Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for naloxegol oxalate

Proprietary Product Name: Movantik

Sponsor: AstraZeneca Pty Ltd

First round CER: April 2015

Second round CER: September 2015

TGA Health Safety Regulation

About the Th erapeutic 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* (the Act), 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>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	adverse event
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BILI	total bilirubin (serum concentration)
BM	bowel motion
BMI	body mass index
BSA	body surface area
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
C-SSRF	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eDiary	Electronic diary
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
HR	hazard ratio

Abbreviation	Meaning
ICH	International Committee on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	independent review committee
ITT	intent-to-treat
LC/MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LAR	laxative adequate responder
LIR	Laxative inadequate responder
LUR	laxative unknown responder
MedDRA	Medical Dictionary for Regulatory Activities
Meu	morphine equivalent units
MRI	magnetic resonance imaging
MTP	Multiple Testing Procedure
NKTR-118	Naloxegol, PEG-naloxol, NKT-10018
NONMEM	Nonlinear Mixed Effects Model
NRS	Numeric Rating Scale
OIC	Opioid-induced constipation
PAC-SYM	Patient Assessment of Constipation Symptoms
PAC-QOL	Patient Assessment of Constipation Quality of Life
PAMORA	Peripherally acting μ-opioid receptor antagonist
PD	pharmacodynamic(s)
PFS	progression-free survival
P-gp	permeability glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)

Abbreviation	Meaning
PP	per protocol
QoL	quality of life
QTc	interval from beginning of QRS complex to end of the T wave; QT corrected
RFBMs	rescue-free bowel movements
SAE	serious adverse event
SBM	spontaneous bowel movement
SGOT	serum glutamic-oxaloacetic transaminase
SOC	system organ class
t1/2	terminal elimination half-life
TEAE	treatment-emergent adverse event
TEAV	treatment-emergent abnormal laboratory values
Tmax	time of maximum observed plasma concentration
ULN	upper limit of normal
Vd	volume of distribution
WHO	World Health Organization

1. Introduction

This is an application to register naloxegol (as oxalate), a new chemical entity, as an oral agent for the treatment of opioid-induced constipation (OIC).

2. Clinical rationale

Constipation is a common problem with OIC. The sponsor notes that prescription and over-the-counter laxatives are commonly used to treat OIC in clinical practice but do not specifically target the opioid mediated mechanisms that cause constipation and are not effective in some people.

> *Comment: The actual incidence of OIC for people in Australia is not given. Further, the incidence of OIC for people using concurrently available laxative therapies appropriately is not given. Lastly an estimate of the proportion of constipation in people taking opiates is due to agonism of the mu receptor (and not underlying disease or physical state) would be helpful.*

The physiological effects of opioids are primarily mediated by three major opioid receptor sub-types: μ, κ and δ. Naloxegol is a competitive μ- and δ-opioid receptor antagonist and a weak partial κ-receptor agonist. Mu (μ) opioid receptors are widely distributed in the CNS and are involved in the perception of pain, and in the myenteric and submucosal plexi of the enteric nervous system where they contribute to peristaltic activity. Thus although the analgesic effects of exogenous opioids rely upon distribution to the CNS, their effect on gut function, one of the reasons the development of OIC, is thought not to be.

> *Comment: There is some evidence that gut function is also controlled by central neural pathways, which would be affected by transport of opiate across the blood brain barrier but not reversed by an antagonist such as a PAMORA that didn't cross. The clinical effect of partial agonism on κ-opioid receptors is not discussed in the clinical submission apart from reference to a rabbit vas deferens assay where naloxegol was shown to have no agonist activity in this assay. The sponsor should discuss the relative contributions of gut opiate to constipation in this population.*

PAMORAs which include naloxegol but also methylnaltrexone, alvimopan and others are a new class of drugs. Naloxegol is PEG naloxol, also known as a PEGylated derivative of naloxone. It is a substrate of the P-gp transporter.

> *Comment: P-gp is important in the transport of many other drugs across the gut wall (and blood brain barrier) and therefore the possibility of drug interactions is high.*

Due to the lack of formal guidance or precedent for defining a clinically relevant difference in OIC response rate for 12 week studies, the sponsor states that the definition of a clinically relevant effect for naloxegol treatment was based on review of literature, on regulatory guidelines available for similar conditions (for example, Irritable Bowel Syndrome),[1] and on consultations with external experts. Based on these factors, the sponsor considered a 10-15% point difference in responder rate, defined by sustained increase in the number of spontaneous bowel movements (SBM) compared with placebo, as a clinically relevant therapeutic gain. In the Camilleri manuscript cited by the sponsor when justifying the choice of endpoint, it is stated that "the bowel function diary has been validated for use in characterising and quantifying constipation symptoms related to opioid use, following guidance from the Food and Drug

[1] US Food and Drug Administration, "Guidance for Industry Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment", May 2012.

Administration (FDA) for patient response outcomes (PRO) instruments… the diary has the advantage that it supports the validity of composite PRO end points (SBM, CSBM [complete spontaneous bowel movement]) favoured by regulatory authorities, as well as symptom severity items identified as relevant by patients… In addition, among patients who reported constipation, the number of SBM discriminates between those who reported varying degrees of symptom severity.[2]

> *Comment: the clinical rationale for drug development given by the Sponsor was disappointing. The other factors that contribute to constipation (and are often remediable) whilst on opioids were not discussed. The Sponsor has implied that constipation on opioids is due to agonism of the mu receptor, likely to be important but not the sole cause. Also, although the Sponsor cites the Camilleri paper as showing that effect of opioid on causing constipation is due to local effects of opioid, on re-reading that article the authors also state "The cause of constipation in opiate users is multi-factorial";[3] for completeness a discussion on the role of central mu-receptor effect on gut function (i.e. role of central neural pathways on gut function) is pivotal to the rationale for developing and using this agent.*

It is difficult to make a decision on the appropriateness of the choice of 10-15% difference in responder rate in the absence of peer reviewed guidelines. It is possible that a greater percentage is more important the lesser number of SBM/week. The PRO instruments appear to have direct clinical relevance and it is unclear why the PRO were not chosen as the primary endpoint in the pivotal clinical studies the expert manuscript quoted (Camilleri et al.)[4] however suggests there is at least some cogniscence (unreferenced) of the link between SBM and PRO.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented biopharmaceutic, clinical pharmacology and clinical trial data to support the application.

The naloxegol biopharmaceutic and clinical pharmacology program included in this submission included 14 completed Phase I studies in 438 volunteers including 24 subjects with mild hepatic impairment and 16 subjects with renal impairment.

The Phase II development programme constituted a single Phase IIb study with 208 randomised patients, guided the choice of the 25 mg but not the 12.5 mg) naloxegol doses used in the Phase III development program.

The Phase III development program included in this submission includes a total of five studies: 2 identical placebo controlled, double blind, 12 week Phase III confirmatory studies (Studies 04 and 05), a double blind, 12 week safety extension study (Study 07) of Study 04, a randomised, open label, 52 week parallel group long term safety study (Study 08), and a placebo controlled double blind study in patients with cancer-related pain and OIC (Study 06).

There were also pooled data for safety, pharmacokinetic (pharmacodynamics [PD] and pharmacokinetics [PK]), exposure outcome modelling and analysis.

[2] Camilleri M, et al. Validation of a bowel function diary for assessing opioid-induced constipation. *Am J Gastroenterol.* 106: 497-506 (2011).
[3] Camilleri M. Opioid-Induced Constipation: Challenges and Therapeutic Opportunities. *Am J Gastroenterol.* 106: 835-842 (2011).
[4] Camilleri M. Opioid-Induced Constipation: Challenges and Therapeutic Opportunities. *Am J Gastroenterol.* 106: 835-842 (2011).

3.1.1.1. Phase I studies (biopharmaceutic and clinical pharmacology)

- 08-PNL-04: "An Open-Label, Randomised, Single-Dose, 2-Treatment, 2-Period, Crossover Study in Healthy Female and Male Subjects to Evaluate NKTR-118 Tablet Bioavailability Relative to NKTR-118 Solution"
- D3820C00025: "A Phase I, open-label, randomised, balanced, single-dose, 2-part study to assess the relative bioavailability of NKTR-118 in 3 formulations under fasted (3-way cross-over) and fed (2-way cross-over) conditions in male and non-fertile female volunteers"
- D3820C00018: "A Phase I, randomised, open-label, 3-way cross-over study in healthy volunteers to demonstrate the bioequivalence of the naloxegol 25 mg commercial and phase III formulations and to assess the effect of food administration on the pharmacokinetics of the commercial formulation"

3.1.1.2. Pharmacokinetics studies

- 05-IN-OX001: "A double-blind, placebo-controlled, dose escalation crossover study to evaluate antagonism of single oral doses of PEG7-Naloxol (naloxegol) on peripheral and central effects of morphine in healthy male volunteers"
- 07-IN-NX002: "A Phase I, double-blind, randomised, placebo-controlled, multiple-dose study to evaluate the safety, tolerability and pharmacokinetics of escalating oral doses of NKTR-118 (naloxegol) in healthy male and female volunteers"

  (Note this study used NKT-10018 which is the same product as NKTR-118).
- D3820C00001: "A Phase I, open-label, single-centre study to assess absorption, distribution, metabolism and excretion after [14C]-labelled oral administration of NKTR-118 (naloxegol) to healthy male volunteers"

3.1.1.3. Studies examining the effect of intrinsic factors

- D3820C00009: "An open-label, parallel-group, phase I study to compare the pharmacokinetics of naloxegol following a single oral dose in subjects with renal impairment and subjects with normal renal function"

3.1.1.4. Naloxegol clinical pharmacology studies

- D3820C00010: "An open-label, single-centre study to assess the pharmacokinetics of NKTR-118 (naloxegol) in patients with impaired hepatic function and healthy volunteers with normal hepatic function following administration of a single dose of 25 mg naloxegol"
- D3820C00020: "A Phase I, randomised, double-blind, placebo-controlled study to assess the safety, tolerability and pharmacokinetics of NKTR-118 (naloxegol) following single and multiple ascending oral dose administration in healthy young and elderly Japanese volunteers, and an open, randomised, crossover study to investigate the effect of food on the pharmacokinetics after single oral doses of naloxegol in healthy male young Japanese volunteers"
- D3820C00011: "A randomised, 2-part, crossover, single centre study to evaluate the effect of quinidine on the pharmacokinetics of NKTR-118 (naloxegol) and the concomitant effect of quinidine and naloxegol on morphine-induced miosis"
- D3820C00012: "An open-label, 1-sequence, 3-period, 3-treatment, crossover study to assess the effects of ketoconazole on the pharmacokinetics of NKTR-118 (naloxegol) in healthy subjects"
- D3820C00015: "An open-label, fixed-sequence, 3-period, 3-treatment, crossover study to assess the effects of rifampin on the pharmacokinetics of naloxegol in healthy subjects"

- D3820C00032: "An open-label, sequential, 3-period study to assess the effects of diltiazem on the pharmacokinetics of naloxegol in healthy subjects"

3.1.1.5. Pharmacodynamics studies

- D3820C00014: "A single centre, randomised, double-blinded, placebo- controlled, open-label, positive-controlled, 4-way cross-over study to assess the effect of a single oral dose naloxegol administration on the QT-interval compared to placebo, using AVELOX (moxifloxacin) as a positive control, in healthy male volunteers"

3.1.1.6. Phase II, safety and efficacy studies

- 07-IN-NX003 (Phase IIb study): "A Phase II, double-blind, randomised, placebo- controlled, multiple-dose, dose escalation study to evaluate the efficacy, safety and tolerability of naloxegol in patients with opioid-induced constipation"

3.1.1.7. Phase III studies

- D3820C00004: "A randomised, double-blind, placebo-controlled study to assess the efficacy and safety of naloxegol in patients with non-cancer related pain and opioid-induced constipation"
- D3820C00005: "A randomised, double-blind, placebo-controlled study to assess the efficacy and safety of naloxegol in patients with non-cancer related pain and opioid-induced constipation"
- D3820C00006: "A randomised, double-blind, placebo-controlled study to assess the efficacy and safety of naloxegol in relieving opioid- induced constipation in patients with cancer-related pain"
- D3820C00007: "A randomised, double-blind, placebo-controlled 12-week extension study to assess the safety and tolerability of naloxegol in patients with non-cancer related pain and opioid- induced constipation"
- D3820C00008: "An open-label 52-week study to assess the long-term safety of naloxegol in opioid-induced constipation (OIC) in patients with non-cancer related pain"

3.2. Paediatric data

The sponsor submitted an application for a Paediatric Investigation Plan (PIP) including a deferral and a waiver for naloxegol for the treatment of OIC in August 2011 (PIP Procedure No. EMEA-001146-PIP01-11). The Paediatric Committee's (PDCO) formal opinion was adopted by the EMA in August 2012. A deferral was agreed regarding the initiation and completion of the naloxegol paediatric study until a juvenile rat toxicology study is complete and PK, safety and efficacy are evaluated in the adult population. An age appropriate formulation will be developed. A waiver was granted for studies in children less than 6 months because of potential incomplete development of the blood brain barrier in this age group.

3.3. Good clinical practice

The sponsor standard operating procedures, quality control measures, and audit programs provide reassurance that the clinical study program was carried out in accordance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, as documented by the International Conference on Harmonisation (ICH), FDA, and EMA. Up-to-date GMP documentation was provided for the three sites (US, Belgium and Sweden).

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each PK topic.

Table 1: Submitted PK studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	D3820C00025
		05-IN-OX001
		D3820C00001
	- Multi-dose	08-PNL-04
		D3820C00018
		07-IN-NX002
		D3820C00020
	Bioequivalence - Single dose	
	- Multi-dose	08-PNL-04
		D3820C00025
		D3820C00018
	Food effect	D3820C00025 D3820C00018 D3820C00020
PK in special populations	Target population - Single dose	
	- Multi-dose	07-IN-NX003 (Phase IIb study)
	Hepatic impairment	D3820C00010
	Renal impairment	D3820C00009
PK interactions	Quinidine Ketaconazole Rifampin Diltiazem Effect on QT	D3820C00011 D3820C00012 D3820C00015 D3820C00032 D3820C00014

None of the PK studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

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

4.2.1. Physicochemical characteristics of the active substance

The following information is derived from the Sponsor's summaries in Module 2. The molecular formula of naloxegol is C34H53NO11 and molecular weight is 652 grams per mole. Naloxegol is a viscous liquid and is soluble in water. Naloxegol oxalate, the salt used in proposed commercial formulation, is a crystalline powder with a formula weight of 742 grams per mole. According to the Biopharmaceutics Classification System (BCS) adopted by the FDA and EMA, naloxegol and naloxegol oxalate are both considered to be highly soluble in aqueous media across the physiologically relevant pH range of 1 to 7.5, with solubilities that exceed 1 mg/mL (naloxegol) and 50 mg/mL (naloxegol oxalate). Naloxegol has 2 pKa values, potentiometrically determined to pKa1=8.4 and pKa2=9.5. Naloxegol is weakly lipophilic, with a logP value of 1.4. The mean in vitro Caco-2 cell monolayer permeability (A - B Papp) was lower for naloxegol than for the high permeability marker pindolol, suggesting low permeability according to the BCS.

Urine recovery results from a 14C-naloxegol mass balance study performed in healthy volunteers (D3820C00001) indicate that at least 16% of a 27 mg dose was absorbed following oral administration of a naloxegol solution. In addition, the presence of oxidative metabolites in faeces suggests that the fraction of the dose absorbed could be higher than the 16% recovered in urine. In the rat, approximately 80% of the dose was absorbed following oral dosing. The high solubility and low permeability indicate that naloxegol is a BCS Class III compound.

4.2.2. Pharmacokinetics in healthy subjects

Data in this section is from the clinical pharmacology and the Phase I studies.

4.2.2.1. Absorption

4.2.2.1.1. Sites and mechanisms of absorption

Naloxegol undergoes rapid absorption from the gut with peak plasma concentrations attained around 2 h (0.5-3 h) after single doses. A secondary plasma concentration peak for all naloxegol formulations was observed in a number of volunteers approximately 0.4 to 3 h after the first peak, more prominent at lower doses (8 mg to 125 mg), which based on the radioactivity study is likely due to enterohepatic recycling. At therapeutic doses, mean terminal elimination half-life values across the clinical pharmacology studies ranged from 6 to 11 h. Naloxegol exposure is dose-proportional at therapeutic doses. Following multiple dosing, steady state is achieved within 2 to 3 days.

4.2.2.2. Bioavailability

4.2.2.2.1. Absolute bioavailability

The following table provides relative bioavailability data – oral solution to a variety of formulated tablets. A comparison of i.v. to oral was not undertaken. The individual studies are summarised.

Table 2: Relative bioavailability data – oral solution to a variety of formulated tablets.

			Comparison: Ratio of geometric least squares means (90% CI)			
Study	**Formulations**		**Pair**	**$AUC_{(0-t)}$**	**$AUC_{(0-\infty)}$**	**C_{max}**
08-PNL-04	Test:	100 mg naloxegol film-coated tablet (batch: 15101.001)	Test/ Reference	1.05 (0.95-1.16)	1.05 (0.95-1.16)	1.01 (0.85-1.21)
	Reference:	100 mg naloxegol from 4% oral aqueous solution (batch: C08J040)				
D3820-C00025	Form 1:	25 mg naloxegol oxalate tablet, fast dissolution (batch: 11-000764AZ)	Form 1/ Form 3	NC	1.06 (0.97-1.17)	1.00 (0.88-1.13)
	Form 2:	25 mg naloxegol oxalate tablet, slow dissolution (batch 11-000441AZ)	Form 2/ Form 3	NC	1.03 (0.94-1.13)	0.97 (0.86-1.10)
	Form 3:	25 mg naloxegol film-coated tablet (Phase I/III) (batch: 17803.002)	Form 1/ Form 2	NC	1.03 (0.94-1.13)	1.03 (0.91-1.16)
D3820-C00018	Test:	25 mg naloxegol oxalate film-coated tablet (Commercial; Biobatch) (batch: 12-001279AZ)	Test/ Reference	0.94 (0.89-1.00)	0.94 (0.89-1.00)	0.92 (0.82-1.04)
	Reference:	25 mg naloxegol film-coated tablet (Phase I/III) (batch: 17803.004)				

A naloxegol aqueous formulation was administered in the initial clinical studies in the development program, including the single-ascending dose study (Study 05-IN-OX001), the multiple-ascending dose study (Study 07-IN-NX002), the absorption/distribution/ metabolism/excretion study (Study D3820C00001) and the Phase IIB study (Study 07-IN-NX003). A relative bioavailability study (Study 08-PNL-04) was conducted to compare a 100 mg liquid dose used in these studies with a 100 mg film-coated tablet formulation. The 90% confidence intervals for the geometric mean tablet- to-solution ratios for Cmax, AUC(0-t), and AUC(0-∞) were within the 80% to 125% interval, indicating bioequivalence between the solution and the tablet formulation. The Cmax of the tablet formulation was 101% compared to the solution, indicating the in vivo dissolution of the tablet formulation was fast. These results verify that in vivo dissolution is not a limiting step for rate or extent of absorption from naloxegol solid formulations that dissolve at a similar rate as the tablet formulations used in the Phase III studies.

Study 08-PNL-04 was conducted using a 100 mg naloxegol film-coated tablet while the Phase I/III studies used 12.5 and 25 mg naloxegol film-coated tablets. The composition of the 100 mg naloxegol film-coated tablet core is identical to those of the 12.5 and 25 mg naloxegol film-coated tablets cores, and the compositions of tablet coatings are similar. In addition, linear or almost linear pharmacokinetics have been demonstrated for both the liquid formulation (from 8 mg to 1000 mg) and the tablet formulation (from 12.5 mg to 100 mg). Doses in the Phase III studies are 12.5 and 25mg.

While the naloxegol film-coated tablet used in the Phase I/III studies contain naloxegol as a free base, the proposed commercial tablet (used in the Phase III studies) contains the crystalline powder naloxegol oxalate salt. The naloxegol free base tablets differ from the proposed commercial tablets not only in the drug substance form but also in composition, excipients, and manufacturing method.

To assess the in vivo impact of these differences, a relative bioavailability study (D3820C00025) was conducted to compare the naloxegol film-coated tablet formulation and 2 different prototype naloxegol oxalate uncoated tablet formulations (with slow and fast dissolution rates).

The composition of the fast dissolution variant tablet is qualitatively the same as the proposed commercial film-coated tablet core, and the percentage proportion of each excipient is similar. However, the naloxegol oxalate relative drug load is lower for the commercial tablet. For the slow dissolution variant tablet, the excipients were the same except for the disintegrant, which was excluded in order to make the dissolution slower. Both naloxegol oxalate tablet variants were manufactured using a roller compaction based method. Bioequivalence was demonstrated across all 3 formulations, with the 90% confidence intervals for the geometric mean tablet-to-tablet ratios for Cmax, AUC(0-t), and AUC(0-∞) within the 80% to 125% bioequivalence limits, indicating that the introduced changes to the composition and the manufacturing method do not translate into changes in the in vivo performance of the tablets. The study results also verify that in vivo dissolution is not a limiting step for rate or extent of absorption from naloxegol oxalate solid formulations as long as the in vitro dissolution is equal to or faster than the dissolution of the slow variant form of the naloxegol oxalate tablet (76% dissolved in 30 minutes).

The naloxegol oxalate film-coated tablet formulation proposed for commercialization is manufactured by a direct compression method. The proposed commercial naloxegol oxalate film-coated tablet was studied in Study D3820C00018, to demonstrate bioequivalence to the Phase I/III naloxegol film-coated tablet and to assess the effect of food on the pharmacokinetics of the commercial naloxegol film-coated tablet. The commercial naloxegol oxalate film-coated tablet was demonstrated to be bioequivalent to the Phase I/III tablet with the 90% confidence intervals for the geometric mean tablet-to-tablet ratios for Cmax, AUC(0-t), and AUC(0-∞) within the 80% to 125% bioequivalence limits.

All of these studies are evaluated and also summarised.

> *Comment: It is noted that a biowaiver is requested for the 12.5 mg naloxegol oxalate film-coated tablet requested in the proposed indication. This is reasonable.*

4.2.2.2.2. Bioequivalence of clinical trial and market formulations

Bioequivalence of naloxegol formulations has been shown in the Phase I studies (summarised above). The pivotal bioequivalence study, D3820C00018 (A phase I, randomised, open-label, 3-way cross-over study in healthy volunteers to demonstrate the bioequivalence of the naloxegol 25 mg commercial and phase III formulations and to assess the effect of food administration on the pharmacokinetics of the commercial formulation) showed that the intended commercial 25 mg naloxegol oxalate tablet is bioequivalent with the 25 mg naloxegol tablet used in the Phase I/III program.

4.2.2.2.3. Bioequivalence of different dosage forms and strengths

These bioequivalence results are supported by in vitro dissolution data. The Sponsor is seeking a biowaiver for the 12.5 mg tablet formulation, based on the similarity in composition and in vitro dissolution profile to the 25 mg tablet and the linear PK observed over the relevant dose range.

4.2.2.2.4. Bioequivalence to relevant registered products

There are currently no relevant registered products in Australia.

4.2.2.2.5. Influence of food

Based on increased bioavailability of naloxegol observed following a high-fat meal (~45% increase for AUC(0-inf) and a ~30% for Cmax), naloxegol should be taken on an empty stomach (i.e. at least 30 min prior to the first meal of the day, or 2 h post-meal) every day.

4.2.2.2.6. Dose proportionality

In the Phase I study D3820C00020 PK was shown to be dose proportional across the dosing range. In young healthy volunteers, the geometric means of AUC and Cmax increased with

ascending dose of 12.5 to 100 mg NKTR-118 with AUC of 81.9 to 731 h·ng/mL and Cmax of 18.3 to 254 ng/mL, respectively. The AUC and Cmax increased approximately dose proportionally. Elderly healthy volunteers showed geometric mean value of 174 h·ng/mL for AUC and 48.8 ng/mL for Cmax after 25 mg NKTR-118, respectively.

Following single dose administration of 25 mg NKTR-118 in the fasted and fed state, the overall exposure to NKTR-118 (AUC) and Cmax after administration of NKTR-118 in the fed state was approximately 1.5-fold greater compared to that in the fasted state.

4.2.2.2.7. Bioavailability during multiple-dosing

In the Phase I study D3820C00020, following multiple dose administration of 12.5 to 100 mg NKTR-118 the steady state exposure to NKTR-118 at 25 mg was higher in the elderly than the young subjects, associated with slightly higher accumulation ratio.

In Study 07-IN-NX002 – a multiple dosing PK study, overall, plasma NKTR-118 concentration-time profiles on Day 8 were between 33% and over 100% higher than on Day 1. Drug was taken BID.

Comment: Accumulation may occur during multiple dosing on a BID regimen.

