Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Fentanyl citrate

Proprietary Product Name: PecFent

Sponsor: ERA Consulting (Australia) Pty Ltd[1]

Date of CER:
30 October 2011

TGA Health Safety Regulation

[1] AstraZeneca Pty Ltd is now the sponsor of this product in Australia.

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, 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 <http://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 <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. List of abbreviations

Abbreviation	Meaning
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve from time zero to infinity
AUC_{0-24}	area under the plasma concentration time curve from time 0 to 24 hours after dosing
AUC_t	area under the plasma concentration time curve from time zero to time of last quantifiable plasma concentration
BMI	body mass index
BP	blood pressure
BTCP	break through cancer pain
CI	confidence interval
CL	confidence limits
C_{max}	maximum plasma concentration
C_{last}	last plasma concentration
CSR	clinical study report
CV(%) or %CV	coefficient of variation expressed as a percentage
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
e-diary	electronic diary
EEG	electro encephalogram
FCNS	fentanyl citrate nasal spray

Abbreviation	Meaning
F_{rel}	relative bioavailability
fL	femptolitre
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IRMS	immediate release morphine sulphate
ITT	intention to treat
IU	International Units
λ_z	apparent terminal phase rate constant
LC/MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LOCF	last observation carried forward
LLOQ or LOQ	lower limit of quantification
LS means	least squares means
MAO	monoamine oxidase
maxTOTPAR	maximum total pain relief
mITT	modified intent-to-treat
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
NasalFent	trade name for FCNS, also called PecFent
OTFC	oral transmucosal fentanyl citrate

Abbreviation	Meaning
PCV	packed cell volume
PDIFF	p-values for differences in LS means
PK	pharmacokinetic
PI	pain intensity
PID	pain intensity difference
PP	per protocol
PR	pain relief
PSUR	Periodic Safety Update Report
SAE	serious adverse event
SAR	seasonal allergic rhinitis
SD	standard deviation
SE	standard error
SGPT	serum glutamate pyruvate transaminase
SPID	summed pain intensity difference
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
T½	terminal half life
T_{max}	time to maximum plasma concentration
TOTPAR	total pain relief
TNSS	total nasal symptom score

2. Clinical rationale

Cancer associated pain is frequently characterised by a highly variable intensity over time, producing for the patient and their clinician the dilemma of whether to use high enough doses of potent analgesics (usually opioids) to control all of the peaks of pain, and risk significantly over treating the patient during the troughs, or to err on the side of caution and leave the patient at risk of "breakthrough" pain. In practice the latter course tends to be predominate, leaving a significant proportion of cancer patients (up to 95% of those with pain) suffering from frequent episodes that are characterised by their severe intensity, rapid onset (mean time to

peak intensity 3 minutes), relatively brief duration (mean 30 minutes) and profound impact on quality of life and burden of care (Portenoy *et al,* 1999).

Attempts to treat breakthrough cancer pain (BTCP) with additional doses of standard, oral opioids are often highly ineffective due to the mismatch between their onset of action (up to 30 minutes) and the typical time course of BTCP episodes, usually resulting merely in unwanted adverse effects (sedation, nausea, constipation) after the episode has ended.

The approval of the oral transmucosal fentanyl product (Actiq®) for BTCP has improved therapeutic options considerably, but the time to onset of effect – 10-15 minutes is still not optimal, and their use can be problematic in a significant proportion of patients suffering from complications of their disease such as xerostomia, mucositis, weakness or poor coordination.

Fentanyl is a well established drug, with over 20 years of clinical use as both an anaesthetic and an analgesic agent. Fentanyl is available in a variety of pharmaceutical forms including: parenteral, transdermal patches and oral transmucosal (lozenge). One oral transmucosal lozenge is approved in Australia – Actiq® (Orphan Australia) for the BTCP indication. A number of other transmucsoal lozenges are approved in the USA and EU (including Effentora®).

Fentanyl nasal spray (FCNS) utilises a new route of administration (intranasal) and pharmaceutical form (nasal spray) for the active ingredient fentanyl citrate; the formulation incorporates PecSys™, a proprietary pectin based drug delivery technology which optimises the profile of fentanyl by modulating absorption, allowing a short time to T_{max} but an attenuated C_{max}.

The development of fentanyl nasal spray was aimed at combing the advantages of the drug fentanyl with the ease of the nasal route of delivery to produce a novel nasal formulation that would be rapidly and efficiently absorbed, thus giving prompt and effective pain relief in a manner which would be simple and convenient and hence highly acceptable to patients.

2.1. Guidance

The following EU Guidance has been adopted in Australia – "Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain: (CPMP/EWP/612/00). This is a general guide for all types of nociceptive pain and does not provide specific guidance for breakthrough cancer pain. It is also noted that no specific pain scale is recommended and the no specific endpoints are recommended.

Adverse events were defined according to EU Guidance – "Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports". The relationship to investigational product was classified using the causality assessment system of the World Health Organisation (WHO) Monitoring Centre, Uppsala, Sweden.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The sponsor submitted 3 studies under the heading *5.3.5.1 Controlled Clinical Trials*; however one of these studies CP041/04 was not a comparative study and was stopped without explanation by the sponsor before enrolment of the planned sample size. This was not considered pivotal or comparative and it is presented in the supportive studies section of this report.

The submission contained the following clinical information:

Module 5

- 4 clinical pharmacology studies, including 4 that provided pharmacokinetic data (CP037/02, CP042/05, CP047/07, and CP048/07)and 0 that provided pharmacodynamic data
- 2 pivotal efficacy/safety studies – CP043/06 and CP 044/06
- 2 other supportive efficacy/safety studies – CP041/04 and CP045/06
- Other: 1 PSURs covering a 6month period (Aug 2010 to Feb 2011), Integrated Summary of Safety and literature references

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

Studies were conducted in Canada, USA, Argentina, India and Europe (UK, Germany, Italy, Spain, Poland, Czech Republic, and France).

Study reports state that studies were conducted in accordance with the local regulatory requirements and the current guidelines:

- The International Conference on Harmonization (ICH) including Good Clinical Practice (GCP);
- The basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312); and
- The principles enunciated in the World Medical Association Declaration of Helsinki (Edinburgh, Scotland, 2000).

All studies required review by appropriate local HRECs and written informed consent before commencement of the trial.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Submitted Pharmacokinetic Studies.

PK topic	Subtopic	Study ID	*Primary objectives
PK in healthy adults	General PK - Single dose - Multi-dose	CP037/02 CP042/05 CP047/07	Comparison of formulations Dose range Dose escalation
	Bioequivalence† - Single dose Multi-dose	Not applicable Not applicable	
	Food effect	Not applicable	
PK in special populations	Target population § Single dose Multi-dose	Not done	
	Hepatic impairment	Not done	
	Renal impairment	Not done	
	Neonates/infants/children/adolescents	Not done	
	Elderly	Not done	
	Other special population – Seasonal Rhinitis	CP048/07	PK profile
Genetic/gender-related PK	Males vs. females	Not done	
	Other genetic variables	Not done	
PK interactions	@ {Drug A}	Not done	
	@ {Drug B}		
	@ {Drug C}		
Population PK analyses	Healthy subjects	Not done	
	Target population	Not done	
	Other	Not done	

* Indicates the primary aim of the study.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

[Information redacted]

4.2. Summary of pharmacokinetics

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

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. *Absorption*

In Study CP042/05 fentanyl was shown to be rapidly absorbed following single dose intranasal administration of fentanyl nasal spray with median T_{max} ranging from 15 to 20 minutes (compared to T_{max} for Actiq® of approximately 90 minutes).

The variability of the pharmacokinetics for fentanyl was considerable following treatment with both fentanyl nasal spray and oral transmucosal fentanyl citrate (OTFC) lozenge.

4.2.1.2. *Bioavailability / Bioequivalence*

4.2.1.2.1. *Selection of formulation*

A Phase 1 study (CP037/02) was conducted in healthy volunteers to compare three prototype 100 µg fentanyl nasal spray formulations under naltrexone blockade, with the oral transmucosal fentanyl citrate (OFTC) lozenge (Actiq 200 µg) as comparator. The prototype nasal formulations were fentanyl-chitosan, fentanyl-pectin and fentanyl-chitosan-poloxamer 188. All fentanyl treatments appeared to be well tolerated both systematically and locally. Fentanyl appeared to be absorbed more rapidly and gave greater C_{max} values when administered nasally compared to the OFTC lozenge; the relative bioavailability of fentanyl nasal spray (pectin formulation) was 132.4% (geometric mean) compared to the OFTC lozenge indicating nasal bioavailability to be greater than the oral transmucosal route. From this study the company chose the fentanyl-pectin nasal formulation for use in the subsequent Phase 1 studies as a clinically significant plasma concentration was quickly reached (median T_{max} = 20 minutes), suggesting that a rapid onset of pain relief may be possible with the pectin formulation. The mean observed C_{max} for this formulation was the lowest of the three nasal formulations (albeit still likely to be an effective concentration). This formulation was assessed as being most likely to match the time course of the typical breakthrough pain episode, delivering fentanyl quickly while producing fewer side effects associated with large, early spikes in plasma concentration.

The key characteristics of this formulation are:

- Its low viscosity enabling delivery from a conventional nasal spray pump
- Its ability to form a soft, mildly adherent gel on contact with the nasal mucosa that modulates the delivery of fentanyl to the systemic circulation to better match the time course of the typical breakthrough pain episode
- Its avoidance of the dripping and running that are a problem with conventional non-gelling, non-modulating nasally administered products.

This formulation is stated to have been used throughout the remaining Phase 1 and Phase 2 and 3 studies.

4.2.1.2.2. *Bioequivalence to relevant registered products*

The relative bioavailability of fentanyl nasal spray (at 100 µg, 200 µg, 400 µg and 800 µg) was compared to the reference product – OFTC lozenge (Actiq® 200 µg) and was assessed in two studies – CP037/02 and CP042/05. The relative bioavailability was calculated on a dose adjusted basis to be approximately 120 – 130%. This difference in bioavailability from the oral transmucosal route is likely to be due principally to the avoidance with the intranasal route of swallowing much of the administered dose from the lozenge.

4.2.1.2.3. *Influence of food*

Not applicable

4.2.1.2.4. *Dose proportionality*

Study CP042/05 demonstrated dose proportionality of single doses for Cmax and AUC_{∞} in the dose range 100 µg to 800 µg fentanyl delivered in the fentanyl-pectin nasal formulation. The departure from dose proportionality seen following the administration of eight immediately consecutive doses to the same nostril indicates a lower than expected availability of fentanyl from such repeated dosing. This is stated as likely due to the limited capacity of the nasal cavity to hold liquid formulations, but may also reflect an overwhelming of the gel forming properties which would lead to the run-off (an impaired absorption) of un-gelled fentanyl.

Comment: The company state that this is a positive result as it indicates an additional safety feature of the formulation but it is disappointing that the study was designed in this way and did not allow for alternate nose dosing which is more in keeping with standard recommendations for nasal delivery and might have provided a different result which removes this potential safety feature.

4.2.1.3. ***Distribution***

The applicant has not provided any studies exploring the distribution of fentanyl nasal spray. They argue that there is no reason to believe that the nasal route of administration would impact on the systemic distribution of fentanyl, so no further studies are considered warranted. The applicant references the review by Dollery (1999), the FDA Summary Basis of approval for Actiq (1998) and the Effentona European Public Assessment Report (2008) to state that Fentanyl is a highly lipophilic and is well distributed beyond the vascular system, with a large apparent volume of distribution.

4.2.1.4. ***Metabolism***

The applicant has not provided any studies exploring the metabolism of fentanyl nasal spray. Using the same references as above they state that fentanyl is metabolised in the liver to norfentanyl by the cytochrome CYP3A4 isoform. Norfentanyl is not pharmacologically active in animal studies. It is more than 90% eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.

4.2.1.5. ***Excretion***

The applicant has not provided any studies exploring the elimination of fentanyl nasal spray. The applicant argues that there is no reason to believe that the nasal route of administration would impact on the elimination of fentanyl, so no further studies are considered warranted. Again using the same references as above the applicant states that less than 7% of an administered dose of fentanyl is excreted unchanged in the urine and only about 1% is excreted unchanged in the faeces. The metabolites are mainly excreted in the urine, while faecal excretion is less important. The total plasma clearance of fentanyl following intravenous administration is approximately 42 l/h.

4.2.2. **Pharmacokinetics in the target population**

No studies were provided comparing the pharmacokinetics in the target population and normal volunteers.

4.2.3. **Pharmacokinetics in other special populations**

No studies were provided in any special populations.

4.2.4. Pharmacokinetic interactions

The applicant provided one study CP048/07 which investigated the pharmacokinetics of Nasalfent in healthy subjects with seasonal allergic rhinitis while asymptomatic, provoked but not treated and provoked and treated with oxymetalozine.

[information redacted]

The applicant provided no other clinical studies exploring possible drug interactions with the nasal formulation of fentanyl. They argue that the possible drug interactions are well documented in the world literature and it would be expected that any systemic drug interactions are similar to other fentanyl formulations.

4.3. Evaluator's overall conclusions on pharmacokinetics

The applicant has provided limited clinical data on the pharmacokinetics of Pecfent but has provided the basic information required for a new route of administration for a well documented substance.

While dose proportionality was seen within the dose range proposed it is noted that there was marked variability in the pharmacokinetics within and between studies. This is noted in passing by the applicant but dismissed as they are strongly recommending that dose titration is carried out on all patients including those switching to fentanyl nasal spray from an oral transmucosal fentanyl citrate product. This recommendation is supported by the literature (DeGregori *et at*, 2010) as it has been found that the clinically effective dose of a fentanyl product for the treatment of breakthrough pain cannot be predicted from the dose of background opioid medication or based on the use of other fentanyl-based products used previously, and so titration to effect is essential.

[information redacted]

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The applicant has not conducted any studies to explore the pharmacodynamics of fentanyl arguing that they are already well documented.

5.2. Summary of pharmacodynamics

The following summary information is derived from the 3 references the applicant used for information on the pharmacology of fentanyl [Dollery (1999), the FDA Summary Basis of approval for Actiq (1998) and the Effentona European Public Assessment Report (2008)].

Fentanyl is an opioid analgesic, interacting predominantly with the opioid μ-receptor. Its primary therapeutic actions are analgesia and sedation. Secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, mitosis, physical dependence and euphoria.

The analgesic effects of fentanyl are related to its plasma level. In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance to opioids. The clinically effective dose of a fentanyl product for the treatment of episodes of breakthrough pain cannot be predicted from the dose of background opioid medication. As a result the dose of fentanyl nasal spray must be individually titrated to achieve the desired effect.

All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients develop tolerance to respiratory depressant effects.

5.3. Evaluator's overall conclusions on pharmacodynamics

The minimal amount of data provided on the pharmacodynamics is appropriate for a well documented substance such as fentanyl.

6. Dosage selection for the pivotal studies

The dosing interval in all the clinical studies was at least 4 hours. This interval was adopted as a reflection of both the findings from the initial single dose Phase 1 studies with fentanyl nasal spray, and from the accepted practice with existing approved fentanyl products of limiting use to treating up to four episodes per day. This interval was further supported by the findings of the multiple dose PK study (CP047/07) which demonstrated that, while increases in Cmax levels seen following a second 100 μg dose of fentanyl nasal spray given at one, two and four hour intervals, they are not seen at the four hour interval. It should be noted that the increases seen after the first dose were not sufficiently large to suggest accumulation or over-exposure, thus indicating an acceptable safety margin for the recommended dose interval of two hours.

The dose range chosen for the clinical studies was based on the dose ranges demonstrated to be clinically effective by the transmucosal route and the bioavailability of fentanyl by the transmucosal route (approx 50%) and by the intranasal route (approx 70-75%). Based on these considerations, the proposed dose range for the clinical studies were in the range of 100 μg, 200 μg, 400 μg and 800 μg, delivered using one or two sprays of two strengths (100 μg per spray and 400 μg per spray). All the clinical trials had an individual dose titration step to establish the appropriate dose for each patient. This is also recommended for the marketed product.

7. Clinical efficacy

7.1. Indication: Breakthrough pain in cancer patients (BTCP)

7.1.1. Pivotal efficacy studies

7.1.1.1. *Study CP043/06*

A Multicentre, Placebo-controlled, Double-blind, Two-phase Crossover Study of Nasalfent (Fentanyl Citrate Nasal Spray- FCNS) in the Treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy.

7.1.1.1.1. *Study design, objectives, locations and dates*

This is a multicentre, randomised, placebo controlled, double blind, crossover study conducted at 58 centres in the USA, Costa Rica and Argentina. The study was conducted between December 2006 and July 2008. The maximum total duration of individual patient participation was approximately 8 weeks.

The primary objective was to demonstrate the efficacy of Nasalfent in the treatment of BTCP in opioid tolerant patients who were receiving regular opioid therapy. Secondary objectives were to demonstrate the speed of action, safety, tolerability and acceptability of Nasalfent in the treatment of BTCP in opioid tolerant patients who were receiving regular opioid therapy.

The study consisted of 4 phases.

- Screening phase (up to 10 days)
- Open, Dose Titration Phase (up to a maximum of 14 days)
- During this phase the dose of Nasalfent was titrated for each patient until 2 consecutive episodes of target BTCP were successfully treated with the same dose without unacceptable adverse events (AEs). Study staff assisted patients in determining their individual effective doses using daily telephone contact. In this phase, patients received an initial dose of 100 µg of Nasalfent, which could then be titrated up to 200 µg, 400 µg, or 800 µg, until an effective dose for each patient was identified.
- Double Blind Treatment Phase (a minimum of 2 days and a maximum of 21 days)
- Patients who successfully completed the open, dose titration phase then entered the double-blind phase. Each patient was supplied with a treatment pack containing 10 "blinded' bottles (each in child-resistant container), which contained in a random order either active Nasalfent, to be administered at the "effective" dose found during Phase 1 (total of 7 bottles), or placebo (total of 3 bottles). The bottles were numbered 1 to 10 and each bottle was used to treat 1 episode of BTCP. For each treated episode, patients recorded a baseline pain intensity (PI) score, then after dosing with blinded study drug, recorded PI and pain relief (PR) at various time points out to 60 minutes, using an electronic diary (e-diary). Assessment also included specific questions about nasal tolerability.
- End of Treatment Phase (occurred between 1 and 14 days after last dose).
- Patients returned to the clinic for final efficacy and safety assessments. Patients who discontinued early or did not enter the double-blind treatment phase but had taken at least 1 dose of study drug also returned for a final assessment.

7.1.1.1.2. *Inclusion and exclusion criteria*

Male or female patients, aged 18 and older, who had a histologically documented diagnosis of a malignant solid tumour or a haematological malignancy causing cancer-related pain were enrolled in the study. Patients had to be taking regular, 24-hour medication (60 mg oral morphine or equivalent opioid) for underlying persistent cancer pain and typically having 1 to 4 episodes of BTCP per day to be eligible for participation.

Patients with uncontrolled or rapidly escalating pain or whose condition was unstable or rapidly deteriorating were not to be enrolled. Additionally, patients with a medical condition (ie respiratory, cardiac, hepatic or renal, neurological or psychiatric) that would have made them unsuitable for the study were excluded. Patients with a history of alcohol or substance abuse or who had radiotherapy or other interventions that could have affected their pain within 30 days were also excluded.

7.1.1.1.3. *Study treatments*

Nasalfent (fentanyl citrate)

Two concentrations were available: 1.57 mg/mL and 6.28 mg/mL fentanyl citrate (equivalent to 1.0 and 4.0 mg/mL of fentanyl base), with each 0.1mL spray providing a dose of 100 µg and 400 µg fentanyl respectively. Details of the formulation was not provided other than to state that it was the pectin formulation designed to modify fentanyl delivery).

Nasalfent was packaged in a multidose Pfeiffer® spray device with the capacity for administration of eight 0.1mL sprays. The device featured a self-advancing counter mechanism and emitted a loud click upon each actuation. Once 8 sprays had been administered, the mechanism locked out to prevent patients attempting to administer further doses from a spent bottle.

Four dose levels were examined in the study: 100 µg, 200 µg, 400 µg, and 800 µg. Up to 4 episodes per day could have been treated with the study drug.

For the Phase 1 (open, dose titration phase) study drug was supplied as 1 bottle of 100 µg, and 1 bottle of 400 µg per spray. For the Phase 2 (double blind, treatment phase) bottles marked 1 through 10 were supplied, each containing either Nasalfent at the strength used for the effective dose (total 7 bottles) or placebo (total 3 bottles), in a randomly designated order.

For the Phase 2, there were therefore 2 possible drug packs:

- Low strength – containing bottles with Nasalfent at 100 µg per spray for patients needing doses of 100 µg or 200 µg
- High strength – containing bottles with Nasalfent at 400 µg per spray for patients needing doses of 400 µg or 800 µg

7.1.1.1.4. *Efficacy variables and outcomes*

The main efficacy variables were:

- SPID at 10, 15, 45, and 60 minutes
- PI scores at 5, 10, 15, 30, 45 and 60 minutes
- Pain Intensity Difference (PID) from baseline at 5, 10, 15, 30, 45, and 60 minutes post dose
- Pain relief (PR) score at 5, 10, 15, 30, 45 and 60 minutes post dose
- Total pain relief (TOTPAR) score at 10, 15, 30, 45, and 60 minutes post dose
- Patient acceptability scores at 30 and 60 minutes post dose
- Pain intensity was recorded in an e-diary using a rating scale of 0 to 10, where 0 represented "no pain" and 10 represented "worst possible pain". The Last Observation Carried Forward (LOCF) method was used to input missing scores for evaluable episodes due to omission or use of rescue medication, prior to calculating the average value for each patient/treatment group. The higher the SPID score the better.
- Pain relief scores were recorded in an e-diary using a 5 point rating scale where 0 = none and 4 = complete pain relief.
- Patient acceptability scores was assessed using a 4 point scale: 1 = not satisfactory, 2 = not satisfied or dissatisfied, 3 = satisfied and 4 = very satisfied. Patient average acceptability score was derived as the averaged acceptability scores across all episodes by treatment group.

The **primary efficacy outcome** was the patient averaged summed pain intensity difference (SPID) from 5 to 30 minutes post-dose.

Other efficacy outcomes included:

- Patient level endpoints:
- Number and percentage of patients in each treatment group with a mean reduction in SPID of ≥2, ≥3, and ≥4 at 10, 15, 30, 45, and 60 minutes post dose
- Number and percentage of patients in each treatment group with a ≥33%, ≥50%, and ≥66% reduction in PI score from baseline at 5, 10, 15, 30, 45, and 60 minutes
- Number and percentage of patients in each treatment group with %max TOTPAR of ≥33%, ≥50%, and ≥66% at 10, 15, 30, 45, and 60 minutes
- Number and percentage of patients in each treatment group with a mean patient acceptability score of >2 and >3 at 30 and 60 minutes post dose

- Rescue medication usage

1. Episode level endpoints

- Episode averaged SPID from time 0 to 30 minutes post dose
- Number and percentage of total treated episodes in each treatment group with a reduction in PI score of ≥1 and ≥2 at 5, 10, 15, 30, 45 and 60 minutes
- Number and percentage of total treated episodes in each treatment group with a reduction in SPID score of ≥2, ≥3 and ≥4 at 10, 15, 30, 45 and 60 minutes
- Number and percentage of total treated episodes in each treatment group with a ≥33%, ≥50%, and ≥66% reduction from baseline in PI score at 5, 10, 15, 30, 45 and 60 minutes post dose
- Episode time for a ≥33%, ≥50%, and ≥66% reduction in PI score within 30 and 60 minutes post dose
- Number and percentage of episodes where a patient experienced no increase in PI at any time point compared to baseline
- Number and percentage of episodes achieving PR scores of ≥1 and ≥2 at 5, 10, 15, 30, 45 and 60 minutes post dose
- Episode time to achieve a PR score of ≥1 and ≥2 in episodes with and without rescue medication
- Number and percentage of episodes in each treatment group with a %max TOTPAR of ≥33%, ≥50%, and ≥66% at 10, 15, 30, 45, and 60 minutes post dose
- Episode time to achieve total pain relief

Number and percentage of total treated episodes in each treatment group with episode acceptability scores of ≥2 and ≥3 at 30 and 60 minutes

- Episode rescue medication usage

7.1.1.1.5. *Randomisation and blinding methods*

Phase 1 was open to establish the dose needed to relieve BTCP episodes. In Phase 2 patients and all study staff were blinded to the medication codes. The 3 placebo bottles were randomly assigned within the 10 bottles supplied to each patient.

Compliance was assessed by reconciling doses recorded on the returned medication and the patient record of usage.

7.1.1.1.6. *Analysis populations*

A total of 139 patients were enrolled which was below the planned enrolment of 180 patients.

The screened population = 139 = all patients who were examined to determine qualifications for entry into the Phase 1 - Open Dose Titration phase of the study

The randomised population = 83 = all patients who were randomly assigned to a double blind treatment sequence.

The safety population = all patients who received at least 1 dose of Nasalfent.

The primary statistical analysis of efficacy was performed on what the applicant calls the modified intent-to-treat (mITT) population. Supportive analyses for efficacy were performed on the mITT and per protocol (PP) population.

The mITT population = 73 = all patients in the randomised population that treated at least 1 mITT evaluable episode with Nasalfent and 1 with placebo, where mITT evaluable episode was

defined as – the patient had treated the episode with study drug, had a baseline and at least 1 post baseline PI measurement, and it was the only episode associated with a single bottle number.

The PP population = 58 = consisted of all patients who were part of the mITT population and in whom:

- At least 2 episodes identified as evaluable PP episodes had been treated, 1 with each of the 2 treatments (Nasalfent or placebo)
- All episodes identified as evaluable PP episodes were treated using part of an ascending sequence of bottle numbers

7.1.1.1.7. *Sample size*

The sample size calculation was based on the US NDA application for Actiq® (fentanyl lozenge). The observed difference between Actiq and placebo for SPID at 30 minutes was 1.5 (4.03 – 2.53) with an estimated common SD of 2.4 (mean of 2.44 and 2.29). The Actiq study had used 2 time points (15 and 30 minutes post dose) for the calculation of SPID 30 minutes, but this study collected data at 2 additional time points – 5 and 10 minutes post dose. Including estimated data from these time points the difference in mean was estimated to be 2.25 with a SD of 4.35. To demonstrate this difference between Nasalfent and placebo with a power of 90% at a significance level of 0.05, a sample size of 80 patients was required for a crossover study. Assuming 33% of patients would not complete the Phase 1 (open, dose titration phase) and an additional 33% would not complete taking the full 10 doses of study drug, 180 patients (about 4-5 patients per site) were needed to be enrolled into the phase 1 (open dose titration) to ensure 80 patients completed the phase 2 (double blind treatment phase).

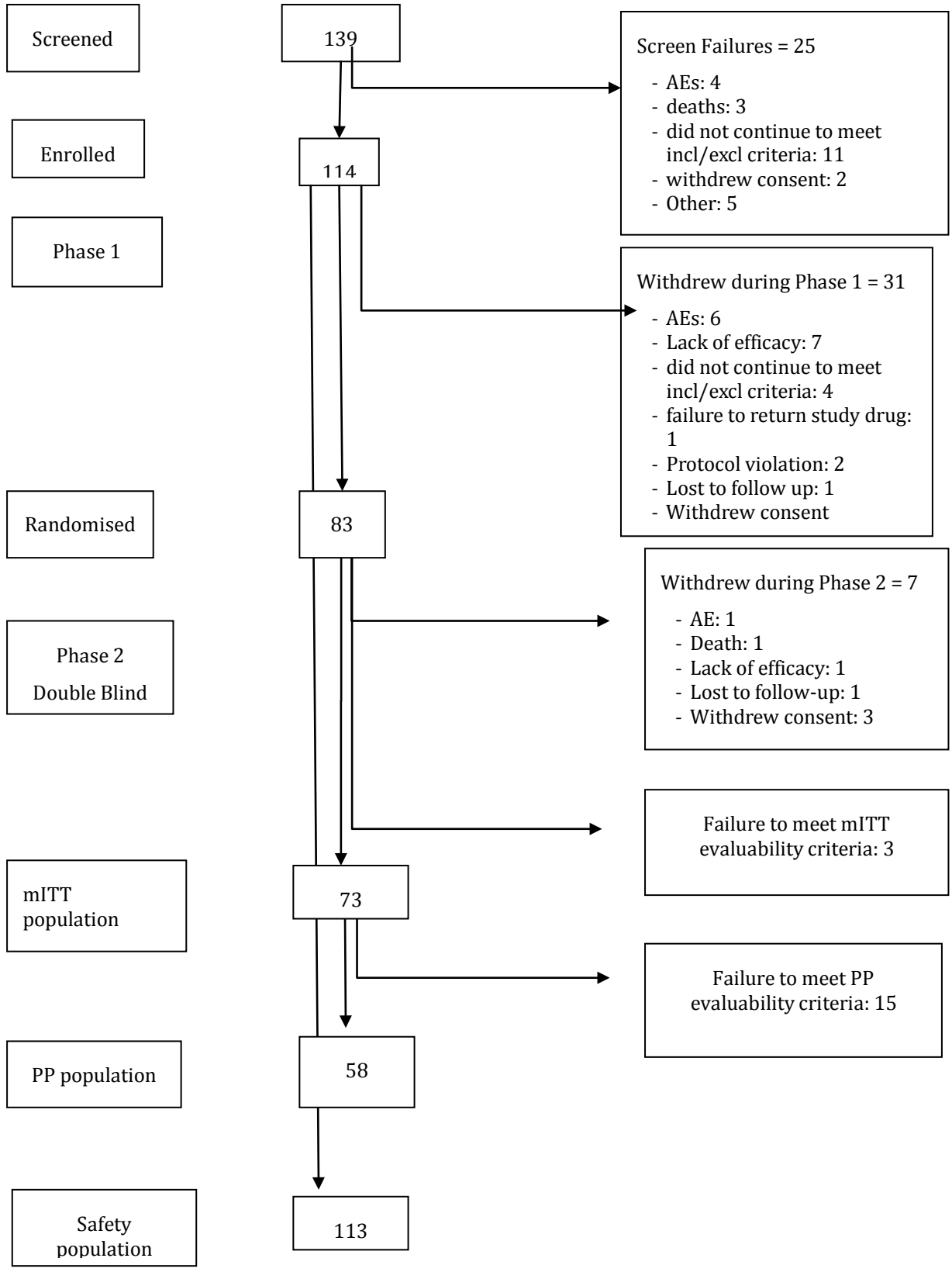
7.1.1.1.8. *Statistical methods*

Data are summarised with descriptive statistics – number (N), mean, standard deviation (SD), standard error (SE), median, minimum and maximum for continuous variables and with counts and percentages of patients for categorical variables.

