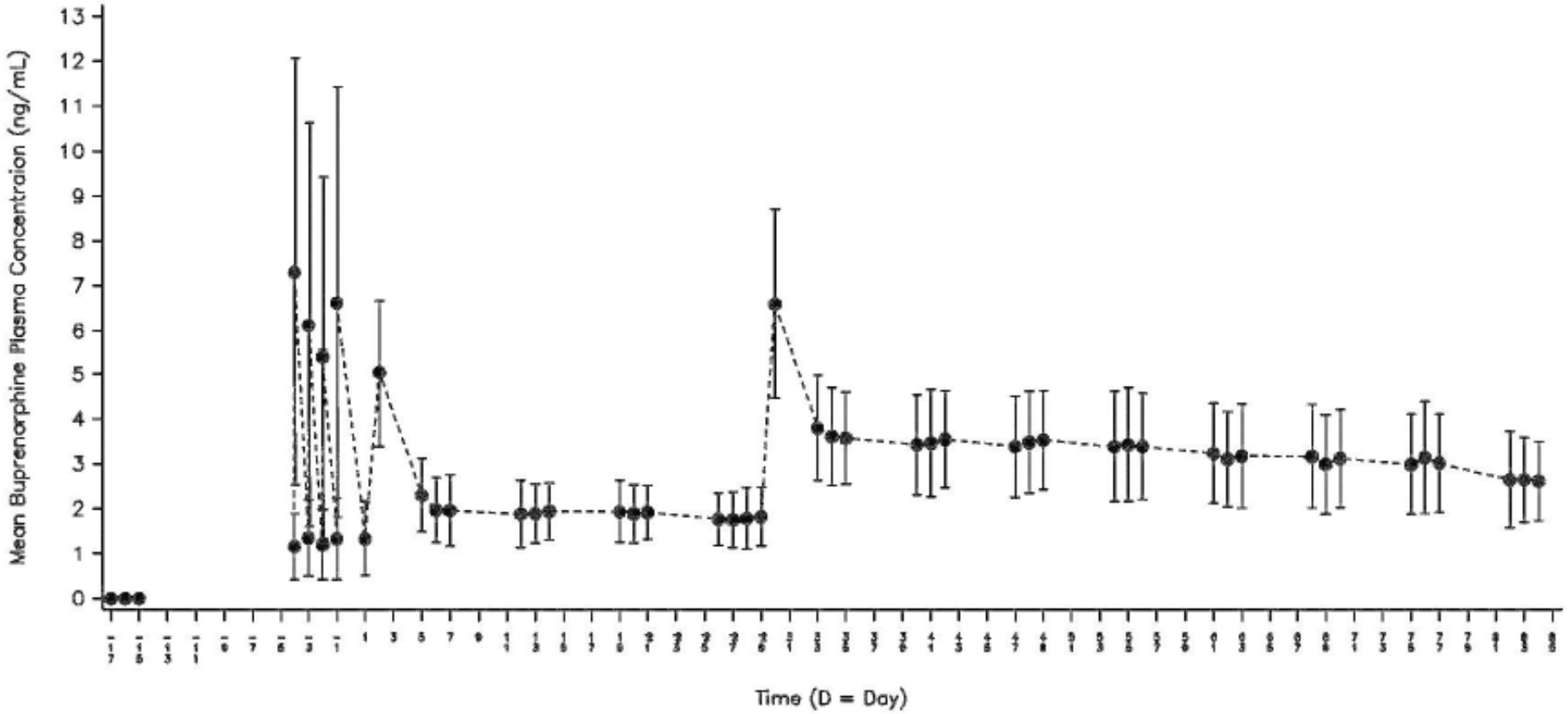
Buprenorphine plasma concentrations from the study were analysed using a population PK modelling approach (in combined analyses M04 and m05 see 21.1.3.4 and 21.1.3.5).

21.1.1.5. Study RB-US-13-0002

A US single centre multiple-dose study of blockade of subjective opioid effects, plasma levels, and safety of subcutaneous injections of depot buprenorphine in subjects with opioid use disorder. See 11.2.2

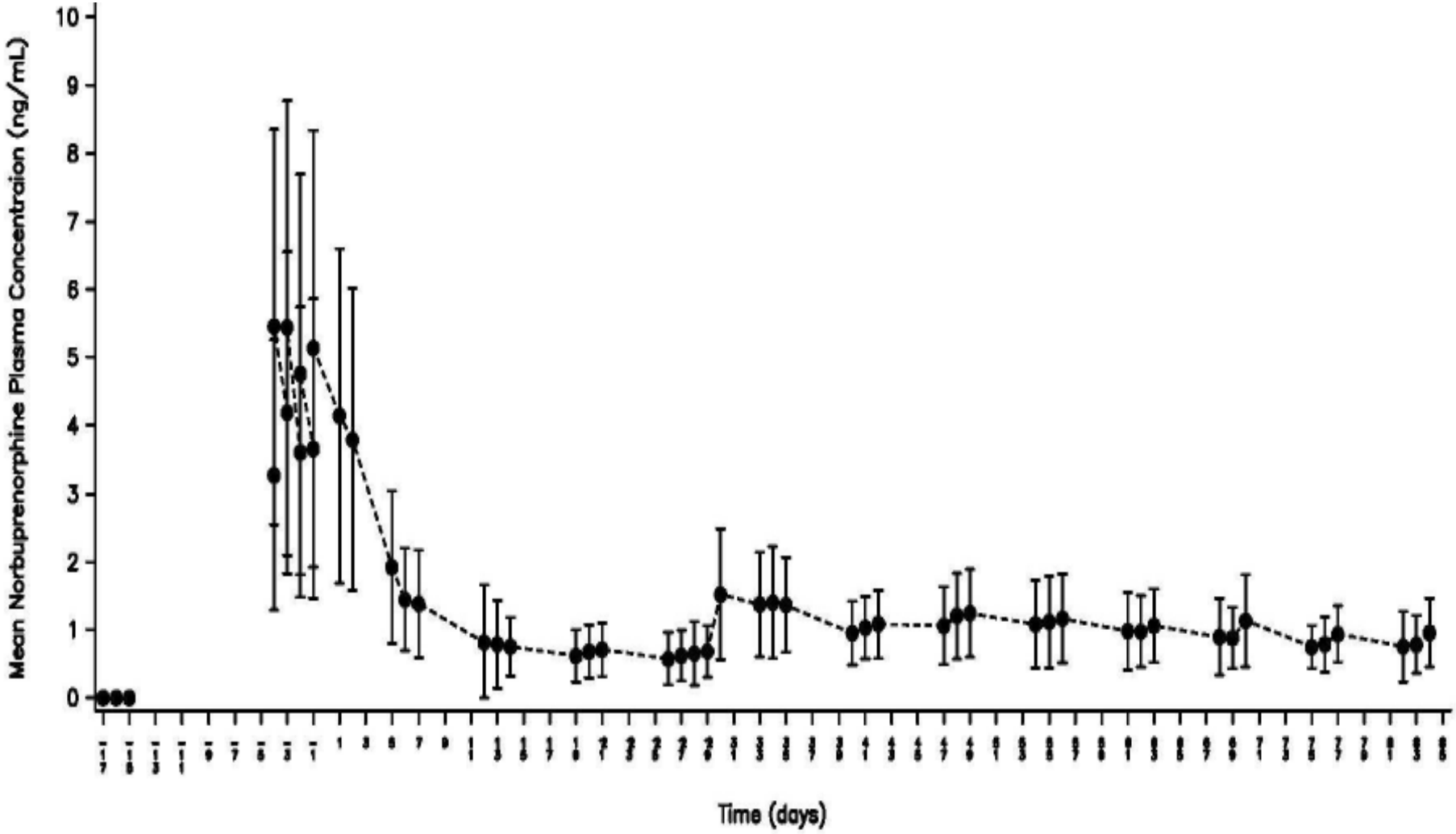
[50] Table S14.2.22 Page 592

Figure 24 Mean (± SD) Buprenorphine Plasma Concentrations vs. Time on a Linear Scale (Pop: ITT)



Source: Figure 1

Figure 25 Mean (± SD) Norbuprenorphine Plasma Concentrations vs.Time on a Linear Scale (Pop: ITT)



Source: Figure 3

Table 41 Buprenorphine Plasma Concentrations Summary-Sublocade (Population: ITT)

Analyte (unit)	Day	Time (hr)	Statistic	RBP-6000 300 mg
Buprenorphine (ng/mL)	Day 1	0	N	37
			Mean (SD)	1.330 (0.8245)
			%CV	62.0
			Median	1.240
			Min, Max	0.154, 3.72
			Geometric Mean	1.073
	Day 2	24	N	38
			Mean (SD)	5.034 (1.6401)
			%CV	32.6
			Median	4.520
			Min, Max	2.89, 11.3
			Geometric Mean	4.815
	Day 29	0	N	30
			Mean (SD)	1.823 (0.6524)
			%CV	35.8
			Median	1.620
			Min, Max	0.975, 3.93
			Geometric Mean	1.725
	Day 30	24	N	30
			Mean (SD)	6.591 (2.1188)
			%CV	32.1
			Median	6.465
			Min, Max	3.69, 13.4
			Geometric Mean	6.289

Subjects received 0mg (placebo), 6 mg, or 18mg hydromorphone on Days 4-7, 11-14, 18-21, 25-28, 32-35, 39-42, 46-49, 53-56, 60-63, 67-70, 74-77, and 81-84. Source: Table 9
Subjects received 8mg to 24mg sublingual Suboxone sublingual film on Day -14 through Day -1.
Subjects received 300mg Sublocade on Day 1 and Day 29 . N = number of subjects

Table 42 Norbuprenorphine Plasma Concentrations Summary-Sublocade (ITT)

Analyte (unit)	Day	Time (hr)	Statistic	RBP-6000 300 mg
Norbuprenorphine (ng/mL)	Day 1	0	N	37
			Mean (SD)	4.142 (2.4530)
			%CV	59.2
			Median	3.320
			Min, Max	0.684, 9.72
			Geometric Mean	3.404
	Day 2	24	N	38
			Mean (SD)	3.802 (2.2160)
			%CV	58.3
			Median	3.220
			Min, Max	1.02, 10.5
			Geometric Mean	3.224
	Day 29	0	N	30
			Mean (SD)	0.686 (0.3812)
			%CV	55.6
			Median	0.605
			Min, Max	0.23, 1.69
			Geometric Mean	0.595
	Day 30	24	N	30
			Mean (SD)	1.522 (0.9635)
			%CV	63.3
			Median	1.190
			Min, Max	0.522, 4.81
			Geometric Mean	1.314

Subjects received 0mg (placebo), 6 mg, or 18mg hydromorphone on Days 4-7, 11-14, 18-21, 25-28, 32-35, 39-42, 46-49, 53-56, 60-63, 67-70, 74-77, and 81-84. Source: Table 9
Subjects received 8mg to 24mg sublingual Suboxone sublingual film on Day -14 through Day -1.
Subjects received 300mg Sublocade on Day 1 and Day 29 . N = number of subjects

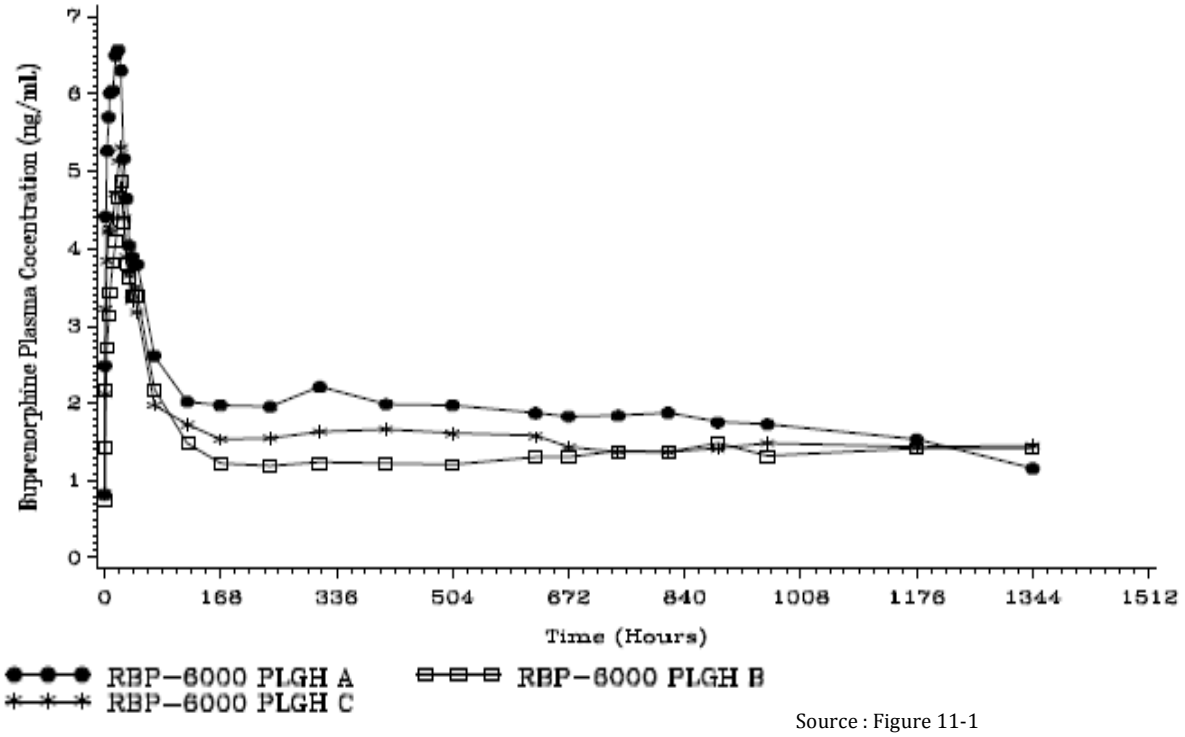
21.1.1.6. Study RB-US-13-0006

A single-centre, randomized, open-label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of depot buprenorphine using poly (dl-lactide-co-glycolide) polymer of two different molecular weights (low and high molecular weights as test treatments) in comparison to intermediate molecular weight (reference treatment) in treatment-seeking subjects with opioid use disorder.

The study was conducted from 22 September 2015 to 10 February 2016 in the US on 47 subjects.

After a single dose of Sublocade, mean concentrations of buprenorphine and norbuprenorphine increased over approximately 48h and then decreased over 48h after peak concentrations. Mean concentrations of buprenorphine and norbuprenorphine remained relatively constant from approximately 7 days post dose to the last sample 56 days post dose. While buprenorphine concentrations of Sublocade PLGH C (14 kDa PLGH polymer) were consistently lower than the low molecular weight treatment (Sublocade PLGH A, 9 kDa PLGH polymer) and higher than the high molecular weight treatment (Sublocade PLGH B, 17 kDa PLGH polymer), all 3 treatments displayed a similar concentration-time profile.

Figure 26 Mean Plasma Concentrations of Buprenorphine (Sublocade Phase) (PK Set)



Source : Figure 11-1

Values below the lower limit of quantification were treated as zero for calculation of summary statistics.
Lower limit of quantitation was 0.05ng/mL for buprenorphine.
Sublocade PLGH A: Sublocade 300mg buprenorphine formulated with 9 kDa PLGH polymer (test treatment), subcutaneous (SC) injection
Sublocade PLGH B: Sublocade 300mg buprenorphine formulated with 17 kDa PLGH polymer (test treatment), SC injection
Sublocade PLGH C: Sublocade 300mg buprenorphine formulated with 14 kDa PLGH polymer (reference treatment), SC injection

21.1.2. Synopses of pharmacodynamics studies

21.1.2.1. PD/PK Study RB-US-13-0002 multiple parameters

This complex study (see also 11.2.2) set out to show that after Sublocade was given hydromorphone, previously shown to be subject desirable in the absence of buprenorphine, was now no more desirable that saline. This was demonstrated with visual analog scales for “Drug Liking" "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High".

Secondary Objectives included:

- To evaluate the correlation between the opioid blockade subjective effects (VAS of "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High") and the reinforcing effects of hydromorphone and simulated mu opioid receptor occupancy (using the maximal effect [E_{max}] model).
- To determine the relationship between plasma concentration and predicted mu opioid receptor occupancy of buprenorphine and both the blockade of the subjective effects of hydromorphone post injection of buprenorphine 300mg (Sublocade).

Predicted mu Opioid Receptor Occupancy (μ-opioid receptor occupancy)

A population PK/PD model was previously developed to model the relationship between buprenorphine plasma concentrations and brain μ-opioid receptor occupancy . [51] The structural

[51] Page 65 CSR

PK/PD model was used to predict μ-opioid receptor occupancy in the current study based on [52]the observed individual buprenorphine plasma concentrations.

The analysis of the Predicted mu Opioid Receptor Occupancy data was not available when the SAP and TFLs for this study were finalised. The data presented in Section 11.2.4 was provided by INDV after the TFLs for this study were finalised.[53]

Individual predictions of μ-opioid receptor occupancy *(were)* generated using a previously developed PK/PD model.[54]

Comment: The published study articles from 2007 and 2003 on which the PK/PD model were based were in the submission as was the online version of the article by Nasser 2014 that described the PK/PD model.

Statistical analysis

The study was performed from 19 November 2013 – 29 July 2014, publication of the 'previously developed' model was September 2014.

The submission as well as the above publications contains INDV-6000-M02 Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy in the brain which also looked at the published study articles from 2007 and 2003. However INDV-6000-M02 report was dated 19 January 2017. (See 21.1.3.1).

Relationship Between Plasma Concentration and Predicted Mu Opioid Receptor Occupancy

[52] Page 65 CSR
[53] CSR page 72
[54] Nasser et al(2014). A Population Pharmacokinetic and Pharmacodynamic Modelling Approach to Support the Clinical Development of RBP-6000, A New, Subcutaneously Injectable, Long-Acting, Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Dependence. Clin. Pharmacokinet 53(9): 813-824. September 2014

Table 43 Effect on Drug Liking and Reinforcing Breakpoint Values Following 18mg and 6mg Hydromorphone Challenges (ITT)

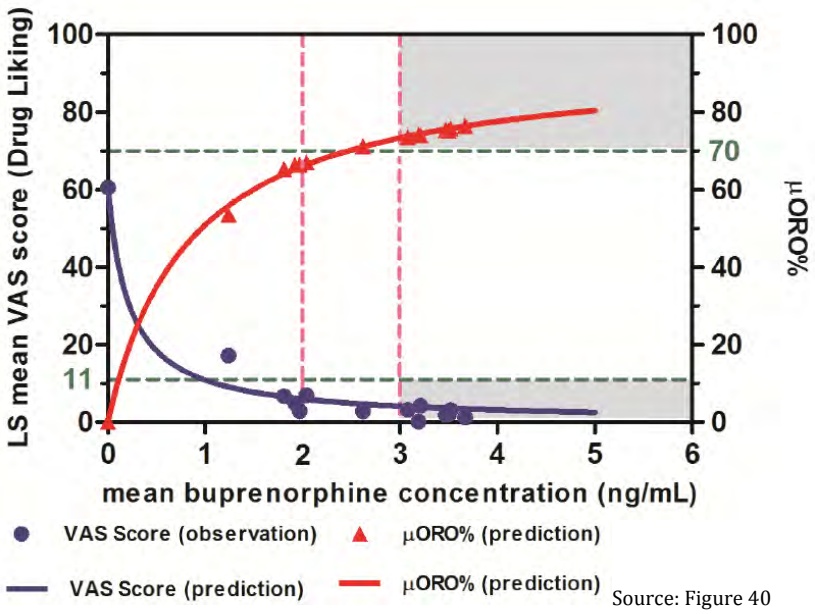
Phase	Week	Buprenorphine Concentration (ng/mL)		Predicted μORO (%)		VAS Scores (Drug Liking) – Change from Placebo, LS Mean (95% CI)		Reinforcing Effects (Breakpoint) – Change from Placebo, LSMean of Log_{10} Transformation (95% CI)	
		18 mg	6 mg	18 mg	6 mg	18 mg vs. placebo	6 mg vs. placebo	18 mg vs. placebo	6 mg vs. placebo
Baseline	–1	0.00	0.00	0.00	0.00	60.61 (52.32, 68.90)	45.36 (37.16, 53.56)	0.89 (0.64, 1.17)	0.93 (0.67, 1.18)
Sublingual	0	1.24	1.32	53.63	54.64	17.17 (10.43, 23.90)	8.20 (1.47, 14.94)	0.84 (0.48, 1.20)	0.58 (0.19, 0.96)
RBP-6000	1	2.04	2.16	67.09	67.88	6.93 (3.24, 10.61)	3.66 (–0.03, 7.34)	0.41 (0.15, 0.67)	0.27 (-0.001, 0.53)
	2	1.97	1.87	66.49	66.06	2.90 (0.33, 5.47)	0.59 (–1.98, 3.15)	0.63 (0.28, 0.99)	0.32 (-0.05, 0.70)
	3	1.92	1.88	66.44	66.00	4.93 (1.02, 8.84)	0.86 (–3.05, 4.78)	0.40 (0.13, 0.66)	0.41 (0.14, 0.69)
	4	1.81	1.78	65.35	65.11	6.68 (1.94, 11.42)	3.32 (–1.43, 8.06)	0.82 (0.53, 1.11)	0.60 (0.31, 0.90)
	5	3.67	3.65	76.42	76.29	1.21 (–0.43, 2.85)	0.74 (–0.94, 2.42)	0.16 (-0.24, 0.56)	-0.04 (-0.47, 0.39)
	6	3.52	3.53	75.69	75.70	3.16 (–0.83, 7.15)	0.35 (–3.62, 4.32)	0.43 (-0.03, 0.88)	0.05 (-0.41, 0.51)
	7	3.47	3.50	75.43	75.64	1.88 (–0.11, 3.87)	–0.15 (–2.16, 1.86)	0.38 (0.043, 0.72)	0.31 (-0.004, 0.63)
	8	3.50	3.37	75.18	74.79	1.93 (–1.79, 5.66)	–1.05 (–4.77, 2.68)	0.37 (-0.05, 0.79)	0.23 (-0.16, 0.61)
	9	3.21	3.12	74.04	73.97	4.17 (–1.84, 10.17)	–0.12 (–6.20, 5.96)	0.48 (-0.14, 1.09)	0.04 (-0.61, 0.69)
	10	3.19	3.04	74.18	73.08	0.13 (–0.50, 0.76)	–0.09 (–0.69, 0.51)	0.20 (-0.22, 0.61)	0.01 (-0.41, 0.44)
	11	3.08	2.99	73.51	73.05	3.24 (–0.35, 6.83)	–0.32 (–3.97, 3.34)	0.32 (-0.29, 0.94)	-0.09 (-0.73, 0.55)
	12	2.62	2.65	71.30	71.31	2.78 (0.61, 4.96)	–0.03 (–2.19, 2.12)	0.69 (0.22, 1.16)	0.26 (-0.25, 0.77)

LS = least squares; μ-opioid receptor occupancy = opioid receptor occupancy; Baseline (Week -1) was defined as Day -17, Day -16, and Day –15. Week 0 (Suboxone sublingual phase) was defined as Day -3, Day -2, and Day -1. Source: Table 13

Following administration of Suboxone during Week 0, increases were observed in buprenorphine plasma concentrations and predicted μ-opioid receptor occupancy with corresponding decreases in mean change from placebo "Drug Liking" VAS scores and log_{10}-transformed mean hydromorphone breakpoint values. The LSMeans change from placebo "Drug

Liking" VAS score for the first week of Sublocade treatment (Injection 1) at the highest hydromorphone dose of 18mg was approximately 7.
After the second Sublocade injection, the LS mean value was further reduced to below 6 with the corresponding 95% CI including 0. Therefore, full blockade is claimed from the first week post first injection through Week 12. Similar effects were observed for the additional VAS scales.

Figure 27 Correlation Between Mean Buprenorphine Concentration and Clinical Effect



Source: Figure 40

The SAP 7.8.4 Predicted Mu Opioid Receptor Occupancy and Opioid Blockade Subjective Effects

It was originally planned in the protocol that a saturable E_{max} model with an additive error model would be used to predict mu opioid receptor occupancy (μ-opioid receptor occupancy) from buprenorphine plasma concentration levels.
The E_{max} model is currently under development. Upon finalization of the model, an addendum to the SAP will be written, and the analysis to be performed will be done at that time. Under the current SAP, no summary or analysis will be done using this model.
Reference for the model was given. The CSR referred to the publication based on the study which under discussion had "The μ-opioid receptor occupancy was predicted using the observed buprenorphine concentrations and the previously published model from Nasser et al."[55]
Naser et al do support the CSR for the use of A saturable E_{max} model was used for predicting the μ-opioid receptor occupancy.

$$\text{μ-opioid receptor occupancy} = \frac{E_{max} \cdot Cp}{EC_{50}+Cp}$$

Were E_{max} is the maximal μ-opioid receptor occupancy, Cp is the buprenorphine plasma concentration, and EC_{50} is the buprenorphine plasma concentration necessary for achieving 50% of the maximal μ-opioid receptor occupancy. The estimated value for E_{max} (standard error) was 91.40 (3.94%) and the estimated value for EC_{50} (standard error) was 0.67 (0.19%) ng/mL.

[55] Nasser , et al. A population pharmacokinetics and pharmacodynamic modelling approach to support the clinical development ofRBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid dependence. Clin Pharmacokinet. 2014;53: 813-824. Also in submission as Study INDV-6000-M02

However the source of support was not found for using An E_{max} inhibitory model was used for describing the relationship between Drug Liking VAS scores and buprenorphine plasma concentrations after 18mg hydromorphone challenge.

21.1.2.2. PD study RB-US-11-0020 multiple assessments

See also 21.1.1.2 for more information.

Pharmacodynamic assessments included the C-SSRS, COWS assessment; the Opioid Craving VAS; urine toxicology screen, and the timeline follow back (TLFB) interview for opiate drug use.

Columbia Suicide Severity Rating Scale

At Screening, 9 subjects (18.8%) responded positively for suicidal ideations at some point in their lives, none within the previous 6 months.

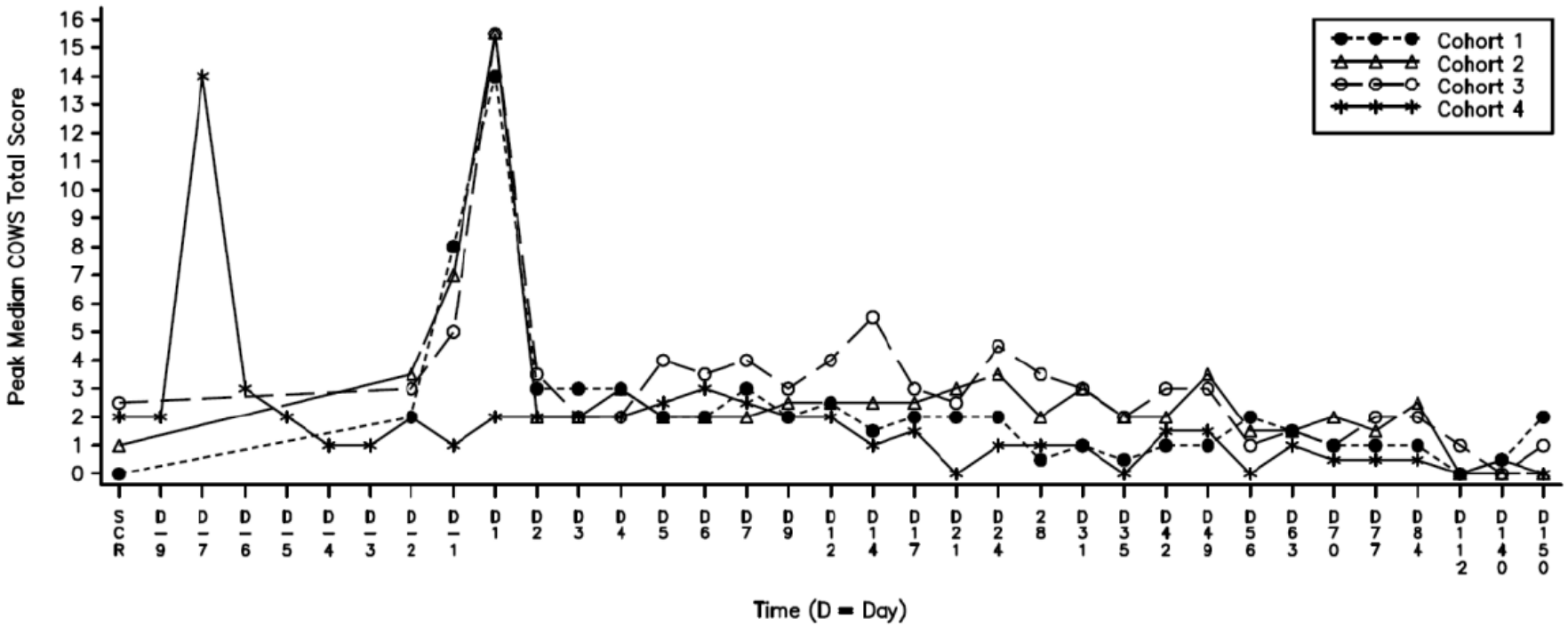
During the study, 3 subjects responded positively on the C-SSRS

Timeline Follow back Interview Data

The number of subjects reporting the use of opioids declined after administration of Sublocade (7 of 48 subjects; 14.6% on Day 25) and rose over time thereafter (14 of 48 subjects; 29.2% on Day 150). Generally, the number of subjects reporting the use of opioids was slightly lower than the number of subjects testing positive for opiates and oxycodone on the urine drug screen.

Clinical Opiate Withdrawal Scale

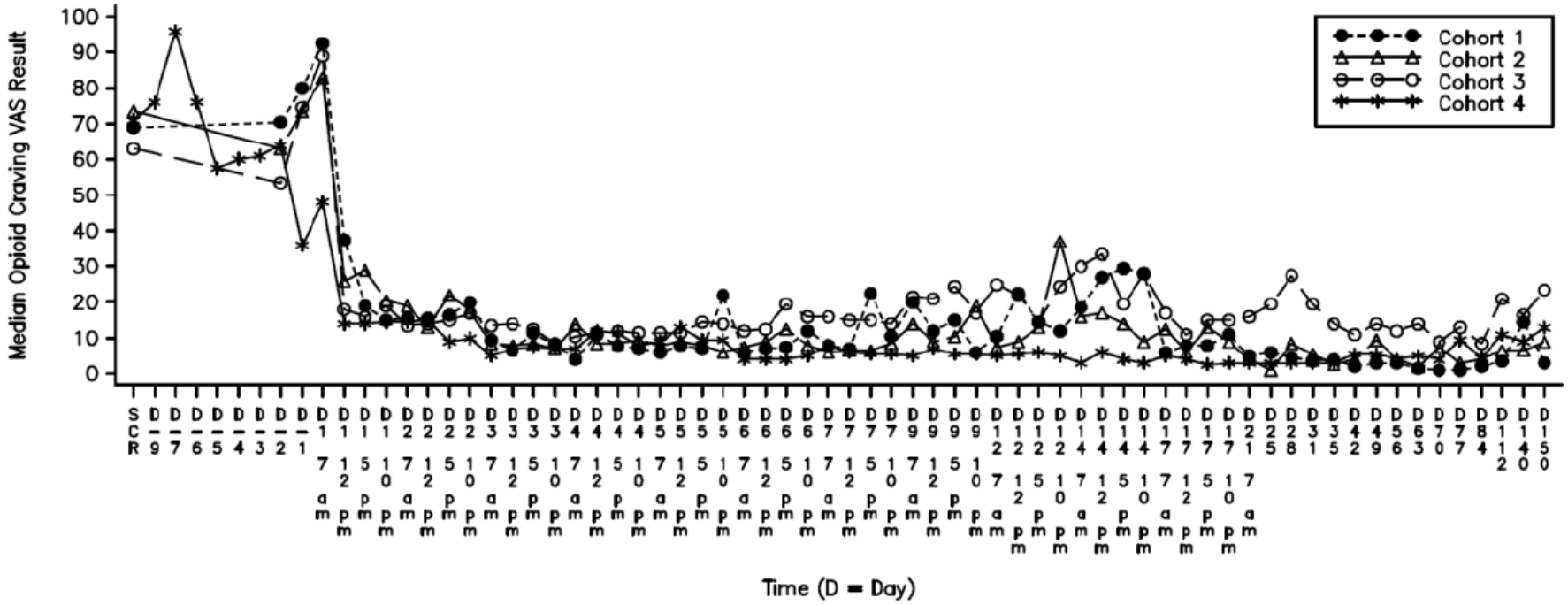
Figure 28 Plot of Median Clinical Opiate Withdrawal Scale Total Score vs.Time (All Cohorts)



Cohort 1 = a single SC injection of Sublocade containing 50mg buprenorphine.
Cohort 2 = a single SC injection of Sublocade containing 100mg buprenorphine.
Cohort 3 = a single SC injection of Sublocade containing 200mg buprenorphine.
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day -7 and 12mg on Days -6 through -1.

Source: Figure 38

Figure 29 Plot of Median Clinical Opioid Craving Visual Analog Scale vs.Time (All Cohorts)



Cohort 1 = a single SC injection of Sublocade containing 50mg buprenorphine. Source: Figure 40
Cohort 2 = a single SC injection of Sublocade containing 100mg buprenorphine.
Cohort 3 = a single SC injection of Sublocade containing 200mg buprenorphine.
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day -7 and 12mg on Days -6 through -1.

21.1.2.3. PD Study RB-US-12-0005 PET substudy

See also 21.1.1.3 for more information.

Positron Emission Tomography Sub-study

The PET imaging sub-study evaluated the mu-opioid receptor availability of subjects who were at steady-state after receiving Sublocade containing 200mg or 300mg buprenorphine.[56]

Initiated in response to US Food and Drug Administration (FDA) feedback.

Subjects who received Sublocade containing either 200mg or 300mg buprenorphine and reached Day 112 (and had received all 4 or 6 planned SC injections, respectively) had the option to participate in a PET imaging sub-study and were required to sign a separate informed consent form prior to participation. It was anticipated that subjects could have needed up to 12 SC injections to complete the PET imaging study, depending on the availability of the PET scan facilities. Subjects were to remain on the same dose of Sublocade (200mg or 300 mg) administered in the main study, which was to be administered every 28 days, until they completed a MRI scan, a PET scan and PK sampling at Week 1 and Week 4 after the last injection. The PK sampling schedule for subjects in the PET imaging sub-study was the same as that for subjects in Cohort 6 in the main study up to Injection 4. Only limited PK samples were collected after Injection 5.

Positron emission tomography data were obtained in 2 subjects dosed under steady-state conditions. One subject received a total of 6 SC injections of 300mg and the other subject received a total of 12 SC injections of 200mg. The subject who received 200mg showed 79% and 75% whole-brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively. The subject who received 300mg showed 92% and 81% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively.[57]

Sponsor comment: These high mu-opioid receptor occupancy values are within the range of those observed following the administration of multiple daily doses of SL buprenorphine (16mg or 32mg) in previously published studies (Greenwald 2003; Greenwald 2007). However, contrarily to daily SL buprenorphine administration, the high mu-opioid receptor occupancy values were maintained over the dosing interval of 28 days. For daily doses of 16mg SL buprenorphine, whole-brain mu-opioid receptor occupancy was reported to be 70% at 4 hours post-dose, but only 46% at 28 hours post-dose.

Secondary endpoints

The COWS total scores, SOWS total scores, VAS scores, CGI-S scale, CGI-I scores showed a reduction from baseline for all treatment cohorts following Subutex SL tablet and Sublocade administration.

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[56] CSR page 55

[57] Subject 001760 (cohort 5, 14 mg of Subutex) receiving 200 mg of RBP-6000 in the PET scan sub-study demonstrated μ-opioid receptor occupancy compared to the average control of 79.4% (whole brain), 72.8% (anterior cingulate cortex), 71.7% (nucleus accumbens), 74.7% (amygdala) on Day 7 following the 12th SC injection of RBP-6000. The same subject's receptor occupancy remained at similar levels on Day 28 following the 12th SC injection of RBP-6000 with 75.1% (whole brain), 69.0% (anterior cingulate cortex), 66.7% (nucleus accumbens), and 67.6% (amygdala).
Subject 001844 (cohort 6, 12 mg of Subutex) receiving 300 mg of RBP-6000 in the PET scan sub-study showed μ-opioid receptor occupancy compared to the average control of 92.4% (whole brain), 87.6% (anterior cingulate), 88.9% (nucleus accumbens), 92.6% (amygdala) on Day 7 following the 6th SC injection of RBP- 6000. The same subject's receptor occupancy remained at 81.4% (whole brain), 77.4% (anterior cingulate cortex), 80.1% (nucleus accumbens), and 79.7% (amygdala) on Day 28 following the 6th SC injection of RBP- 6000. Appendix 16.1.13.3

There were dose and time dependent reductions in self-reported opioid drug use.

The median percentage of urine samples that were negative for opioids over the entire course of the study was 28.6% for Cohort 1 (50mg), 19.1% for Cohort 2 (100mg), 59.4% for Cohort 3 (200mg), 55.6% for Cohort 4 (100mg), 32.1% for Cohort 5 (200mg), and 66.7% for Cohort 6 (300mg).

21.1.3. Synopses of population pharmacokinetics analyses

21.1.3.1. Study INDV-6000-M02 PopPKs and μ-opioid receptor occupancy

Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy in the brain.

The primary goal of this report was to characterize the relationship between buprenorphine plasma concentration and μ-opioid receptor occupancy (μ-opioid receptor occupancy) in the brain and develop a population PK μ-opioid receptor occupancy model.

Higher medication doses are hypothesized to decrease μ-opioid receptor availability (or 'binding potential') and provide agonist replacement that minimizes withdrawal symptoms, promotes clinic attendance, and prevents heroin reinforcement, euphoria, and side effects (Greenwald 2003).

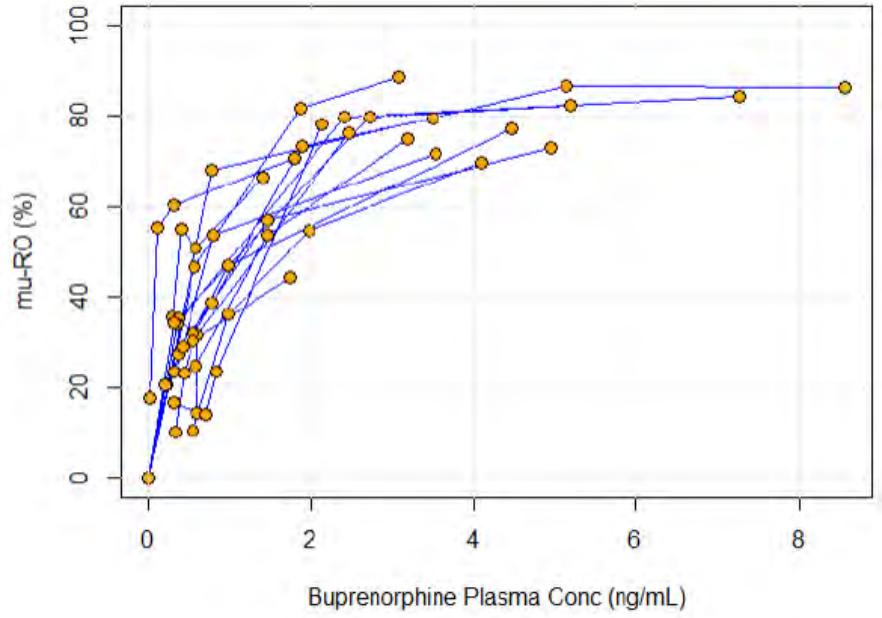
Data Sources

- Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK. Effects of buprenorphine maintenance dose on μ-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology. 2003;28(11):2000-9
  Five heroin-dependent subjects were included in the trial. Each subject was successively maintained on 32, 16, 2, and 0mg daily buprenorphine sublingual tablet doses. Four PET scans with [^{11}C]-carfentanil were conducted on each subject at 4h after the last of 12 daily doses of buprenorphine (32mg, 16mg, 2mg, or placebo). On the 9th day of each maintenance period, blood samples were collected for the measurement of buprenorphine and norbuprenorphine plasma concentrations.
- Greenwald MK, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, Koeppe R, Zubieta JK. Buprenorphine duration of action: μ-opioid receptor availability and pharmacokinetic and behavioural indices. Biol Psychiatry. 2007;61(1):101-10
  Ten heroin-dependent subjects were included in the trial. They were initially maintained for ≥ 2 weeks on 16mg/day buprenorphine given as sublingual tablets. Plasma buprenorphine concentrations, opioid withdrawal symptoms and 4 hydromorphone challenges (24mg) or 4 PET brain scans with [^{11}C]-carfentanil were conducted at 4, 28, 52 and 76h after the last daily buprenorphine dose. Authors' Conclusion: Together with our previous findings, it appears that mu-opioid receptor availability predicts changes in pharmacokinetic and pharmacodynamic measures and that about 50%-60% BUP occupancy is required/or adequate withdrawal symptom suppression (in the absence of other opioids) and hydromorphone blockade.

From both trials, whole-brain imaging results were used to calculate μ-opioid receptor availability.

The 15 subjects had a total of 59 PK/ μ-opioid receptor occupancy data points.

Figure 30 Individual μ-opioid receptor occupancy measurements (mu-RO) vs. the buprenorphine plasma concentrations



Source: Figure 1

Model

The model was based on the assumption that a direct proportionality between buprenorphine plasma concentration and μ-opioid receptor occupancy has been established without equilibration delay. The model used was defined by the equation:

$$\text{μ-opioid receptor occupancy} = \frac{E_{max} \cdot Cp}{EC_{50}+Cp}$$

Were E_{max} is the maximal μ-opioid receptor occupancy, Cp is the buprenorphine plasma concentration, and EC_{50} is the buprenorphine plasma concentration necessary for achieving 50% of the maximal μ-opioid receptor occupancy.

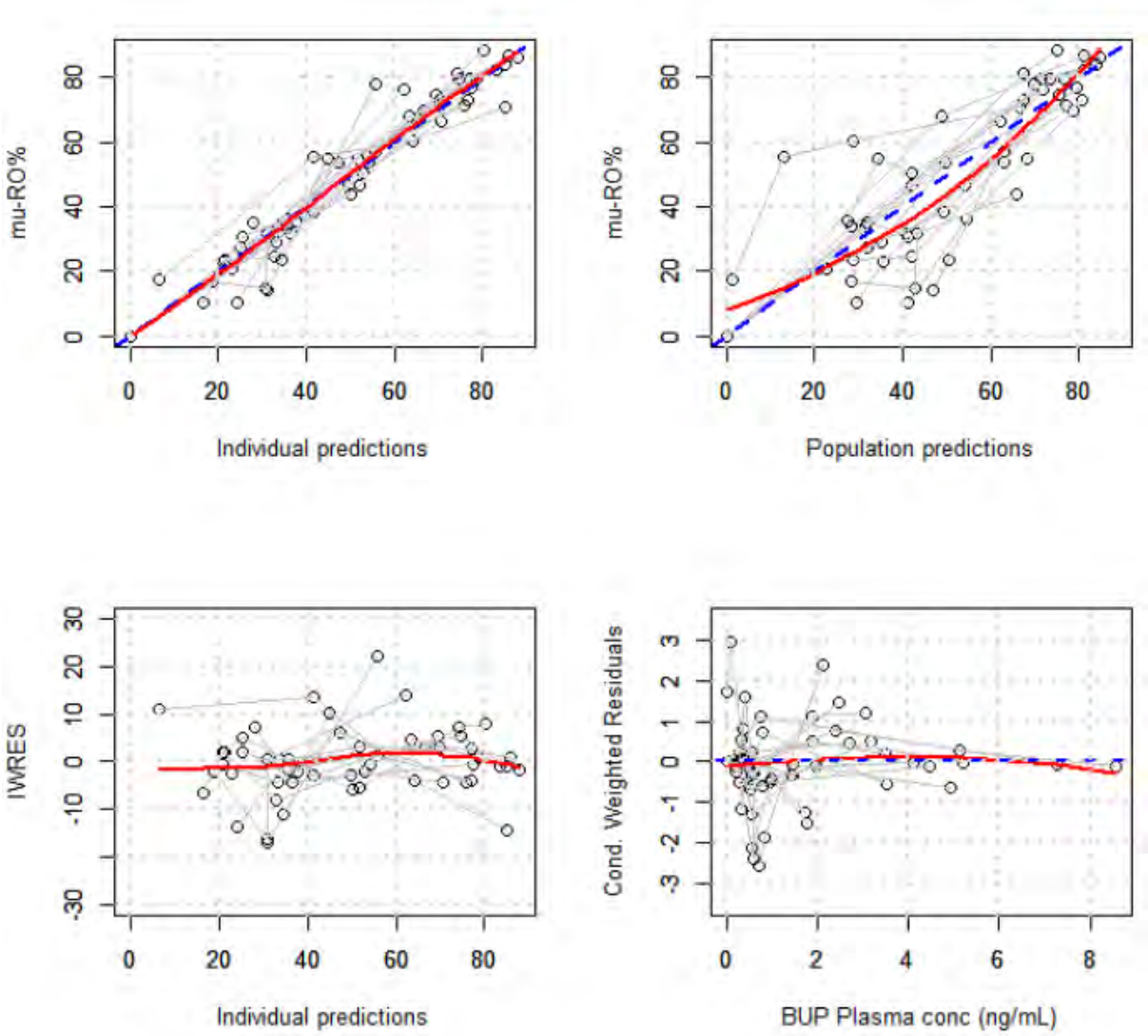
An additive error model option was retained in the final model.

Table 44 Final population parameter estimates

	Emax	EC50	IIV-EC50	Add Err
Parameter estimates	91.40	0.67	0.47	62.50
Standard errors	3.90	0.19	0.25	22.20
RSE(%)	4.30	28.40	54.30	35.50
95% Conf. Interval	83.76-99.04	0.30-1.04		

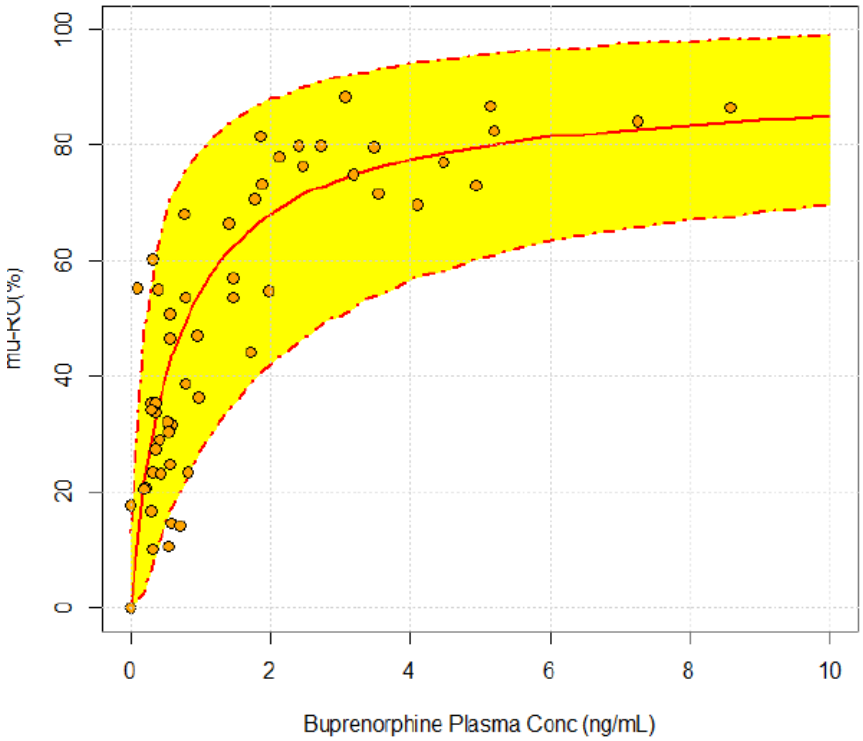
Variance estimates are shown for additive error (Add Err) and EC_{50} inter-individual variability (IIV); RSE: relative standard error; the data available did not permit to estimate the IIV on E_{max}. Source: Table 2

Figure 31 Goodness-of-fit diagnostic plots for the final model



Mu-RO: μ-opioid receptor occupancy; BUP: buprenorphine; IWRES: Individual weighted residuals. Cond. Weighted Residuals: conditional weighted residuals Source: Figure 2

Figure 32 Visual Predictive Check plots for the PK /μ-opioid receptor occupancy model.



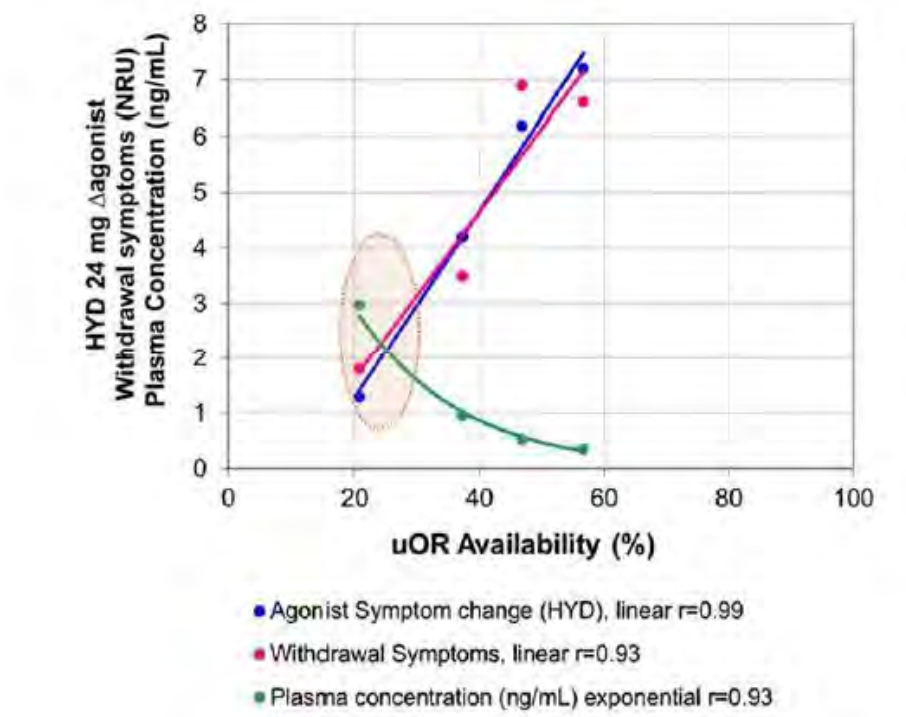
The red lines represent the 5th, 50th, and 95th percentiles of the simulated data, the shaded yellow area represents the 90% prediction intervals. The orange circles are the observed data. Source: Figure 3

Table 45 Bootstrap analysis results based on 500 re-sampled datasets

	Emax	EC50	IIV-EC50	Add Err
Mean	91.41	0.68	0.46	59.88
Percentiles				
0.05%	78.61	0.09	-0.36	-9.91
0.50%	81.40	0.22	-0.18	5.82
2.50%	83.80	0.33	-0.02	19.37
5%	85.02	0.38	0.05	26.30
95%	97.85	0.96	0.88	98.69
97.50%	99.08	1.02	0.96	105.62
99.50%	101.48	1.12	1.11	119.17
99.95%	104.26	1.25	1.29	134.90
Standard error	3.90	0.18	0.25	22.00
Median	91.60	0.67	0.43	57.95
RSE(%)	4.26	26.35	57.73	37.97

RSE: relative standard error Source: Table 3

Figure 33 Observed and Model Predicted Changes in Agonist Effect Following Administration of 24mg Hydromorphone, Observed and Model Predicted Mean Withdrawal Symptoms, and Observed and Model Predicted Buprenorphine Plasma Concentration in Relation to Brain Mu-Opioid Receptor Availability



Dots=mean observations; Solid lines=model predictions by linear or nonlinear regression analysis HYD=hydromorphone
Summary of Clinical Pharmacology Studies Source: individual data from 2 previously published clinical trials (Greenwald 2003; Greenwald 2007) Source : Figure 21

21.1.3.2. Pop PK model & Simulation study INDV6000-m01 (11-0020)

The data for the population PK analysis were obtained from Study RB-US-11-0020.

There were multiple descriptions of the intentions of the report:

The primary goal of this report was to characterize the population pharmacokinetics (PK) of Sublocade after single subcutaneous (SC) injection using the ATRIGEL.[58]

The objective of the modelling and simulation (M & S) project was to inform the design of the clinical phase III program for the treatment of opioid dependence with Sublocade. More specifically, the M & S effort objective was to identify a dose range to be studied that would provide the best balance between clinical efficacy (symptom and functional improvement) and safety.[59]

The Modelling and Simulation objectives were:

- To develop a population PK model that jointly characterizes the disposition of buprenorphine (BUP) and norbuprenorphine (Nor-BUP) after a single SC injection of Sublocade.
- To evaluate the potential effect of selected covariates on the PK of Sublocade.
- To predict the PK profiles of BUP and Nor-BUP after repeated SC injections of Sublocade and to compare the model predictions with the PK levels collected in the multiple

[58] Page 8
[59] Page 10

ascending dose (MAD) study (12-0005: An Open-Label, Multicentre, Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics, and Efficacy Markers of Subcutaneous Injections of Depot Buprenorphine [Sublocade] in Treatment Seeking Opioid-Dependent Subjects).

- To develop a pharmacokinetic/pharmacodynamic (PK/PD) model using published data describing the link between the BUP PK and the μ-opioid receptor occupancy. At this purpose the following stepwise approach was used:
    - Extract μ-opioid receptor occupancy and BUP PK concentration from literature data.
    - Develop a PK/μ-opioid receptor occupancy model.
    - Apply the PK/μ-opioid receptor occupancy model using the population PK model developed for BUP in subjects receiving a single and multiple SC injections of Sublocade to estimate the expected μ-opioid receptor occupancy in a chronic treatment.
- To use trial simulation to investigate alternative doses and dosing regimen scenarios for a chronic (once a month) administration.
- To evaluate alternative study designs and propose an accelerated clinical development plan to streamline Phase I, Phase II and Phase III trials.

The Modelling and Simulation endpoints were:

- The population PK parameters and their associated inter-subject variability, and residual error.
- The identification of significant covariates that impact the PK of Sublocade in the studied population.

The analysis dataset included 36 subjects for a total of 2797 observations. The buprenorphine concentration analysis used was only partly validated.

Base model

The dual absorption process was described by: 1) a first order absorption process associated with the rapid absorption and the first observed peak and 2) a delayed delivery process described by a transit compartment absorption model to mimic the release from the Atrigel Delivery System. This was followed by first-order elimination, and a first-order conversion to Nor-BUP which was subsequently eliminated according to a first-order process.

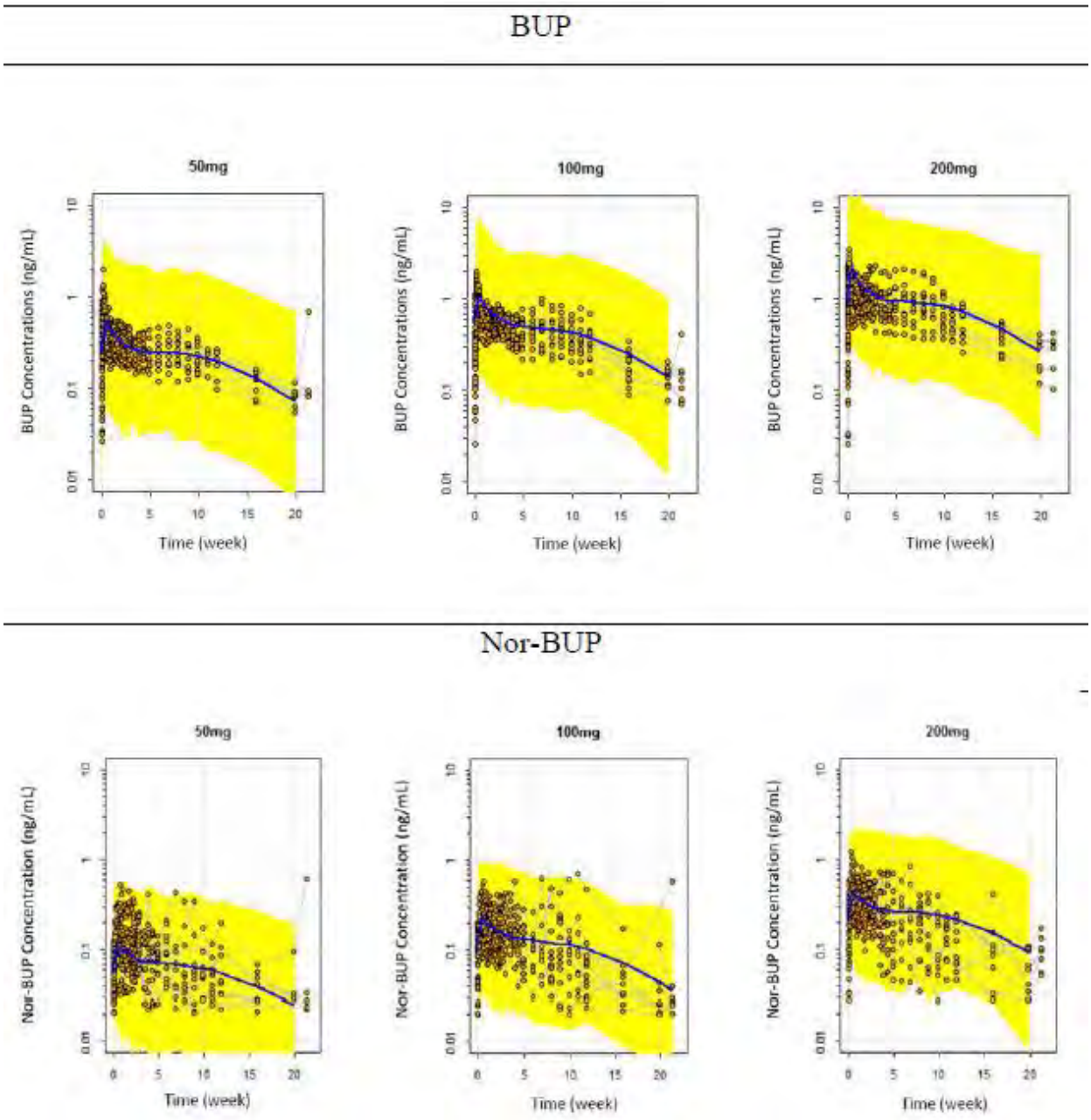
The final model was evaluated using nonparametric bootstrapping, at least 100 datasets were generated. The final model was retested with and without inclusion of the outlier data points.

400 replicates of the original dataset were simulated, based on the final model, and 95% prediction interval was computed based on the simulated datasets.

The Model with a peripheral distribution compartment for Nor-BUP (Model 2) was selected as the base model.

Overall, it was not possible to identify any covariate with significant impact on the population PK variability, given the relatively small number of subjects in the study.

Figure 34 Total Population - Visual Predictive Check Plots for Buprenorphine (BUP) and Norbuprenorphine (Nor-BUP) stratified by Dose

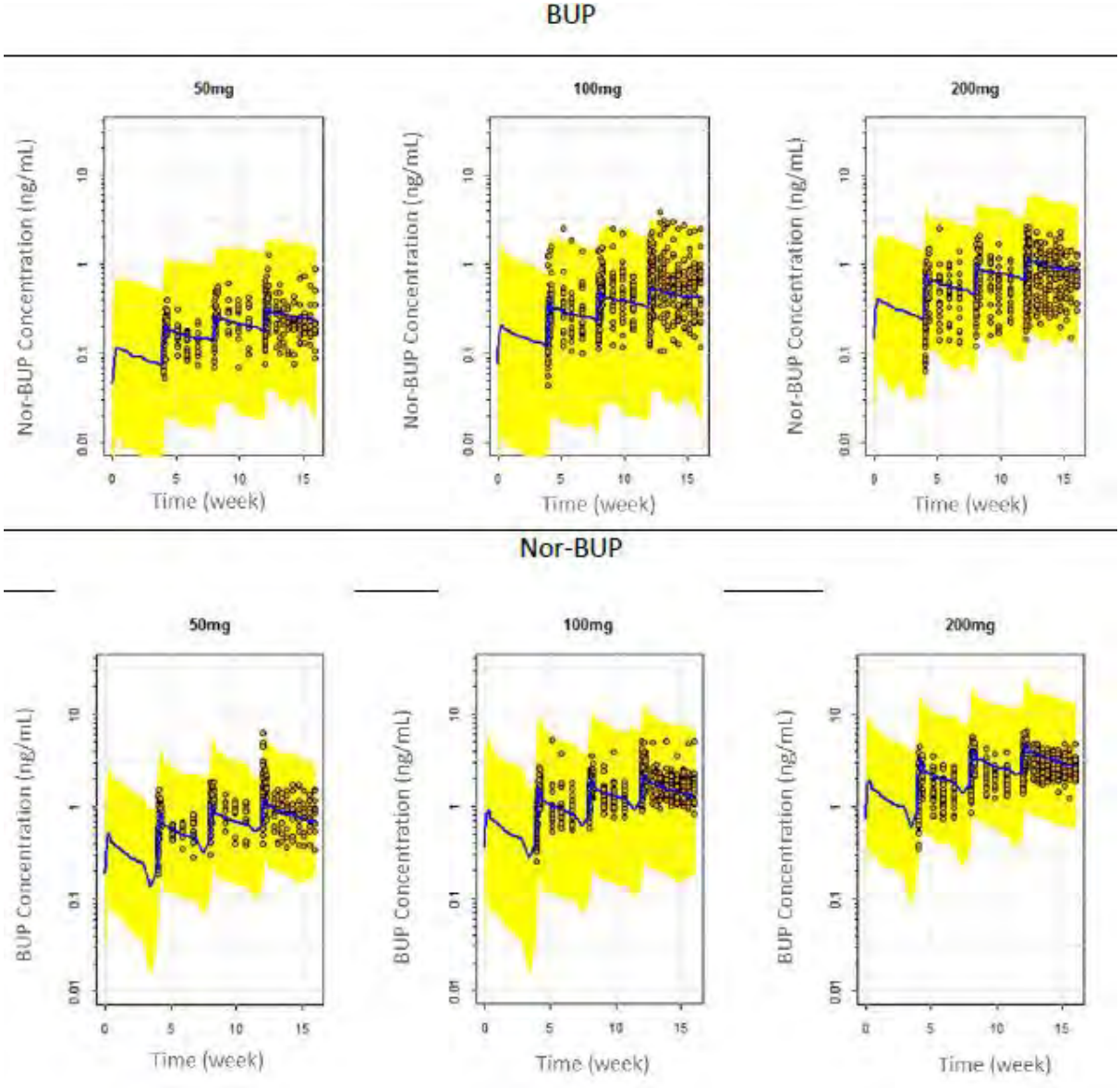


The blue lines are the median predictions, and the shaded yellow areas are the 2.5th and the 97.5th percentiles of the simulated data
Source: Figure 5

The simulated plasma concentrations of BUP and Nor-BUR after repeated SC injections of Sublocade were computed and compared with the observed data collected in the multiple ascending dose study 12-0005 to evaluate the predictive performances of the population PK model developed using the Study 11-0020 data.

In comparison between the simulated concentrations of BUP and Nor- BUP stratified by dose with the observed concentrations in the study 12-0005, the sponsor felt the result indicates the good predictive performances of the population PK model.

Figure 35 Final Model Without Outliers –Simulated Plasma Concentrations of Buprenorphine (BUP) and Norbuprenorphine (Nor-BUP) Stratified by Dose after Repeated Doses of Sublocade (50 mg, 100mg and 200mg) Every 28 Days



The blue lines represent the median predictions, the shaded yellow areas are the 2.5th and the 97.5 th percentiles of the simulated data, and the orange dots the observed concentration in the MAD study (RB-US- 12-0005). Source: Figure 8

The sponsor then undertook a comparison between the level of buprenorphine and the associated μ-opioid receptor occupancy obtained with Probuphine at clinical doses. Probuphine is a subdermal implant not on the ARTG.

21.1.3.3. Pop PK model & Simulation study INDV6000-m03 (12-0005)

For more information on Study 12-0005 see 21.1.1.3.

The main objective of this population PK modelling project was to inform the design of the clinical phase III program in treatment-seeking opioid-dependent subjects by defining and validating population PK model based on study 12-0005.

A total of 89 subjects with 5492 PK measurements were included in the analysis dataset.

Based on analysis of the semi-logarithmic scatter plots of the buprenorphine plasma concentrations vs. time, repeated daily administrations of Subutex during the dose stabilization period (Day -5 to Day -1) were described by a two-compartment model with first-order absorption.

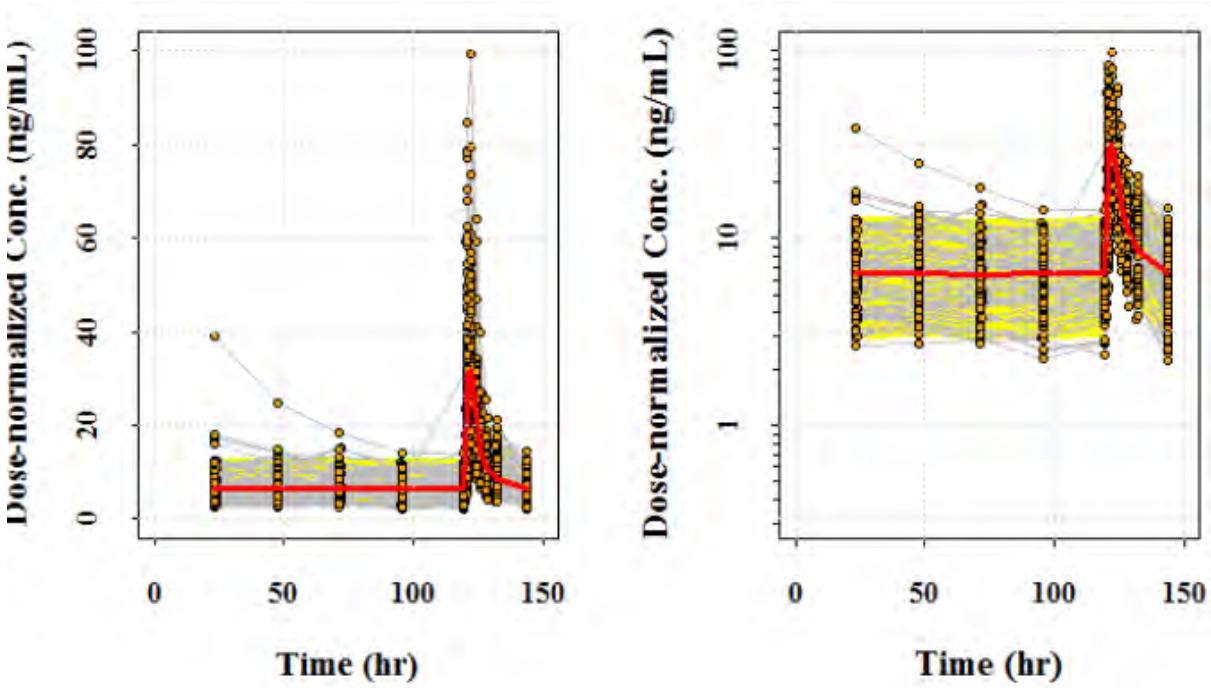
The double-peak kinetics of Sublocade suggested that the likely PK model needed to account for a dual absorption process:

- the first one associated with a rapid delivery from the injection site (first-order absorption process) and
- the second one associated with the slow delivery from the ATRIGEL Delivery System (delayed delivery process described by a transit compartment absorption model).

For disposition the same two-compartment model as for Subutex was used.

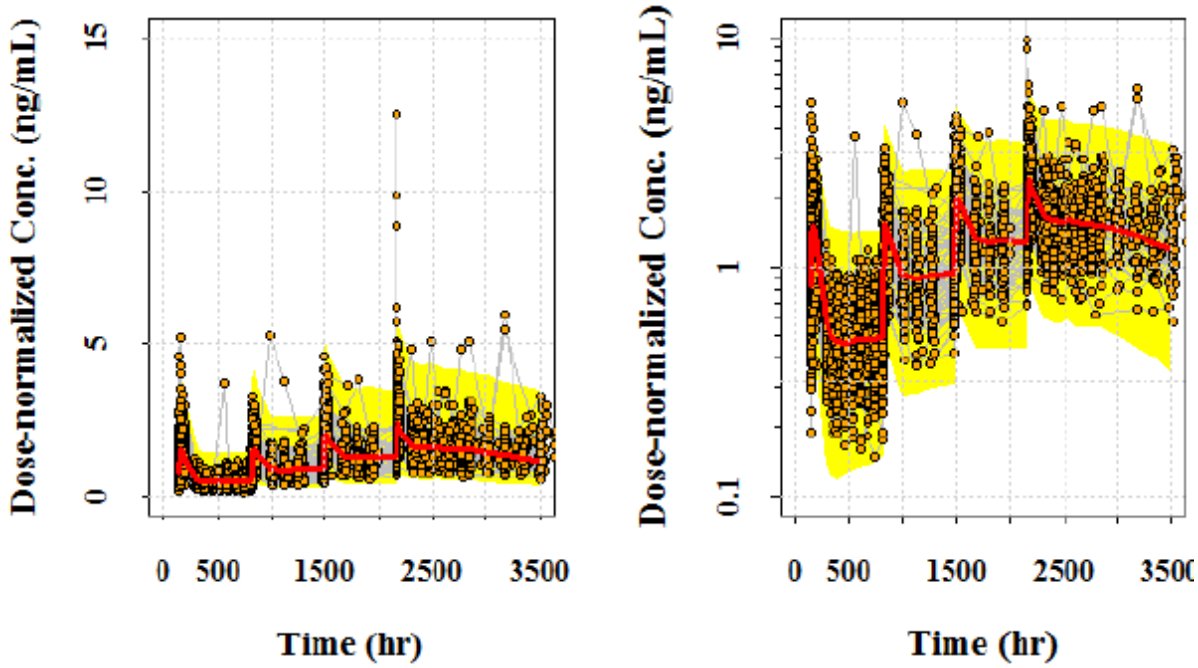
Visual predictive check method was utilized to evaluate the adequacy of the base model, including the effects of statistically significant covariates.

Figure 36 Base model – Dose-normalized Visual Predictive Checks for buprenorphine during the run-in phase with Subutex.



Left: normal scale. Right: semi-log scale. Source: Figure 11

Figure 37 Base model – Dose-normalized Visual Predictive Checks for buprenorphine during Sublocade treatment

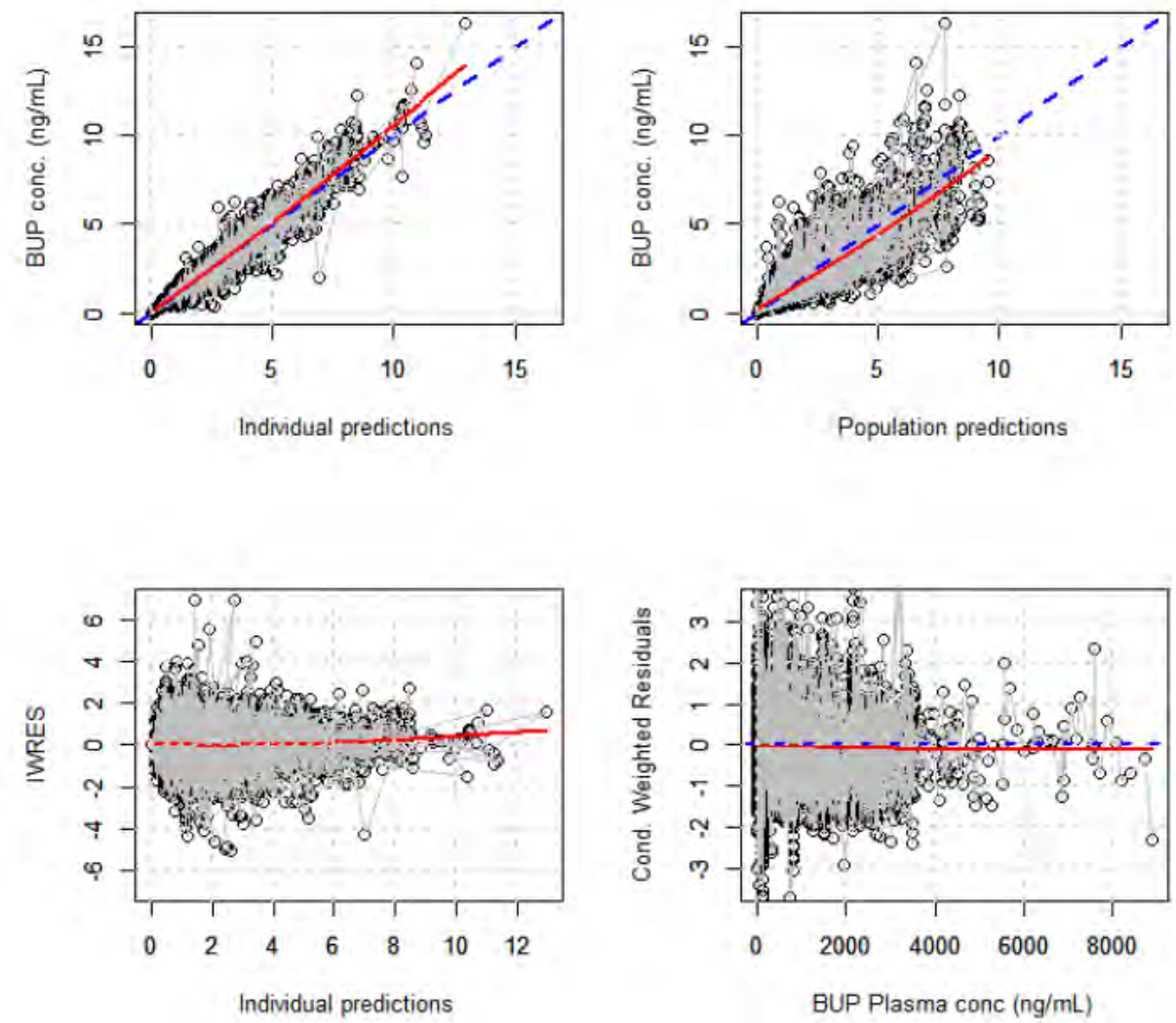


Left: normal scale. Right: semi-log scale. Source: Figure 12

In covariate analysis race was found to significantly affect the V_2[60] value and age was found to affect the k_{12}[61] value in the Subutex model. In the Sublocade model, BMI was found to significantly affect the ka_2[62] value, the rate of absorption decreased with the increase of the BMI value. The expected change in the buprenorphine plasma concentrations associated with the change in the covariate values appears of modest clinical relevance when this change is compared to the level of inter-individual variability estimated in the population PK analysis.

[60] Subutex: apparent volume of distribution of the central compartment
[61] Subutex: first-order absorption rate constant
[62] Sublocade first-order transfer rate constant from depot to the transit compartments

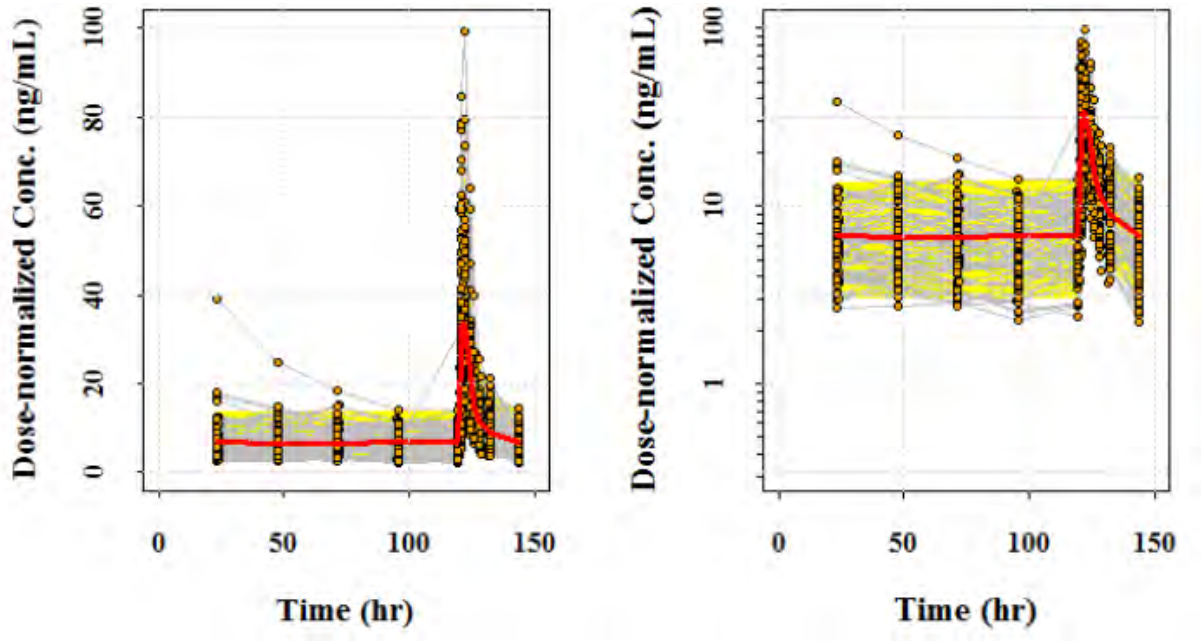
Figure 38 Goodness of fit plots for the final population PK model of buprenorphine (BUP)



Source: Figure 17

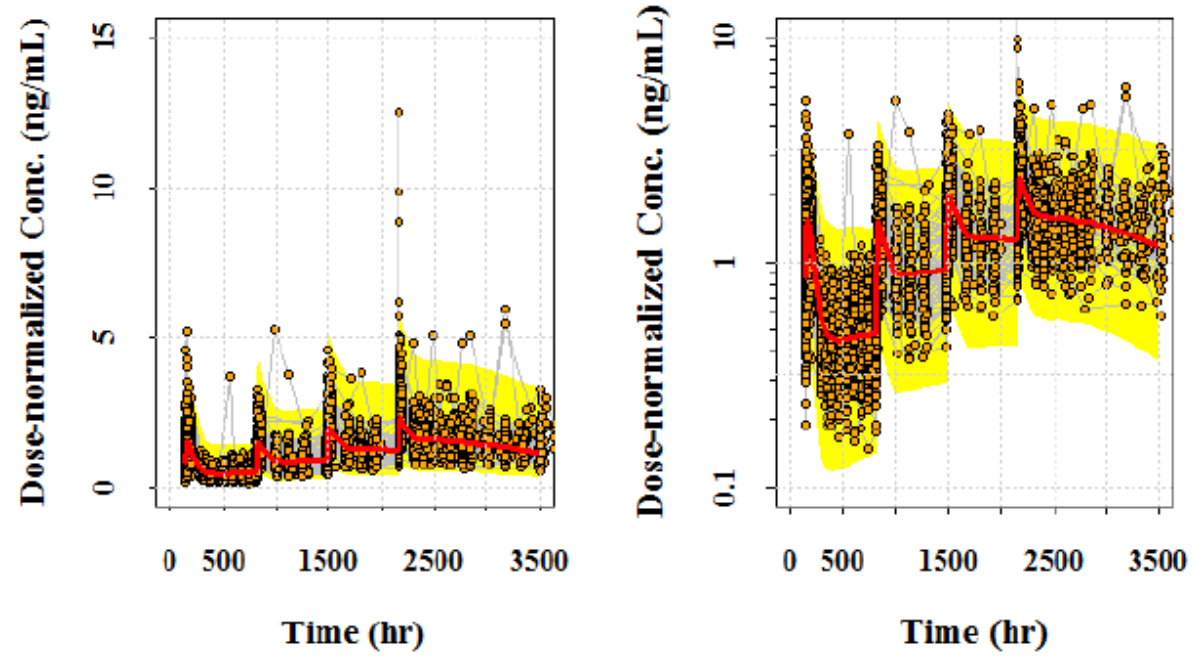
The final model performance/validation and stability was assessed using visual predictive checks.

Figure 39 Final model – Dose-normalized Visual Predictive Checks for buprenorphine during the run-in phase with Subutex.



Left: normal scale. Right: semi-log scale. Source: Figure 18

Figure 40 Final model – Dose-normalized Visual Predictive Checks for buprenorphine during Sublocade treatment



Left: normal scale. Right: semi-log scale. Source: Figure 19

When the relationship between race and V_2 was replaced by the relationship between age and V_2 overall similar fit and parameter estimates were achieved.

21.1.3.4. Pop PK and exposure-response analyses INDV-6000-M04 (Studies 12-005 & 13-0001)

For more information see 21.1.1.3

A population PK model describing simultaneously buprenorphine plasma concentrations after SC injection of Sublocade and sublingual (SL) administration of buprenorphine SL products (Subutex SL tablet or Suboxone SL film) developed from the pooled data of the Phase IIA study (12-0005) and the Phase III double-blind efficacy study (13-0001).

Objectives

i. To develop a population PK model describing buprenorphine plasma concentration-vs-time profiles following repeated Sublocade SC injections and to assess the influence of selected subject characteristics on the PK of Sublocade,

ii. To develop exposure-response relationships between buprenorphine plasma concentration and the selected clinical efficacy variables,

iii. To assess the influence of selected subject characteristics on the PK/PD of Sublocade.

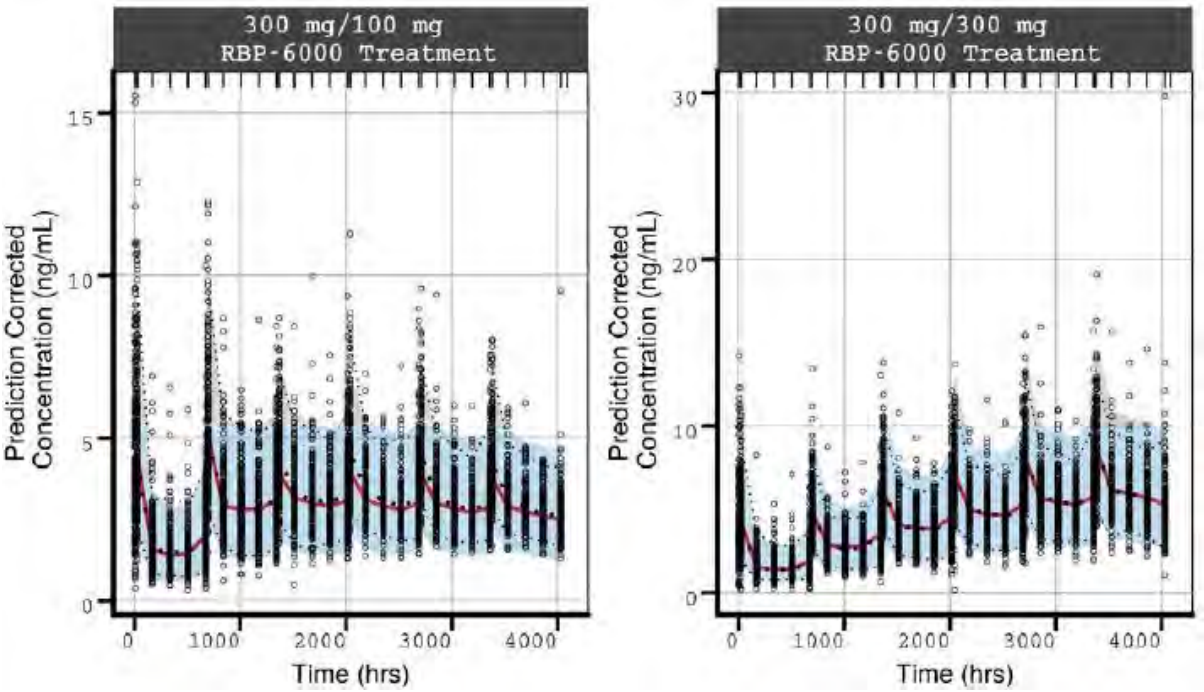
Data included 17,235 observations in 507 subjects from Studies 12-005 & 13-0001 (all 15 subjects from Site 20 in the Phase III efficacy study were excluded from the PK and PK/PD analyses due to site compliance issues.

A non-linear mixed effects modelling approach was used to describe the buprenorphine plasma concentration vs. time profiles following administration of SL buprenorphine (Subutex SL tablet, Suboxone SL film) and SC injection of Sublocade.

Unlike the previous analysis where separate compartmental models were used for Subutex and Sublocade, here a same disposition model was used to fit Subutex and Sublocade data in order to address the flip-flop phenomenon associated with the slow release of buprenorphine from the SC depot. The model was parametrized in clearances and volumes of distribution. The absorption of Sublocade was modelled using the same dual absorption model as previously described (INDV6000-m03 see 21.1.3.3), with the exception that the fraction of Sublocade absorbed by fast (F_2) or slow (F_3) process was not determined by the absorption rate constants (k_{24} and k_{36}) of the two pathways but was estimated.

A total of 17235 observations in 507 subjects were used for population PK modelling.

Figure 41 Prediction-Corrected Visual Predictive Checks for Sublocade Treatment in Study 13-0001



The bold black dotted line represents the median of the observed data; the red solid line represents the median of simulated data; the upper and lower black dotted lines delineate the 90% prediction intervals of the observed data; the light blue shaded area delineates the 90% prediction intervals of the simulated data
Source: Figure 5

A covariate analysis found BMI and sex were the only 2 statistically significant covariates identified with BMI having the only clinically relevant effect (on the early peak of buprenorphine following SC injection – rapid absorption parameter k_{24}). Dose adjustment was not considered necessary.

Illicit Opioid Use

Illicit opioid use was assessed in Study 13-0001 as a composite variable based on urine drug screen (UDS) results combined with subjects self-reports for illicit opioid use as documented on the Timeline Follow back (TLFB) interview.

Illicit opioid use was analysed as a binary variable using logistic regression modelling. Observed data (Figure 42) indicated a clear relationship with buprenorphine plasma concentration that was modelled using an E_{max} relationship. For opioid use, the plateau for maximal response was reached at approximately 2ng/mL, in agreement with a mu-opioid receptor occupancy level of 70%.(21.1.2.1 Study 13-002)[63] Major covariates were identified:

• Subjects using opioids by injectable route at baseline showed a 3.6-fold higher EC_{50} compared to subjects using opioids by non-injectable route at baseline;

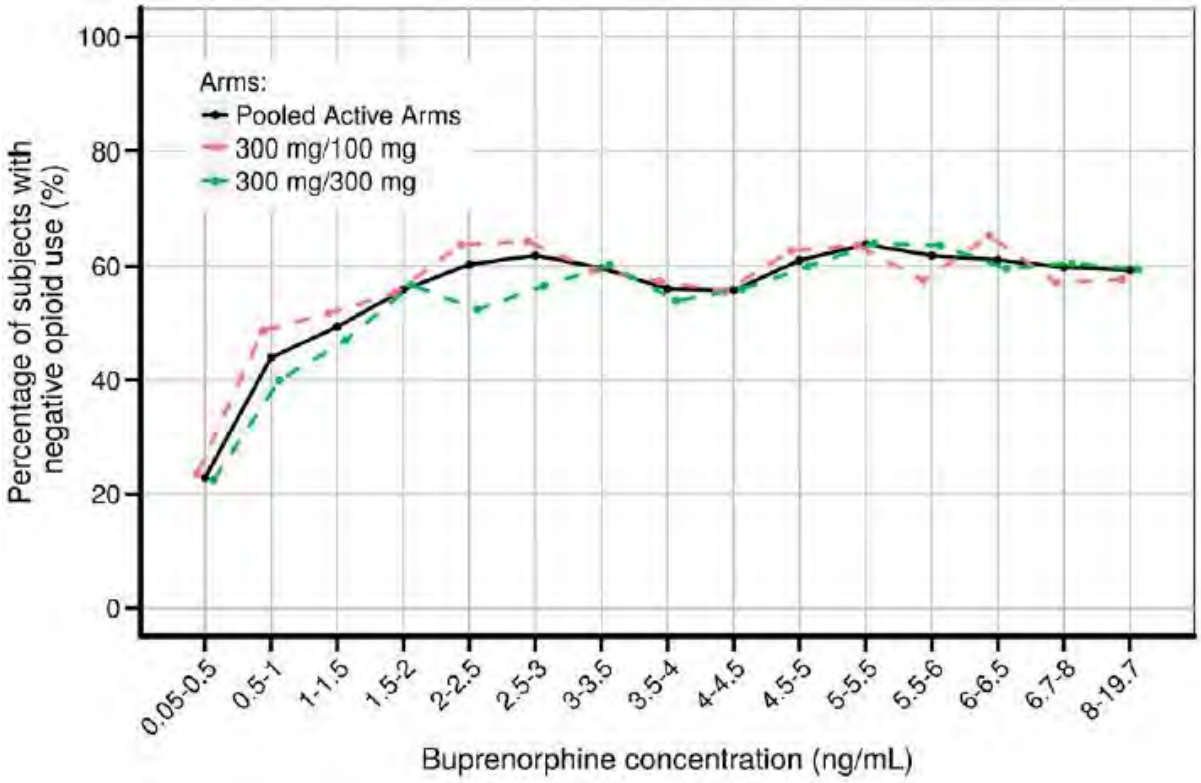
• Subjects who were employed at baseline showed 43% higher maximal drug efficacy (E_{max}) compared to unemployed subjects at baseline;

[63] 'Mu-opioid receptor occupancy predictions were derived using the PK/mu-opioid receptor occupancy model previously published in Nasser et al. (2014)' A Population Pharmacokinetic and Pharmacodynamic Modelling Approach to Support the Clinical Development of RBP-6000, a New, Subcutaneously Injectable, Long-Acting, Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Dependence." Clinical 486 Pharmacokinetics 53 (9): 813–24. doi:10.1007/s40262-014-0155-0.

• Black or African American subjects showed a 31% lower maximal drug efficacy (E_{max}) compared to white subjects and others;

• Subjects with TC and TT genotype for the single nucleotide polymorphism (SNP) rs678849 on the delta-opioid receptor (OPRD1) had their EC50 reduced by 71% and 94%, respectively.

Figure 42 Relationship Between the Percentage of Subjects with Negative Opioid Use and Buprenorphine Plasma Concentration (Study 13-0001).



Solid black curve; percentage of subjects with negative opioid use from the pooled 300 mg/300mg and 300 mg/100mg treatment arms. Dashed curves: percentage of subjects with negative opioid use in the 300 mg/300mg arm (green curve) and 300 mg/100mg arm (red curve)
Source: Figure 9

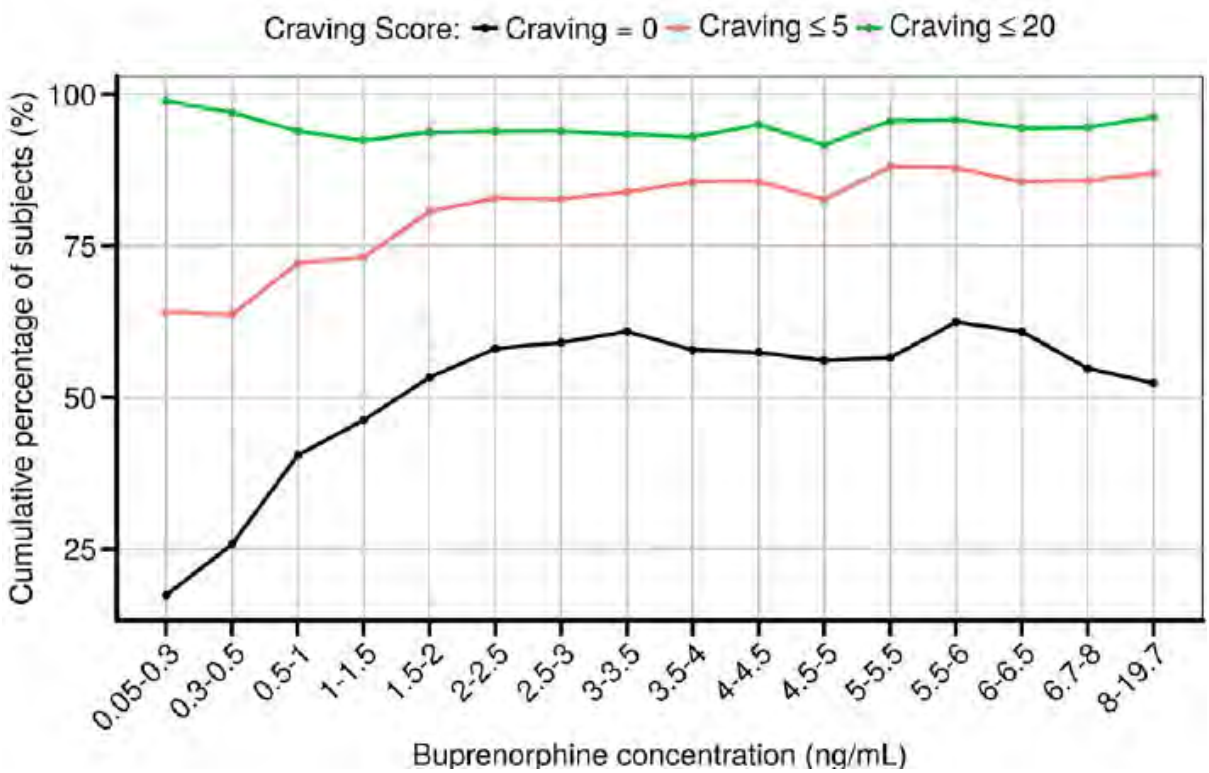
Opioid craving:

Opioid craving was assessed in Study 13-0001 using the Opioid Craving Visual Analogue Scale (VAS).[64]

Categorized data were analysed as an ordinal variable using logistic regression modelling. Observed data (Figure 43) indicated a clear relationship with buprenorphine plasma concentration that was modelled using an E_{max} relationship. For opioid craving the plateau for maximal response was reached at approximately 3ng/mL, consistent with a mu-opioid receptor occupancy level of 75%.

[64] Opioid Craving VAS scores were categorized into 4 ordered categories (0, 1-5, 6-20 and >20) for the purpose of the PK/PD analysis

Figure 43 Relationship Between the Percentage of Subjects in Each Category of Opioid Craving VAS Score and Buprenorphine Plasma Concentration (Study 13-0001).



Curves: percentage of subjects with a craving score of zero (black curve), below 5 (red curve) and below 20 (green curve) form the pooled 300 mg/300mg and 300 mg/100mg treatment arms. Source: Figure 10.

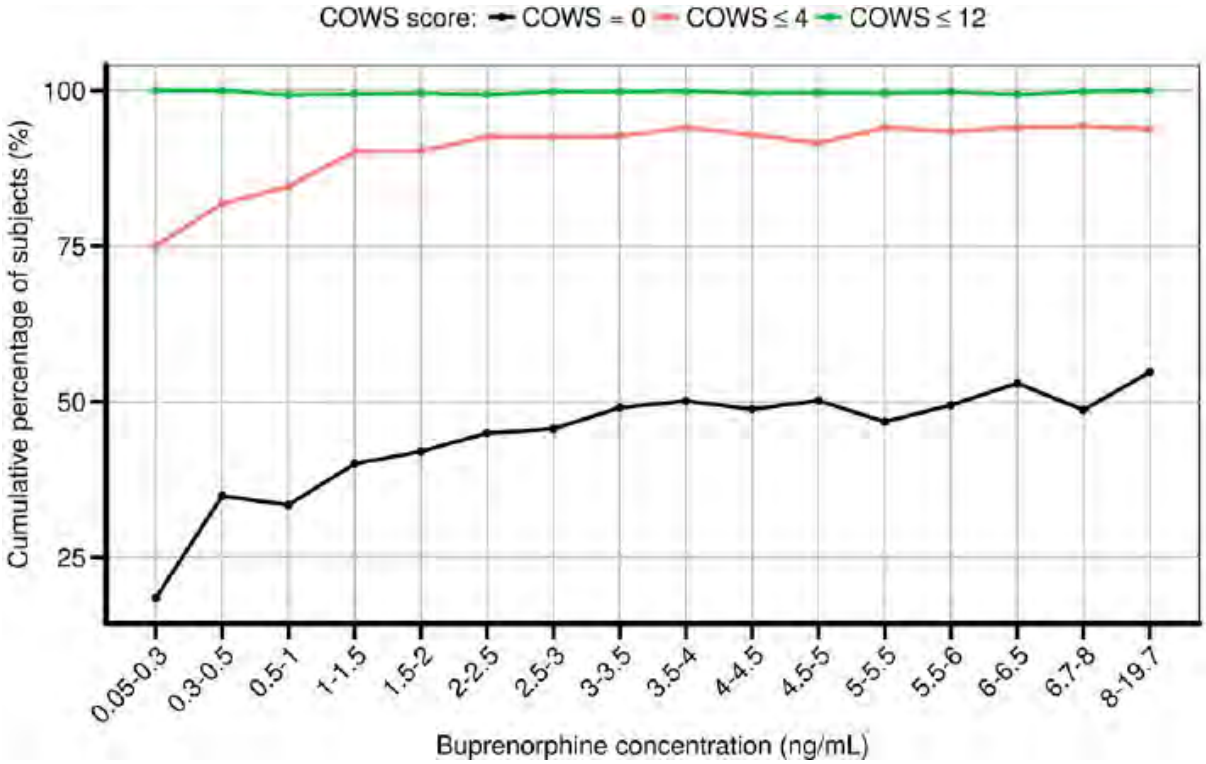
BMI was the only significant covariate identified but had no clinical relevance.

Opioid craving was identified as a major predictor of dropout: an opioid craving score > 20 was associated with an increase in dropout rate of up to 3.0 to 3.6-fold in active treatment arms and placebo arm, respectively, compared to craving ≤ 5.

Clinical Opiate Withdrawal Scale and Subjective Opiate Withdrawal Scale

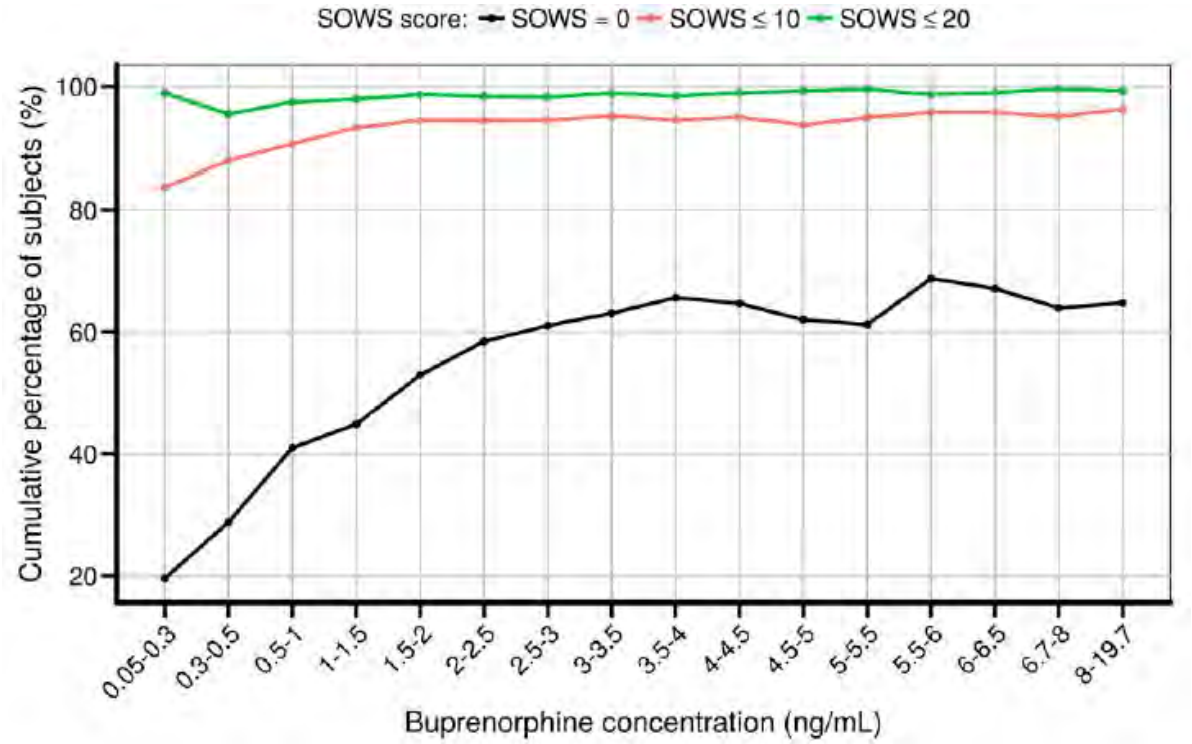
Exposure-response relationships were investigated for COWS (Figure 44) and SOWS (Figure 45). Visually there was a relationship with buprenorphine plasma concentration consistent with an E_{max} model. Empirically, the plateau corresponding to maximal response was reached at approximately 4ng/mL for both COWS and SOWS, consistent with a mu-opioid receptor occupancy level of 78%.

Figure 44 Relationship Between the Cumulative Proportion of Subjects below COWS Score Cut-offs and Buprenorphine Plasma Concentration (Study 13-0001).



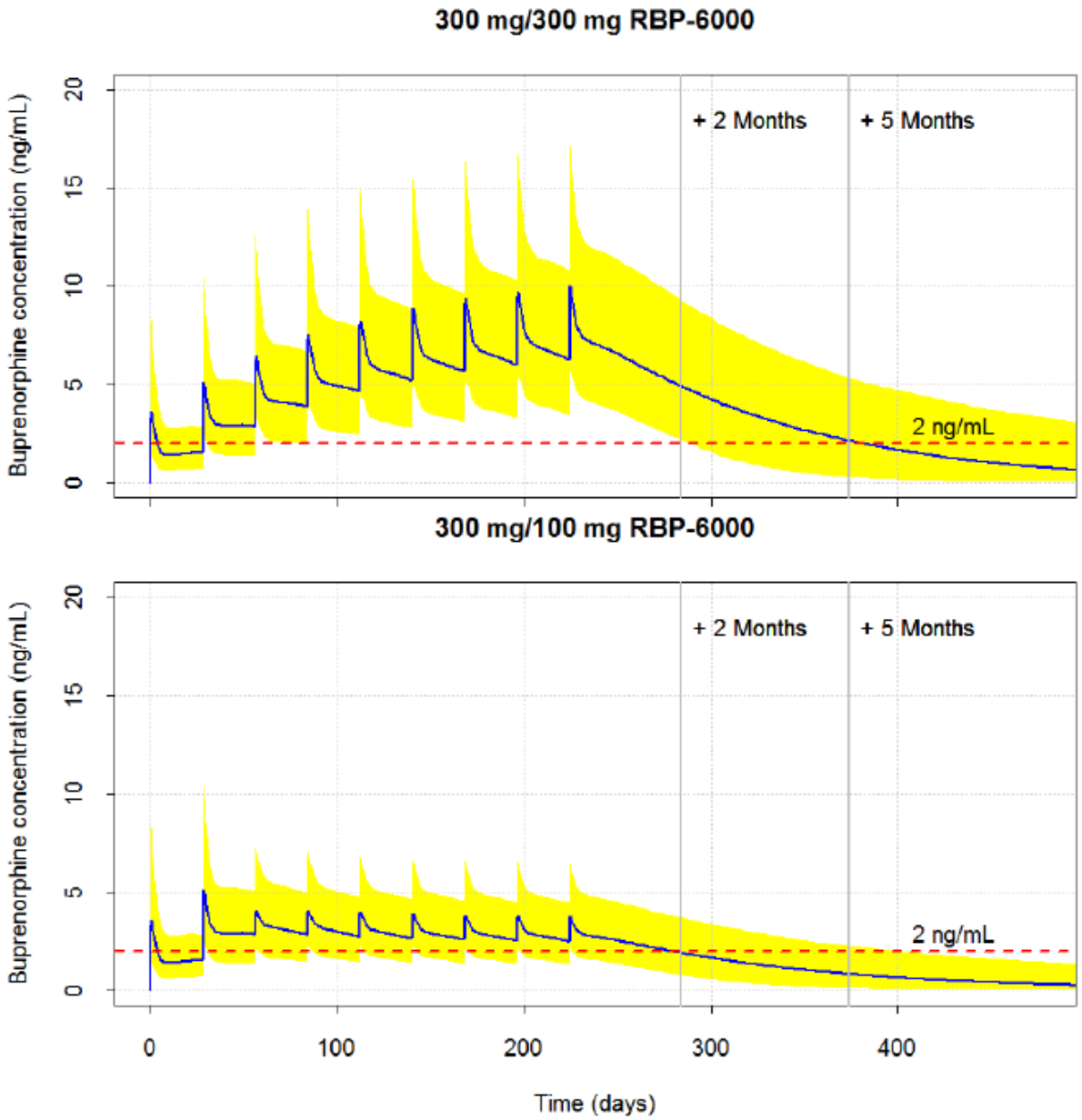
23Solid lines: percentage of subjects with no withdrawal (black curve), a COWS score ≤ 4 (red curve), and a COWS score ≤ 12 (green curve) Source: Figure 22

Figure 45 Relationship Between the Cumulative Proportion of Subjects below Each SOWS Score Cut-offs and Buprenorphine Plasma Concentration (Study 13-0001).



25Solid lines: percentage of subjects with no withdrawal (black curve), a SOWS score ≤ 10 (red curve), and a SOWS score ≤ 20 (green curve) Source: Figure 23

Table 46 Predicted Decrease in Buprenorphine Plasma Concentrations for the 300mg/300mg and 300 mg/100mg Dosing Regimens of Sublocade after the Last SC Injection



Blue curve = medians of the simulated data; Shaded yellow area = 90% prediction intervals of simulated data
A total of 9 SC injections were simulated. The horizontal red dashed line indicates the 2ng/mL minimum concentration required for opioid blockade, as established from modelling and simulation and confirmed by the findings of the opioid blockade study (13-0002). Model used for simulation: INDV-6000-M04 Table 12 Source: Figure 44

21.1.3.5. PopPK analysis NDV-6000-M05 (Studies 12-0005, 13-0001 and 13-0003)

Population pharmacokinetics of Sublocade in treatment- seeking subjects with opioid use disorder combined analysis of studies 12-0005, 13-0001 and 13-0003.

Objectives:

To describe buprenorphine plasma concentrations measured in Study 13-0003 from roll-over and *de novo* subjects for whom PK samples were collected, using the previously developed population pharmacokinetic (PK) model from the combined analysis of Studies 12-0005 and 13-0001.

To refine model estimation from the pooled data of the multiple ascending dose study (12-0005) and the two Phase III studies (13-0001 and 13-0003).

This previously developed population PK model was applied with all parameters fixed to describe the data in subjects of Study 13-0003 for whom PK samples have been obtained. Standard goodness-of-fit plots were generated to assess the adequacy of model predictions compared to observations. Visual predictive checks were also performed. In a second step, model parameter estimation was refined from the full dataset combining data from the three studies: 12-0005, 13-0001, and 13-0003. No additional covariate analysis was performed since no major deviations from the expected PK were observed.

The previously developed population PK model was applied with all parameters fixed to describe the data in Study 13-0003. Goodness-of-fit plots were plotted and showed that overall, the model was able to describe the buprenorphine plasma concentrations observed in Study 13-0003. Visual predictive checks were also performed, indicating that the previously developed model was able to predict long-term buprenorphine plasma concentrations as observed in Study 13-0003.

Since the goodness-of-fit plots and visual predictive check plots did not reveal any major deviation from the expected plasma concentration ranges, the previously developed model was re-estimated using the full dataset combining data from the three studies: 12-0005, 13-0001, and 13-0003. The estimated PK parameter values and their associated variabilities were similar to those of the previous developed model, indicating that the model was robust in predicting data from 570 subjects across 3 different studies and up to 1 year of exposure.

21.1.3.6. INDV-6000-M06 ketoconazole interaction modelling & simulation

Drug-drug interaction modelling & simulation for Subutex and Sublocade with ketoconazole.

The objectives of the modelling work were:

1) to model buprenorphine and norbuprenorphine plasma exposure following SL administration of Subutex and SC injection of Sublocade, to estimate SL and SC bioavailability parameters as well as first-pass effect for SL route,

2) to model the effect of ketoconazole on buprenorphine and norbuprenorphine plasma exposure with the separation of the effects on first-pass and systemic clearance,

3) to predict the effect of ketoconazole on the plasma exposure of Sublocade (for which there is no first-pass effect).

Data used were:

- Individual AUCs from Study 12-0005 and Study P01242.
- Data from the literature relative to physiological blood flows (e.g. hepatic blood flow) as well as buprenorphine systemic clearance (hepatic coefficient of extraction), fraction of buprenorphine metabolized by the CYP 3A4 pathway, and blood-to-plasma ratio.

The following model assumptions were considered:

1) Buprenorphine is extensively metabolized by N-dealkylation to norbuprenorphine primarily through CYP3A4. For the purpose of the analysis, it was assumed that CYP3A4 is the sole cytochrome P450 involved in the conversion of buprenorphine to norbuprenorphine. In the present analysis the fraction of buprenorphine metabolized (f_{met}) was fixed to 0.63, as estimated from Kilford et al. (2009),[65] and the hepatic extraction ratio (E_H) was fixed to 0.9.

[65] Prediction of drug clearance by glucuronidation from in vitro data use of combined cytochrome P450 and UDP- glucuronosyltransferase cofactors in alamethicin-activated human liver microsomes. Kilford PJ, et al Drug Metab Dispos. 2009 Jan;37(1):82-9.

Buprenorphine is a high extraction ratio drug and due to variability in the Q_H, it was decided in previous work to fix E_H to 0.9 which resulted in adequate *in vitro/in vivo* extrapolation.

2) The hepatic blood flow (Q_H) was fixed to 87L/hr (1450mL/min/70 kg);

3) Buprenorphine systemic clearance is essentially equal to buprenorphine hepatic clearance. This is a reasonable assumption since only 1 % of buprenorphine is excreted unchanged in urine (Suboxone sublingual film, Prescribing Information, June 2016).

4) The coefficient of extraction of buprenorphine in the intestines (E_G) was assumed equal to the hepatic coefficient of extraction (E_H).

5) Blood-to-plasma ratio for buprenorphine was set equal to 1 as assumed in earlier work since buprenorphine is a basic compound.

Individual AUCs of buprenorphine and norbuprenorphine from Study 12-0005 following repeated SC injections of Sublocade and administrations of Subutex SL tablets were fitted together with individual AUCs of buprenorphine and norbuprenorphine from Study P01242 in the absence of ketoconazole (control data).

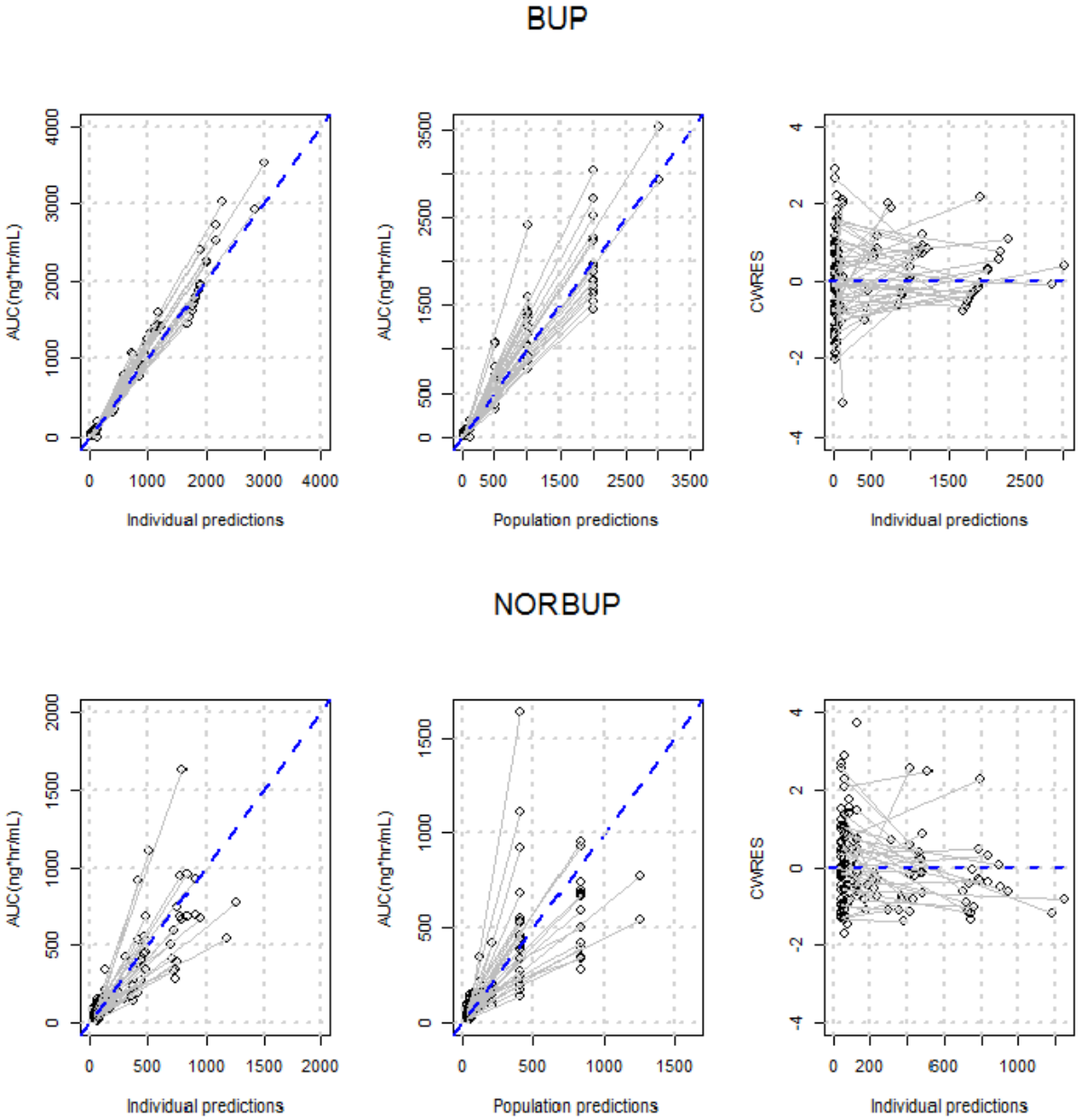
Individual AUCs of buprenorphine and norbuprenorphine from Study P01242 in the presence of ketoconazole were added to the dataset to estimate the effect of ketoconazole on the hepatic clearance component responsible for the conversion of buprenorphine to norbuprenorphine.

The initial model evaluated was the final model of the Step 1 analysis with the inclusion of the ketoconazole effect. The subsequent models evaluated the effect of an IIV term on the model parameters in a step-wise fashion.

The model (Run 06) was retained of the final model.

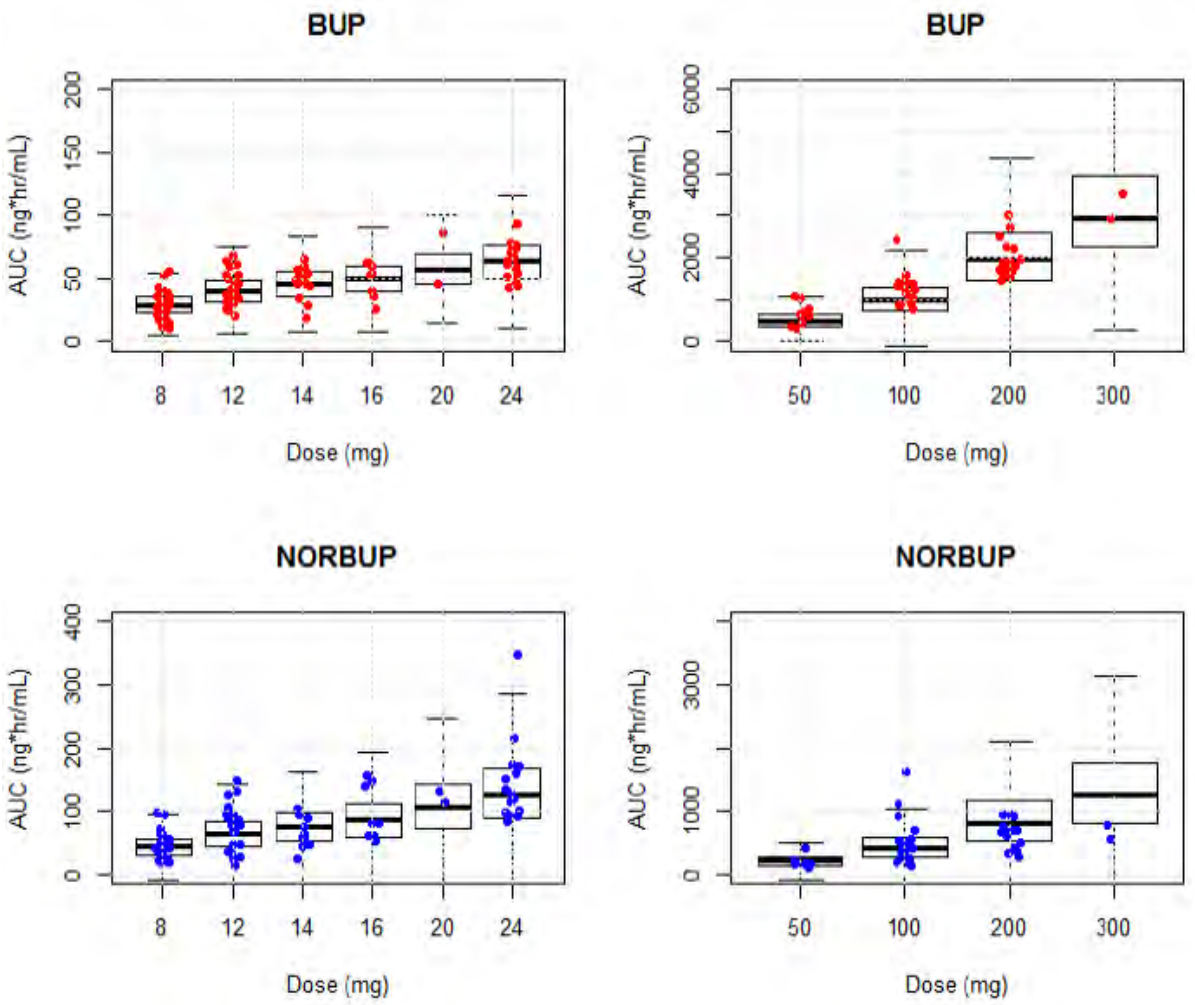
The model predicted a comparatively modest increase (60%) in buprenorphine AUC with concomitant administration of ketoconazole.

Figure 46 Step 2 Analysis: Goodness-of-fit plots for buprenorphine (BUP) and norbuprenorphine (NORBUP)



Dashed blue line: identity line or horizontal line for y=0; dots: observed data; grey line: links individual data. Source:. Figure 6

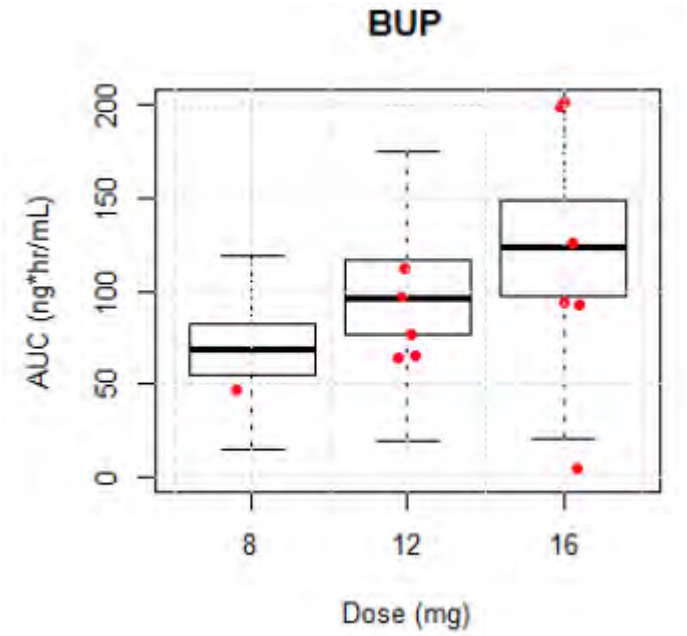
Figure 47 Step 2 Analysis (data without ketoconazole): Visual predictive checks for buprenorphine (BUP) and norbuprenorphine (NORBUP) stratified by dose



Left: Subutex. Right: Sublocade. Source: Figure 7

The red and blue dots represent the observed values. An artefactual spread of the observed AUC values around the nominal dose values has been introduced by the graphical plot procedure in order to better apprehend the dispersion of the data.

Figure 48 Step 2 Analysis (data with ketoconazole): Visual predictive checks for buprenorphine (BUP) stratified by dose



The red dots represent the observed values. Source: Figure 8

Simulations were conducted to predict plasma exposure of buprenorphine and norbuprenorphine following concomitant administrations of ketoconazole (400mg/day) and:

- Sublocade (100mg or 300mg) under steady-state conditions (following 4 SC injections of Sublocade separated by 28 days),
- Subutex SL (8mg, 12mg or 16mg per day) under steady-state conditions.

Table 47 Descriptive statistics on the distribution of the AUC values for Sublocade (100mg and 300mg) following 4 SC injections separated by 28 days, in presence and in absence of ketoconazole, for buprenorphine (BUP) and norbuprenorphine (NORBUP)

Dose	Analyte	Ketoconazole	Mean AUC (ng*hr/mL)	Std Dev	Median	Minimum	Maximum
100 mg	BUP	Without	930.97	349.73	914.15	111.57	2267.30
		With	1471.63	583.33	1399.90	83.33	3384.10
	NORBUP	Without	394.16	192.91	369.33	2.84	1114.30
		With	162.28	77.51	157.23	0.91	539.81
300 mg	BUP	Without	2824.51	1055.66	2746.65	73.01	6298.70
		With	4507.17	1682.55	4381.00	36.51	10741.00
	NORBUP	Without	1228.56	585.07	1177.50	22.07	3699.00
		With	493.42	254.88	474.71	4.22	1341.70

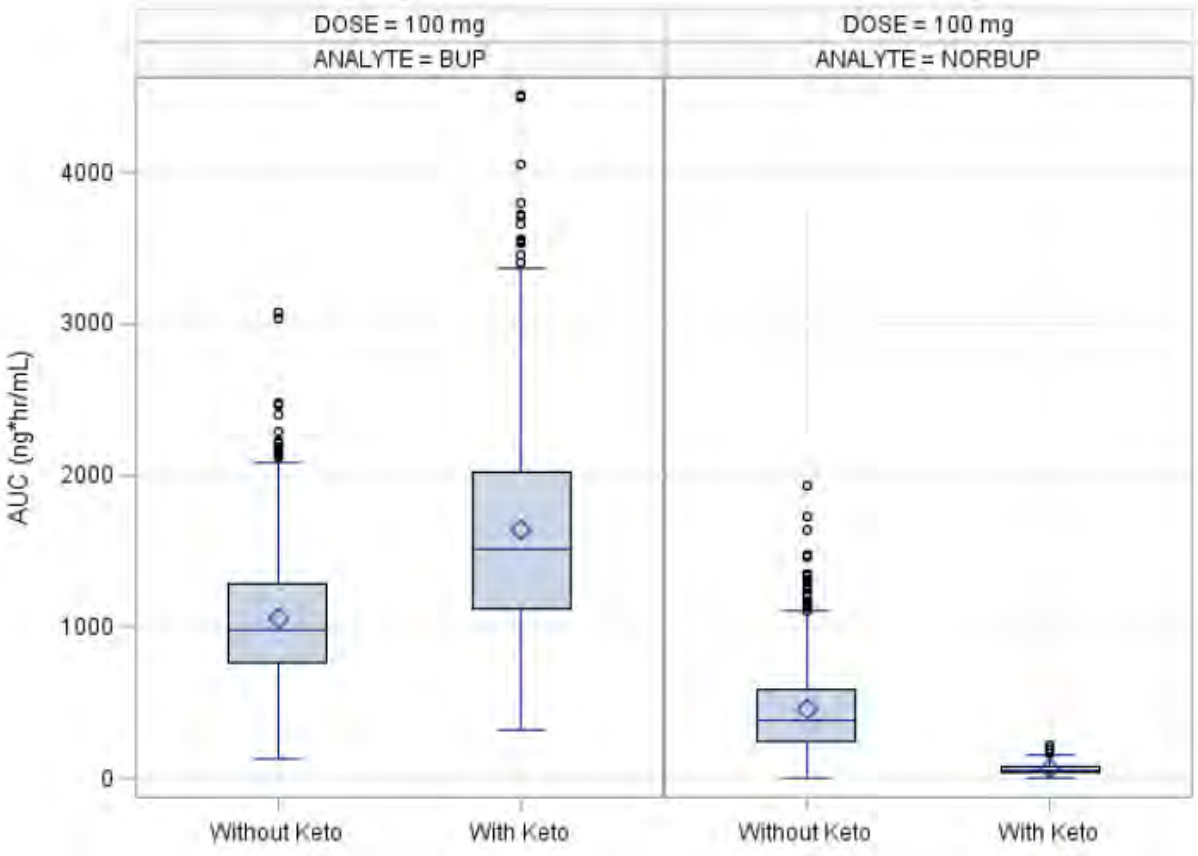
Source: Table 7

Table 48 Ratio of the AUC values for Sublocade in presence and in absence of ketoconazole for buprenorphine (BUP) and norbuprenorphine (NORBUP)

Dose	Analyte	AUC ratio (with keto/without keto)
100 mg	BUP	1.58
	NORBUP	0.41
300 mg	BUP	1.60
	NORBUP	0.40

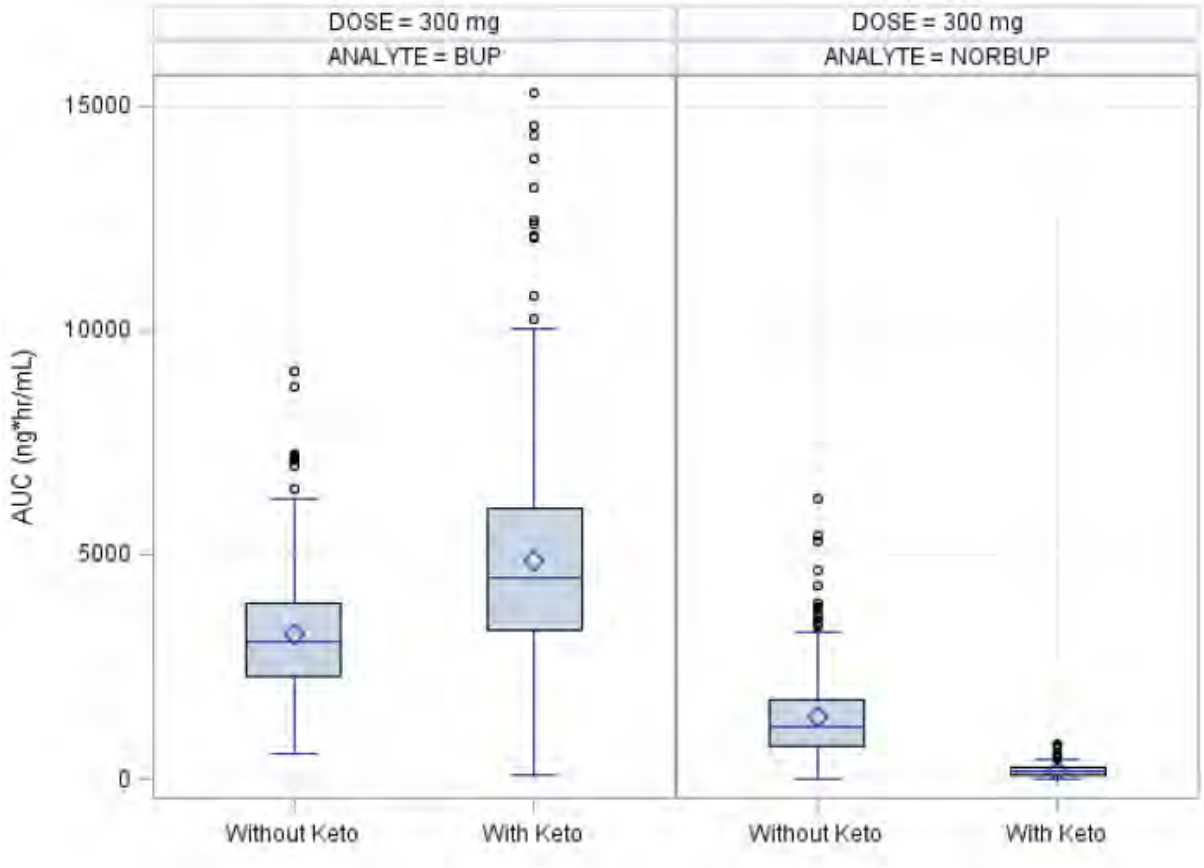
Source: Table 9

Figure 49 Sublocade dose of 100mg. Boxplots of the simulated AUC values following 4 subcutaneous injections of Sublocade separated by 28 days, in presence and in absence of ketoconazole, for buprenorphine (BUP) and norbuprenorphine (NORBUP)



Source: Figure 9

Figure 50 Sublocade dose of 300mg. Boxplots of the simulated AUC values following 4 subcutaneous injections of Sublocade separated by 28 days, in presence and in absence of ketoconazole, for buprenorphine (BUP) and norbuprenorphine (NORBUP)



Source: Figure 10

21.1.3.7. INDV-6000-M07 in vitro-in vivo Correlation

Modelling & Simulation Report *in vitro-in vivo* Correlation evaluation for Sublocade using a population pharmacokinetic modelling approach

Objectives

a) To develop a population pharmacokinetic (PK) model for Sublocade using pooled data from 2 clinical studies (11-0020 and 12-0005) together with historical intravenous (IV) buprenorphine data (CR87/027) for the purpose of *in vitro-in vivo* correlation (IVIVC) assessment;

b) To simulate the mean cumulative absorption profile (% dose absorbed over time) for a single subcutaneous (SC) dose of 100mg of Sublocade based on model and parameter estimates obtained in Step (a);

c) To correlate the mean cumulative absorption profile (from (b)) with the *in-vitro* extended-release (dissolution) profile corresponding to a representative lot of the drug product

4258 buprenorphine plasma concentrations obtained in 121 subjects were available. Buprenorphine plasma concentrations following IV administration were described by a three-compartment model with first-order elimination.

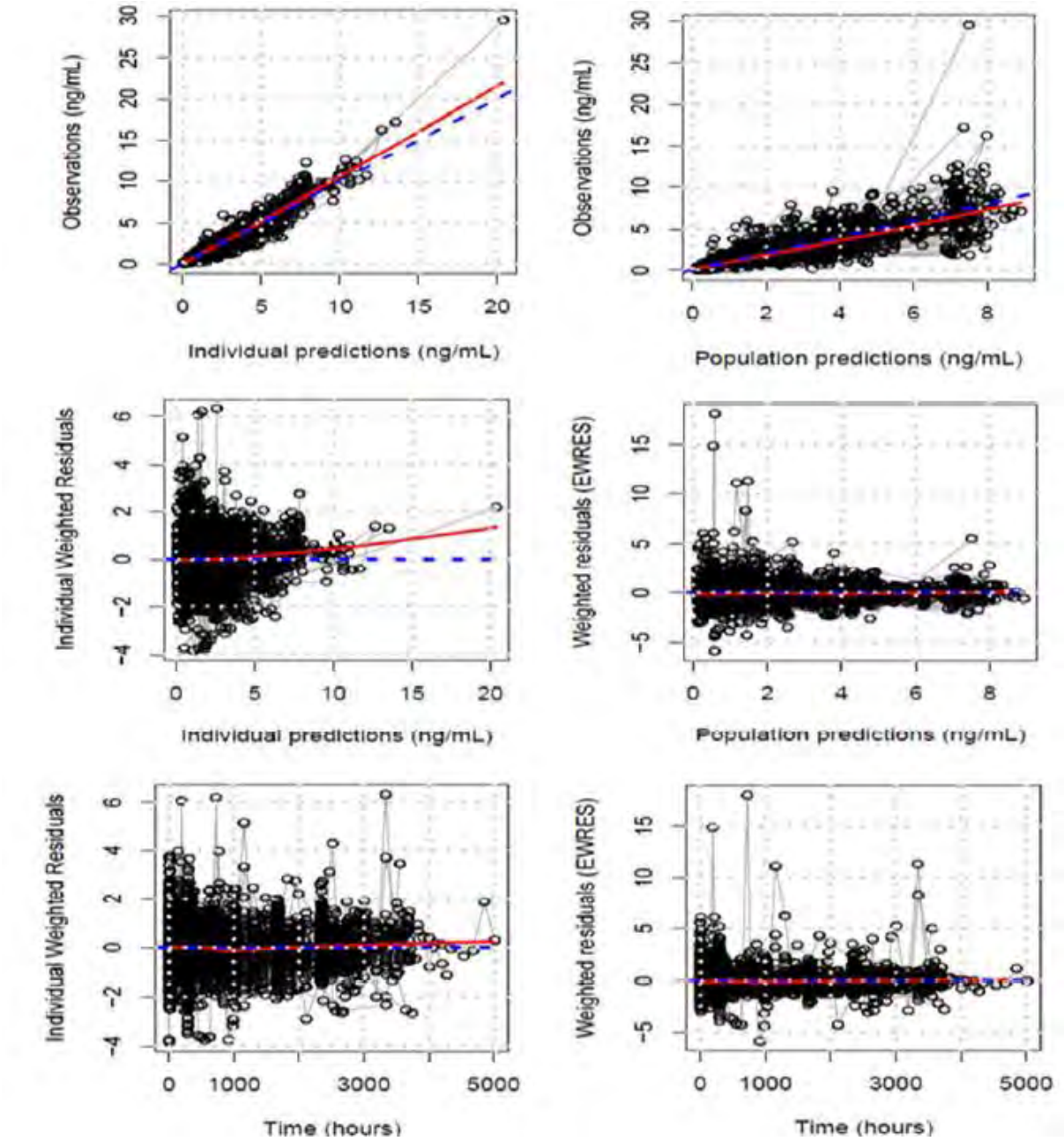
This 3-compartment disposition model was then applied to the analysis of Sublocade and Subutex data in Studies 11-0020 and 12-0005.

A first-order absorption rate constant was used for SL absorption of buprenorphine following administration of Subutex SL tablets.

For Sublocade, the absorption of buprenorphine from the SC injection site was described by a dual absorption model: (i) a first-order absorption to characterize the rapid absorption process associated with the early peak, and (ii) a transit compartment absorption model to mimic the slow delivery of buprenorphine from the SC depot.

Fixed-effect and random-effect parameters for clearance and volumes of distribution were fixed based on the previous estimates obtained by fitting IV data alone. All other model parameters were estimated, with the exception of the variance of FSC (bioavailability of Sublocade) and k_{72} (rate constant from transit to central compartment) which were fixed to 0 and 0.1, respectively.

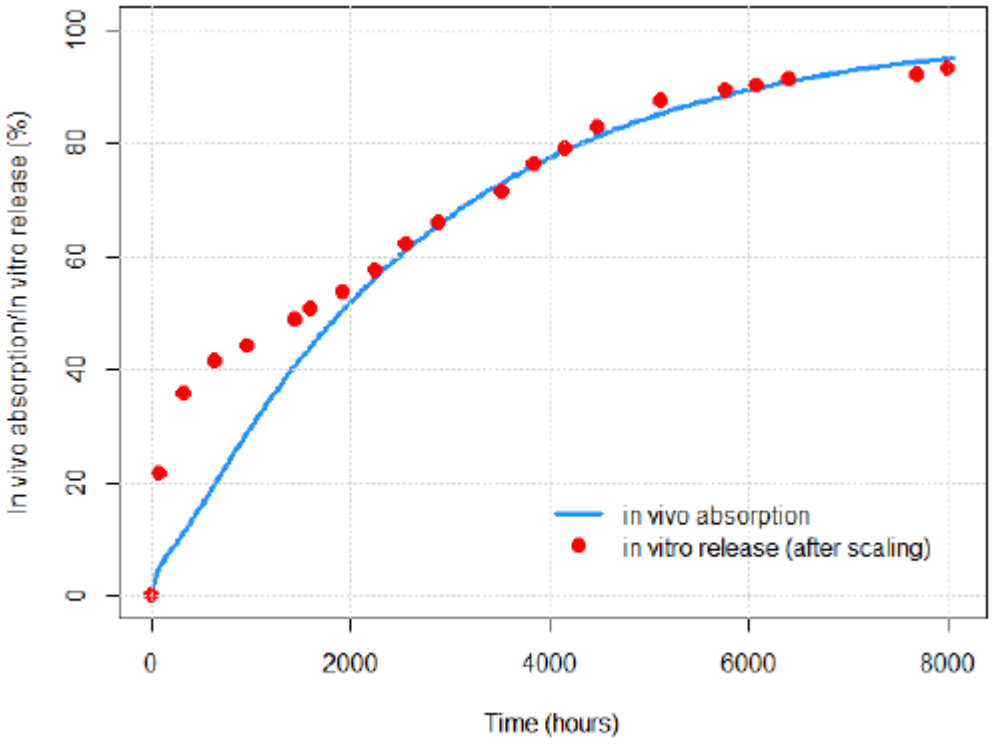
Figure 51 Standard Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Blue dashed line=identity line or y-axis; Red curve=Spline through the data. Data from all studies are shown. Source: Figure 6

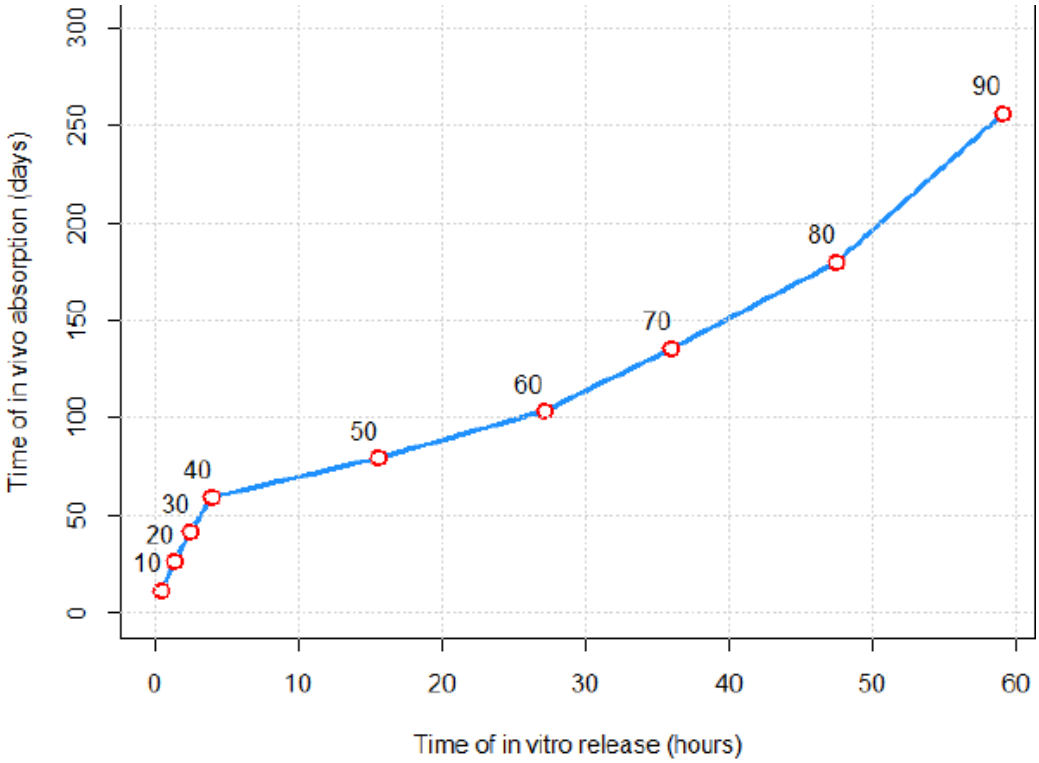
Comparison of *in-vitro* and *in-vivo* data showed a more rapid initial release of drug *in vitro* that was not reflected on the *in-vivo* absorption-time profile. Simple Level A correlation could not be established.

Figure 52 Comparison of Scaled *In-Vitro* Release (Lot 184) and *In-Vivo* Absorption



Blue curve=predicted cumulative absorption profile i*n vivo* based on modelling; Red dots=observed *in-vitro* data
Scaling on both axes was applied to in-vitro data to achieve a reasonable overlay of *in-vitro* and i*n-vivo* profiles Source: Figure 13

Figure 53 Levy Plot Comparing Times to Achieve a Given Percentage of Drug Released *In Vitro* and Absorbed *In Vivo*



Dots correspond to the percentages (10% to 90%) of drug released/absorbed in vitro/in vivo, respectively Source: Figure 14

21.1.3.8. PopPK analysis INDV-6000-Q01 Concentration-QT analysis

Concentration-QT analysis for Sublocade using plasma concentration and ECG data pooled from studies 10-0011, 11-0020, 12-0005, 13-0001, and 13-0006: 1114 subjects.

Objectives:

- To evaluate whether there is a concentration-related effect of buprenorphine and norbuprenorphine on QT interval after accounting for the effect of relevant concomitant medications and illicit drug use on HR and/or QT in opioid-dependent subjects.
- To predict the concentration-related effects of buprenorphine on QTc interval at therapeutic and supra-therapeutic concentration levels.

Matching buprenorphine and norbuprenorphine plasma concentrations and 12-lead electrocardiograms (ECGs) were pooled across clinical studies conducted with Sublocade in opioid-dependent subjects. Concentration-QT models were developed to describe the effects of buprenorphine and norbuprenorphine on corrected QT (QTc) interval, after accounting for the effect of relevant concomitant medications and illicit drug use on heart rate (HR) and/or QT in opioid-dependent subjects.

Table 49 Mean, Median, and 90% CIs for the Geometric C_{max} and the Delta QTc and the Bias-Corrected 90% CI of the Upper Bound

Dose	Geometric Mean C_{max} (ng/mL)			Delta QTc (msec)			
	Mean	Median	90% Confidence Interval	Mean	Median	90% Confidence Interval	Bias-Corrected 90% Confidence Interval
100 mg Q28D	3.44	3.43	3.25 to 3.63	-0.17	-0.16	-0.65 to 0.29	-0.65 to 0.29
300 mg Q28D	8.12	8.12	7.54 to 8.72	-0.40	-0.38	-1.52 to 0.66	-1.52 to 0.67
2x300 mg Q28D	16.2	16.2	15.1 to 17.4	-0.79	-0.75	-3.04 to 1.32	-3.05 to 1.34

Source: Table 3:

After accounting for the covariates that may influence HR and QT in subjects with Opioid Use Disorder an effect of buprenorphine on QT is not seen at therapeutic and supra-therapeutic doses of Sublocade.

22. Attachment: additional evaluation material

22.1. 4.2 DOSE AND METHOD OF ADMINISTRATION

Patients appropriate for Sublocade are adults who have undergone induction on a buprenorphine-containing product. Withdrawal signs and symptoms should be suppressed (COWS ≤ 12) before transitioning to Sublocade.

Dosing and induction of buprenorphine-containing products should be based on instructions in their Product Information.

FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. DO NOT ADMINISTER Sublocade INTRAVENOUSLY OR INTRAMUSCULARLY (see section 4.4 Special Warnings and Precautions for use).

•Only healthcare providers should prepare and administer Sublocade.

•Administer Sublocade monthly with a minimum of 26 days between doses.

• Initiating treatment with Sublocade as the first buprenorphine product has not been studied. Initiate Sublocade treatment only following induction and dose adjustment with a transmucosal buprenorphine containing product.

• Administer each injection only using the syringe and safety needle included with the product.

• Do not administer part of a dose

Recommended dosing

Patients appropriate for Sublocade are adults who have initiated treatment on a transmucosal buprenorphine-containing product. The patient may only be transitioned to Sublocade after stabilisation on transmucosal buprenorphine (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

The recommended dose of Sublocade is 300mg monthly for the first two months. The recommended maintenance dose is 100mg monthly. However patients who do not show a satisfactory clinical response following the second dose can receive a maintenance dose of 300mg monthly.

Buprenorphine plasma levels in the month following the second 300mg dose are maintained with 100mg maintenance dosing. The 300mg maintenance dose achieves higher levels and reaches steady state after the fourth monthly injection (see section 5.2 pharmacokinetic properties).

A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Clinical supervision

Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot.

Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment. For some patients, treatment may continue indefinitely. If considering stopping treatment, the clinical status of the patient should be considered.

If Sublocade is discontinued, its extended-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal or buprenorphine effects and treated appropriately. After steady-state has been achieved (4-6 months), patients discontinuing Sublocade may have detectable plasma levels of buprenorphine for twelve months or longer. The correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

INSTRUCTIONS FOR USE

IMPORTANT INFORMATION:

• For abdominal subcutaneous injection only.

• To be administered by a healthcare professional only.

• Please read the instructions carefully before handling the product.

• Remove Sublocade from the refrigerator prior to administration. The product requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for his or her injection.

• Discard Sublocade if left at room temperature (below 30°C) for longer than 7 days.

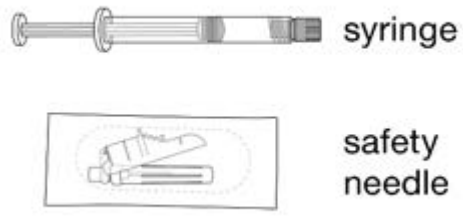
• Do not attach the needle until time of administration.

STEP 1: GETTING READY

Remove the foil pouch and safety needle from the carton. Open the pouch and remove the syringe.

Discard the oxygen absorber pack. It is not needed.

Figure 1

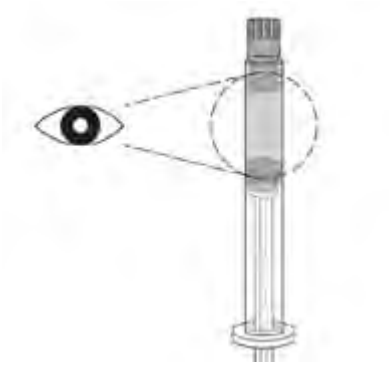


STEP 2: CHECK THE LIQUID CLARITY

Check that the medication for particulate matter and discolouration. Sublocade can range from clear colourless to yellow to amber. Variations of colour within this range do not affect the potency of the product.

If the medication is discoloured or contains particulate matter it should not be used.

Figure 2



STEP 3: ATTACH THE SAFETY NEEDLE

Remove the cap from the syringe and the safety needle supplied in the carton from its sterile package.

Gently twist the needle clockwise until it is tight and firmly attached.

Do not remove the plastic cover from the needle.

Figure 3

STEP 4: PREPARE THE ABDOMINAL INJECTION SITE

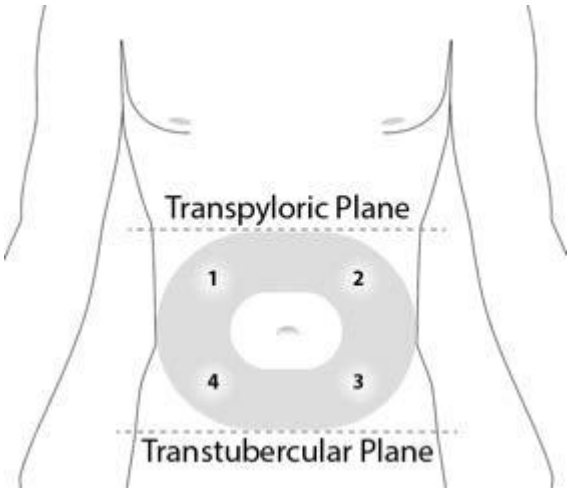
Choose an injection site on the abdomen between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position.

Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.

Clean the injection site well with an alcohol swab.

To avoid irritation, rotate injection sites following a pattern similar to the illustration in Figure 4. Record the location of the injection to ensure that a different site is used at the time of the next injection.

Figure 4



STEP 5: REMOVE EXCESS AIR FROM SYRINGE

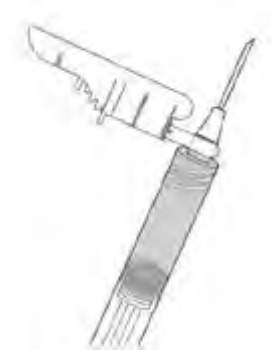
Hold the syringe upright for several seconds to allow air bubbles to rise. Due to the viscous nature of the medication, bubbles will not rise as quickly as those in an aqueous solution.

Remove needle cover and slowly depress the plunger to push out the excess air from the syringe.

• Small bubbles may remain in the medication. Large air gaps, however, can be minimised by pulling back on the plunger rod to pop air bubbles prior to expelling the air very slowly. Air should be expelled very carefully to avoid loss of medication.

If medication is seen at the needle tip, pull back slightly on the plunger to prevent medication spillage.

Figure 5



STEP 6: PINCH THE INJECTION SITE

Pinch the skin around the injection area. Be sure to pinch enough skin to accommodate the size of the needle. Lift the adipose tissue from the underlying muscle to prevent accidental intramuscular injection.

Figure 6

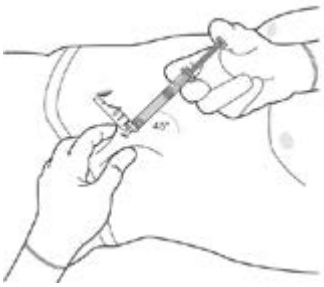
STEP 7: INJECT THE MEDICATION

Sublocade is for subcutaneous injection only. Do not inject intravenously or intramuscularly (see Section 4.4 Special Warnings and Precautions for Use).

Insert needle fully into the abdominal subcutaneous tissue. The actual angle of injection will depend on the amount of subcutaneous tissue.

Use a slow, steady push to inject the medication. Continue pushing until all of the medication is given.

Figure 7



STEP 8: WITHDRAW THE NEEDLE

Withdraw the needle at the same angle used for insertion and release the pinched skin.

Do not rub the injection area after the injection. If there is bleeding, apply a gauze pad or bandage but use minimal pressure.

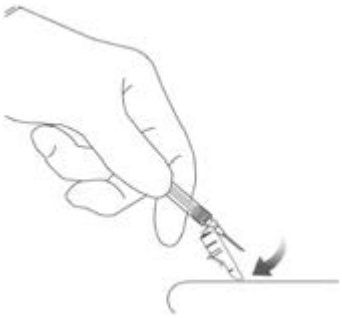
Figure 8

STEP 9: LOCK THE NEEDLE GUARD AND DISCARD THE SYRINGE

Lock the needle guard into place by pushing it against a hard surface such as a table (Figure 9).

Dispose of all syringe components in a secure sharps disposal container.

Figure 9



STEP 10: INSTRUCT THE PATIENT

Advise the patient that they may have a lump for several weeks that will decrease in size over time. Instruct the patient not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.

Removal of the Depot

In the event the depot must be removed, it can be surgically excised by a healthcare professional under local anaesthesia within 14 days of injection. The removed depot should be disposed of carefully

24. Information about the evaluator

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au

Australian Government
Department of Health
Therapeutic Goods Administration

Clinical Evaluation Report

Prescription Medicines Authorisation Branch

Active substance: Buprenorphine

Product name: SUBLOCADE

Sponsor: Indivior Pty Ltd

Submission number: PM-2017-01872-1-1

eSubmission number: e003260

First round PopPK evaluator:
Date of first round report: 4th November 2018
TRIM reference:
Second round PopPK evaluator:
Date of second round report:
TRIM reference:

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
C_{avg}	Average plasma concentration
CGI-I	Clinical Global Impression – Improvement Scale
CGI-S	Clinical Global Impression – Severity of Illness Scale
CL	clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
COWS	Clinical Opioid Withdrawal Scale
CrCL	Creatinine clearance
CWRES	Conditional weighted residuals
CYP3A4	Cytochrome p450 3A4
CYP2C8	Cytochrome P450 2C8
DV	Dependent variable
EBE	Empirical Bayes Estimate
EC_{50}	Concentration at which 50% maximum effect is observed
E_{max}	Maximum effect
EPRED	Expected population prediction (exact method based on Monte Carlo simulations)
EWRES	Expected population weighted residuals (exact method based on Monte Carlo simulations)
FDA	Food and Drug Administration

Abbreviation	Meaning
GOF	Goodness of fit
HCl	Hydrochloride
IPRED	Individual prediction
IIV	Inter-individual variability
IV	Intravenous
IWRES	Individual weighted residuals
Ka	Absorption rate constant
LC-MS/MS	Liquid chromatography and tandem mass spectrometry
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MAR	Missing at random
MOF	Minimum objective function value
NA	Not applicable
NLME	Non-linear mixed effects
NMP	*N*-methyl-*2*-pyrrolidone
NONMEM	Non-linear Mixed Effects Modelling
OFV	Objective function value
OPRM1	Mu-opioid receptor 1
OPRD1	Delta-opioid receptor 1
OPRK1	Kappa-opioid receptor 1
OUD	Opioid use disorder
pcVPC	Prediction-corrected Visual Predictive Check
PD	Pharmacodynamics
PET	Positron emission tomography
PK	Pharmacokinetics

Abbreviation	Meaning
PLGH	Poly(DL-lactide-co-glycolide)
PRED	Population prediction
Q	Intercompartmental clearance
RSE	Relative standard error
RUV	Residual variability
SAEM	Stochastic Approximation Expectation-Maximisation algorithm
SC	Cubcutaneous(ly)
SNP	Single nucleotide polymorphisms
SOWS	Subjective Opiate Withdrawal Scale
TLFB	Timeline Followback interview
T_{max}	Time at which maximum plasma concentration occurs
UDS	Urine drug screen
US	United States of America
UGT	UDP-glucuronosyltransferase
V	Volume of distribution
VAS	Visual analogue scale
VPC	Visual predictive check
WHR	Waist-to-hip ratio
WRES	Weighted residuals

1. Submission details

1.1. Identifying information

Submission number	PM 2018-01872-1-1
eSubmission number	e003260
eSubmission sequences covered in this report	0002
Sponsor	Indivior Pty Ltd
Trade name	SUBLOCADE
Active substance	Buprenorphine

1.2. Submission type

Evaluation of population pharmacokinetic and exposure-response data; and replication of population pharmacokinetic analysis relating to SUBLOCADE (buprenorphine) 100 mg / 300 mg extended release injection.