4.2.2.2.8. Effect of administration timing

Effect of administration timing wasn't explicitly examined (apart from the effects of food) but in 07-IN-NX002, trough plasma NKTR-118 concentrations showed a pattern of am/pm fluctuation.

4.2.2.3. Distribution

4.2.2.3.1. Volume of distribution

After absorption, naloxegol plasma concentrations decline bi-exponentially: naloxegol is distributed into a central and a peripheral compartment, with typical values for apparent volume of 160 L and 266 L, respectively. This is demonstrated in the population pharmacokinetic simulations. The mean apparent volume of distribution during the terminal phase ranged approximately from 968 L to 2140 L across dosing groups and studies.

4.2.2.3.2. Plasma protein binding

Plasma protein binding of naloxegol in humans is low.

4.2.2.3.3. Erythrocyte distribution

The radiolabelled studies suggested erythrocyte distribution was small.

4.2.2.4. Metabolism

4.2.2.4.1. Sites of metabolism and mechanisms / enzyme systems involved

In vitro data indicate that naloxegol is a substrate for cytochrome P450 3A4 (CYP3A4) and that CYP3A is the major CYP enzyme responsible for the metabolism of naloxegol. Naloxegol is also a substrate of the P-gp transporter.

Clinically relevant effects of this metabolism were seen in the pharmacokinetic studies with a P450 inducer (rifampin), P450 inhibitors diltiazem and quinidine and P-gp inhibitor diltiazem. The primary route of naloxegol elimination is via hepatic metabolism, with renal excretion playing a minimal role. In clinical studies, 6 metabolites were found in either faeces, urine and plasma, none of which have been identified as unique or disproportionate human metabolites. The major plasma circulating species is naloxegol.

4.2.2.4.2. Non-renal clearance

Non-renal clearance is predominantly via the faecal (direct and biliary secretion).

4.2.2.4.3. Metabolites identified in humans

Nalexogol plasma NKTR-118-glucuronide concentrations were approximately 100-fold less than plasma NKTR-118 concentrations. Glucuronidation was not affected by dose level or duration of dosing (seen in the PK study 07-IN-NX002).

Interactions with dual modulators with various relative potencies for CYP3A4 and P-gp were studied (there is considerable overlap between CYP3A4 and P-gp inhibitors and inducers). Further CYP3A4 and P-gp genetic expression is variable – and different amounts of the enzyme will account for some of the variability in PK from the same dose.

The significant increase in naloxegol exposure (12.9-fold in AUC and 9.6-fold in Cmax), when naloxegol was co-administered with a dual P-gp/ strong CYP3A4 inhibitor (ketoconazole) is likely to be a result of both inhibition of hepatic metabolism and increased intestinal absorption through inhibition of CYP3A4 enzyme and P-gp transporter in intestinal epithelial cells. When naloxegol was co-administered with a dual P-gp/ moderate CYP3A4 inhibitor (diltiazem), the increase was 3.4-fold in AUC and 2.9-fold in Cmax. The small increase in naloxegol exposure (1.4-fold in AUC and 2.5-fold in Cmax), when co-administered with the dual P-gp/weak CYP3A4 inhibitor (quinidine) is likely mainly driven by the CYP3A4 inhibitory activity of quinidine. Furthermore, there was a significant decrease in naloxegol exposure (AUC decreased by 89 % and Cmax by 76%), when naloxegol was co-administered with dual P-gp/strong CYP3A4 inducer, rifampin.

An analysis of naloxegol patients in the Phase III studies who received strong, moderate or weak CYP3A4 inhibitors (although strong CYP3A4 inhibitors were prohibited in these studies, a few patients received them) uncovered no evidence of a different AE profile compared with the overall population. Furthermore, physiologically-based PK modeling (PBPK) showed an approximately 3-fold increase when naloxegol was co-administered with moderate CYP3A4 inhibitors, and little to minimal impact with most weak CYP3A inhibitors. Additionally, the population PK analysis showed generally similar results i.e. an 8.1-fold higher naloxegol exposure (for AUC and Cmax) with strong CYP3A4 inhibitors, increase in AUC and Cmax by about 60% and 30% with moderate CYP3A4 inhibitors, and little change in naloxegol exposure with weak inhibitors.

Based on available data, as proposed in the Prescribing Information, The Sponsor has recommended concomitant administration of dual P-gp/ strong CYP3A4 inhibitors or strong CYP3A4 inhibitors alone with naloxegol is contraindicated; the naloxegol dose should be decreased to 12.5 mg daily when co-administered with dual P-gp/moderate CYP3A4 inhibitors; no dose adjustment is necessary for dual P-gp/weak CYP3A4 inhibitors when co-administered with naloxegol. Furthermore, naloxegol use is not recommended in patients taking dual P-gp/strong CYP3A4 inducers.

> *Comment: The PI should be modified to state that the drug should not be used with CYP3A4 inducers or inhibitors or P-gp inhibitors. There is no evidence to recommend that using 12.5mg naloxegol with a drug interacting drug is safe or effective and shouldn't be recommended.*

4.2.2.4.4. Renal clearance

Renal clearance is a minor route of elimination for naloxegol. A higher average exposure occurred in subjects with moderate and severe renal insufficiency, driven by 2/8 subjects in each impairment category, the single-dose safety profile of naloxegol in subjects with renal impairment at baseline was similar to patients with normal baseline creatinine clearance values.

> *Comment: However this drug is not given as a single dose.*

In this study it was postulated that higher exposure in these subjects may not be due to a decrease in renal function per se but may be related to other physiological changes (e.g.

hepatic/gut metabolism). Exposure of naloxegol in subjects with end-stage renal disease on dialysis was similar to that in subjects with normal renal function.

The Phase III program allowed participation for patients with moderate renal impairment, and a comprehensive review of available data showed that the AE profile of naloxegol in patients with a baseline creatinine clearance value of <60 mL/min was generally similar to that in patients with normal renal function however, the number of patients in this subgroup was low (n=45). The population PK model did not identify creatinine clearance as an important covariate.

> *Comment: However there were small numbers of patients with renal impairment, especially in categories 3, 4 and 5; thus it is an unknown rather than a negative. Based on the available data, in patients with moderate or severe renal impairment, caution and close monitoring should be used if naloxegol is used, and discontinuation if side effects impacting tolerability occur.*

4.2.2.5. Intra- and inter-individual variability of pharmacokinetics

Because CYP3A4 is variable across the population, and because food and medications have such an effect on the PK, the intra and inter-individual variability of PK is expected to be large.

4.2.3. Pharmacokinetics in the target population

Most of the PK data in this submission was in health volunteers. In the Phase IIb study, PK characteristics of naloxegol at doses of 5, 25 and 50 mg in OIC patients in that clinical trial were comparable to those observed in healthy volunteers.

> *Comment: However the characteristics of that population (07-IN-NX-03) need to be compared to the population likely to be exposed to this product in Australia. In particular use in the cancer population and the PK in this group has not been well studied (and Phase III clinical study 06 in that population was terminated early due to poor recruitment).*

The population PK analysis indicates that patients in the Phase III studies (who had OIC) had about a 30% higher exposure to naloxegol than participants in Phase I studies or the Phase IIb study (many of whom were healthy). The Sponsor suggests that error and uncertainty in dosing and/or sampling times (i.e. rich sampling in Phase IIb study vs. sparse sampling in the Phase III studies), different food consumption patterns, and other underlying medical conditions in the Phase III patient populations may contribute to these differences.

> *Comment: However the patients studied in the PK studies were predominantly healthy and the OIC group were different by very nature of the disease – slow gut transit which can affect drug absorption amongst other PK aspects.*

4.2.4. Pharmacokinetics in other special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

Naloxegol is eliminated extensively by hepatic metabolism. Patients with moderate or severe liver cirrhosis, acute liver disease and clinically important elevations in liver enzymes were excluded from the Phase III program; a small group only of mild or moderate hepatic impairment have had PK sampling.

> *Comment: safety and efficacy have not been established in patients with moderate or severe hepatic impairment, cirrhosis, acute liver disease or clinically important elevations in liver enzymes. These conditions are common in a cancer patient group using regular opiates.*

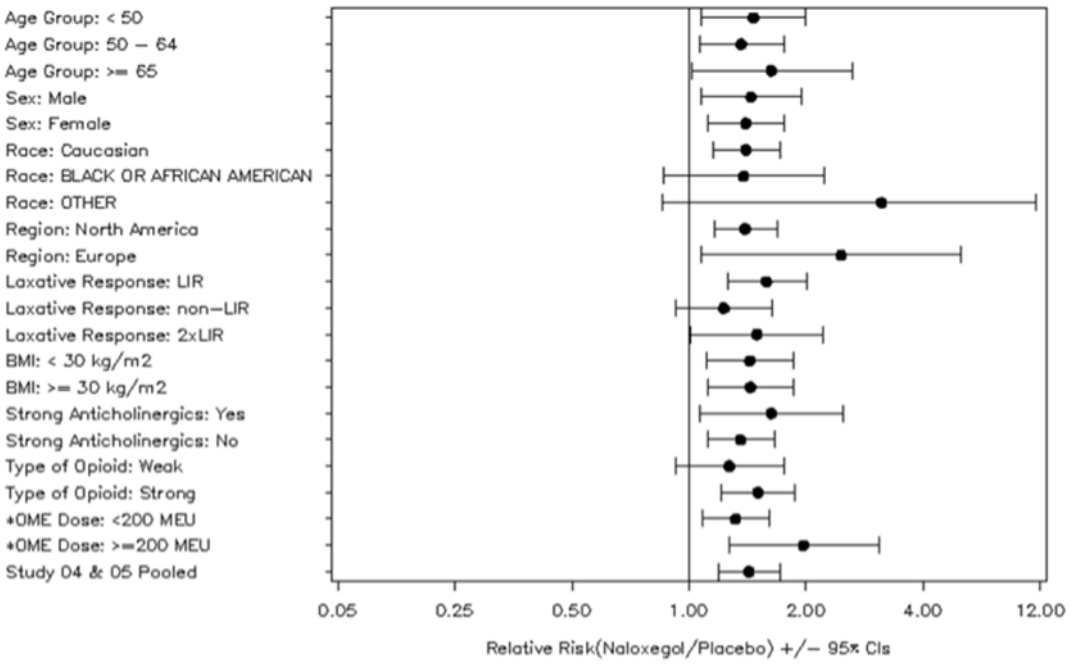
4.2.4.2. Pharmacokinetics in subjects with impaired renal function

This area has been covered above.

4.2.4.3. Pharmacokinetics according to age

The figure below shows the response (naloxegol 25 mg vs. placebo) to study drug during Weeks 1 to 12 in subgroups of interest – pooled data, Studies 04 and 05 (ITT analysis set).

Figure 1: Response (naloxegol 25 mg vs. placebo) to study drug during Weeks 1 to 12 in subgroups of interest – pooled data, Studies 04 and 05 (ITT analysis set).



In the clinical trials, subjects younger than 18 were not exposed to naloxegol. Pooled pharmacokinetic data (mean age 35 years cf. pooled Phase III data (mean age 52 years), an increase in naloxegol exposure was seen with increasing age. Only approximately 10% (n=142) of the naloxegol- treated patients in the Phase III studies were ≥65 years, less than 2% (n=24) were ≥75 years.

> *Comment: The Population PK model did not indicate age as an important covariate, but as with the renal data, it may not fall out as a covariate if there are very small numbers and samples from those patients.*

4.2.4.4. Pharmacokinetics related to genetic factors

The genetics of the CYP3A4 and P-gp have been discussed above.

4.2.4.5. Pharmacokinetics {in other special population / according to other population characteristic}

4.2.4.5.1. Racial group

Nearly 80% of patients enrolled in the naloxegol program were White with remainder being mainly African American. The population PK work found that AUC was significantly lower in African-Americans compared to White volunteers.

4.2.4.5.2. Sex

In the both the pooled pharmacology and the population PK data, sex did not affect naloxegol AUC or Cmax.

4.2.4.5.3. BMI

In the pooled pharmacology data, an increase in naloxegol exposure with increasing BMI was seen. In the Phase III studies, the frequency of AEs for patients receiving naloxegol 25 mg was higher in patients with a BMI ≥30.

A post-hoc BMI categorization requested during an MAA pre-submission meeting (<25 kg/m2 vs ≥25 to <30 kg/m2) showed similar exposure, however this analysis excluded people with a BMI> 30.

4.2.5. Pharmacokinetic interactions

4.2.5.1. Pharmacokinetic interactions demonstrated in human studies

There were a large number of pharmacokinetic parameters noted in the studies supporting this submission.

The significant increase in naloxegol exposure (12.9-fold in AUC and 9.6-fold in Cmax), when naloxegol was co-administered with a dual P-gp/ strong CYP3A4 inhibitor (ketoconazole), may be a result of both inhibition of hepatic metabolism and increased intestinal absorption through inhibition of CYP3A4 enzyme and P-gp transporter in intestinal epithelial cells. When naloxegol was co-administered with a dual P-gp/ moderate CYP3A4 inhibitor (diltiazem), the increase was 3.4-fold in AUC and 2.9-fold in Cmax. The small increase in naloxegol exposure (1.4-fold in AUC and 2.5-fold in Cmax), when co-administered with the dual P-gp/weak CYP3A4 inhibitor (quinidine) is likely mainly driven by the CYP3A4 inhibitory activity of quinidine. Furthermore, there was a significant decrease in naloxegol exposure (AUC decreased by 89 % and Cmax by 76%), when naloxegol was co-administered with dual P-gp/strong CYP3A4 inducer, rifampin.

An analysis of naloxegol patients in the Phase III studies who received strong, moderate or weak CYP3A4 inhibitors (although strong CYP3A4 inhibitors were prohibited in these studies, a few patients received them) uncovered no evidence of a different AE profile compared with the overall population. Furthermore, extensive physiologically-based PK modeling (PBPK) showed an approximately 3-fold increase when naloxegol was co-administered with moderate CYP3A4 inhibitors, and little to minimal impact with most weak CYP3A inhibitors. Additionally, the Population PK analysis showed generally similar results, ie, an 8.1-fold higher naloxegol exposure (for AUC and Cmax) with strong CYP3A4 inhibitors, increase in AUC and Cmax by about 60% and 30% with moderate CYP3A4 inhibitors, and little change in naloxegol exposure with weak inhibitors.

4.2.5.2. Potential effect of other co-administered medications

Post-hoc analysis from Study 11 shows that the PK of naloxegol was not altered when co-administered with a morphine dose of 5 mg/70 kg iv.

Drugs that that reduce GI motility could impact the PK of naloxegol.

However as the dissolution of naloxegol from the intended commercial tablet formulation and its solubility is pH independent, absorption of naloxegol is unlikely to be affected by drugs that increase gastric pH, eg, proton pump inhibitors (PPIs), H2-receptor antagonists, or antacids. In the population PK analysis, inclusion of PPIs as a covariate resulted in little improvement in the model, supporting that PPIs are not likely to affect the PK of naloxegol.

Furthermore, given naloxegol's mechanism of action, antagonism of peripherally acting μ-opioid receptors, naloxegol should not be co-administered with other opioid antagonists. Based on its in vitro enzyme and transporter induction and inhibition profile, naloxegol is not likely to perpetrate pharmacokinetic-based drug-drug interactions.

4.3. Evaluator's conclusions on pharmacokinetics

It should be noted that the conclusions are based on the evaluator's review of each PK study report.

The appendices summarise all of the PK data in pooled form with mathematical extrapolations. This data was helpful to check the actual clinical data and to concur with the modelling.

There were a large number of PK studies. Most of this was in healthy volunteers. Data from groups most likely to be using this therapy was lacking. This was driven by a lack of consideration of the population in Australia most likely to use this therapy, for example, who is currently using chronic opioids? Which groups of these tend to have OIC? What combination of therapies are these people on, as in practice this therapy will be added on to their current medication list? Some of the variables did not reach significance as a covariate in the PK modelling however numbers were very small and there was sparse data for some groups.

Specifically in Australia, these groups of patients are not well represented in the clinical studies. Significant issues that may be relevant to translating the data are:

- the elderly (non-cancer chronic musculoskeletal pain inter alia). A small number (10%) of patients > 65 years were included, and exposure was noted to increases with age. In the Phase I study D3820C00020, following multiple dose administration of 12.5 to 100 mg NKTR-118 the steady state exposure to NKTR-118 at 25 mg was higher in the elderly than the young subjects, associated with slightly higher accumulation ratio.
- those with cancer
- Body Mass Index (BMI) >30
- Ethnic groups other than white
- Children/adolescents
- Renal impairment: CrCl <60, < 30, <15 ml/min as D3820C00009 did show an increase in AUC with increasing dose in renal impairment.
- Chronic dosing (> more than 8 days), that is, in Study 07-IN-NX002: a multiple dosing PK study, overall, plasma NKTR-118 concentration-time profiles on Day 8 were between 33% and over 100% higher than on Day 1. Drug was taken bis in die (BID; twice daily).
- D3820C00010. In this study, the results suggest that after a single dose, exposure of NKTR-118 25 mg does not seem to be dependent on the severity of hepatic impairment (based on their Child-Pugh scores) in patients with mild and moderate hepatic impairment.
- Recommendations to use a half dose for some population groups are not supported by the evidence.

5. Pharmacodynamics

Pharmacodynamic assessments of peripheral and central μ-opioid receptor antagonism via morphine-induced delay in orocecal transit time (OCTT) and miosis indicated that naloxegol at doses from 16 mg to 125 mg antagonizes peripheral opioid effects on the GI tract without antagonizing opioid effects on the CNS. At higher doses, pupil diameter-time profiles after both naloxegol and placebo treatments were superimposable in all but 2 volunteers: 1/6 at 250 mg and 1/6 at 1000 mg had a possible partial attenuation of morphine-induced miosis. Thus at doses of 250 mg and higher, no antagonism of CNS effect was seen in 16/18 volunteers and evidence for possible partial antagonism was seen in only 2 volunteers. As such, naloxegol did not diminish morphine-induced miosis in a dose-dependent manner (see Study 05-IN-0X001).

In Study 11 (D3820C00011), co-administration of naloxegol and P-gp inhibitor quinidine did not antagonize the morphine-induced miosis effect (at morphine doses 5 mg/70 kg, iv), suggesting that P-gp inhibition does not meaningfully affect CNS distribution of naloxegol.

The QT study (Study 14, D3820C00014), which was designed per ICHE14 guidelines to detect any potential signals, confirmed in vitro data findings and showed that naloxegol did not prolong QTcF beyond 10 msec.

5.1. Studies providing PD data

Table 3 shows the studies relating to each PD topic.

Table 3: Submitted PD studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on OIC	07-IN-NX003
Secondary Pharmacology	Effect on antagonism of single oral doses of PEG7-Naloxol on peripheral and central effects of morphine in healthy male volunteers	05-IN-OX001
	The concomitant effect of quinidine and naloxegol on morphine-induced miosis.	D3820C00011
	Effect on QT interval	D3820C00014
Gender other genetic and Age-Related Differences in PD Response	Effect of gender/age	Not undertaken but examined in the context of other studies
Population PD and PK-PD analyses	Healthy subjects	Pooled data
	Target population	Pooled data

None of the PD studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

Most of the PD work is around improved efficacy in constipation.

Naloxegol binds to opioid receptors in the gut. Its efficacy at this effect is covered in the clinical Section. PK-PD analyses are undertaken and presented in the submission.

5.2.1. Pharmacodynamic effects

5.2.1.1. Primary pharmacodynamic effects

Binding to mu (μ) opioid receptors in the gut.

5.2.1.2. Secondary pharmacodynamic effects

Binding to other opioid receptors such as kappa or delta.

5.2.2. Time course of pharmacodynamic effects

The drug has a short half-life and continuous use is required for ongoing benefit.

5.2.3. Relationship between drug concentration and pharmacodynamic effects

Exposure-PD effects (efficacy and safety) are covered in the modelling summaries. Specifically, models were developed characterising the potential exposure-safety relationship between naloxegol exposure and safety endpoints in patients with non-cancer-related pain and OIC based on the data in this submission.

Essentially there appeared to be a clear relationship between dose and concentration and concentration and PD outcomes. It also noted that at the current time there is no evidence to suggest a correlation between the observed drug withdrawal syndrome AEs and naloxegol plasma exposure and no evidence to suggest a correlation between the observed PCI vital signs (SBP and pulse rate) and naloxegol plasma exposure.

5.2.4. Genetic-, gender- and age-related differences in pharmacodynamic response

This work is needed because of the elderly population group that is over-represented in the use of opiates in Australia.

5.2.5. Pharmacodynamic interactions

Two studies examined the effects of nalexogol on opiate effects – miosis, pain score and withdrawal symptoms.

5.3. Evaluator's conclusions on pharmacodynamics

Overall, the PD data is weak for this submission. Information on the effect of gender, BMI, age and race on PD response is necessary due to the population likely to be using this.

6. Dosage selection for the pivotal studies

The doses of naloxegol used in the Phase III program were 12.5 and 25 mg once daily. The naloxegol 25 mg once dose was selected based on efficacy and tolerability demonstrated in the 4 week Phase IIb study (Study 07-IN-NX-003).

That study was a 4 week Phase II dose finding study (5, 25, 50 and 100 mg). The sponsor made the decision to perform a preliminary analysis of the primary endpoint to determine if further dose cohorts were required to define the appropriate Phase III dose at each stage. As a result of this analysis, due to safety issues with the 50 mg dose, a decision was made to end the study after completion of the third cohort. The 25 mg once daily dose was identified as a safe and tolerable dose appropriate for Phase III testing.

The 12.5 mg once daily dose was included in the Phase III program, even though the efficacy data in the Phase II study above was inconsistent in terms of efficacy for all of the parameters and the 5 mg dose showed no efficacy (there was no 12.5 mg dose). Specifically, although the primary endpoint was significant for an average extra 1.6 SBM in the first week compared to placebo in the 25 mg group, P = 0.0020), the secondary endpoint of the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 for both Cohorts 1 and 2 (5 mg and 25 mg) were not statistically significant.

The dose selection was supported by pharmacometric modelling.

Although patients were required to stop their prior laxative regimen at study entry, rescue bisacodyl use was allowed during the studies.

Comment: the evidence for the choice of the 12.5 mg dose in the Phase III studies is weak.

7. Clinical efficacy

7.1. Studies providing efficacy data

Clinical evidence for the efficacy of naloxegol is primarily derived Studies 04 and 05: multinational multicentre, double blind, randomised, placebo controlled, parallel group studies of 2 doses of naloxegol (12.5 mg and 25 mg once daily) and placebo, and a placebo controlled, double blind study in patients with cancer related pain and OIC (Study 06).

A Phase IIb study (07-IN-NX-003) was also included in the Efficacy section.

7.2. Pivotal efficacy studies

The Phase III development program includes a total of three efficacy studies: 2 identical placebo- controlled, double-blind 12-week Phase III confirmatory efficacy studies (Studies 04 and 05) and a placebo-controlled, double- blind study in patients with cancer-related pain and OIC (Study 06).

7.2.1. Study 04 and 05

These two studies will be considered jointly because they had similar design:

- the definition of OIC (based on the Rome III criteria for chronic constipation);
- the primary study endpoint (responder rate, based on frequency of spontaneous bowel movements);
- secondary endpoints (changes in constipation symptoms);
- placebo-controlled design;
- use of a stimulant laxative rescue therapy if the patient had not had an adequate bowel movement within a pre-determined period of time;
- the confirmation of OIC as per the definition during a run-in period before randomisation.

All documentation below applies to both studies unless specifically distinguished.

7.2.1.1. Study design, objectives, locations and dates

- Design: Study 04 and 05 (same title). A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of NKTR-118 in patients with non-cancer-related pain and opioid-induced constipation (OIC). These were Phase III studies.
- Location: Study 04 was carried out in Australia, Germany, Slovakia, and the United States (US). Study 05 had 117 centres (Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden, United Kingdom, and the United States) that randomised patients into the study.
- Dates: First subject enrolled: 14 March 2011 and last subject's last visit was 16 August 2012 for Study 04 and First subject enrolled: 28 March 2011 and last subject last visit was 20 September 2012 for Study 05.

7.2.1.1.1. Primary objectives

- To compare the efficacy of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC.

7.2.1.1.2. Secondary objectives

- To compare the efficacy of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC.

- To compare NKTR-118 12.5 mg and 25 mg with placebo on the daily signs and symptoms associated with OIC (straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and quality of life.

7.2.1.1.3. Safety

- To assess the safety and tolerability of NKTR-118 12.5 mg and 25 mg, when used for the treatment of OIC.

7.2.1.1.4. Exploratory

- To characterize the PK of NKTR-118 and the covariate effect in the targeted disease population, explore the NKTR-118 exposure-response relationship, collect and store DNA for future exploratory research, assess patient health status index and healthcare resource utilization, and assess patients' willingness to take the study drug again.
- To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability, and efficacy) to NKTR-118.