All statistical tests were associated with significance criteria of $\alpha = 0.05$ (2 sided). Confidence intervals (CIs), where detailed, had 95% coverage probability, were 2 sided and were based on normal approximation.

7.1.1.1.9. *Participant flow*

Figure 1 Study CP043/06 - Participant Flow



7.1.1.1.10. *Major protocol violations/deviations*

The study was originally planned to be conducted at 43 centres in the USA but due to poor enrolment this was increased to 58 sites in the USA, Costa Rica and Argentina.

There was only one protocol amendment which was administrative only. The most frequent protocol deviations were: returned drug did not match the episode data entered into the e-diary; spray count discrepancies (usually noted as underuse or overuse of medication – the latter frequently associated with treatment of additional episodes of BTCP) and missed assessments for certain visits.

7.1.1.1.11. *Baseline data*

Summary of Patient Demographic Data – mITT population

Table 2. Study CP043/06 - Baseline Data. Table continued across 2 pages.

Parameter	100 mcg N=8	200mcg N=7	400mcg N=24	800mcg N=34	Total N=73
Age (years)					
N	8	7	24	34	73
Mean (SD)	56.5 (11.89)	46.6 (15.80)	54.3 (11.00)	50.1 (11.42)	51.8 (11.89)
Standard Error	4.20	5.97	2.25	1.96	1.39
Median	59.0	45.0	52.0	50.5	52.0
Min - Max	43-76	27-72	21-73	21-74	21-76
Age (years)					
≤ 60 years	5 (62.5)	6 (85.7)	16 (66.7)	31 (91.2)	58 (79.5)
> 60 years	3 (37.5)	1 (14.3)	8 (33.3)	3 (8.8)	15 (20.5)
Race N (%)					
Caucasian	2 (25.0)	6 (85.7)	18 (75.0)	27 (79.4)	53 (72.6)
Black	2 (25.0)	1 (14.3)	1 (4.2)	3 (8.8)	7 (9.6)
Chinese/ Japanese Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Southeast Asian	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)	2 (2.7)
Other	4 (50.0)	0 (0.0)	5 (20.8)	2 (5.9)	11 (15.1)
Gender N (%)					
Male	4 (50.0)	4 (57.1)	9 (37.5)	21 (61.8)	38 (52.1)

Parameter	100 mcg N=8	200mcg N=7	400mcg N=24	800mcg N=34	Total N=73
Female	4 (50.0)	3 (42.9)	15 (62.5)	13 (38.2)	35 (47.9)
Weight (kg)					
N	8	7	24	34	73
Mean (SD)	72.2 (13.55)	77.2 (18.23)	76.9 (15.81)	84.4 (22.72)	79.9 (19.54)
Standard Error	4. 79	6.89	3. 23	3. 90	2.29
Median	69.6	78.1	78.2	82.1	79.0
Min - Max	57.2-92.2	54.6-97.0	54.0- 114.1	46.0- 147.7	46.0- 147.7
ECOG score1					
0	1 (12.5)	4 (57.1)	2 (8.3)	3 (8.8)	10 (13.7)
1	6 (75.0)	3 (42.9)	13 (54.2)	20 (58.8)	42 (57.5)
2	1 (12.5)	0 (0.0)	9 (37.5)	11 (32.4)	21 (28.8)

Summary of Subject Demographic Characteristics Study CP043/06; [1]ECOG =Eastern Cooperative Oncology Group (ECOG) scores.

7.1.1.1.12. *Results for the primary efficacy outcome*

Primary Endpoint: Summed Pain Intensity Difference at 30 Minutes Post dose (mITT Population).

The mean SPID at 30 minutes post dose was greater for Nasalfent treated episodes (6.57) compared with placebo-treated episodes (4.45); the difference in treatments was highly statistically significant ($p<0.0001$), indicating that the overall degree of pain relief experienced by patients over that 30 minutes was significantly greater following Nasalfent treatment compared to placebo treatment.

Table 3. Study CP043/06 - Primary Efficacy Outcome

Treatment (N = 73)	
Nasalfent	**SPID (30 mins)**
Mean	6.57
SD	4.99
Standard Error	0.58
Median	5.71
Minimum	0.00
Maximum	25.43
Placebo	
Mean	4.45
SD	5.51
Standard Error	0.65
Median	2.67
Minimum	-3.00
Maximum	27.67
P-values[1]	
Treatment	<.0001
Pooled Centre	0.5891
P-values[1]	Additional covariates
Treatment	<0.0001
Pooled Centre	0.7568
Treatment Pooled Centre	0.8821
Age Category	0.6903
Sequence	0.7823
Indicator for Rescue Medication[2]	0.0846

SD = standard deviation; mITT=modified intent-to-treat; Note: Pain Intensity Scores were recorded inane-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'.

[1] P-values from the analysis of covariance (ANCOVA) model; [2] Indicator whether the patient has taken any rescue medication within 30 minutes for any mITT evaluable episode

7.1.1.1.13. *Results for other efficacy outcomes*

Results are given only for the mITT population. The results were similar for the PP population.

- Patient level endpoints

Mean SPID at 5, 10, 15, 45 and 60 minutes post dose

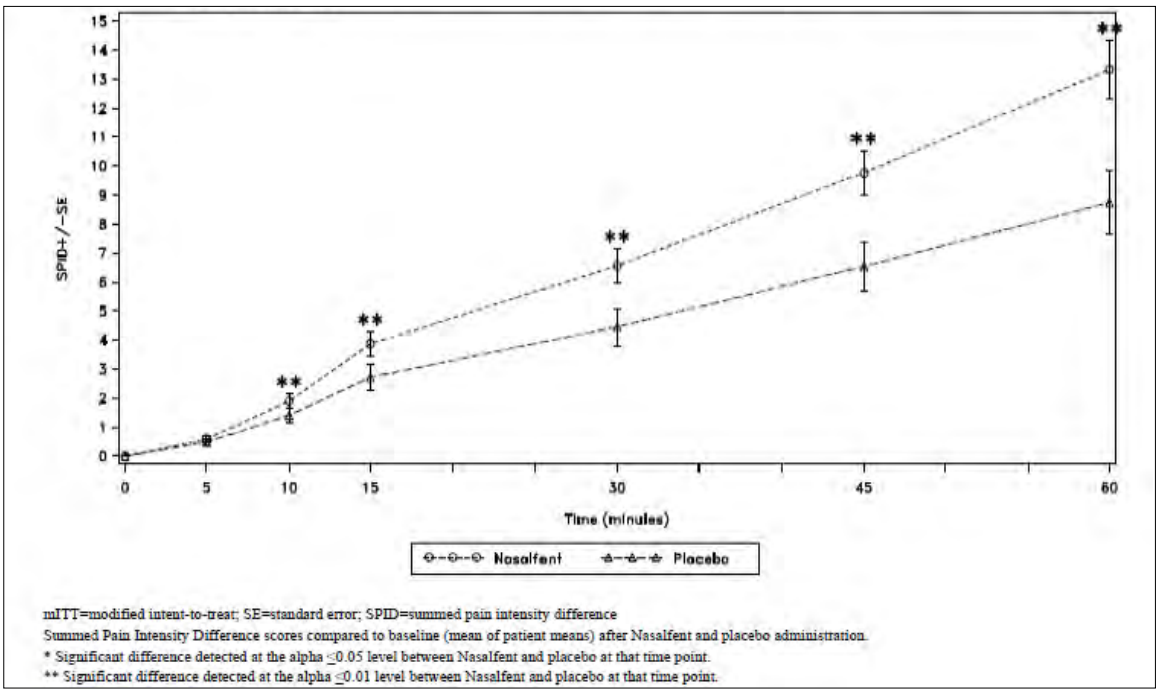
The mean SPID difference between Nasalfent and placebo treated episodes was statistically significant at 10 minutes post dose (p=0.0042) and at each of the subsequent non-primary 15, 45 and 60 minutes endpoints.

Table 4. Study CP043/06 - Mean Values of Summed Pain Intensity Difference by Treatment and Time Point.

mITT Population						
Treatment	**Time in Minutes**					
(N=73)	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Nasalfent						
Mean	0.59	1.90	3.87	6.57	9.77	13.34
SD	0.88	2.08	3.49	4.99	6.65	8.43
Standard Error	0.10	0.24	0.41	0.58	0. 78	0.99
Median	0.25	1.50	3.43	5. 71	8. 71	12.33
Minimum	-0.43	-0.29	-0.14	0.00	0.00	0.7 5
Maximum	4.86	11.71	18.57	25.43	32.29	39.14
Placebo						
Mean	0.48	1.40	2.72	4.45	6.54	8.7 5
SD	1.01	2.29	3. 79	5.51	7.39	9.36
Standard Error	0.12	0.27	0.44	0.65	0.87	1.10
Median	0.00	0.67	1.50	2.67	4.33	6.00
Minimum	-0.50	-1.33	-2.33	-3.00	-2.33	-0.33
Maximum	6.67	13.67	20.67	27.67	34.67	41.67
P-values[1]						
Treatment	0.0709	0.0042	0.0003	<0.0001	<0.0001	<0.0001
Pooled Centre	0.6468	0.5483	0.5669	0.5891	0.6086	0.6173

Note: Pain Intensity Scores were recorded in an e-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain.'1P-values were obtained from an ANCOV A model performed separately at each time point.

Figure 2. Study CP043/06 - Summed Pain Intensity Scores (mean+SE) after Nasalfent and Placebo administration (mITT population).



mITT=modified intent-to-treat; SE=standard error; SPID=summed pain intensity difference
Summed Pain Intensity Difference scores compared to baseline (mean of patient means) after Nasalfent and placebo administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and placebo at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and placebo at that time point.

Pain Intensity Scores at 5, 10, 15, 30, 45, and 60 Minutes

The mean baseline PI scores for Nasalfent- and placebo-treated episodes were comparable (6.89 vs. 6.96, respectively). The mean PI score for Nasalfent-treated episodes was statistically significantly different from that for placebo-treated episodes at the 5-minute time point (p=0.0298), indicating the onset of efficacy at this time. This effect increased over the subsequent time points (10 to 60 minutes post dose), and the differences between PI scores were statistically significantly different (p≤0.0014) between treatments at all subsequent time points.

Table 5. Study CP043/06 - Mean Pain Intensity Score by Treatment and Time Point. Table continued across 2 pages.

mITT Population							
Treatment	**Time in Minutes**						
N=731	**Baseline**	**5 min**	**10 min**	**15 min**	**30min**	**45min**	**60 min**
Nasalfent							
Mean	6.89	6.30	5.58	4.92	4.20	3.70	3.32
SD	1.79	1.83	1.91	1.97	1.96	1.98	2.04
Standard Error	0.21	0.21	0.22	0.23	0.23	0.23	0.24
Median	7.14	6.71	5.67	5.00	4.00	3.43	3.00
Minimum	2.57	2.00	0.00	0.00	0.00	0.00	0.00
Maximum	10.00	9.29	9.29	9.29	8.57	8.50	9.17
Placebo							
Mean	6.96	6.48	6.04	5.64	5.23	4.88	4.74
SD	1.83	1.96	2.07	2.16	2.26	2.27	2.36
Standard Error	0.21	0.23	0.24	0.25	0.26	0.27	0.28
Median	7.33	7.00	6.33	6.00	5.33	5.00	5.00
Minimum	2.00	0.33	0.00	0.00	0.00	0.00	0.00
Maximum	10.00	10.00	10.00	10.00	10.00	10.00	10.00
P-values[1]							
Treatment	0.3176	0.0298	0.0014	<.0001	<.0001	<.0001	<.0001
Pooled Centre	0.9598	0.8473	0.7605	0.8126	0.8116	0.7123	0.6031

mITT = modified intent-to-treat; SD = standard deviation; min = minute; Note: Pain Intensity Scores were recorded in an e-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'. P-values were obtained from an ANCOV A model performed separately at each time point.

Pain Intensity Difference (PID) from baseline to 5, 10, 15, 30, 45, and 60 minutes post dose

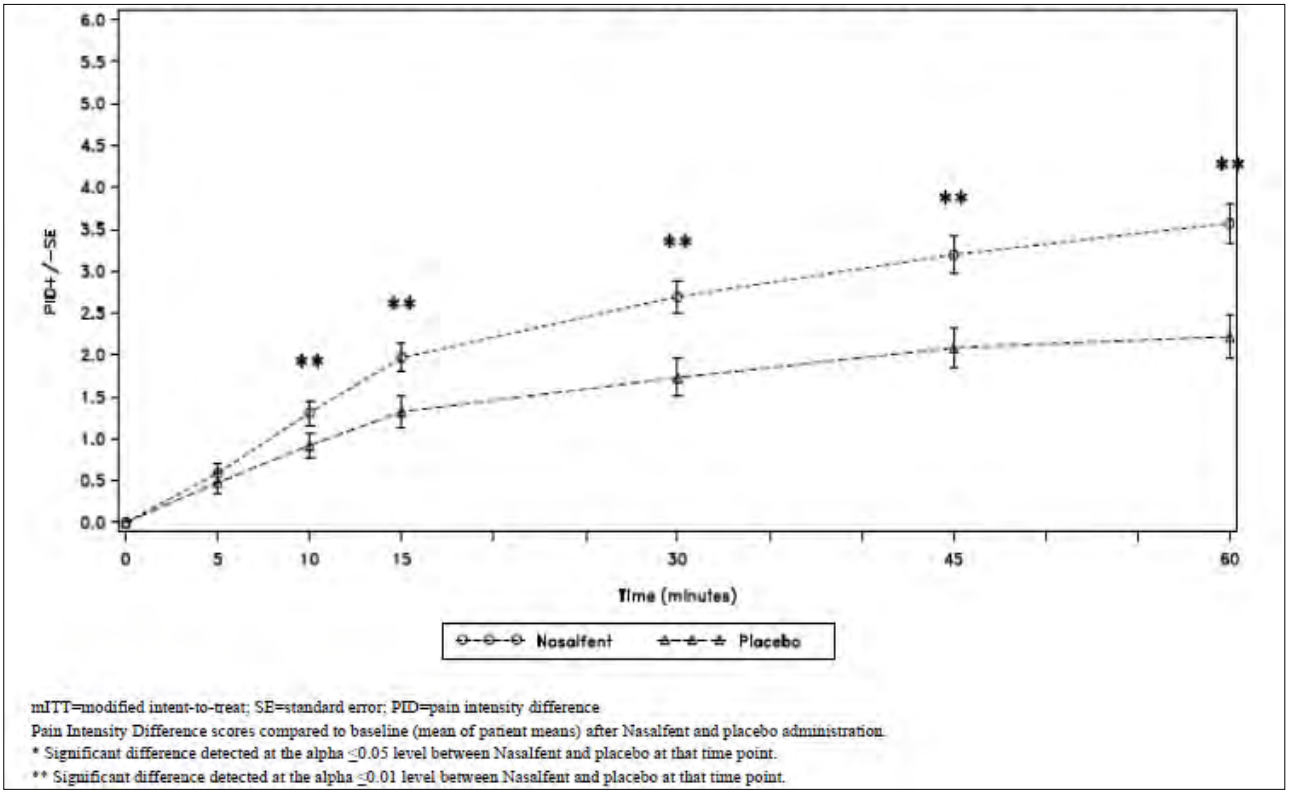
The mean PID was statistically significantly greater for Nasalfent treated episodes than placebo treated episodes in the mITT population at each observed time point from 10 to 60 minutes post dose (p≤0.0023), indicating a greater relief of pain following Nasalfent treatment.

Table 6. Study CP043/06 - Mean PID Values by Treatment and Time Point. Table continued across 2 pages.

mITT Population						
Treatment	**Time in Minutes**					
(N=73)	**5min**	**10 min**	**15min**	**30min**	**45min**	**60min**
Nasalfent						
Mean	0.59	1.31	1.97	2.69	3.20	3.57
SD	0.88	1.27	1.51	1.65	1.85	1.97
Standard Error	0.10	0.15	0.18	0.19	0.22	0.23
Median	0.25	1.14	1.86	2.50	3.00	3.43
Minimum	-0.43	-0.14	0.00	0.00	0.00	-0.17
Maximum	4.86	6.86	6.86	6.86	7.50	9.00
Placebo						
Mean	0.48	0.92	1.32	1.73	2.08	2.22
SD	1.01	1.32	1.57	1.90	2.03	2.14
Standard Error	0.12	0.15	0.18	0.22	0.24	0.25
Median	0.00	0.50	1.00	1.33	1.50	1.67
Minimum	-0.50	-1.00	-1.00	-0.67	0.00	0.00
Maximum	6.67	7.00	7.00	8.00	8.00	8.33
P-values[1]						
Treatment	0.0709	0.0023	<0.0001	<0.0001	<0.0001	<0. 0001
Pooled Centre	0.6468	0.4646	0.5794	0.6795	0.6850	0.6226

mITT = modified intent-to-treat; SD = standard deviation; min = minute; Note: Pain Intensity Scores were recorded in an e-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'. [1] P-values were obtained from an ANCOVA model performed separately at each time point

Figure 3. Study 043/06 – Mean PID Scores at 5 to 60 Minutes Post Dose (Nasalfent and Placebo). mITT population.



mITT=modified intent-to-treat; SE=standard error; PID=pain intensity difference
Pain Intensity Difference scores compared to baseline (mean of patient means) after Nasalfent and placebo administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and placebo at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and placebo at that time point.

Pain relief scores at 5, 10, 15, 30, 45, and 60 minutes post dose

The mean PR score was greater after Nasalfent administration than after placebo administration at all observed time points. The difference was statistically significant at all time points from 10 to 60 minutes ($p \leq 0.0004$).

Table 7. Study CP043/06 - Mean PR Scores by Treatment and Time point

mITT Population						
Treatment	**Time in Minutes**					
(N=73)	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60min**
Nasalfent						
Mean	0.73	1.14	1.49	1.91	2.17	2.32
SD	0.87	0.89	0.89	0.85	0.88	0.89
Standard Error	0.10	0.10	0.10	0.10	0.10	0.10
Median	0.43	1.00	1.43	2.00	2.17	2.43
Minimum	0.00	0.00	0.00	0.00	0.00	0.17
Maximum	4.00	4.00	4.00	4.00	4.00	4.00
Placebo						
Mean	0.66	0.84	1.11	1.29	1.39	1.50
SD	0.93	0.93	1.01	1.16	1.13	1.19
Standard Error	0.11	0.11	0.12	0.14	0.13	0.14
Median	0.33	0.67	1.00	1.00	1.33	1.50
Minimum	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	4.00	4.00	4.00	4.00	4.00	4.00
P-values[1]						
Treatment	0. 2149	0.0002	0.0004	<.0001	<.0001	<.0001
Pooled Centre	0.7 516	0.7771	0.8311	0.9473	0.5144	0.2574

mITT = modified intent-to-treat; SD = standard deviation; PR = pain relief

Note: Pain relief scores were recorded in an e-diary using a 5-point scale (0 = none to 4 = complete).

[1]P-values were obtained from an ANCOVA model performed separately at each time point

Total Pain Relief (TOTPAR) at 10, 15, 30, 45, and 60 minutes

The mean TOTPAR between Nasalfent and placebo treated episodes was statistically significant at 10 minutes post dose and at each of the subsequent observed time points (p≤0.0031), indicating that the significantly greater decreases in PI reported by patients following Nasalfent treatment compared to placebo are consistently reflected in the onset of perceived pain relief.

Table 8. Study CP043/06 - Mean TOTPAR Scores by Treatment and Time point

mITT Population						
Treatment	**Time in Minutes**					
(N=73)	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Nasalfent						
Mean	0.73	1.87	3.36	5.27	7.44	9.76
SD	0.87	1.71	2.51	3.21	3.90	4.56
Standard Error	0.10	0.20	0.29	0.38	0.46	0.53
Median	0.43	1.57	3.02	4.67	7.00	9.67
Minimum	0.00	0.00	0.00	0.00	0.00	0.50
Maximum	4.00	8.00	12.00	16.00	20.00	24.00
Placebo						
Mean	0.66	1.50	2.62	3.91	5.30	6.80
SD	0.93	1.82	2.75	3.74	4.73	5.75
Standard Error	0.11	0.21	0.32	0.44	0.55	0.67
Median	0.33	0.67	1.67	2.67	4.33	6.00
Minimum	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	4.00	8.00	10.67	14.67	18.67	22.67
P-values1						
Treatment	0.2149	0.0031	0.0007	<.0001	<.0001	<.0001
Pooled Centre	0.7516	0.7642	0.7778	0.8399	0.8213	0.7765

mITT = modified intent-to-treat; SD = standard deviation; TOTPAR = total pain relief

Note: Pain relief scores were recorded in an e-diary using a 5-point scale (0 = none to 4 = complete).

[1]P-values were obtained from an ANCOVA model performed separately at each time point.

Patient acceptability scores at 30 and 60 minutes post dose

The overall mean patient averaged acceptability assessment score was significantly greater for Nasalfent as compared with placebo at 30 minutes post dose (2.63 vs 2.01, p<0.0001) and at 60

minutes post dose (2.73 vs 2.02, p<0.0001). The mean assessment scores for the speed of relief and the episode reliability of the nasal spray also favoured Nasalfent over placebo at both 30 and 60 minutes, with statistically significant differences evident at both time points (p<0.0001). In addition, the sensitivity analysis of patient averaged overall acceptability, speed of relief, and reliability of nasal spray assessments demonstrated statistically significant differences between the treatments in favour of Nasalfent at both 30 and 60 minutes post dose (p<0.0001).

Overall, acceptability assessment in the mITT population after the last treated episode demonstrated that 50 (68.5%) patients reported an acceptability assessment score of 3 (satisfied) or 4 (very satisfied) for the ease of use of Nasalfent nasal spray. Similarly, 51 (69.9%) patients reported an acceptability assessment score of 3 (satisfied) or 4 (very satisfied) for the convenience of the nasal spray.

Mean reduction in PI Score ≥1 and ≥2 at 5, 10, 15, 30, 45, and 60 minutes post dose

The number of patients with a mean reduction in the PI score of ≥1 was similar for both treatments after 5 minutes. However, a statistically significantly higher number of patients reporting at least 1 point reduction in PI score following administration of Nasalfent compared with placebo were noted at each time point from 10 to 60 minutes post dose (p≤0.0067). There were a statistically significantly higher number of patients with a mean reduction in PI score of ≥2 after administration of Nasalfent compared with placebo at each observed time point from 15 to 60 minutes post dose (p≤0.0002).

Table 9. Study CP043/06 - Summary of Mean Reduction in Pain Intensity Score ≥1 and ≥2

mITT Population						
Treatment	**Time in Minutes**					
(N=73)	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60min**
Number(%) of Patients with Mean Reduction in PI Score ≥1						
Nasalfent	15	41	53	62	66	70
	(20.5%)	(56.2%)	(72.6%)	(84.9%)	(90.4%)	(95.9%)
Placebo	16	28	38	44	47	47
	(21.90%)	(38.4%)	(52.1%)	(60.3%)	(64.4%)	(64.4%)
P-values[1]	0.7389	0.0067	0.0011	0.0001	<.0001	<.0001
Number(%) of Patients with Mean Reduction in PI Score ≥2						
Nasalfent	5	18	36	46	52	55
	(6.8%)	(24.7%)	(49.3%)	(63.0%)	(71.2%)	(75.3%)
Placebo	5	12	19	26	32	33
	(6.8%)	(16.4%)	(26.0%)	(35.6%)	(43.8%)	(45.2%)
P-values[1]	1.0000	0.0833	0.0002	<.0001	0.0002	<.0001

mITT = modified intent-to-treat; PI = pain intensity; min = minute. [1]P-values from McNemar Test to compare Nasalfent and placebo treatments at each time point.

Mean reduction in SPID Score of ≥2, ≥3 and ≥4 at 10, 15, 30, 45, and 60 minutes post dose

A statistically significantly higher number of patients reported a mean reduction in SPID score of ≥2 following administration of Nasalfent compared with placebo at each time point from 10 to 60 minutes pose dose (p≤0.0116). Significantly more patients also had a mean reduction in SPID score of ≥3 and ≥4 following Nasalfent administration compared with placebo at each time point from 15 to 60 minutes post dose (p≤0.0006 and p≤0.0010, respectively).

Reduction in PI score from baseline by ≥33%, ≥50%, and ≥66% at 5, 10, 15, 30, 45, and 60 minutes post dose

The number of patients with a ≥33% reduction in PI score from baseline was similar following both treatments at 5 and 10 minutes post dose; however, at all time points from 15 to 60 minutes, the number of patients with at least a 33% reduction in PI score after Nasalfent treatment was almost double that after placebo treatment. The difference between treatments was statistically significant at all time points from 15 to 60 minutes post dose (p≤0.0017). Similar results were observed when using a threshold of ≥50% reduction in PI score from baseline (at time points from 30 to 60 minutes post dose) and when using a threshold of ≥66% reduction in PI score from baseline (at 45 and 60 minutes post dose).

Table 10. Study CP043/06 - Summary of Mean Reduction in Pain Intensity Score by ≥33%, ≥50% and ≥66% by Treatment and Time Point.

mITT Population						
Treatment	**Time in Minutes**					
(N=73)	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Number(%) of Patients with Reduction in PI Score ≥33%						
Nasalfent	3	8	28	41	54	55
	(4.1%)	(11.0%)	(38.4%)	(56.2%)	(74.0%)	(75.3%)
Placebo	4	8	14	20	25	32
	(5.5%)	(11.0%)	(19.2%)	(27.4%)	(34.2%)	(43.8%)
P-values[1]	0.3173	1.0000	0.0017	<0.0001	<0.0001	<0.0001
Number(%) of Patients with Reduction in PI Score ≥50%						
Nasalfent	2	7	9	25	35	39
	(2.7%)	(9.6%)	(12.3%)	(34.2%)	(47 .9%)	(53.4%)
Placebo	2	6	7	12	15	15
	(2.7%)	(8.2%)	(9.6%)	(16.4%)	(20.5%)	(20.5%)
P-values[1]	1.0000	0.6547	0.4142	0.0029	<0.0001	<0.0001
Number(%)of Patients with Reduction in PI Score >66%						
Nasalfent		1	6	8	16	23
	(1.4%)	(1.4%)	(8.2%)	(11.0%)	(21.9%)	(31.5%)
Placebo	1	3	5	6	9	10
	(1.4%)	(4.1%)	(6.8%)	(8.2%)	(12.3%)	(13.7%)
P-values[1]	1.0000	0.1573	0.6547	0.4142	0.0348	0.0008

mITT = modified intent-to-treat; P I= pain intensity; min = minute; [1]P-values from McNemar Test to compare Nasalfent and placebo at each time point.

PR scores ≥1 and ≥2 at 5, 10, 15, 30, 45 and 60 minutes post dose

There were a statistically significantly higher number of patients achieving a PR score ≥1 following administration of Nasalfent than following administration of placebo at each observed time point from 10 to 60 minutes post dose (p≤0.0184). Significantly more patients achieved a PR score of ≥2 following administration of Nasalfent than following administration of placebo at 30, 45 and 60 minutes post dose (p≤0.0035).

Achievement of %max TOTPAR of ≥33%, ≥50%, and ≥66% at 10, 15, 30, 45, and 60 minutes post dose

Statistically higher number of patients achieved %max TOTPAR of ≥33% following administration of Nasalfent than following administration of placebo at 45 minutes and 60 minutes post dose (p≤0.0018). A statistically significantly higher number of patients achieved %max TOTPAR of ≥50% at 60 minutes following administration of Nasalfent than following administration of placebo (32.9% vs 20.5%, p=0.0290). No statistically significant difference was observed in the number of patients achieving %max TOTPAR of ≥66% after use of either treatment.