1.3. Drug class and therapeutic indication

Buprenorphine is a synthetic opioid and is a non-selective, mixed agonist-antagonist opioid receptor modulator. It is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist, δ (delta) receptor antagonist and is a very weak partial agonist of the nociceptin receptor. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.

SUBLOCADE also includes the ATRIGEL® Delivery System. ATRIGEL® is an injectable, controlled release carrier system for drugs. The liquid ATRIGEL® / drug product is injected into the subcutaneous space through a small gauge needle or placed into accessible tissue sites through a cannula. Water in the tissue fluids causes the polymer to precipitate and trap the drug in a solid implant. The drug encapsulated within the implant is then released in a controlled manner as the polymer matrix biodegrades with time. ATRIGEL ® contains: 50:50 Poly (DL-lactide-co-glycolide) polymer:*N*-methyl-2-pyrrolidone.

The therapeutic indication is:

Treatment of opioid dependence, within a framework of medical, social and psychological treatment.

1.4. Dosage forms and strengths

- SUBLOCADE 100 mg extended release injection contains buprenorphine 100 mg.
- SUBLOCADE 300 mg extended release injection contains buprenorphine 300 mg.

1.5. Dosage and administration

The following dosing and administration are copied from the product information (PI):

Patients appropriate for SUBLOCADE are adults who have undergone induction on a buprenorphine-containing product. Withdrawal signs and symptoms should be suppressed (COWS ≤12) before transitioning to SUBLOCADE.

Dosing and induction of buprenorphine-containing products should be based on instructions in their Product Information.

FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. DO NOT ADMINISTER SUBLOCADE INTRAVENOUSLY OR INTRAMUSCULARLY (see section 4.4 Special Warnings and Precautions for use).

- Only healthcare providers should prepare and administer SUBLOCADE.
- Administer SUBLOCADE monthly with a minimum of 26 days between doses.
- Initiating treatment with SUBLOCADE as the first buprenorphine product has not been studied. Initiate SUBLOCADE treatment only following induction and dose adjustment with a transmucosal buprenorphine containing product.
- Administer each injection only using the syringe and safety needle included with the product.
- Do not administer part of a dose

Recommended dosing

Patients appropriate for SUBLOCADE are adults who have initiated treatment on a transmucosal buprenorphine-containing product. The patient may only be transitioned to SUBLOCADE after stabilisation on transmucosal buprenorphine (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

The recommended dose of SUBLOCADE is 300 mg monthly for the first two months. The recommended maintenance dose is 100 mg monthly. However patients who do not show a satisfactory clinical response following the second dose can receive a maintenance dose of 300 mg monthly.

Buprenorphine plasma levels in the month following the second 300 mg dose are maintained with 100 mg maintenance dosing. The 300 mg maintenance dose achieves higher levels and reaches steady state after the fourth monthly injection (see section 5.2 pharmacokinetic properties).

A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Clinical supervision

Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot.

Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment. For some patients, treatment may continue indefinitely. If considering stopping treatment, the clinical status of the patient should be considered.

If SUBLOCADE is discontinued, its extended-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal or buprenorphine effects and treated appropriately. After steady-state has been achieved (4-6 months), patients discontinuing SUBLOCADE may have detectable plasma levels of

buprenorphine for twelve months or longer. The correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

INSTRUCTIONS FOR USE

IMPORTANT INFORMATION:

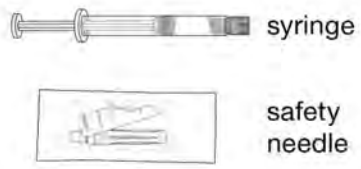
- For abdominal subcutaneous injection only.
- **To be administered by a healthcare professional only.**
- Please read the instructions carefully before handling the product.
- Remove SUBLOCADE from the refrigerator prior to administration. The product requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for his or her injection.
- Discard SUBLOCADE if left at room temperature (below 30°C) for longer than 7 days.
- Do not attach the needle until time of administration.

STEP 1: GETTING READY

Remove the foil pouch and safety needle from the carton. Open the pouch and remove the syringe.

Discard the oxygen absorber pack. It is not needed.

Figure 1

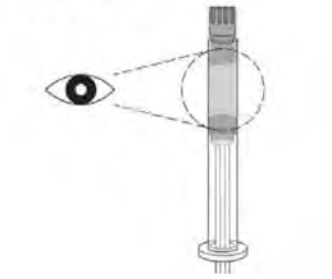


STEP 2: CHECK THE LIQUID CLARITY

Check that the medication for particulate matter and discolouration. SUBLOCADE can range from clear colourless to yellow to amber. Variations of colour within this range do not affect the potency of the product.

If the medication is discoloured or contains particulate matter it should not be used.

Figure 2



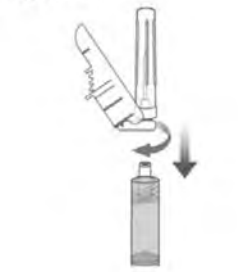
STEP 3: ATTACH THE SAFETY NEEDLE

Remove the cap from the syringe and the safety needle supplied in the carton from its sterile package.

Gently twist the needle clockwise until it is tight and firmly attached.

Do not remove the plastic cover from the needle.

Figure 3



STEP 4: PREPARE THE ABDOMINAL INJECTION SITE

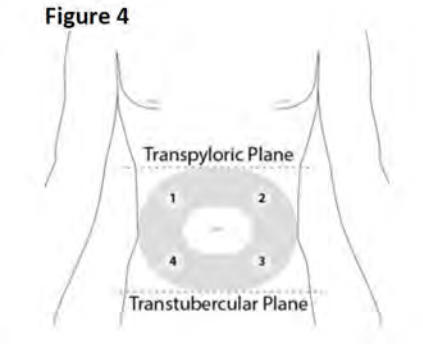
Choose an injection site on the abdomen between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position.

Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.

Clean the injection site well with an alcohol swab.

To avoid irritation, rotate injection sites following a pattern similar to the illustration in Figure 4. Record the location of the injection to ensure that a different site is used at the time of the next injection.

Figure 4



STEP 5: REMOVE EXCESS AIR FROM SYRINGE

Hold the syringe upright for several seconds to allow air bubbles to rise. Due to the viscous nature of the medication, bubbles will not rise as quickly as those in an aqueous solution.

Remove needle cover and slowly depress the plunger to push out the excess air from the syringe.

- Small bubbles may remain in the medication. Large air gaps, however, can be minimised by pulling back on the plunger rod to pop air bubbles prior to expelling the air very slowly. Air should be expelled very carefully to avoid loss of medication.

If medication is seen at the needle tip, pull back slightly on the plunger to prevent medication spillage.

Figure 5

STEP 6: PINCH THE INJECTION SITE

Pinch the skin around the injection area. Be sure to pinch enough skin to accommodate the size of the needle. Lift the adipose tissue from the underlying muscle to prevent accidental intramuscular injection.

Figure 6

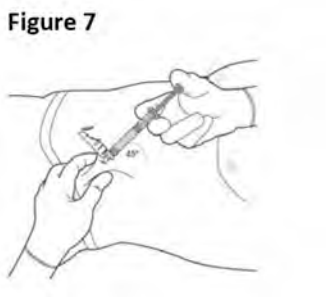
STEP 7: INJECT THE MEDICATION

SUBLOCADE is for subcutaneous injection only. Do not inject intravenously or intramuscularly (see Section 4.4 Special Warnings and Precautions for Use).

Insert needle fully into the abdominal subcutaneous tissue. The actual angle of injection will depend on the amount of subcutaneous tissue.

Use a slow, steady push to inject the medication. Continue pushing until all of the medication is given.

Figure 7



STEP 8: WITHDRAW THE NEEDLE

Withdraw the needle at the same angle used for insertion and release the pinched skin.

Do not rub the injection area after the injection. If there is bleeding, apply a gauze pad or bandage but use minimal pressure.

Figure 8

STEP 9: LOCK THE NEEDLE GUARD AND DISCARD THE SYRINGE

Lock the needle guard into place by pushing it against a hard surface such as a table (Figure 9).

Dispose of all syringe components in a secure sharps disposal container.

Figure 9

STEP 10: INSTRUCT THE PATIENT

Advise the patient that they may have a lump for several weeks that will decrease in size over time. Instruct the patient not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.

Removal of the Depot

In the event the depot must be removed, it can be surgically excised by a healthcare professional under local anaesthesia within 14 days of injection. The removed depot should be disposed of carefully.

1.6. Proposed changes to the product documentation

NA.

2. Background

2.1. Information on the condition being treated

NA.

2.2. Current treatment options

NA.

2.3. Clinical rationale

NA.

2.4. Formulation

2.4.1. Formulation development

NA.

2.4.2. Excipients

- ATRIGEL®: 50:50 Poly (DL-lactide-co-glycolide) polymer:N-methyl-2-pyrrolidone.

2.5. Regulatory history

2.5.1. Australian regulatory history

NA.

2.5.2. Orphan drug designation

NA.

2.5.3. Related submissions

NA.

2.5.4. Overseas regulatory history

NA.

2.6. Guidance

The following guidance applies to the present application:

- Guideline on Reporting the Results of Population Pharmacokinetic Analyses CHMP/EWP/185990/06

2.7. Evaluator's commentary on the background information

Sufficient background information was provided to enable the population pharmacokinetic evaluation.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The population pharmacokinetic dossier contained:

- Report for Study INDV-6000-M05 (population pharmacokinetic study)
- Report for Study INDV-6000-M04 (population pharmacokinetic/pharmacodynamic study)
- Control files and data files for Study INDV-6000-M05

3.2. Paediatric data

There were no paediatric data in the dossier.

3.3. Good clinical practice

The studies appear to have been conducted according to good clinical research practice.

3.4. Evaluator's commentary on the clinical dossier

The population pharmacokinetic dossier contained all of the components requested by the TGA of the Sponsor.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

There were two studies that contributed PK data: Study INDV-6000-M04 and Study INDV-6000-M05. External replication of the analysis was performed for Study INDV-6000-M05.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

NA.

4.2.2. Pharmacokinetics in healthy subjects

The following information is reproduced from the proposed Product Information (PI).

4.2.2.1. Absorption

The pharmacokinetics (PK) of buprenorphine following subcutaneous injection of SUBLOCADE was evaluated in subjects with opioid use disorder after single doses (20 mg to 200 mg) and repeated doses (50 to 300 mg) separated by 28 days for up to 12 injections.

After SUBLOCADE injection, an initial buprenorphine peak was observed and the median T_{max} occurred at 24 hours after injection. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly to a plateau. Steady-state was achieved at 4-6 months. Observed mean buprenorphine concentrations levels for C_{avg}, C_{max} and C_{min} are presented in Table 6.

Table 6 Comparison of Buprenorphine Mean Pharmacokinetic parameters between SUBUTEX and SUBLOCADE

Pharmacokinetic parameters	SUBUTEX daily stabilisation		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg# (1st injection)	100 mg* (steady-state)	300 mg* (steady-state)
$C_{avg,ss}$ (ng/ml)	1.71	2.91	2.19	3.21	6.54
$C_{max,ss}$ (ng/ml)	5.35	8.27	5.37	4.88	10.12
$C_{min,ss}$ (ng/ml)	0.81	1.54	1.25	2.48	5.01

#Exposure after 1 injection of 300 mg SUBLOCADE following 24 mg SUBUTEX stabilisation
*Steady-state exposure after 4 injections of 100 mg or 300 mg SUBLOCADE, following 2 injections of 300 mg SUBLOCADE

4.2.2.2. Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

4.2.2.3. Metabolism

Buprenorphine is metabolised into its major metabolite, norbuprenorphine, primarily by CYP3A4. Norbuprenorphine can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity. Norbuprenorphine steady-state plasma concentrations in humans after subcutaneous injection of SUBLOCADE are low compared to buprenorphine (AUC norbuprenorphine/ buprenorphine ratio of 0.20 to 0.40).

4.2.2.4. Excretion

Buprenorphine is metabolised and eliminated in urine and faeces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of SUBLOCADE ranged from 43 to 60 days as a result of the slow release of buprenorphine from the subcutaneous depot.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuronide conjugated metabolites (70%), the rest being eliminated in urine.

4.2.2.5. Intra and inter individual variability of pharmacokinetics

Study INDV-6000-M05 (Section 19.1.3.1) and Study INDV-6000-M04 (Section 19.1.3.2) describe large interindividual variability for the absorption parameters for buprenorphine when administered as SUBLOCADE. The IIV, expressed as CV%, was 191% for K36 (slow absorption to transit compartment), 73.5% for K64 (absorption from transit compartment to central compartment), 96.1% for K24 (fast absorption) and 47.6% for the fraction absorbed by the fast component. There was less variability in CL: 30.2%. The Sponsor did not determine whether the variability in absorption contributes to variability in exposure.

There were no data describing inter-occasion (intra-individual) variability.

4.2.3. Pharmacokinetics in the target population

The PK studies were conducted in the target population.

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

The Product Information states: "In a pharmacokinetic study with transmucosal buprenorphine, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of SUBLOCADE has not been studied.

Because of the long-acting nature of the product, adjustments to dosages of SUBLOCADE are not rapidly reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing severe hepatic impairment are not candidates for treatment with SUBLOCADE.

Patients who develop moderate to severe hepatic impairment while being treated with SUBLOCADE should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine."

The population pharmacokinetic studies did not provide any additional information regarding hepatic impairment.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

The Product Information states: "Clinical studies of SUBLOCADE did not include subjects with renal impairment. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine."

The population pharmacokinetic studies did not provide any additional information regarding renal impairment.

4.2.4.3. Pharmacokinetics according to age

Age was not a significant covariate for buprenorphine PK with SUBLOCADE in either Study INDV-6000-M04 (Section 19.1.3.2) or INDV-6000-M05 (Section 19.1.3.1). Neither study included children of older persons.

4.2.4.4. Pharmacokinetics related to genetic factors

In Study INDV-6000-M04 (Section 19.1.3.2), polymorphisms of CYP3A4, CYP2C8, UGT1A1 or UGT2B7 did not have a clinically significant effect on the PK of buprenorphine.

4.2.4.5. Pharmacokinetics in other special population / with other population characteristic

In Study INDV-6000-M04 (Section 19.1.3.2) patients with lower BMI had higher peak buprenorphine concentrations. There was a small increase in the rate of absorption from the slow component in females. Neither of these effects were clinically significant.

4.2.5. Population pharmacokinetics

4.2.5.1. Study INDV-6000-M05

See Section 19.1.3.1.

4.2.5.2. Study INDV-6000-M05

See Section 19.1.3.2.

4.2.6. Pharmacokinetic interactions

The population pharmacokinetic studies did not examine drug interactions.

4.2.7. Clinical implications of *in vitro* findings

NA.

4.3. Evaluator's overall conclusions on pharmacokinetics

The Sponsor has adequately characterised the PK of buprenorphine in SUBLOCADE with regard to the absorption and elimination parameters and inter-individual variability. The data in the population pharmacokinetic studies is consistent with the information in the Product Information. There is marked variability in the absorption kinetics of SUBLOCADE but the variability in clearance was similar to that expected from the known PK of buprenorphine.

The Sponsor has not adequately described the effects of the high variability in absorption PK upon exposure to buprenorphine when administered as SUBLOCADE. The Sponsor did not estimate the variability in the secondary PK parameters C_{max}, C_{min} or AUC. Although there is marked variability in absorption this might not contribute to variability in exposure. However, in the absence of determining this variability in exposure this becomes important missing information.

The Sponsor has not adequately described inter-occasion variability in the absorption of buprenorphine from SUBLOCADE. The marked inter-individual variability in absorption of SUBLOCADE indicates potentially significant inter-occasion variability. This is important missing information because it could contribute to unpredictable response from dose to dose.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

There was one study that contributed PKPD data: Study INDV-6000-M04.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

NA.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

For illicit opioid use, Study INDV-6000-M04 (Section 19.1.3.2) estimated an EC_{50} of 1.21 ng/mL, but this increased to 3.78 ng/mL for injectable opioid users. EC_{50} decreased by 71% and 94% respectively for TC and TT genotype for OPRD1. E_{max} was increased by 43% in patients who were employed at baseline, and decreased by 31% in African Americans.

For opioid craving, EC50 was 2.45 ng/mL. E_{max} increased with BMI but this effect was not clinically significant.

COWS and SOWS had a relationship with buprenorphine plasma concentration, with a plateau in effect from 4 ng/mL.

5.2.2.2. Secondary pharmacodynamic effects

Secondary PD effects were not explored in Study INDV-6000-M04 (Section 19.1.3.2).

5.2.3. Time course of pharmacodynamic effects

The maximal effect on craving was achieved by Day 50 with the 300 mg/100 mg dose group and Day 150 with the 300 mg/300 mg dose group.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

As per Section 5.2.2.

5.2.5. Genetic, gender and age related differences in pharmacodynamic response

As per Section 5.2.2.

5.2.6. Pharmacodynamic interactions

PD interactions were not explored in Study INDV-6000-M04 (Section 19.1.3.2).

5.3. Evaluator's overall conclusions on pharmacodynamics

Study INDV-6000-M04 (Section 19.1.3.2) demonstrated the PKPD relationship for buprenorphine in patients with opioid dependency. For patients with injectable illicit opioid use EC_{50} was 3.78 ng/mL. There was a plateau in effect from 4 ng/mL. The study supports the proposed dosing regimen. The study supports the PD information in the Product Information document. The Sponsor has adequately characterised the PKPD relationship for buprenorphine in patients with opioid dependency.

6. Dosage selection for the pivotal studies

NA.

7. Clinical efficacy

NA.

8. Clinical safety

NA.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
The proposed dosing regimen for SUBLOCADE is supported by the PKPD study (INDV-6000-M04)	These results are derived from a PKPD model and would need to be related to the clinical data. SUBLOCADE has an estimated EC_{50} of 1.21 ng/mL for prevention of illicit opioid use, which increases to 3.78 ng/mL for injectable opioid users. EC_{50} decreased by 71% and 94% respectively for TC and TT genotype for OPRD1. E_{max} was increased by 43% in patients who were employed at baseline, and decreased by 31% in African Americans. For opioid craving, EC_{50} was 2.45 ng/mL. E_{max} increased with BMI but this effect was not clinically significant. COWS and SOWS had a relationship with buprenorphine plasma concentration, with a plateau in effect from 4 ng/mL. With the proposed dosing regimen, at steady state plasma concentrations would be expected to be ≥5 ng/mL.

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
SUBLOCADE has complex and highly variable absorption kinetics.	The variability in exposure parameters for SUBLOCADE has not been quantified. The inter-occasion (intra-individual) variability for SUBLOCADE absorption kinetics has not been quantified.

9.3. First round assessment of benefit-risk balance

The population PK and PKPD data do not alter the benefit-risk balance for SUBLOCADE.

10. First round recommendation regarding authorisation

The Population Pharmacokinetic Evaluator has no objection to the authorisation of SUBLOCADE for the indication of:

Treatment of opioid dependence, within a framework of medical, social and psychological treatment.

11. First round comments on product documentation

11.1. First round comments on draft PI (clinical aspects)

The pharmacokinetic and pharmacodynamic information in the PI are supported by the dossier.

11.2. First round comments on draft CMI (clinical aspects)

NA.

11.3. First round comments on draft RMP (Summary of Safety Concerns)

The following important missing information should be included in the safety specification for SUBLOCADE:

- Variability in the secondary PK parameters C_{max}, C_{min} and AUC
- Inter-occasion variability in the absorption of buprenorphine from SUBLOCADE

12. Clinical questions

12.1. Clinical questions

12.1.1. Pharmacokinetics

What is the inter-occasion variability in the absorption parameters of SUBLOCADE (buprenorphine) 100 mg / 300 mg extended release injection?

To what extent does the high variability in absorption of SUBLOCADE contribute to variability in exposure to buprenorphine, as measured by C_{max}, T_{max}, C_{min} and AUC?

12.1.2. Pharmacodynamics

The Population Pharmacokinetic Evaluator has no questions relating to pharmacodynamics.

12.1.3. Efficacy

The Population Pharmacokinetic Evaluator has no questions relating to efficacy.

12.1.4. Safety

The Population Pharmacokinetic Evaluator has no questions relating to safety.

12.1.5. PI and CMI

The Population Pharmacokinetic Evaluator has no questions relating to the PI or CMI.

12.2. Additional expert input

The Population Pharmacokinetic Evaluator has no recommendation for additional expert opinion.

13. First round evaluation errata

13.1. Minor editorial changes

13.2. Minor errors of fact

13.3. Significant errors of fact

14. Second round evaluation

15. Second round benefit-risk assessment

15.1. Second round assessment of benefits

15.2. Second round assessment of risks

15.3. Second round assessment of benefit-risk balance

16. Second round recommendation regarding authorisation

17. Second round comments on product documentation

17.1. Second round comments on draft PI (clinical aspects)

17.2. Second round comments on draft CMI (clinical aspects)

17.3. Second round comments on draft RMP (Summary of Safety Concerns)

18. References

Study INDV-6000-M05, Module 5, Section 5.3.3

Study INDV-6000-M04, Module 5, Section 5.3.4

19. Supporting information, tables and figures

19.1. Clinical pharmacology study synopses

19.1.1. Synopses of pharmacokinetic studies

NA.

19.1.2. Synopses of pharmacodynamics studies

NA.

19.1.3. Synopses of population pharmacokinetics analyses

19.1.3.1. STUDY INDV-6000-M05

Statistical analysis plan

A modelling analysis plan was provided and appears to have been adhered to.

Objectives

- To describe buprenorphine plasma concentrations measured in Study RB-US-13-0003 from roll-over and de novo subjects for whom PK samples were collected, using the previously developed population PK model from the combined analysis of studies RB-US-12-0005 and RB-US-13-0001
- To refine model estimation from the pooled data of the multiple ascending dose Study (RB-US-12-0005) and the two Phase III studies (RB-US-13-0001 and RB-US-13-0003).

Data

The data were obtained from three studies (Table 19.1.3.1.1):

- Study RB-US-12-0005 was a Phase II, ascending dose safety and tolerability study. Patients were induced and stabilised on SUBUTEX SL dosing in the range 8 to 24 mg, and then treated with RBP-6000 in the dose range 50 to 300 mg. There was rich PK sampling up to injection 4 and then sparse sampling.
- Study RB-US-13-0001 was a Phase III, double blind, placebo controlled, 24-week, efficacy and safety study. All patients were initially treated with 300 mg for the first two injections and then either 100 mg or 300 mg for the next four injections. There was sparse PK sampling: on Days 1, 2, 8, 15, 22, 29, 30, 36, 43, 50, 57, 58, 64, 71, 78, 85, 86, 92, 99, 106, 113, 114, 120, 127, 134, 141, 142, 148, 155, 162 and 169.
- Study RB-US-13-0003 was a Phase III long-term open-label safety and tolerability study. Roll-over patients continued on either 100 mg or 300 mg every 28 days. New patients all treated with 300 mg for the first dose, then 100 mg or 300 mg every 28 days. Patients were induced and stabilised on SUBOXONE SL to a minimum dose of 8 mg. There was sparse PK sampling: Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141 and 169 for a total of 12 samples.

There were 570 individual subjects and 19686 plasma concentration observations in the final dataset (Table 19.1.3.1.2). There were 2910 plasma concentrations from sublingual dosing and 16776 from subcutaneous dosing.

There were 387 (67.9%) males, 183 (32.1%) females, 161 (28.2%) Black or African American individuals and the age range was 19 to 64 years (Table 19.1.3.1.3).

Methods

Plasma buprenorphine concentrations were measured using LC-MS/MS assay with LLOQ of 0.050 ng/mL for buprenorphine and 0.040 ng/mL for norbuprenorphine.

Data management and exploratory analysis was performed using SAS and R (Version 1.0.136). The pharmacometric analysis was performed using NONMEM Version 7.3.0 compiled with the GNU Fortran compiler (Version 5.4.0). The analysis was performed using a cluster comprising four computers each with Xeon E5 2698 v3 2.3GHz 16 core CPU's and 16 GB RAM. Perl-speaks-NONMEM (PsN version 4.6.0) was used to operate NONMEM. The estimation method was the Stochastic Approximation Expectation-Maximization (SAEM) method and the Importance Sampling Approach.

The modelling strategy was performed in two stages:

1. First, a previously developed model, using the data from Study PB-US12-0005 and Study RB-US-13-001, was used to fit the data from Study RB-US-13-0003
2. Second, this model was then used to re-estimate the model parameters using the data from all three studies

The previously developed model had the following components (Figure 19.1.3.1.1):

- Two compartments with first-order elimination.
- Sublingual absorption of SUBUTEX modelled as first-order (K14), with relative bioavailability compared to subcutaneous described by F1.
- The relative difference in bioavailability and absorption for the formulation SUBOXONE compared to SUBUTEX described by FRF1 and FRK14 respectively
- Subcutaneous absorption described by a dual absorption model with fast and slow components. The fast component was first order (K24). The slow component had a transit compartment (compartment 6) with first-order absorption (K36) and then first order transfer from the depot to the central compartment (K64).
- The fraction of the dose allocated to the fast component was modelled as F2. However, the methods for estimating this parameter were not clearly described in the methods section.
- Inter-individual variability was modelled on all ten structural parameters, with an omega block structure.
- Covariate effect for BMI on the SC absorption of buprenorphine (effect on K24).
- A covariate effect for BMI on CL was not described in the methods section but was reported in the results and was present in the model code.
- Covariate effect for sex on the subcutaneous absorption of buprenorphine (effect on K36).
- Covariate effect for the higher dose of sublingual buprenorphine on absorption.
- Residual error described by a combined additive and proportional model.

There was no further model development.

The fit of the model was evaluated using goodness-of-fit plots and visual predictive checks (VPCs).

Results

The goodness of fit plots for the Study RB-US-13-0003 data fitted to the model derived from the Study PB-US12-0005 and Study RB-US-13-001 data indicate a good fit for the data to the model (Figure 19.1.3.1.2 and Figure 19.1.3.1.3). The visual predictive check also confirmed a good fit for the model to the data (Figure 19.1.3.1.4). Based on these plots the Sponsor accepted that the previously derived model was suitable for analysing the combined data.

The parameter estimates were derived for the combined dataset and were similar to the original parameter estimates (Table 19.1.3.1.4). The goodness of fit plots were similar to those for the original model and indicate an acceptable fit for the model to the data, and an appropriate specification for the error model (Figure 19.1.3.1.5).

The Sponsor concluded that the model adequately describes the data from all three clinical studies.

There were a number of aspects of the analysis that were apparent from the model code but that were not included in the study report. In the study report the Sponsor did not report the use of allometric scaling for weight on CL, V4, Q or V5. The Sponsor did not report the use of a logit function to estimate the fraction of subcutaneous dose delivered as the fast component. The Sponsor did not report shrinkage.

External replication

The data file supplied was: combineddataset-24mar17-1410

The data file was edited by:

- Deleting all rows that had been "commented-out" with "C" (no rows deleted)
- Deleting rows affected by the IGNORE command:
  - BLQ=1 (seven rows deleted)
  - OUTLIER=1 (26 rows deleted)
  - PK_flag=0 (419 rows deleted)

There were no negative times in the dataset. There were no missing values for gender, age, or BMI. The EVID values were either 0 or 1, so there were no resets in the dataset.

The original data file had 33339 rows. There were no rows that had been "commented-out".

The final dataset had 32887 rows (including column headings), 570 individuals and 19686 observations. There were 387 (67.9%) males, 183 (32.1%) females,

The median (range) number of doses in the dataset was 22 (5 to 46), not including ADDL doses. The median (range) number of plasma concentrations per individual was 39 (0 to 120).

The dataset used by the Sponsor, from the final model output, had 32886 rows (excluding column headings), 570 individuals and 19686 observations. Hence, the datasets used in the Sponsor's analysis and the external replication appear to be the same.

On reading the Sponsor's input file, it appears that for the SUBLOCADE dosing the Sponsor coded the same dose into two dosing compartments at the same time, and then coded a "bioavailability" parameter so that the residual of one dosing compartment equalled the bioavailable fraction in the other. This differs from the schematic presentation of the model which indicates dosing into one compartment. The input file was coded as having compartment 1 (CMT1; sublingual dosing compartment), compartment 2 (CMT2; slow absorption dose compartment), compartment 3 (CMT3; fast absorption dosing compartment) and compartment 4 (CMT4, central compartment). The input file was edited to comply with the Phoenix input file format, which has a separate column for each compartment.

The dosing records also used the ADDL option, and II which indicates the number of additional doses and the dosing interval. The entire ADDL dose was linked to the SC dosing, and all the dosing intervals for the additional doses were 24 hours.

A marker variable was generated to indicate those sublingual doses ≥16 mg.

A marker variable was generated to indicate sublingual formulation (Subuxone = 1, Subutex = 0).

On reading the Sponsor's control file, in the Sponsor's model it appears that the fraction absorbed by the fast phase was modelled using a logit function, and the fraction absorbed by the slow phase is the residual from 1. The code the Sponsor uses for this is:

```
PHI = TVPHI+ETA(6)
F2 = DEXP(PHI)/(1+DEXP(PHI))          ;Fraction of RBP aborbed by 1st phase
F3  = 1 - F2                          ;Fraction absorbed by 2nd phase
```

In the model code, clearance and inter-compartmental clearance were allometrically scaled to weight$^{0.75}$, and normalised to 70kg. Central and peripheral volumes of distribution were scaled to weight and normalised to 70kg.

BMI was centred on 24.8 kg/m^2.

Finally, in the external replication dataset the DV concentration of ng/mL was converted to mg/L.

The external replication model was constructed in four steps:

1. Using the windows menus to construct a two-compartment model with first order elimination, exponential IIV on CL, V1, Q and V2 and Ka, and a combined additive and multiplicative residual error.
2. Using the window's menu to set up the covariate model structure.
3. Using the graphics editor to construct three dose points: one sublingual, a fast subcutaneous absorption and a slow subcutaneous absorption with a transit compartment. There were separate bioavailability parameters for each dose point.
4. Using the text editor to construct the logit function for estimation of the fraction of the subcutaneous dose absorbed by the fast component.

For the external replication, the final model structure is displayed in Figure 19.1.3.1.6 and the model code is displayed in Figure 19.1.3.1.7.

The Sponsor's run-time was 195137 seconds (2.26 days) for the first component of the SAEM iteration and an iteration time of 19074.55 seconds for the second component and 47346.86 seconds for the covariance step (0.77 days). Overall, the run time was three days using a cluster of four computers, each with 16 cores per processor.

The external replication was performed using Phoenix NLME version 8.1. The computations were performed using a single processor with four cores.

Minimisation of the external replication model was attempted using QRPEM which resulted in the following error message:

"Model execution failed.

(2) –

Model not suitable for QRPEM analysis

Possibly nonlinear covariate model or some other unimplemented feature"

Hence, the estimation method used was First Order Conditional Estimation Extended Least Squares (FOCE-ELS) which is similar to First Order Conditional Estimation with Interaction (FOCEI) as used in NONMEM. Using this estimation method the model successfully converged, with a return code of 3, but did not proceed to a covariance step.

A comparison of the parameter estimates from the Sponsor's model and the external replication model is presented in Table 19.1.3.1.5. The estimates for the structural and covariate parameters were similar to the Sponsor's estimates, but the estimates for the random effects were greater in the external replication.

The goodness of fit plots indicate some problems with the external replication model (Figure 19.1.3.1.8). A comparison of the plots of IPRED vs DV and PRED vs DV indicates high shrinkage. IWRES were not normally distributed. However, the plots of CWRES indicate an appropriate specification of the residual error model. The VPC indicated a poor agreement for the predicted to the observed values (Figure 19.1.3.1.9).

Evaluator's comments

The Sponsor's analysis was not conducted and/or reported in accordance with the Guideline on Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06). The Sponsor did not undertake any model development, and did not provide a table of the steps in the development of the structural and error models, or a table for all the steps in the development of the covariate model. All the covariate data were not used in the model development e.g. creatinine clearance was not explored. The model selection criteria were not adequately described and were not acceptable.

However, the data were described in sufficient detail; the methods for imputing missing data and BLQ observations were described and were acceptable. Goodness of fit plots and VPCs were the primary means of model selection and validation. The model validation steps were acceptable and supported the final model.

The model was not described in sufficient detail in the Sponsor's report to enable replication. There were several components of the model apparent in the control file that was not described in the report. These include the logit function used to estimate the fraction of the subcutaneous dose absorbed rapidly; and the allometric scaling of the clearance and volume of distribution parameters. Although the logit function was written into the Sponsor's code, the implementation of the logit function was suboptimal. Boundaries were used for the estimate, although a logit function is designed to make boundaries redundant.

The differences between the Sponsor's and the external replication results are primarily in the estimation of IIV. The difference between the models is that the Sponsor was able to fix some the estimates of IIV in NONMEM and retain the block structure, but in NLME whilst it is possible to fix some of the IIV estimates, the block structure containing these estimates is lost. This is intuitive, because if an estimate of IIV is fixed, it is not possible to adjust or estimate the covariance with other IIV estimates.

Shrinkage was not reported in the study report but can be extracted from the NONMEM output files and is displayed in Table 19.1.3.1.5. For the Sponsor's final model, ETA shrinkage was excessive for Q and K14. In the external replication ETA shrinkage was excessive for all of the IIV parameters.

Both the Sponsor's and the external replication models had a total of 73 parameters. The large number of parameters was due to the complicated error model, with an omega block structure. Each omega (IIV) increased the size of the omega block, and in total the omega block contributed 45 parameters to the model. In addition, there were 10 structural parameters, 10 IIV parameters, two residual error parameters and 6 covariate parameters. Four of the parameters in the external replication model were fixed, and not estimated. Hence, there were 69 parameters estimated in the external replication model. Eight of the parameters in the Sponsor's model were fixed, and not estimated. Hence, there were 65 parameters estimated in the external replication model. These models are both likely to be over-parameterised.

The model could have been simplified in the following way:

- Dropping the IIV parameters for those structural parameters that were fixed: Q, V5, K14 and F1. This would automatically have reduced the number of parameters in the omega block from 45 to 15. The total number of parameters estimated by the Sponsor's model would be reduced to 35.
- Having a block-diagonal omega structure, where an omega block was used only for those parameters likely to be correlated, e.g. CL and V4.

The description of the data from the model indicates a high degree of inter-individual variability in absorption and in distribution for the subcutaneous formulation. However, there has also been a missed opportunity with the Sponsor's model to estimate inter-occasion variability. This would have been of particular interest with the absorption characteristics of the subcutaneous

formulation. It is of clinical interest whether the absorption of buprenorphine from the subcutaneous formulation is predictable from one treatment cycle to the next.

With these issues in mind, the Sponsor's model provided a description of the data that was adequate to use for deriving exposure parameters. However, the Sponsor did not derive these parameters and did not quantify the variability in exposure to buprenorphine (as measured by C_{max}, T_{max}, C_{min} and AUC) following SUBLOCADE. This is clinically relevant information and would be useful to healthcare practitioners prescribing and monitoring SUBLOCADE.

Although the model is an adequate description of the data and suitable for deriving secondary exposure parameters, the model would not be suitable for deriving dosing in different populations or for deriving alternative dosing regimens. In addition, although the model indicates a high degree of variability in PK between individuals there is no information about variability in absorption PK for doses in the same individual.

19.1.3.1. STUDY INDV-6000-M04 (PKPD)

Statistical Analysis Plan

A statistical analysis plan was provided and appears to have been adhered to.

Objectives

- To develop a population PK model describing buprenorphine plasma concentration-vs-time profiles following repeated RBP-6000 SC injections and to assess the influence of selected subject characteristics on the PK of RBP-6000
- To develop exposure-response relationships between buprenorphine plasma concentration and the selected clinical efficacy variables,
- To assess the influence of selected subject characteristics on the PK/PD of RBP-6000.

Data

The data were obtained from Study RB-US-12-0005 and the Phase III double-blind, randomized, efficacy study RB-US-13-0001 (see data, Section 19.1.3.1). In addition to PK measures taken during these studies there was also collection of outcomes data:

- Illicit drug use measured by urine drug screen (UDS) and self-reported illicit drug use. The urine drug screen was for codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Opioid craving visual analogue score (VAS) transformed into a four-category variable
- COWS score
- SOWS score

Genetic variability in response was also evaluated by collecting:

Drug metabolizing genotypes:

- CYP3A4: rs55785340 (CYP3A4*2), rs2740574 (CYP3A4*1B) and rs35599367(CYP3A4*22)
- CYP2C8: rs10509681 (CYP2C8*3)
- UGT1A1: rs8175347 (UGT1A1*28)

Opioid receptor subtype genotypes:

- Opioid receptor mu (OPRM1): rs1799971
- Opioid receptor delta (OPRD1): rs2234918, rs581111 and rs678849
- Opioid receptor kappa (OPRK1): rs1051660
- Dopamine D2 receptor (DRD2): rs1800497

The subject demographic, genetic and baseline characteristics are summarised in Table 19.1.3.2.1 and Table 19.1.3.2.2.

Methods

The dataset was prepared using R (version 3.3.3). Missing data were not imputed. The pharmacometric analysis was performed using NONMEM Version 7.3. Perl-speaks-NONMEM (PsN) was used to interact with NONMEM and R was used for graphical analysis of the NONMEM output. The estimation method was the Stochastic Approximation Expectation-Maximisation (SAEM) method and importance sampling was used to obtain the RSE for the parameter estimates following model estimation with SAEM.

IIV was described using exponential models. Residual error was modelled using a combined additive and proportional error model.

Model selection criteria were stated to be:

- Objective function values (ΔOFV: 3.84, corresponding to a p-value of 0.05 for 1 degree of freedom)
- Goodness-of-fit (GOF) plots. The GOF plots were assessed graphically by evaluation of the agreement between observed and predicted plasma concentrations, the individual predicted profiles vs time, the range of individual weighted residuals (IWRES), conditional weighted residuals (CWRES) and expected weighted residuals (EWRES), and uniformity of the distribution of these residuals about zero across the range of the predicted concentrations.
- The percentage relative standard errors (% RSE) of the parameter estimates and reductions in both IIV and RUV were also used to discriminate between competing models.

The covariate model was performed using an automated procedure in PsN with a forward inclusion (p-value of 0.05) and backward elimination (p-value of 0.01) stepwise approach.

The covariates investigated in the population PK modelling were:

- Demographic characteristics: age, sex, weight, BMI, waist to hip ratio (WHR), African American
- Genetic status with regard to CYP3A4, CYP2C8, UGT1A1 and UGT2B7
- Lab data: AST, ALT, creatinine clearance (CrCL)

The final model was evaluated using VPCs

The covariate analysis for the PD model included demographic characteristics, opioid receptor genotype, route of use of illicit opioids, baseline employment status, baseline health insurance status, baseline depression status, baseline brief pain inventory and clinical global impression of disease severity.

The PKPD analysis was structured as a time to event analysis of either opioid illicit use or opioid craving. The event was characterised as dropout. Both models were E_{max} (direct effect) models with the exposure variable being buprenorphine concentration. PKPD modelling was not performed for the COWS or SOWS scores.

The analysis was performed using NONMEM in the same manner as the PK analysis.

Results

The base PK model was the same as the structural PK model for Study INDV-6000-M05 (Section 19.1.3.1). The parameter estimates are summarised in Table 19.1.3.2.3. The covariate model included covariate effects for BMI on K24 and CL and for SEX on K36. The covariate selection steps are summarised in Figure 19.1.3.2.1. The parameter estimates for the final population PK model are summarised in Table 19.1.3.2.4. The VPC indicates a good fit for the model to the data (Figure 19.1.3.2.2).

The Sponsor developed a dropout model with baseline effects, placebo effect and effects for craving, race, age and CGI (Table 19.1.3.2.5). The model predictions were in good agreement with the observed data from the Kaplan-Meier plot (Figure 19.1.3.2.3).

The Sponsor then developed a PKPD model for illicit opioid use (Table 19.1.3.2.6). This model describes covariate effects for opioid receptor genotype, employment status and African American race. Some of these covariate effects had extremely high %RSE for the estimate: effect on EC_{50} for African American was 910% and on α for TC genotype of OPRD1 was 150%. IIV was high for ED_{50} at 151.2%, and for E_{max} at 38.7%. The model-based predictions were in agreement with the observed values (Figure 19.1.3.2.4)

The Sponsor developed an E_{max} model for opioid craving (Table 19.1.3.2.7). This model describes a covariate effect for BMI. In the model EC_{50} was fixed and not estimated, which limits the model's utility for dose finding. The VPC for the model indicated a good predictive performance relative to observed values (Figure 19.1.3.2.5).

The Sponsor did not perform formal PKPD analysis using COWS score at the outcome measure. However, graphical analysis demonstrated a plateau in effect from a plasma concentration of 4 mg/mL (Figure 19.1.3.2.6). The same relationship was observed with SOWS scores (Figure 19.1.3.2.7).

Evaluator's comments

The Sponsor's analysis was not conducted and/or reported in accordance with the Guideline on Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06). There was no imputation of missing data. BLQ observations were not imputed but were deleted from the dataset. The Sponsor did not provide a table of the steps in the development of the structural and error models, or a table for all the steps in the development of the covariate model. The model selection criteria were not adhered to. Goodness of fit plots and VPCs were the primary means of model selection and validation, but %RSE of the parameter estimates and ETA shrinkage were not considered.

However, the data were described in sufficient detail; the Sponsor provided a log-file of the covariate modelling steps (in lieu of a table); and the model validation steps were acceptable and supported the final model.

The model selection criteria did not include precision of the parameter estimates. As a result of this, parameters with poor precision was included in the final models (e.g. African American effect on EC_{50} had a %RSE of 910%). Although the Sponsor stated %RSE of the parameter estimates would be used as a model selection criterion, this does not appear to have been adhered to.

Shrinkage was not reported and does not appear to have been considered in the construction of the error model. On examining the NONMEM output for the final PK model, ETA shrinkage was 58% for ETA 7 (IIV for absorption rate constant for SL absorption), 48% for ETA 9 (IIV for Q) and 32% for ETA 10 (IIV for peripheral volume of distribution). These IIV parameters were not of major interest in the analysis and could have been deleted without affecting the informativeness of the model. Overall these issues imply that the model was not sufficiently considered or developed.

The modelling strategy did not consider inter-occasion variability. This would be of clinical interest because of the high degree of inter-individual variability in the absorption of the subcutaneous formulation. It is of clinical interest whether this variability also applies between doses. This relates to the predictability of response in each individual patient with subsequent doses.

In the opinion of the Evaluator the Sponsor's model is useful as a descriptive model of the data but is of limited utility in deriving new dosing regimens or in extrapolation to other patient populations.

19.1. Other supporting tables and figures

Table 19.1.3.1.1 Summary of Studies Included in the Analysis (copied from Table 1, Study INDV-6000-M05)

Study No.	Objectives/Design	Dosing Regimen/Subject Number[1]	Population	PK Sampling
RB-US-12-0005	Phase IIA multiple ascending dose safety and tolerability study	Repeated (≥4) SC injections separated by 28 days SUBUTEX/RBP-6000 dose: Cohort 1: 8 mg/50 mg (N=15) Cohort 2: 12 mg/100 mg (N=15) Cohort 3: 24 mg/200 mg (N=15) Cohort 4: 8 mg/100 mg (N=15) Cohort 5: 14 mg/200 mg (N=15) Cohort 6: 8-24 mg/300 mg (N=14) [Subjects were inducted and stabilized over 13 days on SUBUTEX at doses of 8, 12, 14, 24 mg or 8-24 mg prior to receiving RBP-6000] [2 of the 89 subjects participated in the PET Scan sub-study]	Opioid-dependent treatment seeking subjects Males and females 18-65 years of age BMI: 18 – 33 kg/m^2	Rich PK sampling PET sub-study: Rich PK sampling up to injection 4 and sparse PK sampling thereafter. Additional PK sampling prior to each PET Scan.
RB-US-13-0001	Phase III, double-blind, placebo-controlled, 24-week, efficacy, safety and tolerability study	300 mg/300 mg active group: 300 mg for 6 injections separated by 28 +/- 2 days (N = 201) 300 mg/100 mg active group: 300 mg for the first 2 injections followed by 100 mg for the subsequent 4 injections separated by 28+/- 2 days (N = 203) Placebo group: volume-matched to 300 mg/300 mg group or 300 mg/100 mg group) (N = 100)	Opioid-dependent treatment-seeking subjects Males and females 18-65 years of age BMI: 18 – 35 kg/m^2	Sparse PK sampling

Table 19.1.3.1.1 (cont)

Study No.	Objectives/Design	Dosing Regimen/Subject Number[1]	Population	PK Sampling
		Subjects were inducted using SUBOXONE SL film for 3 days, followed by 4- to 11-day SUBOXONE SL film dose adjustment at buprenorphine doses ranging from 8 to 24 mg/day]		
RB-US-13-0003	Phase III long-term open-label safety and tolerability study (extension of Study RB-US-13-0001)	*De novo* subjects: 300 mg for the first SC injection, followed by 300 mg or 100 mg in each of 11 subsequent SC injections separated by 28 +4/-2 days (N = 412) Roll-over subjects (from Study RB-US-13-0001): 300 mg for the first SC injection, followed by 300 mg or 100 mg in each of 5 subsequent SC injections separated by 28 +4/-2 days (N = 257) All subjects were inducted on SUBOXONE SL film for 3 days. Roll-over subjects had to be titrated to a minimum buprenorphine dose of 8 mg by the end of the 3-day induction period regardless of their COWS scores and/or the presence or absence of withdrawal symptoms. After the daily induction visits, all subjects began a 1-to 11-day SUBOXONE SL film dose adjustment period to achieve total doses of buprenorphine between 8 mg to 24 mg	Opioid-dependent treatment-seeking subjects Males and females 18-65 years of age BMI: 18 - 35 kg/m^2	Sparse PK sampling

BMI=body mass index; COWS=Clinical Opiate Withdrawal Scale; N=number of subjects; PET=positron emission tomography; PK=pharmacokinetic; SC=subcutaneous; SL=sublingual

[1] Safety population

Table 19.1.3.1.2 Subjects and Observation Disposition Summary (copied from Table 3, Study INDV-6000-M06)

Study	Arm	Number of Subjects	Number of Subjects w/ PK	Number of PK Observations	Number of SUBOXONE/ SUBUTEX[c] PK Observations	Number of RB-6000 PK Observations
Phase II						
RB-US-12-0005	50 mg (Cohort 1)	15	15	960	210	750
	100 mg (Cohort 2)	15	15	970	210	760
	200 mg (Cohort 3)	15	15	922	210	712
	100 mg (Cohort 4)	15	15	900	209	691
	200 mg (Cohort 5)	15	15	1034	210	824
	300 mg (Cohort 6)	14	14	881	201	680
	300 mg (Subutex only subjects)	14	14	206	206	.
Phase III						
RB-US-13-0001	300 mg/100 mg	194	194	5733	341	5392
	300 mg/300 mg	196	194	5598	329	5269
	Placebo	99	16	31	31	.
RB-US-13-0003	Rollover from active treatment	222	222	2107	221	1886
	De novo	33	31	62	24	38
	Rollover from placebo	32	32	282	25	257
		879[a]	***792[b]***	***19686***	***2910***	***16776***

a: N=625 individuals

b: N=570 individuals

c: SUBUTEX was administered in the run-in phase in Study RB-US-12-0005; SUBOXONE was administered in the run-in phase in Study RB-US-13-0001 and Study RB-US-13-0003

Table 19.1.3.1.3 Demographics Characteristics for Subjects Included in the Population PK Analysis (copied from Table 4, Study INDV-6000-M05)

Characteristic		All Individual Subjects	RB-US-12-0005	RB-US-13-0001	RB-US-13-0003
	N (%)	540 (100.0%)	103 (19.07%)	404 (74.8%)	287 (53.1%)
Age (years)	Mean (SD)	38.8 (11.5)	34.1 (11.9)	39.7 (11.0)	40.8 (11.2)
	Median	37.0	30.0	38.0	39.0
	Min - Max	19.0 - 64.0	19.0 - 60.0	19.0 – 64.0	20.0 – 64.0
Body weight (kg)	Mean (SD)	76.5 (15.5)	72.9 (13.1)	77.5 (15.9)	77.0 (16.2)
	Median	75.0	72.0	75.6	75.0
	Min - Max	46.1 - 132.0	48.1 - 109.1	46.1 - 129.2	46.1 - 132.0
BMI (kg/m^2)	Mean (SD)	25.4 (4.2)	24.7 (3.4)	25.6 (4.3)	25.6 (4.4)
	Median	24.8	24.2	24.9	24.9
	Min - Max	18.0 - 35.0	18.4 - 32.2	18.0 - 34.9	18.0 - 35.0
Sex	Male	387 (67.9%)	72 (69.9%)	270 (66.8%)	193 (32.8%)
	Female	183 (32.1%)	31 (30.1%)	134 (33.2%)	94 (32.8%)
Race	Black or African American	161 (28.2%)	31 (30.1%)	111 (27.5%)	95 (33.1%)
	Others	409 (71.8%)	72 (69.9)	293 (72.5 %)	192 (66.9%)

Table 19.1.3.1.4 Model Parameter Estimates for RBP-6000 Population Pharmacokinetic Model (copied from Table 5, Study INDV-6000-M05)

		Studies RB-US-12-0005 and RB-US-13-0001			Studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003		
		Population Value (θ)	Inter-Individual Variability (ω^2)		Population Value (θ)	Inter-Individual Variability (ω^2)	
Parameter	Description	Estimate (%RSE)	Estimate (%RSE)	%CV	Estimate (%RSE)	Estimate (%RSE)	%CV
CL/F (L/hr)	RBP-6000 apparent elimination clearance	49.8 (2.79)	0.121 (16.4)	35.9	52.0 (1.53)	0.0871 (9.45)	30.2
V4/F (L)	RBP-6000 apparent volume of central compartment	462 (7.45)	0.775 (39.6)	108	433 (26.7)	0.647 (12.2)	95.4
Q/F (L/hr)	RBP-6000 apparent distribution clearance	79.5 (FIXED)	0.334 (FIXED)	63.0	79.5 (FIXED)	0.334 (FIXED)	63.0
V5 (L)	RBP-6000 apparent volume of peripheral compartment	1110 (FIXED)	0.941 (FIXED)	125	1110 (FIXED)	0.941 (FIXED)	125
K14	Sublingual absorption rate constant (h-1)	1.17 (FIXED)	0.190 (FIXED)	45.7	1.17 (FIXED)	0.190 (FIXED)	45.7
K24 (1/hr)	Fast absorption rate constant from SC depot	0.0294 (9.86)	**0.758 (41.0)**	106	0.0276 (5.07)	0.654 (15.7)	96.1
K36 (1/hr)	Slow absorption rate constant from SC depot	0.00370 (8.30)	1.65 (12.6)	205	0.00362 (7.38)	1.54 (10.9)	191
K64 (1/hr)	Rate constant from Transit compartment to Central	0.000480 (5.42)	0.580 (12.3)	88.7	0.000510 (3.73)	0.432 (10.5)	73.5
F1	Relative bioavailability of SUBUTEX compared to RBP-6000	0.185 (FIXED)	0.195 (FIXED)	46.4	0.185 (FIXED)	0.195 (FIXED)	46.4
F2	Fraction of RBP-6000 dose absorbed by fast process	0.0661 (2.84)	0.223 (13.3)	50.0	0.0679 (2.24)	0.204 (11.2)	47.6

Table 19.1.3.1.4 (cont)

Parameter	Description	Studies RB-US-12-0005 and RB-US-13-0001			Studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003		
		Population Value (θ)	Inter-Individual Variability (ω^2)		Population Value (θ)	Inter-Individual Variability (ω^2)	
		Estimate (%RSE)	Estimate (%RSE)	%CV	Estimate (%RSE)	Estimate (%RSE)	%CV
FRK14	Relative change of K14 of SUBUXONE to SUBUTEX	0.898 (28.4)	NA	NA	0.650 (11.2)	NA	NA
FRF1	Relative change of F1 of SUBUXONE to SUBUTEX	1.37 (9.12)	NA	NA	1.47 (3.52)	NA	NA
F1DOSE	Relative change of F1 for dose ≥16mg compared to dose <16mg	0.765 (35.6)	NA	NA	0.765 (FIXED)	NA	NA
BMI on CL	BMI effect on Clearance (power model)	-0.408 (20.8)	NA	NA	-0.364 (20.9)	NA	NA
BMI on K24	BMI effect on fast absorption rate constant from SC depot (power model)	-1.29 (15.0)	NA	NA	-1.32 (13.9)	NA	NA
Sex on K36	Sex effect on slow absorption rate constant from SC depot	0.0759 (139.7)	NA	NA	0.0313 (281.5)	NA	NA
		Residual Variability Estimate (%RSE)			Residual Variability Estimate (%RSE)		
PROP	Proportional residual error	0.190 (0.974)			0.190 (0.658)		
ADD	Additive residual error	0.0378 (13.5)			0.0373 (13.6)		

Table 19.1.3.1.5 Comparison of estimates from the Sponsors and External Replication models

	Sponsor's Estimates			External Replication Estimates		
Parameter	Estimate	IIV (CV%)	Shrinkage	Estimate	IIV (CV%)	Shrinkage
CL/F (L/h)	52.0	30.2	16%	48.0	23.3	41%
V4/F (L)	433	95.4	20%	510	102.7	43%
Q/F (L/h)	79.5 (FIX)	63.0 (FIX)	49%	79.5 (FIX)	190.5	54%
V5 (L)	1110 (FIX)	125 (FIX)	16%	1110 (FIX)	274.6	45%
K14 (h^{-1})	1.17 (FIX)	45.7 (FIX)	50%	1.17 (FIX)	193.7	54%
K24 (h^{-1})	0.0276	96.1	19%	0.0503	207.3	63%
K36 (h^{-1})	0.00362	191	20%	0.0189	400.3	62%
K64 (h^{-1})	0.000510	73.5	28%	0.000811	291.5	54%
F1	0.185 (FIX)	46.4 (FIX)	0%	0.185 (FIX)	87.3	40%
F2	0.0679	47.6	28%	0.0562	84.4	52%
FRK14	0.650			0.556		
FRF1	1.37			1.67		
F1DOSE	0.765			1.04		
BMI on CL	-0.364			-0.0556		
BMI on K24	-1.32			-0.280		
SEX on K36	0.0313			0.292		
PROP	0.190		7.2%	0.0713		35%
ADD (ng/mL)	0.0378			0.001		

Table 19.1.2.2.1 Subject Characteristics for Subjects of Study RB-US-13-0001 Included in the Pharmacometric Analyses (copied from Table 6, Study INDV-6000-M04)

Characteristics	Level	300 mg/100 mg	300 mg/300 mg	Placebo	p-value
N		194	196	99	
Age (years, mean (SD))		40.42 (11.23)	39.34 (10.96)	39.19 (10.96)	0.538
Body weight(kg, mean (SD))		76.23 (15.89)	79.27 (16.11)	75.08 (16.00)	0.058
Body mass index (kg/m^2, mean (SD))		25.18 (4.24)	26.24 (4.36)	25.17 (4.25)	0.029
Waist to hip ratio (WHR, mean (SD))		0.90 (0.08)	0.90 (0.08)	0.90 (0.07)	0.88
Alanine Aminotransferase (IU/L, mean (SD))		26.91 (19.29)	26.61 (17.25)	29.63 (25.64)	0.464
Aspartate Aminotransferase (IU/L, mean (SD))		27.47 (14.24)	26.65 (13.40)	28.57 (18.26)	0.593
Direct bilirubin (mg/dL, mean (SD))		0.15 (0.08)	0.16 (0.10)	0.15 (0.07)	0.723
Total bilirubin (mg/dL, mean (SD))		0.42 (0.20)	0.44 (0.28)	0.42 (0.22)	0.636
Creatinine clearance (mL/min, mean (SD)))		118.92 (32.48)	123.98 (34.35)	123.23 (30.35)	0.294
RACE (N(%))	American Native	4 (2.1)	1 (0.5)	1 (1.0)	0.521
	Black	56 (28.9)	54 (27.6)	20 (20.2)	
	Multiple	2 (1.0)	1 (0.5)	1 (1.0)	
	White	132 (68.0)	140 (71.4)	77 (77.8)	
SEX (N(%))	Female	66 (34.0)	64 (32.7)	35 (35.4)	0.893
	Male	128 (66.0)	132 (67.3)	64 (64.6)	
CGI-S status at Baseline(N(%))	Borderline	2 (1.0)	2 (1.0)	2 (2.0)	0.091
	Markedly ill	67 (34.5)	63 (32.1)	33 (33.3)	
	Mildly ill	8 (4.1)	14 (7.1)	6 (6.1)	
	Moderately ill	72 (37.1)	63 (32.1)	37 (37.4)	
	Normal	19 (9.8)	33 (16.8)	7 (7.1)	
	Severely ill	15 (7.7)	11 (5.6)	2 (2.0)	
	Missing	11 (5.7)	10 (5.1)	12 (12.1)	
Beck Depression Score at Baseline (N(%))	Mild	17 (8.8)	16 (8.2)	8 (8.1)	0.917
	Minimal	45 (23.2)	39 (19.9)	18 (18.2)	
	Moderate	17 (8.8)	19 (9.7)	13 (13.1)	
	Severe	26 (13.4)	25 (12.8)	10 (10.1)	
	Missing	89 (45.9)	97 (49.5)	50 (50.5)	
Health Insurance at Baseline (N(%))	Insured	108 (55.7)	111 (56.6)	52 (52.5)	0.209
	Not insured	77 (39.7)	78 (39.8)	37 (37.4)	
	Missing	9 (4.6)	7 (3.6)	10 (10.1)	
Employment Status at Baseline (N(%))	Employed	55 (28.4)	76 (38.8)	34 (34.3)	0.03
	Unemployed	130 (67.0)	113 (57.7)	55 (55.6)	
	Missing	9 (4.6)	7 (3.6)	10 (10.1)	
Use of Opioids by injection at Baseline (N(%))	No	110 (56.7)	116 (59.2)	49 (49.5)	0.281
	Yes	84 (43.3)	80 (40.8)	50 (50.5)	
CYP2C8*3 (rs10509681) (N(%))	CC	1 (0.5)	2 (1.0)	0 (0.0)	0.553
	TC	23 (11.9)	33 (16.8)	14 (14.1)	
	TT	160 (82.5)	147 (75.0)	81 (81.8)	
	Missing	10 (5.2)	14 (7.1)	4 (4.0)	
CYP3A4*22 (rs35599367) (N(%))	AA	0 (0.0)	1 (0.5)	0 (0.0)	0.774
	GA	9 (4.6)	13 (6.6)	6 (6.1)	
	GG	175 (90.2)	169 (86.2)	89 (89.9)	
	Missing	10 (5.2)	13 (6.6)	4 (4.0)	
CYP3A4*2 (rs55785340) (N(%))	AA	183 (94.3)	183 (93.4)	95 (96.0)	0.654
	GA	1 (0.5)	0 (0.0)	0 (0.0)	

Table 19.1.3.2.1 (cont)

Characteristics	Level	300 mg/100 mg	300 mg/300 mg	Placebo	p-value
	Missing	10 (5.2)	13 (6.6)	4 (4.0)	
CYP3A4*1B (rs2740574) (N(%))	CC	25 (12.9)	26 (13.3)	6 (6.1)	0.25
	TC	36 (18.6)	32 (16.3)	12 (12.1)	
	TT	122 (62.9)	124 (63.3)	76 (76.8)	
	Missing	11 (5.7)	14 (7.1)	5 (5.1)	
DRD2 (rs1800497) (N(%))	AA	9 (4.6)	15 (7.7)	4 (4.0)	0.724
	GA	69 (35.6)	68 (34.7)	34 (34.3)	
	GG	106 (54.6)	100 (51.0)	57 (57.6)	
	Missing	10 (5.2)	13 (6.6)	4 (4.0)	
OPRD1 (rs2234918) (N(%))	CC	43 (22.2)	49 (25.0)	27 (27.3)	0.679
	TC	92 (47.4)	98 (50.0)	46 (46.5)	
	TT	49 (25.3)	36 (18.4)	22 (22.2)	
	Missing	10 (5.2)	13 (6.6)	4 (4.0)	
OPRD1 (rs581111) (N(%))	AA	39 (20.1)	32 (16.3)	18 (18.2)	0.716
	GA	71 (36.6)	82 (41.8)	45 (45.5)	
	GG	74 (38.1)	69 (35.2)	32 (32.3)	
	Missing	10 (5.2)	13 (6.6)	4 (4.0)	
OPRD1 (rs678849) (N(%))	CC	66 (34.0)	68 (34.7)	33 (33.3)	0.855
	TC	80 (41.2)	78 (39.8)	47 (47.5)	
	TT	38 (19.6)	37 (18.9)	15 (15.2)	
	Missing	10 (5.2)	13 (6.6)	4 (4.0)	
OPRK1 (rs1051660) (N(%))	AA	0 (0.0)	5 (2.6)	0 (0.0)	0.09
	CA	32 (16.5)	28 (14.3)	11 (11.1)	
	CC	150 (77.3)	145 (74.0)	82 (82.8)	
	Missing	12 (6.2)	18 (9.2)	6 (6.1)	
OPRM1 (rs1799971) (N(%))	AA	143 (73.7)	157 (80.1)	82 (82.8)	0.355
	GA	40 (20.6)	25 (12.8)	13 (13.1)	
	GG	1 (0.5)	1 (0.5)	0 (0.0)	
	Missing	10 (5.2)	13 (6.6)	4 (4.0)	
UGT2B7*3 (rs12233719) (N(%))	GG	184 (94.8)	183 (93.4)	95 (96.0)	0.628
	Missing	10 (5.2)	13 (6.6)	4 (4.0)	
UGT1A1 (rs8175347) (N(%))	TA5TA5	0 (0.0)	1 (0.5)	0 (0.0)	0.746
	TA5TA6	1 (0.5)	3 (1.5)	3 (3.0)	
	TA5TA7	2 (1.0)	0 (0.0)	1 (1.0)	
	TA5TA8	1 (0.5)	1 (0.5)	0 (0.0)	
	TA6TA6	73 (37.6)	77 (39.3)	42 (42.4)	
	TA6TA7	79 (40.7)	70 (35.7)	39 (39.4)	
	TA6TA8	2 (1.0)	2 (1.0)	1 (1.0)	
	TA7TA7	24 (12.4)	24 (12.2)	10 (10.1)	
	TA7TA8	1 (0.5)	4 (2.0)	0 (0.0)	
	Missing	11 (5.7)	14 (7.1)	3 (3.0)	

Table 19.1.3.2.2 Subject Characteristics for Subjects in Study RB-US-12-0005 Included in the Pharmacometric Analyses (copied from Table 7, Study INDV-6000-M04)

Characteristics	Level	Overall
N		118
Age (years, mean (SD))		34.12 (11.90)
Body weight(kg, mean (SD))		73.01 (13.03)
Body mass index (kg/m^2, mean (SD))		24.68 (3.46)
Alanine Aminotransferase (IU/L, mean (SD))		25.84 (11.70)
Aspertate Aminotransferase (IU/L, mean (SD))		25.24 (6.29)
Direct bilirubin (mg/dL, mean (SD))		0.18 (0.10)
Total bilirubin (mg/dL, mean (SD))		0.49 (0.30)
Creatinine clearance (mL/min, mean (SD)))		120.98 (29.15)
RACE (N(%))	American native	2 (1.7)
	Asian	1 (0.8)
	Black	36 (30.5)
	Unknown	1 (0.8)
	White	78 (66.1)
SEX (N(%))	Female	36 (30.5)
	Male	82 (69.5)

Table 19.1.3.2.3 Final Estimates of the Base Population Pharmacokinetic Model (run029.mod) Developed for the Combined Analysis of Buprenorphine Data from Studies RB-US-12-0005 and RB-US-13- 0001 (copied from Table 11, Study INDV-6000-M04)

PARAMETERS	DESCRIPTIONS	ESTIMATES (RSE%)	VARIANCE (RSE%)	IIV (%)
K14	Sublingual absorption rate constant (h^{-1})	1.17 (FIXED)	0.19 (FIXED)	45.7
K24	Fast absorption rate constant from SC depot ($h^{-}1$)	0.0298 (12)	0.855 (71)	116
K36	Slow absorption rate constant from SC depot (h^{-1})	0.00477 (10)	1.66 (16)	207
K64	Rate constant from Transit compartment to Central (h^{-1})	0.000443 (4)	0.448 (12)	75.2
CL	RBP-6000 apparent elimination clearance (L/h)	49.7 (2.1)	0.123 (30)	36.2
V4	RBP-6000 apparent volume of central compartment (L)	454 (13)	0.799 (66)	111
Q	RBP-6000 apparent distribution clearance (L/h)	79.5 (FIXED)	0.334 (FIXED)	62.9
V5	RBP-6000 apparent volume of peripheral compartment (L)	1110 (FIXED)	0.941 (FIXED)	125
F1	Relative bioavailability of SUBUTEX relative to RBP-6000	0.185 (FIXED)	0.195 (FIXED)	46.4
F2	Fraction of RBP-6000 dose absorbed by fast process	0.0639 (2)	0.19 (15)	45.8
ADD	Additive residual error	0.0361 (16)		
PROP	Proportional residual error	0.19 (1.2)		
FRK14	Fraction of K14 of SUBOXONE relative to SUBUTEX	0.891 (35)		
FRF1	Fraction of F1 of SUBOXONE relative to SUBUTEX	1.38 (8.3)		
F1DOSE	Fraction of F1 for dose $\geq$ 16 mg relative to dose $<$ 16mg	0.733 (34)		

Table 19.1.3.2.4 Estimates of the Final Population Pharmacokinetic Model (run036.mod) for RBP-6000 and SL Buprenorphine Products (SUBUTEX and SUBOXONE) after Combined Analysis of Studies RBUS- 12-0005 and RB-US-13-0001 (copied from Table 12, Study INDV-6000-M04)

PARAMETERS	DESCRIPTIONS	ESTIMATES (RSE%)	VARIANCE (RSE%)	IIV (%)
K14	Sublingual absorption rate constant (h^{-1})	1.17 (FIXED)	0.19 (FIXED)	45.7
K24	Fast absorption rate constant from SC depot ($h^{-}1$)	0.0294 (9.9)	0.758 (41)	107
K36	Slow absorption rate constant from SC depot (h^{-1})	0.0037 (8.3)	1.65 (13)	205
K64	Rate constant from Transit compartment to Central (h^{-1})	0.000483 (5.4)	0.58 (12)	88.6
CL	RBP-6000 apparent elimination clearance (L/h)	49.8 (2.8)	0.121 (16)	35.9
V4	RBP-6000 apparent volume of central compartment (L)	462 (7.4)	0.775 (40)	108
Q	RBP-6000 apparent distribution clearance (L/h)	79.5 (FIXED)	0.334 (FIXED)	62.9
V5	RBP-6000 apparent volume of peripheral compartment (L)	1110 (FIXED)	0.941 (FIXED)	125
F1	Relative bioavailability of SUBUTEX relative to RBP-6000	0.185 (FIXED)	0.195 (FIXED)	46.4
F2	Fraction of RBP-6000 dose absorbed by fast process	0.0661 (2.8)	0.223 (13)	50
ADD	Additive residual error	0.0378 (14)		
PROP	Proportional residual error	0.19 (0.97)		
FRK14	Relative change of K14 of SUBOXONE relative to SUBUTEX	0.898 (28)		
FRF1	Relative change of F1 of SUBOXONE relative to SUBUTEX	1.37 (9.1)		
F1DOSE	Relative change of F1 for dose $\geq$ 16 mg relative to dose $<$ 16mg	0.765 (36)		
$\theta_{bmi} : CL$	Power coefficient for BMI on CL	-0.408 (21)		
$\theta_{bmi} : K24$	Power coefficient for BMI on K24	-1.29 (15)		
$\theta_{female} : K36$	Fractional increase of K36 for Female relative to Male	0.0759 (140)		

Table 19.1.3.2.5 Final Estimates of the Dropout Model (run_DO_24.mod) in Study RB-US-13-0001 (copied from Table 13, Study INDV-6000-M04)

PARAMETERS	DESCRIPTIONS	ESTIMATES (RSE%)
$\beta_{0,TRT}$	Baseline hazard constant for active treatment	0.00459 (17)
$\beta_{0,PBO}$	Baseline hazard constant for placebo treatment	0.0102 (35)
$\beta_{1,TRT:2}$	Coefficient for craving = 1-5 (category 2) in active treatment	0.869 (23)
$\beta_{1,TRT:3}$	Coefficient for craving = 6-20 (category 3) in active treatment	1.29 (28)
$\beta_{1,TRT:4}$	Coefficient for craving > 20 (category 4) in active treatment	2.6 (26)
$\beta_{1,PBO:2}$	Coefficient for craving = 1-5 (category 2) in placebo treatment	0.472 (37)
$\beta_{1,PBO:3}$	Coefficient for craving = 6-20 (category 3) in placebo treatment	0.534 (43)
$\beta_{1,PBO:4}$	Coefficient for craving > 20 (category 4) in placebo treatment	1.72 (32)
β_2	Coefficient for RACE	0.602 (19)
$\beta_{3,PBO}$	Coefficient for Age effect in placebo treatment	-1.64 (27)
$\beta_{4,PBO}$	Coefficient for $CGI - S \leq 3$ in placebo treatment	3.86 (27)
ke_{TRT}	Hazard change rate constant for active treatment	0.00763 (22)
ke_{PBO}	Hazard change rate constant for Placebo treatment	0.00895 (37)

Table 19.1.3.2.6 Parameters Estimates for the Final PK/PD Model (run8.mod) for Illicit Opioid Use in Study RB-US-13-0001 (copied from Table 15, Study INDV-6000-M04)

PARAMETERS	DESCRIPTIONS	ESTIMATES (RSE%)	VARIANCE (RSE%)	SD or IIV(%)
θ_α	The baseline logit for Arms 2 and 3)	-3.3 (16)	6.97 (12)	2.64 (SD)
θE_{max}	Maximal drug effect	4.86 (9.7)	0.139 (63)	38.7
θEC_{50}	Concentration yielding half of E_{max}	1.21 (44)	1.19 (0.77)	151.2
θ_{Arm1}	Relative intercept for Arm1 compared to Arms 2 and 3	0.794 (10)		
$\theta_\alpha(OPRD1_2)$	Fractional change in α for TC genotype of OPRD1(rs678849)	0.133 (150)		
$\theta_\alpha(OPRD1_3)$	Fractional change in α for TT genotype of OPRD1(rs678849)	0.309 (92)		
$\theta EC_{50}(INJUSE)$	Fractional increase of EC_{50} for users of opioids by injectable route	2.57 (47)		
$\theta EC_{50}(OPRD1_2)$	Fractional decrease of EC_{50} for TC genotype of OPRD1(rs678849)	-0.713 (19)		
$\theta EC_{50}(OPRD1_3)$	Fractional decrease of EC_{50} for TT genotype of OPRD1(rs678849)	-0.937 (4)		
$\theta EC_{50}(RACE)$	Fractional decrease of EC_{50} for Blacks/African Americans	-0.113 (910)		
$\theta E_{max}(EMPLY)$	Fractional increase of E_{max} for employed vs. unemployed subjects	0.427 (37)		
$\theta E_{max}(RACE)$	Fractional decrease of E_{max} for Blacks/African Americans	-0.311 (31)		

Table 19.1.3.2.7 Parameters Estimates for the Final PK/PD model (run7.mod) for Opioid Craving in Study RB-US-13-0001 (copied from Table 17, Study INDV-6000-M04)

PARAMETERS	DESCRIPTIONS	ESTIMATES (RSE%)	VARIANCE (RSE%)	SD or IIV(%)
α_1	Baseline value (intercept) of the logit for craving=0 (Arms 2-3)	-2.41 (6.8)	4.42 (9.3)	2.1 (SD)
$\alpha_{1,Arm1}$	Baseline value (intercept) of the logit for craving=0 (Arm 1)	-1.87 (11)		
δ_1	Delta between α_2 and α_1	2.28 (1.7)		
δ_2	Delta between α_3 and α_2	1.85 (2.5)		
E_{max}	Maximal drug effect	2.87 (7.2)	0.7 (14)	101
EC_{50}	Concentration yielding half of E_{max}	2.45 (15)	0 (FIXED)	0 (FIXED)
θ_{BMI}	Exponent of the power model relationship between E_{max} and BMI	0.853 (37)		

Figure 19.1.3.1.1 Structural Model for Buprenorphine after Sublingual and Subcutaneous Administration (copied from Figure 1, INDV-6000-M05)

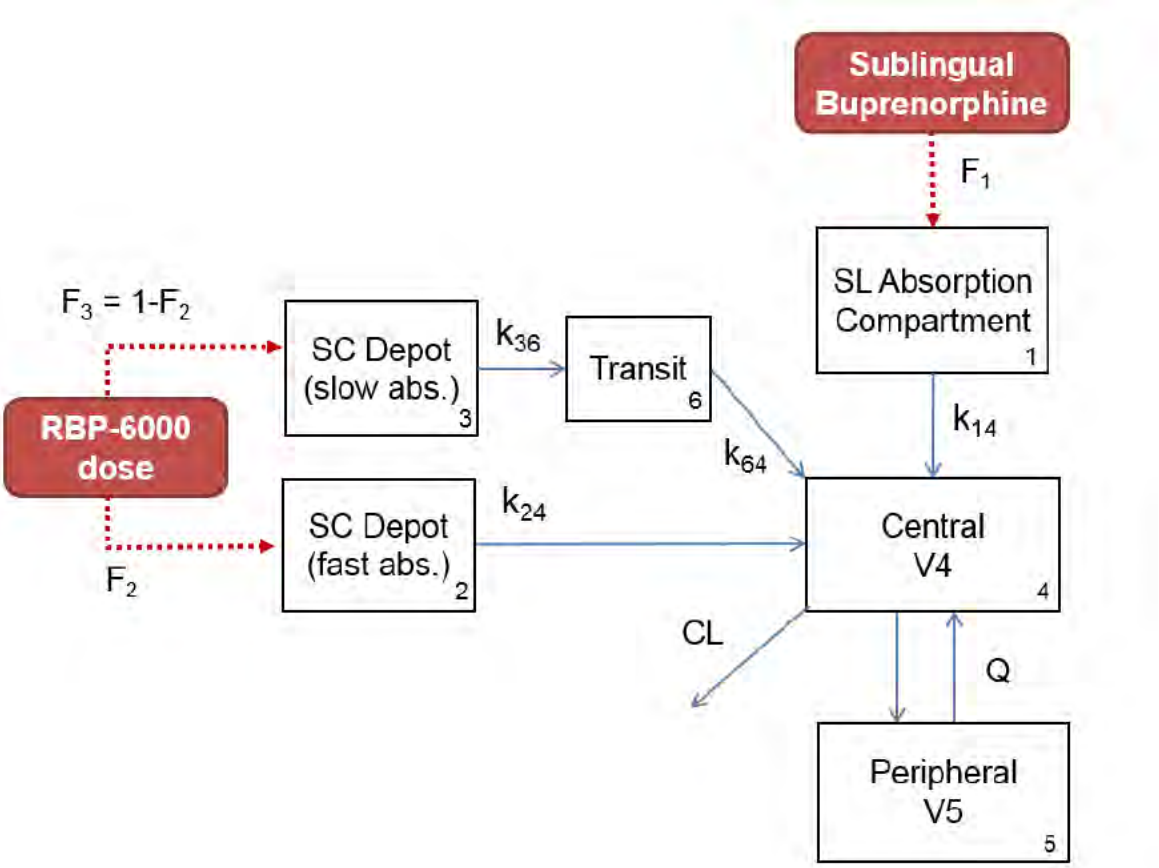
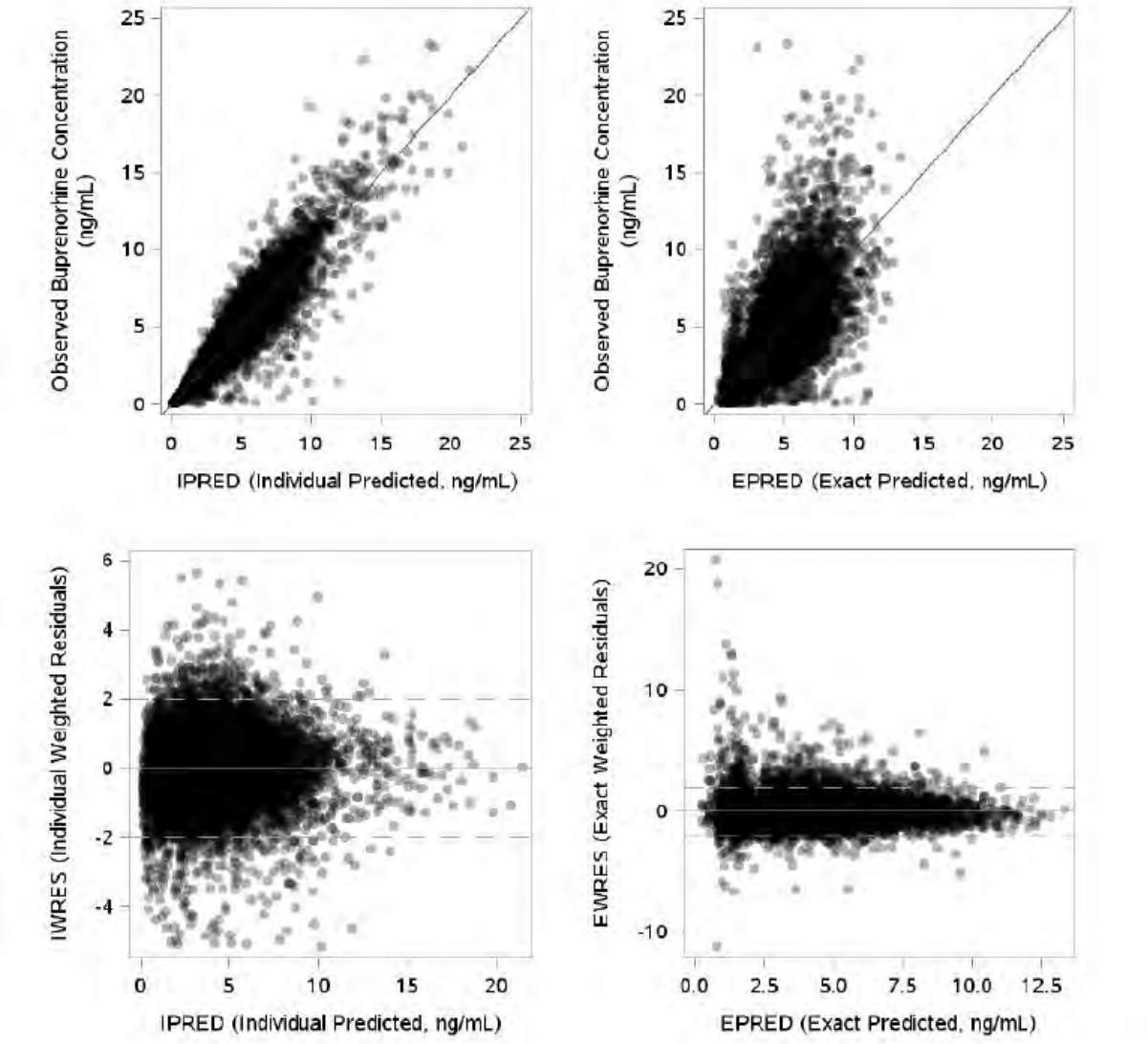
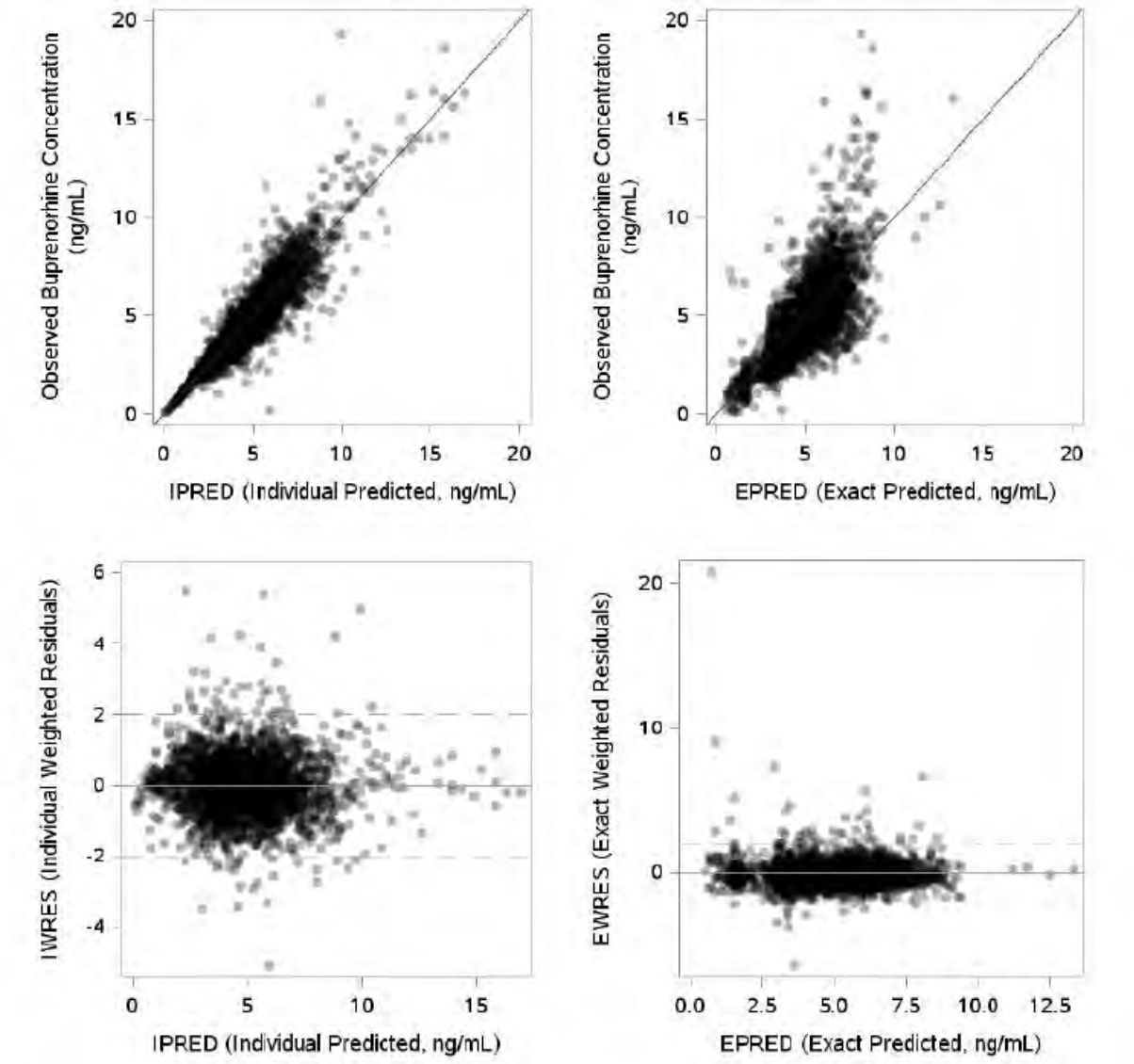


Figure 19.1.3.1.2 Goodness-of-Fit Plots for Phase III Studies Combined (MAXEVAL=0) (copied from Figure 6, Study INDV-6000-M05)



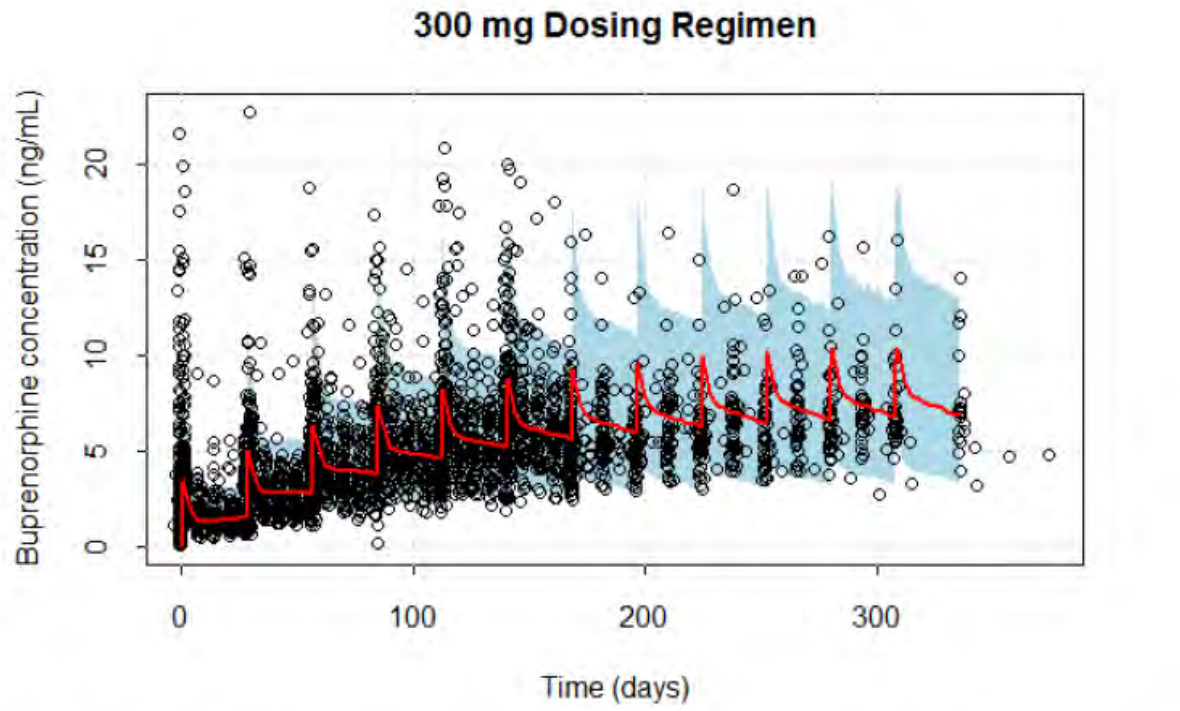
Note:
The blue line (upper panels) represents the line of unity, gray dashed and solid lines (lower panel) are reference lines

Figure 19.1.3.1.3 Goodness-of-Fit Plots for Study RB-US-13-0003 (MAXEVAL=0) (copied from Figure 7, Study INDV-6000-M05)



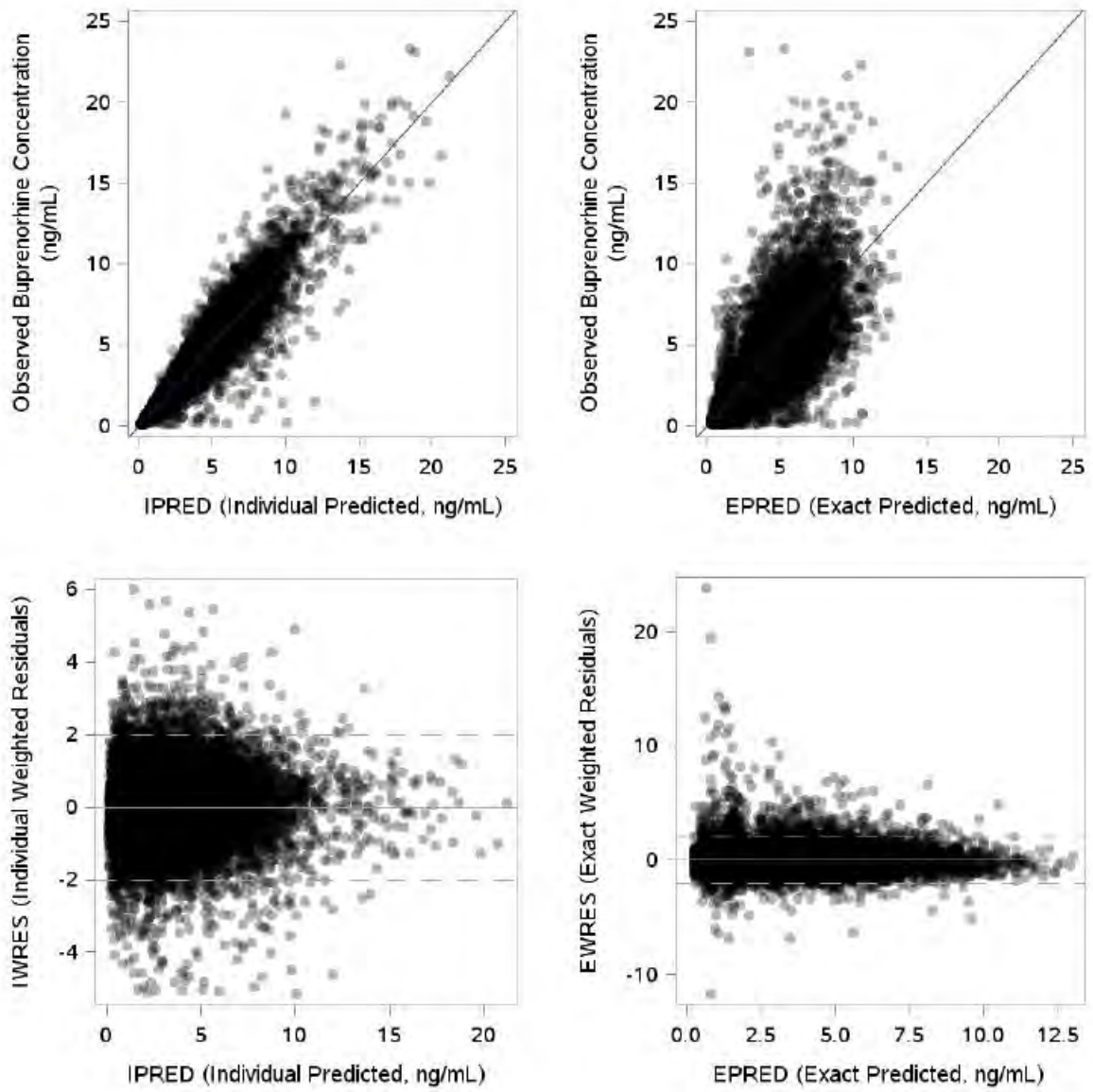
Note:
The blue line (upper panels) represents the line of unity, gray dashed and solid lines (lower panel) are reference lines

Figure 19.1.3.1.4 Visual Predictive Check Plot for Subjects receiving 300 mg RBP-6000 in Studies RB-US-13-0001 and RB-US-13-0003 (copied from Figure 8, Study INDV-6000-M05)



Note: The black circles are observed data from roll-over subjects receiving 300 mg throughout both studies RB-US-13-0001 and RB-US-13-0003 (N=72); Red solid line represents the median of the simulated data; Shaded blue area represents the 90% prediction intervals of the simulated data

Figure 19.1.3.1.5 Goodness-of-Fit Plots for All Studies (re-estimating based on Combined data) (copied from Figure 9, Study INDV-6000-M05)



Note:
The blue line (upper panels) represents the line of unity, gray dashed and solid lines (lower panel) are reference lines

Figure 19.1.3.1.6 Figure 19.1.3.1.6 External replication model structure in NLME

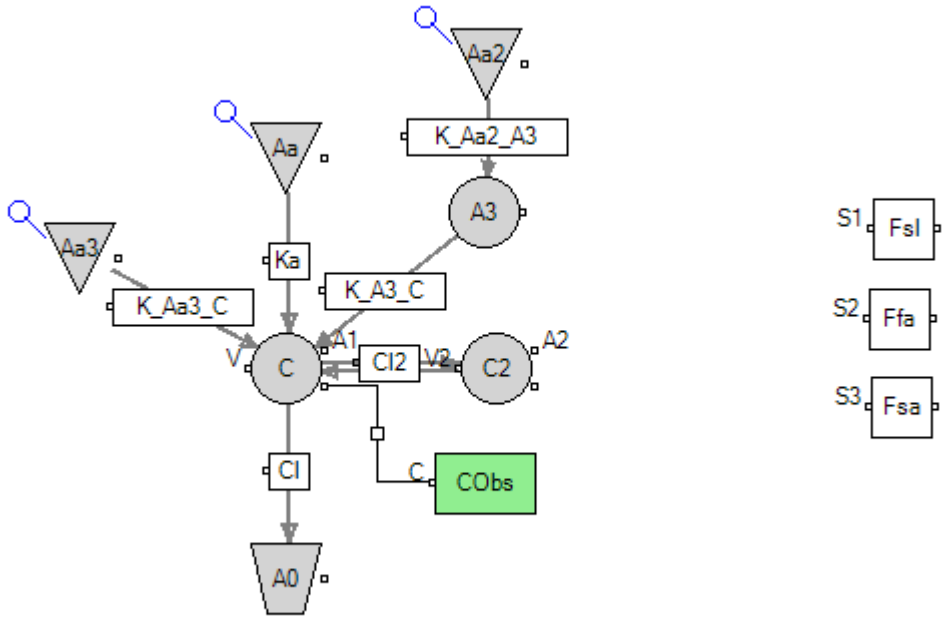


Figure 19.1.3.1.7 External replication model code

```
test(){
        deriv(A1 = - (Cl * C) + (Aa * Ka)- (Cl2 * (C - C2)) + (Aa3 * K_Aa3_C) + (A3 * K_A3_C))
        urinecpt(A0 = (Cl * C))
        deriv(Aa = - (Aa * Ka))
        deriv(A2 = (Cl2 * (C - C2)))
        deriv(Aa2 = - (Aa2 * K_Aa2_A3))
        deriv(A3 = (Aa2 * K_Aa2_A3)- (A3 * K_A3_C))
        deriv(Aa3 = - (Aa3 * K_Aa3_C))
        C = A1 / V
        dosepoint(Aa, bioavail = (Fsl), idosevar = AaDose, infdosevar = AaInfDose, infratevar =
AaInfRate)
        C2 = A2 / V2
        error(CEps = 0.0362917)
        observe(CObs = C + CEps * sqrt(1 + (C)^2 * (CMultStdev/sigma())^2))
        dosepoint(Aa2, bioavail = (Fsa), idosevar = Aa2Dose, infdosevar = Aa2InfDose,
infratevar = Aa2InfRate)
        dosepoint(Aa3, bioavail = (Ffa), idosevar = Aa3Dose, infdosevar = Aa3InfDose, infratevar
= Aa3InfRate)
        stparm(V = tvV * (WEIGHT/70)^dVdWEIGHT * exp(nV))
        stparm(Cl = tvCl * (BMI/24.8)^dCldBMI * (WEIGHT/70)^dCldWEIGHT * exp(nCl))
        stparm(Ka = tvKa * (1+ dkaSLFORM1*(SLFORM==1)) * exp(nKa))
        stparm(V2 = tvV2 * (WEIGHT/70)^dV2dWEIGHT * exp(nV2))
        stparm(Cl2 = tvCl2 * (WEIGHT/70)^dCl2dWEIGHT * exp(nCl2))
        stparm(K_Aa3_C = tvK_Aa3_C * (BMI/24.8)^dK_Aa3_CdBMI * exp(nK_Aa3_C))
        stparm(Fsl = tvFsl * (1+dFsldSLFORM1*(SLFORM==1)) * (1+dFslSL161*(SL16==1)) *
exp(nFsl))
        stparm(Ffa = exp(tvFfa + nFfa)/(1+ exp(tvFfa + nFfa)))
        stparm(Fsa = 1 - exp(tvFfa + nFfa)/(1+ exp(tvFfa + nFfa)))
        stparm(K_Aa2_A3 = tvK_Aa2_A3 * (1+dK_Aa2_A3dFEMALE1*(FEMALE==1)) *
exp(nK_Aa2_A3))
        stparm(K_A3_C = tvK_A3_C * exp(nK_A3_C))
        stparm(CMultStdev = tvCMultStdev)
        fcovariate(SLFORM())
        fcovariate(SL16())
        fcovariate(AGE)
        fcovariate(BMI)
        fcovariate(FEMALE())
        fcovariate(WEIGHT)
        fixef(tvV = c(0, 456.296, ))
        fixef(tvCl = c(0, 49.6328, ))
        fixef(tvKa (freeze) = c(, 1.1670, ))
        fixef(tvV2 (freeze) = c(, 1114.06, ))
        fixef(tvCl2 (freeze) = c(, 79.54, ))
        fixef(tvK_Aa3_C = c(0, 0.0283604, ))
        fixef(tvFsl (freeze) = c(, 0.1847, ))
        fixef(tvFfa = c( , -2.6, ))
        fixef(tvK_Aa2_A3 = c(0, 0.00381785, ))
        fixef(tvK_A3_C = c(0, 0.000470712, ))
        fixef(tvCMultStdev = c(0, 0.19007, ))
        fixef(dFsldSLFORM1(enable=c(0)) = c( , , ))
        fixef(dFslSL161(enable=c(1)) = c(, -0.1, ))
        fixef(dCldBMI(enable=c(2)) = c(, -0.53, ))
```

```
        fixef(dK_Aa3_CdBMI(enable=c(3)) = c(, -2.0, ))
        fixef(dkaSLFORM1 (enable=c(4)) = c(,,))
        fixef(dVdWEIGHT(freeze) = c(, 1, ))
        fixef(dCldWEIGHT(freeze) = c(, 0.75, ))
        fixef(dV2dWEIGHT(freeze) = c(, 1, ))
        fixef(dCl2dWEIGHT(freeze) = c(, 0.75, ))
        fixef(dK_Aa2_A3dFEMALE1(enable=c(4)) = c(, 0.14, ))
        ranef(block(nV, nCl, nKa, nV2, nCl2, nK_Aa3_C, nFsl, nFfa, nK_Aa2_A3, nK_A3_C) = c(1, 0,
1, 0, 0, 1, 0, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1))
}
```

Figure 19.1.3.1.8 Goodness of fit plots for the External Replication model

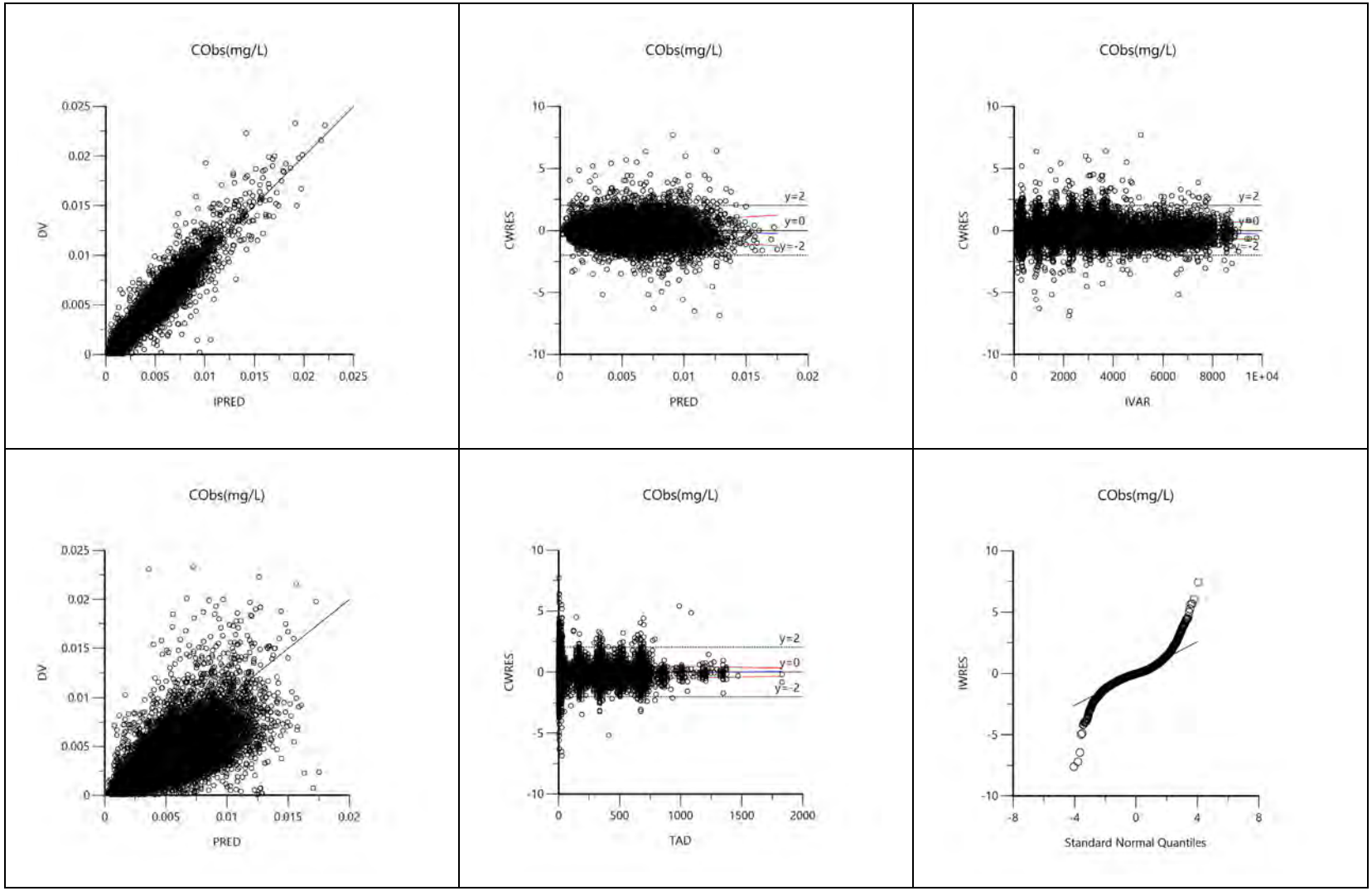


Figure 19.1.3.1.9 VPC for the external replication model

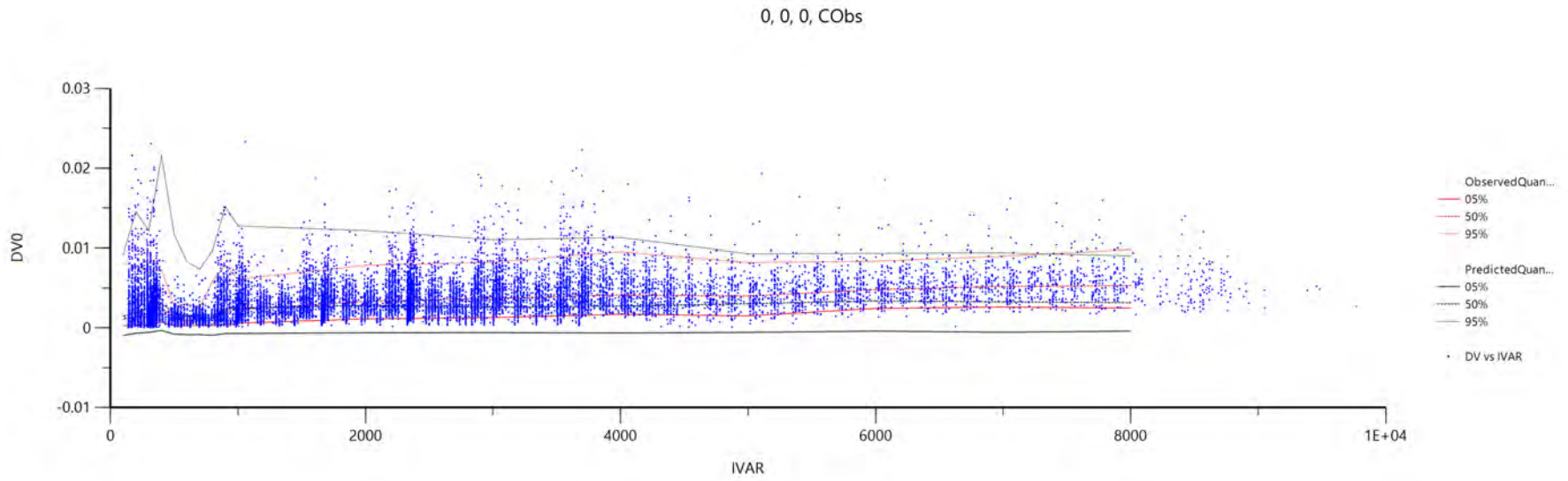


Figure 19.1.3.2.1 Log File for Stepwise Covariate PK Model Building (copied from Appendix 5.1.9, Study INDV-6000-M04)

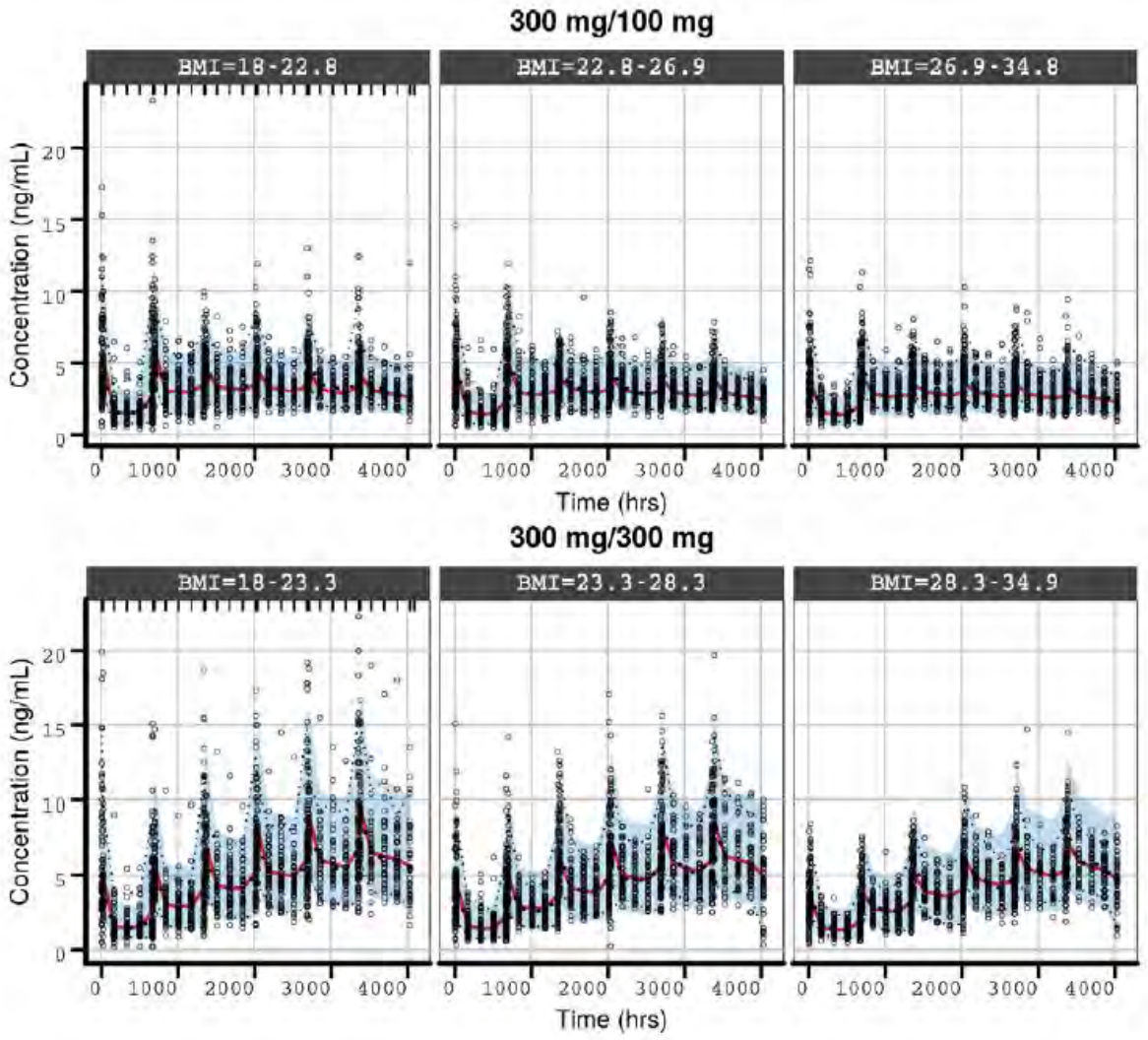
```
--------------------
The ofv of the nonlinear base model :   976.79401       derivatives.mod
The ofv of the linearized base model: 10561.53613       base_model_with_included_relations.mod
--------------------

MODEL           TEST     BASE OFV     NEW OFV         TEST OFV (DROP)    GOAL     dDF    SIGNIFICANT PVAL
CLBMI-5         PVAL  10561.53613  9766.59289           794.94324  >   3.84150    1        YES!  0.00e+00
K24BMI-5        PVAL  10561.53613  9913.02019           648.51593  >   3.84150    1        YES!  0.00e+00
K24SEX-2        PVAL  10561.53613 10047.02472           514.51140  >   3.84150    1        YES!  0.00e+00
K36AGE-5        PVAL  10561.53613 10426.34145           135.19468  >   3.84150    1        YES!  2.99e-31
K36BMI-5        PVAL  10561.53613 10400.77583           160.76029  >   3.84150    1        YES!  7.72e-37
K36SEX-2        PVAL  10561.53613 10559.51156             2.02456  >   3.84150    1              0.154770
K64BMI-5        PVAL  10561.53613 10554.66936             6.86677  >   3.84150    1        YES!  0.008781
K64SEX-2        PVAL  10561.53613 10560.54559             0.99053  >   3.84150    1              0.319610
PHIBMI-5        PVAL  10561.53613  9820.46163           741.07450  >   3.84150    1        YES!  0.00e+00
V4BMI-5         PVAL  10561.53613 10343.30512           218.23100  >   3.84150    1        YES!  2.20e-49

Parameter-covariate relation chosen in this forward step: CL-BMI-5
CRITERION              PVAL < 0.05
BASE_MODEL_OFV       10561.53613
CHOSEN_MODEL_OFV      9766.59289
Relations included after this step:
CL      BMI-5
K24
K36
K64
PHI
V4
--------------------

MODEL           TEST     BASE OFV     NEW OFV         TEST OFV (DROP)    GOAL     dDF    SIGNIFICANT PVAL
K24BMI-5        PVAL   9766.59289  9146.24989           620.34300  >   3.84150    1        YES!  0.00e+00
K24SEX-2        PVAL   9766.59289  9707.59569            58.99720  >   3.84150    1        YES!  1.58e-14
K36AGE-5        PVAL   9766.59289 10191.94000          -425.34711  >   3.84150    1                    9999
K36BMI-5        PVAL   9766.59289  9613.06059           153.53230  >   3.84150    1        YES!  2.93e-35
K36SEX-2        PVAL   9766.59289 10050.39617          -283.80328  >   3.84150    1                    9999
K64BMI-5        PVAL   9766.59289  9766.60650            -0.01361  >   3.84150    1                    9999
K64SEX-2        PVAL   9766.59289  9567.76221           198.83068  >   3.84150    1        YES!  3.76e-45
PHIBMI-5        PVAL   9766.59289  9233.77053           532.82236  >   3.84150    1        YES!  0.00e+00
V4BMI-5         PVAL   9766.59289  9708.92538            57.66751  >   3.84150    1        YES!  3.10e-14

Parameter-covariate relation chosen in this forward step: K24-BMI-5
CRITERION              PVAL < 0.05
BASE_MODEL_OFV        9766.59289
CHOSEN_MODEL_OFV      9146.24989
Relations included after this step:
CL      BMI-5
K24     BMI-5
K36
K64
```

Figure 19.1.3.2.1 (cont)

```
PHI
V4
--------------------

MODEL           TEST     BASE OFV     NEW OFV         TEST OFV (DROP)    GOAL     dDF    SIGNIFICANT PVAL
K24SEX-2        PVAL   9146.24989  9279.04544          -132.79555  >   3.84150   1                 9999
K36AGE-5        PVAL   9146.24989  9145.75304            0.49685   >   3.84150   1             0.480890
K36BMI-5        PVAL   9146.24989  8587.77351          558.47637   >   3.84150   1        YES! 0.00e+00
K36SEX-2        PVAL   9146.24989  9145.66091            0.58897   >   3.84150   1             0.442820
K64BMI-5        PVAL   9146.24989  9146.29112           -0.04123   >   3.84150   1                 9999
K64SEX-2        PVAL   9146.24989  8757.02576          389.22413   >   3.84150   1        YES! 1.22e-86
PHIBMI-5        PVAL   9146.24989  9195.22766          -48.97778   >   3.84150   1                 9999
V4BMI-5         PVAL   9146.24989  9416.22908          -269.97920  >   3.84150   1                 9999

Parameter-covariate relation chosen in this forward step: K36-BMI-5
CRITERION              PVAL < 0.05
BASE_MODEL_OFV        9146.24989
CHOSEN_MODEL_OFV      8587.77351
Relations included after this step:
CL      BMI-5
K24     BMI-5
K36     BMI-5
K64
PHI
V4
```

```
MODEL           TEST     BASE OFV     NEW OFV         TEST OFV (DROP)    GOAL     dDF    SIGNIFICANT PVAL
K24SEX-2        PVAL   8587.77351  8750.96344          -163.18993  >   3.84150   1                 9999
K36AGE-5        PVAL   8587.77351  8587.74229            0.03123   >   3.84150   1             0.859740
K36SEX-2        PVAL   8587.77351  9307.93884          -720.16533  >   3.84150   1                 9999
K64BMI-5        PVAL   8587.77351  9112.97050          -525.19698  >   3.84150   1                 9999
K64SEX-2        PVAL   8587.77351  9268.70706          -680.93354  >   3.84150   1                 9999
PHIBMI-5        PVAL   8587.77351  9163.28089          -575.50738  >   3.84150   1                 9999
V4BMI-5         PVAL   8587.77351  9256.22261          -668.44910  >   3.84150   1                 9999

--------------------
--------------------
Forward search done. Starting backward search inside forward top level directory

MODEL           TEST     BASE OFV     NEW OFV         TEST OFV (DROP)    GOAL     dDF  INSIGNIFICANT PVAL
CLBMI-1         PVAL   8587.77351  9885.47851         -1297.70500  >  -6.63490  -1             0.00e+00
K24BMI-1        PVAL   8587.77351  9525.01400          -937.24048  >  -6.63490  -1             0.00e+00
K36BMI-1        PVAL   8587.77351  8638.66982           -50.89631  >  -6.63490  -1             9.74e-13
```

Figure 19.1.3.2.2 VPC for RBP-6000 Treatment Stratified by BMI Levels in the Phase III Study (copied from Figure 6, Study INDV-6000-M04)



[2]The bold black dotted line represents the median of the observed data; the red solid line represents the median of simulated data; the upper and lower black dotted lines delineate the 90% prediction intervals of the observed data; the light blue shaded area delineates the 90% prediction intervals of the simulated data

Figure 19.1.3.2.3 Model Predictions versus Observations for Dropout Per Treatment Arm in Study RB-US-13-0001 (copied from Figure 11, Study INDV-6000-M04)

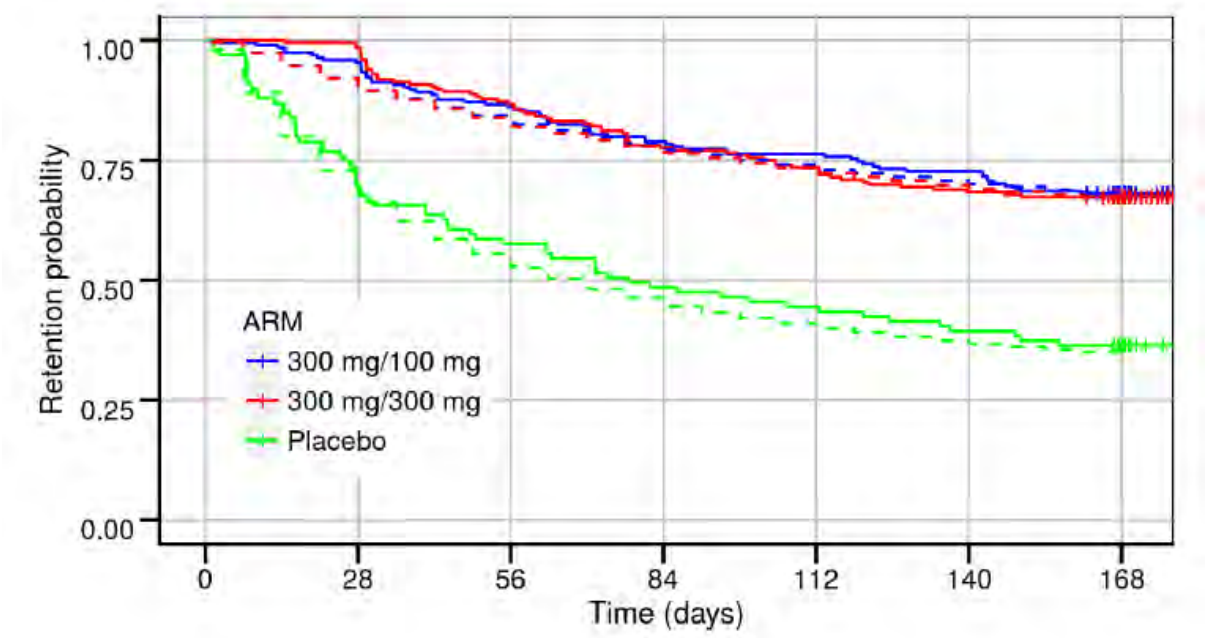


Figure 19.1.2.3.4 Predicted versus Observed Number of Subjects with Negative Opioid Use Per Treatment Arm in Study RB-US-13-0001 (copied from Figure 15, Study INDV-6000-M04)

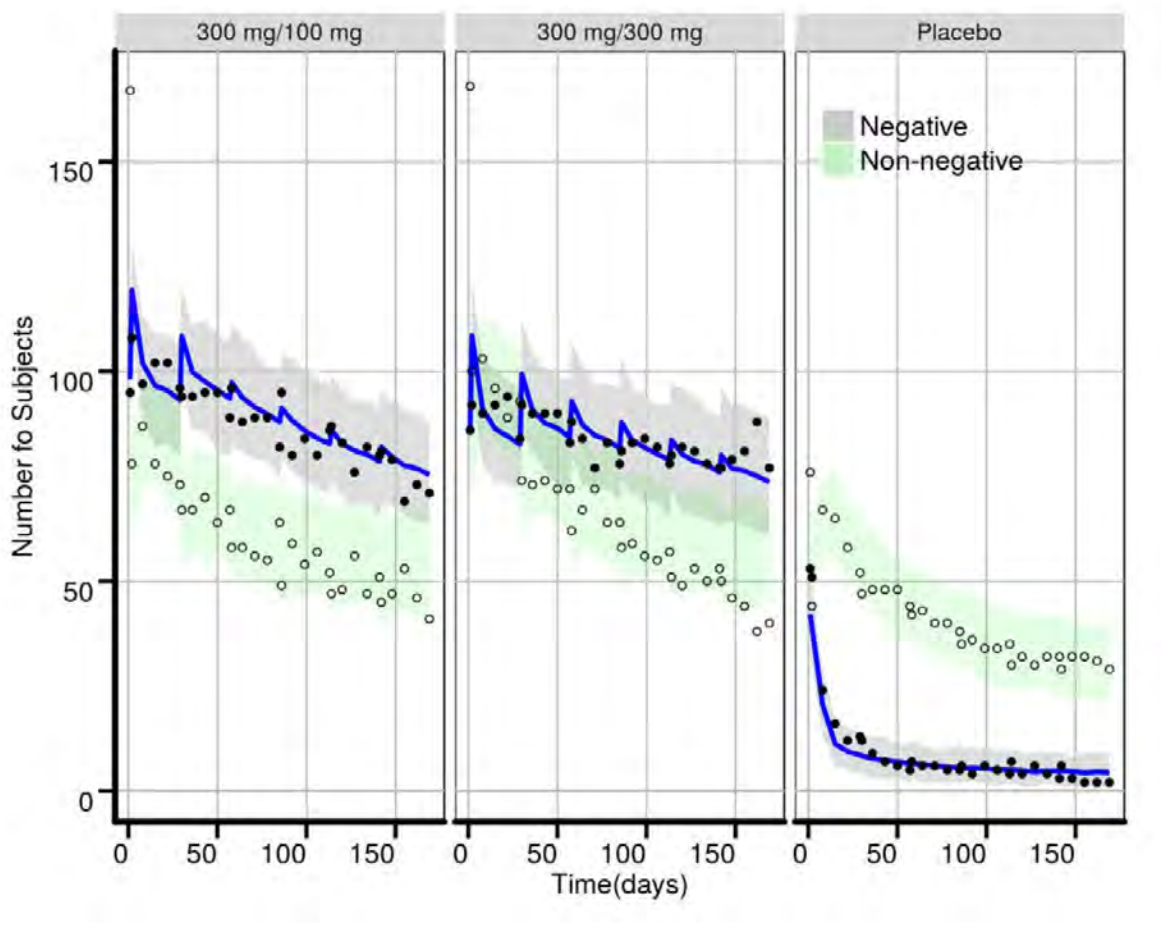


Figure 19.1.3.2.5 Predicted versus Observed Number of Subjects with Zero Craving, Craving Below 5 and Craving Below 20, Per Treatment Arm in Study RB-US-13-0001 (copied from Figure 18, Study INDV-6000-M04)

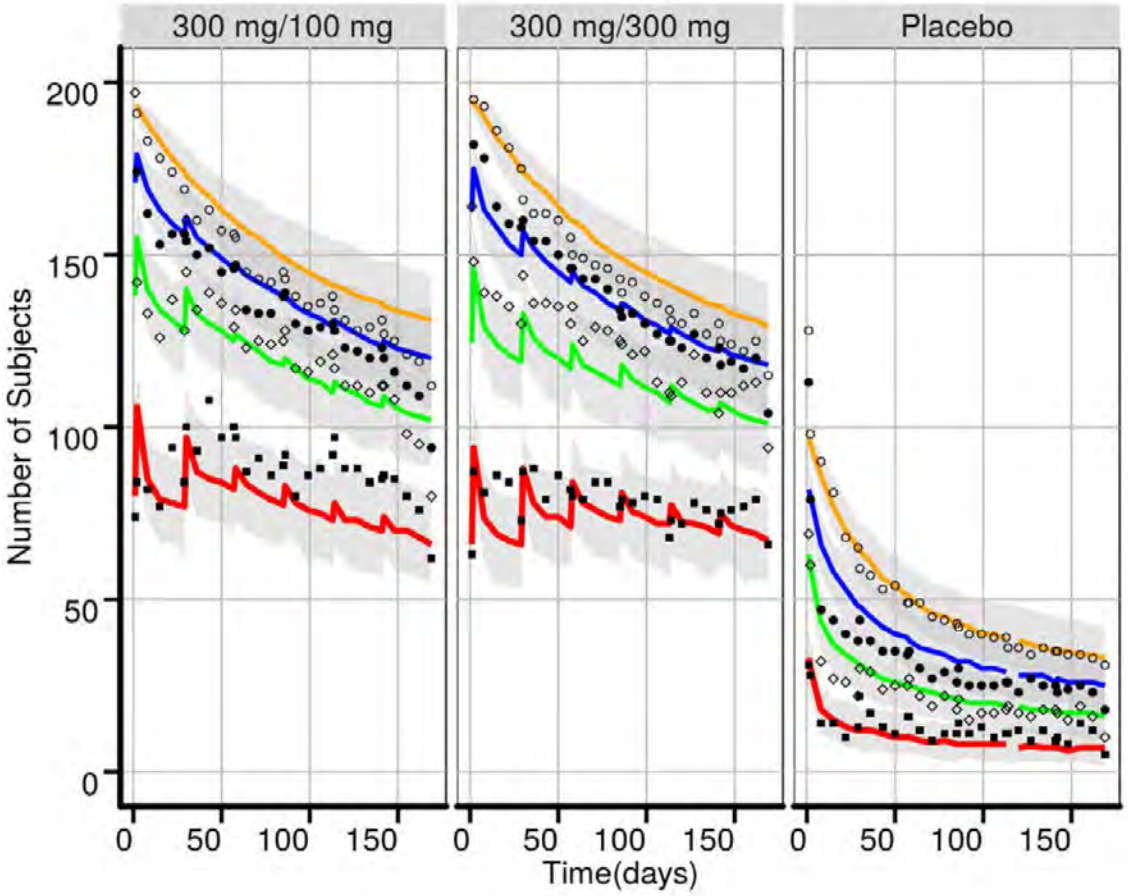


Figure 19.1.3.2.6 Relationship Between the Cumulative Proportion of Subjects below COWS Score Cutoffs and Buprenorphine Plasma Concentration (Study RB-US-13-0001) (copied from Figure 22, Study INDV-6000-M04)

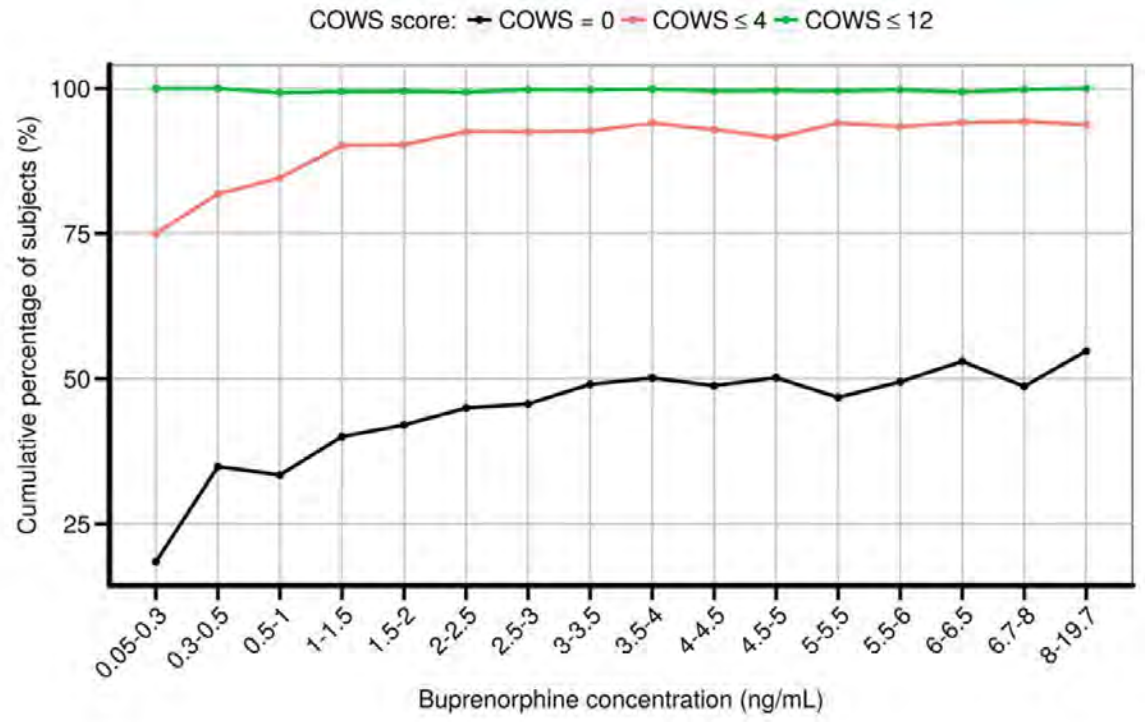
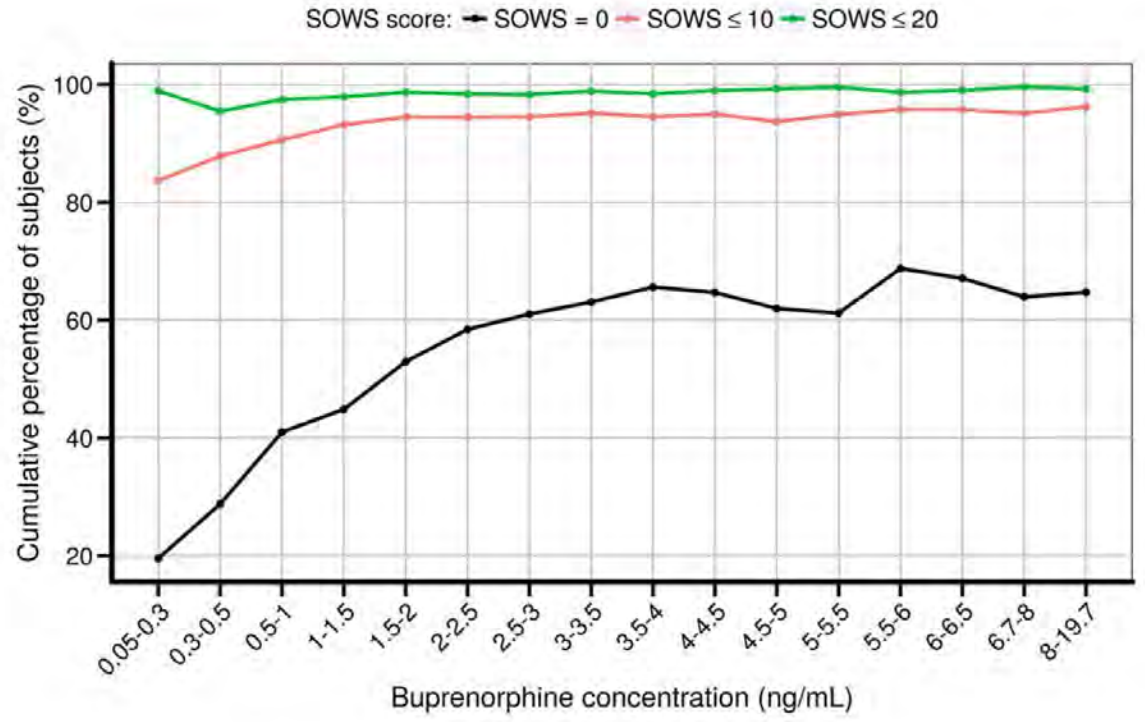


Figure 19.1.3.2.7 Relationship Between the Cumulative Proportion of Subjects below Each SOWS Score Cutoffs and Buprenorphine Plasma Concentration (Study RB-US-13-0001) (copied from Figure 23, Study INDV-6000-M04)



20. Attachment: additional evaluation material

NA

Therapeutic Goods Administration

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https://www.tga.gov.au

Australian Government
Department of Health
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: buprenorphine extended release injection, 100 & 300mg

Product name: SUBLOCADE 100mg & 300 mg

Sponsor: Indivior

Submission number: PM-2018-01872-1

eSubmission number: 003260

File number: E18-284729

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

1. List of tables

2. List of figures

3. List of abbreviations

Abbreviation	Meaning
BUP	buprenorphine
COWS	Clinical Opiate Withdrawal Scale. The COWS is an 11-item, instrument used to assess symptoms of opiate withdrawal. The score on the assessment is the sum of the response for each of the 11 items. A score of 5 to 12 is considered mild withdrawal, 13 to 24 is considered moderate, 25 to 36 is considered moderately severe, and a score exceeding 36 is considered severe withdrawal.
Nor-BUP	norbuprenorphine
Opioid Craving VAS	The Opioid Craving Visual Analog Scale - the VAS was a 100 mm scale
OUD	opioid use disorder
PCC	Percentage Clean Urines
PLGH	50:50 poly(lactide-co-glycolide) with a carboxylic acid end group
RBP-6000	Sublocade
SOWS	The Subjective Opiate Withdrawal Scale is a 16-item scale completed by the subject and used to assess the subject's perception of opiate withdrawal symptoms.
Timeline Follow back Interview	The Timeline Follow back Interview assessed recent drug use. Subjects were asked to estimate, retrospectively, their drug use during the 30 days preceding each visit to the clinical site. Only the frequency of use was captured (i.e., used or did not use).
TEC	Treatment Effectiveness Percentage
μO-RO	mu-opioid receptor occupancy

4. Submission details

4.1. Identifying information

Submission number	PM-2018-01872-1
eSubmission number	003260
Sponsor	Indivior
Trade name	Sublocade 100mg & 300 mg
Active substance	buprenorphine extended release injection, 100 & 300mg

4.2. Submission type

This is a PopPK study based Category 1, type F submission to register a new dosage form of buprenorphine – an extended release injection in two strengths.

4.3. Drug class and therapeutic indication

The approved indication for Subutex Sublingual Tablets is:

> Treatment of opioid dependence, within a framework of medical, social and psychological treatment.

4.4. Dosage forms and strengths

There are multiple buprenorphine preparations registered some with the same Indication as proposed others with different indications e.g. Temgesic Injection and Temgesic Sublingual Tablets indications are:

> Strong analgesic for the short-term (not more than one week) relief of moderate to severe pain, including post-operative and terminal pain. Temgesic Injection should be employed when sublingual administration is not practical e.g. pre- or peri-operatively. It is not recommended for use in children.
>
> Temgesic does not have an approved role in opioid dependence rehabilitation programmes.

The submission proposes registration of the following dosage forms and strengths:

> Buprenorphine extended release injection, 100 & 300mg in pre-filled syringes for single use with an already registered 19G 16mm hypodermic needle for subcutaneous administration.

4.5. Dosage and administration

The proposed section is extensive. It can be found at 22.1. It includes:

> Patients appropriate for Sublocade are adults who have undergone induction on a buprenorphine-containing product. Withdrawal signs and symptoms should be suppressed (COWS ≤ 12) before transitioning to Sublocade.
>
> Dosing and induction of buprenorphine-containing products should be based on instructions in their Product Information.

FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. DO NOT ADMINISTER Sublocade INTRAVENOUSLY OR INTRAMUSCULARLY (see section 4.4 Special Warnings and Precautions for use).

•Only healthcare providers should prepare and administer Sublocade.

•Administer Sublocade monthly with a minimum of 26 days between doses.

• Initiating treatment with Sublocade as the first buprenorphine product has not been studied. Initiate Sublocade treatment only following induction and dose adjustment with a transmucosal buprenorphine containing product.

• Administer each injection only using the syringe and safety needle included with the product.

• Do not administer part of a dose

Recommended dosing

Patients appropriate for Sublocade are adults who have initiated treatment on a transmucosal buprenorphine-containing product. The patient may only be transitioned to Sublocade after stabilisation on transmucosal buprenorphine (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

The recommended dose of Sublocade is 300mg monthly for the first two months. The recommended maintenance dose is 100mg monthly. However patients who do not show a satisfactory clinical response following the second dose can receive a maintenance dose of 300mg monthly.

Buprenorphine plasma levels in the month following the second 300mg dose are maintained with 100mg maintenance dosing. The 300mg maintenance dose achieves higher levels and reaches steady state after the fourth monthly injection (see section 5.2 pharmacokinetic properties).

A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Clinical supervision

Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot.

Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment. For some patients, treatment may continue indefinitely. If considering stopping treatment, the clinical status of the patient should be considered.

If Sublocade is discontinued, its extended-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal or buprenorphine effects and treated appropriately. After steady-state has been achieved (4-6 months), patients discontinuing Sublocade may have detectable plasma levels of buprenorphine for twelve months or longer. The correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

4.6. Proposed changes to the product documentation

Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION and Section 3 PHARMACEUTICAL FORM will of necessity be new.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The addition of a section Risk of serious harm or death with intravenous administration.

Considerable amendments were made including to the Misuse, abuse and diversion section, the Risk of Respiratory and Central Nervous System (CNS) Depression sections, the Managing Risks From Concomitant Use of Benzodiazepines Or Other CNS Depressants With Buprenorphine section, the Opioid Withdrawal Effects section, the Neonatal Abstinence Syndrome section, the Use in hepatic impairment section and the Use in renal impairment section.

New sections: Risks associated with Treatment of Emergent Acute Pain and Use in Patients at Risk for Arrhythmia.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Has been replaced by a Tabular section.

4.6 FERTILITY, PREGNANCY AND LACTATION

The Effects on fertility section is replaced.

The Use in Pregnancy (Category C) and the Use in lactation sections while the subject of a separate current submission, have been modified.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) is of necessity amended.

5.1 PHARMACODYNAMIC PROPERTIES

The Mechanism of action section is modified.

New sections: Plasma concentration and Clinical Response, Clinical trials.

5.2 PHARMACOKINETIC PROPERTIES is mostly new.

5. Background

5.1. Information on the condition being treated

In Australia, death from opioid overdose is increasing, and opioid use in 2012 was estimated to have increased to 15 times that reported in 1992. In 2013 the Australian Bureau of Statistics reported that 668 Australians died (including all ages) from overdose of opioids. Additionally, it was determined that 597 Australians between the ages of 15 and 54 died from accidental overdose of opioids, with 70% of deaths including strong prescription painkillers. Accidental death related to opioid overdose is more likely to affect older Australians. Deaths among 45- to 54-year-olds are now higher than at the peak of the heroin epidemic in 2001. Moreover, according the Australian Bureau of Statistics, heroin was present in 1 in 5 drug-induced deaths in 2016, and has the second lowest median age at death at 41.2 years. Therefore, heroin, heroin-related overdoses and heroin overdoses leading to death still remain a major public health issue in Australia.

According to the Australian National Drug & Alcohol Research Centre, the major cause of opioid deaths has changed over time from heroin to prescription opioids such as oxycodone and fentanyl, and overdose deaths occur in all age groups.

5.2. Current treatment options

Medication-assisted treatment includes methadone (an opioid agonist) or buprenorphine (a partial agonist).

5.3. Clinical rationale

Opioid withdrawal suppression (the prevention of withdrawal symptoms and craving) appears to require ≥ 50% brain mu-opioid receptor occupancy, associated with buprenorphine plasma concentrations ≥ 1ng/mL.

To block the full subjective agonist induced effects (opioid blockade) at least 70% brain mu-opioid receptor occupancy by buprenorphine is required - this being provided by buprenorphine plasma concentrations ≥ 2-3ng/mL.

This level 2ng/mL cannot be maintained over 24h by sublingual buprenorphine, hence the proposed delayed release injection to provide 24h cover.

5.4. Formulation

5.4.1. Formulation development

This application relies not only nonclinical pharmacology information from the approved labelling for buprenorphine products, but also studies from the scientific literature that provide relevant or supporting nonclinical pharmacological data for buprenorphine or the Atrigel Delivery System components (i.e., NMP and PLGH). Indivior has not conducted any new pharmacology studies to support this application.[1]

The Atrigel Delivery System is a non-aqueous solution consisting of a biodegradable polymer, 50:50 poly(DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH) and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP).[2]

The Atrigel Delivery System is on the ARTG e.g. in Bi Eligard cp.

5.4.2. Excipients

The proposed formulation contains the following excipients:

Atrigel Delivery System contains: 50:50 Poly(DL-lactide-co-glycolide) polymer, *N*-methyl-2-pyrrolidone.

5.5. Regulatory history

5.5.1. Australian regulatory history

Temgesic buprenorphine was first placed on the ARTG 30 September 1991.

Subutex sublingual tablets were first placed on the ARTG 2 November 2000.

5.5.2. Related submissions

Submission 2017-02665 to amend the Dosage and Administration section and remove the contraindication for pregnancy and lactation currently being reviewed.

[1] 2.6.2 Pharmacology Written Summary page 4
[2] 2.2 Introduction

5.5.3. Overseas regulatory history

Registration approved US 30/11/17 for 'Treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days. Sublocade should be used as part of a complete treatment plan that includes counselling and psychosocial support.' FDA Cross-Discipline Team Leader Review And Summary Basis for Approval is in the submission.[3]

Applied for in Canada.

5.6. Guidance

- EMA/CHMP/EWP/280/96 Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1).
- CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Guideline on the Investigation of Bioequivalence.
- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a Clinical Investigation of Medicinal Products for Long-Term Use.

6. Contents of the clinical dossier

6.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5

  Clinical pharmacology studies, including:

  - RB-US-10- 0011 An open-label, single-centre, first-in-human study, designed to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of a single SC injection of Sublocade containing 20mg buprenorphine in opioid dependent subjects.
  - RB-US-11-0020 A multicentre, open-label, single ascending-dose study to evaluate the safety, tolerability, and pharmacokinetics of depot buprenorphine in opioid-dependent subjects.
  - RB-US-12-0005 An open-label, multicentre, multiple dose study of the safety, tolerability, pharmacokinetics, efficacy markers, and opioid receptor availability of subcutaneous injections of depot buprenorphine in treatment seeking opioid-dependent subjects.
  - RB-US-13-0006 A single-centre, randomized, open-label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of depot buprenorphine (Sublocade) using poly (dl-lactide-co-glycolide) polymer of two different molecular weights (low and high molecular weights as test treatments) in comparison to intermediate molecular weight (reference treatment) in treatment-seeking subjects with opioid use disorder.
  - CR87/027 A comparative assessment of the bioavailability of buprenorphine administered by the intravenous and sublingual routes.

[3] Module 1/ 111-foreign/ 1114-eval-reports

  - CR96-008 Relative bioavailability study of buprenorphine sublingual liquid and sublingual tablet formulations.
  - P01242 Single centre, Phase 1, open-label, fixed sequence drug interaction' study of ketoconazole in opiate dependent subjects effects of ketoconazole on the pharmacokinetics of sublingual buprenorphine.

- Population pharmacokinetic and/or pharmacodynamic analyses including:
  - INDV-6000-M01 Population PK modelling & simulation report of RB-US-11-0020 A single ascending-dose study of Sublocade in opioid-dependent subjects.
  - INDV-6000-M03 Population pharmacokinetic analysis of buprenorphine after repeated subcutaneous injections of Sublocade in treatment-seeking opioid-dependent subjects in study RB-US-12-0005.
  - NDV-6000-M05 Population pharmacokinetics of Sublocade in treatment-seeking subjects with opioid use disorder combined analysis of studies RB-US-12-0005, RB-US-13-0001 and RB-US-13-0003.
  - INDV-6000-M07 Modelling & Simulation Report *in vitro-in vivo* Correlation evaluation for Sublocade using a population pharmacokinetic modelling approach.
  - INDV-6000-M04 Population pharmacokinetic and exposure-response analyses for buprenorphine after repeated subcutaneous injections of Sublocade in treatment-seeking subjects with opioid use disorder.
  - INDV-6000-M02 Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy in the brain.
  - INDV-6000-M06 Drug-drug interaction modelling & simulation for Subutex and Sublocade with ketoconazole.
  - INDV-6000-Q01 Concentration-QT analysis for Sublocade using plasma concentration and ECG data pooled from studies RB-US-10-0011, RB-US-11-0020, RB-US-12-0005, RB-US-13-0001, and RB-US-13-0006.
- Pivotal efficacy/safety studies.
  - RB-US-13-0001 A randomized, double-blind, placebo-controlled, multicentre study to assess the efficacy, safety, and tolerability of multiple subcutaneous injections of depot buprenorphine (Sublocade 100mg and 300mg) over 24 weeks in treatment-seeking subjects with opioid use disorder.
- Other efficacy/safety studies including:
  - B-US-13-0002 A multiple-dose study of blockade of subjective opioid effects, plasma levels, and safety of subcutaneous injections of depot buprenorphine in subjects with opioid use disorder.
  - INDV-6000-301 An open-label, depot buprenorphine treatment extension study in subjects with opioid use disorder.
  - RB-US-13-0003 an open-label, long-term safety and tolerability study of depot buprenorphine in treatment-seeking subjects with opioid use disorder.
  - RB-US-13-0003 HEOR Health economics and outcomes research (HEOR) report for the RB-US-13-0003 clinical trial.
  - INDV-6000-h01 Health economics and outcomes research endpoints report: a randomized, double-blind, placebo-controlled, multicentre study to assess the

efficacy, safety, and tolerability of multiple subcutaneous injections of depot buprenorphine (Sublocade 100mg and 300mg) over 24 weeks in treatment-seeking subjects with opioid use disorder.

- Other
    - *Integrated Summary of Efficacy*.
    - *Integrated Summary of Safety*.
    - IND-2015-Vail-FTl-503 Rev A a "pre-summative" usability test.
    - Summary of all abuse-related animal and human data, discussion of these data, and conclusions about the drug's abuse potential.
    - FC-FDV-0141R A simulated intravenous *in vitro* study to evaluate local tolerance of intravenous or intra-arterial injection of Sublocade.
    - Expert summary report The risk of QT prolongation associated with the use of buprenorphine containing products.

- Module 1
    - Application letter, application form, draft Australian PI and CMI, FDA-approved product label and FDA Cross-Discipline Team Leader Review and Summary Basis for Approval, RMP.
- Module 2.
    - Introduction, Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Clinical Pharmacology and literature references.

Comment: Almost all the relevant data is there, but oddly study reports are often dated years after publications.

References were not all in the submission and one at least did not appear to exist. The PI annotations often did not reflect the source with much accuracy, or could not be found. All this delays evaluation.

The submission is based on 2 different approaches:

- Based on 2 articles by Grenwald in 2003 & 2007 that measured plasma buprenorphine levels after doses of buprenorphine and the resulting μ-opioid receptor occupancy in the brain using ^{11}C carfentanil PET scans.
  These were then modelled (see 21.1.3.1).
  Based on this model, a buprenorphine plasma concentration of 2 to 3ng/mL was predicted to achieve sufficient μ-opioid receptor occupancy —approximately 70%—to suppress opioid withdrawal signs and symptoms and to block the response to a μ-opioid receptor agonist e.g. hydromorphone.
  The sponsor then undertook to show that this level was consistently achieved (see Figure 1).
- The sponsor also undertook 2 efficacy studies using different endpoints, comparing to placebo (13-0001 and 13-0002).

There are multiple PopPK and PK/PD studies. Mostly the modelling only is found in the CSRs with the results of simulations found in the Clinical Summaries.

6.2. Sponsor's Justification for not providing biopharmaceutic and/or absolute bioavailability data

The sponsor admits a justification is required:

Sublocade is therefore being submitted to the TGA as a major variation to Subutex, type F, for which a head-to-head biopharmaceutical study would be required under strict interpretation of ARGPM Guidance 15.4: Medicines that require biopharmaceutic data – complex intravenous solutions for injection and new dosage form.[4]

The PPF summarises the sponsor's approach to justification:

Although Sublocade is submitted for registration as an alternative to Subutex sublingual tablets as both medicines share the same active ingredient and indication, a head-to-head biopharmaceutic comparison is not relevant due to the difference in the buprenorphine plasma level patterns through time. The efficacy and safety of the products in their common indication is compared in detail on a clinical level in modules 2.5 and 2.7 and conclude to therapeutic comparability, with Sublocade being designed to bring improved adherence to treatment and convenience for patients.[5]

The sponsor argues for bioequivalence based on efficacy:

Efficacy (as measured by urine drug screen and self-reports of illicit opioid use as well as withdrawal symptoms and craving) was maintained when subjects were transitioned from sublingual buprenorphine treatment to Sublocade during the clinical development programme.[6]

Comment: The Clinical Overview has Buprenorphine plasma concentrations required to provide opioid blockade are ≥ 2-3ng/mL. Although SL buprenorphine achieves the 2ng/mL threshold, it is not maintained over the 24-hour dosing interval. For daily doses of 16mg SL buprenorphine, brain mu-opioid receptor occupancy was reported to be 70% at 4 hours post-dose but only 46% at 28 hours post-dose.

6.3. Paediatric data

The submission did not include paediatric data.

6.4. Good clinical practice

While not specifically stated as complying with Good clinical practice in Study CR87-027 the protocol required:[7]

The investigator will submit the study protocol, subject consent form and any other documents as may be requested to an appropriate Ethics or Institutional Review Committee for review and approval.

The articles by Grunwald complied with the Declaration of Helsinki and were Institutional Review Boards of Wayne State University and University of Michigan approved.

[4] Module 1 1.9.2
[5] PPF page 23
[6] Module 1 1.9.2
[7] Page 93 CSR

7. Pharmacokinetics

7.1. Studies providing pharmacokinetic information

Summaries of the pharmacokinetic studies are presented in Section 21.1 of this report. Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1 Submitted PK studies- all studies (except CR87/027) were in Opioid-dependent treatment-seeking subjects.

PK topic	Subtopic	Study ID	*	Synopsis
Single dose	First-in-human	10-0011	*	21.1.1.1
	Single ascending dose	11-0020	*	21.1.1.2
	To assess the relative bioavailability with different MWs of PLGH polymer s†	13-0006	*	21.1.1.4
	Comparative bioavailability of intravenous and sublingual routes†	CR87/027	*	Previous submission
Multi-dose	Multiple ascending dose	12-0005	*	21.1.1.3
	Opioid blockade study	13-0002		21.1.1.4
	Double-blind, placebo-controlled, 24-week, efficacy, safety and tolerability study	13-0001		Only 80 page table in study. Analysis combined at 21.1.3.4 21.1.3.5
	Long-term open label safety and tolerability study (extension of Study RB-US-13-0001)	13-0003		Only listing in study. Analysis combined at 21.1.3.4
	Relative bioavailability of sublingual liquid and sublingual tablet†	CR96-008	*	Previous submission
PK drug interactions	Ketoconazole vs. sublingual	P01242	*	Previous submission
	Modelling & simulation for Subutex and Sublocade with ketoconazole	M06		21.1.3.6
Population PK analyses	Modelling & Simulation Report *in vitro-in vivo* Correlation evaluation	M07	*	21.1.3.7
	Modelling & simulation report single ascending dose study 11-0020	M01	*	21.1.3.1
	Analysis of buprenorphine multiple	M03	*	21.1.3.3

	ascending dose study 12-0005			
	Combined analysis of studies 12-0005, 13-0001 and 13-0003	M05	*	21.1.3.4

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations.

None of the PK studies had deficiencies that excluded their results from consideration; some were related to a previous submission.

7.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

7.2.1. Physicochemical characteristics of the active substance

The following information is derived from the Sponsor's summaries in Module 2.

Sublocade contains 18% buprenorphine base in solution with the Atrigel Delivery System. The Atrigel Delivery System is a non-aqueous solution consisting of a biodegradable polymer with a carboxylic acid end group, 50:50 poly(D,L-lactide-co-glycolide) with a carboxylic acid end group (PLGH), and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). Sublocade forms a solid depot when injected subcutaneously and releases buprenorphine over a month by diffusion as the polymer is hydrolysed and degrades.

7.2.2. Pharmacokinetics in opioid-dependent subjects

7.2.2.1. Absorption

Following SC administration of Sublocade, buprenorphine was rapidly absorbed and peaked at approximately 24 hours post-dose, then declined to a plateau throughout the dosing interval consistent with the slow release of buprenorphine from the Atrigel Delivery System (Studies 11-0020 and 12-0005).

7.2.2.2. Bioavailability

The absolute bioavailability of Sublocade has not been determined in a dedicated clinical study.

However, based on buprenorphine clearance estimates from the literature (Yassen 2007[8]: 93 L/hr; Huestis 2013:[9] 50 - 60 L/hr), the absolute bioavailability of Sublocade is expected to be high, given buprenorphine CL/F values of 63 to 103L/hr following single and repeated SC injections.

7.2.2.3. Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Once absorbed, buprenorphine distributes extensively into the body, as evidenced by a large apparent volume of distribution (V_d/F) with mean values ranging from 96,120 to 154,369L over the dose range of 50 to 200mg (Study 11-0020).[10] The extensively large Vd/F is also because Sublocade is administered as a depot injection, resulting in a large amount of drug being available at the injection site.

[8] Mechanism-Based Pharmacokinetic-Pharmacodynamic Modelling of the Reversal of Buprenorphine-Induced Respiratory Depression by Naloxone Yassen et al Clln Pharmacokinet 2007: 46(!1): 965-980
[9] Intravenous buprenorphine and norbuprenorphine pharmacokinetics in humans M.A. Huestisa et al Drug and Alcohol Dependence 131 (2013) 258– 262
[10] Page 124 Table 11

7.2.2.4. Metabolism

From the Suboxone PI:

> In animals and man buprenorphine is metabolised by Phase 1 (oxidative) and Phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP 3A4. The reported K_m for buprenorphine for CYP 3A4 in human liver microsomes was 89mM, and addition of specific inhibitors of CYP 3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine. There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4 (reported mean K_i in human liver microsomes was 10.3μM and 40.2 μM respectively). Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity and is considered to be an inactive metabolite.

In vitro studies have shown some pharmacological activity associated with norbuprenorphine; however, norbuprenorphine steady-state plasma concentrations in humans after SC injection of Sublocade are low (AUC norbuprenorphine/buprenorphine ratio of 0.23-0.39, based on Study 12-0005).[11] Furthermore, norbuprenorphine is expected to have negligible contribution to brain mu-opioid receptor occupancy given its limited ability to cross the blood-brain barrier.

7.2.2.5. Excretion

The apparent plasma terminal half-life of buprenorphine (mean $t_{½}$) increased slightly with the increase in dose from 50mg to 200mg (1078 hours at 50mg, 1376 hours at 100mg, and 1573 hours at 200mg) (Study 11-0020 page 124). In this study, the CL/F of buprenorphine remained fairly constant over the investigated dose range of 50 to 200mg (64 - 68L/hr).[12] After multiple doses (Study 12-0005), CL/F was also fairly constant over the dose range of 50 to 300mg (81 - 105 L/hr).[13]

7.2.2.6. Intra and inter individual variability of pharmacokinetics

BMI was found to affect the SC absorption of buprenorphine, with higher peak levels of buprenorphine in subjects with a lower BMI. However, these effects were not of sufficient magnitude to suggest that dose adjustments might be necessary.

7.2.3. Population pharmacokinetics

There were multiple models developed. (See 21.1.3).

7.2.4. Pharmacokinetic interactions

7.2.4.1. ketoconazole

A drug-drug interaction population PK model was developed to account for this first-pass effect and to predict the effect of ketoconazole on the PK of Sublocade which bypasses first-pass metabolism. The model predicted a comparatively modest increase (60%) in buprenorphine AUC with concomitant administration of ketoconazole. See 21.1.3.6

7.2.5. Clinical implications of *in vitro* findings

A report on *in vitro-in vivo* Correlation evaluation for Sublocade using a population pharmacokinetic modelling approach found that comparison of *in-vitro* and *in-vivo* data showed a more rapid initial release of drug *in vitro* that was not reflected on the *in-vivo* absorption-time profile. Simple Level A correlation could not be established. (See 21.1.3.7).

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[12] Page 122
[13] Page 185

7.3. Evaluator's overall conclusions on pharmacokinetics

Some proposed insertions in the PI are not supported in the submission. See 15.1.