7.2.1.2. Inclusion and exclusion criteria

7.2.1.2.1. Inclusion

These two studies enrolled adult patients whose OIC diagnosis as per the Rome III criteria was confirmed prospectively with a 2 week daily diary, who were receiving a stable maintenance opioid regimen for non-cancer-related pain and who reported a history of <3 SBMs/week and at least 1 OIC-associated symptom at screening.

7.2.1.2.2. Exclusion

1. Patients with pre-existing constipation for reasons other than opioid treatment, or patients who had diarrhea
2. Patients with potentially weakened integrity of the GI wall, due to risk for bowel perforation;
3. Patients who required concomitant prohibited medication (i.e. strong inhibitors of CYP3A4 or P-gp, opioid antagonists and mixed agonists/antagonists, and laxatives)
4. Patients with potential for blood-brain barrier disruptions (i.e., active multiple sclerosis, advanced Alzheimer's disease, uncontrolled epilepsy)
5. Patients with cancer pain; and
6. Patients with recent history of myocardial infarction (MI), symptomatic congestive heart failure, or any other overt CV disease.
7. Creatinine clearance <60ml/min (changed to <30ml/min during study)

Note that over half of the patients in Studies 04 and 05 were randomised after implementation of Clinical Study Protocol Amendment 2, which, based on Phase I data, changed the creatinine clearance exclusion criterion to <30 mL/min from <60 mL/min, lifted restrictions regarding medications associated with potential QT prolongation (i.e. permitting inclusion of patients taking methadone), and relaxed cardiac exclusion and discontinuation criteria related to risk for ventricular arrhythmia.

Patients were expected to be on a stable maintenance opioid regimen for at least 4 weeks across a wide spectrum of total daily morphine-equivalents: 30 to 1000 morphine equivalent units (meus).

> *Comment: these exclusions are likely to exclude much of the cancer population particularly 2, 3, 4 and 6. Cancer patients were actually excluded from these studies.*

7.2.1.3. Study treatments

NKTR-118 12.5 or 25 mg tablets, or matching placebo, administered once daily (two tablets, one from each bottle 1 hour before eating in the morning), for 12 weeks. Sites had to procure bisacodyl 5 mg tablets for use as laxative rescue medication and to dispense bisacodyl to patients at Visits 2, 3, 4, 5, 6, and 7. Information regarding rescue laxative and opioid medication for breakthrough pain was provided. A list of prohibited laxative therapy was stated in the Protocol as well as a list of prohibited drugs that were opioid agonists/partial antagonists, CYP3A4 and P-gp inhibitors and drugs that prolong QT.

7.2.1.4. Efficacy variables and outcomes

The main efficacy variables were response, pain assessment, changes in opioid dose and evaluation of non-GI withdrawal symptoms to assess impact of naloxegol on antagonising centrally mediated effects of opioids. The primary efficacy outcome in studies 04 and 05 was response (responder/non-responder – increase in SBM) to study drug during Weeks 1 to 12.

One of the main goals of the study was to determine whether NKTR-118 is efficacious in patients who have had inadequate response to laxatives previously. To identify those patients, at Visit 1, each patient's laxative response status was determined based on 4 questions exploring the frequency of laxative use, constipation symptom severity, and laxative side-effects during the previous 2 weeks. The patients were then classified as LIR, LAR, or LUR. Patients who reported having used laxatives over the previous 2 weeks were asked about frequency of laxative use (total days used) and constipation symptom severity.

If the patient reported laxative(s) use on a minimum of 4 days with continued moderate, severe, or very severe stool symptoms in response to at least 1 of the symptom questions, he/she will be classified as LIR. In addition, patients who report side-effects from laxatives were classified as LIR.

If the patient reported laxative(s) use on a minimum of 4 days and reports absent or minimal constipation symptoms (as defined above) over the previous 2 weeks and no associated side effects from laxatives, he/she was classified as LAR.

If the patient reports no use of laxatives over the previous 2 weeks, or reports infrequent use, as defined by less than 4 daily laxative uses over the previous 2 weeks, he/she was classified as LUR.

7.2.1.4.1. Primary efficacy variable

Response (responder/non-responder) to study drug during Weeks 1 to 12, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

7.2.1.4.2. Key secondary efficacy variables

Comparison of the response rate of Weeks 1 to 4 of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs. placebo in the LIR subgroup, calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group and analysed using Chi-Square tests.

Comparison of the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs. placebo, calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group, analysed using CMH tests stratified by response to laxatives at baseline (LIR, LAR, LUR).

Comparison of the regularity during the first 4 weeks of treatment of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs. placebo, analysed using analysis of covariance (ANCOVA), with treatment group and response to laxatives at baseline as fixed effects, and the mean number of days per week with at least 1 SBM during the baseline period as a covariate.

7.2.1.4.3. Additional secondary efficacy variables:

- Change from baseline in the SBMs/week for Weeks 1 to 4 and 1 to 12
- Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours
- Mean number of days per week with at least 1 SBM for Weeks 1 to 12
- Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12
- Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12
- Percentage of days with complete evacuation for Weeks 1 to 4 and 1 to 12
- Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12
- Change from baseline in Patient Assessment of Constipation Symptoms (PAC-SYM) total score and each domain score for Weeks 2, 4, 8, and 12
- Change from baseline in Patient Assessment of Constipation Quality of Life (PAC-QOL) total score and each domain score for Weeks 4 and 12

7.2.1.4.4. Pharmacokinetics

Pharmacokinetics parameters of NKTR-118 will be estimated for individual patients (when possible). These parameters include:

- oral clearance (CL/F)
- absorption rate constant (Ka) and
- area under plasma concentration-time curve from zero to time 24 hours (AUC [0-24])

7.2.1.4.5. Health economics

- Data on the Euroqol 5 Dimension (EQ-5D) questionnaire for Weeks 4 and 12.
- Data on OIC healthcare resource utilization will be captured at the site for economic modelling purposes
- Willingness to Take Drug Again questionnaire for Week 12.

7.2.1.4.6. Definition of outcome variables

7.2.1.4.6.1. PAC-SYM

The PAC-SYM questionnaire is a 12-item questionnaire that evaluates the severity of symptoms of constipation in 3 domains (stool, rectal, and abdominal symptoms) on a 5-point Likert scale ranging from 0 (absent) to 4 (very severe) in the 2 weeks (14 days) prior to assessment. The items of the instrument were developed through literature review and patient interviews. The PAC-SYM is available in several languages that facilitate its use in multinational studies using a linguistic validation process. The patients need to be able to read and to be fluent in the local language. The PAC-SYM will be administered to patients at Visit 3 (randomisation), Visit 5 (Week 2), Visit 6 (Week 4), Visit 7 (Week 8), and Visit 8 (Week 12).

The PAC-SYM questionnaire was completed by patients on the 'SitePad' device provided at the study centre. Study staff logged patients in and provided initial training on how to fill out the questionnaire. With the exception of Visit 3, patients were to fill out the PAC-SYM questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator. A reference to the PAC-SYM was provided (Frank 1999).

7.2.1.4.6.2. PAC-QOL

The PAC-QOL scale is a 28-item self-report instrument designed to evaluate the burden of constipation on patients' everyday functioning and well-being in the 2 weeks (14 days) prior to

assessment. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The development of the PAC-QOL items was informed by both clinician and patient focus groups and the primary validation study evaluated use of the PAC-QOL in the US, Netherlands, Belgium, Canada, and Australia using French and Dutch translations in addition to the original English language based instrument. A reference was supplied (Marquis et al 2005).

The patients need to be able to read and to be fluent in the local language. The instrument can be used to generate an overall score, but is also reported to assess 4 specific constipation-related domains including: 1) Worries and concerns (11 items), 2) Physical discomfort (4 items), 3) Psychosocial discomfort (8 items), and 4) Satisfaction (5 items). PAC-QOL was administered to patients at Visit 3 (randomisation), Week 4 (Visit 6), and Week 12 (Visit 8) and completed by patients on the SitePad device provided at the study centre as per the PAC-SYM methodology.

7.2.1.4.7. Willingness to Take Drug Again Questionnaire

The Willingness to Take Drug Again questionnaire will consist of a yes/no question regarding the patient's willingness to take study drug again. The Willingness to Take Drug Again questionnaire will be completed at Visit 8 (Week 12). The Willingness to Take Drug Again questionnaire was completed by patients on the 'SitePad' device provided at the study centre. Study staff logged patients in and provided initial training on how to fill out the questionnaire. Patients were to fill out the Willingness to Take Drug Again questionnaire prior to any interventions or discussions regarding their OIC with the study staff or the investigator.

7.2.1.4.8. Measurements recorded in eDiary

Patients will be supplied with a handheld eDiary for pilot training, the OIC confirmation period, and the treatment period. At Visit 1, all patients were carefully instructed and trained on how to fill in the eDiary and how to handle the device. The eDiary was completed each day from the evening of Visit 1 to the morning of Visit 8, including days of study visits. The eDiary will include the following daily recordings:

- Date and time of BM (recorded at the time of each BM) Stool consistency (BSS) (recorded at the time of each BM) Straining (recorded at the time of each BM)
- Complete/incomplete evacuation (recorded at the time of each BM)
- Pain level (NRS) recorded each evening for the average and worst pain level that occurred during the previous 24 hours
- Date and time of use of laxative rescue medication (bisacodyl or enema) recorded at the time the medication is taken
- Date and time of use of opioid medication for breakthrough pain recorded at the time the medication is taken (note: daily maintenance opioid regimen would be reported separately on the maintenance opioid dose eCRF).

7.2.1.4.9. Bowel movements

All BMs were recorded as they occur.

7.2.1.4.10. Stool consistency (Bristol Stool Scale)

Patients will rate stool consistency through completion of the BSS after each BM. The BSS is a medical aid designed to classify the form of human feces into 7 categories. It was developed by Heaton at the University of Bristol and was first published in the Scandinavian Journal of Gastroenterology in 1997 (reference provided and checked). The form of the stool depends on the time it spends in the colon. The 7 stool types are:

1. Separate hard lumps, like nuts (hard to pass)
2. Sausage-shaped, but lumpy

3. Like sausage, but with cracks on its surface
4. Like a sausage or snake, smooth and soft
5. Soft blobs with clear cut edges (passed easily)
6. Fluffy pieces with ragged edges, a mushy stool
7. Watery, no solid pieces.

Types 1 and 2 indicate constipation, Types 3 and 4 represent "ideal stools," and Types 5 to 7 are tending towards diarrhea or urgency.

7.2.1.4.11. Straining

The degree of straining with each BM will be recorded at the time of the BM and after the BSS. A single-item straining question, developed and validated through 1:1 interviews with OIC patients was asked via the eDiary. The question was: "How much did you strain during your bowel movement?"

Patients were asked to respond on a 5 point Likert scale choosing one of the following options:

1=Not at all

2=A little bit

3=A moderate amount

4=A great deal

5=An extreme amount.

7.2.1.4.12. Complete/incomplete evacuation

Patients recorded the completeness of evacuation at the time of each BM and after the straining question. A single question on the completeness of evacuation, developed and validated through 1:1 interviews with OIC patients will be asked via the eDiary. "Did you feel like your bowels were completely empty after the bowel movement?" Patients will provide a yes or a no response to the complete/incomplete evacuation question.

7.2.1.4.13. Pain level

Patients rated their pain level at the end of each day, using the NRS for pain.

7.2.1.4.14. Use of laxative rescue medication

All bisacodyl and enema laxative rescue medication was recorded at the time the medication was taken.

7.2.1.4.15. Use of opioid medication for breakthrough pain

Opioid medication for breakthrough pain was recorded in the eDiary at the time the medication is taken. Breakthrough pain medication was recorded on a breakthrough pain medication eCRF; this information was recorded in the eDiary to facilitate daily recording of dosing.

Other definitions:

Confirmed OIC is defined as documented <3 SBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) were excluded. In addition to the SBM frequency criterion, patients had to report ≥1 of the following symptoms in at least 25% of the BMs recorded in the electronic diary during the OIC confirmation period: Bristol Stool Scale (BSS) stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. Patients who had 0 BMs over the 2-week OIC confirmation period were not randomised. In these two efficacy studies a minimum of 50% of patients are to meet criteria for being laxative inadequate responders (LIR).

A responder was defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 9 out of 12 weeks, and at least 3 out of the last 4 weeks. SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours. For the endpoint "mean number of days per week with at least 1 SBM", calculation of the endpoint was clarified to ensure that a day when a patient experienced excessive SBMs (more than 3 SBMs) would not contribute as a day with at least 1 SBM in the analysis. This ensured that patients regularly experiencing excessive BMs on treatment, an undesirable treatment effect, would not bias the analysis towards demonstrating a difference between treatment groups. A responder was defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.

The Sponsor designed a qualitative cross- sectional study solicited feedback from patients with OIC on the questionnaire's usefulness in classifying patients according to their response to laxatives. Both studies were stratified to ensure that a minimum of 50% of the patients in each treatment group was randomised in the laxative inadequate responder (LIR) category.

Demonstration of durability of effect in patients with OIC was required over 12 weeks.

Comment: The section discusses the TGA-Guidance in this area and comments on the appropriateness of the choice of endpoints, particularly the issue of the validation of clinical relevance of a potential increase in SBM from e.g. 3 to 4 SBM/week (for at least 9 out of 12 weeks, and at least 3 out of the last 4 weeks). Two Patient Reported Outcomes (PRO) instruments measuring symptoms of constipation (PAC-SYM) and disease-specific quality of life (PAC-QOL) initially used in the Phase IIb study (07-IN-NX-003) were utilised in these 04 and 05 studies. PRO are likely to be very valid in this disease however it is not clear why, in the absence of clear definitions of what a clinically relevant increase in SBM is (and whether it is change in stool type vs. frequency), that the PRO were not used as primary endpoints. The potential bias of a drug causing multiple evacuations (and therefore increasing the SBM/week but potentially reducing QOL measures) was reasonably addressed in the methods for recording this information.

7.2.1.5. Randomisation and blinding methods

These were randomised and blinded studies. Principal Investigator (PI) or other qualified designee obtained signed informed consent, assigned each potential patient a unique enrollment number, beginning with "E#", a 7-digit number made up of the centre number and the patient number within that centre, determined patient eligibility and randomisation codes distributed and communicated to study sites by use of an IVRS (produced by a computer software program called GRand (AstraZeneca's Global Randomization system) that incorporates a standard procedure for generating random numbers.), stratified by response to laxatives (LIR, LAR, LUR) during the 2 weeks prior to screening. The randomisation procedure was sequential and structured to ensure that a minimum of 50% of patients are LIR. Eligible patients were randomised in balanced blocks to receive NKTR-118 12.5 mg, NKTR-118 25 mg, or matching placebo in a 1:1:1 ratio.

Measures for dealing with randomisation re discontinuation and incorrect allocation were appropriate.

Study treatments were matched and blinded with standard methodology.

Comment: randomisation and blinding was appropriate.

7.2.1.6. Analysis populations

The efficacy analyses utilised the intention to treat (ITT) Analysis Set, consisting of all patients randomised to study treatment that received at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment. The safety analysis set will be the Safety population, defined as all randomised patients who received at least 1 dose of study drug.

The primary analysis was made comparing the response rate of Weeks 1 to 12 of NKTR-118 12.5 mg vs. placebo and NKTR-118 25 mg vs. placebo. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate were analysed using Cochran-Mantel-Haenszel (CMH) tests stratified by response to laxatives at baseline (LIR, laxative adequate responder [LAR], laxative unknown responder [LUR]).

Comment: Efficacy analyses using all randomised patients receiving at least one dose of study drug and one post baseline assessment as defined here is appropriate.

7.2.1.7. Sample size

To detect a difference of 25% in response rate (60% on the two NKTR doses and 35% on placebo), with power=90%, α=0.025 and 2-sided test a sample size of 105 patients per group was needed. However in order to provide an adequate power to detect a treatment difference in the LIR subgroup (assuming LIR is 50% of the total study population), it was recommended that

210 patients per group (total 630 patients for 3 treatment groups) were randomised to the study. The assumptions on expected response rate were referenced from the NKTR-118 Phase II study and from other similar drugs.

Comment: A difference of 25% response rate is reasonable based on the 'response' number in the Phase II study (07-IN-NX-003) and the Sponsor's a prioiri estimate of relevance, however the clinical significance (in terms of patient benefit) of an increase of at least one SBM per week for the percentage that responded was not discussed.

1.1.1.1.1. Statistical methods

The efficacy analyses utilised the ITT Analysis Set, consisting of all patients randomised to study treatment for the duration of their participation in the confirmatory studies. A decision was documented prior to database lock to exclude patients from the ITT analysis set who had previously or concurrently participated in the naloxegol program at another study centre.

To enable the overall Type I error rate to be < 0.05 for the multiple pairwise comparisons versus placebo in the primary and the key secondary endpoints and the two nalexogol , a multiple testing procedure (MTP) with Bonferroni- Holm was undertaken in the order below.

- 12-week responder analysis in the ITT analysis set (primary endpoint, analysed via the Cochran Mantel Haenszel test stratified by baseline laxative response)
- 12-week responder analysis in the LIR subgroup (analysed via the chi-squared test)
- Time to first post dose laxation without laxative use in the previous 24 hours (analysed via a log-rank test, stratified by baseline laxative response)
- Mean number of days per week with at least 1 SBM (analysed via Mixed Model Repeated Measures [MMRM]).

All continuous efficacy endpoints were analysed formally via a MMRM approach. MMRM models adjusted for fixed effects of treatment, baseline value, week, treatment-by-week interaction, baseline laxative responder status and study (where applicable), with centre and patient incorporated via random effects. MMRM is an accepted method for analyzing longitudinal data with missing values and produces unbiased estimates provided the data are missing at random.

Comment: This methodology is reasonable.

7.2.1.8. Participant flow

7.2.1.8.1. Study 04

Of the 1750 enrolled, 652 were randomised and 624 completed the study in the three arms (N=177 in placebo, 174 in the 12.5mg and 173 in the 25mg dose). N=297 entered the extension study.

7.2.1.8.2. Study 05

1969 patients were enrolled and 700 patients completed the OIC confirmation period, were randomised, and entered the double-blind treatment period. Of the randomized patients, 99.6% received treatment, 76.7% completed the study (defined as completing Visit 8 - Week 12 for patients who continued into the long-term safety study, or completing Visit 9 -Week 14 for patients who did not continue into the long-term safety study), and 22.3% received treatment and subsequently discontinued the study. Of the 700 randomized patients, 78 (11.1%) who were included in the intent-to-treat (ITT) analysis set completed the study and continued into the safety study (D3820C00008). 22.3% of the 697 patients who received treatment, discontinued the study: 25.2%, 22.7%, and 18.9% in the NKTR-118 12.5 mg, 25 mg, and placebo groups, respectively. The most common reasons for study withdrawal were subject decision (8.0%) and adverse events (AEs, 6.7%). A greater proportion of patients discontinued treatment due to AEs in the NKTR-118 25 mg group (10.3%) compared with the NKTR-118 12.5 mg group (4.7%) and the placebo group (5.2%).

> *Comment: There were no important features of the participant flow likely to affect the interpretation of the study results apart from the fact that most subjects were from the US and were Caucasian. There were more subjects in the NKTR-118 25mg group that discontinued treatment than the placebo group.*

7.2.1.9. Major protocol violations/deviations

Definitions of all protocol deviations are described in the SAP. In these studies patients were excluded from the per protocol analysis set in similar proportions and for similar reasons across all treatment groups. Of the 652 randomized patients in Study 04, 51 (7.8%) had at least 1 important protocol deviation leading to exclusion from the PP analysis set: 17 (7.8%), 16 (7.4%), and 18 (8.3%) patients in the NKTR-118 25 mg, NKTR-118 12.5 mg, and placebo groups, respectively.

Table 4: Protocol violations/deviations.

	Number (%) of patients[a]			
Important protocol deviation [a]	Placebo (N=217)	NKTR-118 12.5 mg (N=217)	NKTR-118 25 mg (N=218)	Total (N=652)
Number of patients with at least 1 important deviation	18 (8.3)	16 (7.4)	17 (7.8)	51 (7.8)
Did not meet OIC confirmation	5 (2.3)	5 (2.3)	6 (2.8)	16 (2.5)
Did not meet other Inclusion/met exclusion criteria	0	1 (0.5)	1 (0.5)	2 (0.3)
Fewer than 11 days of OIC confirmation	2 (0.9)	2 (0.9)	3 (1.4)	7 (1.1)
Miss-randomizations and errors in treatment dispensing	0	1 (0.5)	0	1 (0.2)
Overlapping participation in studies	3 (1.4)	4 (1.8)	4 (1.8)	11 (1.7)
Randomized and not treated	1 (0.5)	2 (0.9)	0	3 (0.5)
Severe non-compliance to protocol	2 (0.9)	0	5 (2.3)	7 (1.1)
Took Prohibited Medication	7 (3.2)	2 (0.9)	1 (0.5)	10 (1.5)

7.2.1.10. Baseline data

The demographic data of the 04 and 05 studies were similar. Almost all patients were from the US (94%) and were white (79.0%), more were female (62.4%), the mean age was 52.2 years,

only approximately 11% (n=148) of the patients were over the age of 65, and 29 (2.2%) of the patients ≥75 years old, and approximately half of the patients had a BMI ≥30 kg/m2.

> *Comment: These demographics are likely to be quite different to the population in Australian particularly the cancer population, many of whom using high doses of opiates are in the palliative or metastatic population and are likely to have BMI less than 30kg/m².*

Over the 6 months prior to enrolment 84% of the patients used laxatives, 54% were categorised as LIR based on laxative use and constipation symptoms during the 2 weeks prior to screening, and 20% were categorized as 2xLIR. Most patients in the non-LIR population were laxative unknown responders (LURs) (96.6%).

In Studies 04 and 05, the median length of lifetime opioid use was 6 years, and the median duration of current opioid use was 2 years. The most commonly specified primary reasons for pain were back pain, 'other', arthritis and fibromyalgia. Most patients in the 'other' category reported various pain conditions, most of which were characterised by musculoskeletal origin (eg. 'left leg injury, 'degenerative disc disease', 'post-laminectomy syndrome'). The mean daily morphine-equivalent dose ranged from 135.6 meu/day to 143.2 meu/day and from 119.9 meu/day to 151.7 meu/day for the treatment groups in Studies 04 and 05, respectively. At baseline, approximately 79% of patients were receiving <200 meu/day total daily dose of opioids and approximately 67% of patients were taking strong opioids as their maintenance treatment in Studies 04 and 05. The median NRS baseline score in the pooled data for Studies 04 and 05 was 4.8, which suggests that patients' pain level remained moderate despite ongoing opioid treatment.

Approximately 60% of patients had experienced abdominal pain since the start of their ongoing opioid treatment in both studies. The 3 most frequent complaints with constipation were infrequent defecation, straining, and hard stools. At baseline (OIC confirmation period), the mean number of SBMs per week was low (range 1.3 to 1.6) across treatment groups. Symptom burden (straining and stool consistency) was low, and the mean number of days per week with at least 1 SBM was low, ranging from 1.2 to 1.5 across confirmatory studies. Over two thirds of the patients in the Phase III population had moderate/high baseline cardiovascular (CV) risk (categories defined retrospectively, consistent with the minimally restrictive nature of the eligibility criteria.

The mean duration of exposure (approximately 75 days) was similar across the treatment groups in the confirmatory studies, and a total of 887 patients with OIC were exposed to naloxegol. The higher discontinuation rate in the naloxegol 25 mg groups (10.3%) compared with the naloxegol 12.5 mg (4.8%) groups and placebo groups (5.4%) in both studies was driven primarily by withdrawal due to AEs and patient decision.

Given that Studies 04 and 05 were identical in design and recruited comparable populations in terms of demographics and other baseline characteristics, data pooling is justifiable.

7.2.1.11. Results for the primary efficacy outcome (ITT set)

CMH analysis of response rate for Weeks 1 to 12 is shown in Table 5.

Table 5: CMH analysis of response rate for Weeks 1 to 12.

Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo [a]		
			RR	95% CI	p-value
Placebo	214	63 (29.4)	NA	NA	NA
NKTR-118 12.5 mg	213	87 (40.8)	1.380	(1.062, 1.795)	0.015 *
NKTR-118 25 mg	214	95 (44.4)	1.509	(1.168, 1.949)	0.001 *

For the primary efficacy variable, there was a statistically significantly higher response rate in the NKTR-118 25 mg (p=0.001) and 12.5 mg (p=0.015) groups compared with placebo; 15.0

percentage points and 11.4 percentage points higher, respectively, in the NKTR-118 25 mg and 12.5 mg groups, compared with placebo at 12 weeks. The RR estimates patients randomized to the NKTR-118 25 mg groups were more likely to respond than those randomized to placebo. The lower bound of the CI for the 12.5mg is very close to 1.0 (1.062).