Categorical analysis of patient averaged acceptability assessment scores at 30 and 60 minutes post dose

At both 30 minutes and 60 minutes, a greater number of patients reported a mean overall satisfaction score in the range from ≥3 (satisfied to very satisfied) following administration of Nasalfent compared with administration of placebo (30 minutes: 26 [35.6%] vs 13 [17.8%], respectively, and 60 minutes: 31 [42.5%] vs 14 [19.2%], respectively). Similar results were observed for the speed of relief and episode reliability of nasal spray categorical analyses.

Rescue medication usage

Although patients had been requested not to use rescue medication during the first 30 minutes unless absolutely necessary, a small number (8/73 in the mITT population) did so in 11 episodes of BTCP. There was no difference in use of recue medication between the Nasalfent treated and placebo treated patients.

1. Episode level endpoints

For the 83 patients enrolled in the randomised phase of the trial there were a total of 1,354 breakthrough pain episodes were treated 1,125 with Nasalfent and 229 with placebo.

For the mITT population for which efficacy results are provided – a total of 659 episodes were treated with Nasalfent and 200 episodes were treated with placebo.

Treated episodes with a reduction in PI score of ≥1 and ≥2 from baseline at 5, 10, 15, 30, 45, and 60 minutes post dose

A statistically significant increase in the number of episodes with a reduction in PI score ≥1 was observed following administration of Nasalfent compared with administration of placebo at each observed time point from 5 to 60 minutes post dose (p≤0.0355). Statistically significant increases in the number of episodes with a mean reduction in PI score of ≥2 following administration of Nasalfent were also observed compared with administration of placebo at each observed time point from 10 to 60 minutes post dose (p≤0.0110).

Table 11. Study CP043/06 - Number (%) of Episodes with a Reduction in PI Score ≥1 and ≥2 from Baseline by Treatment and Time Point

mITT Population						
Treatment			Time in Minutes			
(N=659)	5min	10 min	15 min	30 min	45 min	60 min
Number(%) of Episodes with Mean Reduction in PI Score ≥1						
Nasalfent	153/459	280/459	336/459	387/459	401/459	409/459
	(33.3%)	(61.0%)	(73.2%)	(84.3%)	(87.4%)	(89.1%)
Placebo	53/200	88/200	111/200	117/200	124/200	127/200
	(26.5%)	(44.0%)	(55.5%)	(58.5%)	(62.0%)	(63.5%)
P-values[1]	0.0355	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Number (%) of Episodes with Mean Reduction in PI Score ≥2						
Nasalfent	60/459	151/459	233/459	302/459	325/459	350/459
	(13.1%)	(32.9%)	(50.8%)	(65.8%)	(70.8%)	(76.3%)
Placebo	23/200	49/200	64/200	80/200	91/200	97/200
	(11.5%)	(24.5%)	(32.0%)	(40.0%)	(45.5%)	(48.5%)
P-values[1]	0.5009	0.0110	<0.0001	<0.0001	<0.0001	<0.0001

mITT = modified intent-to-treat; PI = pain intensity; min = minute; [1]P-values from a multilevel model for binary data wi1h random effects to compare Nasalfent vs. placebo

Mean episode values of SPID and mean episode reduction in SPID values of ≥2, ≥3 and ≥4 at 10, 15. 30, 45, and 60 minutes post dose for all treated episodes

Mean episode values of SPID were greater following Nasalfent administration than following placebo administration for the mITT population, and the differences between the 2 treatments were statistically significant at each observed post dose time point from 15 to 60 minutes ($p \leq 0.0458$).

Table 12. Study CP043/06 - Mean Episode Values of SPID by Treatment and Time Point

mITT Population					
Treatment	**Time in Minutes**				
	10 min	**15 min**	**30 min**	**45 min**	**60 min**
Nasalfent (N=459)					
Mean	1.90	3.85	6.55	9.76	13.33
SD	2.68	4.40	6.25	8.32	10.52
Standard Error	0.13	0.21	0.29	0.39	0.49
Median	1.00	3.00	5.00	8.00	12.00
Minimum	-2.00	-3.00	-4.00	-5.00	-6.00
Maximum	14.00	21.00	28.00	36.00	46.00
Placebo (N=200)					
Mean	1.44	2.80	4.55	6.67	8.93
SD	2.64	4.36	6.37	8.59	10.91
Standard Error	0.19	0.31	0.45	0.61	0. 77
Median	0.00	1.00	2.00	4.00	6.00
Minimum	-3.00	-5.00	-7.00	-8.00	-6.00
Maximum	16.00	24.00	32.00	40.00	48.00
P-values[1]	0.4065	0.0458	0.0001	<0. 0001	<0.0001

mITT = modified intent-to-treat; SD = standard deviation; min = minute. [1]P-values from a multilevel model with random effects to compare Nasalfent vs. placebo

Statistically significant differences were observed between treatments in the numbers of episodes with a mean increase in the SPID score of ≥2, with more episodes following Nasalfent treatment noting a reduction than following placebo treatment at each time point from 10 to 60 minutes post dose (p≤0.0016); the Nasalfent treated episodes also had greater number of episodes with mean increases in SPID score of ≥3 and ≥4 at each time point from 15 to 60 minutes post dose (p≤0.0001).

Table 13. Study CP043/06 - Episode Reductions in SPID (Episode SPID) Score ≥2, ≥3, and ≥4

mITT Population					
Treatment	**Time in Minutes**				
(N=659)	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Number(%) of Episodes with Reduction in SPID Score ≥2					
Nasalfent	188/459	288/459	350/459	392/459	409/459
	(41.0%)	(62.7%)	(76.3%)	(85.4%)	(89.1%)
Placebo	60/200	90/200	112/200	122/200	131/200
	(30.0%)	(45.0%)	(56.0%)	(61.0%)	(65.5%)
P-values[1]	0.0016	<0.0001	<0.0001	<0.0001	<0.0001
Number(%) of Episodes with Reduction in SPID Score ≥3					
Nasalfent	123/459	241/459	318/459	358/459	395/459
	(26.8%)	(52.5%)	(69.3%)	(78.0%)	(86.1%)
Placebo	43/200	70/200	98/200	113/200	124/200
	(21.5%)	(35.0%)	(49.0%)	(56.5%)	(62.0%)
P-values[1]	0.0813	<0.0001	<0.0001	<0.0001	<0.0001
Number(%) of Episodes with Reduction in SPID Score ≥4					
Nasalfent	79/459	189/459	279/459	338/459	373/459
	(17 .2%)	(41.2%)	(60.8%)	(73.6%)	(81.3%)
Placebo	28/200	54/200	80/200	104/200	116/200
	(14.0%)	(27.0%)	(40.0%)	(52.0%)	(58.0%)
P-values[1]	0.2257	<0.0001	<0.0001	<0.0001	<0.0001

mITT = modified intent-to-treat; SPID = summed pain intensity difference; min = minute. [1] P-values from a multilevel model with random effects to compare Nasalfent vs. placebo

Treated episodes with ≥33%, ≥50% and ≥66% reduction in PI score from baseline at 5, 15, 15, 30, 45 and 60 minutes post dose

The number of treated episodes with a ≥33% reduction in PI score from baseline was similar following both treatments at 5 and 10 minutes post dose; however, from 15 minutes through 60 minutes, the number of episodes with this threshold of improvement in PI score was significantly larger following Nasalfent use compared with placebo use ($p<0.001$). Similar results were observed using the threshold of ≥50% and ≥66% reduction in PI score from baseline, but only at 30, 45 and 60 minutes post dose ($p\leq0.0038$).

Table 14. Study CP043/06 - Number (%) of Episodes with Reductions in the Pain Intensity Score ≥33%, ≥50% and ≥66% from Baseline by Treatment and Time Point.

mITT Population						
Treatment	**Time in Minutes**					
N=659	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Number(%) of Episodes with Reduction in PI Score ≥33%						
Nasalfent	36/459	99/459	182/459	275/459	306/459	323/459
	(7.8%)	(21.6%)	(39.7%)	(59.9%)	(66.7%)	(70.4%)
Placebo	11/200	37/200	50/200	67/200	81/200	87/200
	(5.5%)	(18.5%)	(25.0%)	(33.5%)	(40.5%)	(43.5%)
P-values[1]	0.2426	0.3512	<0.0001	<0. 0001	<0.0001	<0.0001
Number (%) of Episodes with Reduction in PI Score ≥50%						
Nasalfent	21/459	49/459	92/459	172/459	229/459	254/459
	(4.6%)	(10.7%)	(20.0%)	(37.5%)	(49.9%)	(55.3%)
Placebo	8/200	16/200	30/200	43/200	55/200	64/200
	(4.0%)	(8.0%)	(15.0%)	(21.5%)	(27.5%)	(32.0%)
P-values[1]	0. 7 067	0.2175	0.0776	<0.0001	<0. 0001	<0.0001
Number (%} of Episodes with Reduction in PI Score ≥66%						
Nasalfent	12/459	28/459	52/459	97/459	141/459	186/459
	(2.6%)	(6.1%)	(11.3%)	(21.1%)	(30.7%)	(40.5%)
Placebo	5/200	8/200	17/200	26/200	39/200	39/200
	(2.5%)	(4.0%)	(8.5%)	(13.0%)	(19.5%)	(19.5%)
P-values[1]	0.9678	0.2150	0.2360	0.0038	0.0003	<0.0001

mITT = modified intent-to-treat; PI = pain intensity; min = minute. [1]P-values from a multilevel model for binary data wi1h random effects to compare Nasalfent vs. placebo

Episode time to achieve ≥33%, ≥50% and ≥66% reductions in PI Score within 30 and 60 minutes post dose

The mean episode time to a reduction ≥33% within 30 minutes was 17.6 minutes following treatment with Nasalfent and 16.0 minutes following treatment with placebo (hazard ratio 2.14, 95% CI: 1.57-2.93). Over 60% of the total episodes reached a ≥33% reduction in PI within 30 minutes of Nasalfent administration compared with 36% of the total episodes following placebo administration.

When the time interval of observation was increased to 60 minutes post dose, more than 70% of the total episodes reached a ≥33% reduction in PI following Nasalfent administration compared with 50% of the total episodes following placebo administration. The mean episode time to a reduction ≥33% within 60 minutes was 22.5 minutes following Nasalfent and 25.6 minutes following placebo (hazard ratio 1.96, 95% CI: 1.50-2.55).

Episodes with no increase in PI at any time point compared to baseline

97.2% of episodes treated with Nasalfent and 96.5% of episodes treated with placebo did not show an increase in PI at any observed time point after baseline.

Episodes achieving a PR score of ≥1, and ≥2 at 5, 12, 15, 30, 45, and 60 minutes post dose

Statistically significantly higher percentage of Nasalfent treated episodes compared with placebo treated episodes achieved PR scores of ≥1 or ≥2 at each observed time point from 10 to 60 minutes post dose (p<0.0001 and p≤ 0.0062, respectively).

Table 15. Study CP043/06 - Number (%) of Episodes Achieving aPR Score of ≥1 and ≥2 by Treatment and Time point.

mITT Population						
Treatment	**5 min**	**10 min**	**15min**	**30min**	**45 min**	**60min**
(N=659)	N=657	N=656	N=659	N=653	N=646	N=639
Number(%) of Episodes Achieving PR Score ≥1						
Nasalfent	198/459	294/458	353/459	387/456	399/453	399/448
	(43.1%)	(64.2%)	(76.9%)	(84.9%)	(88.1%)	(89.1%)
Placebo	75/198	98/198	115/200	116/197	120/193	122/191
	(37.9%)	(49.5%)	(57.5%)	(58.9%)	(62.2%)	(63.9%)
P-values[1]	0.0961	<0.0001	<0.0001	<0.0001	<0.0001	<0. 0001
Number (%) of Episodes Achieving PR Score ≥2						
Nasalfent	82/459	152/458	206/459	281/456	304/453	311/448
	(17.9%)	(33.2%)	(44.9%)	(61.6%)	(67.1%)	(69.4%)
Placebo	32/198	48/198	68/200	75/197	79/193	88/191
	(16.2%)	(24.2%)	(34.0%)	(38.1%)	(40.9%)	(46.1%)
P-values[1]	0.4755	0.0062	0.0021	<0.0001	<0.0001	<0. 0001

mITT = modified intent-to-treat; PR = pain relief; min = minute

[1]P-values from a multilevel model for binary data wi1h random effects to compare Nasalfent vs. placebo

Episode times to achieve PR Scores ≥1 and ≥2 within 30 and 60 minutes post dose

A higher percentage of episodes achieved a PR score of ≥1 within 30 minutes of administration of Nasalfent (88.0%) than placebo (63.0%). The mean episode time to PR score ≥1 within 30 minutes was 10.53 minutes following treatment with Nasalfent and 9.05 minutes following treatment with placebo (hazard ration 2.06, 95% CI: 1.59-2.67). For PR score within 50 minutes, it was 13.0 minutes following treatment with Nasalfent and 12.84 minutes following placebo (hazard ratio 2.17, (95% CI: 1.66-2.85).

A higher percentage of episodes achieved a PR score of ≥2 within 30 minutes of administration of Nasalfent (64.7%) than placebo (43.5%). The mean episode time to PR score ≥2 within 30 minutes was 15.07 minutes for Nasalfent and 12.99 for placebo (hazard ratio 1.79, 95%CI: 1.36-2.35). For PR score ≥2 within 60 minutes, the mean episode time was 20.55 minutes for Nasalfent and 19.02 minutes for placebo (hazard ratio 1.96, 95% CI 1.50-2.58).

Table 16. Study CP043/06 - Episode Times to Pain Relief Score ≥2 within 30 Minutes and 60 Minutes Post dose by Treatment.

mITT Population		
	Nasalfent N=459	**Placebo N=200**
Summary Statistics for Episodes with PR Score ≥2 within 30 Minutes		
N (%)	297 (64.7%)	87 (43.5%)
Mean (SD)	15.07 (9.778)	12.99 (8.972)
Standard Error	0.567	0.962
Median	10.00	10.00
Min	5.0	5.0
Max	30.0	30.0
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.58 (0.140)	1. 786 (1.358 - 2.348)	<0.0001
Summary Statistics for Episodes with PR Score ≥2 within 60 Minutes		
N (%)	352 (76.7%)	102 (51.0%)
Mean (SD)	20.55 (15.862)	19.02 (17.018)
Standard Error	0.845	1.685
Median	15.00	12.50
Min	5.0	5.0
Max	60.0	60.0
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.67 (0.139)	1.963 (1.495 - 2.577)	<0.0001

mITT = modified intent-to-treat; PR = pain relief; HR = hazard ratio; CI = confidence interval; SD =standard deviation; SE = standard error; Min = minimum; Max = maximum. 1P-value is obtained from time to event endpoints survival analysis using a Cox model for multiple correlated events.

Treated episodes with a %max TOTPAR of ≥33%, ≥50%, and ≥66% at 10, 15, 30, 45 and 60 minutes post dose

Statistically significantly more episodes achieved %max TOTPAR of ≥33% at each observed time point from 15 to 60 minutes post dose following Nasalfent administration compared to placebo (p≤0.0014), and similarly for episodes achieving %max TOTPAR of ≥50% at 30, 45 and 60 minutes post dose (p≤0.0125). There was no significant difference in the percentages of episodes achieving the ≥66%.

Table 17. Study CP043/06 - Numbers (%) of Episodes with %max TOTPAR ≥33%, ≥50% and ≥66% by Treatment and Time point.

mITT Population					
Treatment (N=659)	**10 min N=656**	**15 min N=656**	**30min N=650**	**45min N=641**	**60 min N=630**
Number (%) of Episodes with %max TOTPAR ≥33%					
Nasalfent	131/458	190/458	195/455	238/451	275/444
	(28.6%)	(41.5%)	(42.9%)	(52.8%)	(61.9%)
Placebo	49/198	62/198	59/195	72/190	77/186
	(24.7%)	(31.3%)	(30.3%)	(37.9%)	(41.4%)
P-values[1]	0.1770	0.0014	0.0001	<0. 0001	<0. 0001
Number (%) of Episodes with % max TOTPAR ≥50%					
Nasalfent	84/458	100/458	136/455	153/451	172/444
	(18.3%)	(21.8%)	(29.9%)	(33.9%)	(38.7%)
Placebo	30/198	38/198	44/195	44/190	49/186
	(15.2%)	(19.2%)	(22.6%)	(23.2%)	(26.3%)
P-values[1]	0.1786	0.3074	0.0125	0.0002	<0.0001
Number(%) of Episodes with %max TOTPAR ≥66%					
Nasalfent	29/458	45/458	46/455	50/451	78/444
	(6.3%)	(9.8%)	(10.1%)	(11.1%)	(17.6%)
Placebo	14/198	17/198	19/195	20/190	24/186
	(7.1%)	(8.6%)	(9.7%)	(10.5%)	(12.9%)
P-values[1]	0.5331	0.6118	0.9807	0.8510	0.0638

mITT = modified intent-to-treat; TOTPAR = total pain relief; min = minute

[1]P-values from a multilevel model with random effects to compare Nasalfent vs. placebo

Episode times to achieve total pain relief

The mean time for an episode to achieve total pain relief was 37.0 minutes following administration of Nasalfent and 32.6 minutes following placebo (hazard ratio 1.66, 95% CI 1.09 -2.51).

Treated episodes with episode acceptability scores of ≥2 and ≥3 at 30 minutes and 60 minutes post dose

Nasalfent spray had a higher incidence of better acceptability scores per episode as compared to placebo spray. In the categorical analysis, at 30 and 60 minutes pose dose, the number of

episodes with episode acceptability scores ≥3 (satisfied to very satisfied) was greater following treatment with Nasalfent than following treatment with placebo (30 minutes 299/456 [65.6%] vs 74/197 [37.6%] respectively, and 60 minutes: 311/448 [69.4%] vs 75/191 [39.3%] respectively). Similar results were observed for the speed of relief and episode reliability of nasal spray analysis and in the sensitivity analysis, which excluded episodes with rescue medication.

Episode rescue medication usage and time to rescue medication

The proportion of episodes requiring use to rescue medication was significantly lower in Nasalfent treated episodes compared with placebo treated episodes (9.4% vs 20%, respectively, p=0.0002) up to 60 minutes after treatment. A small proportion of patients used rescue medication in the period 0 to 30 minutes despite being requested not to do so unless absolutely necessary (9 [2%] Nasalfent treated and 2 [1%] placebo treated).

It is noted that due to the low number of episodes where rescue medication was used, fit of the statistical models used is questionable and care must be taken when interpreting inferential statistical results.

No rescue medications were required following episodes with either treatment after 1 hour through 4 hours.

Table 18. Study CP043/06 - Episode Rescue Medication Usage up to 1 Hour

mITT Population						
Treatment	**Number(%) of Episodes where Rescue Medication was Used**					
(N=659)	**0-5 min**	**0-10 min**	**0-15 min**	**0-30 min**	**0-45 min**	**0-60 min**
Nasalfent	5/459	6/459	6/459	9/459	22/459	43/459
	(1.1%)	(1.3%)	(1.3%)	(2.0%)	(4.8%)	(9.4%)
Placebo	0/200	0/200	0/200	2/200	16/200	40/200
	(0.0%)	(0.0%)	(0.0%)	(10%)	(8.0%)	(20.0%)
P-values[1]				0.3845	0.0932	0.0002

mITT = modified intent-to-treat; min = minute

[1]P-values from a multilevel model for binary data wi1h random effects to compare Nasalfent vs. placebo for each time point category.

Table 19. Study CP043/06 - Episode Rescue Medication Usage up to 4 Hours

mITT Population			
Treatment	**Treatment**		
(N=659)	**0-30 min**	**30-60 min**	**60 min-4 hrs**
Nasalfent	9/459	34/459	0/459
	(2.0%)	(7 .4%)	(0.0%)
Placebo	2/200	38/200	0/200
	(1.0%)	(19.0%)	(0.0%)
P-values[1]	0.3845	<0.0001	

mITT = modified intent-to-treat; min = minute. [1]P-values from a multilevel model for binary data with random effects to compare Nasalfent vs. Placebo

Table 20. Study CP043/06 - Time to Episode Rescue Medication by Treatment

mITT Population		
Summary Statistics for Episodes Requiring use of Rescue Medication at Any Time		
	Nasalfent	**Placebo**
	N = 459	N = 200
N (%)	43 (9.4%)	40 (20.0%)
Mean(SD)	38.4 (17.44)	44.7 (11.10)
Standard Error	2.66	1.76
Median	41.0	47.5
Min, max	1.0, 60.0	17.0, 60.0
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
-0.80 (0.221)	0.449 (0.291 - 0.692)	0.0003

mITT = modified intent-to-treat; SD = standard deviation

Note: Time to episode rescue medication (minutes) is calculated from the time of study drug over all episodes treated within a treatment group that require rescue medication.

[1]P-value is obtained from time to event endpoints survival analysis using a Cox model for multiple correlated events.

It is noted that since censoring rate is high, caution must be used when interpreting survival analysis results.

Breakthrough pain questionnaire

The mean number of breakthrough pain episodes per day was similar at Visit 4 (end of treatment) compared to Visit 1 (Screening); however, the number of patients reporting severe breakthrough pain episodes was lower at Visit 4 compared to Visit 1 (83.6% vs 72.5%).

Efficacy conclusions

- The primary efficacy endpoint of this study was the SPID from 5 to 30 minutes post dose. BTCP episodes treated with Nasalfent showed a mean SPID that was significantly higher than that for episodes treated with placebo (6.57 vs 4.45, respectively, p<0.0001). This indicates that the overall degree of pain reduction during the 30 minutes period was significantly higher following Nasalfent treatment than following placebo treatment.
- The mean PI score was significantly lower following Nasalfent treatment than following placebo treatment at each observed time point from 5 to 60 minutes post dose.
- All secondary efficacy end points supported the superiority of Nasalfent to placebo.
- The use of rescue medication was significantly lower in Nasalfent treated episodes compared with placebo treated episodes up to 60 minutes after treatment.
- Patients reported significantly greater acceptability and satisfaction scores for Nasalfent spray as compared to placebo spray.

7.1.1.2. ***Study CP044/06***

A Multicentre, Double-Blind, Double-Dummy, Two Phase, Crossover Study of Nasalfent (Fentanyl Citrate Nasal Spray) Compared to Immediate Release Morphine Sulphate (IRMS) Tablets in the Treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy.

7.1.1.2.1. *Study design, objectives, locations and dates*

This is a multicentre, randomised, double blind, double dummy, crossover study conducted in 35 centres in Europe (UK, Germany, Italy, Spain, Poland, Czech Republic, France) and India. The study period was from October 2007 to March 2009.

The study consisted of 4 phases as follows:

- Screening Phase (up to 10 days):
- Open Dose Titration Phase (up to a maximum of 14 days): the dose of Nasalfent was titrated for each patient until 2 consecutive episodes of target BTCP were successfully treated with the same dose without unacceptable adverse events (AEs). Study staff assisted patients in determining their individual effective doses using daily telephone contact. Patients received an initial dose of 100 µg of Nasalfent, which could be titrated up to 200 µg, 400 µg, or 800 µg until an effective dose for each patient was identified.
- Double-blind, double-dummy Treatment Phase (3 to 21 days): Patients treated 10 episodes of BTCP with treatments from blinded samples of both nasal spray and tablets.
- End of Treatment Phase: (between 1 and 14 days after last dose): final assessments were performed in the clinic after 10 episodes of BTCP were completed

7.1.1.2.2. *Inclusion and exclusion criteria*

Key Inclusion criteria:

- male or female patients, aged 18 or older, with a histological documented diagnosis of malignant solid tumour or a haematological malignancy causing cancer related pain
- taking 60 mg of oral morphine or equivalent opioid for at least 1 week as regular, 24 hour medication for their underlying persistent cancer pain
- typically had 1 o 4 episodes of BTCP per day
- had an Eastern Cooperative Oncology Group (ECOG) score of ≤2 and a life expectancy at entry consistent with requirements of study

Key Exclusion criteria:

- opioid or fentanyl intolerance
- using intrathecal or epidural opioids
- having uncontrolled or rapidly escalating pain or whose condition was unstable or rapidly deteriorating
- sleep apnoea or active brain metastases with increased intracranial pressure
- any medical condition (ie respiratory, cardiac, hepatic, or renal, neurological, psychiatric) that would have made them unsuitable for the study
- history of alcohol or substance abuse or who had radiotherapy within 30 days or received treatment with an investigational drug within 4 weeks prior to screening visit
- taking monoamine oxidase inhibitors, those taking antiepileptic medication of other analgesics (where the dose had altered in the preceding 14 to 21 days) or those whose primary source of breakthrough pain was not cancer related

7.1.1.3. ***Study treatments***

7.1.1.3.1. *Nasalfent*

Nasalfent was provided in 2 strengths: 1.57 mg/mL and 6.28 mg/mL fentanyl citrate (equivalent to 1.0 and 4.0 mg/mL of fentanyl base, respectively) with each 0.1 mL spray providing a dose of 100 µg and 400 µg fentanyl respectively.

The solutions were packed into bottles with multi-use delivery Pfeiffer® devices which feature a self advancing counter mechanism and emitted a loud click upon each actuation. These features serve as patient reminders/confirmation that a spray had been administered. Once 8 sprays had been delivered, the mechanism locked out to prevent patients attempting to administer further doses from a spent bottle.

The dose titration phase in this study was the same as for Study CP043/06.

Once the effective dose was determined in the Phase 2 dose titration phase, the "effective" dose for each patient was supplied in the Phase 3 double-blind phase. Possible effective doses were 100 µg, 200 µg, 400 µg and 800 µg. Both the 100 µg and 200 µg doses were administered using a 100 µg/spray "low dose" bottle. The 400 µg and 800 µg were administered using a 400 µg/spray "high dose" bottle. Since the Nasalfent packs come in 2 different strengths (low and high), separate randomisation code lists were generated for each of these 2 dose level drug packs using blocks of 2 sequences (AB or BA).

Immediate Release Morphine Sulphate (IRMS)

The IRMS comparator was Sevredol® (Napp Pharmaceuticals, UK). It comes in 3 strengths: 10 mg, 20 mg and 50 mg of morphine sulphate.

The dose of IRMS was determined according to the established principal of one-sixth of the daily morphine dose equivalent of background opioid medication or the patient's previously "effective" dose of IRMS for BTCP if known prior to study entry.

To preserve the blinding of the study, the tablets were over-encapsulated using a brown size 1 hard gelatine capsule. Placebo capsules were manufactured to match.

The IRMS was dispensed in blister packs containing the appropriate number of encapsulated tablets. Each IRMS blister pack contained 6 capsules allocated to each dose (a total of 60 capsules) consisting of the following:

- 3 of the 50 mg, 2 of the 20 mg and 1 of the 10 mg strengths so that all doses up to 200 mg could be selected from the capsules supplied

- or matching placebo capsules

The blister pack was designed such that the strength of each unmarked capsule in the pack was clearly identified by means of text and colours; capsules were identified as “50 mg”, “20 mg”, and “10 mg” with both active and matched placebo blister packs being identical in appearance. In addition, each blister pack had a panel in which study staff marked which combination of the 6 capsules were to be taken by an individual patient for each episode treated (and against which the actual dose taken could be checked).

7.1.1.3.2. *Efficacy variables and outcomes*

The **primary efficacy outcome** was pain intensity difference 15 minutes after dosing (PID_{15mins}), defined as the recorded difference between PI at that time point and baseline. The PI was measured on a rating scale of 0 to 10 where 0 = no pain and 10 = worst possible pain.

The key efficacy variables were:

- Summed pain intensity difference (SPID) at 10, 15, 30, 45 and 60 minutes post dose
- Pain intensity (PI) at 5, 10, 30, 45, and 60 minutes post dose
- Pain Intensity Difference (PID) at baseline, 5, 10, 30, 45, and 60 minutes post dose
- Pain relief (PR) at 5, 10, 15, 30, 45, and 60 minutes post dose
- Total pain relief (TOTPAR) at 10, 15, 30, 45 and 60 minutes post dose
- Patient acceptability scores at 30 and 60 minutes post dose including overall satisfaction, ease of use, and convenience.

The scales used to measure pain intensity, pain relief and patient acceptability were the same as for study 043/06 (see page 21)

Other efficacy outcomes included:

1. Patient level endpoints

- Number and percentage of all patients in each treatment group with a mean reduction in PI score of ≥1 and ≥2 at 5, 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all patients in each treatment group with a mean SPID score of ≥2, ≥3 and ≥4 at 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all patients in each treatment group with ≥33%, ≥50% and ≥66% reduction in PI score from baseline at 5, 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all patients in each treatment group with a %max TOTPAR score of ≥33%, ≥50% and ≥66% at 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all patients in each treatment group with a mean patient acceptability score of ≥2 and ≥3 at 30 and 60 minutes post dose
- Rescue medication usage and time to rescue medication

2. Episode level endpoints

- Episode PID at 5, 10, 15, 30, 45 and 60 minutes post dose in each treatment group
- Number and percentage of all treated episodes in each treatment group with a reduction in PI score of ≥1 and ≥2 at 5, 10, 15, 30, 45 and 60 minutes post dose
- Number and percentage of all treated episodes in each treatment group with a mean SPID score of ≥2, ≥3 and ≥4 at 10, 15, 30, 45 and 60 minutes post dose

- Number and percentage of all treated episodes in each treatment group with ≥33%, ≥50% and ≥66% reduction in PI score from baseline at 5, 10, 15, 30, 45 and 60 minutes post dose
- Episode time to ≥33%, ≥50% and ≥66% reduction in PI score within 30 and 60 minutes post dose
- Number and percentage of episodes where a patient experiences no increase in PI at any time point compared to baseline
- Number and percentage of episodes achieving a PR score of ≥1 and ≥2 at 5, 10, 15, 30, 45 and 60 minutes post dose
- Episode time to achieve ≥1 and ≥2 PR score within 30 and 60 minutes post dose
- Number and percentage of episodes in each treatment group with a %max TOTPAR score of ≥33%, ≥50% and ≥66% at 10, 15, 30, 45 and 60 minutes post dose
- Episode time to achieve total PR
- Number and percentage of total treated episodes in each treatment group with a episode acceptability score of ≥2 and ≥3 at 30 and 60 minutes post dose
- Episode rescue medication range and time to rescue medication

7.1.1.4. ***Randomisation and blinding methods***

7.1.1.4.1. *Phase 2 – Open dose titration phase*

Each patient was supplied with 1 bottle of 100 µg per spray and 1 bottle of 400 µg per spray. After each dose the patient was instructed to record the dosing details on the e-diary.