8. Pharmacodynamics

8.1. Studies providing pharmacodynamic information

Summaries of the pharmacodynamic studies are presented in Section 21.1 of this report. Table 2 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 2 Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*	Synopsis
Primary Pharmacology	Opioid blockade study	13-0002	*	21.1.2.1
	PET substudy	12-005		21.1.2.3
Secondary Pharmacology	Multiple PD parameters	11-0020		21.1.2.1
	Multiple PD parameters	13-002		21.1.2.1
Population PD and PK-PD analyses	PopPK & Exposure-response analyses after repeated subcutaneous injection Studies 12-005 & 13-0001	MO4	*	21.1.3.4
	Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy	MO2	*	21.1.3.1
	Concentration-QT analysis	NDV-6000-Q01	*	21.1.3.8

* Indicates the primary PD aim of the study.

8.2. Summary of pharmacodynamics

8.2.1. Mechanism of action

From the Suboxone PI:

> Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.
>
> During clinical pharmacology studies in opioid-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, "good effect", and respiratory depression.

8.2.2. Pharmacodynamic effects

8.2.2.1. Primary pharmacodynamic effects

The sponsor submitted Study INDV-6000-M02 (see 21.1.3.1) Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy in the brain.

Based on this model, a buprenorphine plasma concentration of 2 to 3ng/mL was predicted to achieve sufficient μ-opioid receptor occupancy — approximately 70% — to suppress opioid withdrawal signs and symptoms and to block the response to a μ-opioid receptor agonist.

8.2.2.2. Secondary pharmacodynamic effects

Study 13-0002 (see 21.1.2.1). This complex study set out to show that after Sublocade was given hydromorphone, previously shown to be subject desirable in the absence of buprenorphine, was now no more desirable that saline. This was demonstrated with visual analog scales for "Drug Liking" "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High".

Secondary Objectives included:

- To evaluate the correlation between the opioid blockade subjective effects (VAS of "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High") and the reinforcing effects of hydromorphone and simulated mu opioid receptor occupancy (using the maximal effect [E_{max}] model).
- To determine the relationship between plasma concentration and predicted mu opioid receptor occupancy of buprenorphine and both the blockade of the subjective effects of hydromorphone post injection of buprenorphine 300mg (Sublocade).

8.2.3. Pharmacodynamic interactions - QT interval

PopPK analysis INDV-6000-Q01 Concentration-QT analysis (see 21.1.3.8) found no effect of buprenorphine on QT after accounting for the covariates that may influence HR and QT in subjects with opioid use disorder.

The sponsor also submitted a 15 page Expert summary report on The risk of QT prolongation associated with the use of buprenorphine containing Products that found:

The presently published literature does not suggest that buprenorphine is causally associated with QT prolongation and TdP-type ventricular arrhythmias.

and:

There was no strong evidence to demonstrate the extent to which buprenorphine may have contributed to the development of QT prolongation, given the fact that some patients concomitantly received drugs known to prolong the QT interval, as well as had a history of abnormal thyroid function, structural heart disease, bradycardia, hypokalaemia and polysubstance abuse, which confound any interpretation.

8.3. Evaluator's overall conclusions on pharmacodynamics

Among the proposed PI insertions were:

1.

Following sublingual administration, a dose response relationship has been observed for buprenorphine plasma levels and brain mu-opioid receptor occupancy by buprenorphine at 4 hours after dosing. A relationship has also been observed between buprenorphine plasma levels and blockade of subjective opioid agonist symptoms produced by co-administered opioids at 4 hours after dosing. Plasma concentrations of buprenorphine and mu-opioid receptor occupancy decrease between 4 hours and 28 hours post dose correlating with a return of subjective agonist symptoms produced by co-administered opioids, together with opioid withdrawal symptoms and opioid craving.

These statements are from the sponsor's review derived from the two Grunwald Studies. Which are only available in the submission in their published form.

However Study RB-US-13-0002 CSR[14] found 'Scatter plots of the buprenorphine plasma concentration versus the VAS scores for the subjective measures (Drug Liking, Any Drug Effect, Good Drug Effect, Bad Drug Effect, Sedation, and High,) are presented in Figure 37, Figure 38, Figure 39, and Figure 14.2.2.5. Overall, these plots indicate there was a reduction in VAS scores with increased buprenorphine plasma concentration' (see 15.1 for further discussion).
Comment: The proposed insertion relates to the use of sublingual tablets and is not found in the Subutex PI.

2.

In a Positron Emission Tomography (PET) study with Sublocade in 2 subjects (one subject receiving 200mg SC injections and one subject receiving 300mg SC injections) with opioid use disorder, 75 to 92% occupancy of the mu-opioid receptors in the brain was maintained for 28 days following the last dose under steady-state conditions.

This statement is misleading.

The subject who received 200mg showed 79% and 75% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively. The subject who received 300mg showed 92% and 81% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively.[15]

3.

The *(Sublocade opioid blockade)* study evaluated the blockade of subjective opioid effects, pharmacokinetics (PK) and safety of SC injections of Sublocade. Stabilisation doses of SL buprenorphine prior to injection of Sublocade failed to provide full blockade of subjective effects of hydromorphone 18mg IM After Sublocade injections at weeks 0 and 4, on average, subjective effects of both 6 and 18mg doses of hydromorphone were blocked; however wide variability was seen across subjects. Complete blockade continued throughout the 8 weeks of observation that followed the 2nd Sublocade injection.

The primary endpoint was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade). The study failed to meet that endpoint.

For the 18mg hydromorphone to placebo treatment comparison, opioid blockade was observed from Week 1 to Week 3, while at Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade. After the first injection of SC Sublocade, during week 4, a decrease in mean buprenorphine plasma concentration (from 1.9 to 1.8ng/mL) correlated with a 65% μ-opioid receptor occupancy, which corresponded to the increase in VAS scores.

9. Dosage selection for the pivotal studies

Simulations used the population PK model developed from study 11-0020 data (doses of 50 to 300mg) along with the PK/brain mu-opioid receptor occupancy model. Multiple SC injections of Sublocade were simulated for doses ranging from 50 to 300mg. The 300mg dose was the highest dose tested in the clinical development program. The results of these simulations indicated that the C_{max} achieved at an Sublocade dose of 300mg enabled the target of 70% brain mu-opioid receptor occupancy to be reached after the first SC injection. Mean predicted

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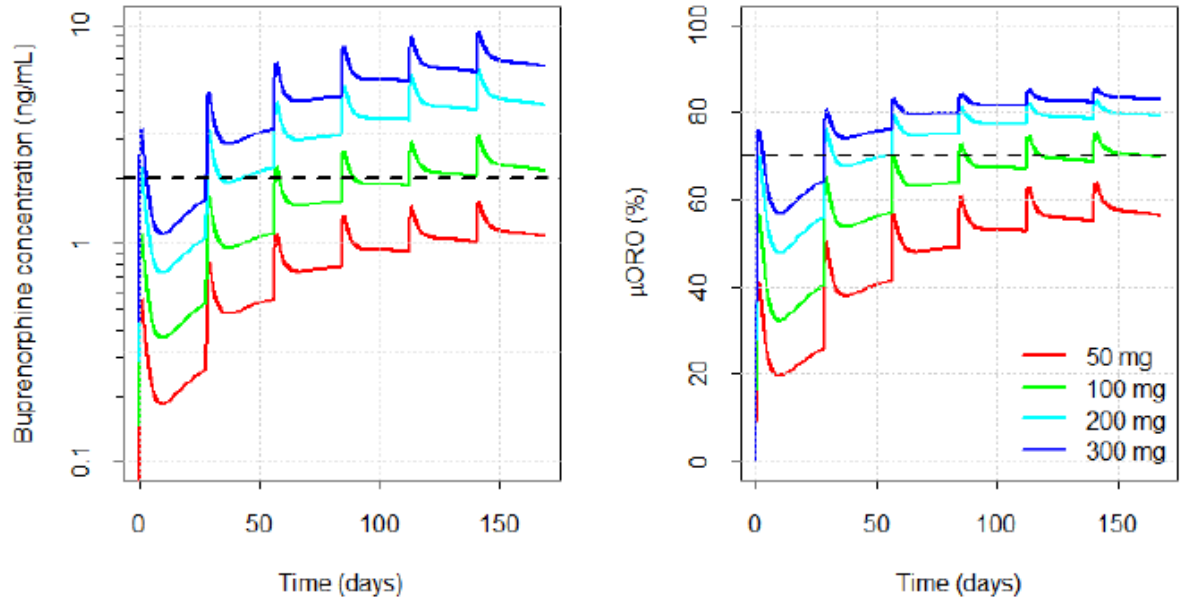
[15] CSR Page 239

receptor occupancy levels were consistently higher than 70% after the second and subsequent injections. The target brain mu-opioid receptor occupancy level could also be reached with the dose of 200mg. However, at this dose, the expected mu-opioid receptor occupancy did not reach the effective level during the first month of treatment. Altogether, these findings supported the choice of 300mg as a starting dose for the treatment of opioid use disorder. The selection of the 300mg dose as an opioid blocking dose was supported by the results from the opioid blockade study.

Simulations also indicated that repeated doses of 100mg of Sublocade provided effective levels of brain mu-opioid receptor occupancy under steady-state conditions. However, given the low predicted levels of brain mu-opioid receptor occupancy after the first and second SC injections at 100mg, the model supported the use of 2 monthly loading doses of 300mg each.[16]

Figure 1 Mean Predicted Buprenorphine Plasma Concentrations and Brain Mu-Opioid Receptor Occupancies After Repeated SC Injections of Sublocade at Various Doses



Left panel = buprenorphine plasma concentrations; Dashed line=2ng/mL
Right panel = mu-opioid receptor occupancy (μ-opioid receptor occupancy); Dashed line=70% μ-opioid receptor occupancy
A total of 6 SC injections given 28 days apart were simulated
Models used for simulation: INDV-6000-M03 Table 10 and INDV-6000-M02 Table 2 Source: Figure 41

[16] Summary of Clinical Pharmacology Studies page 99

11. Clinical efficacy

11.1. Studies providing evaluable efficacy data

Table 3 Efficacy Studies

Study	Description	Synopsis
RB-US-13-0001	A double-blind, placebo-controlled efficacy, safety and tolerability study	11.2.1
RB-US-13-0002	An open-label multiple-dose opioid blockade (OB) study	11.2.2
RB-US-13-0003	A long-term open-label safety and tolerability study	11.2.3
INDV-6000-301	An open-label extension study providing up to 6 months of additional treatment for subjects who completed Study 13-0003 and for whom a new treatment venue had not been identified or arranged	11.2.4

All studies were in opioid dependent subjects

11.2. Pivotal or main efficacy studies

11.2.1. Study 13-0001

A randomized, double-blind, placebo-controlled, multicentre[17] study to assess the efficacy, safety, and tolerability of multiple subcutaneous injections of depot buprenorphine (Sublocade [100mg and 300mg]) over 24 weeks in treatment-seeking subjects with Opioid Use Disorder.

11.2.1.1. Study design, objectives, locations and dates

Carried out from 28 January 2015 to 29 April 2016 in 33 US sites.

Male and female subjects ≥ 18 and ≤ 65 years of age, who were seeking medication-assisted treatment for the treatment of moderate or severe opioid use disorder. 470 subjects planned, 505 randomised, one in error.

The **primary objective** was to assess the efficacy of Sublocade (regimens of SC injections containing either 300mg buprenorphine or 300mg and 100mg buprenorphine) compared with placebo in treatment-seeking subjects with opioid use.

The **secondary objective** of this study was to continue evaluating the safety and tolerability of Sublocade compared with placebo in treatment-seeking subjects with opioid use disorder.

Endpoints

The **primary efficacy endpoint** for this study was the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use (from the TLFB interview) collected from Week 5 through Week 24 in the FAS.

There were 6 subgroup analyses.

There were 11 **secondary efficacy endpoints,** 3 exploratory efficacy endpoints and 11 Supplemental Presentations of efficacy data.

[17] Site 20 was excluded from primary and key secondary efficacy analyses due to compliance issues, but was included in all safety analyses

The **key secondary efficacy endpoint** was changed mid trial on FDA advice:

~~Two key secondary efficacy endpoints for this study will be evaluated to assess clinically relevant differences between treatment and placebo groups. These endpoints are:~~

~~1. Treatment success, which is defined as any subject with ≥75% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 17 and Week 24.~~

~~2. Duration of treatment success, which is defined as the longest sequence of consecutive weeks of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 17 and Week 24.~~

~~Both key secondary efficacy endpoints will be measured during the final 8 weeks of the double-blind phase of the study (Weeks 17 through 24) to allow subjects the greatest amount of time to engage in treatment and attain abstinence, which will be defined as having urine samples negative for opioids as well as self-reports negative for illicit opioid use. This strategy is supported by results from a multiple ascending dose study of RBP- 6000 (RB-US-12-0005), in which self-reported opioid drug use and actual opioid drug use as assessed by urine negative samples decreased following treatment with repeated SC injections of Sublocade. Reductions were the highest at the end of the study, approaching 90% or more by Day 65 (Week 9) following a dose of 300mg Sublocade.~~

<u>The key secondary endpoint in this study is treatment success. A responder is defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24.</u>

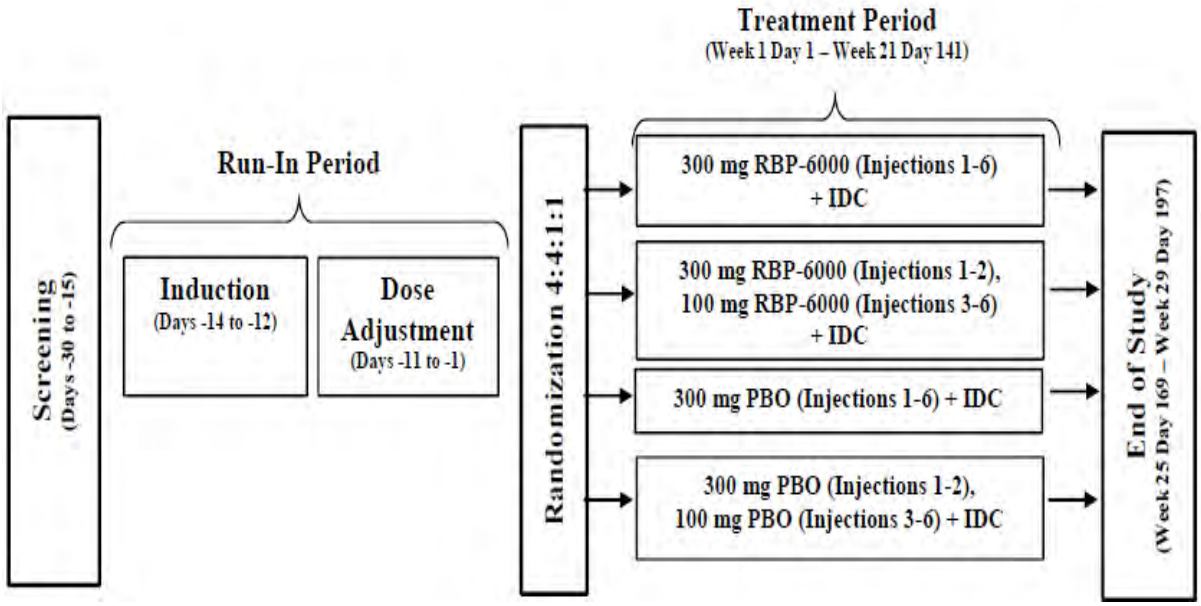
The study comprised:

- Up to 2-week screening period,
- Open-Label Run-in induction Phase with Suboxone sublingual film for 3 days followed by a 4-day to 11-day Suboxone sublingual film open-label run-in dose-adjustment period to achieve buprenorphine doses ranging from 8 to 24mg.
- Double-Blind Treatment Phase with randomisation on Day 1 to 1 of 2 dose regimens of Sublocade or equivalent volume of placebo for 6 SC injections separated by 28 days (± 2). Subjects also received manual-guided behaviour counselling (IDC) at least once per week starting at Day 1 and continuing through the end of the study. Eligible subjects were to be randomised to study treatment in a 4:4:1:1 ratio as follows:
    - Regimen 1: Sublocade 300mg SC every 28 days (± 2) × 6 doses + IDC
    - Regimen 2: Sublocade 300mg SC every 28 days (± 2) × 2 doses + IDC followed by Sublocade 100mg SC every 28 days (± 2) × 4 doses + IDC
    - Placebo Regimen 1: Volume-matched to Regimen #1 + IDC
    - Placebo Regimen 2: Volume-matched to Regimen #2 + IDC.

The design of the trial was also changed mid trial (21 August 2015) on FDA advice:

All randomised subjects who received an injection of study treatment began a 5-day Suboxone sublingual film taper on Day 1. This taper was intended to preserve the blind of the study and to mitigate potential withdrawal signs and symptoms in placebo-treated subjects. A total of 163 randomised subjects received a 5-day Suboxone sublingual film taper.

Figure 2 Study Design



IDC=individual drug counselling: Subjects received IDC during the double-blind treatment period. A total of 163 of the 504 subjects enrolled (32.3%) received a 5-day Suboxone taper as follows: Day 1 (6 mg), Day 2 (4 mg), Day 3 (4 mg), Day 4 (2 mg) and Day 5 (2 mg), according to Amendment 2. Source: Figure 1

11.2.1.2. Analysis populations

Included **Full Analysis Set**:

The Full Analysis Set (FAS) was comprised of all randomised subjects. A randomised subject was defined as any subject that was randomised and allocated study treatment in the IXRS system. This population was used for all efficacy analyses.

11.2.1.3. Sample size

Although there is no true consensus on what constitutes a clinically meaningful difference between placebo and an active treatment in a subject population with opioid use disorder, recent studies suggested that 20% is a clinically meaningful difference.[18] For the purpose of sample size estimation for this study, a slightly smaller treatment difference was assumed to avoid under powering the study. Assuming a placebo response of 15%, a difference of 15% between Sublocade (100mg) and placebo, and a common SD of 30%, the minimum required sample size to achieve at least 90% power using a 2-sided Wilcoxon rank sum test with $\alpha = 5\%$, is 92 subjects per group.

In order to obtain at least 150 completed subjects per active treatment group for inclusion in a long-term safety study (13-0003), and assuming that approximately 20% of the subjects randomised to the active treatment would drop out, the minimum planned sample size was increased to 188 subjects in each active treatment group and 94 subjects in the placebo group.

Hence, a total of 470 subjects were to be randomised in a 4:4:1:1 ratio to Sublocade (300/300mg), Sublocade (300/100mg) or volume-matched placebo (188:188:47:47). Assuming that 20% of the enrolled subjects were to drop out during the Suboxone sublingual film run in phase, approximately 588 subjects were to be enrolled.

11.2.1.4. Statistical methods

The **primary** null (H_0) and research hypotheses (H_a) were as follows:

[18] Page 88

H_0: Neither of the 2 dose regimens of Sublocade (dose Regimen 1: 6 × 300mg or dose Regimen 2: 2 × 300mg + 4 × 100 mg) is superior to placebo at Week 24 with respect to the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24, examined as a cumulative distribution function.

H_a: At least 1 of the 2 dose regimens of Sublocade (dose Regimen 1: 6 × 300mg + or dose Regimen 2: 2 × 300mg + 4 × 100 mg) is superior to placebo at Week 24 with respect to the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use collected from Week 5 through Week 24, examined as a cumulative distribution function.

Since the primary endpoint was not normally distributed, a nonparametric test procedure, the Wilcoxon rank-sum test, was used to compare the treatment groups. To test the 2 primary hypotheses, a truncated Hochberg procedure was used with a truncation parameter of 0, which reduces to Bonferroni. Therefore, the 2 primary hypotheses were tested at $\alpha = 0.025$ level.

The null (H_{10}) and research hypotheses (H_{1a}) for the **key secondary** efficacy endpoint of treatment success were:

- H_{10}: Neither of the 2 dose regimens of Sublocade is superior to placebo with respect to treatment success.
- H_{1a}: At least 1 of the 2 dose regimens of Sublocade is superior to placebo with respect to treatment success.

The Cochran-Mantel-Haenszel (CMH) test was used to test the difference in treatment success rates.

The primary hypotheses were tested. In order to enable a flexible α propagation, a truncated Hochberg procedure was used with a truncation parameter of 0, which reduces to Bonferroni.

If at least 1 of the primary hypotheses was significant, the key secondary hypotheses were to be tested.

Only the 4 comparisons of the 2 primary efficacy and 2 key secondary efficacy endpoints had adjustments for multiplicity.

11.2.1.5. Participant flow

Table 4 Subject Disposition - All Screened Subjects

Category	Total	RBP-6000 300mg/100mg+IDC (N = 203) n (%)	RBP-6000 300mg/300mg+IDC (N = 201) n (%)	Placebo+IDC (N = 100) n (%)
Screened Subjects	1187			
Screen Failures	682			
Screen Failures and entered the Run-in Phase[1]	160			
Screen Failures and not in Run-in Phase	522			
Entered the Run-in Phase[2]	665			
Run-in Failures[3]	161			
Death during Run-in Phase	0			
Randomised	504	203 (100.0)	201 (100.0)	100 (100.0)
Randomised but not treated[4]	0	0 (0.0)	0 (0.0)	0 (0.0)
Randomised and treated	504	203 (100.0)	201 (100.0)	100 (100.0)
Completed	288	125 (61.6)	129 (64.2)	34 (34.0)
Discontinued	216	78 (38.4)	72 (35.8)	66 (66.0)
Reasons for discontinuation				
Lost to follow-up	61	26 (12.8)	23 (11.4)	12 (12.0)
Subject withdrew consent to participate	59	20 (9.9)	21 (10.4)	18 (18.0)
Other[5]	30	17 (8.4)	6 (3.0)	7 (7.0)
Lack of efficacy	26	3 (1.5)	5 (2.5)	18 (18.0)
Adverse event	18	6 (3.0)	10 (5.0)	2 (2.0)
Protocol deviation	7	2 (1.0)	5 (2.5)	0 (0.0)
Withdrawal symptoms	5	1 (0.5)	1 (0.5)	3 (3.0)
Noncompliance with study drug	4	2 (1.0)	0 (0.0)	2 (2.0)
Subject was withdrawn by the investigator	4	1 (0.5)	0 (0.0)	3 (3.0)
Physician decision	2	0 (0.0)	1 (0.5)	1 (1.0)
Death[6]	0	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0	0 (0.0)	0 (0.0)	0 (0.0)

IDC = individual drug counselling

[1] These subjects were in the clinical database as screen failures; however, they also received at least 1 dose of Suboxone SL film.

[2] Includes subjects who received at least 1 dose of Suboxone sublingual film during the run-in phase.

[3] An additional 34 subjects were identified as run-in failures in the datasets but didn't enter the run-in phase. These 34 subjects are not included in the count of run-in failures, as they did not take any run-in medication and are therefore included in the 522 subjects who were "Screen failures and not in run-in phase".

[4] one subject was randomised, but did not receive any study treatment during the double-blind phase, including the Suboxone sublingual film taper.

[5] Discontinuation due to "other" includes site closed by sponsor (n = 9), incarceration (n = 7), relocation (n = 4), noncompliance with study visits/lost to follow-up type reasons (4)

[6] one subject in Sublocade 300 mg/300mg group discontinued due to adverse event that led to death.

Note:2 subjects were run-in failures due to the primary reason of adverse event. The action taken was reported as not applicable as the case report form was intended to capture action taken only with randomised study treatment. Source: Table 13

11.2.1.6. Major protocol violations/deviations

41 subjects had important protocol deviations pertaining to violation of inclusion/exclusion criteria (14 subjects received 300mg/100mg, 17 subjects received 300mg/300mg and 10 subjects received placebo) and 1 subject had a protocol deviation pertaining to receipt of incorrect study treatment (placebo group).

11.2.1.7. Baseline data

Table 5 Demographic and Baseline Characteristics - Full Analysis Set

Subject Characteristics	Sublocade 300mg/100mg+IDC (N = 194)	Sublocade 300mg/300mg+IDC (N = 196)	Placebo+IDC (N = 99)
Age (years)			
n	194	196	99
Mean (SD)	40.4 (11.23)	39.3 (10.96)	39.2 (10.96)
Median	39.0	38.0	38.0
Min, Max	20, 64	19, 64	20, 63
Age (years) by categories (%)			
≥ 18 to < 30	39 (20.1)	43 (21.9)	23 (23.2)
≥ 30 to < 45	84 (43.3)	93 (47.4)	44 (44.4)
≥ 45 to < 60	64 (33.0)	52 (26.5)	30 (30.3)
≥ 60	7 (3.6)	8 (4.1)	2 (2.0)
Sex (%)			
Male	128 (66.0)	132 (67.3)	64 (64.6)
Female	66 (34.0)	64 (32.7)	35 (35.4)
Baseline Weight (kg)			
n	194	196	99
Mean (SD)	76.68 (15.932)	79.65 (16.233)	75.48 (16.143)
Median	74.95	78.05	72.90
Min, Max	45.5, 123.4	47.6, 128.0	48.2, 132.0
Baseline BMI (kg/m^2)			
n	194	196	99
Mean (SD)	25.32 (4.206)	26.35 (4.395)	25.30 (4.266)
Median	24.70	25.50	25.00
Min, Max	18.0, 34.9	18.0, 35.0	17.9, 35.0
Opioid Users at Screening (%)			
Non-injectable Opioid Users	138 (71.1)	136 (69.4)	57 (57.6)
Injectable Opioid Users	84 (43.3)	80 (40.8)	50 (50.5)
Subjects used illicit opioids in addition to run-in medication as indicated by positive UDS on Day 1 (%)	91 (46.9)	104 (53.1)	45 (45.5)
Subjects did not use illicit opioids in addition to run-in medication as indicated by negative UDS on Day 1 (%)	103 (53.1)	92 (46.9)	54 (54.5)

IDC = individual drug counselling Subjects from Site 20 were excluded from the analysis. Source: Table 15 & 16

Results

11.2.1.1. Results for the primary efficacy Endpoint

The primary efficacy endpoint was the Cumulative Distribution Function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24. Both the 300mg/100mg and 300mg/300mg groups were statistically significantly superior to placebo (both $P < 0.0001$); mean (median) percentages were 42.7% (32.5%), 41.3% (30%) and 5% (0%), respectively.

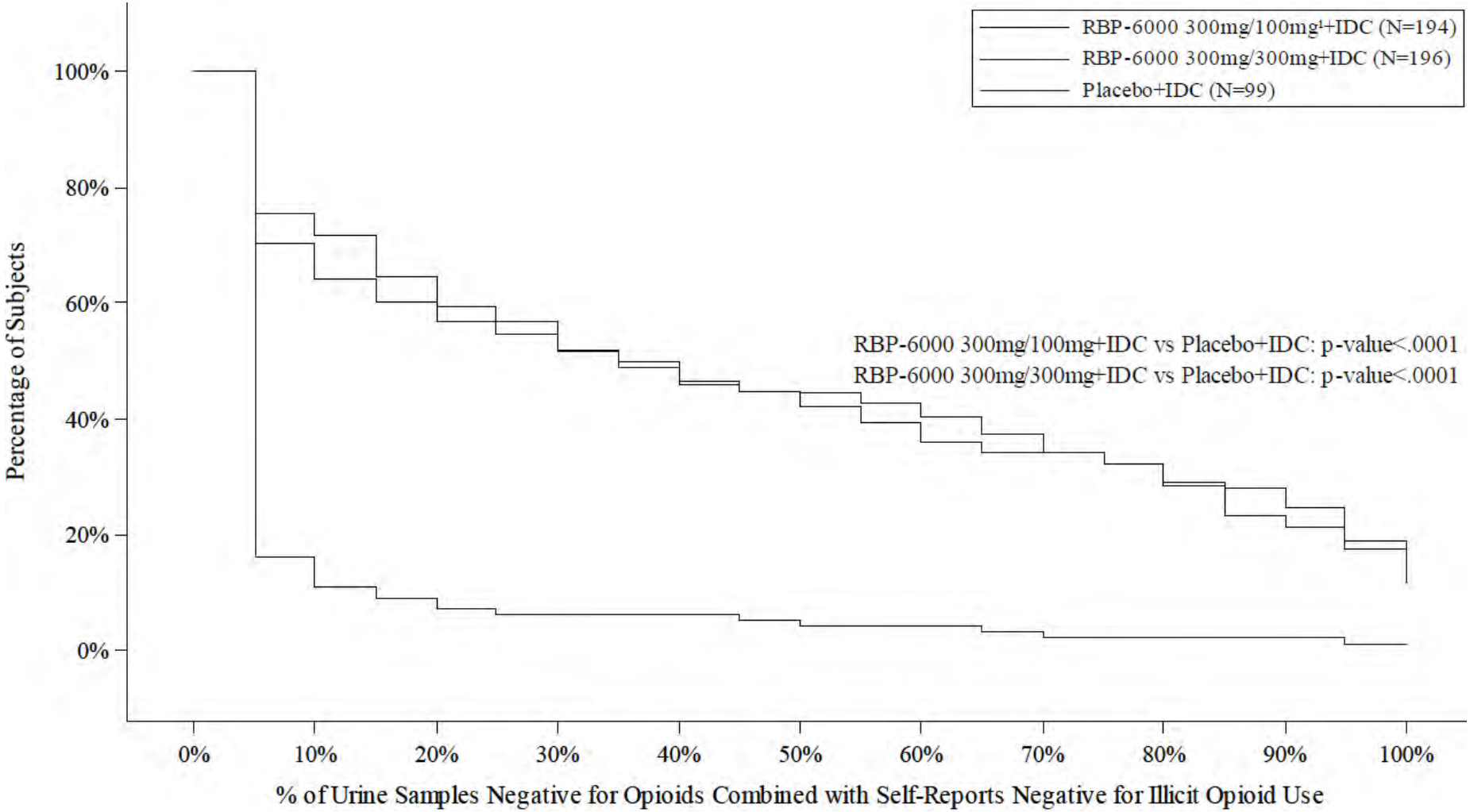
Table 6 Primary Efficacy Endpoint: Cumulative Distribution Function of the Percentage Abstinence From Week 5 Through Week 24 - Full Analysis Set

	Number (%) of Subjects		
Percentage Abstinence	RBP-6000 300mg/100mg+IDC (N = 194)	RBP-6000 300mg/300mg+IDC (N = 196)	Placebo+IDC (N = 99)
≥ 0%	194 (100.0)	196 (100.0)	99 (100.0)
≥ 10%	139 (71.6)	126 (64.3)	11 (11.1)
≥ 20%	115 (59.3)	111 (56.6)	7 (7.1)
≥ 30%	101 (52.1)	101 (51.5)	6 (6.1)
≥ 40%	90 (46.4)	90 (45.9)	6 (6.1)
≥ 50%	86 (44.3)	82 (41.8)	4 (4.0)
≥ 60%	78 (40.2)	70 (35.7)	4 (4.0)
≥ 70%	66 (34.0)	67 (34.2)	2 (2.0)
≥ 80%	55 (28.4)	57 (29.1)	2 (2.0)
≥ 90%	41 (21.1)	48 (24.5)	2 (2.0)
P-value[1] (comparison with Placebo+IDC)	< 0.0001	< 0.0001	
n	194	196	99
Mean (SD)	42.7% (38.50%)	41.3% (39.66%)	5.0% (16.98%)
Median	32.5%	30.0%	0.0%
Min, Max	0%, 100%	0%, 100%	0%, 100%

IDC = individual drug counselling; The primary endpoint, percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use, is "percentage abstinence". Subjects from Site 20 were excluded from the analysis. All missing results for opioids were considered non-negative.

[1] Wilcoxon rank-sum test was used to compare the treatment groups. Each dosing regimen was compared to placebo with respect to the composite primary efficacy endpoint at a significance level of $\alpha = 0.025$. Source: Table 23

Figure 3 Primary Efficacy Endpoint: Cumulative Distribution Function of the Percentage of Subjects Abstinent From Week 5 Through Week 24 – Full Analysis Set



IDC = individual drug counselling Subjects from Site 20 were excluded from the analysis.
All missing results for opioids were considered nonnegative. Depicted data are inverse-cumulative distribution function.
[1] Subjects received Sublocade containing 300mg buprenorphine for the first 2 injections, followed by 4 injections of Sublocade containing 100mg buprenorphine. Source: Figure 3

11.2.1.2. Results for the key secondary efficacy endpoint

The key secondary endpoint in this study was treatment success. A responder was defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24.

Both the 300mg/100mg and300 mg/300mg groups were statistically significantly superior to placebo (both P < 0.0001); percentages were 28.4% and 29.1% vs. 2.0% respectively.

Table 7 Treatment Success - Full Analysis Set

	Number (%) of Subjects				
Key Secondary Efficacy Endpoint	RBP-6000 300mg/100mg+IDC (N = 194)	RBP-6000 300mg/300mg+IDC (N = 196)	Placebo+IDC (N = 99)	*P*-Value[2] (300mg/100 mg+IDC vs Placebo+IDC)	*P*-Value[2] (300mg/300 mg+IDC vs Placebo+IDC)
Treatment Success[1]	55 (28.4)	57 (29.1)	2 (2.0)	< 0.0001	< 0.0001

IDC = individual drug counselling
Subjects from Site 20 were excluded from the analysis.
[1] Treatment success was defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use between Week 5 and Week 24.
[2] The Cochran-Mantel-Haenszel test was used to compare the treatment groups. Source: Table 29

11.2.2. Study 13-0002

A US single centre multiple-dose study of blockade of subjective opioid effects, plasma levels, and safety of subcutaneous injections of depot buprenorphine in subjects with opioid use disorder.

The study was from 19 November 2013 – 29 July 2014, publication[19] was February 2016, but this report is dated 27 February 2017. 39 enrolled, 38 in ITT population.

From the Protocols:

"Based on a review of the protocol by Reckitt Benckiser Pharmaceuticals, Inc. and Vince and Associates Clinical Research, Inc., and feedback from the U.S. Food and Drug Administration (FDA)" the primary objective was modified twice mid trial and all the secondary objectives were modified once.

Comment: These changes were not described in the CSR.

The **primary objective** of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade).

Secondary Objectives:

- To evaluate the reinforcing effects (using Choice Sessions) of the daily randomized hydromorphone challenge dose (relative to money) at weekly time points post injection of buprenorphine 300mg (Sublocade).
- To evaluate the correlation between the opioid blockade subjective effects (VAS of "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and

[19] Nasser et al Sustained-release Buprenorphine (RBP-6000) Blocks the Effects of Opioid Challenge with Hydromorphone in Subjects with Opioid Use Disorder. J Clin Psychopharmacol. 2016 Feb 1;36(1):18-26.

"High") and the reinforcing effects of hydromorphone and simulated mu opioid receptor occupancy (using the maximal effect [E_{max}] model). (See also 21.1.2.1).

- To determine the relationship between plasma concentration and predicted mu opioid receptor occupancy of buprenorphine and both the blockade of the subjective effects of hydromorphone post injection of buprenorphine 300mg (Sublocade). (See also 21.1.2.1).
- To continue evaluating the safety of Sublocade when administered once per month for 2 months as a depot injection of 300mg in individuals who have been inducted and dose stabilized on sublingual (SL) buprenorphine (Suboxone Film) on a dose between 8 and 24 mg/day and in the presence of 6 and 18mg of hydromorphone.

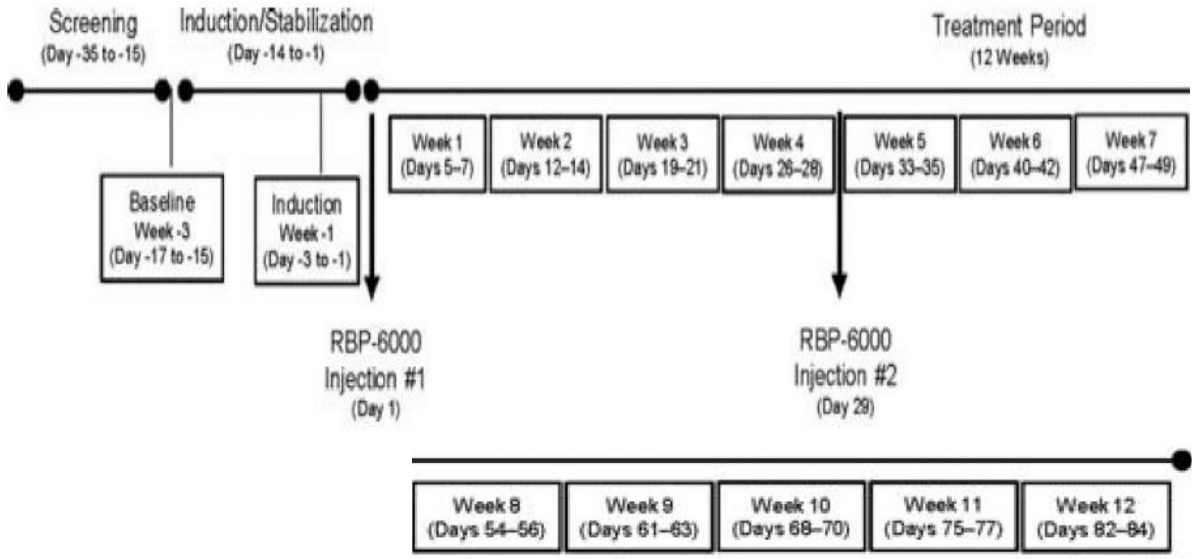
For PKs see 21.1.1.5.

A *post-hoc* analysis was conducted[20] to assess whether the peak (E_{max}) of "Drug Liking" VAS score measured after challenge with IM injections of 6mg and 18mg hydromorphone was not inferior compared to the E_{max} of "Drug Liking" VAS score measured after challenge with placebo at Weeks 1 through 12.

To enter the trial subjects had establish their opiate liking by undertaking a **hydromorphone challenge** of 18mg. [21]

The study comprised an initial 2 weeks on SL Suboxone (buprenorphine and naloxone) followed by 2 injections of Sublocade (depot buprenorphine) 4 weeks apart associated with 12 weeks of observation.

Figure 4 Study design



The boxes represent days of hydromorphone challenge tests they go on out to 12weeks Source: Figure 1 article

Subjects were initially stabilised over 3 days on a dose of 8mg to 24mg of Suboxone sublingual film daily which was continued for the rest of 2 weeks.

On day 1, subjects were administered a single SC injection of Sublocade (300mg) into the abdominal area. A second injection of Sublocade was administered on day 29. The final study visit was 9 weeks after the second injection of Sublocade or after early study termination.

[20] at the request of the US FDA

[21] an acceptable response was defined as having a "Drug Liking" VAS score of at least 40 mm [out of 100 mm on a scale anchored by "none" or "not at all" and "extreme" or "extremely" CSR page 29

Testing for efficacy was done on blocks of 3 consecutive days:

- The last 3 days of Suboxone exposure.
- At the end of every successive week after Sublocade injection.

Following administration of a varying dose of hydromorphone (hydromorphone challenges), subjective effects were measured and Reinforcing Effects Tasks undertaken in order to evaluate opioid blockade.

Hydromorphone challenges

Subjects received one intramuscular injection of placebo (0mg hydromorphone; 0.45% sodium chloride) or 6 or 18mg of hydromorphone (constant 1.8mL volume) in 1 of 6 randomized sequences[22] and 6 VAS assessments and the drug vs. money choice task were conducted.

Reinforcing Effects Tasks were described in the protocol,[23] they are better described in the journal article as Drug Versus Money Choice Task:

At least 5 hours after the baseline and treatment period, randomized hydromorphone challenges subjects completed a 12-trial drug/money choice task. On each trial, the subject could choose to earn 1 of the 12 total hydromorphone (or placebo) unit doses (i.e. 0mg, 0.5mg or 1.5mg per trial) they had received that morning or US $2. To earn each choice, subjects had to click either the "drug" or "money" box displayed on the computer screen. The number of mouse clicks required to receive each reward (drug or money) increased exponentially across trials (5, 40, 70, 120, 180, 260, 395, 555, 775, 1110, 1558, 2160 mouse clicks), according to a progressive ratio schedule of reinforcement. The response requirement for both drug and money increased (independently from one another) until responding ceased, all 12 ratios were completed or the participant chose to work for the alternative option. The "breakpoint" was defined as the highest number of mouse clicks completed to receive the hydromorphone unit dose.

In the initial Suboxone period on the last 3 days of Suboxone treatment, hydromorphone challenges were given 8h prior to Suboxone.

Table 8 Relative and Absolute Treatment Times for Hydromorphone and Suboxone

Drug/Activity	Time to Start Prior to SUBOXONE Sublingual Film	Time to Start Prior to Earned Hydromorphone	Suggested Time
Randomised Hydromorphone Challenge	-8 hours	-6 hours	9 AM
Start of Reinforcing Effects Tasks	-3 hours	-1 hour	2 PM
Hydromorphone earned from Reinforcing Effects Tasks	-2 hours	NA	3 PM
SUBOXONE sublingual film administration	NA	NA	5 PM

Source: Table 1

After the initial Sublocade injection, hydromorphone challenges (in randomized study drug sequences) and 6 VAS assessments and the drug vs. money choice task were conducted on 3 consecutive residential days at the end of each week for a total of 12 weeks. During each 3-day hydromorphone challenge, the clinical staff and subjects remained blinded to the sequence.

[22] Sequence 1: 0 mg (placebo), 6 mg, 18 mg Sequence 2: 6 mg, 18 mg, 0 mg (placebo) Sequence 3: 18 mg, 0 mg (placebo), 6 mg Sequence 4: 0 mg (placebo), 18 mg, 6 mg Sequence 5: 6 mg, 0 mg (placebo), 18 mg Sequence 6: 18 mg, 6 mg, 0 mg (placebo)

[23] E.g. page 426

Statistical analysis

Opioid Blockade Subjective Effects Analysis ("Drug Liking" Visual Analog Scale)

For each hydromorphone challenge week, a mixed-effects model with period (where period is day), hydromorphone sequence, and hydromorphone dose as fixed effects and subject nested within hydromorphone sequence as a random effect were used for analysis. The difference in mean outcome between hydromorphone doses was compared using SAS™ estimate statements.

Opioid blockade was achieved at dose 1 of the hydromorphone challenge if:

the null hypothesis (H_0:M_1-M_0 > d)

was rejected in favour of

the alternative hypothesis (HA: M_1-M_0 ≤ d)

Where

M_0 = the mean response to placebo (0mg hydromorphone)

M_1 = the mean response to hydromorphone challenge dose 1 (6mg hydromorphone)

M_2 = the mean response to hydromorphone challenge dose 2 (18mg hydromorphone),

d is the non-inferiority margin = 11.

Complete hydromorphone blockade was claimed for Sublocade if blockade was achieved for both hydromorphone doses (6mg and 18mg) during each week of testing for the 4 weeks after the first dose of Sublocade.

Each of the above tests was performed at a 2-sided α = 0.05. Since this was an intersection union test, there was no need to adjust for multiple testing, and the overall test was a size-α test

If a significant departure from normality was found in the data, descriptive statistics were provided to assess whether there were sequence, period, or first-order-carryover effects. Chen's t-test for the mean of a skewed distribution was used to test the individual differences between responses to dose 1 and placebo and dose 2 and placebo.

Reinforcing Effects

The ability of Sublocade to attenuate the reinforcing effects of hydromorphone was analysed using the hydromorphone breakpoint value. For each subject, the hydromorphone breakpoint value was determined at each hydromorphone challenge based on the hydromorphone units earned values on the electronic case report form after the completion of each session.

Hydromorphone breakpoint values for all subjects were then analysed by week using a repeated measures mixed-effects model with period, hydromorphone sequence, and hydromorphone dose as fixed effects and subject nested within hydromorphone sequence as a random effect. Difference in mean outcome between hydromorphone doses was compared using SAS™ estimate statements. The purpose of this analysis was to show that there was no difference in breakpoint value between placebo, 6mg hydromorphone and 18mg hydromorphone at each week.

Determination of Sample Size

The sample size calculation formula for testing a non-inferiority hypothesis in a Williams' square design was used, the resulting sample size needed per sequence was n = 4 (with 4 subjects assigned to each sequences of a Williams' 6 x 3 design a minimum of 24 subjects).

For this study, a non-inferiority margin of 11 (δ = 11) was proposed according to Chen (2011).[24]

[24] Analysis of Data from Human Abuse Potential Studies. CPDD 73rd Annual Meeting (presentation). 2011.

Comment: The CSR reference was not provided in the submission nor found in the meeting abstract book on line. A different reference for this in the Summary of Clinical Pharmacology Studies was also not in the submission but the abstract existed online.[25]

There were a total of 27 **major deviations** reported; 3 involved hydromorphone dosing irregularities and there were 24 incidences in which the subjective effects VAS assessments were administered with 95mm scales instead of 100mm scales on Day-17.

Table 9 Summary of Subject Disposition (Population: Safety)

	Overall N = 39 n (%)
Safety Population	39 (100.0)
Completed	30 (76.9)
Withdrew	9 (23.1)
Reason for Withdrawal	
Lost to follow-up	3 (7.7)
Physician decision	3 (7.7)
Withdrawal by subject	3 (7.7)

Source: Table 7

Table 10 Summary of Demographics (Population: Safety)

	Category or Statistic	Overall N=39
Gender - n (%)	Male	35 (89.7)
	Female	4 (10.3)
Age (yr)	N	39
	Mean	34.6
	SD	8.93
	Median	34.0
	Min, Max	20, 55
Weight (kg)	N	39
	Mean	79.55
	SD	11.178
	Median	78.40
	Min, Max	60.9, 102.5
BMI (kg/m^2)	N	39
	Mean	25.35
	SD	3.017
	Median	25.20
	Min, Max	20.7, 31.5

N = number of subjects; n = number of subjects in a subset in a given category
The safety population included all subjects who received at least one dose of Sublocade, Suboxone sublingual film, or hydromorphone (starting with the baseline hydromorphone challenge). Source: Table 8

[25] Chen L, Bonson KR. An equivalence test for the comparison between a test drug and placebo in human abuse potential studies. J Biopharm Stat. 2013 Mar 11;23(2):294-306.

Results

Primary endpoint "Drug Liking" VAS score Weeks 1-4

The study failed to achieve the primary endpoint failing to meet the non-inferiority margin at one time point during the first 4 weeks (18mg hydromorphone at 4 weeks).
During the hydromorphone challenge qualification period (screening, referred here as Week -1), no opioid blockade was observed. After treatment with Suboxone SL film, a decrease in "Drug Liking" VAS scores was observed, but not opioid blockade.
Following SC injection of Sublocade, the "Drug Liking" VAS analysis demonstrated opioid blockade for the 6mg hydromorphone to placebo treatment comparison from Week 1 to Week 4 (Sublocade injection 1 period). For the 18mg hydromorphone to placebo treatment comparison, opioid blockade was observed from Week 1 to Week 3, while at Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade. After the first injection of SC Sublocade, during week 4, a decrease in mean buprenorphine plasma concentration (from 1.9 to 1.8ng/mL) correlated with a 65% μ-opioid receptor occupancy , which corresponded to the slight increase in VAS scores.[26]
Following the second SC injection of Sublocade, opioid blockade was achieved for both the 6mg and 18mg hydromorphone to placebo treatment comparison over the full dosing interval (from Week 5 to Week 8) and was maintained for an additional 4 weeks (from Week 9 to Week 12), despite no further injections of Sublocade.

Secondary Endpoints

Reinforcing effects

For the Reinforcing Effects Tasks analysis, no diminished reinforcing effect of hydromorphone was observed during the hydromorphone qualification challenge period.
The Reinforcing Effects Tasks analysis showed that the reinforcing effects of hydromorphone compared to placebo diminished over the course of the study. Specifically, whereas the LSMeans of the $\log_{10}$ transformed values of the Reinforcing Effects Tasks scores remained for the most part consistent for the placebo (mean = 1.937, SD = 0.2221), the corresponding values for the 6mg and 18mg doses of hydromorphone decreased from baseline through Week 12. For the 6mg dosage, the observed reduction was from approximately 3.093 at baseline to 2.008 at the end of Week 12. For the 18mg dosage, the corresponding range was from 3.058 at baseline to 2.438 at the end of Week 12.
If the 95% CI for the difference in the LSMeans of the $\log_{10}$ transformations of the breakpoint values for the Reinforcing Effects Task scores for either of the active hydromorphone doses (6mg and 18mg) compared to placebo enclosed 0, then there was considered to be no difference between the active dose and placebo. The results indicated that there was no difference between the 6mg dose of hydromorphone and placebo at Weeks 1, 2, and 5 through 12; and no difference between the 18mg dose and placebo at Weeks 5, 6, 8, 9, 10, and 11

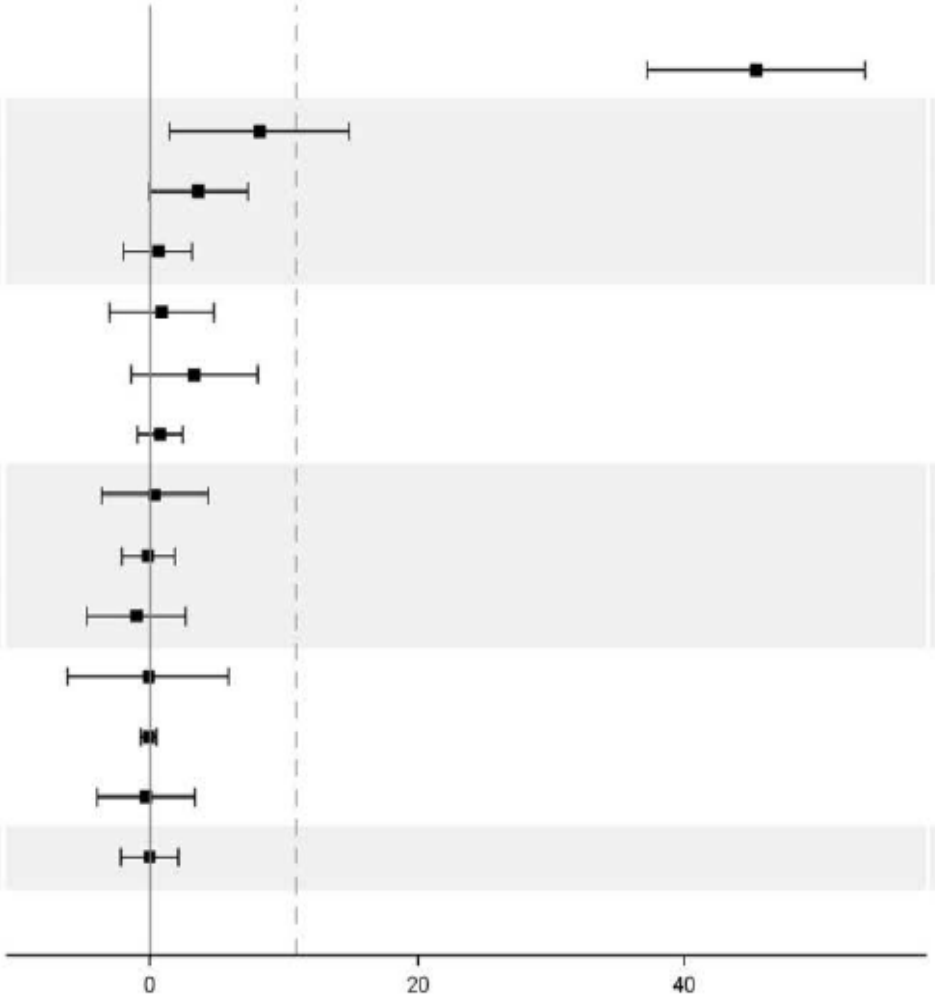
Opioid Blockade Subjective Effects (VAS of "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High")

For the 5 additional VAS analyses, full opioid blockade was observed from Week 1 to Week 12 after Sublocade treatment for both the 6mg and 18mg hydromorphone to placebo treatment comparisons, except for the following 18mg to placebo comparisons: Week 3, Good Drug Effect (upper 95% CI = 11.238); Week 4, High (12.009), Week 4, Any Drug Effect (12.743), and Week 4, Good Drug Effect (12.502).

[26] Publication

Table 11 Plot of Mean Difference and 95% CI for VAS Score: Drug Liking Comparison: 6mg Hydromorphone vs. Placebo

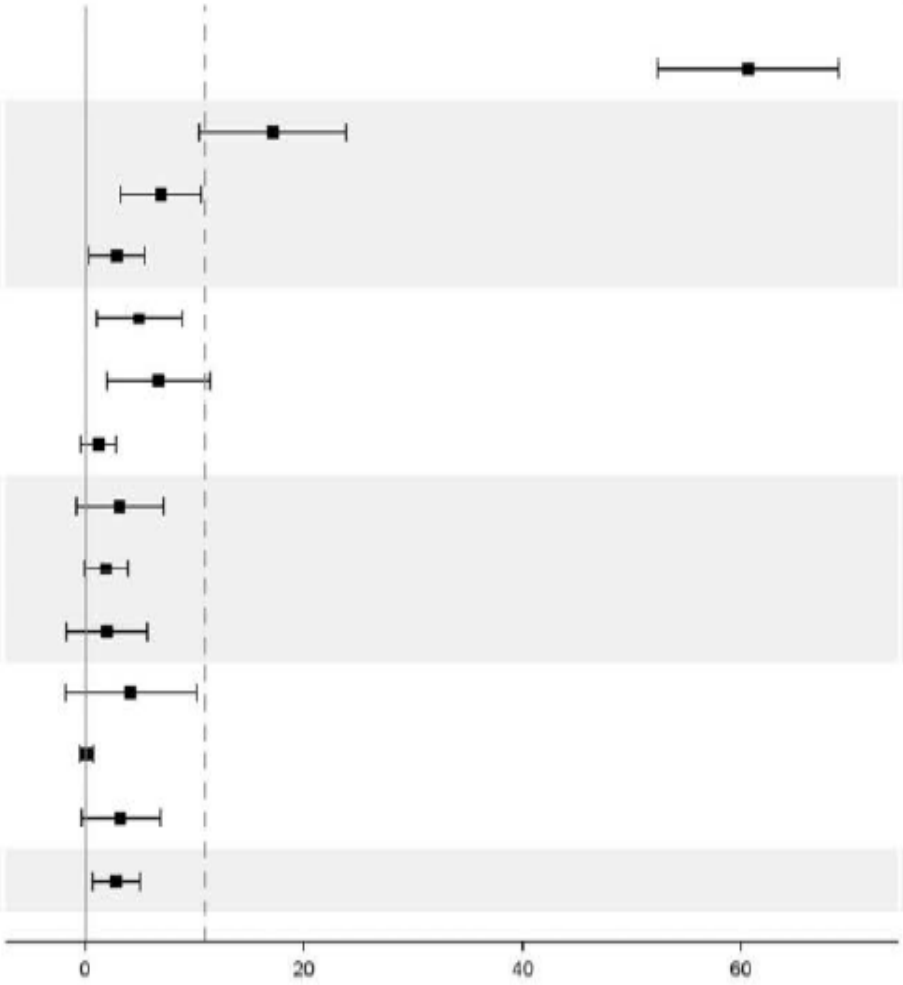
Weeks in Study	LS Means[1]	STDERR[2]	Lower 95% CI	Upper 95% CI
Baseline (Week -1)	45.36	4.11	37.16	53.56
Week 0	8.2	3.38	1.47	14.94
Week 1	3.66	1.85	-0.03	7.34
Week 2	0.59	1.28	-1.98	3.15
Week 3	0.86	1.96	-3.05	4.78
Week 4	3.32	2.37	-1.42	8.06
Week 5	0.74	0.84	-0.94	2.42
Week 6	0.35	1.98	-3.62	4.32
Week 7	-0.15	1	-2.16	1.86
Week 8	-1.04	1.85	-4.77	2.68
Week 9	-0.12	3.01	-6.2	5.95
Week 10	-0.09	0.3	-0.69	0.51
Week 11	-0.32	1.81	-3.97	3.34
Week 12	-0.03	1.07	-2.19	2.12



STDERR = Standard Error of LSMeans difference Dashed line is non-inferiority bound (11). Blockade was achieved for weeks on study if the plot wholly lied left of the non-inferiority bound.
Baseline (pre-buprenorphine treatment phase) was defined as Day -17, Day -16, and Day -15 Week 0 (Suboxone sublingual phase) was defined as Day -3, Day -2, and Day -1
[1] Estimate of Least Squares (LS) Means difference between active drug and placebo (Intent-to-treat population: 38 subjects).
[2] Standard Error of the LSMeans difference between active drug and placebo. Source: Figure 26

Table 12 Plot of Mean Difference and 95% CI - VAS Score: Drug Liking - Comparison: 6mg Hydromorphone vs Placebo (Population: ITT)

Weeks in Study	LS Means[1]	STDERR[2]	Lower 95% CI	Upper 95% CI
Baseline (Week -1)	60.61	4.16	52.32	68.9
Week 0	17.17	3.38	10.43	23.9
Week 1	6.93	1.85	3.24	10.61
Week 2	2.9	1.28	0.33	5.46
Week 3	4.93	1.96	1.02	8.84
Week 4	6.68	2.37	1.94	11.42
Week 5	1.21	0.82	-0.43	2.85
Week 6	3.16	1.99	-0.83	7.15
Week 7	1.88	0.99	0.11	3.87
Week 8	1.93	1.85	-1.79	5.66
Week 9	4.16	2.97	-1.84	10.17
Week 10	0.13	0.31	-0.5	0.76
Week 11	3.24	1.78	-0.35	6.83
Week 12	2.78	1.08	0.61	4.96



STDERR = Standard Error of LSMeans difference Dashed line is non-inferiority bound (11). Blockade was achieved for weeks on study if the plot wholly lied left of the non-inferiority bound.
Baseline (pre-buprenorphine treatment phase) was defined as Day -17, Day -16, and Day -15 Week 0 (Suboxone sublingual phase) was defined as Day -3, Day -2, and Day -1
[1] Estimate of Least Squares (LS) Means difference between active drug and placebo (Intent-to-treat population: 38 subjects).
[2] Standard Error of the LSMeans difference between active drug and placebo. Source: Figure 27

11.2.3. Study 13-0003

An open-label, long-term safety and tolerability study of depot buprenorphine in treatment-seeking subjects with opioid use disorder. Conducted at 39 US sites from 27 July 2015 to 31 January 2017.

The **primary** objective of this study was to assess the long-term safety and tolerability of SC administration of Sublocade in subjects with opioid use disorder

The **secondary** objective of this study was to collect clinical outcome data after SC administration of Sublocade in subjects with opioid use disorder.

Run-in Period

After 14 days of Suboxone SL Subjects who had no significant opioid craving (Opioid Craving VAS of ≤ 20 mm) and no significant withdrawal (COWS score of ≤ 12) were continued into the treatment period.

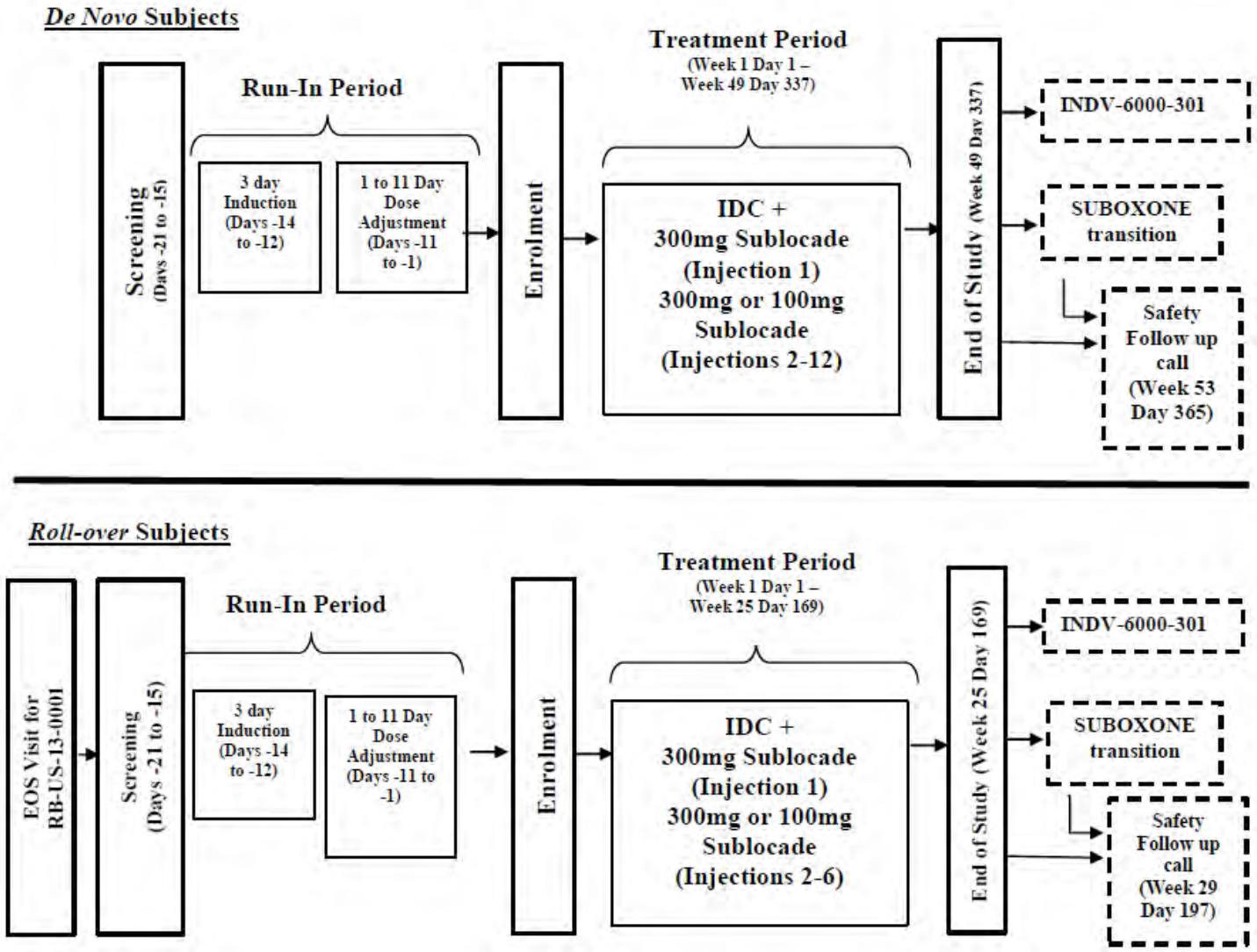
Treatment Period

After an initial 300mg SC injection of Sublocade subsequent 28 day doses of Sublocade could be adjusted down to 100mg with the possibility of adjusting back up to 300 mg.

The *de novo* subjects' maximum duration was up to a 48-week open-label treatment period.

The roll-over subjects' maximum duration was up to a 24-week open-label treatment period.

Figure 5 Study Overview – *de novo* Subjects and Roll-over Subjects



Source: Figure 1

Table 13 Subject Disposition Sublocade treatment

Category	*De novo* Subjects n (%)	Roll-over Subjects n (%)	Total n (%)
Entered Sublocade treatment period[4]	412 (81.1)	257 (96.3)	669 (86.3)
Completed[5,7]	206 (50.0)	200 (77.8)	406 (60.7)
Discontinued[5,7]	206 (50.0)	57 (22.2)	263 (39.3)
Reasons for discontinuation[6]			
Adverse event[8]	11 (2.7)	4 (1.6)	15 (2.2)
Death	0	0	0
Withdrawal symptoms[8]	3 (0.7)	0	3 (0.4)
Lost to follow-up	80 (19.4)	19 (7.4)	99 (14.8)
Non-compliance with study treatment[5]	0	0	0
Physician decision	5 (1.2)	0	5 (0.7)
Subject withdrew consent to participate	67 (16.3)	24 (9.3)	91 (13.6)
Subject was withdrawn from participation by the investigator	7 (1.7)	1 (0.4)	8 (1.2)
Lack of efficacy	0	0	0
Protocol violation	4 (1.0)	4 (1.6)	8 (1.2)
Study terminated by sponsor	0	0	0
Other[9]	28 (6.8)	5 (1.9)	33 (4.9)

[4] The denominator is the number of subjects who entered the run-in period in each subject group Source: Table 11
[5] Non-compliance with study treatment is listed as a protocol violation.
[6] The denominator is the number of subjects who entered the treatment period in each subject group
[7] A Subject missed injection 4 and was not considered to have completed the study, however had an EOS/ET visit listed as Day 337. This subject does not have a reason for discontinuation listed.
A Subject walked out in the middle of the EOS visit and was considered to have discontinued the study, however, the subject received all 12 injections and has an EOS date
[8] Withdrawal symptoms are listed separately from AEs leading to discontinuation. Three subjects had AEs of withdrawal symptoms reported under withdrawal symptoms (not AEs) in this table.
[9] "Other" reasons included incarceration (n = 19), pregnancy (n = 13), and subject unable to continue study due to new job (n = 1)

Table 14 Demographic and Baseline Characteristics – Safety Analysis Set

Subject Characteristics	*De novo* Subjects (N=412)	Roll-over Subjects (N=257)	Total (N=669)
Age (years)[1]			
N	412	257	669
Mean (SD)	38.4 (12.10)	41.6 (11.07)	39.6 (11.81)
Median	36.0	40.0	38.0
Min, Max	19, 65	21, 64	19, 65
Age (years) by categories [n (%)][1]			
≥18 to <30	122 (29.6)	40 (15.6)	162 (24.2)
≥30 to <45	157 (38.1)	114 (44.4)	271 (40.5)
≥45 to <60	107 (26.0)	89 (34.6)	196 (29.3)
≥60	26 (6.3)	14 (5.4)	40 (6.0)
≥65	1 (0.2)	0	1 (0.1)
Sex [n (%)]			
Male	263 (63.8)	169 (65.8)	432 (64.6)
Female	149 (36.2)	88 (34.2)	237 (35.4)
Baseline weight (kg)			
n	412	257	669
Mean (SD)	75.49 (14.658)	78.43 (18.097)	76.62 (16.117)
Median	74.60	74.70	74.70
Min, Max	42.4, 125.0	44.5, 140.2	42.4, 140.2
Baseline BMI (kg/m^2)[2]			
n	412	257	669
Mean (SD)	25.38 (4.286)	26.14 (5.067)	25.67 (4.613)
Median	24.70	25.40	25.00
Min, Max	17.9, 35.8	16.7, 42.3	16.7, 42.3

[1] Age is derived at the time of informed consent using subject date of birth. Source: Table 13
Percentages are based on the number of subjects in the Safety Analysis Set in each subject group.

Results

This study was not powered for efficacy comparisons, and no statistical testing was performed.

Table 15 Cumulative Distribution Function for Percentage Abstinence – Safety Analysis Set

Percentage Abstinent	*De novo* Subjects (N=412) n (%)	Roll-over Subjects (N=257) n (%)
≥ 0%	412 (100)	257 (100)
≥ 10%	315 (76.5)	206 (80.2)
≥ 20%	278 (67.5)	200 (77.8)
≥ 30%	239 (58.0)	189 (73.5)
≥ 40%	217 (52.7)	159 (61.9)
≥ 50%	187 (45.4)	150 (58.4)
≥ 60%	166 (40.3)	137 (53.3)
≥ 70%	132 (32.0)	110 (42.8)
≥ 80%	98 (23.8)	96 (37.4)
≥ 90%	62 (15.0)	74 (28.8)
= 100%	32 (7.8)	47 (18.3)

TLFB = Timeline follow back; UDS = urine drug screen
The percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use, is "percentage abstinence." All missing results for opioids were considered non-negative for opioids. Opioids non-negative indicates detection of codeine, hydrocodone, hydromorphone, methadone, morphine, opiates, oxycodone, and oxymorphone in the UDS and amphetamine/methadone, buprenorphine, methadone, and opioids in the TLFB. Due to an error in the TLFB question, all amphetamine/methadone responses of Use on the TLFB were assumed to be non-negative. Percentages are based on the number of subjects in the Safety Analysis Set in each subject group.
Subjects in the roll-over group participated in this study for 6 months. Subjects in the de novo group participated in this study for 12 months. Source: Table 18

11.2.4. Study INDV-6000-301

An open-label, depot buprenorphine treatment extension study in subjects with opioid use disorder.

There was no primary efficacy endpoint for this study, only exploratory efficacy endpoints.

11.3. Analyses performed across trials: pooled and meta analyses

Study treatment doses and durations and other study parameters precluded pooling of the data.[27]

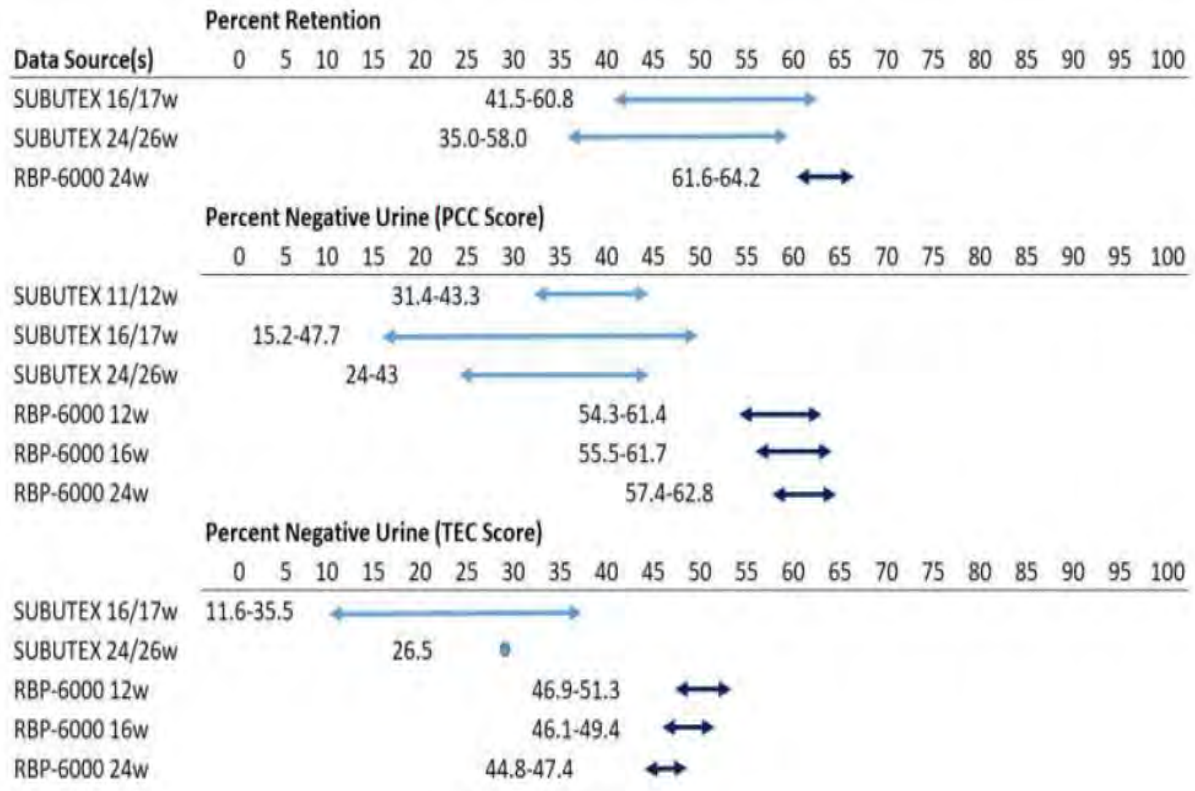
The sponsor compared the results for 13-0001 with those from historical Subutex studies using Percentage Clean Urines (PCC)[28] , Treatment Effectiveness Percentage (TEC)[29] and Retention.[30]

[27] 2.7.3 Summary of Clinical Efficacy page 16
[28] the number of negative ("clean") urine samples for each subject expressed as a percentage of the total number of samples that should have been provided during the time the subject remained in the "maintenance phase" (post induction)
[29] the number of negative ("clean") urine samples for each subject expressed as a percentage of the total number of samples that should have been provided during the full "maintenance phase" (post induction)
[30] the number of subjects remaining in treatment over a given study period expressed as a percentage of the total number of treated subjects

In the Subutex studies the highest mean PCC score was in Study CR88/130 47.7%[31] the highest mean TEC score was 34.5% (same study), the greatest retention rate was Study CR92/099 60.8%.[32]

The PCC and TEC scores for Sublocade calculated for both earlier (Week 6, Week 12) and later (Week 24) timepoints were higher.

Figure 6 Comparison of Percent Retention in Treatment and Opioid-Negative Urine Results (Expressed as PCC and TEC Scores) Between Sublocade (Study 13-0001) and Historical Subutex Studies



PCC = the number of negative ("clean") urine samples for each subject expressed as a percentage of the total number of samples that should have been provided during the time that the subject remained in the "maintenance phase" (post induction);
Retention = the number of subjects remaining in treatment over a given study period expressed as a percentage of the total number of treated subjects;
TEC = the number of negative ("clean") urine samples for each subject expressed as a percentage of the total number of samples that should have been provided during the full "maintenance phase" (post induction); w = weeks
Source: Figure 44 Summary of Clinical Efficacy

11.4. Evaluator's conclusions on clinical efficacy

The study13-0001 was statistically significantly superior to placebo in both the primary efficacy endpoint[33] and the key secondary efficacy endpoint.[34] The study had of the 300mg/100mg

[31] achieved at the end of a 17-week treatment with 8 mg SL buprenorphine
[32] SL buprenorphine d over a 16-weeks at a daily dose of 16 mg
[33] the Cumulative Distribution Function (CDF) of the percentage of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24
[34] Treatment success. A responder is defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Week 5 through Week 24.

group 125/203 completed, for 300mg/300mg 129/201 completed and for placebo 34/100 completed.

Of those randomised 62% on 300mg/100mg, 64.2% on 300mg/300mg and 34% on placebo completed (~12% of each group were lost to follow up).

30/39 completed the study13-0002 which failed to achieve the primary endpoint - failing to meet the non-inferiority margin at one time point during the first 4 weeks (18mg hydromorphone at 4 weeks). After the second injection all such endpoints were met for the following 4 weeks – this is consistent with the time (4 injections) to reach steady state for Sublocade. There appeared to be no precedent trials to 13-0002 with the non-inferiority margin based on an un-submitted article and no p-vales were submitted in support of the results.

Study 13-0003 was not powered for efficacy comparisons, and no statistical testing was performed.

12. Clinical safety

12.1. Studies providing evaluable safety data

12.1.1.1. Pooled Efficacy studies

- Study 13-0001 - a completed efficacy, safety and tolerability study (see 11.2.1).
- Study 13-0003 – a completed long-term safety and tolerability study (see 11.2.3).

These studies were pooled in the Summary of Clinical Safety.

12.1.1.2. Efficacy studies

- Study-13-0002 - a completed multiple-dose efficacy and opioid blockade study (see 11.2.2).

12.1.1.3. Extension Studies

- Study INDV-6000-301 - a completed extension of Study 13-0003, providing up to 6 months of additional treatment for subjects (see 12.2.1).

12.1.1.4. Studies with evaluable safety data: dose finding and pharmacology

- Study 12-0005 - a completed multiple ascending dose safety and tolerability study (see 21.1.1.3).
- Study 11-0020 - a completed single ascending dose safety and tolerability study (see 21.1.1.2).
- Study 13-0006 - a completed single-dose study to assess the relative bioavailability of Sublocade formulated with different MWs of polymer (see 21.1.1.4).
- Study 10-0011 - a completed single-dose first-time-in-human safety and tolerability study (see 21.1.1.1).

12.2. Studies that assessed safety as the sole primary outcome

12.2.1. Study INDV-6000-301

12.2.1.1. Study design, objectives, locations and dates

Conducted from 17 August 2016 to 23 August 2017 in 25 centres.

An open-label, multicentre, depot buprenorphine treatment extension study in subjects with opioid use disorder.

Only subjects who completed the End of Study (EOS) procedures for Study RB-US-13-0003, could be considered for inclusion in this study.

Subjects may have received monthly either an injection dose of 100mg Sublocade or 300mg Sublocade for a total of up to 6 injections.

After enrolment, subjects also received counselling (manual-guided individual behavioural therapy) at each scheduled study visit.

The objective was: To provide ongoing treatment with Sublocade and safety monitoring for subjects who completed the RB-US-13-0003 study and for whom a new treatment venue had not been identified or arranged.

12.2.1.2. Safety variables and outcomes

The injection site was assessed for pain, tenderness, warmth, itching, erythema, inflammation or swelling, and bruising using a 5-point severity scale (Injection Site Grading Scale). In addition, subjects assessed injection site pain using a visual analogue scale (VAS) (referred to as the Injection Site Pain VAS). Subjects were also assessed for adverse events (AEs) and use of concomitant medications. Vital signs were assessed.

12.2.1.3. Participant flow

In the original protocol 600 subjects were to be enrolled, this was modified to 300. Only 208 were screened.

208 subjects entered the treatment period and received at least 1 dose of Sublocade. A total of 166 subjects (79.8%) completed the treatment period by completing the end of study visit. The most common reasons for discontinuation were subject lost to follow-up (45.2% of subjects who discontinued), withdrawal of consent (23.8%), and "other" (21.4%). One subject (2.4%) was withdrawn because of an AE. There were 138 male subjects (66.3%) and 70 female subjects (33.7%). The mean age was 42.1 years (range: 21 to 66 years).

12.2.1.4. Results for Injection Site Reactions and Tolerability Assessments

A customised MedDRA query was utilised to search for TEAEs potentially related to injection site reactions. Injection site reaction TEAEs were reported for 3 subjects (1.4%) overall. All 3 events were mild in severity. No TEAEs pertaining to an injection site reaction were reported as an SAE or led to discontinuation of study treatment.

Injection site tolerability assessments were also performed after each injection. Of the tolerability assessments, mild tenderness at the injection site was the most common reaction, reported in 73 subjects (35.1%). The most common severities of injection site tolerability assessments were none or mild; there were no severe injection site tolerability assessments reported.

Overall, 34 of 208 subjects (16.3%) reported local injection site burning/stinging at least once during the trial. There was a trend for the proportion of subjects reporting burning/stinging to decrease over time with increasing number of injections.

Injection site reactions, whether as TEAEs or as observed by the investigators during tolerability assessments, were not treatment limiting.

12.2.1.5. Results for Withdrawal Symptoms

Overall, 11.5% of subjects had TEAEs potentially pertaining to drug withdrawal symptoms. No terms included in the search were reported in at least 5% of subjects. None of the TEAEs potentially pertaining to drug withdrawal symptoms were reported as an SAE or led to discontinuation of study treatment.

12.2.1.6. Pancreatitis

There were no reports of TEAEs of pancreatitis. There were no TEAEs potentially pertaining to pancreatitis. One subject had simultaneous elevations in lipase and amylase at the end of study/end of treatment visit that were not reported as TEAEs by the investigator.

12.2.1.7. Overall Safety

< 5% of subjects had an AE, mostly mild or moderate in severity. Treatment-emergent AEs were reported in 71 of 208 subjects (34.1%). Most common AEs were in the infections and infestations SOC (13.9% overall), gastrointestinal disorders SOC (6.7% overall), general disorders and administrative site conditions SOC (6.3% overall), and psychiatric disorders SOC (6.3% overall).

23 subjects (11.1%) had ≥ 1 treatment related AE.

There was 1 discontinuation (0.5%) due to an AE (lethargy).

There were 5 subjects (2.4%) with SAEs, none treatment relate. 3 subjects, (1.4%) had pneumonia, the remaining SAEs occurred in 1 subject (0.5%) each.

3 subjects (1.4%) were reported to have TEAEs pertaining to hepatic disorders. TEAEs potentially pertaining to hepatic disorders included ALT increased, AST increased, hepatic enzyme increased and liver function test increased (all reported for 1 subject; 0.5% each).

There were no cases of Hy's Law. 4 subjects (2.2% overall) who had both ALT and AST > 3 x ULN to < 5 x ULN during the study. These 4 subjects had co-existing factors for hepatic enzyme elevation such as an ongoing medical history of hepatitis C, elevated LFTs at screening, alcohol use or concomitant use of hepatotoxic drugs. For all 4 subjects, the hepatic enzymes were elevated at the Screening Visit and remained elevated at the end of study/end of treatment visit.

There were no TEAEs of orthostatic hypotension reported.

There were no TEAEs potentially pertaining to respiratory depression and failure.

TEAEs potentially related to central nervous system depression were reported for 1.9% of subjects.

12.3. Patient exposure

1083 subjects received at least 1 injection of Sublocade.

In Studies 13-0001 and 13-0003 overall, a total of 542 subjects received Sublocade for at least 24 weeks and 291 subjects received Sublocade for at least 48 weeks. The mean (median) duration of exposure to Sublocade was 32.1 (40.0) weeks.

In Study INDV-6000-301 of the 208 subjects who completed study 13-0001 and 13-0003 in which they had already received 12 Sublocade injections, a total of 171 subjects (82.2%) received 6 additional Sublocade injections (a combined total of 18 injections received).

In Study 12-0005 46 subjects received 4 injections of 100 to 300mg, 5 others received > 4.

In Study 13-0002 39 subjects received a single Sublocade 300mg dose and 30 subjects received 2 Sublocade 300mg doses.

In Study 11-0020 24 received a single 100mg dose and 12 a 200mg dose.

In Study 13-0006 subjects received single SC injections of Sublocade 300mg.

Table 16 Individual and Pooled Studies 13-0001 and 13-0003: Study Treatment Exposure by Injection Number

	13-0001			13-0003				Total Sublocade
				Roll–over [a]			De novo [c]	
Injection #	Sublocade 300/100 mg (N = 203) n (%)	Sublocade 300/300 mg (N = 201) n (%)	PBO (N = 100) n (%)	Sublocade 100 →Sublocade 300/Flex [b] (N=112) n (%)	Sublocade 300 →Sublocade 300/Flex [b] (N=113) n (%)	PBO → Sublocade 300/Flex [b] (N=32) n (%)	Sublocade 300/Flex (N=412) n (%)	(N=848) n (%
1	27 (13.3)	26 (12.9)	40 (40.0)	1 (0.9)	5 (4.4)	2 (6.3)	46 (11.2)	101 (11.9)
2	15 (7.4)	15 (7.5)	10 (10.0)	4 (3.6)	7 (6.2)	2 (6.3)	24 (5.8)	56 (6.6)
3	11 (5.4)	12 (6.0)	7 (7.0)	6 (5.4)	7 (6.2)	2 (6.3)	27 (6.6)	52 (6.1)
4	9 (4.4)	14 (7.0)	4 (4.0)	5 (4.5)	6 (5.3)	0	21 (5.1)	44 (5.2)
5	13 (6.4)	5 (2.5)	4 (4.0)	1 (0.9)	6 (5.3)	0	14 (3.4)	30 (3.5)
6	128 (63.1)	129 (64.2)	35 (35.0)	95 (84.8)	82 (72.6)	26 (81.3)	15 (3.6)	75 (8.8)
7	-	-	-	-	-	-	13 (3.2)	20 (2.4)
8	-	-	-	-	-	-	10 (2.4)	20 (2.4)
9	-	-	-	-	-	-	9 (2.2)	22 (2.6)
10	-	-	-	-	-	-	5 (1.2)	16 (1.9)
11	-	-	-	-	-	-	10 (2.4)	18 (2.1)
12	-	-	-	-	-	-	218 (52.9)	394 (46.5)

placebo=placebo Percentage is computed based on the N as a denominator from the respective columns. Source: Tables 14 & 15

Study 13-0001: All subjects in the Sublocade treatment groups were scheduled to receive 2 injections of Sublocade 300 mg. Subjects in the 300/100mg and 300/300mg treatment groups were scheduled to then receive up to 4 injections of Sublocade 100mg or up to 4 injections of Sublocade 300 mg, respectively.

Study 13-0003:

[a]. Roll-over subjects: The treatment groups represent the treatment received in the Ph3DB study and subsequent treatment in Ph3OL study. Subjects received 6 injections in the Ph3DB study; Injection 1 in the Ph3OL study corresponds to their 7th injection

[b]. Sublocade 300/Flex: Represents treatment with an initial injection of Sublocade 300mg followed by up to 5 additional injections using flexible dosing with either Sublocade 300mg or Sublocade 100mg as deemed appropriate by the investigator.

[c]. All de novo subjects received an initial injection of Sublocade 300mg followed by up to 11 additional injections using flexible dosing with either Sublocade 300mg or Sublocade 100mg as deemed appropriate by the investigator.

Total Sublocade includes injections received in 13-0001 plus those in rollover 13-0003 as well as those given *de novo*

12.4. Adverse events

12.4.1.1. Study 13-0001

Treatment-emergent AEs were reported in 76.4% of subjects in the 300/100mg group and 66.7% in the 300/300mg group and in 56.0% the placebo group.

Treatment related AEs to study treatment were in 33.0% of subjects in the 300/100mg and 34.8% in the 300/300mg and in 3.0% of the placebo groups (vs. 2, respectively). Study drug related AEs for ≥ 5% of subjects in any treatment group were injection site pruritus, constipation and injection site pain, reported for 7.4%, 6.4% and 5.4% of subjects in the active total treatment group compared with 4.0%, 0% and 3.0% of subjects in the placebo group, respectively.

Severe AEs were reported in a 7.4%, 6.5% and 4.0% of subjects in the 300/100mg group, 300/300mg group and placebo group, respectively.

SAEs were reported in 2.0%, 3.5% and 5.0% of subjects in the 300/100mg group, 300/300mg group and placebo group, respectively.

On death (gunshot wound) was reported for 1 subject (0.2%) in the 300/300mg group.

AEs leading to study treatment discontinuation were reported in 3.4%, 5.0% and 2.0% of subjects in the 300/100mg group, 300/300mg group and placebo group, respectively. 2 subjects in the 300/100mg group had Drug withdrawal syndrome; 2 subjects in the 300/300mg group had Aspartate aminotransferase increased.

12.4.1.2. Study 13-0003

The overall incidence of TEAEs was 73.3% and 56.4%, respectively, in the *de novo* and roll-over groups.

The only treatment related AEs for ≥ 5% of subjects in either subject group were constipation and injection site pain, reported for 7.2% and 6.7% of subjects overall.

Severe AEs were reported for 8.7% of subjects in the *de novo* subject group and 2.7% of subjects in the roll-over group.

Overall, SAEs were reported for 3.7% of subjects;16 subjects (3.9%) in the *de novo* subject group and 9 subjects (3.5%) in the roll-over subject group. There were 3 SAEs of cellulitis overall and in the *de novo* group 2 accidental overdoses.

AEs led to drug discontinuation for 2.5% of subjects; 13 subjects (3.2%) in the *de novo* group and 4 subjects (1.6%) in the roll-over group.

Table 17 Study 13-0003: TEAEs Leading to Sublocade Dose Reduction

Preferred Term	Sublocade 300/Flex		
	De novo Subjects (N=412) n (%)	Roll-over Subjects (N=257) n (%)	Total (N=669) n (%)
Any TEAE leading to dose reduction	29 (7.0)	17 (6.6)	46 (6.9)
Sedation	2 (0.5)	5 (1.9)	7 (1.0)
Alanine aminotransferase increased	5 (1.2)	1 (0.4)	6 (0.9)
Constipation	4 (1.0)	1 (0.4)	5 (0.7)
Nausea	3 (0.7)	1 (0.4)	4 (0.6)
Fatigue	2 (0.5)	2 (0.8)	4 (0.6)
Aspartate aminotransferase increased	3 (0.7)	1 (0.4)	4 (0.6)
Headache	3 (0.7)	0	3 (0.4)
Lethargy	2 (0.5)	1 (0.4)	3 (0.4)
Somnolence	3 (0.7)	0	3 (0.4)
Injection site pain	1 (0.2)	1 (0.4)	2 (0.3)
Hepatic function abnormal	2 (0.5)	0	2 (0.3)
Gamma-glutamyltransferase increased	2 (0.5)	1 (0.4)	3 (0.4)
Hepatic enzyme increased	1 (0.2)	1 (0.4)	2 (0.3)
Insomnia	2 (0.5)	0	2 (0.3)
Decreased appetite	0	1 (0.4)	1 (0.1)
Muscle twitching	0	1 (0.4)	1 (0.1)
Dizziness	0	1 (0.4)	1 (0.1)
Hypersomnia	1 (0.2)	0	1 (0.1)
Migraine	1 (0.2)	0	1 (0.1)
Euphoric mood	1 (0.2)	0	1 (0.1)
Erectile dysfunction	0	1 (0.4)	1 (0.1)
Flushing	0	1 (0.4)	1 (0.1)

Source: Table 66

12.4.1.3. Study INDV-6000-301

AEs were reported in 71 of 208 subjects (34.1%), most were mild or moderate in severity. One subject had a TEAE (lethargy) leading to treatment discontinuation.

SAEs were reported in 5 subjects (2.4%), 3 subjects, (1.4%) subjects had an SAE of pneumonia.

12.4.1.4. Study 12-0005

89 subjects (100%) receiving Sublocade had an AE. 48 (53.9%) were considered treatment related. 1 AE was severe, 6 (6.7%) were SAEs. 8(9%) led to withdrawal.

12.4.1.1. Study 13-0002

34/39 (87%) subjects had an AE, 25(64%) were treatment related.

12.4.1.2. Study 11-0020

46/48 (95.8%) had AEs, 30 (62.5%) were treatment related, 2 (4.2%) were severe, 7 (14.6%) were SAEs.

12.4.1.3. Study 13-0006

42/47 (89.4%) had AEs, 37 (78.7%) were treatment related, none were severe, 3 (6.4%) were SAEs, 1 led to withdrawal.

12.4.2. Overall AEs

In study 13-0001, No individual TEAEs were reported in > 10% of subjects in the active total, 300/100mg or 300/300mg groups; insomnia was reported in 11.0% of subjects in the placebo group. The most common (reported in ≥ 5% of subjects) TEAEs reported in the active total group were headache, constipation, nausea, injection site pruritus, vomiting, insomnia and upper respiratory tract infection. The percentage of subjects with the most common TEAEs was generally similar across treatment groups, although constipation was reported in only the active treatment groups and upper respiratory tract infection was reported more frequently in the active treatment groups compared with the placebo group. The maximum severity of TEAEs was reported as mild or moderate for most subjects with TEAEs.

In study 13-0003, no individual TEAE was reported in at least 5% of subjects in the roll-over group. TEAEs reported in at least 5% of subjects in the *de novo* subject group included constipation, nausea, injection site pain, insomnia, headache, nasopharyngitis and injection site erythema.

In study INDV-6000-301, no individual TEAE was reported in at least 5% of subjects. The most common TEAEs were similar to those reported in the *de novo* group of study 13-0003 and included constipation, headache, pneumonia and upper respiratory tract infection.

Additional exposure with Sublocade (up to 18 monthly injections of 100mg or 300mg) in study INDV-6000-301 did not reveal any new safety signals.

Frequently reported TEAEs in the Phase 2 and Phase 1 studies did not raise any new safety concerns.

Table 18 Study 13-0001: TEAEs Reported in ≥ 5% of Subjects in Any Treatment Group During the Double-blind Phase

Preferred Term	Active Total (N=404) n (%)	RBP-6000 300mg/100mg (N=203) n (%)	RBP-6000 300mg/300mg (N=201) n (%)	PBO (N=100) n (%)
Any TEAE	289 (71.5)	155 (76.4)	134 (66.7)	56 (56.0)
Headache	36 (8.9)	19 (9.4)	17 (8.5)	6 (6.0)
Constipation	35 (8.7)	19 (9.4)	16 (8.0)	0 (0.0)
Nausea	34 (8.4)	18 (8.9)	16 (8.0)	5 (5.0)
Injection site pruritus	32 (7.9)	13 (6.4)	19 (9.5)	4 (4.0)
Vomiting	30 (7.4)	19 (9.4)	11 (5.5)	4 (4.0)
Insomnia	30 (7.4)	13 (6.4)	17 (8.5)	11 (11.0)
Upper respiratory tract infection	27 (6.7)	15 (7.4)	12 (6.0)	1 (1.0)
Injection site pain	22 (5.4)	10 (4.9)	12 (6.0)	3 (3.0)
Nasopharyngitis	21 (5.2)	11 (5.4)	10 (5.0)	1 (1.0)
Fatigue	20 (5.0)	8 (3.9)	12 (6.0)	3 (3.0)
Anxiety	18 (4.5)	10 (4.9)	8 (4.0)	5 (5.0)
Drug withdrawal syndrome	16 (4.0)	9 (4.4)	7 (3.5)	6 (6.0)
Blood creatine phosphokinase increased	16 (4.0)	11 (5.4)	5 (2.5)	1 (1.0)
Diarrhoea	10 (2.5)	5 (2.5)	5 (2.5)	5 (5.0)

placebo=placebo Source: Table 41

Table 19 Study 13-0003: TEAEs Reported in ≥ 5% of Subjects in Either Subject Group during the Treatment Phase

Preferred Term	RBP-6000 300/Flex		
	De novo Subjects (N=412) n (%)	Roll-over Subjects (N=257) n (%)	Total (N=669) n (%)
Any TEAE	302 (73.3)	145 (56.4)	447 (66.8)
Constipation	47 (11.4)	9 (3.5)	56 (8.4)
Nausea	37 (9.0)	10 (3.9)	47 (7.0)
Injection site pain	39 (9.5)	7 (2.7)	46 (6.9)
Insomnia	27 (6.6)	10 (3.9)	37 (5.5)
Headache	31 (7.5)	5 (1.9)	36 (5.4)
Nasopharyngitis	24 (5.8)	6 (2.3)	30 (4.5)
Injection site erythema	22 (5.3)	5 (1.9)	27 (4.0)

Source: Table 42

12.5. Evaluation of issues with possible regulatory impact

12.5.1. Injection site reaction

AEs

In 13-0001 and 13-0003, 17.2% of Sublocade subjects had at least 1 injection site reaction TAE. Including: injection site pain (7.8%), injection site pruritus (6.6%), injection site erythema (4.8%) and injection site induration (1.4%). No injection site reaction AE was reported as serious. Injection site reaction AEs led to study treatment discontinuation for < 1% of subjects in either.

In study 13-0001, 13.8% of 300/100mg and 18.9% of 300/300mg subjects reported ≥ 1 injection site reaction AE compared with 9.0% in those who received placebo.

Injection site tolerability assessments (grading)

In study 13-0001 and 13-0003, local injection site grading was performed by an observer.[35] Less than 1% of subjects had reports of injection site erythema/redness, induration, pain, or swelling with a maximum intensity of severe. Injection site tenderness with a maximum intensity of severe was reported for < 5% of subjects.

In study INDV-6000-301, mild tenderness at the injection site was the most common reaction, reported in 73 subjects (35.1%). There were no severe injection site tolerability assessments reported.

Subject-reported injection site pain – Visual Analogue Scale (VAS)

Across 13-0001 and 13-0003 Sublocade subjects, the worst mean VAS pain scores (on a 100-mm scale) at any post-injection time point decreased over time; at the 1-minute, 5-minute, 10-minute, 15-minute, 30-minute, 1-hour and 2-hour post-injection time points the worst mean VAS pain scores were 63.0, 29.2, 16.3, 11.2, 8.3, 6.0 and 4.5, respectively.

[35] Injection sites were assessed erythema/redness, induration, pain, swelling and tenderness and each symptom was assigned a severity grade of none (grade 0), mild (grade 1), moderate (grade 2), severe (grade 3) or potentially life-threatening (grade 4).

In study INDV-6000-301, the overall mean worst injection site pain at 1 hour post injection ranged from 0.9 following Injection 5, to 2.5 following Injection 3 using the 100mm VAS scale.

Injection site burning or stinging

Across 13-0001 and 13-0003 Sublocade subjects, nearly all subjects who received Sublocade (95.4%) reported local injection site burning or stinging at one or more 1 minute post-injection assessments when all injections were considered. The percentages of subjects reporting local injection site burning or stinging decreased over time through the 2 hour post-injection assessment. At the 2 hour assessment, 16.2% of subjects reported burning or stinging when all injections were considered.

In study INDV-6000-301, 34 of 208 subjects (16.3%) reported local injection site burning/stinging at least once during the trial. There was a trend for the proportion of subjects reporting burning/stinging to decrease over time with increasing injections.

12.5.2. Liver function and liver toxicity

Treatment-emergent AEs potentially associated with hepatic disorders were reported in 9.3% of subjects exposed to Sublocade in the pooled 13-0001 and 13-0003 studies. In the 13-0001 study, the frequency of TEAEs potentially associated with hepatic disorders was 6.9% in the 300/100mg and 7.5% in the 300/300mg Sublocade treatment groups compared with 1.0% in the placebo group.

In study INDV-6000-301, TEAEs potentially associated with hepatic disorders were reported in 1.4% of subjects exposed to Sublocade for up to 18 months.

12.5.3. Opioid Withdrawal

AEs potentially associated with opioid withdrawal signs and symptoms were commonly reported in subjects exposed to Sublocade in the pooled 13-0001 and 13-0003 studies: 33.4% of subjects reported TEAEs. In study 13-0001, these were observed for similar percentages of subjects across treatment groups (300/100mg 35.0% and 300/300mg 29.9% vs. placebo 36.0%). In study INDV-6000-301, 11.5% of subjects reported TEAEs potentially pertaining to drug withdrawal symptoms.

12.5.4. CNS depression

AEs potentially associated with CNS depression were reported in 10.8% of subjects exposed to Sublocade in the pooled 13-0001 and 13-0003 studies. In the 13-0001 study, these AEs were observed for a greater percentage of subjects in the 300/100mg group (11.8%) than in the 300/300mg group (7.0%) or placebo group (4.0%). All PTs in this special interest topic were reported in < 4% of subjects overall. In study INDV-6000-301, TEAEs potentially related to CNS depression were reported for 1.9% of subjects during the treatment period.

12.5.5. Respiratory Depression

No AEs potentially associated with respiratory depression were reported in any of the Phase 3 studies.

12.5.6. Orthostatic Hypotension

AEs potentially associated with orthostatic hypotension were reported for a small percentage of subjects exposed to Sublocade during the pooled 13-0001 and 13-0003 studies (2.8%). In study 13-0001, these AEs were marginally higher in the 300/100mg group (3.4%) compared with the 300/300mg group (2.5%) and placebo group (2.0%).

A treatment-emergent AE potentially related to orthostatic hypotension (mild dizziness) was reported for 1 subject (0.5%) in study INDV-6000-301.

12.5.7. Acute Pancreatitis

AEs potentially associated with acute pancreatitis were reported for a small percentage of subjects exposed to Sublocade (2.5%) in the pooled 13-0001 and 13-0003 studies. In study 13-0001, these were reported for 2.0% of subjects who received 300/100mg or placebo and at 1.0% in the 300/300mg group. One subject had an event reported as elevated lipase that was coded as pancreatitis.

In study INDV-6000-301, no TEAEs potentially associated with acute pancreatitis were reported.

12.5.8. Clinical Chemistry

While the percentages of subjects with transaminase elevations > 3 x ULN were higher in the Sublocade arms compared with the placebo arm in study 13-0001, the large majority of these cases had coexisting factors for hepatic enzyme elevation such as hepatitis C, chronic alcohol use or history of alcoholic hepatitis/pancreatitis, or elevated LFTs at screening and/or baseline. There were no SAEs potentially pertaining to liver dysfunction in any subject in the study. Findings from the 13-0003 and INDV-6000-301 studies were similar; no signal indicative of hepatic injury was observed during long-term use of Sublocade.

No clinically important effects on adrenocorticotropic hormone (ACTH), FSH or testosterone (total and free) were observed following treatment with Sublocade in either the 13-0001 and 13-0003 studies.

Evaluation of mean values, shifts and TEAEs related to other clinical laboratory parameters across all studies in the Sublocade development program did not reveal any new safety concerns for Sublocade compared with the known safety profile for buprenorphine.

In Study INDV-6000-301 in general, mean values for all haematology parameters remained within the normal range throughout the study. Evaluation of the patterns in shift data for haematology parameters were generally considered not clinically important.

12.5.9. Haematology and haematological toxicity

In study 13-0001 and 13-0003 mean values for haematology parameters predominantly remained within the central laboratory reference range at each time point in all 3 treatment groups with a few minor exceptions that were not considered clinically important.

12.5.10. Electrocardiograph findings and cardiovascular safety

PopPK analysis INDV-6000-Q01 Concentration-QT analysis (see 21.1.3.8) found no effect of Buprenorphine on QT after accounting for the covariates that may influence HR and QT in subjects with opioid use disorder.

The sponsor also submitted a 15 page Expert summary report on The risk of QT prolongation associated with the use of buprenorphine containing Products that found:

The presently published literature does not suggest that buprenorphine is causally associated with QT prolongation and TdP-type ventricular arrhythmias.

and:

there was no strong evidence to demonstrate the extent to which buprenorphine may have contributed to the development of QT prolongation, given the fact that some patients concomitantly received drugs known to prolong the QT interval, as well as had a history of abnormal thyroid function, structural heart disease, bradycardia, hypokalaemia and polysubstance abuse, which confound any interpretation.

12.5.1. Renal Impairment

Based on relevant scientific data, renal impairment is expected to have a limited effect on buprenorphine PK following SC administration of Sublocade. Therefore, a dedicated PK study in subjects with renal impairment with Sublocade was not conducted.

12.6. Other safety issues

12.6.1. Withdrawal and Rebound

No formal evaluation of withdrawal and rebound was included in the Sublocade clinical development program beyond the month following discontinuation of Sublocade. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 or 300mg, respectively).

12.6.2. Safety related to drug-drug interactions and other interactions

In study 13-0001, the percentage of subjects taking at least 1 concomitant CNS depressant medication was similar for the 300/300 mg, 300/100mg and placebo groups, respectively, as follows: 33.0%, 33.8% vs 29.0%. TEAEs potentially associated with CNS depression were reported in similar percentages of subjects across treatment groups for the subset of subjects taking concomitant CNS depressant medications compared with the overall safety population.

Co-administration of CYP3A4 inducers may induce the metabolism of buprenorphine and therefore, may cause an increase in the clearance of the drug, potentially leading to a decrease in buprenorphine plasma concentrations. The effects of CYP3A4 inducers may be dependent on the route of administration of buprenorphine. Buprenorphine is a high extraction ratio drug (hepatic extraction ratio, 0.6 - 0.9). Hence, elimination is expected to be hepatic blood flow-dependent and relatively insensitive to changes in intrinsic clearance (i.e., hepatic metabolism). Since Sublocade is injected SC, the induction of CYP3A4 enzymes is expected to result in minimal decrease in buprenorphine exposure.

12.7. Post marketing experience

Not applicable.

12.8. Evaluator's overall conclusions on clinical safety

Although generally similar to SL buprenorphine, the following points are made:

The safety concerns relate principally to injection reactions. While the polymer is already on the ARTG, it is not so combined with buprenorphine. According to the buprenorphine PI Injection site reaction is rare. The incidence is approximately double that seen with placebo and led to discontinuation in < 1%. The C_{max} seen in PK studies was similar to that seen with SL buprenorphine which carries the warning that it may cause drowsiness, particularly when used together with alcohol or central nervous system depressants, however in Study 13-0001 CNS depression was approximately double that seen with placebo.

The lack of an effect of buprenorphine on QTc in the present analysis is consistent with some reports of buprenorphine from the literature, but not with others including results from a healthy volunteer study and from a study of buprenorphine transdermal system. The discrepancy may be due to differences between subject populations, where healthy volunteers

are more likely to have larger changes in blood pressure and their resulting changes in HR than opioid use disorder subjects.[36]

13. First round benefit-risk assessment

13.1. First round assessment of benefits

The benefits of Sublocade in the proposed usage are:

Indication	
Benefits	Strengths and Uncertainties
A single monthly injection.	There is the possibility of sub-therapeutic dosing in the first months as shown by the failure to meet the noninferiority margin in Study 13-0002. Removal requires surgery. There is a possibility of injection site reactions.
It could be administered only by a health care professional to avoid diversion.	The existing SL buprenorphine treatment is self-administered and could be diverted.

13.2. First round assessment of risks

The risks of Sublocade in the proposed usage are:

Risks	Strengths and Uncertainties
2 cases of accidental overdose occurred.	Once given, prolonged activity would necessitate surgical removal. BMI was found to affect the SC absorption of buprenorphine, resulting in higher peak levels of buprenorphine in subjects with a lower BMI dose adjustments were not considered necessary.
There is the possibility of intravenous or even intra-arterial injection.	The sponsor studied this and found if the Atrigel Delivery System is injected IV or IA, blockage of a blood vessel or vascular occlusion would likely result.

[36] Concentration QT Report page 40

Risks	Strengths and Uncertainties
No direct efficacy comparison with existing SL buprenorphine was made.	
There is an increased exposure.	This does not appear to affect the safety profile, patients are likely to be opioid tolerant

13.3. First round assessment of benefit-risk balance

The benefit-risk balance of Sublocade, given the proposed usage, is favourable.

14. First round recommendation regarding authorisation

Based on clinical evaluation, it is recommended that, subject to an approved PI and the separate statistical evaluation of the PopPK and PK/PD studies, Sublocade be approved for registration for Treatment of opioid dependence, within a framework of medical, social and psychological treatment.

15. First round comments on product documentation

15.1. First round comments on draft PI (clinical aspects)

The clinical aspects of the draft Product Information are not entirely satisfactory and should be revised, having regard to the comments below:

Precautions

Managing Risks From Concomitant Use of Benzodiazepines Or Other CNS Depressants With Buprenorphine

1. The sponsor proposes to insert this section

   ~~Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose, respiratory depression, and death. Medication-assisted treatment of opioid use disorder, however, should not be categorically denied to patients taking these drugs. Prohibiting or creating barriers to treatment can pose an even greater risk of morbidity and mortality due to the opioid use disorder alone.~~

   ~~As a routine part of orientation to buprenorphine treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics and alcohol.~~

   ~~Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at initiation of buprenorphine treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required. There is no evidence to support dose limitations or arbitrary caps of buprenorphine as a strategy to address benzodiazepine use in buprenorphine-treated patients. However, if a patient is sedated at the time of buprenorphine dosing, delay or omit the buprenorphine dose if appropriate.~~

   ~~Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use with buprenorphine. In some cases, monitoring in a higher level~~

~~of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.~~

~~For patients in buprenorphine treatment before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use~~

The justification provided was Information from Subutex + Sublocade US PI. It is not in the Australian Subutex PI.

It is **not** recommended that the proposed insertion be approved.

Neonatal Abstinence Syndrome

2. The sponsor proposes to amend this section:

   Chronic use of buprenorphine by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth. (See Use in Pregnancy). Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

   ~~Advise pregnant women receiving opioid addiction treatment with Sublocade of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. This risk should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance of management of opioid addiction throughout pregnancy.~~

Justification given for the first sentence inserted was 'Same information as for Subutex' and for the added paragraph 'Information from Sublocade US PI' the first statement is correct. The second is not in the Subutex recently reviewed PI.

It is recommended that the proposed insertion as modified by deletion be approved.

Use in Opioid Naïve Patients

3. The sponsor proposes to amend this section:

   There have been reported deaths of opioid naive individuals who received doses as low as 2mg of buprenorphine sublingual tablet for analgesia. Sublocade is not appropriate <u>as an analgesic</u> ~~for use in opioid-naïve patients~~.

The justification provided was Same Information as for Subutex. It is not in the Australian Subutex PI.

It is **not** recommended that the proposed insertion be approved.

Use in hepatic impairment

4. The sponsor proposes to replace this section:

Buprenorphine is extensively metabolised by the liver. The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study, in which a Suboxone 2.0/0.5mg (buprenorphine/naloxone) sublingual tablet was administered to healthy subjects and subjects with varying degrees of hepatic impairment. Plasma levels were found to be elevated for buprenorphine in patients with moderate to severe hepatic impairment (Table 2). Buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function.

Table 2: Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following buprenorphine/naloxone administration (change relative to healthy subjects)

PK parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
BUPRENORPHINE			
Cmax	1.2 fold increase	1.1 fold increase	1.7 fold increase
AUC_{last}	Similar to control	1.6 fold increase	2.8 fold increase

In the same study, changes in C_{max} and AUC_{last} in subjects with HCV infection without hepatic impairment were not clinically significant in comparison to the healthy subjects.

~~In a pharmacokinetic study with transmucosal buprenorphine, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment.~~

This study was not submitted Justification given was 'Information consistent with Subutex PI' it is not.

The existing statement following is not appropriate and should be replaced by the proposed statement:

~~Buprenorphine should be used with caution in patients with moderate to severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Lower initial doses and cautious titration of dosage may be required in patients with severe hepatic impairment~~

Proposed replacement

The effect of hepatic impairment on the pharmacokinetics of SUBLOCADE has not been studied.

Because of the long-acting nature of the product, adjustments to dosages of SUBLOCADE are not rapidly reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing severe hepatic impairment are not candidates for treatment with SUBLOCADE.

Patients who develop moderate to severe hepatic impairment while being treated with SUBLOCADE should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

These latter proposed insertions are supported by the submission.

1. It is recommended that the existing Subutex PI statement be retained except for that relating to use with caution.

2. It is recommended that this usage statement be replaced with that proposed.

Use in renal impairment

5. The sponsor proposes to replace the existing section:

   Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine ~~Subutex~~. Therefore no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min), which may require dose adjustment.

With

> Clinical studies of SUBLOCADE did not include subjects with renal impairment. ~~No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3mg buprenorphine.~~

The reference (Summary of Clinical Pharmacology Studies page 111) in relation to that study also says 'mean buprenorphine-3-glucuronide and norbuprenorphine plasma concentrations were higher in individuals with renal impairment compared to normal healthy subjects.' Thus the proposed statement adds nothing to the existing statement and is incorrect in that there was a difference.

1. It is recommended that the existing Subutex statement be retained with the additional statement on the lack of renal impairment studies.

Use in Patients at Risk for Arrhythmia

6. The sponsor proposes to add this new section:

   Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of Sublocade on the QT interval in five clinical studies including the Phase 3 study. In a Phase 3 study, seven patients had an increase from baseline QTc greater than 60 msec at any time [2/203 patients (1.0%) in the 300 mg/100mg group and 5/201 patients (2.0%) in the 300 mg/300mg group] and one patient in the 300 mg/300mg group was found to have a QTc greater than 500 msec. These QTc findings were all sporadic and transient and none led to aberrant ventricular rhythm. Review of ECG and adverse event data provided no evidence for syncope, seizure, or ventricular tachycardia or fibrillation.

   Consider these observations in clinical decisions when prescribing buprenorphine to patients with hypokalaemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval.

The first proposed paragraph is supported by the submission.

It is recommended that the proposed insertion be approved.

Risks associated with Treatment of Emergent Acute Pain

7. The sponsor proposes to add this new section:

   While on Sublocade, situations may arise where patients need acute pain management, or may require anaesthesia. Treat patients receiving Sublocade with a non-opioid analgesic whenever possible. Patients requiring opioid therapy for analgesia may be treated with a high-affinity full opioid analgesic under the supervision of a physician, with particular attention to respiratory function. Higher doses may be required for analgesic effect. Therefore, a higher potential for toxicity exists with opioid administration.

   If sedation or opioid therapy is required e.g. as part of anaesthesia, patients should be continuously monitored in an anaesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The sedation or opioid therapy should be provided by individuals specifically trained in the use of anaesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.

   Advise patients of the importance of instructing their family members, in the event of emergency, to inform the treating healthcare provider or emergency room staff that the patient is being treated with Sublocade.

   The above guidance should also be considered for any patient who has been treated with Sublocade within the last 6 months.

Only justification offered was 'Information consistent with Sublocade US PI'. It is however consistent with good clinical practice. The reference to sedation is to comply with a multi Australian (& NZ) Colleges document.

It is recommended that the propose insertion as modified by insertions be approved.

Paediatric use

8. The sponsor proposes to amend this section:

   SUBLOCADE is not recommended for use in children. The safety and effectiveness of SUBLOCADE in subjects below the age of 18 has not been established.

   ~~Due to lack of data, patients below the age of 18 should be closely monitored during treatment~~

The last statement is related to off label use.

It is recommended that the propose insertion as modified by deletion be approved.

4.5 Interactions with Other Medicines and Other Forms of Interactions

9. The sponsor proposes to amend this section:

Table 1 - Clinically Significant Drug Interactions

Benzodiazepines and other Central Nervous System depressants	
Examples	Alcohol, Benzodiazepines, Non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, antipsychotics and other opioids (e.g. methadone, analgesics, and antitussives), sedative H1-receptor antagonists, clonidine

Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments. This combination with benzodiazepines may result in death due to respiratory depression of central origin; therefore, patients must be closely monitored when prescribed this combination, and this combination should be avoided in cases where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed Use caution with medicines containing alcohol.
Other Opioid Analgesics	
Clinical Impact:	The analgesic properties of other opioids may be reduced in patients receiving treatment with buprenorphine for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.
Intervention	Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see Section 4.4 Special Warnings and Precautions).
Naltrexone and other opioid antagonists	
Clinical Impact:	Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of SUBLOCADE. Patients maintained on buprenorphine may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations.
CYP3A4 inhibitors	
Examples	Protease inhibitors (like ritonavir, ~~nelfinavir~~, saquinavir or indinavir), azole antifungals like ketoconazole or itraconazole, calcium channel antagonists, and macrolide antibiotics like erythromycin.

Clinical Impact:	The effects of co-administered CYP3A4 inhibitors on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied and the effects may be dependent on the route of administration; however, such interactions have been established in studies using transmucosal buprenorphine. Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4, therefore potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. The concomitant use of sublingual buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects
Intervention	Patients who transfer to SUBLOCADE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate. If patients already on SUBLOCADE require newly-initiated treatment with CYP3A4 inhibitors, patients should be monitored for signs and symptoms of over- medication. Within 2 weeks of SUBLOCADE administration, if signs and symptoms of buprenorphine toxicity or overdose occur but the concomitant medication cannot be reduced or discontinued, it may be necessary to remove the depot and treat the patient with a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilised on SUBLOCADE in the setting of concomitant medication that is a CYP3A4 inhibitor, and the concomitant medication is discontinued, the patient should be monitored for withdrawal. If the dose of SUBLOCADE is not adequate in the absence of the concomitant medication, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments.
CYP3A4 inducers	
Examples	Rifampicin, phenobarbital, carbamazepine, phenytoin.
Clinical Impact:	The effects of co-administered CYP3A4 inducers on buprenorphine exposure in subjects treated with SUBLOCADE have not been studied. Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4; therefore, potential interactions may occur when SUBLOCADE is given concurrently with agents that affect CYP3A4 activity. CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause increased clearance of the drug which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome.
Intervention:	Patients who transfer to SUBLOCADE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inducers should be monitored to ensure that the plasma buprenorphine level provided by SUBLOCADE is adequate. If patients already on SUBLOCADE require newly-initiated treatment with CYP3A4 inducers, the patients should be monitored for withdrawal. If the dose of SUBLOCADE is not adequate and the concomitant medication cannot be reduced or discontinued, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilised on SUBLOCADE in the setting of concomitant medication that is a CYP3A4

	inducer, and the concomitant medication is discontinued, the patient should be monitored for signs and symptoms of over-medication. Within 2 weeks of SUBLOCADE administration, if the dose provided by SUBLOCADE is excessive in the absence of the concomitant inducer, it may be necessary to remove SUBLOCADE and treat the patient with a formulation of buprenorphine that permits dose adjustments
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Examples	Efavirenz, nevirapine, etravirine, delavirdine
Clinical Impact:	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and sublingual buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.
Intervention:	Patients who are on chronic treatment with SUBLOCADE should be monitored for increase or decrease in therapeutic effects if NNRTIs are added to their treatment regimen.
Antiretrovirals: Protease inhibitors (PIs)	
Examples	Atazanavir, ritonavir
Clinical Impact:	Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (~~nelfinavir,~~ lopinavir/ritonavir, ritonavir) have little effect on sublingual buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine after sublingual administration, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving sublingual buprenorphine and atazanavir with and without ritonavir concomitantly.
Intervention:	If treatment with atazanavir with and without ritonavir must be initiated in a patient already treated with SUBLOCADE, the patient should be monitored for signs and symptoms of over-medication. It may be necessary to remove the depot and treat the patient with a sublingual buprenorphine product that permits rapid dose adjustments.
~~Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs)~~	
~~Clinical Impact:~~	~~Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.~~
~~Intervention:~~	~~None~~

The recommended insertions are for consistency with the Subutex PI.

Of the recommended deletions:

- Nelfinavir, delavirdine not on ARTG. Nelfinavir subsequent proposed insertion says it has little effect on SL buprenorphine.
- The proposes insertion on NRTIs is not an interaction.

The sponsor has proposed additional insertions based on the US PI that are considered acceptable.

It is recommended that the proposed insertions as modified by deletion and insertion be approved.

Changes to remove the contraindication for pregnancy and lactation are in Submission 2017-02665, were initially currently being reviewed and have now been approved 30 August 2018.

4.7 Effects on Ability to Drive and Use Machines

10. The sponsor proposes to amend this section:

    Buprenorphine may influence the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness or impaired thinking, especially during the first few days following treatment and dose adjustment. If used with alcohol or central nervous system depressants the effect is likely to be more pronounced (See section 4.4 Special warnings and precautions for use). Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that SUBLOCADE does not adversely affect their ability to engage in such activities.

    There is an increased level of buprenorphine for 3 days after each injection, buprenorphine levels accumulate during the first two months and are maintained with the 100mg dose; further accumulation occurs with the 300mg maintenance dose, which achieves steady-state after the fourth monthly injection.

It is recommended that the proposed insertion as modified by rearrangement and insertion of a further warning be approved.

4.8 Adverse Effects (Undesirable Effects)

Post-marketing experience with buprenorphine

11. The sponsors propose to include under this section:

    ~~In cases of intravenous or intentional misuse, local reactions, such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections have been reported.~~

This has no relevance to Sublocade (see 13.2).

It is **not** recommended that the proposed insertion be approved.

4.9 Overdose

12. The sponsor proposes to include under this section:

    ~~Clinicians should consider the potential role and contribution of buprenorphine, other opioids, and other CNS depressant drugs in a patient's clinical presentation.~~ Clinical data are limited with regards to the possible surgical removal of the depot as only two cases of surgical removal were reported in premarketing clinical studies.

The first statement is redundant.

It is recommended that the proposed insertion as modified by deletion be approved.

5.1 Pharmacodynamic Properties - Plasma concentration and Clinical Response

13. The sponsor proposes to insert:

    The Sublocade opioid blockade study evaluated the blockade of subjective opioid effects, pharmacokinetics (PK) and safety of SC injections of Sublocade. Stabilisation doses of SL buprenorphine prior to injection of Sublocade failed to provide full blockade of subjective effects of hydromorphone 18mg I.M. ~~After Sublocade injections at weeks 0 and 4, on average, subjective effects of both 6 and 18mg doses of hydromorphone were blocked; however wide variability was seen across subjects. Complete blockade continued throughout the 8 weeks of observation that followed the 2nd Sublocade injection~~.

The **primary objective** of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior to the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade).

At Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade.

These deletions are secondary end points, the study failed to achieve its primary objective.

It is recommended that the proposed insertion as modified by deletion be approved.

14. The sponsor proposes to insert:

    ~~Figure 11 illustrates the relationship between buprenorphine plasma level and drug liking after 18mg hydromorphone I.M.~~

This was the result of a *post hoc* analysis.[37]

It is **not** recommended that the proposed insertion be approved.

Clinical trials

15. The sponsor proposes to insert:

    Opioid blockade study (13-0002)

    The study evaluated the blockade of subjective opioid effects, PK and safety of SC injections of SUBLOCADE in 39 subjects with opioid use disorder (not treatment-seeking).

    <u>The primary objective of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior to the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade).</u>

    <u>At Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade. In the 4 weeks following the</u>

[37] Figure 11 was page 134 Summary of Clinical Efficacy

second injection all such endpoints were met. This is consistent with the time (4 injections) to reach steady state for Sublocade.

~~The peak (E_{max}) effect of "Drug Liking" Visual Analogue Scale (VAS) measurement after challenge with I.M. injections of 6mg and 18mg hydromorphone (HM) was not inferior (i.e., shown to be not substantially more likeable) compared to the E_{max} of "Drug Liking" VAS, measured after challenge with placebo (at weeks 1 through 4 following the first injection of 300mg Sublocade). The noninferiority (NI) margin, the largest difference allowed for the 6 or 18mg HM VAS to exceed the placebo VAS (the maximum VAS recorded following IM injection of 0mg HM) before being considered significant, was set at 20. Based on comparison to the historical response to opioid agonists in unblocked subjects, a difference of less than 20 points (on a unipolar scale) between the mean maximum response to hydromorphone and the mean maximum placebo response for the same challenge was considered to indicate near-complete blockade.~~

The deleted paragraph was the result of a *post hoc* analysis.[38]

It is recommended that the proposed insertion as modified by insertion and deletion be approved.

16. The sponsor proposes to insert:

    ~~All 12 weeks of the treatment period demonstrated blockade for both 6mg and 18mg following SUBLOCADE injections. However, wide variation can be seen in isolated measurements from individual subjects, described in section "Plasma concentration and clinical response".~~ For comparison, stabilisation doses of SL buprenorphine in Week 0 failed to provide full blockade to 18mg of HM. ~~Complete blockade continued throughout the 8 weeks of observation that followed the 2nd SUBLOCADE injection.~~

The **primary objective** of this study was to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge with 6mg (Dose 1) and 18mg (Dose 2) hydromorphone is noninferior to the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300mg (Sublocade).

At Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade.

The deletions relate to secondary end points.

It is recommended that the proposed insertion as modified by deletions be approved.

17. Proposed Figure 10 is based on Figure 5 Summary of Clinical Pharmacology Studies page 49.
18. Proposed Figure 11. Median (95% Confidence Interval) of Placebo-Corrected Drug Liking VAS Scores by Hydromorphone Dose and by Week is based on Figure 33 page 135 Summary of Clinical Efficacy and is the result of a *post hoc* analysis.

It is **not** recommended that the proposed insertion be approved.

[38] page 134 Summary of Clinical Efficacy

Efficacy study (13-0001)

19. The sponsor proposes to insert:

    Efficacy was evaluated over Weeks 5 to 24 based on weekly urine drug screens combined with self-reported use of illicit opioid use. A "grace period" was applied for Weeks 1 through 4 to allow patients to stabilise in treatment. During this period, opioid use, if it occurred, was not considered in the analysis. Missing urine drug screen samples and/or self-reports during weeks 5-24 were counted as positive for illicit opioids. The key secondary endpoint was treatment success (responder), defined as any subject with ≥80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use (opioid-free weeks) from Week 5 through Week 24. ~~Weekly assessments of other markers of efficacy were also collected: Opioid Craving VAS, Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), Clinical Global Impression – Severity (CGI-S) Scale, Clinical Global Impression – Improvement (CGI-I) Scale.~~

As well as 2 key secondary endpoints there were a further 10 secondary endpoints these latter had no allowances for multiplicity.

It is recommended that the proposed insertion as modified by deletion be approved.

20. The sponsor proposes to insert:

    Based on the cumulative distribution function (CDF) of the percentage of urine samples negative for illicit opioids combined with self-reports of negative for illicit opioid is collected from week 5 through week 24 (Table 3), regardless of dose, SUBLOCADE was superior to the placebo group with statistical significance.

    The proportion of patients achieving treatment success (defined as patients with ≥ 80% opioid-free weeks) was statistically significantly higher in both groups receiving SUBLOCADE compared to the placebo group.

    ~~Secondary endpoints included the Opioid Craving VAS, COWS and SOWS, CGI-S, CGI-I. These consistently reached statistical significance compared to placebo for the 300/300mg group; however, statistical significance compared to placebo was not seen in the 300/100mg group for the Opioid Craving VAS, COWS, and SOWS.~~

As well as 2 key secondary endpoints there were a further 10 secondary endpoints with no allowances for multiplicity.

It is recommended that the proposed insertion as modified by deletion be approved.

21. The sponsor proposes to insert:

    Analysis of the dropout pattern in Study 13-0001 indicated that opioid craving was a major predictor of dropout. An opioid craving score > 20 was associated with an increase in dropout rate of up to 3.0 and 3.6-fold in active treatment arms and placebo arm, respectively, compared to craving ≤ 5.

This is supported by the submission.[39]

Dropout of subjects from the study was modelled using survival (time-to-event) analysis. Treatment effect was modelled to account for a 2 times lower dropout rates in Sublocade treatment arms (300mg/300mg: 36%; 300mg/100mg: 38%) compared to placebo (66%).

[39] Summary of Clinical Pharmacology Studies page 84

Covariate analysis identified opioid craving as a significant predictor of dropout: an opioid craving VAS score > 20 was associated with an increase in dropout rate of up to 3.0 to 3.6 - fold in active treatment arms and placebo arm, respectively, compared to craving VAS scores ≤ 5.

It is recommended that the proposed insertion be approved.

22. The sponsor proposes to insert Figure 12. This is supported by the submission.
23. The sponsor proposes to insert Table 3:

Most of this is supported by Table 23 in the CSR (see Table 1 Table 6 above).

However the final line

= 100%	25 (13)	23 (12)	1 (1.0)

Is not in that Table.

Please supply the source for the final line in Table 3. The sponsor's response indicated it was from Table 23 Summary of Clinical Efficacy. It is recommended that the insertion be approved.

24. The sponsor proposes to insert Table 4. This is supported by the submission.
25. The sponsor proposes to insert Table 5:

This table gives the results for 5 of the 10 secondary endpoints with no provision for multiplicity.

It is **not** recommended the proposed Table 5 insertion be approved.

26. The sponsor proposes to insert:

~~In addition, the effect of SUBLOCADE on the following health economics and outcomes research endpoints (HEOR) was prospectively assessed as part of the initial study design; health status, (EQ-5D-5L), health related quality of life (SF-36®-v2), medication satisfaction questionnaire (MSQ), health care resource utilization (HCRU) and employment status and health insurance (ESHI).~~

~~At the end of the study (Week 25), mean scores in the general health, vitality, social functioning, role, emotional and mental health domains as assessed by the SF-36 scale were significantly higher in each of the active treatment groups compared to placebo. At Week 25, significantly fewer subjects in the active treatment groups reported problems on EQ-5D-5L mobility for 300 mg/300mg (10.0%; P = 0.010) and 300 mg/100mg (12.7%; P = 0.048) versus placebo (17.9%). In addition, significantly fewer subjects reported problems with anxiety/depression at Week 25 in the 300 mg/300mg (23.1%) versus placebo (43.6%) group (P = 0.010).~~

~~Subjects in both active treatment groups had a statistically significantly higher mean medication satisfaction score compared to subjects in the placebo group at all time points. When analysed by level of medication satisfaction, more subjects in the active treatment groups were satisfied, very satisfied, or extremely satisfied compared to the placebo group at Week 25 (87.7% versus 46.2%, P < 0.001, SUBLOCADE 300 mg/300mg versus placebo; 88.1% versus 46.2%, P < 0.001, 300 mg/100mg versus placebo).~~

As well as 2 key secondary endpoints there were a further 10 secondary endpoints with no allowances for multiplicity.

It is **not** recommended that the proposed insertion be approved.

5.1 Pharmacodynamic Properties - Plasma concentration and Clinical Response

27. The sponsor proposes to insert:

~~Following sublingual administration, a dose response relationship has been observed for buprenorphine plasma levels and brain mu-opioid receptor occupancy by buprenorphine at 4 hours after dosing. A relationship has also been observed between buprenorphine plasma levels and blockade of subjective opioid agonist symptoms produced by co-administered opioids at 4 hours after dosing. Plasma concentrations of buprenorphine and mu-opioid receptor occupancy decrease between 4 hours and 28 hours post dose correlating with a return of subjective agonist symptoms produced by co-administered opioids, together with opioid withdrawal symptoms and opioid craving~~.

These statements are from the sponsor's review derived from the two Grunwald Studies. Which are only available in the submission in their published form.

However Study 13-0002 CSR[40] found 'Scatter plots of the buprenorphine plasma concentration versus the VAS scores for the subjective measures (Drug Liking, Any Drug Effect, Good Drug Effect, Bad Drug Effect, Sedation, and High,) are presented in Figure 37, Figure 38, Figure 39, and Figure 14.2.2.5. Overall, these plots indicate there was a reduction in VAS scores with increased buprenorphine plasma concentration.'

Comment: The proposed insertion relates to the use of sublingual tablets and is not found in the Subutex PI. An appropriate statement that relates to the use of Sublocade would be:

> In Opioid blockade study (13-0002) overall, scatter plots of the buprenorphine plasma concentration versus the VAS scores for the subjective measures (Drug Liking, Any Drug Effect, Good Drug Effect, Bad Drug Effect, Sedation, and High,) indicate there was a reduction in VAS scores with increased buprenorphine plasma concentration.

1. It is **not** recommended that the proposed insertion be approved.
2. It is recommended that the above insertion be made.

28. The sponsor proposes to insert:

> In a Positron Emission Tomography (PET) study with Sublocade in 2 subjects (one subject receiving 200mg SC injections and one subject receiving 300mg SC injections) with opioid use disorder, ~~75 to 92%~~ 79% & 92% occupancy of the mu-opioid receptors in the brain at day 7 ~~was maintained for 28 days to~~ following the last dose under steady-state conditions was maintained for 28 days to 75 & 81%.

This statement is misleading.

The subject who received 200mg showed 79% and 75% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively. The subject who received 300mg showed 92% and 81% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively.[41]

It is recommended that the proposed insertion as modified by deletion and insertion be approved.

[40] Page 130

[41] CSR Page 239

5.2 Pharmacokinetic Properties - Absorption

29. The sponsor proposes to insert Table 6:

Table 6 Comparison of Buprenorphine Mean Pharmacokinetic parameters between SUBUTEX and SUBLOCADE.

Pharmacokinetic parameters	SUBUTEX daily stabilisation		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg# (1st injection)	100 mg* (steady-state)	300 mg* (steady-state)
$C_{avg,ss}$ (ng/ml)	1.71	2.91	2.19	3.21	6.54
$C_{max,ss}$ (ng/ml)	5.35	8.27	5.37	4.88	10.12
$C_{min,ss}$ (ng/ml)	0.81	1.54	1.25	2.48	5.01

#Exposure after 1 injection of 300mg SUBLOCADE following 24mg SUBUTEX stabilisation.

*Steady-state exposure after 4 injections of 100mg or 300mg SUBLOCADE, following 2 injections of 300mg SUBLOCADE.

$$C_{avg,ss} = \frac{AUC_{0\text{-}T,ss}}{T}$$

Proposed Table 6 is sourced from Study 13-0001 based on the description *Steady-state exposure after 4 injections of 100mg or 300mg Sublocade, following 2 injections of 300mg Sublocade.

CSR for 13-0001[42] says only Raw PK and PGx data are briefly summarised in this CSR.

The 2.7.2 Summary of Clinical Pharmacology Studies[43] says Summary statistics of buprenorphine and norbuprenorphine plasma concentrations are provided per Sublocade treatment arm in CSR 13-0001 Table S14.2.22. Buprenorphine plasma concentrations from that study were analysed using a population PK modelling approach (Section 2.7.2.3.2.3).

Table S14.2.22 Plasma Concentration Summary – Sublocade 300mg/300mg+IDC Subjects Full Analysis Set is a *post hoc* analysis as its caption says only of plasma concentrations not PK parameters, nor are these parameters found in the PK model report INDV-6000-M04.

Table 16[44] has some of these parameters.

The following comparisons at steady state show a C_{max} with 100mg Sublocade similar to Subutex but with 300mg it is almost double, C_{min} with 100mg Sublocade is in the range of 2-3ng/mL for 70% μ-opioid receptor occupancy, while for 300mg it is well above it.

Table 20 Comparison steady state Subutex SL Tablet vs. Sublocade C_{max} and C_{min}

Formulation	Study	Dose (mg)	Cohort	N	C_{max} (ng/mL)	C_{min} (ng/mL)
Subutex SL Tablet	12-0005	8	1	15	3.52	0.52
		8	4	15	3.96	0.57

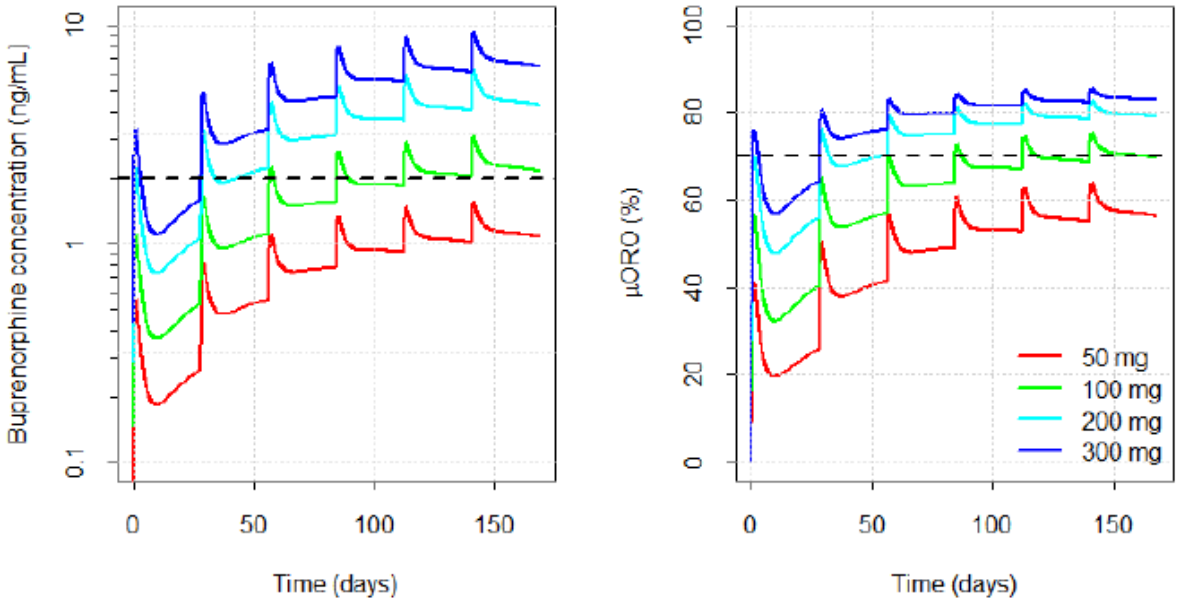
[42] Page 144
[43] Page 57
[44] Page 109 Summary of Clinical Pharmacology Studies

		12	2	15	5.35	0.81
		14	5	15	5.26	0.92
Sublocade	13-0001	100	6 SC injections (observed)	102	4.88	2.48
			6 SC injections (model)	194	4.11	2.74
		300	6 SC injections (observed)	102	10.12	5.01
			6 SC injections (model)	196	8.68	5.11

Source: Table 16 Summary of Clinical Pharmacology Studies

In Study 13-0001 on Day 29 after the first injection (see Table 41) mean C_{min} was 1.82ng/mL, below the range of 2-3ng/mL for 70% μ-opioid receptor occupancy, but the range was 0.98 to 3.93ng/mL. This is reflected in the modelling.

Figure 7 Mean Predicted Buprenorphine Plasma Concentrations and Brain Mu-Opioid Receptor Occupancies After Repeated SC Injections of Sublocade at Various Doses



Left panel = buprenorphine plasma concentrations; Dashed line=2ng/mL
Right panel = mu-opioid receptor occupancy (μ-opioid receptor occupancy); Dashed line=70% μ-opioid receptor occupancy
A total of 6 SC injections given 28 days apart were simulated
Models used for simulation: INDV-6000-M03 Table 10 and INDV-6000-M02 Table 2 Source: Figure 41

1. It is recommended that the sponsor clearly identify the source of the Table 6.3. The sponsor satisfactorily indicated the source and in doing so corrected an error in $C_{min,ss}$ 300mg 1st injection

2. It is recommended that an explanatory note on the derivation of C_{avg} be added.

Excretion

30. The sponsor proposes to insert:

Buprenorphine is metabolised and eliminated in urine and faeces. The apparent terminal plasma half-life of buprenorphine following subcutaneous injection of SUBLOCADE ranged from ~~43 to 60~~ 45 to 66 days as a result of the slow release of buprenorphine from the subcutaneous depot.

Study 11-0020 page 124.

It is recommended that the proposed insertion as modified by deletion and insertion be approved.

15.2. First round comments on draft CMI (clinical aspects)

The clinical aspects of the draft Consumer Medicine Information are not entirely satisfactory and should be revised, having regard to the comments below:

When you must not use it

1. The sponsor proposes to delete:

If you have serious problems with your liver, or if your doctor detects the development of such a problem during treatment.

The existing PI has:

Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing severe hepatic impairment are not candidates for treatment with SUBLOCADE.

It is **not** recommended that the proposed deletion be approved.

Taking Other Medicines

2. Please add to the list

- Medicines containing alcohol

How much to use

3. The sponsor proposes to insert:

SUBLOCADE is only for adults ~~and children over the age of 16 years~~.

This is not consistent with the PI.

It is recommended that the proposed insertion as modified by deletion be approved.

Side effects

4. The sponsor proposes to delete:

- fatigue, ~~weakness, numbness~~

Fatigue is in the PI.

It is **not** recommended that all the proposed deletion be approved.

15.3. First round comments on draft RMP (Summary of Safety Concerns)

The Clinical aspects of the draft Risk Management Plan are satisfactory.

16. Clinical questions

16.1. Clinical questions

16.1.1. PI and CMI

1. Please supply the source for the final line in Table 3.
2. Please clearly identify the source of the Table 6.

17. Second round evaluation

QUESTION 1 The sponsor's response indicated it was from Table 23 Summary of Clinical Efficacy.

It is recommended that the insertion be approved.

QUESTION 2 1. The sponsor satisfactorily indicated the source and in doing so corrected an error in $C_{min,ss}$ 300mg 1st injection. Instead of the proposed equation the sponsor proposes to insert a word equivalent. The sub-note numbering varied within the response.

Table 6. Comparison of Buprenorphine Mean Pharmacokinetic Parameters Between SUBUTEX and SUBLOCADE

Pharmacokinetic parameters	SUBUTEX daily stabilization		SUBLOCADE		
Mean	12 mg (steady-state)	24 mg (steady-state)	300 mg[1] (1st injection)	100 mg[2] (steady-state)	300 mg[2] (steady-state)
$C_{avg,ss}$ (ng/ml)	1.71	2.91	2.19	3.21	6.54
$C_{max,ss}$ (ng/ml)	5.35	8.27	5.37	4.88	10.12
$C_{min,ss}$ (ng/ml)	0.81	1.54	~~1.25~~1.86[3]	2.48	5.01

[1] Exposure after 1 injection of 300mg SUBLOCADE following 24mg SUBUTEX stabilization

[2] Steady-state exposure after 4 injections of 100mg or 300mg SUBLOCADE, following 2 injections of 300mg SUBLOCADE

[3] $C_{avg,ss}$ represents the average of plasma concentrations calculated as AUC_{tau}/tau where tau is 24 hours for SUBUTEX daily administration and tau is 28 days for SUBLOCADE injections

~~$C_{avg,ss} = \frac{AUC_{0-T,ss}}{T}$~~

[4] C_{min} on Day 29 (end of dosing interval)

It is recommended that the proposed table as modified be approved.

18. Second round benefit-risk assessment

No new clinical information was submitted in response to questions. Accordingly, the risk/benefit of Sublocade are unchanged from those identified in Section 13.1

19. Second round recommendation regarding authorisation

The recommendation is unchanged from round 1.

20. Second round comments on product documentation

20.1. Second round comments on draft PI (clinical aspects)

The sponsor has satisfactorily met the first round recommendations **1-4**.

5. Use in renal impairment

The sponsor accepts the modification in recommendation 5 but proposes a modification:

> Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine ~~less than 1% is excreted unchanged in urine.~~ Therefore no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min), which may require dose adjustment.

Justification given was Information added for completeness.

In 2.7.2 Summary of Clinical Pharmacology Studies the sponsor refers to this as a result from a mass balance study reported in the Suboxone SL Film Prescribing Information 2018. This is incorrect. The Australian Suboxone SL PI does not contain this information.

It is not recommended that the proposed insertion be approved.

The sponsor has satisfactorily met the first round recommendations **6-9.**

10. Effects on Ability to Drive and Use Machines

The sponsor had proposed inserting within the existing Subutex PI section:

Buprenorphine levels accumulate during the first two months and are maintained with the 100 mg dose; further accumulation occurs with the 300 mg maintenance dose, which achieves steady-state after the fourth monthly injection.

This evaluator recommended moving it to follow the existing statement and adding a comment as:

> Buprenorphine may influence the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness or impaired thinking, especially during the first few days following treatment and dose adjustment. If used with alcohol or central nervous system depressants the effect is likely to be more pronounced (See section 4.4 Special warnings and precautions for use). ~~Buprenorphine levels accumulate during the first two months and are maintained with the 100 mg dose; further accumulation occurs with the 300 mg maintenance dose, which achieves steady-state after the fourth monthly injection.~~

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that SUBLOCADE does not adversely affect their ability to engage in such activities.

There is an increased level of buprenorphine for 3 days after each injection. Buprenorphine levels ~~accumulate~~ increase during the first two months ~~after the first two 300mg injections~~ and are maintained with the 100mg dose; further accumulation occurs with the 300mg maintenance dose, which achieves steady-state after the fourth monthly injection.

This evaluator apologises for not being more specific about the sentence move, which in the sponsor response has been duplicated (see the first deletion above and the last sentence). The sponsor proposes to further modify the statement without justification. The change of ~~accumulate~~ for increase is grammatical and acceptable. The change of during the first two months to after the first two 300mg injections requires justification.

It is recommended that the proposed insertion as modified by rearrangement and insertion and deletion (above) be approved.

The sponsor has satisfactorily met the first round recommendations **11-14.**

PHARMACODYNAMIC PROPERTIES (items **15 to 29** in the first round)

The sponsor has made multiple changes to this section in response to the recommendations.

The following are new changes:

Related to items **13 & 16** the sponsor further deleted and inserted:

The SUBLOCADE opioid blockade study evaluated the blockade of subjective opioid effects, pharmacokinetics (PK) and safety of SC injections of SUBLOCADE and the results are presented in the Clinical Trials section. . ~~Stabilisation doses of SL buprenorphine prior to injection of SUBLOCADE failed to provide full blockade of subjective effects of hydromorphone 18 mg I.M~~

This deletion is only partially duplicated in the Clinical Trials section, page 18 of the PI.

For comparison, stabilisation doses of SL buprenorphine in Week 0 failed to provide full blockade ~~to~~ of subjective effects of 18 mg of hydromorphone.

1. It is recommended that the proposed deletion and insertion be approved.

2. It is recommended that the last sentence under Opioid blockade study (13-0002) be modified as above.

Item **15**.The sponsor proposes deletion of the recommended text and insertion of:

~~At Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade. In the 4 weeks following the second injection all such endpoints were met. This is consistent with the time (4 injections) to reach steady state for Sublocade.~~

Following SC injection of Sublocade, the "Drug Liking" VAS analysis demonstrated opioid blockade ~~for the 6mg hydromorphone to placebo treatment comparison~~ from Week 1 to Week 4 (SUBLOCADE injection 1 period). For the 18mg hydromorphone to placebo treatment comparison, ~~opioid blockade was observed from Week 1 to Week 3, however~~ the study did not meet ~~it's~~ the primary endpoint as at Week 4 the upper bound of the 95% CI (11.418) was above the pre-defined non-inferiority margin (11) for demonstrating opioid blockade.

~~After the first injection of SC SUBLOCADE, during week 4, a decrease in mean buprenorphine plasma concentration (from 1.9 to 1.8ng/mL) correlated with a predicted 65% μ-opioid receptor occupancy, which corresponded to the slight increase in VAS scores.~~

Following the second SC injection of SUBLOCADE, opioid blockade was achieved for both the 6mg and 18mg hydromorphone to placebo treatment comparison over the full dosing interval (from Week 5 to Week 8) This is consistent with the time (4 injections) to reach steady state for Sublocade. ~~and was maintained for an additional 4 weeks (from Week 9 to Week 12), despite no further injections of SUBLOCADE.~~

The primary objective of this study is to demonstrate that the "Drug Liking" visual analog scale (VAS) measured after challenge **with 6mg (Dose 1) and 18 mg (Dose 2)** hydromorphone is noninferior to the "Drug Liking" visual analog scale (VAS) measured after challenge with placebo at weeks 1-4 post first injection of buprenorphine 300 mg. The end point relates to both 6mg & 18mg doses results not them individually.

The study failed its primary endpoint, μ - opioid receptor occupancy was a secondary objective of a failed trial, likewise maintenance from week 9-12.

It is recommended that the proposed deletion and insertion as modified by insertion and deletion (highlighted above) be approved.

30. (The sponsor's response of using geometric means for Excretion justifies the retention of the existing 43-60 days.

20.2. Second round comments on draft CMI (clinical aspects)

The sponsor has met the clinical recommendations.

Page 3 Things to be careful of

The sponsor proposes to insert:

Treating pain, emergencies and anaesthesia

While on SUBLOCADE situations may arise where you need to be treated for pain or may require anaesthesia. SUBLOCADE can interfere with the action of some pain treatments. It is important you inform your health care provider that you are treated with SUBLOCADE. Tell your family or friends that, in the event of emergency, they should inform the treating healthcare provider or emergency room staff that you are being treated with SUBLOCADE. After stopping SUBLOCADE you should continue to inform your health care providers you have been treated with SUBLOCADE for 6 months after your last dose as SUBLOCADE effect can last for a long time.

Justification given was Section added to be in compliance with PI and erroneously omitted in previous CMI.

It is recommended that he proposed insertion be approved.

20.3. Second round comments on draft RMP (Summary of Safety Concerns)

The sponsor has made changes to the PI & CMI based on the RMP evaluator's recommendations, including a black box warning. Clinical aspects appear satisfactory.

20. References

Not applicable.

21. Supporting information, tables and figures

21.1. Clinical pharmacology study synopses

21.1.1. Synopses of pharmacokinetic studies

21.1.1.1. PK study RB-US-10-0011

An open-label, single-centre, first-in-human study, designed to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of a single SC injection of Sublocade containing 20mg buprenorphine in opioid dependent subjects.

The 20mg dose was investigated to evaluate the safety and tolerability of buprenorphine in the ATRIGEL delivery system and not necessarily to evaluate any therapeutic dose.[45]

Conducted from 30 November 2010 to 31 May 2011 in the US. 12 subjects were enrolled with 6 completing (6 withdrawn at subjects request). Subjects were generally healthy aged 18 to 60 years inclusive, opioid dependent.

Primary Objectives :

- To assess the safety and tolerability of a single subcutaneous (SC) injection of Sublocade containing 20mg buprenorphine in opioid-dependent subjects.
- To characterize the PK profile of a single SC injection of Sublocade containing 20mg of buprenorphine in opioid-dependent subjects.
- To facilitate the determination of an appropriate dose of Sublocade for subsequent studies.

On Study Day 1, subjects received a single SC injection of Sublocade containing 20mg buprenorphine after a 2 hour fast, blood samples for determination of buprenorphine and norbuprenorphine levels were collected 15 minutes prior to and then at 0.5, 1, 2, 4, 6, 8 and 12h after injection.

Blood for PK was collected once per day during Days 2 to 32 Subjects were administered oral methadone during Days 25 to 30 of residential treatment.

During the inpatient portion of the study (Days -2 to 30), subjects who displayed clinically significant signs of opioid withdrawal were treated with oral hydromorphone.

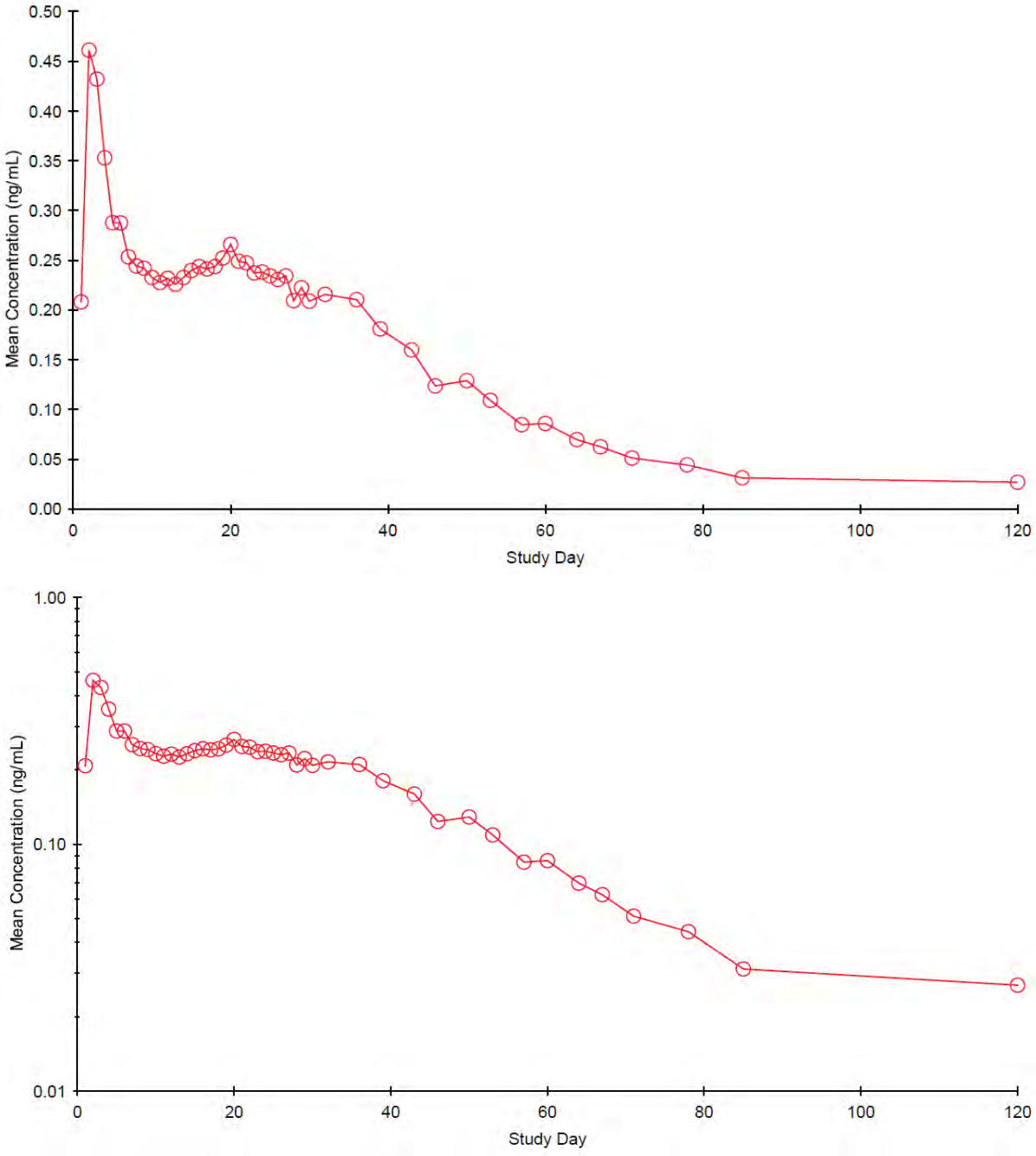
From Study Day 30 subjects were treated as outpatients and blood collected for PKs on Study Days 32, 36, 39, 43, 46, 50, 53, 57, 60, 64, 67, 71, 78, and 85 for and monitored for safety, withdrawal and illicit drug use. Subjects whose buprenorphine plasma concentrations were not below 100pg/mL by Day 85, continued to come to the CU weekly (Day 92, 99, 106, 113), until buprenorphine plasma levels were below 100pg/mL up to Day 120.

Buprenorphine peaked on Day 2 (0.461 ± 0.134ng/mL), and all subjects had buprenorphine concentrations below 100pg/mL by Day 85. There was substantial intrasubject and intersubject variability in norbuprenorphine plasma concentrations throughout the sampling period. Quantifiable norbuprenorphine concentrations were observed at 0.5h.

[45] Page 161 CSR

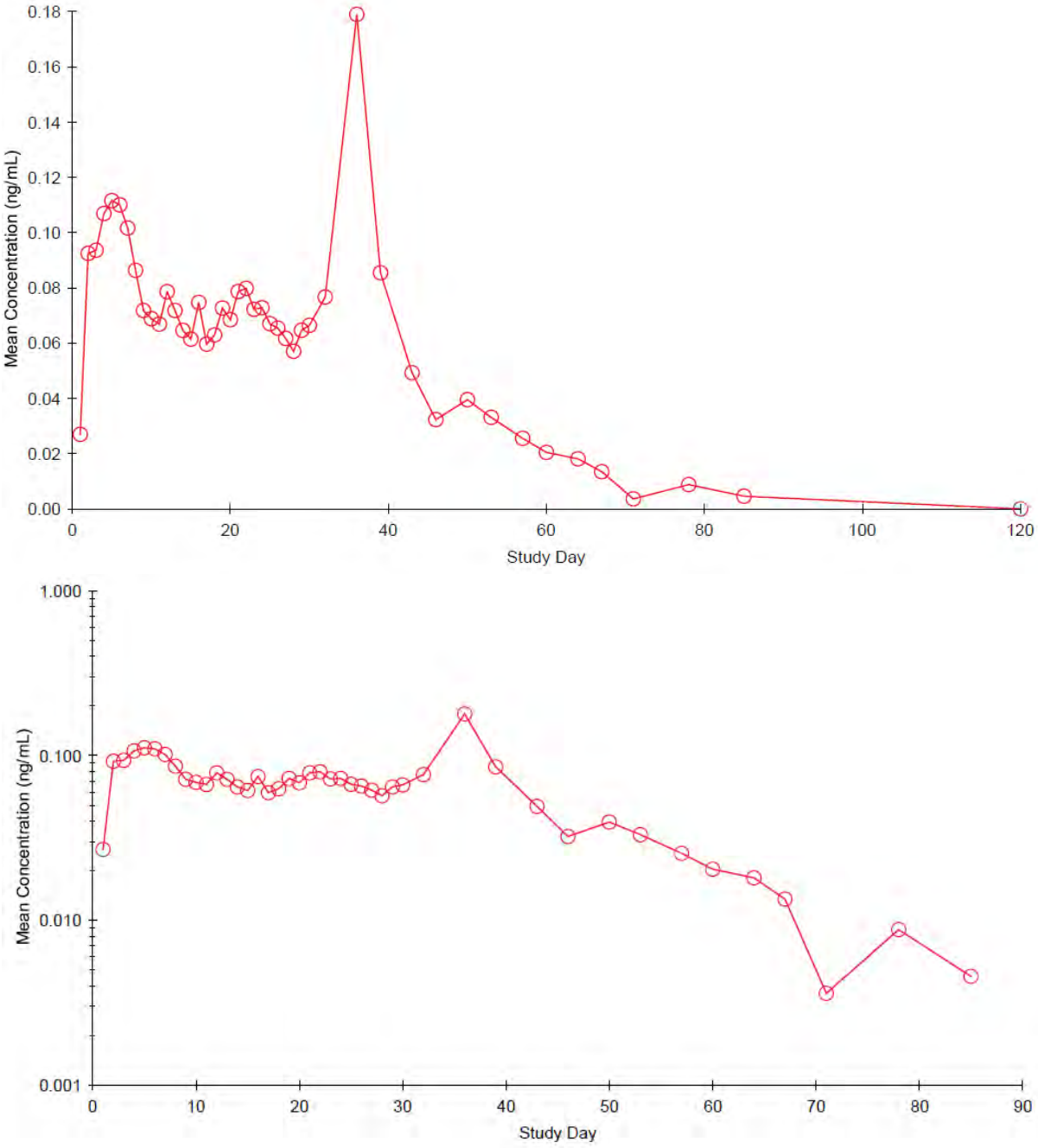
Analysis used a liquid chromatograph tandem mass spectroscopy (LC-MS-MS) procedure validated for a range of 0.025 to 10.0ng/mL for buprenorphine and 0.020 to 8.00ng/mL for norbuprenorphine.