This is demonstrated more easily in the sponsor provided bar graph. Here is can be seen the placebo response rate is approximately 30%.

Figure 2. Percentage patients responding.

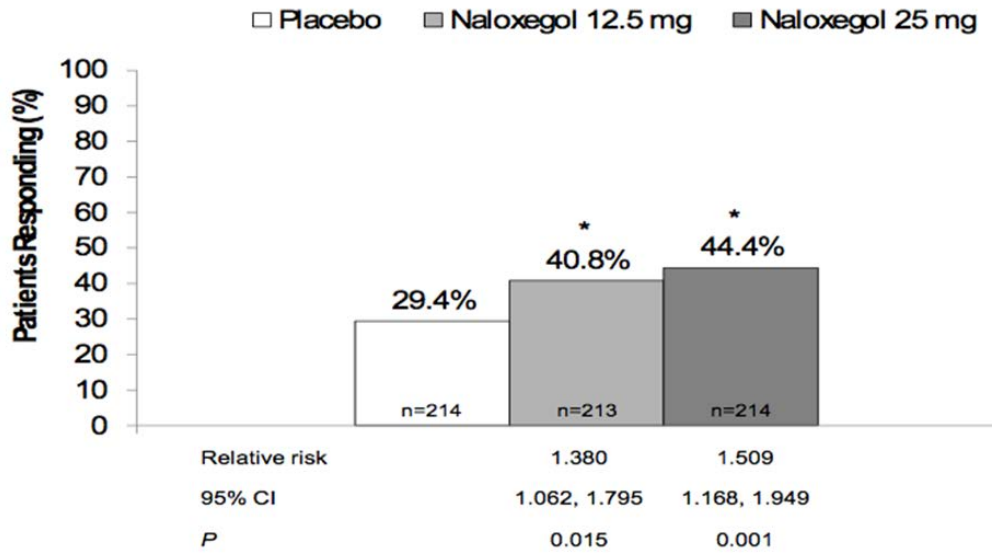
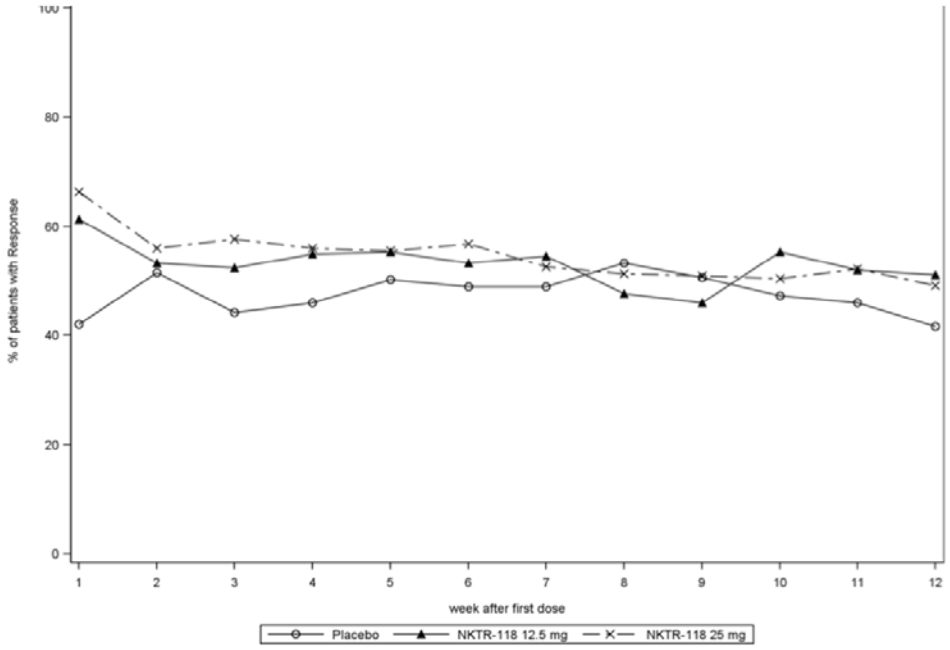


Table 6: Study 05 CMH analysis of response rate for Weeks 1 to 12 (Intent-to-treat analysis set).

Treatment Group	n	Number (%) of patients responding	Comparison versus Placebo [a]		
			RR	95% CI	p-value
Placebo	232	68 (29.3)	NA	NA	NA
NKTR-118 12.5 mg	232	81 (34.9)	1.188	(0.911,1.548)	0.202
NKTR-118 25 mg	232	92 (39.7)	1.348	(1.045,1.739)	0.021

The primary endpoint is positive for the 25mg dose. The 95% CI are very close to 1.

Figure 3. Percentage of patients who have at least 3 SBMs/week and at least 1 SBM/week increase over baseline (Intent-to-treat analysis set).



Note: The denominator for the percentages is the ITT analysis set, and patients who discontinued the study were automatically counted as non-improvers in the weeks following their discontinuation.

Comment: Using the MTP, the results are statistically significant for the primary endpoint for both studies in the 25mg dose. However the clinical relevance is not clear. In Study 05, the NKTR-118 12.5 mg dose did not demonstrate statistical significance for the primary outcome (p=0.202) so interpretation of the significance of positive results is difficult.

7.2.1.12. Results for other efficacy outcomes

In the pre-specified LIR subgroup, in Study 04, statistically significant higher response rates were observed in the NKTR-118 12.5 mg and 25 mg groups compared with placebo over 12 weeks in patients with OIC who had inadequate response to laxatives in the past (p=0.028 and 0.002, respectively, ITT analysis).

Table 7: Study 04 results.

Endpoint	Baseline laxative response	n [a]	Placebo (N = 214)	n [a]	NKTR-118 12.5 mg (N = 213)	n [a]	NKTR-118 25 mg (N = 214)
Response, n [b] (%)	LIR	118	34 (28.8)	115	49 (42.6)	117	57 (48.7)
	Non-LIR	96	29 (30.2)	98	38 (38.8)	97	38 (39.2)
Time (hrs) to first SBM,	LIR	116	43.4 (25.2,48.2)	114	20.6 (8.1, 23.5)	117	5.4 (3.9, 10.7)
Median (95% CI)	Non-LIR	93	34.8 (25.2, 49.5)	97	20.3 (7.7, 24.2)	96	6.9 (4.8, 21.3)
Change from baseline:							
SBMs/week,	LIR	118	2.0 (2.36)	114	2.6 (2.27)	117	3.5 (2.84)
Mean (SD)	Non-LIR	93	1.9 (1.90)	97	2.5 (2.10)	95	2.9 (2.22)
Days/week with	LIR	118	1.6 (1.63)	114	2.2 (1.76)	117	2.7 (1.76)
≥1 SBM, Mean (SD)	Non-LIR	93	1.6 (1.57)	97	2.1 (1.65)	95	2.4 (1.68)
Mean degree of	LIR	118	-0.6 (0.89)	114	-0.7 (0.83)	117	-0.8 (0.85)
straining, Mean (SD)	Non-LIR	93	-0.6 (0.76)	97	-0.6 (0.79)	95	-0.7 (0.91)
Mean stool consistency,	LIR	118	0.5 (1.32)	114	0.6 (1.04)	117	0.8 (1.18)
Mean (SD)	Non-LIR	93	0.6 (1.20)	97	0.5 (1.22)	95	0.6 (1.33)
% days/wk with	LIR	118	17.5 (22.22)	114	24.5 (23.47)	117	28.8 (25.60)
≥1 CSBM, Mean (SD)	Non-LIR	93	18.2 (21.70)	97	19.5 (22.93)	95	26.0 (24.62)

Similar results were seen in Study 05.

Table 8: Study 05 results.

Endpoint	Baseline laxative response	n [a]	Placebo (N = 232)	n [a]	NKTR-118 12.5 mg (N = 232)	n [a]	NKTR-118 25 mg (N = 232)
Response, n [b] (%)	LIR	121	38 (31.4))	125	53 (42.4)	124	58 (46.8)
	Non-LIR	111	30 (27.0)	107	28 (26.2)	108	34 (31.5)
Time (hrs) to first SBM,	LIR	117	38.2 (28.9, 57.4)	122	12.8 (6.4, 21.9)	120	18.1 (6.5, 22.8)
Median (95% CI)	Non-LIR	111	33.9 (26.6, 47.1)	106	21.8 (12.4, 25.4)	107	8.9 (6.0, 22.3)
Change from baseline:							
SBMs/week,	LIR	120	2.2 (2.31)	122	2.7 (2.08)	121	3.6 (3.31)
Mean (SD)	Non-LIR	111	1.9 (1.97)	106	2.4 (2.63)	105	2.7 (2.64)
Days/week with	LIR	120	1.7 (1.74)	122	2.3 (1.65)	121	2.7 (1.90)
≥1 SBM, Mean (SD)	Non-LIR	111	1.6 (1.58)	106	1.8 (1.58)	105	2.1 (1.57)
Mean degree of	LIR	120	-0.5 (0.82)	122	-0.7 (0.90)	121	-0.8 (0.99)
straining, Mean (SD)	Non-LIR	111	-0.5 (0.77)	106	-0.6 (0.83)	105	-0.8 (0.90)
Mean stool consistency,	LIR	120	0.4 (1.24)	122	0.6 (1.20)	121	0.9 (1.35)
Mean (SD)	Non-LIR	111	0.2 (1.25)	106	0.5 (1.23)	105	0.8 (1.28)
% days/wk with	LIR	120	15.1 (20.83)	122	25.4 (24.93)	121	30.4 (28.89)
≥1 CSBM, Mean (SD)	Non-LIR	111	17.9 (20.75)	106	19.0 (21.16)	105	22.1 (23.70)

In the overall population and the LIR subgroup, there was no statistically significant interaction between response rate and baseline opioid dose in either Study.

In the pre-specified LIR subgroup in Study 05, the number and % of responders was: 38 (31.4), 53 (42.4) and 58 (46.8) in the placebo, NKTR-118 12.5 mg and 25 mg treatment groups, respectively, significant for the 25mg group only (p=0.014).

In Study 04, a statistically significant shorter median time to first post-dose SBM was observed in the NKTR- groups compared with placebo (p<0.001 for both comparisons), time in hours: 34.8 (95% CI 25.2, 49.5), 20.3 (7.7, 24.2) and 6.9 (4.8, 21.3) hours in the placebo, 12.5 and 25mg groups respectively. In 05 the time to first post-dose laxation was statistically significantly shorter for the NKTR-118 25 mg group compared with placebo (p<0.001) but not the 12.5mg dose.

In Study 04, there was a statistically significant increase in the mean number of days per week with at least 1 SBM at Week 12 in the NKTR-118 12.5 mg and 25 mg treatment groups compared with placebo (p<0.001 for both comparisons). In Study 05, there was a statistically significant increase in the mean number of days per week with at least 1 SBM at Week 12 in the NKTR-118 25 mg group, but not in the 12.5 mg group, compared with placebo: 0.68; 95% CI (0.37 0.98); p<0.001.

In Study 04 the NKTR-118 25 mg but not the 12.5mg group, statistical improvement was observed for all individual OIC symptoms assessed (straining, stool consistency, days/weeks with CSBM) p=0.008, 0.042, and p<0.001, respectively). The mean straining scores decreased over Weeks 1 to 12, with no difference to placebo in the 12.5mg group but a statistically greater reduction in the MMRM-estimated Least-Squares Mean changes from baseline (standard error of the mean [SEM]) of greater than 0.5 points seen with increasing doses of NKTR-118 (-0.73 [0.05], -0.64 [0.05], and -0.54 [0.05] for the 25 mg, 12.5 mg, and placebo groups, respectively). The 25 mg group showed an improvement in intensity of straining compared with placebo of -0.18 (p=0.008). In terms of stool consistency, over Weeks 1 to 12, the MMRM-estimated Least-Squares Means (SEM) indicated an increase in stool consistency in all treatment groups, with statistically significant increases seen with only in the 25mg group - an improvement in BSS ratings compared with placebo of 0.18 (p=0.042). The significance of a 0.18 change in a 7-point scale is not discussed. In Study 05 for the NKTR-118 25 mg and 12.5 mg treatment groups,

improvement versus placebo was seen for straining and stool consistency but not CSBM based on the daily diary data.

In Study 04, a percentage change in the complete spontaneous bowel movement (CSBM) was seen in all groups, the 25 mg group showing a statistically significant increase in percent number of days with a CSBM/week compared with placebo of 8.59 ($p<0.001$). The clinical significance of an 8.59% increase in percent days per week with a CSBM was not discussed. There were statistically significant differences in the CSBM in the 05 Study, with a 11.76% (7.62,15.91) increase in days per week with a CSBM.

There was an increase in mean SBMs per week of nearly one extra SBM in the NKTR-118 25 mg and half in the 12.5 mg groups compared with placebo (0.99; $p<0.001$, and 0.54; $p=0.011$, respectively); 4.4 SBMs per week in the NKTR-118 25 mg group compared with 3.9 and 3.4 SBMs per week in the NKTR-118 12.5 mg and placebo groups, respectively.

Predictability of response to study drug based on the first 12 hours shows there was no clear relationship between response in the first 12 hours and response over 12 weeks for the NKTR-118 25 mg group ($p=0.430$). In the NKTR-118 12.5 mg and placebo groups, patients who had a SBM within the first 12 hours were more likely to be considered responders over 12 weeks compared with patients who did not have an SBM within 12 hours ($p<0.001$ and $p=0.007$, respectively).

Rescue medication use: over the 12-week study period, the median number of times that patients used bisacodyl as a rescue laxative was 1.0 for the NKTR-118 25 mg group, 2.0 for the NKTR-118 12.5 group, and 4.0 for placeboin the 04 study. In Study 05, the mean bisacodyl dose per week was 7.9mg in the placebo and 6.1 and 6.6mg in the 12.5 and 25mg naloxegol groups respectively; median 3.2mg in the placebo and 1.0 and 1.1mg in both naloxegol groups respectively. In the Study 04, the proportion of patients who used bisacodyl at least once was lower in the NKTR-118 25 mg (117 patients; 54.7%) and 12.5 mg (135 patients; 63.4%) groups compared with the placebo group (154 patients; 72.0%). No formal statistical analysis was conducted for this measure. The number and percentage of patients that used an enema 1 time or more than once during the study were low in the ITT analysis set and similar across treatment groups.

In Study 04, statistical improvement in the severity of symptoms of constipation in OIC patients by Week 12 was observed only in the rectal domain of PAC-SYM in the NKTR-118 25 mg ($p= 0.003$) treatment group compared with placebo. There was no relevant difference in the level of improvement for the abdominal domain or stool domain of the three domain PAC-SYM across treatment groups by Week 12, or in the 12.5mg dose. The overall score was not different between the three groups at Week 12. In Study 05, only the rectal (25mg dose only) and stool domains (both doses) but not the abdominal domain of the PAC-SYM showed statistical improvement at Week 12 (total score at week 12 significant in the 25mg dose).

This table shows the summary score for Study 04.

Table 9: PAC-SYM, NKTR-118 treatment groups versus placebo (Intent-to-treat analysis set), repeated measures analysis.

Scale	Time point	Treatment Group	n	LS Means (SEM)	Difference versus Placebo [a]		
					LS Mean	95% CI	p-value
Total score	Week 2	Placebo	197	-0.51 (0.04)	NA	NA	NA
		NKTR-118 12.5 mg	194	-0.65 (0.05)	-0.14	(-0.25, -0.02)	0.018
		NKTR-118 25 mg	191	-0.68 (0.05)	-0.17	(-0.29, -0.05)	0.004
	Week 4	Placebo	193	-0.60 (0.05)	NA	NA	NA
		NKTR-118 12.5 mg	194	-0.70 (0.05)	-0.10	(-0.22, 0.03)	0.125
		NKTR-118 25 mg	181	-0.70 (0.05)	-0.10	(-0.23, 0.03)	0.121
	Week 8	Placebo	183	-0.64 (0.05)	NA	NA	NA
		NKTR-118 12.5 mg	183	-0.75 (0.05)	-0.11	(-0.25, 0.02)	0.098
		NKTR-118 25 mg	175	-0.76 (0.05)	-0.13	(-0.26, -0.01)	0.062
	Week 12	Placebo	173	-0.69 (0.05)	NA	NA	NA
		NKTR-118 12.5 mg	171	-0.76 (0.05)	-0.08	(-0.21, 0.06)	0.273
		NKTR-118 25 mg	158	-0.81 (0.05)	-0.12	(-0.26, 0.02)	0.089

Study 05
Total Score

Week 12	Placebo	184	-0.63 (0.05)	NA	NA	NA
	NKTR-118 12.5 mg	173	-0.75 (0.05)	-0.12	(-0.26, 0.01)	0.080
	NKTR-118 25 mg	165	-0.81 (0.05)	-0.18	(-0.32, -0.04)	0.011

Study 04
Total Score

Treatment Group		n	LS Means (SEM)	Difference versus Placebo [a]		
				LS Mean	95% CI	p-value
Week 12	Placebo	174	-0.89 (0.09)	NA	NA	NA
	NKTR-118 12.5 mg	172	-0.91 (0.09)	-0.02	(-0.25, 0.20)	0.831
	NKTR-118 25 mg	159	-1.06 (0.09)	-0.18	(-0.41, 0.06)	0.141

In Study 04, there was no relevant difference in the level of improvement in patient satisfaction and quality of life as measured by the total and domain scores of the PAC-QOL across treatment groups by Week 12.

Week 12 was statistically significant for the 05 study, however the clinical relevance of a 0.5 LS means change from baseline was not clear.

Table 10: Study 05 results, Week 12.

Week 12	Placebo	185	-0.81 (0.09)	NA	NA	NA
	NKTR-118 12.5 mg	168	-1.12 (0.09)	-0.31	(-0.54, -0.07)	0.011
	NKTR-118 25 mg	167	-1.30 (0.09)	-0.49	(-0.73, -0.25)	<0.001

Comment: A statistically significant improvement in the LIR group receiving 25 and 12.5mg naloxegol was seen in the 04 but only in those receiving 25 but not 12.5mg in the LIR group in 05. This is consistent with the primary endpoint. Statistically significant shorter median time to first post-dose SBM was observed in the 25mg NKTR- groups compared with placebo. In 04 there was a statistically significant increase in the mean

number of days per week with at least 1 SBM at Week 12 in the NKTR-118 treatment groups compared with placebo (p<0.001 for both comparisons).

In the NKTR-118 25 mg but not the 12.5mg group, statistical improvement was observed for all individual OIC symptoms assessed in the 04 and 05 group. In Study 04, in terms of stool consistency, over Weeks 1 to 12, statistically significant increases seen with only in the 25mg group - an improvement in BSS ratings compared with placebo of 0.18 (p=0.042). The significance of a 0.18 change in a 7 point scale is not discussed. The 25 mg group showed a statistically significant increase in percent number of days with a CSBM/week compared with placebo of 8.59% in the 04 and 11.76% in the 05 group. The clinical significance of an extra 8-11% days per week with a CSBM was not discussed.

There was an increase in mean SBMs per week of nearly one extra SBM in the NKTR-118 25 mg and half in the 12.5 mg groups compared with placebo; 4.4 SBMs per week in the NKTR-118 25 mg group compared with 3.9 and 3.4 SBMs per week in the NKTR-118 12.5 mg and placebo groups, respectively. These small fractional increases of SBM or fractions of days with a CSBM are not discussed. The significance of a 0.18 change in a 7-point BSS scale on symptoms is not discussed for example.

In the patient relevant endpoints measured by PAC-SYM and PAC-QOL there were no differences between placebo and either of the doses of nalexegol in the 04 Study apart from the rectal domain of the PAC-SYM. Improvements on the rectal and stool domain were seen in Study 05 in the 25mg dose and showed a statistical improvement of 0.5 points on the QoL score, the clinical relevance of which was not clear.

7.2.2. Study 06

Title: A Randomised, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NKTR-118 in Relieving Opioid-Induced Constipation (OIC) in Patients with Cancer-Related Pain

7.2.2.1. Design

A Phase III multicentre, randomised, double-blind, placebo-controlled, study of the efficacy, safety, and tolerability of NKTR-118 in patients with OIC in cancer was planned (4 week treatment phase for Part A and 12 weeks for Part B). The study consisted of 2 Parts: Part A and Part B. Part A was a double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of NKTR-118 12.5 mg and 25 mg in the treatment of OIC in cancer patients with pain related to malignancy over a 4-week period. Malignancy-related pain included pain directly related to a tumor or pain resulting from the direct treatment of a tumor (e.g. neuropathic pain as a result of tumor resection, mucositis, or peripheral neuropathic pain as a result of chemotherapy or radiation therapy). All patients were to have the opportunity to transition from Part A (the double-blind portion of the study) to Part B (the active treatment extension), provided they met the relevant criteria. Part B was to be an active treatment extension to assess the safety and tolerability of NKTR-118 in the treatment of OIC in cancer-related pain during an additional 12 weeks of treatment.

Approximately 672 patients were planned to be enrolled to obtain 336 randomized patients at approximately 150 centres in the United States and 15 other countries. However due to slow recruitment, the study was stopped. At the time, 14 patients only had been enrolled at 11 centres in the US, Poland, and the Czech Republic; these were randomised across the 3 treatment groups. As this was fewer than 5% of the planned number, there were insufficient number of patients to perform the protocol specified formal statistical analyses.

7.2.2.2. Patient group

Patients (≥18 years or older) with a histologically or cytologically confirmed neoplasm and with a life expectancy of ≥3 months who were receiving a stable maintenance opioid regimen (total daily dose of ≥30 mg of oral morphine, or equi-analgesic amount[s] of 1 or more other opioid

therapies) for a minimum of 4 weeks prior to screening for cancer-related pain with no anticipated change in opioid dose requirement as a result of disease progression over the proposed 4-week study period were eligible to be randomised. The target population must have reported a history of <3 rescue-free bowel movements (RFBMs)/week and at least 1 OIC associated symptom at screening and have a confirmed diagnosis of OIC. A RFBM was defined as a bowel movement (BM) without rescue laxatives in the previous 24 hours. Confirmed OIC was defined as documented <3 RFBMs/week on average over the 2-week OIC confirmation period. In addition to the RFBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the BMs recorded in the electronic diary (eDiary) during the OIC confirmation period: Bristol Stool Scale (BSS) stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. Patients who had 0 BMs in the 7 days prior to randomisation were ineligible.

7.2.2.3. Primary Objective

- To compare the efficacy of NKTR-118 12.5 and 25 mg with placebo in the treatment of patients who have OIC in pain related to malignancy in a 4-week double-blind study (Part A).

7.2.2.4. Secondary Objective

- To compare NKTR-118 12.5 mg and 25 mg with placebo on the daily signs and symptoms associated with OIC (degree of straining, sensation of incomplete evacuation, and stool consistency), symptoms of constipation, and overall quality of life over a 4-week double-blind study (Part A).
- To characterize the maintenance of effect of NKTR-118 over a 12-week extension (Part B).

7.2.2.5. Safety

- To assess the safety and tolerability of NKTR-118 12.5 and 25 mg, when used for the treatment of OIC.

7.2.2.6. Exploratory

To characterize the PK of NKTR-118 and the covariate effect in the targeted disease population, explore the NKTR-118 exposure-response relationship, collect and store DNA for future exploratory research, and to assess patient health status index.

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to NKTR-118.

7.2.2.7. Efficacy and Safety Data

Due to the small number, data is described only.

Three out of 5 patients in the NKTR-118 25 mg group, 4 out of 5 patients in the NKTR-118 12.5 mg group, and 2 out of 4 patients in the placebo group demonstrated response.

No deaths, other serious AEs (SAEs), or discontinuations due to AEs occurred during the study.

During Part A of the study, 2 patients (40.0%) in the NKTR-118 25 mg group, 3 patients (60.0%) in the NKTR-118 12.5 mg group, and 2 patients (50.0%) in the placebo group reported AEs - the most common AEs during Part A were from the system organ class (SOC) of gastrointestinal (GI) disorders (2/5 patients [40%] in the NKTR-118 12.5 mg group, 1/5 patients (20%) in the NKTR-118 25 mg group, and 0 patients in the placebo group).

Treatment-emergent AEs in the GI SOC during Part A included the preferred terms of haematochezia and nausea in the NKTR-118 12.5 mg group and nausea in the NKTR-118 25 mg group.

During Part B of the study, 4 patients (66.7%) in the NKTR-118 25 mg group and 1 patient (33.3%) in the NKTR-118 12.5 mg group reported AEs. No AE preferred term was observed in more than a single patient during Part B.

Comment: the poor recruitment and early cessation for this study as compared with recruitment for the non-cancer populations could suggest that pain relief concerns, or concerns regarding the multifactorial nature of constipation in cancer, and/or concern regarding GI side effects from an opiate Mu antagonist are contributory. The Sponsor needs to give more detail on the actual reason for lack of recruitment. As high morphine doses are common in this group and constipation is common the failure to complete a Phase III study in this population is viewed by the Evaluator as a risk for the proposed indication of all OIC.