7.1.1.4.2. *Phase 3 – Double-blind, double-dummy phase*

Each patient was supplied with 2 separate drug packs: 1 for Nasalfent containing 10 blinded bottles and 1 for IRMS containing blinded blisters of encapsulated tablets.

The 10 bottles from the Nasalfent pack and the corresponding blisters from the IRMS pack were used together in the order in which they were numbered (Dose 01 to Dose 10) for each of the 10 episodes of BTCP being treated. For each dose, this provided treatment with either Nasalfent combined with placebo capsules or IRMS capsules combined with placebo nasal spray. Each patient was randomly allocated to one of 2 treatment sequences (where N = Nasalfent and S = IRMS):

A: S N S N N S S N S N

B: N S N S S N N S N S

The 2 sequences were balanced with no more than 2 consecutive periods of the same treatment.

7.1.1.4.3. *Analysis populations*

A total of 135 patients were enrolled (below planned enrolment of 180 patients) and 110 patients entered the Phase 2 open dose titration phase. A total of 84 patients completed the Phase 2 and entered the Phase 3 treatment phase. A total of 79 patients completed the study.

Screened population = 135 = all patients who were examined to determine qualifications for entry into the Open, Dose- Titration Phase (Phase 2) of the study.

Randomised population = 110 = all patients who were randomly assigned to the Double-blind, double dummy Treatment Phase (Phase 3)

mITT population = 79 = all patients in the randomised population that had treated at least 1 mITT-evaluable episode with Nasalfent and 1 with IRMS. A mITT evaluable episode is defined as an episode treated with either Nasalfent spray and placebo capsule or IRMS capsule and placebo spray; and a patient had a baseline and at least 1 post baseline PI measurement; and it was the

only episode associated with a single bottle number and a single blister pack row. Both the bottle number used for the episode and the blister pack row must have non-missing records in the dataset for an episode to be considered mITT evaluable

PP population = 72 = all patients who were part of the mITT population and in whom – at least 2 episodes identified as evaluable PP episodes had been treated, 1 with each of the two treatments (Nasalfent or IRMS) and all episodes identified as evaluable PP episodes were treated using part of an ascending sequence of bottle and blister numbers whose numbers matched.

Safety population = 106 = all patients who received at least 1 dose of the study drug (Nasalfent or IRMS)

The primary statistical analyses of efficacy were performed on the mITT population. All secondary efficacy analyses were performed on the mITT and PP populations. The safety analyses were performed on the safety population.

7.1.1.4.4. *Sample size*

The study design was based on that used for demonstrating efficacy for Actiq® (fentanyl lozenge). For the endpoint of PID, a p-value <0.008 was demonstrated at each time point. Since it was expected that the PID_{15mins} with Nasalfent would be larger than with Actiq, it was estimated that the ratio of the effect size to SE would be about 3.15 for a similar sample size of 75 patients. Assuming 33% of patients would not complete the phase 2 dose titration phase and an additional 33% would discontinue prior to taking all 10 doses of the study drug, 180 patients (about 3-4 per site) were needed to enter the phase 3 to ensure 80 patients completed Phase 3 (double-blind phase).

7.1.1.4.5. *Statistical methods*

The primary efficacy end point was PID_{15mins}, defined as the recorded difference between PI at the baseline and the 15 minute time point. The primary end point was analysed using analysis of covariance (ANCOVA). The PID_{15mins} score was the dependent variable and the model contained terms for treatment groups (Nasalfent and IRMS) and study centre. The centre was created by pooling the sites. The generalised least squares estimates for the 2 treatment groups were obtained with a random effect for patients. The generalised least squares of the estimates of the overall mean and the type 2 tests of fixed effects for treatment and pooled study centre were determined. Covariates for age category (≤60 years, >60 years), sequence, treatment pooled centre, and use of rescue medication were also examined.

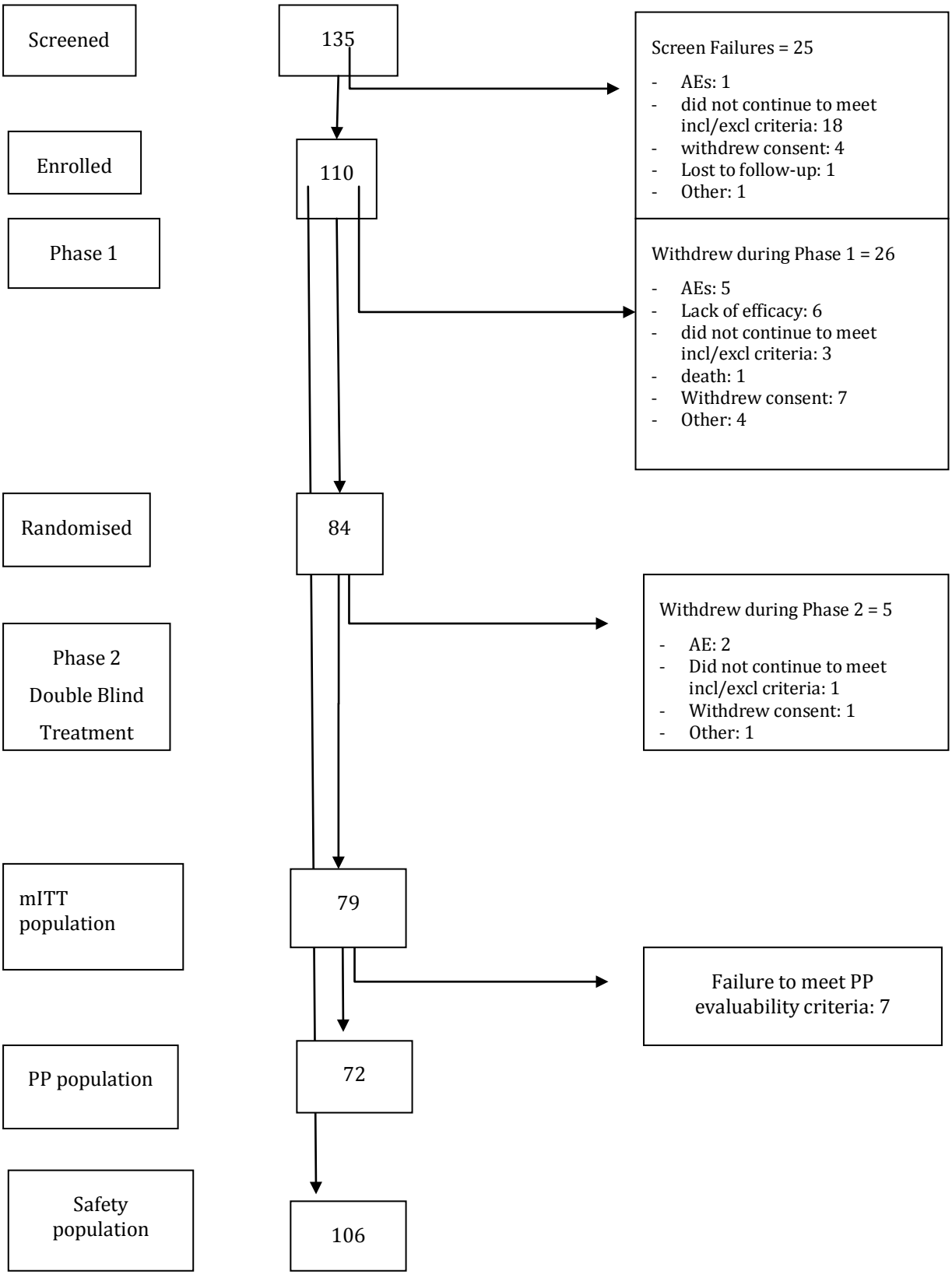
Summary statistics for the continuous end points (SPID at 10, 15, 45 and 60 mins; TOTPAR at 10, 15, 30, 45 and 60 mins; PI at 5, 10, 15, 30, 45 and 60 mins; PID at 5, 10, 15, 30, 45 and 60 mins; and PR at 5, 10, 15, 30, 45 and 60 mins) included sample size (n), mean, standard deviation (SD), standard error (SE) and minimum and maximum values by Nasalfent and IRMS. SPID at 10, 15, 45 and 60 mins and TOTPAR at 10, 15, 30, 45 and 60 mins were analysed using a similar ANCOVA model as for the primary end point analysis described above. Differences in PID at 5, 10, 15, 30, 45 and 60 mins and PR at 5, 10, 15, 30, 45 and 60 mins between treatments (Nasalfent and IRMS) at each time point and patient averaged acceptability scores were analysed using a Wilcoxin signed rank test. For many endpoints, analyses of patient and episode means were also conducted.

All hypothesis testing was conducted using 2-sided tests with alpha set at the 0.05 level of significance. Data were summarised by Nasalfent dose level (all doses, 100 µg, 200 µg, 400 µg and 800 µg) and IRMS. Descriptive statistics (mean, median, SD, SE, minimum and maximum, frequencies, percentages) were used to describe baseline characteristics for treatment doses (Nasalfent 100 µg, 200 µg, 400 µg and 800 µg), treatments (Nasalfent and IRMS) and all patients. Summary statistics for categorical patient-level end points included number and

percentage for each response category. Categorical episode end points were summarised, by treatment doses and for all patients, by treatments.

Mean, SD, SE, median and range of time was provided for time to event end points. In addition, as the Nasalfent and IRMS episode time to events could have been correlated within patient, time to event end points were analysed using a Cox model for multiple correlated events.

7.1.1.4.6. *Participant flow*



7.1.1.4.7. *Major protocol violations/deviations*

The protocol violations/deviations were: inappropriate use of study drug or inappropriate way of recording in e-diary (21 patients), missed or delayed assessments for certain visits (10 patients), missed entries or inappropriate way of filling BTCP questionnaire (9 patients), inappropriately filled ICF or use of wrong ICF version (6 patients), missed visits or visits outside the window period (4 patients) entry into study despite not satisfying inclusion/exclusion criteria (4 patients), missed telephone calls (3 patients), and returned drug did not match the episode data entered into the e-diary, delay in SAE report (1 patient each). Some patients reported more than one protocol deviation.

These deviations did not appear to confound results.

7.1.1.4.8. *Baseline data*

Table 21. Study CP044/06 – Baseline Data. Table continued across 2 pages.

mITT Population					
Summary of Subject Demographic Characteristics - Double-Blind. Double-Dummy Treatment Phase					
	100 mcg N=16	**200 mcg N=18**	**400mcg N=30**	**800mcg N=15**	**Total N=79**
Age (years) N	16	18	30	15	79
Mean (SD)	58.4 (10.38)	55.8 (12.20)	54.6 (12.50)	58.9 (10.89)	56.5 (11.66)
Standard Error	2.59	2.87	2.28	2.81	1.31
Median	58.5	57.5	56.5	61.0	58.0
Min -Max	41-76	39-79	32- 82	37-77	32- 82
Age (years)					
>60 years	7 (43.8)	5 (27.8)	10 (33.3)	8 (53.3)	30 (38.0)
≥ 60 years	9 (56.3)	13 (72.2)	20 (66.7)	7 (46.7)	49 (62.0)
Race N (%)					
Caucasian	5 (31.3)	9 (50.0)	12 (40.0)	8 (53.3)	30 (38.0)
Black	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Chinese / Japanese Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Southeast Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other - Indian	10 (62.5)	9 (50.0)	18 (60.0)	8 (53.3)	45 (57.0)

mITT Population					
Summary of Subject Demographic Characteristics - Double-Blind. Double-Dummy Treatment Phase					
Gender N (%)					
Male	6 (37.5)	10 (55.5)	17 (56.7)	10 (66.7)	43 (54.4)
Female	10 (37.5)	8 (44.4)	13 (43.3)	5 (33.3)	36 (45.6)
Weight (kg)					
N	16	18	30	15	79
Mean (SD)	51.1 (13.42)	60.5 (19.48)	59.6 (16.11)	61.3 (22.45)	58.4 (17.84)
Standard Error	3.36	4.59	2.94	5.80	2.01
Median	48.0	54.3	56.3	58.5	55.0
Min -Max	30.0-78.0	36.0-98.0	38.0-102.0	35.0-109.0	30.0-109.0
ECOG score[1]					
0	0 (0.0)	1 (5.6)	2 (6.7)	1 (6.7)	4 (5.1)
1	10 (62.5)	11 (61.1)	18 (60.0)	9 (60.0)	48 (60.8)
2	6 (37.5)	6 (33.3)	10 (33.3)	5 (33.3)	27 (34.2)
[1]ECOG =Eastern Cooperative Oncology group (ECOG) scores. Date of Reporting Dataset Creation: 15MAY2009.					

The demographics of the patients were similar during the double blind treatment phase (Phase 3) to those during the open, titration phase (Phase 2) and between the Safety population and the mITT population.

7.1.1.4.9. *Results for the primary efficacy outcome*

Results are given only for the mITT population. The results were similar for the PP population.

Pain Intensity Difference at 15minutes (PID_{15mins}) post dose

The mean PID at 15 minutes post dose was greater for Nasalfent-treated episodes (3.02) compared with IRMS treated episodes (2.69); the difference in treatments was statistically significant (p=0.0396). The treatment by centre interaction was not statistically significant.

A sensitivity analysis was done for PID at 15 minutes, calculated for the mITT population "as randomised" instead of "as treated". A similar statistically significant treatment difference (p=0.0071) was observed between Nasalfent and IRMS treated episodes in this population.

Table 22. Study CP044/06 - Primary Endpoint-PID at 15 Minutes Post Dose. Table continued across 2 pages.

mITT Population	
Treatment (N=79)	**Pain Intensity Difference at 15 Minutes**
Nasalfent	
Mean	3.02
SD	1.84
Standard Error	0.21
Median	2.60
Minimum	0.00
Maximum	8.00
IRMS	
Mean	2.69
SD	1.63
Standard Error	0.18
Median	2.40
Minimum	0.00
Maximum	7.80
P-values[1]	
Treatment	0.0396
Pooled Centre	0.2080
P-values[1]	Additional covariates
Treatment	0.0690
Pooled Centre	0.2345
Treatment Pooled Centre	0.0693
IRMS Dose Allocated or Previously Identified	0.8949
Indicator for Rescue Medication[2]	0.4204
Age Category	0.6622
Sequence	0.9714
SD = standard deviation; mITT = modified intent-to-treat; IRMS = immediate-release morphine sulphate	

Note: Pain Intensity Scores were recorded in an e-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'.

[1] P-values from the analysis of covariance (ANCOVA) model

[2] Indicator whether the patient has taken any rescue medication within 15 minutes for any mITT evaluable episode

7.1.1.4.10. *Results for other efficacy outcomes*

Mean PID values at 5, 10, 30, 45, and 60 minutes post dose

The mean PID was statistically greater for Nasalfent treated episodes than IRMS treated episodes in the mITT population at each observed time point from 15 to 60 minutes post dose (p≤0.0396), indicating a greater relief of pain following Nasalfent treatment.

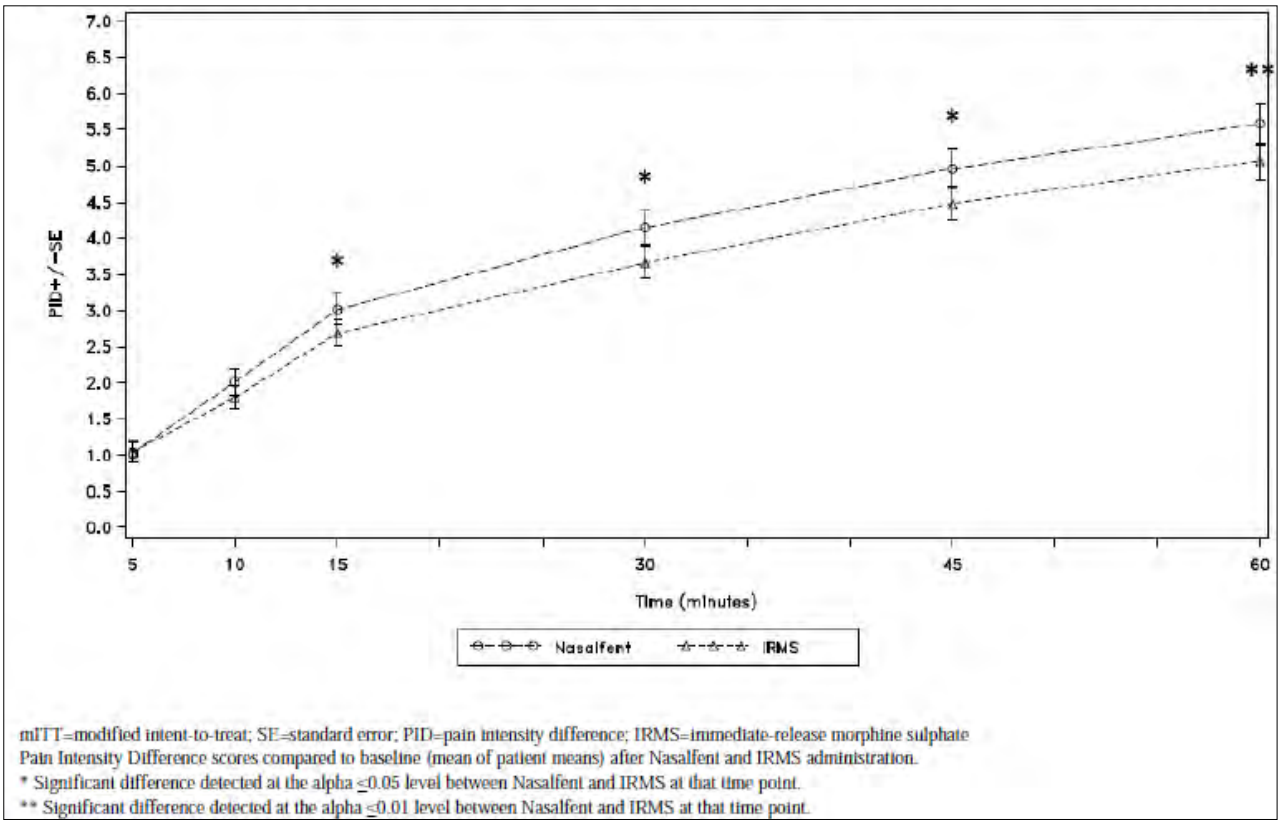
Table 23. Study CP044/06 - Mean PID values by Treatment and Time Point. Table continued across 2 pages.

mITT Population						
Treatment	**Mean PID Values at Different Time Points**					
(N = 79)	5 min	10 min	15 min	30 min	45 min	60min
Nasalfent						
Mean	1.04	2.02	3.02	4.15	4.96	5.59
SD	1.19	1.55	1.84	2.14	2.35	2.53
Standard Error	0.13	0.17	0.21	0.24	0.26	0.28
Median	0.80	1.60	2.60	4.20	5.20	5.80
Minimum	-0.20	-0.20	0.00	0.00	0.00	0.00
Maximum	6.80	7.80	8.00	9.40	9.60	9.60
IRMS						
Mean	1.05	1.80	2.69	3.66	4.48	5.07
SD	1.27	1.39	1.63	1.95	2.06	2.28
Standard Error	0.14	0.16	0.18	0.22	0.23	0.26
Median	0.60	1.40	2.40	3.60	4.20	5.00
Minimum	-0.25	0.00	0.00	0.00	0.60	0.60
Maximum	7.40	7.60	7.80	9.00	9.80	9.80
P-values						
Treatment	0.8986	0.0844	0.0396	0.0141	0.0130	0.0036
Pooled Centre	0.2071	0.3978	0.2080	0.0069	<0.0001	<0.0001

mITT = modified intent-to-treat; SD = standard deviation; min = minute; PID = pain intensity difference; IRMS = immediate release morphine sulphate. Note: Pain Intensity Scores were recorded in an e-diary on a rating scale of 0

to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'. [1] P-values were obtained from an ANCOVA model performed separately at each time point

Figure 4. Study CP044/06 - Mean PID Values at 5, 10, 30, 45 and 60 Minutes. mITT population.



mITT=modified intent-to-treat; SE=standard error; PID=pain intensity difference; IRMS=immediate-release morphine sulphate
Pain Intensity Difference scores compared to baseline (mean of patient means) after Nasalfent and IRMS administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and IRMS at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and IRMS at that time point.

Mean SPID at 10, 15, 30, 45 and 60 minutes post dose

The mean SPID difference between Nasalfent and IRMS treated episodes was statistically significant at 45 minutes (p=0.0331) and 60 minutes post dose (p=0.0191) but not at 30 minutes (p=0.0566).

Table 24. Study CP044/06 - Mean Values of SPID by Treatment and Time Point.

mITT Population						
Treatment	**Mean SPID Values at Different Time Points**					
(N=79)	5 min	10 min	15 min	30 min	45 min	60 min
Nasalfent						
Mean	1.04	3.05	6.07	10.22	15.18	20.77
SD	1.19	2.64	4.33	6.17	8.16	10.31
Standard Error	0.13	0.30	0.49	0.69	0.92	1.16
Median	0.80	2.40	4.80	9.00	14.80	21.40
Minimum	-0.20	-0.40	-0.40	0.40	1.00	1.00
Maximum	6.80	14.60	22.60	30.40	38.60	47.00
IRMS						
Mean	1.05	2.85	5.54	9.21	13.69	18.76
SD	1.27	2.56	4.02	5.67	7.31	9.21
Standard Error	0.14	0.29	0.4 5	0.64	0.82	1.04
Median	0.60	2.20	4.75	8.00	12.60	17.20
Minimum	-0.25	0.00	0.00	0.40	1.00	1.60
Maximum	7.40	15.00	22.60	30.20	37.80	46.80
P-values						
Treatment	0 .8986	0.3177	0.1325	0.0566	0.0331	0.0191
Pooled Centre	0.2071	0.3241	0.3593	0.2026	0.0551	0.0112

SPID = summed pain intensity difference; mITT = modified intent-to-treat; min = minute; IRMS = immediate release morphine sulphate; SD = standard deviation. Note: Pain Intensity Scores were recorded in ane-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain.'[1]P-values were obtained from an ANCOVA model performed separately at each time point.

Mean PI scores at 5, 10, 15, 30, 45 and 60 minutes post dose

The mean baseline PI scores for Nasalfent and IRMS treated episodes were statistically different (7.76 vs 7.65, respectively, p=0.027). The mean PI score was lower for Nasalfent treated episodes than for IRMS treated episodes at all subsequent time points after 10 minutes. The difference was statistically significant at the 30 minute time point (p=0.0456), and this effect increased over the subsequent time points (45 to 60 minutes post dose), and the differences

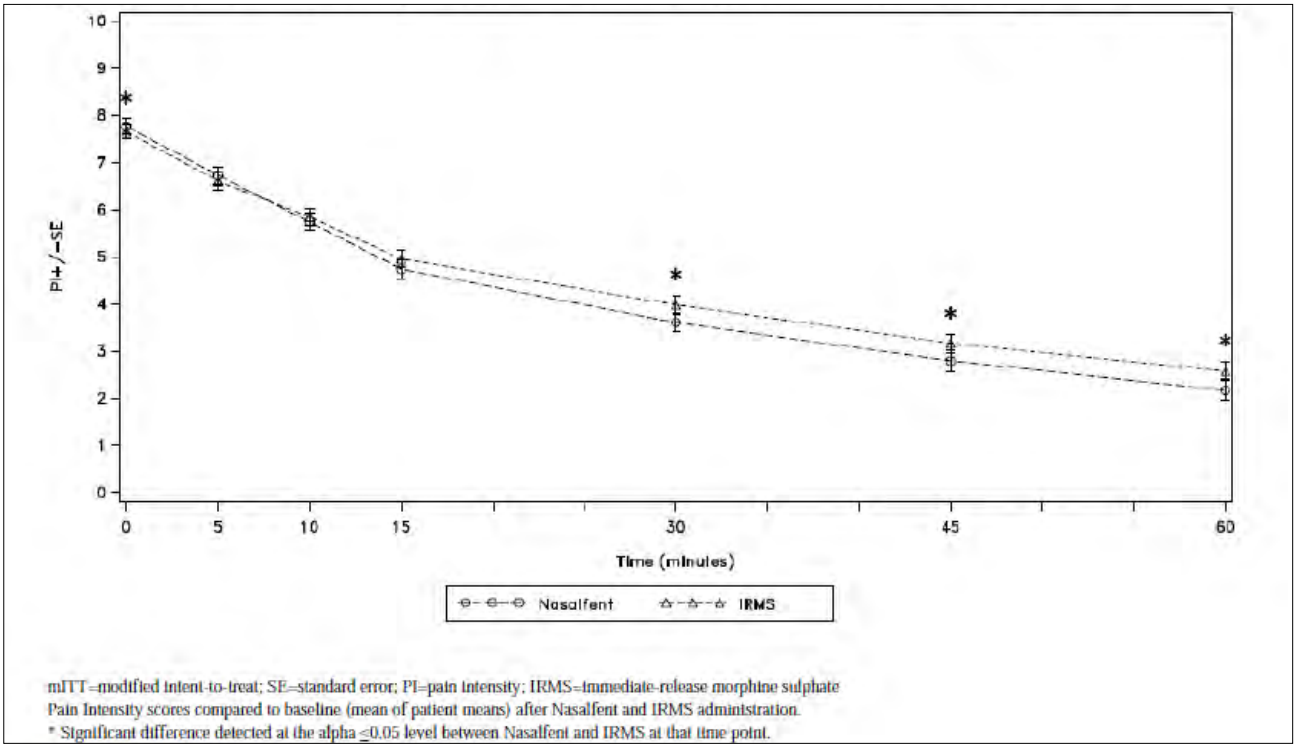
between PI scores were statistically significant (p≤0.0401) between treatments at all these time points.

Table 25. Study CP044/06 - Mean PI Scores by Treatment and Time Point

mITT Population							
Treatment	**Mean PI Scores at Different Time Points**						
N=79							
Nasalfent	**Baseline**	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Mean	7.76	6.72	5.74	4.74	3.61	2.79	2.17
SD	1.42	1.63	1.65	1.72	1.86	1.96	2.05
Standard Error	0.16	0.18	0.19	0.19	0.21	0.22	0.23
Median	8.00	7.00	6.00	5.20	3.60	2.40	1.40
Minimum	2.60	1.80	1.00	0.60	0.00	0.00	0.00
Maximum	10.00	0.00	9.00	8.00	9.00	8.00	7.00
IRMS							
Mean	7.65	6.60	5.85	4.95	3.98	3.16	2.57
SD	1.37	1.60	1.60	1.55	1.69	1.68	1.82
Standard Error	0.15	0.18	0.18	0.17	0.19	0.19	0.20
Median	8.00	7.00	6.20	5.20	4.20	3.20	2.40
Minimum	2.80	1.20	1.00	0.40	0.00	0.00	0.00
Maximum	9.80	9.20	8.20	7.60	8.00	7.00	7.40
P-values							
Treatment	0.0270	0.2253	0.3778	0.1464	0.0456	0.0401	0.0152
Pooled Centre	0.0017	0.0002	0.0071	0.1813	0.5559	0.0723	0.0110

mITT = modified intent-to-treat; SD = standard deviation; min = minute; PI = pain intensity; IRMS = immediate release morphine sulphate. Note: Pain Intensity Scores were recorded in an e-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'. 1P-values were obtained from an ANCOVA model performed separately at each time point.

Figure 5. Study CP044/06 - Mean PI scores at 5, 10, 15, 30, 45 and 60 Minutes Post Dose. mITT population.



Mean PR scores at 5, 10, 15, 30, 45 and 60 minutes post dose

The mean PR score was greater after Nasalfent administration than after IRMS administration at all observed time points. The difference was statistically significant at time points from 30 to 60 minutes ($p \leq 0.0050$).