Figure 8 Mean Buprenorphine Concentration-Time Profiles after Administration of a Single Subcutaneous (SC) Injection of Sublocade Containing 20mg Buprenorphine



Source: Figure 3

Figure 9 Mean Norbuprenorphine Concentration-Time Profiles after Administration of a Single SC Injection of Sublocade Containing 20mg Buprenorphine



Source: Figure 4

As can be seen from the above figures there was an initial burst of absorption followed by a secondary more sustained peak plasma concentration.

Table 21 Initial Burst Pharmacokinetic Parameters of Buprenorphine

Parameter	n	Mean	SD	CV%
T_{max} (day)	6	1.04	0.78	75.00
C_{max} (ng/mL)	6	0.550	0.166	30.16
AUC_{0-30} (day*ng/mL)	6	7.516	1.892	25.17

Source: Table 19

Table 22 Overall PK Parameters of Buprenorphine

Parameter	n	Mean	SD	CV%
T_{max} (day)	6	1.04	0.78	75.00
C_{max} (ng/mL)	6	0.550	0.166	30.16
$AUC_{0\text{-}85days}$ (day*ng/mL)	6	13.29	3.547	26.68
AUC_{last} (day*ng/mL)	6	14.20	4.149	29.21
AUC_{inf} (day*ng/mL)	2	15.78	2.799	17.74
AUC_{Extrap} (%)	2	4.52	0.87	19.33
λ_z (day^{-1})	2	0.0445	0.0240	54.03
$T_{1/2}$ (day)	2	18.24	9.86	54.03
T_{last} (day)	6	95.00	28.36	29.85
C_{last} (ng/mL)	6	0.0431	0.0200	46.52

Source: Table 20

Table 23 Initial Burst PK Parameters of Norbuprenorphine

Parameter	n	Mean	SD	CV%
T_{max} (day)	6	6.67	9.14	137.04
C_{max} (ng/mL)	6	0.144	0.0566	39.23
$AUC_{0\text{-}30}$ (day*ng/mL)	6	2.184	1.153	52.79

Source: Table 21

Table 24 Overall PK Parameters of Norbuprenorphine

Parameter	n	Mean	SD	CV%
T_{max} (day)	6	19.17	17.39	90.75
C_{max} (ng/mL)	6	0.231	0.127	54.90
$AUC_{0\text{-}85days}$ (day*ng/mL)	6	4.339	1.885	43.45
AUC_{last} (day*ng/mL)	6	4.224	1.932	45.74
AUC_{inf} (day*ng/mL)	1	4.981	NC	NC
AUC_{Extrap} (%)	1	6.75	NC	NC
λ_z (day^{-1})	1	0.0642	NC	NC
$T_{1/2}$ (day)	1	10.79	NC	NC
T_{last} (day)	6	63.33	17.01	26.86
C_{last} (ng/mL)	6	0.0556	0.0708	127.39

Source: Table 22

Urine drug screening results showed that buprenorphine was detectable in the urine of all subjects starting on Day 2 and continued to be positive in 5 subjects at Day 85, when plasma levels were all below 100pg/mL.

Safety:

12 subjects experienced drug withdrawal syndrome.

10 subjects experienced injection site pain, 5 experienced rebound hypertension, 4 experienced constipation, 3 experienced headache and 2 experienced injection site warmth, increased respiratory rate, and upper respiratory tract infection.

In the completers all AEs were felt not treatment related except injection site pain (6 mild), Rebound hypertension (2 mild), Respiratory rate increased (2 mild), Hepatic enzyme increased (1 moderate), constipation (1 mild) and Tinnitus (1 mild).

The one SAE, psychosocial stress leading to prolonged hospitalization that occurred in this study was not considered to be related to the study drug.

Increases above the ULN for all haematology or coagulation parameters except WBC were less than 1.5-fold the ULN. In one subject, WBCs were elevated 2.2- fold above the ULN. Decreases in haematology parameters were generally within 10% of the LLN. No changes in haematology parameters or coagulation parameters were considered clinically significant.

Alkaline phosphatase increases ranged from 1.1 to 1.7 x ULN. ALT increases ranged from 1.1 to 7.4 x ULN. AST increases ranged from 1.1 to 8.0 x ULN.

These elevated liver function tests were primarily due to one Subject and were considered a grade 2 moderate severity TEAE. They started on Study Day 27 and resolved on Day 56. This subject had alkaline phosphatase, AST and ALT within normal laboratory limits at baseline.

Another Subject had 3.7 x ULN ALT and another Subject had 3.1 x ULN ALT, but these elevations were not considered clinically significant.

Increased liver function tests in Subject ID 132 that were reported as a TEAE.

BUN was slightly decreased in two subjects 0.9 x LLN. Glucose levels were decreased in all subjects as much as 0.62 x LLN; however, glucose levels were below the LLN for all subjects at baseline.

Five of the twelve subjects who received study drug injections had blood pressure increases after study drug injection considered to be clinically significant that were reported as mild rebound hypertension.

21.1.1.2. PK study RB-US-11-0020

A Phase 1, single-centre,[46] open-label, single ascending-dose study, designed to evaluate the safety, tolerability, and PK profile of a single SC injection of Sublocade containing 50mg, 100mg, or 200mg of buprenorphine.

Conducted from 10 July 2012 to 16 February 2013 in the US. 51 subjects were Included and Dosed and 35 completed.

Primary objectives:

- To assess the safety and tolerability of single subcutaneous (SC) injections of Sublocade (50mg, 100mg, and 200mg), administered as buprenorphine, in opioid-dependent subjects.
- To characterize the pharmacokinetics (PK) of single SC injections of Sublocade.
- To evaluate the safety and PK of Sublocade when administered as a single SC injection of 100mg of buprenorphine after up to 12mg daily dosing of Suboxone (buprenorphine/naloxone) sublingual (SL) tablets (Suboxone SL) for 7 days in opioid-dependent subjects.

Secondary objective was to explore pharmacodynamic (PD) markers using the Columbia Suicide Severity Rating Scale (C-SSRS), Clinical Opiate Withdrawal Scale (COWS), and Opioid Craving Visual Analog Scale (VAS) total scores.

[46] The study CSR and protocol are labelled as multicentre, however the Design section (page 43) describe it as single centre and 16.1.4 List and Description of Investigators and Other Important Participants in the Study shows all subjects enrolled in a single site.

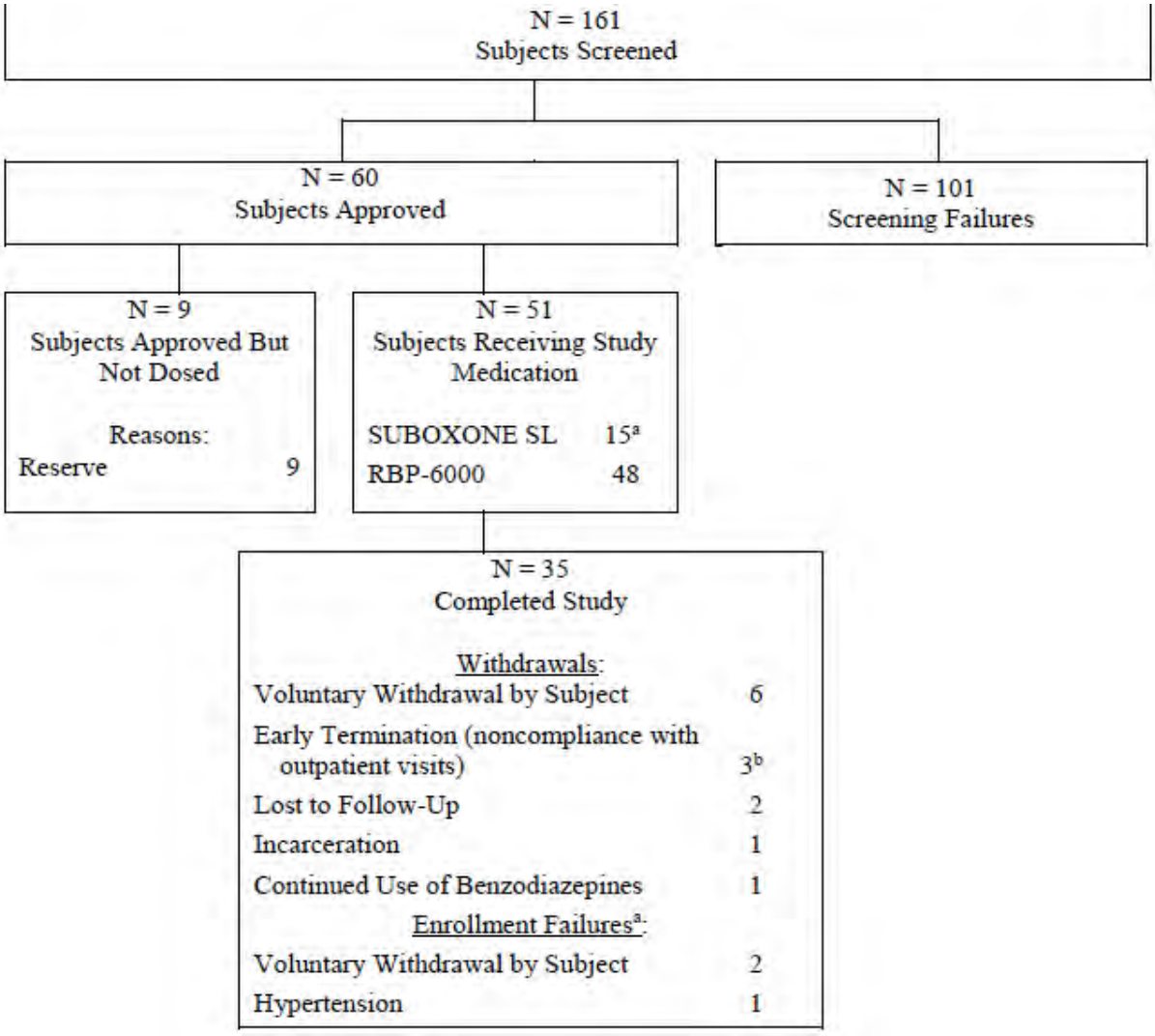
Cohorts 1-3 were admitted on Day -2 and were confined for 23 days. Upon admission, non-opioid rescue medications to treat the signs and symptoms of withdrawal were initiated, as clinically appropriate. In these 3 cohorts, 12 subjects per cohort received Sublocade containing 50mg, 100mg, or 200mg buprenorphine, with safety, tolerability, and available PK data reviewed prior to dose escalation.

Cohort 4 were admitted on Day -9 and were confined for 30 days. 15 subjects enrolled in cohort 4 and after 7 consecutive days of up to 12mg daily dosing of Suboxone SL Tablets, 3 enrolment failures meant 12 subjects then received a single SC injection of 100mg buprenorphine Sublocade.

Subjects were discharged from the study following the end of study visit as early as 1 week after plasma buprenorphine concentration fell below 100pg/mL. If plasma buprenorphine concentrations were above 100pg/mL on Day 140, subjects were discharged from the study after the end of study visit on Day 150.

During the inpatient portion of the study (from Day 11 post injection), subjects who displayed clinically significant signs of opioid withdrawal were treated with oral hydromorphone. Methadone was allowed, beginning on Day 16 only if hydromorphone was not being used concurrently on that day to aid the ability of individual subjects to abstain from illicit drug use.

Figure 10 Summary of Subject Disposition



N = number of subjects Source: Figure 3

[a] Three subjects received Suboxone SL only and were not administered Sublocade.

[b] Includes Subject 001330 who lived out of area and was unable to comply with visit schedule.

There were problems with the concentration analyses. It was planned to undertake the analysis using a validated procedure for samples using K_2EDTA as the anticoagulant. By error all samples were collected using K_3EDTA as the anticoagulant. Once the error was discovered, a method for the quantitation of samples collected in K_3EDTA tubes was partially validated.

Results

Buprenorphine

Buprenorphine exposure (AUC_{0-48} and C_{max}) during Day 1 to Day 3 (initial burst period) increased with increasing dose of Sublocade, from 50mg to 200mg in Cohorts 1-3.

Cohort 4, which received Suboxone SL for 7 days prior to dosing with 100mg Sublocade, showed a similar AUC_{0-48} and C_{max} as Cohort 3 (200mg Sublocade). Median t_{max} for the initial burst period was 24h in Cohorts 1-3, and 18h in Cohort 4.

In the secondary peak and overall periods, $AUC_{Day3-28}$, $AUC_{Day1-29}$, AUC_{0-inf}, and C_{max}, increased with the increasing dose of Sublocade in Cohorts 1-3, while Cohort 4 results were between those of Cohorts 2 and 3.

The secondary peak median t_{max} was 144h, 228h, and 264h at 50 mg, 100 mg, and 200 mg, respectively. Median t_{max} was 180h in Cohort 4.

In the overall profile, median t_{max} was 24h for Cohorts 1-3 and 18h for Cohort 4.

Apparent clearance (CL/F) was fairly constant at the 50 mg, 100 mg, and 200mg doses.

Apparent volume of distribution (V_d/F) increased with the increase in Sublocade dose (96120L, 127235L and 154369L for 50mg, 100mg, and 200mg doses respectively).

For buprenorphine, mean t½ increased slightly with the increase in dose (1078h at 50mg, 1376h at 100mg, and 1573h at 200mg).

Overall, the degree of fluctuation of buprenorphine plasma concentrations was similar between all cohorts. Swing increased with the dose between Cohorts 1-3, while the lowest swing value was observed in Cohort 4.

Norbuprenorphine

Norbuprenorphine AUCs, and $C_{max,}$ in the initial burst, secondary peak period, and the overall profile increased with increasing dose of Sublocade, with Cohort 4 showed much greater AUC_{last} compared to Cohort 2 and 3.

Median t_{max} for the initial burst period was 48h in Cohorts 1-3, and 5h in Cohort 4

Median t_{max} in the secondary peak period was 144h in Cohort 4, and 300h for Cohorts 1 and 2 and 264h in Cohort 3.

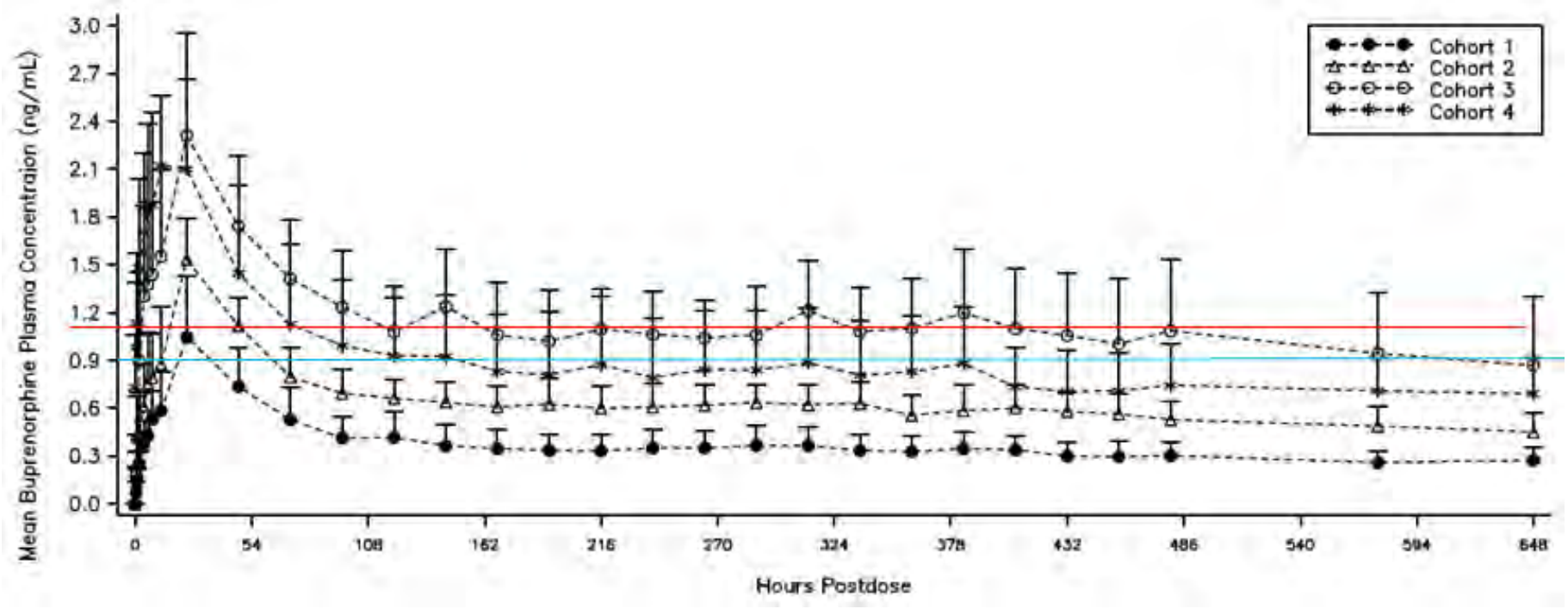
Overall, geometric mean $AUC_{Day1-29}$ of norbuprenorphine for Cohort 4 was greater by 3.1 fold and 1.7 fold compared to Cohort 2 and Cohort 3, respectively.

Geometric mean C_{max} for Cohort 4 was 7.5-fold and 4-fold greater compared to Cohort 2 and Cohort 3, respectively.

Mean t½ was 1510h, 980h, 1156h, and 847h for Cohorts 1-4, respectively.

Fluctuation was similar between Cohorts 1-3 in the overall profile. Swing was lowest in Cohort 1, but comparable between Cohorts 2 and 3. Cohort 4 norbuprenorphine had the highest percent fluctuation and swing compared to other cohorts.

Figure 11 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 28

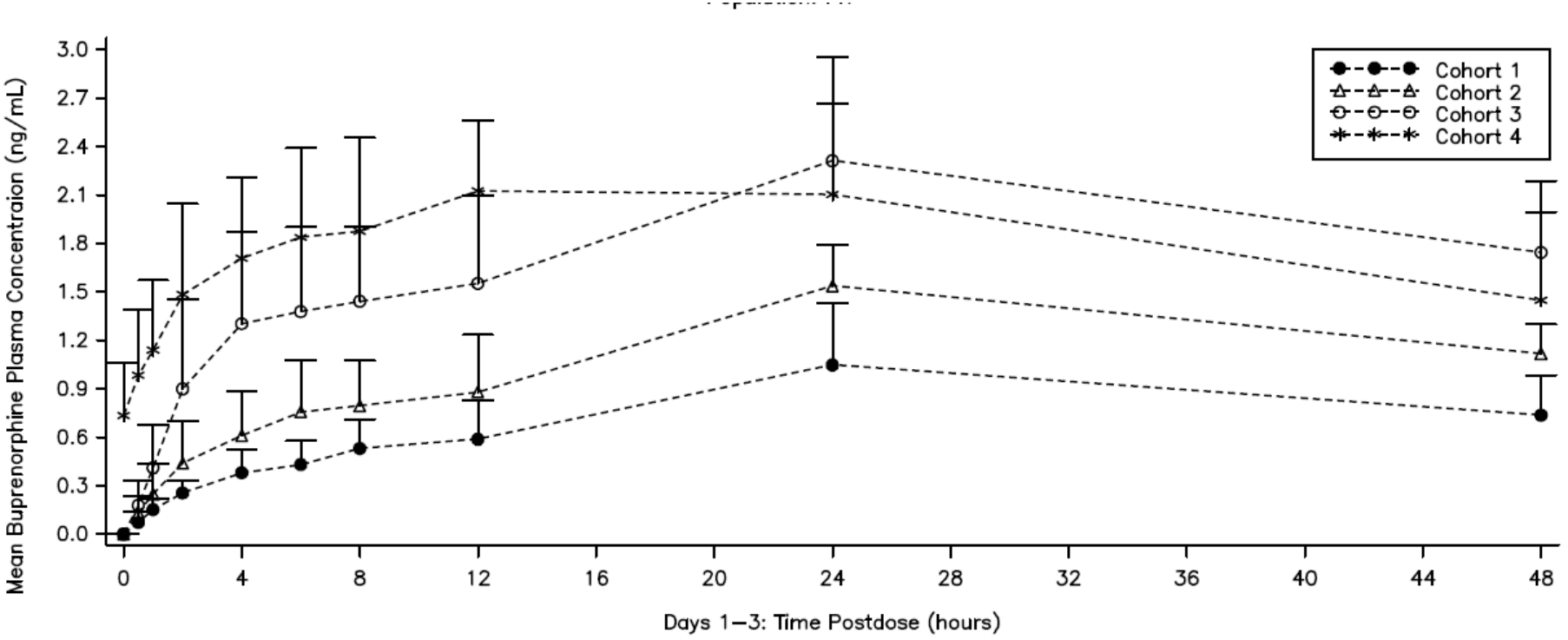


Cohort 1: Sublocade containing 50mg Buprenorphine Source: Figure 14.2.2. 1 .4
Cohort 2: Sublocade containing 100mg Buprenorphine
Cohort 3: Sublocade containing 200mg Buprenorphine The red line is at ~1.1ng/mL i.e. mean C_{avg}
Cohort 4: 7 days of SL Suboxone dosing (6 days at 12mg daily) followed by Sublocade containing 100mg Buprenorphine the blue line is at ~0.95ng/mL i.e. . mean C_{avg}

Comment: The concentration of 2-3ng/mL for 70% μ-opioid receptor occupancy is not achieved except in the early days. The sponsor defined both C_{avg} and $C_{avg\ Day\ 3\text{-}28}$ in the Statistical Analysis Plan[47] but in the CER only referred to C_{avg}. As can be seen for Cohorts 3 & 4 neither result particularly reflect plasma concentrations, at times either being well above or below the observed results. C_{avg} is a mathematical concept, not a measurement, which for comparative purposes only serves to diminish absolute values of differences in AUCs.

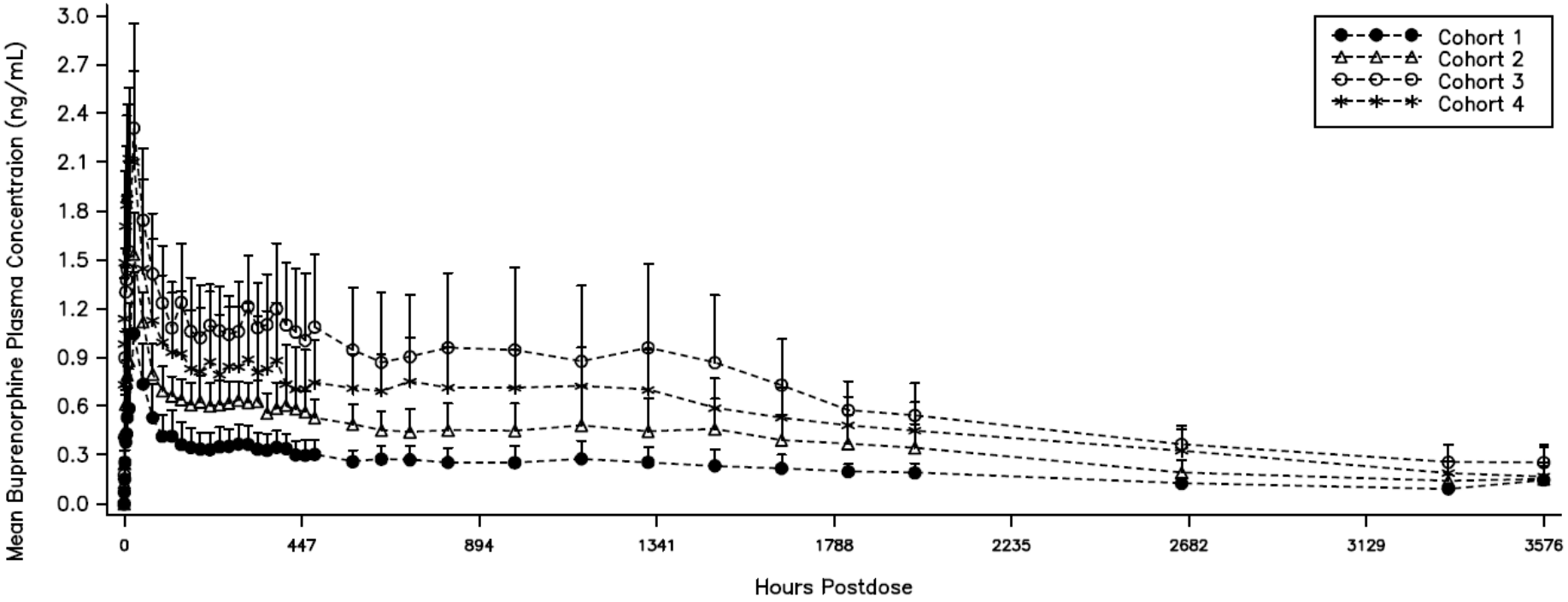
[47] Page 9 C_{avg} = The average of plasma concentrations calculated as $AUC_{Day\ 1\text{-}29}$/28 days and $C_{avg\ Day\ 3\text{-}28}$ = The average of plasma concentrations in the plateau (day 3 to day 28),calculated as $AUC_{Day\ 3\text{-}28}$/time Mean results were found in Table 11 CER

Figure 12 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 3



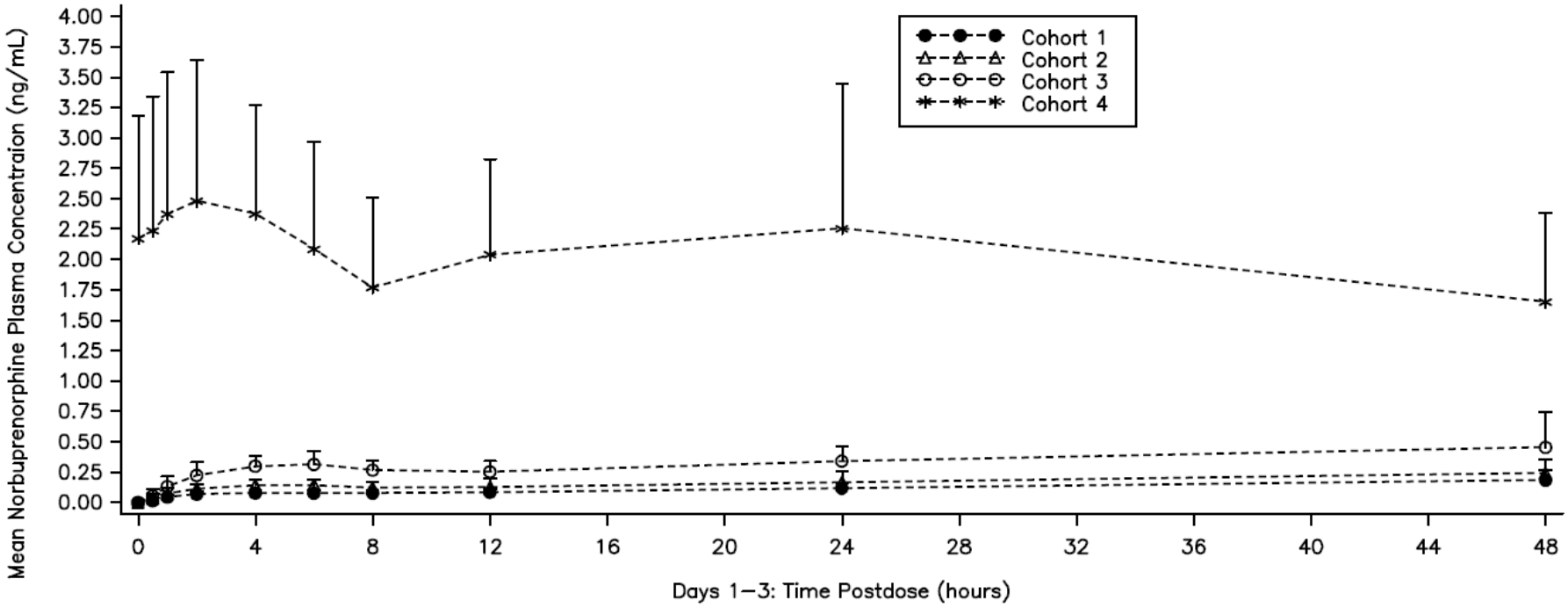
Cohort 1: Sublocade containing 50mg Buprenorphine
Cohort 2: Sublocade containing 100mg Buprenorphine
Cohort 3: Sublocade containing 200mg Buprenorphine
Cohort 4: 7 days of SL Suboxone dosing (6 days at 12mg daily) followed by Sublocade containing 100mg Buprenorphine Source: Figure 14.2.2. 1 .2

Figure 13 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 150



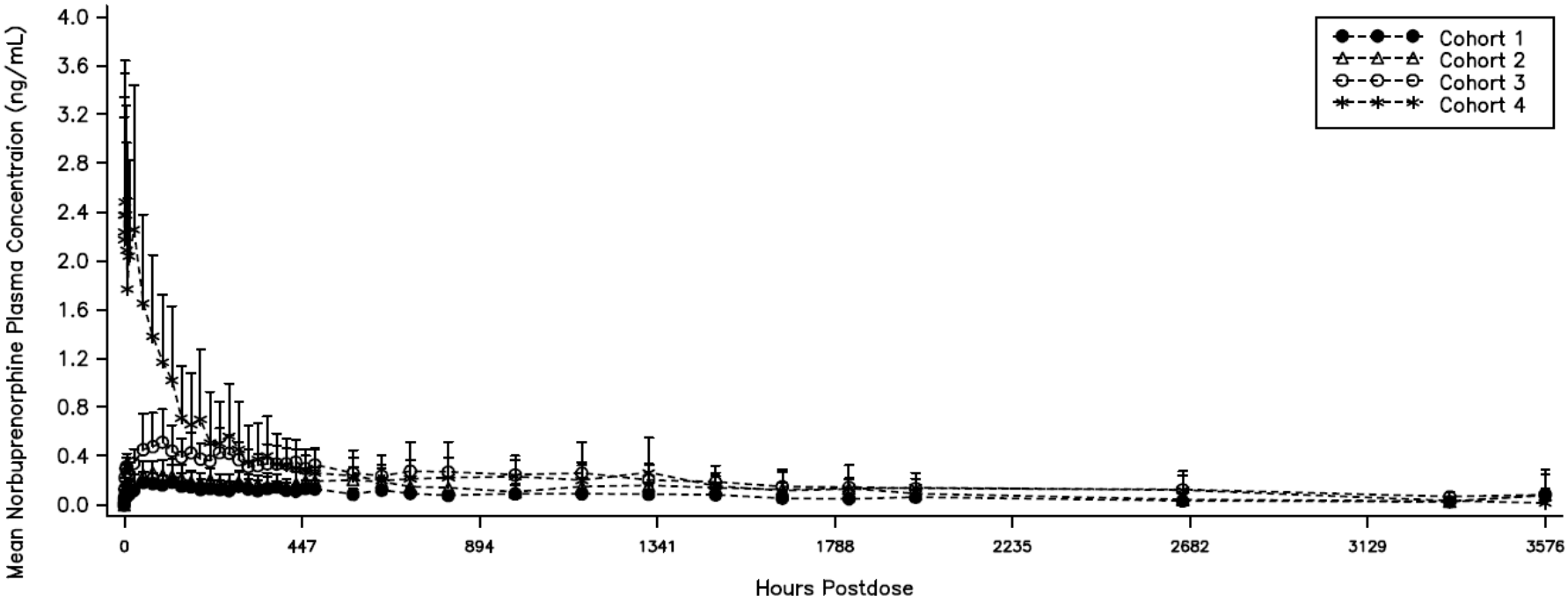
Cohort 1: Sublocade containing 50mg Buprenorphine
Cohort 2: Sublocade containing 100mg Buprenorphine
Cohort 3: Sublocade containing 200mg Buprenorphine
Cohort 4: 7 days of SL Suboxone dosing (6 days at 12mg daily) followed by Sublocade containing 100mg Buprenorphine Source: Figure 14.2.2. 1 .3

Figure 14 Plot of Mean (+ SD) Norbuprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to 3



Cohort 1 = a single SC injection of Sublocade containing 50mg buprenorphine.
Cohort 2 = a single SC injection of Sublocade containing 100mg buprenorphine.
Cohort 3 = a single SC injection of Sublocade containing 200mg buprenorphine.
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day -7 and 12mg on Days -6 through -1. Source: Figure 14.2.2.3.2

Figure 15 Plot of Mean (+ SD) Norbuprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to 150



Cohort 1 = a single SC injection of Sublocade containing 50mg buprenorphine.
Cohort 2 = a single SC injection of Sublocade containing 100mg buprenorphine.
Cohort 3 = a single SC injection of Sublocade containing 200mg buprenorphine.
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day -7 and 12mg on Days -6 through -1. Source: Figure 14.2.2.3.3

Table 25 Summary Statistics of Buprenorphine Plasma PK Parameters (Study 11-0020)

Parameter	Statistic	RBP-6000			SUBOXONE + RBP-6000
		Cohort 1 50 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 100 mg
AUC_{0-inf} (ng*hr/mL)	N	8	9	8	8
	Geometric Mean	846.78	1528.74	2919.43	2117.26
	%CV	22.9	19.3	25.7	29.4
CL/F (L/hr)	N	10	11	10	NC
	Geometric Mean	62.90	64.38	66.57	
	%CV	24.4	21.5	25.8	
C_{avg} (ng/mL)	N	12	12	12	10
	Geometric Mean	0.36	0.62	1.11	0.91
	%CV	27.4	16.6	25.7	32.5
C_{max} (ng/mL)	N	12	12	12	12
	Geometric Mean	1.00	1.52	2.38	2.23
	%CV	35.6	16.4	20.9	23.2
C_{min} (ng/mL)	N	12	12	12	12
	Geometric Mean	0.05	0.08	0.11	0.23
	%CV	56.1	44.3	67.8	64.3
T_{max} (hr)	N	12	12	12	12
	Median	24.00	24.00	24.00	18.00
	Min, Max	4.00, 24.03	24.00, 48.00	4.00, 144.00	4.00, 24.00
$t_{½}$ (hr)	N	10	11	10	10
	Geometric Mean	1036.76	1234.43	1429.41	1140.51
	%CV	27.2	47.3	49.6	16.7

NC=not calculated Source: Table 4Summary of Clinical Pharmacology Studies
Cohort 1=single SC injection of Sublocade containing 50mg buprenorphine
Cohort 2=single SC injection of Sublocade containing 100mg buprenorphine
Cohort 3=single SC injection of Sublocade containing 200mg buprenorphine
Cohort 4=once daily dosing with SL Suboxone, 8mg (2-, 4-mg doses approximately 3 hours apart) on Day -7 and 12mg on Day -6 through Day -1 followed by single SC injection of Sublocade containing 100mg Buprenorphine

Table 26 Summary Statistics of Norbuprenorphine Plasma PK Parameters (Study 11-0020)

Parameter	Statistic	RBP-6000			SUBOXONE + RBP-6000
		Cohort 1 50 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 100 mg
AUC_{0-inf} (ng*hr/mL)	N	3	7	5	7
	Geometric Mean	327.07	476.34	733.15	686.90
	%CV	33.5	51.6	34.4	36.2
AUC_{last} (ng*hr/mL)	N	12	12	12	12
	Geometric Mean	194.69	348.42	583.84	589.54
	%CV	72.2	62.2	45.0	60.2
C_{max} (ng/mL)	N	12	12	12	12
	Geometric Mean	0.22	0.34	0.64	2.53
	%CV	60.3	50.4	40.2	42.5
T_{max} (hr)	N	12	12	12	12
	Median	204.00	468.09	264.03	5.00
	Min, Max	48.00, 3581.02	48.00, 1825.80	4.00, 1130.60	2.00, 48.00
$t_{½}$ (hr)	N	4	7	6	7
	Geometric Mean	1383.80	856.74	1146.28	603.36
	%CV	49.3	52.6	14.1	68.7
M:P Ratio $RAUC_{last}$	N	12	12	12	12
	Geometric Mean	0.27	0.24	0.23	0.41
	%CV	48.0	54.1	36.6	97.6
M:P Ratio RC_{max}	N	12	12	12	12
	Geometric Mean	0.20	0.20	0.24	1.00
	%CV	50.3	54.8	42.3	43.4

M:P Ratio RC_{max} = Metabolite-to-parent ratio on C_{max} Source: Table 5 Summary of Clinical Pharmacology Studies
M:P Ratio $RAUC_{last}$ = Metabolite-to-parent ratio on AUC_{last}
Cohort 1=single SC injection of Sublocade containing 50mg buprenorphine
Cohort 2=single SC injection of Sublocade containing 100mg buprenorphine
Cohort 3=single SC injection of Sublocade containing 200mg buprenorphine
Cohort 4=once daily dosing with SL Suboxone, 8mg (2-, 4-mg doses approximately 3 hours apart) on Day -7 and 12mg on Day -6 through Day -1 followed by single SC injection of Sublocade containing 100mg buprenorphine

Pre-treatment with Suboxone SL slightly increased the exposure to buprenorphine and considerably increased exposure to norbuprenorphine (geometric mean $AUC_{Day1-29}$ and C_{max} were greater than Cohort 2 by 3 fold and 7.5 fold, respectively) after administration of Sublocade. Metabolite to parent (norbuprenorphine/buprenorphine) ratios of AUC_{last} and C_{max} were also considerably higher in Cohort 4 compared to Cohorts 1-3. Metabolite to parent C_{max} and C_{avg} ratios were lower after administration of Sublocade than following administration of Suboxone SL. The metabolite to parent C_{max} (geometric mean) ratio was ~0.2 for all the 3 doses in Cohorts 1-3 following administration of Sublocade compared to 0.87 following administration of Suboxone SL and 1.0 in Cohort 4 (Suboxone SL and Sublocade). The ratio of C_{avg} (R_{Cavg}) for buprenorphine and norbuprenorphine were 1.5251 and 4.1959, respectively,

which further explains the greater exposure to norbuprenorphine compared to buprenorphine after pre-treatment with Suboxone SL in Cohort 4.

Table 27 Summary Statistics of Buprenorphine and Norbuprenorphine Plasma PK Parameters for Cohort 4 During Treatment with Suboxone SL

Parameter	Statistic	Buprenorphine	Norbuprenorphine
$C_{max,ss}$ (ng/mL)	n	13	13
	Mean	4.3223	4.5115
	%CV	44.0	61.4
	Median	3.6000	3.6000
	Min,Max	1.980, 7.930	2.010, 11.600
	Geometric Mean	3.9670	3.9163
$T_{max,ss}$ (hr)	n	13	13
	Median	1.0000	1.0000
	Min,Max	0.500, 2.000	1.000, 12.067
AUC_{0-24} (hr*ng/mL)	n	13	13
	Mean	34.417	66.435
	%CV	34.9	51.3
	Median	31.956	61.698
	Min,Max	13.19, 60.49	26.10, 136.89
	Geometric Mean	32.410	58.885
C_{avg} (SL) (ng/mL)	n	13	13
	Mean	1.4340	2.7681
	%CV	34.9	51.3
	Median	1.3315	2.5708
	Min,Max	0.550, 2.520	1.087, 5.704
	Geometric Mean	1.3504	2.4536
R_{Cavg} (SL)	n	10	11
	Mean	1.6398	4.5992
	%CV	44.9	47.0
	Median	1.3902	3.8391
	Min,Max	0.987, 3.417	2.406, 8.589
	Geometric Mean	1.5251	4.1959
RCmax,ss	n		13
	Mean		1.0218
	%CV		54.3
	Median		1.0228
	Min, Max		0.302, 2.182
	Geometric Mean		0.8730

R_{Cavg} Ratio of Suboxone C_{avg}/Sublocade C_{avg} Source: Table 13
$R_{Cmax,ss}$ Ratio of C_{max} norbuprenorphine/C_{max} buprenorphine (C_{max} was converted to molar concentration; buprenorphine MW: 467.64, norbuprenorphine MW: 413.55)
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day-7 and 12mg on Days -6 to -1.

With the increase in dose of Sublocade from 50mg to 200mg, mean buprenorphine exposure parameters in the initial period (C_{max} and AUC_{0-48}), secondary period ($AUCD_{ay3-28}$ and Cm_{ax}), and entire profile (C_{max}, C_{avg}, $AUC_{Day1-29}$, AUC_{last}, and AUC_{0-inf}), increased less than proportionally to dose, where the difference of the slope from unity was statistically significant for all the above exposure parameters except for AUC_{last} and AUC_{0-inf} in the overall profile. Mean norbuprenorphine exposure parameters in the initial burst period (C_{max} and AUC_{0-48}), secondary

peak period ($AUC_{Day3-28}$ and C_{max}), and entire profile (C_{max}, C_{avg}, $AUC_{Day1-29}$, AUC_{last}, and AUC_{0-inf}) increased less than proportionally to dose, but the difference of slope from unity was statistically significant only for initial burst parameters.

Table 28 Statistical Analysis of Dose Proportionality for Buprenorphine

Phase	PK Parameter	Estimate (beta1)	p-value	90% CI of Slope
Initial Burst	C_{max} (ng/mL)	0.620	<.001	(0.501, 0.739)
	AUC_{0-48} (hr*ng/mL)	0.641	<.001	(0.525, 0.756)
Secondary Peak	C_{max} (ng/mL)	0.828	0.044	(0.688, 0.967)
	$AUC_{Day\ 3-28}$ (hr*ng/mL)	0.846	0.043	(0.721, 0.970)
Overall	C_{max} (ng/mL)	0.626	<.001	(0.509, 0.744)
	C_{avg} (ng/mL)	0.819	0.014	(0.700, 0.937)
	$AUC_{Day\ 1-29}$ (hr*ng/mL)	0.819	0.014	(0.700, 0.937)
	AUC_{last} (hr*ng/mL)	0.889	0.171	(0.754, 1.023)
	AUC_{0-inf} (hr*ng/mL)	0.893	0.208	(0.751, 1.035)

Source: Table 14

Table 29 Statistical Analysis of Dose Proportionality for Norbuprenorphine

Phase	PK Parameter	Estimate (beta1)	p-value	90% CI of Slope
Initial Burst	C_{max} (ng/mL)	0.673	0.016	(0.455, 0.891)
	AUC_{0-48} (hr*ng/mL)	0.741	0.025	(0.555, 0.927)
Secondary Peak	C_{max} (ng/mL)	0.804	0.183	(0.561, 1.048)
	$AUC_{Day\ 3-28}$ (hr*ng/mL)	0.775	0.089	(0.558, 0.992)
Overall	C_{max} (ng/mL)	0.764	0.124	(0.511, 1.017)
	C_{avg} (ng/mL)	0.768	0.075	(0.555, 0.981)
	$AUC_{Day\ 1-29}$ (hr*ng/mL)	0.768	0.075	(0.555, 0.981)
	AUC_{last} (hr*ng/mL)	0.792	0.178	(0.537, 1.047)
	AUC_{0-inf} (hr*ng/mL)	0.587	0.068	(0.220, 0.954)

Source: Table 15

Confounding

Although the use of *cannabis sativa* was prohibited during the study, multiple subjects continued to use cannabis throughout the study. Throughout the entire duration of the study, cannabis use ranged from 17-75%, 0-42%, 8-83%, and 7-33% (8 to 33% by *post hoc* analysis) of subjects in Cohorts 1-4, respectively. The impact of continued cannabis use on study integrity could not be determined, because buprenorphine and cannabinoids are both metabolized by CYP3A4, and cannabinoids are known to induce and inhibit CYP3A4.13.

21.1.1.3. PK study RB-US-12-0005

An open-label multiple dose study of the safety, tolerability, pharmacokinetics, efficacy markers, and opioid receptor availability of subcutaneous injections of depot buprenorphine (Sublocade) in treatment seeking opioid-dependent subjects.

This was described as multicentred (e.g. on title page) but Appendix 16.1.4.1 List of Investigators gives only a single centre in the US. Conducted from 05 October 2012 to 05 May 2014. Cohort 6 was added by amendment 4 (18 June 2013).

90 subjects were planned to be enrolled with at least 6 subjects per cohort completing the study. A total of 89 subjects received both Subutex SL tablet and Sublocade and were included in the PK, pharmacodynamic (PD) and safety evaluations.

The primary objectives of this study were:

- To assess the safety and tolerability of multiple subcutaneous (SC) injections of 50mg, 100mg, 200mg and 300mg doses of buprenorphine in Sublocade in treatment seeking opioid-dependent subjects who were inducted and then stabilised on a Subutex sublingual (SL) tablet dose of 8mg, 12mg, 14mg, 24mg or 8-24mg[48] prior to transfer.
- To evaluate the multiple dose pharmacokinetics (PK) of buprenorphine and norbuprenorphine after SC injections of 50mg, 100mg, 200mg and 300mg doses of buprenorphine in Sublocade in treatment seeking opioid-dependent subjects who were inducted and then stabilised on a Subutex SL tablet dose of 8mg, 12mg, 14mg, 24mg or 8-24mg.
- To compare the steady-state PK of buprenorphine and norbuprenorphine after SC doses of Sublocade relative to the corresponding Subutex SL tablet doses.

The secondary objectives of this study were to evaluate the overall clinical response to Subutex SL tablet and to Sublocade with respect to the following:

- The Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), Opioid Craving Visual Analog Scale (VAS), Clinical Global Impression - Severity scale (CGI-S), and Clinical Global Impression - Improvement scale (CGI-I) total scores.
- Illicit opioid and non-opioid drug use as measured by urine drug screen results.
- The Columbia-Suicide Severity Rating Scale (C-SSRS).

The study population consisted of male and female subjects aged ≥ 18 to ≤ 65 years who met DSM-IV-TR criteria for opioid-dependence at screening and were seeking opioid-dependence treatment.

Subjects entered an open-label Subutex SL tablet induction and stabilisation period to achieve stable[49] daily doses.

For Cohorts 1-5 they were 8mg, 12mg, 14mg, or 24mg during a 13-day inpatient (Day -14 to Day -1) period. They then received 4 SC injections of Sublocade separated by 28 days.

For Cohort 6 the stable doses were 8 - 24mg (variable) followed by 6 SC injections of Sublocade separated by 28 days

- Cohort 1: 50mg Sublocade (8mg Subutex SL tablet)
- Cohort 2: 100mg Sublocade (12mg Subutex SL tablet)
- Cohort 3: 200mg Sublocade (24mg Subutex SL tablet)
- Cohort 4: 100mg Sublocade (8mg Subutex SL tablet)
- Cohort 5: 200mg Sublocade (14mg Subutex SL tablet)
- Cohort 6: 300mg Sublocade (8 to 24mg Subutex SL tablet)

Any subject who reached a total daily dose of 24mg of Subutex SL tablet during the stabilisation period, was receiving Sublocade injections and required rescue medication for opioid

[48] The "8-24mg" Subutex designator refers to the range of doses of Subutex SL tablet allowed for Cohort 6 subjects. These subjects were on 1 of the following doses of Subutex SL tablet at the time of transfer to Sublocade: 8mg, 12mg, 16mg, 20mg or 24mg

[49] subjects were considered stable if they had a COWS score of < 12 and an Opioid Craving VAS score of < 20 mm from Day -5 through Day 1 predose

withdrawal symptoms (e.g., Subutex SL tablet or methadone) was discontinued from the study for a lack of efficacy.

Plasma concentrations of buprenorphine and norbuprenorphine were quantified using validated LC-MS/MS methods validated for a range of 0.0500 to 25.0ng/mL for buprenorphine and 0.0400 to 20.0ng/mL for norbuprenorphine.

Results

Buprenorphine

Following the first dose of Sublocade, buprenorphine plasma concentrations rose to a peak at a median time of 20h post-dose and declined to a plateau throughout Day 1 to Day 29. Similar results were seen for subsequent doses of Sublocade.

Mean plasma concentrations of buprenorphine showed an apparent increase with the dose from 50mg to 300mg following all injections of Sublocade. Within each dose level, mean concentrations of buprenorphine increased with every injection from Injections 1 to 4.

The mean pre-dose concentrations (C_{trough}) also increased from Injection 1 to 4 for buprenorphine.

Nor-buprenorphine

After Injection 1 of Sublocade, norbuprenorphine concentrations showed peak concentrations 6 to 12h post dose. There was a secondary peak that was at 24 to 48h post dose.

Following Injection 2, 3 and 4, norbuprenorphine concentrations peaked at 48h, with a secondary peak from Day 42 to Day 48, on Day 65, and on Day 93 to Day 101 after the SC Injections 2, 3 and 4, respectively. Following the secondary peaks concentrations declined to a plateau throughout the dosing interval.

Mean plasma concentrations of the metabolite, norbuprenorphine, showed an apparent increase with the dose from 50mg to 300mg following all injections of Sublocade. For each dose level, mean concentrations of norbuprenorphine increased with every injection, from Injections 1 to 4.

For norbuprenorphine, the pre-dose concentrations (C_{trough}) following Sublocade SC injections were much lower when compared with the pre-dose concentrations prior to the first SC injection, i.e., following Subutex SL tablet administration during the stabilisation phase.

Table 30 Summary of Subject Disposition: Subjects Who Received Both Subutex Sublingual Tablet and Sublocade (Population: Safety)

	Subutex SL; Sublocade							
	Cohort 1 8 mg; 50 mg (N = 15) n (%)	Cohort 2 12 mg; 100 mg (N = 15) n (%)	Cohort 3 24 mg; 200 mg (N = 15) n (%)	Cohort 4 8 mg; 100 mg (N = 15) n (%)	Cohort 5[b,c] 14 mg; 200 mg (N = 15) n (%)	Cohort 6[d] 8-24 mg; 300 mg (N = 14) n (%)	Overall (N = 89) n (%)	PET Imaging Sub-study[e] (N = 2) n (%)
Safety Population	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	14 (100.00)	89 (100.00)	2 (100.00)
PK Population	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	14 (100.00)	89 (100.00)	2 (100.00)
PD Population	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	15 (100.00)	14 (100.00)	89 (100.00)	2 (100.00)
Completed to Day 113[a]	10 (66.67)	10 (66.67)	9 (60.00)	7 (46.67)	9 (60.00)	6 (42.86)	51 (57.30)	2 (100.00)
Withdrew from Main Study	5 (33.33)	5 (33.33)	6 (40.00)	8 (53.33)	6 (40.00)	8 (57.14)	38 (42.70)	0 (0.0)
Reason for Withdrawal								
Adverse Event	1 (6.67)	0 (0.0)	1 (6.67)	2 (13.33)	2 (13.33)	2 (14.29)	8 (8.99)	0 (0.0)
Lost To Follow-Up	0 (0.0)	3 (20.00)	4 (26.67)	1 (6.67)	1 (6.67)	5 (35.71)	14 (15.73)	0 (0.0)
Physician Decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by Subject	1 (6.67)	0 (0.0)	1 (6.67)	1 (6.67)	1 (6.67)	1 (7.14)	5 (5.62)	0 (0.0)
Noncompliance with Study Drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Violation	3 (20.00)	1 (6.67)	0 (0.0)	4 (26.67)	2 (13.33)	0 (0.0)	10 (11.24)	0 (0.0)
Other	0 (0.0)	1 (6.67)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.12)	0 (0.0)

[a] A completed subject in the main study was defined in the Statistical Analysis Plan (SAP) as anyone who completed study treatment through Day 113. Cohort 6 was added by protocol amendment; initially, subjects could receive up to 4 injections (Day 113 completion) and subsequent to an additional amendment could receive up to 6 injections (study treatment through Day 141). Subjects in Cohorts 3, 5 and 6 who completed the main study were eligible to enrol in the PET imaging sub-study (see footnote e).

[b] Four subjects in Cohort 5 consented to receive additional doses of Sublocade to be eligible for participation in the PET imaging sub-study. PET imaging was completed for 1 of the 4 subjects. This subject received 12 injections of Sublocade.

[c] One subject in Cohort 5 (001789) completed the main study, enrolled in the PET imaging sub-study and received 7 injections of Sublocade. The subject subsequently experienced an SAE of thyroid cancer and was discontinued from the PET imaging sub-study but was counted as having completed the main study.

[d] Two subjects in Cohort 6 consented to receive additional doses of Sublocade to be eligible for participation in the PET imaging sub-study. Both subjects received 6 doses of Sublocade. PET imaging was completed for 1 of the 2 subjects.

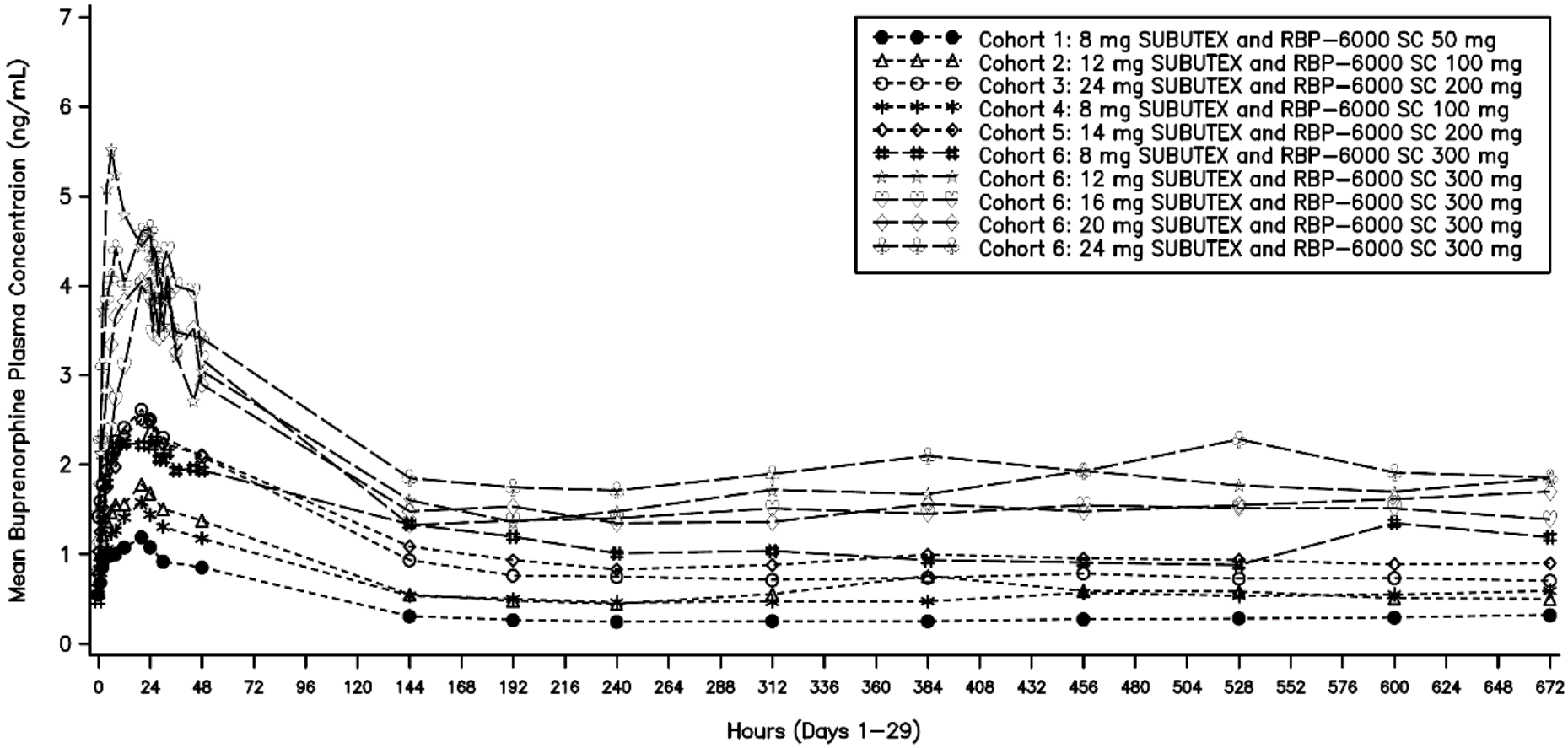
[e] Subjects who received Sublocade containing 200mg or 300mg buprenorphine (Cohorts 3, 5 or 6) and reached Day 112 (and had received all 4 or 6 planned SC injections) had the option to consent to participate in the PET imaging sub-study in which they remained on their assigned Sublocade dose SC injections at 28-day intervals until they completed an MRI, PET scan and PK samples at Week 1 and Week 4 post injection. It was anticipated that subjects could receive up to 12 injections of Sublocade to complete the PET imaging sub-study, depending on the availability of the PET imaging facilities. A total of 6 subjects who completed the main study consented to participate in the PET imaging sub-study; 2 subjects completed the sub-study. Source: Table 11

Table 31 Summary of Demographics for Subjects Who Received Both Subutex Sublingual Tablet and Sublocade (Population: Safety)

		SUBUTEX SL: Sublocade						
	Category or Statistic	Cohort 1 8 mg; 50 mg (N = 15) n (%)	Cohort 2 12 mg; 100 mg (N = 15) n (%)	Cohort 3 24 mg; 200 mg (N = 15) n (%)	Cohort 4 8 mg; 100 mg (N = 15) n (%)	Cohort 5 14 mg; 200 mg (N = 15) n (%)	Cohort 6 8-24 mg; 300 mg (N = 14) n (%)	Overall (N = 89) n (%)
Gender - n (%)	Male	12 (80.0)	10 (66.7)	10 (66.7)	9 (60.0)	9 (60.0)	10 (71.4)	60 (67.4)
	Female	3 (20.0)	5 (33.3)	5 (33.3)	6 (40.0)	6 (40.0)	4 (28.6)	29 (32.6)
Age (yr)	n	15	15	15	15	15	14	89
	Mean	36.5	31.1	30.1	36.1	36.2	32.9	33.8
	SD	11.36	11.14	11.21	14.87	12.85	11.00	12.10
	Median	34.0	30.0	24.0	32.0	31.0	28.0	30.0
	Min, Max	24, 60	20, 55	19, 54	20, 59	19, 56	22, 56	19, 60
Weight (kg)	n	15	15	15	15	15	14	89
	Mean	71.12	73.71	68.08	74.43	73.16	74.64	72.50
	SD	12.929	10.411	9.900	15.995	12.753	16.825	13.159
	Median	71.40	72.30	67.70	73.00	73.60	73.60	71.60
	Min, Max	56.4, 100.9	56.3, 97.7	51.6, 87.3	52.3, 109.1	50.0, 94.1	48.1, 107.0	48.1, 109.1
	Median	22.50	23.80	24.10	23.90	26.50	25.25	24.20
	Min, Max	19.4, 29.5	20.9, 31.3	19.8, 27.2	19.7, 32.2	19.1, 31.6	18.4, 30.9	18.4, 32.2
Other Opioid Use (yr)	n	12	11	12	11	11	10	67
	Mean	6.75	6.18	4.17	5.27	8.36	6.30	6.15
	SD	5.545	4.191	2.887	3.927	9.770	8.693	6.165
	Median	5.00	6.00	4.50	6.00	5.00	3.50	5.00
	Min, Max	1.0, 17.0	2.0, 15.0	1.0, 11.0	1.0, 13.0	1.0, 36.0	1.0, 30.0	1.0, 36.0
Heroin Use (yr)	n	12	9	11	14	10	9	65
	Mean	11.25	9.78	5.00	11.64	10.70	8.56	9.62
	SD	10.463	11.454	5.604	12.549	7.987	12.471	10.292
	Median	9.50	4.00	3.00	7.50	11.50	2.00	6.00
	Min, Max	1.0, 36.0	1.0, 30.0	1.0, 20.0	1.0, 43.0	1.0, 26.0	1.0, 40.0	1.0, 43.0

Source: Table 12

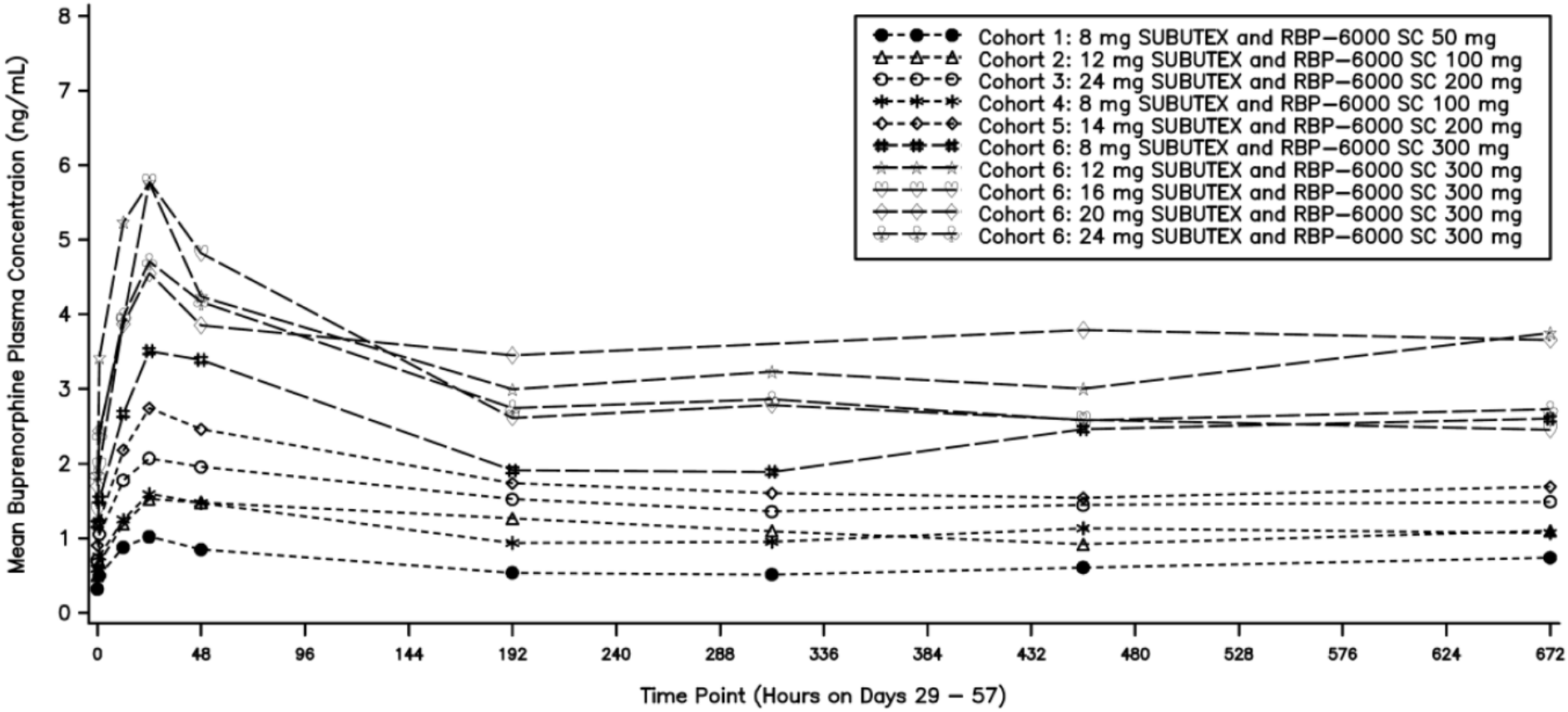
Figure 16 Mean Buprenorphine Plasma Concentrations vs. Time on a Linear Scale Post Sublocade SC Injection 1 from Study Day 1 to Day 29 (672h) (Pop: PK)



Source: Figure 6

Comment: The sponsor uses both **D**ays and hours for description of time. They are not concurrent, thus two days or48h (from time of injection will) occur on **D**ay 3. Reinjection at 28 days will occur on **D**ay 29.

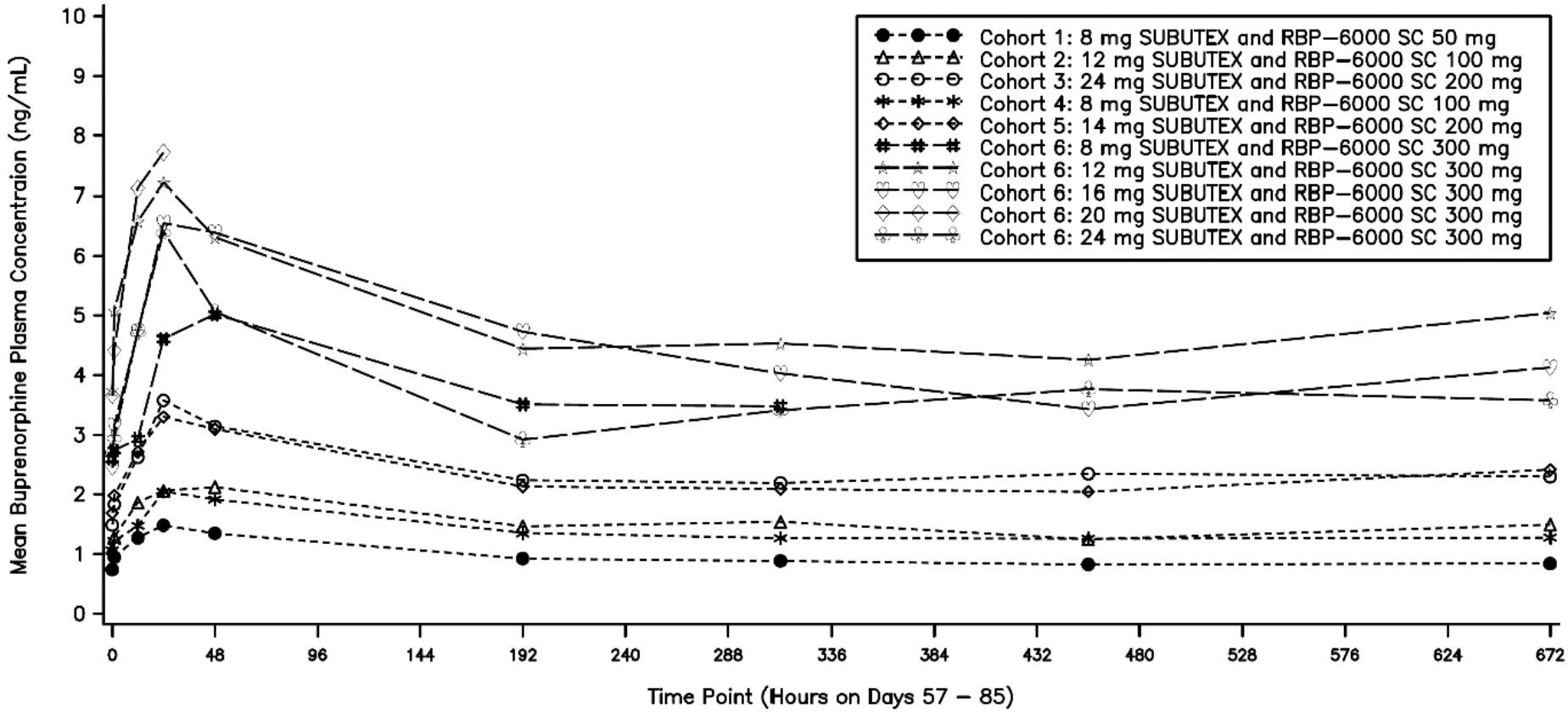
Figure 17 Mean Buprenorphine Plasma Concentrations vs. Time on a Linear Scale Post Sublocade SC Injection 2 from Study Day 29 to Day 57 (672h) (Pop: PK)



Source: Figure 8

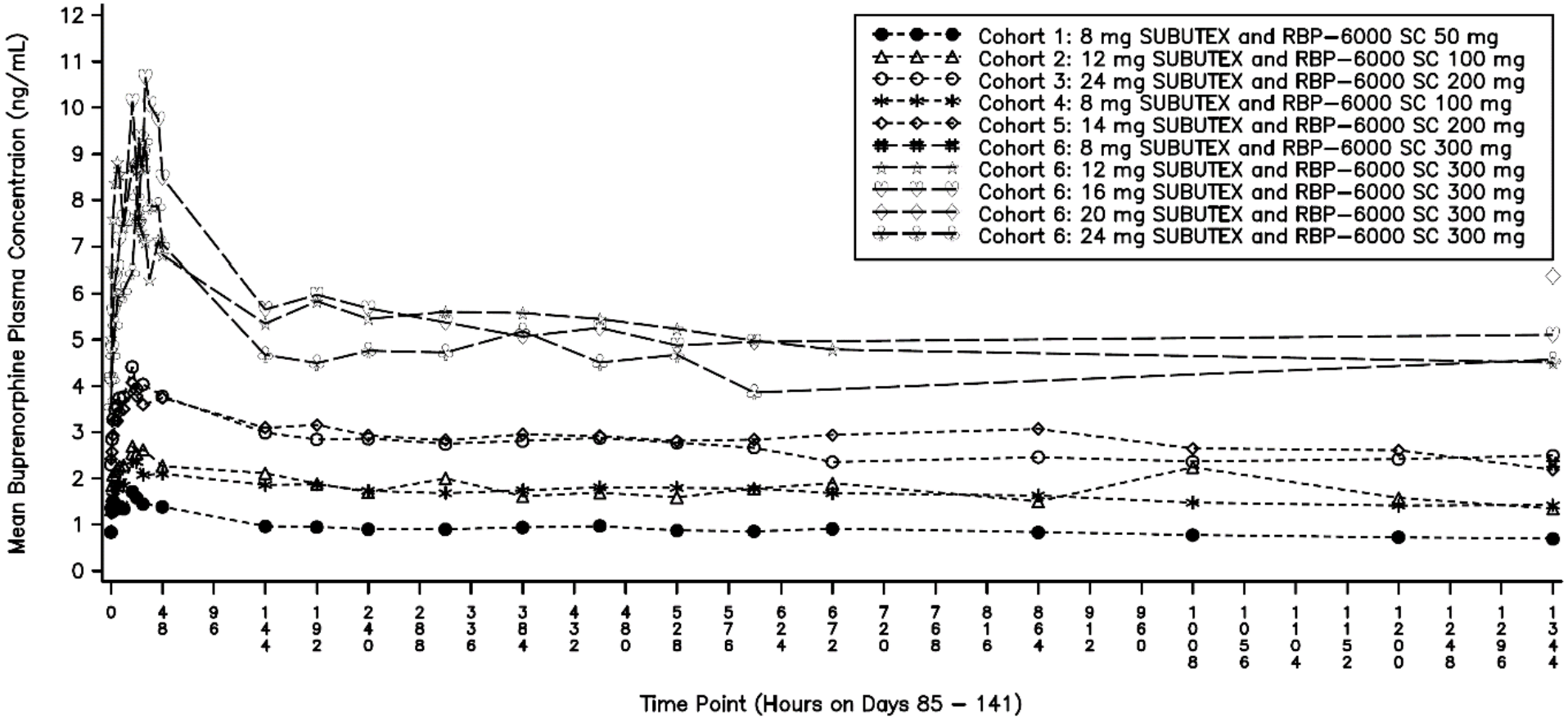
Mean Buprenorphine Plasma Concentrations versus Time on a Linear Scale

Figure 18 Post Sublocade SC Injection 3 from Study Day 57 to Day 85 (672h) (Pop: PK)



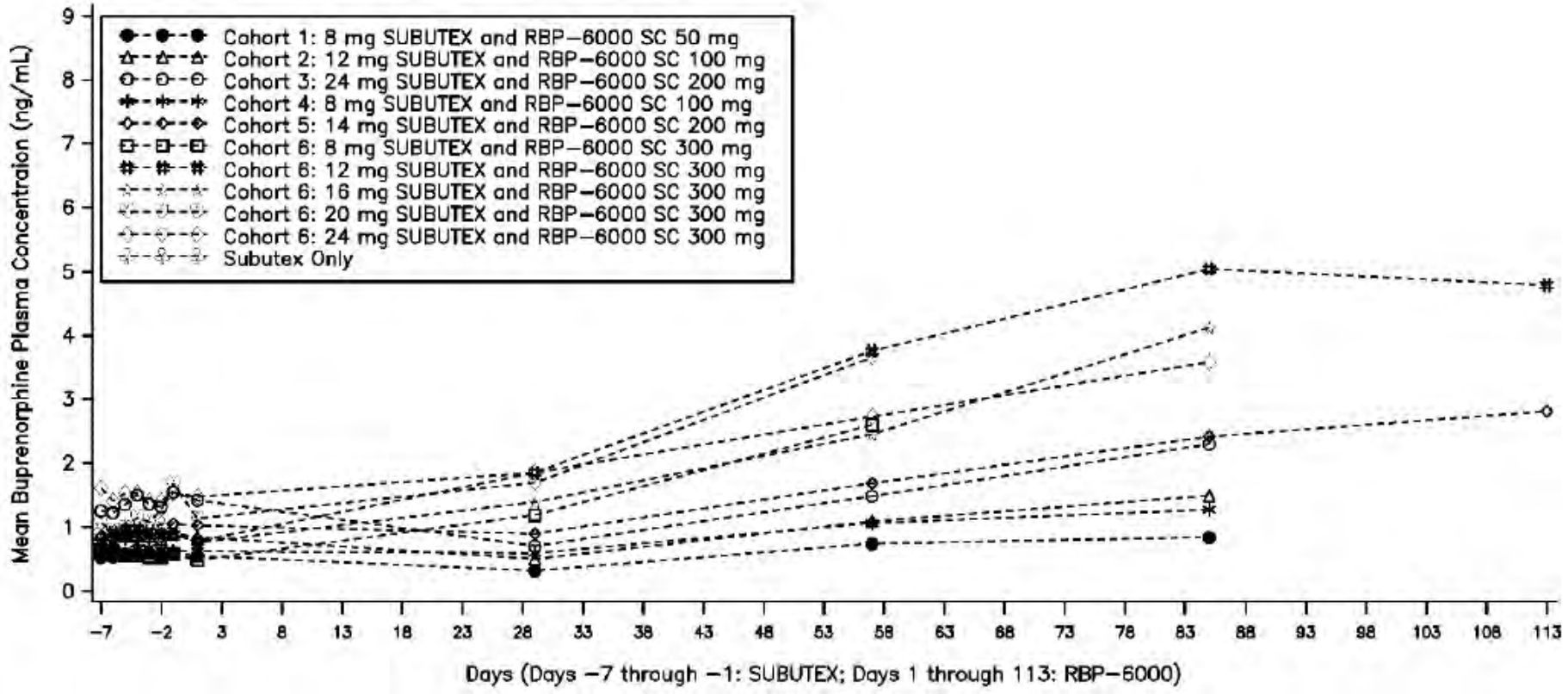
Source: Figure 10

Figure 19 Mean Buprenorphine Plasma Concentrations vs. Time on a Linear Scale Post Sublocade SC Injection 4 from Study Day 85 to Day 141 (Pop: PK)



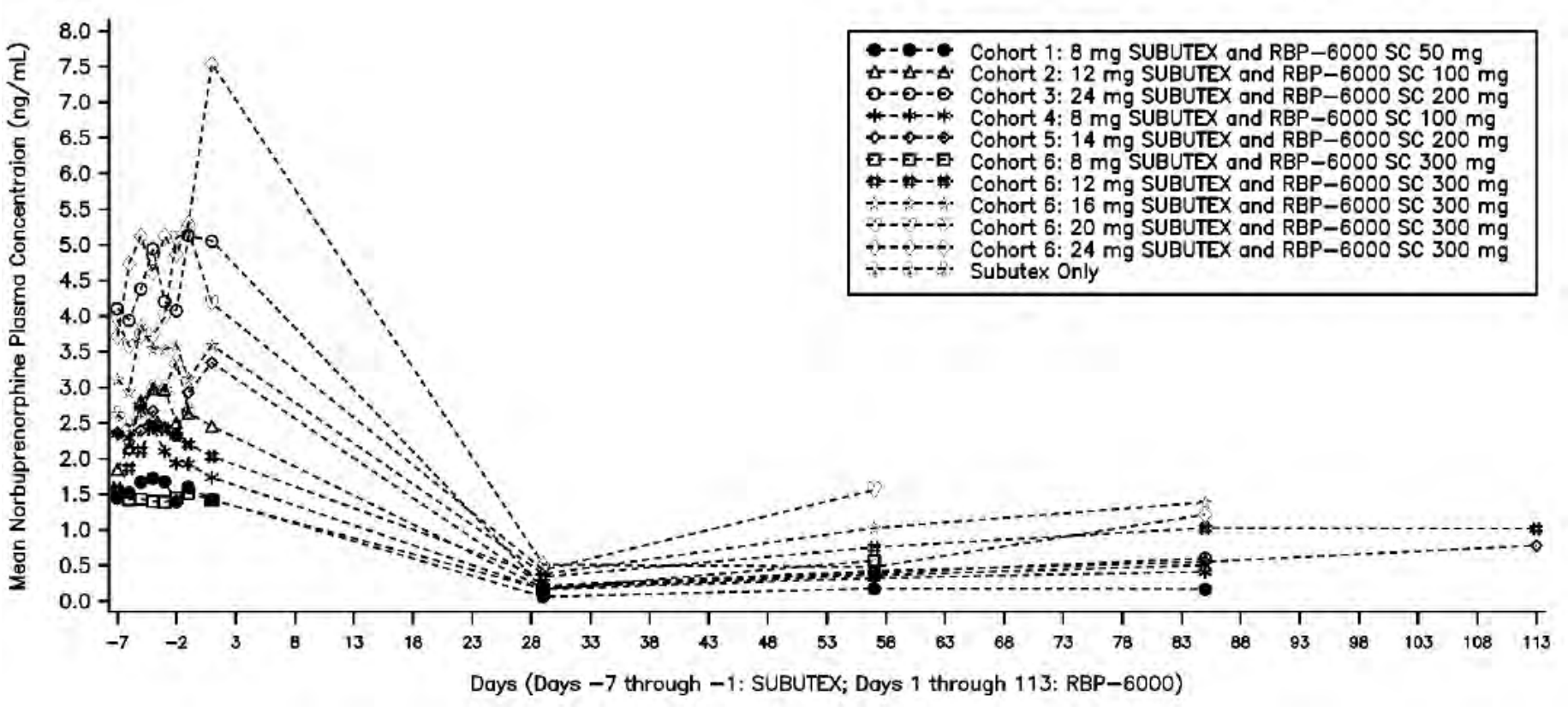
Source: Figure 12

Figure 20 Mean Predose (C_{trough}) Buprenorphine Plasma Concentrations vs. Time on a Linear Scale Following Subutex SL and Sublocade SC Injection Administration (Study Days -7 to -1, 1, 29, 57, 85, and 113) (Pop: PK)



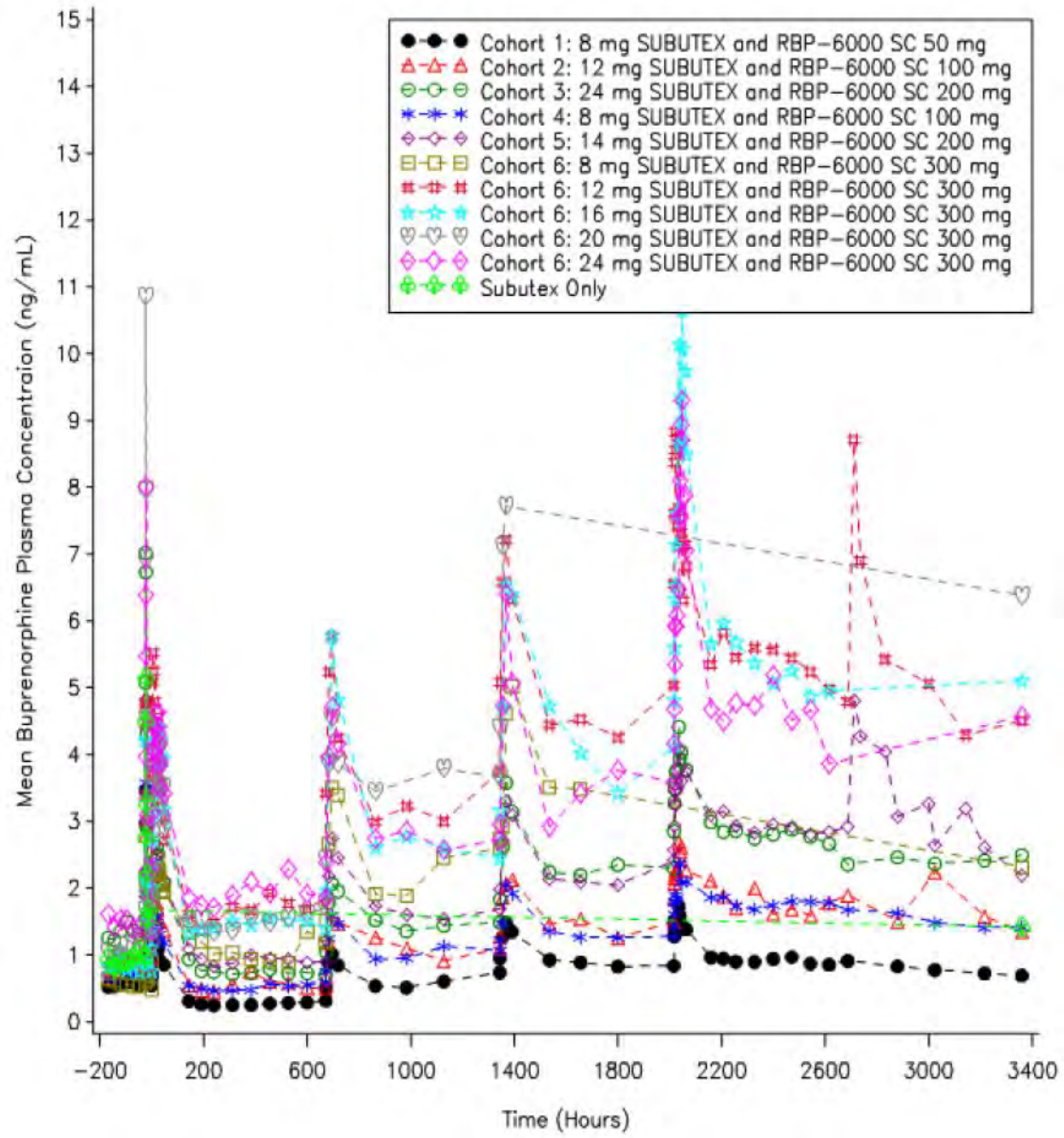
Source: Figure 16

Figure 21 Mean Predose (C_{trough}) Norbuprenorphine Plasma Concentrations vs. Time on a Linear Scale Following Subutex SL and Sublocade SC Injection Administration (Study Days -7 to -1, 1, 29, 57, 85, and 113) (Pop: PK)



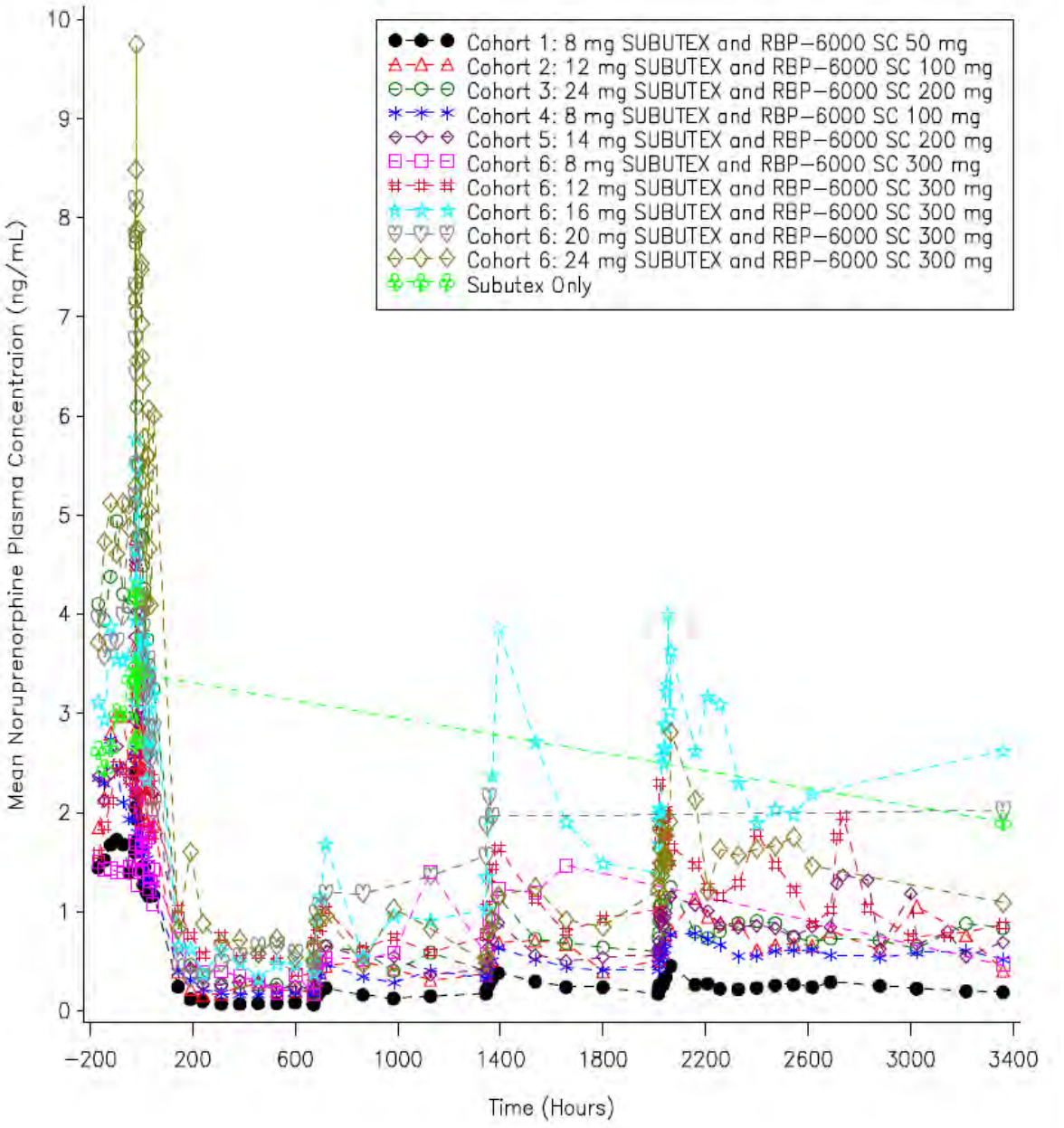
Source: Figure 27

Figure 22 Mean Buprenorphine Plasma Concentrations by Scheduled Sampling Time for All Cohorts Study Days -7 to 141 on a Linear Scale (Pop: PK)



Source: Figure 14

Figure 23 Mean Norbuprenorphine Plasma Concentrations by Scheduled Sampling Time for All Cohorts Study Days -7 to 141 on a Linear Scale (Pop: PK)



Source: Figure 25

PK Parameters

Comment: The CSR provided extensive tabular summary results. Briefer summaries of those tables are provided in the Summary of Clinical Pharmacology Studies and are reproduced below.

Of concern in those tables is the use of C_{avg} for comparison. As can be seen from the following definitions, when for comparison $AUC_{0-\tau}$ is used, using C_{avg} also achieves nothing except to divide any difference by 28x24.

The sponsor defined 3 different C_{avg} rather than using AUCs for comparison:

- $C_{avg, ss}$ = Average plasma concentration on Study Day -1, calculated as AUC_{0-24}/ 24h
- $C_{avg, Day\ 2-28}$ = The average of plasma concentrations in the plateau, calculated as $AUC_{Day2-28}$/ time, where time was 624h.

- C_{avg} = The average of plasma concentrations calculated as AUC_{tau}/ tau (assuming tau = 28 days) for Injections 1, 4, and 6 (for Cohort 6, as applicable).

Table 32 Summary Statistics of Buprenorphine Plasma PK Parameters (Study 12-0005)

			Subutex; Sublocade					
Parameter	Day	Statistic	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
			8 mg; 50 mg	12 mg; 100 mg	24 mg; 200 mg	8 mg; 100 mg	14 mg; 200 mg	8-24 mg; 300 mg
AUC_{0-24hr} (ng*hr/mL)	Day 1	N	15	15	14	15	12	14
		Geo Mean	24.09	34.33	53.08	29.50	48.90	79.89
		CV%	25.9	38.8	30.8	41.6	23.0	33.7
	Day 85	N	11	12	11	10	8	7
		Geo Mean	33.13	54.06	87.70	46.77	79.67	173.78
		CV%	41.2	27.8	30.0	20.2	22.6	24.3
AUC_{0-48hr} (ng*hr/mL)	Day 1	N	15	15	15	15	15	14
		Geo Mean	45.43	68.19	105.48	59.51	102.63	157.50
		CV%	24.7	35.1	27.8	32.5	21.6	29.1
	Day 85	N	11	11	11	10	11	6
		Geo Mean	66.41	109.70	180.06	97.19	170.14	374.10
		CV%	35.1	26.3	26.0	18.1	17.0	21.3
AUC_{tau} (ng*hr/mL)	Day 1	N	15	14	13	14	14	11
		Geo Mean	240.62	442.11	610.63	394.19	726.67	1218.90
		CV%	22.3	30.8	35.5	32.2	29.6	30.7
	Day 85	N	10	11	9	8	7	2
		Geo Mean	622.70	1217.72	1887.78	1249.05	2013.34	3216.49
		CV%	38.1	34.1	23.6	19.8	22.7	13.3
C_{avg} (ng/mL)	Day 1	N	15	14	13	14	14	11
		Geo Mean	0.36	0.66	0.91	0.59	1.08	1.81
		CV%	22.3	30.8	35.5	32.2	29.6	30.7
	Day 85	N	10	11	9	8	7	2
		Geo Mean	0.93	1.81	2.81	1.86	3.00	4.79
		CV%	38.1	34.1	23.6	19.8	22.7	13.3
C_{max} (ng/mL)	Day 1	N	15	15	14	15	15	14
		Geo Mean	1.29	1.87	2.64	1.59	2.78	4.60
		CV%	34.3	40.8	28.8	36.8	24.9	29.8
	Day 85	N	11	12	11	10	11	7
		Geo Mean	1.84	2.96	4.36	2.52	4.32	9.38
		CV%	69.0	28.2	28.9	18.7	21.0	24.3

C_{min} (ng/mL)	Day 1	N	15	15	14	15	15	14
		Geo Mean	0.20	0.36	0.55	0.38	0.67	0.76
		CV%	27.0	26.7	42.8	47.6	31.4	44.9
	Day 85	N	11	12	11	10	11	7
		Geo Mean	0.54	1.22	2.07	1.15	2.17	3.99
		CV%	28.0	28.3	22.1	23.8	28.7	17.2
T_{max} (hr)	Day 1	N	15	15	14	15	11	7
		Median	20.00	20.00	20.00	20.00	20.00	20.00
		Min, Max	4.00, 20.05	4.00, 414.17	6.00, 30.00	4.00, 48.00	6.00, 48.00	4.00, 32.00
	Day 85	N	11	12	11	10	11	7
		Median	20.00	20.00	20.08	24.00	24.00	24.00
		Min, Max	2.00, 24.00	12.00, 315.95	8.00, 30.08	4.00, 529.83	4.00, 48.00	4.00, 36.00
CL/F (L/hr)	Day 85	N	11	12	11	10	8	5
		Geo Mean	79.95	82.21	102.72	85.34	101.88	79.62
		CV%	40.5	25.8	22.3	24.1	27.9	19.6
Rac(AUC)	Day 85	N	10	11	9	8	7	2
		Geo Mean	2.40	2.69	3.34	3.28	2.72	3.55
		CV%	37.5	18.6	26.9	27.2	30.5	15.8

Rac(AUC)=accumulation index in terms of AUC calculated as ratio of AUCtau Injection 4/ AUCtau Injection 1
Cohort 1=8mg Subutex and Sublocade 50 mg.
Cohort 2=12mg Subutex and Sublocade 100 mg.
Cohort 3=24mg Subutex and Sublocade 200 mg.
Cohort 4=8mg Subutex and Sublocade 100 mg
Cohort 5=14mg Subutex and Sublocade 200 mg
Cohort 6=8mg Subutex and Sublocade 300 mg Source: Table 7 Summary of Clinical Pharmacology Studies

Table 33 Summary Statistics of Norbuprenorphine Plasma PK Parameters (Study 12-0005)

			Subutex; Sublocade					
Parameter	Day	Statistic	Cohort 1 8 mg; 50 mg	Cohort 2 12 mg; 100 mg	Cohort 3 24 mg; 200 mg	Cohort 4 8 mg; 100 mg	Cohort 5 14 mg; 200 mg	Cohort 6 8-24 mg; 300 mg
AUC_{tau} (ng*hr/mL)	Day 1	N	11	12	13	14	14	11
		Geo Mean	163.72	312.68	516.15	248.86	361.55	618.79
		CV%	44.9	43.8	32.6	31.1	52.6	62.4
	Day 85	N	10	11	9	8	7	2
		Geo Mean	166.94	417.39	521.66	424.24	654.28	648.84
		CV%	50.2	84.5	44.6	33.7	24.8	24.3
C_{max} (ng/mL)	Day 1	N	15	15	14	15	15	14
		Geo Mean	1.51	2.38	5.28	1.84	3.39	3.84
		CV%	45.6	51.0	34.6	39.8	58.1	68.1
	Day 85	N	11	12	11	10	11	7
		Geo Mean	0.43	1.09	1.39	0.88	1.38	2.51
		CV%	60.2	81.4	31.4	32.9	41.6	45.3
T_{max} (hr)	Day 1	N	15	15	14	15	15	14
		Median	8.00	6.00	2.53	6.00	4.00	4.00
		Min, Max	0.00, 48.00	0.00, 457.15	0.00, 30.00	0.00, 30.00	0.00, 30.00	0.00, 36.00
	Day 85	N	11	12	11	10	11	7
		Median	48.00	48.00	48.00	182.81	30.07	12.00
		Min, Max	1.00, 408.52	4.00, 604.77	6.00, 456.80	8.00, 629.07	4.00, 459.00	6.00, 48.00

Cohort 1=8mg Subutex and Sublocade 50 mg.
Cohort 2=12mg Subutex and Sublocade 100 mg.
Cohort 3=24mg Subutex and Sublocade 200 mg.
Cohort 4=8mg Subutex and Sublocade 100 mg
Cohort 5=14mg Subutex and Sublocade 200 mg
Cohort 6=8mg Subutex and Sublocade 300 mg

Source: Table 8 Summary of Clinical Pharmacology Studies

Dose Proportionality

Overall, the results show that buprenorphine plasma exposure increased slightly less than dose proportionally. A 6-fold increase in dose resulted in approximately a 5.1-fold and 5.2-fold increase in buprenorphine C_{max} and AUC_{tau}, respectively. For norbuprenorphine, plasma exposure increased with the increase in dose from 50 to 300mg, at a rate that was less than dose-proportional.

Table 34 Statistical Analysis of Dose Proportionality (Study 12-0005)

RBP-6000 Dose Range	Analyte	Parameter (unit)	Injection Number	Slope Estimate (beta1)	P-value[a]	90% CI of Slope	Critical Region
50 - 300 mg	Buprenorphine	C_{max} (ng/mL)	1	0.675	<0.001	(0.573, 0.776)	(0.875, 1.125)
			4	0.779	0.003	(0.659, 0.898)	(0.875, 1.125)
			6	0.891	0.874	(-2.542, 4.325)	(0.875, 1.125)
		AUC_{tau} (ng*hr/mL)	1	0.826	0.003	(0.731, 0.922)	(0.875, 1.125)
			4	0.823	0.023	(0.697, 0.950)	(0.875, 1.125)
	Norbuprenorphine	C_{max} (ng/mL)	1	0.645	<0.001	(0.482, 0.808)	(0.875, 1.125)
			4	0.857	0.213	(0.666, 1.047)	(0.875, 1.125)
			6	0.880	0.924	(-5.459, 7.218)	(0.875, 1.125)
		AUC_{tau} (ng*hr/mL)	1	0.711	0.003	(0.553, 0.869)	(0.875, 1.125)
			4	0.804	0.171	(0.568, 1.041)	(0.875, 1.125)

[a] Dose proportionality was to be declared if the 90% CI was contained entirely within the critical region
Subjects were dosed with Subutex SL tablets followed by SC injections of Sublocade.
Power Model: ln(PK) = ln(beta0) + beta1*ln(Dose) + C, where PK is the pharmacokinetic parameter tested, ln(beta0) is the y intercept, beta1 is the slope and C is an error term Source: Table 9 Summary of Clinical Pharmacology Studies

Comparison with SL Subutex

After 4 SC injections of Sublocade, buprenorphine average plasma concentrations (C_{avg}) for the 100mg and 200mg doses were similar to the steady-state C_{avg} concentrations observed following daily Subutex administration at 12mg and 24mg, respectively. The C_{max} following Sublocade administration was lower than the C_{max} observed following Subutex administration.

Table 35 Buprenorphine Plasma C_{max}, C_{min}, AUC Subutex SL & Sublocade

Parameter	Time point	Statistic	Cohort 1 8 mg; 50 mg	Cohort 2 12 mg; 100 mg	Cohort 3 24 mg; 200 mg	Cohort 4 8 mg; 100 mg	Cohort 5 14 mg; 200 mg	Cohort 6 Total; 300 m
Sublingual Buprenorphine (Subutex) at steady state								
Cmax,ss (ng/mL)	DAY -1 DOSE	n	15	15	15	15	15	14
		Mean	3.521	5.350	7.571	3.964	5.260	5.813
		SD	1.0407	1.7340	3.0928	1.9131	1.5595	3.4264
		%CV	29.6	32.4	40.9	48.3	29.6	58.9
		Median	3.520	4.690	6.530	3.240	5.280	5.585
		Min,Max	1.09, 5.90	3.05, 9.45	4.48, 16.30	1.44, 7.94	1.87, 7.61	1.51, 14.10
		Geometric Mean	3.341	5.112	7.084	3.551	4.996	4.920
Cmin,ss (ng/mL)	DAY -1 DOSE	n	15	15	15	15	15	14
		Mean	0.524	0.806	1.385	0.568	0.920	0.927
		SD	0.2212	0.3638	0.4806	0.2367	0.2800	0.4667
		%CV	42.2	45.1	34.7	41.7	30.4	50.4
		Median	0.473	0.821	1.230	0.473	0.925	0.907
		Min,Max	0.20, 0.83	0.27, 1.45	0.73, 2.30	0.22, 0.94	0.39, 1.34	0.40, 1.76
		Geometric Mean	0.477	0.721	1.308	0.519	0.875	0.815
AUCtau,ss (hr*ng/mL)	DAY -1 DOSE	n	15	15	15	15	15	14
		Mean	28.452	40.971	63.019	30.029	46.681	46.628
		SD	7.9415	12.6823	16.4068	12.8676	11.8403	23.2554
		%CV	27.9	31.0	26.0	42.9	25.4	49.9
		Median	28.571	37.086	60.138	28.778	48.952	43.632
		Min,Max	12.48, 42.69	20.29, 60.93	43.52, 94.00	11.17, 55.51	18.84, 64.77	14.83, 86.26
		Geometric Mean	27.273	39.039	61.142	27.484	44.875	40.830
Sublocade								
AUC 0-48 (hr*ng/mL)	DAY 1 DOSE	n	15	15	15	15	15	14
		Mean	46.855	72.453	109.029	62.395	104.868	164.511
		SD	11.5533	25.4451	30.2598	20.3054	22.6943	47.8237
		%CV	24.7	35.1	27.8	32.5	21.6	29.1
		Median	49.568	70.786	104.765	59.319	98.468	159.227
		Min,Max	24.55, 71.16	34.71, 119.57	71.48, 176.90	35.21, 108.75	70.37, 147.60	83.26, 235.95
		Geometric Mean	45.425	68.190	105.476	59.514	102.630	157.500
Cmax (INT) (ng/mL)	DAY 1 DOSE	n	15	15	15	15	15	14
		Mean	1.352	1.916	2.755	1.686	2.861	4.817
		SD	0.4641	0.6773	0.7630	0.6200	0.7136	1.4337
		%CV	34.3	35.4	27.7	36.8	24.9	29.8
		Median	1.280	1.850	2.620	1.530	2.670	4.750
		Min,Max	0.66, 2.61	0.94, 3.12	1.71, 4.61	0.87, 3.14	1.80, 4.11	2.41, 6.74
		Geometric Mean	1.287	1.801	2.665	1.588	2.781	4.604
Cmax (INT) (ng/mL)	DAY 85 DOSE	n	11	12	11	10	11	7
		Mean	2.085	2.958	4.526	2.549	4.404	9.637
		SD	1.4381	0.9624	1.3078	0.4797	0.9231	2.3409
		%CV	69.0	32.5	28.9	18.8	21.0	24.3
		Median	1.650	2.885	4.230	2.380	4.040	9.840
		Min,Max	1.10, 6.26	1.58, 5.05	2.88, 6.64	2.10, 3.43	3.02, 6.16	6.46, 12.60
		Geometric Mean	1.835	2.820	4.360	2.511	4.317	9.383
Cmin (ng/mL)	DAY 1 DOSE	n	15	15	14	14	15	13
		Mean	0.206	0.388	0.600	0.388	0.714	1.244
		SD	0.0556	0.1145	0.2623	0.1554	0.2315	0.4455
		%CV	27.0	29.5	43.7	40.1	32.4	35.8
		Median	0.207	0.381	0.497	0.345	0.626	1.130
		Min,Max	0.09, 0.30	0.23, 0.74	0.30, 1.29	0.17, 0.71	0.42, 1.12	0.66, 2.27
		Geometric Mean	0.198	0.375	0.555	0.362	0.683	1.177

$AUC_{0-\tau}$ for Subutex was not defined but is probably 0-24h Source Tables 13,15 & 17 CSR

The total exposure within the first 24h ($AUC_{0\text{-}24hr}$) observed after the first SC injection of Sublocade was similar to the corresponding steady-state $AUC_{0\text{-}24hr}$ estimates following Subutex administration on Day -1 within the same cohort. The $AUC_{24\text{-}48hr}$ following the first SC injection of Sublocade were also similar.

Table 36 Statistical Analysis of Plasma PK Parameters: Subutex versus Sublocade (Study 12-0005)

Cohort, SUBUTEX, RBP-6000	PK Parameter	Injection Number	Geometric LSMean		Geometric LSMean Ratio Test/Ref (%)
			SUBUTEX (Reference)	RBP-6000 (Test)	
Cohort 1 8 mg, 50 mg	C_{avg} (ng/mL)	1	1.14	0.36	31.5
		4	1.14	0.89	78.5
	C_{max} (ng/mL)	1	3.34	1.29	38.5
		4	3.34	1.73	51.7
Cohort 2 12 mg, 100 mg	C_{avg} (ng/mL)	1	1.63	0.66	40.3
		4	1.63	1.78	109.7
	C_{max} (ng/mL)	1	5.11	1.87	36.6
		4	5.11	2.85	55.7
Cohort 3 24 mg, 200 mg	C_{avg} (ng/mL)	1	2.55	0.91	35.6
		4	2.55	2.89	113.6
	C_{max} (ng/mL)	1	7.08	2.65	37.4
		4	7.08	4.39	62.0
Cohort 4 8 mg, 100 mg	C_{avg} (ng/mL)	1	1.15	0.59	51.9
		4	1.15	1.94	169.7
	C_{max} (ng/mL)	1	3.55	1.59	44.7
		4	3.55	2.59	72.8
Cohort 5 14 mg, 200 mg	C_{avg} (ng/mL)	1	1.87	1.08	58.0
		4	1.87	2.93	156.6
		6	1.87	3.99	213.6
	C_{max} (ng/mL)	1	5.00	2.78	55.7
		4	5.00	4.26	85.3
		6	5.00	4.77	95.4
Cohort 6 12 mg, 300 mg	C_{avg} (ng/mL)	1	1.68	1.75	104.3
		4	1.68	4.79	284.5
	C_{max} (ng/mL)	1	4.68	6.01	128.6
		4	4.68	9.51	203.3
		6	4.68	7.58	162.0

Source: Table 10 Summary of Clinical Pharmacology Studies

Table 37 Statistical Analysis of C_{min} (ng/mL) Injection No. 1 Subutex Sublingual Tablet vs. Sublocade

	Geometric LSMean		Geometric LSMean Ratio Test/Reference (%)	90% CI of Geometric Mean Ratio Test/Reference (%)
	Subutex SL (Reference)	Sublocade (Test)		
Cohort 1, 8 mg, 50 mg	0.48	0.20	41.5	(33.3, 51.7)
Cohort 2, 12 mg, 100 mg	0.72	0.36	50.5	(43.2, 59.0)
Cohort 3, 24 mg, 200 mg	1.31	0.55	41.7	(35.8, 48.5)
Cohort 4, 8 mg, 100 mg	0.52	0.37	72.2	(61.7, 84.5)
Cohort 5, 14 mg, 200 mg	0.87	0.67	76.6	(66.7, 87.9)
Cohort 6, 12 mg, 300 mg	0.71	0.70	98.8	(60.4, 161.4)

Source: Table 23 CSR

Achieving Steady state

For Subutex SL tablet, buprenorphine achieved steady state by Day -7 in all dose groups except for the 12mg dose for which steady-state was achieved on Day -6.

Steady-state for buprenorphine following multiple SC injections was achieved by Day 57 (Injection 3) in the 50mg dose group, by Day 85 (Injection 4) in the 300mg dose group, and by Day 141 (Injection 6) for the 200mg dose group. Steady-state was not achieved for the 100mg dose group but data were only available for 4 SC injections.

Table 38 Assessment of Steady-State of Sublocade (Study 12-0005)

RBP-6000	Day	N	Geometric LS Mean	% Ratio of Geometric LS Means	P-value
50 mg RBP-6000	Day 29	15	0.30	39.2	<0.001
	Day 57	12	0.68	82.8	0.200[a]
	Day 85	11	0.80	96.0	0.815
	Day 113	10	0.83		
100 mg RBP-6000	Day 29	27	0.52	39.2	<0.001
	Day 57	24	1.05	69.8	<0.001
	Day 85	22	1.35	81.3	0.033
	Day 113	19	1.66		
200 mg RBP-6000	Day 29	27	0.76	30.7	<0.001
	Day 57	24	1.53	54.8	<0.001
	Day 85	22	2.28	76.3	0.013
	Day 113	16	2.53	78.1	0.088
	Day 141	3	3.00	85.9	0.537[a]
	Day 169	3	3.49		
300 mg RBP-6000	Day 29	11	1.55	36.0	<0.001
	Day 57	10	2.92	61.5	0.007
	Day 85	7	4.23	86.0	0.472[a]
	Day 113	2	4.70	93.5	0.834
	Day 141	2	5.41	115.7	0.730
	Day 169	1	4.68		

[a] This was the first non-significant comparison at the 0.1 level; steady-state was attained.
Source: Table 11 Summary of Clinical Pharmacology Studies

Evaluator Comment on Study PKs: The PKs show that the subjects received every 28 days a substantial rapid rise in plasma buprenorphine lasting >3days followed by a steady level for the rest of the 28 days.

Safety

Of 35 that received only Subutex SL tablets, 24 subjects (68.6%) had AEs. Those for > 2 subjects were: drug withdrawal syndrome (12 subjects, 34.3%), headache (8 subjects, 22.9%), constipation (6 subjects, 17.1%) and vomiting (3 subjects, 8.6%). The majority of TEAEs were moderate in severity (18 subjects, 51.4%). 1 severe AE (limb abscess) occurred in the 24mg group. There were no study drug related AEs to, no deaths , no SAEs and no withdrawals due to AEs.

All of the 89 that received both Subutex SL tablet and Sublocade reported AEs.

The most common were: drug withdrawal syndrome (67 subjects, 75.3%), headache (45 subjects, 50.6%), constipation (41 subjects, 46.1%), musculoskeletal pain (35 subjects, 39.3%), and anxiety (34 subjects, 38.2%).

The majority of TEAEs were moderate in severity (88 subjects, 98.9%). 1 AE was considered severe (deep vein thrombosis), which occurred in Cohort 5 (200mg).

There was 1 report of suicidal ideation in Cohort 3 (200mg), which was considered moderate in severity and not related to study drug.

There were 9 SAEs reported in 6 subjects; none of which were considered to be related to study drug. There were no deaths and 8 (9.0%) subjects were withdrawn from the study due to AEs. The number of subjects with at least 1 TEAE decreased as a function of the number of injections received from Injection 1 (89.9%) through Injection 7 (33.3%; n = 3; n ≤ 2 for subsequent injections).

Injection Site reactions overall appeared to increase in frequency with increased dose but the numbers are small.

Injection site reactions were reported in 88 (98.9%) subjects. The majority of injection site reactions were of moderate severity with a total of 5 (5.6%) injection site reactions (all for injection site pain) being severe. The number of subjects with at least 1 injection site reaction remained relatively constant as a function of the number of injections. The plots of injection site pain on the VAS demonstrated that by about 10 to 15 minutes after an injection, the pain had generally resolved.

Table 39 Overall Summary of Injection Site Reactions by System Organ Class and Preferred Term: Subjects Who Received Both Subutex Sublingual Tablet and Sublocade (Population: Safety)

	SUBUTEX SL; RBP-6000						All Subjects All Cohorts (N = 89) n (%)
System Organ Class Preferred Term[a] Severity	Cohort 1 50 mg (N = 15) n (%)	Cohort 2 100 mg (N = 15) n (%)	Cohort 3 200 mg (N = 15) n (%)	Cohort 4 100 mg (N = 15) n (%)	Cohort 5 200 mg (N = 15) n (%)	Cohort 6 300 mg (N = 14) n (%)	
Overall							
Total Subjects with at Least one Injection Site Reaction	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	13 (92.9)	88 (98.9)
Mild	4 (26.7)	1 (6.7)	6 (40.0)	4 (26.7)	2 (13.3)	2 (14.3)	19 (21.3)
Moderate	10 (66.7)	14 (93.3)	9 (60.0)	9 (60.0)	11 (73.3)	11 (78.6)	64 (71.9)
Severe	1 (6.7) (Injection Site Pain)	0 (0.0)	0 (0.0)	2 (13.3) (Injection Site Pain)	2 (13.3) (Injection Site Pain)	0 (0.0)	5 (5.6)
General Disorders and Administration Site Conditions	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	13 (92.9)	88 (98.9)
Injection Site Pain	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)	13 (92.9)	88 (98.9)
Injection Site Erythema	7 (46.7)	13 (86.7)	12 (80.0)	9 (60.0)	14 (93.3)	11 (78.6)	66 (74.2)
Injection Site Swelling	1 (6.7)	9 (60.0)	6 (40.0)	5 (33.3)	9 (60.0)	10 (71.4)	40 (44.9)
Injection Site Warm	2 (13.3)	4 (26.7)	4 (26.7)	3 (20.0)	7 (46.7)	4 (28.6)	24 (27.0)
Injection Site Haematoma	4 (26.7)	8 (53.3)	6 (40.0)	6 (40.0)	10 (66.7)	6 (42.9)	40 (44.9)
Injection Site Pruritus	6 (40.0)	11 (73.3)	7 (46.7)	6 (40.0)	11 (73.3)	6 (42.9)	47 (52.8)

N = total number of subjects exposed per cohort; n = number of subjects in a subset in a given category; Source: Table 40
Subjects were dosed with Subutex SL tablet followed by SC injections of Sublocade containing buprenorphine.

In contrast to the above Table the following Table was extracted from a listing Table 6 of Overall Treatment-Emergent Adverse Events by System Organ Class and Preferred Term that Occurred in 2 or more Subjects: Subjects Who Received Both SUBUTEX Sublingual Tablet and RBP-6000 (Population: Safety)

Table 40 Injection Site reactions extracted from Table 6 of Overall TEAs ≥ 2 subjects

	SUBUTEX SL; RBP-6000						All Subjects All Cohorts (N=89) n (%)
System Organ Class Preferred Term[a]	Cohort 1 50 mg (N=15) n (%)	Cohort 2 100 mg (N=15) n (%)	Cohort 3 200 mg (N=15) n (%)	Cohort 4 100 mg (N=15) n (%)	Cohort 5 200 mg (N=15) n (%)	Cohort 6 300 mg (N=14) n (%)	
Injection Site Dermatitis	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)	2 (2.2)
Injection Site Pruritus	1 (6.7)	2 (13.3)	2 (13.3)	0 (0.0)	0 (0.0)	3 (21.4)	8 (9.0)
Injection Site Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (7.1)	2 (2.2)
Injection Site Pain	0 (0.0)	0 (0.0)	1 (6.7)	1 (6.7)	0 (0.0)	1 (7.1)	3 (3.4)

N = total number of subjects exposed per cohort; n = number of subjects in a subset in a given category;
Subjects were dosed with Subutex SL tablet followed by SC injections of Sublocade containing buprenorphine.
A treatment-emergent adverse event was any event not present prior to exposure to study drug or any event already present that worsened in either intensity or frequency following exposure to study drug.
'n' is the number of subjects with at least 1 treatment-emergent adverse event in a given category. Source: Table 36

21.1.1.4. Study RB-US-13-0001

The Plasma Concentration Summary[50] is some 80 pages. There was no other summary.

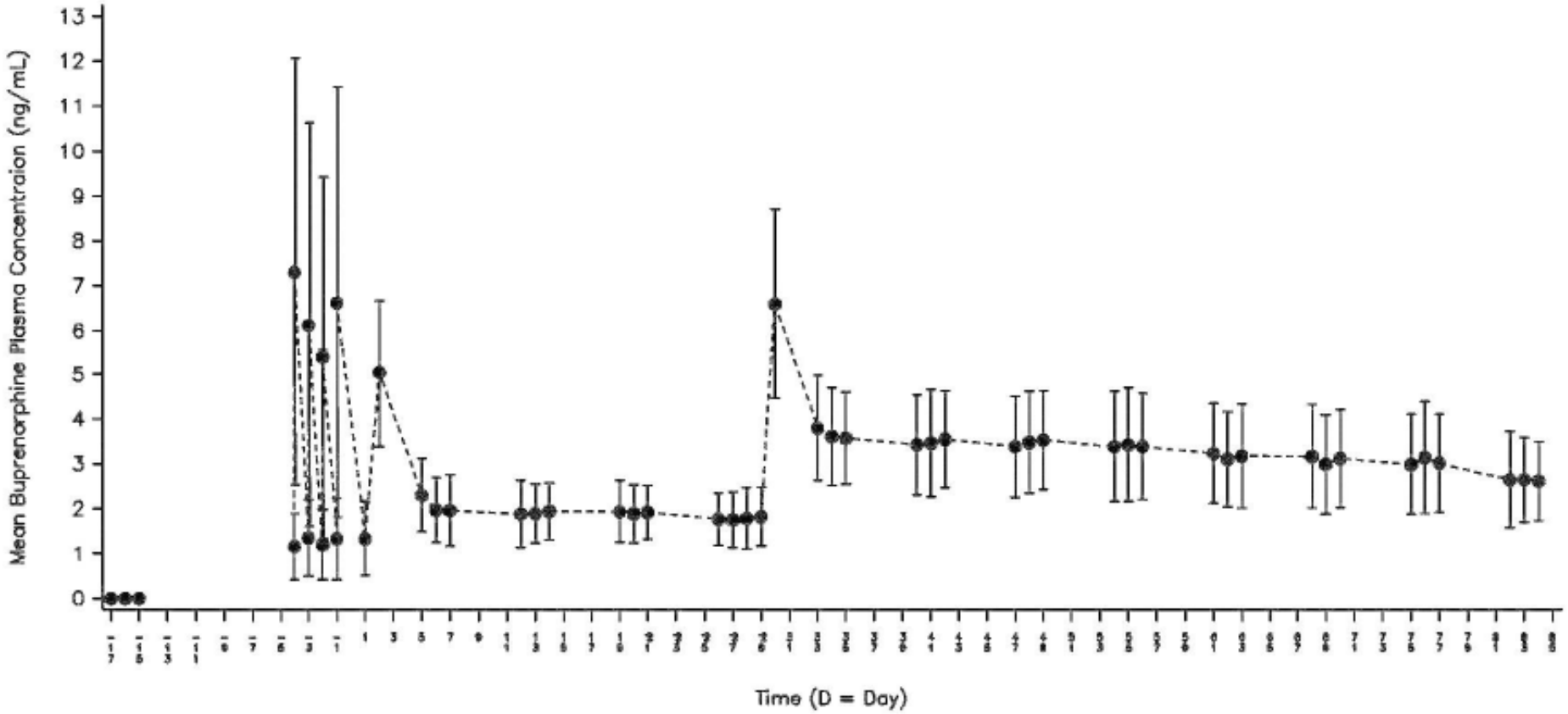
Buprenorphine plasma concentrations from the study were analysed using a population PK modelling approach (in combined analyses M04 and m05 see 21.1.3.4 and 21.1.3.5).

21.1.1.5. Study RB-US-13-0002

A US single centre multiple-dose study of blockade of subjective opioid effects, plasma levels, and safety of subcutaneous injections of depot buprenorphine in subjects with opioid use disorder. See 11.2.2

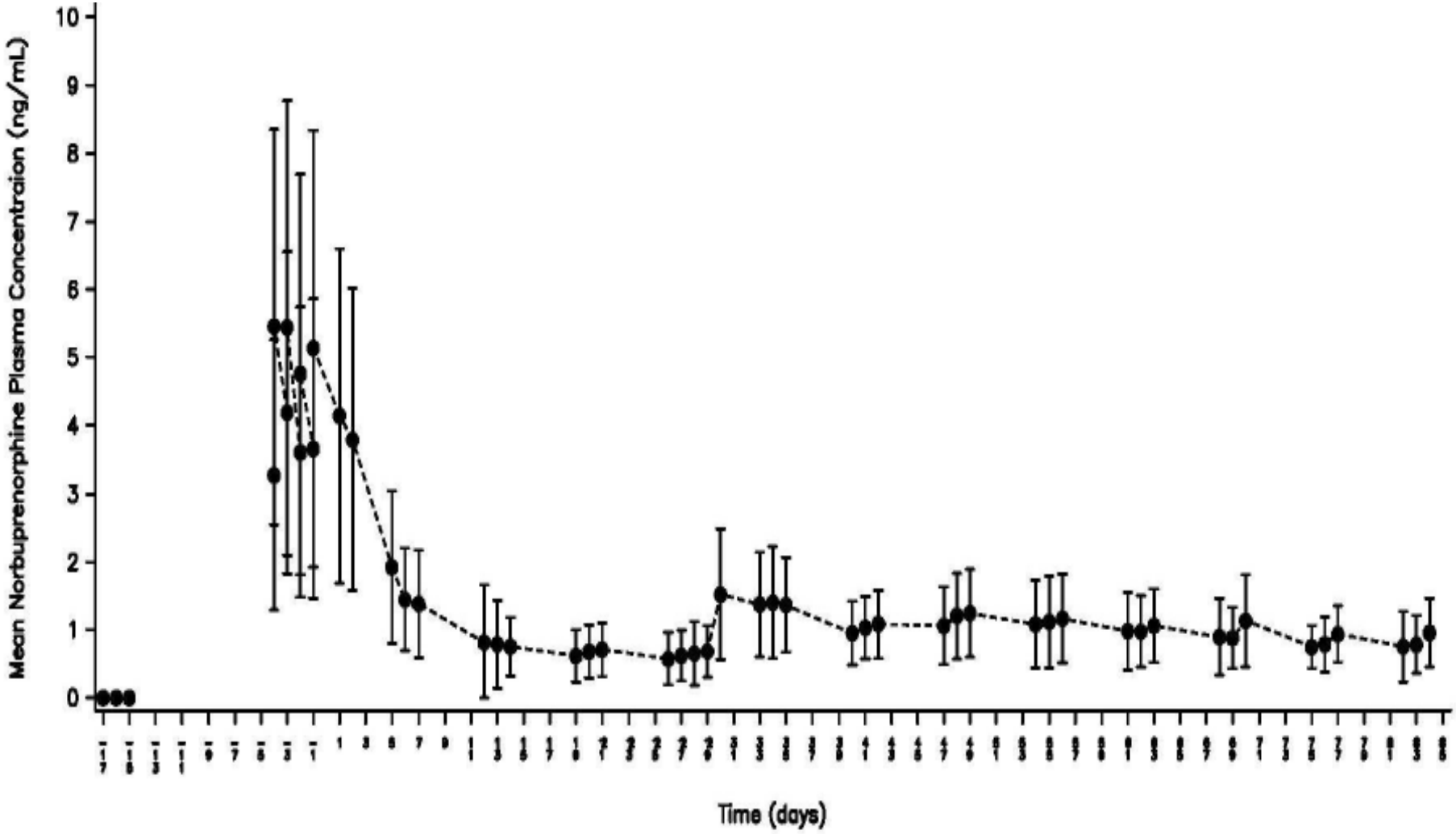
[50] Table S14.2.22 Page 592

Figure 24 Mean (± SD) Buprenorphine Plasma Concentrations vs. Time on a Linear Scale (Pop: ITT)



Source: Figure 1

Figure 25 Mean (± SD) Norbuprenorphine Plasma Concentrations vs.Time on a Linear Scale (Pop: ITT)



Source: Figure 3

Table 41 Buprenorphine Plasma Concentrations Summary-Sublocade (Population: ITT)

Analyte (unit)	Day	Time (hr)	Statistic	RBP-6000 300 mg
Buprenorphine (ng/mL)	Day 1	0	N	37
			Mean (SD)	1.330 (0.8245)
			%CV	62.0
			Median	1.240
			Min, Max	0.154, 3.72
			Geometric Mean	1.073
	Day 2	24	N	38
			Mean (SD)	5.034 (1.6401)
			%CV	32.6
			Median	4.520
			Min, Max	2.89, 11.3
			Geometric Mean	4.815
	Day 29	0	N	30
			Mean (SD)	1.823 (0.6524)
			%CV	35.8
			Median	1.620
			Min, Max	0.975, 3.93
			Geometric Mean	1.725
	Day 30	24	N	30
			Mean (SD)	6.591 (2.1188)
			%CV	32.1
			Median	6.465
			Min, Max	3.69, 13.4
			Geometric Mean	6.289

Subjects received 0mg (placebo), 6 mg, or 18mg hydromorphone on Days 4-7, 11-14, 18-21, 25-28, 32-35, 39-42, 46-49, 53-56, 60-63, 67-70, 74-77, and 81-84. Source: Table 9
Subjects received 8mg to 24mg sublingual Suboxone sublingual film on Day -14 through Day -1.
Subjects received 300mg Sublocade on Day 1 and Day 29 . N = number of subjects

Table 42 Norbuprenorphine Plasma Concentrations Summary-Sublocade (ITT)

Analyte (unit)	Day	Time (hr)	Statistic	RBP-6000 300 mg
Norbuprenorphine (ng/mL)	Day 1	0	N	37
			Mean (SD)	4.142 (2.4530)
			%CV	59.2
			Median	3.320
			Min, Max	0.684, 9.72
			Geometric Mean	3.404
	Day 2	24	N	38
			Mean (SD)	3.802 (2.2160)
			%CV	58.3
			Median	3.220
			Min, Max	1.02, 10.5
			Geometric Mean	3.224
	Day 29	0	N	30
			Mean (SD)	0.686 (0.3812)
			%CV	55.6
			Median	0.605
			Min, Max	0.23, 1.69
			Geometric Mean	0.595
	Day 30	24	N	30
			Mean (SD)	1.522 (0.9635)
			%CV	63.3
			Median	1.190
			Min, Max	0.522, 4.81
			Geometric Mean	1.314

Subjects received 0mg (placebo), 6 mg, or 18mg hydromorphone on Days 4-7, 11-14, 18-21, 25-28, 32-35, 39-42, 46-49, 53-56, 60-63, 67-70, 74-77, and 81-84. Source: Table 9
Subjects received 8mg to 24mg sublingual Suboxone sublingual film on Day -14 through Day -1.
Subjects received 300mg Sublocade on Day 1 and Day 29 . N = number of subjects

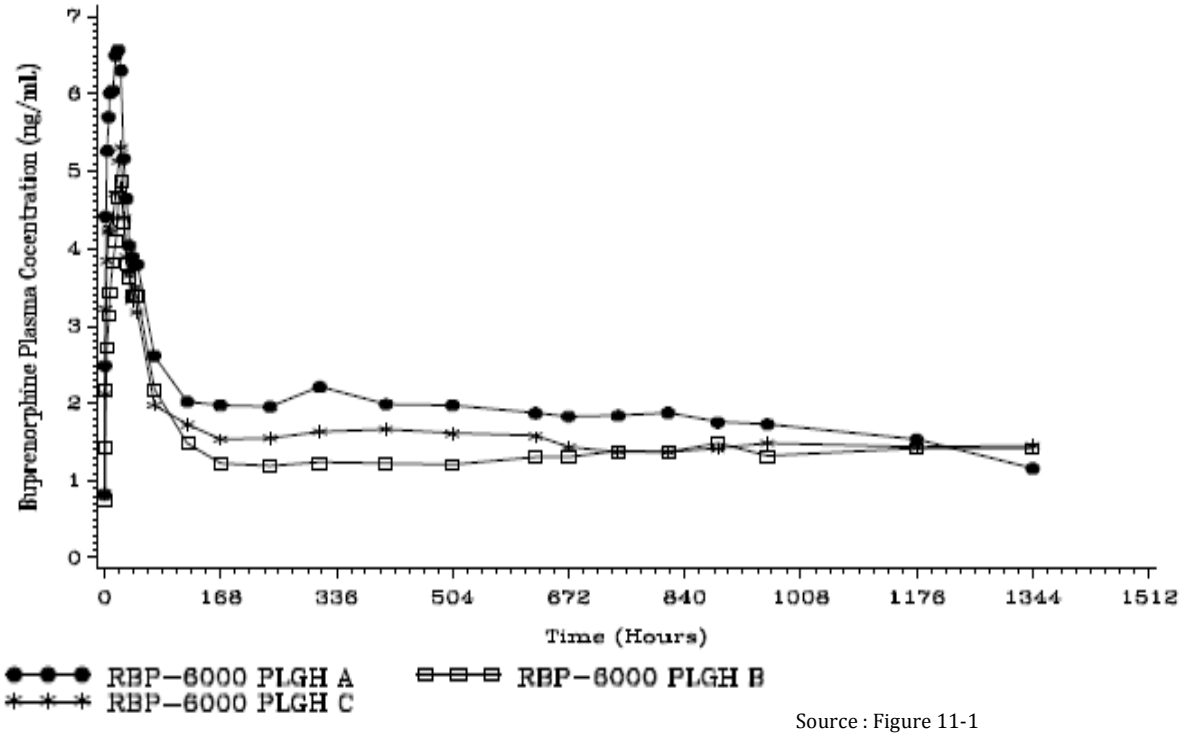
21.1.1.6. Study RB-US-13-0006

A single-centre, randomized, open-label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of depot buprenorphine using poly (dl-lactide-co-glycolide) polymer of two different molecular weights (low and high molecular weights as test treatments) in comparison to intermediate molecular weight (reference treatment) in treatment-seeking subjects with opioid use disorder.

The study was conducted from 22 September 2015 to 10 February 2016 in the US on 47 subjects.

After a single dose of Sublocade, mean concentrations of buprenorphine and norbuprenorphine increased over approximately 48h and then decreased over 48h after peak concentrations. Mean concentrations of buprenorphine and norbuprenorphine remained relatively constant from approximately 7 days post dose to the last sample 56 days post dose. While buprenorphine concentrations of Sublocade PLGH C (14 kDa PLGH polymer) were consistently lower than the low molecular weight treatment (Sublocade PLGH A, 9 kDa PLGH polymer) and higher than the high molecular weight treatment (Sublocade PLGH B, 17 kDa PLGH polymer), all 3 treatments displayed a similar concentration-time profile.

Figure 26 Mean Plasma Concentrations of Buprenorphine (Sublocade Phase) (PK Set)



Source : Figure 11-1

Values below the lower limit of quantification were treated as zero for calculation of summary statistics.
Lower limit of quantitation was 0.05ng/mL for buprenorphine.
Sublocade PLGH A: Sublocade 300mg buprenorphine formulated with 9 kDa PLGH polymer (test treatment), subcutaneous (SC) injection
Sublocade PLGH B: Sublocade 300mg buprenorphine formulated with 17 kDa PLGH polymer (test treatment), SC injection
Sublocade PLGH C: Sublocade 300mg buprenorphine formulated with 14 kDa PLGH polymer (reference treatment), SC injection

21.1.2. Synopses of pharmacodynamics studies

21.1.2.1. PD/PK Study RB-US-13-0002 multiple parameters

This complex study (see also 11.2.2) set out to show that after Sublocade was given hydromorphone, previously shown to be subject desirable in the absence of buprenorphine, was now no more desirable that saline. This was demonstrated with visual analog scales for “Drug Liking" "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High".

Secondary Objectives included:

- To evaluate the correlation between the opioid blockade subjective effects (VAS of "Any Drug Effect", "Good Drug Effect", "Bad Drug Effect", "Drug Liking", "Sedation", and "High") and the reinforcing effects of hydromorphone and simulated mu opioid receptor occupancy (using the maximal effect [E_{max}] model).
- To determine the relationship between plasma concentration and predicted mu opioid receptor occupancy of buprenorphine and both the blockade of the subjective effects of hydromorphone post injection of buprenorphine 300mg (Sublocade).

Predicted mu Opioid Receptor Occupancy (μ-opioid receptor occupancy)

A population PK/PD model was previously developed to model the relationship between buprenorphine plasma concentrations and brain μ-opioid receptor occupancy . [51] The structural

[51] Page 65 CSR

PK/PD model was used to predict μ-opioid receptor occupancy in the current study based on [52]the observed individual buprenorphine plasma concentrations.

The analysis of the Predicted mu Opioid Receptor Occupancy data was not available when the SAP and TFLs for this study were finalised. The data presented in Section 11.2.4 was provided by INDV after the TFLs for this study were finalised.[53]

Individual predictions of μ-opioid receptor occupancy *(were)* generated using a previously developed PK/PD model.[54]

Comment: The published study articles from 2007 and 2003 on which the PK/PD model were based were in the submission as was the online version of the article by Nasser 2014 that described the PK/PD model.

Statistical analysis

The study was performed from 19 November 2013 – 29 July 2014, publication of the 'previously developed' model was September 2014.

The submission as well as the above publications contains INDV-6000-M02 Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy in the brain which also looked at the published study articles from 2007 and 2003. However INDV-6000-M02 report was dated 19 January 2017. (See 21.1.3.1).

Relationship Between Plasma Concentration and Predicted Mu Opioid Receptor Occupancy

[52] Page 65 CSR
[53] CSR page 72
[54] Nasser et al(2014). A Population Pharmacokinetic and Pharmacodynamic Modelling Approach to Support the Clinical Development of RBP-6000, A New, Subcutaneously Injectable, Long-Acting, Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Dependence. Clin. Pharmacokinet 53(9): 813-824. September 2014

Table 43 Effect on Drug Liking and Reinforcing Breakpoint Values Following 18mg and 6mg Hydromorphone Challenges (ITT)

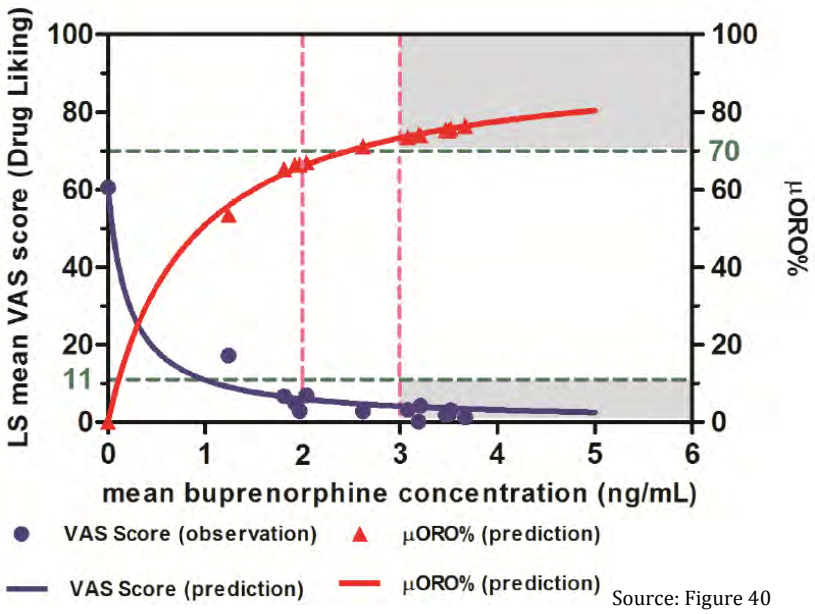
Phase	Week	Buprenorphine Concentration (ng/mL)		Predicted μORO (%)		VAS Scores (Drug Liking) – Change from Placebo, LS Mean (95% CI)		Reinforcing Effects (Breakpoint) – Change from Placebo, LSMean of Log_{10} Transformation (95% CI)	
		18 mg	6 mg	18 mg	6 mg	18 mg vs. placebo	6 mg vs. placebo	18 mg vs. placebo	6 mg vs. placebo
Baseline	–1	0.00	0.00	0.00	0.00	60.61 (52.32, 68.90)	45.36 (37.16, 53.56)	0.89 (0.64, 1.17)	0.93 (0.67, 1.18)
Sublingual	0	1.24	1.32	53.63	54.64	17.17 (10.43, 23.90)	8.20 (1.47, 14.94)	0.84 (0.48, 1.20)	0.58 (0.19, 0.96)
RBP-6000	1	2.04	2.16	67.09	67.88	6.93 (3.24, 10.61)	3.66 (–0.03, 7.34)	0.41 (0.15, 0.67)	0.27 (-0.001, 0.53)
	2	1.97	1.87	66.49	66.06	2.90 (0.33, 5.47)	0.59 (–1.98, 3.15)	0.63 (0.28, 0.99)	0.32 (-0.05, 0.70)
	3	1.92	1.88	66.44	66.00	4.93 (1.02, 8.84)	0.86 (–3.05, 4.78)	0.40 (0.13, 0.66)	0.41 (0.14, 0.69)
	4	1.81	1.78	65.35	65.11	6.68 (1.94, 11.42)	3.32 (–1.43, 8.06)	0.82 (0.53, 1.11)	0.60 (0.31, 0.90)
	5	3.67	3.65	76.42	76.29	1.21 (–0.43, 2.85)	0.74 (–0.94, 2.42)	0.16 (-0.24, 0.56)	-0.04 (-0.47, 0.39)
	6	3.52	3.53	75.69	75.70	3.16 (–0.83, 7.15)	0.35 (–3.62, 4.32)	0.43 (-0.03, 0.88)	0.05 (-0.41, 0.51)
	7	3.47	3.50	75.43	75.64	1.88 (–0.11, 3.87)	–0.15 (–2.16, 1.86)	0.38 (0.043, 0.72)	0.31 (-0.004, 0.63)
	8	3.50	3.37	75.18	74.79	1.93 (–1.79, 5.66)	–1.05 (–4.77, 2.68)	0.37 (-0.05, 0.79)	0.23 (-0.16, 0.61)
	9	3.21	3.12	74.04	73.97	4.17 (–1.84, 10.17)	–0.12 (–6.20, 5.96)	0.48 (-0.14, 1.09)	0.04 (-0.61, 0.69)
	10	3.19	3.04	74.18	73.08	0.13 (–0.50, 0.76)	–0.09 (–0.69, 0.51)	0.20 (-0.22, 0.61)	0.01 (-0.41, 0.44)
	11	3.08	2.99	73.51	73.05	3.24 (–0.35, 6.83)	–0.32 (–3.97, 3.34)	0.32 (-0.29, 0.94)	-0.09 (-0.73, 0.55)
	12	2.62	2.65	71.30	71.31	2.78 (0.61, 4.96)	–0.03 (–2.19, 2.12)	0.69 (0.22, 1.16)	0.26 (-0.25, 0.77)

LS = least squares; μ-opioid receptor occupancy = opioid receptor occupancy; Baseline (Week -1) was defined as Day -17, Day -16, and Day –15. Week 0 (Suboxone sublingual phase) was defined as Day -3, Day -2, and Day -1. Source: Table 13

Following administration of Suboxone during Week 0, increases were observed in buprenorphine plasma concentrations and predicted μ-opioid receptor occupancy with corresponding decreases in mean change from placebo "Drug Liking" VAS scores and log_{10}-transformed mean hydromorphone breakpoint values. The LSMeans change from placebo "Drug

Liking" VAS score for the first week of Sublocade treatment (Injection 1) at the highest hydromorphone dose of 18mg was approximately 7.
After the second Sublocade injection, the LS mean value was further reduced to below 6 with the corresponding 95% CI including 0. Therefore, full blockade is claimed from the first week post first injection through Week 12. Similar effects were observed for the additional VAS scales.

Figure 27 Correlation Between Mean Buprenorphine Concentration and Clinical Effect



Source: Figure 40

The SAP 7.8.4 Predicted Mu Opioid Receptor Occupancy and Opioid Blockade Subjective Effects

It was originally planned in the protocol that a saturable E_{max} model with an additive error model would be used to predict mu opioid receptor occupancy (μ-opioid receptor occupancy) from buprenorphine plasma concentration levels.
The E_{max} model is currently under development. Upon finalization of the model, an addendum to the SAP will be written, and the analysis to be performed will be done at that time. Under the current SAP, no summary or analysis will be done using this model.
Reference for the model was given. The CSR referred to the publication based on the study which under discussion had "The μ-opioid receptor occupancy was predicted using the observed buprenorphine concentrations and the previously published model from Nasser et al."[55]
Naser et al do support the CSR for the use of A saturable E_{max} model was used for predicting the μ-opioid receptor occupancy.

$$\text{μ-opioid receptor occupancy} = \frac{E_{max} \cdot Cp}{EC_{50}+Cp}$$

Were E_{max} is the maximal μ-opioid receptor occupancy, Cp is the buprenorphine plasma concentration, and EC_{50} is the buprenorphine plasma concentration necessary for achieving 50% of the maximal μ-opioid receptor occupancy. The estimated value for E_{max} (standard error) was 91.40 (3.94%) and the estimated value for EC_{50} (standard error) was 0.67 (0.19%) ng/mL.

[55] Nasser , et al. A population pharmacokinetics and pharmacodynamic modelling approach to support the clinical development ofRBP-6000, a new, subcutaneously injectable, long-acting, sustained-release formulation of buprenorphine, for the treatment of opioid dependence. Clin Pharmacokinet. 2014;53: 813-824. Also in submission as Study INDV-6000-M02

However the source of support was not found for using An E_{max} inhibitory model was used for describing the relationship between Drug Liking VAS scores and buprenorphine plasma concentrations after 18mg hydromorphone challenge.

21.1.2.2. PD study RB-US-11-0020 multiple assessments

See also 21.1.1.2 for more information.

Pharmacodynamic assessments included the C-SSRS, COWS assessment; the Opioid Craving VAS; urine toxicology screen, and the timeline follow back (TLFB) interview for opiate drug use.

Columbia Suicide Severity Rating Scale

At Screening, 9 subjects (18.8%) responded positively for suicidal ideations at some point in their lives, none within the previous 6 months.

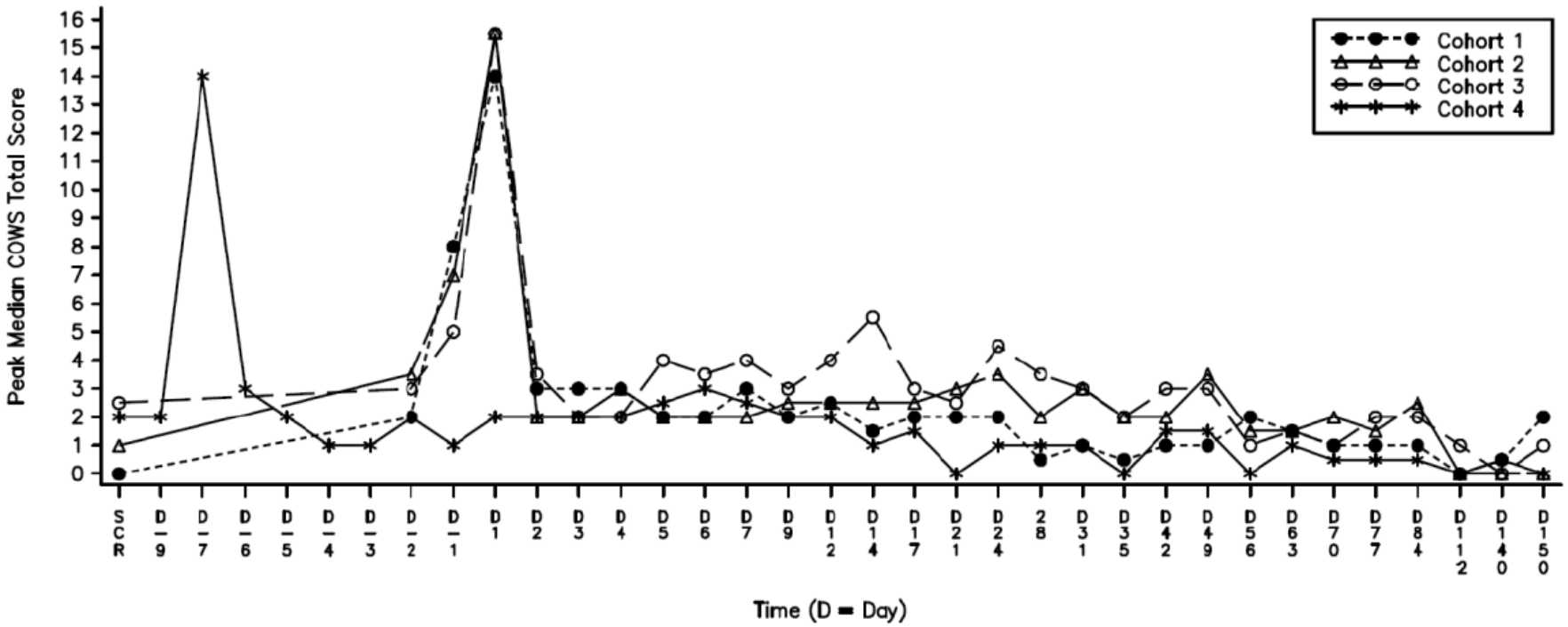
During the study, 3 subjects responded positively on the C-SSRS

Timeline Follow back Interview Data

The number of subjects reporting the use of opioids declined after administration of Sublocade (7 of 48 subjects; 14.6% on Day 25) and rose over time thereafter (14 of 48 subjects; 29.2% on Day 150). Generally, the number of subjects reporting the use of opioids was slightly lower than the number of subjects testing positive for opiates and oxycodone on the urine drug screen.

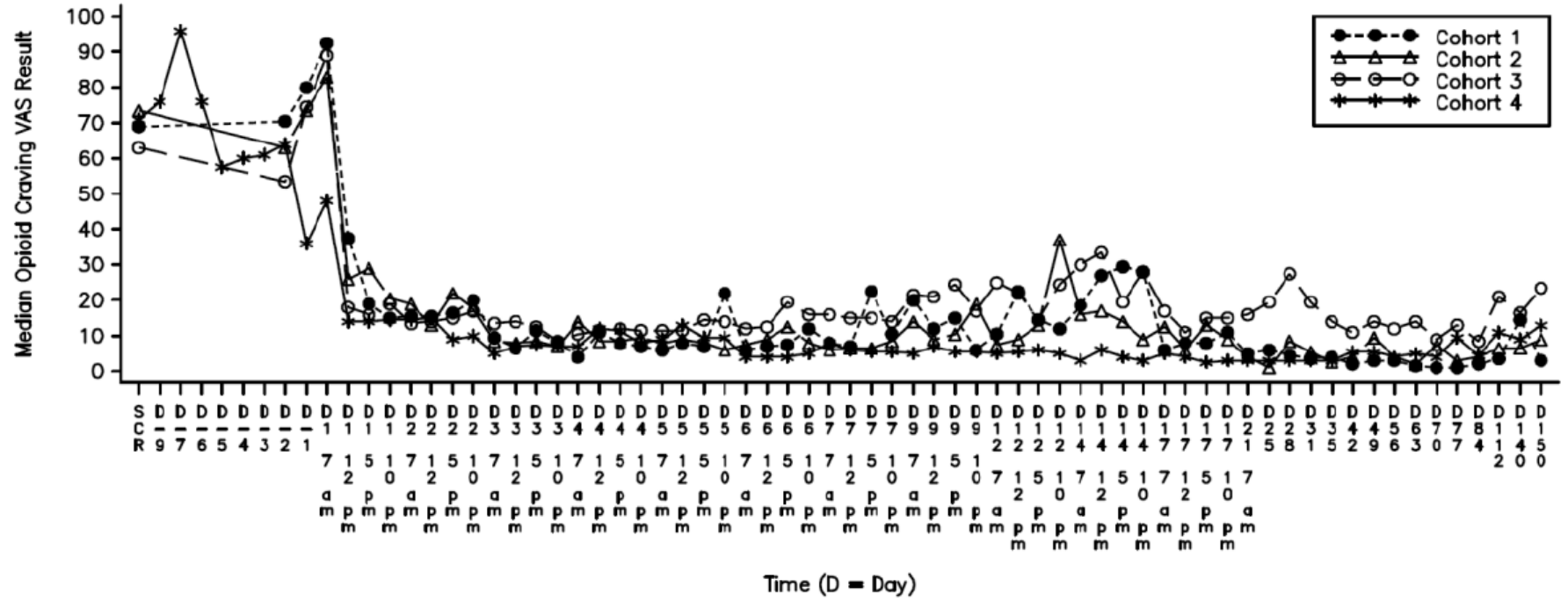
Clinical Opiate Withdrawal Scale

Figure 28 Plot of Median Clinical Opiate Withdrawal Scale Total Score vs.Time (All Cohorts)



Cohort 1 = a single SC injection of Sublocade containing 50mg buprenorphine. Source: Figure 38
Cohort 2 = a single SC injection of Sublocade containing 100mg buprenorphine.
Cohort 3 = a single SC injection of Sublocade containing 200mg buprenorphine.
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day -7 and 12mg on Days -6 through -1.

Figure 29 Plot of Median Clinical Opioid Craving Visual Analog Scale vs.Time (All Cohorts)



Cohort 1 = a single SC injection of Sublocade containing 50mg buprenorphine. Source: Figure 40
Cohort 2 = a single SC injection of Sublocade containing 100mg buprenorphine.
Cohort 3 = a single SC injection of Sublocade containing 200mg buprenorphine.
Cohort 4 = QD dosing with Suboxone SL, 8mg (two 4mg doses approximately 3 hours apart) on Day -7 and 12mg on Days -6 through -1.

21.1.2.3. PD Study RB-US-12-0005 PET substudy

See also 21.1.1.3 for more information.

Positron Emission Tomography Sub-study

The PET imaging sub-study evaluated the mu-opioid receptor availability of subjects who were at steady-state after receiving Sublocade containing 200mg or 300mg buprenorphine.[56]

Initiated in response to US Food and Drug Administration (FDA) feedback.

Subjects who received Sublocade containing either 200mg or 300mg buprenorphine and reached Day 112 (and had received all 4 or 6 planned SC injections, respectively) had the option to participate in a PET imaging sub-study and were required to sign a separate informed consent form prior to participation. It was anticipated that subjects could have needed up to 12 SC injections to complete the PET imaging study, depending on the availability of the PET scan facilities. Subjects were to remain on the same dose of Sublocade (200mg or 300 mg) administered in the main study, which was to be administered every 28 days, until they completed a MRI scan, a PET scan and PK sampling at Week 1 and Week 4 after the last injection. The PK sampling schedule for subjects in the PET imaging sub-study was the same as that for subjects in Cohort 6 in the main study up to Injection 4. Only limited PK samples were collected after Injection 5.

Positron emission tomography data were obtained in 2 subjects dosed under steady-state conditions. One subject received a total of 6 SC injections of 300mg and the other subject received a total of 12 SC injections of 200mg. The subject who received 200mg showed 79% and 75% whole-brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively. The subject who received 300mg showed 92% and 81% whole brain mu-opioid receptor occupancy on the 7th and 28th days post-injection, respectively.[57]

Sponsor comment: These high mu-opioid receptor occupancy values are within the range of those observed following the administration of multiple daily doses of SL buprenorphine (16mg or 32mg) in previously published studies (Greenwald 2003; Greenwald 2007). However, contrarily to daily SL buprenorphine administration, the high mu-opioid receptor occupancy values were maintained over the dosing interval of 28 days. For daily doses of 16mg SL buprenorphine, whole-brain mu-opioid receptor occupancy was reported to be 70% at 4 hours post-dose, but only 46% at 28 hours post-dose.

Secondary endpoints

The COWS total scores, SOWS total scores, VAS scores, CGI-S scale, CGI-I scores showed a reduction from baseline for all treatment cohorts following Subutex SL tablet and Sublocade administration.

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[56] CSR page 55

[57] Subject 001760 (cohort 5, 14 mg of Subutex) receiving 200 mg of RBP-6000 in the PET scan sub-study demonstrated μ-opioid receptor occupancy compared to the average control of 79.4% (whole brain), 72.8% (anterior cingulate cortex), 71.7% (nucleus accumbens), 74.7% (amygdala) on Day 7 following the 12th SC injection of RBP-6000. The same subject's receptor occupancy remained at similar levels on Day 28 following the 12th SC injection of RBP-6000 with 75.1% (whole brain), 69.0% (anterior cingulate cortex), 66.7% (nucleus accumbens), and 67.6% (amygdala).
Subject 001844 (cohort 6, 12 mg of Subutex) receiving 300 mg of RBP-6000 in the PET scan sub-study showed μ-opioid receptor occupancy compared to the average control of 92.4% (whole brain), 87.6% (anterior cingulate), 88.9% (nucleus accumbens), 92.6% (amygdala) on Day 7 following the 6th SC injection of RBP- 6000. The same subject's receptor occupancy remained at 81.4% (whole brain), 77.4% (anterior cingulate cortex), 80.1% (nucleus accumbens), and 79.7% (amygdala) on Day 28 following the 6th SC injection of RBP- 6000. Appendix 16.1.13.3

There were dose and time dependent reductions in self-reported opioid drug use.

The median percentage of urine samples that were negative for opioids over the entire course of the study was 28.6% for Cohort 1 (50mg), 19.1% for Cohort 2 (100mg), 59.4% for Cohort 3 (200mg), 55.6% for Cohort 4 (100mg), 32.1% for Cohort 5 (200mg), and 66.7% for Cohort 6 (300mg).

21.1.3. Synopses of population pharmacokinetics analyses

21.1.3.1. Study INDV-6000-M02 PopPKs and μ-opioid receptor occupancy

Modelling of the relationship between buprenorphine plasma concentrations and μ-opioid receptor occupancy in the brain.

The primary goal of this report was to characterize the relationship between buprenorphine plasma concentration and μ-opioid receptor occupancy (μ-opioid receptor occupancy) in the brain and develop a population PK μ-opioid receptor occupancy model.

Higher medication doses are hypothesized to decrease μ-opioid receptor availability (or 'binding potential') and provide agonist replacement that minimizes withdrawal symptoms, promotes clinic attendance, and prevents heroin reinforcement, euphoria, and side effects (Greenwald 2003).

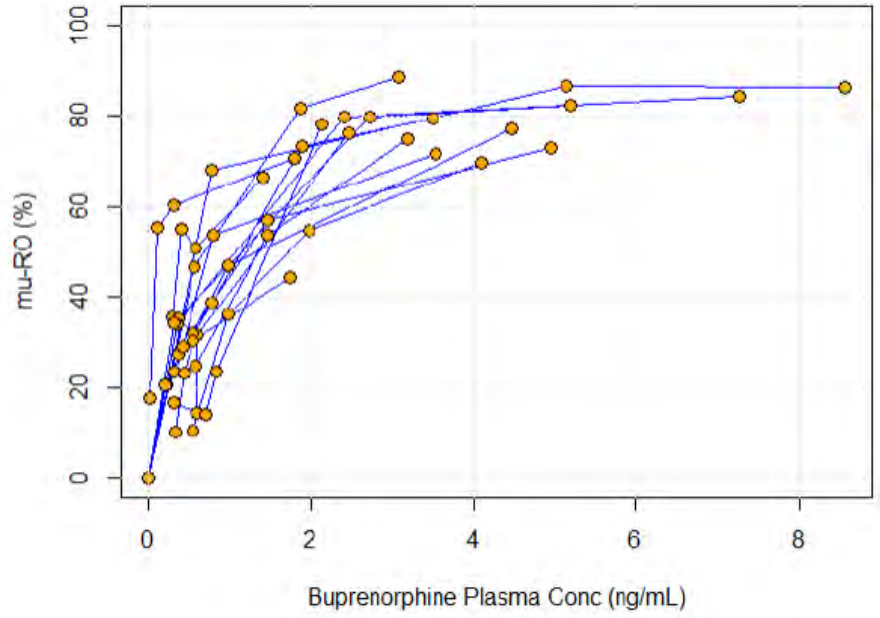
Data Sources

- Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK. Effects of buprenorphine maintenance dose on μ-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology. 2003;28(11):2000-9
  Five heroin-dependent subjects were included in the trial. Each subject was successively maintained on 32, 16, 2, and 0mg daily buprenorphine sublingual tablet doses. Four PET scans with [^{11}C]-carfentanil were conducted on each subject at 4h after the last of 12 daily doses of buprenorphine (32mg, 16mg, 2mg, or placebo). On the 9th day of each maintenance period, blood samples were collected for the measurement of buprenorphine and norbuprenorphine plasma concentrations.
- Greenwald MK, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, Koeppe R, Zubieta JK. Buprenorphine duration of action: μ-opioid receptor availability and pharmacokinetic and behavioural indices. Biol Psychiatry. 2007;61(1):101-10
  Ten heroin-dependent subjects were included in the trial. They were initially maintained for ≥ 2 weeks on 16mg/day buprenorphine given as sublingual tablets. Plasma buprenorphine concentrations, opioid withdrawal symptoms and 4 hydromorphone challenges (24mg) or 4 PET brain scans with [^{11}C]-carfentanil were conducted at 4, 28, 52 and 76h after the last daily buprenorphine dose. Authors' Conclusion: Together with our previous findings, it appears that mu-opioid receptor availability predicts changes in pharmacokinetic and pharmacodynamic measures and that about 50%-60% BUP occupancy is required/or adequate withdrawal symptom suppression (in the absence of other opioids) and hydromorphone blockade.