7.2.3. Study 07-IN-NX-003

7.2.3.1. Study design, objectives, locations and dates

Title: A Phase II, double-blind, randomised, placebo- controlled, multiple-dose, dose escalation study to evaluate the efficacy, safety and tolerability of naloxegol in patients with opioid-induced constipation.

7.2.3.2. Design

- A multicentre, randomised, double-blind, placebo-controlled, multiple-dose, dose-escalation study of the efficacy, safety, and tolerability of NKTR-118 in patients with OIC. Note naloxegol is also referred to as PEG-naloxol (NKTR-118) in this study.

7.2.3.2.1. Primary Objective

- To evaluate the efficacy of PEG-naloxol (NKTR-118) at various dose levels, with efficacy defined as the change from baseline in the number of spontaneous bowel movements (SBMs) per week.

7.2.3.2.2. Secondary Objectives

- To evaluate the safety and tolerability of NKTR118, to identify an effective dose that preserves opioid-conferred analgesia.
- Delineate the dose-response for NKTR-118 across a range of underlying opioid doses, with response defined as the change in SBMs per week from baseline.
- Characterise the pharmacokinetics (PK) of NKTR-118 in patients

7.2.3.2.3. Location and Dates

A total of 54 clinical sites in 4 countries screened or randomised at least 1 patient in this study: 38 in the United States, 7 in Germany, 5 in Romania, and 4 in Canada; dates of recruitment: 04 Jan 2008 – 24 Mar 2009.

7.2.3.3. Inclusion and exclusion criteria

This study enrolled male and female patients ≥ 18 years of age on a stable opioid dose of 30 mg/day to 1000 mg/day who had OIC (defined as ≤ 5 SBMs over the 2-week OIC screening period, which corresponded to < 3 SBMs/week). Only those patients who met these criteria in the 2 week screening period were randomised and entered a 1- week on-study, single-blind placebo run-in period, followed by 4 weeks of randomised double blind treatment with NKTR-118 or placebo. Patients were randomised within each cohort in a 1:1 ratio (active:placebo).

This study planned to enroll up to 4 sequential dose cohorts comprising approximately 240 patients. Approximately 16 patients per cohort were planned for inclusion in the PK substudy.

Enrolment of the next successive cohort began only after an independent Dose Evaluation Safety Committee (DESC) had examined the safety data from the current cohort, including a

review of all individual occurrences of clinically significant pain progression (CSPP), occurrences of possible opioid withdrawal, change in Numeric Rating Scale (NRS) pain score for the cohort, any change in mean daily opioid use for individual patients and overall, and specific adverse events (AEs) of special interest at each cohort level.

7.2.3.4. Study treatments

The doses of NKTR-118 for Cohorts 1, 2, 3, and 4, respectively, were originally scheduled to be 5 mg, 25 mg, 50 mg, and 100 mg once daily; however, upon review of safety data from the 50 mg cohort, the DESC recommended against a fourth dose cohort at 100 mg i.e. due to safety concerns that 50 mg once daily dose should be the top recommended dose. In Amendment 6.0, the dose of the fourth cohort was changed from 100 to 38 mg once daily, however the amendment did not go ahead except for the revisions to the final statistical analysis plan (SAP) i.e. no 38mg dose.

Comment: The choice of doses and recommendation to use 38mg as a final dose cohort was noted as well as the actual final doses chosen for the Phase III studies which were 25 and 12.5 mg.

7.2.3.5. Efficacy variables and outcomes

The primary efficacy outcome was the change from baseline in SBMs/week to the end of the first week of double-blind study drug administration.

Other efficacy outcomes included:

- Change from Baseline in SBMs/Week During Weeks 2, 3, and 4
- Change from Baseline in SBMs/Week Across the 28-day Double-Blind Period
- Time to First Laxation
- Laboratory Evaluation of FSH, LH, Testosterone, Prolactin, and Estradiol
- Health Outcomes Assessments: PAC-SYM, PAC-QOL, and SF-36.

A PK substudy was conducted in conjunction with the main study, in which approximately 16 patients were to be included per cohort, with the intent that approximately 8 patients receiving NKTR-118 would be included in this substudy.

7.2.3.6. Randomisation and blinding methods

Each screened patient was assigned a unique patient number. Eligibility was determined after both screening periods (initial and OIC) at Week 1, Day 1 upon completion of the OIC screening period. Patients were randomised, received a unique randomization number, and entered the placebo run-in period followed by the 4-week randomized treatment period. Randomization numbers were distributed and communicated to sites by use of an IVRS operated by Perceptive Informatics, a division of PAREXEL. Randomisation was stratified by total daily opioid dose at screening in MEU (low, 30 to 100 MEU; high, > 100 to 1000 MEU).

Study medication (NKTR-118 and placebo) bottles, bottle cartons, and syringe cartons were prepared for dosing and labelled according to applicable regulations, containing at least the following information: the protocol number, blinded name/code of the drug, the route of administration, the patient number, patient initials, date of dispensing, lot number, expiry date and any required per country/region cautionary statements. Syringes were labelled with the protocol number, blinded name/code of the drug, patient number, date of dispensing, and expiry date.

Comment: Randomisation and blinding methods are appropriate.

7.2.3.7. Analysis populations

- Modified Intent-to-Treat Population: The MITT analysis population consisted of all randomized patients who received at least 1 dose of double-blind study treatment, had a baseline value and Visit 6 evaluable data (where Visit 6 was the Week 1 visit during the double-blind study treatment period). Patients were analysed by treatment received. The MITT population was the primary population for all efficacy analyses.
- Per-Protocol Population: The per-protocol population included all MITT patients except patients with major protocol deviations. After SAP finalisation it was determined that the per- protocol analysis of efficacy endpoints will not significantly add value to efficacy analysis conclusions based on the MITT population, was not conducted nor reported.
- Safety Population: The safety population consisted of all randomised patients who took at least 1 dose of placebo run-in study treatment or blinded study medication. Unless otherwise stated, all safety analyses were based on this population.
- Pharmacokinetic Population: Nektar Clinical Pharmacology identified the patients eligible for inclusion in the PK population and provided the list to Synteract. Details of the PK analyses were included in a separate analysis plan, which was prepared by Nektar Clinical Pharmacology. The PK population was based on the PK substudy and included 5 patients in Cohort 1 (5 mg), 12 patients in Cohort 2 (25 mg), and 5 patients in Cohort 3 (50 mg). The PK population included all patients in this substudy who received NKTR-118 and had relatively complete individual analyte concentration-time profiles that allowed computation of meaningful PK parameter values. All PK summaries and analyses were based on the PK population. Data was provided in the CSR and included in the PK summary of this evaluation (Tables 18-20, population PK).

7.2.3.8. Sample size

There were a total of 207 randomised patients who received at least 1 dose of placebo run-in medication in this study. There were 5, 12, and 5 patients with evaluable PK data in the 5, 25, and 50 mg dose groups, respectively, within the PK analysis population.

7.2.3.9. Statistical methods

Statistical Analysis: Analysis of the primary endpoint was conducted based on the modified intent-to-treat (MITT) population, summarised by cohort and treatment group using the Wilcoxon rank sum test was used to compare the treatment groups (NKTR-118 vs. placebo) within each cohort. The Wilcoxon signed rank test was used for the within group comparisons.

7.2.3.10. Major protocol violations/deviations

There were 56 protocol violations (major and minor assessed together) in 208 subjects, relatively comparable between placebo and the three different doses.

7.2.3.11. Baseline data

The majority of patients in the MITT population were female (62.2%) and Caucasian (86.5%). The mean patient age was 49.7 (range of 21 to 80 years). Height and weight were comparable across groups. A total of 194 patients received at least 1 dose of double-blind study medication.

7.2.3.12. Results for the primary efficacy outcome

The primary endpoint for this study was change from baseline in SBMs/week to the end of the first week of double-blind study drug administration.

For Cohort 1 (5 mg), the mean change in SBMs/week from baseline to the end of Week 1 was not statistically significant. For Cohort 2 (25 mg), the mean change in SBMs/week from baseline to the end of Week 1 was 3.6 for NKTR-118 patients and 1.9 for placebo patients (an extra 1.6

SBM/week, P = 0.0020). For Cohort 3 (50 mg), there was also a statistically significant difference (and extra 2.5 SBM/week, P = 0.0001).

Post hoc it was noted that an increase of approximately 4 SBMs/week from baseline was seen in some patients but only with the 2 higher doses of NKTR-118 (25 mg and 50 mg).

7.2.3.13. Results for other efficacy outcomes

7.2.3.13.1. Secondary Efficacy Endpoints

- Change from Baseline in SBMs/Week During Weeks 2, 3, and 4

For Cohort 1 and 2 (5 mg and 25mg), the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 <1 extra SBM/week and were not statistically significant, although they were if only two of the time-points were used (Week 3 and 4). For Cohort 3 (50 mg), the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 were 4.3, 5.2, and 3.9 for NKTR-118 patients and 1.0, 1.1, and 0.7 for placebo patients, respectively, statistically significant (P = <0.0001, P = <0.0001, and P = 0.0002, respectively).

- Change from Baseline in SBMs/Week Across the 28-day Double-Blind Period was not statistically significant for Cohort 1 (5mg), but was for Cohort 2 (25 mg), the mean change in SBMs/week from baseline across the 28-day double blind period was 3.2 for NKTR-118 patients and 1.7 for placebo patients, (P = 0.0022) and for Cohort 3 (50 mg), 4.6 for NKTR-118 patients and 1.2 for placebo patients, p <0.0001.
- Time to First Laxation was not statistically significantly different between NKTR-118 (5 mg) and placebo groups, but was in the NKTR-118 (25 mg) and (50 mg) cohorts compared to placebo with respective P = 0.0012 and P = 0.0016. The median time to first laxation for NKTR-118 (25 mg) vs. placebo was 6.6 vs. 48.6 hours and was 2.9 vs. 44.9 hours for NKTR-118 (50 mg) vs. placebo.
- Laboratory Evaluation of FSH, LH, Testosterone, Prolactin, and Estradiol showed no clinically significant changes in the levels of the 5 reproductive hormones evaluated in this study in patients treated with placebo or NKTR-118 across the 3 cohorts.
- Health Outcomes Assessments: PAC-SYM, PAC-QOL, and SF-36.

Statistical improvements were seen in some of the PAC-SYM symptoms for some of the doses at some of the time points. NKTR-118 patients in Cohort 2 (25 mg) had statistically significant mean scores vs. placebo for rectal symptoms at Week 2 (P = 0.0496), stool symptoms at Weeks 2 and 4 (P = 0.0100 and P = 0.0335, respectively), and total score (P = 0.0163). NKTR-118 patients in Cohort 3 (50 mg) had statistically significant mean scores vs. placebo for rectal symptoms at Week 4 (P = 0.0116). There were no other clinically meaningful differences between placebo and NKTR-118 scores within cohorts or between NKTR-118 doses.

The PAC-QOL showed similar variability and lack of dose-response. At double-blind Day 1, mean scores across all treatments and cohorts ranged from 2.8 to 3.2. However, at double-blind Weeks 2 and 4, NKTR-118 patients in all cohorts reported greater satisfaction compared with placebo patients (mean scores at Week 2 of 2.2 for 5 mg and 1.8 for 25 mg and 50 mg patients vs. 2.7 for all placebo cohorts; yet mean scores at Week 4 of 2.4, 2.0, and 2.2 for 5 mg, 25 mg, and 50 mg, respectively, vs. 2.6 for placebo Cohort 1 [5 mg] and 2.8 for placebo Cohorts 2 [25 mg] and 3 [50 mg]). Besides the satisfaction domain, there were no trends between placebo and NKTR-118 scores within cohorts or between NKTR-118 doses.

There were no significant differences in mean SF-36 scale scores between NKTR-118 5 mg and placebo patients. NKTR-118, 25 mg patients experienced statistically significant SF-36 scale scores that were higher than placebo for physical functioning, mental health, social functioning, and vitality only at some post-dose time-points e.g. in the 25mg group, mean SF-36 scores were statistically significant vs. placebo for the physical functioning (P = 0.0307) and mental health (P

= 0.0398) scales at Week 2, At Week 4, NKTR-118 patients in Cohort 2 (25 mg) had statistically significant scores vs. placebo for the social functioning (P = 0.0224) and mental health (P = 0.0311) scales. When the LOCF analysis was run, NKTR-118 25 mg patients had statistically significant scores vs. placebo for the vitality (P = 0.0451), social functioning (P = 0.0151), and mental health (P = 0.0215) scales. At double-blind Day 1, mean SF-36 scale scores were statistically significant for NKTR-118 patients in Cohort 3 (50 mg) vs. placebo (P = 0.0287) for the mental health scale only; this was not seen at subsequent visits for NKTR-118 patients in Cohort 3 (50 mg).

For the SF-36 mean component summary scores, NKTR-118 in Cohort 3 (50 mg) was significant vs. placebo (P = 0.0493) for the mental component at Day 1, and NKTR-118 in Cohort 2 (25 mg) was significant vs. placebo (P = 0.0339) for the mental component at Week 2. No other statistically significant differences were noted.

Post hoc analysis showed that the proportion of responders (i.e. patients who showed an increase of ≥ 2 SBMs/week from baseline) across the 28-day double-blind period was significantly higher in the NKTR- 118 group vs. placebo group in both the 25 mg (75% vs. 26%) and 50 mg cohorts (92% vs. 29%; *P* = 0.0003 and *P* = 0.0001, respectively) but not the 5mg dose.

> *Comment: Other health outcome assessments are suggestive, but not consistent across the time-points or increasing with increasing dose in the PAC-QOL, PAC-SYM or the SF-36. The post hoc analysis suggested that if a parameter of ≥ 2 SBMs/week from baseline was chosen, there are significantly more responders in the NKTR- 118 group in the 25 and 50mg doses. It is noted that there appears to be no relationship between responder and PRO.*

7.2.3.14. Pharmacokinetics

NKTR-118 was rapidly absorbed independent of dose and duration of dosing. Systemic exposure to NKTR-118 was dose proportional, and the elimination rate was independent of dose. Pharmacokinetic steady-state was achieved rapidly with no appreciable accumulation occurring after once daily dosing. There were no differences in PK characteristics between males and females.

Glucuronidation of NKTR-118 is a minor metabolic pathway. No metabolite exceeded 10% in abundance relative to parent NKTR-118 in plasma or urine and no metabolite accumulated after 28 days of dosing. Further, no indication of induction or inhibition of any metabolic pathway was observed during the 28-day dosing period.

The following table shows the mean NKTR-118 PK parameters in the evaluable PK population.

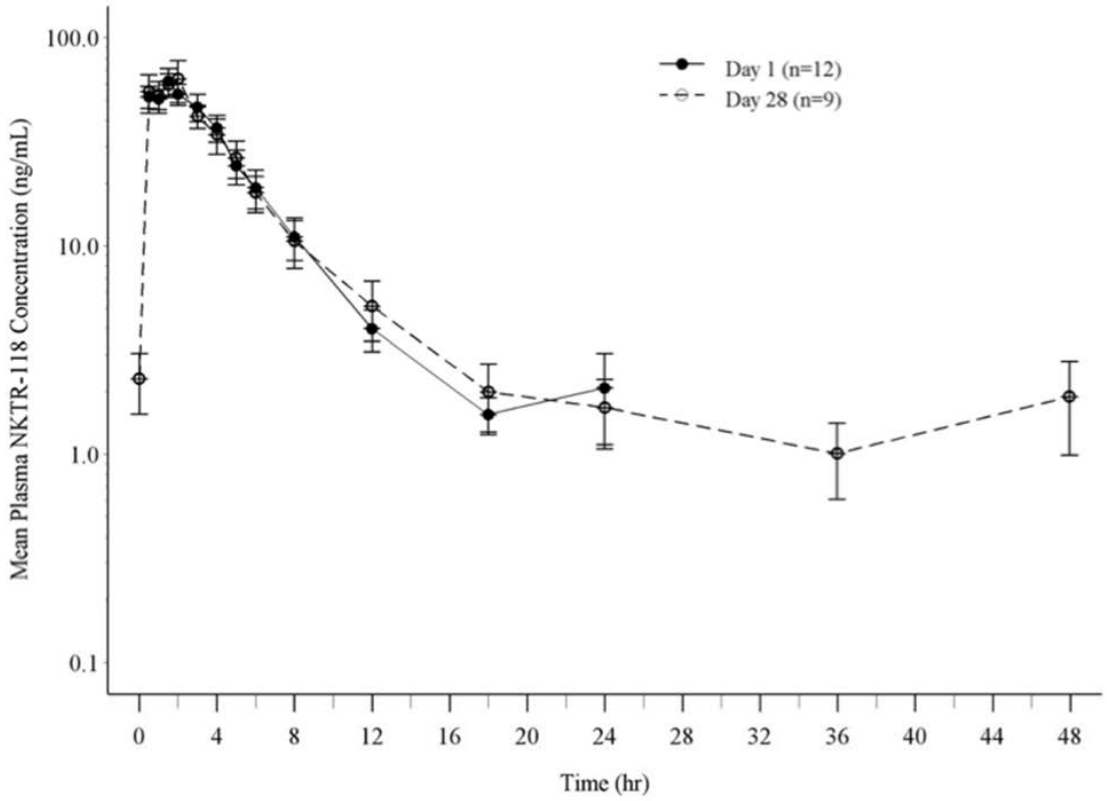
Table 11: Mean (CV%) NKTR-118 PK Parameters: Evaluable PK Population N: number of patients with evaluable PK data. CV%: Coefficient of variation, expressed as percent of mean value. NC: not calculated for Day 1.

Day	Dose(mg)	N	Tmax(hr)	Cmax(ng/mL)	AUC(0-24)(hr*ng/mL)	T1/2 (hr)
1	5	5	1.7 (84.7)	9.1 (52.2)	34.01 (48.8)	NC
	25	12	1.5 (61.1)	70.6 (42.3)	327.7 (47.7)	NC
	50	5	1.5 (91.3)	123.7 (36.3)	426.8 (22.1)	NC
28	5	4	1.5 (81.7)	8.0 (49.2)	39.0 (23.1)	17.4 (8.3)
	25	9	1.4 (43.9)	81.1 (45.7)	334.8 (51.4)	14.1 (4.9)
	50	4	1.6 (101.7)	100.0 (41.9)	403.6 (36.7)	20.3 (10.3)

A 10 fold increase in AUC was seen between the 5mg and 25mg with slightly increased AUC with a doubling of that dose to 50mg.

The following graph summarises the concentrations vs. time for Day 1 and 28 in the 25mg group.

Figure 4: PK analysis population: mean (+/- SEM) plot of NKTR-118 plasma concentration versus time for Day 1 and 28 on a log-linear scale (dose group = 25 mg).



Following review of 8 AEs of special interest and the aggregate safety data from patients in Cohort 3 (50 mg), the DESC recommended against dose escalation to a fourth dose cohort at 100 mg (patients would withdraw).

Mean daily opioid levels remained relatively steady from baseline throughout double-blind treatment for all cohorts. There were no statistically significant changes from baseline in the mean daily opioid levels between the NKTR-118 arm and placebo arm in Cohort 2 (25 mg) and Cohort 3 (50 mg); however statistically significant differences were seen between the NKTR-118 arm and placebo arm in Cohort 1 (5 mg).

Opioid withdrawal was measured by a change in the total Clinical Opioid Withdrawal Scale (COWS) score between the NKTR-118 and placebo groups. There was no statistically significant difference in the total COWS score between NKTR- 118 vs. placebo in the double-blind treatment period in Cohort 1 (5 mg) and Cohort 2 (25 mg). However, in Cohort 3 (50 mg), a statistically significant difference in total COWS score was noted between the NKTR- 118 and placebo groups, but only at Day 1 of the double-blind treatment period. A post hoc analysis demonstrated that this increase in Day 1 total COWS score for the NKTR-118, 50 mg dose group was primarily due to increases in the GI component scores for the patients experiencing an increase in COWS score from baseline, consistent with the finding that patients in the 50 mg dose group receiving NKTR-118 experienced more GI side effects than those receiving placebo. When the GI component of the COWS instrument was removed from calculation of total COWS scores for both the NKTR-118 and placebo groups in the 50 mg cohort, there was no longer any significant difference in COWS score between the NKTR-118 and placebo groups indicating a lack of increase in the components of the scale that reflect CNS withdrawal.

> *Comment: Whilst it is reasonable to remove the COWS scores it is noted that GI symptoms can reflect COW.*

Mean pain on average over the last 24 hours and worst mean pain in the last 24 hours as measured by NRS remained relatively consistent from baseline through post-dose time-points for all 3 cohorts.

Mean bisacodyl rescue medication use was numerically lower for the NKTR-118 arms of Cohort 2 (25 mg) and Cohort 3 (50 mg) vs. placebo at all post-dose time-points; however, a statistical comparison was not done.

No differences in mean clinical laboratory parameters were noted between NKTR-118 and placebo. Vital signs, PE results, and ECG findings were largely normal with no trend detected.

The NKTR-118 dose cohorts of 5 mg and 25 mg were generally well tolerated; however, GI AEs occurred more frequently in the 50 mg once daily cohort.

> *Comment: An increase in responder rate was seen in the 25mg and 50mg group with an extra 1.6 SBM/week and extra 2.5 SBM/week, respectively. However this was not associated with improved symptoms nor QOL. A 10 fold increase in AUC between the 5mg and 25mg with slightly increased AUC with a doubling of dose to 50mg. Commonly reported side effects are GI in nature (abdominal pain, diarrhea, and nausea) and most frequent in the 50 mg cohort.*

7.3. Analyses performed across trials (pooled & meta analyses)

The evaluator reviewed pooled analyses and used them to check the statements on pooled efficacy items of interest or concern in the summary sections of each trial.

7.4. Evaluator's conclusions on efficacy

Overall, there was an increase in the primary endpoint SBM/week of 1-2 on average in the 25 mg group in the pivotal studies. Efficacy was also seen in the Phase II study where the dose of 50 mg was studied.

However, there are some important caveats to make regarding the interpretation of the statistical significance of the primary endpoints. The fact that there were more subjects in the NKTR-118 25 mg group that discontinued treatment and that had adverse events (AEs) than placebo will be covered in the Safety section.

7.4.1. Demographics

Firstly, most subjects in the efficacy studies were from the US and were Caucasian. In the pivotal studies, approximately half of the patients had a BMI ≥30 kg/m^2. The relevance of this to the Australian population and to the cancer population specifically is unclear.

7.4.2. Relationship of statistical response to clinical outcome

The clinical significance (in terms of patient benefit) of the statistically significantly increased number who responded to therapy compared to placebo (increase of at least one SBM per week) was not explicit. There was an increase in mean SBMs per week of nearly one extra SBM in the NKTR-118 25 mg and half in the 12.5 mg groups compared with placebo; 4.4 SBMs per week in the NKTR-118 25 mg group compared with 3.9 and 3.4 SBMs per week in the NKTR-118 12.5 mg and placebo groups, respectively. These small fractional increases of SBM or fractions of days with a CSBM are not discussed.

7.4.3. Relationship of change in individual OIC symptoms to clinical status

In Study 04, stool consistency measurement, over Weeks 1 to 12, statistically significant increases are seen only with only in the 25 mg group and in Bristol Stool Scale (BSS) ratings compared with placebo of only 0.18 ($p = 0.042$). The significance of a 0.18 change in a 7-point scale is not clear. The 25 mg group showed a statistically significant increase in percent number

of days with a CSBM/week compared with placebo of 8.59% in the 04 and 11.76% in the Study 05 group. The clinical significance of an extra 8-11% of days per week with a CSBM was not clear.

7.4.4. Relationship of change in individual OIC symptoms clinical status to responder rate (primary outcome)

In the patient relevant endpoints measured by the Patient Assessment of Constipation Symptom Questionnaire (PAC-SYM) and the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL), there were no differences between placebo and either of the doses of nalexegol in the 04 Study apart from the rectal domain of the PAC-SYM. Improvements on the rectal and stool domain were seen in Study 05 in the 25 mg dose and showed a statistical improvement of 0.5 points on the QoL score, the clinical relevance of this was not clear, nor was the relationship of response (and increase of 1 or more SBM/week) to the QoL.