Table 26. Study CP044/06 - Mean PR Scores by Treatment and Time Point.

mITT Population						
Treatment	**Mean PR Scores at Different Time Points**					
(N=79)	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Nasalfent						
Mean	0.90	1.38	1.84	2.46	2.84	3.14
SD	0.83	0.80	0.86	0.86	0.87	0.88
Standard Error	0.09	0.09	0.10	0.10	0.10	0.10
Median	0.80	1.20	1.80	2.50	3.00	3.25
Minimum	0.00	0.00	0.00	0.00	0.00	1.00
Maximum	3.50	3.50	3.80	4.00	4.00	4.00
IRMS						
Mean	0.83	1.27	1.68	2.17	2.53	2.86
SD	0.89	0.88	0.90	0.93	0.90	0.90
Standard Error	0.10	0.10	0.10	0.11	0.10	0.10
Median	0.60	1.00	1.60	2.23	2.78	3.00
Minimum	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	4.00	4.00	4.00	4.00	4.00	4.00
P-values						
Treatment	0.1924	0.0686	0.0731	0.0050	0.0014	0.0024
Pooled Centre	0.0057	0.0275	0.3215	0.1365	0.0239	0.0045

mITT = modified intent-to-treat; SD = standard deviation; PR = pain relief; IRMS = immediate release morphine sulphate; min = minute. Note: Pain relief scores were recorded in an e-diary using a 5-point scale (0 none to 4 complete). [1] P-values were obtained from an ANCOVA model performed separately at each time point

Mean TOTPAR scores at 10, 15, 30, 45 and 60 minutes post dose

The mean TOTPAR difference between Nasalfent and IRMS treated episodes was statistically significant at 15 minutes post dose and at each of the subsequent observed time points ($p \leq 0.0350$). The mean TOTPAR values by pooled centre were statistically significant at 5, 10 and 15 minutes (p-values 0.0057, 0.0095 and 0.0357 respectively), indicating the pooled centre

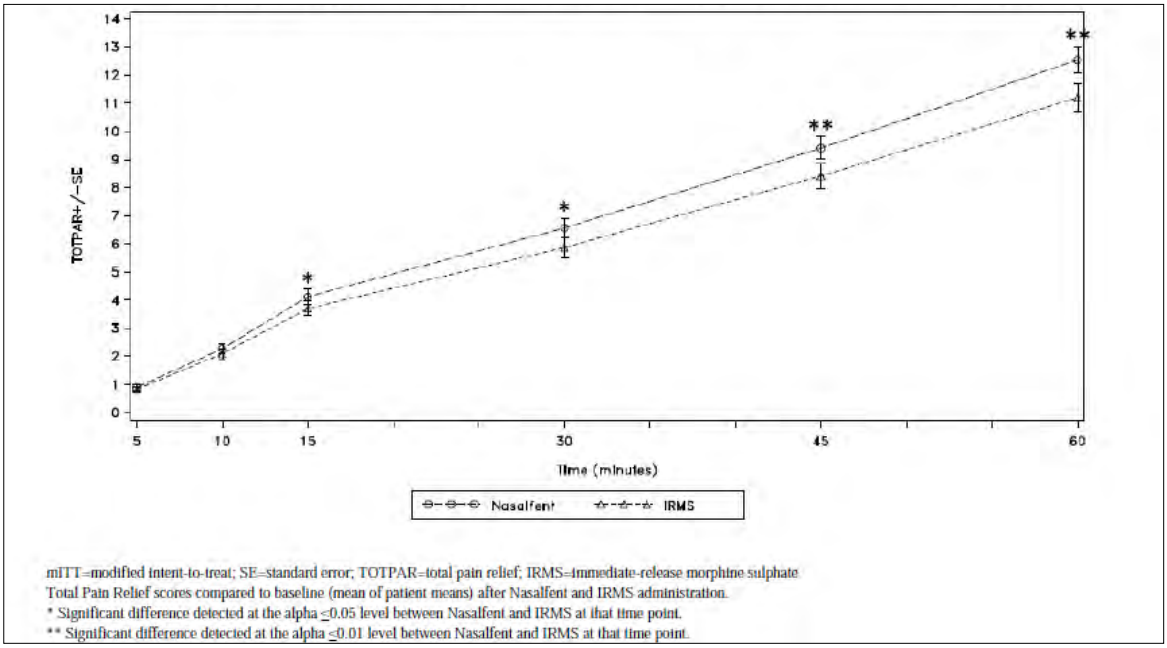
related differences influence the comparison. The differences between treatment groups increased over time in the mITT population. This suggests that the significantly greater decreases in PI reported by patients following Nasalfent treatment compared to IRMS are consistently reflected in the onset of perceived pain relief.

Table 27. Study CP044/06 - Mean TOTPAR Scores by Treatment and Time Point

mITT Population						
Treatment	Mean TOTPAR Scores at Different Time points					
(N=79)	5 min	10 min	15 min	30min	45 min	60 min
Nasalfent						
Mean	0.90	2.28	4.11	6.57	9.40	12.54
SD	0.83	1.56	2.29	2.94	3.56	4.18
Standard Error	0.09	0.18	0.26	0.33	0.40	0.47
Median	0.80	2.00	3.60	5.80	9.00	12.60
Minimum	0.00	0.00	0.00	1.00	2.10	3.10
Maximum	3.50	7.00	10.50	14.50	18.50	22.50
IRMS						
Mean	0.83	2.10	3.70	5.88	8.41	11.20
SD	0.89	1.70	2.34	3.10	3.81	4.46
Standard Error	0.10	0.19	0.26	0.35	0.43	0.51
Median	0.60	1.80	3.10	5.60	8.55	11.80
Minimum	0.00	0.00	0.00	0.00	0.20	0.40
Maximum	4.00	8.00	11.20	15.00	19.00	23.00
P-values						
Treatment	0.1924	0.0554	0.0350	0.0121	0.0048	0.0027
Pooled Centre	0.0057	0.0095	0.0357	0.0680	0.0894	0.0795

mITT = modified intent-to-treat; SD = standard deviation; TOTPAR = total pain relief; IRMS = immediate release morphine sulphate; min = minute. Note: Pain relief scores were recorded in an e-diary using a 5-point scale (O=none to 4=complete). 1 P-values were obtained from an ANCOVA model performed separately at each time point.

Figure 6. Study CP044/06 – Mean TOTPAR Score 5 to 60 Minute Post Dose. mITT population



mITT=modified intent-to-treat; SE=standard error; TOTPAR=total pain relief; IRMS=immediate-release morphine sulphate
Total Pain Relief scores compared to baseline (mean of patient means) after Nasalfent and IRMS administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and IRMS at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and IRMS at that time point.

Patient acceptability scores at 30 and 60 minutes post dose

The overall mean acceptability assessment score was significantly greater for Nasalfent as compared with IRMS at 30 minutes post dose (2.91 vs 2.64, p<0.0088) and at 60 minutes post dose (3.01 vs 2.73, p<0.0113). The mean assessment scores for the relief of pain and the episode reliability of the nasal spray also favoured Nasalfent over IRMS at both 30 and 60 minutes, with statistically significant differences evident at both time points (p≤0.0126). In addition, the sensitivity analysis of patient averaged overall acceptability, speed of relief, and reliability of nasal spray assessments demonstrated statistically significant differences between the treatments in favour of Nasalfent at both 30 and 60 minutes post dose (p≤0.0151).

Table 28. Study CP044/06 - Patient-Averaged Acceptability Assessments: Summary Statistics. Table continued across 2 pages.

mITT Population					
Question	**Time point**	**Acceptability Assessment score[1]**	**Nasalfent N=79**	**IRMS N=78**	**P-value[2]**
How satisfied are you overall with the nasal spray you have used to treat this episode of BTCP?	30min	N	79	78	0.0088
		Mean (SD)	2.91 (0.521)	2.64 (0.572)	
		Standard Error	0.059	0.065	
		Median	3.00	2.80	
		Min, Max	1.8, 4.0	1.0, 4.0	
	60 min	N	79	77	0.0113
		Mean (SD)	3.01 (0.508)	2.73 (0.564)	

mITT Population					
Question	**Time point**	**Acceptability Assessment score[1]**	**Nasalfent N=79**	**IRMS N=78**	**P-value[2]**
		Standard Error	0.057	0.064	
		Median	3.00	3.00	
		Min, Max	1.8, 4.0	1.2, 4.0	
How satisfied are you with the speed of relief you gained with the spray in the treatment of this episode of BTCP?	30min	N	79	78	0.0037
		Mean (SD)	2.92 (0.544)	2.62 (0.604)	
		Standard Error	0.061	0.068	
		Median	3.00	2.80	
		Min, Max	1.4, 4.0	1.0, 4.0	
	60 min	N	79	77	0.0068
		Mean (SD)	3.01 (0.552)	2.72 (0.574)	
		Standard Error	0.062	0.065	
		Median	3.00	3.00	
		Min, Max	1.8, 4.0	1. 2, 4.0	
How satisfied are you with the reliability of the nasal spray in the treatment of this episode of BTCP?	60min	N	79	77	0.0126
		Mean (SD)	3.03 (0.503)	2.74 (0.570)	
		Standard Error	0.057	0.065	
		Median	3.00	3.00	
		Min, Max	2.0, 4.0	1.2, 4.0	

mITT = modified intent-to-treat; SD = standard deviation; BTCP = breakthrough cancer pain; Min = minimum; Max = maximum; min = minute; IRMS = immediate release morphine sulphate. [1]Acceptability assessment score was recorded as 1 (not satisfied), 2 (not satisfied or dissatisfied), 3 (satisfied) and 4 (very satisfied). [2]P-value from Wilcoxon rank sum test to compare Nasalfent and IRMS treatments

- Patient level end points

Mean reduction in PI score at ≥1 and ≥2 at 5, 10, 15, 30, 45, and 60 minutes post dose

The number of patients with a mean reduction in the PI score ≥1 was similar for both treatments at each time point from 5 to 60 minutes after dosing. There was a statistically significantly higher number of patients with a mean reduction in PI score of ≥2 after administration of Nasalfent compared with administration of IRMS at 15 minutes post dose (p=0.0290) but not at subsequent time points.

Mean SPID values of ≥2, ≥3 and ≥4 at 10, 15, 30, 45, and 60 minutes post dose

The number of patients with mean SPID values of ≥2, ≥3 and ≥4 was similar for both treatments at each time point from 10 to 60 minutes after dosing.

Reduction in PI score from baseline by ≥33%, ≥50%, and ≥66%, at 5, 10, 15, 30, 45, and 60 minutes post dose

The number of patients with a mean reduction in the PI scores of ≥33% was similar for both treatments at each time point from 5 minutes to 60 minutes after dosing, with no statistically significant differences observed between treatment groups. There was a statistically significantly higher number of patients with a mean reduction in PI score of ≥50% after administration of Nasalfent compared with IRMS at 15 and 30 minutes post dose ($p \leq 0.0499$). Similarly there was a statistically significantly higher number of patients with a mean reduction in PI score of ≥66% after administration of Nasalfent compared with IRMS at each time point from 30 to 60 minutes post dose ($p \leq 0.0455$).

Table 29. Study CP044/06 - Summary of Mean Reduction in PI Score by ≥33%, ≥50% and ≥66% by Treatment and Time Point

mITT Population						
Treatment	**Number (%) of Patients with Mean Reduction in PI Score ≥33%**					
(N=79)	**5 min**	**10 min**	**15 min**	**30min**	**45 min**	**60 min**
Nasalfent	6	20	44	63	67	68
	(7.6%)	(25.3%)	(55.7%)	(79.7%)	(84.8%)	(86.1%)
IRMS	7	17	40	57	65	70
	(8.9%)	(21.5%)	(50.6%)	(72.2%)	(82.3%)	(88.6%)
P-values[1]	0.6547	0.3657	0.3711	0.1088	0.4795	0.4795
Number (%) of Patients with Mean Reduction in PI Score ≥50%						
Nasalfent	1	11	22	44	54	59
	(1.3%)	(13.9%)	(27.8%)	(55.7%)	(68.4%)	(74.7%)
IRMS	2	7	14	34	50	57
	(2.5%)	(8.9%)	(17.7%)	(43.0%)	(63.3%)	(72.2%)
P-values[1]	0.3173	0.1025	0.0325	0.0499	0.2482	0.4795
Number {%) of Patients with Mean Reduction in PI Score ≥66%						
Nasalfent	1	2	8	25	42	50
	(1.3%)	(2.5%)	(10.1%)	(31.6%)	(53.2%)	(63.3%)
IRMS	1	1	6	17	29	42
	(1.3%)	(1.3%)	(7.6%)	(21.5%)	(36.7%)	(53.2%)
P-values[1]	1.0000	0.3173	0.4142	0.0455	0.0029	0.0455

mITT = modified intent-to-treat; PI = pain intensity; min = minute; IRMS = immediate-release morphine sulphate. [1]P-values from McNemar Test to compare Nasalfent and IRMS at each time point

PR scores at ≥1 and ≥2 at 5, 10, 15, 30, 45, and 60 minutes post dose

There were a slightly higher number of patients achieving PR scores ≥1 and ≥2 following administration of Nasalfent than following administration of IRMS at each observed time point from 5 to 60 minutes post dose. However, the difference was only statistically significant at 30 minutes for the number of patients achieving ≥2 PR score.

Achievement of %max TOTPAR of ≥33%, ≥50% and ≥66% at 10, 15, 30, 45, and 60 minutes post dose

Statistically significantly higher number of patients achieved %max TOTPAR of ≥33% following administration of Nasalfent than following IRMS at 45 minutes and 60 minutes post dose

(p≤0.0201). A statistically significantly higher number of patients achieved %max TOTPAR of ≥50% at 60 minutes following administration of Nasalfent than following IRMS (59.5% vs 48.1%, p=0.0455). No statistically significant difference was observed in the number of patients achieving %max TOTPAR of ≥66% after use of either treatment.

Table 30. Study CP044/06 – Number (%) of Patients Achieving %maxTOTPAR ≥33%, ≥50% and ≥66% by Treatment and Time Point

mITT Population					
Treatment	**Number(%) of Patients Achieving %maxTOTPAR ≥33%**				
(N=79)	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Nasalfent	27/79	36/79	52/79	66/79	68/79
	(34.2%)	(45. 6%)	(65.8%)	(83.5%)	(86.1%)
IRMS	22/79	30/78	43/78	50/78	57/77
	(27.8%)	(38.5%)	(55.1%)	(64.1%)	(74.0%)
P-values	0.0588	0.2513	0.0593	0.0001	0.0201
Number(%) of Patients Achieving %maxTOTPAR ≥50%					
Nasalfent	12/79	16/79	23/79	31/79	47/79
	(15.2%)	(20.3%)	(29.1%)	(39.2%)	(59.5%)
IRMS	11/79	14/78	22/78	28/78	37/77
	(13.9%)	(17.9%)	(28.2%)	(35.9%)	(48.1%)
P-values[1]	0.3173	0.7055	1.0000	0.6374	0.0455
Number(%) of Patients Achieving %maxTOTPAR ≥66%					
Nasalfent	4/79	7/79	9/79	15/79	17/79
	(5.1%)	(8.9%)	(11.4%)	(19.0%)	(21.5%)
IRMS	4/79	4/78	6/78	10/78	11/77
	(5.1%)	(5.1%)	(7.7%)	(12.8%)	(14.3%)
P-values[1]	1.0000	0.3173	0.4142	0.2482	0.2482

mITT = modified intent-to-treat; TOTPAR = total pain relief; min = minute; IRMS = immediate release morphine sulphate

[1]P-values from McNemar Test to compare Nasalfent and IRMS at each time point

Mean Patient Acceptability Score of ≥2 and ≥3 at 30 and 60 Minutes Post Dose

At both 30 and 60 minutes post dose a greater number of patients reported a mean overall satisfaction score of ≥3 (satisfied to very satisfied) following administration with Nasalfent compared with IRMS (30 minutes: 51 [64.6%] vs 37 [47.4%], respectively, and at 60 minutes: 55 [69.6%] vs 44 [57.1%], respectively). Similar results were observed for the speed of relief and the episode reliability of nasal spray.

Rescue medication usage

There was no statistically significant difference in rescue medication usage between the two treatment groups. Although patients had been requested not to use rescue medication during the first 15 minutes unless absolutely necessary, a small number (3) did so in the Nasalfent

treated episodes. No patients took rescue medication during the first 15 minutes following IRMS treated episodes.

1. Episode level end points

In the mITT population there were 372 episodes treated with Nasalfent and 368 episodes treated with IRMS.

Episode pain intensity difference at 5, 10, 15, 30, 45, and 60 minutes post dose in each treatment group

The mean episode values of PID were greater following Nasalfent administration than following IRMS administration and the differences were statistically significant at each observed post dose time point from 10 to 60 minutes (p≤0.0432).

Table 31. Study CP044/06 - Episode Pain Intensity Difference (PID)

mITT Population						
Treatment	**Mean PID Values at Different Time Points**					
N=740	**5 min**	**10 min**	**15 min**	**30min**	**45 min**	**60 min**
Nasalfent						
N	372	372	372	372	372	372
Mean (SD)	1.07 (1.43)	2.06 (1.88)	3.09 (2.22)	4.26 (2.51)	5.09 (2.72)	5.73 (2.84)
IRMS						
N	368	368	368	368	368	368
Mean (SD)	1.01 (1.57)	1.81 (1.78)	2.71 (2.07)	3.69 (2.33)	4.54 (2.50)	5.13 (2.66);
P-values[1]	0.5993	0.0432	0.0022	<0.0001	<0.0001	<0.0001

mITT = modified intent-to-treat; PID = pain intensity difference; min = minute; IRMS = immediate release morphine sulphate; SD = standard deviation. [1]P-values from a multilevel model for binary data with random effects to compare Nasalfent vs. IRMS

All total episodes in each treatment group with a reduction in PI score of ≥1 and ≥2 from baseline at 5, 10, 15, 30, 45, and 60 minutes post dose

A significantly higher number of episodes with a reduction in PI score of ≥1 was observed following administration of Nasalfent compared with administration of IRMS at 5 minutes (p=0.0326) and 30 minutes post dose (p=0.0306) but not at 10 minutes (p=0.0616) or 15 minutes (p=0.1140). A significantly higher number of episodes with a mean reduction in PI score of ≥2 following administration of Nasalfent were also observed compared with administration of IRMS at 10 minutes (p=0.0181) and 15 minutes (p=0.0183) post dose.

Table 32. Study CP044/06 - Number (%) of Episodes with a Reduction in PI Score ≥1 and ≥2 from Baseline by Treatment and Time Point

mITT Population						
Treatment	**Mean PID Values at Different Time Points**					
(N=740)	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Number (%) of Episodes with Mean Reduction in PI Score ≥1						
Nasalfent	214/372	309/372	341/372	356/372	360/372	360/372
	(57.5%)	(83.1%)	(91.7%)	(95.7%)	(96.8%)	(96.8%)
IRMS	189/368	290/368	327/368	340/368	350/368	349/368
	(51.4%)	(78.8%)	(88.9%)	(92.4%)	(95.1%)	(94.8%)
P-values[1]	0.0326	0.0616	0.1140	0.0306	0.1900	0.1363
Number (%) of Episodes with Mean Reduction in PI Score ≥2						
Nasalfent	94/372	195/372	281/372	323/372	332/372	340/372
	(25.3%)	(52.4%)	(75.5%)	(86.8%)	(89.2%)	(91.4%)
IRMS	84/368	167/368	255/368	305/368	326/368	329/368
	(22.8%)	(45.4%)	(69.3%)	(82.9%)	(88.6%)	(89.4%)
P-values[1]	0.3021	0.0181	0.0183	0.0656	0.6791	0.2594

mITT = modified intent-to-treat; PI = pain intensity; min = minute; IRMS = immediate release morphine sulphate.

[1] P-values from a multilevel model for binary data with random effects to compare Nasalfent vs. IRMS.

All total treated episodes in each treatment group with mean SPID values of ≥2, ≥3, and ≥4 at 10, 15, 30, 45, and 60 minutes post dose

Statistically significant differences were observed between treatments in the number of episodes with mean SPID value of ≥2, with more episodes achieving this threshold following Nasalfent treatment than following IRMS treatment at 10 minutes and 45 minutes post dose ($p \leq 0.0398$); the Nasalfent treated episodes also had greater numbers of episodes with mean SPID value of ≥3 at 10 minutes and 15 minutes ($p \leq 0.0348$) and ≥4 at each time point from 10 to 30 minutes post dose ($p \leq 0.0338$).

Table 33. Study CP044/06 - Episodes with SPID (Episode SPID) Scores ≥2, ≥3, and ≥4

mITT Population					
Treatment	**Number (%) of Episodes with Mean SPID Score ≥2**				
(N =740)	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
Nasalfent	241/372	322/372	347/372	3611372	361/372
	(64.8%)	(86.6%)	(93.3%)	(97.0%)	(97.0%)
IRMS	213/368	306/368	335/368	347/368	350/368
	(57.9%)	(83.2%)	(91.0%)	(94.3%)	(95.1%)
P-values[1]	0.0146	0.0972	0.1613	0.0398	0.1233
Number (%) of Episodes with Mean SPID Score >3					
Nasalfent	174/372	289/372	336/372	349/372	360/372
	(46.8%)	(77.7%)	(90.3%)	(93.8%)	(96.8%)
IRMS	150/368	260/368	322/368	342/368	348/368
	(40.8%)	(70.7%)	(87.5%)	(92.9%)	(94.6%)
P-values[1]	0.0348	0.0064	0.1208	0.5067	0.0870
Number (%) of Episodes with Mean SPID Score >4					
Nasalfent	124/372	242/372	324/372	343/372	356/372
	(33.3%)	(65.1%)	(87.1%)	(92.2%)	(95.7%)
IRMS	102/368	209/368	302/368	338/368	345/368
	(27.7%)	(56.8%)	(82.1%)	(91.8%)	(93.8%)
P-values[1]	0.0338	0.0043	0.0196	0.7474	0.1558

mITT = modified intent-to-treat; SPID = summed pain intensity difference; min = minute; IRMS = immediate release morphine sulphate. [1] P-values from a multilevel model with random effects to compare Nasalfent vs. IRMS

All total treated episodes in each treatment group with ≥33%, ≥50%, and ≥66%, reduction in PI score from baseline to 5, 10, 15, 30, 45, and 60 minutes post dose

The number of treated episodes with a ≥33% reduction in PI score from baseline was significantly larger following Nasalfent compared with IRMS at 10 minutes and 15 minutes post dose (p≤0.0357). Similar results were observed using the thresholds of ≥50% reduction in PI score from baseline at 15 and 30 minutes (p≤0.0019) and using the thresholds of 66% reduction in PI score from baseline at 30, 45 and 60 minutes post dose (p≤0.0008).

Table 34. Study CP044/06 – Number (%) of Episodes with Reductions in the Pain Intensity Score ≥33%, ≥50% and ≥66% from Baseline by Treatment and Time Point

mITT Population						
Treatment	**Number (%) of Episodes with Mean Reduction in PI Score ≥33%**					
(N=740)	**5 min**	**10 min**	**15 min**	**30min**	**45 min**	**60 min**
Nasalfent	46/372	126/372	206/372	283/372	309/372	316/372
	(12.4%)	(33.9%)	(55.4%)	(76.1%)	(83.1%)	(84.9%)
IRMS	47/368	104/368	174/368	269/368	299/368	314/368
	(12.8%)	(28.3%)	(47.3%)	(73.1%)	(81.3%)	(85.3%)
P-values[1]	0.9230	0.0357	0.0056	0.1999	0.3571	0.9564
Number (%) of Episodes with Mean Reduction in PI Score ≥50%						
Nasalfent	20/372	66/372	137/372	225/372	263/372	282/372
	(5.4%)	(17. 7%)	(36.8%)	(60.5%)	(70.7%)	(75.8%)
IRMS	19/368	56/368	105/368	178/368	247/368	278/368
	(5.2%)	(15.2%)	(28.5%)	(48.4%)	(67.1%)	(75.5%)
P-values1	0.8010	0.1999	0.0019	<0.0001	0.0943	0. 7073
Number (%) of Episodes with Mean Reduction in PI Score ≥66%						
Nasalfent	7/372	24/372	62/372	129/372	202/372	247/372
	(1.9%)	(6.5%)	(16.7%)	(34. 7%)	(54.3%)	(66.4%)
IRMS	11/368	22/368	50/368	95/368	154/368	205/368
	(3.0%)	(6.0%)	(13.6%)	(25.8%)	(41.8%)	(55.7%)
P-values[1]	0.2376	0.6616	0.1189	0.0008	<0.0001	<0.0001

mITT = modified intent-to-treat; PI = pain intensity; min = minute; IRMS = immediate release morphine sulphate

[1]P-values from a multilevel model for binary data with random effects to compare Nasalfent vs. IRMS

Episodes with no increase in PI at any time point compared to baseline

98.4% (366/372) episodes following Nasalfent treatment and 96.7% (356/368) episodes following IRMS treatment were not associated with an increase in PI at any observed time point after baseline.

Episodes achieving ≥1 and ≥2 PR scores at 5, 10, 15, 30, 45, and 60 minutes post dose

A statistically significantly higher percentage of Nasalfent treated episodes compared with IRMS treated episodes achieved PR scores of ≥1 at 5, 10, and 30 minutes post dose (p≤0.0238) and ≥2 at 15, and 30 minutes post dose (p≤0.0181).

Table 35. Study CP044/06 - Number (%) of Episodes Achieving aPR Score of ≥1 and ≥2 by Treatment and Time Point

mITT Population						
Treatment	**Number(%) of Episodes Achieving PR Score ≥1**					
(N=740)	**5 min**	**10 min**	**15 min**	**30min**	**45 min**	**60 min**
Nasalfent	227/312	304/371	330/367	346/363	342/351	345/351
	(61.0%)	(81.9%)	(89.9%)	(95.3%)	(95.8%)	(96.6%)
IRMS	190/368	276/365	312/363	333/364	341/362	337/356
	(51.6%)	(75.6%)	(86.0%)	(91.5%)	(94.2%)	(94.7%)
P-values[1]	0.0009	0.0110	0.0508	0.0238	0.2812	0.2333
Number (%) of Episodes Achieving PR Score ≥2						
Nasalfent	75/312	146/371	221/367	299/363	312/351	326/351
	(20.2%)	(39.4%)	(60.2%)	(82.4%)	(87.4%)	(91.3%)
IRMS	74/368	127/365	194/363	260/364	302/362	311/356
	(20.1%)	(34.8%)	(53.4%)	(71.4%)	(83.4%)	(87.4%)
P-values[1]	0.9782	0.1125	0.0181	<0.0001	0.0629	0.0695

mITT = modified intent-to-treat; PR = pain relief; min = minute; IRMS = immediate release morphine sulphate. [1]P-values from a multilevel model for binary data with random effects to compare Nasalfent vs. IRMS

Number and percentage of episodes in each treatment group with a %maxTOTPAR of ≥33%, ≥50% and ≥66% at 10, 15, 30, 45, and 60 minutes post dose

Statistically significantly more episodes achieved %maxTOTPAR of ≥33% at each observed time point from 15 to 60 minutes post dose following Nasalfent administration compared to IRMS ($p \leq 0.0111$), and at 45 and 60 minutes post dose for episodes achieving %maxTOTPAR of ≥50% ($p \leq 0.0016$). There was no significant difference in the percentage of episodes achieving %maxTOTPAR of ≥66%.

Table 36. Study CP044/06 - Number (%) of Episodes Achieving a PR Score of ≥1 and ≥2 by Treatment and Time Point

mITT Population						
Treatment	**Number(%) of Episodes Achieving PR Score ≥1**					
(N=740)	**5 min**	**10 min**	**15 min**	**30min**	**45 min**	**60 min**
Nasalfent	227/312	304/371	330/367	346/363	342/351	345/351
	(61.0%)	(81.9%)	(89.9%)	(95.3%)	(95.8%)	(96.6%)
IRMS	190/368	276/365	312/363	333/364	341/362	337/356
	(51.6%)	(75.6%)	(86.0%)	(91.5%)	(94.2%)	(94. 7%)
P-values[1]	0.0009	0.0110	0.0508	0.0238	0.2812	0.2333
Number (%) of Episodes Achieving PR Score ≥2						
Nasalfent	75/312	146/371	221/367	299/363	312/351	326/351
	(20.2%)	(39.4%)	(60.2%)	(82.4%)	(87.4%)	(91.3%)
IRMS	74/368	127/365	194/363	260/364	302/362	311/356
	(20.1%)	(34.8%)	(53.4%)	(71.4%)	(83.4%)	(87.4%)
P-values[1]	0.9782	0.1125	0.0181	<0.0001	0.0629	0.0695

mITT = modified intent-to-treat; PR = pain relief; min = minute; IRMS = immediate release morphine sulphate. [1] P-values from a multilevel model for binary data with random effects to compare Nasalfent vs. IRMS

Total treated episodes in each treatment group with episode acceptability scores of ≥2 and ≥3 at 30 and 60 minutes post dose

Nasalfent spray had a higher incidence of better acceptability scores per episode compared to IRMS spray. In the categorical analysis, at 30 and 60 minutes post dose, the number of episodes with episode acceptability scores ≥3 (satisfied to very satisfied) was greater following treatment with Nasalfent than following treatment with IRMS (30 minutes: 303/363 [83.5%] vs 262/364 [72.0%], respectively, and 60 minutes: 312/357 [87.4%] vs 269/356 [75.6%], respectively). Similar results were observed for the speed of relief and episode reliability of nasal spray analysis and in the sensitivity analysis, which excluded episodes with rescue medication.

Episode rescue medication usage

The proportion of episodes requiring the use of rescue medication was not statistically significantly different (p=0.5715) in Nasalfent treated episodes compared with IRMS treated episodes (3.0% vs 3.8%, respectively) from 0 – 60 minutes after treatment. A small number of patients used rescue medication prior to 15 minutes post dose despite having been requested not to do so unless absolutely necessary (4 [1.1%] Nasalfent treated episodes and no IRMS

treated episode). Rescue medication was required for 1 episode following Nasalfent treatment and for 2 episodes following IRMS treatment from 1 to 4 hours post dose.