From both trials, whole-brain imaging results were used to calculate μ-opioid receptor availability.

The 15 subjects had a total of 59 PK/ μ-opioid receptor occupancy data points.

Figure 30 Individual μ-opioid receptor occupancy measurements (mu-RO) vs. the buprenorphine plasma concentrations



Source: Figure 1

Model

The model was based on the assumption that a direct proportionality between buprenorphine plasma concentration and μ-opioid receptor occupancy has been established without equilibration delay. The model used was defined by the equation:

$$\text{μ-opioid receptor occupancy} = \frac{E_{max} \cdot Cp}{EC_{50}+Cp}$$

Were E_{max} is the maximal μ-opioid receptor occupancy, Cp is the buprenorphine plasma concentration, and EC_{50} is the buprenorphine plasma concentration necessary for achieving 50% of the maximal μ-opioid receptor occupancy.

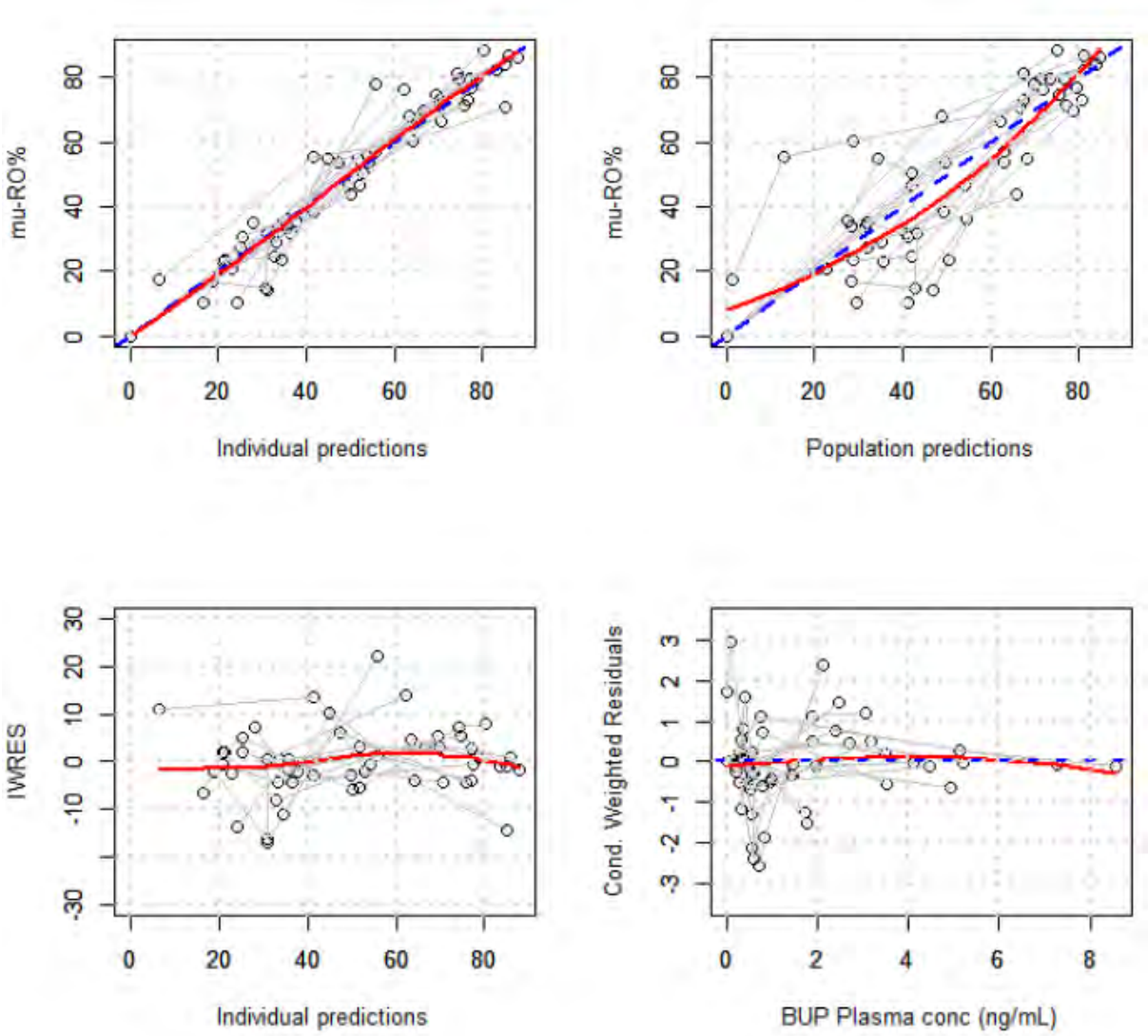
An additive error model option was retained in the final model.

Table 44 Final population parameter estimates

	Emax	EC50	IIV-EC50	Add Err
Parameter estimates	91.40	0.67	0.47	62.50
Standard errors	3.90	0.19	0.25	22.20
RSE(%)	4.30	28.40	54.30	35.50
95% Conf. Interval	83.76-99.04	0.30-1.04		

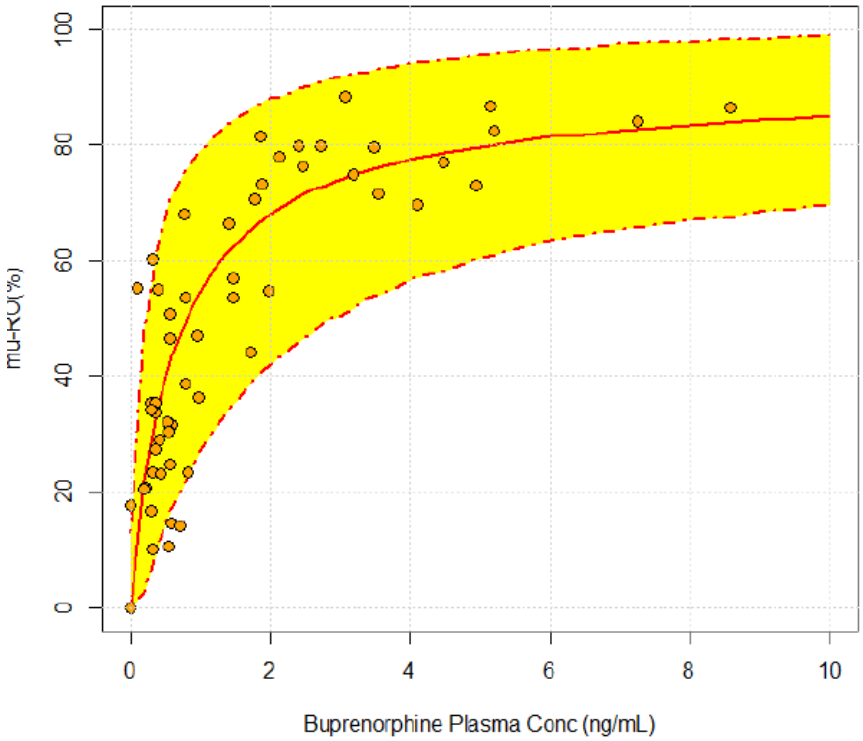
Variance estimates are shown for additive error (Add Err) and EC_{50} inter-individual variability (IIV); RSE: relative standard error; the data available did not permit to estimate the IIV on E_{max}. Source: Table 2

Figure 31 Goodness-of-fit diagnostic plots for the final model



Mu-RO: μ-opioid receptor occupancy; BUP: buprenorphine; IWRES: Individual weighted residuals. Cond. Weighted Residuals: conditional weighted residuals Source: Figure 2

Figure 32 Visual Predictive Check plots for the PK /μ-opioid receptor occupancy model.



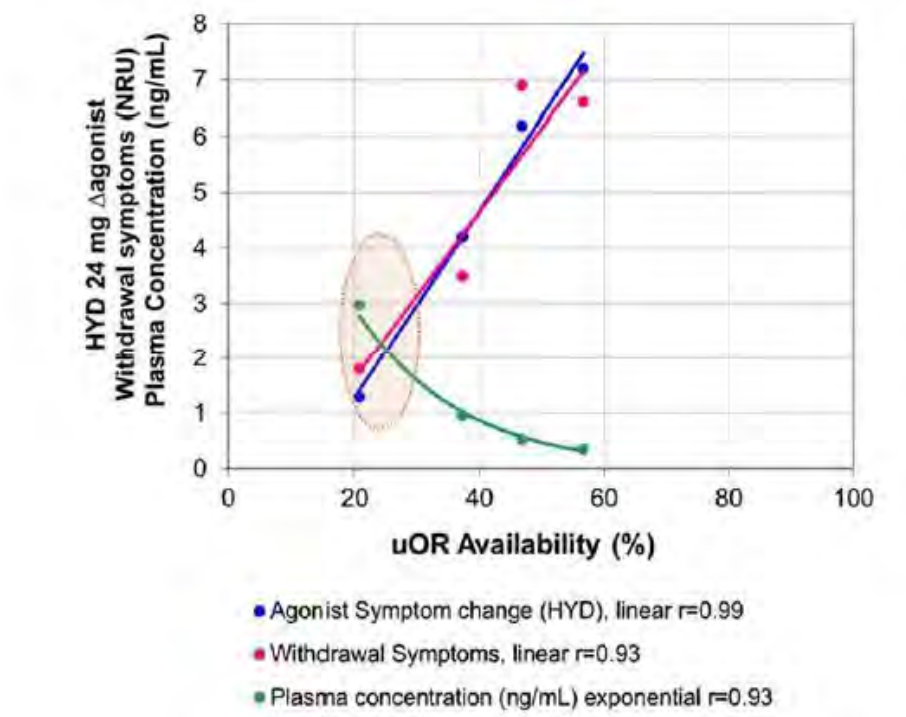
The red lines represent the 5th, 50th, and 95th percentiles of the simulated data, the shaded yellow area represents the 90% prediction intervals. The orange circles are the observed data. Source: Figure 3

Table 45 Bootstrap analysis results based on 500 re-sampled datasets

	Emax	EC50	IIV-EC50	Add Err
Mean	91.41	0.68	0.46	59.88
Percentiles				
0.05%	78.61	0.09	-0.36	-9.91
0.50%	81.40	0.22	-0.18	5.82
2.50%	83.80	0.33	-0.02	19.37
5%	85.02	0.38	0.05	26.30
95%	97.85	0.96	0.88	98.69
97.50%	99.08	1.02	0.96	105.62
99.50%	101.48	1.12	1.11	119.17
99.95%	104.26	1.25	1.29	134.90
Standard error	3.90	0.18	0.25	22.00
Median	91.60	0.67	0.43	57.95
RSE(%)	4.26	26.35	57.73	37.97

RSE: relative standard error Source: Table 3

Figure 33 Observed and Model Predicted Changes in Agonist Effect Following Administration of 24mg Hydromorphone, Observed and Model Predicted Mean Withdrawal Symptoms, and Observed and Model Predicted Buprenorphine Plasma Concentration in Relation to Brain Mu-Opioid Receptor Availability



Dots=mean observations; Solid lines=model predictions by linear or nonlinear regression analysis HYD=hydromorphone
Summary of Clinical Pharmacology Studies Source: individual data from 2 previously published clinical trials (Greenwald 2003; Greenwald 2007) Source : Figure 21

21.1.3.2. Pop PK model & Simulation study INDV6000-m01 (11-0020)

The data for the population PK analysis were obtained from Study RB-US-11-0020.

There were multiple descriptions of the intentions of the report:

The primary goal of this report was to characterize the population pharmacokinetics (PK) of Sublocade after single subcutaneous (SC) injection using the ATRIGEL.[58]

The objective of the modelling and simulation (M & S) project was to inform the design of the clinical phase III program for the treatment of opioid dependence with Sublocade. More specifically, the M & S effort objective was to identify a dose range to be studied that would provide the best balance between clinical efficacy (symptom and functional improvement) and safety.[59]

The Modelling and Simulation objectives were:

- To develop a population PK model that jointly characterizes the disposition of buprenorphine (BUP) and norbuprenorphine (Nor-BUP) after a single SC injection of Sublocade.
- To evaluate the potential effect of selected covariates on the PK of Sublocade.
- To predict the PK profiles of BUP and Nor-BUP after repeated SC injections of Sublocade and to compare the model predictions with the PK levels collected in the multiple

[58] Page 8
[59] Page 10

ascending dose (MAD) study (12-0005: An Open-Label, Multicentre, Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics, and Efficacy Markers of Subcutaneous Injections of Depot Buprenorphine [Sublocade] in Treatment Seeking Opioid-Dependent Subjects).

- To develop a pharmacokinetic/pharmacodynamic (PK/PD) model using published data describing the link between the BUP PK and the μ-opioid receptor occupancy. At this purpose the following stepwise approach was used:
    - Extract μ-opioid receptor occupancy and BUP PK concentration from literature data.
    - Develop a PK/μ-opioid receptor occupancy model.
    - Apply the PK/μ-opioid receptor occupancy model using the population PK model developed for BUP in subjects receiving a single and multiple SC injections of Sublocade to estimate the expected μ-opioid receptor occupancy in a chronic treatment.
- To use trial simulation to investigate alternative doses and dosing regimen scenarios for a chronic (once a month) administration.
- To evaluate alternative study designs and propose an accelerated clinical development plan to streamline Phase I, Phase II and Phase III trials.

The Modelling and Simulation endpoints were:

- The population PK parameters and their associated inter-subject variability, and residual error.
- The identification of significant covariates that impact the PK of Sublocade in the studied population.

The analysis dataset included 36 subjects for a total of 2797 observations. The buprenorphine concentration analysis used was only partly validated.

Base model

The dual absorption process was described by: 1) a first order absorption process associated with the rapid absorption and the first observed peak and 2) a delayed delivery process described by a transit compartment absorption model to mimic the release from the Atrigel Delivery System. This was followed by first-order elimination, and a first-order conversion to Nor-BUP which was subsequently eliminated according to a first-order process.

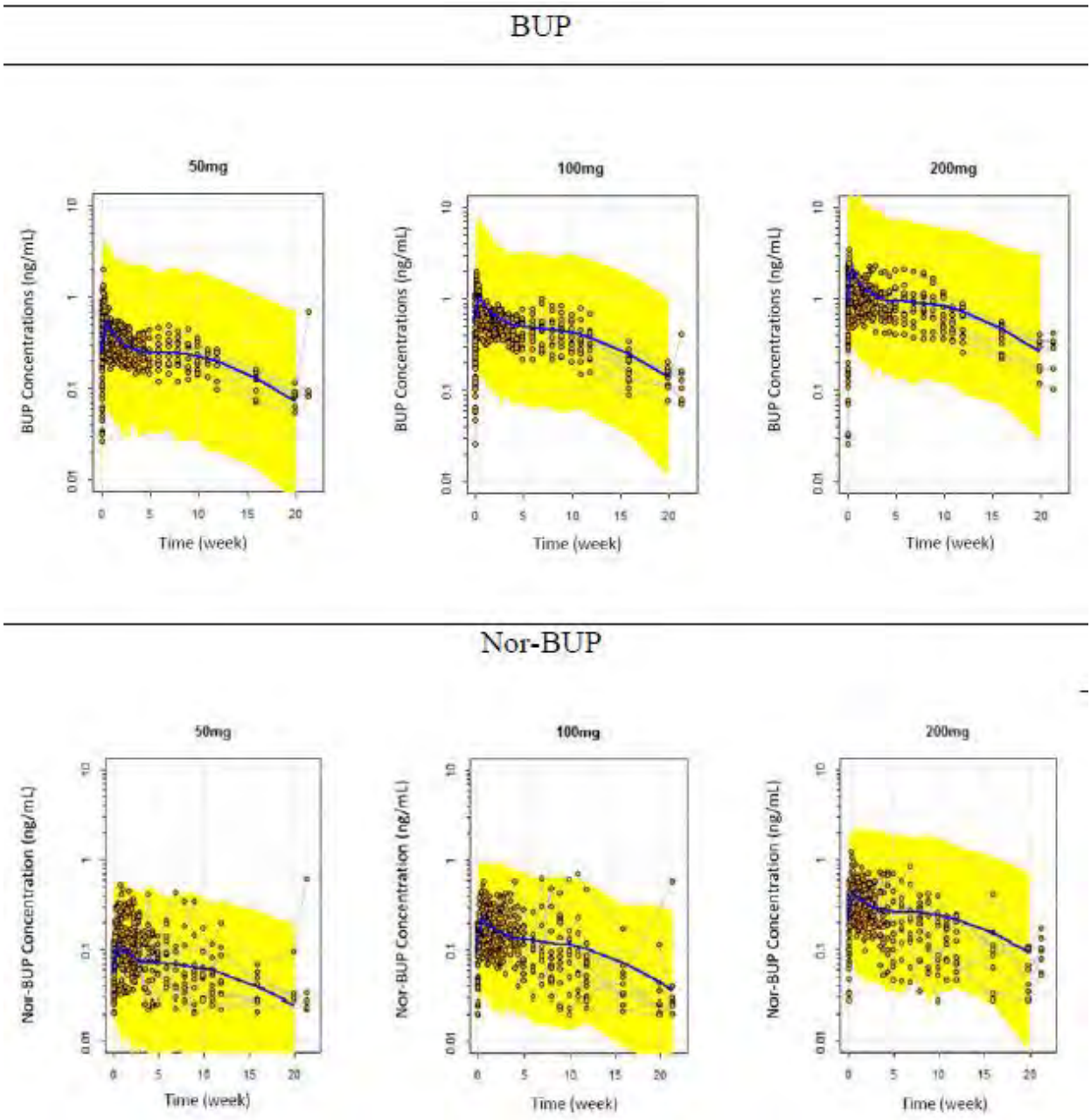
The final model was evaluated using nonparametric bootstrapping, at least 100 datasets were generated. The final model was retested with and without inclusion of the outlier data points.

400 replicates of the original dataset were simulated, based on the final model, and 95% prediction interval was computed based on the simulated datasets.

The Model with a peripheral distribution compartment for Nor-BUP (Model 2) was selected as the base model.

Overall, it was not possible to identify any covariate with significant impact on the population PK variability, given the relatively small number of subjects in the study.

Figure 34 Total Population - Visual Predictive Check Plots for Buprenorphine (BUP) and Norbuprenorphine (Nor-BUP) stratified by Dose

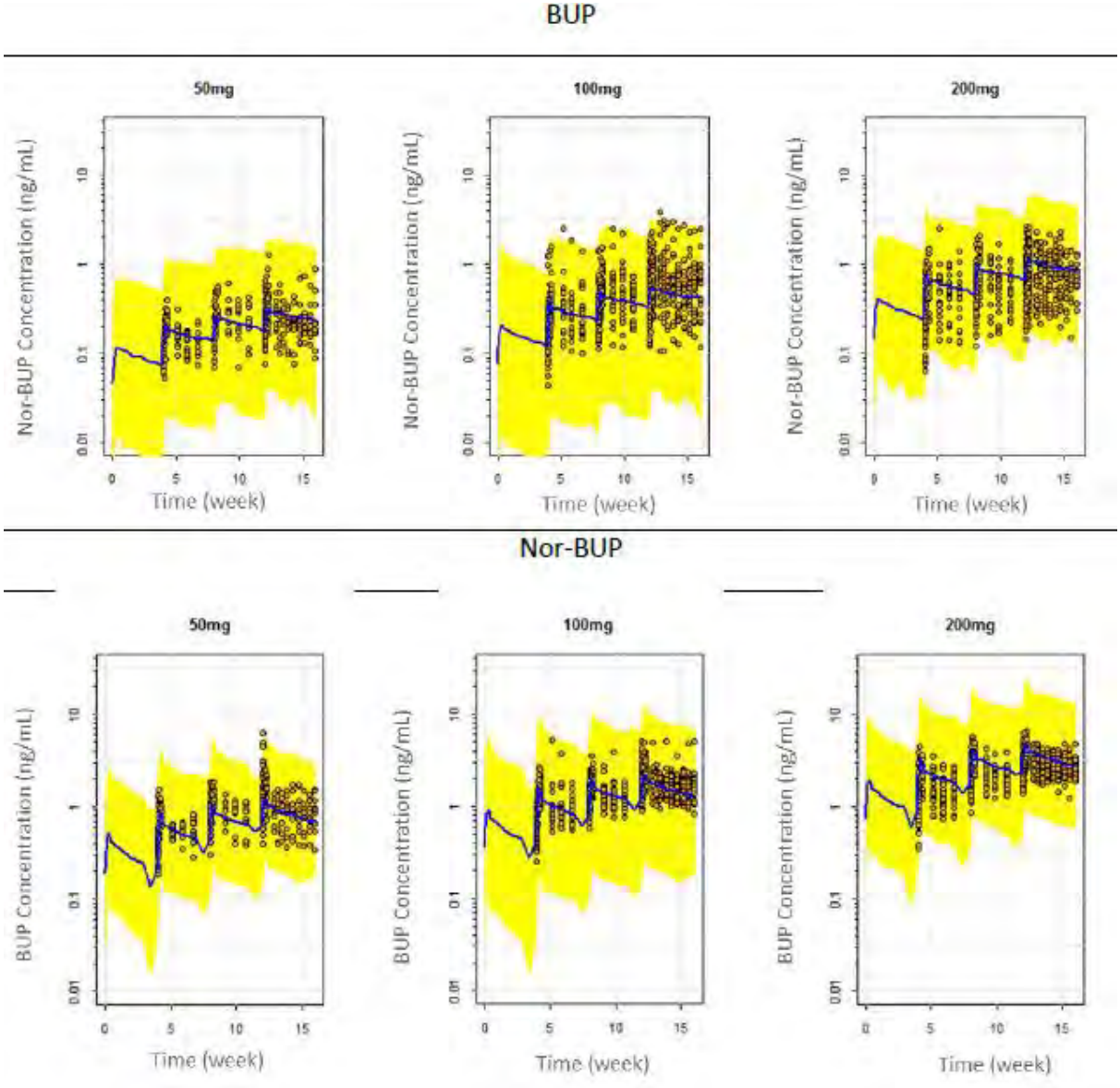


The blue lines are the median predictions, and the shaded yellow areas are the 2.5th and the 97.5th percentiles of the simulated data
Source: Figure 5

The simulated plasma concentrations of BUP and Nor-BUR after repeated SC injections of Sublocade were computed and compared with the observed data collected in the multiple ascending dose study 12-0005 to evaluate the predictive performances of the population PK model developed using the Study 11-0020 data.

In comparison between the simulated concentrations of BUP and Nor- BUP stratified by dose with the observed concentrations in the study 12-0005, the sponsor felt the result indicates the good predictive performances of the population PK model.

Figure 35 Final Model Without Outliers –Simulated Plasma Concentrations of Buprenorphine (BUP) and Norbuprenorphine (Nor-BUP) Stratified by Dose after Repeated Doses of Sublocade (50 mg, 100mg and 200mg) Every 28 Days



The blue lines represent the median predictions, the shaded yellow areas are the 2.5th and the 97.5 th percentiles of the simulated data, and the orange dots the observed concentration in the MAD study (RB-US- 12-0005). Source: Figure 8

The sponsor then undertook a comparison between the level of buprenorphine and the associated μ-opioid receptor occupancy obtained with Probuphine at clinical doses. Probuphine is a subdermal implant not on the ARTG.

21.1.3.3. Pop PK model & Simulation study INDV6000-m03 (12-0005)

For more information on Study 12-0005 see 21.1.1.3.

The main objective of this population PK modelling project was to inform the design of the clinical phase III program in treatment-seeking opioid-dependent subjects by defining and validating population PK model based on study 12-0005.

A total of 89 subjects with 5492 PK measurements were included in the analysis dataset.

Based on analysis of the semi-logarithmic scatter plots of the buprenorphine plasma concentrations vs. time, repeated daily administrations of Subutex during the dose stabilization period (Day -5 to Day -1) were described by a two-compartment model with first-order absorption.

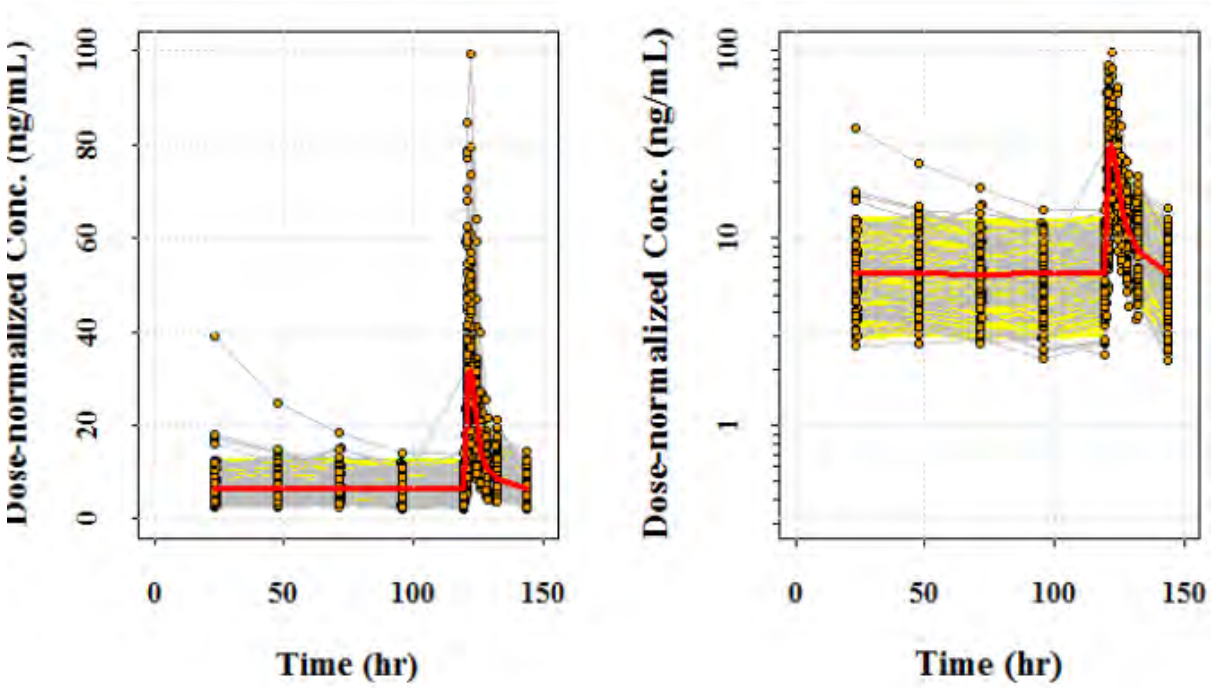
The double-peak kinetics of Sublocade suggested that the likely PK model needed to account for a dual absorption process:

- the first one associated with a rapid delivery from the injection site (first-order absorption process) and
- the second one associated with the slow delivery from the ATRIGEL Delivery System (delayed delivery process described by a transit compartment absorption model).

For disposition the same two-compartment model as for Subutex was used.

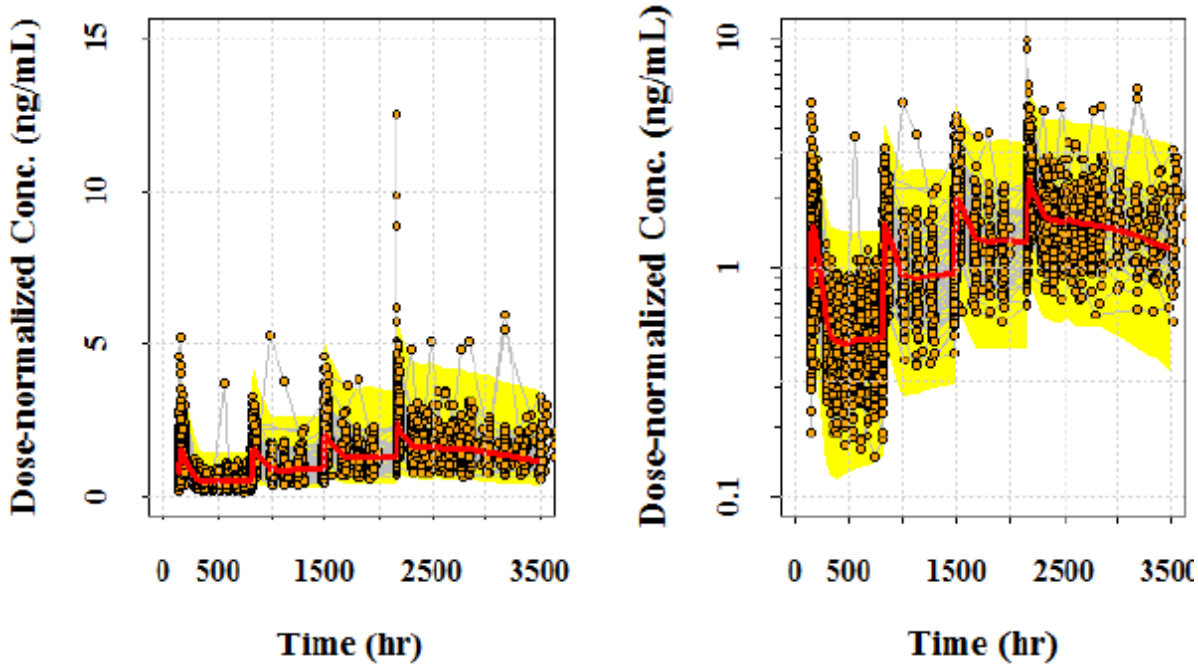
Visual predictive check method was utilized to evaluate the adequacy of the base model, including the effects of statistically significant covariates.

Figure 36 Base model – Dose-normalized Visual Predictive Checks for buprenorphine during the run-in phase with Subutex.



Left: normal scale. Right: semi-log scale. Source: Figure 11

Figure 37 Base model – Dose-normalized Visual Predictive Checks for buprenorphine during Sublocade treatment

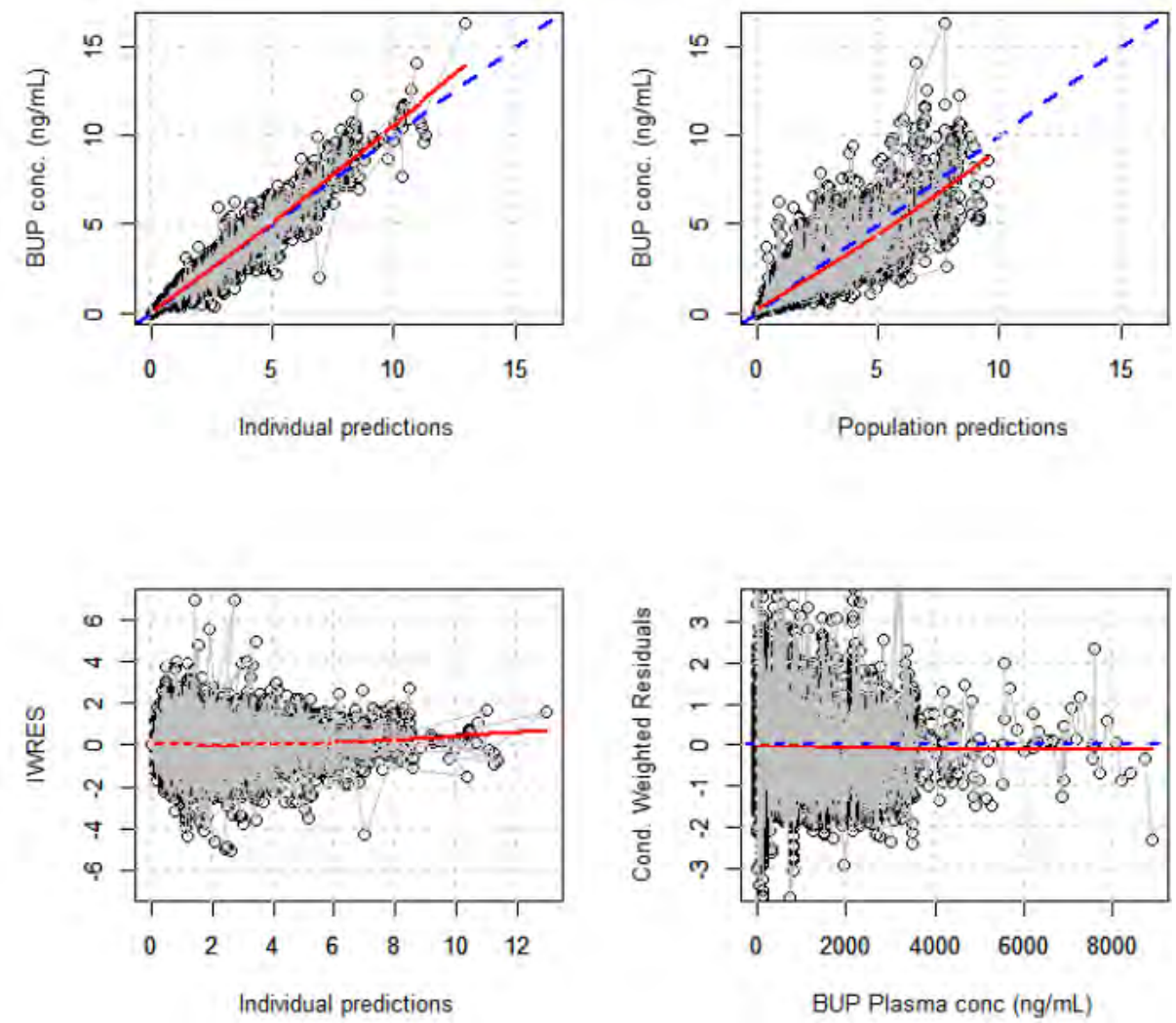


Left: normal scale. Right: semi-log scale. Source: Figure 12

In covariate analysis race was found to significantly affect the V_2[60] value and age was found to affect the k_{12}[61] value in the Subutex model. In the Sublocade model, BMI was found to significantly affect the ka_2[62] value, the rate of absorption decreased with the increase of the BMI value. The expected change in the buprenorphine plasma concentrations associated with the change in the covariate values appears of modest clinical relevance when this change is compared to the level of inter-individual variability estimated in the population PK analysis.

[60] Subutex: apparent volume of distribution of the central compartment
[61] Subutex: first-order absorption rate constant
[62] Sublocade first-order transfer rate constant from depot to the transit compartments

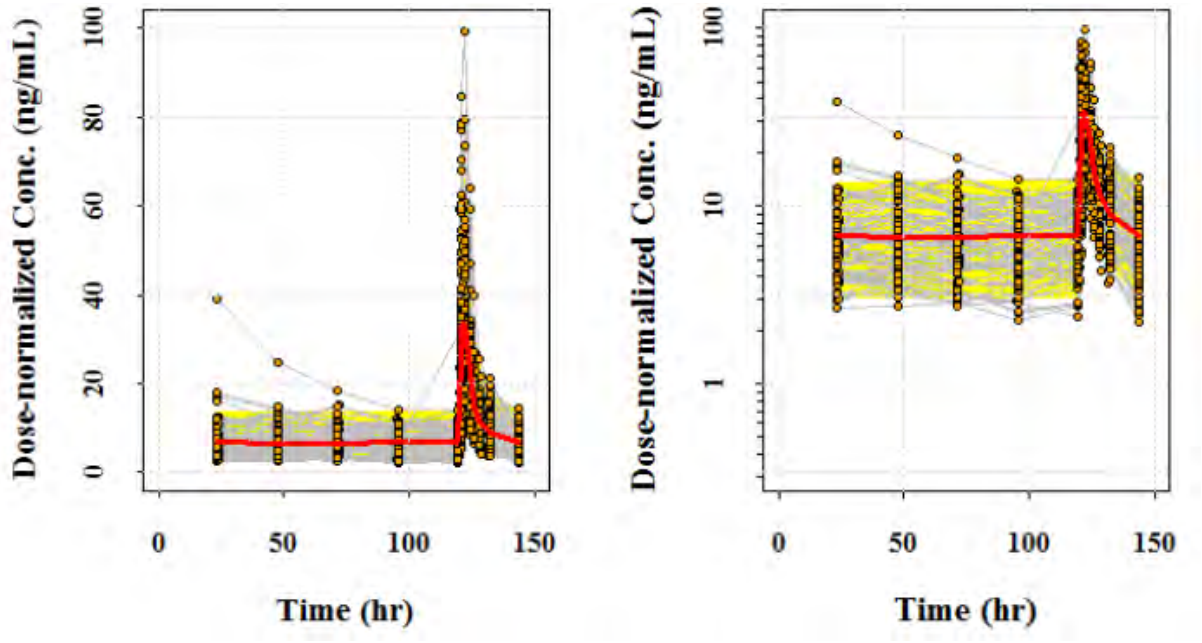
Figure 38 Goodness of fit plots for the final population PK model of buprenorphine (BUP)



Source: Figure 17

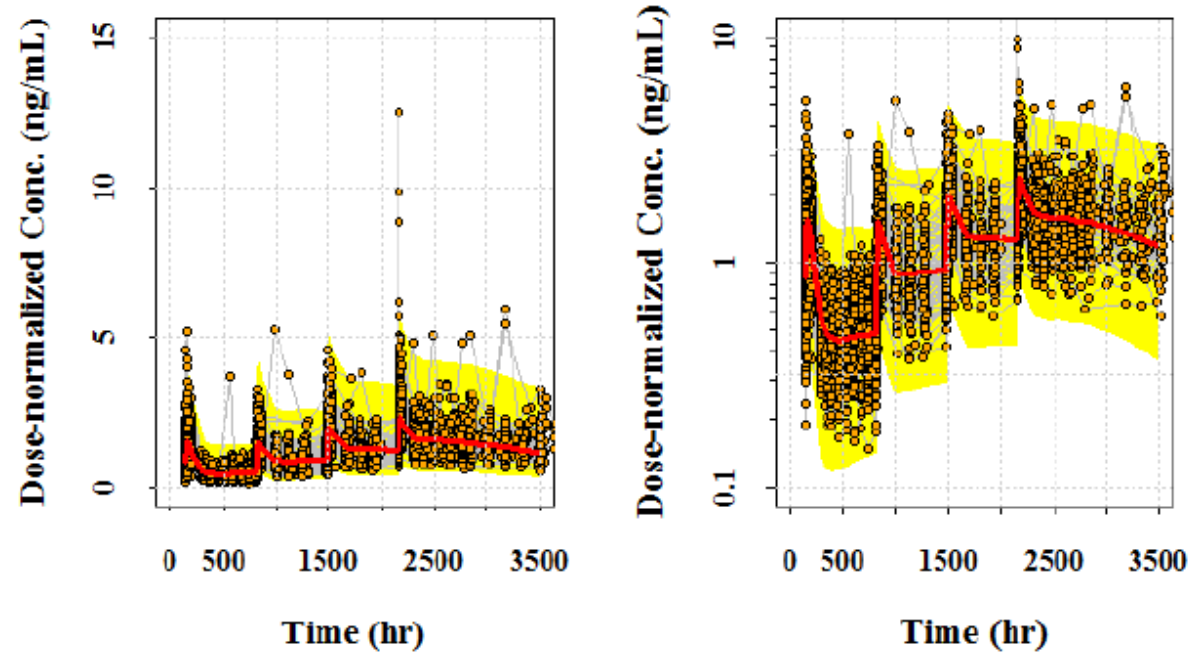
The final model performance/validation and stability was assessed using visual predictive checks.

Figure 39 Final model – Dose-normalized Visual Predictive Checks for buprenorphine during the run-in phase with Subutex.



Left: normal scale. Right: semi-log scale. Source: Figure 18

Figure 40 Final model – Dose-normalized Visual Predictive Checks for buprenorphine during Sublocade treatment



Left: normal scale. Right: semi-log scale. Source: Figure 19

When the relationship between race and V_2 was replaced by the relationship between age and V_2 overall similar fit and parameter estimates were achieved.

21.1.3.4. Pop PK and exposure-response analyses INDV-6000-M04 (Studies 12-005 & 13-0001)

For more information see 21.1.1.3

A population PK model describing simultaneously buprenorphine plasma concentrations after SC injection of Sublocade and sublingual (SL) administration of buprenorphine SL products (Subutex SL tablet or Suboxone SL film) developed from the pooled data of the Phase IIA study (12-0005) and the Phase III double-blind efficacy study (13-0001).

Objectives

i. To develop a population PK model describing buprenorphine plasma concentration-vs-time profiles following repeated Sublocade SC injections and to assess the influence of selected subject characteristics on the PK of Sublocade,

ii. To develop exposure-response relationships between buprenorphine plasma concentration and the selected clinical efficacy variables,

iii. To assess the influence of selected subject characteristics on the PK/PD of Sublocade.

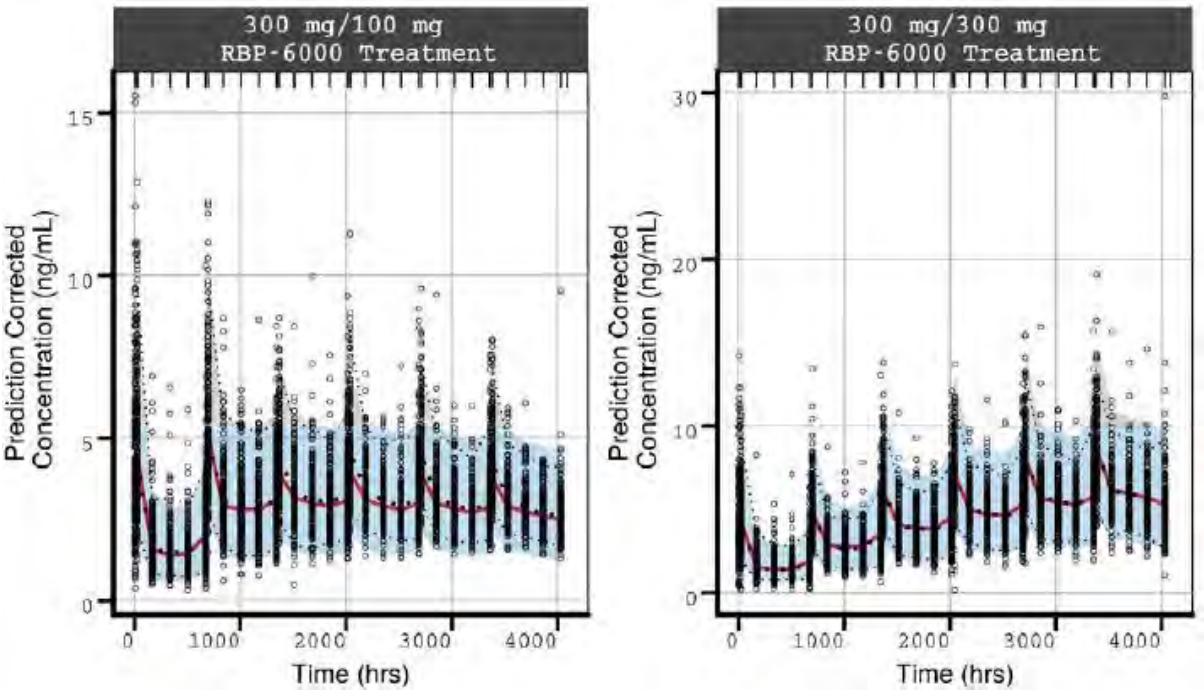
Data included 17,235 observations in 507 subjects from Studies 12-005 & 13-0001 (all 15 subjects from Site 20 in the Phase III efficacy study were excluded from the PK and PK/PD analyses due to site compliance issues.

A non-linear mixed effects modelling approach was used to describe the buprenorphine plasma concentration vs. time profiles following administration of SL buprenorphine (Subutex SL tablet, Suboxone SL film) and SC injection of Sublocade.

Unlike the previous analysis where separate compartmental models were used for Subutex and Sublocade, here a same disposition model was used to fit Subutex and Sublocade data in order to address the flip-flop phenomenon associated with the slow release of buprenorphine from the SC depot. The model was parametrized in clearances and volumes of distribution. The absorption of Sublocade was modelled using the same dual absorption model as previously described (INDV6000-m03 see 21.1.3.3), with the exception that the fraction of Sublocade absorbed by fast (F_2) or slow (F_3) process was not determined by the absorption rate constants (k_{24} and k_{36}) of the two pathways but was estimated.

A total of 17235 observations in 507 subjects were used for population PK modelling.

Figure 41 Prediction-Corrected Visual Predictive Checks for Sublocade Treatment in Study 13-0001



The bold black dotted line represents the median of the observed data; the red solid line represents the median of simulated data; the upper and lower black dotted lines delineate the 90% prediction intervals of the observed data; the light blue shaded area delineates the 90% prediction intervals of the simulated data
Source: Figure 5

A covariate analysis found BMI and sex were the only 2 statistically significant covariates identified with BMI having the only clinically relevant effect (on the early peak of buprenorphine following SC injection – rapid absorption parameter k_{24}). Dose adjustment was not considered necessary.

Illicit Opioid Use

Illicit opioid use was assessed in Study 13-0001 as a composite variable based on urine drug screen (UDS) results combined with subjects self-reports for illicit opioid use as documented on the Timeline Follow back (TLFB) interview.

Illicit opioid use was analysed as a binary variable using logistic regression modelling. Observed data (Figure 42) indicated a clear relationship with buprenorphine plasma concentration that was modelled using an E_{max} relationship. For opioid use, the plateau for maximal response was reached at approximately 2ng/mL, in agreement with a mu-opioid receptor occupancy level of 70%.(21.1.2.1 Study 13-002)[63] Major covariates were identified:

• Subjects using opioids by injectable route at baseline showed a 3.6-fold higher EC_{50} compared to subjects using opioids by non-injectable route at baseline;

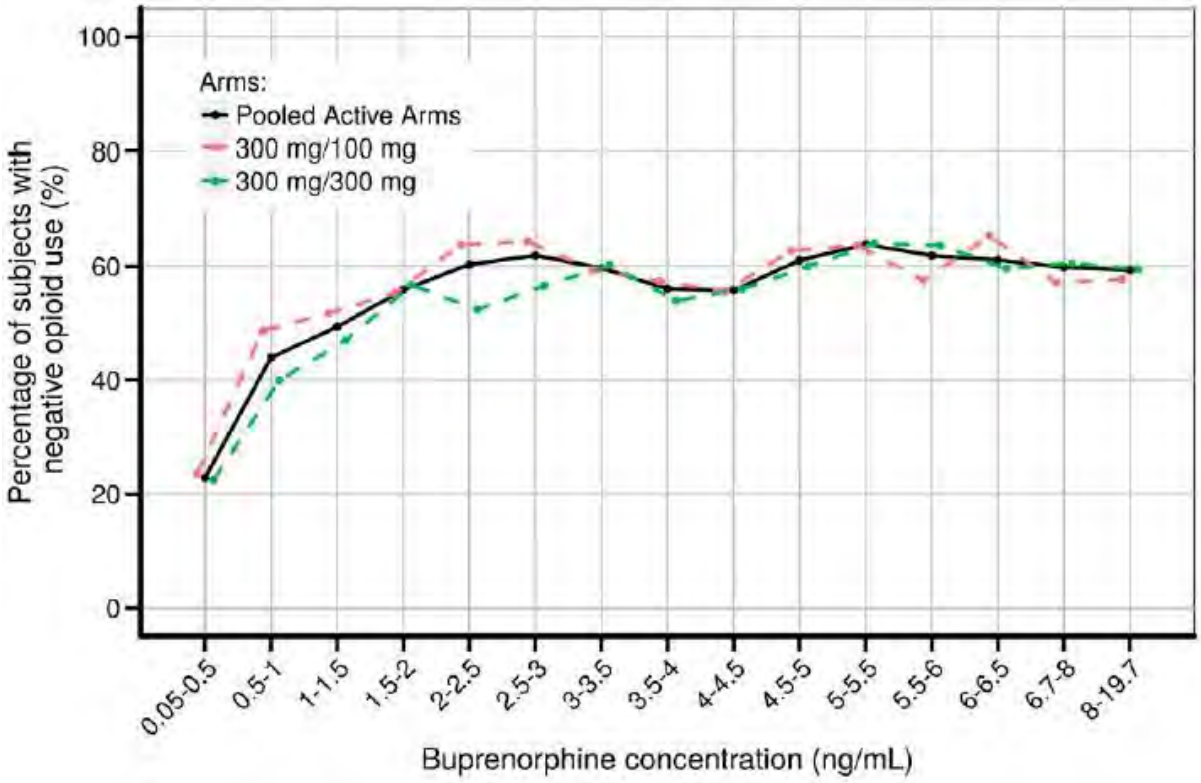
• Subjects who were employed at baseline showed 43% higher maximal drug efficacy (E_{max}) compared to unemployed subjects at baseline;

[63] 'Mu-opioid receptor occupancy predictions were derived using the PK/mu-opioid receptor occupancy model previously published in Nasser et al. (2014)' A Population Pharmacokinetic and Pharmacodynamic Modelling Approach to Support the Clinical Development of RBP-6000, a New, Subcutaneously Injectable, Long-Acting, Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Dependence." Clinical 486 Pharmacokinetics 53 (9): 813–24. doi:10.1007/s40262-014-0155-0.

• Black or African American subjects showed a 31% lower maximal drug efficacy (E_{max}) compared to white subjects and others;

• Subjects with TC and TT genotype for the single nucleotide polymorphism (SNP) rs678849 on the delta-opioid receptor (OPRD1) had their EC50 reduced by 71% and 94%, respectively.

Figure 42 Relationship Between the Percentage of Subjects with Negative Opioid Use and Buprenorphine Plasma Concentration (Study 13-0001).



Solid black curve; percentage of subjects with negative opioid use from the pooled 300 mg/300mg and 300 mg/100mg treatment arms. Dashed curves: percentage of subjects with negative opioid use in the 300 mg/300mg arm (green curve) and 300 mg/100mg arm (red curve)
Source: Figure 9

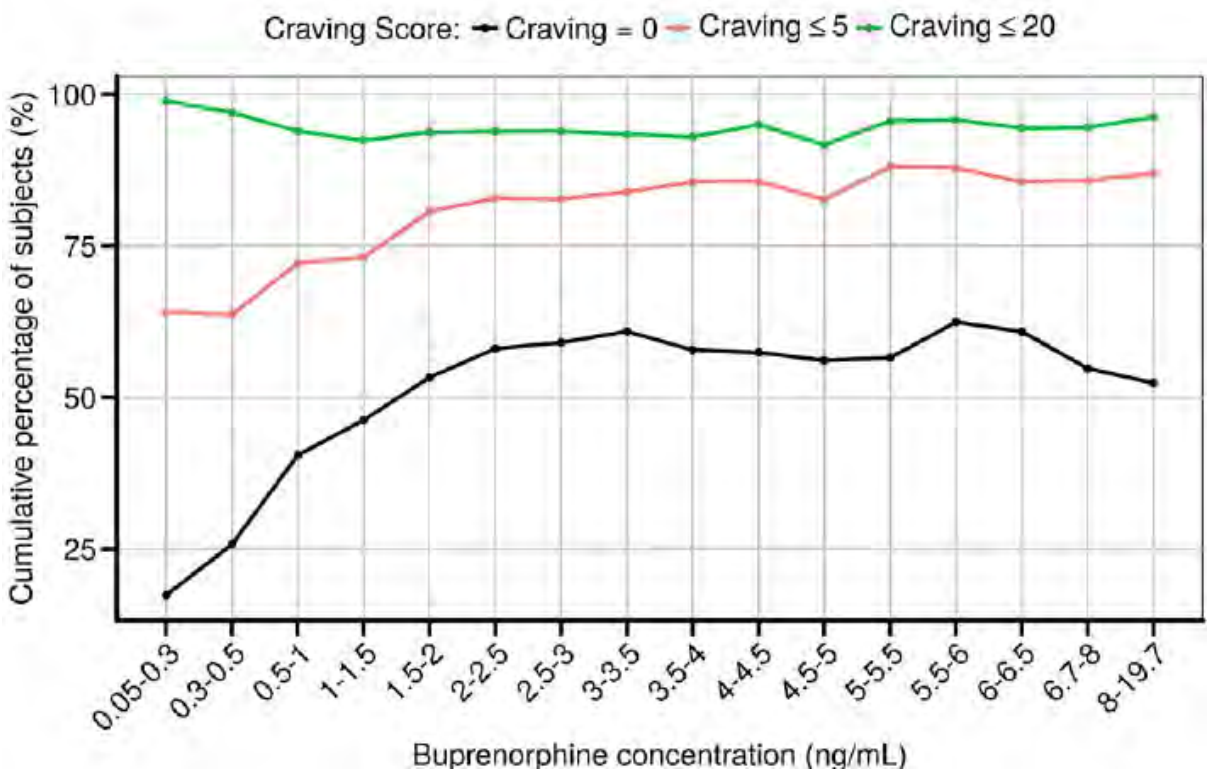
Opioid craving:

Opioid craving was assessed in Study 13-0001 using the Opioid Craving Visual Analogue Scale (VAS).[64]

Categorized data were analysed as an ordinal variable using logistic regression modelling. Observed data (Figure 43) indicated a clear relationship with buprenorphine plasma concentration that was modelled using an E_{max} relationship. For opioid craving the plateau for maximal response was reached at approximately 3ng/mL, consistent with a mu-opioid receptor occupancy level of 75%.

[64] Opioid Craving VAS scores were categorized into 4 ordered categories (0, 1-5, 6-20 and >20) for the purpose of the PK/PD analysis

Figure 43 Relationship Between the Percentage of Subjects in Each Category of Opioid Craving VAS Score and Buprenorphine Plasma Concentration (Study 13-0001).



Curves: percentage of subjects with a craving score of zero (black curve), below 5 (red curve) and below 20 (green curve) form the pooled 300 mg/300mg and 300 mg/100mg treatment arms. Source: Figure 10.

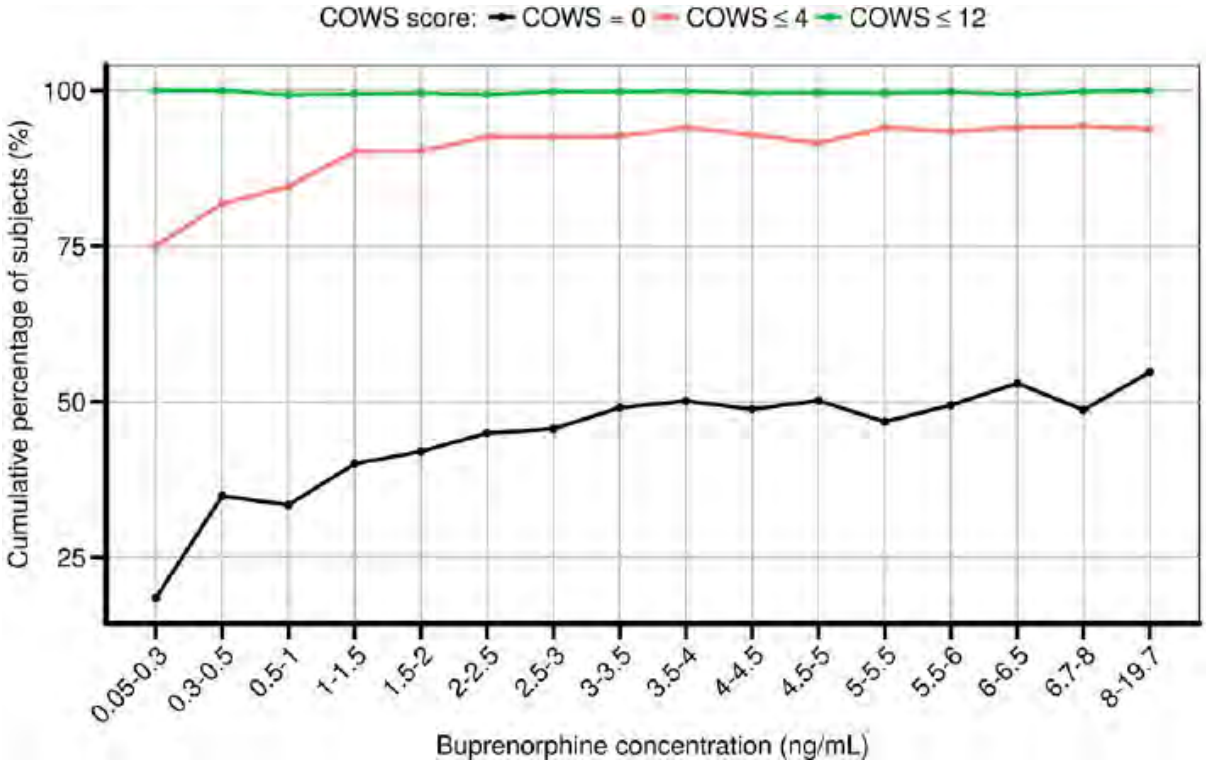
BMI was the only significant covariate identified but had no clinical relevance.

Opioid craving was identified as a major predictor of dropout: an opioid craving score > 20 was associated with an increase in dropout rate of up to 3.0 to 3.6-fold in active treatment arms and placebo arm, respectively, compared to craving ≤ 5.

Clinical Opiate Withdrawal Scale and Subjective Opiate Withdrawal Scale

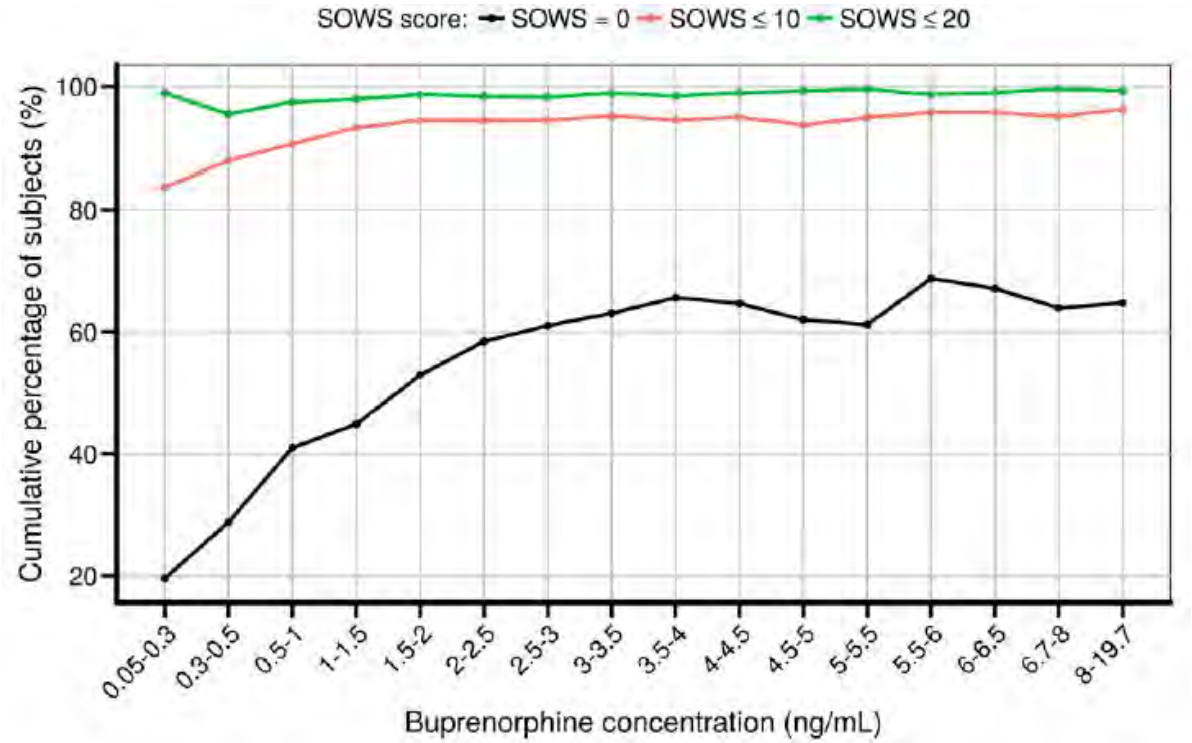
Exposure-response relationships were investigated for COWS (Figure 44) and SOWS (Figure 45). Visually there was a relationship with buprenorphine plasma concentration consistent with an E_{max} model. Empirically, the plateau corresponding to maximal response was reached at approximately 4ng/mL for both COWS and SOWS, consistent with a mu-opioid receptor occupancy level of 78%.

Figure 44 Relationship Between the Cumulative Proportion of Subjects below COWS Score Cut-offs and Buprenorphine Plasma Concentration (Study 13-0001).



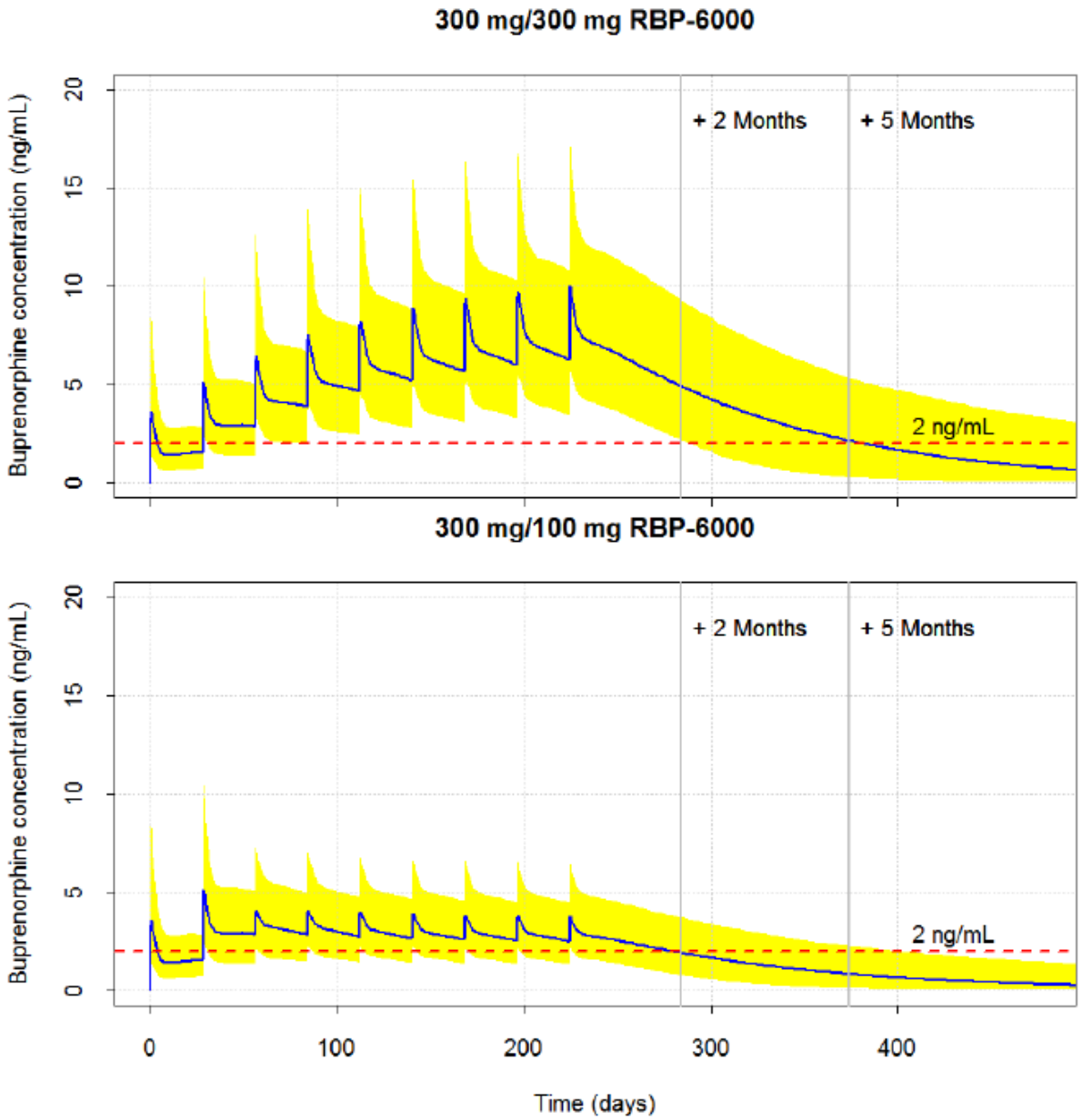
23Solid lines: percentage of subjects with no withdrawal (black curve), a COWS score ≤ 4 (red curve), and a COWS score ≤ 12 (green curve) Source: Figure 22

Figure 45 Relationship Between the Cumulative Proportion of Subjects below Each SOWS Score Cut-offs and Buprenorphine Plasma Concentration (Study 13-0001).



25Solid lines: percentage of subjects with no withdrawal (black curve), a SOWS score ≤ 10 (red curve), and a SOWS score ≤ 20 (green curve) Source: Figure 23

Table 46 Predicted Decrease in Buprenorphine Plasma Concentrations for the 300mg/300mg and 300 mg/100mg Dosing Regimens of Sublocade after the Last SC Injection



Blue curve = medians of the simulated data; Shaded yellow area = 90% prediction intervals of simulated data
A total of 9 SC injections were simulated. The horizontal red dashed line indicates the 2ng/mL minimum concentration required for opioid blockade, as established from modelling and simulation and confirmed by the findings of the opioid blockade study (13-0002). Model used for simulation: INDV-6000-M04 Table 12 Source: Figure 44

21.1.3.5. PopPK analysis NDV-6000-M05 (Studies 12-0005, 13-0001 and 13-0003)

Population pharmacokinetics of Sublocade in treatment- seeking subjects with opioid use disorder combined analysis of studies 12-0005, 13-0001 and 13-0003.

Objectives:

To describe buprenorphine plasma concentrations measured in Study 13-0003 from roll-over and *de novo* subjects for whom PK samples were collected, using the previously developed population pharmacokinetic (PK) model from the combined analysis of Studies 12-0005 and 13-0001.

To refine model estimation from the pooled data of the multiple ascending dose study (12-0005) and the two Phase III studies (13-0001 and 13-0003).

This previously developed population PK model was applied with all parameters fixed to describe the data in subjects of Study 13-0003 for whom PK samples have been obtained. Standard goodness-of-fit plots were generated to assess the adequacy of model predictions compared to observations. Visual predictive checks were also performed. In a second step, model parameter estimation was refined from the full dataset combining data from the three studies: 12-0005, 13-0001, and 13-0003. No additional covariate analysis was performed since no major deviations from the expected PK were observed.

The previously developed population PK model was applied with all parameters fixed to describe the data in Study 13-0003. Goodness-of-fit plots were plotted and showed that overall, the model was able to describe the buprenorphine plasma concentrations observed in Study 13-0003. Visual predictive checks were also performed, indicating that the previously developed model was able to predict long-term buprenorphine plasma concentrations as observed in Study 13-0003.

Since the goodness-of-fit plots and visual predictive check plots did not reveal any major deviation from the expected plasma concentration ranges, the previously developed model was re-estimated using the full dataset combining data from the three studies: 12-0005, 13-0001, and 13-0003. The estimated PK parameter values and their associated variabilities were similar to those of the previous developed model, indicating that the model was robust in predicting data from 570 subjects across 3 different studies and up to 1 year of exposure.

21.1.3.6. INDV-6000-M06 ketoconazole interaction modelling & simulation

Drug-drug interaction modelling & simulation for Subutex and Sublocade with ketoconazole.

The objectives of the modelling work were:

1) to model buprenorphine and norbuprenorphine plasma exposure following SL administration of Subutex and SC injection of Sublocade, to estimate SL and SC bioavailability parameters as well as first-pass effect for SL route,

2) to model the effect of ketoconazole on buprenorphine and norbuprenorphine plasma exposure with the separation of the effects on first-pass and systemic clearance,

3) to predict the effect of ketoconazole on the plasma exposure of Sublocade (for which there is no first-pass effect).

Data used were:

- Individual AUCs from Study 12-0005 and Study P01242.
- Data from the literature relative to physiological blood flows (e.g. hepatic blood flow) as well as buprenorphine systemic clearance (hepatic coefficient of extraction), fraction of buprenorphine metabolized by the CYP 3A4 pathway, and blood-to-plasma ratio.

The following model assumptions were considered:

1) Buprenorphine is extensively metabolized by N-dealkylation to norbuprenorphine primarily through CYP3A4. For the purpose of the analysis, it was assumed that CYP3A4 is the sole cytochrome P450 involved in the conversion of buprenorphine to norbuprenorphine. In the present analysis the fraction of buprenorphine metabolized (f_{met}) was fixed to 0.63, as estimated from Kilford et al. (2009),[65] and the hepatic extraction ratio (E_H) was fixed to 0.9.

[65] Prediction of drug clearance by glucuronidation from in vitro data use of combined cytochrome P450 and UDP- glucuronosyltransferase cofactors in alamethicin-activated human liver microsomes. Kilford PJ, et al Drug Metab Dispos. 2009 Jan;37(1):82-9.

Buprenorphine is a high extraction ratio drug and due to variability in the Q_H, it was decided in previous work to fix E_H to 0.9 which resulted in adequate *in vitro/in vivo* extrapolation.

2) The hepatic blood flow (Q_H) was fixed to 87L/hr (1450mL/min/70 kg);

3) Buprenorphine systemic clearance is essentially equal to buprenorphine hepatic clearance. This is a reasonable assumption since only 1 % of buprenorphine is excreted unchanged in urine (Suboxone sublingual film, Prescribing Information, June 2016).

4) The coefficient of extraction of buprenorphine in the intestines (E_G) was assumed equal to the hepatic coefficient of extraction (E_H).

5) Blood-to-plasma ratio for buprenorphine was set equal to 1 as assumed in earlier work since buprenorphine is a basic compound.

Individual AUCs of buprenorphine and norbuprenorphine from Study 12-0005 following repeated SC injections of Sublocade and administrations of Subutex SL tablets were fitted together with individual AUCs of buprenorphine and norbuprenorphine from Study P01242 in the absence of ketoconazole (control data).

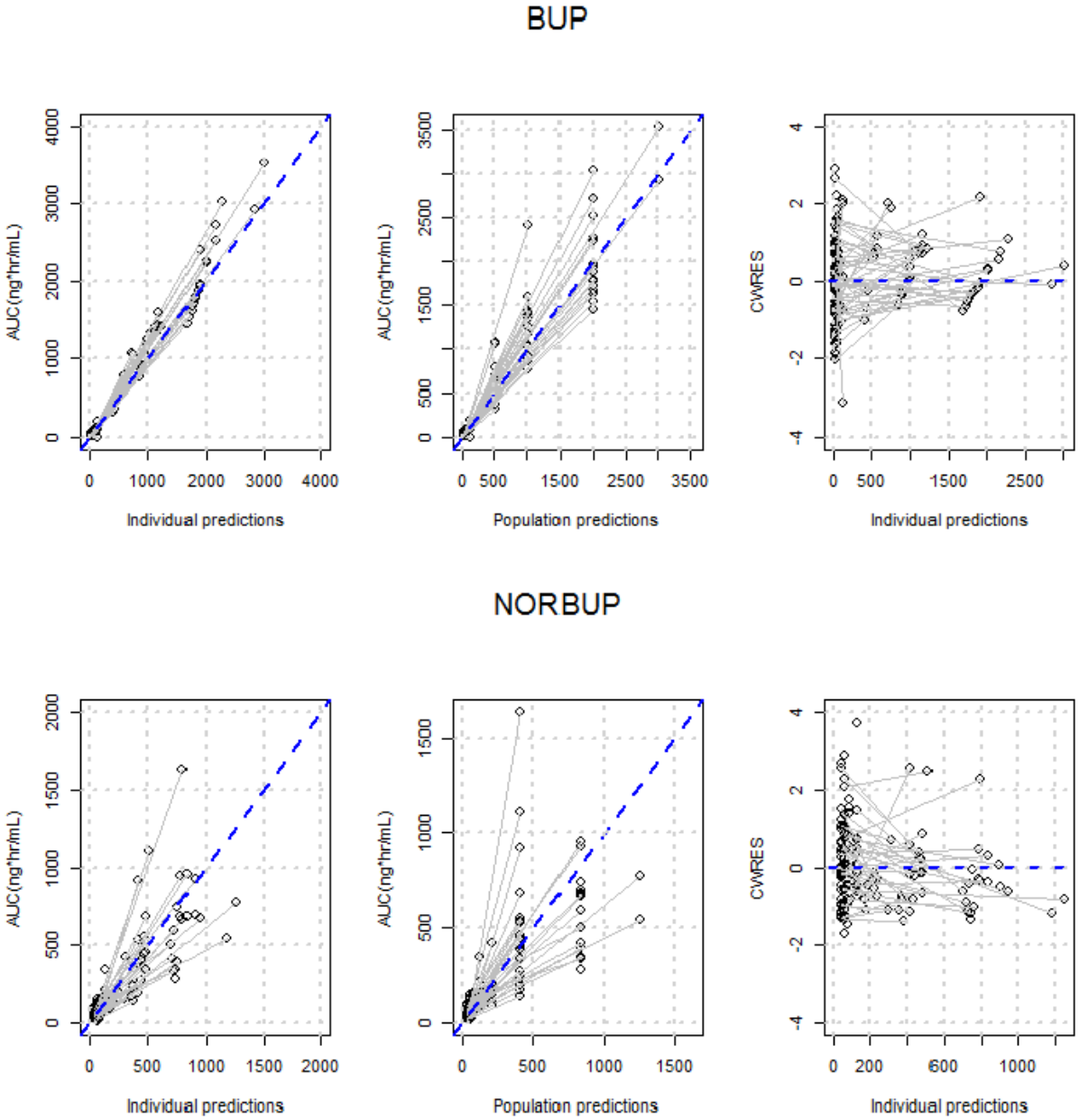
Individual AUCs of buprenorphine and norbuprenorphine from Study P01242 in the presence of ketoconazole were added to the dataset to estimate the effect of ketoconazole on the hepatic clearance component responsible for the conversion of buprenorphine to norbuprenorphine.

The initial model evaluated was the final model of the Step 1 analysis with the inclusion of the ketoconazole effect. The subsequent models evaluated the effect of an IIV term on the model parameters in a step-wise fashion.

The model (Run 06) was retained of the final model.

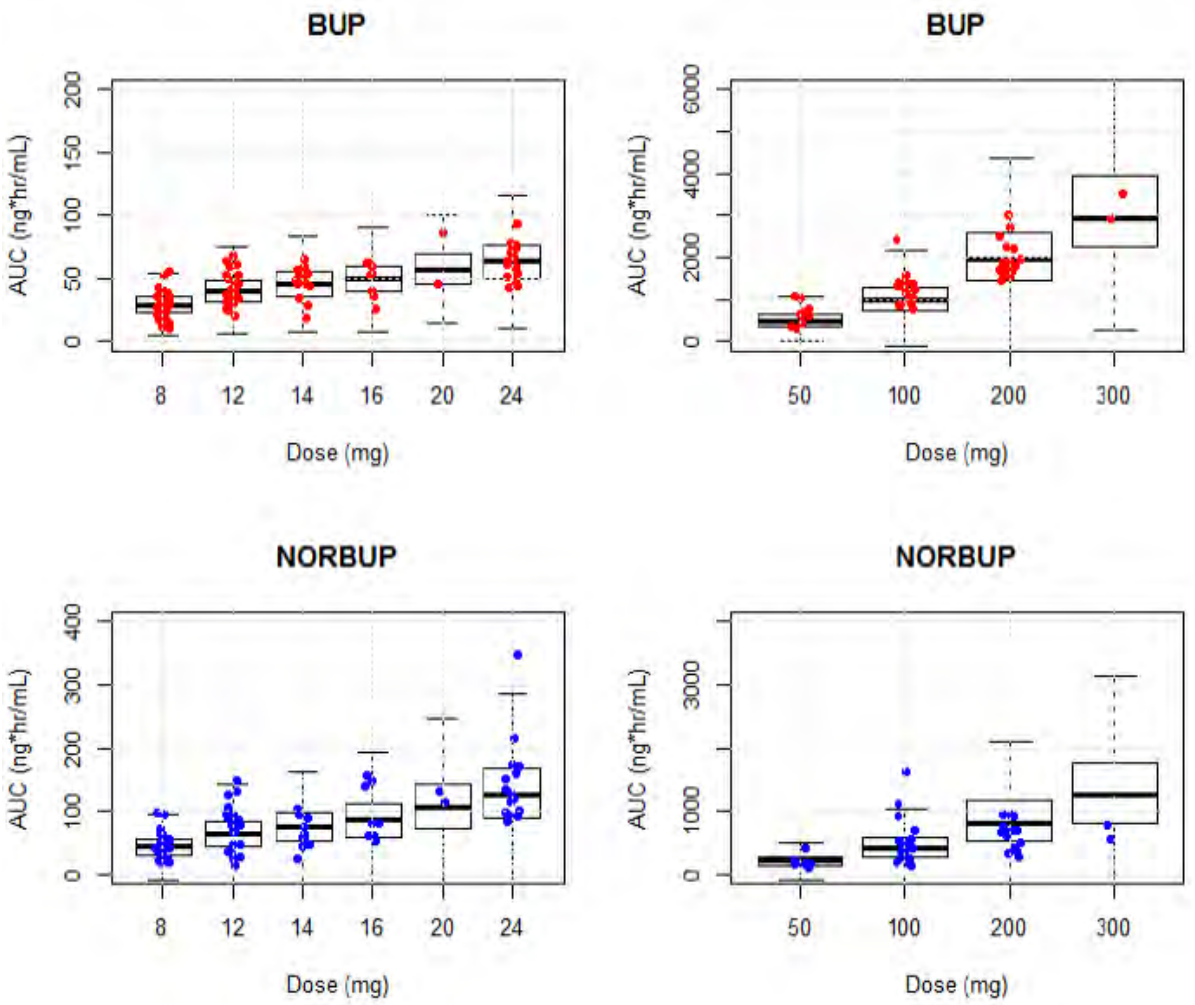
The model predicted a comparatively modest increase (60%) in buprenorphine AUC with concomitant administration of ketoconazole.

Figure 46 Step 2 Analysis: Goodness-of-fit plots for buprenorphine (BUP) and norbuprenorphine (NORBUP)



Dashed blue line: identity line or horizontal line for y=0; dots: observed data; grey line: links individual data. Source:. Figure 6

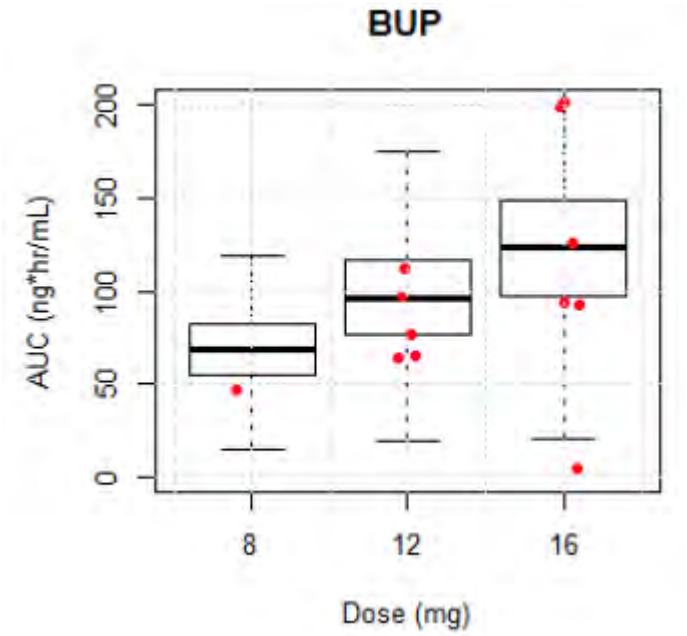
Figure 47 Step 2 Analysis (data without ketoconazole): Visual predictive checks for buprenorphine (BUP) and norbuprenorphine (NORBUP) stratified by dose



Left: Subutex. Right: Sublocade. Source: Figure 7

The red and blue dots represent the observed values. An artefactual spread of the observed AUC values around the nominal dose values has been introduced by the graphical plot procedure in order to better apprehend the dispersion of the data.

Figure 48 Step 2 Analysis (data with ketoconazole): Visual predictive checks for buprenorphine (BUP) stratified by dose



The red dots represent the observed values. Source: Figure 8

Simulations were conducted to predict plasma exposure of buprenorphine and norbuprenorphine following concomitant administrations of ketoconazole (400mg/day) and:

- Sublocade (100mg or 300mg) under steady-state conditions (following 4 SC injections of Sublocade separated by 28 days),
- Subutex SL (8mg, 12mg or 16mg per day) under steady-state conditions.

Table 47 Descriptive statistics on the distribution of the AUC values for Sublocade (100mg and 300mg) following 4 SC injections separated by 28 days, in presence and in absence of ketoconazole, for buprenorphine (BUP) and norbuprenorphine (NORBUP)

Dose	Analyte	Ketoconazole	Mean AUC (ng*hr/mL)	Std Dev	Median	Minimum	Maximum
100 mg	BUP	Without	930.97	349.73	914.15	111.57	2267.30
		With	1471.63	583.33	1399.90	83.33	3384.10
	NORBUP	Without	394.16	192.91	369.33	2.84	1114.30
		With	162.28	77.51	157.23	0.91	539.81
300 mg	BUP	Without	2824.51	1055.66	2746.65	73.01	6298.70
		With	4507.17	1682.55	4381.00	36.51	10741.00
	NORBUP	Without	1228.56	585.07	1177.50	22.07	3699.00
		With	493.42	254.88	474.71	4.22	1341.70

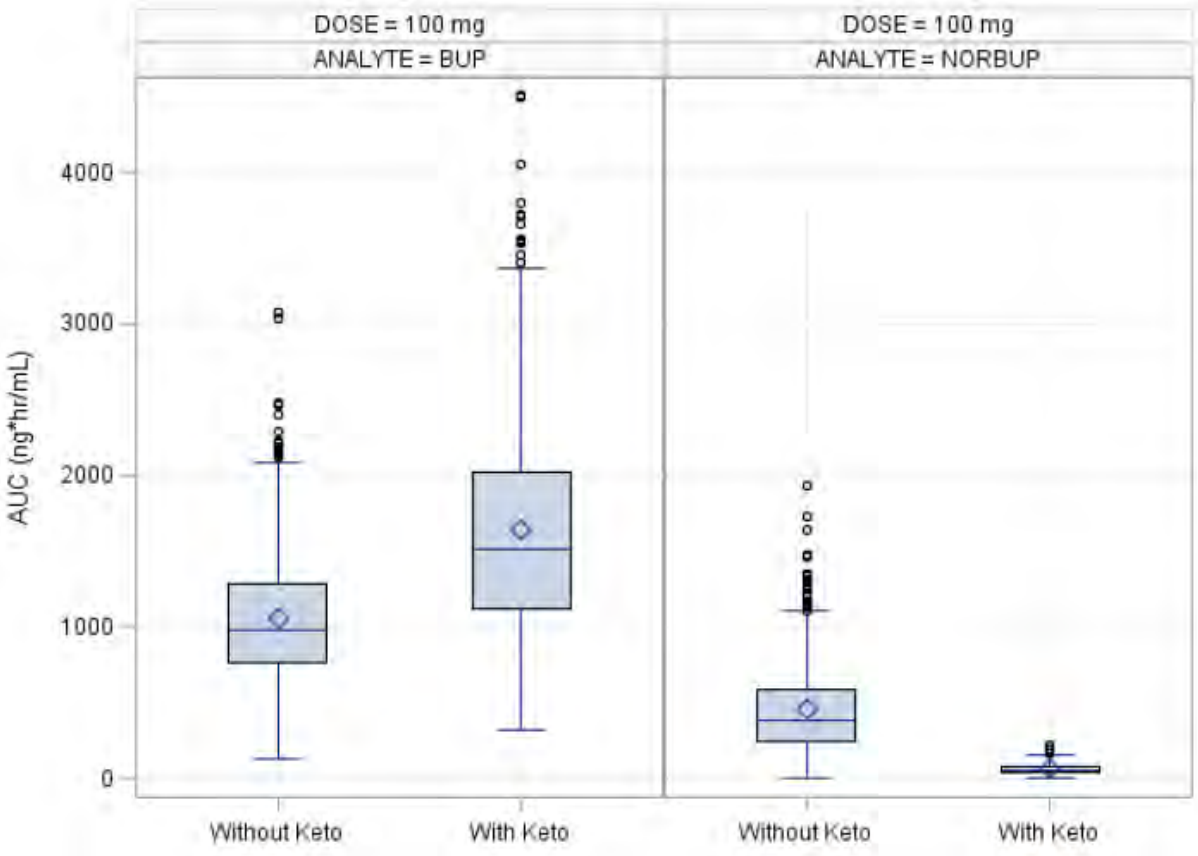
Source: Table 7

Table 48 Ratio of the AUC values for Sublocade in presence and in absence of ketoconazole for buprenorphine (BUP) and norbuprenorphine (NORBUP)

Dose	Analyte	AUC ratio (with keto/without keto)
100 mg	BUP	1.58
	NORBUP	0.41
300 mg	BUP	1.60
	NORBUP	0.40

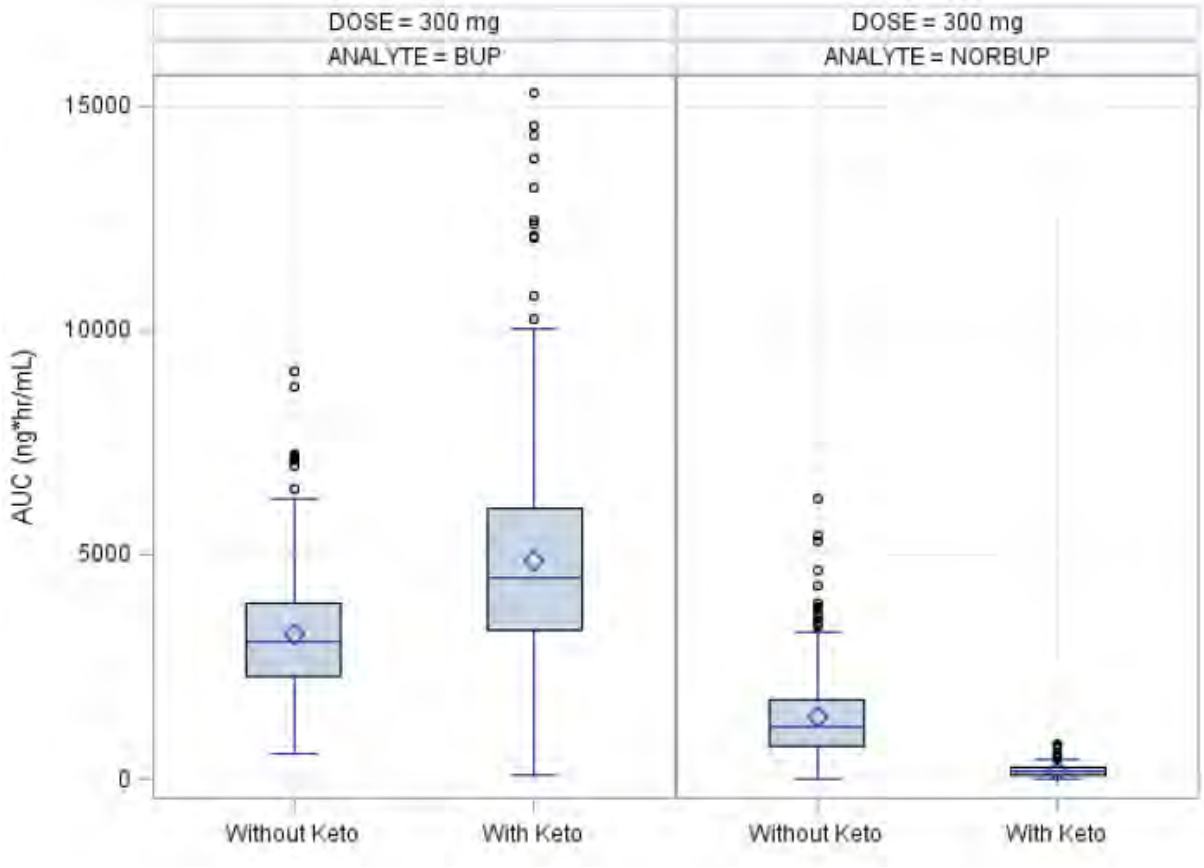
Source: Table 9

Figure 49 Sublocade dose of 100mg. Boxplots of the simulated AUC values following 4 subcutaneous injections of Sublocade separated by 28 days, in presence and in absence of ketoconazole, for buprenorphine (BUP) and norbuprenorphine (NORBUP)



Source: Figure 9

Figure 50 Sublocade dose of 300mg. Boxplots of the simulated AUC values following 4 subcutaneous injections of Sublocade separated by 28 days, in presence and in absence of ketoconazole, for buprenorphine (BUP) and norbuprenorphine (NORBUP)



Source: Figure 10

21.1.3.7. INDV-6000-M07 in vitro-in vivo Correlation

Modelling & Simulation Report *in vitro-in vivo* Correlation evaluation for Sublocade using a population pharmacokinetic modelling approach

Objectives

a) To develop a population pharmacokinetic (PK) model for Sublocade using pooled data from 2 clinical studies (11-0020 and 12-0005) together with historical intravenous (IV) buprenorphine data (CR87/027) for the purpose of *in vitro-in vivo* correlation (IVIVC) assessment;

b) To simulate the mean cumulative absorption profile (% dose absorbed over time) for a single subcutaneous (SC) dose of 100mg of Sublocade based on model and parameter estimates obtained in Step (a);

c) To correlate the mean cumulative absorption profile (from (b)) with the *in-vitro* extended-release (dissolution) profile corresponding to a representative lot of the drug product

4258 buprenorphine plasma concentrations obtained in 121 subjects were available. Buprenorphine plasma concentrations following IV administration were described by a three-compartment model with first-order elimination.

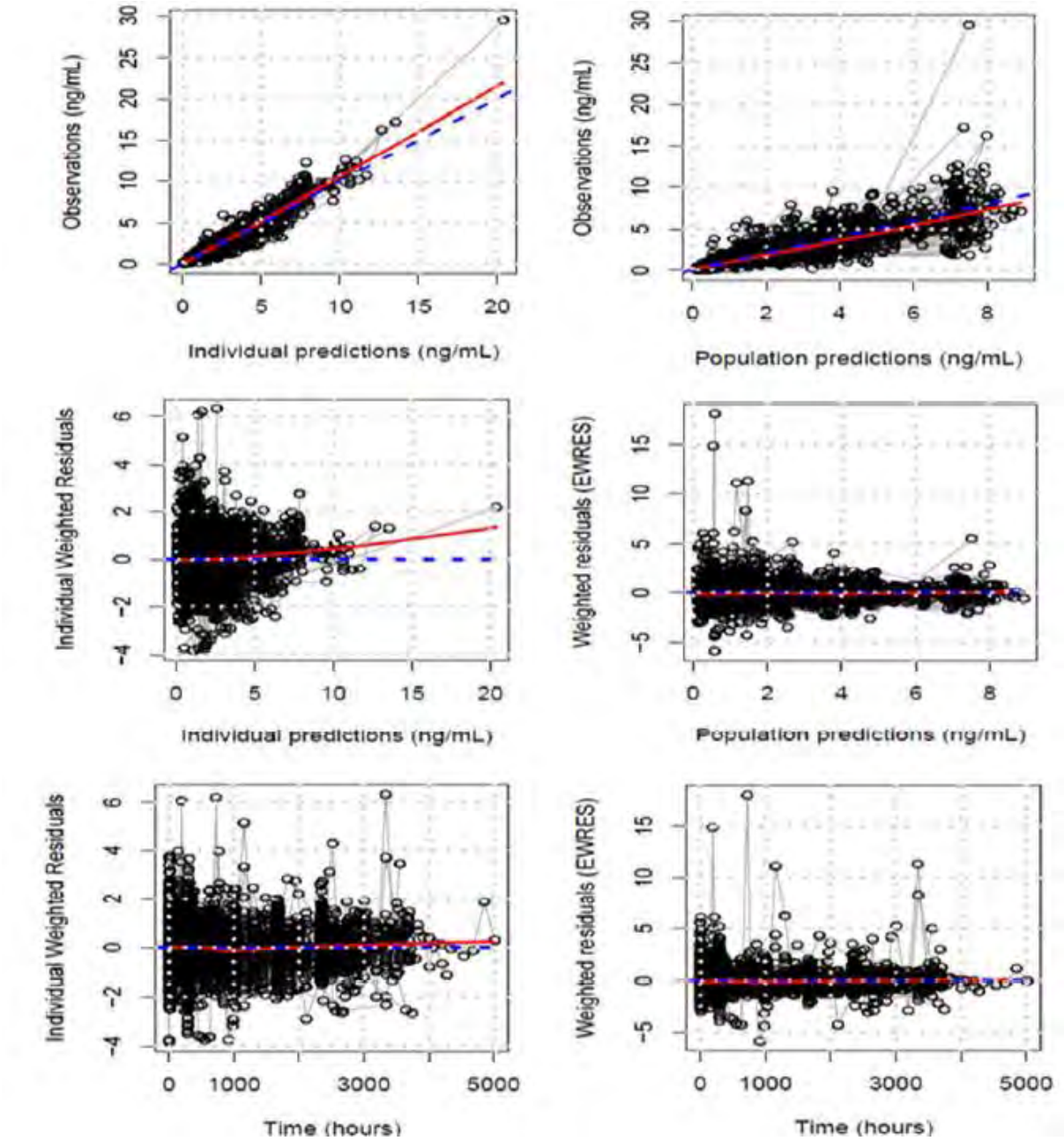
This 3-compartment disposition model was then applied to the analysis of Sublocade and Subutex data in Studies 11-0020 and 12-0005.

A first-order absorption rate constant was used for SL absorption of buprenorphine following administration of Subutex SL tablets.

For Sublocade, the absorption of buprenorphine from the SC injection site was described by a dual absorption model: (i) a first-order absorption to characterize the rapid absorption process associated with the early peak, and (ii) a transit compartment absorption model to mimic the slow delivery of buprenorphine from the SC depot.

Fixed-effect and random-effect parameters for clearance and volumes of distribution were fixed based on the previous estimates obtained by fitting IV data alone. All other model parameters were estimated, with the exception of the variance of FSC (bioavailability of Sublocade) and k_{72} (rate constant from transit to central compartment) which were fixed to 0 and 0.1, respectively.

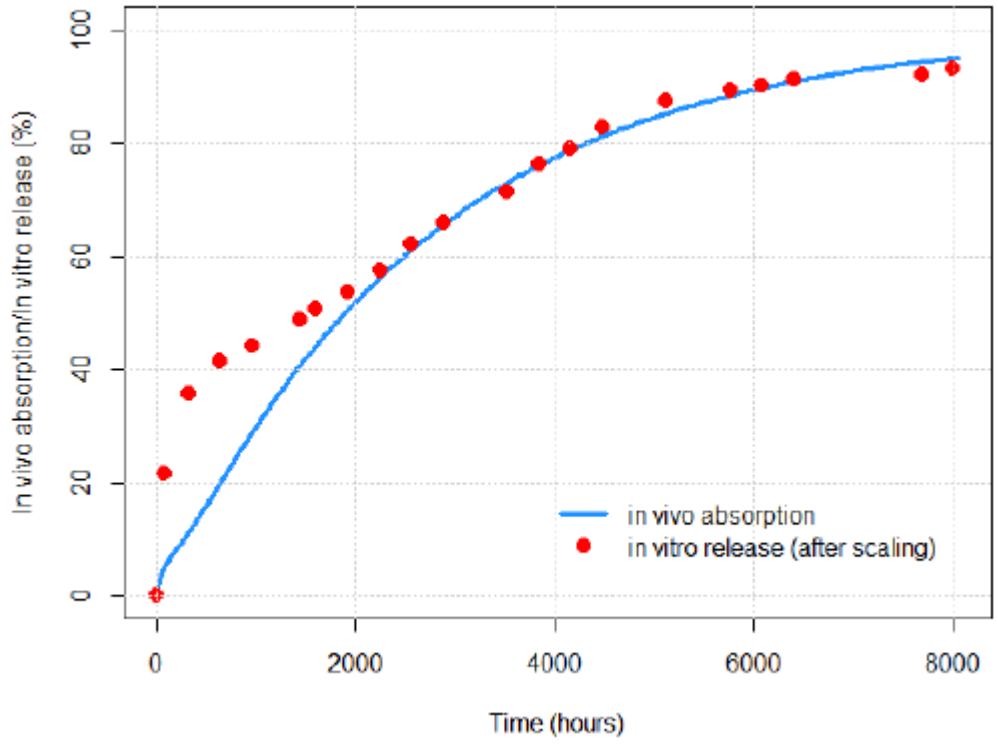
Figure 51 Standard Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Blue dashed line=identity line or y-axis; Red curve=Spline through the data. Data from all studies are shown. Source: Figure 6

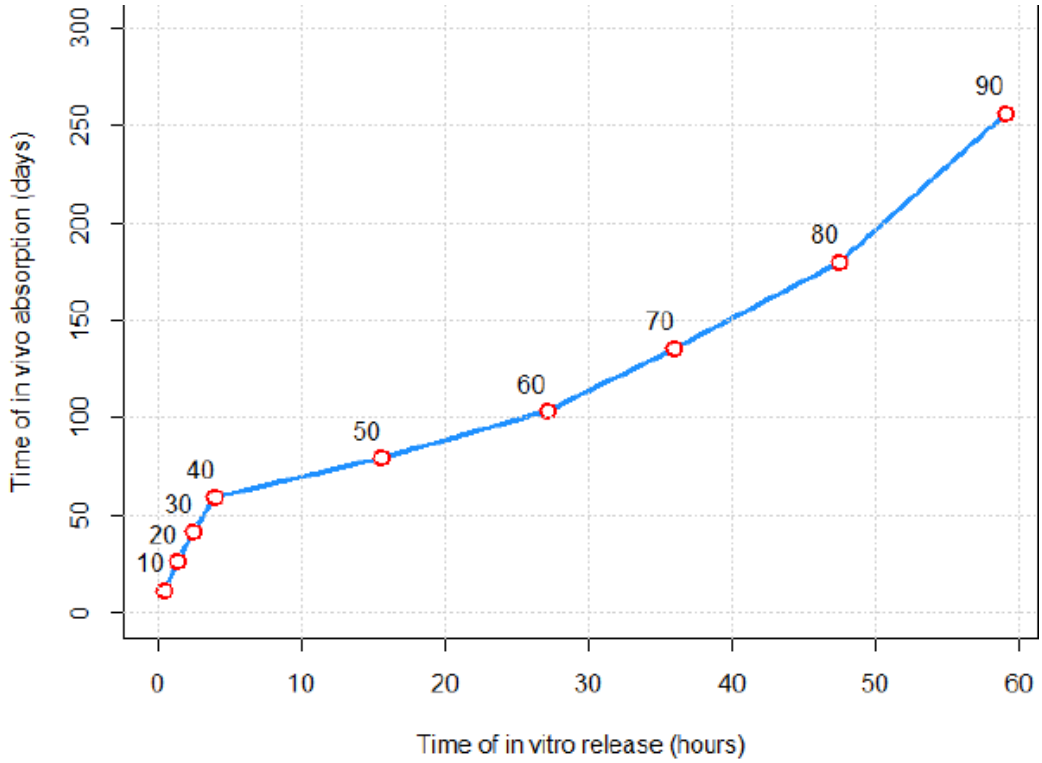
Comparison of *in-vitro* and *in-vivo* data showed a more rapid initial release of drug *in vitro* that was not reflected on the *in-vivo* absorption-time profile. Simple Level A correlation could not be established.

Figure 52 Comparison of Scaled *In-Vitro* Release (Lot 184) and *In-Vivo* Absorption



Blue curve=predicted cumulative absorption profile i*n vivo* based on modelling; Red dots=observed *in-vitro* data
Scaling on both axes was applied to in-vitro data to achieve a reasonable overlay of *in-vitro* and i*n-vivo* profiles Source: Figure 13

Figure 53 Levy Plot Comparing Times to Achieve a Given Percentage of Drug Released *In Vitro* and Absorbed *In Vivo*



Dots correspond to the percentages (10% to 90%) of drug released/absorbed in vitro/in vivo, respectively Source: Figure 14

21.1.3.8. PopPK analysis INDV-6000-Q01 Concentration-QT analysis

Concentration-QT analysis for Sublocade using plasma concentration and ECG data pooled from studies 10-0011, 11-0020, 12-0005, 13-0001, and 13-0006: 1114 subjects.

Objectives:

- To evaluate whether there is a concentration-related effect of buprenorphine and norbuprenorphine on QT interval after accounting for the effect of relevant concomitant medications and illicit drug use on HR and/or QT in opioid-dependent subjects.
- To predict the concentration-related effects of buprenorphine on QTc interval at therapeutic and supra-therapeutic concentration levels.

Matching buprenorphine and norbuprenorphine plasma concentrations and 12-lead electrocardiograms (ECGs) were pooled across clinical studies conducted with Sublocade in opioid-dependent subjects. Concentration-QT models were developed to describe the effects of buprenorphine and norbuprenorphine on corrected QT (QTc) interval, after accounting for the effect of relevant concomitant medications and illicit drug use on heart rate (HR) and/or QT in opioid-dependent subjects.

Table 49 Mean, Median, and 90% CIs for the Geometric C_{max} and the Delta QTc and the Bias-Corrected 90% CI of the Upper Bound

Dose	Geometric Mean C_{max} (ng/mL)			Delta QTc (msec)			
	Mean	Median	90% Confidence Interval	Mean	Median	90% Confidence Interval	Bias-Corrected 90% Confidence Interval
100 mg Q28D	3.44	3.43	3.25 to 3.63	-0.17	-0.16	-0.65 to 0.29	-0.65 to 0.29
300 mg Q28D	8.12	8.12	7.54 to 8.72	-0.40	-0.38	-1.52 to 0.66	-1.52 to 0.67
2x300 mg Q28D	16.2	16.2	15.1 to 17.4	-0.79	-0.75	-3.04 to 1.32	-3.05 to 1.34

Source: Table 3:

After accounting for the covariates that may influence HR and QT in subjects with Opioid Use Disorder an effect of buprenorphine on QT is not seen at therapeutic and supra-therapeutic doses of Sublocade.

22. Attachment: additional evaluation material

22.1. 4.2 DOSE AND METHOD OF ADMINISTRATION

Patients appropriate for Sublocade are adults who have undergone induction on a buprenorphine-containing product. Withdrawal signs and symptoms should be suppressed (COWS ≤ 12) before transitioning to Sublocade.

Dosing and induction of buprenorphine-containing products should be based on instructions in their Product Information.

FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. DO NOT ADMINISTER Sublocade INTRAVENOUSLY OR INTRAMUSCULARLY (see section 4.4 Special Warnings and Precautions for use).

•Only healthcare providers should prepare and administer Sublocade.

•Administer Sublocade monthly with a minimum of 26 days between doses.

• Initiating treatment with Sublocade as the first buprenorphine product has not been studied. Initiate Sublocade treatment only following induction and dose adjustment with a transmucosal buprenorphine containing product.

• Administer each injection only using the syringe and safety needle included with the product.

• Do not administer part of a dose

Recommended dosing

Patients appropriate for Sublocade are adults who have initiated treatment on a transmucosal buprenorphine-containing product. The patient may only be transitioned to Sublocade after stabilisation on transmucosal buprenorphine (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

The recommended dose of Sublocade is 300mg monthly for the first two months. The recommended maintenance dose is 100mg monthly. However patients who do not show a satisfactory clinical response following the second dose can receive a maintenance dose of 300mg monthly.

Buprenorphine plasma levels in the month following the second 300mg dose are maintained with 100mg maintenance dosing. The 300mg maintenance dose achieves higher levels and reaches steady state after the fourth monthly injection (see section 5.2 pharmacokinetic properties).

A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Clinical supervision

Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot.

Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment. For some patients, treatment may continue indefinitely. If considering stopping treatment, the clinical status of the patient should be considered.

If Sublocade is discontinued, its extended-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal or buprenorphine effects and treated appropriately. After steady-state has been achieved (4-6 months), patients discontinuing Sublocade may have detectable plasma levels of buprenorphine for twelve months or longer. The correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

INSTRUCTIONS FOR USE

IMPORTANT INFORMATION:

• For abdominal subcutaneous injection only.

• To be administered by a healthcare professional only.

• Please read the instructions carefully before handling the product.

• Remove Sublocade from the refrigerator prior to administration. The product requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for his or her injection.

• Discard Sublocade if left at room temperature (below 30°C) for longer than 7 days.

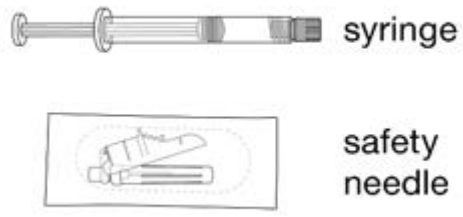
• Do not attach the needle until time of administration.

STEP 1: GETTING READY

Remove the foil pouch and safety needle from the carton. Open the pouch and remove the syringe.

Discard the oxygen absorber pack. It is not needed.

Figure 1

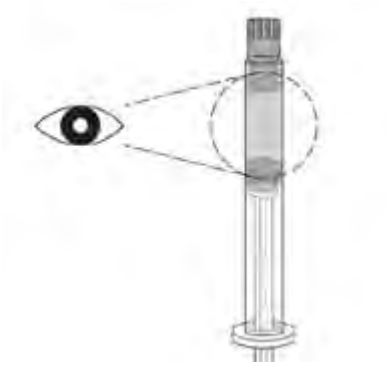


STEP 2: CHECK THE LIQUID CLARITY

Check that the medication for particulate matter and discolouration. Sublocade can range from clear colourless to yellow to amber. Variations of colour within this range do not affect the potency of the product.

If the medication is discoloured or contains particulate matter it should not be used.

Figure 2



STEP 3: ATTACH THE SAFETY NEEDLE

Remove the cap from the syringe and the safety needle supplied in the carton from its sterile package.

Gently twist the needle clockwise until it is tight and firmly attached.

Do not remove the plastic cover from the needle.

Figure 3

STEP 4: PREPARE THE ABDOMINAL INJECTION SITE

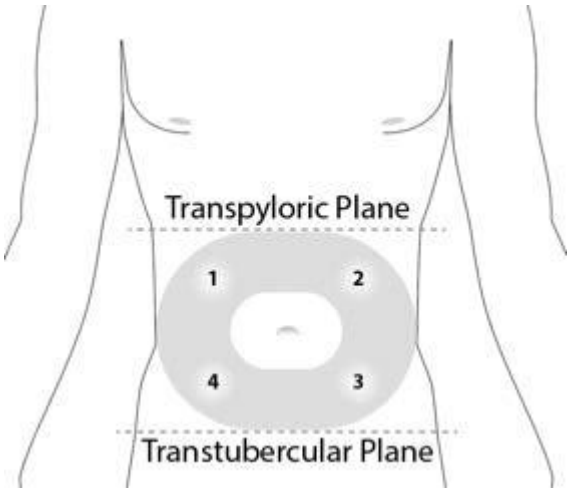
Choose an injection site on the abdomen between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position.

Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.

Clean the injection site well with an alcohol swab.

To avoid irritation, rotate injection sites following a pattern similar to the illustration in Figure 4. Record the location of the injection to ensure that a different site is used at the time of the next injection.

Figure 4



STEP 5: REMOVE EXCESS AIR FROM SYRINGE

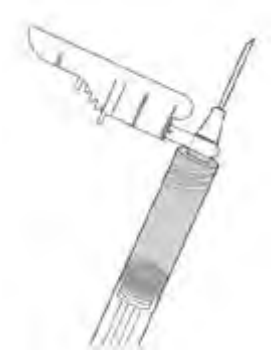
Hold the syringe upright for several seconds to allow air bubbles to rise. Due to the viscous nature of the medication, bubbles will not rise as quickly as those in an aqueous solution.

Remove needle cover and slowly depress the plunger to push out the excess air from the syringe.

• Small bubbles may remain in the medication. Large air gaps, however, can be minimised by pulling back on the plunger rod to pop air bubbles prior to expelling the air very slowly. Air should be expelled very carefully to avoid loss of medication.

If medication is seen at the needle tip, pull back slightly on the plunger to prevent medication spillage.

Figure 5



STEP 6: PINCH THE INJECTION SITE

Pinch the skin around the injection area. Be sure to pinch enough skin to accommodate the size of the needle. Lift the adipose tissue from the underlying muscle to prevent accidental intramuscular injection.

Figure 6

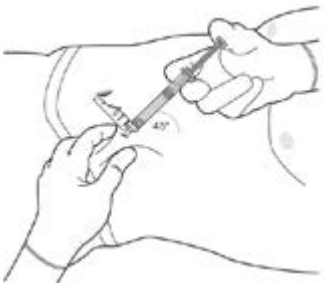
STEP 7: INJECT THE MEDICATION

Sublocade is for subcutaneous injection only. Do not inject intravenously or intramuscularly (see Section 4.4 Special Warnings and Precautions for Use).

Insert needle fully into the abdominal subcutaneous tissue. The actual angle of injection will depend on the amount of subcutaneous tissue.

Use a slow, steady push to inject the medication. Continue pushing until all of the medication is given.

Figure 7



STEP 8: WITHDRAW THE NEEDLE

Withdraw the needle at the same angle used for insertion and release the pinched skin.

Do not rub the injection area after the injection. If there is bleeding, apply a gauze pad or bandage but use minimal pressure.

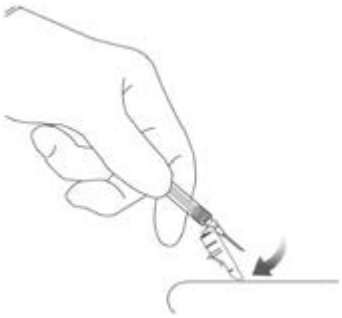
Figure 8

STEP 9: LOCK THE NEEDLE GUARD AND DISCARD THE SYRINGE

Lock the needle guard into place by pushing it against a hard surface such as a table (Figure 9).

Dispose of all syringe components in a secure sharps disposal container.

Figure 9



STEP 10: INSTRUCT THE PATIENT

Advise the patient that they may have a lump for several weeks that will decrease in size over time. Instruct the patient not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.

Removal of the Depot

In the event the depot must be removed, it can be surgically excised by a healthcare professional under local anaesthesia within 14 days of injection. The removed depot should be disposed of carefully

24. Information about the evaluator

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au

Australian Government
Department of Health
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: Buprenorphine

Product name: SUBUTEX/BUPRADEX/SUBUTEX FDT

Sponsor: Indivior Pty Ltd

Submission numbers: PM-2017-02665-1-1 ;

PM-2017-02666-1-1

eSubmission numbers: e002631; Sequence: 000;

e00 2528 Sequence 0001

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning
AHRQ	US Agency for Healthcare Research and Quality
AID	Absolute Infant Dose
COWS	Clinical Opiate Withdrawal Scale
C_{MAX}	Maximum Concentration
CI	Confidence Interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
ITT	Intention-to-Treat
LBW	Low Birth Weight
NAS	Neonatal Abstinence Syndrome
OBS	Observational
OUD	Opioid Use Disorder
PT	Preferred Term
RCT	Randomised Controlled Trial
RID	Relative Infant Dose
RR	Relative Risk
SGA	Small for Gestational Age
TME	Targeted Medical Event
WMD	Weighted Mean Difference

List of tables

List of figures

1. Submission details

1.1. Identifying information

Submission number	PM-2017-02665-1-1; PM-2017-02666-1-1
eSubmission number	e002631; e002585
eSubmission sequences covered in this report	0000 and 0001
Sponsor	Indivior Pty Ltd
Trade name	SUBUTEX/BUPRADEX/SUBUTEX FDT; SUBOXONE/ BUPRADONE/ SUBOXONE SUBLINGUAL FILM
Active substance	Buprenorphine

1.2. Submission type

This is a Category 1 Major Variation Application: Type F, changes to the product information requiring the evaluation of data. This is a literature based submission.

1.3. Drug class and therapeutic indication

Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.

The approved indication is for "treatment of opioid dependence within a framework of medical, social and psychological treatment".

1.4. Dosage forms and strengths

Table 1 Dosage forms and strengths

Products	**ARTG #**
SUBUTEX buprenorphine 0.4 mg (as hydrochloride) tablet blister pack	76661
SUBUTEX buprenorphine 2 mg (as hydrochloride) tablet blister pack	76662
SUBUTEX buprenorphine 8 mg (as hydrochloride) tablet blister pack	76663
SUBUTEX buprenorphine 0.4mg (as hydrochloride) tablet jar/can	76773
SUBUTEX buprenorphine 2mg (as hydrochloride) tablet jar/can	76774
SUBUTEX buprenorphine 8mg (as hydrochloride) tablet jar/can	76775

BUPRADEX buprenorphine 0.4mg (as hydrochloride) tablet blister pack	152475
BUPRADEX buprenorphine 2mg (as hydrochloride) tablet blister pack	152476
BUPRADEX buprenorphine 8mg (as hydrochloride) tablet blister pack	152477
SUBUTEX FDT buprenorphine 8 mg (as hydrochloride) tablet blister pack	134405
SUBUTEX FDT buprenorphine 16 mg (as hydrochloride) tablet blister pack	134407

Products	**ARTG #**
SUBOXONE 2/0.5 sublingual tablet blister pack	120159
SUBOXONE 8/2 sublingual tablet blister pack	120160
BUPRADONE 2/0.5 buprenorphine (as hydrochloride) 2 mg and naloxone (as hydrochloride) 0.5 mg sublingual tablet	152483
BUPRADONE 8/2 buprenorphine (as hydrochloride) 8 mg and naloxone (as hydrochloride) 2 mg sublingual tablet	152484
SUBOXONE SUBLINGUAL FILM 2/0.5 buprenorphine (as hydrochloride) 2mg / naloxone (as hydrochloride) 0.5mg soluble film sachet	163443
SUBOXONE SUBLINGUAL FILM 8/2 buprenorphine (as hydrochloride) 8mg / naloxone (as hydrochloride) 2mg soluble film sachet	163444
SUBOXONE SUBLINGUAL FILM 4/1 buprenorphine (as hydrochloride) 4mg / naloxone (as hydrochloride) 1mg soluble film sachet	211117
SUBOXONE SUBLINGUAL FILM 12/3 buprenorphine (as hydrochloride) 12mg / naloxone (as hydrochloride) 3mg soluble film sachet	211120

1.5. Dosage and administration

The Dosage and Administration section has been reproduced from the Subutex PI with the proposed amendments tracked. Similar changes are proposed for this section in the PIs for SUBUTEX/ BUPRADEX and SUBUTEX FDT. Existing text is shown in plain script. Changes proposed by the Sponsor are shown in green text.

DOSAGE AND ADMINISTRATION

Treatment with TRADENAME is intended for adults and children aged 16 years or over who have agreed to be treated for opioid dependence. When initiating TRADENAME treatment, the physician should be aware of the partial agonist profile of the molecule to the μ opioid receptor, which can precipitate withdrawal in opioid-dependent patients if given too soon after the administration of heroin, methadone or another opioid. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective and clear signs of withdrawal are evident. The route of administration of TRADENAME is sublingual. The sublingual formulation is not designed to be split or broken. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug.

Method of Administration

BUPRADEX should be placed under the tongue until dissolved. This usually occurs within 2 to 10min. Patients should not swallow or consume food or drink until the tablet is completely dissolved. ~~The initial dose of TRADENAME may precipitate a mild abstinence syndrome in opioid-dependent subjects. This may last up to 24 hours, but resolves with continued daily administration of TRADENAME~~. A dose is made up from BUPRADEX 2 mg and BUPRADEX 8 mg, which may be

placed sublingually all at the same time or in two divided portions; the second portion to be placed sublingually directly after the first portion has dissolved.

Starting TRADENAME

Following treatment induction, the patient should be rapidly stabilised on an adequate maintenance dose by titrating to clinical effect. An adequate maintenance dose holds the patient in treatment and suppresses opioid withdrawal effects, and is guided by reassessment of the clinical and psychological status of the patient.

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective and clear signs of withdrawal are evident.

Patients taking ~~Street~~ Heroin (or Other Short-acting Opioids): When treatment starts the dose of TRADENAME should be taken at least 6 hours after the patient last used opioids ~~or~~ and when the ~~early~~ objective signs of withdrawal appear. The Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment however clinical assessment of withdrawal symptoms with consideration of the patient's baseline presentation is important, particularly for patients in mild withdrawal (COWS score of ≤12).The recommended starting dose is 4 mg TRADENAME on day one, with a possible additional 4 mg depending on the individual patient's requirement. The suggested total dose for Day One is in the range of 8- 12 mg TRADENAME.

Patients on Methadone: Before starting treatment with TRADENAME, the maintenance dose of methadone should be reduced to ~~30 mg per day~~the minimum daily dose that the patient can tolerate. The first dose of TRADENAME should be taken at least 24 hours after the patient last used methadone. The initial 4-8mg TRADENAME induction dose should ideally be administered when ~~the early~~ objective withdrawal signs are evident (COWS >12). The suggested target total dose for Day One is in the range of 8- 12 mg TRADENAME.

During the initiation of treatment, closer dosing supervision is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

Dose adjustment in hepatic impairment

In patients with severe hepatic impairment, consider reducing the starting and titration doses by half compared to patients with normal liver function, and monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

No dose adjustment is necessary for patients with moderate hepatic impairment, although TRADENAME should be used with caution in these patients. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

No dosage adjustment is needed in patients with mild hepatic impairment.

Dosage Adjustment and Maintenance

The dose of BUPRADEX should be increased progressively according to the clinical effect in the individual patient ~~and should not exceed a maximum daily dose of 32 mg.~~ The dosage is adjusted in increments or decrements of 2 – 8 mg buprenorphine to a level that maintains the patient in treatment and suppresses opioid withdrawal effects according to reassessments of the clinical and psychological status of the patient.

In clinical studies many patients were stabilized on a daily maintenance dose of 12 mg/3 mg to 16 mg/4 mg of buprenorphine, although some patients may require higher doses. A maximum daily

dose of 32 mg should not be exceeded. During maintenance therapy, it may be necessary to periodically restabilise patients to new maintenance doses in response to changing patient needs.

Less than daily dosing

For patients who require supervised dosing, a less-than daily dosing regimen may facilitate supervised dosing in patients with opioid dependence that is uncomplicated by concomitant dependence on other agents with central nervous system (CNS) activity, including alcohol.

After a satisfactory stabilisation has been achieved, the frequency of dosing may be decreased to every-other-day at twice the individually titrated daily dose. Patients on < 8 mg/day may not find less-than-daily dosing adequate.

In some patients, three times a week (for example on Monday, Wednesday and Friday) may be used. The dose on Monday and Wednesday may be twice the daily dose, and the dose on Friday may be three times the individually titrated daily dose. However the dose given on any one day should not exceed 32 mg.

The patient should be observed following the first multi-dose administration to initiate the less-than daily dosing regimen and whenever treated with high doses. Patients who sporadically use concomitant CNS-active medications or substances should be monitored closely.

Reducing Dosage and Stopping Treatment

The decision to discontinue therapy with TRADENAME should be made as part of a comprehensive treatment plan. A gradual dose taper over a period of 21 days is shown in Table 4.

Note: changes to allow for buccal administration have also been included in the PIs for SUBOXONE FILM (buprenorphine/ naloxone) only.

~~Place SUBOXONE SUBLINGUAL FILM under the tongue. If an additional SUBOXONE SUBLINGUAL FILM is necessary to achieve the prescribed dose, place it sublingually on the opposite side from the first film, and in a manner to minimise overlapping as much as possible. If more than two films are required, place the next film or films after the first two have dissolved. The soluble film must be kept under the tongue until completely dissolved, which takes on average between 4 and 8 minutes.~~

Sublingual Administration

Place one film under the tongue, close to the base on the left or right side. If an additional film is necessary to achieve the prescribed dose, place an additional film sublingually on the opposite side from the first film. Place the film in a manner to minimize overlapping as much as possible. The film must be kept under the tongue until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it under the tongue on either side after the first 2 films have dissolved.

Buccal Administration

Place one film on the inside of the right or left cheek. If an additional film is necessary to achieve the prescribed dose, place an additional film on the inside of the opposite cheek. The film must be kept on the inside of the cheek until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it on the inside of the right or left cheek after the first two films have dissolved.

1.6. Proposed changes to the product documentation

The Sponsor is proposing 2 changes to the product information:

- *Change 1: removal of the contraindication for pregnancy and lactation (Type F)*
- *Change 2: revision of dosage and administration section (Type F)*

Proposed changes to the Dosage and Administration section of the PIs are as follows:

i. Inclusion of the Clinical Opiate Withdrawal Scale (COWS) as an objective assessment of withdrawal prior to commencing induction therapy;
ii. Amendment to the recommended starting dose for buprenorphine from '4 mg' to '4 to 8 mg', and specifying target dose range on day one being 8 to 12 mg in total;
iii. Specifying that increases or decreases in buprenorphine maintenance dose should be in increments of 2 to 8 mg, according to patient response during the dose stabilisation phase;
iv. Specify the usual maintenance dose of buprenorphine as 12 to 16 mg, although some patients may require higher doses (to a maximum of 32 mg), and alert prescribers to the need to reassess maintenance dose over time;
v. Allowing switching to from methadone to buprenorphine at daily doses of methadone greater than the current 30 mg, No specific maximum dose of methadone above which switching should not occur is proposed to be included in the revised PI.
v. Provide recommendations for less than once daily maintenance dosing using this formulation.

- *Change 3* (for SUBOXONE film only) – add buccal route of administration.

2. Background

2.1. Information on the condition being treated

Opioids are natural or synthetic substances that act at one of the three opioid receptor systems (mu, kappa and delta). Opioids have analgesic and central nervous system depressant effects as well as the potential to cause euphoria. In the United States, 5.1 million people (1.9 percent of persons age 12 or older) were estimated in 2015 to have used heroin at some point in their lives (Strain E, 2017). Opioid addiction is associated with increased mortality compared with the general population, principally due to higher rates of overdose and trauma. Opioid Use Disorder (OUD) is classically a relapsing, remitting illness. Individuals with OUD can misuse prescribed opioid medications or illicitly obtained heroin (Strain E, 2017). Multiple obstetric complications have been associated with opiate-dependence in pregnancy, although it is unclear whether this is due to the direct effects of opiates or associated poor ante-natal care. The complications include:

- Abruption placentae
- Foetal death
- Intra-amniotic infection
- Foetal growth restriction
- Foetal passage of meconium
- Preeclampsia
- Premature labour and delivery
- Premature rupture of membranes
- Placental insufficiency
- Miscarriage
- Postpartum haemorrhage
- Septic thrombophlebitis

(Change G, 2017).

An infant born to a mother with opiate use pregnancy is at risk of neonatal abstinence syndrome (NAS). NAS is not completely understood and includes a spectrum of signs indicating neonatal behavioural dysregulation. The characteristic signs of NAS reflect dysfunction in four

domains: state control and attention, motor and tone control, sensory integration, and autonomic functioning (Jansson L, 2017). Seizures can occur in 2-11% of infants. NAS can be objectively measured using a variety of instruments, the most common being the Finnegan Neonatal Abstinence Scoring System. An oral solution of morphine can be given to the infant if they display significant NAS signs despite supportive therapy (Jansson L, 2017).

2.2. Current treatment options

Opioid therapy substitution is considered the standard of care for pregnant women with OUD. In the US, opioid therapy substitution can occur with methadone or buprenorphine. Methadone substitution treatment has been associated with an increased risk of adverse neonatal outcomes, such as NAS, preterm birth <32 weeks of gestation, small for gestational age infants (SGA) or low birth weight (LBW), decreased head circumference, jaundice, thrombocytosis, arrhythmia, and admission to a neonatal intensive care unit (Seligman N and Berghella V, 2017). Buprenorphine use in pregnancy is less studied than methadone. Buprenorphine may pose a lower risk of overdose mortality than methadone. For the newborn, in utero exposure to buprenorphine rather than methadone may result in a lower risk of preterm birth, higher birth weight, and larger head circumference. It may also be associated a lower rate and severity of neonatal withdrawal (Berghella et al, 2017).

2.3. Clinical rationale

Since its international birth date, there has been considerable clinical experience with buprenorphine to treat OUD, including use in pregnancy and lactation. There is also published literature on use of buprenorphine in pregnant and lactating women. Thus, the contraindication of buprenorphine in pregnant and lactating women may be inconsistent with best medical practice and warrants further review.

2.4. Formulation

2.4.1. Formulation development

Not applicable. No changes to buprenorphine/ naloxone sublingual film formulation were made to accompany the proposed buccal route of administration.

2.4.2. Excipients

Not applicable.

2.5. Regulatory history

2.5.1. Australian regulatory history

SUBUTEX was first registered on the ARTG in Nov 2000. SUBUTEX FDT was first registered on the ARTG in Oct 2007. BUPRADEX was first registered on the ARTG in Feb 2009.

2.5.2. Orphan drug designation

Not applicable.

2.5.3. Related submissions

The changes proposed in this submission are also applicable to the Sponsor's buprenorphine/naloxone combination medicines indicated for the treatment of opioid dependence, which are the subject of a separate Category 1 application (Submission ID: PM-

2017-02666-1). The supporting documentation is identical for all changes that are common between the two Category 1 applications.

2.5.4. Overseas regulatory history

An overview of current foreign regulatory status with respect to removal of the contraindication for pregnancy and lactation proposed in the current application (i.e. Change 1) is provided in the table below:

Table 2 Foreign regulatory status

Region/Country	Location of *Pregnancy and Lactation*	Status	Approval Year
US	Precautions	Approved since initial approval	2002
UK	*Pregnancy:* Precautions *Breastfeeding:* Contraindication	Pregnancy has been approved as a precaution since initial approval	February 1998
Sweden	Precautions	Approved since initial approval	Oct 1999
France/Netherlands	Precautions	Approved since initial approval	July 1995

The proposed changes to dosage and administration section of the PI in the current application (i.e. Change 2) are to align with current global Core Company Data Sheet are similar to those currently approved in the rest of the world. These changes have been variously submitted and approved at different times in different regions. An assurance is provided by the Sponsor that the above changes have not been deferred, withdrawn or rejected in any region or country.

2.6. Guidance

Not applicable.

2.7. Evaluator's commentary on the background information

The background information is satisfactory.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

Module 1: administrative and prescribing information, lifecycle management tracking table, information relating to pharmacovigilance, information relating to paediatrics and foreign regulatory information.

Module 2: Clinical overview – Dosing; Clinical overview – Pregnancy and Lactation; Summary of clinical efficacy; Summary of clinical safety; literature references; and synopses of individual studies.

Module 5: Literature references

3.2. Paediatric data

The Sponsor is not submitting data to support use in a paediatric population. However, the indication of Pregnancy and Lactation contains infant data where the infants were exposed to buprenorphine in utero or via breast feeding.

3.3. Good clinical practice

The submission was a literature-based application.

3.4. Evaluator's commentary on the clinical dossier

The clinical dossier is satisfactory.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information for use in lactation

The Sponsor identified 2 published articles that were pivotal to the indication Use in Lactation; both studies were graded as Level III-2 evidence (comparative, non-randomised trials). Both of these studies aimed to investigate the infant dose of buprenorphine after exposure via breast milk. The two studies are presented as follows.

Lindemalm S., Nydert P., Svensson J.-O, Stahle L., Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. Journal of Human Lactation 2009; 25 (2): 199-205.

Study design

This was an open observational study with the aim of investigating the transfer of buprenorphine and its main active metabolite, nor-buprenorphine, into human milk and to determine the drug dose and effects in exposed infants.

Six women with OUD were recruited into the study. All women were maintained on buprenorphine during their pregnancies. None of the mothers had HIV infection, and all had negative urine toxicological tests for narcotics after the initiation of the buprenorphine maintenance therapy. Serological tests for hepatitis C were positive in all women. All pregnancies and births were uneventful. The mothers and infants stayed at the hospital for a minimum period of 7 days after the delivery for observation of NAS in the infant.

Methods

Breastfeeding was established at the maternity ward (in general, 5 to 8 days after the delivery) and repeated venous blood samples were obtained from 6 mothers during the 12-hour period starting just prior to the first daily dose and then at 1, 2, 3, 4, 6, 8, and 12 hours after the dose of buprenorphine. No blood samples were taken from the infants. The infants were breastfed on demand, and a sample of milk was collected 6 to 8 times from the mothers during approximately 24 hours. The weight of the infant was measured before and after nursing to estimate the ingested milk volume. Urine (10 mL) was sampled from the infants (4-20 hours) and mothers (5-12 hours) after the morning dose of buprenorphine was taken by the mother. All infants were followed up in the clinic 1 month after discharge from the hospital. The somatic growth (changes in weight, length, and head circumference measurements) and the general development (skin colour and firmness, heart—breath rates, muscle tonus, central nervous irritability signs according to Finnegan score of abstinence, history in sleep and wakeful cycles

during the last 24-hour period) of the infants were assessed 1 month after discharge from the hospital by the same senior paediatrician.

Liquid chromatography/mass spectrometry (LC/MS) was used to quantify buprenorphine levels in collected plasma, milk, and urine. Area under the milk concentration-time curves (milk AUC_{0-24}) and mother plasma concentration-time curves (mother AUC_{0-24}) were calculated using the mixed log linear trapezoidal rule, and if the 24-hour sample was missing, the researchers used the last value carried forward. The buprenorphine and nor-buprenorphine infant dose intake during 24 hours was calculated by multiplying the breast milk concentration (mol/L) with the molecular weight of buprenorphine (467.65 g/mol) and nor-buprenorphine (413.65 g/mol) and the weight difference before and after breast milk intake, assuming a density of 1000 g/L of breast milk. The calculated total infant dose was performed under the assumption of equivalent activity.

Results
Four infants showed signs of NAS, manifested at the second day of life. The symptoms were of mild grade, and pharmacological treatment with morphine replacement therapy was necessary in 1 infant. No other neonatal adaptive problems occurred during the first week of life. The measured plasma peak concentrations in mothers varied from 9.4 to 38.7 nmol/L for buprenorphine and from 10.9 to 38.2 nmol/L for nor-buprenorphine. The area under the concentration curve (24 hours) varied from 0.06 to 0.20 (mg.h/L) in milk and 0.03 to 0.10 in plasma for buprenorphine and from 0.03 to 0.15 in milk and 0.06 to 0.22 (mg.h/L) in plasma for nor-buprenorphine. Buprenorphine and nor-buprenorphine were found in low levels in the infants' urine. Breastfed infants were exposed to a calculated buprenorphine dose per kg bodyweight less than 1% (0.18%-0.77%), with an average milk/plasma area under the curve of 1.7 (range, 1.1-2.8) for buprenorphine and 0.7 (range, 0.4-1.2) for nor-buprenorphine.
The development of the infants 1 month after discharge from the hospital was uneventful, and all had normal weight gain.

Conclusions
Breastfed infants were exposed to a calculated buprenorphine dose per kg bodyweight of less than 1%. No signs of abnormal development were found in the infants at the time of discharge from the hospital when the breastfeeding was established or at the follow-up review at 1 month. The researchers concluded that this data supported the use of buprenorphine in breast feeding, but close monitoring of the infant was required.

Ilett K.F., Hackett L.P., Gower S., Doherty D.A., Hamilton D., Bartu A.E. Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breast milk during maternal buprenorphine substitution treatment. Breastfeeding Medicine 2012; 7 (4): 269-274.

Study design

The aim of this study was to estimate the dose of buprenorphine and its primary metabolite nor-buprenorphine that a breastfed infant would receive during maternal maintenance treatment with buprenorphine. It was an open observational study.

Methods
Seven women with OUD were recruited from a single centre in Australia. The women were visited at home 3 weeks after birth and provided with a sample collection kit consisting of labelled sample tubes, a data collection sheet and information forms. The infants were weighed at this visit. A 2-page questionnaire was delivered to the mother requesting information on the commencement of breastfeeding and duration of breastfeeding. Mothers were asked to rate their breastfeeding pattern as ''all breastfeeds,'' ''nearly all breastfeeds,'' ''about half are

breastfeeds,'' or ''only one breastfeed per day.' Data was obtained on maternal age, weight, birth, and buprenorphine dose. Infant data included gestational age, 1-minute and 5-minute Apgar scores, evidence of NAS in hospital and at follow-up, birth weight, and weight at follow-up and breastfeeding. The Modified Finnegan Scale was used to assess severity of NAS. Mothers were instructed to take their daily dose of buprenorphine at 8am, and to collect up to 12 samples of breast milk (4mL) over a 24-hour period. A urine sample was also collected on the study day and screened for amphetamines, benzodiazepines, cocaine metabolites, opiates and carboxylic acid. Buprenorphine and nor-buprenorphine in milk (1 mL) were quantified by an ultraperformance liquid chromatography (UPLC)–electrospray interface–tandem mass spectrometry (MS/MS) assay.

The milk concentration–time datasets were subjected to non-compartmental pharmacokinetic analysis to calculate area under the curve (AUC) for 0–24 hours and average concentration (C_{avg}), defined as AUC for 0–24 hours/24, across the 24-hour dose interval. Milk creamatocrit was measured and absolute infant dose (AID), defined as C_{avg} · daily milk intake, and relative infant dose (RID), defined as 100 · AID/weight-adjusted maternal daily dose via milk were calculated, assuming a milk intake of 0.15 L/kg/day.

Results
The mothers' mean age was 31 years, with a mean weight of 72.8 kg. Median buprenorphine dose was 7 mg, with a range from 2.4 to 24mg once daily. The urine drug screen conducted on the study day revealed that two subjects were negative for all drugs, whereas another two were negative for amphetamines, opiates, and cocaine, two were positive for benzodiazepines, and four were positive for THC. Their infants were four girls and three boys, with normal Apgar scores. Three infants required transfer to a special Level 2 nursery. Four infants had NAS scores of 9 and above, but only one required pharmacological treatment with morphine. On discharge from the hospital, five infants were exclusively breastfed, and two were supplemented with formula. At follow-up 2 infants had NAS scores of 2, and 1 had a score of 8? The mean age and weight were 1.12 months and 4.32 kg, respectively, on the study day. All were tracking according to their expected weight-for-age percentiles from birth to the study day and were exhibiting normal sleep patterns. One infant was still being treated with morphine at 5 weeks of age.

There was wide inter-subject variability in milk C_{avg}. This was 10.3-fold for buprenorphine. The mean maximum concentration (C_{max}) of buprenorphine in milk was 9.1 (4.8–13.4) µg/L at 4.2 (2.1–6.3) hours after dosing, whereas for nor-buprenorphine the maximum concentration was 2.1 (0.9– 3.3) µg/L at 4.0 (2.1–5.8) hours after dosing. Mean (95% confidence interval) nor-buprenorphine concentration in milk and AID values (1.94 [0.79–3.08] µg/L and 0.29 [0.12–0.46] µg/kg/day, respectively) were approximately half those for buprenorphine (3.65[1.61–5.7] µg/L and 0.55 [0.24–0.85] µg/kg/day, respectively). Similarly, the mean RID values were 0.18% (0.11–0.25%) for nor-buprenorphine and 0.38% (0.23–0.53%) for buprenorphine. The breastfed infants showed no adverse effects and were progressing as expected.

Conclusion
The estimated RID values were 0.18% (0.11–0.25%) for nor-buprenorphine and 0.38% (0.23–0.53%) for buprenorphine based on samples of breast milk collected from the mother. No adverse events were detected in the infants.

4.2. Studies providing pharmacokinetic information for buccal administration of buprenorphine/ naloxone

The buccal route is supported by seven (7) phase 1 pharmacokinetic (PK) studies, and a phase 2 safety and tolerability study showing the buccal route to have similar pharmacokinetics, safety,

and tolerability profiles as compared to the sublingual route of administration in a range of dosage strengths from 2 mg/0.5 mg to 16 mg/4 mg buprenorphine/naloxone combination. All data pertaining to the buccal route submitted in this application were previously provided to the TGA for review under the Category 1 application for SUBOXONE SUBLINGUAL FILM (PM-2009-01902-3-1) and are provided again, with the exception of study 20-293-SA. Study 20-293-SA is a new study that is being submitted in this application.

Study 20-293-SA was a dose proportionality study was conducted to compare the rate and extent of absorption of five dosages (2/0.5 mg, 4/1 mg (2 x 2/0.5 mg), 8/2 mg, 12/3 mg, and 16/4 mg) of buccally applied film. The objective of this single-dose, open-label, randomized, 3-period, 5-treatment, 3-way crossover study was to compare the rate and extent of absorption of five dosages (2/0.5 mg, 4/1 mg (2 x 2/0.5 mg), 8/2 mg, 12/3 mg, and 16/4 mg) of buprenorphine/naloxone film strip (buccal) investigational formulations, manufactured by MonoSol Rx, LLC for Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours. Data from 32 to 36 subjects for each treatment were included in the pharmacokinetic analysis.

Exposure to buprenorphine, naloxone, and norbuprenorphine increased with buccal doses of buprenorphine/naloxone in the film strips. Based on linear regression of the dose-normalized values of Cmax, AUClast, and AUCinf, there was a less than proportional increase in exposure to buprenorphine with increasing dose; the negative slope in the regression line appeared to be due to slightly higher values for two subjects after administration of 2/0.5 mg and 8/2 mg. However, linear regression analysis indicated that the increase in peak and overall exposure to naloxone was slightly greater than proportional with increasing dose. Peak and overall systemic exposure to norbuprenorphine was proportional to the administered dose in buprenorphine film strips.

4.3. Summary of pharmacokinetics

These studies confirm buprenorphine is excreted into breast milk. The two studies used different methodologies to assess an estimated infant dose of buprenorphine after exposure via breast milk. In Lindemalm et al (2009) buprenorphine and nor-buprenorphine were found in low levels in the infants' urine. Breastfed infants were exposed to a calculated buprenorphine dose per kg bodyweight less than 1% (0.18%-0.77%). In Ilett et al (2012) the estimated RID values were 0.18% (0.11–0.25%) for nor-buprenorphine and 0.38% (0.23–0.53%) for buprenorphine based on data obtained from breast milk.

4.4. Evaluator's overall conclusions on pharmacokinetics

In both studies the RID was <1%, which is below the 10% margin which is classically accepted as safe for infant exposure to a drug via breast milk. These studies support the removal of lactation as a contraindication and replacement with precautionary advice.

The new study for buccal administration of SUBOXONE film supported the proposed additional route of administration. This product can be administered either sublingually or buccally with a similar PK profile throughout the dose range.

5. Pharmacodynamics

No data.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

No dose finding studies were submitted. For the indication of Use in Pregnancy and Lactation, the doses of buprenorphine varied across trials and tended to reflect local prescribing practices.

6.2. Evaluator's conclusions on dose finding for the pivotal studies

Not applicable.

7. Clinical efficacy

7.1. Use in Pregnancy and Lactation

The Sponsor identified 6 published studies which were pivotal to the Use in Pregnancy indication. Of these, 3 studies were Level I evidence (evidence from a systematic review of all relevant RCTs) and 3 studies were Level II evidence (evidence from properly designed RCTs). All 6 studies have been evaluated. Of note, there is some overlap in the data set. The 3 systematic reviews all included the same 3 RCTs (Jones et al 2005, Jones et al 2010 and Fischer et al 2006), which have been assessed as pivotal to the application and thus have been evaluated separately in addition to inclusion in the systematic reviews.

The systematic review by Zedler et al (2016) also included 15 observational trials. Brogly et al (2014) included 9 cohort studies. Minozzi et al (2013) only included the 3 RCTs. There are 7 secondary (non-pivotal) publications which are all either sub-studies or secondary analyses of one of the RCTs (Jones et al 2010). There are two other secondary studies, both prospective comparative observational cohort studies (Binder 2008, Kahila 2008), and 4 supportive studies. All of the non-pivotal studies are considered supportive and were not individually evaluated.

It is important to note that the primary comparator in these studies is methadone. Methadone is not contraindicated in pregnancy or during lactation in Australia. It is an acceptable comparator.

7.1.1. Study ID

Zedler B.K, Mann A.L, Kim M.M, Amick H, R, Joyce A.R, Murrelle E.L and Jones H.E. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. Addiction. 2016 Dec;111(12):2115-2128

7.1.1.1. Study design, objectives, locations and dates

The study by Zedler et al (2016) was a systematic review designed to assess the safety of buprenorphine compared with methadone to treat pregnant women with OUD and provide quantitative treatment effect estimates for selected pregnancy outcomes. This study focussed on birth outcomes and not NAS. The researchers searched the PubMed and Embase databases and the Cochrane Database of Systematic Reviews from their inception through to Feb 2015.

7.1.1.2. Inclusion and exclusion criteria

Studies were included in the systematic review if they met the following criteria:

- Were randomised controlled trials (RCTs) or observational studies (case-control or cohort)

- Enrolled opioid-dependent women
- Compared buprenorphine or buprenorphine-naloxone with methadone
- Reported original data on one or more specified pregnancy related outcomes

7.1.1.3. Study treatments

The study treatments were buprenorphine or buprenorphine-naloxone treated subjects compared to methadone treated subjects.

7.1.1.4. Efficacy variables and outcomes

The pregnancy outcomes were:

- Spontaneous foetal death
- All foetal death
- Foetal growth outcomes (birth weight, low birth weight, small for gestational age, intrauterine growth restriction, head circumference)
- Foetal/congenital anomalies
- Sudden infant death syndrome
- Foetal/child neurodevelopment
- Maternal adverse events (AEs) during pregnancy

7.1.1.5. Randomisation and blinding methods

The review consisted of 3 randomised trials, although the method of randomisation is not specified. There were 15 cohort studies.

7.1.1.6. Analysis populations

Three RCTs (n = 223) and 15 cohort observational trials (n = 1923) met the inclusion criteria.

7.1.1.7. Sample size

The total sample size was 2146 patients, although the sample size for each outcome varied according to how many studies investigated that particular outcome.

7.1.1.8. Statistical methods

Two researchers extracted data independently from each included paper into standardised tables and resolved discrepancies by consensus. Studies were categorised as RCTs or observational trials based on the elements as reported. For RCTs, the researchers assessed randomisation adequacy, allocation concealment, missing outcome data, selective outcome reporting and blinding of participants, study personnel and assessors according to standards of the US Agency for Healthcare Research and Quality (AHRQ). The unit of analysis was pregnancies or live births, depending on the outcome. The researchers conducted a meta-analyses of the unadjusted study data using random effects models to account for heterogeneity among the studies and estimated unadjusted treatment effects as weighted mean differences (WMDs) for continuous outcomes and risk ratios (RRs) for binary outcomes.

Statistical significance was defined as a 95% confidence interval (CI) for the pooled effect that did not include zero for WMDs or 1.0 for RRs. The researchers anticipated a large amount of missing data based upon on the challenges of this study population. To account for this, the researchers decided to include only unadjusted outcome data as available from studies with low or medium risk of bias in the main analyses. To examine the stability of the main estimates, sensitivity analyses were conducted by including high risk of bias studies or imputing missing binary data under best- and worst-case scenarios. Observational studies were combined with similar study methods and clinical variability and calculated summary treatment effect estimates separately by study design. Inconsistency (heterogeneity) across studies was evaluated using the I^2 statistic. For comparisons with 10 or more studies funnel plots were

evaluated to assess potential publication bias. Strength of evidence for each outcome was based on guidance established by AHRQ using five domains: study limitations, directness, consistency, precision and reporting bias. The assigned grade (high, moderate, low, insufficient) represents the degree of confidence in the effect estimates for an outcome.

7.1.1.9. Results for the primary efficacy outcome

In the meta-analyses using unadjusted data and methadone as comparator, buprenorphine was associated with lower risk of preterm birth [RCT risk ratio (RR) =0.40, 95% confidence interval (CI)=0.18, 0.91; Observational (OBS) RR=0.67, 95% CI=0.50, 0.90], greater birth weight [RCT weighted mean difference (WMD)=277 g, 95% CI=104, 450; OBS WMD=265 g, 95% CI=196, 335] and larger head circumference [RCT WMD=0.90 cm, 95% CI=0.14, 1.66; OBS WMD=0.68 cm, 95% CI=0.41, 0.94]. No treatment differences were observed for spontaneous foetal death, foetal/congenital anomalies and other foetal growth measures, although the power to detect such differences may have been inadequate due to small sample sizes.

Table 3 Summary of Efficacy results (Zedler)

Outcome	**Number of studies (pregnancies or live births)**	**Summary effect (95% CI)**	**Strength of evidence**
Spontaneous foetal death			
RCT	2 (187)	RR = 0.26 (0.03-2.31)	Low
Observational	3 (271)	RR = 1.17 (0.32-4.27)	Low
Foetal/Congenital Anomalies			
RCT	1 (131)	RR = 0.42 (0.02-10.08)	Insufficient
Observational	4 (933)	RR = 1.18 (0.39-3.62)	Low
Preterm birth			
RCT	3 (166)	RR = 0.40 (0.18-0.91)	Low
Observational	7(1343)	RR = 0.67 (0.50-0.90)	Moderate
Birth Weight, g			
RCT	2 (150)	WMD = 324 (32-617)	Low
Observational	6 (1085)	WMD = 265 (195-335)	Moderate
Low Birth Weight			
Observational	2 (222)	0.51 (0.17-1.59)	Low

Small for Gestational Age RCT Observational	 1 (131) 2 (692)	 RR = 0.63 (0.06-6.77) RR = 0.67 (0.34-1.31)	 Insufficient Low
Intrauterine Growth Restriction Observational	 2 (385)	 RR = 0.80 (0.57-1.12)	 Low
Head Circumference, cm RCT Observational	 2 (150) 5 (960)	 WMD = 0.9 (0.14-1.66) WMD = 0.68 (0.41-0.94)	 Low Moderate
Sudden Infant Death Syndrome Observational	 1 (83)	 0% BUP Vs 6% METH (p=0.19)	 Insufficient
Neurodevelopment foetus RCT Observational	 1 (175) 2 (198)	 Foetal heart rate and motor activity suppression: BUP<METH (p<0.05) Visual latency at 52 months of age BUP<METH (p=0.02)	 Insufficient Insufficient
Non-serious maternal adverse events RCT	 1 (175)	 77% BUP Vs 93% METH (p=0.003)	 Insufficient
Serious Maternal adverse events RCT	 1 (175)	 9% BUP Vs 16% METH (p=0.19)	 Insufficient

7.1.1.10. Evaluator commentary

The evaluation of the RCTs produced evidence that was either low or insufficient to draw robust conclusions. The significant findings (i.e., findings of a moderate strength of evidence) were limited to observational studies for only some of the outcomes.
Buprenorphine treatment of maternal opioid use disorder during pregnancy was not associated with greater harms than methadone treatment, and moderately strong evidence indicated lower risk of preterm birth, greater birth weight and larger head circumference with buprenorphine. The latter two findings may due to the fact that methadone is causally associated with small birth weight babies.

7.1.2. Study ID

Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. Am J of Epidemiol. 2014, Vol 180, No 7, 673-686.

7.1.2.1. Study design, objectives, locations and dates

This study was a systematic review. The goals of this study were to conduct a systematic review of the published literature and perform an analysis of the association of prenatal buprenorphine maintenance therapy versus methadone maintenance therapy exposure on the neonate. Computerised searches were performed in PubMed, the Cochrane Central Register of Controlled Trials and the Cochrane database, and included publications from January 2000 through October 2013. Twelve published studies met the inclusion criteria; all were cohort studies or RCTs.

7.1.2.2. Inclusion and exclusion criteria

The inclusion criteria were comparative studies of buprenorphine versus methadone exposure during pregnancy and effect on neonatal outcomes.

7.1.2.3. Study treatments

The study treatments were buprenorphine or methadone in pregnant women, administered once daily. The method of prenatal agonist therapy administration differed across studies: in most of the RCTs, buprenorphine and methadone were administered by observed daily dosing at the study clinics; in the US cohort studies, only methadone was administered by observed daily dosing; in cohort studies from France, women receiving methadone had stricter follow-up than those receiving buprenorphine; in other European studies, take-home doses of both treatments was permitted; and in some studies, treatment administration was not described.

7.1.2.4. Efficacy variables and outcomes

Binary outcomes were pharmacological treatment for NAS, preterm birth (<37 weeks' gestation), and illicit maternal opioid use detected late in pregnancy. Continuous outcomes were the mean difference in length of hospital stay, length of NAS treatment, amount of morphine used to treat NAS, gestational age at birth, and neonatal birth weight, body length, and head circumference.

7.1.2.5. Randomisation and blinding methods

Four studies were RCT, although the method of randomisation is not specified.

7.1.2.6. Analysis populations

Not applicable.

7.1.2.7. Sample size

A total of 515 buprenorphine-exposed and 855 methadone-exposed neonates were included in the analysis. Most summary estimates were based on fewer neonates because of data availability.

7.1.2.8. Statistical methods

Most studies reported crude estimates, and these were included in the analysis. Sensitivity analyses were performed to assess heterogeneity, publication bias, and confounding. Summary estimates were calculated separately by study design (RCT vs. cohort study) to examine

consistency with overall estimates. Although the number of comparative studies included was small, the researchers recalculated summary estimates excluding 1 study at a time to see if the summary estimates were heavily influenced by a particular study.

Heterogeneity among studies was statistically assessed with the Cochran Q statistic and Galbraith plots and was quantified by the I^2 statistic. Publication bias was visually examined using funnel plots. Cohort studies have consistently suggested that confounding by indication would likely occur via use of buprenorphine versus methadone as the former is more likely to be prescribed in more stable opioid-dependent pregnant women. Therefore, the researchers concluded that methadone exposure could exacerbate poor outcomes (confounding by indication) and buprenorphine could augment better outcomes due to the differences in the study population. The researchers estimated what they believed to be plausible values for the prevalence of confounding by indication (0.40), where methadone exposure corresponded to a harmful effect and buprenorphine exposure corresponded to a positive effect (assuming the studies were not randomised).

7.1.2.9. Participant flow

Three of the 4 RCTs had considerable dropout rates across treatment arms and conducted per-protocol analysis as the primary analysis. No other information is provided on participant flow.

7.1.2.10. Results for the primary efficacy outcome

The unadjusted NAS treatment risk was lower (risk ratio = 0.90, 95% confidence interval (CI): 0.81, 0.98) and mean length of hospital stay shorter (−7.23 days, 95% CI: −10.64, −3.83) in buprenorphine-exposed versus methadone-exposed neonates. In treated neonates, NAS treatment duration was shorter (−8.46 days, 95% CI: −14.48, −2.44) and morphine dose lower (−3.60 mg, 95% CI: −7.26, 0.07) in those exposed to buprenorphine. Buprenorphine-exposed neonates had higher mean gestational age and greater weight, length, and head circumference at birth. Fewer women treated with buprenorphine used illicit opioids near delivery (risk ratio = 0.44, 95% CI: 0.28, 0.70). Simulations suggested that confounding by indication could account for some of the observed differences.

7.1.2.11. Evaluator commentary

Buprenorphine demonstrated superior foetal outcomes compared to methadone. The risk of NAS was slightly reduced in buprenorphine exposed infants, and the mean length of hospital stay was significantly shorter. Buprenorphine-exposed neonates had higher mean gestational age and greater weight, length, and head circumference at birth. This may be due to methadone being causally associated with a decrease in these outcomes.

7.1.3. Study ID

Minozzi Silvia, Amato Laura, Bellisario Cristina, Ferri Marica, Davoli Marina. Maintenance agonist treatments for opioid-dependent pregnant women. Cochrane Database of Systematic Reviews 2013 NO: 12 DOI: 10.1002/14651858.CD006318.pub3

7.1.3.1. Study design, objectives, locations and dates

This study was from the Cochrane Database of Systematic Reviews and was designed to assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions for child health status, neonatal mortality, retaining pregnant women in treatment and reducing the use of substances. Due to the broad objective criteria, not all findings are relevant to this submission (for e.g., articles not evaluating buprenorphine). The researchers searched the Cochrane Drugs and Alcohol Group Trials Register (September 2013), PubMed (1966 to September 2013), CINAHL (1982 to September 2013), reference lists of relevant

papers, sources of ongoing trials, conference proceedings and national focal points for drug research. Only four RCTs with 271 participants satisfied the inclusion criteria for this review. Three compared methadone with buprenorphine (223 participants) and one compared methadone with oral slow-release morphine (48 participants). The latter is not relevant to this submission and is not considered further.

7.1.3.2. Inclusion and exclusion criteria

The inclusion criteria were any RCTs assessing the efficacy of any maintenance pharmacological treatment for opiate-dependent pregnant women.

7.1.3.3. Study treatments

Three trials compared a methadone dose of between 20 and 140 mg/day with a buprenorphine dose of between 2 and 32 mg/day.