7.4.5. Concerns

- Concerns relating to lack of OIC data in the cancer population: patients with cancer were excluded from the pivotal trial and the 06 cancer OIC study was closed with only 14 subjects.
- Concerns regarding the choice of dose for pivotal study: the choice of 25 mg for the pivotal study is clear but not the 12.5 mg dose. This correlates with the 12.5 mg dose having poor clinical efficacy.
- Choice of primary endpoint: PRO are likely to be very valid in this disease however it is not clear why, in the absence of a clear definition of what a clinically relevant increase in SBM is (nor whether it is change in stool type versus frequency), that the PRO were not used as primary endpoints.
- Efficacy is subpopulation such as elderly (only 2% older than 75 years in the pivotal study and AUC in the elderly increased), patients with moderate-severe renal impairment (dialysis population and PK are different to patients with CrCl between 15 and 30 ml/min). There is no evidence in the cancer population or in children.
- There is no long term efficacy data greater than 12 weeks which is problematic as the condition for which the opiate is prescribed (which can contribute to the constipation) is a long term condition.

8. Clinical safety

8.1. Studies providing safety data

The following studies provided evaluable safety data:

- The Phase II Study 07-IN-NX-003
- The two Phase III efficacy and safety studies (04 and 05)
- A 12 week double blind safety extension study (Study 07- D3820C00007) of Study 04
- A randomised 52 week open label parallel group long term safety study (Study 08 - D3820C00008)
- A study in OIC in Cancer (Study 07)
- Phase I and PK studies

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

Incidence, nature, and intensity of adverse events (AEs), treatment-related AEs, serious adverse events (SAEs), AEs leading to discontinuation, and specific safety areas of interest

- Change from baseline in the mean daily opioid dose for Weeks 1 to 4 and 1 to 12
- Change from baseline in the mean Numeric Rating Scale (NRS) pain score for Weeks 1 to 4 and 1 to 12
- Observed values and change from baseline in composite score in modified Himmelsbach scale for the evaluation of centrally mediated opioid withdrawal symptoms at 2 hours after first dose of study drug, and at Weeks 1, 4, and 12 (reference provided)
  - Changes in vital signs and physical examination
  - Changes in laboratory assessments (i.e. chemistry, hematology, and urinalysis
  - Changes in electrocardiograms (ECGs)

8.1.2. AEs of Special Interest

In the pivotal 04 and 05 AEs of particular interest, including selected CV events (i.e. MACE events, congestive heart failure), AEs potentially related to blood pressure changes, serious GI events adjudicated for bowel perforation, AEs potentially related to abuse liability, and AEs potentially related to opioid withdrawal) were assessed by central adjudication. In Study 04, there were nil CV events were judged to be related to IP however hypotension was considered to be likely to be related in two cases, one case of orthostatic hypotension thought to be possibly related. There were no serious GI events adjudicated for perforation and AEs potentially related to opioid withdrawal were identified as a special interest AE category in the SAP (COWS - all 3 AEs identified were coded to the MedDRA term of drug withdrawal syndrome as these were reported as verbatim terms of opioid withdrawal by the PI). Overall the frequency of AEs identified as drug withdrawal by the investigator was low and similar across treatment groups. The proportion of patients with AEs of abuse potential was 2.3% (5 patients), 4.7% (10 patients), and 5.2% (11 patients) in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, during the randomised treatment period.

In Study 05, the same AEs were of special interest and although cases were referred to adjudication, most were thought unrelated to study medication. The only one of note to report was the risk of withdrawal.

Table 12: Number (%) of patients with AEs of opioid withdrawal, treatment period only or post-treatment follow-up (Safety analysis set).

	Number (%) of patients [a]		
Topic/preferred term	Placebo (N = 231)	NKTR-118 12.5 mg (N = 230)	NKTR-118 25 mg (N = 232)
Number of patients with at least 1 of opioid withdrawal related AE	0	1 (0.4)	4 (1.7)
Drug withdrawal syndrome	0	1 (0.4)	4 (1.7)

8.1.3. Pivotal studies that assessed safety as a primary outcome

A 12-week double-blind safety extension study (Study 07- D3820C00007) of Study 04 and a randomised 52-week open-label parallel-group long-term safety study (Study 08 - D3820C00008) assessed safety as a primary outcome. These studies are described below, "Other studies evaluable for safety only".

8.1.4. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data from a single study.

Study 07-IN-NX-003 provided four week data on dose escalation of 5-100mg once daily.

In this Study, in both the 5 mg and 25 mg groups TEAE rate was mildly increased, in Cohort 3 (50 mg), 85% of patients reported TEAEs as compared to 56% in the placebo arm. Most TEAEs occurring in patients treated with NKTR-118 were reported as either Grade 1 or 2 in severity. Sixteen patients in Cohort 1 (5 mg), 16 patients in Cohort 2 (25 mg) and 23 patients in Cohort 3 (50 mg) experienced at least 1 TEAE that was assessed as being causally related to the study drug. The majority of study drug (NKTR- 118) related TEAEs reported within all 3 cohorts were in the System Organ Class (SOC) of GI disorders - diarrhoea, abdominal pain, and nausea.

Five of 194 patients (2.5%) who entered the double-blind study period, 1 in each of the active arms (except placebo 25mg) experienced a total of 7 SAEs. Of these 7 SAEs, 4 were experienced by patients in the NKTR-118 arm and 3 were reported in the placebo group. Of the 4 SAEs experienced by NKTR-118 patients, 1 SAE reported in Cohort 3 (50 mg) was assessed as being related to the study drug NKTR-118 (TEAE) - abdominal cramping occurred shortly after administration of the first dose of the study drug. The most frequent study drug-related Grade 3/4 TEAE reported across all 3 dose cohorts was abdominal pain. Less than 15% of patients in the NKTR-118 group who entered the double-blind study period experienced Grade 3 TEAEs. A total of 4 patients experienced Grade 4 TEAEs during the study, 2 in the NKTR-118 arm of Cohort 1 (5 mg) and Cohort 2 (25 mg), respectively and 2 in the placebo arm of Cohort 1 (5 mg). Patient 43003, randomized to NKTR-118 arm in Cohort 2 (25 mg), experienced an AE of pulmonary embolism that had a fatal outcome, assessed by the investigator as being unrelated to the IP.

In addition to TEAEs and SAEs, an independent DESC also reviewed specific AEs of interest that were identified within the protocol; namely events that qualified for CSPP, MSOW with and without a documented COWS score of ≥ 13, and all treatment-related AEs that led to study drug discontinuation and early termination from the study. The DESC reviewed per patient safety data on an ongoing basis and aggregate safety data for each cohort after 40 patients within a cohort had completed the first week of double-blind study treatment. Following DESC review, if no safety concerns were identified, the DESC provided written recommendation to proceed with dose escalation to the next. Following review of 8 AEs of special interest and the aggregate safety data from patients in Cohort 3 (50 mg), the DESC recommended **against** dose escalation to 100 mg.

8.1.5. Study D3820c00007 (Extension Study)

Title: A Randomized, Double-Blind, Placebo-Controlled 12-Week Extension Study to Assess the Safety and Tolerability of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)

8.1.5.1. Design

This was a 12-week extension of the Phase III, multicentre, double-blind, randomized, placebo-controlled, parallel group 12 week study D3820C00004 to evaluate the safety and tolerability of NKTR-118 12.5 mg and 25 mg with placebo in the treatment of OIC in patients with non-cancer-related pain. Patients continued on their randomized dose from the D3820C00004 study. No formal sample size calculation was performed for this long-term safety study. Sample size was determined by the number of patients enrolled from the previous study (Study 04).

8.1.5.2. Dates/Location

First subject enrolled into D3820C00007 extension 07 July 2011. The last subject of the last visit in D3820C00007 extension was enrolled on 13 September 2012. This study was conducted in 52 study centres in the United States (US).

8.1.5.3. Objectives

8.1.5.3.1. Primary

- To compare NKTR-118 12.5 mg and 25 mg with placebo regarding long-term safety and tolerability in the treatment of OIC using descriptive statistics.

8.1.5.3.2. Secondary

- To assess the impact of NKTR-118 12.5 mg and 25 mg on symptoms of constipation and quality of life.

8.1.5.3.3. Exploratory

- To assess patient health status index and healthcare resource utilization.

8.1.5.4. Statistics

Results were summarized using frequency and percentages for categorical data and n, mean, standard deviation, median, minimum, maximum for continuous data.

The safety analysis set was used to assess the safety and tolerability. All randomised patients who received at least 1 dose of study drug in the current study were included in the safety analysis set, with the exception of patients who were found to have randomised multiple times within the programme at different centres.

The efficacy analyses were based on a modified Intent-to-Treat analysis set that included all randomised patients who received at least 1 dose of study drug in the current study and had at least 1 post-baseline efficacy measurement (PAC-SYM or PAC-QOL)

8.1.5.4.1. Population

A total of 302 patients rolled over from Study D3820C00004 and continued in the double-blind treatment period at 52 study centres in the US. 297 (98.3%) of those received treatment, 245 (81.1%) completed the study, and 46 (15.2%) received treatment and subsequently discontinued the study. The treatment groups were generally balanced in terms of discontinuations: 15 (15.2%), 17 (17.5%), and 14 (13.2%) patients in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, discontinued the study. The most common reasons for study withdrawal were patient decision (20 patients; 6.6%) and adverse events (AEs) (11 patients; 3.6%).

A total of 6 additional patients completed the study, but had previously or concurrently participated in the NKTR-118 program at another study centre and were excluded from the safety analysis set.

Treatment groups were reasonably comparable across analysis sets with respect to: disposition; protocol deviations; demographic and baseline characteristics (assessed prior to randomisation in Study D3820C00004); prior and concomitant medications, including the pattern of laxative classes taken prior to study entry, satisfaction with laxative classes, and the pattern of related severity of symptoms; rescue medication and treatment compliance. All enrolled patients were from the US.

There was a notable imbalance across the treatment groups in the number of patients with ongoing GI events from the preceding study (Study D3820C00004), with no patients in the placebo group reported with any ongoing GI events compared with 13 (13.3%) and 8 (8.4%) patients in the NKTR-118 25 mg and 12.5 mg groups, respectively. The most common ongoing GI event was abdominal pain, which was reported more frequently in the NKTR-118 25 mg group.

8.1.5.4.2. Summary of efficacy results

The change in mean domain scores of the PAC-SYM and individual domains observed in the 12-week pivotal study (Study D3820C00004) was maintained in this extension study i.e. di not improve despite continuing on the IP. They did not differ amongst the three groups i.e. at entry into this extension study, patients in each treatment group had a change in total PAC-SYM scores of -0.8 points compared to baseline (improvement of symptoms). These improvements were maintained at the final on-treatment assessment in each group (mean changes from baseline of -0.8, -0.9, and -0.9 in the placebo, 12.5 mg, and 25 mg NKTR-118 groups, respectively).

At entry into this extension study, each treatment group had similar changes in the mean total and individual domains of the PAC-QOL domain scores (improvement in quality of life) compared to baseline (-0.8, -1.0, -0.8 in the placebo, 12.5 mg, and 25 mg groups, respectively). These changes did not improve at the final on-treatment assessment (-0.8, -1.0 and -0.9 in the placebo, 12.5 mg, and 25 mg groups, respectively).

8.1.5.4.3. Summary of safety results

The following table presents the number and percentage of patients who had at least 1 AE in any category during the randomized treatment and follow-up periods.

Table 13: Number (%) of patients who had at least 1 AE in any category during the treatment period or post-treatment follow-up (Safety analysis set).

AE Category	Number (%) patients [a]		
	Placebo (N = 100)	NKTR-118 12.5 mg (N = 94)	NKTR-118 25 mg (N = 97)
Any AE	33 (33.0)	32 (34.0)	40 (41.2)
Any AE with outcome = death	0	1 (1.1)	0
Any SAE (including events with outcome = death)	5 (5.0)	6 (6.4)	6 (6.2)
Any AE leading to permanent discontinuation of IP	3 (3.0)	4 (4.3)	4 (4.1)

The percentages are based on the number of patients in the Safety analysis set in each treatment group. AEs that started on or after the first dose of IP in the current D3820C00007 study are included and patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

The most common treatment-emergent AEs (TEAEs) in the NKTR-118 treatment groups were arthralgia and diarrhoea, which occurred at a higher frequency in the NKTR-118 treatment groups compared with placebo.

There was no obvious difference observed for the type or frequency of SAEs across treatment groups and the incidence of discontinuations of IP due to an AE (DAEs) and the type or frequency of DAEs across treatment groups was similar.

There was no obvious difference across treatment groups with respect to the incidence of cardiovascular (CV) AEs. There was 1 CV event adjudicated as MACE in the NKTR-118 12.5 mg group (adjudicated as 'Cardiovascular death') and 1 other CV event of interest in the NKTR-118 25 mg group (adjudicated as 'Heart failure requiring hospitalisation'). Neither event was considered by the investigator to be related to IP. There was no notable imbalance in AEs related to changes in blood pressure and there were no AEs adjudicated as bowel perforation events.

NKTR-118 was not associated with clinically important changes in centrally mediated opioid withdrawal signs and there were no clinically important changes for average pain intensity scores in any treatment group (assessed by the NRS). In this Study analysis of mean daily opioid dose showed no clinically important increase or decrease in any of the treatment groups.

There was no obvious clinically important changes in laboratory, vital signs, ECG, or physical examination variables, including the immediate post-dose time period in the 12.5 and 25mg groups or in outliers for systolic blood pressure, diastolic blood pressure, heart rate, or QTcF at any time point throughout the study or suicidal behaviour or ideation as assessed by C-SSRS and AEs.

In all treatment groups, including placebo, there were no improvements in PAC-SYM and PAC-QOL domains observed in the 12-week confirmatory study.

> *Comment: no extra QOL or symptomatic benefit was seen in patients who took the IP for a further 12 weeks although the benefit was maintained on continuous use. There was a new TEAE reported – arthralgia.*

8.1.6. Study D3820c00008 (Extension Study)

8.1.6.1. Design

This was a Phase III, 52-week, multi-centre, open-label, randomised, parallel group, safety and tolerability study of NKTR-118 versus usual care in the treatment of OIC in patients with non-cancer-related pain. This was to have been a study with global participation, but all patients ended up being enrolled from the US. Eligible patients were randomized in a 2:1 ratio to receive either NKTR-118 25 mg daily (QD) or Usual Care treatment for OIC.

8.1.6.2. Study Dates

First subject randomised 18 April 2011, last subject last visit: 03 December 2012.

8.1.6.3. Locations

Of the 247 study centres selected for this study, 213 screened at least 1 patient and 184 randomised patients into the study. This study was conducted in the United States.

8.1.6.4. Objectives

8.1.6.4.1. Primary

To assess the long-term safety and tolerability of NKTR-118 25 mg.

8.1.6.4.2. Secondary

To evaluate the long-term safety and tolerability of NKTR-118 25 mg compared with usual care using descriptive statistics (patients in usual care followed a laxative treatment regimen for OIC determined by the investigator according to his/her best clinical judgment, excluding peripheral μ-opioid antagonists).

8.1.6.4.3. Exploratory

To collect and store deoxyribonucleic acid (DNA) for future exploratory research, and assess healthcare resource utilization.

8.1.6.5. Target subject population and sample size

Patients entering the study could enrol directly from 12-week pivotal study D3820C00005, directly from the 3-month safety extension (Study D3820C00007) of the 12-week pivotal study D3820C00004, or could be "new patients" who had not previously participated in a NKTR-118 study. Patients who enrolled from a previous study had no break or pause in treatment.

All patients were required to have been receiving a stable maintenance opioid regimen (total daily dose of 30 to 1000 mg of oral morphine, or equi-analgesic amounts of 1 or more other

opioid therapies for a minimum of 4 weeks) for non-cancer-related pain and to have reported a history of <3 spontaneous bowel movements (SBMs)/week and at least 1 OIC associated symptom at screening and a confirmed diagnosis of OIC, at the time of randomization into their initial NKTR-118 study.

Confirmed OIC was defined as: Documented <3 SBMs/week on average over the 2-week OIC confirmation period (for roll-over patients this referred to the OIC confirmation period of the previous pivotal study). Patients with uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) were excluded. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the BMs recorded in the electronic diary (eDiary) during the OIC confirmation period: Bristol Stool Scale (BSS) stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. Patients who had 0 BMs over the 2-week OIC confirmation period were not randomized.

No formal sample size calculation was performed for this long-term safety study. The sample size determination was based on the regulatory exposure requirement (ICH E1 [1994]) that at least 300 patients had to complete 6 months of treatment with NKTR-118 25 mg and the number of patients randomised could have been adjusted during the study in order to achieve approximately 100 patients with at least 12 months of exposure to NKTR-118.

8.1.6.6. Statistical methods

No formal statistical analyses were planned for any of the endpoints collected in this study. Differences between open-label NKTR-118 25 mg and usual care were assessed using descriptive statistics.

Summaries for the assessment of long-term safety were presented separately by new and rollover patients.

8.1.6.7. Subject population

A total of 2393 patients enrolled, of which 2309 were new patients and 84 were roll-over patients. Of the 2309 new patients who entered the initial study period, 760 patients completed the OIC confirmation period, were randomized, and entered the open-label treatment period. In addition, 84 roll-over patients were also randomized. Of the 844 randomized new patients and roll-over patients, 99.5% received treatment, 61.1% completed the study (defined as completing the 2-week follow-up visit after the 52-week treatment period), and 34.1% received treatment and subsequently discontinued the study. Overall, 393 and 317 patients had at least 6 and 12 months exposure to NKTR-118 25 mg, respectively, in this study, which met the specified exposure requirements.

Of the 844 patients randomized, a total of 288 patients (34.1%) who received treatment discontinued the study for any reason: 36.8% in the NKTR-118 25 mg group, and 28.8% in the Usual Care group. The most common reasons for study withdrawal were patient decision (12.8%) and AE (7.2%). A greater proportion of patients withdrew due to AE in the NKTR-118 25 mg group (9.9%) compared with the Usual Care group (1.8%), primarily driven by GI AEs.

Overall, there were no imbalances between the NKTR-118 25 mg and Usual Care treatment groups in terms of patient characteristics that could have a potential influence on the results and their interpretation. The treatment groups were generally balanced with respect to: disposition; protocol deviations; demographic and baseline characteristics; pre-, post-, and concomitant medications, including the pattern of laxative classes taken prior to study entry; satisfaction with laxative classes, and the pattern of related severity of symptoms.

Patient characteristics for new and roll-over patients were generally similar. Patients in the Usual Care treatment group were treated according to the investigator's clinical judgment with most patients taking laxatives (79%) at the start of the treatment period, and 73% continuing on their initial laxative treatment during the study. All randomised patients were from the US.

8.1.6.8. Summary of efficacy results

Efficacy was not an endpoint in the study.

8.1.6.9. Summary of safety results

The following table presents the number and percentage of patients who had at least 1 AE in any category during the randomized treatment and follow-up periods.

Table 14: Number (%) of patients who had at least 1 AE in any category during the treatment period or post-treatment follow-up (Safety analysis set).

AE category	Number (%) patients [a]	
	Usual Care (N = 270)	NKTR-118 25 mg (N = 534)
Any AE	195 (72.2)	437 (81.8)
Any AE with outcome = death	1 (0.4)	1 (0.2)
Any SAE (including events with outcome = death)	30 (11.1)	51 (9.6)
Any AE leading to permanent discontinuation of IP	NA	56 (10.5)

The most common treatment-emergent AEs in the NKTR-118 25 mg treatment group were: abdominal pain, diarrhoea, nausea, headache, and flatulence and occurred more frequently in the NKTR-118 25 mg treatment group compared with the Usual Care group.

Two deaths of unknown cause were reported, neither of which was considered by the investigator to be related to study treatment.

The most common AEs leading to discontinuation of IP in the NKTR-118 25 mg treatment group were gastrointestinal AEs.

There were obvious differences between treatment groups with respect to events affecting the cardiovascular system; centrally mediated opioid withdrawal signs as assessed by the Modified Himmelsbach scale, or by analysis of relevant AEs potentially related to withdrawal.

There were no obvious differences between treatment groups with respect to suicidal behaviour or ideation as assessed by the Columbia-Suicide Severity Rating Scale and AEs. NKTR-118 was not associated with AEs potentially related to abuse liability.

There were no obvious clinically important changes from baseline in average pain intensity scores in either treatment group, as measured by the NRS and analysis of mean daily opioid dose showed no clinically important increase or decrease in either treatment group.

The IP was not associated with clinically important changes in laboratory, vital signs, electrocardiogram, or physical examination variables.

8.1.6.10. Clinical pharmacology studies

One point highlighted is that in the dose-finding study 07-IN-NX002 a relationship was observed between NKTR-118 dose level and the incidence of dizziness (0% at 25mg BID (60 mg BID but 33% at 125 mg BID: and 50% at 250 mg BID (placebo 25%).

Overall 67% of subjects receiving the highest dose (250 mg BID (q12h)) reported dizziness or orthostatic dizziness. Also of note was that myalgia was reported by 0 out of 8 placebo recipients and 2 out of 6 (33%) subjects who received the highest dose of NKTR-118. This dose whilst 20-fold higher than the 25mg dose, has concentrations that could theoretically be reached if a potent CYP3A4 or P-gp inhibitor was given concurrently.

This study also noted that plasma NKTR-118 concentration-time profiles on Day 8 were between 33% and over 100% higher than on Day 1, suggesting accumulation at higher doses.

8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.3. Patient exposure

Duration of exposure for pivotal Studies 04 and 05 are shown in Tables 15 and 16.

Table 15: Pivotal Study 04 – Duration of Exposure.

	Placebo (N = 213)	NKTR-118 12.5 mg (N = 211)	NKTR-118 25 mg (N = 214)
Duration of exposure (days)			
n	213	211	214
Mean	77.5	77.4	74.3
SD	20.75	21.58	25.21
Median	85.0	85.0	85.0
Min	2	4	1
Max	95	113	101
Total patient exposure [a]	16510	16323	15895

Table 16: Pivotal Study 05 – Duration of Exposure.

	Placebo (N=231)	NKTR-118 12.5 mg (N=230)	NKTR-118 25 mg (N=232)
Duration of exposure (days)			
n	231	230	232
Mean	76.1	75.9	72.4
SD	22.68	22.86	27.24
Median	85.0	85.0	85.0
Min	1	1	1
Max	98	112	104
Total patient exposure [a]	17579	17456	16801

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Study 04

Overall, 173 (79.4%), 174 (80.2%), and 177 (81.6%) patients in the NKTR-118 25 mg, NKTR-118 12.5 mg, and placebo groups, respectively, completed the study. For all 3 treatment groups, more treatment discontinuations occurred during the first 6 weeks of treatment: 32 (15.0%), 20 (9.5%), and 21 (9.9%) patients in the NKTR-118 25 mg, NKTR-118 12.5 mg, and placebo groups, respectively, discontinued treatment up to and including Week 6 of treatment. From Week 7, up to and including Week 12, 9 (4.2%), 14 (6.6%), and 12 (5.6%) patients in the NKTR-118 25 mg, NKTR-118 12.5 mg, and placebo groups, respectively, discontinued the study.

Table 17: Number (%) of patients who had at least 1 AE in any category during the treatment period or post-treatment follow-up (Safety analysis set).

AE category	Number (%) patients [a]		
	Placebo (N = 213)	NKTR-118 12.5 mg (N = 211)	NKTR-118 25 mg (N = 214)
Any AE	100 (46.9)	104 (49.3)	131 (61.2)
Any AE with outcome = death	0	2 (0.9)	0
Any SAE (including events with outcome = death)	11 (5.2)	11 (5.2)	7 (3.3)
Any AE leading to discontinuation of IP	12 (5.6)	9 (4.3)	22 (10.3)

8.4.1.2. Study 05

More patients in the NKTR-118 25 mg group had at least 1 AE compared with the NKTR-118 12.5 mg and placebo groups (160 (69.0%), 137 (59.6%), and 136 (58.9%) respectively). A higher proportion of patients in the NKTR-118 25 mg group discontinued IP due to an AE compared with the NKTR-118 12.5 mg and placebo groups (24 (10.3%), 12 (5.2%), and 12 (5.2%) patients respectively, discontinued IP due to an AE.

8.4.2. Other studies

Safety from the Phase IIb and safety extension studies has been previously described. Overall there were common GI side effects. The only new AE reported was arthralgia.

8.4.3. Treatment-related adverse events (adverse drug reactions)

8.4.3.1. Study 04

Medical review of individual AEs of general potential interest, in line with the ICH definition of other significant AEs, which a) were reported in patients randomized to NKTR-118, and b) are not described in detail elsewhere in this CSR, identified the following AEs: ECG QT prolonged, tracheitis, neuropathy peripheral, and suicidal ideation, each reported by 1 patient in the NKTR-118 25 mg group.

8.4.3.2. Study 05

Medical review of individual AEs of general potential interest, in line with the ICH definition of other significant AEs, which a) were reported in patients randomized to NKTR-118, and b) are not described in detail elsewhere in this CSR, identified the following AEs: hypertensive crisis (1 patient in the NKTR-118 12.5 mg group), neuropathy peripheral (1 patient in NKTR-118 12.5 mg group), pancytopenia (1 patient in the NKTR-118 12.5 mg group), (interstitial lung disease (1 patient in the NKTR-118 25 mg group), renal failure acute (1 patient in the NKTR-118 12.5 mg group), drug hypersensitivity (2 patients in the NKTR-118 25 mg group), hypersensitivity (1 patient in the NKTR-118 25 mg group), and suicidal ideation (1 patient each in the NKTR-118 25 mg and 12.5 mg groups).