Episode time to achieve ≥33%, ≥50%, ≥66% reduction in PI score within 30 and 60 minutes post dose

Over 77% of the total episodes reached a ≥33% in PI within 30 minutes of Nasalfent administration compared with 74% of the total episodes following IRMS administration. The mean episode time to a ≥33% reduction was 16.1 minutes following Nasalfent and 17.5 minutes following IRMS (hazard ratio 1.205; 95% CI: 1.022 – 1.420; p=0.0263). Censorship of the episode data was high. Similar results were observed for ≥50% and ≥66% reductions in PI score within 30 minutes post baseline with significant hazard ratios (p=0.0047 and p=0.0196 respectively).

When the time interval of observation was increased to 60 minutes post dose. 87.9% of the total episodes reached a ≥33% reduction in PI following Nasalfent administration compared with 88.59% of the total episodes following IRMS administration. The mean episode time to a reduction ≥33% within 60 minutes was 19.8 minutes following Nasalfent and 22.8 minutes following IRMS; the difference was not statistically significant (hazard ratio 1.123; 95% CI: 0.975 – 1.294; p=0.1069). Similar results were observed for ≥50% reduction in PI score within 60 minutes post baseline. However, statistically significant results were observed for ≥66% reductions in PI score within 60 minutes post baseline (hazard ratio 1.342; 95% CI: 1.106 – 1.628; p=0.0.0263. Censorship of the episode data was high.

Table 37. Time to Episode Reduction in Pain Intensity Score ≥33%, ≥50%, and ≥66% within 30 Minutes. Table continued across 2 pages.

mITT Population		
	Nasalfent	**IRMS**
	N=372	**N=368**
Summary Statistics for Episodes with ≥33% reduction in PI Score within 30 Minutes		
N (%)	290 (77.96%)	273 (74.18%)
Mean (SD)	16.1 (9.18)	17.5 (9.83)
Standard Error	0.54	0.60
Median	15.0	15.0
Min	5	5
Max	30	30
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.19(0.084)	1.205(1.022-1.420)	0.0263
Summary Statistics for Episodes with ≥50% reduction in PI Score within 30 Minutes		
N (%)	233(62.63%)	185(50.27%)
Mean (SD)	19.1 (9.35)	19.0 (9.57)
Standard Error	0.61	0.70
Median	15.0	5.0
Min	5	5
Max	30	30
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.36(0.127)	1.430 (1.116-1.833)	0.0047
Summary Statistics for Episodes with ≥66% reduction in PI Score within 30 Minutes		
N (%)	136 (36.56%)	100 (27.17%)
Mean (SD)	21.9 (9.09)	20.8 (9.68)
Standard Error	0.78	0.97

mITT Population		
	Nasalfent	**IRMS**
Median	30.0	22.5
Min	5	5
Max	30	30
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.37(0.157)	1.442 (1.060-1.962)	0.0196

mITT = modified intent-to-treat; PI = pain intensity; HR = hazard ratio; CI = confidence interval; SD = standard deviation; SE = standard error; Min = minimum; Max = maximum; IRMS = immediate release morphine sulphate

[1] P-value is obtained from time to event endpoints survival analysis using a Cox model for multiple correlated events.

Episode time to achieve ≥1 and ≥2 pain relief score within 30 and 60 minutes post baseline

A higher percentage of episodes achieved a PR score of ≥1 within 30 minutes of administration of Nasalfent (97.6%) then IRMS (94.0%). The mean episode time to PR score ≥1 within 30 minutes was 8.33 minutes following Nasalfent and 8.99 minutes following IRMS (hazard ratio 1.423; 95% CI: 1.135 – 1.785; p=0.0023). For episodes associated with a PR score ≥1 within 60 minutes, time to relief was 8.81 minutes following Nasalfent and 10.17 minutes following IRMS (hazard ratio 1.418; 95% CI: 1.138 – 1.767; p=0.0.0018).

Table 38. Study CP044/06 - Episode Times to Pain Relief Score ≥1 and ≥2 within 30 Minutes and 60 Minutes Post Dose by Treatment. Table continued across 2 pages.

mITT Population		
	Nasalfent	**IRMS**
	N= 372	**N=368**
Summary Statistics for Episodes with PR Score ≥1 within 30 Minutes		
N (%)	363 (97.6%)	346 (94.0%)
Mean (SD)	8.33 (5.996)	8.99 (6.161)
Standard Error	0.315	0.331
Median	5.00	5.00
Min	5.0	5.0
Max	30.0	30.0
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.35 (0.116)	1.423 (1.135 - 1. 785)	0.0023
Summary Statistics for Episodes with PR Score ≥1 within 60 Minutes		
N (%)	367 (98. 7%)	356 (96. 7%)
Mean (SD)	8.81 (7.567)	10.17 (9.313)
Standard Error	0.395	0.494
Median	5.00	5.00
Min	5.0	5.0
Max	60.0	60.0
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.35 (0.112)	1.418 (1.138- 1.767)	0.0018
Summary Statistics for Episodes with PR Score ≥2 within 30 Minutes		
N (%)	319 (85.8%)	274 (74.5%)
Mean (SD)	15.33 (9.399)	14.84 (9.321)
Standard Error	0.526	0.563

mITT Population		
	Nasalfent	**IRMS**
Median	15.00	15.00
Min	5.0	5.0
Max	30.0	30.0
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.31 (0.102)	1.366 (1.117- 1.669)	0.0023
Summary Statistics for Episodes with PR Score ≥2 within 60 Minutes		
N (%)	349 (93.8%)	335 (91.0%)
Mean (SD)	18.35 (13.516)	21.04 (15.895)
Standard Error	0. 724	0.868
Median	15.00	15.00
Min	5.0	5.0
Max	60.0	60.0
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.25 (0.093)	1.285 (1.071- 1.541)	0.0070

mITT = modified intent-to-treat; PR = pain relief; HR = hazard ratio; CI = confidence interval; SD = standard deviation; SE=standard error; Min=minimum; Max=maximum; IRMS=immediate-release morphine sulphate. [1] P-value is obtained from time to event endpoints survival analysis using a Cox model for multiple correlated events.

Episode time to achieve total pain relief

A higher percentage of episodes were associated with total pain relief following Nasalfent (50.5%) administration than following IRMS (34.0%). The mean time for an episode to achieve total pain relief was 42.8 minutes following administration of Nasalfent and 40.9 minutes following IRMS (hazard ratio 1.602; 95% CI: 1.259 – 2.059; p=0.0001). Censorship of episode data for those episodes with a total pain relief score of 4 was high. It is noted that when interpreting survival analysis estimates care must be taken due to high censoring percentage. In the hazard ratio estimates are for Nasalfent vs. IRMS groups, when number of events is low, the validity of model assumptions is questionable.

Table 39. Study CP044/06 - Episode Times to Achieve Total Pain Relief by Treatment

mITT Population		
	Nasalfent	**IRMS**
	N=372	**N=368**
Summary Statistics for Episodes that Achieved Total Pain Relief		
N (%)	188 (50.5%)	125 (34.0%)
Mean (SD)	42.8 (16.46)	40.9 (18.08)
Standard Error	1.20	1.62
Median	45.0	45.0
Min	5	5
Max	60	60
Survival Analysis Estimates		
Estimate (SE)	**HR (95% CI)**	**P-value[1]**
0.47 (0.123)	**1.602 (1.259- 2.038)**	**0.0001**

mITT = modified intent-to-treat; SD = standard deviation; CI = confidence interval; HR = hazard ratio; SE = standard error; Min = minimum; Max = maximum; IRMS = immediate-re1ease morphine sulphate. [1] P-value is obtained from time to event endpoints survival analysis using a Cox model for multiple correlated events.

Time to rescue medication

The mean time to rescue medication was 24.9 minutes following Nasalfent treatment and 39.4 minutes following IRMS treatment (hazard ratio 1.1612; 95% CI: 0.484 – 2.782; difference not significant).

Breakthrough pain questionnaire

The mean number of breakthrough pain episodes per day was similar at Visit 4 (end of treatment) compared to Visit 1 (Screening); however, the number of patients reporting severe breakthrough pain episodes was lower at Visit 4 compared to Visit 1 (79.7% vs 74.0%).

Efficacy Conclusions

- The primary efficacy end point was the PID at 15 minutes post dose. With Nasalfent treatment the mean PID score was significantly higher than with IRMS treatment (3.02 vs 2.69, p=0.0396) indicating a higher degree of pain reduction with Nasalfent at 15 minutes
- The superiority of Nasalfent over IRMS appeared as early as 5 minutes after dosing in the episode based analyses, with statistically significant differences in the percentage of episodes showing a beneficial change in PI and PR scores following Nasalfent treatment than following IRMS (p=0.0326 and p=0.009 respectively)
- At the 10 minutes post dose the episode based analyses showed statistically significant differences in a range of end points:
  - PID (p=0.0432)
  - Percentage of episodes with≥1 point improvement in PR (p=0.011)
  - Percentage of episodes with≥2 point improvement in PI (p=0.0181)
  - Percentage of episodes with≥33% improvement in PI (p=0.0357)

7.1.2. Other efficacy studies

7.1.2.1. *Study 041/04: Summary*

7.1.2.1.1. *Objectives*

To determine the efficacy, acceptability to patients and safety and tolerability of the pectin formulation of nasal fentanyl solution for the relief of breakthrough pain in cancer patients.

7.1.2.1.2. *Methodology*

Design: this is a phase 2, open label, non-comparative, multi-centre, in-patient study conducted at 3 centres in Canada from July 2004 to January 2006.

Patients were dosed with a nasal fentanyl solution for up to a maximum of 7 episodes of breakthrough pain. Pain relief and pain intensity were assessed by the patient. The study was conducted in two parts. Part 1 involved a dose escalation sequence to identify the efficacious dose. Part 2 used the efficacious dose from Part 1 for 4 episodes of breakthrough pain.

Entry criteria: the main inclusion criteria were:

- Pain due to cancer requiring the use of strong opioids regularly and as required to relieve episodes of breakthrough pain
- Breakthrough pain of at least moderate severity (pain score ≥2 on 5 point scale)
- Subjects were inpatients aged over 18 years of age and well enough to participate

The main exclusion criteria were known tolerance to opioids and/or presence of history of nasal problems including polyps, congestion of nasal obstruction.

Treatments: The patients were dosed using the following regimen:

Table 40. Study 041/04 Dosing Regimen

Episode of BTP	Strength Used	1st Dose	2nd Dose	3rd Dose	Max Cumulative Dose
Ist BTP	0.25 mg/mL	25 µg	25 µg	50 µg	100 µg
2nd BTP	1.0 mg/mL	100 µg	100 µg	200 µg	400 µg
3rd BTP	4.0 mg/mL	400 µg	400 µg	-	800 µg
4th -·7th	Use the effective dose attained in Part I (Ist - 3rd BTP)				

Data collection and analysis: Pain intensity was assessed using a 5 point scale and pain relief using a 9 point scale. Safety was assessed by reported adverse events.

"Effective" relief of breakthrough pain was assessed by:

- Reduction in the pain score
- Time to meaningful pain relief
- Onset of pain relief
- Duration of pain relief

Pain intensity and pain relief were recorded at regular intervals for up to 4 hours after dosing. The secondary measures were nasal and other symptom scores (eg levels of sedation, giddiness, nausea) collected as reported for 4 hours after dosing in Part 2 and an overall satisfaction rating.

7.1.2.1.3. *Study participants*

Planned: up to 40 patients to allow a minimum of 20 to complete the study.

Enrolled: 29 patients were consented and 23 started Part 1, 18 completed Part 1. 3 obtained no pain relief at highest dose (800 µg). 15 patients entered Part 2 but 3 failed to complete all 4 episodes of BTCP required in the assessment. These 3 patients were included in efficacy assessment.

Completed: 12 patients completed all 4 assessments in Part 2. 55 episodes of BTCP in 15 patients were included in efficacy assessment.

Analysed: 15 patients were analysed for efficacy and all 23 dosed patients were considered for safety.

The study intended to complete 20 patients. However, the study was stopped by the sponsor prior to its scheduled completion. No explanation is provided for why the study was stopped.

The demographic data for the 15 patients who were included in the efficacy data were:

- Age: 59 ± 9 yrs (range 43-75 yrs, median 61 yrs)
- Race: 13 Caucasian (86.7%), 2 Native (13.3%)
- Gender: 8 female (53.3%) and 7 male (46.7%)

7.1.2.1.4. *Results*

Analysis of run-in dose-response (Part 1)

All doses of nasal fentanyl were effective in at least one patient. The following represents the frequency of the successful dose for each of the patients in the data set.

Table 41. Study 041/04 – Part 1 Dose Response

Dose	Frequency	% of Total	Cumulative %
25 µg	3	20.00%	20.00%
50 µg	3	20.00%	40.00%
100 µg	1	6.67%	46.67%
200 µg	2	13.33%	60.00%
400 µg	4	26.67%	86.67%
800 µg	2	13.33%	100.00%

At their individual selected dose, all 15 patients analysed for efficacy experienced meaningful pain relief.

Figure 7. Study 041/04 – Mean Patient PID compared to baseline Population: Efficacy

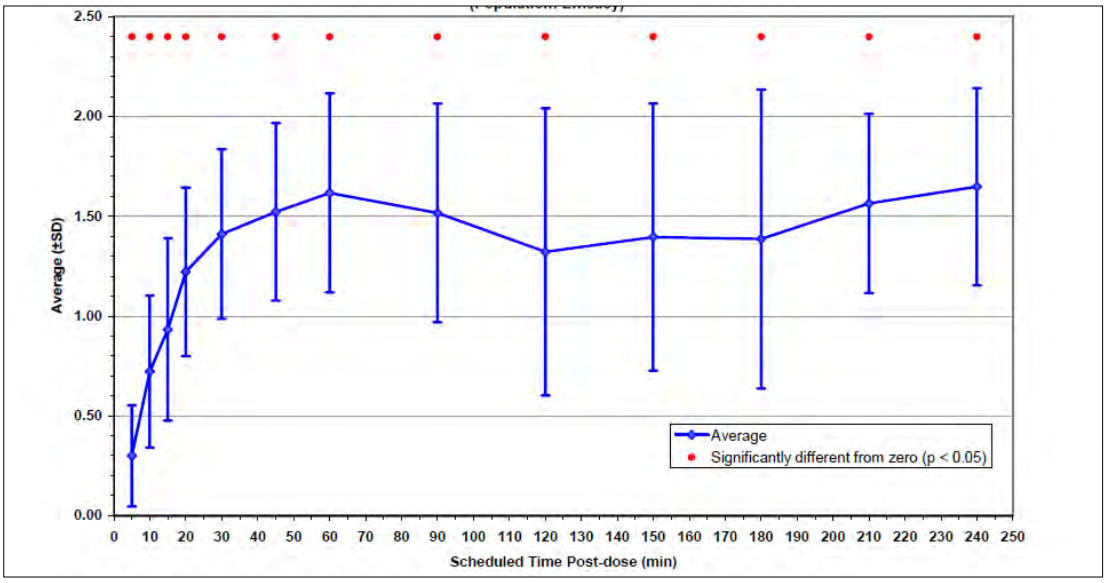
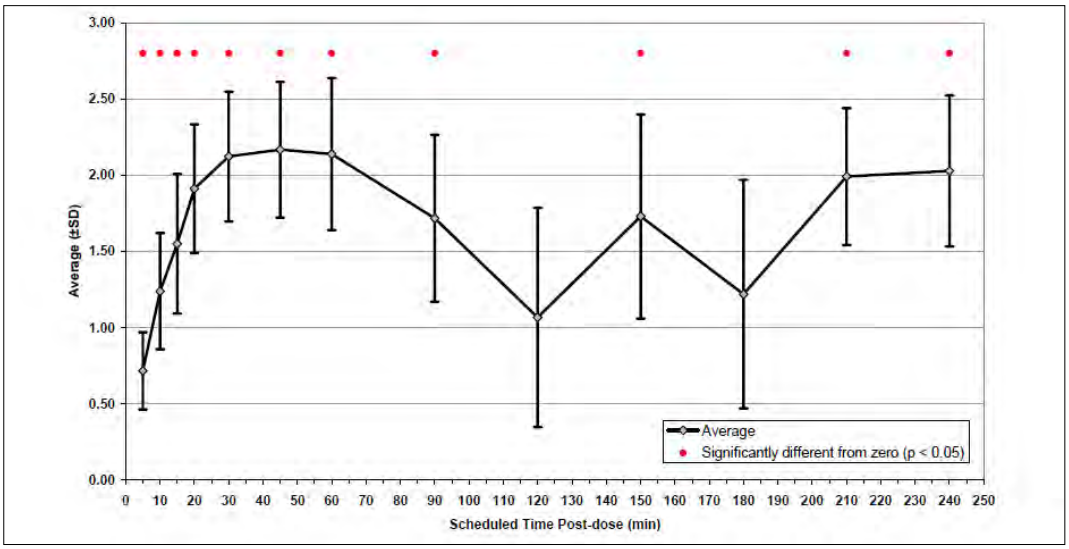


Figure 8. Study 041/04 - Mean Patient PR Score Population: Efficacy



On average patients experienced changes in PID and PR within 5 minutes of dosing. Maximal mean (± SD) patient PID (1.6 ± 0.5) and PR (2.2 ± 0.9) scores were reached at 60 minutes and 45 minutes post dose respectively (median 60 and 30 min post dose). PIDs remained significantly different from baseline between the time of maximal effect (60 minutes) and the end of the assessment period (240 minutes) despite a reduction in the number of patients assessed. PR scores remained significantly different from baseline between the mean time of maximal effect (45 mins) and 90 mins.

The median (25, 75% quartiles) time to onset of pain relief and time to onset of meaningful time relief was 9.3 mins (8.3, 16.3) and 32.0 mins (26.0, 41.8) based on per patient analysis and 10.0 (6.0, 17.0) and 46.0 (22.0, 218.0) based on per episode analysis. The mean (± SD) duration of meaningful pain relief was 86.0 ± 59.6 mins.

Ten (10) out of 13 patients (77%) who responded to the overall satisfaction question rated the drug-product as “good” or “better”.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

The applicant has provided no analyses of efficacy across trials.

7.1.4. Evaluator's conclusions on clinical efficacy for breakthrough cancer pain

Applicant has provided two pivotal studies to support the efficacy of the Nasalfent (nasal spray fentanyl citrate) in the treatment of BTCP. The first study compared Nasalfent to placebo and demonstrated superiority to placebo consistently in all the endpoints. The second study compared Nasalfent to an approved fentanyl lozenge and demonstrated comparable efficacy with statistically significant improvement in the onset of action.

The two pivotal studies did not have the same primary efficacy outcome:

- Placebo comparison study (CP043/06) – SPID from 5 to 30 minutes
- Active comparison study (CP044/06) - PID at 15 minutes

However, both studies included a range of secondary outcomes which were similar in the two studies.

Study numbers were small and the company did not use a true ITT analysis. The use of the modified ITT results in less patients being available for analysis; however the results showed statistical significance in favour of the fentanyl nasal spray. The improvement in onset of action is relevant to the patient population.

Overall, efficacy for the fentanyl nasal spray has been demonstrated.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, CP043/06 and CP044/06, the following safety data were collected:

- General adverse events (AEs) were assessed by the standard procedures. Patients were closely observed and questioned for any kind of AE during study procedures and throughout the study period with non-leading questions. They were instructed to immediately report any symptoms and signs arising between formal observations or visits to study staff. The following information regarding each AE was collected: date and time of onset and resolution (duration); intensity (mild, moderate or severe); outcome; and whether the AE caused withdrawal from the study.

  The investigator was asked to assess the causal relationship between the AE and the investigational product using the following guidance:

  - **Not related**: sufficient information existed to indicate that causality was unrelated to investigational product (eg event due to extraneous cause such as underlying medical condition, other therapeutic interventions, environmental factors, etc)
  - **Remote:** the time from the investigational medicinal product administration to occurrence of AE make a relationship improbable, but not impossible. The AE was unlikely to have been produced by the patient's underlying medical conditions, environmental or toxic factors, or other therapeutic interventions
  - **Possible:** The AE followed a reasonable temporal sequence from the investigational product administration. It is unlikely to have been produced by the patient's underlying medical conditions, environmental or toxic factors, or other therapeutic interventions

- **Probable:** The AE followed a reasonable temporal sequence from the investigational product administration, or was associated with established drug concentration in body tissues; improved on stopping or reducing the investigational product dosage (de-challenge); and could not reasonably be explained by the study patient's underlying medical conditions, environmental or toxic factors, or other therapeutic interventions
- **Definite:** Same criteria as "probable" but the AE reappears on repeated exposure (re-challenge)
- An adverse event that was assessed by the Investigator as being possibly, probably or definitely related to the associated study medication was defined as an adverse reaction.

  The definition of serious and unexpected adverse reactions were the same as is given in the Australian guidelines (TGA, 2006).

- AEs of particular interest, including:
- Objective nasal examination was assessed by the study physician at screening and at end of study. Assessment included obstruction (on 3 point scale), inflammation (on 3 point scale), presence of discharge, side most affected overall and colour of mucosa.
- Subjective nasal assessment was assessed by the patient one hour after each dose of study drug and at the final study visit on a 3 point scale. Assessment included stuffy/blocked nose, runny nose, itching or sneezing, crusting or dryness of nose, burning or discomfit of nose, bleeding, cough, postnasal drip, sore throat and taste disturbance
- Laboratory tests, including standard haematology, biochemistry, and urinalysis were performed at screening and at end of study.
- Physical Examination and vital signs, including measurements of heart rate, systolic and diastolic blood pressure, and respiration rate were assessed at screening and at end of study.
- Urine pregnancy tests were performed at screening to ensure female patients of childbearing potential were not pregnant

8.1.2. Pivotal studies that assessed safety as a primary outcome

Studies CP045/06 was a pivotal study that assessed safety as a primary outcome. This study is described in Section 7.1.5.

8.1.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- Study CP41/04 provided data on adverse events and patient well being, assessed by observation and questionnaire.

8.1.4. Other studies evaluable for safety only

8.1.4.1. *Clinical pharmacology studies*

Note: In Pharmacokinetic studies fentanyl was always administered after naltrexone.

Study CP037/02: Safety and tolerability were assessed by a local nasal tolerance questionnaire, completed after each nasal dose, and by monitoring other adverse events throughout the study.

Study CP042/05: Local tolerability was assessed by a reatogenicity questionnaire throughout and completing an overall assessment of the acceptability of nasal dosing at the end of each nasal treatment. There was also a topical safety assessment by an ENT specialist suing a conventional rating scale at the beginning and end of the study, and clinical nasal assessment by the study physician.

Study CP047/07: Safety and tolerability were evaluated by physical examination, vital signs, (pulse, blood pressure, respiratory rate, temperature and oxygen saturation), clinical laboratory

tests (haematology, biochemistry and urinalysis), 12 lead ECGs and adverse event questioning. The tolerability of intranasal administration was determined by nasal assessments and reactogenicity questionnaire.

Study CP048/07: Safety and tolerability was assessed by monitoring adverse events throughout the study, plus a standard symptom questionnaire that was completed before dosing and the reactogenicity questionnaire completed prior to an after each fentanyl nasal spray. A topical safety assessment was conducted by an ENT specialist at the beginning and end of the study.

8.1.5. Pivotal studies that assessed safety as a primary outcome

8.1.5.1. *Study CP045/06*

8.1.5.1.1. *Study design, objectives, locations and dates*

*Objectives***:** To provide continued access to Nasalfent for patients who had gained clinical benefit from its use during their participation in the efficacy trial program and to provide additional data on the long term safety of Nasalfent in the treatment of patients with BTCP.

The study was reported in 1 study report and two addendums. The first study report detailed the inclusion of new patients to the study and described the safety assessment of the initial subset of patients from January 2007 to April 2009. The first addendum dated December 2009 presented the long term safety data to September 2009 and the second dated August 2010 presented the long term safety data on the patients remaining in the study (61 patients) from October 2009 to March 2010.

*Design***:** This was an open label study conducted at 91 centres worldwide (Argentina, Canada, Costa Rica, Czech Republic, France, Germany, UK, India, Italy, Poland, Spain and the USA). The design of the study for new patients was similar to the design of the previous efficacy studies described above with 4 phases:

- Screening phase (up to 10 days)
- Open, Dose Titration Phase – (up to maximum of 14 days) - the dose of Nasalfent was titrated until 2 consecutive treated episodes of BRCP were successfully treated with the same dose without acceptable adverse events.
- Open Label Treatment Phase (16 weeks) – Each patient was supplied with up to a 4 week supply of Nasalfent. Patients were instructed to self-administer the effective dose of Nasalfent established during the Dose Titration Phase. Nasalfent was used to treat a maximum of 4 episodes of target BTCP per day with at least 4 hours between each use of Nasalfent. If pain relief was inadequate after 30 minutes or if a separate episode of BTCP occurred before the mandated 4 hours had elapsed then the patient was instructed to use their rescue medication. Patients were monitored by weekly telephone calls to review safety and adjust dose levels if needed and patients returned to clinic for visits at weeks 4, 8 and 12 to assess safety and tolerability.
- End of Treatment Phase (between 1 and 14 days after last dose) – patients returned to clinic for final acceptability and safety assessments.

For patients previously enrolled in Study CP043/06 and CP044/06 the main study consisted of the Open-label Treatment Phase and the End of Treatment Phase.

At the end of the study patients could continue in an open-ended long term access/extension arm and continue treatment with Nasalfent until it was no-longer required, or until the product was commercially available in their country. Only safety data (AE reporting) and study drug reconciliation was conducted in the extension phase.

8.1.5.1.2. *Inclusion and exclusion criteria*

Male or female patients aged 18 years or older, who had histologically documented diagnosis of a malignant solid tumour or a haematological malignancy. Patients had to be taking regular 24 hour medication (60 mg oral morphine or equivalent opioid) for underlying persistent cancer-related pain and typically having 1 to 4 episodes of BTCP per day. Patients had to have completed their required participation in the earlier phases of Study CP045/06 prior to "rolling over" into the extension period.

8.1.5.1.3. *Study treatments*

Two concentrations of the pectin formulation of fentanyl citrate were available: 1.57 mg/mL and 6.28 mg/mL (equivalent to 1.0 and 4.0 mg/mL of fentanyl base, respectively), with each 0.1 mL spray providing a dose of 100 µg or 400 µg fentanyl respectively. Four dose levels were examined in the study: 100 µg, 200 µg, 400 µg and 800 µg.

8.1.5.1.4. *Safety variables and outcomes*

The main efficacy variables were:

- Adverse events
- Objective nasal examination by the study physician
- Subjective nasal assessment by the patient

A primary efficacy outcome was not identified for the study.

Other efficacy outcomes included:

- Withdrawal due to AEs
- Physical examination including vital signs
- Laboratory assessments
- Use of concomitant medication
- Study drug compliance
- Acceptability assessments - end points were:
  - Overall satisfaction
  - Ease of use
  - Convenience

    Each acceptability end point was assessed using a 4 point scale as: 1 (not satisfied), 2 (not satisfied or dissatisfied), 3 (satisfied) and/or 4 (very satisfied). Acceptability assessment also included examination of rescue medication usage.

For the long term extension study only the following safety parameters were assessed:

- Adverse events
- Withdrawal due to AEs
- Use of concomitant medication
- Study drug compliance

8.1.5.1.5. *Randomisation and blinding methods*

This was an open label study with no randomisation.

8.1.5.1.6. *Analysis populations*

The ITT Safety Population was defined as all patients newly enrolled and previously enrolled in studies CP043/06 and CP 044/06 who had received at least one dose of Nasalfent. It comprised 403 patients - consisting of all 356 patients who were entered into the Open-Label Treatment Phase, plus 2 patients who were entered directly into the Extension Period from the Open-Dose Titration Phase, plus 45 withdrawn patients exposed during the Open-Dose Titration Phase (51 patients minus 6 patients who were dispensed Nasalfent treatment but did not take any).

8.1.5.1.7. *Sample size*

The sample size was based on the expectation of enrolling sufficient number of patients to ensure that 500 patients were eventually exposed to Nasalfent across the entire clinical study program, and that 150 of these had been dosed for 3 or more months (≥90 days).

8.1.5.1.8. *Statistical methods*

Results are summarised overall and by dose using frequencies and percentages as well as mean, median, range, SD, SE minimum and maximum.

For summary purposes, verbatim AE terms recorded were mapped to preferred terms and body systems using the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0. All AEs were listed, but only treatment emergent adverse events (TEAE) were summarised.