7.1.3.4. Efficacy variables and outcomes

Primary outcomes
For the woman
1. Drop-out from treatment, as measured by the number of women who had dropped out at the end of the intervention
2. Use of primary substance of abuse
2.1 Use of primary substance as measured by the number of women using heroin during or at the end of treatment (self-report or urine analysis results)
2.2. Use of primary substance at follow-up as measured by the number of women using heroin at the end of follow-up (after childbirth)
3. *Obstetric outcomes*
3.1 Third trimester bleeding
3.2 Foetal distress and meconium aspiration
3.3 Caesarean section
3.4 Abnormal presentation
3.5 Medical complications at delivery
3.6 Breastfeeding following delivery
3.7 Puerperal morbidity

For the child
4. Health status measured as:
4.1 Birth weight
4.2 APGAR score (Activity, Pulse, Grimace, Appearance and Respiration score)
4.3 Neonatal abstinence syndrome, measured using the Finnegan scale
4.4 Prenatal and neonatal mortality
Secondary outcomes
5. Side effects for the mother
6. Side effects for the child

7.1.3.5. Randomisation and blinding methods

All 3 studies were RCTs. One study was an open study, whilst the remaining were double-blind.

7.1.3.6. Sample size

Methadone versus buprenorphine was compared in 3 trials with 223 participants

7.1.3.7. Statistical methods

Two authors independently performed the 'Risk of bias' assessment for RCTs and CCTs using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*. The recommended approach for assessing risk of bias in studies included in Cochrane Reviews is a two-part tool, addressing seven specific domains, namely: sequence generation and

allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. The overall quality of evidence was evaluated using the GRADE system:

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: any estimate of effect is very uncertain.

The researchers analysed dichotomous outcomes by calculating the RR for each trial with the uncertainty in each result being expressed by its confidence interval. Continuous outcomes were analysed by calculating the mean difference (MD) or the standardised mean difference (SMD) with 95% CI. Heterogeneity was assessed by means of the I^2 statistic and Chi^2 test for heterogeneity. The cut points were an I^2 value > 50% and a P value of the Chi^2 test of < 0.1.

7.1.3.8. Participant flow

The 3 trials were at high risk of attrition bias because the attrition rate was high (30-40%) and unbalanced between the groups.

7.1.3.9. Results for the primary efficacy outcome

Methadone versus buprenorphine: the drop-out rate from treatment was lower in the methadone group (risk ratio (RR) 0.64, 95% CI 0.41 to 1.01, three studies, 223 participants). There was no statistically significant difference in the use of primary substance between methadone and buprenorphine (RR 1.81, 95% CI 0.70 to 4.69, two studies, 151 participants). For both, the quality of evidence was judged as low. Birth weight was higher in the buprenorphine group in the two trials that could be pooled (mean difference (MD) -365.45 g (95% CI -673.84 to -57.07), two studies, 150 participants). The third study reported that there was no statistically significant difference. For APGAR score, neither of the studies which compared methadone with buprenorphine found a significant difference. For both, the quality of evidence was judged as low. Many measures were used in the studies to assess NAS. The number of newborns treated for NAS did not differ significantly between groups. The quality of evidence was judged as very low. The authors concluded they did not find sufficient significant differences between methadone and buprenorphine to determine that one treatment is superior to another for all relevant outcomes.

7.1.3.10. Results for other efficacy outcomes

Use of primary substance of abuse: 2 trials were pooled with 151 participants; the result was not statistically significant. No study reported on substance abuse at follow up.

Obstetric outcomes

Data was not recorded for third trimester bleeding.

Pre-term delivery: in 1 study, 3 children were delivered prematurely in the methadone group and two in the buprenorphine group. In a second study, 1 infant was born pre-term in the methadone group. In the third study, there were 19% pre-term deliveries in the methadone group and 7% in the buprenorphine group. The result was not statistically significant.

Foetal distress and meconium aspiration: In 1 study there was 1 case of meconium aspiration in the buprenorphine group.

Caesarean section: in 1 study, there was 1 caesarean section in each group. In the second study, there were 2 cases of planned caesarean section at week 40 in the buprenorphine group. In the

third study, there were 37% caesarean sections in the methadone group and 29% in the buprenorphine group. The result was not statistically significant.

Abnormal presentation: In one study, all births were normal presentation. In the second study this event was not reported on. In the third study, there were 14% abnormal foetal presentations in the methadone group and 5% in the buprenorphine group. The result was not statistically significant.

Medical complications at delivery: In one study, 1 subject required vacuum extraction due to prolonged delivery. No medical complications were reported in the second study. In the third study there were 51% medical complications at delivery in the methadone group and 31% in the buprenorphine group (p=0.03).

Breast feeding following delivery: data was not reported in any of the studies.

Puerperal morbidity: No cases of puerperal morbidity were reported in 2 of the studies and data was not collected in the third.

Infant outcomes

Prenatal and neonatal mortality: In one study there was one sudden intrauterine death at 38 weeks of pregnancy and one late abortion at 28 weeks of pregnancy, both in the methadone group. In the first woman urine toxicology revealed 66% opioid-positive results, 48% cocaine-positive results and 16% benzodiazepine-positive results over the study period. Cigarette consumption was a mean of 35 per day. In the second woman all urine toxicology results were negative.

Adverse Events

No side effects for the mothers were reported in 2 studies. In the third study there were 14/ 89 (16%) serious adverse events in the methadone group and 8/86 (9%) in the buprenorphine group (RR 1.69, 95% CI 0.75 to 3.87). There were also 83/89 (93%) non-serious adverse events in the methadone group and 66/86 (77%) in the buprenorphine group (RR 4.77, 95% CI 0.59 to 38.49). The results were not statistically significant.

No side effects for the child were reported in 2 studies. In the third study there were 6/73 (8%) serious adverse events in the methadone group and 1/58 (2%) in the buprenorphine group (RR1.22, 95%CI 1.07 to 1.38), which was in favour of buprenorphine. There were also 34/73 (47%) non-serious adverse events in the methadone group and 29/58 (50%) in the buprenorphine group (RR 1.08, 95%CI 0.74 to 1.59). The results were not statistically significant.

7.1.3.11. Evaluator commentary

This was a high quality metaanalysis but the quality of evidence for all positive findings was low to very low. There was no robust evidence that buprenorphine is superior to methadone as a treatment option for opioid dependent pregnant women. Given it is proposed to remove the contraindication of use in pregnancy for buprenorphine it is not necessary that superiority be demonstrated. The limited published data that was assessed in this metaanalysis suggests that buprenorphine is no worse than methadone in pregnancy.

7.1.4. Study ID

Jones HE, Johnson RE, Jasinski DR, O'Grady KE, Chisholm CA, Choo RE, Crocetti M, Dudas R, Harrow C, Huestis MA, Jansson LM, Lantz M, Lester BM, Milio L. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. Drug and Alcohol Dependence 2005; 79: 1-10.

7.1.4.1. Study design, objectives, locations and dates

This study was designed to compare the NAS in neonates of methadone and buprenorphine maintained pregnant opioid-dependent women and to provide preliminary safety and efficacy data for a larger multi-centre trial. The study was a controlled, randomised, double-blind double-dummy design. Participants were recruited from heroin-dependent patients admitted between May 2000 and March 2003, inclusive, to the residential unit of the Centre for Addiction and Pregnancy, a multi-disciplinary treatment program. Patients were admitted to a separate facility 7 days before their estimated due date. Neonates were kept as inpatients and observed for NAS for 4 days. Neonates treated for NAS were discharged following 24 hour of no medication and NAS scores $\leq$ 8. Following hospital discharge, NAS observations were continued through to day 10 in the original drug treatment facility.

7.1.4.2. Inclusion and exclusion criteria

Inclusion criteria were: 21–40 years of age; estimated gestational age by sonogram of 16–30 weeks; DSM-IV diagnosis of current opioid dependence; requesting maintenance pharmacotherapy; recent self-reported opioid use (more than 4 days of use in the past 7 days); and an opiate-positive urine sample at intake.

Exclusion criteria were: a urine positive for undocumented methadone during intake; a current DSM-IV diagnosis of alcohol abuse or dependence; self-reported use of benzodiazepines (more than seven times per month and/or more than once a week); currently taking medication for another Axis I disorder; presence of a serious concurrent medical illness contraindicating study participation; diagnosis of pre-term labour; evidence of foetal malformation; positive HIV test; or positive sickle cell trait.

7.1.4.3. Study treatments

Participants received methadone for 3–5 days until signing written informed consent. Following this, participants were switched from daily methadone to an equivalent dose of immediate-release morphine divided into 4 daily doses. Once randomised, participants were switched from their individualised dose of immediate-release morphine onto an equivalent dose of double-blind study medication. This first day total dose for methadone ranged from 20–60 mg to 8–12 mg for buprenorphine. Medications were administered double-blind and double-dummy (i.e., each dosing day 12 sublingual tablets followed by 40 ml of oral liquid were administered). A participant assigned to active methadone received 12 sublingual placebo tablets followed by her dose of methadone (20–100 mg) in 40 ml liquid, while a study participant assigned to active buprenorphine received her dose (4–24 mg) in 12 sublingual buprenorphine tablets followed by 40 ml of placebo liquid.

Doses of 60 mg methadone and 12 mg buprenorphine were selected as target doses. A flexible (i.e., individualised) dosing schedule was used. Double-blind medication dose increases or decreases were made through clinical decisions based on compliance in taking medication, participant request, urine toxicology and participant self-reports of opioid withdrawal symptoms or craving. Dose changes were made no more often than every 2 weeks unless clinically indicated. A unit dose increase or decrease was 5–10 mg of methadone and 2mg of buprenorphine. To maintain the double-blind, the actual dose changes were known only to pharmacy staff. Across medication groups, an average of 3.5 dose increases were made (range 0–6), 3.7 for methadone and 3.3 for buprenorphine until delivery.

Treatment of NAS: Treatment with NAS was initiated when NAS scores were $\geq$ 9. Morphine solution, equivalent to morphine 0.02 mg/drop, was administered to the infant. Doses of

morphine were given every 3–5 h with feeding. Neonates scoring 9–12 received 2 drops, those scoring 13–16 received 4 drops and those scoring 17–20 received 6 drops. Weaning was initiated after a neonate was maintained on a stable dose for 48h. Neonates were reduced in medication by one drop per day if every score for 24 h was 8 or below. If scores were nine or greater at any time that day, weaning was deferred.

7.1.4.4. Efficacy variables and outcomes

7.1.4.5. Primary outcome measures included:

(1) number of neonates requiring morphine drops for NAS;
(2) peak NAS score, using the modified 19-item Finnegan Scale;
(3) total amount of morphine drops administered to treat NAS; and
(4) total days of neonatal hospital stay from delivery until discharge from the hospital.

Secondary outcome measures obtained from the medical record included birth-weight, head circumference, length, prematurity, gestational age at delivery, sex, Apgar scores at 1 min and 5 min, neonatal and maternal urine toxicology (tested for opioids, cocaine, barbiturates, and benzodiazepines), type of birth, birth presentation, use of anaesthesia, and maternal days of hospital stay in the postpartum unit. Maternal secondary outcome measures included: the average number of days in treatment from day of randomisation until delivery to document equivalent drug exposure; the overall percentage of urine samples positive during treatment for each illicit drug and Complete Blood Counts and Blood Chemistry Panels performed at study entry and every 4 weeks until study discharge.

7.1.4.6. Randomisation and blinding methods

Subjects were assigned to one of the two treatment groups using a computerised dynamic balanced randomisation. The study was double-blind.

7.1.4.7. Analysis populations

All analyses were performed on subjects who completed the study (n=20).

7.1.4.8. Sample size

A total of 30 women were randomized to methadone (n = 15) and buprenorphine (n = 15). The final sample size enrolled in treatment at delivery was 11 women stabilized on methadone and 9 women stabilized on buprenorphine.

7.1.4.9. Statistical methods

Alpha was set at .05 for each of the four primary analyses. In the case of the binary outcome variable treated for NAS, a chi-square goodness of fit test was conducted. The discrete outcome variables of total amount of opioid agonist medication administered to treat NAS and length of neonatal stay in the hospital were assumed to follow a Poisson distribution and thus Poisson regressions were conducted.

7.1.4.10. Participant flow

Of the 30 randomised patients, 20 delivered while enrolled in the study; the remaining 10 dropped out during the study. Of those randomised to buprenorphine reasons for drop-out included discharged for medical condition (n = 1), missed consecutive dosing days (n = 4), and elected to withdraw (n = 1). Of those randomised to methadone reasons for discharge included missed consecutive dosing days (n=3) and elected to withdraw (n = 1). No significant demographic differences were observed between completers and non-completers. All subsequent analyses utilise only the completer sample. One buprenorphine-maintained mother delivered twins. Data for variables known to be altered by twin status (i.e., gestational age at delivery, birth weight, head circumference, and length) were therefore not included in the statistical analyses

7.1.4.11. Baseline data

Table 4 Baseline Demographic Characteristics (Jones 2005)

Measure	Methadone (n = 11)	Buprenorphine (n = 9)	F or χ^2 (d.f.)	p
Demographics				
Mean age	30.3 (1.1)	30.0 (1.2)	0.03 (1, 18)	0.871
Race (%)			1.89 (2)	0.390
African–American	63.6	88.9		
White	27.3	11.1		
Other	9.1	0.0		
Mean estimated gestational at entry	23.6 (1.17)	22.8 (1.27)	0.20 (1, 18)	0.663
Mean years of education	10.0 (1.1)	10.33 (1.3)	.04 (1, 18)	0.844
Employment (%)			3.61 (2)	0.165
Unemployed seeking	72.7	33.3		
Unemployed not seeking	27.3	55.6		
Homemaker	0	11.1		
Drug use				
Cocaine use (past 30 days) (%) 63.6		88.9	1.68 (1)	0.195
Opioid use >4× day (%) 54.5		55.6	0.002 (1)	0.964
**Days of alcohol use in past 30 days	1.0 (0.53)	0.78 (0.49)	0.10 (1, 17)	0.761
Nicotine use in past 30 days (%) 81.8		77.8	–	–
Income				
Public assistance in past month ($)	94.9 (75.7)	114.0 (52.9)	0.809 (1, 17)	0.381
Pregnancy history				
Mean previous number of pregnancies	3.9 (0.68)	5.2 (0.87)	1.45 (1, 18)	0.245
Mean previous number of full term deliveries	2.45 (0.52)	3.22 (0.65)	0.87 (1, 18)	0.363
Mean previous number of pre-term deliveries	0.18 (0.12)	0.44 (0.21)	1.28 (1, 18)	0.273
Mean previous number of miscarriages/induced abortions	0.91 (0.34)	1.11 (0.42)	0.14 (1, 18)	0.712
Mean number of living children	2.64 (0.48)	3.44 (0.60)	1.14 (1, 18)	0.301
Medical complications				
% Positive for hepatitis C 18.2 11.1 – –				

Notes: The initial five participants were stratified using five strata of age (18–29 or 30–40); cocaine use past month (0–3 or 4–8); alcohol use past month (0 or >1 day); opioid use (3 or >3 times per day); or liver disease (yes/no). The remaining 25 participants were stratified using strata described before. The strata were reduced and changed following the advice of the Data Safety Monitoring Board.
Values in parenthesis are S.E. values.

7.1.4.12. Results for the primary efficacy outcome

Twenty percent of buprenorphine-exposed and 45.5% of methadone-exposed neonates were treated for NAS (p = .23). The total amount of medication administered to treat NAS in methadone-exposed neonates was three times greater than for buprenorphine-exposed neonates (p = .13). Buprenorphine exposed neonates remained in the hospital for a significantly (p = .021) shorter period of time (1.3 days difference) than methadone-exposed neonates. One buprenorphine-exposed neonate and two methadone-exposed neonates were admitted to the NICU and spent 2, 4 and 7 days, respectively. None of the NICU admissions were due to opioid withdrawal. Importantly, daily peak NAS total scores over all observation days did not significantly differ between groups (p = .25).

7.1.4.13. Results for other efficacy outcomes

Buprenorphine-exposed neonates were not statistically significantly heavier at birth than the methadone-exposed neonates. On average, buprenorphine-exposed neonates weighed 528 g more than the methadone-exposed group. Group means were not statistically significantly for head circumference or length. Gestational age at delivery and Apgar scores at 1 min and 5 min were similar between the two treatment groups. None of the neonates were observed to have illicit drugs in their urine at delivery. All but one birth in each group were vaginal, all births were normal presentation, use of anaesthesia and maternal length of hospital stay were similar

among groups. Only one mother (methadone treated) was positive for any illicit drugs (opiates) at delivery. No complications were observed and mothers from both treatment groups were discharged from the hospital after a similar time period. No major or minor congenital abnormalities were observed in either group.

The average doses at delivery for methadone and buprenorphine were 79.1 mg and 18.7 mg, respectively. Low rates of illicit drug use prior to delivery were observed during the study in both groups. Methadone and buprenorphine groups had percentages of urine samples positive for opioid (15.6, 16.7), cocaine (11.2, 15.2), benzodiazepines (0.4, 2.5), amphetamine (0, 0), and marijuana (7.5, 0), respectively. Eight of 11 methadone and 7 of 9 buprenorphine maintained women were negative from all illicit drugs for 4 weeks or more prior to delivery. Complete Blood Counts and Blood Chemistry Panels showed similar pregnancy related changes and were comparable between groups.
Adverse events were similar for both medications and included typical opioid- or pregnancy-like effects with the most common being vomiting, fever, pain, constipation, headache, and insomnia.

7.1.4.14. Evaluator commentary

This was a well-designed study that was limited by the low number of completers (n=20). No firm conclusions regarding differences between methadone and buprenorphine can be drawn regarding the results due to the low power of the study.

7.1.5. Study ID

Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G. Neonatal abstinence syndrome after methadone or buprenorphine exposure. The New England journal of medicine 2010; 363:2320-31

7.1.5.1. Study design, objectives, locations and dates

This was a double-blind, double-dummy, flexible-dosing, randomised, controlled study in which buprenorphine and methadone were compared for use in the care of 175 pregnant women with opioid dependency at eight international sites (6 in the United States and 1 each in Austria and Canada). The study ran from between May 2005 and Oct 2008. The study was referred to as the Maternal Opioid Treatment: Human Experimental Research (MOTHER) project.

7.1.5.2. Inclusion and exclusion criteria

The inclusion criteria were opioid-dependent women between the ages of 18 and 41 years with a singleton pregnancy between 6 and 30 weeks of gestation, no medical or other conditions contraindicating participation, were not subject to pending legal action that might prevent their participation, had no disorders related to the use of benzodiazepines or alcohol, and did not plan to give birth outside the hospital at the study site.

7.1.5.3. Study treatments

Before randomisation, all participants received rapid-release morphine as inpatients to achieve medical stabilisation. A blinded, individualised dosing schedule was used for the study medications, and a double-blind method was used to implement dose-unit increases or decreases (with dose adjustments of 2 mg for buprenorphine and 5 or 10 mg for methadone). Dose adjustments entailed clinical decisions based on medication adherence, the participant's request, urine toxicology results, and self-reported symptoms of withdrawal or craving. Participants were required to receive daily medications under observation in the study clinic. They always received seven tablets (three in the size of an 8-mg tablet and four in the size of a 2-mg tablet) to place under the tongue for 5 minutes, or until the tablets dissolved. Each tablet contained buprenorphine or placebo. After receiving these tablets, participants received liquid containing methadone or placebo (40 ml at U.S. sites and 50 ml in Vienna).

7.1.5.4. Efficacy variables and outcomes

The five primary neonatal outcome measures were the number of neonates requiring treatment for NAS, peak NAS score, total amount of morphine needed for treatment of NAS, length of hospital stay, and head circumference. The seven secondary neonatal outcomes were the number of days during which medication was given for NAS, weight and length at birth, preterm birth (defined as birth at <37 weeks of gestation), gestational age at delivery, and 1-minute and 5-minute Apgar scores. The nine secondary maternal outcomes were caesarean section, weight gain, abnormal foetal presentation during delivery, anaesthesia during delivery, the results of drug screening at delivery, medical complications at delivery, study discontinuation, amount of voucher money earned for drug-negative tests, and number of prenatal obstetrical visits. Adverse events for all participants were collected.

NAS assessment was performed for a minimum period of 10 days after birth. Hospitalised neonates were examined every 4 hours by trained staff. Neonates discharged from the hospital before postnatal day 10 were expected to reside with the mother in a residential setting, where the evaluation was continued. NAS scores were obtained twice daily, at least 8 hours apart, with the use of a modified Finnegan scale (called the MOTHER NAS scale), which includes 28 items; 19 items were used for scoring and medication decisions. Scores on the modified scale range from 0 to 42, with higher scores indicating more severe withdrawal.

7.1.5.5. Randomisation and blinding methods

Seven sites contributed randomised data; one site screened participants but did not complete randomisation. The method of randomisation was not specified. The study was a double-blind double –dummy design, outlined in 7.2.5.3.

7.1.5.6. Analysis populations

The study population was divided into those who were randomised and those who completed the study. Analyses of neonatal outcomes were based on the subjects who completed the study

7.1.5.7. Sample size

A total of 175 underwent randomisation (86 in the buprenorphine group and 89 in the methadone group).

7.1.5.8. Statistical methods

Bonferroni's principle was used to set the family wise alpha level at 0.01 (nominal alpha level, 0.05 ÷ 5) for each of the five primary outcome measures at the time of the initial study design; an interim analysis requested by the data safety and monitoring board resulted in a recalculation of the alpha level on the basis of the O'Brien–Fleming spending function, such that the end-of trial alpha level was 0.0091 for each primary outcome measure. Bonferroni's principle was also used to set the family-wise alpha level at 0.003125 (nominal alpha level, 0.05 ÷ 16) for the secondary outcome measures. Poisson regression analyses were conducted for the total amount of morphine needed to treat NAS, neonatal length of stay in the hospital, number of days of treatment for NAS, estimated gestational age at delivery, amount of money earned for drug-negative tests, number of prenatal obstetrical visits, and Apgar scores at 1 minute and 5 minutes. Ordinary least-squares regression analyses were conducted for the peak score on the NAS scale during the assessment period, infant head circumference, and infant weight and length at birth. Logistic-regression analyses were conducted for the remaining dichotomous variables.

7.1.5.9. Participant flow

Of the 86 subjects assigned to receive buprenorphine, 28 discontinued the study (26 had voluntary reasons and 2 had involuntary reasons). Fifty-eight buprenorphine subjects

completed the study. Of the 89 subjects assigned to methadone, 16 withdrew (10 had voluntary reasons and 6 had involuntary reasons). The drop-out rates were high and unbalanced between the groups, complicating interpretation of the results.

7.1.5.10. Baseline data

Among the 131 participants who completed the study there were no significant differences between the buprenorphine and methadone groups with respect to any of the baseline characteristics.

7.1.5.11. Results for the primary efficacy outcome

The percentage of neonates requiring NAS treatment did not differ significantly between groups (P = 0.26), nor did the groups differ significantly with respect to the peak NAS score (P = 0.04) or head circumference (P = 0.04).
There were significant differences for the total amount of morphine needed for the treatment of NAS and the length of the hospital stay for neonates. On average, neonates exposed to buprenorphine required 89% less morphine than did neonates exposed to methadone (mean total doses of 1.1 mg and 10.4 mg, respectively; P<0.0091), and spent, on average, 43% less time in the hospital (10.0 vs. 17.5 days, respectively; P<0.0091).

7.1.5.12. Results for other efficacy outcomes

One of the 7 neonatal secondary outcome measures differed significantly between groups: neonates exposed to buprenorphine spent, on average, 58% less time in the hospital receiving medication for NAS than did those exposed to methadone (4.1 days vs. 9.9 days, P<0.003125). There were no significant differences in any of the nine maternal secondary outcomes. The methadone group had higher rates of non-serious maternal events overall (P = 0.003) and of non-serious maternal cardiovascular events in particular (P = 0.01). There was no significant difference with respect to any serious maternal or neonatal adverse events or any non-serious neonatal adverse events

7.1.5.13. Evaluator commentary

Infants exposed to buprenorphine required significantly less morphine for the treatment of NAS, a significantly shorter period of NAS treatment, and a significantly shorter hospital stay than did infants with prenatal exposure to methadone. However, buprenorphine exposure did not cause a reduction in the number of neonates requiring NAS treatment, peak NAS score, head circumference, any other neonatal outcome, or any maternal outcome. Women who were taking buprenorphine were more likely to discontinue treatment for voluntary reasons.

7.1.6. Study ID

Fischer G, Ortner R, Rohrmeister K, Jagsch R, Baewert A, Langer M, Aschauer H. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. Addiction (Abingdon, England) 2006; 101: 275 -81.

7.1.6.1. Study design, objectives, locations and dates

This was a randomised, double-dummy, double, flexible dose study conducted in 14 subjects. The aim was to evaluate the efficacy and safety of methadone versus buprenorphine treatment in pregnant opioid dependent women in terms of:

- the frequency and amount of additional opioids used by the mother as measured by urine toxicology;
- the frequency and amount of use of other substances of abuse (such as cocaine and benzodiazepines) by the mother as measured by urine toxicology;
- retention in treatment as measured by completion of the study;
- the severity and duration of the NAS as measured by the Finnegan Scale

The study took place in Vienna, Austria from 2000 to 2002.

7.1.6.2. Inclusion and exclusion criteria

Opioid-dependent pregnant women older than 18 years, who presented at the addiction clinic of the Medical University Vienna were included in the study if they provided informed consent and were willing to follow the protocol and to avoid use of illegal drugs whenever possible. Study entry was between weeks 24 and 29 of pregnancy. All subjects considered for entry had opioid-positive urine toxicology, but a cocaine-, benzodiazepine- and methadone-negative urinalysis result in addition to a negative result on an alcohol breath analyser at the screening visit. Women with tetrahydrocannabinol (THC)-positive urine toxicology results were allowed to enter the study. Women were excluded if they had severe somatic or other severe psychiatric diseases or a high-risk pregnancy.

7.1.6.3. Study treatments

During screening, all subjects were maintained on oral slow-release morphine. Subjects were admitted to the clinic for a minimum of 3 days during the induction of methadone or buprenorphine treatment in order to achieve 24-hour care. Subjects received either 8 mg buprenorphine or 40 mg methadone at the onset of moderate withdrawal symptoms on day 1. Doses were titrated according to a predefined titration algorithm: day 1 dosing was followed by either 55 mg methadone or 12 mg buprenorphine if withdrawal was present. Dose titration increments to 70, 85 and 100 mg per day were available during induction onto methadone (depending on clinical status) and increments to 16, 20 and 24 mg per day were available during buprenorphine induction (matched with placebo tablets/solution). The dosing schedule applied during the titration period of 5 days. However, flexible dosing was allowed during the entire study period, depending upon clinical wellbeing and Wang withdrawal score. Doses of buprenorphine were between 8 and 24 mg/day and doses of methadone ranged between 40 and 100 mg/day throughout the study.

7.1.6.4. Efficacy variables and outcomes

The European Addiction Severity Index was assessed on day 1 of treatment. Hamilton Depression scores, Wang Withdrawal scores (range 0–45) and the visual analogue scores for craving were assessed daily during the titration period and weekly during the entire investigational period; the self-reported number of cigarettes smoked daily was also obtained. Urine samples were taken twice-weekly throughout the study. Gynaecological investigations were undertaken on day 1, weeks 28, 32, 36 and 38 of pregnancy, and at the expected time of delivery. Following delivery, the women were investigated for congenital infections and anomalies. Neonates were observed for a minimum of 10 days on an in-patient basis under blinded conditions for the mothers' treatment condition and scored every 4 hours using the Finnegan scale (range 0–45). Infants with scores higher than 10 points were treated with oral morphine drops, according to body weight and total NAS score. Routine birth data (gestational age, weight, length, head circumference and Apgar score standardised 1, 5 and 10 minutes after delivery; range 0–10) were documented.

7.1.6.5. Randomisation and blinding methods

The study was double-blind. Randomisation was performed by the pharmacy department.

7.1.6.6. Analysis populations

Efficacy analyses took place on subjects who completed the study.

7.1.6.7. Sample size

A total of 18 subjects were enrolled and 14 completed the study (6 in the methadone group and 8 in the buprenorphine group).

7.1.6.8. Statistical methods

Given the small sample sizes, inferential statistics have been included to a limited extent, mostly for baseline comparisons; Fisher's exact tests were used for baseline comparisons of categorical variables. Data on interval level scales were analysed using *t*-tests for independent samples, or the Mann–Whitney test was used for highly skewed non-parametric data.

7.1.6.9. Participant flow

There were 4 drop-outs during the study – 1 subject in the methadone group experienced a stillbirth, a second had a late abortion and 2 subjects did not comply with scheduled study visits.

7.1.6.10. Major protocol violations/deviations

Two subjects did not comply with scheduled study visits.

No baseline data was provided.

7.1.6.11. Results for the primary efficacy outcome

All children were healthy, but five (*n* = 3 methadone, *n* = 2 buprenorphine) were delivered prematurely before week 37 of pregnancy; one was delivered at week 34, one at week 35 and three at week 36. There was no significant difference in birth weights (mean 2820 g) between the two treatment groups, either for premature or mature deliveries (*P* =0.489). Apgar scores ranged from 8.5 at 1 minute to 10 at both 5 minutes and 10 minutes in both groups and for both premature and full term neonates, with no difference found between treatment groups. Of the 14 neonates, 6 (3 in each treatment group) experienced no more than mild NAS and did not require treatment with morphine. For the 8 neonates who required treatment for their NAS symptoms, neonates of methadone maintained mothers required treatment on average 12 hours earlier (mean 60 hours after last dose of study medication, range 52–68; SD 11.3) than those born to the buprenorphine maintained group (mean after 72 hours; range 35–109; SD 35.2) (*P* = 0.537). The mean duration of treatment for NAS was 5.3 (range 4–7; SD 1.5) and 4.8 days (range 1–8; SD 2.9) in the methadone and buprenorphine groups, respectively (*P* = 0.766). There was no difference in the mean cumulative dose of morphine required to manage NAS in the two groups (methadone: 2.71 ± 1.68 mg; buprenorphine: 2.00 ± 2.00 mg; *P* = 0.640). Finnegan scores of neonates from mothers with high rates of cigarette use (greater than 10 per day) appeared to be higher than those from mothers who reported smoking less than 10 cigarettes per day.

7.1.6.12. Evaluator commentary

This is a small study with limited power to detect any positive associations. No statistically significant differences were found with respect to any of the outcomes.

7.1.7. Other efficacy studies in Pregnancy and Lactation

There are 7 secondary (non-pivotal) publications which are all either sub-studies or secondary analyses of one of the RCTs (Jones et al 2010). There are two other secondary studies, both prospective comparative observational cohort studies (Binder 2008, Kahila 2008), and 4 supportive studies.

The seven studies, either secondary analysis or a sub-study of Jones et al 2010 focused on NAS outcomes using the modified Finnegan scale reported in the original Jones 2010 et al study, but extending the analysis to include individual items included in the overall NAS scale, the relationship between dose of opioid replacement treatment and NAS outcomes, and the potential impact of ethnicity and rural verses urban location on NAS outcomes. Some of these studies evaluated the impact of opioid replacement during pregnancy on foetal heart rate, biophysical profiles of the neonate and neurobehavioral outcomes using the NICU Network Neurobehavioral Scale. These studies were less statistically reliable than the original Jones et al 2010 study.

Of the 2 prospective observational cohort studies, one compared pregnancy and birth outcomes, including NAS in infants exposed to buprenorphine, methadone or heroin. The other compared the effect or buprenorphine and methadone on neonatal biochemical markers, including hypoxic stress via cord serum samples and cord blood pH. The outcomes of these studies are consistent with the findings of the pivotal studies and are supportive only.

7.1.8. Analyses performed across trials: pooled and meta analyses

See Section 7.5.

7.1.9. Evaluator's conclusions on efficacy during use in pregnancy and lactation

- There is overlap between safety and efficacy assessments, as many maternal and foetal outcomes can be considered both a measure of efficacy but also a safety issue (for example, the development of NAS).
- Brogley et al (2014) estimated that the unadjusted NAS treatment risk was lower (risk ratio = 0.90, 95% confidence interval (CI): 0.81, 0.98) and mean length of hospital stay shorter (−7.23 days, 95% CI: −10.64, −3.83) in buprenorphine-exposed versus methadone-exposed neonates. In treated neonates, NAS treatment duration was shorter (−8.46 days, 95% CI: −14.48, −2.44) and morphine dose lower (−3.60 mg, 95% CI: −7.26, 0.07) in those exposed to buprenorphine. Buprenorphine-exposed neonates had higher mean gestational age and greater weight, length, and head circumference at birth. Fewer women treated with buprenorphine used illicit opioids near delivery (risk ratio = 0.44, 95% CI: 0.28, 0.70).
- Across the neonatal parameters evaluated, Minozzi et al (2013) found few differences between treatments. For all positive findings the quality of evidence was assessed as low to very low due to insufficient information and no robust conclusions can be drawn.
- Zedler et al (2016) analysed a wide range of birth outcomes with exception of NAS. Zedler et al (2016) identified no statistically or clinically significant difference between buprenorphine exposed infants and methadone exposed infants in the risk estimates for spontaneous foetal death, with the estimated RR (95% CI) calculated as RR = 0.26 (0.03 to 2.25) based on RCT; RR=1.52 (0.28 to 8.28) based on the OBS. The RR and ranges calculated for foetal/congenital anomalies based on RCT and OBS where 0.42 (0.02 to 10.08) and 1.18 (0.39 to 3.62) respectively. The analysis demonstrated that there were fewer pre-term births (RR=0.40 (0.18 to 0.91) RCTs; RR=0.67 (0.50 to 0.90) OBS) with buprenorphine exposure compared to methadone exposure. Also babies exposed to buprenorphine had significantly higher birth weight (Weighted Mean Difference (WMD) = 324 RCTs; WMD=265 OBS) and head circumference (WMD=0.90 RCTs; WMD-0.68 OBS) than those exposed to methadone. Zedler et al (2016) produced more firm findings, with positive findings graded as moderate strength of evidence for the observational trials.
- Of the 3 RCTs, the most powerful was the MOTHER project by Jones et al (2010), which had a larger cohort. Jones et al (2010) demonstrated that buprenorphine was statistically significantly superior to methadone for two NAS measures: the total amount of morphine used to treat NAS and the length or neonatal hospital stay. Secondary outcomes such as delivery type, gestational age, birth weight, Apgar scores, head circumference, and infant length were consistent between the buprenorphine exposed and methadone exposed infants and were generally reported within normal range.
- Small studies to assess superiority of one treatment over another were generally underpowered and failed to determine a statistically significant difference between treatments for major efficacy / safety endpoints. Equivalence of outcomes cannot be concluded on the basis of underpowered superiority studies.

7.2. Change in Dosage and Administration

The primary objectives of the clinical efficacy component of the changes to the Dosage and Administration sections of the PIs were:

- To demonstrate that the proposed changes to the buprenorphine induction regimen, dosage increments during treatment stabilisation, and the recommended maintenance dose generally necessary to maintain opioid withdrawal or craving control, have no detrimental impact on the overall efficacy of this medicine when used to treat opioid dependence.
- To demonstrate that buprenorphine may be administered to opioid dependent subjects less than once daily, while maintaining levels of efficacy similar to a once daily regimen.
- To demonstrate that the Clinical Opiate Withdrawal Scale (COWS) is a valid instrument with sufficient sensitivity to detect opioid withdrawal, and that a score of > 12 is a reasonable point at which to commence buprenorphine treatment. The use of this scale therefore enhances efficacy of this treatment.

7.2.1. Amendments to starting dose, flexible dosing adjustment and maintenance dose recommendations

The complete list of publications retrieved is in Table 1below. Of the 19 publications, Mattick 2003 supports the proposed additional amendment to the Subutex PI only to allow for less than once daily maintenance dosing. All studies except that by Oreskovich 2005 were conducted in subjects receiving buprenorphine maintenance treatment for opioid dependence. Oreskovish was conducted in subjects undergoing detoxification rather than maintenance treatment with buprenorphine. It was included because it provides comparative information on the proposed larger induction dose recommendation. All RCT, except Oreskovich 2005 used a short induction phase, a flexible dose stabilisation phase and a longer term maintenance phase to compare the dosages of buprenorphine and methadone, and relative efficacy outcomes.

7 of the 9 RCTs used buprenorphine sublingual, and 2 used buprenorphine plus naloxone sublingual as the test medication arm. 7 of these studies compared the buprenorphine containing regimen to methadone, usually administered as a solution. The duration of the studies ranged from 5 days to 6 months, with 6 studies treating the subjects for 3 months or more. The 9 RCTs treated a total of 1,478 subjects, with 992 assigned to buprenorphine-containing medications. Inclusion of the 8 secondary studies increased total subject numbers to 4,071 with approximately 1,600 assigned to buprenorphine-containing medications.

9 studies are non-comparative, not randomised or do not include key aspects relevant to all proposed dosing changes, while providing important data complementary to the other reports. Those studies will not be further discussed in this report. These studies are listed below.

Study category	Type of evidence (NHMRC 1999)	References Submitted
PIVOTAL	**LEVEL II** Evidence from properly designed randomized controlled trials (RCT)	Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction 2003; 98: 441-452. Petitjean S, Stohler R, Deglon J-J, Livoti S, Waldvogel D, Uehlinger C, Ladewig D. Double-blind randomized trial of s buprenorphine and methadone in opiate dependence. Drug and Alcohol Dependence 2001; 62: 97-104. Kakko J, Gronbladh L, Svanborg KD, von Wachenfeldt J, Ruck C, Rawlings B, Nilsson L-H, Heilig M. A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: A randomised controlled trial. American Journal of Psychiatry 2007; 164: 797-803. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Comparison of buprenorphine and methadone in the treatment of opioid dependence. The American Journal of Psychiatry 1994; 151: 1025-1030.
SUPPORTIVE	**LEVEL II** Evidence from properly designed randomized controlled trials (RCT)	Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine versus methadone in the treatment of opioid-dependent cocaine users. Psychopharmacology 1994; 116: 401-406. Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomised trial. International Journal of Neuropyschopharmacology 2008; 11: 641-653. Jones HE, Johnson RE, Jasinski DR, O'Grady KE, Chisholm CA, Choo RE, Crocetti M, Dudas R, Harrow C, Huestis MA, Jansson LM, Lantz M, Lester BM, Milio L. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. Drug and Alcohol dependence 2005; 79: 1-10. Hillhouse M, Canamar CP, Doraimani G, Thomas C, Hasson A, Ling W. Participant characteristics and buprenorphine dose. The American Journal of Drug and Alcohol Abuse 2011; 37: 453-459. *(Secondary analysis)* Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, Thomas C, Jenkins J, Hasson A, Annon J, Saxon A, Slzer J, Boverman J, Bilangi R. Buprenorphine tapering schedule and illicit opioid use. Addiction 2008; 104: 256-265. *(Primary study)* Oreskovich MR, Saxon AJ, Ellis MLK, Malte CA, Reoux JP, Know PC. A double-blind, double-dummy, randomized, prospective pilot study of the partial Mu opiate agonist, buprenorphine, for acute

		detoxification from heroin. Drug and Alcohol Dependence 2005; 77: 71-79.
SECONDARY	LEVEL II Evidence from properly designed randomized controlled trials (RCT)	Amass L, Pukeleviciene V, Subata E, a Almeida AR, Pieri MC, D'Egidio P, Stankova Z, Costa A, Smyth BP, Sakoman S, Wei Y, Strang J. A prospective, randomized, multicenter acceptability and safety study of direct buprenorphine/naloxone induction in heroin-dependent individuals. Addiction (Abingdon, England) 2012; 107: 142-51. Fischer G., Ortner R., Rohrmeister K, Jagsch R, Baewert A, Langer M, Aschauer H. Methadone versus buprenorphine in pregnant addicts: A double-blind, double-dummy comparison study. Addiction 2006; 101: 275-281. Magura S., Lee J.D., Hershberger J, joseph H, Marsch L, Shropshire C, Rosenblum A. Buprenorphine and methadone maintenance in jail and post-release: A randomized clinical trial. Drug and Alcohol Dependence 2009; 99: 222-230.
SECONDARY	LEVEL III-1 Evidence obtained from well-designed pseudo-randomised controlled trials	Compton P.A., Wesson D.R., Charuvastra V.C., Ling W. Buprenorphine as a pharmacotherapy for opiate addiction: What dose provides a therapeutic response? American Journal on Addictions 1996: 5: 220-230. Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, Ling W. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction (Abingdon, England) 2014; 109: 79-87. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, Gardin J, Griffin ML, Gourevitch MN, Haller DL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, Somoza EC, Sonne SC, Ling W. Adjunctive counselling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence. Archive of general Psychiatry 2011; 68: 1238-1246.
SECONDARY	LEVEL III-2 Evidence obtained from comparative, non-randomised studies	Gerra G., Borella F., Zaimovic A., Moi G, Bussandri M, Bubici C, Bertacca S. Buprenorphine versus methadone for opioid dependence: Predictor variables for treatment outcome. Drug and Alcohol Dependence 2004; 75: 37-45. Pinto H., Maskrey V., Swift L., Rumball D, Wagle A, Holland R. The SUMMIT Trial: A field comparison of buprenorphine versus methadone maintenance treatment. Journal of Substance Abuse Treatment 2010; 39: 340-352.
	LEVEL IV Evidence obtained from case series studies	Verthein U., Prinzleve M., Farnbacher G., Haasen C., Krausz M. Treatment of opiate addicts with buprenorphine: A prospective naturalistic trial. Addictive Disorders and their Treatment 2004; 3: 58-70.

7.2.1.1. Pivotal studies for change in dose regime

Due to the number of studies emphasis has been placed on the 4 pivotal studies. These were all Level II evidence (properly designed randomised, controlled trials).

Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction 2003; 98: 441-452.

This was a multicentre, double-blind, double dummy, randomised, two arm, parallel-group trial comparing the safety and efficacy of sublingual buprenorphine tablets with methadone oral solution using flexible dosing, in adult patients seeking treatment for opioid dependence. It was undertaken in 3 outpatient clinics in Sydney and Adelaide, Australia. This study was designed to assess the difference in retention of participants between the buprenorphine or methadone treated subjects when using a maintenance dose based on clinical response. Patients were randomized to receive buprenorphine or methadone over a 13-week treatment period in a double-blind, double-dummy trial.

The study enrolled 405 subjects aged 18 years or older, who lived within commuting distance of a study clinic, appeared mentally competent to give informed consent and had a current diagnosis of opioid dependence using the criteria in the 4th edition of the DSM Diagnostic and Statistical Manual of Mental Disorders, were eligible for recruitment. The exclusion criteria included treatment with methadone maintenance during the preceding 30 days, in a previous study of buprenorphine, current use of anticonvulsants, disulfiram or antipsychotic medicines, serious acute medical illness which could make participation medically hazardous. Pregnant or nursing women, or deemed likely to become pregnant were also excluded.

Patients received buprenorphine or methadone as indicated clinically using a flexible dosage regime. Induction doses across all sites were set at 20–40 mg oral methadone and 2–6 mg buprenorphine. During weeks 1–6, patients were dosed daily. Buprenorphine doses up to 32 mg daily and methadone doses up to 150 mg daily were permitted. From weeks 7–13, buprenorphine patients received double their Week 6 dose on alternate days. The maximum daily buprenorphine dose remained 32 mg when alternate dosing was introduced. This resulted in patients previously receiving from 16 – 32 mg buprenorphine daily going on to receive 32 mg every alternate day. The starting dose of buprenorphine used to induce subjects in this study was 2 to 6mg. If the participant complained that their withdrawal symptoms were not adequately controlled during this period, dosage adjustments could be made. Efficacy was assessed by treatment retention, urine testing for opioids and withdrawal symptoms. Self-reported drug use, alcohol consumption, feelings associated with illicit opioid use and adverse events were also recorded. A maximum daily dose of 32mg buprenorphine was applied to the maintenance phase.

ITT analyses showed no significant difference in completion rates at 13 weeks. Patients in the buprenorphine group were retained in treatment for a mean of 59.2 days (SD = 35.9) compared with a mean of 66.8 days (SD = 33.1) in the methadone group. Overall, 54.8% of the 394 patients who received at least one dose of medication completed the 13-week trial. 59% of methadone patients completed the trial compared with 50% buprenorphine patients. This difference was not statistically significant. Methadone was superior to buprenorphine in time to termination over the 13-week period (Wald $\chi^2 = 4.371$, df = 1, p= 0.037), but not separately for the single-day or alternate-day dosing phases. There were no significant between-group differences in morphine-positive urines, or in self-reported heroin or other illicit drug use. The majority (85%) of the buprenorphine patients transferred to alternate-day dosing were maintained in alternate-day dosing. The authors concluded that buprenorphine did not differ from methadone in its ability to suppress heroin use, but retained approximately 10% fewer patients. This poorer retention was due possibly to too-slow induction onto buprenorphine. For the majority of patients, buprenorphine can be administered on alternate days.

Petitjean S et al. Double-blind randomised trial of buprenorphine and methadone in opiate dependence. Drug and Alcohol Dependence 62 (2001) 97-104.

This study compared the safety and efficacy of sublingual buprenorphine tablets with oral methadone in a population of opioid-dependent individuals in a double-blind, randomized, 6-week trial using a flexible dosing procedure. 58 patients seeking treatment for opioid dependence were recruited in 3 outpatient facilities in Switzerland and randomly assigned to substitution with buprenorphine or methadone.

The buprenorphine and the methadone group consisted of 27 and 31 patients, respectively. Buprenorphine was administered as a sublingual tablet in doses of 2 or 8 mg day, methadone was prepared as an oral solution. The initial daily dose of buprenorphine was 4 mg (day 1–3). On day 4 of treatment, the participants were eligible to receive double-blind dose increases or decreases. At patients' request and physicians' assessment the dose could be increased to 8 mg on day 4, to 12 mg on day 8 and to 16 mg on day 15. If over-medication was evident, the dose was reduced. In the methadone group, subjects started with 30-mg oral methadone and doses were adjusted according to the same schedule and criteria. Maximum daily doses were 60 mg on day 4, 90 mg on day 8 and 120 mg on day 15. Dose changes were made by steps of 30 mg methadone or 4 mg buprenorphine, respectively.

The retention rate was significantly better in the methadone maintained group (90 vs. 56%; $p< 0.001$). Subjects completing the study in both the treatment groups had similar proportions of opioid positive urine samples (buprenorphine 62%; methadone 59%) and positive urine specimens, as well as mean heroin craving scores decreased significantly over time ($p=0.035$ and $p< 0.001$). The proportion of cocaine-positive toxicology results did not differ between groups. At week six mean stabilisation doses were 10.5 mg per day for the sublingual buprenorphine tablet, and 69.8 mg per day for methadone, respectively. Patient performance during maintenance was similar in both the groups.

The authors opined that the high attrition rate in the buprenorphine group during the induction phase might reflect inadequate induction doses. It was concluded that buprenorphine is a viable alternative for methadone in short-term maintenance treatment for heroin dependence if treatment induction is done with adequate dosages.

Evaluator comment – a major issue with this study appears to be induction dose regimens. Dose adjustment during the induction period was every 4 days. This is very slow. The current PIs for Suboxone and Subutex allow for more frequent dose adjustment to clinical effect during the induction period.

Kakko J. et al. A Stepped Care Strategy Using Buprenorphine and methadone versus Conventional Methadone Maintenance in Heroin Dependence: A Randomized Controlled Trial. American Journal of Psychiatry 2007; 164:797-803.

The authors compared adaptive, buprenorphine-based stepped care to optimal methadone maintenance treatment. This randomised controlled trial was undertaken 2004–2006. It consisted of a 24-day uniform double-blind induction phase followed by single-blind flexible dosing based on structured clinical criteria, for a total of 6 months. A double-blind 24-day induction phase provided uniform dose escalation and stabilisation for both arms (methadone maintenance treatment: 10 days to reach 70 mg/day of methadone; stepped therapy: 2 days to reach 16 mg/day of buprenorphine/naloxone). To avoid precipitating withdrawal, buprenorphine/naloxone was given upon the appearance of withdrawal symptoms, ≥8 hours after the last heroin intake.

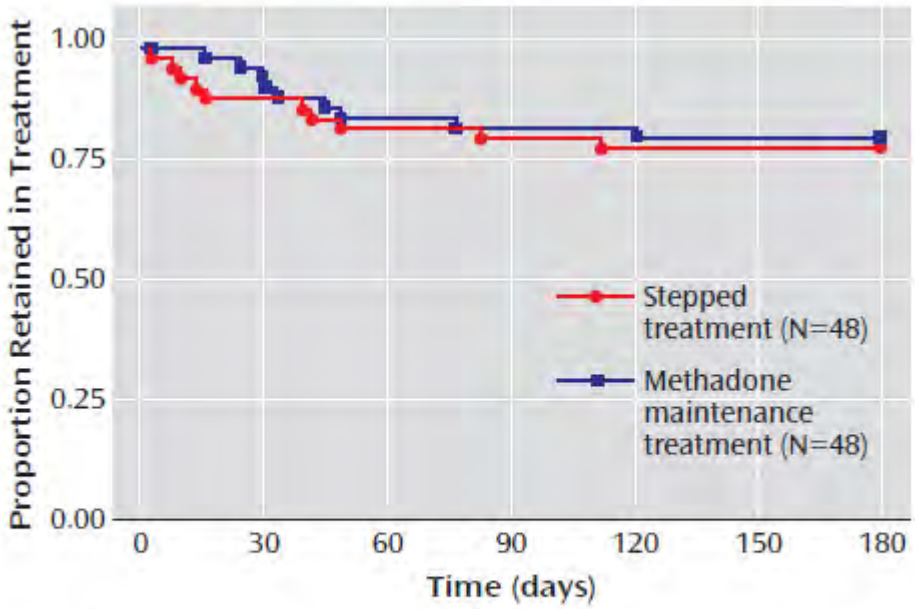
After induction patients entered the maintenance phase. Within that phase, a transition was permitted. A transition was a dose increase or, in subjects receiving 32 mg/day of buprenorphine/naloxone, switching to methadone. Criteria for transitions were the following—within the preceding 2 weeks: ≤2 missed visits, self-reported insufficient blockade of craving, self-reported withdrawal symptoms on nadir, or any urine sample positive for illicit opiates and

no signs of overdosing (cognitive impairment, sedation, respiratory depression). Methadone maintenance treatment was allowed transitions in 10-mg increments to 120 mg/day. Stepped therapy allowed transitions, in 8-mg increments, to 32 mg/day. If this was insufficient, a rapid switch followed; patients received 50 mg/day of methadone the day after the last buprenorphine/naloxone dose, followed by 10-mg increases every second day to 90 mg/day. After this, the methadone maintenance therapy protocol above was followed.

Patients met with case managers at least weekly for counselling and to provide information for dose adjustments. A slip (self-reported drug intake or any positive urine sample) led to the progression of 1) a dose increase; 2) if insufficient (i.e., indicators of slip/relapse continued to occur), or the maximum dose had been reached, intensified counselling to two and then three times a week. When 4 weeks' stability in treatment had been achieved, defined by all-negative urine tests, but no earlier than after 3 months, patients were allowed take-away doses for weekends. With additional completed 4 weeks of stability, take-away doses were dispensed twice weekly, and after an additional 4 weeks of stability, once weekly. In case of relapse, daily supervised administration resumed. Patients were withdrawn from the study if they were absent from scheduled visits for more than a week; verbally or physically threatened or abused staff or patients; dealt drugs; or engaged in illicit drug use. The study group comprised 96 subjects aged >20 years with heroin dependence for at least 1 year(48 per arm, 64 in Stockholm, 32 in Uppsala, Sweden). The primary outcome was patient survival. The primary outcome measure was retention in treatment. This was analysed by using Cox proportional hazard regression, with age, duration of heroin use, and gender as covariates.

Results are shown below:

Figure 1 Comparison of a Novel Stepped Strategy for Treatment of Heroin Dependence Versus High Quality Conventional methadone Maintenance Treatment (Kakko)



[a] Retention in treatment was equivalent in both arms (adjusted odds ratio=1.02, 95% CI=0.65–1.50; test for noninferiority at $\delta \geq 0.15$, $z=-1.7$, $p<0.05$). For detailed statistics, see Results.

116 subjects were screened, and 96 (83%) were randomly assigned from September 2004 to July 2005. Overall retention was 78% with retention virtually identical between arms.

Evaluator comment This study was very comprehensive and used opiate replacement therapy as part of a comprehensive treatment program. The induction and maintenance dose regimens also permitted more flexible dosing that in the studies by Mattick and Petitjean described

earlier in this subsection. It is notable that buprenorphine/ naloxone compared more favourably with morphine when administered with the more flexible induction and maintenance dose regimen that applied in this study. Although the study was quite small it was sufficient to determine equivalence of retention rates within the δ of ± 15%.

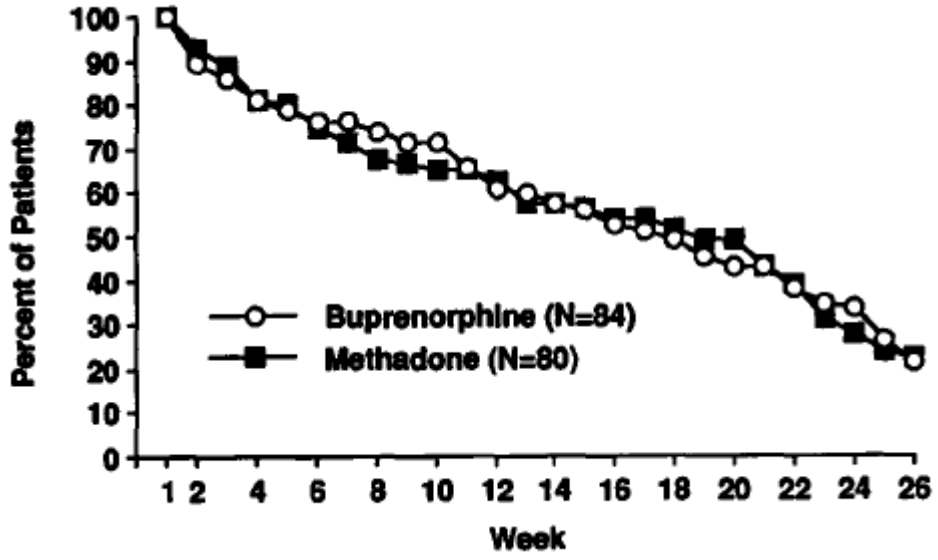
Strain E.C et al. Comparison of Buprenorphine and methadone in the Treatment of Opioid Dependence. American journal of Psychiatry 1994; 151: 1025 – 1030.

This study compared the efficacy of buprenorphine and methadone in the treatment of opioid dependence. Study subjects were (n=164) relatively treatment-naive, opioid-dependent patients who were randomised assigned to a 26-week treatment program of methadone or buprenorphine treatment.

Dosing was double-blind and double-dummy. Patients were stabilised on a regimen of either methadone, 50 mg, or buprenorphine, 8 mg, with dose changes possible through week 16 of treatment. During the first 4 days of treatment (induction), patients received daily doses of 20, 30, 40, and 50 mg of methadone, or 2, 4, 6, and 8 mg of buprenorphine. Stabilisation doses were either 50 mg of methadone or 8 mg of buprenorphine. Beginning in the third week of treatment and continuing through week 16, participants were eligible to receive double-blind dose increases and decreases. During the last 10 weeks of treatment, the week 16 dose was tapered, decreasing at a rate of 10% per week. Subjects and staff were unaware of the phases or details of the dosing schedule and were simply instructed that all patients would be detoxified to placebo by the end of the 6 months. Dose changes (weeks 3-16) were made in increments of 10 mg for methadone and 2 mg for buprenorphine. The maximum number of dose increases was four (i.e., a maximum of 90 mg of methadone or 16 mg of buprenorphine), and the increases were spaced at least 1 week apart.

Urine samples were collected three times a week, and weekly counselling was provided. Buprenorphine (mean dose=8.9 mg/day) and methadone (mean dose=54 mg/day) were equally effective in sustaining retention in treatment, compliance with medication, and counselling regimens. Retention rates by study week are shown in the figure below:

Figure 2 Percent of Patients Assigned to Buprenorphine or Methadone Who Remained in Treatment at Each Week. (Strain)



Retention was defined as the total number of days between admission and discharge, or the last day of the flexible dosing period if the patient remained in treatment beyond week 16. In both groups 56% of patients remained in treatment through the 16-week flexible dosing period i.e. prior to dose tapering. Overall opioid-positive urine sample rates were 55% and 47% for

buprenorphine and methadone groups, respectively; cocaine-positive urine sample rates were 70% and 58%. Evidence was obtained for the effectiveness of dose increases in suppressing opioid, but not cocaine, use among those who received dose increases. The authors concluded that this study provides further support for the utility of buprenorphine as a new medication in the treatment of opioid dependence and demonstrates efficacy equivalent to that of methadone when used during a clinically guided flexible dosing procedure.

Evaluator comment The results of this study were very disappointing. Clearly the majority of patients with opiate dependence do not respond to blinded withdrawal of opiate. It does show that the poor retention occurred with both methadone and buprenorphine both during the maintenance period and after commencement of dose tapering. The induction and maintenance dose regimens for buprenorphine was also more rigid that the currently recommended regimens. That may have contributed to the poor retention.

7.2.1.2. Other efficacy studies for change in dose regimen

Oreskovich MR et al. A double-blind, double-dummy, randomised, prospective pilot study of the partial Mu opiate agonist, buprenorphine for acute detoxification from heroine. Drug and Alcohol Dependence 2005;77:71-79.

This study compared 2 buprenorphine dosing schedules with clonidine in 30 heroin users who met the DMS-VI criteria for opioid dependence and achieved a COWS score of 13 (moderate withdrawal) were randomised to receive:

- higher dose buprenorphine (HD, 8-8-8-4-2 mg/day on days 1–5),
- lower dose buprenorphine (LD, 2-4-8-4-2 mg/day on days 1–5), or
- clonidine (C, 0.2-0.3-0.3-0.2-0.1 mg QID on days 1–5)

COWS scores were obtained four times each day. Twenty-four hours after randomisation,

the suppression of withdrawal, defined by four consecutive COWS scores <12, were: C = 11%, LD = 40%, and HD = 60%.

Evaluator comment This study was cited in the Clinical Overview as support for the proposed induction dose regimen of 8 to 12 mg buprenorphine on the first day of treatment however that regimen was not used in this study. The study does support the use of regular review of patients undergoing induction treatment and adjustment of dose according to COWS scores. This evaluator considers that given the variability in previous exposure to opiates in patients undergoing induction treatment that close observation and adjustment of buprenorphine dose would be required, particularly in the first 24 hours of treatment to avoid either precipitating opiate withdrawal or providing more buprenorphine than needed at induction.

Soyka et al. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomised study. International Journal of Neuropsychopharmacology (2008), 11,641-653.

This was a 6-month, randomised, flexible-dose study comparing the effects of methadone and buprenorphine on retention rate and substance use in a sample of 140 opioid-dependent, primarily heroin-addicted patients who had been without opioid substitution therapy in the 4 weeks prior to the study. The major aims were to compare the efficacy of buprenorphine and methadone in a flexible dosing regimen and to identify possible predictors of outcome. Mean daily dosages after the induction phase were 44–50 mg for methadone and 9–12 mg for buprenorphine. Results from this study indicate a favourable outcome, with an overall retention rate of 52.1% and no significant differences between treatment groups (55.3% vs. 48.4 %).

This study used OWS to assess withdrawal symptoms daily for the first 7 days then weekly. The mean dose of methadone on Day 1 was 34.7 mg and this had increased to 44.7 (S.D.=20.1) mg at the end of the induction period (end Day 7). The mean dose of buprenorphine on Day 1 was 9.8 mg on day 0 and this had increased to 12.1 at the end of the induction period. During the induction phase)Days 1 – 7) withdrawal symptoms were consistently more severe in the buprenorphine group than the methadone group.

Evaluator comment This study suggests that a buprenorphine dose higher than 10 mg is likely to be needed for many opiate-addicted patients presenting for treatment with buprenorphine substitution therapy.

Hillhouse et al. Participant Characteristics and Buprenorphine Dose. The American Journal of Drug and Alcohol Abuse, 37:453-459, 2011.

This study was a secondary analysis of data collected in a comparison of buprenorphine taper schedules conducted as part of the National Institute on Drug Abuse's Clinical Trials Network to assess whether participant baseline characteristics are associated with buprenorphine dose.

After 3 weeks of flexible dosing with Suboxone, 516 participants were categorised by dose provided in the final dosing week (9.3% received a final week dose of 8 mg buprenorphine, 27.3% received 16 mg, and 63.4% received 24 mg). Findings show that final week dose groups differed in baseline demographic and drug use characteristics including education, heroin use, route of drug administration, withdrawal symptoms, and craving. These groups also differed in opioid use during the four dosing weeks, with the lowest use in the 8 mg group and highest use in the 24 mg group ($p < .0001$).

This study also used the COWS scale to assess severity of withdrawal signs and symptoms. Mean COWS at baseline by final induction dose was 6.75 in the 8 mg dose group, 8.42 in the 16 mg dose group and 8.77 in the 24 mg dose group. Induction occurred over the first 3 days of the study. Opioid use was measured by the Treatment Effectiveness Score (TES). The TES is computed as the percentage of opioid-negative urine analysis tests over the number of possible tests (6) during the treatment period.

The initial dose of study drug was determined by each study physician, but typically ranged between 2 and 4 mg buprenorphine, with a maximum 8 mg dosage for the first day. The usual dose for day 2 was 12 mg and the usual dose for day 3 was 16 mg. Doses could then be adjusted in 4 mg increments at weekly visits up to 24 mg daily. All participants were on a daily dose of 8, 16, or 24 mg by the fourth week.

The higher dose group (i.e. 24 mg daily) had significantly greater clinically observed withdrawal symptoms compared with the 8 mg daily group. Physicians were given the opportunity to provide dosage based on the apparent needs of each participant, and flexible dosing for 3 weeks allowed titration up or down based on the specific participant's needs. Despite a 3-week period to identify an appropriate clinical dose, the 24 mg group had the highest rate of continued opioid use compared with the 8 and 16 mg dose groups. Additionally the TES was used to measure opioid use from induction through the end of the 4-week treatment phase. The mean TES of the 8 mg group was 66%, the mean TES of the 16 mg group was 53%, and the mean TES of the 24 mg group was 42%. A significant association was found between final week dose group and TES after controlling for the baseline characteristics which differed by dose group (mean years of education, heroin use in the past month, COWS, and VAS) ($F = 11.61$; $p < .0001$).

Evaluator comment This analysis showed that patients with more severe withdrawal effects require higher buprenorphine doses both for induction and maintenance treatment. Higher doses of buprenorphine were also associated with less use of opiates during the study.

These results support flexible dosing and indicate that despite flexible dosing physicians may be under-dosing some patients, resulting in higher use of opiates and higher withdrawal rates from treatment.

These results are specific to the group of patients in the study. It isn't clear if the same degree of dependence would be present in opiate-dependent populations in other countries with different social support systems and availability of illicit drugs. For this reason the dosage and administration recommendations should emphasise monitoring of individual patients and adjustment of dose according to response to minimise withdrawal symptoms. The maintenance dose should then be similar to the daily dose at the end of the induction period.

Ling W. et al. Buprenorphine tapering schedule and illicit opioid use. Addiction. 2008; 104:256-265.

This was a randomised, parallel-group, open-label study to compare the effects of a short or long taper schedule after buprenorphine stabilisation on participant outcomes as measured by opioid-free urine tests at the end of each taper period. All procedures were identical for all participants until the taper period. Tapering occurred over either 7 or 28 days. The study was conducted in 11 outpatient treatment programs in the USA.

Non-blinded dosing with Suboxone® during the 1-month stabilisation phase included 3 weeks of flexible dosing as determined appropriate by the study physicians. Flexible dosing was limited to a maximum of 8 mg on Day 1, 12 mg on Day 2 and 16 mg on Day 3. The maximum maintenance dose was 24 mg daily. A fixed dose was required for the final week before beginning the taper phase. Illicit opioid use was assessed by measuring opioid in urine samples. At the end of the taper, 44% of the 7-day taper group (n = 255) provided opioid-free urine specimens compared to 30% of the 28-day taper group (n = 261; P = 0.0007). There were no differences at the 1-month and 3-month follow-ups (7-day = 18% and 12%; 28-day = 18% and 13%, 1 month and 3 months, respectively). The author's concluded that for individuals terminating buprenorphine pharmacotherapy for opioid dependence, there appears to be no advantage in prolonging the duration of taper.

Evaluator comment While flexible dosing was used in this study the maximum dose was less than the approved maximum dose in Australia and the initial flexible induction regimen was less flexible than is recommended in the current dosing recommendations. The authors stated that they were aware that inadequate dosing may have been responsible for some dropout during the stabilisation period.

Compton P.A. et al. Buprenorphine as a Pharmacotherapy for Opiate Addiction - What Dose Provides a Therapeutic Response? American journal on Addictions 1996; 5:220-230.

The introduction to this study stated to the effect that there is no agreed primary efficacy measure in studies of the efficacy of various opiate treatment programs. Outcome measure have included % of opiate-free urines produced by each dosing regimen, subjective opiate craving, retention in treatment, withdrawal symptoms, and self-reports of opiate use.

In this study effectiveness was assessed based on subject behaviours which the authors considered indicated an effective dose of opiate maintenance pharmacotherapy or that are indicators of what the authors consider to be pharmacological stability in treatment. These criteria included opiate use, clinical attendance, symptom response and toxicity. Thus drug effectiveness was not based on a comparison of group outcomes but rather on how well the desired outcomes were achieved. The objective was to determine at what dose or range of doses buprenorphine produces a therapeutic response indicating good medication effect.

100 consecutively admitted opiate-addicted patients seeking buprenorphine maintenance at one treatment centre in the USA were enrolled in one of 2 buprenorphine protocols, one evaluating the duration of buprenorphine's action over 48- and 72- hour intervals and the other exploring the efficacy of buprenorphine administered on a 3-times-per-week dosing schedule. Before manipulation of the dosing schedule, both protocols required that subjects be effectively stabilised on a therapeutic dose. The induction dose was 8 mg daily for 1 week then adjustment either weekly or every second week up to a maximum daily dose of 32 mg.

Pharmacological response was assessed based on a Clinical Stabilisation Score (CSS) which was calculated weekly for each subject. This was a composite score which included measures of illicit opiates in urine, clinical attendance and a self-report of symptoms reflecting opiate toxicity and opiate withdrawal. The maximum CSS was 6. Subjects with scores of 5 or 6 for 3 consecutive weeks (indicating negative urine sample for opioids, clinic attendance and no symptoms of withdrawal or toxicity) for 3 consecutive weeks were considered stable. Doses of buprenorphine were adjusted within the dose range according to the reason for lower CSS i.e. if toxicity was present the dose was reduced, if opioids were in urine or withdrawal symptoms were reported the dose was increased.

34 subjects achieved pharmacological stabilisation within 16 weeks of buprenorphine treatment. 80% of subjects who stabilised required 12 mg or more of buprenorphine per day with a mean of 14.6 mg. The authors stated that these findings provide further evidence that doses above 8 mglday of buprenorphine may be required for subjects to significantly reduce opiate use. The authors also noted that because it is a partial agonist, buprenorphine may not effectively substitute for heroin in persons with severe opiate dependence or prolonged history of methadone maintenance treatment.

Evaluator comment The authors of this study intended to assess a 3-times per week dosing schedule for subjects who had stabilised on a daily dose of buprenorphine. 34/100 subjects achieved pharmacological stabilisation. The report did not then provide a breakdown of the relative effectiveness of the 3-times-per-week dose regimen compared with the daily dose regimen. Given that only 34 subjects could have been assessed this would be too small for any meaningful assessment of the two dosing regimens.

7.2.2. Less than once daily dosing

10 published studies were submitted to support the proposed less than once daily dosing schedule. The studies are listed below. The Study by Mattick in Table 1 also provided data to support alternative day administration.

Table 5 Published Studies Supporting Less Than Once Daily Dosing

Study category	Type of evidence (NHMRC 1999)	References Submitted
PIVOTAL	LEVEL II Evidence from properly designed randomized controlled trials (RCT)	Amass L, Bickel WK, Higgins ST, Badger GJ. Alternative-day dosing during buprenorphine treatment of opioid dependence. Life Sciences 1994; 54: 1215-1228. Amass L, Bickel WK, Crean JP, Blake J Higgins ST. Alternative-day buprenorphine dosing is preferred to daily dosing by opioid-dependent humans. Psychopharmacology 1998; 136: 217-225. Bickel WK, Amass L, Crean JP, Badger GJ. Buprenorphine dosing every 1, 2, or 3 days in opioid-dependent patients. Psychopharmacology 1999; 146: 111-118. Perez de los Cobos J, Martin S, Etcheberrigaray A, Trujols J, Battle F, Tejero A, Queralto JM, Casas M. A controlled trial of daily versus thrice weekly buprenorphine administration for the treatment of opioid dependence. Drug and Alcohol Dependence 2000; 59: 223-233. Marsch LA, Bickel WK, Badger GJ, Jacobs EA. Buprenorphine treatment for opioid dependence: the relative efficacy of daily, twice and thrice weekly dosing. Drug and Alcohol Dependence 2005; 77: 195-204. Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR. Thrice-Weekly versus daily buprenorphine maintenance. Biological Psychiatry 2000; 47: 1072-1079.
SECONDARY	LEVEL II Evidence from properly designed randomized controlled trials (RCT)	Gross A, Jacobs EA, Petry NM, Badger GJ, Bickel WK. Limits to buprenorphine dosing: a comparison between quintuple and sextuple the maintenance dose every 5 days. Drug and alcohol dependence 2001; 64: 111-6. Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens in the treatment of opioid dependence. Clinical pharmacology and therapeutics 1999; 66: 306-14.
		Petry NM, Bickel WK, Badger GJ. A comparison of four buprenorphine dosing regimens using open-dosing procedures: is twice-weekly dosing possible? Addiction (Abingdon, England) 2000; 95: 1069-77.
	LEVEL III-1 Evidence obtained from well-designed pseudo-randomised controlled studies	O'Connor P.G., Oliveto A.H., Shi J.M. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. American Journal of Medicine 1998; 105: 100-105.

In the Clinical Overview it was also stated that the potential for buprenorphine to be administered less than once daily is supported by its long mean half-life (34.6 hours) and the pharmacokinetic principle which suggests that the optimal dosing interval of any medicine can be based on half-life.

6 of the 10 studies were randomised and controlled with a total of 333 subjects in the 6 studies combined. The average daily maintenance dose of buprenorphine in these studies ranged from 2mg to 24mg, and the single largest less than daily mean dose was 47.1mg when administered in a thrice weekly regimen.

The outcome measures used to compare efficacy used self-rated withdrawal and opioid effects using validated scales in 5 of the 6 RCTs, 4 used illicit drug and/or opioid positive urine samples and 3 used retention in treatment as either primary or secondary efficacy outcome measures. Other parameters compared included observer rated withdrawal and opioid effects and pupil diameter. The 6 studies considered pivotal are briefly outlined below. The supportive studies do not add substantially to the evidence for the utility and effectiveness of the proposed less than once daily dose regimens and will not be further reviewed for efficacy.

Amass let al. Alternative-day dosing during buprenorphine treatment of opioid dependence. Life Sciences 1994; 54: 1215-1228

This was a small placebo-controlled, crossover trial in 13 opioid-dependent outpatients. Study participants received 21 days of daily sublingual buprenorphine and 21-days of alternate-day buprenorphine at twice the daily maintenance rate every other day and placebo on the interposed day. Observer and subject-rated measures of opioid agonist and withdrawal effects, pupillary diameter and dose identifications were collected daily.

10/13 (77%) subjects completed the study with the maximum daily dose of 8 mg. Of these 10, 8 participated in the crossover. In these 8 subjects no clinically significant differences in measures of outcome were observed. The authors stated that this alternate-day schedule permits patients to attend the clinic less frequently without the risk of diversion associated with take-home doses, may be cost-effective for programs, and may be useful in settings in which travel to the clinic is a barrier to treatment.

Evaluator comment This study is too small to provide much useful information regarding differences in clinical outcomes from the 2 dose regimens. However, the maximum maintenance dose for daily dosing was only 8 mg buprenorphine, suggesting any alternate daily dose regimen would be suitable only for those who had been stabilised on relatively low doses of buprenorphine.

Amass et al. Alternate-day buprenorphine dosing is preferred to daily dosing by opioid-dependent humans. Psychopharmacology 1998; 136: 217-225.

The purpose of this study was to replicate and extend prior findings with alternate-day buprenorphine administration using double the daily maintenance dose (Amass et al. 1994a; above). 4 possible dose regimens were examined in 18 opioid-dependent outpatients (blind daily/ open daily/ blind alternate-day/open alternate-day). Induction doses of from 2 to 8 mg buprenorphine/ 70 kg /day for 3 days were given based on prior history of opioid use and response to initial dosing. Maintenance doses were then given for days 4 – 13. That 10-day maintenance period was the treatment baseline for all outcome measures. Subjects were paid for attendance for negative opioid tests with additional payment for completion of the study.

10/18 (56%) subjects completed one exposure to the 4 treatment conditions and 7 of these participated in a replication and a phase where subjects could be exposed to alternate daily dosing schedules. 6 of the 7 preferred alternate daily dosing.

Evaluator comment This is another small study with few observations. It is clear that most patients prefer to not visit a clinic daily. In this study few patients had clinically significant withdrawal effects on the alternate day when they received no buprenorphine. Again the maximum daily dose of buprenorphine was only 8 mg.

Bickel WK et al. Buprenorphine dosing every 1,2,or 3 days in opioid-dependent patients. Psychopharmacology 1999; 146: 111-118.

This study was conducted to examine whether triple the maintenance dose can be administered every 72 h without opioid withdrawal or intoxication. 16 opioid-dependent outpatients who had been induced on buprenorphine doses of from 2 to 8 mg/ 70kg daily each received three conditions (1) the maintenance dose of buprenorphine every 24 h, (2) double the maintenance dose every 48 h, and (3) triple the maintenance dose every 72 h under double-blind placebo-controlled conditions. Each condition was imposed in a random sequence for 21–22 days. Self-report and observer measures were taken at 24-h intervals. Subjects were paid for participation, opioid abstinence and completion of the study.

It was reported that there were no significant differences observed on measures of opioid agonist and withdrawal effects between the dosing conditions. 24 hours after administration of triple the maintenance dose, significant effects were observed in 8 opioid agonist measures. Also, 72 h after administration of triple the maintenance dose, significant effects were observed on four measures of withdrawal. The authors did not consider these agonist and withdrawal effects to be excessive.

Evaluator comment In this study toxicity and withdrawal effects were evident on every third day dosing for patients who had been stabilised on daily buprenorphine doses of from 2 to 8 mg/70 mg/day. This study is presented as a pivotal study supporting the proposed inclusion of the following statement in the PI In some patients, three times a week (for example on Monday, Wednesday and Friday) may be used. The dose on Monday and Wednesday may be twice the daily dose, and the dose on Friday may be three times the individually titrated daily dose. However the dose given on any one day should not exceed 32 mg.

This evaluator considers that if 72 hour dosing intervals are to be considered this should only occur in patients who are stable and ideally at doses of no more than 8 mg, though it would be acceptable to trial patients stable on somewhat higher doses. If unsuccessful then patients should resume daily dosing.

Perez de los Cobos J. et. Al A controlled trial of daily versus thrice weekly buprenorphine administration for the treatment of opioid dependence. Drug and Alcohol Dependence 2000; 59: 223-233.

A total of 60 treatment-seeking opioid addicts were randomly assigned to take buprenorphine tablets sublingually either every day (8 mg) or thrice-weekly (16 mg on Mondays and Wednesdays and 24 mg on Fridays) over the course of a 12-week, double-blind, parallel trial. Efficacy was measured primarily by treatment retention and urine testing for opioids. The buprenorphine dosing schedule had no significant effect on treatment retention. Patients who took buprenorphine daily stayed in the study an average of 69.8 days, and those who took it thrice weekly stayed 71.8 days (F(1, 58)-0.12, P-0.72). The study was completed by 19 patients from the daily dosing group (63%), and 21 (70%) from the thrice-weekly dosing group (χ^2 (1)=0.30, p=0.58). The rates of opioid-positive urine tests were significantly higher among those subjects who were given buprenorphine thrice weekly (58.5%) than among those who took it daily (46.6%). Additionally opioid abstinence for ≥4 weeks was found in 36.6% of daily dosing patients compared with 13.3% of thrice-weekly dosing. The authors considered that the results indicate the advisability of daily doses of buprenorphine, at least at the beginning of a maintenance programme.

Evaluator comment This study did not support dosing every third day.

Marsch LA et.al. Buprenorphine treatment for opioid dependence: the relative efficacy of daily, twice and thrice weekly dosing. Drug and Alcohol Dependence 2005; 77:195-204.

This randomised clinical trial evaluated the relative efficacy of three buprenorphine dosing schedules. 134 opioid-dependent adults were randomly assigned to receive buprenorphine 7, 3 or 2 days per week for 24 weeks. Daily maintenance doses were 4, 8, 10, or 12 mg of sublingual buprenorphine solution. Participants who attended the clinic daily received a maintenance dose of buprenorphine daily. Participants who attended the clinic thrice weekly received double their maintenance dose on Monday and Wednesday, followed by a triple dose on Friday. Participants who attended the clinic twice weekly received quadruple their maintenance dose of buprenorphine on Monday and triple their maintenance dose on Friday.

Primary outcome measures were treatment retention and both opiate and cocaine abstinence as measured via objective urinalysis testing. For the first 14–18 days of treatment (depending on intake day), participants completed an induction phase where they were titrated to daily doses of from 4 to 12 mg depending upon the severity of the participant's dependence (as determined by self-reported level of opiate use, participant weight, and participant and observer reports of withdrawal/agonist effects during the first week of treatment). After induction participants were randomised to one of the 3 treatment regimens.

The mean daily buprenorphine dose after induction was between 7.2 and 7.5 mg across the 3 dose regimen groups. There was little difference in treatment retention rates across the 3 treatment regimens with 69%, 73% and 64% of participants in the daily 3x per week and 2 x per week respectively retained in treatment for the 24 weeks of the maintenance period. Similarly there was no clinically significant difference in the proportion of negative opioid urine tests across the treatment regimens with negative tests at 73%, 70% and 73% of tests in the daily, 3 x per week and 2 x per week dosing groups respectively.

Evaluator comment In this study for individuals stabilised on around 8 mg buprenorphine daily there appeared to be little difference in outcomes between daily and every third day treatment regimens. I note that this group had particularly high retention and negative opioid urine test rates regardless of treatment regimen compared with patients in most of the other studies. The reason for this difference is not known.

Schottenfeld RS et.al. Thrice-Weekly versus daily buprenorphine maintenance. Biological Psychiatry 2000; 47: 1072-1079.

After a 3-day induction, opioid-dependent patients (n = 92) were randomly assigned to daily clinic attendance and 12-weeks maintenance treatment with sublingual buprenorphine administered double-blind either daily (n = 45; 16 mg/70 kg) or thrice weekly (n = 47; 34 mg/ 70 kg on Fridays and Sundays and 44 mg/70 kg on Tuesdays). Outcome measures included retention, results of 33/week urine toxicology tests, and weekly self-reported illicit drug use.

Average weight-adjusted weekly doses were 17.9 mg daily in the daily schedule and 36.4 mg (on Sundays and Fridays) and 47.1 mg (on Tuesdays) in the thrice-weekly group. Retention was 71% in the daily and 77% in the 3x/week conditions. The proportion of opioid-positive urine tests decreased significantly from baseline in both groups and averaged 57% (daily) and 58% in 3x/week groups. There were no significant differences between groups in self-reported number of bags of heroin used for any day of the week, including Thursdays (48–72 hours following the last buprenorphine dose for subjects in the 33/week condition), or in medication compliance (92%, 91%) and counselling attendance (82%, 82%).

Cocaine use increased in both groups over the course of the study. The proportion of subjects achieving 3 or more consecutive weeks of abstinence from cocaine was 51.1% and 55.3% in the daily and thrice weekly groups, respectively.

Evaluator comment The thrice weekly dose exceeded the current maximum daily dose of 32 mg buprenorphine. It is considered that no additional effect is achieved with doses above 32 mg however it would allow a longer period with buprenorphine above the level at which withdrawal symptoms were likely to occur. It is noted that the higher doses used in the thrice weekly dose regimen in this study have not been included in the proposed amendments to the dose regimen.

7.2.3. COWS as an Objective Measure of Withdrawal Symptoms

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item clinician-administered scale assessing opioid withdrawal. The assessment criteria and scoring system for COWS is in section 19. The maximum score is 48 with scores from 5 to 12 considered mild withdrawal, from 13 – 24 as moderate, 25 to 36 as moderately severe and more than 36 as severe withdrawal. Patients should not exceed the lowest score in most categories without exhibiting some observable sign or symptom of withdrawal.

5 published papers describing 4 studies (Nielsen 2014 and Weiss 2010 report on the same trial) were identified as providing data relevant to the use of COWS score of >12 as a suitable point at which to commence buprenorphine treatment for opiate withdrawal symptoms. These papers are listed below:

Table 5 Published studies supporting the use of the COWS

Revision of Dosage Regimen

Study category	Type of evidence (NHMRC 1999)	References Submitted
	LEVEL II Evidence from properly designed randomized controlled trials (RCT)	Tompkins DA, Bigelow GE, Harrison JA, Johnson RE, Fudala PJ, Strain EC. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. Drug and Alcohol Dependence 2009; 105: 154-159. Oreskovich MR, Saxon AJ, Ellis MLK, Malte CA, Reoux JP, Know PC. A double-blind, double-dummy, randomized, prospective pilot study of the partial Mu opiate agonist, buprenorphine, for acute detoxification from heroin. Drug and Alcohol Dependence 2005; 77: 71-79.
	LEVEL III-1 Evidence obtained from well-designed pseudo-randomised controlled studies	Nielsen S, Hillhouse M, Weiss RD, Mooney L, Sharpe Potter J, Lee J, Gourevitch MN, Ling W. The relationship between primary prescription opioid and buprenorphine-naloxone induction outcomes in a prescription opioid dependent sample. American Journal of Addiction 2014; 23: 343-8. Weiss RD, Potter JS, Provost SE, Huang Z, Jacobs P, Hasson A, Lindblad R, Connery HS, Prather K, Ling W. A multi-site, two-phase, prescription opioid addiction treatment study (POATS): Rationale, design, and methodology. Contemporary Clinical Trials 2010; 31: 189-199. (Methods Paper)
	LEVEL IV Evidence obtained from case series	Ang-Lee K, Oreskovich MR, Saxom AJ, Jaffe C, Meredith C, Ellis MLK, Malte CA, Know PC. Single dose of 24 milligrams of buprenorphine for heroin detoxification: an open label study of five inpatients. Journal of Pyschoactive Drugs 2006; 38: 505-512.

Of the 4 studies, 2 are RCT. Of these, the study by Oreskovich (2005), was also included as a supportive study in the induction, flexible dosing and maintenance dose section of the evaluation report. COWS was also used in the Hillhouse (2011) study but there was no score minimum COWS required prior to commencement of buprenorphine induction and the mean COWS at baseline were <12. In the Hillhouse study mean baseline COWS scores (prior to induction and by final induction dose) were 6.75 in the 8 mg dose group, 8.42 in the 16 mg dose group and 8.77 in the 24 mg dose group.

Tompkins DA et. al. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices again the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument

Though commonly used in clinical practice, it has not been systematically validated. This study was intended to compare the COWS in comparison to the validated Clinical Institute Narcotic Assessment (CINA) scale. 46 opioid-dependent volunteers were enrolled in a residential trial and stabilised on morphine 30mg given subcutaneously four times daily. Subjects then underwent double-blind, randomised challenges of intramuscularly administered placebo and naloxone (0.4 mg) on separate days, during which the COWS, CINA, and visual analogue scale (VAS) assessments were concurrently obtained. Subjects completing both challenges were included. Correlations between mean peak COWS and CINA scores as well as self-report VAS questions were calculated.

Mean peak COWS and CINA scores of 7.6 and 24.4, respectively, occurred on average 30 min post-injection of naloxone. Mean COWS and CINA scores 30 min after placebo injection were 1.3 and 18.9, respectively. The Pearson's correlation coefficient for peak COWS and CINA scores during the naloxone challenge session was 0.85 ($p < 0.001$). Peak COWS scores also correlated well with peak VAS self-report scores of bad drug effect ($r = 0.57$, $p < 0.001$) and feeling sick ($r = 0.57$, $p < 0.001$), providing additional evidence of concurrent validity. Placebo was not associated with any significant elevation of COWS, CINA, or VAS scores, indicating discriminant validity. Cronbach's alpha for the COWS was 0.78, indicating good internal consistency (reliability).

Evaluator comment While this study validates COWS for scores of up to around 7 to 8 the COWS is a 48 point scale and this study didn't assess the validity of the higher scores proposed prior to commencement of buprenorphine for the treatment of opioid dependence. It has no bearing on the proposal to commence buprenorphine treatment at the threshold COWS score of 12. It is notable that the mean COWS scores 30 minutes after naloxone were well below the proposed score for commencement of buprenorphine for treatment of opiate withdrawal effects. This suggests that the threshold COWS score for commencement of treatment should be lower than the proposed minimum score of 12.

Oreskovich MR et. Al. A double-blind, double-dummy, randomized, prospective pilot study of the partial Mu opiate agonist, buprenorphine, for acute detoxification from heroin. Drug and Alcohol Dependence 77 (2005) 71- 79.

This study is described in section 7.2.1.2. It is notable that the heroin users enrolled in this study required a COWS score of 13 (moderate withdrawal) prior to study entry. Suppression of withdrawal was defined as 4 consecutive COWS scores of <12 obtained over a 24 hour period.

Evaluator comment While this study defined suppression of withdrawal symptoms as consecutive COWS scores of <12 that is not consistent with no symptoms of withdrawal. It is not clear that optimum management of opioid dependence would be achieved by accepting mild withdrawal symptoms as a target for treatment or a level at which treatment with buprenorphine could commence.

7.2.4. Evaluator's conclusions on clinical efficacy for changes to Dosage and Administration

Change in dose regimen: The proposed changes to the dose regimens differ somewhat from the current recommendations in the National Guideline.

Heroin and short-acting opioids: For patients taking heroin or other short-acting opioids it has been proposed to state that the total target dose for Day one of induction is in the range of 8 – 12 mg buprenorphine. The Guideline does not specifically recommend total daily doses of more than 8 mg on Day one of treatment. The following is stated:

- For the patient with mild withdrawal (subjective symptoms but no signs of opioid withdrawal that would produce a score less than 8 with the COWS), provide an initial dose of 4mg, with the possibility of a subsequent dose of 4mg after 1-2 hours ('split dosing' reduces the risk of precipitated withdrawal);
- For the patient with moderate or severe withdrawal at the time of the first dose, an initial dose of 8mg is appropriate;
- Lower doses (e.g. 2 or 4mg total on day 1) are suited to those with low or uncertain levels of opioid dependence, with high risk polydrug use (alcohol, benzodiazepines) or with other severe medical complications. Seek specialist advice if concerned.

The aim of induction treatment is to minimise withdrawal signs and symptoms so it seems reasonable to titrate the total daily dose to symptoms and also allow a second dose 1 – 2 hours after an initial dose of 8 mg for patients who present with moderate or severe withdrawal. The PI should be amended so it is clear which patient group could receive up to 12 mg buprenorphine on Day 1 of induction and the timing of that higher total daily dose.

Methadone: For patients on methadone it is proposed to suggest and initial buprenorphine dose of 4 – 8 (rather than the current 4 mg) and also that the target total dose of buprenorphine for Day 1should be in the range 8 – 12 mg. The guidelines note that withdrawal often does not occur until more than 24 hours after the last dose of methadone. The size of the last dose of methadone is less important than the time since the last dose, as determined by withdrawal. Patients at low risk of complications from transitioning to buprenorphine include those with methadone doses less than 60 mg daily rather than the 30 mg daily which is specified in the current buprenorphine substitution PI but has been proposed for removal. The Guideline also recommends that for induction these patients need frequent monitoring and buprenorphine should be dispensed in multiple doses over the first 4 to 6 hours of the transfer.
Further specific instructions regarding dosing, dependent on the severity of withdrawal symptoms are provided in the Guideline and these allow for initial total daily doses of up to 16 mg buprenorphine.

It is recommended that this section of the PI be amended to provide more detail on the timing of dosing, adjustment according to severity of withdrawal and to allow for total daily doses of up to 16 mg buprenorphine on day of transition from morphine maintenance treatment.

Dose adjustment in maintenance: It is proposed to specify the size of dose increments (from 2 – 8 mg), to note that many patients in clinical trials were stabilised on daily doses of 12 – 16 mg buprenorphine but that higher doses may be needed. This section is consistent with the National Guidelines. Minor amendments to improve readability of this section have been recommended.

Less than once daily dosing: The need for longer than daily dosing frequencies appears to be due to the desire to avoid take-away doses of buprenorphine. The terminal half-life of buprenorphine is less than 48 hours which suggests that alternate day dosing would not be optimal. Dosing every 72 hours would be even less optimal. The evidence supporting these alternative regimens is very limited. The studies are small, the withdrawal rates high and the level of use of illicit drugs in conjunction with the buprenorphine maintenance regimens are generally high. Some studies showed mild toxicity and withdrawal symptoms when the proposed alternative dosing regimens were used. Additionally given maximum effect of buprenorphine occurs at doses of around 32 mg daily. The higher doses used in some of the studies for alternate and every third day dosing would have extended the duration of effect but were unlikely to have increased the maximum effect beyond that seen with up to 16 mg daily. The proposed changes to the PI state that patients stabilised on <8mg daily may not find less than daily dosing adequate. I think this is a typographic error and should be those on >8 mg daily. The studies assessing these revised dose intervals were generally in patients with daily buprenorphine dose requirements of 4 to 8 mg. It is likely that blood levels of buprenorphine would fall below maintenance requirements for patients needing higher daily maintenance doses.

While there is no objection to the proposal to allow less than daily dosing I recommend it be limited to patients stabilised on no more than 8 mg buprenorphine daily. If withdrawal or toxicity signs and symptoms are evident or reported then patients should be recommenced on a daily dosing regimen. Furthermore I recommend the proposed schedules for less than daily dosing be amended to be consistent with the National Guideline section A4.3.1 i.e. Patients interested in less than daily dosing should first be stabilised on daily dosing before trying alternate-day dosing for two weeks. If this is successful, the patient can then be tried on a three-times-a-week regimen. If a patient cannot be stabilised on such dosing regimens due to the onset of withdrawal, cravings, side effects or features of intoxication, they should be returned to a more frequent dosing regimen.

Alternate-day or four-times-a-week regimens involve attending the pharmacy for dosing on alternate days (i.e. a dose every 48 hours), or attending four times a week (with 3x48 hour doses and 1x24 hour dose each week, e.g. Mon, Tues, Thurs, Sat). The advantage of the latter approach (4 times a week) is that the patient attends regularly each week, with less likelihood of attendance errors on the patient's part and dosing errors by the pharmacist.

COWS: For individuals switching from illicit opiates to maintenance treatment with buprenorphine withdrawal can be precipitated on induction of buprenorphine if it is commenced soon after the use of a full opioid agonist. This can be a barrier for some patients commencing and engaging in treatment. For this reason it is important that buprenorphine substitution not be commenced until there are some signs of withdrawal. The sponsor has proposed a COWS score of >12 prior to commencement. This is consistent with no more than mild withdrawal signs and symptoms and is consistent with the COWS score than is currently suggested in the National Guidelines for medication-Assisted Treatment of Opioid Dependence[1] .

Those guidelines recommend deferral of the first dose of buprenorphine until the patient is experiencing mild to moderate withdrawal (anxiety, abdominal or joint pain, dilated pupils, sweating). Mild to moderate withdrawal symptoms is consistent with a COWS score of 5 to 12.

[1] http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/AD14DA97D8EE00E8CA257CD1001E0E5D/$File/National_Guidelines_2014.pdf

8. Clinical safety

As this was a literature based submission safety data were limited. Available safety data are presented below.

8.1. Use in Pregnancy and Lactation

8.1.1. Pivotal and/or main efficacy studies

The only pivotal efficacy study that explicitly investigated AEs was by Jones et al (2010). The other pivotal studies indirectly evaluated safety through their efficacy analysis; for example, development of NAS, APGAR scores, pre-term birth etc. The evaluation of these efficacy and safety parameters is found in Section 7.

8.1.2. Patient exposure

A total of 131 patients were exposed to study treatment in Jones et al (2010).

8.1.3. Adverse events

Below is a table of all AEs from Jones et al (2010), and includes both maternal and foetal AEs.

Table 6 Adverse events from Jones et al 2010

Adverse Event	**Maternal**		**Neonatal**	
	Methadone (N= 89)	Buprenorphine (N= 86)	Methadone (N=73)	Buprenorphine (N=58)
Serious events	*number (percent)*			
Abnormal foetal health	3 (3)	0		
Abnormal laboratory values	0	0	0	0
Cardiovascular symptoms	1 (1)	0	2 (3)	1 (2)
Gastrointestinal symptoms	1 (1)	1 (1)	0	1 (2)
Genitourinary symptoms	0	1 (1)	0	1 (2)
Illicit drug use	1 (1)	1 (1)		
Musculoskeletal symptoms	0	0	0	1 (2)
Neurologic symptoms	0	0	0	1 (2)
Obstetrical symptoms	6 (7)	2 (2)	1 (1)	1 (2)
Postsurgical problems	0	0	0	1 (2)
Psychological problems	1 (1)	0		
Psychosocial problems	1 (1)	0		
Respiratory symptoms	1 (1)	0	2 (3)	0
Sexually transmitted diseases	1 (1)	0	0	0
Skin conditions	0	1 (1)	0	0
Sleep disturbances	0	1 (1)		
Other	0	0	1 (1)	1 (2)
Any serious adverse event	14 (16)	8 (9)	6 (8)	1 (2)
Nonserious events				
Abnormal appetite	2 (2)	0	4 (6)	1 (2)
Abnormal foetal health	6 (7)	4 (5)		
Abnormal laboratory values	10 (11)	8 (9)	0	0
Blood-borne disorders	5 (6)	1 (1)	0	1 (2)
Cardiovascular symptoms	29 (33)	14 (16)	8 (11)	4 (7)
Endocrinologic symptoms	5 (6)	3 (4)	1 (1)	1 (2)
Eye, ear, nose, or throat problems	12 (14)	15 (17)	1 (1)	1 (2)

Fever	3 (3)	2 (2)	0	0
Gastrointestinal symptoms	60 (67)	47 (55)	5 (7)	4 (7)
Genitourinary symptoms	23 (26)	16 (19)	1 (1)	0
Hematopoietic or lymphatic symptoms	14 (16)	15 (17)	17 (23)	14 (24)
Illicit drug use	10 (11)	8 (9)	3 (4)	5 (9)
Dental problems	22 (25)	15 (17)	1 (1)	2 (4)
Musculoskeletal symptoms	38 (43)	28 (33)	3 (4)	1 (2)
Neuromuscular symptoms	33 (37)	29 (34)	0	0
Neurologic symptoms	16 (18)	12 (14)	0	0
Obstetrical problems	29 (33)	23 (27)	3 (4)	4 (7)
Postsurgical problems	16 (18)	8 (9)	3 (4)	0
Psychological problems	24 (27)	21 (24)		
Psychosocial problems	4 (5)	5 (6)		
Respiratory symptoms	29 (33)	31 (36)	14 (19)	12 (21)
Sexually transmitted diseases	8 (9)	8 (9)	1 (1)	1 (2)
Skin conditions	16 (18)	12 (14)	7 (10)	2 (4)
Sleep disturbances	24 (27)	20 (23)		
Somatic symptoms	19 (21)	9 (11)		
Other	4 (5)	3 (4)	2 (3)	3 (5)
Any non-serious adverse event	83 (93)	66 (77)	34 (47)	29 (50)

* An alpha level of 0.05 was selected for each test of significance. Adverse events related to neonatal appetite included weight loss, need for nutritional support, and feeding intolerance. Cardiovascular events included rapid or slow heart rate and high or low blood pressure. Neonatal obstetrical events included asynclitic presentation and acrocyanosis. Psychosocial events included any stressful life event (e.g., stress surrounding moving, eviction, or death of a family member). A serious adverse event was defined as death or substantial risk of death of the mother or the infant or any medical event that a study investigator or the data and safety monitoring board judged to be serious because it might jeopardise the participant or might require intervention (e.g., hospitalisation or extension of hospitalisation). Two women in the methadone group had multiple serious adverse events (1 had a positive serologic test for syphilis, over- night hospitalisation, and suspected premature rupture of foetal membrane; the other had lack of housing and depression), and 12 women in this group had a single serious adverse event (2 cases each of foetal-heart-rate deceleration, pre- mature labour, and miscarriage and 1 case each of decreased blood flow to the foetus, pathological cardiotocographic de- celeration, heroin and cocaine overdose, gastroenteritis requiring hospitalisation, amniorrhexis, and pneumonia). Two women in the buprenorphine group had multiple serious adverse events (1 had multicystic kidney and positive drug- screening urinalysis leading to hospitalisation; the other had vaginal bleeding and preterm labour), and 6 women in this group had a single serious adverse event (2 cases of vaginal bleeding and 1 case each of methicillin-resistant *Staphylo• coccus aureus*, gastric haemorrhage, hospitalisation for removal of vaginal condyloma, and false labour). One neonate in the methadone group had multiple serious adverse events (2 surgeries for dextrocardia), and 4 neonates in this group had a single serious adverse event (1 case each of premature delivery [after which the neonate died], suspected apnoea, respiratory distress, and cyanosis). One neonate in the buprenorphine group had all 8 serious adverse events listed in the table (e.g., multiple surgeries, renal failure, and hypoxic ischaemic encephalopathy) and subsequently died.

The methadone group had higher rates of non-serious maternal events overall (P = 0.003) and of non-serious maternal cardiovascular events in particular (P = 0.01). The authors concluded that the two treatment groups did not differ significantly with respect to any serious or non-serious maternal or neonatal adverse events.

8.1.4. Treatment related adverse events (adverse drug reactions)

There was no assessment of whether the AEs were treatment related in Jones et al (2010). It is difficult to discern whether the AEs are due to the study drugs, concomitant maternal health issues, illicit drug use or the lack of antenatal care associated with this study population.

8.1.5. Deaths and other serious adverse events

In Jones et al 2010 there were 2 deaths, 1 each in the buprenorphine group and 1 in the methadone group. In the methadone group 1 infant had a pre-term delivery and subsequently died. In the buprenorphine group, 1 infant had multiple serious AEs (multiple surgeries, renal failure, hypoxic ischaemic encephalopathy) and also died.

8.2. Changes to Dosing and Administration

Significant increases in exposure to buprenorphine or naloxone have not been proposed in the amendments to the dose regimens. The current maximum dose of 32 mg daily remains in place.

The safety summary presented adverse event (ADE) data reported in three pivotal RCT and three supportive RCT, which evaluated the safety and efficacy of buprenorphine, and buprenorphine plus naloxone when administered according to the proposed changes to the starting dose, a flexible, clinically based maintenance dose titration regimen and in a usual maintenance dose ranging from 12 to 16 mg daily.

Five of the RCTs in this summary investigated buprenorphine for maintenance therapy of opioid dependence. These studies included 348 adult subjects of both sexes, who were treated with daily doses of ranging from 2 to 32mg daily, for between 6 weeks and 6 months. The sixth study, (Oreskovich 2005) enrolled 30 patients with acute heroin dependency who were treated with buprenorphine or clonidine for detoxification rather than for maintenance therapy. As such, the duration of dosing was only five days. Given the different products, patient characteristics and that the studies were in either induction or maintenance treatment it was not appropriate to pool safety results from these studies.

The largest of these studies was by Mattick. A total of 405 patients were recruited and a flexible dosing regimen was used with doses given in increments of 2 mg or 8 mg. Treatment emergent adverse events (ADEs) which occurred at an incidence of more than 5% were tabulated by system organ classification and event and are shown below.

Table 7 Treatment-Emergent Adverse Events (TEAE) with incidence of ≥5% (Mattick)

Adverse event	*Methadone (n = 202)*	*Buprenorphine (n = 192)*
Body as a whole		
Pain	31 (15%)	27 (14%)
Headache	23 (11%)	25 (13%)
Pain abdomen	23 (11%)	14 (7%)
'Flu' syndrome	20 (10%)	14 (7%)
Chills	14 (7%)	13 (7%)
Withdrawal syndrome	12 (6%)	21 (11%)
Accidental injury	12 (6%)	6 (3%)
Pain back	10 (5%)	12 (6%)
Cardiovascular		
Palpitations	9 (5%)	12 (6%)
Digestive system		
Nausea	33 (16%)	33 (17%)
Constipation	29 (14%)	20 (10%)
Vomiting	16 (8%)	16 (8%)
Musculoskeletal system		
Spasm general	12 (6%)	11 (8%)
Nervous system		
Insomnia	20 (10%)	25 (13%)
Anxiety	15 (7%)	9 (5%)
Somnolence	18 (9%)	9 (5%)
Depression	9 (5%)	12 (6%)
Respiratory system		
Rhinitis	12 (6%)	9 (5%)
Yawn	10 (5%)	9 (5%)
Skin and appendages		
Sweat	29 (14%)	28 (15%)
Special senses		
Lacrimation	11 (5%)	6 (3%)

Symptoms shown have an incidence of 5% in either randomized group.

Of the 96 patients who discontinued buprenorphine in this study, 3 did so due to an adverse event. Serious ADEs for the group given buprenorphine were: one case of allergic reaction, assault on a patient, motor vehicle accident, serious pneumonia and suicide attempt. Four cases of overdose on heroin or heroin plus benzodiazepines were also reported from the patients assigned buprenorphine. For the patients assigned methadone treatment one serious case of acute hepatitis C and two serious assaults on patients were reported. The AEs are generally consistent with degrees of withdrawal syndrome rather than effects of either methadone or buprenorphine. While serious AEs were reported it is not clear these can be attributed to either methadone or buprenorphine.

More limited reporting of adverse events was available from the other published study reports. These were smaller studies. No new suspected adverse effects were apparent from the limited data presented in the reports, with signs and symptoms of opiate withdrawal predominating in the AEs reported.

8.3. Post marketing experience

Postmarketing surveillance population-based linkage studies

Two population-based cohort record-linkage studies were conducted utilising existing nationwide administrative and health records in Denmark and Sweden.
One of the population based cohort studies reviewed over 950,000 pregnancies which occurred in Denmark between 1997 and 2001. The study aimed to examine selected pregnancy and birth outcomes, as well as NAS, among pregnancies exposed to buprenorphine and methadone. The data used in the linked analysis were collected prospectively between 1997 and 2011 in the Danish Medical Birth Registry, the Registry of Medicinal Products Statistics, the National Patient Registry and the Registry of Drug Abusers Undergoing Treatment.

A total of 158 pregnancies reported prenatal exposure to buprenorphine, 197 to methadone and 28 to heroin as the only opioid involved. The data demonstrated an increased likelihood of adverse birth outcomes among pregnant opioid users compared to the general population. There were 4 cases of stillbirth among the 197 methadone-exposed pregnancies, and no cases of stillbirth among buprenorphine or heroin-exposed pregnancies. The investigators reported a doubling of risk or greater in preterm birth, low birth weight, and congenital malformation in users of buprenorphine and methadone during pregnancy as compared with pregnancies with no reported opioid use, and a doubling of risk of SGA for methadone exposure. The increased risk for most birth outcomes was lower in buprenorphine exposed than in methadone exposed pregnancies.

The percentage of infants in which NAS was reported was higher in methadone-exposed pregnancies (54.9%) when compared to buprenorphine-exposed pregnancies (4.6%). Sixteen infants who had been exposed prenatally to a buprenorphine formulation were born with a congenital anomaly. A total of 13 infants were exposed to monotherapy (without other opioids). In addition, one set of twins was born to a mother who had taken Suboxone (containing buprenorphine and naloxone), and one infant was born to a mother who had taken Subutex (buprenorphine), heroin, morphine and methadone during pregnancy. Eight of these 16 infants had cardiac defects. The other eight infants presented with an accessory finger, AV malformation of the upper extremity, arthrogryposis, hydronephosis, peripheral vascular malformation NOS, plagiocephaly, hypertrophic pyloric stenosis (one infant each). Six of the seven mothers giving birth to infants with cardiac defects were age 35 or older. There was no particular pattern to the types of malformations other than the predominance of cardiac defects. The report did mention the statistical precision was relatively low as many of the estimates of effect were based on small numbers for a given outcome and uncontrolled confounding by other lifestyle factors could be present.

The other population based study reviewed around 750,000 pregnancies recorded in Sweden between 2005 and 2011. This study was performed using prospectively collected population-based data from the Swedish Medical Birth Register, which covers all births in Sweden. Information on drug exposure during pregnancy, maternal characteristics (i.e., age, parity, smoking, hepatitis, cohabitation status, EGA at first visit to prenatal health care), and birth and infant diagnoses (e.g., stillbirth, neonatal death, malformations) was obtained by using the unique national Personal Identification Number. This information was linked to data from the Prescribed Drug Register, the nationwide Cause of Death Register, and the Patient Register. Birth outcomes were reported according to drug exposure as Suboxone, Subutex, buprenorphine, or methadone. There were 176 pregnancies exposed to Suboxone plus Subutex (n=36), Subutex alone (n=139), or Suboxone alone (n=1) and there were 52 pregnancies exposed to methadone.

In the exposed group, there were fourteen infants with at least one major malformation; 7 (5%) in pregnancies exposed to Subutex, six (11.5%) with methadone exposure, and 1 (3%) with exposure to Suboxone and Subutex. No stillbirth, neonatal deaths, or deaths within the first year of life occurred among the infants born to mothers taking buprenorphine or methadone. NAS developed in 23.3% (95 % CI: 17.4, 30.4) of infants born to mothers taking Suboxone/Subutex, 24.5% (95% CI 17.7, 32.6) of infants of mothers taking Subutex alone, and 38.5% (95% CI 25.6, 53.0) of infants born to mothers taking methadone. The risk of caesarean section, preterm birth, SGA, LBW, major congenital malformation and any congenital malformation were not significantly elevated among pregnancies exposed to buprenorphine compared to the general population. Relative Risk (RR) for caesarean section, preterm birth, major congenital malformations, and any congenital malformations were significantly elevated for methadone-exposed pregnancies, but not in mothers exposed to buprenorphine. The increase observed in most birth outcomes (except SGA) was numerically lower in buprenorphine-exposed than in methadone-exposed pregnancies. As with the Danish study, the statistical precision was considered to be relatively low and uncontrolled confounding by other lifestyle factors could be present.

Post market pharmacovigilance review

The Indivior pharmacovigilance safety database was examined from June 1 1982 through November 15 2014 in order to identify all likely pregnancy-related Individual Case Safety Reports involving an exposure to a buprenorphine product (e.g., buprenorphine NOS, Suboxone, Subutex, Temgesic, Lepetan, Buprenex). Pregnancy cases were identified by 3 criteria: the case contained a preferred term (PT) that indicated exposure during pregnancy, case age onset at < 1 year to be classified as a neonate and the pregnancy indicator variable was yes. Cases were divided into cases including one or more Targeted Medical Events (TME) of interest for pregnancy (TME cases, n=2,435) or non-TME cases (n=7,524). Non-TME cases are those in which (1) only exposure to buprenorphine during pregnancy was reported with no mention of an adverse event, (2) exposure with a pregnancy-related event that was not a TME was reported (e.g. non-serious nausea and vomiting in pregnancy), or (3) exposure with non-pregnancy-related event (e.g. motor vehicle accident, fracture, etc.) are reported.

A total of 396 women were reported to have experienced pregnancy loss. This includes cases of spontaneous abortion, miscarriage or foetal death. Of the 396 cases of pregnancy loss, only Suboxone use was reported during pregnancy in 160 cases (40%), only Subutex use in 107 cases (27%), and in 127 cases (32%) both Suboxone and Subutex were reported to have been used during pregnancy. In 2 additional women the use of only low-dose buprenorphine during pregnancy was reported. There were 36 reports of infant deaths of all types. Fourteen were reported as SIDS (none of these were premature). Among the others there were 7 with both prematurity and congenital anomaly, 2 who were premature (without congenital anomaly), 5 term infants with a congenital anomaly, 5 who were term and did not have any congenital anomaly and 3 with insufficient information (including no information about gestational age at birth or details of the death). Two cases of mixed drug overdose and one case of hepatic failure due to acute fatty liver of pregnancy resulted in the deaths of the pregnant woman and foetus in each case.

A total of 257 women were reported to have experienced premature delivery. Mean gestational age at birth among the premature infants was 33.8 weeks in the 165 infants with data available. (Range: 25-36.9 weeks). Mean birth weight was 2149.7 grams in the 140 infants with data available (Range: 595-5613 grams). Low birth weight (i.e., ≤2500 g) was reported in 96 premature infants (38.1%). Sixty-one (24.2%) had NAS and 14 (5.6%) had jaundice. Twenty-five premature infants (9.9%) had a respiratory disorder.

A total of 379 women exposed to buprenorphine were reported to have experienced a complication during pregnancy, labour, delivery, or the postpartum period in addition to, or other than prematurity or foetal mortality. The product used was Subutex only in 34% of reports, Suboxone only in 26.9%, and both Subutex and Suboxone in 38.3% of cases. In 3 cases, only low-dose buprenorphine exposure was reported. In 47 cases a complication involving the foetus was reported (21 of these also reported a maternal complication); 51 cases reported a postpartum complication (16 also reported another complication) and 161 cases reported complications of labour and delivery (28 of them also reported another complication). Decreased foetal heart rate and foetal growth restriction were reported in 11 cases each (2.9% each), foetal distress in 8 cases (2.1%) and nuchal cord in 7 cases (1.8%). Most case reports reported very little information.

A structural or congenital anomaly was reported in 159 infants or foetuses that were exposed to buprenorphine during gestation. In 131 cases (82.4%) the anomaly was reported in a live-born infant and in 28 cases the foetus did not survive to birth. Almost all of the reports involved use of Subutex only (n=92), 20% involved Suboxone only (n=32), 21% Suboxone plus Subutex (n=33), and three reports involved a low-dose buprenorphine formulation only. The most commonly reported congenital/foetal anomalies were cardiovascular in 36.5% of cases (n=58), musculoskeletal in 21.4% (n=34), neural tube/central nervous system (CNS) in 17.6% (n=28), orofacial/skull in 15.7% (n=25) and chromosomal abnormalities in 10.7% (n=17).

A total of 944 infants born to mothers taking buprenorphine during pregnancy were reported to have experienced NAS. Most of the reports noted exposure to buprenorphine during pregnancy only (n=796, 84.3%), and in 145 (15.4%) exposure was during pregnancy and breastfeeding. There were 26 cases reporting children with various developmental delays. Most of the cases reported were poorly documented and relatively non-specific. In 13 cases, a speech and/or language disorder was reported (including one case who also had a cleft palate without mention of whether the speech delay was related to the malformation and one who had cerebral palsy). Six of the 26 infants were premature and/or had low birth weight. Three children had Autism Spectrum Disorder. There was one child with physical growth retardation (staturoponderal) and abnormal behaviour.

As expected, frequencies of these AEs could not be estimated as exposure (the denominator) is unknown. There is no evidence that these safety issues are higher than the background rate. In summary, no clear patterns were identified that would constitute a new safety signal.

8.4. Evaluator's overall conclusions on clinical safety

- The postmarketing surveillance population-based linkage studies demonstrated no evidence of a new safety issue in infants exposed to buprenorphine. Analysis was limited by uncontrolled confounding and the small number of outcomes for any outcome.
- Examination of the Sponsor safety database did not demonstrate evidence of a safety signal for maternal or foetal AEs. Analysis was limited by uncontrolled confounding, small numbers for outcomes and unknown frequency of AEs
- It is noted that pregnant women with OUD constitute a high risk population due to concomitant illnesses, continuing substance abuse in many cases, poor lifestyle choices, lack of ongoing medical attention and a generally chaotic and unhealthy lifestyle. These factors could all contribute to adverse maternal and foetal outcomes.
- Alternatives to buprenorphine treatment include methadone, which is more studied in this population but also associated with safety concerns (such as LBW infants and pre-term birth). Ongoing abuse with illicit opiates is associated with multiple serious foetal and maternal adverse outcomes.

- The proposed changes to the dosing recommendations generally involve more monitoring and only minor increases in the total dose of buprenorphine on some days and no increase in the maximum daily dose. Given this no new safety issues were likely to be identified and none were evident in the papers presented.

9. First round benefit-risk assessment

9.1. First round assessment of benefits – Use in Pregnancy and Lactation

Indication	
Benefits	**Strengths and Uncertainties**
• In general buprenorphine maintenance treatment appears to result in less risk to the neonate than methadone treatment. • Child-birth for patients on buprenorphine rather than methadone maintenance was associated with fewer pre-term births, higher birth weights, length and head circumference as well as shorter hospital stays for those neonates. • There is international experience with the use of buprenorphine in pregnancy • Buprenorphine offers an alternative to methadone or continued substance abuse • Post-marketing studies and a review of the Sponsor safety database did not indicate evidence of new safety issues associated with buprenorphine exposure during pregnancy • In two studies examining infant exposure to buprenorphine via breast milk, the RID was <1%, which is below the 10% margin which is classically accepted as safe for infant exposure to a drug via breast milk.	

9.1. First round assessment of benefits – Change in Dose Regime and Buccal administration

Indication	
Benefits	**Strengths and Uncertainties**
The proposed changes to the dose regimen allow for somewhat increased flexibility in dosing and are generally consistent with the current National Guidelines for medication – Assisted Treatment of Opioid Dependence. The proposed changes will result in more specific and detailed instruction on dosing. For SUBOXONE film the additional route of administration (buccal) will provide an alternative method of administration for individuals who prefer buccal to sublingual administration.	A larger range of patients will be eligible for treatment using the revised dosing recommendations.

9.2. First round assessment of risks – Use in Pregnancy and Lactation

Risks	Strengths and Uncertainties
• In a Cochrane Systematic Review by Minozzi et al (2013) the researchers found there was insufficient evidence or low to very low evidence to separate buprenorphine and methadone in terms of efficacy and safety in for use in pregnancy • Analysis of post market safety data was complicated by unknown frequency of AEs (due to unknown exposure), uncontrolled confounding and low number of outcomes for AEs	

9.1. First round assessment of risks – Change in dose regime and buccal administration

Risks	Strengths and Uncertainties
It is possible the revised dosing recommendations may be interpreted such that some patients who would currently be considered too high a risk for conversion to buprenorphine treatment e.g. patients taking more than 30 mg methadone daily, may undergo unsuccessful attempted conversion to buprenorphine. This would cause unnecessary withdrawal symptoms. No substantial additional risks appear to be associated with buccal rather than sublingual administration for SUBOXONE film.	Present a concise overview of the strength of Provided patients and their healthcare providers discuss the risks of transition to buprenorphine and agree on the treatment the risks associated with transition would be minimised. The highest risk of unsuccessful conversion to buprenorphine is in those patients who take unknown illicit medications and / or who have high levels of dependence of long acting opioids. Close supervision of these patients should mitigate the risks of using buprenorphine in these patients.

9.2. First round assessment of benefit-risk balance – Use in Pregnancy and Lactation

The benefit-risk balance for removal of use of buprenorphine in Pregnancy and Lactation as a contraindication and replacement with precautionary advice is favourable.

9.3. First round assessment of benefit-risk balance – Change in Dose Regime and buccal administration

The benefit-risk balance for revision of the Dosage and Administration instructions is favourable. Additional minor amendments to the proposals to improve readability and consistency with the National Guidelines for medication-Assisted Treatment of Opioid Dependence have been recommended.

10. First round recommendation regarding authorisation

Pending negotiation of the Product Information documents it is recommended that the changes be approved.

11. First round comments on product documentation

11.1. First round comments on draft PI

Only those sections of the draft PIs in which amendments are recommended have been reproduced below. Existing text is shown in plain script. Changes proposed by the Sponsor are shown in green. Text recommended for inclusion by the evaluator is shown in red.

Use in Pregnancy (Category C)
Treatment with buprenorphine during pregnancy was associated with difficult parturition and fetotoxicity, including post-implantation loss and decreased post-natal survival, in rats and rabbits at systemic exposures similar to the maximum anticipated human exposure (32 mg/day). Evidence for teratology was not evident in animal studies.

Maternal oral administration at high doses (80 mg/kg/day) during gestation and lactation resulted in a delayed postnatal development of some neurological functions (surface righting reflex and startle response) in neonatal rats with a NOEL of 8 mg/kg/day PO (representing a systemic exposure of ~30% of the maximum anticipated clinical exposure). Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

~~There are no adequate and well controlled studies of TRADENAME in pregnant women.~~
Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Data on the use of buprenorphine in pregnancy, and its impact on the mother and foetus, are limited. Data from randomised, controlled trials and observational studies do not indicate an increased risk of maternal or foetal adverse outcomes compared to methadone.

Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. ~~TRADENAME are contraindicated in pregnant women (see **CONTRAINDICATIONS**).~~

Use in Lactation
Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. Decreases in postnatal survival, growth and development were also observed in animals treated with buprenorphine during lactation. In two studies of thirteen women, buprenorphine was found in low levels in human breast milk. In both studies the estimated infant dose was <1% of the maternal dose. Because buprenorphine passes into the mother's milk, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. ~~TRADENAME should not be used in breast-feeding women.~~

DOSAGE AND ADMINISTRATION

Patients taking ~~Street~~ Heroin (or Other Short-acting Opioids): When treatment starts the dose of TRADENAME should be taken at least 6 hours after the patient last used opioids ~~or~~ and when the ~~early~~ objective signs of withdrawal appear. The Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment however clinical assessment of withdrawal symptoms with consideration of the patient's baseline presentation is important, particularly for patients in mild withdrawal (COWS score of 5-≤12).The recommended starting dose is 4 mg TRADENAME on day one, with a possible additional 4 mg depending on the individual patient's requirement. For patients with moderate or severe withdrawal at the time of the first dose, an initial dose of 8mg is appropriate with an additional 4 mg depending on the individual patient's requirement to a total maximum of 12 mg on Day 1.

Lower doses (e.g. 2 or 4mg total on Day 1) are suited to those with low or uncertain levels of opioid dependence, with high risk polydrug use (alcohol, benzodiazepines) or with other severe medical complications. Seek specialist advice if concerned. The suggested total dose for Day One is in the range of 8- 12 mg TRADENAME.

Patients on Methadone*:* Before starting treatment with TRADENAME, the maintenance dose of methadone should be reduced to ~~30 mg per day~~the minimum daily dose that the patient can tolerate. The first dose of TRADENAME should be taken at least 24 hours after the patient last used methadone. ~~The initial 4-8mg TRADENAME induction dose should ideally be administered when the early objective withdrawal signs are evident (COWS >12). The suggested target total dose for Day One is in the range of 8- 12 mg TRADENAME.~~ An initial dose of 2 mg TRADENAME should be administered when moderate withdrawal is apparent (COWS ≥13). An additional dose of 6 mg TRADENAME cam be administered one hour later if the initial dose does not precipitate withdrawal.
Supplementary doses can be administered every one to three hours according to withdrawal severity:
• 0mg if there is no or minimal withdrawal (COWS<6);
• 4mg if there is mild withdrawal (COWS 6-12);
• 8mg if there is moderate to severe withdrawal (COWS≥13).

The suggested target total dose for Day One is in the range of 8 – 16 mg TRADENAME.

During the initiation of treatment patients need frequent monitoring. TRADENAME should be dispensed in multiple doses over the first 4 to 6 hours of the transfer. ~~closer~~ ~~D~~osing supervision is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

Dosage Adjustment and Maintenance

The dose of TRADENAME should be increased progressively according to the clinical effect in the individual patient ~~and should not exceed a maximum daily dose of 32 mg.~~ The dosage is adjusted in increments or decrements of 2 – 8 mg buprenorphine to a level that maintains the patient in treatment and suppresses opioid withdrawal effects according to reassessments of the clinical and psychological status of the patient.

~~In clinical studies many patients were stabilized on a daily maintenance dose of 12 mg/3 mg to 16 mg/4 mg of buprenorphine, although some patients may require higher doses. A maximum daily dose of 32 mg should not be exceeded~~. Most patients require daily buprenorphine doses in the range 12 -24 mg to achieve stabilisation, although some patients require higher (e.g. up to 32mg/day) or lower (4-8 mg/day) doses to achieve their treatment goals. During maintenance therapy, it may be necessary to periodically restabilise patients to new maintenance doses in response to changing patient needs.

Less than daily dosing

For patients who require supervised dosing, a less-than daily dosing regimen may facilitate supervised dosing in patients with opioid dependence that is uncomplicated by concomitant dependence on other agents with central nervous system (CNS) activity, including alcohol.

After a satisfactory stabilisation has been achieved, the frequency of dosing may be decreased to every-other-day at twice the individually titrated daily dose. Patients on ~~<~~ >8 mg/day may not find less-than-daily dosing adequate and these dose regimens are not recommended for patients stabilised on >12 mg TRADENAME daily.

In some patients, three times a week (for example on Monday, Wednesday and Friday) may be used. The dose on Monday and Wednesday may be twice the daily dose, and the dose on Friday may be three times the individually titrated daily dose. However the dose given on any one day should not exceed 32 mg.

The patient should be observed following the first multi-dose administration to initiate the less-than daily dosing regimen and whenever treated with high doses. Patients who sporadically use concomitant CNS-active medications or substances should be monitored closely.

The proposed changes referring to buccal administration for SUBOXONE film (including the change to the tradename) are acceptable without amendment.

11.2. First round comments on draft CMI (clinical aspects)

11.3. First round comments on draft RMP (Summary of Safety Concerns)

12. Clinical questions

No questions

12.1. Additional expert input

Not required

13. First round evaluation errata

13.1. Minor editorial changes

13.2. Minor errors of fact

13.3. Significant errors of fact

14. References

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15. Supporting information, tables and figures

Table 9 COWS criteria and scoring system

Resting pulse rate (beats/ minute)– measured after patient is sitting or lying for one minute 0 pulse rate ≤80 1 pulse rate 81 – 100 2 pulse rate 101 – 120 4 pulse rate >120	**GI Upset**: over last 30 minutes 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhoea 5 multiple episodes of diarrhoea or vomiting
Sweating: over past 30 minutes not accounted for by room temperature or patient activity 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** observation of outstretched hands 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness Observation during assessment 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/ arms 5 unable to sit still for more than a few seconds	**Yawning** Observation during assessment 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/ minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability**0 none 1 patient reports increasing irritability of anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficulty
Bone or Joint aches If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny nose or tearing Not accounted for by cold symptoms or allergies 0 not present	

1 nasal stuffiness or unusually moist eyes 4 nose constantly running / tears streaming down cheeks.	

16. Information about the evaluator

This evaluation was completed by two internal evaluators.

Therapeutic Goods Administration

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Australian Government
Department of Health
Therapeutic Goods Administration

Risk Management Plan Evaluation Report

Buprenorphine (SUBLOCADE)

Submission No: PM-2018-01872-1-1

Sponsor: Indivior Pty Ltd

Round 1: 29 November 2018
Round 2: 12 March 2019
Post-Round 2: 06 June 2019

s22 [redacted]

s22 [redacted]

TGA Health Safety Regulation

RISK MANAGEMENT PLAN EVALUATION REPORT

Submission type: Major variation — new dose form
Sponsor: Indivior Pty Ltd
Generic name: **Buprenorphine**
Trade name: **SUBLOCADE**
Dose form and strength: Extended release injection; 100 mg and 300 mg
Drug class: Opioid partial agonist

Submission No; eSubmission ID: PM-2018-01872-1-1; e003260
RMP file No: E18-298353
TRIM reference: D18-11218807

EU-RMP Version: Rounds 1 and 2 – Version 1.0; date 12 March 2018; DLP 31 December 2017.
ASA Version: Round 1 – Version 1; date May 2018.
Round 2 – Version 2; January 2019.
Post Round 2 – Version 2.1; March 2019.
s22 [redacted]

Evaluator: s22 [redacted]
Peer Reviewer:

Date authorised: 29 November 2018 [Round 1]
12 March 2019 [Round 2]
06 June 2019 [Post Round 2]
s22 [redacted]

RMP referral to ACM: Not referred to ACM

Pharmacovigilance activities:	Routine
Risk minimisation Activities	Routine
	Healthcare professional education
	Patient education
	Restricted distribution
Black Triangle Scheme:	No

s22 [redacted]

s22 [redacted]

SUMMARY

- Indivior Pty Ltd has applied to register a new dose form and strength of buprenorphine (Sublocade) as an extended release subcutaneous injection, 100mg and 300mg. Sublocade is proposed for the treatment of opioid dependence, within a framework of medical, social and psychological treatment. The dosage of Sublocade is 300 mg monthly for the first 2 months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient.

- Indivior Pty Ltd has submitted EU-RMP version 1.0 (dated 12 March 2018; DLP 31 December 2017) and ASA version 1 (dated May 2018) in support of this application. The ASA was updated to version 2 (January 2019) at round 2. The sponsor has submitted ASA version 2.1 (March 2019) at post-round 2. The sponsor has submitted ASA version 3.0 (September 2019) at post-round 2 reconciliation.

- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below:

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	CNS depression including respiratory depression/respiratory failure	✓	–	✓	✓
	Hepatitis, hepatic events, use in patients with hepatic impairment	✓	–	✓	✓
	Local tolerability: injection site reactions	✓	–	✓	✓
	Drug withdrawal syndrome including neonatal withdrawal	✓	–	✓	✓
	Misuse/abuse	✓	–	✓	✓
	Overdose*	✓	–	✓	✓
Important potential risks	Use in pregnancy and lactation*	✓	–	✓	✓
Missing information	Use in children/adolescents (< 18 years old)	✓	–	✓	–
	Use in elderly patients (≥ 65 years old)	✓	–	✓	–

*ASA specific safety concerns

- The proposed summary of safety concerns has been revised as requested by the RMP evaluator in round 1 (see section 5.2) and is deemed acceptable. The sponsor has separated out 'overdose' as a stand-alone important identified risk and added 'use in pregnancy and lactation' as an important potential risk. The sponsor has also simplified the wording relating to the important identified risks of 'hepatitis, hepatic events, use in patients with hepatic impairment' and 'misuse/abuse' (see section 2.4).

- The sponsor has not proposed any additional pharmacovigilance activities. This is considered acceptable.

- The sponsor has proposed additional risk minimisation activities in the form of HCP and patient educational materials. This is considered acceptable.

- The sponsor has committed to provide the TGA with an updated restricted access plan to limit supply in the first six months to approved prescribers and an evaluation plan once discussions with state/territory health departments are completed and prior to supply.
- The sponsor has committed to developing and providing the TGA with specific strategies for risk minimisation of supply of Sublocade beyond the initial restricted access scheme. This is to be provided to the TGA prior to expanded supply beyond of the initial restricted access period.

NEW AND OUTSTANDING RECOMMENDATIONS – POST ROUND 2

The recommendations made in the round 1 evaluation, along with consideration of the sponsor response, are located in section 5.2 (recommendations 1 to 10). The recommendations made in the round 2 evaluation, along with consideration of the sponsor response, are located in section 6 (recommendations 7, 8 and 11). The recommendations made in the post round 2 evaluation, along with the sponsor response, are located in section 7 (recommendations 7 and 8). The recommendations made in the post round 2 reconciliation evaluation, along with consideration of the sponsor response, are located in section 8 (recommendations 7 and 8).

There are no new recommendations.

Wording for conditions of registration

The SUBLOCADE EU-Risk Management Plan (RMP) (version 1.0, dated 12 March 2018, data lock point 31 December 2017), with Australian Specific Annex (version 2.1, dated March 2019), included with submission PM-2018-01872-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

s22 [redacted]

Additional conditions of registration that may be applicable in this instance (for Delegate consideration):

To ensure that the proposed educational materials will adequately mitigate the risks associated with the use of Sublocade, the sponsor should provide mock-ups to the TGA for review. This material must be acceptable to the TGA before the supply of Sublocade begins.

The sponsor must implement a restricted access scheme to ensure that distribution of Sublocade is limited, in the first 6 months of supply, to prescribers in hospital and specialist drug rehabilitation clinics who have demonstrated that they have reviewed the educational materials. The plan for this scheme must be considered adequate to the TGA before the supply of Sublocade begins.

The sponsor should implement additional risk minimisation on commencement of supply of Sublocade beyond the restricted access scheme. The evaluation of the restricted access scheme and educational materials and the revised risk minimisation plan must be considered acceptable to the TGA before the restricted access scheme concludes and broader supply of Sublocade commences.

Pharmacists should dispense Sublocade to the prescribing doctor and not directly to the patient.

Other advice to the Delegate

The sponsor has provided an acceptable distribution plan for the initial restricted access period and adequate evaluation plan to assess the suitability of the educational materials and develop a distribution plan for beyond the restricted access period.

MAIN BODY

1. BACKGROUND

Indivior Pty Ltd has applied to register a new dose form and strength of buprenorphine (Sublocade) as an extended release subcutaneous injection, 100mg and 300mg. The sponsor advises that Sublocade will be used in the same patient population and will share the same therapeutic indications as the sublingual tablet version Subutex (also sponsored by Indivior Pty Ltd). Subutex is currently approved for the treatment of opioid dependence, within a framework of medical, social and psychological treatment and is available in three different strengths.

Indivior Pty Ltd has submitted EU-RMP version 1.0 (dated 12 March 2018; DLP 31 December 2017) and ASA version 1 (dated May 2018) in support of this application. The sponsor has submitted ASA version 2 (dated January 2019) at round 2. The sponsor has submitted ASA version 2.1 (March 2019) at post-round 2. The sponsor has submitted ASA version 3.0 (September 2019) at post-round 2 reconciliation.

1.1. INDICATION

The proposed indication as stated in the draft PI is as follows:

> *Treatment of opioid dependence, within a framework of medical, social and psychological treatment.*

This indication is consistent with that of the reference product, Subutex.

1.2. DOSAGE AND ADMINISTRATION

The draft PI advises that patients appropriate for Sublocade are adults who have initiated treatment on a transmucosal buprenorphine-containing product and that the patient may only be transitioned to Sublocade after stabilisation on transmucosal buprenorphine.

The recommended dosing regimen for Sublocade is 300 mg monthly for the first 2 months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient.

The full proposed dosage and administration information is provided in Appendix 1.

1.3. OVERSEAS REGULATORY STATUS

The sponsor has advised that Sublocade extended release injection has been approved/submitted in the countries listed in the table below.

Country	Regulatory Status	Date	Indications
U.S.A.	Approved	30/11/2017	Treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days. SUBLOCADE should be used as part of a complete treatment plan that includes counseling and psychosocial support.
Canada	Approved	21/11/2018	Treatment of moderate to severe opioid use disorder in adults. SUBLOCADE should be used as part of a complete treatment plan that includes counselling and psychosocial support.
EU (DCP for FR, BE, PT, CZ, LU, LV, LI and CY)	Evaluation ongoing	08/11/2018	Treatment of opioid addiction, within a comprehensive therapeutic monitoring framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents 15 years of age and older, who have agreed to be treated for opioid addiction.
National submissions in UK, DE, SE, DK, NO, FI, IT.	Evaluation ongoing	14/11/2018 - 27/11/2018	Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

1.4. QUALITY OF THE SUBMISSION

There is an inconsistency within the ASA between the information provided in the table in Section 3.1 for the entry *Misuse/abuse (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV use, extraction, overdose* and that for the same entry in the table under Section 4. The former states that there are no additional risk minimisation activities for this risk, however Table 4 identifies two additional risk minimisation activities for the risk. The sponsor should amend the ASA to ensure consistency. It is also noted that the EU-RMP does not propose additional risk minimisation activities for this risk. This was resolved by the sponsor at round 2.

2. SAFETY SPECIFICATION

2.1. NONCLINICAL ADVICE ON SAFETY SPECIFICATION

The nonclinical evaluation states that:

> *"Key safety concerns arising from the nonclinical data are adequately identified in the Safety Specification of the Risk Management Plan (Part II, Module SII)."*

2.2. CLINICAL ADVICE ON SAFETY SPECIFICATION

The Clinical Evaluator provided comment that the summary of safety concerns appears satisfactory.

2.3. PROPOSED SUMMARY OF SAFETY CONCERNS - ROUND 1

The sponsor has proposed the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	CNS depression including respiratory depression/respiratory failure
	Hepatitis, hepatic events, use in patients with hepatic impairment ~~(effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation)~~
	Local tolerability: injection site reactions
	Drug withdrawal syndrome including neonatal withdrawal
	Misuse/abuse ~~(risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION)~~**; IV use, extraction, overdose**
Missing information	Use in children/adolescents (< 18 years old)
	Use in elderly patients (≥ 65 years old)

It is suggested that the sponsor remove the words highlighted in the table above in red with a strike-through, as they are superfluous to the name of the risk.

The sponsor should amend the summary of safety concerns so that *misuse/abuse* and *overdose* are separate important identified risks. Although the risk with IV use could be associated with an intention of abuse, it could also stem from an administration error. Furthermore, IV use is associated with specific safety issues caused by the product forming a solid mass in a blood vessel. Overdose

may occur, for example, if a patient was prescribed other opioids for pain relief and were not aware of the risk of overdose from concomitant use.

The sponsor should include '*use in pregnancy and lactation'* as an important potential risk, given that there are limited data on the impacts of buprenorphine on mother, foetus and breastfeeding infants.

2.4. ROUND 2 - SUMMARY OF KEY CHANGES TO SAFETY SPECIFICATION

Changes from ASA version 1 to version 2	RMP evaluator comment
Amended 'Misuse/abuse' and 'Overdose' as separate important identified risks	This satisfies recommendation 2 and is acceptable.
Added Use in pregnancy and lactation as an important potential risk	This satisfies recommendation 1 and is acceptable.
Amended wording from 'Hepatitis, hepatic events, use in patients with hepatic impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation)' to 'Hepatitis, hepatic events, use in patients with hepatic impairment'	This satisfies recommendation 3 and is acceptable.
Amended wording from 'Misuse/abuse (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV use, extraction, overdose' to 'Misuse/abuse'	This satisfies recommendation 3 and is acceptable.

The sponsor has addressed and resolved the issues identified in section 2.3. The summary of safety concerns is acceptable.

3. PHARMACOVIGILANCE PLAN

3.1. ROUND 1 - PROPOSED PHARMACOVIGILANCE PLAN

The sponsor has proposed routine pharmacovigilance for all safety concerns. Specific adverse drug reaction follow-up forms have been proposed for the following safety concerns:

- CNS depression
- Respiratory depression/Respiratory failure
- Overdoses involving benzodiazepines and/or alcohol
- Fatal overdose
- Drug interactions
- Lack of drug effect
- Misuse/Abuse
- Off-label use
- Medication error
- Injection site reactions and injection site infection
- Hepatic events / Drug related hepatic disorders
- Drug withdrawal syndrome
- Neonatal withdrawal
- Paediatric accidental exposure / Paediatric intoxication
- Elderly population

- Transmission of an infectious agent via product

No additional pharmacovigilance activities have been proposed.

3.2. ADEQUACY OF PROPOSED PHARMACOVIGILANCE PLAN

Routine pharmacovigilance measures proposed are considered suitable to monitor the risks associated with this medicine.

3.3. PLANNED STUDIES

There are no planned studies proposed.

3.4. ROUND 2 - SUMMARY OF CHANGES TO THE PHARMACOVIGILANCE PLAN

There have been no changes to the pharmacovigilance plan in the updated ASA. This is acceptable.

4. RISK MINIMISATION PLAN

4.1. CONSIDERATION OF PART II: MODULE SVI

The sponsor has proposed routine risk minimisation activities for all safety concerns. Although the sponsor has stated in the ASA that it does not propose additional risk minimisation activities, it has also described educational material addressing some of the safety concerns, for health professionals and consumers. Clarification is required on whether or not additional risk minimisation materials implemented for the sponsor's other buprenorphine-containing products will be updated with information about Sublocade (see sections 1.4 and 4.1.3).

4.1.1.1. Potential for misuse for illegal purposes

The sponsor states the following in Part II of the EU-RMP:

> *Since BUPRENORPHINE EXTENDED-RELEASE INJECTION is required to be administered in a healthcare setting and is not made directly available to patients, its potential for misuse, abuse and diversion is minimised. Its format as an injectable depot also reduces its abuse potential.*

The RMP evaluator considers this statement to be reasonable and notes that *misuse/abuse* is included in the summary of safety concerns.

The sponsor states in the cover letter and in section 3.3 of the ASA, that it intends to engage with State and territory health departments to allow managed distribution of the product to healthcare professionals and not directly to patients, in order to reduce the risk of diversion, misuse and intravenous administration. The sponsor has undertaken to provide TGA with a copy of the letter sent to State/Territory health departments to initiate discussion on the new regulatory policy framework for extended-release buprenorphine.

4.1.1.2. Medication Errors

The potential for medication errors is discussed in the ASA. Sublocade is intended for subcutaneous injection only and carries risk of serious injury or death if administered intravenously or intramuscularly. The sponsor has proposed routine risk activities that minimise this risk, including

that administration be undertaken by healthcare professionals only, and warning statements on label packaging and in the proposed PI, including the following in section 4.4 of the PI:

> *Intravenous injection presents significant risk of serious harm or death as SUBLOCADE forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. Do not administer intravenously or intramuscularly.*

Given the very serious risks if administered intravenously, routine risk minimisation activities alone are not considered adequate for addressing this risk. The sponsor should implement additional risk minimisation measures for health care professionals and patients that address the risk of IV administration and other risks associated with the dosage formulation (see 4.1.3).

ROUND 1 - PLANNED RISK MINIMISATION ACTIVITIES

Routine risk minimisation activities have been proposed for all of the safety concerns. The sponsor states that [*r*]*outine risk minimisation activities as described in Part V.1 of the EU-RMP are sufficient to manage the safety concerns of SUBLOCADE.*

4.1.2. Product labelling

4.1.2.1. Product Information

The information contained in the PI for Sublocade appears consistent with that in the US Prescribing Information[1]. However, it is noted that the foreign product information provided by the sponsor, contains a boxed warning that includes the following warning statement:

> *WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY*
>
> *Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously. (5.1)*

The proposed Australian PI does not contain this warning as a boxed warning. It is recommended that the sponsor amends the Australian PI to include the above boxed warning with a corresponding cross-reference to the relevant section of the body of the PI that contains more detailed information.

The sponsor has advised in its cover letter, that the full approved Product Information is intended to be included as a package insert in the carton as required by current legislation for injectables.

The evaluator notes that there is an application under evaluation to remove the pregnancy contraindication for Subutex (PM-2017-02665-1-1). The wording of section 4.6 in the proposed PI for Sublocade reflects the changes requested to the Subutex PI.

4.1.2.2. Consumer medicine information

The following warning statement in the PI regarding risk of serious harm or death with intravenous administration is only partially communicated in the CMI. The PI states the following:

[1] US FDA Prescribing Information, (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209819s000lbl.pdf)

Risk of serious harm or death with intravenous administration

Intravenous injection presents significant risk of serious harm or death as SUBLOCADE forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. Do not administer intravenously or intramuscularly.

While the CMI states the following:

SUBLOCADE forms a depot following subcutaneous injection. Serious harm could result if injected intravenously. SUBLOCADE must not be injected intravenously or intramuscularly.

The sponsor should extend the warning in the CMI to include communication of the risk of *death* associated with intravenous administration.

Additionally, subsequent to the recommendation in section 4.1.2.1 above to include a boxed warning in the PI, a similar prominent boxed warning should also be placed at the beginning of the CMI, in a manner that provides sufficient information for a consumer to understand the risks or to prompt a conversation with a healthcare professional.

The risk of Neonatal Abstinence Syndrome is communicated in the PI but is not mentioned in the CMI. The sponsor should align the CMI with information in the PI under the subheading *Neonatal Abstinence Syndrome,* albeit with appropriate tailoring to the consumer.

4.1.3. Additional risk minimisation activities

The sponsor has proposed that:

… Indivior will provide HCPs with detailed educational materials on the Instructions for Use to ensure correct administration of the product. These materials are currently in preparation and will be forwarded to TGA when available and finalised at a later date.

The sponsor has also proposed the following educational material for patients:

… a product-specific patient information brochure designed to be given by prescribers to patients who have been prescribed SUBLOCADE. This brochure will cover information about the safety concerns identified. It will also encourage patients to report adverse experiences and drug misuse to HCPs.

The product-specific patient information brochure is currently in preparation and will be forwarded to TGA when available and finalised at a later date.

The evaluator considers that additional risk minimisation activities for health professionals and patients for this new formulation of buprenorphine are warranted for all of the important identified risks.

The evaluator also considers that the supply of Sublocade should be restricted for the first six months to prescribers in hospitals and specialist drug rehabilitation clinics who have demonstrated that they have reviewed the educational materials. Such a program would allow specialist prescribers to gain experience with the formulation so that they can provide experience-informed clinical advice to other prescribers and general practitioners when the product is made available for broader prescriber groups. The sponsor should commit to implementation of a restricted access program, and should provide to the TGA, prior to registration of this product, a plan for the restricted access program, which should include a description of how and to whom educational materials will

be distributed, and how the sponsor will ensure that the product is only supplied to prescribers in hospitals and specialist drug rehabilitation clinics. The plan should also describe how the sponsor will ensure adequate review and implementation of the additional risk minimisation activities based on early experience prior to supply to a broader group of prescribers.

s22 [redacted]

4.1.4. Evaluation of effectiveness of additional risk minimisation activities

The sponsor should develop an evaluation plan for the recommended restricted access program, and submit this to the TGA for review prior to registration of this product. The sponsor has proposed to evaluate its educational materials for healthcare professionals (HCP) using a survey and to evaluate its educational materials for consumers through readability testing.

The proposals to conduct a survey for HCPs, and readability testing of consumer materials, are considered acceptable. The sponsor should provide details of how these will be conducted, prior to registration. The plan for evaluating the HCP materials should be considered in light of recommendation 7, in particular to allow the educational materials to be reviewed and amended, if necessary, on the basis of experience during the first 6 months of supply and prior to broader supply.

4.2. ROUND 2 - SUMMARY OF CHANGES TO THE RISK MINIMISATION PLAN

The recommendations made in the round 1 evaluation, along with consideration of the sponsor response, are located in Section 5.2 (recommendations 1 to 10).

The sponsor has:

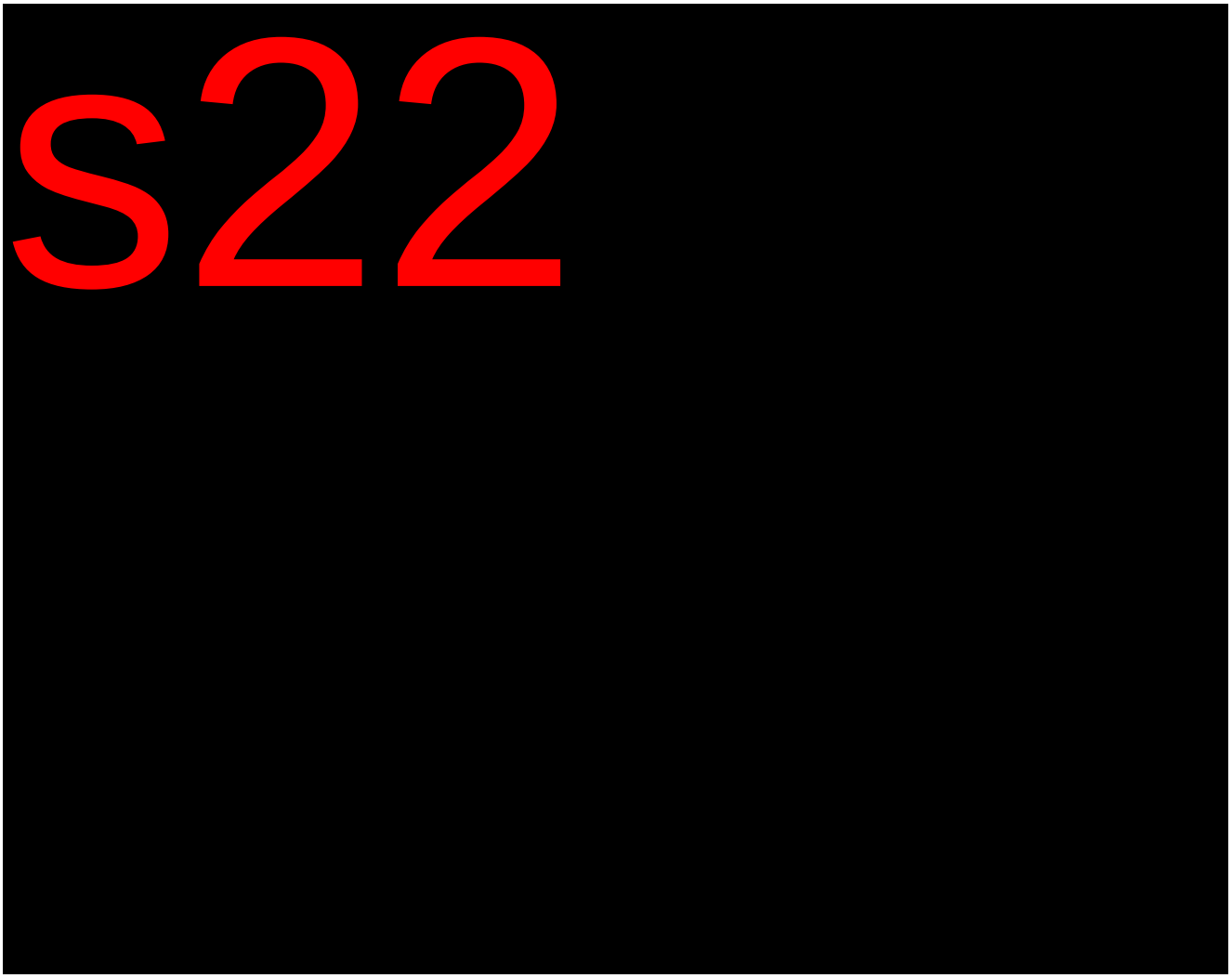
- aligned sections 3.1 and 4 of the ASA for consistency by including: restricted access of supply, educational materials and activities with state health regulators as additional risk minimisation activities (see section 1.4)
- added educational materials as an additional risk minimisation materials for the following risks: CNS depression including respiratory depression/respiratory failure; hepatitis, hepatic events, use in patients with hepatic impairment; local tolerability: injection site reactions; drug withdrawal syndrome (including neonate withdrawal); misuse/abuse; overdose; and use in pregnancy and lactation
- added: limitation of the supply, State and Territory health regulator activities and a black box warning in the CMI and PI to address the misuse/abuse safety concern
- included the black box warning in the PI
- amended the CMI to include the black box warning, information on risk of intravenous use and neonatal abstinence syndrome
- proposed a draft restricted access plan for the first 6 months which will require review after discussions and negotiations are had with the state/territory health departments. These are to be provided to the TGA once developed for evaluation prior to supply

- committed to developing and providing a distribution plan for access beyond the initial restricted access period. This is to be provided to the TGA prior to the expansion of the initial restricted access period
- advised that additional risk minimisation materials will not be implemented for the sponsor's other buprenorphine-containing products regarding information about Sublocade
- provided a plan for reviewing and evaluating educational materials which is acceptable. Any changes to the educational material are to be provided to the TGA for evaluation before supply.

5. ROUND 2 EVALUATION

5.1. ACM ADVICE

This RMP is not being referred to the ACM.



7.1. RECONCILIATION OF ROUND 1 RECOMMENDATIONS

The sponsor has provided the following response.

Recommendation 1: The following safety concern should be added to the summary of concerns as an important potential risk: • *Use in pregnancy and lactation*.
Sponsor's response: The sponsor accepts the recommendation and "Pregnancy and lactation" has been added to the Australian-specific annex (ASA) as a potential risk.
RMP evaluator comment: **The summary of safety concerns in the ASA has been amended as requested. Pregnancy and lactation are adequately addressed in the PI. This is acceptable.**
Recommendation 2: The sponsor should amend the summary of safety concerns so that *misuse/abuse* and *overdose* are separate important identified risks.
Sponsor's response: The sponsor accepts the recommendation and the change has been implemented in the ASA.
RMP evaluator comment: The summary of safety concerns in the ASA has been amended as requested.
Recommendation 3: It is suggested that the sponsor remove the following words that appear in the summary of safety concerns, as they are superfluous to the name of the risks. • (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation) • (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION);
Sponsor's response: The sponsor accepts the recommendation and the wording has been removed from the ASA.
RMP evaluator comment: The summary of safety concerns in the ASA has been amended as requested.
Recommendation 4: The sponsor should amend the ASA to ensure consistency between section 3.1 of the ASA and Table 4 of the ASA (see section 1.4 for more detail).
Sponsor's response: Section 3.1 of the ASA has been modified to reflect the same information present in section 4 of the ASA. Additionally, the restriction on supply for the first 6 months only to prescribers familiar with Medication Assisted Treatment for Opioid Dependence (MATOD) (detailed in Recommendation 7) has been added to sections 3.1 and section 4 of the ASA to reflect the evaluator's comments.
RMP evaluator comment: The sponsor has amended the various sections of ASA to ensure consistency. This is acceptable.
Recommendation 5: It is recommended that the PI be amended to include a boxed warning pertaining to the risk of serious harm or death of intravenous administration in line with the foreign prescribing information (see section 4.1.2).
Sponsor's response: The sponsor accepts the recommendation with note about the slight change in wording to remove US specific information regarding the US REMS.
RMP evaluator comment: The sponsor has included the boxed warning in the PI as requested. This is acceptable.
Recommendation 6: The sponsor should align the CMI to the PI for the following risks: a) Include a boxed warning as per Recommendation 5 above; b) Extend the warning to include communication of the risk of death associated with intravenous administration;

c) Neonatal Abstinence Syndrome.

Sponsor's response: The CMI has been amended as recommended by the evaluator.

RMP evaluator comment: The sponsor has amended the CMI as requested to include the boxed warning and aligned the three points above. This is acceptable.

Recommendation 7: Additional risk minimisation is required for health professionals and patients for this new formulation of buprenorphine for all of the important identified risks. The sponsor should submit the proposed patient educational materials and should propose suitable materials for health professionals. The sponsor should also submit a plan for a restricted access scheme to limit supply in the first six months to prescribers in hospitals and specialist drug rehabilitation clinics who can demonstrate that they have reviewed the educational materials. The plan should include an estimate of the extent of use of Sublocade by specialist prescribers during the initial 6 months of supply, as a benchmark to determine whether actual specialist experience in the first 6 months is sufficient to inform advice to non-specialist prescribers, and a plan for evaluating the effectiveness of the scheme in restricting use of the product to the intended prescriber group and supporting safe use of the product. The proposed educational materials and distribution plan should be provided as part of a revised ASA and must be considered acceptable to the TGA before the supply of Sublocade begins.

Sponsor's response: The following is a summary of the full response (see Appendix 3).
Indivior agrees with the importance of educational materials addressing the important identified risks. Draft educational materials are attached to the ASA. These materials will undergo review and amendment as described in the response to Recommendation 10 below.

Indivior agrees with the proposal to restrict access to clinicians who have demonstrated an understanding of both opioid dependence treatment and requirement for health care professional only handling of SUBLOCADE. Access to buprenorphine and methadone is currently highly regulated by each state and in the submitted ASA Indivior committed to working with state regulators to facilitate the timely development of state specific policies and regulations controlling the prescription and distribution of SUBLOCADE.

Indivior has contacted state health departments (see attached letters) to inform the departments on the need to plan for the future availability of extended release buprenorphine injections. Meetings with state health departments were requested and to date have taken place in Victoria, South Australia, Queensland, New South Wales and Northern Territory. The meetings focused on the following issues:

- *Regulatory and policy options to ensure patients do not handle the product*
- *Which medical practitioners may be authorised to prescribe extended release buprenorphine injections and whether there would be a state-based training requirement to be fulfilled*
- *Direct supply of extended release buprenorphine injections to a medical practice (without a requirement for pharmacy dispensing) and associated security and drug accountability criteria a medical practice may have to observe*

Following on from the meetings, Indivior is aware that some states have now formed advisory groups to discuss the issues in more detail.

It is currently unclear when state/territory departments may formalise processes. To pro-actively ensure that the evaluator's concerns are adequately addressed, independently of any state/territory decisions, Indivior proposes to proactively initiate a program of restricted access to ensure appropriate systems are in place at the time of SUBLOCADE approval. This program will address the aspects of restricted access identified by the evaluator:

- *restricted access scheme to limit supply to prescribers in hospitals and specialist drug rehabilitation clinics, and*
- *restricted access scheme to limit supply to prescribers who can demonstrate that they have reviewed the educational materials.*

The risks identified for SUBLOCADE are largely similar to existing MATOD treatments with the important additional risk related to patient access and intravenous administration. Similar to current state regulations for oral MATOD, the restricted access scheme will address not just the prescriber experience and location but also the

process for distribution and administration, noting that commonly for existing oral products the prescriber of treatment is not involved in the distribution or administration of the treatment.

<u>Limiting supply to prescribers in hospitals and specialist drug rehabilitation clinics</u>
The wording used by the evaluator has a potential to lead to confusion as it does not fully reflect the current treatment models that exist in Australia.

To properly administer a restricted access scheme, a clear definition of approved prescribers is essential. The defined group of prescribers will have appropriate expertise in treatment of opioid dependence. It is also important that the defined group of prescribers allows for equitable access between states and for rural and remote patients. Within the current treatment framework, restricting supply to prescribers in hospitals and specialist drug rehabilitation clinics may not achieve the objectives of the restricted access scheme.

Clinicians in hospitals do not commonly perform the function of prescriber for maintenance therapy of opioid dependence. Government-run outpatient clinics are typically not necessarily located within a hospital. These clinics may have different names usually along the lines of "drug and alcohol service".

Private hospital involvement in treatment of opioid dependence is commonly associated with short term detoxification or withdrawal treatment rather than the provision of ongoing maintenance therapy.

<u>Current MATOD treatment models</u>

Treatment of patients with MATOD requires a prescriber who medically manages the patient, including writing prescriptions, and a dispensing point where the patient receives the medication. The available medications are methadone, buprenorphine (Subutex®) and buprenorphine plus naloxone (Suboxone Film®).