Table 18: Study 04 – Number (%) of patients who had at least 1 AE for a preferred term occurring in ≥2% of patients in any treatment group during the treatment period only, by preferred term (Safety analysis set).

Preferred term	Number (%) patients [a]		
	Placebo (N = 213)	NKTR-118 12.5 mg (N = 211)	NKTR-118 25 mg (N = 214)
Patients with any AE	97 (45.5)	101 (47.9)	129 (60.3)
Abdominal pain	7 (3.3)	18 (8.5)	27 (12.6)
Diarrhoea	9 (4.2)	7 (3.3)	20 (9.3)
Nausea	10 (4.7)	15 (7.1)	16 (7.5)
Flatulence	4 (1.9)	9 (4.3)	12 (5.6)
Abdominal pain upper	4 (1.9)	3 (1.4)	11 (5.1)
Hyperhidrosis	1 (0.5)	0	9 (4.2)
Headache	4 (1.9)	5 (2.4)	8 (3.7)
Back pain	5 (2.3)	0	7 (3.3)
Upper respiratory tract infection	6 (2.8)	6 (2.8)	6 (2.8)
Vomiting	7 (3.3)	3 (1.4)	6 (2.8)
Abdominal distension	4 (1.9)	7 (3.3)	5 (2.3)
Fall	5 (2.3)	3 (1.4)	3 (1.4)

The SOCs with the greatest frequency of AEs were: Gastrointestinal Disorders (NKTR-118 25 mg 77 patients [36.0%]; NKTR-118 12.5 mg 51 patients [24.2%]; placebo 42 patients [19.7%]), Infections and Infestations (NKTR-118 25 mg 34 patients [15.9%]; NKTR-118 12.5 mg 27 patients [12.8%]; placebo 28 patients [13.1%]), and Investigations (NKTR-118 25 mg 15 patients [7.0%]; NKTR-118 12.5 mg 16 patients [7.6%]; placebo 17 patients [8.0%]).

For the NKTR-118 25 mg group, abdominal pain (27 patients; 12.6%) and diarrhoea (20 patients; 9.3%) were the most frequently reported AEs in the SOC of Gastrointestinal Disorders; upper respiratory tract infection (6 patients; 2.8%) and bronchitis (4 patients; 1.9%) were the most frequently reported AEs in the SOC of Infections and Infestations; and blood glucose increased (3 patients; 1.4%), alanine aminotransferase increased (2 patients; 0.9%), and liver function test abnormal (2 patients; 0.9%) were the most frequently reported AEs in the SOC of Investigations.

Nine patients in the NKTR-118 25 mg group reported events of hyperhidrosis (4.2%) during the treatment period. Six of the 9 events began on Day 1 of treatment. All events except 1 were mild or moderate in intensity. One event was assessed as severe in intensity and resulted in study discontinuation, and 1 other moderate event resulted in study discontinuation. Seven of the 9 events resolved (4 events resolved within 1 day of onset), and 2 remained ongoing at the time of study completion.

Table 19: Patients who had at least 1 AE by SOC and PT, treatment period only (Safety set).

System organ class/preferred term	Number (%) of patients[a] Placebo (N=213)	NKTR-118 12.5 mg (N=211)	NKTR-118 25 mg (N=214)
Patients with any AE	97 (45.5)	101 (47.9)	129 (60.3)
GASTROINTESTINAL DISORDERS	42 (19.7)	51 (24.2)	77 (36.0)
ABDOMINAL PAIN	7 (3.3)	18 (8.5)	27 (12.6)
DIARRHOEA	9 (4.2)	7 (3.3)	20 (9.3)
NAUSEA	10 (4.7)	15 (7.1)	16 (7.5)
FLATULENCE	4 (1.9)	9 (4.3)	12 (5.6)
ABDOMINAL PAIN UPPER	4 (1.9)	3 (1.4)	11 (5.1)
VOMITING	7 (3.3)	3 (1.4)	6 (2.8)
ABDOMINAL DISTENSION	4 (1.9)	7 (3.3)	5 (2.3)
ABDOMINAL TENDERNESS	0	1 (0.5)	3 (1.4)
ABDOMINAL PAIN LOWER	0	1 (0.5)	2 (0.9)
ABDOMINAL DISCOMFORT	0	2 (0.9)	1 (0.5)
DRY MOUTH	1 (0.5)	1 (0.5)	1 (0.5)
GASTROOESOPHAGEAL REFLUX DISEASE	1 (0.5)	1 (0.5)	1 (0.5)
ERUCTATION	0	1 (0.5)	1 (0.5)
RECTAL HAEMORRHAGE	2 (0.9)	0	1 (0.5)
CONSTIPATION	1 (0.5)	0	1 (0.5)
ABDOMINAL HERNIA	0	0	1 (0.5)
ABDOMINAL RIGIDITY	0	0	1 (0.5)
FOOD POISONING	0	0	1 (0.5)
GASTRITIS	0	0	1 (0.5)
HIATUS HERNIA	0	0	1 (0.5)
PAINFUL DEFAECATION	0	0	1 (0.5)
PEPTIC ULCER	0	0	1 (0.5)
SIGMOIDITIS	0	0	1 (0.5)
TOOTH DISORDER	0	0	1 (0.5)
DYSPEPSIA	2 (0.9)	1 (0.5)	0
FAECAL INCONTINENCE	0	1 (0.5)	0
TOOTHACHE	0	1 (0.5)	0

For events of abdominal pain in the NKTR-118 25 mg group, 22 of 27 patients had onset of the event within the first week of treatment, and of those 22 patients, 16 had an event duration of longer than 1 week. For events of diarrhoea in the NKTR-118 25 mg group, 8 of 20 patients had onset of the event within the first week of treatment, and of those 8 patients, 3 had an event duration of longer than 1 week. For events of nausea in the NKTR-118 25 mg group, 11 of 16 patients had onset of the event within the first week of treatment, and of those 11 patients, 2 had an event duration of longer than 1 week. For events of flatulence in the NKTR-118 25 mg group, 11 of 12 patients had onset of the event within the first week of treatment, and of those 11 patients, 9 had an event duration of longer than 1 week. Of the patients who were reported with GI AEs of abdominal pain, diarrhoea, and nausea during the treatment period: 19.2% (10/52 patients), 5.6% (2/36 patients), and 2.4% (1/41 patients), respectively, had events considered to be severe in intensity.

The frequencies of AEs in any category during the randomised treatment and follow-up periods for patients categorized as LIR and non-LIR at baseline were generally comparable with the overall safety analysis set in both subgroups (LIR and non-LIR), more patients in the NKTR-118 25 mg group were reported to have at least 1 AE compared with the NKTR-118 12.5 mg and placebo groups.

Table 20: Study 05 – Adverse events by system organ class and preferred term (summarised in descending order).

Preferred term	Number (%) patients [a]		
	Placebo (N = 231)	NKTR-118 12.5 mg (N = 230)	NKTR-118 25 mg (N = 232)
Patients with any AE	130 (56.3)	130 (56.5)	154 (66.4)
Abdominal pain	18 (7.8)	25 (10.9)	44 (19.0)
Diarrhoea	10 (4.3)	18 (7.8)	21 (9.1)
Nausea	10 (4.3)	14 (6.1)	20 (8.6)
Vomiting	6 (2.6)	7 (3.0)	14 (6.0)
Flatulence	7 (3.0)	4 (1.7)	14 (6.0)
Headache	8 (3.5)	12 (5.2)	12 (5.2)
Back pain	4 (1.7)	12 (5.2)	12 (5.2)
Pain in extremity	1 (0.4)	5 (2.2)	7 (3.0)
Sinusitis	2 (0.9)	3 (1.3)	7 (3.0)
Nasopharyngitis	1 (0.4)	2 (0.9)	7 (3.0)
Abdominal pain upper	3 (1.3)	5 (2.2)	6 (2.6)
Abdominal distension	5 (2.2)	4 (1.7)	6 (2.6)
Fatigue	3 (1.3)	3 (1.3)	6 (2.6)
Hypertension	2 (0.9)	2 (0.9)	6 (2.6)
Upper respiratory tract infection	6 (2.6)	3 (1.3)	5 (2.2)
Anxiety	4 (1.7)	5 (2.2)	4 (1.7)
Dizziness	5 (2.2)	8 (3.5)	3 (1.3)
Fall	3 (1.3)	6 (2.6)	1 (0.4)
Blood thyroid stimulating hormone increased	0	5 (2.2)	0

Six patients in the NKTR-118 groups reported events of hyperhidrosis during the treatment period: 4 (1.7%) patients in the NKTR-118 25 mg group and 2 (0.9%) patients in the NKTR-118 12.5 mg group. Three of the 6 events began on Day 1 of treatment. All events except 1 were mild or moderate in intensity. One event was assessed as severe in intensity, and 2 moderate events resulted in study discontinuation. Five of the 6 events resolved (4 events resolved within 1 week of onset), and 1 remained ongoing at the time of study completion. Twelve (5.7%) patients in the NKTR-118 group, 12 (5.7%) patients in the NKTR-118 12.5 mg group and 4 (1.2%) patients in the placebo group reported AE of back pain during the treatment period. Seven (3%) patients in the NKTR-118 group, 5 (2.2%) patients in the NKTR-118 12.5 mg group and 1 (0.4%) in the placebo group reported AE of pain in extremity during the treatment period. There were no imbalances between the treatment groups in terms of the AE of back pain or pain in extremity leading to discontinuation of the study. Most AEs of back pain and pain in extremity were not associated with start of the treatment but occurred after the first week of treatment in the NKTR-118 and placebo treatment groups.

Gastrointestinal AEs of abdominal pain, diarrhoea, and nausea were more common in the NKTR-118 groups compared with the placebo group, while GI AEs of flatulence and vomiting were more common in the NKTR-118 25 mg group only, compared with NKTR-118 12.5 mg and placebo.

8.4.4. Deaths and other serious adverse events

8.4.4.1. Study 04

There were 2 deaths in the 12.5mg group, both judged to be non-related to IP - non-small cell lung cancer and a cardiac valve replacement complication.

8.4.4.2. Study 05

There were no deaths during the study.

A total of 8 (3.4%), 14 (6.1%), and 12 (5.2%) patients in the NKTR-118 25 mg, 12.5 mg, and placebo groups, respectively, were reported to have at least 1 SAE.

8.4.5. Discontinuation due to adverse events

8.4.5.1. Study 04

See Table 21.

Table 21: Study 04 – Number (%) of patients who had an AE leading to permanent discontinuation of IP, by preferred term during the treatment period (Safety analysis set).

Preferred term	Number (%) patients [a]		
	Placebo (N = 213)	NKTR-118 12.5 mg (N = 211)	NKTR-118 25 mg (N = 214)
Patients with any AE leading to discontinuation of IP	12 (5.6)	9 (4.3)	22 (10.3)
Diarrhoea	0	0	6 (2.8)
Abdominal pain	1 (0.5)	1 (0.5)	4 (1.9)
Abdominal pain upper	0	0	3 (1.4)
Hyperhidrosis	0	0	2 (0.9)

These are the 4 most reported AEs. In the 25mg group there was1 case each of nausea flatulence hypotension fatigue yawning abdominal distension abdominal rigidity back pain drug effect decreased headache hepatic enzyme increased liver function test abnormal musculoskeletal pain myalgia myocardial infarction non-cardiac chest pain, pain in extremity renal cancer stage I, rhinorrhoea viral infection; in the 12.5mg group 2 patients had dizziness and 1 each of abdominal discomfort acute myocardial infarction atrial fibrillation confusional state, crying dehydration hypokalaemia hyponatraemia laceration orthostatic hypotension rash syncope upper respiratory tract infection.

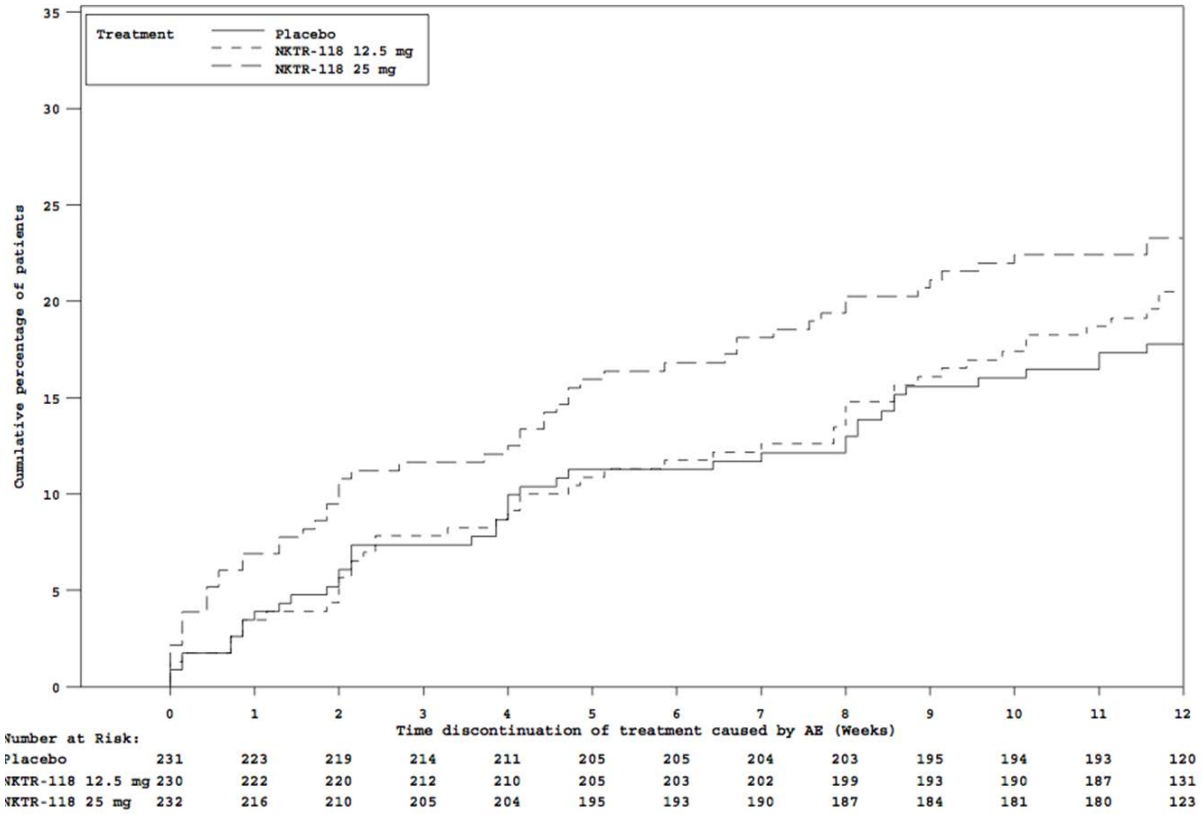
8.4.5.1. Study 05

See Table 22.

Table 21: Study 05 – Number (%) of patients who had an AE leading to permanent discontinuation of IP, by preferred term during the treatment period.

Preferred term	Number (%) patients [a]		
	Placebo (N = 231)	NKTR-118 12.5 mg (N = 230)	NKTR-118 25 mg (N = 232)
Patients with any AE leading to discontinuation of IP	12 (5.2)	12 (5.2)	24 (10.3)
Abdominal pain	0	3 (1.3)	9 (3.9)
Diarrhoea	3 (1.3)	4 (1.7)	8 (3.4)
Nausea	1 (0.4)	2 (0.9)	4 (1.7)
Vomiting	1 (0.4)	2 (0.9)	4 (1.7)
Hyperhidrosis	1 (0.4)	0	2 (0.9)
Abdominal pain upper	0	0	2 (0.9)
Back pain	1 (0.4)	1 (0.4)	1 (0.4)
Depression	0	1 (0.4)	1 (0.4)
Gastrointestinal pain	0	1 (0.4)	1 (0.4)
Neck pain	0	1 (0.4)	1 (0.4)
Arthritis	0	0	1 (0.4)
Chills	0	0	1 (0.4)
Decreased appetite	0	0	1 (0.4)
Drug dependence	0	0	1 (0.4)
Drug withdrawal syndrome	0	0	1 (0.4)
Faecal incontinence	0	0	1 (0.4)
Feeling jittery	0	0	1 (0.4)
Headache	0	0	1 (0.4)
Hepatic function abnormal	0	0	1 (0.4)
Influenza like illness	0	0	1 (0.4)
Joint range of motion decreased	0	0	1 (0.4)
Lethargy	0	0	1 (0.4)
Liver function test abnormal	0	0	1 (0.4)
Myalgia	0	0	1 (0.4)
Rash	0	0	1 (0.4)

Figure 5: Kaplan-Meier plot of time discontinuation of treatment for any reason (SAS).



8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Study 04

One patient who had normal transaminases at screening developed AST and ALT > 5 x ULN during the study. The transaminases resolved while the patient stayed on the 12.5mg dose. It was judged as probably related to IP but patient had history of paracetamol abuse.

A study narrative is included as although it does not meet Hy law but has been assessed as liver disease related to IP.

- Patient # [information redacted]: This patient [information redacted] showed an elevation in ALT and AST values >5x ULN during treatment. Screening ALT was 37 IU/L (reference range 6-37 IU/L) and AST was 44 IU/L (reference range 10-36 IU/L). Baseline (randomization) ALT was 22 IU/L and AST was 20 IU/L. The patient had been randomized to NKTR-118 12.5 mg. On Day 29, the patient's ALT was 77 IU/L and AST was 73 IU/L. On Day 56, the patient's alkaline phosphatase level was 159 IU/L (reference range 40-100 IU/L), ALT was 117 IU/L and AST was 56 IU/L. The site replied to a query that the patient exhibited no signs or symptoms of liver dysfunction, nor had any other problems or changes during the study. There were no documented risk factors for elevated liver function tests. Laboratory tests were repeated on Days 62 and 68, with liver function tests gradually normalizing.

  On Day 90 (last day of treatment) the patient's ALT was 233 IU/L, AST was 215 IU/L, and alkaline phosphatase was 182 IU/L. AEs of ALT elevation, AST elevation, and alkaline phosphatase elevation were reported. The PI assessed the AEs as related to IP; however, the dosage of IP was not changed and no treatment was required. The AEs were unresolved at study completion. The patient completed the study and rolled over to the 12-week extension

study (Study D3820C00007) and continued on NKTR-118 12.5 mg. Two days later, the patient had a hepatitis panel drawn, which was negative for hepatitis A, B, and C. The PI commented that the "patient has history of long term use of acetaminophen medications, but no other liver risk history." The patient completed the 12-week extension study on Day 189 post-randomisation.

8.5.1.2. Study 05

A similar case in the 25mg group was unresolved at end of Day 87 despite drug being stopped.

- Patient # [information redacted]: This patient [information redacted] showed an elevation in ALT and AST values >5x ULN during treatment. At the randomization visit, ALT and AST were elevated at 63 and 62 IU/L, respectively. On Day 57, the patient had an AE of worsening of liver function, considered severe in intensity and assessed by the PI as related to the IP. At that time, ALT and AST were elevated at 269 and 243 IU/L, respectively. Retest on Day 63 showed ALT and AST of 390 and 365 IU/L, respectively. The IP was permanently discontinued on Day 64. On Day 66, ALT and AST were 388 and 338 IU/L, respectively. On Day 71, ALT and AST remained elevated at 345 and 364 IU/L, respectively. Total bilirubin was within normal limits throughout the study except for slight elevation at 1.3 mg/dL on Day 71. The patient was reported to be asymptomatic. The patient was reported to have started a strenuous exercising program (3 hours per day) with the use of weight loss supplement "lipozene" on Day 33. The AE did not require treatment and was unresolved at the time the patient was withdrawn from the study (Day 87).

8.5.2. Kidney function

Nil in either study

8.5.3. Other clinical chemistry

Nil in either study

8.5.4. Haematology

Nil in either study

8.5.5. Electrocardiograph

In Study 04, the proportion of patients with PCI QRS values (≥140 msec) during the treatment period was greater in the NKTR-118 groups compared with the placebo group: 8 (3.7%) and 8 (3.8%) patients in the NKTR-118 25 mg and 12.5 mg groups, respectively, compared with 3 (1.4%) patients in the placebo group. In addition, the proportion of patients with a PCI QTcF interval (≥450 msec and a ≥30 msec increase from baseline) was greater in the NKTR-118 groups compared with the placebo group: 4 (1.9%) patients in both the NKTR-118 25 mg and 12.5 mg groups, compared with 2 (0.9%) patients in the placebo group. There were no other marked differences across the treatment groups.

During the treatment period, 1 (0.5%) patient in the NKTR-118 12.5 mg group had a QTcF ≥500 ms and a ≥60 ms increase from baseline in the QTcF interval (narrative provided below) and 1 (0.5%) patient in the placebo group had a QTcF ≥500 ms and a ≥30 ms increase from baseline in the QTcF interval. A total of 3 (1.4%) patients in the NKTR-118 12.5 mg group had a heart rate of ≥120 bpm, compared with no patients in the NKTR-118 25 mg and placebo groups.

In Study 05, the proportion of patients with a PCI QTcF interval (≥450 msec and a ≥30 msec increase from baseline) was greater in the NKTR-118 groups compared with the placebo group: 6 (2.6%) patients in the NKTR-118 25 mg group and 3 (1.3%) patients in the NKTR-118 12.5 mg group, compared with 1 (0.4%) patient in the placebo group. During the treatment period, 1 patient in the NKTR-118 25 mg group had a ≥60 ms increase from baseline in the QTcF interval (narrative provided below). One patient in the NKTR-118 25 mg group and 1 patient in the

placebo group had a heart rate of ≥120 bpm, compared with no patient in the NKTR-118 25 mg group.

8.5.6. Numeric Rating Scale (NRS): changes in pain level

In the Pivotal study 04 there were no statistically significant differences between NKTR-118 groups and placebo in either average or worst pain scores. Furthermore, the 2-sided 95% CIs of the difference in LS Means (NKTR-118/placebo) ranged from -0.24 to +0.23. For both the average and worst pain scores, LS Means for each treatment group over time were similar.

Mean daily opioid dose remained stable during the study. Over both Weeks 1 to 4 and Weeks 1 to 12 the mean and upper and lower quartiles for the mean daily opioid dose appeared similar across treatment groups.

In Study 05, over both Weeks 1 to 4 and Weeks 1 to 12 the mean and upper and lower quartiles for the average and worse NRS pain score were generally similar between treatment groups.

8.5.7. Vital signs

In both 04 and 05 changes in vital signs, weights were similar across the three groups.

8.6. Post-marketing experience

Nil

8.7. Safety issues with the potential for major regulatory impact

There are potential issues with safety, especially when used outside of the non cancer population or healthy populations studied in these trials. Pharmacovigilance should be undertaken if the product has a favourable decision.

These include GI side effects and bowel perforation (latter not seen in the pivotal studies), hypotension, increase in pain, hyperhidrosis and other symptoms of changes in the autonomic nervous system.

Populations at risk are the elderly, cancer patients and those with organ dysfunction.

Opioid withdrawal was reported in the pivotal clinical study (Study 04).

8.7.1. Liver toxicity

There were two cases of elevation in transaminases in the pivotal studies. Although not meeting criteria for 'Hy's law', vigilance and monitoring should occur, specifically in a chronic pain setting where other medications are commonly co-ingested and over a period of time.

8.7.2. Haematological toxicity

Nil concern from the trial data submitted.

8.7.3. Serious skin reactions

Nil concern from the trial data submitted.

8.7.4. Cardiovascular safety

Nil concern from the trial data submitted.

8.7.5. Unwanted immunological events

Nil concern from the trial data submitted.

8.8. Other safety issues

Nil concern from the trial data submitted.

8.8.1. Safety in special populations

Nil concern from the trial data submitted apart from that highlighted above.

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

Nil concern from the trial data submitted.

The IP clearly interacts with drugs that are P450 CYP3A4 inhibitors and inducers and P-gp inhibitors and this combination (and concomitant foods that are inhibitors and inducers) should not be used together.

8.9. Post marketing data

Nil

8.10. Evaluator's conclusions on safety

It is noted that in both of the extension studies, all patients were from the US as were a large majority of people in the pivotal studies. The relationship of that population to disease incidence and management in comparison to Australia was not made. The relationship of the demographics and relationship to likely population in Australia was not made.

Overall, the IP showed increased AEs compared to placebo, in a dose-response relationship. Most AEs were GI and some were judged as severe in intensity.