8.1.5.1.9. *Participant flow*

Figure 9. Study CP045/6 - Patient Source and Disposition during Screening and Titration

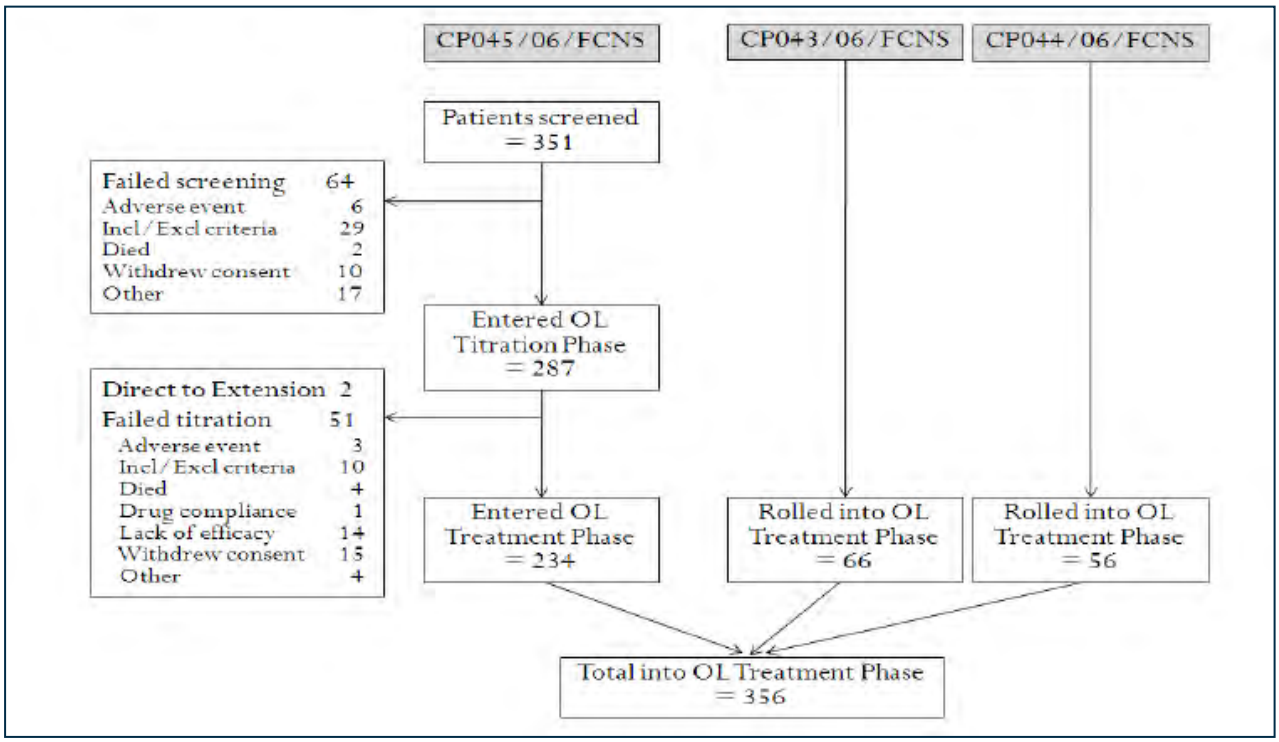


Figure 10. Study CP045/06 – Patient Disposition during First Extension Period

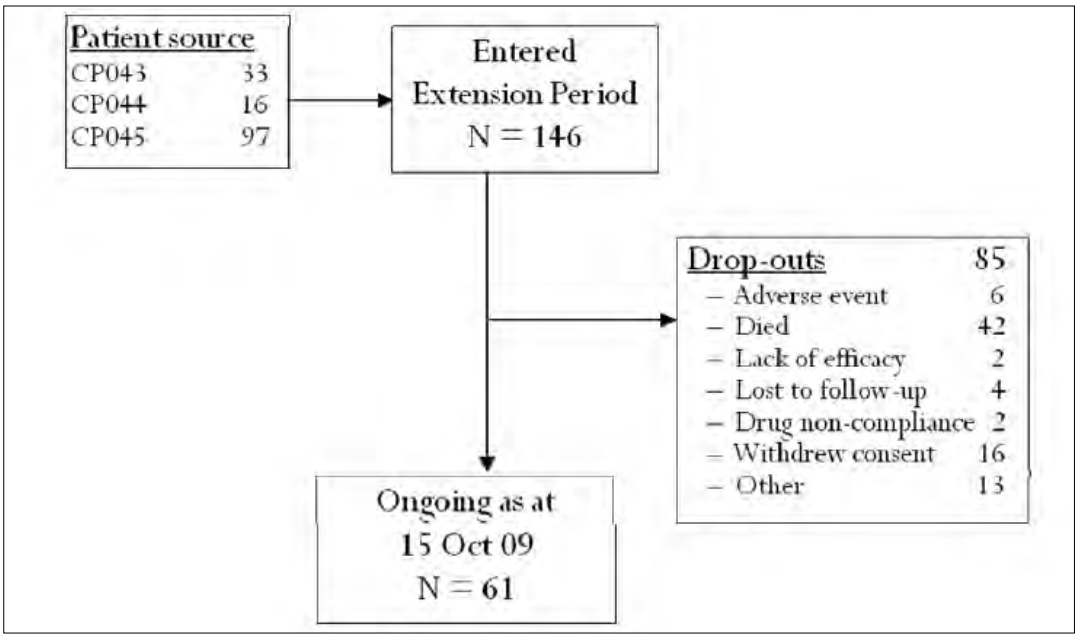
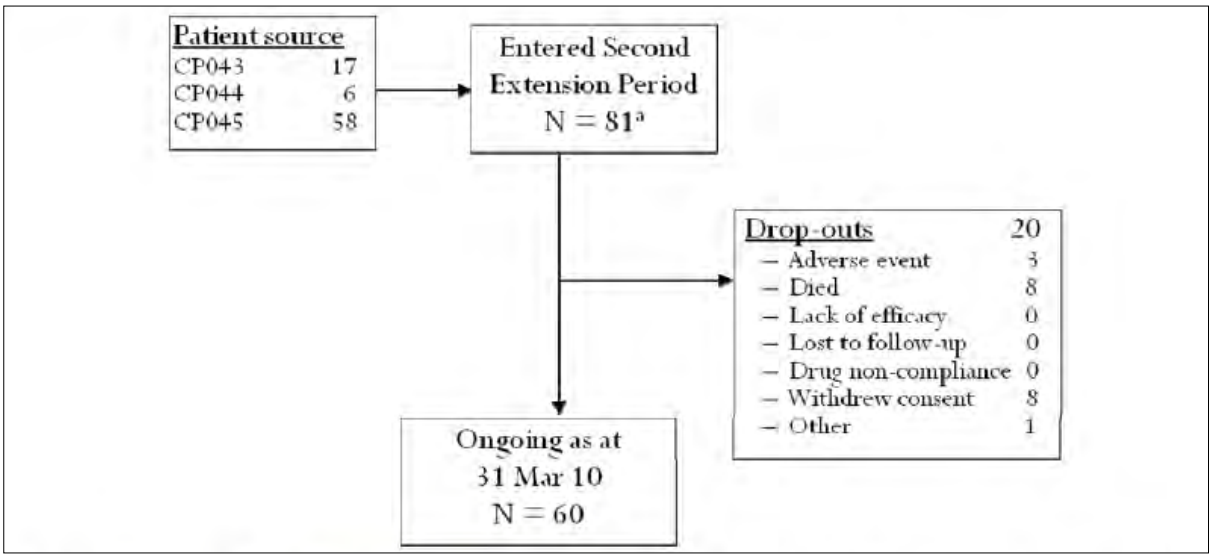


Figure 11. Study CP045/06 – Patient Disposition during Second Extension Period to 31 March 2010



*Includes a patient who died during the First Extension period but had an SAE reported late during this period.

8.1.5.1.10. *Major protocol violations/deviations*

The most frequent protocol deviations were as follows: returned drug did not match episode data entered into e-diary, spray count discrepancies (usually noted as underuse or overuse of medication – the later frequently associated with treatment of additional episodes of BTCP, missed assessment for certain visits, not observing the 4 hour period for rescue medication usage, patients. It is stated that these deviation did not appear likely to confound the study results.

8.1.5.1.11. *Baseline data*

A majority of patients in the ITT Safety Population were Caucasian 214 (53.1%); 129 (32.0%) were Indian. The proportion of male patients participating in the study was slightly higher than

female patients (male: 53.1% and female: 46.9%). The mean age was 53.8 years with 26.1% of the population over the age of 60 years. Most patients (71.5%) had a baseline ECOG score of 0 or 1 indicating a high level of functioning.

8.1.5.1.12. *Results for the primary safety outcome*

There was no stated single primary safety outcome.

8.1.5.1.13. *Results for other safety outcomes*

A total of 42,227 BTCP episodes were treated (23,936 episodes for newly treated patients; 12,538 episodes from Study CP043/06 and 5,753 episodes from Study CP044/06.

A total of 403 patients were included in the ITT population, and 355 patients entered into the Open-label Treatment Phase. By the time of Database lock for the main study (report dated Aug 2009) 100 of these patients had entered the Extension Phase, with 73 continuing to receive treatment at that time. In the first addendum (dated Dec 2009) 146 patients had entered the Extension phase and in the second addendum (dated Aug 2010) 81 patients were analysed. No overall summary of the results is presented.

The results were generally consistent in the 3 reports and for simplicity the results of the main study are reported here with comments where appropriate from the addendum reports.

The doses patients were on in the main study are seen below.

Table 42. Study CP045/06 – Patient Exposure - Dose

Summary of all BTCP Episodes Treated with Nasalfent				
Study Phase	**Episodes for Newly Enrolled Patients**			
Open, Dose Titration Phase	N (%)			
Total	1332			
100 µg	413 (31.0)			
200 µg	371 (27.9)			
400 µg	372 (27.9)			
800 µg	176 (13.2)			
Open-Label Treatment Phase	**Episodes for Newly Enrolled Patients**	**Episodes for Patients in Study CP043/06**	**Episodes for Patients in Study CP044/06**	**Total**
Total	23936	12538	5753	42227
100 µg	3747 (15.7)	1276 (10.2)	315 (5.5)	5338 (12.6)
200 µg	5020 (21.0)	406 (3.2)	1285 (22.3)	6711 (15.9)
400 µg	6900 (28.8)	4385 (35.0)	2612 (45.4)	13897 (32.9)
800 µg	8269 (34.5)	6471 (51.6)	1541 (26.8)	16281 (38.6)

Table 43. Study 045/06 – Patient Exposure - Time

Duration of Exposure to Nasalfent by Study Phase (ITT Population)

	Number of Patients (N[%]) Exposed within Duration Range by Phase and Dose					
Study Phase	**1-7 Days**	**8-14 Days**	**15-28 Days**	**29-90 Days**	**>90 Days**	**Total**
Open, Dose-Titration Phase (only)[a]						
Total	251	21	0	0	0	272
100 µg	247 (100.0)	0	0	0	0	247
200 µg	210 (99.5)	1 (0.5)	0	0	0	211
400µg	153(98.7)	2(1.3)	0	0	0	155
800 µg	80 (100.0)	0	0	0	0	80
Open-Label Treatment Phase(Titrated Dose Maintained)						
Total	19	18	54	101	108	300
100 µg	2 (4.2)	5 (10.4)	6 (12.5)	18 (37.5)	17 (35.4)	48
200 µg	2 (3.4)	6 (10.2)	18 (30.5)	19 (32.2)	14 (23.7)	59
400 µg	12 (12.6)	3 (3.2)	13 (13.7)	35 (36.8)	32 (33.7)	95
800 µg	3 (3.1)	4(4.1)	17(17.3)	29 (29.6)	45 (45.9)	98
Open-Label Treatment Phase(Titrated Dose Changed)[a]						
Total	0	0	2	21	18	41
100 µg	0	0	0	6 (100.0)	0	6
200 µg	1 (4.2)	2 (8.3)	5 (20.8)	14 (58.3)	2 (8.3)	24
400 µg	5 (14.7)	2 (5.9)	10 (29.4)	17 (50.0)	0	34
800 µg	1 (5.0)	3 (15.0)	7 (35.0)	9 (45.0)	0	20
All						
Total	63	18	49	129	138	397[b]
100 µg	209(79.5)	3(1.1)	9 (3.4)	23(8.7)	19(7.2)	263
200 µg	158 (66.1)	6 (2.5)	22 (9.2)	34 (14.2)	19 (7.9)	239
400 µg	100 (46.5)	6 (2.8)	22 (10.2)	53 (24.7)	34 (15.8)	215
800 µg	30 (20.8)	6 (4.2)	21 (14.6)	41 (28.5)	46 (31.9)	144

[a] Patients in the Open, Dose-Titration Phase and Open-Label Treatment Phase (titrated dose changed) were exposed to more than 1 dose. Patients in all phases by dose could have been exposed to more than 1 dose. For exposure tables, titrated dose maintained/changed was established based one-diary episode dose assignments.

[b] 5 Patients were not included in the analysis as no data on the e-diary treated episodes were available for these patients.

8.1.6. Adverse events

TEAEs were reported by 76.9% of patients in the ITT Population and were distributed across levels of severity (19.9% mild, 25.8% moderate and 31.3% severe). A total of 99 (24.6%) patients reported treatment-related TEAEs, which were generally mild or moderate in severity.

More patients experienced TEAEs, treatment-related TEAEs, SAEs and treatment withdrawals at the Nasalfent 800 mcg dose than the other dose levels. However, this was probably related to the longer duration of exposure and thus the greater number of episodes treated with this dose. The most frequently reported TEAEs were either attributed to disease progression (13.9% patients) or were events usually associated with opioids such as fentanyl (ie, vomiting, nausea, dizziness, and constipation). No pattern of concern in the incidence of AEs after administration of additional rescue medication was apparent.

8.1.7. Deaths

Overall, 80 deaths (4 during the Open, Dose-Titration Phase; 59 during the Open-Label Treatment Phase, 14 following withdrawal, and an additional 3 following study completion) were reported. The deaths of 33 patients were attributed directly to disease progression, while the rest were caused by a wide range of expected complications of advanced cancer. Only 2 patients who died had associated AEs considered to be remotely (septic shock) or possibly (constipation, intestinal perforation, and peritonitis) related to study drug.

In the first addendum, an additional 43 deaths were reported. The deaths were either attributed to disease progression, or to a wide range of expected complications of advanced cancer. Only 1 patient who died had an AE considered to be 'possibly' related to study drug; this was an AE of severe vomiting that occurred after 282 days' treatment with Nasalfent. The patient continued to use study drug until her death over two months later from 'disease progression'.

In the second addendum, and additional 7 deaths were reported. The deaths were either attributed directly to disease progression, or to a wide range of expected complications of advanced cancer. None of the deaths followed an AE considered to be 'possibly' related to study drug.

8.1.8. Serious AEs

Nonfatal SAEs were reported in 61 (15.1%) patients overall. Of the 20 patients who discontinued treatment due to an AE, 6 were due to disease progression. Withdrawals due to AEs were distributed across dose groups (Nasalfent 100 μg: 3 patients; 200 μg: 6 patients; 400 μg: 4 patients and 800 μg: 7 patients). In 11 of these cases, AEs associated with withdrawal were not considered to be related to study drug. Of the remaining cases, 4 patients had AEs resulting in withdrawal largely considered to be at least possibly related to study drug but were not unexpected with chronic opioid treatment (eg, nausea and constipation).

8.1.9. Laboratory tests

There were no treatment-emergent changes in laboratory or clinical safety parameters that were suggestive of safety issues associated with acute or long-term Nasalfent treatment.

8.1.10. Nasal assessments

Objective nasal examinations were undertaken to determine treatment effect on the nasal mucosa. There was no consistent pattern of findings from these examinations that would indicate Nasalfent is associated with changes in nasal obstruction, inflammation, discharge, or colour of mucosa, even after treatment in excess of four months. In patient subjective assessments, no consistent pattern of abnormal nasal symptoms such as stuffy or blocked nose, runny nose, itching or sneezing, crusting or dryness of nose, burning or discomfort, nasal bleeding, cough, postnasal drip, sore throat, or taste disturbance was reported.

8.1.11. Device usage

The small number of potential device malfunctions reported (up to 4.2% in the Open Dose-Titration Phase and 1.8% in the Open-Label Treatment Phase) did not seem to cause patients any problems. A significant number of the reported malfunction events (0.9%) were likely to reflect patient inexperience in the use of the device, such as not recognizing spray delivery, rather than true device malfunction. This conclusion is supported by the observed fall in the

percentage of overall reports during the Open, Dose-Titration Phase (4.2%) compared to the Open-Label Treatment Phase (1.8%).

8.1.12. Drug abuse

Two patients in the study were reported to have abused the study medication, and both patients had large positive spray discrepancies (ie, had used more sprays than were accounted for by the reported number of treated episodes in the e-diary). Although there were a number of other patients with large positive discrepancies between treated episodes of BTCP and the number of sprays actually used, the majority of cases in this patient population seemed likely to be due to failure of compliance with the use of the e-diary to record episodes, rather than with the use of Nasalfent, or due to failure (in a few cases) of the e-diary itself.

No further cases of drug abuse were reported in the addendums, although 3 patients were withdrawn in the first extension phase due to concerns over misuse – over frequent dosing in 2 patients and drug seeking behaviour in one patient. No patients were withdrawn in the second extension phase due to concerns over misuse.

8.1.13. Patient compliance with reporting

The mean number of discrepancies in the number of sprays for the Open, Dose-Titration Phase and Open-Label Treatment Phase derived from e-diary data, were 0.7 and 31.7, respectively. The mean compliance for the Open, Dose-Titration Phase and Open-Label Treatment Phase, was 127.4% and 129.6%, respectively. Assessment of individual patient histories indicates that this was predominantly caused by under-reporting in the e-diary of appropriately treated episodes. SAEs and deaths are to be expected in this cancer population over a period of 5 months. The majority of these events were unlikely to be related to Nasalfent treatment, but rather due to events associated with the progression of cancer or its treatment. The AEs associated with withdrawal were largely considered to be at least possibly related to study drug and are not unexpected with fentanyl treatment (eg, nausea, vomiting, and constipation).

8.1.14. Patient acceptability

At the episode level, for 60 minutes assessment during Open-Label Treatment Phase, patients reported being “satisfied” or “very satisfied” with Nasalfent for 89.7% of episodes treated. Patients were also satisfied or very satisfied with the speed at which relief came in 90.0% of episodes. Levels of satisfaction were not affected by dose level.

Between 89% and 98% of patients reported being satisfied or very satisfied with its ease of use, convenience and reliability. These acceptability findings were consistent throughout the 12 weeks of observation for these parameters. The majority of episodes were treated with Nasalfent 800 mcg (16281 [38.6%]) or Nasalfent 400 mcg (13897 [32.9%]) during the Open-Label Treatment Phase. Across all dose levels, 93.99% of episodes treated with Nasalfent did not require rescue medication within 60 minutes, and 93.75% of episodes within 240 minutes. Where rescue medication was used, there was a trend to decreased rescue medication usage as treatment duration increased (Weeks 13 to 16 [5.02% of episodes] compared with Weeks 0 to 4 [7.42% of episodes]).

8.2. Patient exposure

Table 44. Healthy subject Exposure – Pharmacology Studies

	Number of Healthy Subjects Receiving Fentanyl Nasal Spray				
Dose	**CP037/02**	**CP042/05**	**CP047/07**	**CP048/07**	**Total**
100 µg	18	16	12	45	91
100 µg x 2 (4 hrs apart)			11		
100 µg x 2 (2 hrs apart)			10		
100 µg x 2 (1 hr apart)			10		
100 µg x 8 (consecutive)			10		
200 µg		14			
400 µg		13			
800 µg		12			

Table 45. Total Duration of Exposure to Fentanyl Nasal Spray (FNS) by Dose – Efficacy/Safety Studies

	Number(%) of Subjects	Days (%) of FNS Exposure	Subject Years (%) of FNS Exposure
Total Subjects[a]	506	27,040	74.0
100 µg	460 (90.9)	4,559 (16.9)	12.5 (16.9)
200 µg	387 (76.5)	5,215 (19.3)	14.3 (19.3)
400 µg	318 (62.8)	8,529 (31.5)	23.4 (31. 5)
800 µg	182 (36.0)	8,798 (32.5)	24.1 (32. 5)
Long Term Subjects[b]	153	18,078	49. 5
100 µg	140 (91.5)	2,857 (15. 8)	7.8 (15.8)
200 µg	130 (85.0)	3,138 (17.4)	8.6 (17.4)
400 µg	110 (71.9)	5,541 (30.7)	15.2 (30.7)
800 µg	67(43. 8)	6,582 (36.4)	18.0 (36.4)

a. Subjects could have been exposed to more than 1 dose.

b. Long-term treatment was defined as ≥90 days of treatment.

Table 46. Duration of Exposure to Fentanyl Nasal Spray by Dose and Duration of Exposure

	Number of Subjects Exposed at Any Dose within Specified Duration Range				
All Subjects[a]	1-7 days	8-14 days	15-28 days	29-89 days	>90 days
Total (N=506)	123	41	57	132	153
	Number(%) of Subjects Exposed at Specific Dose within Duration Range (Subjects could be exposed to more than 1dose and/or duration)				
100 µg (N=460)	394 (85. 7)	9 (2.0)	14 (3.0)	23 (5.0)	20 (4.3)
200 µg (N=387)	294 (76.0)	11 (2.8)	22 (5.7)	39(10.1)	21 (5.4)
400 µg (N=318)	192 (60.4)	10 (3.1)	22 (6.9)	56 (17.6)	38(11.9)
800 µg (N=182)	60 (33.0)	7 (3.8)	22(12.1)	44 (24.2)	49 (26.9)

a. Only subjects that had treated episodes with either 100, 200, 400 or 800 meg dose were included; subjects were exposed to more than 1 dose.

8.3. Adverse events

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

Because of the naltrexone block used in the pharmacokinetic studies in healthy volunteers the safety reporting provided by the applicant has been divided into 'Pivotal Studies'=Phase 2/3 and 'other studies'=Phase 1. This has been repeated in this report as it appears appropriate in analysing safety:

- Pivotal studies (CP043/06, CP044/06, CP041/04, CP045/06)
- Other studies (CP37/02, CP042/05, CP047/07, CP048/07)

8.3.1.1. *Pivotal studies*

During the Phase 2/3 studies, 289 (75.4%) subjects reported one or more adverse events. Adverse events were experienced by higher proportion of subjects receiving 400 µg (43.6%) and 800 µg (62.1%) than subjects receiving 100 µg (31.0%) or 200 µg (28.0%). This is likely a reflection of the higher numbers of episodes treated with the higher doses.

Most adverse events were mild or moderate in intensity: 142 (27.5%) subjects had severe adverse events at some point during the studies.

Table 47. Adverse Event Incidence

Category of Adverse Event	FINAL Total N=516
Number (%) of Subjects with at Least One AE	**389 (75.4)**
Number (%) of Subjects with at Least One Mild AE	291 (56.4)
Number (%) of Subjects with at Least One Moderate AE	226 (43.8)
Number (%) of Subjects with at Least One Severe AE	142 (27.5)
Number (%) of Subjects with at Least One Treatment-Related AE	**149 (28.9)**
Number (%) of Subjects with at Least One Not Related AE	326 (63.2)
Number (%) of Subjects with at Least One Remotely Related AE	53 (10.3)
Number (%) of Subjects with at Least One Possibly Related AE	103 (20.0)
Number (%) of Subjects with at Least One Probably Related AE	51 (9.9)
Number (%) of Subjects with at Least One Definite Related AE	22 (4.3)
Number (%) of Subjects with at Least One Serious AE	134 (26.0)
Number (%) of Subjects with at Least One Serious, Treatment-Related AE	7 (1.4)
Number (%) of Subjects with at Least One AE Leading to Interruption of Treatment	48 (9.3)
Treatment	74 (14.3)
Number (%) of Subjects with at Least One AE Resulting in Death	83 (16.1)
Number (%) of Subjects with at Least One Treatment-Related AE Resulting in Death	2 (0.4)
Total Number of AEs	**1726**
Total Number (%) of Treatment-Related AEs	368 (21.3)
Total Number (%) of Serious AEs	219 (12.7)
Total Number (%) of Serious, Treatment-Related AEs	14 (0.8)

Table 48. Adverse Events Reported by > 2.5% of All Subjects in Descending Order of Incidence – Phase 2/3 Studies

Preferred Term	N (%)				
	100 µg (N=484)	200 µg (N=389)	400 µg (N=319)	800 µg (N=182)	Total (N=516)
Subjects with>1 AE	150 (31.0)	109 (28.0)	139 (43.6)	113(62.1)	389 (75.4)
Vomiting	20 (4.1)	20 (5.1)	21 (6.6)	14(7.7)	71 (13.8)
Nausea	23(4.8)	15 (3.9)	12 (3.8)	14 (7.7)	63 (12.2)
Disease progression	16 (3.3)	8 (2.1)	16 (5.0)	26(14.3)	62 (12.0)
Constipation	23(4.8)	6 (1.5)	14 (4.4)	8 (4.4)	50 (9.7)
Dizziness	16 (3.3)	14 (3.6)	8 (2.5)	9 (4.9)	42 (8.1)
Somnolence	10(2.1)	8 (2.1)	14(4.4)	7 (3.8)	36 (7.0)
Pyrexia	7 (1.4)	6 (1.5)	9 (2.8)	7 (3.8)	28 (5.4)
Pain	5 (1.0)	4(1.0)	8 (2.5)	8 (4.4)	24 (4.7)
Dyspnoea	9 (1.9)	4 (1.0)	5 (1.6)	5 (2.7)	23 (4.5)
Diarrhoea	7 (1.4)	4 (1.0)	6 (1.9)	6 (3.3)	22 (4.3)
Headache	9 (1.9)	7 (1.8)	2 (0.6)	2(1.1)	20 (3.9)
Anaemia	1 (0.2)	8 (2.1)	4 (1.3)	6 (3.3)	19 (3.7)
Fatigue	3 (0.6)	3 (0.8)	9 (2.8)	5 (2.7)	19 (3.7)
Oedema peripheral	1 (0.2)	5 (1.3)	7 (2.2)	6 (3.3)	19 (3.7)
Dehydration	1 (0.2)	7 (1.8)	4 (1.3)	7 (3.8)	18 (3.5)
Anxiety	4 (0.8)	3 (0.8)	7 (2.2)	3 (1.6)	17 (3.3)
Insomnia	2 (0.4)	6 (1.5)	6 (1.9)	3 (1.6)	17 (3.3)
Asthenia	4 (0.8)	3 (0.8)	7 (2.2)	2(1.1)	16(3.1)
Epistaxis	6 (1.2)	3 (0.8)	3 (0.9)	5 (2.7)	15 (2.9)
Cough	4 (0.8)	0 (0.0)	7 (2.2)	3 (1.6)	14 (2.7)
Pharyngolaryngeal pain	4 (0.8)	5 (1.3)	3 (0.9)	3 (1.6)	14 (2.7)

In the long term study (CP045/06) a total of 131 (85.6%) of the 153 long term patients had at least one adverse event. At the 100, 200 and 400 µg dose levels, the majority of patients did not report adverse events. Severity of AEs was mild or moderate for the majority of patients reporting AEs, and most patients did not have an AE considered by the investigator to be

treatment related. The following table shows the AE reported by >2.5% of the long term subjects and demonstrates a similar AE profile as in the short term treated patients (see table above).

AEs reported by ≥5% of long term patients were disease progression, vomiting, nausea, constipation, dizziness, diarrhoea, somnolence, pain, Pharyngolaryngeal pain, pyrexia, and rhinorrhoea.

Table 49. Adverse Events Reported by >2.5% of All Long Term Subjects in Total Descending Order of Incidence- Phase 2/3 Studies

Preferred Term	N (%)				
	100 µg (N=144)	200 µg (N=130)	400 µg (N=110)	800 µg (N=67)	Total (N=l53)
Subjects with ≥ 1 AE	38 (26.4)	30(23.1)	47 (42.7)	52 (77.6)	131 (85.6)
Disease progression	8 (5.6)	2 (1.5)	5 (4.5)	11 (16.4)	24 (15.7)
Vomiting	5 (3.5)	2 (1.5)	7 (6.4)	10 (14.9)	23 (15.0)
Nausea	2 (1.4)	4 (3.1)	5 (4.5)	8 (11.9)	19 (12.4)
Constipation	7 (4.9)	1 (0.8)	6 (5.5)	2 (3.0)	15 (9.8)
Dizziness	4 (2.8)	6 (4.6)	1 (0.9)	4 (6.0)	13 (8.5)
Diarrhoea	3 (2.1)	1 (0.8)	3 (2.7)	4 (6.0)	11 (7.2)
Somnolence	3 (2.1)	2 (1.5)	5 (4.5)	3 (4.5)	11 (7.2)
Pain	2 (1.4)	2 (1.5)	2 (1.8)	5 (7.5)	10 (6.5)
Pharyngolaryngeal pain	3 (2.1)	4 (3.1)	1 (0.9)	2 (3.0)	9 (5.9)
Pyrexia	3 (2.1)	0 (0.0)	4 (3.6)	2 (3.0)	9 (5.9)
Rhinorrhoea	2 (1.4)	2 (1.5)	0 (0.0)	4 (6.0)	8 (5.2)
Oedema peripheral	0 (0.0)	0 (0.0)	3 (2.7)	4 (6.0)	7 (4.6)
Cancer pain	1 (0.7)	0 (0.0)	3 (2.7)	3 (4.5)	6 (3.9)
Dysgeusia	3 (2.1)	1 (0.8)	1 (0.9)	1 (1.5)	6 (3.9)
Headache	3 (2.1)	1 (0.8)	0 (0.0)	2 (3.0)	6 (3.9)
Insomnia	1 (0.7)	1 (0.8)	3 (2.7)	1 (1.5)	6 (3.9)
Nasal discomfort	2 (1.4)	2 (1.5)	2 (1.8)	1 (1.5)	6 (3.9)
Anaemia	0 (0.0)	2 (1.5)	2 (1.8)	1 (1.5)	5 (3.3)
Asthenia	0 (0.0)	2 (1.5)	2 (1.8)	1 (1.5)	5 (3.3)
Dehydration	0 (0.0)	2 (1.5)	2 (1.8)	2 (3.0)	5 (3.3)
Epistaxis	2 (1.4)	2 (1.5)	1 (0.9)	2 (3.0)	5 (3.3)
Fatigue	2 (1.4)	0 (0.0)	3 (2.7)	1 (1.5)	5 (3.3)
Gastritis	2 (1.4)	1 (0.8)	2 (1.8)	0 (0.0)	5 (3.3)
Nasopharyngitis	2 (1.4)	1 (0.8)	0 (0.0)	2 (3.0)	5 (3.3)
Pruritus	1 (0.7)	1 (0.8)	1 (0.9)	2 (3.0)	5 (3.3)
Urinary tract infection	1 (0.7)	0 (0.0)	2 (1.8)	2 (3.0)	5 (3.3)
Abdominal pain	1 (0.7)	0 (0.0)	3 (2.7)	0 (0.0)	4 (2.6)
Anxiety	0 (0.0)	1 (0.8)	2 (1.8)	1 (1.5)	4 (2.6)
Arthralgia	0 (0.0)	0 (0.0)	3 (2.7)	1 (1.5)	4 (2.6)
Bronchitis	0 (0.0)	1 (0.8)	2 (1.8)	1 (1.5)	4 (2.6)
Confusional state	0 (0.0)	0 (0.0)	2 (1.8)	2 (3.0)	4 (2.6)
Cough	1 (0.7)	0 (0.0)	3 (2.7)	0 (0.0)	4 (2.6)
Infection	1 (0.7)	0 (0.0)	2 (1.8)	2 (3.0)	4 (2.6)
Non-cardiac chest pain	1 (0.7)	1 (0.8)	2 (1.8)	0 (0.0)	4 (2.6)
Upper respiratory tract infection	1 (0.7)	0 (0.0)	2 (1.8)	1 (1.5)	4 (2.6)

8.3.1.2. ***Other studies***

During the Phase 1 studies 73 (73%) subjects experienced one or more adverse events and 62 (62%) had events that were considered by the investigator to be treatment-related.