<u>Dispensing sites</u>

The distribution and administration scheme for SUBLOCADE will require modification from the current process and will need to facilitate subcutaneous administration without patients handling the product.
Within the current MATOD treatment framework, this may be achieved with delivery of SUBLOCADE directly from a warehouse to the medical practice where the product will be administered or to a pharmacy for distribution to an approved administration point.

<u>Proposed prescriber criteria for restricting supply in first 6 months to prescribers in hospitals and specialist drug rehabilitation clinics</u>

As noted above, MATOD is not usually provided in a service within a specialist drug rehabilitation clinic. Indeed, this terminology is not usually used within the sector. To identify settings with specialised experience in the treatment of opioid dependence, it is proposed to use criteria for both the prescriber and the administration setting.

It is proposed that prescribing is restricted in the first 6 months to prescribers who meet at least one of the following criteria:
• A member of The Chapter of Addiction Medicine (AChAM) - a Chapter of the Royal Australasian College of Physicians (RACP); or
• A member of The Faculty of Addiction Psychiatry (FAP) – a RANZCP group; or
• Prescribers who have completed an accreditation course administered by State/Territory governments and prescribe MATOD to 50 or more patients

Note prescribers are required to register patients treated with MATOD therefore the number of patients they treat is defined and recorded.

This restriction will ensure that all prescribers are suitably experienced and specialised in the treatment of opioid dependence. Given logistic challenges and state requirements on security and drug accountability, the actual number of administration sites in the first 6 months is likely to be low within the private sector. It is anticipated that government clinics, a proportion of private clinics and 20-40 private medical practices will offer administration services.

It is noted that in the long term, due to security and drug accountability requirements for holding drugs at a medical office, there is a high probability that prescribers with low patient numbers may opt to refer to other services that are willing to meet these requirements.

Administration location

To ensure that the product is managed within a setting where awareness of appropriate patient and product management can be reasonably assured, it is further proposed that the administration location be restricted to sites with a substantial focus on the treatment of opioid dependence. These sites will be defined as:
- *Sites associated with public or private hospitals; or*
- *Sites with sole or dual private prescriber practices where at least one prescriber meets eligibility criteria; or multiple prescriber practices with 2 or more prescribers operating from the prescribing location meet the eligibility criteria.*

Prescribers who can demonstrate that they have reviewed the educational materials

Educational materials will be available in hardcopy and on an Indivior managed website for health care professional education; further details are provided in the ASA. Indivior field medical and sales staff will facilitate access to the relevant educational materials. Following review of educational materials, health care professionals will be invited to complete a form acknowledging review of these materials. The record of completion will be maintained in a database.

Restricted access distribution scheme

Prescribers who have met eligibility criteria and completed the record of educational material review will be approved to order stock of SUBLOCADE for delivery to sites meeting the location eligibility criteria.

Community pharmacies who are accredited with state health departments to dispense MATOD and have completed the record of educational material review will also be eligible to order stock of SUBLOCADE for distribution to approved prescriber's sites meeting the location eligibility criteria. Pharmacies will be provided with access to approved prescriber lists to enable the screening of orders and restriction of delivery to approved sites.

Wholesalers (or pre-wholesalers) will be provided with access to approved pharmacy and prescriber lists to enable the screening of orders and restriction of delivery to approved sites. This is subject to legal review for privacy and liability concerns.

Assessment of specialist experience during initial restricted access scheme

A number of approaches to benchmarking of specialist experience during the initial restricted access scheme have been considered, including
- *Target number of units distributed developed based on target number of patients*
- *Target number of units distributed developed based on target number of clinicians*
- *Target number of prescribers with experience*
- *Target number of prescribers "approved"*
- *Target number of prescribers "approved" and survey of approved prescribers to assess knowledge of product*

The number of units distributed is a simple but blunt instrument to assess prescriber experience. Target number of prescribers with experience may be challenging to assess if a substantial proportion of experience occurs in public clinics in NSW and Qld where limited visibility of individual prescriber experience will be available.

It is therefore proposed that a target number of approved prescribers (those completing review of educational material) be determined, and a sample of these prescribers be surveyed to assess sufficiency of specialist experience during initial restricted access scheme to inform advice to nonspecialist prescribers. This would provide an assessment of both quantity and the quality of experience. A more detailed description of this assessment will be developed with input from specialist prescribers and with reference to the final agreed specialist prescriber definition.

Evaluating the effectiveness of the scheme to limit supply

Routine pharmacovigilance activities will contribute to the assessment of the scheme to limit supply.

A plan for evaluating the effectiveness of the scheme in restricting use of the product to the intended prescriber group will be developed and submitted once confirmation that the proposed restricted access scheme is considered acceptable to TGA.

RMP evaluator comment:
The sponsor has provided mock ups of the educational material for HCPs and patients that address the majority of the safety concerns and are generally acceptable. The important identified risk of 'Overdose' is adequately addressed in the PI and CMI however has not been addressed in the educational materials (as per the additional risk minimisation plan of the ASA) and should be included. s22 [redacted]

The sponsor proposes to make educational materials available in hard copy and electronically via their website which is acceptable.

The sponsor has proposed that prescribing is restricted in the first 6 months to prescribers who have reviewed the educational materials (and have a record of completion) and meet at least one of the following criteria which is acceptable:

- **a member of The Chapter of Addiction Medicine (AChAM) - a Chapter of the Royal Australasian College of Physicians (RACP); or**
- **a member of The Faculty of Addiction Psychiatry (FAP) – a RANZCP group; or**
- **have completed an accreditation course administered by State/Territory governments and prescribe MATOD to 50 or more patients.**

The sponsor has proposed that the administration location be restricted to sites defined as follows which is acceptable:

- **sites associated with public or private hospitals; or**
- **sites with sole or dual private prescriber practices where at least one prescriber meets eligibility criteria; or multiple prescriber practices with 2 or more prescribers operating from the prescribing location meet the eligibility criteria.**

The sponsor proposes that access to Sublocade be restricted to the following which is acceptable:

- **approved prescribers**
- **accredited community pharmacies who have reviewed the education materials and obtained a record of completion (pharmacies will have access to approved prescriber lists to enable screening and restriction of delivery to approved sites)**
- **wholesalers (or pre-wholesalers) will be provided with access to approved pharmacy and prescriber lists to enable screening of orders and restriction of delivery to approved sites.**

The above initial restricted access plan may require adjustments after the sponsor meets and negotiates with state/territory health departments. The sponsor is requested to provide the related access plans to the TGA for evaluation prior to supply.

In order to estimate the extent of use by specialist prescribers in the first 6 months of supply the sponsor has proposed that a target number of approved prescribers be determined. A sample of these will be surveyed to assess sufficiency of specialist experience during the restricted access scheme to inform advice to non-specialist prescribers. This is acceptable. The sponsor also commits to develop a more detailed description of this assessment and this should be provided to the TGA once developed.

The sponsor has committed to developing a plan for evaluating the effectiveness of the restricted access scheme. This can only occur once the proposed restricted access scheme is considered acceptable. This evaluation plan is to be submitted to the TGA for evaluation.

Recommendation 8: The sponsor should provide a plan for reviewing, implementing and evaluating additional risk minimisation for supply of Sublocade beyond the restricted access program. This plan must be considered acceptable to the TGA before the restricted access scheme concludes and broader supply of Sublocade commences.

Sponsor's response: As outlined above, the supply of MATOD is highly regulated at a state level and Indivior has proactively engaged with State governments to develop policy/regulations to manage the supply of SUBLOCADE. The development of State specific policy/regulations will be highly influential on the longer term model for restricted access to SUBLOCADE. Notwithstanding this regulatory influence, the proposed initial restricted supply scheme is scalable with revision of the approved prescriber criteria which may include the option to include all prescribers completing state accreditation programs or all prescribers completing review of educational materials. It is important that the restricted access scheme achieve the dual objectives of management of risks and facilitating access to treatment. Current restricted supply schemes for MATOD are a barrier to treatment for many patients.

Specific strategies for risk minimisation of supply of SUBLOCADE beyond the restricted access scheme will be developed and submitted in the future.

RMP evaluator comment: The sponsor has stated that the initial restricted supply scheme is scalable and plans to develop and provide specific strategies for risk minimisation of supply of Sublocade in the future. This plan must be submitted to the TGA and considered acceptable before the restricted access scheme concludes and broader supply of Sublocade commences.

Recommendation 9: The sponsor should clarify whether or not additional risk minimisation materials implemented for the sponsor's other buprenorphine-containing products will be updated with information about SUBLOCADE (see sections 1.4 and 4.1.3).

Sponsor's response: Risk minimisation materials implemented for Indivior's other buprenorphine-containing products will not be updated with information about SUBLOCADE as they relate specifically to sublingual buprenorphine. SUBLOCADE materials will include brief information related to the use of Indivior's other buprenorphine-containing products.

RMP evaluator comment: The sponsor's response is noted.

Recommendation 10: Prior to registration, the sponsor should provide details of how its proposed readability testing of consumer educational materials and its survey for HCPs, will be conducted. The plan for evaluating the HCP materials should be revised in light of recommendation 7, in particular to allow the educational materials to be reviewed and amended, if necessary, on the basis of experience during the first 6 months of supply and prior to broader supply.

Sponsor's response: Educational materials will be tested for the effectiveness of their risk minimisation activities. This evaluation will be subject to a protocol which will assess the process used for the risk minimisation activity and the overall outcome. The tested populations will include s47 [redacted] *that assesses the effectiveness of the applicable materials.*

Such effectiveness would be assessed using the following:

s47 [redacted]

During the restricted supply period, Indivior will undertake a s47 [redacted].
RMP evaluator comment: The sponsor's response is noted and acceptable. The sponsor is requested to send any updated materials, if applicable, to the TGA for review before supply is extended beyond the initial restricted supply period.

8. POST-ROUND 2 EVALUATION

The sponsor has amended the CMI as requested below, however not provided any further information regarding the distribution and restricted access plan.

Recommendation 7 and Recommendation 8: (See section 5.2 for full details). The distribution and restricted access plans proposed by the sponsor are acceptable in theory however discussions and negotiations will need to be made between the sponsor and state/territory health departments. The outcomes of these discussions and negotiations will further define the restricted access plan(s). The proposed restricted access plan(s) and related evaluation plans must be submitted to the TGA for evaluation before implementation.
Sponsor's response: no formal response from the sponsor.
RMP evaluator comment: **This recommendation is considered to be outstanding as no formal response with further information has been received by the sponsor and is referred to the delegate.**
Recommendation 11: The CMI requires amending, specifically: • the tradename in the header of the document needs to be changed from 'Subutex' to 'Sublocade' • the position of the information proposed in the clean Sublocade CMI 'After using Sublocade' section does not seem appropriate. Consideration should be given to the relevance of this information and relocating the information to the 'How to use' section of the CMI. Further, the wording in the approved Subutex CMI 'After using Subutex' seems applicable and consideration should be given to including similar wording in the Sublocade CMI 'After using Sublocade' section. • the information relating to the storage of Sublocade should be included under a specific heading in the CMI (e.g. Presentation and Storage or similar). The sponsor is required to amend the draft CMI and submit it to the TGA for evaluation.
Sponsor's response: No formal response from the sponsor.
RMP evaluator comment: The sponsor has submitted an amended CMI as requested with the updated ASA version 2.1 which is acceptable.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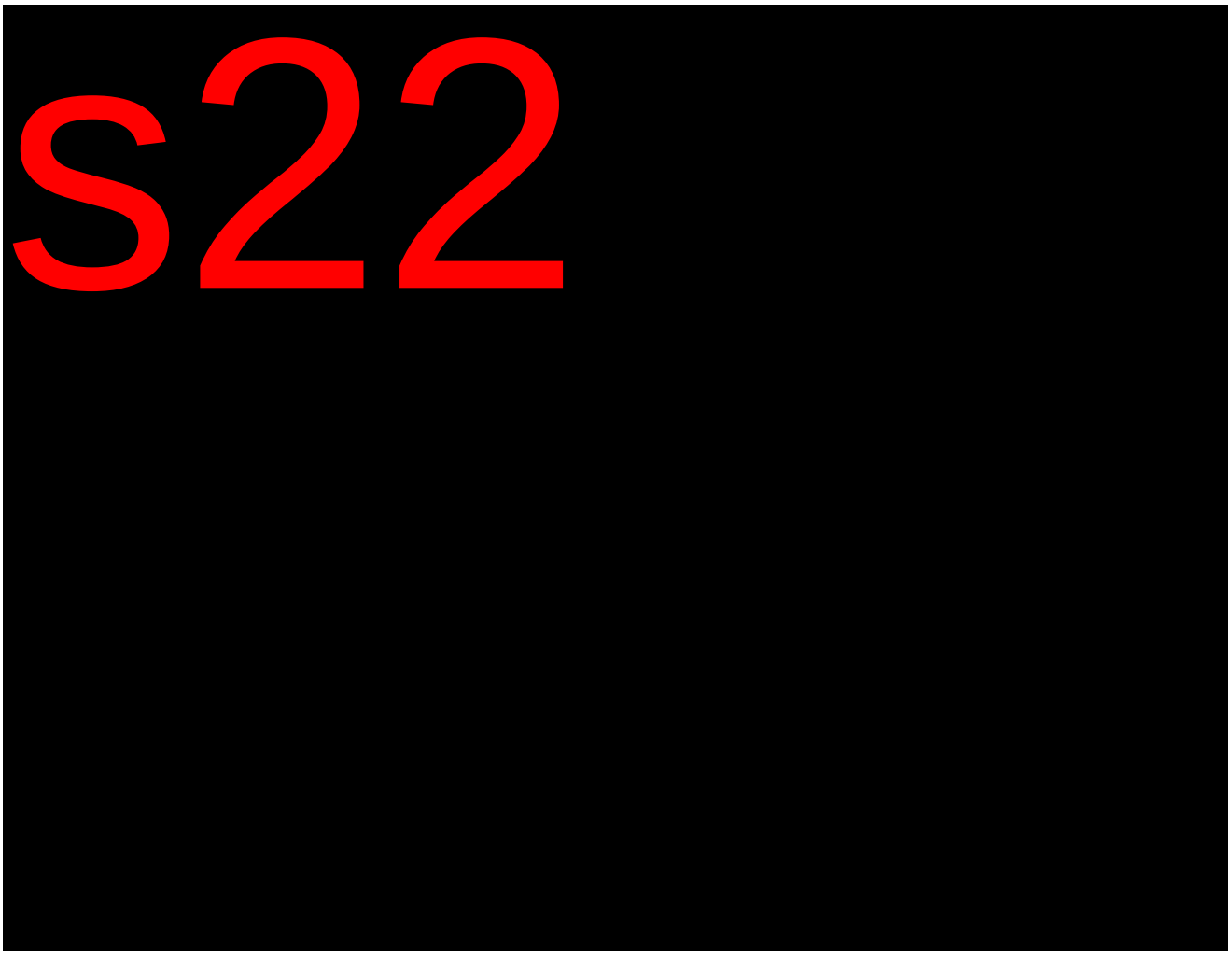
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APPENDIX 1 – GLOSSARY

ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-Specific Annex
CMI	Consumer Medicine Information
DLP	Data Lock Point
FDA	Food and Drug Authority (USA)
HCP	Health Care Professional
MATOD	Medication assisted treatment of opioid dependence
PI	Product Information
PIP	Paediatric Investigation Plans
PSUR	Periodic Safety Update Report
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration

APPENDIX 2 – DOSAGE AND ADMINISTRATION INFORMATION

Patients appropriate for SUBLOCADE are adults who have undergone induction on a buprenorphine- containing product. Withdrawal signs and symptoms should be suppressed (COWS ≤12) before transitioning to SUBLOCADE. Dosing and induction of buprenorphine-containing products should be based on instructions in their Product Information.

FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. DO NOT ADMINISTER SUBLOCADE INTRAVENOUSLY OR INTRAMUSCULARLY (see section 4.4 Special Warnings and Precautions for use).

- Only healthcare providers should prepare and administer SUBLOCADE.
- Administer SUBLOCADE monthly with a minimum of 26 days between doses.

- Initiating treatment with SUBLOCADE as the first buprenorphine product has not been studied. Initiate SUBLOCADE treatment only following induction and dose adjustment with a transmucosal buprenorphine containing product.
- Administer each injection only using the syringe and safety needle included with the product.
- Do not administer part of a dose

Recommended dosing

Patients appropriate for SUBLOCADE are adults who have initiated treatment on a transmucosal buprenorphine-containing product. The patient may only be transitioned to SUBLOCADE after stabilisation on transmucosal buprenorphine (see Section 5.1 Pharmacodynamic Properties – Clinical trials).
The recommended dose of SUBLOCADE is 300 mg monthly for the first two months. The recommended maintenance dose is 100 mg monthly. However patients who do not show a satisfactory clinical response following the second dose can receive a maintenance dose of 300 mg monthly.
Buprenorphine plasma levels in the month following the second 300 mg dose are maintained with 100 mg maintenance dosing. The 300 mg maintenance dose achieves higher levels and reaches steady state after the fourth monthly injection (see section 5.2 pharmacokinetic properties).
A patient who misses a dose should receive the next dose as soon as possible, with the following dose given no less than 26 days later. Occasional delays in dosing up to 2 weeks are not expected to have a clinically significant impact on treatment effect.

Clinical supervision

Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot.
Due to the chronic nature of opioid use disorder, the need for continuing medication-assisted treatment should be re-evaluated periodically. There is no maximum recommended duration of maintenance treatment. For some patients, treatment may continue indefinitely. If considering stopping treatment, the clinical status of the patient should be considered.

If SUBLOCADE is discontinued, its extended-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal or buprenorphine effects and treated appropriately. After steady-state has been achieved (4-6 months), patients discontinuing SUBLOCADE may have detectable plasma levels of buprenorphine for twelve months or longer. The correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

INSTRUCTIONS FOR USE

IMPORTANT INFORMATION:

- For abdominal subcutaneous injection only.
- To be administered by a healthcare professional only.
- Please read the instructions carefully before handling the product.

- Remove SUBLOCADE from the refrigerator prior to administration. The product requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for his or her injection.
- Discard SUBLOCADE if left at room temperature (below 30°C) for longer than 7 days.
- Do not attach the needle until time of administration.

STEP 1: GETTING READY

Remove the foil pouch and safety needle from the carton. Open the pouch and remove the syringe.
Discard the oxygen absorber pack. It is not needed.

Figure 1

STEP 2: CHECK THE LIQUID CLARITY

Check that the medication for particulate matter and discolouration. SUBLOCADE can range from clear colourless to yellow to amber. **Variations of colour within this range do not affect the potency of the product.**
If the medication is discoloured or contains particulate matter it should not be used.

Figure 2

STEP 3: ATTACH THE SAFETY NEEDLE

Remove the cap from the syringe and the safety needle supplied in the carton from its sterile package.
Gently twist the needle clockwise until it is tight and firmly attached.
Do not remove the plastic cover from the needle.

Figure 3

STEP 4: PREPARE THE ABDOMINAL INJECTION SITE

Choose an injection site on the abdomen between the transpyloric and transtubercular planes with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment). It is recommended that the patient is in the supine position.
Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.
Clean the injection site well with an alcohol swab.
To avoid irritation, rotate injection sites following a pattern similar to the illustration in Figure 4. Record the location of the injection to ensure that a different site is used at the time of the next injection.

Figure 4

STEP 5: REMOVE EXCESS AIR FROM SYRINGE

Hold the syringe upright for several seconds to allow air bubbles to rise. Due to the viscous nature of the medication, bubbles will not rise as quickly as those in an aqueous solution.
Remove needle cover and slowly depress the plunger to push out the excess air from the syringe.

- Small bubbles may remain in the medication. Large air gaps, however, can be minimised by pulling back on the plunger rod to pop air bubbles prior to expelling the air very slowly. Air should be expelled very carefully to avoid loss of medication.

If medication is seen at the needle tip, pull back slightly on the plunger to prevent medication spillage.

Figure 5

STEP 6: PINCH THE INJECTION SITE

Pinch the skin around the injection area. Be sure to pinch enough skin to accommodate the size of the needle. Lift the adipose tissue from the underlying muscle to prevent accidental intramuscular injection.

Figure 6

STEP 7: INJECT THE MEDICATION

SUBLOCADE is for subcutaneous injection only. Do not inject intravenously or intramuscularly (see Section 4.4 Special Warnings and Precautions for Use).
Insert needle fully into the abdominal subcutaneous tissue. The actual angle of injection will depend on the amount of subcutaneous tissue.
Use a slow, steady push to inject the medication. Continue pushing until all of the medication is given.

Figure 7

STEP 8: WITHDRAW THE NEEDLE

Withdraw the needle at the same angle used for insertion and release the pinched skin.
Do not rub the injection area after the injection. If there is bleeding, apply a gauze pad or bandage but use minimal pressure.
Figure 8

STEP 9: LOCK THE NEEDLE GUARD AND DISCARD THE SYRINGE

Lock the needle guard into place by pushing it against a hard surface such as a table (**Figure 9**).
Dispose of all syringe components in a secure sharps disposal container.
Figure 9

STEP 10: INSTRUCT THE PATIENT

Advise the patient that they may have a lump for several weeks that will decrease in size over time. Instruct the patient not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.

Removal of the Depot

In the event the depot must be removed, it can be surgically excised by a healthcare professional under local anaesthesia within 14 days of injection. The removed depot should be disposed of carefully.

APPENDIX 3 – SPONSOR'S FULL RESPONSE TO RECOMMENDATION 7

Indivior agrees with the importance of educational materials addressing the important identified risks. Draft educational materials are attached to the ASA. These materials will undergo review and amendment as described in the response to Recommendation 10 below.

Indivior agrees with the proposal to restrict access to clinicians who have demonstrated an understanding of both opioid dependence treatment and requirement for health care professional only handling of SUBLOCADE. Access to buprenorphine and methadone is currently highly regulated by each state and in the submitted ASA Indivior committed to working with state regulators to facilitate the timely development of state specific policies and regulations controlling the prescription and distribution of SUBLOCADE. Indivior has contacted state health departments (see attached letters) to inform the departments on the need to plan for the future availability of extended release buprenorphine injections. Meetings with state health departments were requested and to date have taken place in Victoria, South Australia, Queensland, New South Wales and Northern Territory. The meetings focused on the following issues:

- Regulatory and policy options to ensure patients do not handle the product
- Which medical practitioners may be authorised to prescribe extended release buprenorphine injections and whether there would be a state-based training requirement to be fulfilled
- Direct supply of extended release buprenorphine injections to a medical practice (without a requirement for pharmacy dispensing) and associated security and drug accountability criteria a medical practice may have to observe

Following on from the meetings, Indivior is aware that some states have now formed advisory groups to discuss the issues in more detail.

It is noted that extended release buprenorphine injections do not easily fit into existing state regulator models and require the development of new policies that focus upon the development of services that will provide the "administration" of extended release buprenorphine injections. To be able to administer, this will involve a prescriber who is authorised by a state/territory department AND a physical location that can meet the security and drug accountability requirements for a schedule 8 medication. At present, with the exception of NSW, government drug and alcohol MATOD services provide very limited dispensing services and may require suitable time to plan and make modifications for the appropriate storage of a schedule 8 medication. Private medical services will require time and support to be able to meet the requirements to be able to administer extended release buprenorphine injections at their premises.

It is currently unclear when state/territory departments may formalise processes. To pro-actively ensure that the evaluator's concerns are adequately addressed, independently of any state/territory decisions, Indivior proposes to proactively initiate a program of restricted access to ensure appropriate systems are in place at the time of SUBLOCADE approval. This program will address the aspects of restricted access identified by the evaluator:

- restricted access scheme to limit supply to prescribers in hospitals and specialist drug rehabilitation clinics, and
- restricted access scheme to limit supply to prescribers who can demonstrate that they have reviewed the educational materials.

The risks identified for SUBLOCADE are largely similar to existing MATOD treatments with the important additional risk related to patient access and intravenous administration. Similar to current state regulations for oral MATOD, the restricted access scheme will address not just the prescriber experience and location but also the process for distribution and administration, noting that commonly for existing oral products the prescriber of treatment is not involved in the distribution or administration of the treatment.

<u>Limiting supply to prescribers in hospitals and specialist drug rehabilitation clinics</u>

The wording used by the evaluator has a potential to lead to confusion as it does not fully reflect the current treatment models that exist in Australia.

To properly administer a restricted access scheme, a clear definition of approved prescribers is essential. The defined group of prescribers will have appropriate expertise in treatment of opioid dependence. It is also important that the defined group of prescribers allows for equitable access between states and for rural and

remote patients. Within the current treatment framework, restricting supply to prescribers in hospitals and specialist drug rehabilitation clinics may not achieve the objectives of the restricted access scheme.

Clinicians in hospitals do not commonly perform the function of prescriber for maintenance therapy of opioid dependence. Government-run outpatient clinics are typically not necessarily located within a hospital. These clinics may have different names usually along the lines of "drug and alcohol service".
Private hospital involvement in treatment of opioid dependence is commonly associated with short term detoxification or withdrawal treatment rather than the provision of ongoing maintenance therapy.

The term drug rehabilitation clinic can reflect a number of different treatment settings and frameworks. Healthdirect, a national, government-owned, not-for-profit organisation supporting access to health information describe that

> *"rehabilitation programs usually take place in community-based treatment centres or residential rehabilitation services. Residential rehabilitation services allow you to stay in a special clinic for a number of days or weeks."*

Healthdirect refer users to the ADIN network to identify Drug and alcohol rehabilitation services. A search of this directory for opioid rehabilitation identifies 57 services. Only a small minority of these services provide access to MATOD.

Current MATOD treatment models

Treatment of patients with MATOD requires a prescriber who medically manages the patient, including writing prescriptions, and a dispensing point where the patient receives the medication. The available medications are methadone, buprenorphine (Subutex®) and buprenorphine plus naloxone (Suboxone Film®).

A prescriber is

a) a medical practitioner or Nurse Practitioner who has undertaken an accreditation course and is able to prescribe methadone or buprenorphine products, or
b) a medical practitioner who has not undergone formal training however under state policy is able to prescribe Suboxone® for up to 5 patients (SA and Victoria), 20 patients (NSW) (Subutex® or Suboxone®), or
c) a medical practitioner who has undertaken a Suboxone only training course (WA) and can prescribe for up to 5 patients.

A dispensing point is

a) Community pharmacy accredited to dispense MATOD
b) Government drug and alcohol service
c) Private licensed dispensing clinic (only exist in NSW and Queensland)
d) Correctional institution
e) Private or public hospital-based service

The National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD) collection is a set of jurisdictional data that includes information about:

- clients accessing pharmacotherapy for the treatment of opioid dependence
- prescribers participating in the delivery of pharmacotherapy treatment
- dosing sites providing pharmacotherapy drugs to clients

The data from the 2017 NOPSAD survey represent the most recent available data. On the survey day in 2017, almost 50,000 patients received pharmacotherapy treatment for their opioid dependence at 2,732 dosing points around Australia. Of these patients, 17,986 (40.21%) were on buprenorphine products – Subutex and Suboxone. There were 3,074 prescribers of opioid pharmacotherapy drugs. It is noted that the majority of patients receiving treatment are in the private sector and in one state (Victoria) there is no formal public sector drug and alcohol services.

Medical Management and Prescribing

Medical management and prescribing for patients with opioid dependence occurs in various settings including public and private clinics and medical practices.

Table 1 provides information on the number of public clinics in each state/territory and the proportion of the overall MATOD patients. This table shows that the majority of patients are in NSW, Queensland and Victoria and highlights the differences in system structures with Victoria having no or limited public facilities due to a historic decision by the Victorian government to close all government drug and alcohol services.

Table 2 describes the number of patients managed by prescribers in different settings. Of those treated with buprenorphine products, 67% were being treated by a private prescriber usually within a private medical practice or at a few sites within a private psychiatric service (hospital or outpatient clinic). Public prescribers work within the public health system or within corrective services and include medical practitioners and Nurse Practitioners. The distribution of prescribers varies by State and Territory (Table 3). Of the 3,074 prescribers in Australia, almost half (1,474) are in Victoria where there are no formal public prescribers or government clinics.

Table 1. State/territory summary NOPSAD Data 2017

State	NSW	VIC	QLD	WA	SA	TAS	ACT	NT	TOTAL
Total MATOD Patients	41.5%	28.6%	13.3%	7.0%	5.8%	1.5%	2.0%	0.3%	100.0%
Total BUP Patients	30.3%	35.8%	18.1%	6.6%	5.4%	2.0%	1.2%	0.6%	100.0%
Public Clinics	35	6	12	1	3	2	1	2	56
Private Clinics	12	0	8	0	0	0	0	0	20

Table 2: 2017 NOPSAD data - Prescriber setting x patient x treatment type

	Methadone	Buprenorphine (all types)	Total
Number			
Public Prescriber	7663	5498	13161
Private Prescriber	21231	12047	33278
Public/Private Prescriber	22	83	105
Correctional Facility	2890	358	3248
Total	**31806**	**17986**	**49792**
Percentage			
Public Prescriber	24.1	30.6	26.4
Private Prescriber	66.8	67	66.8
Public/Private Prescriber	0.1	0.5	0.2
Correctional Facility	9.1	2	6.5
Total	**100**	**100**	**100**

Table 3: Prescribers, by prescriber type, states and territories, NOPSAD 2017

Prescriber type 2017	NSW	Vic	Qld	WA	SA	Tas	ACT	NT	Total
Number									
Public prescriber	212	—	91	24	29	13	6	14	389
Private prescriber	608	1,454	124	83	203	22	66	—	2,560
Public/private prescriber	—	—	—	—	—	2	1	—	3
Correctional facility	38	20	7	18	6	1	1	—	91
Not stated	—	—	31	—	—	—	—	—	31
Total	**858**	**1,474**	**253**	**125**	**238**	**38**	**74**	**14**	**3,074**
Percent									
Public prescriber	24.7	—	36.0	19.2	12.2	34.2	8.1	100.0	12.7
Private prescriber	70.9	98.6	49.0	66.4	85.3	57.9	89.2	—	83.3
Public/private prescriber	—	—		—	—	5.3	1.4	—	0.1
Correctional facility	4.4	1.4	2.8	14.4	2.5	2.6	1.4	—	3.0
Not stated	—	—	12.3	—	—	—	—	—	1.0
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

A further analysis of prescribers indicates that on the "snapshot" day in 2017

- 808 prescribers were not treating any patients
- 1,310 prescribers were treating between 1-5 patients
- 10.24% (315) of prescribers were treating at least 50 patients; together these prescribers manage 48.72% of all methadone and buprenorphine patients in Australia

This information is summarised in Figure 1 and Table 4 where the data highlights that there is a large number of prescribers managing few patients, this likely represents prescribers with a broad general practice or who have specialised in different areas of practice such as pain physicians.

There is a smaller cohort of prescribers who have specialised their practice in management of opioid dependence and gained substantial experience in this area with a larger number of patients. The distribution of prescriber loads varies across states and territories (Table 5), however in general the three cohorts described above exist in all areas.

It is noted that the most experienced prescribers with the highest case-loads are often in the private sector and almost exclusively this is the case in Victoria.

Figure 1. Clients receiving pharmacotherapy treatment on a snapshot day per prescriber, states and territories 2017

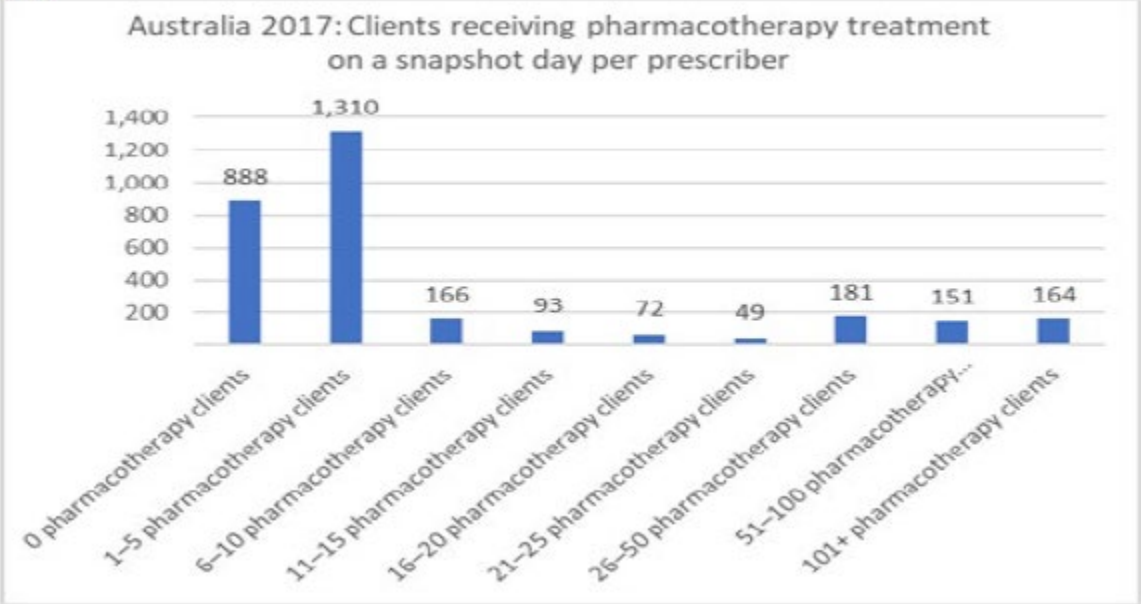


Table 4: Clients receiving pharmacotherapy treatment on a snapshot day per prescriber, states and territories, 2017

Clients per prescriber 2017	NSW	Vic	Qld	WA	SA	Tas	ACT	NT	Total	Total (%)
0 pharmacotherapy clients	—	728	143	—	—	—	17	—	888	28.9
1–5 pharmacotherapy clients	522	465	38	56	174	16	32	7	1,310	42.6
6–10 pharmacotherapy clients	56	60	14	15	12	5	4	—	166	5.4
11–15 pharmacotherapy clients	32	27	6	8	7	1	8	4	93	3.0
16–20 pharmacotherapy clients	21	27	7	7	5	2	2	1	72	2.3
21–25 pharmacotherapy clients	15	15	4	3	7	1	2	2	49	1.6
26–50 pharmacotherapy clients	78	51	10	13	17	8	4	—	181	5.9
51–100 pharmacotherapy clients	71	43	7	14	9	5	2	—	151	4.9
101+ pharmacotherapy clients	63	58	24	9	7	—	3	—	164	5.3
Total	**858**	**1,474**	**253**	**125**	**238**	**38**	**74**	**14**	**3,074**	**100.0**

Specialist Setting

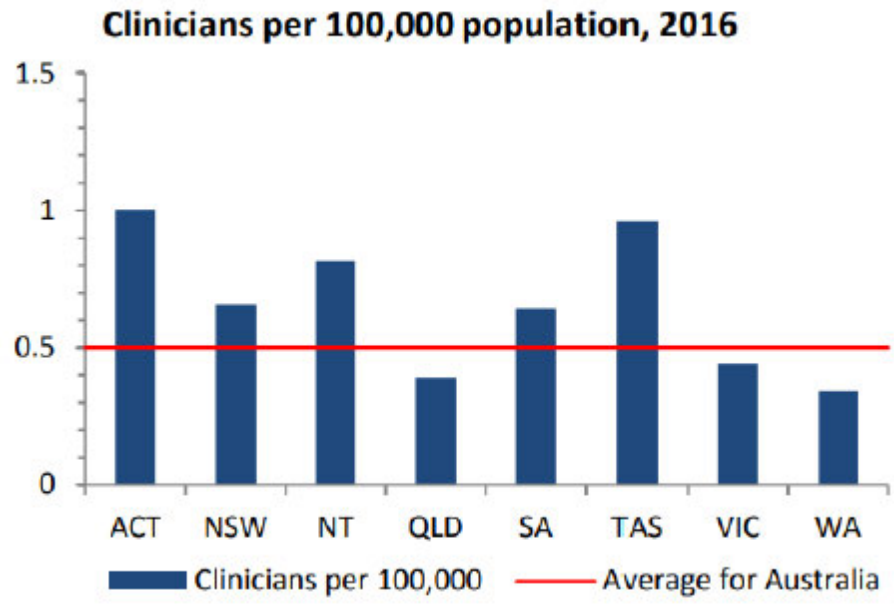
There are a limited number of specialists in the area of addiction medicine. In the clear majority of cases they will be either

- A member of The Chapter of Addiction Medicine (AChAM) - a Chapter of the Royal Australasian College of Physicians (RACP), or
- A member of The Faculty of Addiction Psychiatry (FAP) – a RANZCP group

Although all of the above specialists may have some experience with opioid dependence, this may be limited (especially in the case of psychiatrists) as they may specialise in other addictive behaviours (e.g. alcohol, gambling, cannabis).

The distribution of specialists is not representative of the Australian population. Victoria and Western Australia have less than 0.5 specialists per 100,000 population (Figure 2). Specialist availability in rural, regional remote areas of Australia is very limited or non-existent (Table 5).

Figure 2. Addiction medicine 2016 Factsheet – Clinicians per 100,000 population, 2016



Source: Addiction medicine 2016 Factsheet Australian Government

Table 5. Addiction medicine 2016 Factsheet

Location of clinicians by remoteness, Modified Monash Model (MMM*)							
MMM category	1	2	3	4	5	6	7
%	86.7	6.2	4.7	0.8	-	1.6	-

* Further information on the Modified Monash Model is available at doctorconnect.gov.au

Source: Addiction medicine 2016 Factsheet Australian Government (to be reconfigured for copyright)

There are in addition physicians who have specialised in the area of addiction who have come from other backgrounds e.g. Neurology and General Practice. These clinicians have completed state accreditation requirements to prescribe MATOD and have specialised experience working in practices with a substantial focus on the treatment of opioid dependence.

Dispensing Sites

The main model utilised in Australia for distribution and administration of MATOD involves the dispensing of medication for daily supervised medication, with a risk assessment to determine whether "takeaway" doses for self-administration are permissible. Table 6 summarises the settings of dispensing sites. In general, public (8.3% of patients) and private clinic (7.8%) dispensing account for a relatively small part of the overall delivery of medications to patients. Community pharmacies dose 72.7% of patients. NSW is an outlier in this regard with a comparatively higher proportion of public clinic dispensing sites. Private dispensing clinics ONLY exist in NSW and Queensland. There is minimal dispensing of buprenorphine in correctional facilities.

Table 6. Clients receiving pharmacotherapy treatment on a snapshot day, by dosing point site and pharmacotherapy type 2017

Dosing site	Methadone N (%)	Buprenorphine N (%)	Total N (%)
Public clinic	2,647 (8.4)	1,464 (8.1)	4,111 (8.3)
Private clinic	2,609 (8.2)	1,252 (6.9)	3,861 (7.8)
Pharmacy	22,164 (70.0)	14,017 (77.7)	36,181 (72.7)
Correctional facility	2,964 (9.4)	347 (1.9)	3,311 (6.6)
Hospital	366 (1.2)	228 (1.3)	594 (1.2)
Other	39 (0.1)	177 (1.0)	216 (0.4)
Not stated	895 (2.8)	559 (3.1)	1,454 (3.0)
Total	**31,684**	**18,044**	**49,728**

Source: AIHW NOPSAD 2017 Table S13: Clients receiving pharmacotherapy treatment on a snapshot day, by dosing point site and pharmacotherapy type, 2006 to 2017

Only one residential treatment service in Australia has a license to dispense MATOD within its premises. As noted above, rehabilitation services are generally aimed at assisting clients to achieve and maintain abstinence and usually exclude those on MATOD or require them to undertake a withdrawal management program as part of the admittance process. In a very limited number of services, clients may be able to continue MATOD treatment although still receiving doses from community settings – this is usually logistically challenging.

The distribution and administration scheme for SUBLOCADE will require modification from the current process and will need to facilitate subcutaneous administration without patients handling the product. Within the current MATOD treatment framework, this may be achieved with delivery of SUBLOCADE directly from a warehouse to the medical practice where the product will be administered or to a pharmacy for distribution to an approved administration point.

<u>Proposed prescriber criteria for restricting supply in first 6 months to prescribers in hospitals and specialist drug rehabilitation clinics</u>

As noted above, MATOD is not usually provided in a service within a specialist drug rehabilitation clinic. Indeed, this terminology is not usually used within the sector. To identify settings with specialised experience in the treatment of opioid dependence, it is proposed to use criteria for both the prescriber and the administration setting.

It is proposed that prescribing is restricted in the first 6 months to prescribers who meet at least one of the following criteria:

- A member of The Chapter of Addiction Medicine (AChAM) - a Chapter of the Royal Australasian College of Physicians (RACP); or
- A member of The Faculty of Addiction Psychiatry (FAP) – a RANZCP group; or
- Prescribers who have completed an accreditation course administered by State/Territory governments and prescribe MATOD to 50 or more patients

Note prescribers are required to register patients treated with MATOD therefore the number of patients they treat is defined and recorded.

This restriction will ensure that all prescribers are suitably experienced and specialised in the treatment of opioid dependence. Given logistic challenges and state requirements on security and drug accountability, the

actual number of administration sites in the first 6 months is likely to be low within the private sector. It is anticipated that government clinics, a proportion of private clinics and 20-40 private medical practices will offer administration services.

It is noted that in the long term, due to security and drug accountability requirements for holding drugs at a medical office, there is a high probability that prescribers with low patient numbers may opt to refer to other services that are willing to meet these requirements.

Administration location

To ensure that the product is managed within a setting where awareness of appropriate patient and product management can be reasonably assured, it is further proposed that the administration location be restricted to sites with a substantial focus on the treatment of opioid dependence. These sites will be defined as

- Sites associated with public or private hospitals; or
- Sites with sole or dual private prescriber practices where at least one prescriber meets eligibility criteria; or multiple prescriber practices with 2 or more prescribers operating from the prescribing location meet the eligibility criteria.

Prescribers who can demonstrate that they have reviewed the educational materials

Educational materials will be available in hardcopy and on an Indivior managed website for health care professional education; further details are provided in the ASA. Indivior field medical and sales staff will facilitate access to the relevant educational materials. Following review of educational materials, health care professionals will be invited to complete a form acknowledging review of these materials. The record of completion will be maintained in a database.

Restricted access distribution scheme

Prescribers who have met eligibility criteria and completed the record of educational material review will be approved to order stock of SUBLOCADE for delivery to sites meeting the location eligibility criteria.
Community pharmacies who are accredited with state health departments to dispense MATOD and have completed the record of educational material review will also be eligible to order stock of SUBLOCADE for distribution to approved prescriber's sites meeting the location eligibility criteria.
Pharmacies will be provided with access to approved prescriber lists to enable the screening of orders and restriction of delivery to approved sites.

Wholesalers (or pre-wholesalers) will be provided with access to approved pharmacy and prescriber lists to enable the screening of orders and restriction of delivery to approved sites. This is subject to legal review for privacy and liability concerns.

Assessment of specialist experience during initial restricted access scheme

A number of approaches to benchmarking of specialist experience during the initial restricted access scheme have been considered, including

- Target number of units distributed developed based on target number of patients
- Target number of units distributed developed based on target number of clinicians
- Target number of prescribers with experience
- Target number of prescribers "approved"
- Target number of prescribers "approved" and survey of approved prescribers to assess knowledge of product

The number of units distributed is a simple but blunt instrument to assess prescriber experience.
Target number of prescribers with experience may be challenging to assess if a substantial proportion of experience occurs in public clinics in NSW and Qld where limited visibility of individual prescriber experience will be available.

It is therefore proposed that a target number of approved prescribers (those completing review of educational material) be determined, and a sample of these prescribers be surveyed to assess sufficiency of specialist experience during initial restricted access scheme to inform advice to nonspecialist prescribers. This would provide an assessment of both quantity and the quality of experience. A more detailed description

of this assessment will be developed with input from specialist prescribers and with reference to the final agreed specialist prescriber definition.

Evaluating the effectiveness of the scheme to limit supply

Routine pharmacovigilance activities will contribute to the assessment of the scheme to limit supply.

A plan for evaluating the effectiveness of the scheme in restricting use of the product to the intended prescriber group will be developed and submitted once confirmation that the proposed restricted access scheme is considered acceptable to TGA.

EU RISK MANAGEMENT PLAN FOR BUPRENORPHINE EXTENDED-RELEASE INJECTION FOR SUBCUTANEOUS USE[a]

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP:31 December 2017

Date of final sign off: 12 March 2018

Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable, as this is the first RMP for BUPRENORPHINE EXTENDED-RELEASE INJECTION.

Other RMP versions under evaluation:	Not applicable
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:	Not applicable
Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable

EEA QPPV name: s22 [redacted]

EEA QPPV signature: s22 [redacted]

[a]BUPRENORPHINE EXTENDED RELEASE INJECTION will be used throughout the document.

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List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicology
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
APA	American Psychiatric Association
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
API	Active Pharmaceutical Ingredient
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control
CHO	Chinese Hamster Ovary
CNS	Central Nervous System
DDD	Defined Daily Dose
DSI	DNA Synthesis Inhibition
DSM	Diagnostic and Statistical Manual
EEA	European Economic Area
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EU	European Union
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GLP	Good Laboratory Practices
HBV	Hepatitis B Virus
HCl	Hydrochloride
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICD	International Statistical Classification of Diseases
ICSR	Individual Case Safety Report
IDU	Injection Drug User
INN	International Nonproprietary Name
INR	International Normalised Ratio
IV	Intravenous
LBW	Low Birth Weight
LFT	Liver Function Test
MAD	Multiple-Ascending-Dose
MAH	Marketing Authorisation Holder
MAOI	Monoamine oxidase inhibitors
MAT	Medication-Assisted Treatment
MTD	Maximum Tolerated Dose
NAS	Neonatal Abstinence Syndrome
NESARC	National Epidemiologic Survey of Alcohol and Related Conditions
NICU	Neonatal Intensive Care Unit

NMP	N-methyl-pyrrolidone
NOAEL	No Observed Adverse Effect Level
NMPOUD	Nonmedical Prescription Opioid Use Disorder
NOWS	Neonatal opioid withdrawal syndrome
NSDUH	National Survey on Drug Use and Health
OAMT	Opioid Agonist Maintenance Treatment
OB	Opioid Blockade
OUD	Opioid Use Disorder
PASS	Post-authorisation Safety Study
PLGH	Poly (lactide-co-glycolide)
PK	Pharmacokinetic(s)
PT	Preferred Term
PTD	Patient Treatment Days
PTY	Patient Treatment Years
PhV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SC	Subcutaneous(ly)
TEAE	Treatment Emergent Adverse Event
TK	Toxicokinetic(s)
UDS	Unscheduled DNA Synthesis
UK	United Kingdom
ULN	Upper Limit Normal
UNODC	United Nations Office on Drugs and Crime
USA	United States of America
WHO	World Health Organization
XR-NTX	Extended-Release Naltrexone
Z drugs	Zolpidem, Zopiclone, and Zaleplon

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) **(INN or common name)**	BUPRENORPHINE (EXTENDED-RELEASE INJECTION) FOR SUBCUTANEOUS USE[a]
Pharmacotherapeutic group(s) (ATC Code)	Group: Other nervous-system drugs, drugs used in addictive disorders (N07BC01 - buprenorphine)
Marketing Authorisation Holder (MAH)	Indivior UK Limited
Medicinal products to which this RMP refers	BUPRENORPHINE EXTENDED-RELEASE INJECTION
Invented name(s) in the European Economic Area (EEA)	TBD[b]
Marketing authorisation procedure	National or Decentralised procedure Mutual Recognition/Decentralised procedure
Brief description of the product	Chemical class: Buprenorphine is a white or almost white crystalline powder, free from any visible particulate contamination. Chemically, buprenorphine is (2S)-2-[17-(Cyclopropyl methyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol. The ATRIGEL® Delivery System is a biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP).
	Summary of mode of action: Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.
	Important information about its composition: BUPRENORPHINE EXTENDED-RELEASE INJECTION is a colourless to yellow to amber sterile solution and is available as a solution consisting of the Active Pharmaceutical Ingredient (API), buprenorphine base, and the ATRIGEL Delivery System. BUPRENORPHINE EXTENDED-RELEASE INJECTION is injected as a liquid, and the subsequent precipitation of the poly (DL-lactide-co-glycolide) polymer creates a solid depot which contains buprenorphine. After initial formation of the depot, buprenorphine is released via diffusion from, and the biodegradation of, the depot.

	The ATRIGEL® Delivery System is a biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, NMP.
Hyperlink to the Product Information	Refer to Module 1.3.1
Indication(s) in the EEA	Current (if applicable): Not applicable
	Proposed (if applicable): BUPRENORPHINE EXTENDED-RELEASE INJECTION is indicated for the treatment of moderate to severe opioid use disorder. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used as part of a complete treatment plan that includes counselling and psychosocial support.
Dosage in the EEA	Current (if applicable): Not applicable
	Proposed (if applicable): BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be dispensed directly to a healthcare provider for administration by a healthcare provider. The recommended dose of BUPRENORPHINE EXTENDED-RELEASE INJECTION following induction with transmuscosal buprenorphine is 300 mg monthly for the first two months. The subsequent doses may be 100 mg or 300 mg monthly based on the clinical condition of the patient.
Pharmaceutical form(s) and strengths	Current (if applicable): Not applicable
	Proposed (if applicable): BUPRENORPHINE EXTENDED-RELEASE INJECTION is a colourless to yellow to amber sterile solution and is available as a solution consisting of the API, buprenorphine base, and the ATRIGEL Delivery System. The ATRIGEL® Delivery System is a biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, NMP. Each 0.5 mL solution for injection in a prefilled syringe contains 100 mg buprenorphine (as buprenorphine base) in 1 mL syringe. Each 1.5 mL solution for injection in a prefilled syringe contains 300 mg buprenorphine (as buprenorphine base) in 2.25 mL syringe.

	Each dose is provided in a prefilled syringe with a 19 Gauge 5/8-inch (16 mm) needle.
Is/will the product be subject to additional monitoring in the EU?	No

[a] BUPRENORPHINE EXTENDED RELEASE INJECTION will be used throughout the document.
[b] In the EU, the product name is under proposal. In Canada, the proposed name is SUBLOCADE.

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication: Opioid Use Disorder

Incidence and Prevalence

Opioid use disorder (OUD) (as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA 2013)) and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), is a neurobehavioural syndrome characterised by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological and/or physical consequences. OUD is an international healthcare crisis of near epidemic proportions.

As stated in the 2017 World Drug Report by United Nations Office on Drugs and Crime (UNODC), the number of past-year users of opiates and individuals who misused prescription opioids worldwide was estimated at 35.1 million people (range 28.3 to 42.7 million), of whom 17.7 million were estimated to have used opiates (heroin and opium) (UNODC 2017). In 2014, there were approximately 69 000 deaths from an opioid involved overdose worldwide (Knipper 2017).

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2017 report, an estimated 1.4 million people received treatment for illicit drug use in the European Union during 2015 (1.6 million including Norway and Turkey). Opioid users represent the largest group undergoing specialised treatment and consume the greatest share of available treatment resources, mainly in the form of substitution treatment. Differences between countries can be very large, however, with opioid users accounting for more than 90% of treatment entrants in Estonia and less than 5% in Hungary. The latest data show that heroin use accounts for the majority, around 80%, of new opioid-related treatment demands in Europe. In addition, the overall decline in treatment demand related to heroin, observed since 2007, is no longer evident. Of particular concern is the increasing European estimate for drug overdose deaths, which has now risen for the third consecutive year; heroin is implicated in many of these deaths. Also in Europe, problems related to highly potent synthetic opioids appear to be growing, as indicated by increasing reports of non-fatal intoxications and deaths received by the Early Warning System (EMCDDA 2017).

While heroin still remains the most commonly used opioid in Europe, and opioid for the use of which most people seek treatment, there has been an increase in treatment demand related to prescription opioids (UNODC 2017). In 2015, 17 European countries reported that more than 10 percent of all opioid treatment admissions were for problems related to opioids other than heroin. The most common opioids for the use of which treatment was sought were methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone. In some countries, non-heroin opioids represent the most common form of opioid use among treatment entrants (EMCDDA 2017).

Other countries also experiencing an increase in opioid use and opioid related harms include Canada with a death rate of opioid-related deaths of 8.8 per 100 000 population (Health Canada 2016), and Australia with an opioid related death rate of 0.78 to 1.19 deaths/100 000 population over 10 years (Blanch 2014). In the USA, from 2000 to 2013, the age-adjusted rate for overdose deaths involving heroin nearly quadrupled from 0.7 deaths per 100 000 in 2000 to 2.7 deaths per 100 000 in 2013 (Hedegaard 2015).

Demographics of the target population and risk factors for the disease

In the global burden of disease study, the prevalence of opioid dependence is higher among males than females, 0.30% and 0.14%, respectively (Degenhardt 2014).

Male opioid users were more likely to also use other illicit drugs; female opioid users were more likely to also abuse other prescription drugs (Wu 2010).

In 2015, the average prevalence of high-risk opioid use among adults (15–64) was estimated at 0.4% of the EU population, the equivalent of 1.3 million high-risk opioid users in Europe. Five countries account for three quarters (76%) of the estimated high-risk opioid users in the EU (Germany, Spain, France, Italy, United Kingdom [UK]). About 191 000 patients who entered specialised treatment in Europe reported opioids as their primary drug, 37 000 of whom were first-time entrants. Primary heroin users accounted for 79% of first-time primary opioid users entering treatment. Among heroin users in EU, the mean age at first use is 23 years, while the mean age at first treatment is 34 years. Among first-time patients entering drug treatment in 2015 with heroin as their primary drug, the male to female ratio was approximately 4:1 (EMCDDA 2017).

Risk factors for opioid dependence include: a personal history of substance abuse, family history of substance abuse, young age, a history of preadolescent sexual abuse, psychological stress, polysubstance abuse, poor social support, non-functional status caused by pain, exaggeration of pain, and unclear cause of pain (NIDA 2007).

Scientists estimate that genetic factors account for between 40 and 60 percent of a person's vulnerability to addiction; this includes the effects of environmental factors on the function and expression of a person's genes. A person's stage of development and other medical conditions they may have are also factors. Adolescents and people with psychiatric illnesses are at greater risk of drug abuse and addiction than the general population (NIDA 2014).

Predictors of dependence on opioid medications among pain patients include substance abuse-related diagnoses, positive toxicology for opioids, and other medical diagnoses. Other patients at risk include those with idiopathic pain (no clear aetiology) or high levels of psychological distress or disability (Miller 2004).

The main existing treatment options

Opioid use disorder generally has a chronic and relapsing course and therefore a long-term relapse prevention treatment should be implemented for individuals who stop the use of opioids (UNODC-WHO 2017). Psychosocially assisted treatment refers to the combination of specific pharmacological and psychosocial measures, aimed at reducing or ceasing opioid use, preventing future harms associated with opioid use by decreasing the risk of complications and relapse, improving quality of life, well-being and social functioning of the OUD patient. While the psychosocial measures are varied, only a few specific medications are used for the treatment of OUD (WHO 2009).

The two, main pharmacological therapeutic strategies to address OUD are:

- Opioid Agonist Maintenance Treatment (OAMT) with long-acting opioids (methadone or buprenorphine)
- Detoxification followed by relapse-prevention treatment using opioid antagonist (naltrexone) (UNODC 2017).

Methadone and buprenorphine are effective evidence-based medications currently used in the treatment of OUD and have been placed on the WHO model list of essential medicines (WHO 2009).

The primary aim of OAMT is to reduce the use of illicit opioids and manage abstinence by preventing withdrawal symptoms, reducing drug craving, and decreasing effects of additional opioids if they are consumed (UNODC-WHO 2017).

Methadone is the most common treatment in Europe (Segrec 2017) which addresses the symptoms and signs of opioid withdrawal, reduces craving, and may mitigate euphoria (Dematteis 2017). In Europe, methadone is received by around two-thirds (63%) of substitution clients (EMCDDA 2017). A further 35% of clients are treated with buprenorphine-based medications, which is the principal substitution drug in 8 countries (EMCDDA 2017). Other substances, such as slow-release morphine or diacetylmorphine (heroin), are more rarely prescribed, being received by an estimated 2% of substitution clients in Europe (EMCDDA 2017).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Long-term studies of opioid dependent individuals indicate opioid dependence to be a chronic relapsing condition. Estimates suggest a 2-5% annual remission rate, for example, 2 to 5% will stop using opioids in any one year (Lintzeris 2015).

The natural history of opioid dependence, if untreated, is morbidity and mortality. The main causes of death in this population are overdose and/or suicide, trauma, and infectious diseases (such as hepatitis C-related liver disease, HIV infection and endocarditis). Much of the overdose-related mortality associated with dependence on opioids is linked to use of other sedative drugs such as benzodiazepines and antidepressants and the use of alcohol which is a sedative as well. Effective treatment is associated with a 3-5-fold reduction in mortality (Lintzeris 2015).

Important co-morbidities

Hepatitis

People who inject drugs are at a risk for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections through the sharing of needles and drug preparation equipment (CDC 2012). Current research shows that the prevalence of HCV is high among opioid dependent individuals. In fact, prior research showed that 80% of a sample of opioid dependent patients were positive for HCV antibody, and almost 67% were chronically infected (Murphy 2015). Chronic HCV infection can lead to long-term consequences including deaths and cases of severe liver disease, including cirrhosis and cancer, among an ageing population of high-risk drug users (EMCDDA 2017).

Across Europe, HCV is highly prevalent among injecting drug users. For every 100 people infected with HCV, 75-80 will develop chronic infection (EMCDDA 2017). A study was conducted in Spain which showed the incidence of HCV infection among injection drug users (IDUs) was found to be 39.8/100 person-years, and was 52.9/100 person-years among those who continued injecting during the follow up period. Thus, the anti-HCV prevalence among the sample of injection drug users was close to the highest reported in the world (Vallejo 2015).

HIV/AIDS

Drug injection continues to play a role in the transmission of HIV. In 2007, it was estimated that there were 15.9 million IDUs worldwide, and 3 million of these IDUs were living with HIV (Grebely 2011).

In 2013, the average rate of newly reported HIV diagnoses associated with injection drug use was 2.5 per million population, and there were 769 notifications of new acquired immune deficiency syndrome (AIDS) cases in Europe attributable to injection drug use (EMCDDA 2015). In 2010, approximately 1 700 people died of HIV/AIDS attributable to injection drug use in Europe (EMCDDA 2015).

Psychiatric disorders

A high prevalence of psychiatric comorbidities, especially depressive, anxiety, and personality disorders, in opioid dependent patients, is well established (Roncero 2016).

A study to determine the prevalence of psychiatric disorders among young IDUs outside of a treatment setting found that major depression was the most prevalent disorder with an estimated lifetime rate of 25% (95% CI: 16.9-34.9) for men and 31% (95% CI: 21.2-42.1%) for women (Mackesy-Amiti 2012). A recent study showed a very high prevalence of psychiatric (comorbidities anxiety disorder, mood disorder, non-opioid substance use disorder, or personality disorder) among patients seeking treatment for co-occurring opioid use disorder and chronic pain. Most participants in this study (81%) met the criteria for at least 1 psychiatric comorbidity, and the majority of participants (59%) met the criteria for at least 2 (Barry 2016).

Chronic pain

The use of opioid analgesics to treat chronic non-cancer pain, which is defined as pain lasting a least 3 months, has increased 3-fold since the early 1990s and has brought with it an epidemic of nonmedical opioid use, opioid overdose, and opioid use disorder (Barry 2016). The intersection between pain management, opioid dependence, and addictive behaviour inflates the challenges of treating both opioid addiction and chronic pain (Dennis 2015). Thus, clinicians report difficulty managing patients with chronic pain and opioid use disorder (Barry 2016).

Part II: Module SII - Nonclinical Part of the Safety Specification

Buprenorphine is an opioid partial agonist/antagonist with a high affinity for the mu- and kappa-receptors of the brain. Buprenorphine exerts its effect via high affinity binding to, and very slow rate of dissociation from mu receptors in the central nervous system. As a partial agonist, buprenorphine possesses a lower ceiling potential for respiratory depression, coma and death, making it a feasible treatment for opioid dependence. In a number of tests, the maximum physiological agonist response to buprenorphine does not increase despite an increase in dose (e.g., profile characterised by a bell-shaped or flattened dose-response, which reflects a limited or decreased efficacy of the drug at the upper end of the dose response curve). This effect is not seen with full opioid receptor agonists, and has subsequently been referred to as a 'ceiling effect' for buprenorphine. These properties may account for a long duration of action, the unpredictability of reversal by opioid antagonists, and a relatively low level of manifested physical dependence.

The toxicity profile of BUPRENORPHINE EXTENDED-RELEASE INJECTION and the ATRIGEL Delivery System (including high exposures to poly(lactide-co-glycolide) (PLGH) and N-methyl-2-pyrrolidone (NMP)) have been evaluated in a series of Good Laboratory Practice (GLP)-compliant studies, which evaluated systemic toxicity, local toxicity, genotoxicity and reproductive toxicity. The components of the ATRIGEL Delivery System were nonmutagenic when assessed in genotoxicity studies and in absence of preneoplastic lesions in the toxicity bridging studies in rats and dogs with BUPRENORPHINE EXTENDED-RELEASE INJECTION. No evidence of systemic toxicity was observed up to 6 and 9 months of monthly repeat-dosing in rats and dogs, respectively, and local reactions were typical of foreign body responses, ranging from no reaction to mild irritation. A full reproductive and developmental toxicity battery of studies was conducted to evaluate the safety and determine the toxicity profile of BUPRENORPHINE EXTENDED-RELEASE INJECTION and the ATRIGEL Delivery System under clinically relevant conditions by utilising the same dosing regimen that is used in the clinic; one subcutaneous (SC) dose administered once a month (~28 days in the animal studies). Results of these studies confirm the safe use of this product as safety margins at the no-observed-adverse-effect level (NOAEL) in single- and repeat-dose studies in rats and dogs ranged from 6- to 12-times higher. In fertility, embryo-foetal development and pre-/postnatal development studies in rats and rabbits, safety margins were 10-times or higher the highest proposed human dose (e.g., 22.8 mg/kg ATRIGEL Delivery system or 13.9 mg/kg NMP and 8.9 mg/kg PLGH; assumes a 60-kg individual). A summary of key safety findings from the BUPRENORPHINE EXTENDED-RELEASE INJECTION nonclinical studies are provided in the table below.

Table 2: Key Safety Findings from Nonclinical Studies

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
Single-Dose Findings	

Key Safety Findings (From Nonclinical Studies)	**Relevance to Human Usage**
BUPRENORPHINE EXTENDED-RELEASE INJECTION In a single study in rats, a dose-related higher severity (to mild or moderate) of vacuolar degeneration of pancreatic acinar cells was noted.	This finding was attributed to stress on the animals and was not considered adverse since it is a common incidental finding in rats and was observed in many of the control animals. The clinical relevance to human usage is not expected based on the high exposure multiples at which effects occurred in the single-dose studies.
ATRIGEL Delivery System In single-dose rat, rabbit, and dog toxicity studies conducted to compare the toxicological profile of the ATRIGEL Delivery System to that of a saline control, swelling was observed at the injection site of all animals receiving the ATRIGEL Delivery System. ATRIGEL Delivery System-related findings were limited to the injection site and were characterised by the presence of well delineated granulomas.	Injection site reactions are well characterised, single subcutaneous doses of ATRIGEL Delivery System are unlikely to present any significant risk to humans.
Repeat-Dose Findings	
BUPRENORPHINE EXTENDED-RELEASE INJECTION s47	s47
In rats, clinical observations including, urine stained fur, aggressive behaviour, decreased activity, broken/cracked teeth, lower body weight (males) and food consumption, all of which are consistent with the previously reported pharmacological effects of buprenorphine in rats.	Consistent with the previously reported pharmacological effects of buprenorphine in rats. These are monitorable clinical signs.
Elevated levels of stress levels supported by pathologically higher adrenal gland and decreased thymus weights.	The higher levels of stress coupled with the pharmacological effects of buprenorphine likely exacerbated the expected prevalence of this commonly observed background pancreatic histopathology in rat toxicity studies.
ATRIGEL Delivery System s47	The clinical relevance to human usage is not expected based on the high exposure multiples at which effects occurred in the repeat-dose studies.

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
s47	
s47	The clinical relevance to human usage is not expected based on the high exposure multiples at which effects occurred in the repeat-dose studies.
Reproductive Findings	
Dosing strategy Reproductive and developmental toxicity studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION were conducted in rats and rabbits. Pivotal studies were each conducted with 3 dose levels of BUPRENORPHINE EXTENDED-RELEASE INJECTION, 3 control groups administered the corresponding amount of ATRIGEL Delivery System and a single saline vehicle control group. A daily dosing schedule with BUPRENORPHINE EXTENDED-RELEASE INJECTION would not be clinically appropriate for these developmental and reproductive toxicity studies. Instead, BUPRENORPHINE EXTENDED-RELEASE INJECTION was administered in each study to with a goal of allowing for sustained exposure during the appropriate sensitive period(s) of development (e.g., organogenesis and/or early lactation) with an expected pharmacological response that would be well tolerated.	
Embryo Foetal Developmental Findings	
BUPRENORPHINE EXTENDED-RELEASE INJECTION In the fertility and embryo-foetal rat study, clinical signs indicative of maternal toxicity were observed during the gestation period and consisted of lower body weight, body weight gain, and food consumption. These findings were observed in the 900 mg/kg buprenorphine group as well as the corresponding high dose ATRIGEL group (4 244 mg/kg). Adverse treatment-related developmental effects	Because animal reproductive toxicity studies are not always predictive, the results from rat and rabbit infertility and embryo-foetal development toxicity studies with BUPRENORPHINE EXTENDED-RELEASE INJECTION suggest that BUPRENORPHINE EXTENDED-RELEASE INJECTION should

Key Safety Findings (From Nonclinical Studies)	Relevance to Human Usage
were observed in the mid- (2 829 mg/kg) and high- (4 244 mg/kg) ATRIGEL control groups and at 600 and 900 mg/kg buprenorphine. Mean foetal body weights in the high-ATRIGEL control group and at 900 mg/kg buprenorphine were statistically lower and considered adverse. In addition, a higher litter incidence of external malformations was observed in the mid- and high-ATRIGEL control groups and at 600 and 900 mg/kg buprenorphine and consisted predominately of malformations of the head which also correlated with skeletal malformations of the skull in these same dose groups. The results of this study indicate that toxicity can be induced by high doses of both the ATRIGEL Delivery System as well as BUPRENORPHINE EXTENDED-RELEASE INJECTION. Similar findings were noted in female rabbits receiving high doses of BUPRENORPHINE EXTENDED-RELEASE INJECTION or ATRIGEL Delivery System alone. Clinical signs indicative of maternal toxicity were observed during the gestation period and consisted of lower body weight gain and food consumption. These findings were observed in the high-ATRIGEL control group (1783 mg/kg) and the 155 and 390 mg/kg BUPRENORPHINE EXTENDED-RELEASE INJECTION administered group. Three females aborted and ten females had total litter resorption (100% post implantation loss) in the high-ATRIGEL control group and three females aborted and eight females had total litter resorption (100% post implantation loss) at 390 mg/kg buprenorphine. A higher incidence of litters with external malformations, visceral, and skeletal malformations as well as variations were observed in the high-ATRIGEL control group and at 390 mg/kg buprenorphine and were likely due to the high exposure to NMP. In addition, at 155 mg/kg buprenorphine, a higher incidence of litters with skeletal malformations was observed.	be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Infertility Findings	
In the rat fertility and embryo-foetal study, a total of 7 males were either euthanised due to moribundity or were found dead during the study between Days 40 and 60. Several of these animals exhibited one or more of the following clinical signs: lower activity, dehydration, hunched posture, cold to the touch, thin body condition, red material around the eyes, nose, and/or mouth, salivation, difficult breathing, red urine, tremors, and vocalisation. After 3 dose cycles, fraternal toxicity was observed in all of the BUPRENORPHINE EXTENDED-RELEASE INJECTION administered groups (300, 600, and 900 mg/kg buprenorphine) and included moribundity/mortality at 900 mg/kg buprenorphine and lower body weight, body weight gain, and food consumption at all dose levels.	Because animal reproductive toxicity studies are not always predictive, the results from rat and rabbit reproductive toxicity studies with BUPRENORPHINE EXTENDED-RELEASE INJECTION suggest that BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Key Safety Findings (From Nonclinical Studies)	**Relevance to Human Usage**
Treatment-related reductions in testes and epididymis weights were noted in the high-ATRIGEL control group and at 900 mg/kg buprenorphine. Also, a higher incidence of small thymus was noted macroscopically. Male survival in the ATRIGEL control groups (low and mid) and at 300 and 600 mg/kg buprenorphine were unaffected by treatment. Male fertility and reproduction indices were lower in the high-ATRIGEL control group and at 900 mg/kg buprenorphine as evidenced by abnormal sperm parameters (low motility, low mean number of sperm, and higher percentage of abnormal sperm).	
Buprenorphine Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure approximately 70-times the maximum human dose of BUPRENORPHINE EXTENDED-RELEASE INJECTION of 300 mg buprenorphine over 28 days [calculated using 0.179 mg/day/kg]) or up to 5 mg/kg/day IM or SC (estimated exposure approximately 4.5-times the maximum human dose of BUPRENORPHINE EXTENDED-RELEASE INJECTION of 300 mg buprenorphine over 28 days [calculated using 0.179 mg/day/kg]).	Because animal reproductive toxicity studies are not always predictive, the results from rat and rabbit infertility and embryo-foetal development toxicity studies with BUPRENORPHINE EXTENDED-RELEASE INJECTION suggest that BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Genotoxicity Findings	
Buprenorphine Buprenorphine was studied in a series of tests using gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (S. cerevisiae) for recombinant, gene convertant, or forward mutations, in Bacillus subtilis “rec” assay, in Chinese hamster ovary (CHO) cells for clastogenicity, in Chinese hamster bone marrow and spermatogonia cells, and in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (E. coli) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [3H] thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice. Given the negligible potential for carcinogenicity is expected for buprenorphine, the equivocal genetic toxicity finding noted with buprenorphine indicates that there is low risk for buprenorphine to produce genetic toxicity in humans.	

Key Safety Findings (From Nonclinical Studies)	**Relevance to Human Usage**
	Given the weight of evidence from the genetic toxicity studies, BUPRENORPHINE EXTENDED-RELEASE INJECTION is not considered a genotoxicant.
ATRIGEL Delivery System The ATRIGEL Delivery System was evaluated in the *in vivo* rat micronucleus test at a dose level of 2 000 mg/kg. Animals treated with ATRIGEL alone showed normal background levels of micronuclei. The components of the ATRIGEL Delivery System were considered to be non-mutagenic when assessed in the core battery of genotoxicity studies with ELIGARD® (leuprolide acetate for injectable suspension), including the rat micronucleus study.	The ATRIGEL Delivery System is not considered a genotoxicant.
Carcinogenicity Findings	
Carcinogenicity studies have not been conducted with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Two SUBUTEX® (buprenorphine hydrochloride) / SUBOXONE® (buprenorphine hydrochloride/naloxone hydrochloride) carcinogenicity studies with buprenorphine have been conducted with oral (dietary) administration in mice. It was concluded from these studies that buprenorphine is noncarcinogenic in mice at dietary doses up to 100 mg/kg/day, and when buprenorphine was administered to mice for 99 weeks at dosages of up to 2.0 mg/kg/day. Two SUBOXONE/SUBUTEX carcinogenicity studies with buprenorphine have been conducted in rats employing the oral (dietary) route of administration. In one study, statistically significant dose-related higher incidence of testicular Leydig cell tumours in buprenorphine administered male groups were seen, according to the trend test adjusted for survival. Pairwise comparison of the high dose with control did not show statistical significance. No other significant tumorigenic or carcinogenic findings were seen. In the second study, no biologically significant changes seen in haematology, serum chemistry or urinalysis were considered biologically significant or treatment-related, though some variations occurred.	Macroscopic findings were unremarkable. Some tissues in males showed dose-related higher incidence in non-neoplastic lesions including unilateral and bilateral Leydig cell hyperplasia which was higher in all treated groups. With the exception of these Leydig cell lesions, none of the non-neoplastic lesions showed progression to neoplastic lesions. Negligible potential for carcinogenicity is expected for buprenorphine as a result of BUPRENORPHINE EXTENDED-RELEASE INJECTION use.
Mutagenicity	
BUPRENORPHINE EXTENDED-RELEASE INJECTION No evidence of mutagenic potential for SC BUPRENORPHINE EXTENDED-RELEASE INJECTION was found in *in vivo* SC micronucleus test using rats' marrow erythrocytes when tested at the maximum tolerated dose (MTD) equivalent to 500 mg buprenorphine/kg (or	No higher risk of mutagenicity is expected for buprenorphine as a result of BUPRENORPHINE EXTENDED-RELEASE INJECTION use.

Key Safety Findings (From Nonclinical Studies)	**Relevance to Human Usage**
approximately 448 times the recommended human monthly SC dose of 300 mg of buprenorphine).	
ATRIGEL Delivery System No evidence of mutagenic potential for SC ATRIGEL Delivery System was found in this *in vivo* SC micronucleus test in rats, when tested at 2 000 mg/kg which represent approximately 1792 times the recommended human monthly SC dose.	No higher risk of mutagenicity is expected as a result of use of the ATRIGEL Delivery System.
Other toxicity-related information or data	Not applicable

In conclusion, based on the results of the above nonclinical data accumulated over the course of the BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical development programme, no additional nonclinical data appear to be needed.

Buprenorphine has been used extensively as an individual single entity or in combination with naloxone in humans. The pharmacology, pharmacodynamics, absorption, distribution, metabolism, excretion and toxicology (ADMET) of this molecule has been characterised sufficiently in both animals and humans.

Based on previous investigations of safety and efficacy of buprenorphine, a review of published literature, nonclinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION and components of the ATRIGEL Delivery System, as well as a review of the safety of the primary excipient NMP, the nonclinical information summarised are considered adequate to support the intended clinical use of BUPRENORPHINE EXTENDED-RELEASE INJECTION for opioid dependence at the maximum dose of 300 mg buprenorphine administered SC once monthly.

Part II: Module SIII - Clinical Trial Exposure

Table 3: Completed and Ongoing Clinical Trials in Development Programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION

Phase Count	Phase of Study	Protocol Number	Number of Subjects Screened	Number of Subjects Treated
Phase I: 3	Phase I	RB-US-10-0011	39	12
	Phase I	RB-US-11-0020	161	48
	Phase I	RB-US-13-0006	67	47
Phase II:2	Phase II	RB-US-13-0002	342	39
	Phase IIA	RB-US-12-0005	360	89
Phase III:3	Phase III	RB-US-13-0001	1 187	404
	Phase III	RB-US-13-0003	994	444
	Phase III	INDV-6000-301[a]	-	-
Total			**3 150**	**1 083**

Subjects who were dosed and reported in the RB-US-13-0001 study are not represented in the RB-US-13-0003 totals (de novo [n=412] and roll-over placebo [n=32]).
[a] To prevent duplicate reporting, the ongoing, open-label extension study INDV-6000-301 is not included since all of these subjects were treated in RB-US-13-0001 or RB-US-13-0003.

Table 4: Duration of Exposure- Completed Clinical Trial Exposure for BUPRENORPHINE EXTENDED-RELEASE INJECTION

Indication: Opioid Use Disorder			
Duration of exposure (at least)	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**
1-30 days	312	2 712	7.43
31-90 days	165	11 901	32.58
91-180 days	130	17 925	49.08
181-360 days	476	144 788	396.41
Total	**1 083**	**177 326**	**485.49**

INDV-6000-301 study is not included as the study is ongoing

Exposure duration was calculated for each subject who was exposed to at least one dose of BUPRENORPHINE EXTENDED-RELEASE INJECTION as
(1) For Subjects who received BUPRENORPHINE EXTENDED-RELEASE INJECTION treatment within only one study: date of last dose – date of 1st dose +1 day
(2) For Subjects who rolled over from either BUPRENORPHINE EXTENDED-RELEASE INJECTION treatment groups in RB-US-13-0001 study to RB-US-13-0003 study: date of Last dose in RB-US-13-0003 study – date of 1st dose in RB-US-13-0001 study + 1 day
Exposure duration was summed over all subjects within individual exposure duration categories to generate PTD and PTY

Indication: Opioid Use Disorder			
Duration of exposure (at least)	**Persons**	**Patient treatment days (PTD)**	**Patient treatment years (PTY)**

Subjects who rolled over from the BUPRENORPHINE EXTENDED-RELEASE INJECTION 300/300 mg and 300/100 mg dosage groups in RB-US-13-0001 study to the RB-US-13-0003 study were included in the treatment group to which they were assigned in the RB-US-13-0001 study. This includes 42 subjects in the 300/300 mg rollover group who received at least one 100 mg dose in RB-US-13-0003. Note that these subjects had been exposed to the 300 mg dose throughout RB-US-13-0001, and for most doses in RB-US-13-0003.

Table 5: Cumulative Exposure to BUPRENORPHINE EXTENDED-RELEASE INJECTION by Dose

Indication: Opioid Use Disorder			
Dose of exposure (dose of BUPRENORPHINE EXTENDED-RELEASE INJECTION)	**Persons**	**Patient Treatment Days (PTD)**	**Patient Treatment Years (PTY)**
20 mg	12	12	0.03
50 mg	27	1 091	2.99
100 mg	54	2 098	5.74
200 mg	42	2 507	6.86
300 mg	100	1 837	5.03
300/100 mg	203	40 187	110.03
300/300 mg	201	38 936	106.6
300/Flexible	444	90 658	248.21
Total	**1 083**	**177 326**	**485.49**

INDV-6000-301 study is not included as the study is ongoing
Exposure duration was calculated for each subject who was exposed to at least one dose of BUPRENORPHINE EXTENDED-RELEASE INJECTION as
(1) For Subjects who received BUPRENORPHINE EXTENDED-RELEASE INJECTION treatment within only one study: date of last dose – date of 1st dose +1 day
(2) For Subjects who rolled over from either BUPRENORPHINE EXTENDED-RELEASE INJECTION treatment groups in RB-US-13-0001 study to RB-US-13-0003 study: date of Last dose in RB-US-13-0003 study – date of 1st dose in RB-US-13-0001 study + 1 day
Exposure duration was summed over all subjects within individual exposure duration categories to generate PTD and PTY
Subjects who rolled over from the BUPRENORPHINE EXTENDED-RELEASE INJECTION 300/300 mg and 300/100 mg dosage groups in RB-US-13-0001 study to the RB-US-13-0003 study were included in the treatment group to which they were assigned in the RB-US-13-0001 study. This includes 42 subjects in the 300/300 mg rollover group who received at least one 100 mg dose in RB-US-13-0003. Note that these subjects had been exposed to the 300 mg dose throughout RB-US-13-0001, and for most doses in RB-US-13-0003.

Table 6: Cumulative Exposure to BUPRENORPHINE EXTENDED-RELEASE INJECTION by Age Group and Gender

Indication: Opioid Use Disorder						
Age group (years of age)	**Persons**		**Patient treatment days (PTD)**		**Patient treatment years (PTY)**	
	M	F	M	F	M	F

18 - < 35	319	168	43 324	25 725	118.61	70.43
35 - < 45	181	90	27 070	17 603	74.11	48.19
45 - < 55	127	60	24 198	12 891	66.25	35.29
55 - ⩽ 65	106	32	19 915	6 600	54.52	18.07
Total	**733**	**350**	**114 507**	**62 819**	**313.50**	**171.99**

INDV-6000-301 study is not included as the study is ongoing
Exposure duration was calculated for each subject who was exposed to at least one dose of BUPRENORPHINE EXTENDED-RELEASE INJECTION as
(1) For Subjects who received BUPRENORPHINE EXTENDED-RELEASE INJECTION treatment within only one study: date of last dose – date of 1st dose +1 day
(2) For Subjects who rolled over from either BUPRENORPHINE EXTENDED-RELEASE INJECTION treatment groups in RB-US-13-0001 study to RB-US-13-0003 study:
date of Last dose in RB-US-13-0003 study – date of 1st dose in RB-US-13-0001 study + 1 day
Exposure duration was summed over all subjects within individual exposure duration categories to generate PTD and PTY
Subjects who rolled over from the BUPRENORPHINE EXTENDED-RELEASE INJECTION 300/300 mg and 300/100 mg dosage groups in RB-US-13-0001 study to the RB-US-13-0003 study were included in the treatment group to which they were assigned in the RB-US-13-0001 study. This includes 42 subjects in the 300/300 mg rollover group who received at least one 100 mg dose in RB-US-13-0003. Note that these subjects had been exposed to the 300 mg dose throughout RB-US-13-0001, and for most doses in RB-US-13-0003.

Table 7: Cumulative Exposure to BUPRENORPHINE EXTENDED-RELEASE INJECTION by Ethnic or Racial Origin

Indication: Opioid Use Disorder			
Ethnic/racial origin	**Persons**	**Patient Treatment Days (PTD)**	**Patient Treatment Years (PTY)**
American Indian or Alaskan Native	8	1 178	3.23
Asian	5	348	0.95
Black or African-American	296	53 555	146.63
White	764	120 132	328.9
Other	9	2 028	5.55
Missing	1	85	0.23
Total	**1 083**	**177 326**	**485.49**

INDV-6000-301 study is not included as the study is ongoing
Exposure duration was calculated for each subject who was exposed to at least one dose of BUPRENORPHINE EXTENDED-RELEASE INJECTION as
(1) For Subjects who received BUPRENORPHINE EXTENDED-RELEASE INJECTION treatment within only one study: date of last dose – date of 1st dose +1 day
(2) For Subjects who rolled over from either BUPRENORPHINE EXTENDED-RELEASE INJECTION treatment groups in RB-US-13-0001 study to RB-US-13-0003 study: date of Last dose in RB-US-13-0003 study – date of 1st dose in RB-US-13-0001 study + 1 day
Exposure duration was summed over all subjects within individual exposure duration categories to generate PTD and PTY
Subjects who rolled over from the BUPRENORPHINE EXTENDED-RELEASE INJECTION 300/300 mg and 300/100 mg dosage groups in RB-US-13-0001 study to the
RB-US-13-0003 study were included in the treatment group to which they were assigned in the RB-US-13-0001 study. This includes 42 subjects in the 300/300 mg rollover group who received at least one 100 mg dose in RB-US-13-0003. Note that these subjects had been exposed to the 300 mg dose throughout RB-US-13-0001, and for most doses in RB-US-13-0003.

Cumulatively, there have been 8 clinical trials (7 completed, 1 ongoing) in the development programme conducted with BUPRENORPHINE EXTENDED-RELEASE INJECTION, which included 3 Phase I studies, 2 Phase II studies, and 3 Phase III studies. A total of 1 083 subjects from the completed clinical trials have received BUPRENORPHINE EXTENDED-RELEASE INJECTION. One open-label long-term safety extension study (INDV-6000-301) is ongoing at the time of database lock but has not been included in the tables since all subjects previously participated in RB-US-13-0001 and/or RB-US-13-0003 and have therefore already been included in exposure numbers.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Use in Children/Adolescents Less Than 18 Years Old

Reason for exclusion: The safety and effectiveness of BUPRENORPHINE EXTENDED-RELEASE INJECTION have not been established in paediatric patients. Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it.

Is it considered to be included as missing information? Yes

Geriatric Use (Elderly Patients Greater Than or Equal To 65 years old)

Reason for exclusion: Clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between geriatric and younger patients.

Is it considered to be included as missing information? Yes

Pregnant or Breastfeeding Women

Reason for exclusion: Chronic exposure to buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Is it considered to be included as missing information? No

Rationale: Although pregnant women were excluded from the clinical development programme, there were a total of 22 pregnancies reported, 1 of which involved a report of neonatal drug withdrawal syndrome in a male neonate.

Additionally, a post-authorisation safety study (PASS) study was conducted to monitor pregnancy outcomes associated with exposure to SUBOXONE, SUBUTEX and methadone among pregnant opioid dependent women using medical registries in Sweden and Denmark from 2005 to 2011. In Sweden, in general, women exposed to SUBUTEX or methadone more often delivered preterm and C-sections were more common, when compared to the total population. There were 34 infants with neonatal abstinence syndrome (NAS) exposed to SUBUTEX. In

Denmark, among the 571 823 mothers who gave birth during the study period; 564 exposed infants in 557 pregnancies were identified. Compared with the nonexposed, all recorded opioid use was associated with greater prevalence of preterm birth prevalence ratios were 3.5 (95% CI: 0.6<20.1) in SUBUTEX exposed and low birth weight (LBW) prevalence ratios 4.6 (95% CI: 0.8<26.7) in SUBUTEX exposed. No stillbirths occurred in SUBUTEX only exposed pregnancies.

Patients Who Have Been Shown to be Hypersensitive to Buprenorphine or Any Component of the ATRIGEL Delivery System

Reason for exclusion: Cases of hypersensitivity to buprenorphine containing products have been reported both in clinical trials and in the postmarketing experience. Cases of bronchospasm, angioneurotic oedema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine is a contraindication to the use of BUPRENORPHINE EXTENDED-RELEASE INJECTION.

Is it considered to be included as missing information? No

Rationale: A history of hypersensitivity to buprenorphine is a contraindication to the use of BUPRENORPHINE EXTENDED-RELEASE INJECTION.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. However, given the extended post-marketing experience of the component products, for example, over 30 years for buprenorphine, the detection of signals for uncommon, rare or very rare adverse events would be less of a concern for BUPRENORPHINE EXTENDED-RELEASE INJECTION.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 8: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Use in children/adolescents (< 18 years old)	Children were not included in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION.
Use in elderly patients (≥ 65 years old)	The clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects.

Type of Special Population	Exposure
Pregnant women	Pregnant women were excluded from the BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical development programme. However, there were a total of 22 pregnancies reported during the BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical development programme (21 study subjects and 1 partner of a study subject), all of which were discontinued from the study upon notification of pregnancy. There was 1 report of NOWS in a male neonate. The gestational outcome of the 22 pregnancies include the following: Livebirths (n=7; 1 NOWS; 2 premature deliveries; 3 with no complications; 1 resolved complications [baby tested positive for buprenorphine and was admitted to the neonate intensive care unit]), elective termination (n=3), Unknown (n=11), and spontaneous abortion (n=1).
Breastfeeding women	Not included in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION.
Patients with hepatic impairment	Patients with hepatic impairment have not been studied in BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical trials. For BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical studies, only subjects who met the following criteria would be included in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION: Total bilirubin ≤ 1.5 x the upper limit of normal (ULN), alanine aminotransferase (ALT) ≤3 x ULN, aspartate aminotransferase (AST) ≤3 x ULN, serum creatinine ≤ 2 x ULN, international normalised ratio (INR) ≤ 1.5 x ULN.
Patients with renal impairment	Patients with renal impairment were not included in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION.
Patients with cardiovascular impairment	Patients with cardiovascular impairment were not included in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION.
Immunocompromised patients	Immunocompromised patients were not included in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION.
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with a disease severity different from inclusion criteria in clinical trials were not included in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION.

<table>
<tr><th>Type of Special Population</th><th>Exposure</th></tr>
<tr><td>Population with relevant different ethnic origin for BUPRENORPHINE EXTENDED-RELEASE INJECTION</td><td>Exposure to BUPRENORPHINE EXTENDED-RELEASE INJECTION by Ethnic Origin
<table>
<tr><th>Ethnic/Racial Origin</th><th>Persons</th><th>Patient Treatment Days (PTD)</th><th>Patient Treatment Years (PTY)</th></tr>
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<tr><td>Total</td><td>1 083</td><td>177 326</td><td>485.49</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION.</td></tr>
</table>

Part II: Module SV - Post-authorisation Experience

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Since BUPRENORPHINE EXTENDED-RELEASE INJECTION is required to be administered in a healthcare setting and is not made directly available to patients, its potential for misuse, abuse and diversion is minimised. Its format as an injectable depot also reduces its abuse potential.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission for BUPRENORPHINE EXTENDED-RELEASE INJECTION

Table 9: Safety Concerns in the Initial RMP Submission for BUPRENORPHINE EXTENDED-RELEASE INJECTION

Important identified risks	• CNS depression including respiratory depression/respiratory failure • hepatitis, hepatic events, use in patients with hepatic impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation) • local tolerability: injection site reactions • drug withdrawal syndrome including neonatal withdrawal • misuse/abuse (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV use, extraction, overdose
Missing information	• use in children/adolescents (< 18 years old) • use in elderly patients (≥ 65 years old)

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following risks are not considered important for BUPRENORPHINE EXTENDED-RELEASE INJECTION:

Orthostatic hypotension is not considered an important risk. Buprenorphine, like other opioids, may produce orthostatic hypotension in ambulatory patients. s47 [redacted]

Acute pancreatitis is not considered an important risk. Monitoring of pancreatic functioning was conducted in several clinical studies due to a nonclinical safety finding of pancreatic acinar cell s47 [redacted]

s47 [redacted]

Use in patients with a head injury and increase in intracranial pressure is not considered an important risk since it is already a well-known opioid class effect. Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure, which may cause seizures, so opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure.

Peripheral oedema is not considered an important risk. Although peripheral oedema has been frequently reported with buprenorphine/naloxone sublingual tablets and film, peripheral oedema

s47 [redacted]

Reason for Not Including an Identified or Potential risk in the List of Safety Concerns in the RMP:

The following known risks require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers:

- orthostatic hypotension
- acute pancreatitis
- use in patients with head injury and increase in intracranial pressure
- peripheral oedema

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk 1: CNS Depression (including respiratory depression/respiratory failure)

Risk-benefit impact:

Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effects of buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. Additionally, due to additive effects of CNS depressants, the concomitant use of non-benzodiazepine or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

Based on experience with morphine, monoamine oxidase inhibitors (MAOIs) may increase the effects of buprenorphine in BUPRENORPHINE EXTENDED-RELEASE INJECTION. Additionally, buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose, respiratory depression, and death. Patients should be warned of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. No respiratory failure or respiratory depression was reported in the BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical development programme.

CNS depression (e.g. drowsiness, coma), including respiratory depression and respiratory failure, is classified as an important identified risk.

Important Identified Risk 2: Hepatitis, Hepatic Events and Use in Patients with Hepatic Impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation)

Risk-benefit impact: The effect of hepatic impairment on the pharmacokinetics (PK) of BUPRENORPHINE EXTENDED-RELEASE INJECTION has not been studied. However, the effect of hepatic impairment on the PK of sublingual buprenorphine has been evaluated in a PK study. While no clinically significant changes have been observed in subjects with mild hepatic impairment, the plasma levels have been shown to be higher and half-life values have been shown to be longer for buprenorphine in subjects with moderate and severe hepatic impairment.

In the BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical development programme, adverse reactions commonly associated with BUPRENORPHINE EXTENDED-RELEASE INJECTION (in ≥ 5% of subjects) included increased hepatic enzymes; however, these subjects had confounding factors, including ongoing medical history of Hepatitis B or C and did not meet the conditions for an actual Hy's Law case.

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving sublingual buprenorphine in clinical trials and through postmarketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with HBV and HCV, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role.

Hepatitis, hepatic events, use in patients with hepatic impairment is classified as an important identified risk.

Important Identified Risk 3: Drug Withdrawal Syndrome including neonatal withdrawal

Risk-benefit impact: Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type characterised by withdrawal signs and symptoms upon discontinuation. The withdrawal syndrome is milder than that seen with full agonists and may be delayed in onset. Considering the long half-life, any withdrawal signs and symptoms that may occur would be expected to be delayed. Chronic exposure to buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorised or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognised and treated in the neonate.

Thus, drug withdrawal syndrome is to be classified as an important identified risk.

Important Identified Risk 4: Local Tolerability: Injection Site Reactions

Risk-benefit impact: Injection site pain and pruritus were some of the most commonly reported adverse drug reactions during the BUPRENORPHINE EXTENDED-RELEASE INJECTION pivotal clinical studies reported in ≥ 5% of subjects. In most cases, injection site reactions have been mild to moderate in severity, usually presenting early in the course of treatment, which is consistent with observations in previous local irritation ATRIGEL studies.

Thus, local tolerability: injection site reactions is to be classified as an important identified risk.

Important Identified Risk 5: Misuse/abuse (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV use, extraction, overdose

BUPRENORPHINE EXTENDED-RELEASE INJECTION contains buprenorphine, a controlled substance that can be abused in a manner similar to other opioids. Buprenorphine is sought by people with opioid use disorders and is subject to criminal diversion.

The most frequently reported postmarketing adverse event observed with buprenorphine sublingual tablets was misuse or abuse. Many, but not all, postmarketing reports regarding coma and death involved misuse by self-injection or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol.

There is a risk of serious harm or death with intravenous administration of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Intravenous injection presents significant risk of serious harm or death as BUPRENORPHINE EXTENDED-RELEASE INJECTION forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously.

BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. No accounts of subjects removing or attempting to

remove the depot after administration of BUPRENORPHINE EXTENDED-RELEASE INJECTION were reported in clinical studies. No events of drug misuse, abuse, or diversion have been reported in BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical studies.

Thus, misuse/abuse is to be classified as an important identified risk.

Missing Information 1: Use in Children/Adolescents (Less Than 18 Years Old)

Risk-benefit impact: The safety and effectiveness of BUPRENORPHINE EXTENDED-RELEASE INJECTION have not been established in paediatric patients. Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it.

Thus, the use of BUPRENORPHINE EXTENDED-RELEASE INJECTION in children/adolescents < 18 years old is classified as missing information.

Missing Information 2: Use in Elderly Patients (Greater Than or Equal to 65 Years Old)

Risk-benefit impact: Clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between geriatric and younger patients.

Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients, the decision to prescribe BUPRENORPHINE EXTENDED-RELEASE INJECTION should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose.

Thus, the use of BUPRENORPHINE EXTENDED-RELEASE INJECTION in elderly patients ≥ 65 years old is classified as missing information.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the first RMP for BUPRENORPHINE EXTENDED-RELEASE INJECTION.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Table 10: Important Identified Risk: CNS Depression Including Respiratory Depression/Respiratory Failure

Potential mechanisms	Respiratory depression is the leading mechanism of death in fatal overdose. Suppression of respiratory function is a dose-dependent property of opioids. Alcohol and benzodiazepines interact with buprenorphine hydrochloride (HCl) (Jones 2004). Severe alcohol intoxication, alcohol withdrawal syndrome, and delirium tremens are associated with the risk of respiratory depression. Concomitant use of alcohol and buprenorphine HCl increases the risk of respiratory depression. The mechanisms of developing respiratory depression from opioid use are self-potentiating in that hypoventilation impairs gas exchange, resulting in increased carbon dioxide (hypercapnia) and decreased oxygen (hypoxia) and pH (respiratory acidosis). In turn, suppression of the chemoreceptor responses to increased carbon dioxide levels blunt the normally protective central response which would increase breathing efforts. This "vicious cycle" may result in profoundly low oxygen (hypoxemia) and/or respiratory arrest (Jungquist 2011). Buprenorphine may cause drowsiness, particularly when used together with alcohol or CNS depressants such as benzodiazepines, tranquilisers, sedatives or hypnotics. One of the most serious problems with opioids is that overdose can give rise to respiratory depression, coma, and death. Buprenorphine in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death.
Evidence sources(s) and strength of evidence	Due to additive effects of CNS depressants, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death. Opioids can reduce respiration in a dose dependent manner. In non-clinical studies, buprenorphine caused mild respiratory depression, with slight, dose-related decreases in blood pH (~7.42-7.35) and pO_2 (~80-55 mmHg), and increased pCO_2 (~38-50 mmHg) in rats. These results confirmed the expected narcotic-like effects of buprenorphine on respiration. Additionally, non-clinical studies have shown that the combination of benzodiazepines and buprenorphine increased buprenorphine-induced respiratory depression. Respiratory depression has occurred during post-marketing surveillance. Death due to respiratory depression has been reported, particularly when buprenorphine was used in combination with benzodiazepines, or when buprenorphine was not used according to prescribing information.
Characterisation of risk	*Clinical Development Programme* Phase III studies: In the pooled Phase III studies, 10% of subjects had TEAEs potentially associated with CNS depression. The preferred terms for TEAEs potentially associated with CNS depression in at least 1% of subjects included: somnolence (3.2%), sedation (2.7%), dizziness (1.9%) and lethargy (1.2%). In the Phase III double-blind study, none of the TEAEs potentially associated with CNS depression were serious except for 1 case of accidental

	overdose in the placebo group. In the Phase III long-term safety study, there were no overdoses of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Three subjects (<1.0%) had a reported overdose with other substances, heroin, diazepam and trazodone (1 subject each). Phase II studies: In the multiple-ascending-dose (MAD) study, no dose-related trends were observed overall or relative to individual preferred terms (PTs). Dizziness was the only PT for TEAEs potentially associated with CNS depression reported for > 1 subject in this study (4 subjects; 1 subject in Cohort 2 [stabilised on SUBUTEX 12 mg then BUPRENORPHINE EXTENDED-RELEASE INJECTION 100 mg, 6.7%], 2 subjects in Cohort 4 [stabilised on SUBUTEX 8 mg then BUPRENORPHINE EXTENDED-RELEASE INJECTION 100 mg, 13.3%] and 1 subject in Cohort 6 [stabilised on a dose of SUBUTEX 8-24 mg then BUPRENORPHINE EXTENDED-RELEASE INJECTION 300 mg, 6.7%]). In the opioid blockade (OB) study, 30.8% of subjects had TEAEs potentially associated with CNS depression. The most common TEAE by PT was sedation (23.1%). None of the TEAEs potentially associated with CNS depression in Phase II studies were serious or led to withdrawal from the study. Phase I studies: In the pooled Phase I studies, 14.0% of subjects had TEAEs potentially associated with CNS depression. The PTs for TEAEs potentially associated with CNS depression in at least 1.0% of subjects were dizziness (8.4%) and somnolence, syncope and vision blurred (1.9% each). Respiratory depression/respiratory failure was not specifically reported in BUPRENORPHINE EXTENDED-RELEASE INJECTION clinical trials. No overdoses of BUPRENORPHINE EXTENDED-RELEASE INJECTION were reported. There was a low incidence (<1.0%) of overdose of other substances in Phase 3 studies as described above. None were fatal.
Risk factors and risk groups	The risk for CNS depression is increased in patients who are on prescription medications for anxiety/depression and those with habitual alcohol intake. Risk factors for developing respiratory failure includes smoking tobacco products, excessive alcohol intake, a family history of respiratory disease or conditions, injury to the spine, brain, or chest, and immunocompromised patients (Macon 2017). Other risk factors include concomitant use of CNS depressants and respiratory illness.
Preventability	Use BUPRENORPHINE EXTENDED-RELEASE INJECTION with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Due to its extended-release characteristics, if BUPRENORPHINE EXTENDED-RELEASE INJECTION is discontinued as a result of compromised respiratory function, monitor patients for ongoing buprenorphine effects for several months. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be prescribed with caution to patients taking benzodiazepines or other drugs that

	act on the CNS, regardless of whether these drugs are taken on the advice of a healthcare provider or are being abused/misused. If it is anticipated that patients will begin taking benzodiazepines or other drugs after beginning treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION, healthcare providers should assess the risks and benefits of initiating BUPRENORPHINE EXTENDED-RELEASE INJECTION for those patients and should consider starting treatment with a lower dose of benzodiazepines or CNS depressants. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments.
Impact on the risk-benefit impact of the product	With the risk minimisation measures in place for the risk of CNS depression, it is expected that the impact on the risk-benefit balance is low.
Public health impact	Fatal overdose among opioid abusers, particularly increased in the presence of sedative agents, is a known public health problem. Prescriber, patient, caregiver education is a useful tool to increase community awareness of the risk of fatal overdose.

Table 11: Important Identified Risk: Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment (Effects of This Risk May Be Increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION Because of Long-Term Depot Formulation)

Potential mechanisms	The metabolic pathway of pain relief medications, including opioids, pass through the liver (oxidation, dealkylation, conversion, and combining). Therefore, in patients with reduced hepatic function, the metabolic pathways are affected and the toxicity probability of these drugs increases (Soleimanpour 2016). Buprenorphine has a high hepatic extraction ratio, and as such, its clearance is mainly dependent on hepatic blood flow and not affected by the changes of intrinsic clearance. Buprenorphine does not undergo first-pass metabolism following subcutaneous injection of BUPRENORPHINE EXTENDED-RELEASE INJECTION. The clearance of buprenorphine (>60 L/h) approaches hepatic blood flow. Because buprenorphine is metabolised by the liver, its activity may be increased and/or extended in those individuals with impaired hepatic function

	or otherwise altered in those receiving agents known to interact with this enzyme. Infection is primarily due to IV drug abuse.
Evidence source(s) and strength of evidence	Cases of acute hepatic injury have been reported in opioid dependent patients, both in clinical trials and in post-marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role. The effect of hepatic impairment on the pharmacokinetics of sublingual buprenorphine has been evaluated in a pharmacokinetic study. While no clinically significant changes have been observed in subjects with mild hepatic impairment, the plasma levels have been shown to be higher and half-life values have been shown to be longer for buprenorphine in subjects with moderate to severe hepatic impairment.
Characterisation of risk	*Clinical Development Programme* Phase III studies: In the pooled Phase III studies, 8.7% of subjects exposed to BUPRENORPHINE EXTENDED-RELEASE INJECTION had TEAEs potentially associated with hepatic disorders. The preferred terms for TEAEs potentially associated with hepatotoxicity in at least 1% of subjects were the following: gamma-glutamyltransferase increased (4.1%), aspartate aminotransferase increased (3.5%), alanine aminotransferase increased (2.9%) and liver function test (LFT) increased (1.4%). Phase II studies: In the MAD study, TEAEs potentially associated with hepatic disorders were reported in a larger percentage of subjects in Cohort 4 (stabilised on SUBUTEX 8 mg then BUPRENORPHINE EXTENDED-RELEASE INJECTION 100 mg, 33.3%) compared with the other cohorts (0 to 13.3%) and none of these events were reported for Cohort 6 (stabilised on SUBUTEX 8 to 24 mg then BUPRENORPHINE EXTENDED-RELEASE INJECTION 300 mg). Preferred terms reported in more than 1 subject in this study were the following: alanine aminotransferase increased (6 subjects), LFT increased (5 subjects), aspartate aminotransferase increased (3 subjects) and hepatic enzyme increased. There was no dose-related trend either overall or by individual preferred terms. In the OB study, 1 subject had a TEAE potentially associated with hepatic disorders (2.6%, LFT increased). None of the TEAEs potentially associated with hepatic disorders in Phase II studies were serious. Phase I studies: In the pooled Phase I studies, 13.1% of subjects had TEAEs potentially associated with hepatic disorders. The PTs for TEAEs potentially associated with hepatotoxicity in at least 1.0% of subjects were the following: LFT increased (6.5%), blood bilirubin increased (3.7%) and alanine aminotransferase increased (2.8%).

	No subjects met the criteria for a potential Hy's Law case.
Risk factors and risk groups	Patients who are positive for viral hepatitis or having existing liver dysfunction are at greater risk of liver injury.
Preventability	Patients who are positive for viral hepatitis, on concomitant medicinal products and/or have existing liver dysfunction are at greater risk of liver injury and these underlying factors must be taken into consideration before prescribing buprenorphine and during treatment. Liver function tests, prior to initiation of treatment, are recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. An aetiological evaluation is recommended when a hepatic adverse event is suspected. Depending on the findings, the medicinal product may be discontinued and the patient closely monitored for response to discontinuation and treated appropriately for withdrawal in order to maintain continued abstinence. If the treatment is continued, hepatic function should be monitored closely. The plasma levels of buprenorphine may be higher in patients with hepatic impairment. Patients should be monitored for overtreatment that may require dose adjustment. Because buprenorphine levels cannot be rapidly adjusted, patients with pre-existing severe hepatic impairment are not candidates for treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Patients who develop moderate to severe hepatic impairment while being treated with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. If signs and symptoms of toxicity or overdose occur within 2 weeks of BUPRENORPHINE EXTENDED-RELEASE INJECTION administration, removal of the depot may be performed.
Impact on the risk-benefit impact of the product	With the risk minimisation measures in place for the risk of hepatitis, hepatic events, use in patients with hepatic impairment, it is expected that the impact on the benefit-risk balance of BUPRENORPHINE EXTENDED-RELEASE INJECTION remains positive.
Public health impact	Hepatitis is a common health concern among opioid dependent injection drug users. However, the public health impact is low, as the risk can be largely minimised if the product is used as per the reference safety information.

Table 12: Important Identified Risk- Local Tolerability: Injection Site Reactions

Important Identified Risk: Local Tolerability: Injection Site Reactions	
Potential mechanisms	An injection site reaction is inflammation in or damage to the tissue surrounding where a drug was injected. There are two types of injection site reactions: a local allergic reaction called a flare reaction, and a more severe reaction characterised by damage to the tissue due to extravasation. Extravasation is leakage of a small amount of drug from the blood vessel

	where it was injected. Symptoms for both reactions typically include redness, tenderness, warmth, and itching, but the consequences of extravasation are more severe and may include pain, blistering, and severe skin damage (UNM Health 2016).
Evidence source(s) and strength of evidence	Multiple Injection site reactions (e.g. induration, erythema, bruising, oedema, pruritus and local pain at the injection site) have been observed in clinical trials and non-clinical studies for BUPRENORPHINE EXTENDED-RELEASE INJECTION. For instance, BUPRENORPHINE EXTENDED-RELEASE INJECTION single-dose toxicity/toxicokinetic (TK) studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION were conducted in rats and dogs (RBLS-R02-60-09 and RBLS-C01-60-09, respectively). As with the rats, the injection site reactions observed in the high dose dogs (ATRIGEL 285 mg/kg males/279 mg/kg females) and control dogs (ATRIGEL 362 mg/kg males/361 mg/kg females) included swelling, abrasion, reddening and raised areas or masses and correlated with increasing volume of the ATRIGEL. In RB-US-11-0020, 46 of 48 subjects (95.8%) reported a total of 320 injection site reactions. Most injection site reactions were assessed as mild in severity (34 subjects; 70.8%); however, 1 subject (2.1%) reported severe swelling at the injection site. Additionally, in a MAD study in opiate dependent subjects (RB-US-12-0005), 5 subjects experienced an injection site reaction of severe injection site pain. In an imaging study in opiate dependent subjects designed to determine the amount of opioid-blockade (RB-US-13-0002), 3 subjects experienced an injection site reaction of severe injection site tenderness.
Characterisation of risks	*Clinical trial programme* In Phase III studies: A total of 82 subjects overall (12.3%) were reported to have TEAEs pertaining to injection site reactions; 61 subjects (14.8%) in the *de-novo* subject group and 21 subjects (8.2%) in the roll-over subject group. The most common preferred terms overall pertaining to injection site reactions were injection site pain (41 subjects; 6.1%), injection site erythema (26 subjects; 3.9%), and injection site pruritus (26 subjects; 3.9%). Two subjects (0.3%) had adverse events (AE) pertaining to injection site reactions that led to discontinuation. No AE pertaining to injection site reaction was reported as an SAE. In Phase II studies: In the MAD study, at least 1 injection site reaction TEAE was reported for 1 to 4 subjects per cohort. Injection site pruritus was the most commonly reported TEAE by PT. In the OB study, at least 1 injection site reaction TEAE was reported for 3 subjects (7.7%). None of these injection site reaction TEAEs were serious or led to withdrawal from the study. In Phase I studies: In the pooled Phase I studies, at least 1 injection site reaction TEAE was reported for 29.9% of subjects. Preferred terms for injection site reaction TEAEs in at least 5% of subjects were the following: injection site pain (14.0%), injection site pruritus (7.5%) and injection site erythema (5.6%).

Risk factors and risk groups	Risk factors for injection site reactions given subcutaneously include injecting the medicine in the same spot twice in a row (Case-Lo 2015).
Preventability	BUPRENORPHINE EXTENDED-RELEASE INJECTION is for abdominal subcutaneous injection only and must NOT be administered intravenously or intramuscularly. BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be administered monthly with a minimum of 26 days between doses. Each injection should be administered only using the syringe and safety needle included with the product. To avoid irritation, rotate injection sites.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of local tolerability: injection site reactions, it is expected that the impact on the risk-benefit balance of BUPRENORPHINE EXTENDED-RELEASE INJECTION is low.
Public health impact	The potential public health impact of injection site reaction with BUPRENORPHINE EXTENDED-RELEASE INJECTION use is expected to be minimal.

Table 13: Important Identified Risk: Drug Withdrawal Syndrome (Including Neonatal Withdrawal)

Potential mechanisms	Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type characterised by withdrawal signs and symptoms upon discontinuation. The withdrawal syndrome is milder than that seen with full agonists and may be delayed in onset. Considering the long half-life, any withdrawal signs and symptoms that may occur would be expected to be delayed. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 or 300 mg, respectively). The severity of withdrawal can vary depending on severity of preceding opioid abuse.
Evidence source(s) and strength of evidence	Drug withdrawal syndrome was the most common AE reported in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION; however, it was not considered related to BUPRENORPHINE EXTENDED-RELEASE INJECTION. Additionally, withdrawal signs and symptoms were not observed in the month following discontinuation of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Symptoms of opioid withdrawal (dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhoea, pupillary dilation, piloerection, or sweating, diarrhoea, yawning, fever, insomnia) may cause clinically significant distress

	or impairment in social, occupational, or other important areas of functioning (DSM-V). NOWS is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorised or illicit. Neonatal withdrawal has been reported in infants of women treated with buprenorphine during pregnancy.
Characterisation of risks	*Clinical trial programme:* Treatment-emergent AEs potentially associated with opioid withdrawal signs and symptoms were commonly reported in subjects exposed to BUPRENORPHINE EXTENDED-RELEASE INJECTION in the pooled Phase 3 studies. In the Phase III double-blind study, these were observed for similar percentages of subjects across treatment groups (300/100 mg 35.0% and 300/300 mg 29.9% vs placebo 36.0%). There was no evidence that BUPRENORPHINE EXTENDED-RELEASE INJECTION induced withdrawal. Additionally, withdrawal signs and symptoms were not observed in the month following discontinuation of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Phase III studies: In the pooled Phase III studies, 32.2% of subjects had TEAEs potentially associated with opioid withdrawal signs and symptoms. The PT, Drug withdrawal syndrome, was reported in a total of 26 subjects (3.1%) overall. Other PTs for TEAEs potentially associated with opioid withdrawal signs and symptoms in at least 1.0% of subjects were the following: nausea (9.4%), insomnia (7.7%), vomiting (6.4%), anxiety (4.4%), arthralgia (2.6%), diarrhoea (2.0%), dizziness and hyperhidrosis (each 1.9%), decreased appetite (1.7%), hypertension and muscle spasms (each 1.5%), pruritus (1.2%), and depression and myalgia (each 1.1%). Phase II studies: In the MAD study, Drug withdrawal syndrome (PT) was reported in 14 subjects. Other PTs reported in > 1 subject in this study included the following: anxiety, vomiting, nausea, diarrhoea, insomnia, restlessness, tachycardia, dizziness and pyrexia. In the OB study, 59.0% of subjects had TEAEs potentially associated with opioid withdrawal signs and symptoms. Drug withdrawal syndrome was not reported as a TEAE in this study. Preferred terms for TEAEs potentially associated with opioid withdrawal signs and symptoms reported in > 1 subject in this study were the following: anxiety (30.8%), nausea (28.2%), vomiting (23.1%), diarrhoea (10.3%), and tachycardia and dizziness (each 5.1%). None of the TEAEs potentially associated with opioid withdrawal signs and symptoms in Phase II studies were serious. Phase I studies: In the pooled Phase I studies, 56.1% of subjects had TEAEs potentially associated with opioid withdrawal signs and symptoms. Drug withdrawal syndrome was reported for 19 subjects (17.8%). Other PTs for TEAEs potentially associated with opioid withdrawal signs and symptoms in at least 5.0% of subjects were the following: nausea (15.0%), diarrhoea (12.1%), vomiting (12.1%), insomnia (11.2%), yawning (9.3%), dizziness (8.4%), irritability and restlessness (each 6.5%), arthralgia and myalgia and

	rhinorrhoea (each 5.6%). None of the TEAEs potentially related to opioid withdrawal signs and symptoms in Phase I studies were reported as serious. During the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION, out of 22 reported pregnancies, there was 1 known report of neonatal drug withdrawal syndrome in a male neonate. All subjects were discontinued from the study upon notification of pregnancy.
Risk factors and risk groups	Chronic administration of buprenorphine produces dependence, characterised by withdrawal upon abrupt discontinuation or rapid taper.
Preventability	If BUPRENORPHINE EXTENDED-RELEASE INJECTION is discontinued, its extended-release characteristics should be considered and the patient should be monitored for several months for signs and symptoms of withdrawal and treated appropriately. NOWS is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorised or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognised and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly. Advise pregnant women receiving opioid addiction treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION of the risk of NOWS and ensure that appropriate treatment will be available. This risk should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance of management of opioid addiction throughout pregnancy. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of drug withdrawal syndrome, it is expected that the impact on the risk-benefit balance of BUPRENORPHINE EXTENDED-RELEASE INJECTION is low.
Public health impact	No negative public health impact is expected due to risk of withdrawal associated BUPRENORPHINE EXTENDED-RELEASE INJECTION use. The increasing incidence of neonatal abstinence syndrome accounts for 3% of admissions to neonatal intensive care units (NICUs) (Tolia 2015).

Table 14: Important Identified Risk: Misuse/Abuse (Risk Reduced by Use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV use, Extraction, Overdose

Potential mechanisms	Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. Scenarios in which BUPRENORPHINE EXTENDED-RELEASE INJECTION can be misused/abused. ≠ misuse/abuse of stolen drug ≠ extraction of buprenorphine and misuse/abuse of extracted buprenorphine ≠ misuse/abuse by healthcare professionals (e.g. physicians, nurses, technicians) or storage handling people ≠ misuse/abuse of residual buprenorphine in syringe (if not properly disposed)
Evidence source(s) and strength of evidence	Opioids are the most commonly abused type of prescription drug and appear to be the largest contributor of increases in the prevalence of prescription drug abuse in the USA (McHugh 2015). Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, postmarketing reports regarding coma and death involved misuse by self-injection by the intravenous route or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Intravenous injection presents significant risk of serious harm or death as BUPRENORPHINE EXTENDED-RELEASE INJECTION forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. The most frequently reported postmarketing adverse event observed with buprenorphine sublingual tablets was drug misuse or abuse.
Characterisation of risks	*Clinical trial programme:* Because BUPRENORPHINE EXTENDED-RELEASE INJECTION is required to be administered in a healthcare setting and is not made directly available to patients, its potential for misuse, abuse and diversion is minimised. Furthermore, no accounts of subjects removing or attempting to remove the depot after administration of BUPRENORPHINE EXTENDED-RELEASE INJECTION were reported in clinical studies.
Risk factors and risk groups	Risk factors associated with opioid abusers include 18-25-year olds, the male gender, patients with psychiatric disorders (including depression and bipolar

	disorder), exposure to violence and sexual abuse, a patient with a history of substance abuse, and a family history of substance abuse (Brady 2016).
Preventability	BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION and to monitor all patients for progression of opioid use disorder and addictive behaviours.
Impact on the risk-benefit balance of the product	With the risk minimisation measures in place for the risk of misuse/abuse, it is expected that the impact on the risk-benefit balance of BUPRENORPHINE EXTENDED-RELEASE INJECTION is low.
Public health impact	Opioid abuse is a major public health concern and is associated with a high level of morbidity and mortality in Europe (EMCDDA 2017). Since the prevalence of opioid abuse and misuse has increased globally, leading to an increase in deaths from overdose and individuals seeking treatment for opioid use disorders, a number of policy and educational initiatives have been implemented to help providers and patients, prescribe and use opioids more responsibly (Brady 2016). These include increasing access to effective treatments and harm reduction strategies including education, monitoring opioid cost and supply, strategic reimbursement for clinicians, and targeted research funding (Hawk 2015). The spread of blood borne viral infections and death due to respiratory depression constitute known public health problems posed by IV opioid abuse.

SVII.3.2. Presentation of the Missing Information

Missing Information: Use in Children/Adolescents (Less Than 18 Years Old)

The safety and effectiveness of BUPRENORPHINE EXTENDED-RELEASE INJECTION have not been established in paediatric patients. Children must be protected against exposure.

Missing Information: Use in Elderly Patients (Greater Than or Equal To 65 Years Old)

Clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects.

Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients, the decision to prescribe BUPRENORPHINE EXTENDED-RELEASE INJECTION should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose.

Part II: Module SVIII - Summary of the Safety Concerns

Table 15: Summary of Safety Concerns for BUPRENORPHINE EXTENDED-RELEASE INJECTION

Important identified risks	≠ CNS depression including respiratory depression/respiratory failure ≠ hepatitis, hepatic events, use in patients with hepatic impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation) ≠ local tolerability: injection site reactions ≠ drug withdrawal syndrome including neonatal withdrawal ≠ misuse/abuse (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV use, extraction, overdose
Missing information	≠ use in children/adolescents (< 18 years old) ≠ use in elderly patients (≥ 65 years old)

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance (PhV) includes review of information regarding adverse events reported with the use of BUPRENORPHINE EXTENDED-RELEASE INJECTION from individual case safety report (ICSR) review, signal detection, aggregate reports review, and literature reviews.

Table 16: Routine Pharmacovigilance Activities

CNS Depression (Including Respiratory Depression/Respiratory Failure)		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of CNS depression (including effects on driving ability and respiratory depression/respiratory failure) as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation)		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of hepatitis, hepatic events, use in patients with hepatic impairment as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Local Tolerability: Injection Site Reactions		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of injection site reactions/risks of injection administration as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events

Drug Withdrawal Syndrome Including Neonatal Withdrawal		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of drug withdrawal syndrome (including neonatal withdrawal) as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Misuse/Abuse (risk reduced by in use in BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV Use, Extraction, Overdose		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of misuse and/or abuse (e.g. IV use, extraction, overdose) as an important safety concern	Routine PhV	Monitor for a change in the nature, severity, or frequency of these events
Use in Children/Adolescents Less Than 18 Years Old		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of usage in paediatric patients (younger than 18 years old) as an important safety concern	Routine PhV	Monitor adverse events, detect, and evaluate signals among paediatric patients (younger than 18 years old) related to the use of BUPRENORPHINE EXTENDED-RELEASE INJECTION
Use in Elderly Patients (Greater Than or Equal to 65 Years Old)		
Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Ongoing monitoring of usage in elderly patients as an important safety concern	Routine PhV	Monitor adverse events, detect, and evaluate signals among the elderly population

Routine PhV activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for BUPRENORPHINE EXTENDED-RELEASE INJECTION

Appendix 4 includes special interest group questionnaires for the purpose to obtain additional, structured information. These questionnaires will facilitate the capture of clinically relevant and complete information at the time of the initial report.

Other forms of routine PhV activities for any safety concerns

No other forms of routine PhV activities are currently being conducted for any safety concerns for BUPRENORPHINE EXTENDED-RELEASE INJECTION.

III.2 Additional Pharmacovigilance Activities

There are no additional PhV activities planned to date to assess effectiveness of risk minimisation measures for BUPRENORPHINE EXTENDED-RELEASE INJECTION.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable

Part IV: Plans for Post-authorisation Efficacy Studies

There are currently no planned or ongoing post-authorisation efficacy studies for BUPRENORPHINE EXTENDED-RELEASE INJECTION that are conditions of the marketing authorisation or that are specific obligations.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table 17: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
CNS depression including respiratory depression/respiratory failure	Routine risk communication: Section 4.4 and 4.5 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION Company Core Data Sheet (CCDS) Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 recommends to warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Use BUPRENORPHINE EXTENDED-RELEASE INJECTION with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Section 4.5 Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments. Other routine risk minimisation measures beyond the Product Information: None
Hepatitis, hepatic events, use in patients with hepatic impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation)	Routine risk communication: Sections 4.2 and 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 recommends that patients who develop moderate to severe hepatic impairment while being treated with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. If signs and symptoms of toxicity or overdose occur within 2 weeks of BUPRENORPHINE EXTENDED-RELEASE INJECTION administration, removal of the depot may be required. Section 4.4 recommends that liver function tests, prior to initiation of treatment are recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. An aetiological evaluation is recommended when a

	hepatic adverse event is suspected. Patients with pre-existing severe hepatic impairment are not candidates for treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. *Use in patients with impaired hepatic function* In a pharmacokinetic study, the buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of BUPRENORPHINE EXTENDED-RELEASE INJECTION has not been studied. Because of the long-acting nature of the product, adjustments to dosages of BUPRENORPHINE EXTENDED-RELEASE INJECTION are not rapidly reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing severe hepatic impairment are not candidates for treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Patients who develop moderate to severe hepatic impairment while being treated with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Other routine risk minimisation measures beyond the Product Information: None
Local Tolerability: Injection Site Reactions	Routine risk communication: Section 4.2, 4.8 and Appendix A of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 states BUPRENORPHINE SUBCUTANEOUS INJECTION is for abdominal subcutaneous injection only and must NOT be administered intravenously or intramuscularly. BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be administered monthly with a minimum of 26 days between doses. Each injection should be administered only using the syringe and safety needle included with the product. Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot. Section 4.8: Injection site erythema, injection site pain and injection site pruritus occurred in ≥2% of subjects in Phase 3 clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Appendix A: Instructions for Use, gives healthcare providers detailed instructions on how to administer BUPRENORPHINE EXTENDED-RELEASE INJECTION, from removal from the refrigerator to instructing patients on the care of the injection site following healthcare provider administration. Other routine risk minimisation measures beyond the Product Information: None

Drug withdrawal syndrome (including neonatal withdrawal)	Routine risk communication: Section 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 states to advise pregnant women receiving opioid addiction treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION of the risk of NOWS and ensure that appropriate treatment will be available. This risk should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly. Withdrawal signs and symptoms were not observed in the month following discontinuation of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Considering the long half-life, any withdrawal signs and symptoms that may occur would be expected to be delayed. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 or 300 mg, respectively). Patients who elect to discontinue treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for several months for signs and symptoms of withdrawal and treated appropriately. Other routine risk minimisation measures beyond the Product Information: None
Misuse/Abuse (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV Use, Extraction, Overdose	Routine risk communication: Sections 4.2 and 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 states that BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot. Section 4.4 states Intravenous injection presents significant risk of serious harm or death as BUPRENORPHINE SUBCUTANEOUS INJECTION forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. Do not administer BUPRENORPHINE EXTENDED-RELEASE INJECTION intravenously or intramuscularly. Monitor all patients for progression of opioid use disorder and addictive behaviours. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION and to monitor all patients for progression of opioid use disorder and addictive behaviours.

	Other routine risk minimisation measures beyond the Product Information: None.
Use in Children/Adolescents (<18 years old)	Routine risk communication: Sections 4.2 and 4.6 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 states that the safety and effectiveness of BUPRENORPHINE EXTENDED-RELEASE INJECTION have not been established in paediatric patients. Section 4.6 states chronic exposure to buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Other routine risk minimisation measures beyond the Product Information: None
Use in Elderly Patients (≥ 65 years old)	Routine risk communication: Section 4.2 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 states that clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between geriatric and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients, the decision to prescribe BUPRENORPHINE EXTENDED-RELEASE INJECTION should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose. Other routine risk minimisation measures beyond the Product Information: None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of BUPRENORPHINE EXTENDED-RELEASE INJECTION.

V.3. Summary of Risk Minimisation Measures

Table 18: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
CNS depression (including respiratory depression/respiratory failure)	Routine risk minimisation measures: Section 4.4 and 4.5 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Hepatitis, hepatic events, use in patients with hepatic impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation)	Routine risk minimisation measures: Sections 4.2 and 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Local Tolerability: Injection Site Reactions	Routine risk minimisation measures: Section 4.2, 4.8 and Appendix A of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Drug withdrawal syndrome (including neonatal withdrawal)	Routine risk minimisation measures: Section 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Misuse/Abuse (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV Use, Extraction, Overdose	Routine risk minimisation measures: Sections 4.2 and 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities
Use in Children/Adolescents (<18 years old)	Routine risk minimisation measures: Sections 4.2 and 4.6 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS	Routine PhV activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: No additional risk minimisation measures	
Use in Elderly Patients (≥ 65 years old)	Routine risk minimisation measures: Section 4.2 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Additional risk minimisation measures: No additional risk minimisation measures	Routine PhV activities

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for BUPRENORPHINE EXTENDED-RELEASE INJECTION

This is a summary of the RMP for BUPRENORPHINE EXTENDED-RELEASE INJECTION. The RMP details important risks of BUPRENORPHINE EXTENDED-RELEASE INJECTION, how these risks can be minimised, and how more information will be obtained about the BUPRENORPHINE EXTENDED-RELEASE INJECTION risks and uncertainties (missing information).

The product information for BUPRENORPHINE EXTENDED-RELEASE INJECTION provides essential information to healthcare professionals and patients on how BUPRENORPHINE EXTENDED-RELEASE INJECTION must be used.

Important new concerns or changes to the current concerns will be included in updates of the BUPRENORPHINE EXTENDED-RELEASE INJECTION RMP.

I. The Medicine and What it is Used For

BUPRENORPHINE EXTENDED-RELEASE INJECTION is indicated for the treatment of moderate to severe opioid use disorder.

BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used as part of a complete treatment plan that includes counselling and psychosocial support.

BUPRENORPHINE EXTENDED-RELEASE INJECTION is given by a subcutaneous injection in the abdomen.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of BUPRENORPHINE EXTENDED-RELEASE INJECTION, with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- ≠ Specific information, such as warnings, precautions, and advice on correct use, in the product label addressed to patients and healthcare professionals.
- ≠ Inclusion of important advice on the medicine’s packaging.
- ≠ The authorised pack size and the amount of medicine in a pack is chosen to ensure that the medicine is used correctly.

≠ The medicine's legal status and the way a medicine is supplied to the patient (e.g. with or without prescription).

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of BUPRENORPHINE EXTENDED-RELEASE INJECTION is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of BUPRENORPHINE EXTENDED-RELEASE INJECTION are risks that need risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 19: List of Important Risks and Missing Information for BUPRENORPHINE EXTENDED-RELEASE INJECTION

Important identified risks	≠ CNS depression including respiratory depression/respiratory failure ≠ hepatitis, hepatic events, use in patients with hepatic impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term depot formulation) ≠ local tolerability: injection site reactions ≠ drug withdrawal syndrome including neonatal withdrawal ≠ misuse/abuse (risk reduced by use of BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV use, extraction, overdose
Missing information	≠ use in children/adolescents (<18 years old) ≠ use in elderly patients (≥ 65 years old)

II.B Summary of Important Risks

Table 20: Summary of Important Risks

CNS Depression (including respiratory depression/respiratory failure)	
Evidence for linking the risk to the medicine	Due to additive effects of CNS depressants, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death. Opioids can reduce respiration in a dose dependent manner. In non-clinical studies, buprenorphine caused mild respiratory depression, with slight, dose-related decreases in blood pH (~7.42-7.35) and pO_2 (~80-55 mmHg), and increased pCO_2 (~38-50 mmHg) in rats. These results confirmed the expected narcotic-like effects of buprenorphine on respiration. Additionally, non-clinical studies have shown that the combination of benzodiazepines and buprenorphine increased buprenorphine-induced respiratory depression. Respiratory depression has occurred during post-marketing surveillance. Death due to respiratory depression has been reported, particularly when buprenorphine was used in combination with benzodiazepines, or when buprenorphine was not used according to prescribing information.
Risk factors and risk groups	The risk for CNS depression is increased in patients who are on prescription medications for anxiety/depression and those with habitual alcohol intake. Risk factors for developing respiratory failure includes smoking tobacco products, excessive alcohol intake, a family history of respiratory disease or conditions, injury to the spine, brain, or chest, and immunocompromised patients (Macon 2017). Other risk factors include concomitant use of CNS depressants and respiratory illness.
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 recommends to warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Use BUPRENORPHINE EXTENDED-RELEASE INJECTION with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments.

	Additional risk minimisation measures: None
Hepatitis, Hepatic Events, Use in Patients with Hepatic Impairment (effects of this risk may be increased in BUPRENORPHINE EXTENDED-RELEASE INJECTION because of long-term deport formulation)	
Evidence for linking the risk to the medicine	Cases of acute hepatic injury have been reported in opioid dependent patients, both in clinical trials and in post-marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role. The effect of hepatic impairment on the pharmacokinetics of sublingual buprenorphine has been evaluated in a pharmacokinetic study. While no clinically significant changes have been observed in subjects with mild hepatic impairment, the plasma levels have been shown to be higher and half-life values have been shown to be longer for buprenorphine in subjects with moderate to severe hepatic impairment.
Risk factors and risk groups	Patients who are positive for viral hepatitis or having existing liver dysfunction are at greater risk of liver injury.
Risk minimisation measures	Routine risk minimisation measures Section 4.2 recommends that patients who develop moderate to severe hepatic impairment while being treated with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. If signs and symptoms of toxicity or overdose occur within 2 weeks of BUPRENORPHINE EXTENDED-RELEASE INJECTION administration, removal of the depot may be required. Section 4.4 recommends that liver function tests, prior to initiation of treatment are recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. An aetiological evaluation is recommended when a hepatic adverse event is suspected. Patients with pre-existing severe hepatic impairment are not candidates for treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. *Use in patients with impaired hepatic function* In a pharmacokinetic study, the buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of BUPRENORPHINE EXTENDED-RELEASE INJECTION has not been studied. Because of the long-acting nature of the product, adjustments to dosages of BUPRENORPHINE EXTENDED-RELEASE INJECTION are not rapidly

	reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing severe hepatic impairment are not candidates for treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Patients who develop moderate to severe hepatic impairment while being treated with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Additional risk minimisation measures: None
Local Tolerability: Injection Site Reactions	
Evidence for linking the risk to the medicine	Multiple Injection site reactions (e.g. induration, erythema, bruising, oedema, pruritus and local pain at the injection site) have been observed in clinical trials and non-clinical studies for BUPRENORPHINE EXTENDED-RELEASE INJECTION. For instance, BUPRENORPHINE EXTENDED-RELEASE INJECTION single-dose toxicity/TK studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION were conducted in rats and dogs (RBLS-R02-60-09 and RBLS-C01-60-09, respectively). As with the rats, the injection site reactions observed in the high dose dogs (ATRIGEL 285 mg/kg males/279 mg/kg females) and control dogs (ATRIGEL 362 mg/kg males/361 mg/kg females) included swelling, abrasion, reddening and raised areas or masses and correlated with increasing volume of the ATRIGEL. In RB-US-11-0020, Overall, 46 of 48 subjects (95.8%) reported a total of 320 injection site reactions. Most injection site reactions were assessed as mild in severity (34 subjects; 70.8%); however, 1 subject (2.1%) reported severe swelling at the injection site. Additionally, in a MAD study in opiate dependent subjects (RB-US-12-0005), 5 subjects experienced an injection site reaction of severe injection site pain. In an imaging study in opiate dependent subjects designed to determine the amount of opioid-blockade (RB-US-13-0002), 3 subjects experienced an injection site reaction of severe injection site tenderness.
Risk factors and risk groups	Currently, most SC injection volumes of therapeutic compounds that are greater than 1 mL have been associated with tolerability issues such as increased injection pain, high SC back pressure from the tissue site, site leakage, and injection-site reactions (Jorgensen 1996, Heise 2014). Risk factors for injection site reactions given subcutaneously include injecting the medicine in the same spot twice in a row (Case-Lo 2015).
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 states BUPRENORPHINE SUBCUTANEOUS INJECTION is for abdominal subcutaneous injection only and must NOT be administered intravenously or intramuscularly. BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be administered monthly with a minimum of 26 days between doses. Each injection should be administered only using the syringe and safety needle included with the product.

	Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot. Section 4.8: Injection site erythema, injection site pain and injection site pruritus occurred in ≥2% of subjects in Phase 3 clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Appendix A: Instructions for Use, gives healthcare providers detailed instructions on how to administer BUPRENORPHINE EXTENDED-RELEASE INJECTION, from removal from the refrigerator to instructing patients on the care of the injection site following healthcare provider administration. BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. Additional risk minimisation measures: None
Drug Withdrawal Syndrome including neonatal withdrawal	
Evidence for linking the risk to the medicine	Drug withdrawal syndrome was the most common AE reported in the clinical development programme for BUPRENORPHINE EXTENDED-RELEASE INJECTION; however, it was not considered related to BUPRENORPHINE EXTENDED-RELEASE INJECTION. Additionally, withdrawal signs and symptoms were not observed in the month following discontinuation of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Symptoms of opioid withdrawal (dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhoea, pupillary dilation, piloerection, or sweating, diarrhoea, yawning, fever, insomnia) may cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (DSM-V). NOWS is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorised or illicit. Neonatal withdrawal has been reported in infants of women treated with buprenorphine during pregnancy.
Risk factors and risk groups	Chronic administration of buprenorphine produces dependence, characterised by withdrawal upon abrupt discontinuation or rapid taper.
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 states to advise pregnant women receiving opioid addiction treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION of the risk of NOWS and ensure that appropriate treatment will be available. This risk should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly.

	Withdrawal signs and symptoms were not observed in the month following discontinuation of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Considering the long half-life, any withdrawal signs and symptoms that may occur would be expected to be delayed. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 or 300 mg, respectively). Patients who elect to discontinue treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for several months for signs and symptoms of withdrawal and treated appropriately. Additional risk minimisation measures: None
Misuse/Abuse (risk reduced by in use in BUPRENORPHINE EXTENDED-RELEASE INJECTION); IV use, extraction, overdose	
Evidence for linking the risk to the medicine	Opioids are the most commonly abused type of prescription drug and appear to the largest contributor of increases in the prevalence of prescription drug abuse in the US (McHugh 2015). Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, postmarketing reports regarding coma and death involved misuse by self-injection by the intravenous route or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Intravenous injection presents significant risk of serious harm or death as BUPRENORPHINE EXTENDED-RELEASE INJECTION forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. The most frequently reported postmarketing adverse event observed with buprenorphine sublingual tablets was drug misuse or abuse.
Risk factors and risk groups	Patients abusing buprenorphine, especially IV abusers, polysubstance abusers, combining the use of buprenorphine with alcohol, benzodiazepines, and other drugs, are at high risk for overdose and associated respiratory depression.
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 states that BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot.

	Section 4.4 states Intravenous injection presents significant risk of serious harm or death as BUPRENORPHINE SUBCUTANEOUS INJECTION forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. Do not administer BUPRENORPHINE EXTENDED-RELEASE INJECTION intravenously or intramuscularly. Monitor all patients for progression of opioid use disorder and addictive behaviours. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION and to monitor all patients for progression of opioid use disorder and addictive behaviours Additional risk minimisation measures: None
Use in Children/Adolescents (Less Than 18 Years Old)	
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 states that the safety and effectiveness of BUPRENORPHINE EXTENDED-RELEASE INJECTION have not been established in paediatric patients. Section 4.6 states chronic exposure to buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Additional risk minimisation measures: None
Use in Elderly (Patients Greater Than or Equal To 65 Years Old)	
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 states that clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between geriatric and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients, the decision to prescribe BUPRENORPHINE EXTENDED-RELEASE INJECTION should

	be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose. Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of BUPRENORPHINE EXTENDED-RELEASE INJECTION.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for BUPRENORPHINE EXTENDED-RELEASE INJECTION.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not Applicable

Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

Not applicable since there are no additional PhV activities proposed in Part III of this RMP.

Annex 3 – Protocols for Proposed, On-going and Completed Studies in the Pharmacovigilance Plan

Not applicable

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

SPECIAL INTEREST QUESTIONS FOR BUPRENORPHINE CONTAINING PRODUCT

CNS DEPRESSION

1. Please specify if the event started after or before the intake of product *[name of INDV product(s) or name of active ingredient(s)]*.

2. What were the signs and symptoms? (e.g. drowsiness, dizziness, blurred vision, impaired thinking, etc.)

3. Did the symptom(s) of CNS depression affect the ability to drive?

4. During treatment with product, has the patient/subject been involved in any road traffic accidents while driving?

5. When did the symptom(s) of CNS depression occur? Please provide start and stop dates.

6. How severe were the CNS depression symptoms (e.g. mild, moderate, or severe)?

7. Please specify the dosage, route of administration, frequency and strength of the product given to the patient/subject.

8. Was there a history of concomitant use of alcohol or other CNS depressants (e.g. benzodiazepines)? If so, please provide details, including indication and dosing information.

9. Please specify if the patient/subject has a past medical history or concurrent medical condition of any CNS disorders.

10. What treatment was received for the event of CNS depression and what was the outcome? Please provide the resolution date, if available.

11. Has product been taken since the event of CNS depression? If yes, did CNS depression reoccur?

12. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

RESPIRATORY DEPRESSION/RESPIRATORY FAILURE

1. Please specify if the event started after or before the intake of product *[name of INDV product(s) or name of active ingredient(s)]*.

2. What were the signs and symptoms? (e.g. inability to breathe, bluish coloration in the skin, restlessness, anxiety, confusion, altered consciousness, rapid shallow breathing, racing heart, profuse sweating, etc.)

3. When did the symptom of respiratory depression/respiratory failure occur? Please provide start and stop dates.

4. Please specify the dosage, route of administration, frequency and strength of the product given to the patient/subject.

5. Was there a history of breathing problems before the event (e.g. asthma, COPD or other respiratory diseases)?

6. Please specify if the patient/subject have any family history of any respiratory problem (e.g. asthma, COPD or other respiratory diseases)?

7. Was there a history of use of alcohol or other CNS depressants (e.g. benzodiazepines)? If so, please provide dosing information.

8. Was there an event of CNS depression?

9. What treatment was received for the event of respiratory depression/respiratory failure and what was the outcome? Please provide the resolution date.

10. Has product been taken since the event of respiratory depression/respiratory failure? If yes, did respiratory depression/respiratory failure reoccur?

11. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

OVERDOSES INVOLVING BENZODIAZEPINES AND/OR ALCOHOL

1. Please clarify what drug was overdosed. What were the symptoms of overdose? Does the patient/subject have symptoms of respiratory insufficiency?

2. Did the patient/subject have any prior episode of overdose?

3. What other drugs were being taken (prescription medications, street drugs, over the counter medications, herbal supplements, alcohol)? Please include name, indication for use, dose, frequency, start/stop date.

4. Were benzodiazepines and/or alcohol taken along with product *[name of INDV product(s) or name of active ingredient(s)]*?

5. Please provide product dosing information, including frequency and start/stop dates.

6. Was the patient/subject sent to the ER? Was he/she admitted to the hospital?

7. Was any treatment received? If so, please describe the treatment given.

8. Did the patient/subject recover and symptoms resolve? If so, please provide resolution dates. If the overdose was fatal, was an autopsy performed?

9. (ask only if fatal overdose) If an autopsy was performed, [please provide autopsy and toxicology findings (for HCP reporters)] or [may we request a copy of the autopsy report (for consumer reporters)].

10. Please provide any significant prior medical history.

11. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

FATAL OVERDOSE

1. Please specify if an autopsy was done. If yes, please provide autopsy results and toxicology report. If not, please provide possible primary cause of death.

2. Please specify if product *[name of INDV product(s) or name of active ingredient(s)]* was identified as being in the patient's/subject's system. If yes, please specify the dose and route of administration.

3. Was there a reported cause of death? If so, please provide.

4. Is there any evidence to suggest that the overdose was intentional or accidental? What were the circumstances surrounding the overdose (e.g. party, binging, suicidal intent)?

5. What were the symptoms of the fatal overdose? Was there severe respiratory insufficiency? Please describe the event.

6. Did the patient/subject have any prior episode of overdose?

7. Please provide relevant medical history (e.g. asthma, COPD, respiratory distress, etc.)? If so, please describe.

8. What other drugs were being taken (prescription medications, street drugs, over-the-counter medications, herbal supplements, alcohol)? Please include name, indication for use, dose, frequency, start/stop date?

9. Please specify if the patient/subject took benzodiazepines and/or consumed alcohol and/or any other CNS depressant along with product.

10. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

DRUG INTERACTIONS

1. Please specify the dosage, route of administration, frequency and strength of the product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

2. What type of drug interactions patient/subject experienced (e.g. drug-drug interaction, drug-food interactions, or drug interaction with some agent)?

3. Were any other medication(s) or agent started with product (concomitant medication). If yes, please provide dose and start/stop dates of concomitant medication(s).

4. What were the signs and symptoms of drug interactions?

5. How long was the duration between the administration of product and appearance of signs and symptoms of drug interactions?

6. How severe was drug interaction (e.g. mild, moderate, or severe)?

7. Does patient/subject experience any adverse event due to drug interactions. If yes, what were the signs and symptoms?

8. Does patient/subject experienced lack of drug effect due to drug interactions. If yes, please describe in detail.

9. Did patient/subject receive any treatment for drug interaction? If yes, please describe in detail.

10. Did this drug interactions result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

11. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

LACK OF DRUG EFFECT

1. Please specify the dosage, route of administration, frequency and strength of product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

2. What were the signs and symptoms indicating a lack of drug effect?

3. Has the patient/subject experienced lack of drug effect in past for this product?

4. Please specify if the patient/subject has any family history of lack of drug effect for this product?

5. Were any other medication(s) or agent started with this product (concomitant medication). If yes, please provide medication's dose and start/stop dates.

6. Did the event result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

7. What was the next step taken since the event of lack of drug effect? (e.g. informed as a quality compliant or switched to another product, etc.)

8. Has product been taken since the event of lack of drug effect? If yes, did lack of drug effect reoccur?

9. If a consumer reports, may we contact your physician? If yes, please provide name and contact information.

MISUSE/ABUSE

1. How is product *[name of INDV product(s) or name of active ingredient(s)]* being used (e.g. injection, intranasal, etc.) and for how long? What was it prescribed for?

2. If taking product not as prescribed (e.g. injection, intranasal, etc.), have there been any unfavorable side effects? If yes, what symptoms have been experienced?

3. How was product obtained (e.g. prescription, obtained from a friend, bought off the street)?

4. What dose of product was being used?

5. What other medications/substances have been used (e.g. alcohol, benzodiazepines, or other opioids such as methadone, oxycontin, vicodin, etc.)?

6. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

OFF-LABEL USE

1. Please specify the dosage, route of administration, frequency and strength of the product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

2. (**only if reported as "off label use"**) What was the type of off label use (unapproved indication, unapproved age group, unapproved dosage or dosing regimen, or unapproved route of administration)? Please explain.

3. Is the off label use of product still continuing?

4. Has/did the patient/subject experience any adverse event due to off label use? If yes, please describe in detail.

5. Did this off label use result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

6. Is the patient on any other medications or illicit drugs? If yes, please provide medication's dose and start/stop dates.

7. If a consumer reports, may we contact your physician? If yes, please provide name and contact information.

MEDICATION ERROR

1. Please specify the dosage, route of administration, frequency and strength of the product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

2. What type of medication error patient/subject experienced (e.g. related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, dispensing, distribution, or administration)?

3. Does patient/subject experience any adverse event due to medication error. If yes, what were the signs and symptoms?

4. Does patient/subject experienced lack of drug effect due to medication error. If yes, please describe in detail.

5. Were any other medication(s) or agent started with product (concomitant medication). If yes, please provide dose and start/stop dates of concomitant medication(s).

6. Did this medication error result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

7. What was the next step taken after the event of medication error?

8. If a consumer reports, may we contact your physician? If yes, please provide name and contact information.

INJECTION SITE REACTIONS AND INJECTION SITE INFECTION

1. What was the type of Injection site reactions (Injection site pain, Injection site erythema, Injection site pruritus, Injection site induration, Injection site reaction, Injection site discomfort, Injection site infection, Injection site hematoma, Injection site swelling, etc.)?

2. Please specify the dosage, route of administration, frequency and strength of the injection containing product *[name of INDV product(s) or name of active ingredient(s)]* given to the patient/subject.

3. What were the signs and symptoms of Injection site reactions?

4. How long was the duration between the administration of injection containing product and appearance of Injection site reactions?

5. How severe was Injection site reactions (e.g. mild, moderate, or severe)?

6. Does patient/subject experience any other adverse events along with Injection site reactions. If yes, what were they?

7. Does patient/subject have any past medical history of Injection site reactions from any injection administration?

8. Did patient/subject receive any treatment for Injection site reactions? If yes, please describe in detail.

9. Did this drug interactions result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

10. Was there any administration error observed during the time of administration?

11. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

HEPATIC EVENTS / DRUG RELATED HEPATIC DISORDERS

1. Were baseline liver function tests done prior to starting product *[name of INDV product(s) or name of active ingredient(s)]*? If yes, please provide results.

2. Did the hepatic enzymes increase after taking product? Please provide lab results (e.g. AST, ALT, ALP, total bilirubin, INR). If yes, on which day after the start on product were the increased enzymes detected?

3. Did the event result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

4. Please specify if the patient/subject underwent any additional relevant laboratory/diagnostic investigations. If yes, please specify the findings.

5. Is there a history of hepatitis (e.g. Hepatitis A, B or C, etc.), HIV infection, or any other viral infection? If so, please provide relevant medical history and/or relevant treatment/concomitant medications.

6. Please specify if the patient/subject consumed alcohol. If so, how much a day and for how long.

7. Please specify the dosage, route of administration, frequency and strength of product given to the patient/subject.

8. Was product stopped after hepatic enzymes increased? If yes, did the event resolve? If yes, please provide the date of resolution. What was the outcome?

9. Was product restarted after the event resolved? If yes, did the hepatic enzymes increase after the re-start of product?

10. Please specify if the patient/subject was taking any hepatotoxic drugs (e.g. acetaminophen, aspirin, NSAIDs, steroids, antibiotics, oral contraceptives, statins, herbal medicines, etc.) before the onset of hepatic event. If yes, please provide medication's dose and start/stop dates.

11. Please specify if the patient/subject underwent any relevant laboratory/diagnostic investigations. If yes, please specify the findings.

12. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

DRUG WITHDRAWAL SYNDROME

1. When did withdrawal begin?

2. Had there been a recent switch of medications (e.g. methadone to Suboxone tablet/film, Suboxone tablet to Suboxone film, Subutex to Suboxone tablet, Suboxone/Subutex to generic Suboxone, etc.)?

3. Was there a change in dosing (e.g. 16 mg to 24 mg)? If yes, please provide start and stop dates. How long after change in dosing did the withdrawal symptoms start?

4. When did withdrawal symptoms occur? (e.g. within 6 hours, or within 24 hours, etc.). Please provide start and stop dates.

5. Was medical attention or treatment received for the withdrawal? If yes, describe.

6. Have withdrawal symptoms been experienced before?

7. Have withdrawal symptoms resolved? If yes, please provide stop date.

8. How severe were the withdrawal symptoms (e.g. mild, moderate, or severe)?

9. Does patient/subject believe the withdrawal symptoms were caused by product?

10. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

NEONATAL WITHDRAWAL *(topic is specific for buprenorphine containing products)*

1. What medications were taken during the pregnancy? Please include name, dose, frequency and indication used for.

2. When was product *[name of INDV product(s) or name of active ingredient(s)]*?

3. Did the mother have a recent switch of medications (e.g. methadone to Suboxone tablet/film, Suboxone tablet to Suboxone film, Subutex to Suboxone tablet, Suboxone/Subutex to generic Suboxone, etc.)?

4. What were the signs and symptoms of neonatal withdrawal (agitation, apnoea, blood pressure increased, bradycardia, convulsion, crying, dehydration, diarrhoea)?

5. Was there a change in dosing (e.g. 16 mg to 24 mg)? If yes, please provide start date of new dosage and stop date of previous dosage.

6. When was the neonate diagnosed with withdrawal? Was diagnosis made by a physician?

7. How severe were the withdrawal symptoms (e.g. mild, moderate, severe)?

8. Was treatment received for withdrawal? If so, please provide name, dose, start/stop dates of treatment.

9. How long was the baby in the hospital due to withdrawal?

10. Did all of the symptoms resolve prior to discharge?

11. Is the baby feeding well and meeting growth and development milestones?

12. If a consumer report, may we contact your physician and/or pediatrician? If yes, please provide name and contact information.

PEDIATRIC ACCIDENTAL EXPOSURE / PEDIATRIC INTOXICATION

1. How old was the child exposed to product *[name of INDV product(s) or name of active ingredient(s)]*?

2. Please specify the dosage, route of administration, frequency and strength of the product child was exposed to.

3. What signs and symptoms did the child experience and for how long?

4. Was a physician seen? Was treatment received? If so, provide treatment details.

5. Did the child require lifesaving equipment for the treatment of intoxication?

6. Was the child hospitalized? If so, please provide dates of hospitalization and discharge.

7. Did the child recover? If so please provide the resolution date along with treatment received and outcome.

8. Was there any additional drug along with product child exposed to? If yes, please provide the dosage, route of administration, frequency and strength.

9. How many times was the child exposed?

10. Does the child still have any symptoms now?

11. How is the child overall growing and meeting all milestones?

12. If a consumer report, may we contact the child's physician/pediatrician? If yes, please provide name and contact information.

ELDERLY POPULATION

1. Please specify the event(s) the patient/subject experienced at the time of reporting.

2. Please specify if the patient/subject presented with the event(s) prior to starting product *[name of INDV product(s) or name of active ingredient(s)]*.

3. Please specify if the event(s) worsened since starting product.

4. Please specify if the patient/subject has any history of psychiatric illness/medical illness (diabetes, hypertension etc.), hospitalizations, operations, drug use etc. If yes, please specify the illness, duration and if it is still ongoing/recovered.

5. Please specify the dosage, route of administration, frequency and strength of the product given to the patient/subject.

6. Please specify if the patient/subject has a history of tobacco use i.e. chewing/smoking etc. If yes, please specify on an average how many cigarettes are smoked each day/week or how many times tobacco is chewed each day/week.

7. Please specify if the patient/subject consumes alcohol. If yes, for how long and how much per day?

8. Please specify if the patient/subject had a history of use of drugs such as cocaine, cannabis, LSD, amphetamine, etc.

9. Please specify the treatment or any other concomitant medication(s) that the patient/subject was taking. Please specify the start date, stop date and action taken.

10. Did the patient/subject stop taking product? If yes, please specify if the patient's/subject's condition improved after stopping the drug.

11. Please specify if the patient/subject underwent any relevant laboratory/diagnostic investigations. If yes, please specify the findings.

12. Please specify final outcome of the event(s) (e.g. completely recovered, condition improving, not recovered, etc.)

13. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

TRANSMISSION OF AN INFECTIOUS AGENT VIA PRODUCT

1. Please specify if the event started after or before the intake of product *[name of INDV product(s) or name of active ingredient(s)]*. Please provide start and stop dates of event. If unable to provide the start and stop date, then describe the duration between start of medication and occurrence of event (days/weeks/months/years).

2. Please specify the dosage, route of administration, frequency and strength of the product given to the patient/subject.

3. What treatment was received for this event? Please provide the outcome of the event. If the patient/subject completely recovered, please specify the resolution date.

4. What were the signs and symptoms? How severe were the symptoms (e.g. mild, moderate, or severe)?

5. Was there any medication error reported for product? Describe the type of medication error (e.g. change in color, change in texture, packaging, dispensing, distribution, or administration).

6. Please provide the LOT number and/or batch number of the product *[name of INDV product]*.

7. Please provide the action taken to the product *[name of INDV product]*.

8. Please provide detailed information about the infection. Was it systemic or localized (e.g. Injection site infection)? Please specify if the patient/subject underwent any relevant laboratory/diagnostic investigations. If yes, please specify the findings.

9. Did the event result in an ER visit or hospitalization? If yes, what was the duration of hospitalization?

10. If a consumer report, may we contact your physician? If yes, please provide name and contact information.

Annex 5 - Protocols for Proposed and On-going Studies in RMP Part IV

Not applicable

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable

Annex 7 – Summary of Changes to the Risk Management Plan Over Time

Not applicable, as this is the first RMP for BUPRENORPHINE EXTENDED-RELEASE INJECTION.

Annex 9 – Other Supporting Data (Including Referenced Material)

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SUBLOCADE

Australian Specific Annex
to the
EU Risk Management Plan

March 2019
Version 2.1

Indivior Pty Ltd
78 Waterloo Rd
Macquarie Park NSW 2113

Contents

Australian-Specific Annex

1. Introduction

1.1. Purpose of Australian Specific Annex for this Risk Management Plan

This Australian Specific Annex (ASA) was written in accordance with the format recommended in the TGA guideline *Risk Management Plans for medicines and biologics* version 3.1 dated November 2017.

It is an annex to the *EU Risk Management Plan for Buprenorphine Extended Release injection* version 1.0 dated 12 March 2018. This EU-RMP was written in accordance with the EU *Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2).*

This ASA was prepared for TGA to:

- discuss the relevance to the Australian market of the content of the EU Risk Management Plan (EU-RMP), and
- describe the additional steps taken in Australia to identify and minimise the safety risks associated with this treatment.

1.2. Registration history

Buprenorphine for the treatment of opioid dependence has been available in Australia both in single component products (Subutex tablets) and in combination with naloxone (Suboxone) as sublingual tablets and film since 2000.

The current ASA refers to a new dosage form of buprenorphine (extended release injection, tradename SUBLOCADE) to be administered as a once-monthly injection. The product is being registered in dosage strengths of 100 mg and 300 mg as a major variation (new dosage form/new strength) to the Subutex registration with which it will share identical indications for use:

> *Treatment of opioid dependence, within a framework of medical, social and psychological treatment.*

The regulatory status of SUBLOCADE in other countries is described in the table on the following page.