In the Phase II study, in both the 5 mg and 25 mg group treatment emergent adverse event (TEAE) rate was mildly increased, and in the 50 mg group, 85% of patients reported TEAEs as compared to 56% in the placebo arm. Sixteen patients in Cohort 1 (5 mg), 16 patients in Cohort 2 (25 mg) and 23 patients in Cohort 3 (50 mg) experienced at least 1 TEAE that was assessed as being causally related to the study drug, the majority of which included diarrhoea, abdominal pain and nausea. However the most frequent study drug related Grade 3/4 TEAE reported across all 3 dose cohorts was abdominal pain.

Following review of 8 AEs of special interest in this study, the Dose Evaluation Safety Committee (DESC) recommended against dose escalation to 100 mg due to GI safety concerns.

In extension study 07, more AEs were reported in the 25 compared to the 12.5 mg and placebo groups.

The most common TEAEs in the NKTR-118 treatment groups were arthralgia and diarrhoea, which occurred at a higher frequency in the NKTR-118 treatment groups compared with placebo.

The pivotal studies overall showed that more patients in the NKTR-118 25 mg group had at least 1 AE compared with the NKTR-118 12.5 mg and placebo groups.

In both pivotal studies the most common TEAEs among patients in the NKTR-118 treatment groups (abdominal pain, diarrhoea, and nausea) were from the GI System Organ Class (SOC), and occurred most frequently in the NKTR-118 25 mg treatment group. The proportion of patients with diagnostic adverse events (DAEs) and common GI AEs (abdominal pain, diarrhoea) was also higher in the 25 mg dose group of NKTR-118 compared with both placebo and the 12.5 mg dose group. The most common DAEs were GI AEs.

A higher rate of severe GI AEs was also observed in the NKTR-118 25 mg group compared with the 12.5 mg and placebo treatment groups.

A new AE of hyperhidrosis was reported during the treatment period. In the 04 Study, six of the 9 events began on Day 1 of treatment. One event was assessed as severe in intensity and resulted in study discontinuation, and 1 other moderate event resulted in study discontinuation. Hyperhidrosis was reported more commonly in the 25 mg compared to 12.5 mg groups

The pivotal Study 04 reported three episodes of significant withdrawal (measured by COWS) coded to the MedDRA term of drug withdrawal syndrome. In Study 05, withdrawal symptoms were also reported.

More patients in the NKTR-118 25 mg treatment group had the AE of drug withdrawal reported compared with the other treatment groups (4 in the NKTR-118 25 mg, 1 in the NKTR-118 12.5 mg and none in the placebo group).

One patient did develop transaminitis while on the IP. This requires pharmacovigilance. Small electrocardiogram (ECG) changes were reported which, while being of uncertain significance, require pharmacovigilance.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of naloxegol in the proposed usage are:

- In non-cancer patients with OIC, a statistically significant increase in responder rate over placebo (increase by 1 or more SBM/week)

9.2. First round assessment of risks

The risks of naloxegol in the proposed usage are:

- Minimal effect on symptoms and quality of life.
- No clinical data in the cancer population
- Paucity of data in the elderly and in racial groups represented in Australia (who may have different dietary or genetic P450 and P-gp expression).
- Non-morphine effects on constipation not addressed
- Significant GI side effects
- Significant inter and intra patient PK variability
- Withdrawal effects of opioids
- Lack of real clinical data in patients with severe renal or liver disease
- Significant changes in exposure when taken concurrently with P450CYP 3A4 inducers or inhibitors or P-gp inhibitors (including food)

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of naloxegol is unfavourable given the proposed usage, but could become favourable if the changes recommended are adopted.

Specifically, if the indication was changed to use in non-cancer pain only in patients and for whom an extra SBM/week correlate with symptom improvement. Subjects should unresponsive to other currently available therapies. The 25 mg only dose should be available.

10. First round recommendation regarding authorisation

Rejection of the submission due to the following major reasons:

- Rationale for the therapy in Australia not given, particularly the difference in the cancer and non cancer populations
- Clinical relationship of increase in SBM or 1 or more per week is not clear.
- Lack of relationship between increase in SBM or 1 or more per week and symptoms.
- Side effect profile including risk of withdrawal, compared to placebo, prominent.

There are other factors which are highlighted in the Questions below which could be addressed and if so may not be reasons for rejection.

11. Clinical questions

- Post marketing safety data was not provided. Is it available?
- The actual incidence of OIC for people in Australia is not given. Further, the incidence for people using current therapies appropriately is not given. Currently, clinical practice appears to be to start patients on coloxyl and senna and lactulose when opioids are started. Some patients do get constipated, sometimes related to dehydration of another factor. When underlying contributors have been addressed, macrogol is available. Some patients cannot tolerate macrogol, and then may have access to other oral agents or enemas. Can the sponsor describe the place in therapy in Australia? The sponsor should discuss the relative contributions of gut opiate to constipation in the cancer and non-cancer populations.
- Patients who don't respond to these current therapies may have a mechanical obstruction or pseudoileus. Can the sponsor provide number of patients that are likely to be needing treatment in Australia?
- Can the sponsor discuss why the naloxegol was not compared to or extrapolated from standard therapy in Australia?
- Regarding the definition of responders (noting the lack of current CHMP Guidance), while noting the advice was from authoritative bodies, the clinical relevance of, for example, 4 SBM/week for 3 out of 4 weeks as opposed to 3 SBM/week is unclear. It is possibly more unclear in the cancer population on opiates who are often more concerned about symptoms and QoL, that is, reduced hospital admissions than number of SBMs/week.
- It is noted that applications were submitted in Canada and Switzerland in 2013. Is there any follow-up for those applications?

12. Second round evaluation

12.1. Issues addressed

12.1.1. Minimal effect on symptoms and QoL

12.1.1.1. Sponsor response

AstraZeneca's position is that the therapeutic benefit Movantik 25 mg offers is clinically meaningful for patients. It is demonstrated via the primary responder endpoint, which represents a sustained improvement in SBM frequency versus placebo, and supported by all multiplicity protected secondary endpoints, other secondary endpoints that are important for

patients, and the analysis of response incorporating symptom data. Overall, the studies were not powered to assess for significant differences between Movantik and placebo for quality of life parameters. Patients suffering chronic OIC are likely to notice and value even shorter periods of lesser improvements. The risks of Movantik recorded in the clinical programme notably are most commonly reversible upon drug discontinuation, not serious, and unlikely to result in permanent sequelae.

These consistent improvements were seen despite a substantial placebo response.

12.1.1.2. Evaluator response

The evaluator notes the study was not powered to examine improvements in the quality of life. However it appears the main reason to treat this condition, which as the Sponsor notes causes significant effects on quality of life, is improvement in quality of life. The placebo effect, which results in no difference compared to naloxegol for many of the endpoints, is noted. In distinction to the symptomatic nature of this problem, with effects on QoL, the clinical relevance of the primary endpoint of one extra SBM per week for 3 out of 4 is not made. That is, it is not clear if the three extra bowel motions per month improved QOL in the population who had a benefit.

12.1.2. No clinical data in the cancer population

12.1.2.1. Sponsor response

See the responses in the following sections of this document.

12.1.2.2. Evaluator response

This information in following sections does not provide clinical data requested. It hypothesises that the benefit and toxicity is likely to be the same as non cancer OIC.

12.1.3. Paucity of data in the elderly

12.1.3.1. Sponsor response

While there is a small effect of age on the PK of naloxegol (approximately 0.7% increase in AUC for every year increase in the age range studied [18 to 78 years of age]), the magnitude of this change in unlikely to be clinically meaningful. Therefore, no dose adjustment is recommended based on age. This recommendation is supported by clinical findings: Movantik was generally safe and well tolerated in patients ≥65 years of age in both the 12 week pool and after longer exposure. The safety profile in these elderly patients is similar to that seen in younger patients with regard to frequency and type of AEs as well as changes in vital signs, ECGs, and clinical laboratory parameters.

12.1.3.2. Evaluator response

It is unclear where the 0.7% per year comes from as the table shows there were no patients over 65 in any of the PD or biopharmaceutical studies. There were only 13 people in the 65-74 group and 5 in the 75-84 and 0 over 85s only in the PK studies, and in the efficacy/safety studies, 207 were in the 65-74, 40 in the 65-74 and nil over 80. There is thus minimal data in the over 65 age group.

AstraZeneca proposes the following language for inclusion in the *PHARMACOLOGY, Pharmacokinetics, Special populations* section of the proposed PI.

> *Age and gender*
>
> *Patients over 65 years of age have been well represented in the Phase III studies. There is a small effect of age on the pharmacokinetics of naloxegol (approximately 0.7% increase in AUC for every year increase in the age range evaluated in the clinical studies [18 to 78 years of age]). Clinical studies of Movantik did not include sufficient numbers of patients aged 75 years or over to determine whether they respond differently than younger patients; however, the magnitude of the small change in PK observed with age is unlikely*

to be clinically meaningful. No dose adjustment is recommended for the elderly patients as this age group has been well represented in the phase III trials.

There is no gender effect on the pharmacokinetics of naloxegol.

The evaluator believes this is misleading. Rather it is recommended to state "patients over 65 years of age have been poorly represented in the Phase II and III studies. There were no patients over 65 in any of the PD or the biopharmaceutical studies, 13 in the 65-74 age groups, 5 only in the 75-84 group and 0 over 85s only in the PK studies, and in the efficacy/safety studies 207 in the 65-74, 40 in the 65-74 and nil over 80. This drug has thus not been well studied in the 65-84 age group and care should be taken if using in this population. The drug has not been studied in any form in the population over 85 and is not recommended".

12.1.4. Paucity of data in racial groups represented in Australia (who may have different dietary or genetic P450 and P-gp expression)

12.1.4.1. Sponsor response

Polymorphism data on P-gp are controversial and genotype has been shown to have little impact on cytochrome P450 3A (CYP3A4)/5 activities. Consequently, the effects of the polymorphism of CYP3A4 and P-gp are usually not investigated in most drug development programmes. In addition, there are no known issues with genotype or single nucleotide polymorphisms for CYP3A4 or P-gp; therefore, it is expected that exposure and the pattern of safety and efficacy in the Australian population will be similar to what has been studied in North America and Europe. In alignment with the findings of the Risk Management Plan (RMP) reviewer, AstraZeneca's position is that the results of the clinical studies are expected to be broadly applicable to the Australian population.

12.1.4.2. Evaluator response

The evaluator notes that there is little evidence to assume the patient population using the drug in Australia will be broadly similar to those in the clinical trials. For example, the prevalence of Black Americans in the US and the large East Asian, Indigenous and Southern Asian populations in Australia. Dietary issues affect P450 and P-gp expression as well as racial differences; this is thus very likely to have effects on the PK parameters and drug concentrations.

It is normal practice for physicians to monitor the response of their patients to the dose prescribed, and it is anticipated that patients will be monitored as per standard of care. AstraZeneca acknowledges that data on racial groups in Australia are limited and proposes to include analyses of relevant cases, which will be provided in the annual Periodic Benefit-Risk Evaluation Report (PBRER).

It is important to evaluate this in the PBRER. In addition it should state in the PI that there is a paucity of data in racial groups represented in Australia thus care should be taken with additional efficacy and toxicity monitoring.

12.1.5. Non-morphine effects on constipation not addressed

12.1.5.1. Sponsor response

AstraZeneca acknowledges that the pathophysiology of OIC is multifactorial; however, the extent of clinical efficacy demonstrated with Movantik and other peripherally acting μ- opioid receptor antagonists (PAMORAs) suggests that inhibition of opioid signalling in the periphery only is sufficient to manage OIC. While there may be a small contribution to constipation from central opioid effects, it is pivotal to exclude inhibition of signalling in/to the brain as not to interfere with pain management and not to cause opioid withdrawal. Clinical data demonstrate relief from OIC with Movantik use, while not interfering with analgesia or causing opioid withdrawal to any significant degree.

12.1.5.2. Evaluator response

This response acknowledging the difficulties in blocking peripheral versus central opioid effects and the complexity of constipation in people using chronic opioids is noted.

12.1.6. Significant GI side effects

12.1.6.1. Sponsor response

GI AEs are not unexpected with Movantik, given its pharmacologic and physiologic effects (reversal of impaired GI motility and decreased intestinal fluid absorption). The incidence of AEs of abdominal pain and diarrhoea was dose-ordered; most of these events began within the first 7 days of receiving Movantik, and the majority of the events resolved while the patients were on study treatment. Clinically important GI AEs (that is, serious GI AEs, discontinuations due to GI AEs, and GI AEs of severe intensity for the preferred terms of abdominal pain, abdominal pain upper, abdominal pain lower, diarrhoea, nausea, vomiting, and flatulence) are an identified risk associated with Movantik. GI perforation, a potential risk associated with Movantik, was not observed in the development program.

12.1.6.2. Evaluator response

These clinically significant GI AEs are noted in the clinical evaluation report.

12.1.7. Significant inter and intra patient PK variability

12.1.7.1. Sponsor response

Inter subject PK variability was calculated as approximately 50% in a Phase I bioequivalence study using data from the proposed commercial tablet administered under fasting conditions to normal healthy volunteers. This variability is lower than the inter subject variability reported for statins.

12.1.7.2. Evaluator response

There is now tens of thousands of patients and patient years data with statins. It is difficult to see how the comparison of a significant pharmacological problem to another drug in a different drug class overrides the acknowledgement and management of the issue with this drug.

12.1.8. No estimates of intra subject PK variability were performed in volunteers or patients. No analyses of inter and intra patient PK variability were performed in the Phase III studies, as PK data were collected using sparse sampling techniques

12.1.8.1. Sponsor response

AstraZeneca acknowledges that data on exposure in OIC patients in Australia are minimal (n = 1, Study 04) and proposes to include analyses of relevant cases, which will be provided in the annual PBRER.

12.1.8.2. Evaluator response

This is helpful but unclear how this would be undertaken. Will the sponsor be proposing to measure PK at steady state in patients as part of a Phase IV study?

12.1.9. Withdrawal effects of opioids

12.1.9.1. Sponsor response

Naloxegol, a peripherally acting opioid antagonist with limited CNS penetrance, would not be expected to produce signs of interference with the central analgesic effects of opioids. Opioid withdrawal syndrome was uncommon in the clinical trial program, was generally not severe or serious, and did not cause discontinuation. AstraZeneca agrees that this is, nonetheless, an identified risk and proposes the following language for inclusion in the PRECAUTIONS section of

the proposed PI, which is in alignment with the European Summary of Product Characteristics (SmPC).

> *Opioid withdrawal syndrome*
>
> *Cases of opioid withdrawal syndrome have been reported in the Movantik clinical programme (DSM-5). Opioid withdrawal syndrome is a cluster of three or more of the following signs or symptoms: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhoea, pupillary dilation, piloerection or sweating, diarrhoea, yawning, fever, or insomnia. Opioid withdrawal syndrome typically develops within minutes to several days following administration of an opioid antagonist. If opioid withdrawal syndrome is suspected the patient should discontinue Movantik and contact their physician.*

12.1.9.2. Evaluator response

This is appropriate, however as it is possible for inhibition of P-gp in the brain to cause transport into the CNS, the line

> *Naloxegol, a peripherally acting opioid antagonist with limited CNS penetrance, would not be expected to produce signs of interference with the central analgesic effects of opioids*

should be rewritten as

> *Naloxegol is a peripherally acting opioid antagonist. In the usual clinical situation limited CNS penetrance occurs, thus it would not be expected to produce signs of interference with the central analgesic effects of opioids. However if the blood-brain barrier is disturbed of there is inhibition of the transport P-gp, signs of central analgesic antagonism is likely.*

12.1.10. Lack of real clinical data in patients with severe renal or liver disease

12.1.10.1. Sponsor response

AstraZeneca acknowledges that clinical data on OIC patients with severe renal or liver disease are limited and proposes to include analyses of relevant cases, which will be provided in the annual PBRER.

A brief summary of the available data is provided below:

Overall, in severe renal impaired subjects, AUC and Cmax of naloxegol increased by 117% and 84%, respectively, compared to patients with normal renal function (Study D3820C00009). However, in 2 out of 8 subjects (in both the moderate and severe renal impairment groups but not in the end stage renal failure group) up to 10 fold increases in the exposure of naloxegol were observed.

Despite the higher average exposure in moderately and severely renal function impaired subjects, no clinically meaningful differences were observed in the frequencies or patterns of AEs. In the Phase III pivotal studies, the AE profile of naloxegol in patients with a baseline creatinine clearance value of <60 mL/min was generally similar to that in patients with normal renal function; however, the number of patients in this subgroup was low (n = 45; there were only 36 naloxegol treated patients in this subgroup in the Phase IIb/III pool). No clinically meaningful differences were observed in the frequencies or patterns of AEs.

In subjects with mild or moderate hepatic impairment, the mean naloxegol AUC was 17% and 18% lower than observed in healthy subjects. Cmax was not significantly impacted by mild or moderate hepatic impairment. The safety and tolerability profile of naloxegol in patients with mild or moderate hepatic impairment at baseline is similar to patients with normal baseline liver function values. There were no clinically relevant changes in laboratory, vital sign, ECG, or physical exam data in the subjects evaluated (Study 10). There is no data in subjects with severe hepatic impairment.

Please also refer to the proposed PI text that is noted in the response.

12.1.10.2. Evaluator response

This is reasonable. However, after "No clinically meaningful differences were observed in the frequencies or patterns of AEs" should be added "however, numbers were small".

12.1.11. Significant changes in exposure when taken concurrently with P450 inducers or inhibitors or P-gp inhibitors (including food)

12.1.11.1. Sponsor response

Naloxegol is a sensitive substrate of CYP3A4 and its disposition can be expected to be affected by inhibitors or inducers of this enzyme. Drug-drug interaction studies conducted with a strong, moderate, and weak CYP3A4 inhibitor (ketoconazole, diltiazem, and quinidine, respectively) demonstrated changes in exposure consistent with the class of inhibition (that is, strong: >5 fold increase in AUC, moderate: 2 to 5 fold increase in AUC, and weak: 1.25 to <2 fold increase in AUC. The mean increase in AUC when naloxegol was administered with ketoconazole, diltiazem, or quinidine was approximately 13 fold, 3.4 fold and 1.39 fold, respectively. There is considerable overlap between CYP3A4 and P-gp inhibitors and inducers, and each of the CYP3A4 inhibitors identified above is also classified as an inhibitor of P-gp of which naloxegol is also a substrate.

Rifampin is an inducer of CYP3A4 and P-gp and co-administration with naloxegol resulted in an approximate 1.9 fold decrease in naloxegol AUC compared to naloxegol given alone.

Studies of interactions between naloxegol and morphine, ketoconazole, rifampin, quinidine, and dilitazem have been conducted as part of the naloxegol clinical development program. These findings are presented in detail. The safety profile of naloxegol in these studies was similar to that of the Phase III clinical development program.

AstraZeneca has taken steps to manage the potential for significant changes in exposure to naloxegol caused by CYP3A4/P-gp inhibitors and inducers by:

- contraindicating co-administration of Movantik and strong CYP3A4/P-gp inhibitors
- recommending against co-administration of Movantik with strong CYP3A4/P-gp inducers
- recommending that the starting dose of Movantik be reduced to 12.5 mg when co-administered with a moderate CYP3A4/P-gp inhibitor.

Co-administration of naloxegol with a high fat or a low fat meal resulted in modest increases in mean AUC of approximately 45% and 50%, respectively. The clinical studies have shown that exposure (that is, AUC) increases by 42% to 55% and maximum plasma concentration increases by 30% to 47% when a 25 mg dose of naloxegol is administered after eating a meal, compared with fasting conditions. The DOSAGE AND ADMINISTRATIONS section of the proposed PI recommends that Movantik is taken once daily in the morning on an empty stomach. AstraZeneca acknowledge that specific dietary constituents (for example, grapefruit juice, star fruit, St. John's wort) can affect CYP3A4 or P-gp and merit specific label language as noted in the PHARMACOKINETICS section of the proposed PI.

The following information is already included in the PRECAUTIONS section of the proposed PI as follows:

> *CYP3A4 inducers*
>
> *Movantik should be avoided in patients who are taking strong CYP3A4 inducers (e.g. carbamazepine, rifampicin, St. John's wort) (see INTERACTIONS WITH OTHER MEDICINES).*
>
> *AstraZeneca proposes the text for the DOSAGE AND ADMINISTRATION, Special Populations section of the proposed PI.*

12.1.11.2. Evaluator response

This is noted; however, the evaluator still requests a removal the word 'strong'.

12.1.12. First round assessment of benefit-risk balance

12.1.12.1. Sponsor response

AstraZeneca believe that the totality of naloxegol data provides evidence for durable and consistent benefits for patients with OIC, which outweigh the observed risks.

12.1.12.2. Evaluator response

Please see evaluator summary below.

12.1.13. Side effect profile including risk of withdrawal, compared to placebo

12.1.13.1. Sponsor response

The side effect profile of Movantik is benign and well characterised, and has demonstrated an acceptable safety and tolerability profile both the 25 and 12.5 mg doses. With the exception of GI AEs, discussed further below, AEs with Movantik occurred at low frequencies and were not appreciably different than placebo. The only area of interest where a notable and consistent imbalance versus placebo was identified in the clinical trials was GI AEs. GI adverse drug reactions are not unexpected with naloxegol given its pharmacologic and physiologic effects. The incidence of AEs of abdominal pain and diarrhoea was dose-ordered; most of these events began within the first 7 days of receiving naloxegol and most resolved while the patients were still on study treatment. Clinically important GI AEs (that is, GI SAEs, GI DAEs, and GI events of severe intensity for the preferred terms (PTs) of abdominal pain, abdominal pain upper, abdominal pain lower, diarrhoea, nausea, vomiting, and flatulence) is an identified risk associated with naloxegol. GI perforation, a potential risk associated with naloxegol, was not observed in the development program.

In the Phase III program, analysis of modified Himmelsbach opioid withdrawal scale scores (mHS) demonstrated no treatment imbalance in withdrawal symptoms. A minor imbalance in the number of AEs of opioid withdrawal (naloxegol 25 mg: 5 [1.1%]; naloxegol 12.5 mg: 1 [0.2%]; placebo 1 [0.2%]) was noted to be primarily driven by a small number of patients (n = 4) in the naloxegol 25 mg group with AEs of opioid withdrawal who were receiving methadone as their primary opioid. Theoretically, CNS opioid antagonism could occur in OIC patients with clinical conditions known to disrupt the blood brain barrier (for example, active multiple sclerosis, advanced Alzheimer's disease, uncontrolled epilepsy). However, these patients were specifically excluded from the clinical program and therefore this has not been conclusively demonstrated in clinical trials. As AEs associated with CNS opioid antagonism is a potential risk in patients with potential for blood-brain barrier disruptions, and if prescribed naloxegol, such patients could be at risk for opioid withdrawal and/or impaired analgesia.

12.1.13.2. Evaluator response

The significant GI side effects were noted in the clinical evaluation report.

The incidence of withdrawal, while noted in the clinical trials as low, may be more prominent when used in a nonclinical trial setting. As such, ensuring it is clear in the PI and RMP are important.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits of Movantik are unchanged from those identified in the first round assessment.

13.2. Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Movantik are unchanged from those identified in the first round assessment.

13.3. Second round assessment of benefit-risk balance

The assessment of risk-benefit is unchanged from the first round conclusions.

14. Second round recommendation regarding authorisation

The evaluator recommends rejecting the submission due to the following major reasons:

- Rationale for the therapy in Australia not given, particularly the difference in the cancer and non cancer populations

This has been justified in the Section 31 response by an assumption that the population is broadly similar to the clinical trial population. Assumptions were made that the cancer population ought to have similar efficacy and safety as the non cancer population, to naloxegol.

Neither assumptions were well justified. However, it is noted that there are several million people in Australia with constipation and taking opioids who would be eligible to take the therapy if registered.

The cancer issue is particularly difficult as there is no data and yet there are a large number of theoretical concerns both about whether there is a need (that is, low recruitment to studies and current availability in Australia of effective therapies in this group), as well as concerns about efficacy and safety in this group.

- Clinical relationship of increase in SBM or 1 or more per week is not clear.

The clinical relevance of this (as opposed to QOL) is still not clear. QOL data provided is not convincing to the evaluator, and in addition was not a primary endpoint.

- Lack of relationship between increase in SBM or 1 or more per week and symptoms.

This was not addressed satisfactorily.

- Side effect profile including risk of withdrawal, compared to placebo, prominent.

This was addressed by agreeing to some changes in the RMP and changes in the PI; however, many of the requested PI changes were not agreed by the sponsor.

Overall, the clinical relevance of the endpoint is unclear. The QoL data was underpowered and not clearly beneficial across all domains. The side effect profile for GI effects is dominant. For this reason, the risk-benefit is positive and the requested indication is not recommended.

15. References

- Camilleri M, Rothman M, Ho K. Validation of a bowel function diary for assessing opioid-induced constipation. Am J Gastroenterol 2011;106:497–506.
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