Country	Regulatory Status	Date	Indications
U.S.A.	Approved	30/11/2017	Treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days. SUBLOCADE should be used as part of a complete treatment plan that includes counseling and psychosocial support.
Canada	Approved	21/11/2018	Treatment of moderate to severe opioid use disorder in adults. SUBLOCADE should be used as part of a complete treatment plan that includes counselling and psychosocial support.
EU (DCP for FR, BE, PT, CZ, LU, LV, LI and CY)	Evaluation ongoing	08/11/2018	Treatment of opioid addiction, within a comprehensive therapeutic monitoring framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents 15 years of age and older, who have agreed to be treated for opioid addiction.
National submissions in UK, DE, SE, DK, NO, FI, IT.	Evaluation ongoing	14/11/2018 - 27/11/2018	Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

1.3. History of RMPs submitted in Australia

No previous RMPs/ASAs have been submitted in Australia for SUBLOCADE extended release injection for monthly administration.

Indivior Pty Ltd has submitted RMPs for its sublingual buprenorphine only and buprenorphine + naloxone combination products for the treatment of opioid addiction, the latest version of which is dated April 2018.

For the EU, a specific RMP addressing the monthly buprenorphine injection (Buprenorphine Extended Release Injection) has been created and is included in the submission application.

1.4. Epidemiology of the population to be treated in Australia

Part II, Mod. S.1 Epidemiology of the Indication and Target Population is identical in the EU-RMP and in this ASA.

Note that only incidence and prevalence rates of treated population are available due to the nature of opioid dependence which makes it difficult to estimate the true incidence and prevalence of the condition, including non-treated opioid dependent persons.

The EU-RMP indicates that the Australian population is moving towards a prescription opioid problem and is consistent with trends seen in other countries (Blanch 2014). In 2016, 0.2% of the population over 14 years of age reported using heroin in the past 12 months while 3.6% misused opioid pharmaceuticals. (NDSHS 2016). Fentanyl use has increased since 2000; however, adjusted mortality rates (per million DDD prescribed) remain lower relative to other opioids such as oxycodone (Berecki-Gisolf 2017).

In the 5 years between 2011 and 2015, 3,601 people died from overdose due to an opioid. This represents a 1.6-fold increase compared with the 5 years 2001-2005. Accidental death from pharmaceutical opioids was responsible for most opioid-related deaths between 2011 and 2015. The rate of accidental deaths due to opioids per capita is 7.3 deaths per 100,000 in rural areas and 5.8 per 100,000 in metropolitan areas. (Penington Institute 2017).

In 2016, the number of opiate replacement therapy (ORT) patients doubled (48,900 people) compared to 1998 (24,657 people). The growth was approximately 5% each year between 1998 and 2010 and an overall 6% over 6 years from 2010 (NOPSAD 2016). In June 2016, the number of ORT patients in the general population was 2.0 clients per 1,000 people. In 1998, the rate was 1.3 and increased to 2.1 in 2010, then remained at this level until dropping to 2.0 in 2015 (NOPSAD 2016).

Of the 48,900 clients who received pharmacotherapy treatment in June 2016, close to two-thirds (64%) were male. The median age of clients across all drug types was 42 years, with the majority (68%) being aged between 30 and 49 years. Almost one in ten clients (9%) was identified as Indigenous.

2. Pharmacovigilance plan

2.1. Pharmacovigilance organisation in Australia

Indivior Pty Ltd follows Indivior UK Ltd global pharmacovigilance systems for the management of adverse events arising from Australia as well as those arising from anywhere around the world.

It complies with the TGA guideline Pharmacovigilance responsibilities of medicine sponsors - Australian recommendations and requirements, v2, September 2017.

2.2. Routine pharmacovigilance activities

In Part III.1, the EU-RMP states "Routine pharmacovigilance includes review of information about adverse events with the use of RBP-6000 and SUBUTEX from ICSR review, signal detection, aggregate reports review, and literature reviews".

Indivior Pty Ltd follows Indivior UK Ltd global pharmacovigilance systems for the management of adverse events arising from Australia as well as those arising from anywhere around the world. It complies with the Australian recommendations and requirements and includes:

- Systems and processes to ensure that information regarding individual case safety reports and other safety related information (including overdose, prescription or medication error, abuse/misuse, lack of efficacy, unexpected benefit and transmission of an infectious agent via a medicinal product, possible interactions and use during pregnancy or lactation) and serious adverse events from clinical trials is collected and collated in an accessible manner.
- Preparation of reports for regulatory authorities including expedited adverse drug reaction reports, Development Safety Update Reports, Periodic Safety Update Reports and Risk Management Plans.
- Continuous monitoring of the safety profile of a medicinal product throughout its life including literature searches, signal detection, issue evaluation and escalation, labelling activities, and liaison with regulatory authorities.

2.3. Pharmacovigilance activities for safety concerns specific to Australia

No specific safety concerns are foreseen for Australia in addition to those identified in the EU-RMP, hence pharmacovigilance activities specifically tailored to Australia are not deemed necessary.

Routine pharmacovigilance activities listed in Part V.3 of the EU-RMP will be applied to Australia.

2.4. Studies referenced in the pharmacovigilance plan of the RMP

No specific pharmacovigilance activities / studies are planned in the EU-RMP.

3. Risk minimisation plan

3.1. How risk minimisation activities will be implemented in Australia.

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
CNS Depression including respiratory depression / respiratory failure	**Routine activities** Routine risk communication: Section 4.4 and 4.5 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION Company Core Data Sheet (CCDS) Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 recommends to warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Use BUPRENORPHINE EXTENDED-RELEASE INJECTION with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Section 4.5 Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In	**Routine activities** Routine risk communication: Section 4.4 and 4.5 of the SUBLOCADE Product Information (PI) Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.4:* Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBLOCADE. SUBLOCADE should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression or kyphoscoliosis). *Section 4.5:* Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or	Education material

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	others, gradually tapering a patient off a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments. **Additional activities** None	decreasing to the lowest effective dose may be appropriate. Similarly, cessation of other CNS depressants is preferred when possible. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments **Additional activities** Education material	
Hepatitis, hepatic events, use in patients with hepatic impairment	**Routine activities** Routine risk communication: Sections 4.2 and 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 recommends that patients who develop moderate to severe hepatic impairment while being treated with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. If signs and symptoms of toxicity or overdose occur within 2 weeks of BUPRENORPHINE	**Routine activities** Routine risk communication: Section 4.4 of the SUBLOCADE PI Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.4, Hepatitis, hepatic events:* Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicines (see section 4.5 Interactions) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. A biological and etiological	Education material

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	EXTENDED-RELEASE INJECTION administration, removal of the depot may be required. Section 4.4 recommends that liver function tests, prior to initiation of treatment are recommended to establish a baseline. Periodic monitoring of liver function during treatment, is also recommended. An etiological evaluation is recommended when a hepatic adverse event is suspected. Patients with pre-existing severe hepatic impairment are not candidates for treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. *Use in patients with impaired hepatic function* In a pharmacokinetic study, the buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of BUPRENORPHINE EXTENDED RELEASE INJECTION has not been studied. Because of the long-acting nature of the product, adjustments to dosages of BUPRENORPHINE EXTENDED-RELEASE INJECTION are not rapidly reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, patients with	evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicine may be discontinued. If treatment is continued, hepatic function should be monitored closely. *Section 4.4, Use in hepatic impairment:* In a pharmacokinetic study with transmucosal buprenorphine, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of SUBLOCADE has not been studied. Because of the long-acting nature of the product, adjustments to dosages of SUBLOCADE are not rapidly reflected in plasma buprenorphine levels. Because buprenorphine levels cannot be rapidly decreased, patients with pre-existing severe hepatic impairment are not candidates for treatment with SUBLOCADE. Patients who develop moderate to severe hepatic impairment while being treated with SUBLOCADE should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.	

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	pre-existing severe hepatic impairment are not candidates for treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION. Patients who develop moderate to severe hepatic impairment while being treated with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. **Additional activities** None.	**Additional activities** Education material	
Local Tolerability: Injection Site Reactions	**Routine activities** Routine risk communication: Section 4.2, 4.8 and Appendix A of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 states BUPRENORPHINE SUBCUTANEOUS INJECTION is for abdominal subcutaneous injection only and must NOT be administered intravenously or intramuscularly. BUPRENORPHINE EXTENDED RELEASE INJECTION should only be prepared and administered by a healthcare provider. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be administered monthly with	**Routine activities** Routine risk communication: Section 4.2 and 4.8 of the SUBLOCADE PI Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2: SUBLOCADE is for abdominal subcutaneous injection only and must NOT be administered intravenously or intramuscularly. Only healthcare providers should prepare and administer SUBLOCADE. Administer SUBLOCADE monthly with a minimum of 26 days between doses. Administer each injection only using the syringe and safety needle included with the product	Education material

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	a minimum of 26 days between doses. Each injection should be administered only using the syringe and safety needle included with the product. Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot. Section 4.8: Injection site erythema, injection site pain and injection site pruritus occurred in ≥2% of subjects in Phase 3 clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Appendix A: Instructions for Use, gives healthcare providers detailed instructions on how to administer BUPRENORPHINE EXTENDED-RELEASE INJECTION, from removal from the refrigerator to instructing patients on the care of the injection site following healthcare provider administration. **Additional activities** None.	Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot. Section 4.8: Injection site erythema, injection site pain and injection site pruritus occurred in ≥2% of subjects in Phase 3 clinical studies of SUBLOCADE. Section 4.2: Instructions for Use, gives healthcare providers detailed instructions on how to administer SUBLOCADE, from removal from the refrigerator to instructing patients on the care of the injection site following healthcare provider administration. **Additional activities** Education material	
Drug withdrawal syndrome (including neonatal withdrawal)	**Routine activities** Routine risk communication: Section 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS	**Routine activities** Routine risk communication: Section 4.4 of the SUBLOCADE PI Routine risk minimisation activities recommending	Education material

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 states to advise pregnant women receiving opioid addiction treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION of the risk of NOWS and ensure that appropriate treatment will be available. This risk should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly. Withdrawal signs and symptoms were not observed in the month following discontinuation of BUPRENORPHINE EXTENDED-RELEASE INJECTION. Considering the long half-life, any withdrawal signs and symptoms that may occur would be expected to be delayed. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 or 300 mg, respectively). Patients who elect to discontinue treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION should be monitored for several months for signs and	specific clinical measures to address the risk: *Section 4.4 Neonatal abstinence syndrome:* Advise pregnant women receiving opioid addiction treatment with SUBLOCADE of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. This risk should be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance of management of opioid addiction throughout pregnancy. *Section 4.4 Opioid withdrawal effects*: Withdrawal signs and symptoms were not observed in the month following discontinuation of SUBLOCADE. Considering the long half-life, any withdrawal signs and symptoms that may occur would be expected to be delayed. Model simulations indicate that steady-state buprenorphine plasma concentrations decreased slowly over time following the last injection and remained at therapeutic levels for 2 to 5 months on average, depending on the dosage administered (100 or 300 mg, respectively). Patients who elect to discontinue treatment with SUBLOCADE should be monitored for withdrawal signs and symptoms. Consider transmucosal buprenorphine if needed to	

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	symptoms of withdrawal and treated appropriately. **Additional activities** None.	treat withdrawal after discontinuing SUBLOCADE. **Additional activities** Education material	
Misuse/Abuse	**Routine activities** <u>Routine risk communication:</u> Sections 4.2 and 4.4 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Section 4.2 states that BUPRENORPHINE EXTENDED-RELEASE INJECTION should only be prepared and administered by a healthcare provider. Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot. Section 4.4 states Intravenous injection presents significant risk of serious harm or death as BUPRENORPHINE SUBCUTANEOUS INJECTION forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thromboembolic events, including life threatening pulmonary emboli, could result if administered intravenously. Do not administer	**Routine activities** <u>Routine risk communication:</u> Black box warning in PI and CMI. Sections 4.2 and 4.4 of the SUBLOCADE PI: <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> *Black box warning:* RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously. (see section 4.4). *Section 4.2:* Only healthcare providers should prepare and administer SUBLOCADE. Periodic assessment is necessary to determine effectiveness of the treatment plan and overall patient progress. When evaluating the patient, examine the injection site for signs of infection or evidence of tampering or attempts to remove the depot. *Section 4.4 Risk of serious harm or death with*	Additional activities for Australia: i) Limitation of supply in the first 6 months. ii) Educational program. iii) Activities with State Health Regulators.

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	BUPRENORPHINE EXTENDED RELEASE INJECTION intravenously or intramuscularly. Monitor all patients for progression of opioid use disorder and addictive behaviours. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with BUPRENORPHINE EXTENDED-RELEASE INJECTION and to monitor all patients for progression of opioid use disorder and addictive behaviours. **Additional activities** None.	*intravenous administration:* Intravenous injection presents significant risk of serious harm or death as SUBLOCADE forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. Do not administer intravenously or intramuscularly. *Section 4.4 Risk of Respiratory/CNS depression:* Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBLOCADE. *Section 4.4 Misuse, Abuse and diversion:* To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and patient follow-up visits with clinical monitoring appropriate to the patient's level of stability should be conducted. **Additional activities** Limitation of supply in the first 6 months of supply to prescribers familiar with MATOD#. Educational program. Activities with State Health Regulators.	
Overdose	**Routine activities** Routine risk communication: Section 4.9 of the BUPRENORPHINE	**Routine activities** Routine risk communication: Section 4.9 of the SUBLOCADE PI.	Education material

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.9 states that in the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be considered as indicated. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary. Clinicians should consider the potential role and contribution of buprenorphine, other opioids, and other CNS depressant drugs in a patient's clinical presentation. Clinical data are limited with regards to the possible surgical removal of the depot. Two cases of surgical removal were reported in premarketing clinical studies.	Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.9:* The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus. In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation following standard intensive care measures. The patient should be transferred to an environment within which full resuscitation facilities are available. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose. The long duration of action of buprenorphine should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. Ongoing IV	

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
		infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required. Clinical data are limited with regards to the possible surgical removal of the depot as only two cases of surgical removal were reported in premarketing clinical studies. **Additional activities** Education material	
Use in pregnancy and lactation	**Routine activities** <u>Routine risk communication:</u> Section 4.6 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Section 4.6 states chronic exposure to buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used during pregnancy only if the	**Routine activities** <u>Routine risk communication:</u> Section 4.6 of the SUBLOCADE PI <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> *Section 4.6:* Buprenorphine readily crosses the placental barrier and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory	Education Material

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	potential benefit justifies the potential risk to the foetus. *Breast-feeding*: Buprenorphine and its metabolites are excreted in human breast milk. Caution should be exercised when BUPRENORPHINE (ER) SUBCUTANEOUS INJECTION is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BUPRENORPHINE (ER) SUBCUTANEOUS INJECTION and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Advise breastfeeding women taking buprenorphine products to monitor the infant for increased drowsiness and breathing difficulties. **Additional activities** None.	depression or withdrawal syndrome in neonates. Data on the use of buprenorphine in pregnancy, and its impact on the mother and foetus, are limited. Data from randomised, controlled trials and observational studies do not indicate an increased risk of maternal or foetal adverse outcomes compared to methadone. *Use in lactation* Because buprenorphine passes into the mother's milk, the development and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBLOCADE and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. **Additional activities** Education Material	
Use in Children/Adolescents <18 years old	**Routine activities** <u>Routine risk communication:</u> Sections 4.2 and 4.6 of the BUPRENORPHINE EXTENDED-RELEASE INJECTION CCDS <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Section 4.2 states that the safety and effectiveness of BUPRENORPHINE EXTENDED-RELEASE INJECTION have not been	**Routine activities** <u>Routine risk communication:</u> Sections 4.2 and 4.6 of the SUBLOCADE PI <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> *Section 4.4 Paediatric use:* SUBLOCADE is not recommended for use in children. The safety and effectiveness of SUBLOCADE in subjects below the age of 18 has not been established. Due to	-----

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	established in paediatric patients. Section 4.6 states chronic exposure to buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates. BUPRENORPHINE EXTENDED-RELEASE INJECTION should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. **Additional activities** None.	lack of data, patients below the age of 18 should be closely monitored during treatment. *Section 4.6:* Buprenorphine readily crosses the placental barrier and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates. Data on the use of buprenorphine in pregnancy, and its impact on the mother and foetus, are limited. Data from randomised, controlled trials and observational studies do not indicate an increased risk of maternal or foetal adverse outcomes compared to methadone. **Additional activities** None.	
Use in Elderly Patients (≥ 65 years old)	**Routine activities** Routine risk communication: Section 4.2 of the BUPRENORPHINE	**Routine activities** Routine risk communication: Section 4.4 of the SUBLOCADE PI. Routine risk minimisation	-----

Safety Concerns or Missing information	Risk Minimisation activities (routine and additional) proposed in the EU-RMP	Risk minimisation activities (routine and additional) proposed for Australia	Difference between EU and Australian activities with justification
	EXTENDED-RELEASE INJECTION CCDS Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 states that clinical studies of BUPRENORPHINE EXTENDED-RELEASE INJECTION did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between geriatric and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients, the decision to prescribe BUPRENORPHINE EXTENDED-RELEASE INJECTION should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose. **Additional activities** None.	activities recommending specific clinical measures to address the risk: *Section 4.4 Use in the elderly* The safety and efficacy of buprenorphine in elderly patients over 65 years have not been established. **Additional activities** None.	

MATOD – medication assisted treatment of opioid dependence

To manage the safety concerns of SUBLOCADE routine risk minimisation activities as described in Part V.1 of the EU-RMP will be applied in Australia and will be supplemented with local activities as described below.

Educational activities

Information about the safety risks identified is included in the Product Information (PI) and Consumer Medicine Information (CMI) which the Company will make available to

healthcare professionals (HCPs) and patients respectively, both as per regulatory obligations such as the publication of PIs on the TGA website, and through proactive publication in reference manuals such as MIMS, prescribing software and the electronic distribution of the CMI.

All of Indivior's educational activities are conducted in compliance with the principles of the current Edition of the Medicines Australia Code of Conduct, which promotes responsible promotion of medicines through, amongst other means, disclosing full PI to HCPs. The PI includes information and warning about the ongoing safety concerns identified above.

This Risk Minimisation Plan for Australia therefore covers the following three audiences receiving targeted information:

- Physicians, pharmacists and other HCPs
- Patients
- Controls over SUBLOCADE distribution (State regulators)

Educational Material for Healthcare Professionals

Indivior currently supplies materials for the education of HCPs covering the areas of pharmacology, adverse effects, interactions and contraindications to ensure understanding of its current sublingual buprenorphine and buprenorphine + naloxone products. These materials have been provided to TGA with the Buprenorphine ASA and are not provided again since not specifically relevant to SUBLOCADE.

For SUBLOCADE specifically, Indivior will provide HCPs with detailed educational materials on the Instructions for Use to ensure correct administration of the product. A copy of the draft SUBLOCADE Instructions for Use is provided in Att. 1. Indivior will also provide information regarding the distribution and storage requirements. The Patient Booklet will be provided to Healthcare professionals.

The educational materials mentioned above will be provided in hardcopy and on a health care professional website (www.turntohelp.com.au). Indivior field medical staff and medical representatives will facilitate access to and understanding of education materials. During the initial restricted access scheme, health care professionals will be invited to complete a form acknowledging review of materials and understanding of key risks.

Educational Material for Patients

Indivior will produce a product-specific patient information brochure designed to be given by prescribers to patients who have been prescribed SUBLOCADE. This brochure will cover information about the safety concerns identified. It will also encourage patients to report adverse experiences and drug misuse to HCPs.

A draft proposed version of the product-specific patient information brochure is provided in Att. 2.

Legal status of buprenorphine and controls over its distribution

Buprenorphine is listed in Schedule 8 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSMP), hence it is treated as a Controlled Drug – "Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence".

As such, it is labeled with the following warnings which reduce its risk of diversion and misuse:

- Controlled Drug
- Possession without authority is illegal

- Keep out of reach of children

Relevant regulations in most circumstances require that it is prescribed only by physicians who are accredited by relevant State Health Authorities.

Its importation into and distribution within Australia is authorised and monitored by the Drug Control Section of the Therapeutic Goods Administration at three levels:

- Import licences (Regulation 5 of the Customs (Prohibited Imports) Regulations 1956) indicating the amount to be imported for the year and that Indivior must obtain annually;
- Import permits for each batch to be imported into Australia must be obtained by Indivior
- Weekly reporting of drug movements at each step of the supply chain by wholesalers, by distributors and by pharmacies.

Controls over SUBLOCADE distribution

a) State Regulators

In view of the risk of incorrect administration and possible diversion/misuse of the product, Indivior recommends that SUBLOCADE should not be made available to patients directly but only to HCPs who will administer the product to patients.

This recommendation requires a change to the current accessibility scheme to ensure the distribution system will allow managed supply. To this purpose, Indivior has contacted each State Health Regulator for a change in requirements and creation of an appropriate regulatory policy framework. Meetings with state health departments were requested and to date have taken place in Victoria, South Australia, Queensland, New South Wales and Northern Territory.

Noting that the development of state regulations can be a long process, Indivior will proactively initiate a program of restricted access to ensure appropriate systems are in place at the time of SUBLOCADE approval. This program will address the aspects of restricted access as detailed below.

b) Restricted access plan for first 6 months of supply

i) Identification of prescribers

In view of the identified risks, Indivior proposes a restricted access scheme to limit supply in the first 6 months only to prescribers familiar with administration of medication assisted treatment for opioid dependence (MATOD).

Supply of SUBLOCADE therefore will be restricted to:

- A member of The Chapter of Addiction Medicine (AChAM) - a Chapter of the Royal Australasian College of Physicians (RACP); or
- A member of The Faculty of Addiction Psychiatry (FAP) – a RANZCP group; or
- Prescribers who have completed an accreditation course administered by State/Territory governments and prescribe MATOD to 50 or more patients.

This restriction will ensure that all prescribers are suitably experienced and specialised in the treatment of opioid dependence. Given logistic challenges and state requirements on security and drug accountability, the actual number of administration sites is likely to be low within the private sector. It is anticipated that

government clinics, a proportion of private clinics and 20-40 private medical practices will offer administration services.

To ensure that the product is managed within a setting where awareness of appropriate patient and product management can be reasonably assured, it is further proposed that the location of the prescriber be restricted to:

- Sites associated with public or private hospitals; or
- Sites with sole or dual private prescriber practices where at least one prescriber meets eligibility criteria; or multiple prescriber practices with 2 or more prescribers operating from the prescribing location meet the eligibility criteria

ii) Eligibility criteria for use of SUBLOCADE

To be eligible to prescribe SUBLOCADE, healthcare professionals will need to review education materials and complete a form acknowledging review of materials, understanding of key risks and the restricted access supply scheme. The record of completion form will be maintained in a database suitable for administration of the distribution process.

Educational materials will be available in hardcopy and on an Indivior managed website for health care professional education. Indivior field medical staff and medical representatives will facilitate access to and understanding of educational materials.

Prescribers who have met eligibility criteria and completed the record of educational material review will be approved to order stock of SUBLOCADE for delivery to sites meeting the location eligibility criteria.

Pharmacies who are accredited with state health departments to dispense MATOD and have completed the record of education material review will also be eligible to order stock of SUBLOCADE for distribution to approved prescriber's sites meeting the location eligibility criteria.

Wholesalers (or pre-wholesalers) will be provided with access to approved pharmacy and prescriber lists to enable the screening of orders and restriction of delivery to approved sites. This is subject to legal review for privacy and liability concerns.

iii) Assessment of specialist experience

It is proposed that a target number of approved prescribers (those completing review of educational material) be determined and a sample of these prescribers be surveyed to assess sufficiency of specialist experience during initial restricted access scheme to inform advice to non-specialist prescribers. This would provide an assessment of both quantity and the quality of experience. A more detailed description of this assessment will be developed with input from specialist prescribers and with reference to the final agreed specialist prescriber definition.

iv) Evaluating the effectiveness of the scheme to restrict supply

Routine pharmacovigilance activities will contribute to the assessment of the scheme to limit supply.

A plan for evaluating the effectiveness of the scheme in restricting use of the product to the intended prescriber group will be developed and submitted once confirmation that the proposed restricted access scheme is considered acceptable to TGA.

3.2. Potential for medication errors or other risks if applicable

Due to the formulation, the product is intended for abdominal subcutaneous administration only. This information is mentioned in the PI, CMI and product packaging in the following sections:

Black box warning on PI and CMI:

***WARNING**: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION*
Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously. (see section 4.4).

Section 4.4 of the PI:

Intravenous injection presents significant risk of serious harm or death as SUBLOCADE forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously. Do not administer intravenously or intramuscularly.

Section 4.2 of the PI:

FOR ABDOMINAL SUBCUTANEOUS INJECTION ONLY. DO NOT ADMINISTER SUBLOCADE INTRAVENOUSLY OR INTRAMUSCULARLY (see section 4.4 Special Warnings and Precautions for use).

Clear boxed warning on packaging (outer carton and pouch):

Warning: Serious harm or death could result if injected intravenously.

Since SUBLOCADE is required to be administered in a healthcare setting and is not made available directly to patients, its potential for misuse, abuse and diversion is reduced. Its format as an injectable depot also reduces its abuse potential.

3.3. How risk minimisation activities will be evaluated in Australia.

It can be considered that in time, the Pharmacovigilance plan enables monitoring the safety concerns of treatment and the efficacy of the risk minimisation activities. The undercover nature of the condition treated and of the main safety concerns linked to diversion and illicit use of opioids used in medication assisted therapy of opioid dependence may limit the effectiveness of the Risk Management Plan. While it is anticipated that diversion will be limited with SUBLOCADE, this risk cannot be excluded.

The effectiveness of risk minimisation activities in Australia will be evaluated through the measures described below.

Educational materials

Readability testing

The current educational materials on disease state and general buprenorphine pharmacology will not require further evaluation as this was part of the Buprenorphine ASA submitted to TGA.

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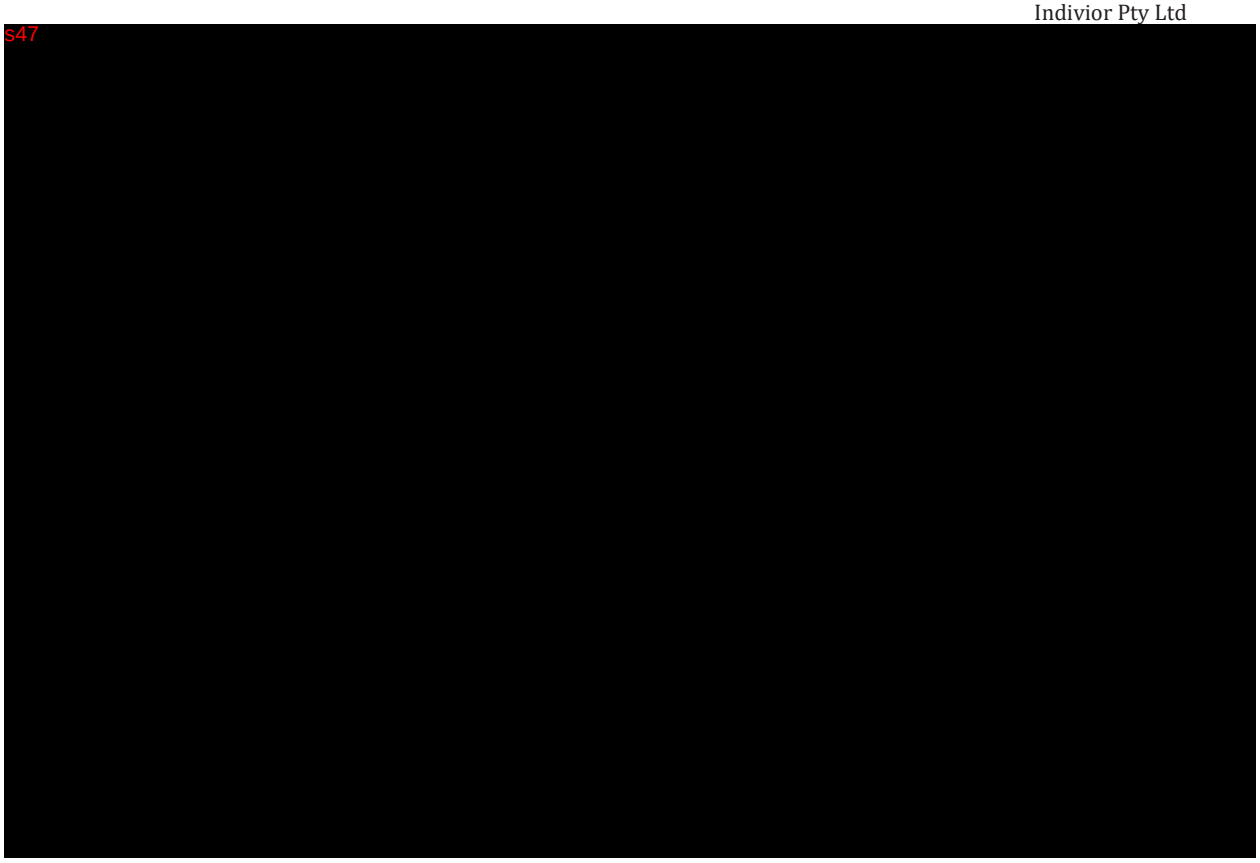

Review of materials based on clinical experience

During the restricted supply period, Indivior will undertake a qualitative review of HCP material with a focus group of SUBLOCADE experienced prescribers.

Controls over SUBLOCADE distribution

After the initial 6 months of supply, it is proposed that distribution of SUBLOCADE be broadened. A plan for reviewing, implementing and evaluating risk minimisation for supply of SUBLOCADE beyond the restricted access program will be developed.

As outlined above, the supply of MATOD is highly regulated at a state level and Indivior has proactively engaged with State governments to develop regulations to manage the supply of SUBLOCADE. The development of State specific regulations will be highly influential on the longer term model for restricted access to SUBLOCADE. Notwithstanding this regulatory influence, the proposed initial restricted supply scheme is scalable with revision of the approved prescriber criteria which may include the option to include all prescribers completing state accreditation programs or all prescribers completing review of educational materials. It is important that the restricted access scheme achieve the dual objective of management of risks and facilitating access to treatment.

Specific strategies for risk minimisation of supply of SUBLOCADE beyond the restricted access scheme will be developed and submitted in the future.

4. Summary of the RMP

Safety Concerns or Missing information	Pharmacovigilance activities (routine and additional) proposed for Australia	Risk minimisation activities (routine and additional) proposed for Australia
CNS Depression including respiratory depression / respiratory failure	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Section 4.4 and 4.5 of the PI (warnings on use of benzodiazepines and other CNS depressants) **Additional activities** Education material
Hepatitis, hepatic events, use in patients with hepatic impairment	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Section 4.4 of the PI (hepatitis and use in hepatic impairment). **Additional activities** Education material
Local Tolerability: Injection Site Reactions	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Section 4.2 and 4.8 of the PI (Instructions for Use and Adverse events) **Additional activities** Education material
Drug withdrawal syndrome (including neonatal withdrawal)	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Section 4.4 of the PI (Neonatal abstinence syndrome + Opioid withdrawal effects) **Additional activities** Education material
Misuse/Abuse	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Sections 4.2 and 4.4 of the PI: (administration by HCPs only, risk with intravenous administration, risk of CNS depression). Inclusion of a black box warning in the PI. **Additional activities** Limitation of supply in the first 6 months to prescribers familiar with MATOD.

Safety Concerns or Missing information	Pharmacovigilance activities (routine and additional) proposed for Australia	Risk minimisation activities (routine and additional) proposed for Australia
		Educational program. Activities with State Health Regulators
Overdose	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Section 4.9 of the PI (overdose) **Additional activities** Education material
Use in pregnancy and lactation	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Section 4.6 of the PI. **Additional activities** Education material
Use in Children/Adolescents <18 years old	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Sections 4.2 and 4.6 of the PI (Paediatric use, pregnancy) **Additional activities** None.
Use in Elderly Patients (≥ 65 years old)	**Routine activities** Routine Pharmacovigilance **Additional activities** None	**Routine activities** Section 4.4 of the PI (Use in the elderly) **Additional activities** None.

5. Person responsible for this RMP and contact details

s22

Indivior Pty Ltd

78 Waterloo Rd

MACQUARIE PARK NSW 2113

Tel: +s22 - Mobile: s22

Email: s22 @indivior.com

6. References

1) Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. Br J Clin Pharmacol. 2014;78(5):1159-66.

2) Berecki-Gisolf J, Hassani-Mahmooei B, Clapperton A, McClure R. Prescription opioid dispensing and prescription opioid poisoning: Population data from Victoria, Australia 2006-2013. Aust NZ J Public Health. 2017;41:85-91.

3) Roxburgh A, Burns L, Drummer o Trends in fentanyl prescriptions and fentanyl-related mortality in Australia Drug Alcohol Rev 2013;32:269–275

4) National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD) collection: 2016 report, Australian Institute of Health and Welfare

5) National Drug Strategy Household Survey (NDSHS) 2016 key findings (AIHW) (http://www.aihw.gov.au/alcohol-and-other-drugs/data-sources/ndshs-2016/key-findings)

6) **Australia's Annual Overdose Report** 2017 (http://www.penington.org.au/overdoseday)

Attachments

1. Draft Instructions for Use
2. Draft Patient Information Brochure

SUBLOCADE® (buprenorphine) 100/300 mg extended release injections

Instructions for use

This booklet is for healthcare professionals who are administering SUBLOCADE extended release injections. The information in this guide is designed to help support the safe use of SUBLOCADE extended release injections for the treatment of opioid dependence within a framework of medical, social and psychological treatment.

Please read all instructions in this booklet carefully before injecting SUBLOCADE.

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION;[1]

Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo embolic events, including life threatening pulmonary emboli, if administered intravenously.

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Focus on you.

Sublocade®
buprenorphine
extended-release injection

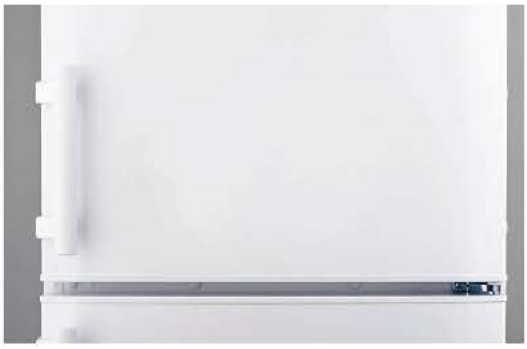
Important information[2]

- SUBLOCADE is for abdominal subcutaneous injection only.
- SUBLOCADE should be administered by a healthcare professional only.
- Do not administer SUBLOCADE intravenously or intramuscularly,
- Remove SUBLOCADE from the refrigerator prior to administration. SUBLOCADE requires at least 15 minutes to reach room temperature. Do not open the foil pouch until the patient has arrived for his or her injection.
- Discard SUBLOCADE if left at room temperature (below 30°C) for longer than 7 days.
- Do not attach the needle until time of administration.

Intravenous injection presents significant risk of serious harm or death as SUBLOCADE forms a solid mass upon contact with body fluids. Occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, could result if administered intravenously.

Storing SUBLOCADE

- Refrigerate at 2–8 °C.
- Do not freeze.
- Once outside the refrigerator, SUBLOCADE may be stored in its original packaging at room temperature (below 30°C) for up to 7 days prior to administration.
- Discard SUBLOCADE if left at room temperature for longer than 7 consecutive days.

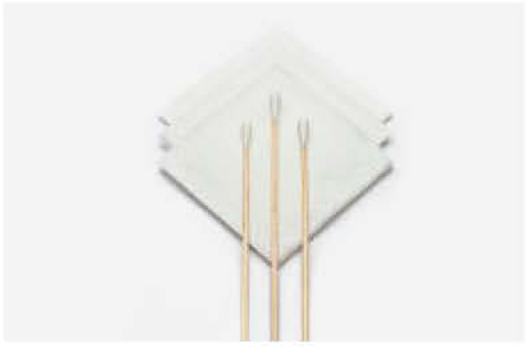


Required materials

- Collect the following materials before removing

SUBLOCADE from its packaging:

  - alcohol swabs
  - gauze pad and/or bandages
  - sharps disposal container.



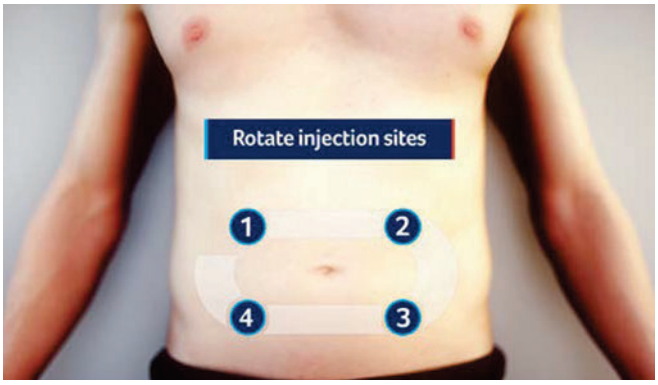
Getting ready

- Remove SUBLOCADE from the refrigerator prior to administration.

  SUBLOCADE requires at least 15 minutes to reach room temperature.
- Do not open the foil pouch until the patient has arrived for his or her injection.
- Do not attach the needle until time of administration.

Selecting and preparing an abdominal injection site

- Choose an injection site on the abdomen between the transpyloric and transtubercular planes (See Step 4 with adequate subcutaneous tissue that is free of skin conditions (e.g. nodules, lesions, excessive pigment).
- Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred in any way.
- It is recommended that the patient is in the supine position.
- Clean the injection site well with an alcohol swab.
- To avoid irritation, rotate injection sites following a pattern similar to the one shown here.
- Record the location of the injection to ensure that a different site is used at the time of the next injection.



Important information after the injection

- Do not rub the injection area after the injection.
- If there is bleeding, apply a gauze pad or bandage but use minimal pressure.
- Advise the patient that they may have a lump for several weeks that will decrease in size over time.
- Instruct the patient not to rub or massage the injection site and to be aware of the placement of any belts or clothing waistbands.
- Dispose of all syringe components in a secure sharps disposal container.

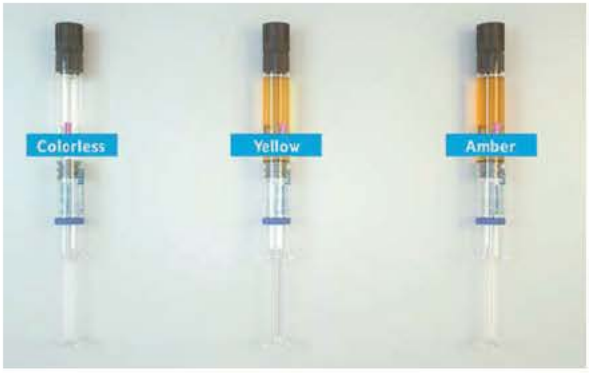
Preparation[2]

STEP 1
Remove SUBLOCADE syringe from packaging

- Remove the foil pouch and safety needle from the carton.
- Open the pouch and remove the syringe.
- Discard the oxygen absorber pack: it is not needed.

STEP 2
Check the liquid clarity

- Check SUBLOCADE for particulate matter and discolouration.
- SUBLOCADE can range from clear colourless to yellow to amber.
- Variations of colour within this range do not affect the potency of SUBLOCADE.
- SUBLOCADE should not be used if it is discoloured or contains particulate matter.

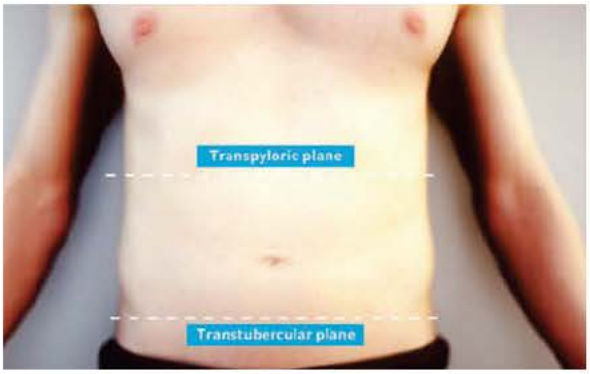


STEP 3
Attach the safety needle

- Remove the cap from the syringe and remove the safety needle supplied in the carton from its sterile package.
- Gently twist the needle clockwise until it is tight and firmly attached.
- Do not remove the plastic cover from the needle.

STEP 4
Prepare the abdominal injection site

- Select the injection site on the abdomen between the transpyloric and transtubercular planes and clean well with an alcohol swab.



STEP 5
Remove excess air from the syringe

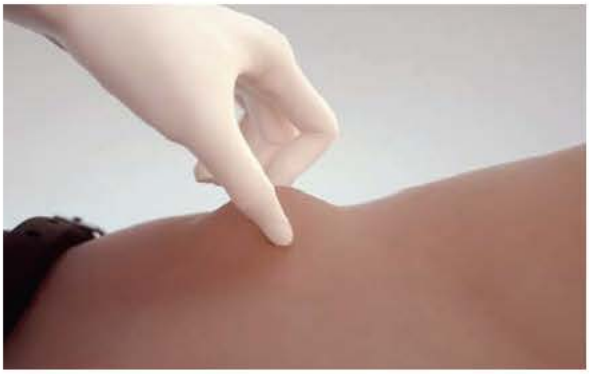
- Hold the syringe upright for several seconds to allow air bubbles to rise.
- Due to the viscous nature of SUBLOCADE, bubbles will not rise as quickly as those in an aqueous solution.
- Remove needle cover and slowly depress the plunger to push out the excess air from the syringe.

- Small bubbles may remain in SUBLOCADE.
- Large air gaps can be minimised by pulling back on the plunger rod to pop air bubbles prior to expelling the air very slowly.
- If SUBLOCADE is seen at the needle tip, pull back slightly on the plunger to prevent spillage.

Injection[2]

STEP 6
Pinch the injection site

- Pinch the skin around the injection area.
- Be sure to pinch enough skin to accommodate the size of the needle.
- Lift the adipose tissue from the underlying muscle to prevent accidental intramuscular injection.



STEP 7
Inject SUBLOCADE

- Insert the needle fully into the abdominal subcutaneous tissue.
- The actual angle of the injection will depend on the amount of subcutaneous tissue.
- Use a slow, steady push to inject SUBLOCADE.
- Continue pushing until all SUBLOCADE is administered.

STEP 8
Withdraw the needle

- Withdraw the needle at the same angle used for insertion and release the pinched skin.
- Do not rub the injection area after the injection.

Disposal[2]

STEP 9

Lock the needle guard and discard the syringe

- Lock the needle guard into place by pushing it against a hard surface such as a table.
- Dispose of all syringe components in a secure sharps disposal container.

Important Safety Information

Buprenorphine is an opioid and may cause CNS depression including respiratory depression/ respiratory failure. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBLOCADE. In the event of overdose the major symptom requiring intervention is respiratory depression. Support adequate respiratory exchange. Naloxone is recommended and higher than usual doses may be required. The patient should be transferred to an environment within which full resuscitation facilities are available. Consider the long duration of effect of Sublocade when assessing overdose treatment and monitoring duration. Consider the effects of other prescribed or unprescribed CNS depressants.

Drug Withdrawal Syndrome including Neonatal Withdrawal can occur following discontinuation of buprenorphine. Withdrawal may be delayed or attenuated in patients treated with SUBLOCADE due to the long duration of action however neonatal withdrawal would be expected to occur on a similar time frame and severity as sublingual buprenorphine.

Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. Attempts to nonmedically extract the buprenorphine dose may cause harm. Inadvertent or intentional IV use may cause harm or death. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and patient follow-up visits with clinical monitoring appropriate to the patient's level of stability should be conducted.

Buprenorphine is cleared predominantly by hepatic metabolism. Because SUBCLOCADE dose cannot be rapidly decreased, do not use SUBLOCADE in patients with severe hepatic impairment. Cases of acute hepatic injury have been reported in opioid-dependent patients treated with buprenorphine products, both in clinical trials and post marketing adverse reaction reports. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis or have existing liver dysfunction are at greater risk of liver injury.

PI PLACEHOLDER

References: 1. SUBLOCADE® Approved Product Information, XXXXX. 2. SUBLOCADE® Consumer Medicine Information Leaflet XXXXX.

Information for patients

This booklet contains important safety information.

Please read it in full and ask your doctor if you have any questions.

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Sublocade®
buprenorphine
extended-release injection

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION;

Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo embolic events, including life threatening pulmonary emboli, if administered intravenously.

Contents

Who is this booklet for?

This booklet is for people 16 years of age and older, who are dependent on opioids (such as heroin, morphine, oxycodone or codeine), who have started treatment on a daily buprenorphine-containing product and will start treatment with SUBLOCADE.[1] It contains information about SUBLOCADE, how it works and how you use it as part of your treatment.

If you are dependent on opioids, it means that you:[2]

- are using opioids more regularly than you should, in larger amounts than you should or in ways that have become a problem in your life
- may not be able to stop using opioids, even when you want to.

SUBLOCADE treatment is provided by healthcare professionals only. A supportive healthcare team (usually a doctor and a pharmacist, but may also include a drug and alcohol health specialist) is an essential part of any good treatment program. Support groups, family members and friends can also help you as you go through treatment. Printed information (like this booklet) does not replace the need for professional advice and a good relationship with your doctor.

Support groups, family members and friends can help you as you go through treatment.

About SUBLOCADE

SUBLOCADE is the brand name of a medication for treating people who are dependent on opioids.[1] It is a type of treatment known as a long-acting injectable or LAI. It's called this because SUBLOCADE is designed to deliver its active ingredient at a controlled rate over a one-month period.[1]

The active ingredient of SUBLOCADE is buprenorphine and it is available in two strengths:

- 100 mg buprenorphine
- 300 mg buprenorphine.

Buprenorphine[1]

Buprenorphine works by binding with the receptors in your brain where opioids would normally attach. By blocking these receptors, buprenorphine reduces the effects of opioids, so you do not feel the same 'high'. Buprenorphine binding to opioid receptors also suppresses cravings and withdrawal symptoms helping you to break free from opioid dependence.

How SUBLOCADE works in the body

Extended release[1]

SUBLOCADE comes as a clear, colourless to yellow to amber solution in a pre-filled syringe. When the SUBLOCADE solution comes into contact with body fluids, it hardens to form a solid mass called a depot. This depot then releases buprenorphine at a controlled rate over a one-month period. SUBLOCADE is designed to be injected just underneath the skin of your abdomen, where the depot will form and release buprenorphine, slowly shrinking as it does so.

Images are for illustrative purposes only and may not accurately depict the subject matter.

Because SUBLOCADE forms a solid depot upon contact with body fluids, it must not be injected into a vein or into a muscle. **Serious side effects, including death, can occur if SUBLOCADE is injected into a vein or muscle.**[1]

Treatment with SUBLOCADE

When will I be given SUBLOCADE?[1]

Before receiving SUBLOCADE, you must first undergo induction treatment with a buprenorphine-containing product that is dissolved in your mouth, either under the tongue or inside of your cheek. Induction treatment will usually span several days. After the first SUBLOCADE dose you will no longer receive other buprenorphine containing products and SUBLOCADE will be administered once each month.

What dose will I be given?[1]

Your doctor will decide what dose of SUBLOCADE to prescribe and you should always follow medical advice. It is important to see your doctor regularly and raise any issues or concerns you have, particularly if you have withdrawal symptoms or cravings.

Can I use other drugs?

It is very dangerous to use benzodiazepines (such as sleeping pills or tranquillisers) or alcohol. Some people have died when using benzodiazepines, other depressants, alcohol or other opioids at the same time as medications containing buprenorphine.[1]

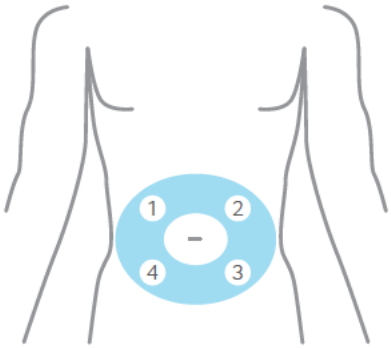
During your treatment, your doctor may ask you to take a urine test – this is to help them adjust your treatment. This may be to ensure the dose of SUBLOCADE is high enough, but also to ensure you are not in danger of other drugs interacting with your treatment.

A urine test can detect benzodiazepines (such as Valium® or Xanax®), cocaine, amphetamines, cannabis and opioids (such as buprenorphine, heroin, morphine or methadone).[3]

How is SUBLOCADE given?[1]

SUBLOCADE is to be prepared and injected by a healthcare professional only – you should not inject it yourself. This means you need to visit your healthcare professional once every month to receive your SUBLOCADE treatment.

SUBLOCADE is injected underneath the skin of your abdomen, in the area around your belly button. Every time you go for an injection, it should be given in a different place to the previous one – the numbers in the below image show where you may receive injections over four months.



After injection:

You will notice a small lump at the injection site for several weeks. This is the depot that is releasing the buprenorphine into your system.

- Do not rub or massage the injection site.
- Do not try to remove the depot.
- Be careful not to wear clothing or accessories that will rub the depot (such as waistbands or belts).

You must wait a minimum of 26 days before your next injection. **If you have any side effects during this time it is very important to tell your doctor straight away. See the side effects section of this booklet for more information.**

Who should avoid SUBLOCADE?

Allergy to buprenorphine[1]

Do not use SUBLOCADE if you are allergic to buprenorphine or any other ingredient in SUBLOCADE. Allergy can show up as rashes, hives and itchy skin. Very occasionally, allergy causes a severe reaction (such as problems breathing due to airway constriction and anaphylactic shock). If you have any of these reactions when taking SUBLOCADE, tell your doctor immediately.

SUBLOCADE will not be given if:[1]

- you are under 16 years of age
- you are allergic to buprenorphine or any of the inactive ingredients
- you are intoxicated due to central nervous system depressant medicines (e.g. tranquillisers, sedative hypnotics, narcotic analgesics, anti-anxiety medicines, antipsychotics), alcohol or have delirium tremens (the 'shakes' and hallucinations)
- you have serious breathing problems.

What are the dispensing arrangements?

SUBLOCADE is a long-acting treatment option. It must be administered by a healthcare professional, so you cannot get take-away doses.[1]

What happens if I miss a dose?[1]

If you miss a dose you should go to your healthcare professional as soon as possible to receive the missed dose. Once you have received the catch-up dose, continue treatment with the following dose given no less than 26 days later.

What if I need pain relief?[1]

SUBLOCADE can interfere with some pain treatments. In case you need to be treated for pain, are in an emergency or if you need anaesthesia you should:

- inform your healthcare provider that you are being treated with SUBLOCADE
- tell your family and friends that in the event of an emergency, they need to inform the treating healthcare provider/emergency room staff that you are being treated with SUBLOCADE.

After stopping SUBLOCADE you should continue to inform healthcare providers that you have been treated with SUBLOCADE for 6 months since your last dose (as the buprenorphine can remain in your system for a long time).

Stopping treatment

How long you spend on treatment varies from person to person. Your treatment team can help you decide when is the best time for you to come off treatment. It is usually when you have made significant progress in your treatment plan and you are ready. Coming off treatment is not as simple as just stopping your medications. It involves improvements in other aspects of your life, such as social, emotional and physical wellbeing. It's important to continue to speak to your doctor about coming off treatment and to form a plan together to prevent the chances of relapse.[3]

It is important to note that due to the extended-release properties of SUBLOCADE, its effects can last for a while after discontinuation of treatment. Buprenorphine may remain in your bloodstream at therapeutic levels for 2–5 months and at detectable levels for 12 months or longer.[1] This means that you may not experience withdrawal symptoms for a while after stopping treatment. But if you do experience withdrawal symptoms or are concerned about them during this time, you may be prescribed a buprenorphine-containing medication that dissolves in your mouth.[1]

Opioid dependence is a complex and chronic condition. As such, you may benefit from continuing to see your doctor to check in, and in case you feel you are beginning to slide back towards drug use, restarting your medication may be an option.[3] It's important to remember this does not mean you have failed. By monitoring your health and taking action, you are succeeding in taking control back over your life.

Important safety information

Because SUBLOCADE forms a solid mass when it comes into contact with body fluid, it **SHOULD NOT** be injected into a vein or into muscle. Doing so can cause serious tissue damage or death from the depot forming in muscle tissues, travelling through the veins to your heart or brain. This is why SUBLOCADE can only be injected by a healthcare professional.[1]

Attempting to remove the depot, misuse it or pass it on to another person, in any way, should not be attempted. Attempts to inject a depot that has been removed from a person into your veins would result in serious harm.[1]

What are the side effects of SUBLOCADE?[1]

Like all medicines, SUBLOCADE may have unwanted side effects. The following list includes many of the common side effects reported with SUBLOCADE. Do not be alarmed by this list as you may experience some or none of these side effects. If you think you are experiencing any of the following side effects, you should tell your doctor immediately.

Some of the most common side effects reported with the use of buprenorphine were:

- difficulty sleeping, anxiety
- fatigue, weakness, numbness
- pain in the abdomen, back, arms, legs, joints and muscles, leg cramps, muscle weakness
- abnormal liver function
- flu-like symptoms such as chills, fever, sore throat, coughing, runny nose and sweating
- upset stomach and diarrhoea
- reactions at the injection site (redness, pain, itching, nodule just under the skin).

If any of the following happen, tell your doctor immediately or go to Accident and Emergency at your nearest hospital. You may need urgent medical attention.

- There have been rare cases of life-threatening severe hypersensitive reactions with symptoms of severe difficulty in breathing, swelling of the face, lips, mouth or throat.

- Some cases of severe liver problems have occurred during treatment. If you develop severe fatigue, have no appetite or if your skin or eyes look yellow, you have light coloured bowel motions or dark coloured urine, tell your doctor immediately.

If you take too much (overdose)

- The medicine will be given to you under medical supervision; it is therefore unlikely that you will be given too much. Taking too much can cause drowsiness and affect your breathing, this can be dangerous if it is severe. Taking SUBLOCADE with sleeping tablets, anti-anxiety medication or alcohol can increase the risk. If you think that you or anyone else may have received too much SUBLOCADE, immediately telephone your doctor or National Poison Centre (in Australia telephone 13 11 26).

Use in pregnancy and breastfeeding[1]

You can take SUBLOCADE whilst pregnant or breastfeeding, but the benefits of your treatment versus the risks to your baby need to be assessed. Use of SUBLOCADE during pregnancy may result in your baby experiencing withdrawal symptoms after they are born. Not all babies exposed to SUBLOCADE will have withdrawal symptoms. Talk to your doctor if you become pregnant or plan to become pregnant during treatment with SUBLOCADE. Your doctor will help you consider the risks and benefits of continued treatment and plan for monitoring your baby following birth. Due to the long duration of buprenorphine effect your baby will be monitored for several days at the end of pregnancy for effects on breathing and for withdrawal symptoms.

If you become pregnant, decide to breastfeed or are planning to become pregnant, you must discuss the risks and benefits of treatment with your doctor and obstetrician.

Removal of SUBLOCADE[1]

If you experience any side effects, decide to discontinue treatment or for any other reason need to have the SUBLOCADE depot removed, you must see your doctor within 14 days of injection. The depot can only be removed through minor surgery, which must be performed by a healthcare professional under local anaesthesia. The depot will then be disposed of by the healthcare professional.

If you are not within the 14-day period or experience sudden and dangerous side effects, the buprenorphine in the SUBLOCADE depot may be counteracted with other medications. Because of the extended-release formulation of SUBLOCADE, these medications may need to be administered continuously.

Where to go to for support

Your healthcare treatment team

A healthcare team aims to bring the different aspects of treatment together to offer you the medication, and professional and personal support you need. Your treatment team may include:

- your doctor (who prescribes and administers SUBLOCADE)
- your counsellor, case worker or other health professionals
- a nurse for administration and reviewing your progress.

If you are unhappy with any part of your drug treatment, talk to your treatment team.

It is important to have a good relationship with your treatment team. For treatment with SUBLOCADE to be effective, you must have adequate medical supervision. You will need to regularly see your treating doctor (who is trained to provide SUBLOCADE treatment) to review how your treatment is going. During the initial stage of treatment, you may need to see your doctor more often, until your dose is stabilised.

Counselling

Counselling can help you with treatment and other issues. This includes helping you:

- change your pattern of drug use
- manage cravings
- prevent cravings
- avoid situations that might trigger drug use.

Drug and alcohol clinics offer their clients one-on-one or group-based counselling. Other support agencies may also provide private counselling. These generally charge fees, but some offer special rates that are more affordable to people with low income. Talk to your doctor or see the contact information at the back of this book about where to find counselling. For more information, you can also contact your local community health centre or area health service.

Narcotics Anonymous

Narcotics Anonymous (NA) is a not-for-profit organisation supporting people for whom drugs have become a major problem. The only requirement for membership is the desire to stop using.

Other support

It is important to have support during (and after) your treatment. Support may come from family or friends, caseworkers, community services providers or specialist drug treatment services.

The combination of support that is helpful will differ from person to person; seeking support that suits your particular situation can really benefit your treatment experience.

Notes

Use this space to keep track of any symptoms or side effects you experience

Date

Date

References:

1. SUBLOCADE® (buprenorphine) Approved Product Information, xxxxxx.
2. World Health Organisation. Dependence syndrome. Available at: www.who.int/substance_abuse/terminology/definition1/en/. Accessed January 2019.
3. Gowing L *et al.* National Guidelines for Medication-Assisted Treatment of Opioid Dependence April 2014. Commonwealth of Australia.

Useful contacts

Confidential and anonymous 24-hour Alcohol and Drug Information Services (ADIS) provide counselling and referral recommendations. Here is a list of contacts for each state:

Australian Capital Territory	(02) 6207 9977
New South Wales	(02) 9361 8000
New South Wales (Toll Free)	1800 422 599
Northern Territory (Toll Free)	1800 131 350
Darwin	(08) 8922 8399
Alice Springs	(08) 8951 7580
Queensland (Toll Free)	1800 177 833
South Australia	(08) 8363 8618
Adelaide	1300 131 340
Tasmania (Toll Free)	1800 811 994
Hobart	(03) 9416 1818
Victoria (Toll Free)	1800 888 236
Western Australia	(08) 9442 5000
Western Australia (Toll Free)	1800 198 024

Australian Government
Department of Health
Therapeutic Goods Administration

The Managing Director
Indivior Pty Ltd
78 Waterloo Rd
Macquarie Park NSW 2113

Clinical File: 2014/005042
PI File:2008/008042
Submission No.: PM-2018-03877-1-1
Data: e002585 - (0009)

Attention: s22 [redacted]

Dear Sir/Madam,

REQUEST UNDER s. 9D(1) FOR VARIATION TO COMPLETE/CORRECT ENTRY IN THE ARTG AND CHANGE TO THE APPROVED PRODUCT INFORMATION

I refer to your request under subsection 9D(1) of the *Therapeutic Goods Act 1989* (the Act) dated 10 September 2018 to vary the entry of:

- AUST R 163443 - SUBOXONE FILM 2/0.5 buprenorphine (as hydrochloride) 2mg / naloxone (as hydrochloride dihydrate) 0.5mg soluble film sachet
- AUST R 163444 - SUBOXONE FILM 8/2 buprenorphine (as hydrochloride) 8mg / naloxone (as hydrochloride dihydrate) 2mg soluble film sachet
- AUST R 211117 - SUBOXONE FILM 4/1 buprenorphine (as hydrochloride) 4mg / naloxone (as hydrochloride dihydrate) 1mg soluble film sachet
- AUST R 211120 - SUBOXONE FILM 12/3 buprenorphine (as hydrochloride) 12mg / naloxone (as hydrochloride dihydrate) 3mg soluble film sachet

(referred to hereinafter as the product(s)) in the Australian Register of Therapeutic Goods (the ARTG) as described in **Attachment 2a.**

You also asked that the approved Product Information (PI) for the product(s) be varied under subsection 25AA(4) of the Act to reflect any variation made under subsection 9D(1).

Subsections 9D(1), 25AA(4) and 25AA(4A) of the Act can be found online at the following link: **https://www.legislation.gov.au/Series/C2004A03952**

Decision

As delegate of the Secretary of the Department of Health, I am varying the entry in the ARTG for this product(s) under subsection 9D(1) as requested on the basis that the relevant information currently in the entry is incorrect and that the variations requested would correct the entry.

As delegate of the Secretary of the Department of Health, I am approving the text of the PI under subsection 25AA(4) as set out at **Attachment 2a and 2b** to take account of my decision under subsection 9D(1) on the basis that the only changes made to the most recently approved PI were those set out in your request of 10 September 2018.

Date of effect

The date of effect of the variation is the date of this approval letter. The "Date of revision" or "date of most recent amendments" included in the PI is to be the date of this letter.

Action required of you

The approved PI at **Attachment 2b** must be lodged with the TGA **within 2 weeks** of the date of approval of the variation. If the related Consumer Medicine Information (CMI) document needs to be changed as a consequence of the change to the approved PI, it must also be lodged with the TGA **within 2 weeks** of the date of the changed PI.

The documents must be lodged in the TGA eBusiness Services system. Information on how to lodge these documents is available at www.ebs.tga.gov.au. The documents must be in text PDF format –scanned PDF documents will **not** be accepted by the system.

Review rights

Details of review rights for the decision under subsection 9D(1) and 25AA(4) are provided at **Attachment 1**.

Your obligations in relation to Product Information etc.

You are reminded that an approved PI for a medicine cannot be changed without the approval of the Secretary under subsection 25AA(4) of the Act.

You are also reminded that the Consumer Medicine Information must comply with the requirements set out in the Therapeutic Goods Regulations 1990 which includes the obligation of ensure the CMI that must be supplied with the medicine is 'consistent with' the approved PI.

Please do not hesitate to contact me if you have any further queries regarding this matter.

Yours faithfully,

Electronically signed and authorised by
s22
Delegate of the Secretary

Clinical Evaluation Section 1
Prescription Medicines Authorisation Branch
Email: s22 @tga.gov.au

3 October 2018

Attachments:

1. Review rights
2. Approved product information for:
   a. SUBOXONE FILM buprenorphine (as hydrochloride) / naloxone (as hydrochloride dihydrate) soluble film sachet (changes highlighted)
   b. SUBOXONE FILM buprenorphine (as hydrochloride) / naloxone (as hydrochloride dihydrate) soluble film sachet (clean)

Attachment 1

Request for reconsideration of an initial decision

This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister within 90 days and be accompanied by any information that you wish to have considered. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate to an officer of the Department with the appropriate delegation.

Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the notification is made of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

A request for reconsideration should be made in writing, signed and dated by the person requesting reconsideration, should be titled **"<insert person/company name> - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989***" and should include the following:

- a copy of the initial decision notification letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: '**minister.hunt.DLO@health.gov.au**' and copied to '**decision.review@health.gov.au**'

Requests for reconsideration that include dossiers (or similar bulk material) that cannot easily be attached to the request given first by email, may then be submitted on a USB drive or CD sent by express post or registered mail to:

Mail: **Minister for Health**
Suite M1 40
c/- Parliament House
CANBERRA ACT 2600

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you

can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

ATTACHMENT 2A

AUSTRALIAN PRODUCT INFORMATION

SUBOXONE FILM (BUPRENORPHINE/NALOXONE)

1 NAME OF THE MEDICINE

SUBOXONE FILM contains buprenorphine (as hydrochloride) and naloxone (as hydrochloride dihydrate) at a ratio of 4:1 buprenorphine: naloxone (ratio of free bases).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SUBOXONE FILM is available in four dosage strengths:

2 mg buprenorphine (as hydrochloride) + 0.5 mg naloxone (as hydrochloride dihydrate)
4 mg buprenorphine (as hydrochloride) + 1 mg naloxone (as hydrochloride dihydrate)
8 mg buprenorphine (as hydrochloride) + 2 mg naloxone (as hydrochloride dihydrate) and
12 mg buprenorphine (as hydrochloride) + 3 mg naloxone (as hydrochloride dihydrate).

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg /mL at 37°C, pH 4.1). Chemically, it is 21- Cyclopropyl-7α-[(S) -1- hydroxy-1, 2, 2 -trimethylpropyl]-6, 14-endo-ethano-6, 7, 8, 14-tetrahydrooripavine hydrochloride. Buprenorphine hydrochloride has the molecular formula C29 H41 NO4 HCl and the molecular weight is 504.09. The CAS number is 53152-21-9.

Naloxone hydrochloride is a white to slightly off-white powder that exists as the dihydrate and is soluble in water, in dilute acids and in strong alkali. Chemically, it is (-)-17-Allyl-4, 5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. Naloxone hydrochloride has the molecular formula C19 H21 NO4 HCl .2H2O and the molecular weight is 399.87.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

SUBOXONE FILM is a soluble film intended for sublingual and or buccal administration only.
SUBOXONE FILM is supplied as an orange rectangular soluble film with a white printed logo in four dosage strengths:

- "N2" for 2/0.5 mg buprenorphine/naloxone
- "N4" for 4/1 mg buprenorphine/naloxone*
- "N8" for 8/2 mg buprenorphine/naloxone and
- "N12" for 12/3 mg buprenorphine/naloxone*.

* Not supplied

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of opioid dependence within a framework of medical, social and psychological treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with SUBOXONE FILM is intended for adults and children aged 16 years or over who have agreed to be treated for opioid dependence.

SUBOXONE FILM and SUBOXONE TABLET do not meet all criteria for bioequivalence (see section 5.2 Pharmacokinetic Properties). Patients being switched between tablets and soluble films may therefore require dosage adjustment.

The routes of administration of SUBOXONE FILM is sublingual and buccal only. The film formulation is not designed to be split or broken.

SUBOXONE FILMS should not be swallowed whole as this reduces the bioavailability of the medicine. Physicians must advise patients that the sublingual and buccal route are the only effective and safe route of administration for this medicine.

Please note: The following instructions refer to the buprenorphine content of each dose.

Method of Administration

Sublingual Administration

Place one film under the tongue, close to the base on the left or right side. If an additional film is necessary to achieve the prescribed dose, place an additional film sublingually on the opposite side from the first film. Place the film in a manner to minimize overlapping as much as possible. The film must be kept under the tongue until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it under the tongue on either side after the first 2 films have dissolved.

Buccal Administration

Place one film on the inside of the right or left cheek. If an additional film is necessary to achieve the prescribed dose, place an additional film on the inside of the opposite cheek. The film must be kept on the inside of the cheek until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it on the inside of the right or left cheek after the first two films have dissolved.

No food or drink should be consumed until the film is completely dissolved. SUBOXONE FILM should NOT be chewed, swallowed, or moved from placement.

Starting SUBOXONE FILM

An adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal symptoms due to inadequate dosage.

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use and the degree or level of opioid dependence.

Due to naloxone exposure being somewhat higher following buccal administration than sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimise naloxone exposure and to reduce the risk of precipitated withdrawal.

Induction onto SUBUTEX (buprenorphine tablets) is recommended when there is doubt about the level of dependence or previous opioid use, to avoid precipitating opioid withdrawal. Patients can be switched to SUBOXONE FILM on the third day.

When initiating buprenorphine treatment, the physician should be aware of the partial agonist profile of the molecule to the μ opioid receptors, which can precipitate withdrawal in opioid-dependent patients if given too soon after the administration of heroin, methadone or another opioid. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective and clear signs of withdrawal are evident.

Patients taking Heroin (or Other Short-acting Opioids)

When treatment starts the dose of SUBOXONE FILM should be taken at least 6 hours after the patient last used opioids and when the objective signs of withdrawal appear. The Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment however clinical assessment of withdrawal symptoms with consideration of the patient's baseline presentation is important, particularly for patients in mild withdrawal (COWS score of 5-12). The recommended starting dose is 4-8 mg SUBOXONE FILM on Day One, with a possible additional 4 mg depending on the individual patient's requirement. The suggested target total dose for Day One is in the range of 8-12 mg SUBOXONE FILM. For patients with moderate or severe withdrawal at the time of the first dose, an initial dose of 8 mg may be appropriate with an additional 4 mg depending on the individual patient's requirement to a total maximum of 12 mg on Day 1.

Lower doses (e.g. 2 or 4 mg total on Day 1) are suited to those with low or uncertain levels of opioid dependence, with high risk polydrug use (alcohol, benzodiazepines) or with other severe medical complications. Seek specialist advice if concerned.

Patients on Methadone

Before starting treatment with SUBOXONE FILM, the maintenance dose of methadone should be reduced to the minimum methadone daily dose that the patient can tolerate. The first dose of SUBOXONE FILM should be taken at least 24 hours after the patient last used methadone. An initial dose of 2 mg SUBOXONE FILM may be administered when moderate withdrawal is apparent (COWS ≥ 13). An additional dose of 6 mg SUBOXONE FILM can be administered one hour later if the initial dose does not precipitate withdrawal. Supplementary doses can be administered every 1 to 3 hours according to withdrawal severity:

- 0 mg if there is no or minimal withdrawal (COWS < 5);
- 4 mg if there is mild withdrawal (COWS 5-12);
- 8 mg if there is moderate to severe withdrawal (COWS ≥ 13).

The suggested target total dose for Day One is in the range of 8 – 16 mg SUBOXONE FILM. A maximum daily dose of 32 mg should not be exceeded.

During the initiation of treatment, patients need frequent monitoring. SUBOXONE FILM should be dispensed in multiple doses over the first 4 to 6 hours of the transfer. Dosing supervision is recommended to ensure proper placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

Switching between treatments for opioid dependence

Patients should be closely monitored during the switching period from buprenorphine or methadone to buprenorphine/naloxone since withdrawal symptoms have been reported.

Switching between SUBOXONE FILM strengths

The sizes and the compositions of the four units of SUBOXONE FILMs, i.e., 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE FILMs to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be monitored for over-dosing or under-dosing. For this reason, pharmacist should not substitute one or more film strengths for another without approval of the prescriber.

Switching between sublingual and buccal sites of administration

The systematic exposure of buprenorphine between buccal and sublingual administration of SUBOXONE FILM is similar. Therefore, once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under or overdosing.

Dose adjustment in hepatic impairment

Use of SUBOXONE FILM is contraindicated in patients with severe hepatic impairment.

SUBOXONE FILM may not be appropriate for patients with moderate hepatic impairment. SUBOXONE FILM may be used with caution for maintenance treatment in patients with moderate hepatic impairment, who have initiated treatment on a buprenorphine-only product. Patients with moderate hepatic impairment prescribed SUBOXONE should be monitored for signs and symptoms of precipitated opioid withdrawal. In addition, lower initial doses and cautious titration of dosage may be required in patients with moderate hepatic impairment.

No dosage adjustment is needed in patients with mild hepatic impairment.

Dosage Adjustment and Maintenance

The dose of SUBOXONE FILM should be adjusted progressively according to the clinical effect in the individual patient. The dosage is adjusted in increments or decrements of 2 – 8 mg buprenorphine to a level that maintains the patient in treatment and suppresses opioid withdrawal effects according to reassessments of the clinical and psychological status of the patient.

Most patients require daily buprenorphine doses in the range 12-24 mg to achieve stabilisation, although some patients require higher (e.g. up to 32 mg/day) or lower (4-8 mg/day) doses to achieve their treatment goals. During maintenance therapy, it may be necessary to periodically restabilise patients to new maintenance doses in response to changing patient needs.

Less than daily dosing

After a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

In some patients, after a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

The patient should be observed following the first multi-dose administration to initiate the less-than-daily dosing regimen, and whenever treated with high doses. Patients who sporadically use concomitant CNS-active medications or substances should be monitored closely.

Reducing Dosage and Stopping Treatment

The decision to discontinue therapy with SUBOXONE FILM should be made as part of a comprehensive treatment plan. A possible gradual dose taper over a period of 21 days is shown in Table 1.

Table 1.	**Gradual dose taper schedule**		
Week	**20 mg Maintenance dose**	**16 mg Maintenance dose**	**8 mg Maintenance dose**
1	16 mg	12 mg	8 mg
2	8 mg	8 mg	4 mg
3	4 mg	4 mg	4 mg

4.3 CONTRAINDICATIONS

Hypersensitivity to buprenorphine or naloxone or any other component of the soluble film.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency (Child-Pugh C).
Acute intoxication with alcohol or other CNS depressant.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

SUBOXONE FILM should be administered with caution in debilitated patients and those with impairment of hepatic, pulmonary, or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (e.g. Addison's disease); CNS depression or coma; toxic psychoses; acute alcoholism; or delirium tremens.

Buprenorphine increases intracholedochal pressure as do other opioids. Therefore, caution should be exercised when SUBOXONE FILM is to be administered to patients with dysfunction of the biliary tract.

As with other opioids, caution is advised in patients using buprenorphine and having hypotension, prostatic hypertrophy or urethral stenosis.

Opioids may produce orthostatic hypotension in ambulatory patients.

As with other mu-opioid receptor agonists, the administration of SUBOXONE FILM may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Use in the elderly

The safety and efficacy of buprenorphine in elderly patients over 65 years have not been established.

Misuse, abuse and diversion

SUBOXONE can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. SUBOXONE misuse by someone other than the intended patient poses the additional risk of new opioid dependent individuals using buprenorphine as the primary opioid of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft, including in the home. Sub-optimal treatment with SUBOXONE may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with SUBOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines. To minimise risk of misuse, abuse or diversion, appropriate precautions should be taken when prescribing and dispensing SUBOXONE, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

Patients dependent upon concomitant CNS-active substances, including alcohol, should not be treated with the increased doses required by the less-than-daily dosing regimen intended for use in a supervised dose setting. Patients with sporadic use of concomitant non-opioid medications should be monitored closely, and all patients dosed on a less-than-daily basis should be observed following the first multi-dose administration when initiating less-than-daily dosing or whenever treated with high doses.

Respiratory Depression

SUBOXONE FILM is intended for sublingual or buccal use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when buprenorphine was used in combination with benzodiazepines, in opioid naïve individuals, or when buprenorphine was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBOXONE FILM.

In the event of depression of respiratory or cardiac function, see section 4.9 Overdose.

SUBOXONE FILM should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis).

SUBOXONE FILM may cause severe, possible fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

CNS Depression

SUBOXONE may cause drowsiness, particularly when used together with alcohol or other central nervous system depressants (such as benzodiazepines, tranquillisers, sedatives or hypnotics (see section 4.5 Interactions). When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. SUBOXONE FILM should be used cautiously with MAOIs, based on experience with morphine.

Hepatitis, Hepatic Events

Cases of acute hepatic injury have been reported in opioid-dependent patients, both in clinical trials and post marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose-related, and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, liver enzyme abnormalities, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues, or drug misuse by injection) could promote the occurrence of such hepatic injuries. These co-factors must be taken into account before prescribing SUBOXONE FILM and during treatment monitoring. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicines (see section 4.5 Interactions) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicine may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to opioid dependence. If treatment is continued, hepatic function should be monitored closely.

Use in hepatic Impairment

Buprenorphine and naloxone are extensively metabolised by the liver. The effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study, in which a SUBOXONE 2.0/0.5 mg (buprenorphine/naloxone) sublingual tablet was administered to healthy subjects and subjects with varying degrees of hepatic impairment. Plasma levels were found to be elevated for buprenorphine and naloxone in patients with moderate to severe hepatic impairment (Table 2). Patients with severe hepatic impairment experienced substantially greater increases in exposure to naloxone relative to buprenorphine, and patients with moderate hepatic impairment experienced greater increases in exposure to naloxone relative to buprenorphine. The clinical impact in terms of efficacy/safety is unknown, but is likely to be greater for those with severe hepatic impairment than those with moderate hepatic impairment.

The doses of buprenorphine and naloxone in SUBOXONE cannot be individually titrated. As such, SUBOXONE should be avoided in patients with severe hepatic impairment. Use of SUBOXONE may not be appropriate in those with moderate hepatic impairment. It may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine-only product. Patients with moderate hepatic impairment should be monitored for signs and symptoms of precipitated opioid withdrawal. In addition, lower initial doses and cautious titration of dosage may be required in patients with moderate hepatic

impairment. As with all patients treated with SUBOXONE, liver function tests should be monitored prior to and during treatment. See also section 4.2 Dose and Method of administration.

Table 2: Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following buprenorphine/naloxone administration (change relative to healthy subjects)

PK parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
BUPRENORPHINE			
Cmax	1.2 fold increase	1.1 fold increase	1.7 fold increase
AUC_{last}	Similar to control	1.6 fold increase	2.8 fold increase
NALOXONE			
Cmax	Similar to control	2.7 fold increase	11.3 fold increase
AUC_{last}	0.2 fold increase	3.2 fold increase	14 fold increase

In the same study, changes in Cmax and AUClast of buprenorphine and naloxone in subjects with HCV infection without hepatic impairment were not clinically significant in comparison to the healthy subjects.

Use in renal impairment

Renal elimination plays a relatively small role (~30%) in the overall clearance of SUBUTEX. Therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min), which may require dose adjustment.

Head Injury and Increased Intracranial Pressure

SUBOXONE FILM, like other potent opioids may itself elevate cerebrospinal fluid pressure, which may cause seizures, and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased, or history of seizure. SUBOXONE FILM can produce miosis and changes in the level of consciousness, or changes in the perception of pain as a symptom of disease and may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.

Opioid Withdrawal Effects

Because SUBOXONE FILM contains naloxone, it is highly likely to produce marked and intense opioid withdrawal symptoms if injected by patients treated with SUBUTEX or SUBOXONE or by persons dependent on full opioid agonists such as heroin, oxycodone, morphine or methadone.

SUBOXONE FILM may produce withdrawal symptoms in opioid dependent subjects if it is administered too soon after another opioid. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed.

Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and studies in animals, as well as clinical experience, have shown that buprenorphine may produce dependence, but at a lower level than morphine. Consequently, it is important to follow the recommendations in section 4.2 Dose and Method of administration. Withdrawal symptoms may also be associated with suboptimal dosing.

Neonatal Abstinence Syndrome

Chronic use of buprenorphine by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, apnoea, convulsions

or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth (see section 4.6 Use in Pregnancy). Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Allergic Reactions

Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic oedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to SUBOXONE FILM use.

Paediatric Use

SUBOXONE FILM is not recommended for use in children. The safety and effectiveness of SUBOXONE FILM in subjects below the age of 16 has not been established. Due to limited amount of available data, patients between 16 and 18 years of age should be closely monitored during treatment.

Effects on Laboratory Tests

Athletes should be aware that this medicine may cause a positive reaction to "anti-doping" tests.

Use in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received doses as low as 2 mg of buprenorphine sublingual tablet for analgesia. SUBOXONE is not appropriate as an analgesic.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Alcohol

Alcohol increases the sedative effect of buprenorphine/naloxone. SUBOXONE should not be used together with alcoholic drinks, and must be used cautiously with medicines containing alcohol (see section 4.4 Special Warnings and Precautions for Use).

Benzodiazepines

This combination may result in death due to respiratory depression of central origin; therefore, patients must be closely monitored when prescribed this combination, and this combination should be avoided where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed (see section 4.4 Special Warnings and Precautions for Use).

Other central nervous system depressants

Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. The reduced level of alertness can make driving and using machinery dangerous. Examples include opioids (e.g. methadone, analgesics, and antitussives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine (see section 4.4 Special Warnings and Precautions for Use).

Opioid analgesics

The analgesic properties of other opioids such as methadone and level III analgesics may be reduced in patients receiving treatment with buprenorphine/naloxone for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving SUBOXONE. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma

levels are declining. Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see section 4.4 Special Warnings and Precautions for Use).

Naltrexone and other opioid antagonists

Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of SUBOXONE FILM. Patients maintained on SUBOXONE FILM may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations.

CYP3A4 inhibitors

An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving SUBOXONE FILM should be closely monitored, and may require dose reduction if combined with potent CYP3A4 inhibitors e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, azole antifungals like ketoconazole or itraconazole, calcium channel antagonists, and macrolide antibiotics.

CYP3A4 inducers

Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in under-treatment of opioid dependence with buprenorphine; therefore, it is recommended that patients receiving SUBOXONE FILM should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, and rifampicin) are co-administered.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There were no effects on mating performance or fertility in rats following buprenorphine treatment at oral doses 20 times the maximum clinical dose of 32 mg/day (based on mg/m2). Dietary administration of SUBOXONE TABLETS to rats at doses of 47 mg/kg/day or greater (estimated respective buprenorphine and naloxone exposures 14 and 24 times the anticipated clinical exposure, based on plasma AUC) resulted in reduced female conception rates. A dietary dose of 9.4 mg/kg/day (twice the anticipated clinical exposure for both buprenorphine (based on AUC) and naloxone (based on mg/m2) had no adverse effect on fertility.

Use in Pregnancy – Pregnancy Category C

In rats, oral administration of buprenorphine at doses up to 20 times the maximum clinical dose of 32 mg/day (based on mg/m2) prior to and during gestation and lactation resulted in reduced implantation, fewer live births, and reduced pup weight gain and survival. There was no evidence of teratogenicity in rats and rabbits following parenteral administration of buprenorphine during the period of organogenesis, although there was embryofoetal toxicity, and reduced pup viability and developmental delays in rats. There was no evidence of teratogenicity in rats and rabbits following oral or intramuscular administration of maternally toxic doses of combinations of buprenorphine + naloxone during the period of organogenesis, although post-implantation losses were increased. In rats, oral (20 times maximum clinical dose, based on mg/m2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response).

Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. SUBOXONE FILM should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Continued use of

heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

Data on the use of buprenorphine in pregnancy, and its impact on the mother and foetus, are limited. Data from randomised, controlled trials and observational studies do not indicate an increased risk of maternal or foetal adverse outcomes compared to methadone.

Use in Lactation

Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. In rats, oral (20 times maximum clinical dose, based on mg/m2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response). The no effect level for developmental effects was twice the maximum clinical dose, based on mg/m2. In two studies of thirteen women, buprenorphine was found in low levels in human breast milk. In both studies the estimated infant dose was <1% of the maternal dose. Because buprenorphine is excreted into human milk, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBOXONE FILM and any potential adverse effects on the breastfed child from the treatment or the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SUBOXONE may influence the ability to drive and use machinery when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions). Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SUBOXONE therapy does not adversely affect their ability to engage in such activities.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Safety Study of SUBOXONE FILM

The clinical safety of SUBOXONE FILM was evaluated in a trial (RB-US-07-0001) of 382 patients stabilised on SUBOXONE TABLETS for at least 30 days and then switched to SUBOXONE FILM for maintenance treatment. Two hundred and forty-nine (249) patients completed at least 12 weeks of dosing with the SUBOXONE FILM. Patients received SUBOXONE FILM sublingually or buccally in a 1:1 ratio (N=194 sublingually, N=188 buccally). Adjunctive treatment was "treatment as usual" with varying levels of counselling and behavioural treatment. Treatment was conducted on an outpatient basis. Among all patients who received SUBOXONE FILM either sublingually or buccally, the most common treatment emergent adverse events were oral mucosal erythema, sinusitis, nausea, toothache, pain and upper respiratory tract infection. The most common treatment emergent adverse event for the patients administered SUBOXONE FILM sublingually was upper respiratory tract infection (4 patients, 2.1%) and for patients administered SUBOXONE FILM buccally were oral mucosal erythema (6 patients, 3.2%), nausea (4 patients, 2.1%) and sinusitis (4 patients, 2.1%). All other adverse events were reported in 3 (1.5% or 1.6%, respectively) or fewer patients.

Adverse events reported to occur to at least 1% of patients being treated with SUBOXONE FILM in this trial are shown in Table 3.

Table 3 Adverse Events (≥1%) by Body System and Treatment Group in Study RB-US-07-0001, Sublingual and Buccal Administration

System Organ Class Preferred term	**Sublingual N=194**	**Buccal N=188**
Infections and Infestations		
Sinusitis	3 (1.5%)	4 (2.1%)
Upper respiratory tract infection	4 (2.1%)	2 (1.1%)
Pharyngitis streptococcal	2 (1.0%)	2 (1.1%)
Urinary tract infection	3 (1.5%)	1 (0.5%)
Influenza	2 (1.0%)	1 (0.5%)
Tooth abscess	2 (1.0%)	0 (0%)
Nasopharyngitis	0 (0%)	3 (1.6%)
Cellulitis	0 (0%)	2 (1.1%)
Gastrointestinal Disorders		
Glossodynia	3 (1.5%)	1 (0.5%)
Hypoaesthesia oral	2 (1.0%)	1 (0.5%)
Nausea	3 (1.5%)	3 (1.6%)
Oral mucosal erythema	2 (1.0%)	6 (3.2%)
Toothache	2 (1.0%)	4 (2.1%)
Vomiting	3 (1.5%)	2 (1.1%)
Gastrooesophageal reflux disease	1 (0.5%)	3 (1.6%)
Constipation	1 (0.5%)	2 (1.1%)
Musculoskeletal and Connective Tissues Disorders		
Back pain	3 (1.5%)	1 (0.5%)
Arthralgia	2 (1.0%)	0 (0%)
Musculoskeletal pain	2 (1.0%)	0 (0%)
Muscle spasms	0 (0%)	2 (1.1%)
Psychiatric Disorders+		
Stress	2 (1.0%)	1 (0.5%)
Drug dependence (craving)	0 (0%)	2 (1.1%)
Injury, Poisoning and Procedural Complications		
Skin laceration	2 (1.0%)	1 (0.5%)
Road traffic accident	0 (0%)	2 (1.1%)
General Disorders and Administration Site Conditions		
Pain	3 (1.5%)	3 (1.6%)
Oedema peripheral	1 (0.5%)	2 (1.1%)
Nervous System Disorders		
Headache	2 (1.0%)	3 (1.6%)
Migraine	1 (0.5%)	2 (1.1%)

System Organ Class Preferred term	Sublingual N=194	Buccal N=188
Renal and Urinary Disorders		
Nephrolithiasis	2 (1.0%)	2 (1.1%)
Metabolism and Nutrition Disorders		
Gout	1 (0.5%)	2 (1.1%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0 (0%)	2 (1.1%)
Skin and Subcutaneous Tissue Disorders		
Dermatitis contact	2 (1.0%)	0 (0%)
Pregnancy, Puerperium and Perinatal Conditions		
Pregnancy	2 (1.0%)	0 (0%)

* AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 terminology.

Clinical trials of SUBOXONE TABLETS

Adverse events reported to occur to at least 1% of patients being treated in clinical trials of SUBOXONE TABLETS (CR96/013 + CR96/014) are shown in Tables 4 and 5.

Table 4. Adverse Events (≥1%) by Body System and Treatment Group in Study CR96/013

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine/naloxone) TABLETS 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) TABLETS 16 mg/day N=103 n (%)	Placebo N=107 n (%)	All Subjects (N = 317) n (%)
Body as a Whole				
Abscess	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)	19 (6.0%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)	24 (7.6%)
Fever	3 (2.8%)	3 (2.9%)	4 (3.7%)	10 (3.2%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)	93 (29.3%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)	25 (7.9%)
Accidental Injury	2 (1.9%)	5 (4.9%)	5 (4.7%)	12 (3.8%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)	63 (19.9%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)	31 (9.8%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)	24 (7.6%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)	86 (27.1%)
Cardiovascular System				
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)	21 (6.6%)

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine/naloxone) TABLETS 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) TABLETS 16 mg/day N=103 n (%)	Placebo N=107 n (%)	All Subjects (N = 317) n (%)
Digestive System				
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)	24 (7.6%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)	25 (7.9%)
Dyspepsia	4 (3.7%)	5 (4.9%)	5 (4.7%)	14 (4.4%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)	42 (13.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)	21 (6.6%)
Metabolic/Nutritional Disorders				
Peripheral Edema	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)
Musculoskeletal System				
Myalgia	4 (3.7%)	1 (1.0%)	1 (0.9%)	6 (1.9%)
Nervous System				
Agitation	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Anxiety	3 (2.8%)	5 (4.9%)	4 (3.7%)	12 (3.8%)
Dizziness	5 (4.7%)	3 (2.9%)	4 (3.7%)	12 (3.8%)
Hyperkinesia	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Hypertonia	2 (1.9%)	0	2 (1.9%)	4 (1.3%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)	54 (17.0%)
Nervousness	5 (4.7%)	6 (5.8%)	4 (3.7%)	15 (4.7%)
Paresthesia	3 (2.8%)	3 (2.9%)	0	6 (1.9%)
Somnolence	8 (7.5%)	4 (3.9%)	2 (1.9%)	14 (4.4%)
Thinking Abnormal	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Tremor	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)
Respiratory System				
Cough Increased	1 (0.9%)	2 (1.9%)	2 (1.9%)	5 (1.6%)
Pharyngitis	2 (1.9%)	4 (3.9%)	1 (0.9%)	7 (2.2%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)	29 (9.1%)
Skin And Appendages				
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)	39 (12.3%)
Special Senses				
Amblyopia	3 (2.8%)	1 (1.0%)	0	4 (1.3%)

Lacrimation Disorder	0	4 (3.9%)	6 (5.6%)	10 (3.2%)
Urogenital System				
Dysmenorrhea	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)
Urinary Tract Infection	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

Table 5. Adverse Events (≥1%) by Body System and Treatment Group in Study CR96/014

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)
Body as a Whole	
Abscess	17 (3.6%)
Allergic Reaction	8 (1.7%)
Asthenia	48 (10.2%)
Chills	44 (9.3%)
Cyst	7 (1.5%)
Edema, Face	8 (1.7%)
Fever	36 (7.6%)
Flu Syndrome	89 (18.9%)
Headache	202 (42.8%)
Infection	5 (1.1%)
Infection, Viral	5 (1.1%)
Accidental Injury	72 (15.3%)
Malaise	9 (1.9%)
Neck Rigid	5 (1.1%)
Pain	197 (41.7%)
Pain, Abdomen	77 (16.3%)
Pain, Back	132 (28.0%)
Pain, Chest	23 (4.9%)
Pain, Neck	12 (2.5%)
Withdrawal Syndrome	194 (41.1%)
Cardiovascular System	
Hypertension	17 (3.6%)
Migraine	13 (2.8%)
Vasodilation	29 (6.1%)
Digestive System	
Abscess, Periodontal	10 (2.1%)
Anorexia	16 (3.4%)
Constipation	115 (24.4%)
Diarrhea	50 (10.6%)
Dyspepsia	45 (9.5%)
Flatulence	11 (2.3%)
Gastrointestinal Disorder	
Liver Function Abnormal	18 (3.8%)
Nausea	76 (16.1%)

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)
Stomatitis	5 (1.1%)
Tooth Disorder	37 (7.8%)
Ulcer, Mouth	6 (1.3%)
Vomiting	61 (12.9%)
Hemic/Lymphatic System	
Anemia	7 (1.5%)
Ecchymosis	6 (1.3%)
Lymphadenopathy	5 (1.1%)
Metabolic/Nutritional Disorders	
Peripheral Edema	24 (5.1%)
Hyperglycemia	5 (1.1%)
Weight Decreased	15 (3.2%)
Musculoskeletal System	
Arthralgia	20 (4.2%)
Arthritis	5 (1.1%)
Leg Cramps	13 (2.8%)
Joint Disorder	9 (1.9%)
Myalgia	31 (6.6%)
Nervous System	
Agitation	10 (2.1%)
Anxiety	65 (13.8%)
Depression	70 (14.8%)
Dizziness	33 (7.0%)
Dream Abnormalities	9 (1.9%)
Drug Dependence	9 (1.9%)
Hypertonia	9 (1.9%)
Insomnia	138 (29.2%)
Libido Decreased	9 (1.9%)
Nervousness	42 (8.9%)
Paresthesia	28 (5.9%)
Somnolence	40 (8.5%)
Thinking Abnormal	6 (1.3%)
Tremor	7 (1.5%)
Respiratory System	
Asthma	21 (4.4%)
Bronchitis	9 (1.9%)
Cough Increased	36 (7.6%)
Dyspnea	9 (1.9%)
Lung Disorder	10 (2.1%)
Pharyngitis	64 (13.6%)
Pneumonia	12 (2.5%)
Respiratory Disorder	7 (1.5%)
Rhinitis	75 (15.9%)
Sinusitis	7 (1.5%)
Sputum Increased	5 (1.1%)
Yawn	6 (1.3%)

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)
Skin and Appendages	
Acne	5 (1.1%)
Dermatological Contact	5 (1.1%)
Herpes Simplex	6 (1.3%)
Nodule, Skin	6 (1.3%)
Pruritus	11 (2.3%)
Skin Dry	6 (1.3%)
Sweat	74 (15.7%)
Urticaria	6 (1.3%)
Special Senses	
Amblyopia	5 (1.1%)
Conjunctivitis	14 (3.0%)
Eye Disorder	8 (1.7%)
Lacrimation Disorder	14 (3.0%)
Pain, Ear	8 (1.7%)
Urogenital System	
Dysmenorrhea	19 (4.0%)
Dysuria	9 (1.9%)
Hematuria	8 (1.7%)
Impotence	11 (2.3%)
Urinary Tract Infection	19 (4.0%)
Urine Abnormality	12 (2.5%)
Vaginitis	11 (2.3%)

The most common (≥10%) adverse events reported were those related to withdrawal symptoms (e.g. insomnia, headache, constipation, nausea, abdominal pain, diarrhoea, muscle aches, anxiety, sweating). In patients with marked opioid dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

Note - Patients enrolled in study RB-US-07-0001 on the soluble film were on a stable buprenorphine treatment prior to study initiation, while patients enrolled in studies CR96/013 and CR96/014 were buprenorphine-naïve individuals. As a result, the number of AEs observed in study RB-US-07-0001 is likely to be lower than that observed in studies CR96/013 and CR96/014.

Post-marketing experience with buprenorphine alone

Post-marketing experience with buprenorphine alone has been associated with the following side effects: respiratory depression (see section 4.4 Special Warnings and Precautions for Use) and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, foetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, urinary retention, vertigo, drug dependence, headache, nausea, vomiting, drug withdrawal syndrome, peripheral oedema, heart rate and rhythm disorders, and deaths.

Cases of hepatitis, jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, and elevations in hepatic transaminases have been reported with buprenorphine use (see section 4.4 Special Warnings and Precautions for Use).

In cases of intravenous misuse of buprenorphine, local reactions, sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections have been reported.

Cases of acute or chronic hypersensitivity have been reported with buprenorphine with symptoms including rashes, hives, pruritus and reported cases of bronchospasm, angioneurotic oedema, and anaphylactic shock (see section 4.4 Special Warnings and Precautions for Use and section 4.3 Contraindications).

Very rare (<0.01%) side effects: loss of consciousness, cognitive disorders, psychosis, hallucinations, suicidal ideation, disorders of pregnancy (such as miscarriage and termination of pregnancy, premature birth, placental abruption, prolonged labour), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, decreased oxygen saturation, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, cleft palate, Klinefelter's Syndrome, intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, infant respiratory distress syndrome and subarachnoid bleeding), heart murmur, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders, pulmonary oedema, septic shock, infections (including sepsis, septic arthritis and septic embolus, staphylococcal sacroileitis, brain abscess, pneumonia and endocarditis and amniotic fluid infection) events associated with intravenous misuse (such as cutaneous ulceration, eschar, lividoid and necrotic lesions and penile and scrotal lesion), aphasia, aphonia, slurred speech, diplopia, facial palsy, ascites and lympodoema, pulmonary oedema, pulmonary artery thrombosis, pericardial effusion, shock, cerebrovascular accident, Popeye syndrome, intracranial haemorrhage, nephropathy, colic, denutrition splenic infarction, electrolyte imbalance (such as hyperkalaemia, hyponatraemia and hypoglycaemia), deaths (including death from suicide and sudden infant death syndrome) and unusual reactions. The actual incidence of all cases is extremely low and must be taken in consideration with the co-morbidities, life-style, environmental factors, and concomitant illicit and licit opioid use of the population under treatment.

Post-marketing experience with SUBOXONE TABLETS

A post-marketing study looking at injecting practices in Australia suggested that the combination of buprenorphine and naloxone is less commonly injected than buprenorphine alone.

Additionally, post-marketing experience with SUBOXONE TABLETS for treatment of opioid dependence has been associated with the following side effects: anxiety, hyperhidrosis, syncope, insomnia, reduced feeling, anorexia (see also Tables 4 and 5 above), amnesia, convulsions, blood in vomit, fatigue, jaundice, swollen joints, miscarriage, shortness of breath, and suicide ideation. Treatment with SUBOXONE has been associated with orthostatic hypotension.

Additionally, post-marketing experience with SUBOXONE TABLETS for treatment of opioid dependence has been associated very rarely (<0.01%) with the following side effects: attempted suicide, disorders of pregnancy (such as premature birth), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, macrocephaly, meconium staining and aspiration, decreased oxygen saturation, neonatal aspiration, asphyxia, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, low birth weight, Klinefelter's Syndrome, mitochondrial disease, abnormal behaviour, developmental delay, developmental speech disorder intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, subarachnoid bleeding and sudden infant death syndrome), pancreatitis, loss of consciousness, depression of consciousness, coordination disturbance, hallucinations, psychosis, mental disturbance and altered mental state, cerebral oedema, heart rate and rhythm disorders, septic shock, infections (including sepsis, pneumonia, chorioamniotitis and amniotic fluid infection) events associated with intravenous misuse (such as cellulitis), blurred vision, papilloedema, ascites and peripheral oedema, renal failure, adrenal insufficiency, electrolyte imbalance (such as hyperkalaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia and hypoglycaemia) and deaths (including death from suicide and sudden infant death syndrome). The actual incidence of all cases is extremely low and must be taken in consideration with the co-morbidities, life-style,

environmental factors, and concomitant illicit and licit opioid use of the population under treatment.

Post-marketing experience with SUBOXONE FILM

Post-marketing experience with SUBOXONE FILM for the treatment of opioid dependence has been most frequently associated with the following; adverse reactions appearing in at least 1% of

Table 6: Spontaneous adverse drug reactions collected through post-marketing surveillance reported by body system

System Organ Class	Preferred term
Nervous system disorders	Headache
Gastrointestinal disorders	Glossitis Nausea Stomatitis Tongue disorder Vomiting
Skin and subcutaneous disorders	Rash
General disorders and administration site conditions	Drug ineffective Drug withdrawal syndrome Oedema peripheral

reports by healthcare professionals are included in Table 6.

4.9 OVERDOSE

Manifestations of acute overdose include miosis, sedation, hypotension, respiratory depression and death. Nausea and vomiting may be observed.

The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment

In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation following standard intensive care measures. The patient should be transferred to an environment within which full resuscitation facilities are available.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of SUBOXONE FILM should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.

During clinical pharmacology studies in opioid dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, "good effect", and respiratory depression.

Naloxone is an antagonist at μ (mu), δ (delta), and κ (kappa) opioid receptors**.** Because of its almost complete first pass metabolism, naloxone administered orally, sublingually or buccally has no detectable pharmacological activity. However, when administered intravenously to opioid dependent persons, the presence of naloxone in SUBOXONE FILM produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

Clinical Trials

Efficacy of buprenorphine in combination with naloxone was demonstrated with SUBOXONE TABLETS. No clinical efficacy studies have been conducted with SUBOXONE FILM.

All trials used buprenorphine in conjunction with psychosocial counselling as part of a comprehensive opioid dependence treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

Clinical pharmacology studies on SUBOXONE TABLETS demonstrate an aversive effect if SUBOXONE TABLETS are misused by the injection route by opioid dependent patients.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuronidation in the small intestine and the liver. The use of SUBOXONE FILM by the oral route is therefore inappropriate. SUBOXONE FILMS are for sublingual and/or buccal administration. Table 7 shows the pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after administration of SUBOXONE FILM in randomised, crossover studies. Overall, there was wide variability in the sublingual absorption of buprenorphine and naloxone. SUBOXONE FILM and SUBOXONE TABLET do not meet all criteria for bioequivalence. Patients being switched between tablets and soluble films may therefore require dosage adjustment (see Dosage and Administration).

In several pharmacokinetic studies following the administration of different dosages, a dose of one or two of the 2 mg/0.5 mg SUBOXONE FILMS administered sublingually or buccally showed comparable relative bioavailability to the same total dose of SUBOXONE TABLETS. In contrast, one 8 mg/2 mg and one 12 mg/3 mg SUBOXONE FILM administered sublingually or buccally showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE TABLETS. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE FILMS (total dose of 12 mg/ 3 mg) administered sublingually showed comparable relative bioavailability to the same total dose of SUBOXONE TABLETS, while buccally administered SUBOXONE FILMS showed higher relative bioavailability. Table 8, below, illustrates the relative increase in exposure to buprenorphine and naloxone associated with SUBOXONE FILMS compared to SUBOXONE TABLETS, and shows the effect of route of administration.

Table 7. Pharmacokinetic parameters (Mean ± SD) of buprenorphine and naloxone following SUBOXONE FILM administration				
PK Parameter	**SUBOXONE Film Dose (mg)**			
	2 mg/0.5 mg	**4 mg / 1 mg**	**8 mg / 2 mg**	**12 mg / 3 mg**
Buprenorphine				
C_{max} (ng/mL)	0.947 ± 0.374	1.40 ± 0.687	3.37 ± 1.80	4.55 ± 2.50
T_{max} (h) Median, (min-max)	1.53 (0.75 - 4.0)	1.50 (0.5, 3.0)	1.25 (0.75 - 4.0)	1.50 (0.5, 3.0)
AUC_{inf} (ng.hr/mL)	8.654 ± 2.854	13.71 ± 5.875	30.45 ± 13.03	42.06 ± 14.64
$t_{1/2}$ (hr)	33.41 ± 13.01	24.30 ± 11.03	32.82 ± 9.81	34.66 ± 9.16
Norbuprenorphine				
C_{max} (ng/mL)	0.312 ±0.140	0.617 ±0.311	1.40 ±1.08	2.37 ±1.87
T_{max} (h) Median, (min-max)	1.38 (0.5 - 8.0)	1.25 (0.5, 48.0)	1.25 (0.75 - 12.0)	1.25 (0.75, 8.0)
AUC_{inf} (ng.hr/mL)	14.52 ±5.776	23.73 ±10.60	54.91 ±36.01	71.77 ±29.38
$t_{1/2}$ (hr)	56.09 ±31.14	45.96 ±40.13	41.96 ±17.92	34.36 ±7.92
Naloxone				
C_{max} (ng/mL)	0.054 ± 0.023	0.0698 ± 0.0378	0.193 ± 0.091	0.238 ± 0.144
T_{max} (h) Median, (min-max)	0.75 (0.5 - 2.0)	0.75 (0.5, 1.5)	0.75 (0.5 - 1.25)	0.75 (0.50, 1.25)
AUC_{inf} (ng.hr/mL)	0.137 ± 0.043	0.204 ± 0.108	0.481 ± 0.201	0.653 ± 0.309
$t_{1/2}$ (hr)	5.00 ± 5.52	3.91 ± 3.37	6.25 ± 3.14	11.91 ± 13.80

Table 8. Changes in Pharmacokinetic Parameters for SUBOXONE FILM Administered Sublingually or Buccally in Comparison to SUBOXONE TABLET								
Dosage	PK Parameter	**Increase in Buprenorphine**			PK Parameter	**Increase in Naloxone**		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 x 2 mg/0.5 mg	C_{max}	22%	25%	-	C_{max}	-	-	-
	$AUC_{0\text{-last}}$	-	19%	-	$AUC_{0\text{-last}}$	-	-	-
2 x 2 mg/0.5 mg	C_{max}	-	21%	21%	C_{max}	-	17%	21%
	$AUC_{0\text{-last}}$	-	23%	16%	$AUC_{0\text{-last}}$	-	22%	24%
1 x 8 mg/2 mg	C_{max}	28%	34%	-	C_{max}	41%	54%	-
	$AUC_{0\text{-last}}$	20%	25%	-	$AUC_{0\text{-last}}$	30%	43%	-

1 x 12 mg/3 mg	C_{max}	37%	47%	-	C_{max}	57%	72%	9%
	$AUC_{0\text{-last}}$	21%	29%	-	$AUC_{0\text{-last}}$	45%	57%	-
1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg	C_{max}	-	27%	13%	C_{max}	17%	38%	19%
	$AUC_{0\text{-last}}$	-	23%	-	$AUC_{0\text{-last}}$	-	30%	19%

Note: 1. '–' represents no change when the 90% confidence intervals for the geometric mean ratios of the C_{max} and $AUC_{0\text{-last}}$ values are within the 80% to 125% limit. 2. There is no data for the 4 mg/1 mg strength film; it is compositionally proportional to 2 mg/0.5 mg strength film and has the same size of 2 x 2 mg/0.5 mg film strength.

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours). Following intravenous administration, naloxone is rapidly distributed (distribution half-life of around 4 minutes).

Buprenorphine is highly lipophilic which leads to rapid penetration of the blood-brain barrier. The medicine is around 96% protein bound primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism

In animals and man buprenorphine is metabolised by Phase 1 (oxidative) and Phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP 3A4. In in vitro metabolic studies, addition of specific inhibitors of CYP 3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine (see also section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions). There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity and is considered to be an inactive metabolite.

Naloxone undergoes direct glucuroconjugation to naloxone-3-glucuronide as well as N-dealkylation and reduction of the 6-oxo group.

Excretion

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase (refer to Table 1), due in part to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite, and in part to the highly lipophilic nature of the molecule. Naloxone has a short elimination half-life (refer to Table 7).

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine. Naloxone is excreted in the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In genotoxicity studies using buprenorphine and naloxone (9:2), assays for bacterial gene mutations and chromosomal damage (human lymphocytes in vitro and rat micronucleus test in vivo) were negative.

Carcinogenicity

In mice, no evidence for carcinogenicity due to buprenorphine was noted in life-time studies at dietary doses of up to 100 mg/kg/day, which equates to ca 14-fold human exposure at the maximum recommended clinical dose of 32 mg based on body surface area.

In rats, statistically significant (trend test adjusted for survival) dose-related increases in testicular interstitial (Leydig) cell tumours occurred at a dietary buprenorphine dose of 55 mg/kg/day (16 fold the maximal recommended human sublingual dose of 32 mg, on a mg/m2 basis); the no-effect dose was 5.4 mg/kg/day (twice the maximal human dose, on a mg/m2 basis). The carcinogenic potential of naloxone alone has not been investigated in long term animal studies.

In a 2-year dietary study with SUBOXONE TABLETS in rats, Leydig cell adenomas were found at doses of 6-115 mg/kg/day, associated with respective exposures (plasma AUC) to buprenorphine and naloxone of 2-21 fold, and up to 58 fold, anticipated human exposure. A NOEL was not established in the study.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each soluble film contains acesulfame potassium, citric acid, maltitol solution, hypromellose, polyethylene oxide, sodium citrate, lime flavour, Sunset Yellow FCF and a white printing ink.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

12 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25oC.

6.5 NATURE AND CONTENTS OF CONTAINER

Each soluble film is packed in an individual child resistant polyethylene terephthalate (PET)/low density polyethylene (LDPE)/aluminium/ethylene acrylic acid (EAA) or PET/LDPE/aluminium/LDPE sachet. There are 28 sachets in a pack.

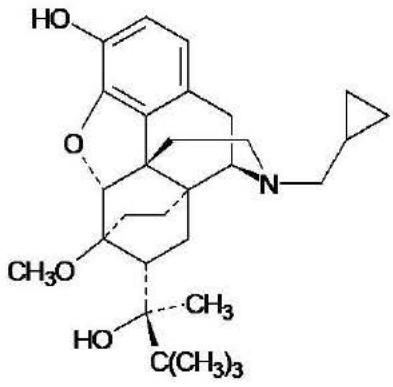
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

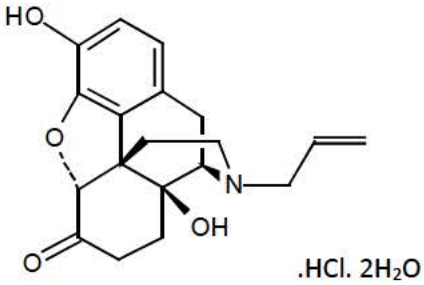
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structures of buprenorphine hydrochloride and naloxone hydrochloride dihydrate are:



.HCl



.HCl. $2H_2O$

Buprenorphine hydrochloride

Naloxone hydrochloride dihydrate

CAS number

The CAS number of buprenorphine hydrochloride is 53152-21-9.

The CAS number of naloxone hydrochloride dihydrate is 51481-60-8.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 - Controlled Drug

8 SPONSOR

Indivior Pty Ltd
78 Waterloo Road
Macquarie Park NSW 2113
Australia

For adverse event reporting please contact:
Indivior Pty Ltd
+800-270-81901
PatientSafetyRoW@indivior.com

9 DATE OF FIRST APPROVAL

2 November 2000

10 DATE OF REVISION

~~30 August~~ xxxx 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat of PI
4.2 4.3 4.6	Removal of pregnancy and lactation from contraindications and changes to dose and method of administration

AUSTRALIAN PRODUCT INFORMATION

SUBOXONE FILM (BUPRENORPHINE/NALOXONE)

1 NAME OF THE MEDICINE

SUBOXONE FILM contains buprenorphine (as hydrochloride) and naloxone (as hydrochloride dihydrate) at a ratio of 4:1 buprenorphine: naloxone (ratio of free bases).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SUBOXONE FILM is available in four dosage strengths:

2 mg buprenorphine (as hydrochloride) + 0.5 mg naloxone (as hydrochloride dihydrate)
4 mg buprenorphine (as hydrochloride) + 1 mg naloxone (as hydrochloride dihydrate)
8 mg buprenorphine (as hydrochloride) + 2 mg naloxone (as hydrochloride dihydrate) and
12 mg buprenorphine (as hydrochloride) + 3 mg naloxone (as hydrochloride dihydrate).

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg /mL at 37°C, pH 4.1). Chemically, it is 21- Cyclopropyl-7α-[(S) -1- hydroxy-1, 2, 2 -trimethylpropyl]-6, 14-endo-ethano-6, 7, 8, 14-tetrahydrooripavine hydrochloride. Buprenorphine hydrochloride has the molecular formula C29 H41 NO4 HCl and the molecular weight is 504.09. The CAS number is 53152-21-9.

Naloxone hydrochloride is a white to slightly off-white powder that exists as the dihydrate and is soluble in water, in dilute acids and in strong alkali. Chemically, it is (-)-17-Allyl-4, 5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. Naloxone hydrochloride has the molecular formula C19 H21 NO4 HCl .2H2O and the molecular weight is 399.87.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

SUBOXONE FILM is a soluble film intended for sublingual and or buccal administration only.
SUBOXONE FILM is supplied as an orange rectangular soluble film with a white printed logo in four dosage strengths:

- "N2" for 2/0.5 mg buprenorphine/naloxone
- "N4" for 4/1 mg buprenorphine/naloxone*
- "N8" for 8/2 mg buprenorphine/naloxone and
- "N12" for 12/3 mg buprenorphine/naloxone*.

* Not supplied

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of opioid dependence within a framework of medical, social and psychological treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with SUBOXONE FILM is intended for adults and children aged 16 years or over who have agreed to be treated for opioid dependence.

SUBOXONE FILM and SUBOXONE TABLET do not meet all criteria for bioequivalence (see section 5.2 Pharmacokinetic Properties). Patients being switched between tablets and soluble films may therefore require dosage adjustment.

The routes of administration of SUBOXONE FILM is sublingual and buccal only. The film formulation is not designed to be split or broken.

SUBOXONE FILMS should not be swallowed whole as this reduces the bioavailability of the medicine. Physicians must advise patients that the sublingual and buccal route are the only effective and safe route of administration for this medicine.

Please note: The following instructions refer to the buprenorphine content of each dose.

Method of Administration

Sublingual Administration

Place one film under the tongue, close to the base on the left or right side. If an additional film is necessary to achieve the prescribed dose, place an additional film sublingually on the opposite side from the first film. Place the film in a manner to minimize overlapping as much as possible. The film must be kept under the tongue until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it under the tongue on either side after the first 2 films have dissolved.

Buccal Administration

Place one film on the inside of the right or left cheek. If an additional film is necessary to achieve the prescribed dose, place an additional film on the inside of the opposite cheek. The film must be kept on the inside of the cheek until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it on the inside of the right or left cheek after the first two films have dissolved.

No food or drink should be consumed until the film is completely dissolved. SUBOXONE FILM should NOT be chewed, swallowed, or moved from placement.

Starting SUBOXONE FILM

An adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal symptoms due to inadequate dosage.

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use and the degree or level of opioid dependence.

Due to naloxone exposure being somewhat higher following buccal administration than sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimise naloxone exposure and to reduce the risk of precipitated withdrawal.

Induction onto SUBUTEX (buprenorphine tablets) is recommended when there is doubt about the level of dependence or previous opioid use, to avoid precipitating opioid withdrawal. Patients can be switched to SUBOXONE FILM on the third day.

When initiating buprenorphine treatment, the physician should be aware of the partial agonist profile of the molecule to the μ opioid receptors, which can precipitate withdrawal in opioid-dependent patients if given too soon after the administration of heroin, methadone or another opioid. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective and clear signs of withdrawal are evident.

Patients taking Heroin (or Other Short-acting Opioids)

When treatment starts the dose of SUBOXONE FILM should be taken at least 6 hours after the patient last used opioids and when the objective signs of withdrawal appear. The Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment however clinical assessment of withdrawal symptoms with consideration of the patient's baseline presentation is important, particularly for patients in mild withdrawal (COWS score of 5-12). The recommended starting dose is 4-8 mg SUBOXONE FILM on Day One, with a possible additional 4 mg depending on the individual patient's requirement. The suggested target total dose for Day One is in the range of 8-12 mg SUBOXONE FILM. For patients with moderate or severe withdrawal at the time of the first dose, an initial dose of 8 mg may be appropriate with an additional 4 mg depending on the individual patient's requirement to a total maximum of 12 mg on Day 1.

Lower doses (e.g. 2 or 4 mg total on Day 1) are suited to those with low or uncertain levels of opioid dependence, with high risk polydrug use (alcohol, benzodiazepines) or with other severe medical complications. Seek specialist advice if concerned.

Patients on Methadone

Before starting treatment with SUBOXONE FILM, the maintenance dose of methadone should be reduced to the minimum methadone daily dose that the patient can tolerate. The first dose of SUBOXONE FILM should be taken at least 24 hours after the patient last used methadone. An initial dose of 2 mg SUBOXONE FILM may be administered when moderate withdrawal is apparent (COWS ≥ 13). An additional dose of 6 mg SUBOXONE FILM can be administered one hour later if the initial dose does not precipitate withdrawal. Supplementary doses can be administered every 1 to 3 hours according to withdrawal severity:

- 0 mg if there is no or minimal withdrawal (COWS < 5);
- 4 mg if there is mild withdrawal (COWS 5-12);
- 8 mg if there is moderate to severe withdrawal (COWS ≥ 13).

The suggested target total dose for Day One is in the range of 8 – 16 mg SUBOXONE FILM. A maximum daily dose of 32 mg should not be exceeded.

During the initiation of treatment, patients need frequent monitoring. SUBOXONE FILM should be dispensed in multiple doses over the first 4 to 6 hours of the transfer. Dosing supervision is recommended to ensure proper placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

Switching between treatments for opioid dependence

Patients should be closely monitored during the switching period from buprenorphine or methadone to buprenorphine/naloxone since withdrawal symptoms have been reported.

Switching between SUBOXONE FILM strengths

The sizes and the compositions of the four units of SUBOXONE FILMs, i.e., 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE FILMs to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be monitored for over-dosing or under-dosing. For this reason, pharmacist should not substitute one or more film strengths for another without approval of the prescriber.

Switching between sublingual and buccal sites of administration

The systematic exposure of buprenorphine between buccal and sublingual administration of SUBOXONE FILM is similar. Therefore, once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under or overdosing.

Dose adjustment in hepatic impairment

Use of SUBOXONE FILM is contraindicated in patients with severe hepatic impairment.

SUBOXONE FILM may not be appropriate for patients with moderate hepatic impairment. SUBOXONE FILM may be used with caution for maintenance treatment in patients with moderate hepatic impairment, who have initiated treatment on a buprenorphine-only product. Patients with moderate hepatic impairment prescribed SUBOXONE should be monitored for signs and symptoms of precipitated opioid withdrawal. In addition, lower initial doses and cautious titration of dosage may be required in patients with moderate hepatic impairment.

No dosage adjustment is needed in patients with mild hepatic impairment.

Dosage Adjustment and Maintenance

The dose of SUBOXONE FILM should be adjusted progressively according to the clinical effect in the individual patient. The dosage is adjusted in increments or decrements of 2 – 8 mg buprenorphine to a level that maintains the patient in treatment and suppresses opioid withdrawal effects according to reassessments of the clinical and psychological status of the patient.

Most patients require daily buprenorphine doses in the range 12-24 mg to achieve stabilisation, although some patients require higher (e.g. up to 32 mg/day) or lower (4-8 mg/day) doses to achieve their treatment goals. During maintenance therapy, it may be necessary to periodically restabilise patients to new maintenance doses in response to changing patient needs.

Less than daily dosing

After a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

In some patients, after a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

The patient should be observed following the first multi-dose administration to initiate the less-than-daily dosing regimen, and whenever treated with high doses. Patients who sporadically use concomitant CNS-active medications or substances should be monitored closely.

Reducing Dosage and Stopping Treatment

The decision to discontinue therapy with SUBOXONE FILM should be made as part of a comprehensive treatment plan. A possible gradual dose taper over a period of 21 days is shown in Table 1.

Table 1.	**Gradual dose taper schedule**		
Week	**20 mg Maintenance dose**	**16 mg Maintenance dose**	**8 mg Maintenance dose**
1	16 mg	12 mg	8 mg
2	8 mg	8 mg	4 mg
3	4 mg	4 mg	4 mg

4.3 CONTRAINDICATIONS

Hypersensitivity to buprenorphine or naloxone or any other component of the soluble film.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency (Child-Pugh C).
Acute intoxication with alcohol or other CNS depressant.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

SUBOXONE FILM should be administered with caution in debilitated patients and those with impairment of hepatic, pulmonary, or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (e.g. Addison's disease); CNS depression or coma; toxic psychoses; acute alcoholism; or delirium tremens.

Buprenorphine increases intracholedochal pressure as do other opioids. Therefore, caution should be exercised when SUBOXONE FILM is to be administered to patients with dysfunction of the biliary tract.

As with other opioids, caution is advised in patients using buprenorphine and having hypotension, prostatic hypertrophy or urethral stenosis.

Opioids may produce orthostatic hypotension in ambulatory patients.

As with other mu-opioid receptor agonists, the administration of SUBOXONE FILM may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Use in the elderly

The safety and efficacy of buprenorphine in elderly patients over 65 years have not been established.

Misuse, abuse and diversion

SUBOXONE can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. SUBOXONE misuse by someone other than the intended patient poses the additional risk of new opioid dependent individuals using buprenorphine as the primary opioid of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft, including in the home. Sub-optimal treatment with SUBOXONE may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with SUBOXONE may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines. To minimise risk of misuse, abuse or diversion, appropriate precautions should be taken when prescribing and dispensing SUBOXONE, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

Patients dependent upon concomitant CNS-active substances, including alcohol, should not be treated with the increased doses required by the less-than-daily dosing regimen intended for use in a supervised dose setting. Patients with sporadic use of concomitant non-opioid medications should be monitored closely, and all patients dosed on a less-than-daily basis should be observed following the first multi-dose administration when initiating less-than-daily dosing or whenever treated with high doses.

Respiratory Depression

SUBOXONE FILM is intended for sublingual or buccal use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when buprenorphine was used in combination with benzodiazepines, in opioid naïve individuals, or when buprenorphine was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBOXONE FILM.

In the event of depression of respiratory or cardiac function, see section 4.9 Overdose.

SUBOXONE FILM should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis).

SUBOXONE FILM may cause severe, possible fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

CNS Depression

SUBOXONE may cause drowsiness, particularly when used together with alcohol or other central nervous system depressants (such as benzodiazepines, tranquillisers, sedatives or hypnotics (see section 4.5 Interactions). When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. SUBOXONE FILM should be used cautiously with MAOIs, based on experience with morphine.

Hepatitis, Hepatic Events

Cases of acute hepatic injury have been reported in opioid-dependent patients, both in clinical trials and post marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose-related, and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, liver enzyme abnormalities, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues, or drug misuse by injection) could promote the occurrence of such hepatic injuries. These co-factors must be taken into account before prescribing SUBOXONE FILM and during treatment monitoring. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicines (see section 4.5 Interactions) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicine may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to opioid dependence. If treatment is continued, hepatic function should be monitored closely.

Use in hepatic Impairment

Buprenorphine and naloxone are extensively metabolised by the liver. The effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study, in which a SUBOXONE 2.0/0.5 mg (buprenorphine/naloxone) sublingual tablet was administered to healthy subjects and subjects with varying degrees of hepatic impairment. Plasma levels were found to be elevated for buprenorphine and naloxone in patients with moderate to severe hepatic impairment (Table 2). Patients with severe hepatic impairment experienced substantially greater increases in exposure to naloxone relative to buprenorphine, and patients with moderate hepatic impairment experienced greater increases in exposure to naloxone relative to buprenorphine. The clinical impact in terms of efficacy/safety is unknown, but is likely to be greater for those with severe hepatic impairment than those with moderate hepatic impairment.

The doses of buprenorphine and naloxone in SUBOXONE cannot be individually titrated. As such, SUBOXONE should be avoided in patients with severe hepatic impairment. Use of SUBOXONE may not be appropriate in those with moderate hepatic impairment. It may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine-only product. Patients with moderate hepatic impairment should be monitored for signs and symptoms of precipitated opioid withdrawal. In addition, lower initial doses and cautious titration of dosage may be required in patients with moderate hepatic

impairment. As with all patients treated with SUBOXONE, liver function tests should be monitored prior to and during treatment. See also section 4.2 Dose and Method of administration.

Table 2: Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following buprenorphine/naloxone administration (change relative to healthy subjects)

PK parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
BUPRENORPHINE			
Cmax	1.2 fold increase	1.1 fold increase	1.7 fold increase
AUC_{last}	Similar to control	1.6 fold increase	2.8 fold increase
NALOXONE			
Cmax	Similar to control	2.7 fold increase	11.3 fold increase
AUC_{last}	0.2 fold increase	3.2 fold increase	14 fold increase

In the same study, changes in Cmax and AUClast of buprenorphine and naloxone in subjects with HCV infection without hepatic impairment were not clinically significant in comparison to the healthy subjects.

Use in renal impairment

Renal elimination plays a relatively small role (~30%) in the overall clearance of SUBUTEX. Therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min), which may require dose adjustment.

Head Injury and Increased Intracranial Pressure

SUBOXONE FILM, like other potent opioids may itself elevate cerebrospinal fluid pressure, which may cause seizures, and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased, or history of seizure. SUBOXONE FILM can produce miosis and changes in the level of consciousness, or changes in the perception of pain as a symptom of disease and may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.

Opioid Withdrawal Effects

Because SUBOXONE FILM contains naloxone, it is highly likely to produce marked and intense opioid withdrawal symptoms if injected by patients treated with SUBUTEX or SUBOXONE or by persons dependent on full opioid agonists such as heroin, oxycodone, morphine or methadone.

SUBOXONE FILM may produce withdrawal symptoms in opioid dependent subjects if it is administered too soon after another opioid. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed.

Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and studies in animals, as well as clinical experience, have shown that buprenorphine may produce dependence, but at a lower level than morphine. Consequently, it is important to follow the recommendations in section 4.2 Dose and Method of administration. Withdrawal symptoms may also be associated with suboptimal dosing.

Neonatal Abstinence Syndrome

Chronic use of buprenorphine by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, apnoea, convulsions

or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth (see section 4.6 Use in Pregnancy). Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Allergic Reactions

Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic oedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to SUBOXONE FILM use.

Paediatric Use

SUBOXONE FILM is not recommended for use in children. The safety and effectiveness of SUBOXONE FILM in subjects below the age of 16 has not been established. Due to limited amount of available data, patients between 16 and 18 years of age should be closely monitored during treatment.

Effects on Laboratory Tests

Athletes should be aware that this medicine may cause a positive reaction to "anti-doping" tests.

Use in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received doses as low as 2 mg of buprenorphine sublingual tablet for analgesia. SUBOXONE is not appropriate as an analgesic.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Alcohol

Alcohol increases the sedative effect of buprenorphine/naloxone. SUBOXONE should not be used together with alcoholic drinks, and must be used cautiously with medicines containing alcohol (see section 4.4 Special Warnings and Precautions for Use).

Benzodiazepines

This combination may result in death due to respiratory depression of central origin; therefore, patients must be closely monitored when prescribed this combination, and this combination should be avoided where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed (see section 4.4 Special Warnings and Precautions for Use).

Other central nervous system depressants

Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. The reduced level of alertness can make driving and using machinery dangerous. Examples include opioids (e.g. methadone, analgesics, and antitussives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine (see section 4.4 Special Warnings and Precautions for Use).

Opioid analgesics

The analgesic properties of other opioids such as methadone and level III analgesics may be reduced in patients receiving treatment with buprenorphine/naloxone for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving SUBOXONE. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma

levels are declining. Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see section 4.4 Special Warnings and Precautions for Use).

Naltrexone and other opioid antagonists

Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of SUBOXONE FILM. Patients maintained on SUBOXONE FILM may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations.

CYP3A4 inhibitors

An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving SUBOXONE FILM should be closely monitored, and may require dose reduction if combined with potent CYP3A4 inhibitors e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, azole antifungals like ketoconazole or itraconazole, calcium channel antagonists, and macrolide antibiotics.

CYP3A4 inducers

Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in under-treatment of opioid dependence with buprenorphine; therefore, it is recommended that patients receiving SUBOXONE FILM should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, and rifampicin) are co-administered.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There were no effects on mating performance or fertility in rats following buprenorphine treatment at oral doses 20 times the maximum clinical dose of 32 mg/day (based on mg/m2). Dietary administration of SUBOXONE TABLETS to rats at doses of 47 mg/kg/day or greater (estimated respective buprenorphine and naloxone exposures 14 and 24 times the anticipated clinical exposure, based on plasma AUC) resulted in reduced female conception rates. A dietary dose of 9.4 mg/kg/day (twice the anticipated clinical exposure for both buprenorphine (based on AUC) and naloxone (based on mg/m2) had no adverse effect on fertility.

Use in Pregnancy – Pregnancy Category C

In rats, oral administration of buprenorphine at doses up to 20 times the maximum clinical dose of 32 mg/day (based on mg/m2) prior to and during gestation and lactation resulted in reduced implantation, fewer live births, and reduced pup weight gain and survival. There was no evidence of teratogenicity in rats and rabbits following parenteral administration of buprenorphine during the period of organogenesis, although there was embryofoetal toxicity, and reduced pup viability and developmental delays in rats. There was no evidence of teratogenicity in rats and rabbits following oral or intramuscular administration of maternally toxic doses of combinations of buprenorphine + naloxone during the period of organogenesis, although post-implantation losses were increased. In rats, oral (20 times maximum clinical dose, based on mg/m2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response).

Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. SUBOXONE FILM should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Continued use of

heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

Data on the use of buprenorphine in pregnancy, and its impact on the mother and foetus, are limited. Data from randomised, controlled trials and observational studies do not indicate an increased risk of maternal or foetal adverse outcomes compared to methadone.

Use in Lactation

Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. In rats, oral (20 times maximum clinical dose, based on mg/m2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response). The no effect level for developmental effects was twice the maximum clinical dose, based on mg/m2. In two studies of thirteen women, buprenorphine was found in low levels in human breast milk. In both studies the estimated infant dose was <1% of the maternal dose. Because buprenorphine is excreted into human milk, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBOXONE FILM and any potential adverse effects on the breastfed child from the treatment or the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SUBOXONE may influence the ability to drive and use machinery when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions). Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SUBOXONE therapy does not adversely affect their ability to engage in such activities.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Safety Study of SUBOXONE FILM

The clinical safety of SUBOXONE FILM was evaluated in a trial (RB-US-07-0001) of 382 patients stabilised on SUBOXONE TABLETS for at least 30 days and then switched to SUBOXONE FILM for maintenance treatment. Two hundred and forty-nine (249) patients completed at least 12 weeks of dosing with the SUBOXONE FILM. Patients received SUBOXONE FILM sublingually or buccally in a 1:1 ratio (N=194 sublingually, N=188 buccally). Adjunctive treatment was "treatment as usual" with varying levels of counselling and behavioural treatment. Treatment was conducted on an outpatient basis. Among all patients who received SUBOXONE FILM either sublingually or buccally, the most common treatment emergent adverse events were oral mucosal erythema, sinusitis, nausea, toothache, pain and upper respiratory tract infection. The most common treatment emergent adverse event for the patients administered SUBOXONE FILM sublingually was upper respiratory tract infection (4 patients, 2.1%) and for patients administered SUBOXONE FILM buccally were oral mucosal erythema (6 patients, 3.2%), nausea (4 patients, 2.1%) and sinusitis (4 patients, 2.1%). All other adverse events were reported in 3 (1.5% or 1.6%, respectively) or fewer patients.

Adverse events reported to occur to at least 1% of patients being treated with SUBOXONE FILM in this trial are shown in Table 3.

Table 3 Adverse Events (≥1%) by Body System and Treatment Group in Study RB-US-07-0001, Sublingual and Buccal Administration

System Organ Class Preferred term	**Sublingual N=194**	**Buccal N=188**
Infections and Infestations		
Sinusitis	3 (1.5%)	4 (2.1%)
Upper respiratory tract infection	4 (2.1%)	2 (1.1%)
Pharyngitis streptococcal	2 (1.0%)	2 (1.1%)
Urinary tract infection	3 (1.5%)	1 (0.5%)
Influenza	2 (1.0%)	1 (0.5%)
Tooth abscess	2 (1.0%)	0 (0%)
Nasopharyngitis	0 (0%)	3 (1.6%)
Cellulitis	0 (0%)	2 (1.1%)
Gastrointestinal Disorders		
Glossodynia	3 (1.5%)	1 (0.5%)
Hypoaesthesia oral	2 (1.0%)	1 (0.5%)
Nausea	3 (1.5%)	3 (1.6%)
Oral mucosal erythema	2 (1.0%)	6 (3.2%)
Toothache	2 (1.0%)	4 (2.1%)
Vomiting	3 (1.5%)	2 (1.1%)
Gastrooesophageal reflux disease	1 (0.5%)	3 (1.6%)
Constipation	1 (0.5%)	2 (1.1%)
Musculoskeletal and Connective Tissues Disorders		
Back pain	3 (1.5%)	1 (0.5%)
Arthralgia	2 (1.0%)	0 (0%)
Musculoskeletal pain	2 (1.0%)	0 (0%)
Muscle spasms	0 (0%)	2 (1.1%)
Psychiatric Disorders+		
Stress	2 (1.0%)	1 (0.5%)
Drug dependence (craving)	0 (0%)	2 (1.1%)
Injury, Poisoning and Procedural Complications		
Skin laceration	2 (1.0%)	1 (0.5%)
Road traffic accident	0 (0%)	2 (1.1%)
General Disorders and Administration Site Conditions		
Pain	3 (1.5%)	3 (1.6%)
Oedema peripheral	1 (0.5%)	2 (1.1%)
Nervous System Disorders		
Headache	2 (1.0%)	3 (1.6%)
Migraine	1 (0.5%)	2 (1.1%)

System Organ Class Preferred term	Sublingual N=194	Buccal N=188
Renal and Urinary Disorders		
Nephrolithiasis	2 (1.0%)	2 (1.1%)
Metabolism and Nutrition Disorders		
Gout	1 (0.5%)	2 (1.1%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0 (0%)	2 (1.1%)
Skin and Subcutaneous Tissue Disorders		
Dermatitis contact	2 (1.0%)	0 (0%)
Pregnancy, Puerperium and Perinatal Conditions		
Pregnancy	2 (1.0%)	0 (0%)

* AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 terminology.

Clinical trials of SUBOXONE TABLETS

Adverse events reported to occur to at least 1% of patients being treated in clinical trials of SUBOXONE TABLETS (CR96/013 + CR96/014) are shown in Tables 4 and 5.

Table 4. Adverse Events (≥1%) by Body System and Treatment Group in Study CR96/013

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine/naloxone) TABLETS 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) TABLETS 16 mg/day N=103 n (%)	Placebo N=107 n (%)	All Subjects (N = 317) n (%)
Body as a Whole				
Abscess	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)	19 (6.0%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)	24 (7.6%)
Fever	3 (2.8%)	3 (2.9%)	4 (3.7%)	10 (3.2%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)	93 (29.3%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)	25 (7.9%)
Accidental Injury	2 (1.9%)	5 (4.9%)	5 (4.7%)	12 (3.8%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)	63 (19.9%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)	31 (9.8%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)	24 (7.6%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)	86 (27.1%)
Cardiovascular System				
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)	21 (6.6%)

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine/naloxone) TABLETS 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) TABLETS 16 mg/day N=103 n (%)	Placebo N=107 n (%)	All Subjects (N = 317) n (%)
Digestive System				
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)	24 (7.6%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)	25 (7.9%)
Dyspepsia	4 (3.7%)	5 (4.9%)	5 (4.7%)	14 (4.4%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)	42 (13.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)	21 (6.6%)
Metabolic/Nutritional Disorders				
Peripheral Edema	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)
Musculoskeletal System				
Myalgia	4 (3.7%)	1 (1.0%)	1 (0.9%)	6 (1.9%)
Nervous System				
Agitation	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Anxiety	3 (2.8%)	5 (4.9%)	4 (3.7%)	12 (3.8%)
Dizziness	5 (4.7%)	3 (2.9%)	4 (3.7%)	12 (3.8%)
Hyperkinesia	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Hypertonia	2 (1.9%)	0	2 (1.9%)	4 (1.3%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)	54 (17.0%)
Nervousness	5 (4.7%)	6 (5.8%)	4 (3.7%)	15 (4.7%)
Paresthesia	3 (2.8%)	3 (2.9%)	0	6 (1.9%)
Somnolence	8 (7.5%)	4 (3.9%)	2 (1.9%)	14 (4.4%)
Thinking Abnormal	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Tremor	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)
Respiratory System				
Cough Increased	1 (0.9%)	2 (1.9%)	2 (1.9%)	5 (1.6%)
Pharyngitis	2 (1.9%)	4 (3.9%)	1 (0.9%)	7 (2.2%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)	29 (9.1%)
Skin And Appendages				
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)	39 (12.3%)
Special Senses				
Amblyopia	3 (2.8%)	1 (1.0%)	0	4 (1.3%)

Lacrimation Disorder	0	4 (3.9%)	6 (5.6%)	10 (3.2%)
Urogenital System				
Dysmenorrhea	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)
Urinary Tract Infection	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

Table 5. Adverse Events (≥1%) by Body System and Treatment Group in Study CR96/014

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)
Body as a Whole	
Abscess	17 (3.6%)
Allergic Reaction	8 (1.7%)
Asthenia	48 (10.2%)
Chills	44 (9.3%)
Cyst	7 (1.5%)
Edema, Face	8 (1.7%)
Fever	36 (7.6%)
Flu Syndrome	89 (18.9%)
Headache	202 (42.8%)
Infection	5 (1.1%)
Infection, Viral	5 (1.1%)
Accidental Injury	72 (15.3%)
Malaise	9 (1.9%)
Neck Rigid	5 (1.1%)
Pain	197 (41.7%)
Pain, Abdomen	77 (16.3%)
Pain, Back	132 (28.0%)
Pain, Chest	23 (4.9%)
Pain, Neck	12 (2.5%)
Withdrawal Syndrome	194 (41.1%)
Cardiovascular System	
Hypertension	17 (3.6%)
Migraine	13 (2.8%)
Vasodilation	29 (6.1%)
Digestive System	
Abscess, Periodontal	10 (2.1%)
Anorexia	16 (3.4%)
Constipation	115 (24.4%)
Diarrhea	50 (10.6%)
Dyspepsia	45 (9.5%)
Flatulence	11 (2.3%)
Gastrointestinal Disorder	
Liver Function Abnormal	18 (3.8%)
Nausea	76 (16.1%)

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)
Stomatitis	5 (1.1%)
Tooth Disorder	37 (7.8%)
Ulcer, Mouth	6 (1.3%)
Vomiting	61 (12.9%)
Hemic/Lymphatic System	
Anemia	7 (1.5%)
Ecchymosis	6 (1.3%)
Lymphadenopathy	5 (1.1%)
Metabolic/Nutritional Disorders	
Peripheral Edema	24 (5.1%)
Hyperglycemia	5 (1.1%)
Weight Decreased	15 (3.2%)
Musculoskeletal System	
Arthralgia	20 (4.2%)
Arthritis	5 (1.1%)
Leg Cramps	13 (2.8%)
Joint Disorder	9 (1.9%)
Myalgia	31 (6.6%)
Nervous System	
Agitation	10 (2.1%)
Anxiety	65 (13.8%)
Depression	70 (14.8%)
Dizziness	33 (7.0%)
Dream Abnormalities	9 (1.9%)
Drug Dependence	9 (1.9%)
Hypertonia	9 (1.9%)
Insomnia	138 (29.2%)
Libido Decreased	9 (1.9%)
Nervousness	42 (8.9%)
Paresthesia	28 (5.9%)
Somnolence	40 (8.5%)
Thinking Abnormal	6 (1.3%)
Tremor	7 (1.5%)
Respiratory System	
Asthma	21 (4.4%)
Bronchitis	9 (1.9%)
Cough Increased	36 (7.6%)
Dyspnea	9 (1.9%)
Lung Disorder	10 (2.1%)
Pharyngitis	64 (13.6%)
Pneumonia	12 (2.5%)
Respiratory Disorder	7 (1.5%)
Rhinitis	75 (15.9%)
Sinusitis	7 (1.5%)
Sputum Increased	5 (1.1%)
Yawn	6 (1.3%)

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)
Skin and Appendages	
Acne	5 (1.1%)
Dermatological Contact	5 (1.1%)
Herpes Simplex	6 (1.3%)
Nodule, Skin	6 (1.3%)
Pruritus	11 (2.3%)
Skin Dry	6 (1.3%)
Sweat	74 (15.7%)
Urticaria	6 (1.3%)
Special Senses	
Amblyopia	5 (1.1%)
Conjunctivitis	14 (3.0%)
Eye Disorder	8 (1.7%)
Lacrimation Disorder	14 (3.0%)
Pain, Ear	8 (1.7%)
Urogenital System	
Dysmenorrhea	19 (4.0%)
Dysuria	9 (1.9%)
Hematuria	8 (1.7%)
Impotence	11 (2.3%)
Urinary Tract Infection	19 (4.0%)
Urine Abnormality	12 (2.5%)
Vaginitis	11 (2.3%)

The most common (≥10%) adverse events reported were those related to withdrawal symptoms (e.g. insomnia, headache, constipation, nausea, abdominal pain, diarrhoea, muscle aches, anxiety, sweating). In patients with marked opioid dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

Note - Patients enrolled in study RB-US-07-0001 on the soluble film were on a stable buprenorphine treatment prior to study initiation, while patients enrolled in studies CR96/013 and CR96/014 were buprenorphine-naïve individuals. As a result, the number of AEs observed in study RB-US-07-0001 is likely to be lower than that observed in studies CR96/013 and CR96/014.

Post-marketing experience with buprenorphine alone

Post-marketing experience with buprenorphine alone has been associated with the following side effects: respiratory depression (see section 4.4 Special Warnings and Precautions for Use) and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, foetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, urinary retention, vertigo, drug dependence, headache, nausea, vomiting, drug withdrawal syndrome, peripheral oedema, heart rate and rhythm disorders, and deaths.

Cases of hepatitis, jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, and elevations in hepatic transaminases have been reported with buprenorphine use (see section 4.4 Special Warnings and Precautions for Use).

In cases of intravenous misuse of buprenorphine, local reactions, sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections have been reported.

Cases of acute or chronic hypersensitivity have been reported with buprenorphine with symptoms including rashes, hives, pruritus and reported cases of bronchospasm, angioneurotic oedema, and anaphylactic shock (see section 4.4 Special Warnings and Precautions for Use and section 4.3 Contraindications).

Very rare (<0.01%) side effects: loss of consciousness, cognitive disorders, psychosis, hallucinations, suicidal ideation, disorders of pregnancy (such as miscarriage and termination of pregnancy, premature birth, placental abruption, prolonged labour), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, decreased oxygen saturation, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, cleft palate, Klinefelter's Syndrome, intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, infant respiratory distress syndrome and subarachnoid bleeding), heart murmur, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders, pulmonary oedema, septic shock, infections (including sepsis, septic arthritis and septic embolus, staphylococcal sacroileitis, brain abscess, pneumonia and endocarditis and amniotic fluid infection) events associated with intravenous misuse (such as cutaneous ulceration, eschar, lividoid and necrotic lesions and penile and scrotal lesion), aphasia, aphonia, slurred speech, diplopia, facial palsy, ascites and lympodoema, pulmonary oedema, pulmonary artery thrombosis, pericardial effusion, shock, cerebrovascular accident, Popeye syndrome, intracranial haemorrhage, nephropathy, colic, denutrition splenic infarction, electrolyte imbalance (such as hyperkalaemia, hyponatraemia and hypoglycaemia), deaths (including death from suicide and sudden infant death syndrome) and unusual reactions. The actual incidence of all cases is extremely low and must be taken in consideration with the co-morbidities, life-style, environmental factors, and concomitant illicit and licit opioid use of the population under treatment.

Post-marketing experience with SUBOXONE TABLETS

A post-marketing study looking at injecting practices in Australia suggested that the combination of buprenorphine and naloxone is less commonly injected than buprenorphine alone.

Additionally, post-marketing experience with SUBOXONE TABLETS for treatment of opioid dependence has been associated with the following side effects: anxiety, hyperhidrosis, syncope, insomnia, reduced feeling, anorexia (see also Tables 4 and 5 above), amnesia, convulsions, blood in vomit, fatigue, jaundice, swollen joints, miscarriage, shortness of breath, and suicide ideation. Treatment with SUBOXONE has been associated with orthostatic hypotension.

Additionally, post-marketing experience with SUBOXONE TABLETS for treatment of opioid dependence has been associated very rarely (<0.01%) with the following side effects: attempted suicide, disorders of pregnancy (such as premature birth), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, macrocephaly, meconium staining and aspiration, decreased oxygen saturation, neonatal aspiration, asphyxia, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, low birth weight, Klinefelter's Syndrome, mitochondrial disease, abnormal behaviour, developmental delay, developmental speech disorder intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, subarachnoid bleeding and sudden infant death syndrome), pancreatitis, loss of consciousness, depression of consciousness, coordination disturbance, hallucinations, psychosis, mental disturbance and altered mental state, cerebral oedema, heart rate and rhythm disorders, septic shock, infections (including sepsis, pneumonia, chorioamniotitis and amniotic fluid infection) events associated with intravenous misuse (such as cellulitis), blurred vision, papilloedema, ascites and peripheral oedema, renal failure, adrenal insufficiency, electrolyte imbalance (such as hyperkalaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia and hypoglycaemia) and deaths (including death from suicide and sudden infant death syndrome). The actual incidence of all cases is extremely low and must be taken in consideration with the co-morbidities, life-style,

environmental factors, and concomitant illicit and licit opioid use of the population under treatment.

Post-marketing experience with SUBOXONE FILM

Post-marketing experience with SUBOXONE FILM for the treatment of opioid dependence has been most frequently associated with the following; adverse reactions appearing in at least 1% of

Table 6: Spontaneous adverse drug reactions collected through post-marketing surveillance reported by body system

System Organ Class	Preferred term
Nervous system disorders	Headache
Gastrointestinal disorders	Glossitis Nausea Stomatitis Tongue disorder Vomiting
Skin and subcutaneous disorders	Rash
General disorders and administration site conditions	Drug ineffective Drug withdrawal syndrome Oedema peripheral

reports by healthcare professionals are included in Table 6.

4.9 OVERDOSE

Manifestations of acute overdose include miosis, sedation, hypotension, respiratory depression and death. Nausea and vomiting may be observed.

The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment

In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation following standard intensive care measures. The patient should be transferred to an environment within which full resuscitation facilities are available.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of SUBOXONE FILM should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.

During clinical pharmacology studies in opioid dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, "good effect", and respiratory depression.

Naloxone is an antagonist at μ (mu), δ (delta), and κ (kappa) opioid receptors**.** Because of its almost complete first pass metabolism, naloxone administered orally, sublingually or buccally has no detectable pharmacological activity. However, when administered intravenously to opioid dependent persons, the presence of naloxone in SUBOXONE FILM produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

Clinical Trials

Efficacy of buprenorphine in combination with naloxone was demonstrated with SUBOXONE TABLETS. No clinical efficacy studies have been conducted with SUBOXONE FILM.

All trials used buprenorphine in conjunction with psychosocial counselling as part of a comprehensive opioid dependence treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

Clinical pharmacology studies on SUBOXONE TABLETS demonstrate an aversive effect if SUBOXONE TABLETS are misused by the injection route by opioid dependent patients.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuronidation in the small intestine and the liver. The use of SUBOXONE FILM by the oral route is therefore inappropriate. SUBOXONE FILMS are for sublingual and/or buccal administration. Table 7 shows the pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after administration of SUBOXONE FILM in randomised, crossover studies. Overall, there was wide variability in the sublingual absorption of buprenorphine and naloxone. SUBOXONE FILM and SUBOXONE TABLET do not meet all criteria for bioequivalence. Patients being switched between tablets and soluble films may therefore require dosage adjustment (see Dosage and Administration).

In several pharmacokinetic studies following the administration of different dosages, a dose of one or two of the 2 mg/0.5 mg SUBOXONE FILMS administered sublingually or buccally showed comparable relative bioavailability to the same total dose of SUBOXONE TABLETS. In contrast, one 8 mg/2 mg and one 12 mg/3 mg SUBOXONE FILM administered sublingually or buccally showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE TABLETS. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE FILMS (total dose of 12 mg/ 3 mg) administered sublingually showed comparable relative bioavailability to the same total dose of SUBOXONE TABLETS, while buccally administered SUBOXONE FILMS showed higher relative bioavailability. Table 8, below, illustrates the relative increase in exposure to buprenorphine and naloxone associated with SUBOXONE FILMS compared to SUBOXONE TABLETS, and shows the effect of route of administration.

Table 7. Pharmacokinetic parameters (Mean ± SD) of buprenorphine and naloxone following SUBOXONE FILM administration				
PK Parameter	**SUBOXONE Film Dose (mg)**			
	2 mg/0.5 mg	**4 mg / 1 mg**	**8 mg / 2 mg**	**12 mg / 3 mg**
Buprenorphine				
C_{max} (ng/mL)	0.947 ± 0.374	1.40 ± 0.687	3.37 ± 1.80	4.55 ± 2.50
T_{max} (h) Median, (min-max)	1.53 (0.75 - 4.0)	1.50 (0.5, 3.0)	1.25 (0.75 - 4.0)	1.50 (0.5, 3.0)
AUC_{inf} (ng.hr/mL)	8.654 ± 2.854	13.71 ± 5.875	30.45 ± 13.03	42.06 ± 14.64
$t_{1/2}$ (hr)	33.41 ± 13.01	24.30 ± 11.03	32.82 ± 9.81	34.66 ± 9.16
Norbuprenorphine				
C_{max} (ng/mL)	0.312 ±0.140	0.617 ±0.311	1.40 ±1.08	2.37 ±1.87
T_{max} (h) Median, (min-max)	1.38 (0.5 - 8.0)	1.25 (0.5, 48.0)	1.25 (0.75 - 12.0)	1.25 (0.75, 8.0)
AUC_{inf} (ng.hr/mL)	14.52 ±5.776	23.73 ±10.60	54.91 ±36.01	71.77 ±29.38
$t_{1/2}$ (hr)	56.09 ±31.14	45.96 ±40.13	41.96 ±17.92	34.36 ±7.92
Naloxone				
C_{max} (ng/mL)	0.054 ± 0.023	0.0698 ± 0.0378	0.193 ± 0.091	0.238 ± 0.144
T_{max} (h) Median, (min-max)	0.75 (0.5 - 2.0)	0.75 (0.5, 1.5)	0.75 (0.5 - 1.25)	0.75 (0.50, 1.25)
AUC_{inf} (ng.hr/mL)	0.137 ± 0.043	0.204 ± 0.108	0.481 ± 0.201	0.653 ± 0.309
$t_{1/2}$ (hr)	5.00 ± 5.52	3.91 ± 3.37	6.25 ± 3.14	11.91 ± 13.80

Table 8. Changes in Pharmacokinetic Parameters for SUBOXONE FILM Administered Sublingually or Buccally in Comparison to SUBOXONE TABLET								
Dosage	PK Parameter	**Increase in Buprenorphine**			PK Parameter	**Increase in Naloxone**		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 x 2 mg/0.5 mg	C_{max}	22%	25%	-	C_{max}	-	-	-
	$AUC_{0\text{-last}}$	-	19%	-	$AUC_{0\text{-last}}$	-	-	-
2 x 2 mg/0.5 mg	C_{max}	-	21%	21%	C_{max}	-	17%	21%
	$AUC_{0\text{-last}}$	-	23%	16%	$AUC_{0\text{-last}}$	-	22%	24%
1 x 8 mg/2 mg	C_{max}	28%	34%	-	C_{max}	41%	54%	-
	$AUC_{0\text{-last}}$	20%	25%	-	$AUC_{0\text{-last}}$	30%	43%	-

1 x 12 mg/3 mg	C_{max}	37%	47%	-	C_{max}	57%	72%	9%
	$AUC_{0\text{-last}}$	21%	29%	-	$AUC_{0\text{-last}}$	45%	57%	-
1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg	C_{max}	-	27%	13%	C_{max}	17%	38%	19%
	$AUC_{0\text{-last}}$	-	23%	-	$AUC_{0\text{-last}}$	-	30%	19%

Note: 1. '–' represents no change when the 90% confidence intervals for the geometric mean ratios of the C_{max} and $AUC_{0\text{-last}}$ values are within the 80% to 125% limit. 2. There is no data for the 4 mg/1 mg strength film; it is compositionally proportional to 2 mg/0.5 mg strength film and has the same size of 2 x 2 mg/0.5 mg film strength.

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours). Following intravenous administration, naloxone is rapidly distributed (distribution half-life of around 4 minutes).

Buprenorphine is highly lipophilic which leads to rapid penetration of the blood-brain barrier. The medicine is around 96% protein bound primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism

In animals and man buprenorphine is metabolised by Phase 1 (oxidative) and Phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP 3A4. In in vitro metabolic studies, addition of specific inhibitors of CYP 3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine (see also section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions). There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity and is considered to be an inactive metabolite.

Naloxone undergoes direct glucuroconjugation to naloxone-3-glucuronide as well as N-dealkylation and reduction of the 6-oxo group.

Excretion

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase (refer to Table 1), due in part to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite, and in part to the highly lipophilic nature of the molecule. Naloxone has a short elimination half-life (refer to Table 7).

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine. Naloxone is excreted in the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In genotoxicity studies using buprenorphine and naloxone (9:2), assays for bacterial gene mutations and chromosomal damage (human lymphocytes in vitro and rat micronucleus test in vivo) were negative.

Carcinogenicity

In mice, no evidence for carcinogenicity due to buprenorphine was noted in life-time studies at dietary doses of up to 100 mg/kg/day, which equates to ca 14-fold human exposure at the maximum recommended clinical dose of 32 mg based on body surface area.

In rats, statistically significant (trend test adjusted for survival) dose-related increases in testicular interstitial (Leydig) cell tumours occurred at a dietary buprenorphine dose of 55 mg/kg/day (16 fold the maximal recommended human sublingual dose of 32 mg, on a mg/m2 basis); the no-effect dose was 5.4 mg/kg/day (twice the maximal human dose, on a mg/m2 basis). The carcinogenic potential of naloxone alone has not been investigated in long term animal studies.

In a 2-year dietary study with SUBOXONE TABLETS in rats, Leydig cell adenomas were found at doses of 6-115 mg/kg/day, associated with respective exposures (plasma AUC) to buprenorphine and naloxone of 2-21 fold, and up to 58 fold, anticipated human exposure. A NOEL was not established in the study.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each soluble film contains acesulfame potassium, citric acid, maltitol solution, hypromellose, polyethylene oxide, sodium citrate, lime flavour, Sunset Yellow FCF and a white printing ink.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

12 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25oC.

6.5 NATURE AND CONTENTS OF CONTAINER

Each soluble film is packed in an individual child resistant polyethylene terephthalate (PET)/low density polyethylene (LDPE)/aluminium/ethylene acrylic acid (EAA) or PET/LDPE/aluminium/LDPE sachet. There are 28 sachets in a pack.

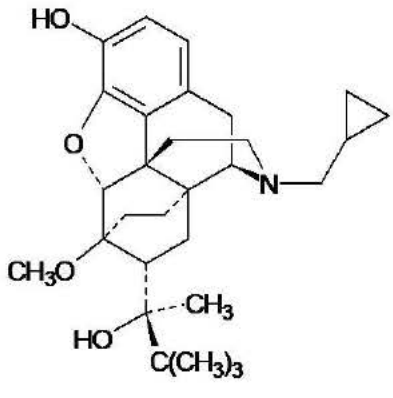
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

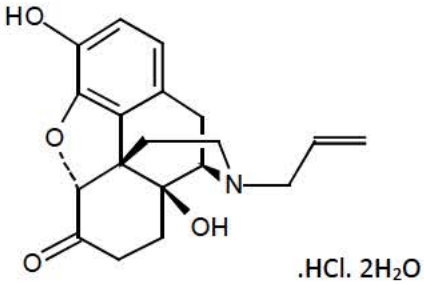
Chemical structure

The chemical structures of buprenorphine hydrochloride and naloxone hydrochloride dihydrate are:



.HCl

Buprenorphine hydrochloride



.HCl. $2H_2O$

Naloxone hydrochloride dihydrate

CAS number

The CAS number of buprenorphine hydrochloride is 53152-21-9.

The CAS number of naloxone hydrochloride dihydrate is 51481-60-8.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 - Controlled Drug

8 SPONSOR

Indivior Pty Ltd
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Macquarie Park NSW 2113
Australia

For adverse event reporting please contact:
Indivior Pty Ltd
+800-270-81901
PatientSafetyRoW@indivior.com

9 DATE OF FIRST APPROVAL

2 November 2000

10 DATE OF REVISION

xxxx 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat of PI
4.2 4.3 4.6	Removal of pregnancy and lactation from contraindications and changes to dose and method of administration