Table 50. Overall Summary of Adverse Events – Phase I Studies

Number (%) of Subjects	Total (N=100)
Number (%) of subjects with ≥1 AE	73 (73.0)
Number (%) of subjects with ≥1 mild AE	71 (71.0)
Number (%) of subjects with ≥1 moderate AE	30 (30.0)
Number (%) of subjects with ≥1 severe AE	4 (4.0)
Number (%) of subjects with ≥1 treatment-related AE	62 (62.0)
Number (%) of deaths	0 (0.0)
Number (%) of deaths due to treatment-related AEs	0 (0.0)
Number (%) of subjects with ≥1 SAE	2 (2.0)
Number (%) of subjects with ≥1 treatment-related SAE	0 (0.0)
Number (%) of subjects with ≥1 AE leading to withdrawal from study	3 (3.0)
Number (%) of subjects with ≥1 treatment-related AE leading to withdrawal from study	0 (0.0)
Note: Treatment-related adverse events are defined as those reported as probably, possibly, definite, or with unknown relationship to study treatment. Adverse events of missing intensity are considered severe.	

Table 51. Adverse Events Reported by > 2.5% of All Subjects in Descending Order of Incidence - Phase 1 Studies

Preferred Term	Total (N=100)
Number(%) of subjects with >1 AE	73 (73.0)
Rhinorrhoea	36 (36.0)
Headache	34 (34.0)
Rhinitis	32 (32.0)
Nausea	22 (22.0)
Dizziness	17 (17.0)
Vomiting	15 (15.0)
Fatigue	12 (12.0)
Somnolence	12 (12.0)
Pharyngolaryngeal pain	10 (10.0)
Epistaxis	8 (8.0)
Nasal congestion	8 (8.0)
Abdominal pain upper	7 (7.0)
Cough	7 (7.0)
Dysgeusia	6 (6.0)
Feeling hot	6 (6.0)
Malaise	6 (6.0)
Nasopharyngitis	5 (5.0)
Tremor	5 (5.0)
Anorexia	4 (4.0)
Chest pain	4 (4.0)
Feeling abnormal	4 (4.0)
Abdominal pain	3 (3.0)
Catheter site pain	3 (3.0)
Diarrhoea	3 (3.0)
Nasal discomfort	3 (3.0)
Sneezing	3 (3.0)

The high incidence of rhinorrhoea and rhinitis was due to the subjects with seasonal allergic rhinitis who were enrolled into Study CP048/07 and who had allergen challenges. It should be remembered that all subjects received naltrexone and some also received oxymetazoline for one of the three arms of the study.

The majority of adverse events were mild or moderate in intensity. Severe AEs included 2 events of rhinitis and 1 event of lymphadenopathy, ear congestion, vomiting, chest pain, balance disorder, headache, dyspnoea, nasal oedema, nasal septum disorder, nasal ulcer and rhinorrhoea.

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

8.3.2.1. *Pivotal studies*

During the Phase 2/3 studies, 28.9% of subjects experienced adverse events that were assessed by the investigator as possibly, probably, or definitely treatment related. The most common events included:

- Dizziness 6.2%

- Vomiting 4.8%
- Somnolence 4.8%
- Nausea 4.5%
- Constipation 2.9%

Subjects treated a total of 45,599 episodes of BTCP during the Phase 3 studies; 343 (0.75%) of these episodes had adverse events that were considered by the investigator to be possibly or probably rated to treatment.

8.3.2.2. *Other studies*

In the phase 1 studies 62% of the subjects experienced 1 or more AEs that were assessed by the investigator as treatment related. The most commonly reported AEs were rhinitis, headache, rhinorrhoea, and nausea.

The majority of treatment related AEs were mild or moderate in intensity. Severe AEs included one event each of vomiting, rhinitis, balance disorder, headache and rhinorrhoea.

8.3.3. Deaths and other serious adverse events

8.3.3.1. *Pivotal studies*

8.3.3.1.1. *Deaths*

Table 52. Summary of Deaths by Study Phase-Phase 2/3 Studies

	Titration Phase (N=107)	Titrated Dose-Maintained Population (N=346)	Titrated Dose-Changed Population (N=64)	All (N=523)
Total deaths	10 (9.3)[a]	69 (19.9)	9 (14.1)	88 (16.8)
Withdrawn due to death (ie, died while on-study)	5 (4.7)	57 (16.5)[b]	3 (4.7)	65 (12.4)[b]
Death following withdrawal	5 (4.7)	11 (3.2)	2 (3.1)	18 (3.4)
Death following completion	NA	2 (0.6)[b]	4 (6.3)	6(1.1)[b]

a. Includes 1 subject (510501) w1th a non-treatment-emergent AE with fatal outcome.

b. Subject 390801 was withdrawn due to death during Study CP045/06 and also had an AE with fatal outcome reported in Study CP043/06 after completion of that study.

A total of 88 (16.8%) patient deaths were reported during the Phase II/III studies. These deaths included two patients from Study CP041/04) who were receiving 50 mcg FCNS, one subject (in Study CP043/06) with a fatal adverse event associated with placebo, one patient (in Study CP044/06) with a fatal adverse event associated with IRMS, and one patient who died due to a non-treatment emergent adverse event (urinary tract infection) following withdrawal from Study CP045/06.

Sixty-five (12.4%) patients died while on-study, 18 (3.4%) patients died following withdrawal, and six (1.1%) patients died after they completed their respective studies. An additional six patients died following participation in Study CP041/04 and no adverse event was associated with the death. The last dose of FCNS taken by these patients was 25 mcg, 50 mcg, 200 mcg, and 400 mcg in one patient each, and 800 mcg in two patients. These deaths occurred between three and 25 days following the last dose of study medication.

Two patients had AEs that resulted in death that were assessed by the investigator as possibly treatment related. One patient developed anuria, cardiovascular insufficiency, and hypotension during the dose titration phase and one dose maintained patient developed constipation, intestinal perforation, and peritonitis.

A total of 15 (9.8%) long-term patients died, 9 of whom died due to disease progression. None of the deaths were considered by the investigator to be due to treatment-related adverse events.

8.3.3.1.2. *Serious adverse events*

A total of134 (26.0%) patients experienced SAEs during the pivotal studies. The most frequent SAE was disease progression (36 patients 7%). Seven (1.4%) patients had treatment related SAEs.

A total of 22 (4.3%) patients experienced SAEs during the dose titration phase of the studies. 15 (2.9%) had non-fatal SAEs. The SAEs included disease progression in 4 (0.8%) patients, pneumonia in 3 (0.6%) patients and anaemia and dyspnoea in 2 (0.4%) patients each. All other SAEs were reported for a single patient.

A total of 99 (28.6%) patients experienced SAEs during dose maintained treatment phase of the studies. 45 (13.0%) patients had non-fatal SAEs. The most common SAE overall was disease progression (7.8%); all other SAEs were reported by fewer than 2% of all dose maintained subjects. Most SAEs were considered to be severe in intensity.

Three (0.9%) patients had SAEs during the dose maintained treatment that were assessed by the investigator as possibly or probably treatment related. One patient had SAEs that resulted in death (noted above) that were possibly treatment related. Two patients had non-fatal SAEs (dyspnoea in a 200 µg treated patient); cyanosis, loss of consciousness and upper airway obstruction in a 400 µg treated patient, that were possibly or probably treatment related.

Table 53. Serious Adverse Events Reported by ≥ 2 Subjects in Descending Order of Overall Incidence, Dose-Maintained Population-Phase 2/3 Studies.

Preferred Term	N (%)				
	100 µg (N=61)	200 µg (N=68)	400 µg (N=109)	800 µg (N=108)	Total (N=346)
Subjects with ≥1 SAE	16 (26.2)	23 (33.8)	35 (32.1)	25 (23.1)	99 (28.6)
Disease progression	6 (9.8)	5 (7.4)	7 (6.4)	9 (8.3)	27 (7.8)
Cardio-respiratorarrest	0 (0.0)	2 (2.9)	4 (3.7)	0 (0.0)	6 (1.7)
Pain	0 (0.0)	1 (1.5)	2 (1.8)	3 (2.8)	6 (1.7)
Breast cancer	1 (1.6)	0 (0.0)	3 (2.8)	0 (0.0)	4 (1.2)
Constipation	2 (3.3)	1 (1.5)	1 (0.9)	0 (0.0)	4 (1.2)
Dyspnoea	2 (3.3)	1 (1.5)	0 (0.0)	1 (0.9)	4 (1.2)
Nausea	1 (1.6)	0 (0.0)	0 (0.0)	2 (1.9)	3 (0.9)
Pulmonary embolism	2 (3.3)	0 (0.0)	1 (0.9)	0 (0.0)	3 (0.9)
Vomiting	0 (0.0)	1 (1.5)	0 (0.0)	2 (1.9)	3 (0.9)
Anaemia	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.9)	2 (0.6)
Back pain	1 (1.6)	0 (0.0)	1 (0.9)	0 (0.0)	2 (0.6)
Bradycardia	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.9)	2 (0.6)
Chronic obstructive pulmonary disease	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.9)	2 (0.6)
General physical health deterioration	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)	2 (0.6)
Hypoxia	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	2 (0.6)
Loss of consciousness	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	2 (0.6)
Mental status changes	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)	2 (0.6)
Mouth haemorrhage	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)	2 (0.6)
Multi-organ failure	0 (0.0)	1 (1.5)	1 (0.9)	0 (0.0)	2 (0.6)
Pancreatic carcinoma	0 (0.0)	1 (1.5)	1 (0.9)	0 (0.0)	2 (0.6)
Renal failure acute	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.9)	2 (0.6)
Respiratory failure	0 (0.0)	1 (1.5)	1 (0.9)	0 (0.0)	2 (0.6)
Sepsis	0 (0.0)	1 (1.5)	0(0.0)	1 (0.9)	2 (0.6)

A total of 36 (23.5%) long-term subjects had SAEs; 26 (17.0%) long-term subjects had non-fatal SAEs. Three subjects, two in 400 μg and one in 800 μg) had treatment-related non-fatal SAEs, each considered by the investigator to be possibly related to fentanyl nasal spray. The most common SAEs were disease progression (9 patients) and pain (3 patients).

8.3.3.2. ***Other studies***

8.3.3.2.1. *Deaths*

No subjects died during the Phase 1 studies.

8.3.3.2.2. *Serious adverse events*

Two subjects in the Phase 1 studies had non-fatal SAEs: one subject had mild chest pain and one subject became pregnant. Both SAEs were non-fatal and mild in intensity.

8.3.4. **Discontinuation due to adverse events**

8.3.4.1. ***Pivotal studies***

Seventy-four (14.3%) subjects had adverse events that led to discontinuation of treatment in the phase 2/3 studies. The most common reasons were: disease progression (22 patients, 4.5%), cardio-respiratory arrest and vomiting (6 patients, 1.2% each) and nausea (5 patients, 1.0%). 23 (4.5%) of these patients had adverse events that were assessed as possibly, probably or definitely treatment-related.

In the long term study a total of 7 patients had adverse events leading to discontinuation of treatment; the only AE leading to discontinuation of treatment in >1 subject was disease progression.

8.3.4.2. ***Other studies***

In the phase 1 studies 4 subjects were withdrawn from the studies due to adverse events, one of whom withdrew after naltrexone dosing (due to vomiting) and never received fentanyl. One subject was withdrawn after receiving a single 100 μg dose of FCNS due to non-specific chest pain, assessed as mild and considered not related to study drug; one subject was withdrawn after receiving a single 100 μg dose of FCNS due to an allergic reaction; and one subject was withdrawn prior to dosing with FCNS in the second phase of Study CP048/07 due to palpitation after having the provocation of their seasonal allergic rhinitis induced under laboratory conditions and following treatment with oxymetazoline. The subject had successfully completed the first phase of the study, receiving a single 100 μg dose of FCNS.

8.3.5. **Laboratory tests**

It is noted that with a patient population with severe, frequently end-stage malignant disease, the interpretation of laboratory tests is confounded by the impact of the underlying disease and its medical management. In addition, 30% of the patients in the studies were using fentanyl long term for treatment of background pain, at doses considerably higher than the doses of FCNS used for the BTCP.

8.3.6. **Liver function**

8.3.6.1. ***Pivotal studies***

Patients with screening test results indicating significant liver dysfunction were excluded from the clinical trials No clinically significant changes in liver function tests were identified in the Phase 2/3 studies.

8.3.6.2. ***Other studies***

No clinically significant changes in liver function tests were identified in the Phase 1 studies. No pharmacokinetic studies in patients with liver dysfunction were submitted.

8.3.7. Kidney function

8.3.7.1. *Pivotal studies*

Patients with screening test results indicating significant renal dysfunction were excluded from the clinical trials. No clinically significant changes in kidney function tests were identified in the Phase 2/3 studies.

8.3.7.2. *Other studies*

No clinically significant changes in liver function tests were identified in the Phase 1 studies in normal healthy volunteers. No pharmacokinetic studies in patients with kidney dysfunction were submitted.

8.3.8. Other clinical chemistry

8.3.8.1. *Pivotal studies*

No clinically significant changes in other routine chemistry tests were identified in the Phase 2/3 studies.

8.3.8.2. *Other studies*

No clinically significant changes in other routine chemistry tests were identified in the Phase 1 studies.

8.3.9. Haematology

8.3.9.1. *Pivotal studies*

No clinically significant changes in other routine haematology tests were identified in the Phase 2/3 studies.

8.3.9.2. *Other studies*

No clinically significant changes in other routine haematology tests were identified in the Phase 1 studies.

8.3.10. Urinalysis

8.3.10.1. *Pivotal studies*

No clinically significant changes in routine urinalysis tests were identified in the Phase 2/3 studies.

8.3.10.2. *Other studies*

No clinically significant changes in routine urinalysis tests were identified in the Phase 2/3 studies.

8.3.11. Vital signs

8.3.11.1. *Pivotal studies*

Vital sign data collected from subjects in the Phase 2/3 studies were included in the safety database. In general, the mean changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and weight) from Screening to End of Treatment were small and not clinically significant.

Two subjects reported adverse events (hypotension and weight decreased) associated with vital sign abnormalities that were assessed as possibly treatment related during the Open, Dose-Titration Phase of Study CP044/06 and during the Open-Label Treatment Phase of Study CP045/06, respectively.

8.3.11.2. *Other studies*

No clinically significant changes in vital signs were identified in the Phase 1 studies.

8.3.12. Nasal local symptoms and tolerability

8.3.12.1. *Pivotal studies*

Objective nasal examinations were conducted on subjects in the Phase 3 studies by either an ENT specialist or appropriately trained clinician before, during and after treatment with FCNS. At the End of Treatment, one subject had moderate obstruction and no subject had moderate or severe inflammation or discharge.

Table 54. Objective Nasal Examination at Screening and End of Treatment Phase (Phase 3 Studies). Table continued across 2 pages.

Parameter	Category	Screening (N=500) N (%)	End of Treatment (N=346) N (%)
Obstructiona	Absent	481 (96.2)	337 (97.4)
	Mild	17 (3.4)	8 (2.3)
	Moderate	2 (0.4)	1 (0.3)
	Severe	0 (0.0)	0 (0.0)
Inflammationb	Absent	485 (97.0)	332 (96.0)
	Mild	15 (3.0)	14 (4.0)
	Moderate	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Discharge present	None	466 (93.2)	334 (96.5)
	Mild	33 (6.6)	12 (3.5)
	Moderate	0 (0.0)	0 (0.0)
	Severe	1 (0.2)	0 (0.0)
Colour of mucosa	Normal	465 (93.0)	330 (95.4)
	Pale	14 (2.8)	5 (1.4)
	Red	17 (3.4)	8 (2.3)
	Blue	0 (0.0)	0 (0.0)
	Other	4 (0.8)	3 (0.9)
Side most affected	Left	20 (4.0)	4 (1.2)
	Right	12 (2.4)	7 (2.0)
	Both equally	30 (6.0)	28 (8.1)

Parameter	Category	Screening (N=500) N (%)	End of Treatment (N=346) N (%)
	N/A	438 (87.6)	307 (88.7)

N/A = not applicable. a Obstruction was recorded as: 0 = absent (No effect observed), 1 = mild (Mild mucosal thickening), 2 = moderate (Oedema, narrowing of airways) or 3 = severe (Significant /severe obstruction).

b Inflammation was recorded as: 0 = absent (No effect observed), 1 = mild (Some crusting or blood staining), 2 = moderate (Marked crusting, fresh blood, pus or cyanotic mucosa) or 3 = severe (Septal perforation or mucosal ulceration).

Subjective nasal tolerability assessments were completed by subjects in the Phase 3 studies during and after treatment with FNS. The parameters assessed were symptoms of stuffy/blocked nose, runny nose, itching, sneezing, crusting or dryness, burning or discomfort, bleeding, cough, post-nasal drip, sore throat, and taste disturbance. These symptoms were scored using a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe).

Table 55. Subjective Nasal Examination at Screening and End of Treatment Phase (Phase 3 Studies). Table continued across 2 pages.

Parameter	Category	Screening (N=475) N (%)	End of Treatment (N=287) N (%)
Bleeding (nose)	Absent	470 (98.9)	283 (98.6)
	Mild	4 (0.8)	4 (1.4)
	Moderate	1 (0.2)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Burning or discomfort (nose)	Absent	459 (96.6)	278 (96.9)
	Mild	15 (3.2)	6 (2.1)
	Moderate	0 (0.0)	3 (1.0)
	Severe	1 (0.2)	0 (0.0)
Cough	Absent	424 (89.3)	253 (88.2)
	Mild	40 (8.4)	31 (10.8)
	Moderate	9 (1.9)	3 (1.0)
	Severe	2 (0.4)	0 (0.0)
Crusting or dryness (nose)	Absent	426 (89.7)	258 (89.9)
	Mild	41 (8.6)	25 (8.7)

Parameter	Category	Screening (N=475) N (%)	End of Treatment (N=287) N (%)
	Moderate	8 (1.7)	3 (1.0)
	Severe	0 (0.0)	1 (0.3)
Itching or sneezing	Absent	458 (96.4)	277 (96.5)
	Mild	14 (2.9)	10 (3.5)
	Moderate	2 (0.4)	0 (0.0)
	Severe	1 (0.2)	0 (0.0)
Postnasal drip	Absent	432 (90.9)	260 (90.6)
	Mild	38 (8.0)	24 (8.4)
	Moderate	4 (0.8)	2 (0.7)
	Severe	1 (0.2)	1 (0.3)
Runny nose	Absent	430 (90.5)	258 (89.9)
	Mild	38 (8.0)	25 (8.7)
	Moderate	6 (1.3)	2 (0.7)
	Severe	1 (0.2)	2 (0.7)
Sore throat	Absent	427 (89.9)	268 (93.4)
	Mild	37 (7.8)	14 (4.9)
	Moderate	7 (1.5)	4 (1.4)
	Severe	4 (0.8)	1 (0.3)
Stuffy nose	Absent	400 (84.2)	267 (93.0)
	Mild	49 (10.3)	16 (5.6)
	Moderate	25 (5.3)	4 (1.4)
	Severe	1 (0.2)	0 (0.0)
Taste disturbance	Absent	390 (82.1)	250 (87.1)
	Mild	57 (12.0)	30 (10.5)
	Moderate	23 (4.8)	5 (1.7)

Parameter	Category	Screening (N=475) N (%)	End of Treatment (N=287) N (%)
	Severe	5 (1.1)	2 (0.7)

In the long term study, no significant changes were observed with regard to obstruction, inflammation, presence of discharge, colour of mucosa, or side most affected from Screening to End of Treatment.

8.3.12.2. *Other studies*

Not applicable

8.3.13. Overdose

8.3.13.1. *Pivotal studies*

Overdose was defined as acute over administration of study drug ie administration of 2 or more doses within a short time interval (during the course of one BTCP episode), as opposed to longer term over usage at the intended dose. Overdose defined in this way was also used as a marker for aberrant drug related behaviours.

During the Phase 2/3 studies, 516 patients treated a total of 45,599 BRCP episodes with FCNS. Adverse events, study drug reconciliation reports, telephone contact reports during titration, and protocol and protocol deviation/violation reports were reviewed for any evidence of overdose, as defined above. Of the 45, 599 episodes treated, only 11 possible or actual incidents of overdosing were observed.

One patient who was identified as an overdose later emerged as being at risk for potential abuse, although this does not appear to have been presaged by or related to the overdoing incident.

Review of the remaining overdose incidents indicate that most incidents of potential or actual overdose resulted from subject uncertainty over whether the spray had actually been delivered. The fine, low-volume spray with which FCNS is delivered is emitted at relatively low speed and is frequently not felt by the recipient. Although patients were instructed that they might not feel the spray being administered, some repeated administration if they did not feel the spray. While overall, few potential cases of device malfunction were reported (n=325) approximately half of the reported malfunctions were that the device did not appear to administer the dose.

Intentional administration of more sprays certainly resulted in two of the three clinical overdoses, and probably the third, in addition to several of the over administration incidents. Clearly, precise and unambiguous training on this point is essential, and this should be repeatedly emphasised in the advice provided to the patient when the drug is prescribed.

The additional safety features of the spray, namely the loud click and the advancing spray counter, are specifically intended to give the user corroborative evidence of the administration of the spray, independent of any sensation of its arrival in the nose. These features appear to have led to successful use of the product by the patients as there was a low incidence of overdose.

It is noted that the majority of the patients in the studies (who were opioid tolerant at entry) appeared to be able to tolerate over-administration of 100% of the intended dose, as evidenced by 5 of the 7 incidents were this degree of over-administration appeared to have occurred without producing any clinically evident adverse effects.

8.3.13.2. *Other studies*

Not applicable as each dose was dispensed by study staff and not by subjects in Phase 1 studies.

8.3.14. Unintentional exposure

8.3.14.1. *Pivotal studies*

A total of 17,182 spray bottles of FNS were dispensed during the three Phase 3 trials (not including the Extension Period of CP045/06). Each spray bottle of FCNS was supplied in a polyethylene canister fitted with a child-resistant closure mechanism requiring a 2-movement unlocking action for removal. Investigators and study staff impressed upon patients at all appropriate points in the studies, the need to supervise and safeguard their study medication supplies carefully, including returning each bottle to its child resistant container following each use, and to return all supplies to the site pharmacy at the next appropriate visit.

Patients were trained and repeatedly reminded about the high risk of adverse effect or even death should the study medication get into the hands of a child or other person, and were told always to return the spray bottle to its child-resistant container after every use. During the clinical program there have been no reports of access to FCNS by children or others. In view of the potency of fentanyl in opioid-naïve children, it is highly unlikely that exposure in children could have occurred without clinical consequences being reported. No incidents of exposure in household members were reported.

8.3.14.2. *Other studies*

Not applicable as subjects were dose at the research facility and did not take medication home.

8.3.15. Drug abuse potential

8.3.15.1. *Pivotal studies*

The clinical studies had strict procedures for dispensing product and reconciling returned trial supplies. For each bottle returned in the titration, double-blind and open-label treatment phases of the studies a comparison was made between the number of sprays administered as indicated by the counter on each bottle, and the number of episodes recorded as treated in the e-diary.

One patient was withdrawn from Study CP045/06 for the adverse event of intentional drug misuse. This patient had completed Study CP043/06, during which there was no evidence of drug misuse (the patient's total spray discrepancy for the trial was 2 sprays). The total spray discrepancy for this patient during CP045/06 was 86 sprays (145.3% of the expected spray use).

Another patient in Study CP045/06 had the AE of drug abuse recorded at a routine visit on 05th Sep 2007, but continued in the study. On 26th Sep 2007, a telephone contact between the site and the patient reported "subject admitted taking/abusing all 80 doses", and he was withdrawn from the trial (although for the AE of nausea and diarrhoea). The patient's overall positive spray discrepancy for this trial was 46 sprays (143.4% of the expected spray use).

In both cases, supervision by the responsible investigator identified the potential problem before clinically important sequelae arose.

No investigator reported any specific concerns over abuse or diversion for any of the other patients within the trial programme, although this cannot be completely excluded for the patients with larger positive discrepancies. It is noted that dose discrepancy was the most common protocol deviation in all the studies. However, it is likely that in this population any use of medication outside the protocol was for extra episodes of breakthrough pain that were not recorded in the e-diary.

A potent opioid like fentanyl has a significant potential for abuse, and its proper control and supervision is well known in clinical use. However, such abuse is accepted to be unusual in the

terminal cancer population (Ballantyne, 2007). The data from the fentanyl nasal spray trials to date support this assertion, and indicate that the patients targeted by the proposed indication are not likely to abuse or divert the product.

8.3.15.2. *Other studies*

Not applicable as subjects only dosed at study site.

8.4. Postmarketing experience

One PSUR was included in the submission covering the period 31-Aug-2010 to 28-Feb-2011.

PecFent was approved in the European Union via the centralised procedure on 31 August 2010. The product was launched in the United Kingdom on 4 October 2010, and is currently marketed in three countries UK, Ireland (launch: 18 October 2010) and Germany (launch: 22 November 2010).

From launch on 4 October 2010 to 31 December 2010, 5885 bottles of the 100 mcg strength and 4525 bottles of the 400 mcg strength have been sold in the EU (ex-factory). Information on the number of bottles actually prescribed is unknown due to the lag in companies obtaining prescribing information.

Estimated post-marketing exposure to PecFent has been calculated as an average of between 11,528 and 34,915 "patient days" of treatment during the PSUR period based on available sales data and fentanyl citrate defined daily dose.

Six adverse reports have been received by the company in this time. The reports were:

- one serious spontaneous unlisted case of a female patient of an unknown age who experienced visual disturbance (black spots) whilst taking PecFent (fentanyl citrate) for an unreported indication. The prescriber stopped the treatment with PecFent and outcome of the event was unknown. The patient was said to be "…very sick…" and terminal, was taking a variety of largely unspecified medications and the case is without much detail. The company physician assessed the causal relationship as possible on the basis of the implied temporal relationship.
- five medically confirmed reports concerning non-serious listed adverse events.

To date, there have been no new safety signals and no reports of accidental exposure, overdose, or misuse/abuse.

8.5. Evaluator's overall conclusions on clinical safety

Safety data has been appropriately collected in all the clinical trials. While the total number of patients studied is not large fentanyl is a well documented substance and no new safety issues have emerged with the nasal spray formulation. It is noted that the nasal spray was administered concomitantly with the patient's regular opioid medication in all cases and the high background rate of adverse events in this patient population makes assessment of safety of the nasal formulation difficult.

Local nasal tolerability appears satisfactory.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of FCNS in the proposed usage are:

- Fentanyl is a well established drug with over 20 years of clinical use.
- A total of 45,599 episodes of BTCP were treated with FCNS at doses ranging from 100 to 800 µg in a total of approximately 500 patients. The average duration of therapy was 73 days, with 153 subjects being treated for between 90 and 159 days.
- The studies used well-established and validated measures of efficacy and demonstrated that FCNS has a fast onset of action, with onset of efficacy evident from as early as 5 minutes after administration (on some endpoints), and reached clinically meaningful levels within 10 minutes. The effect was maintained throughout the typical (up to 60 minutes) duration of a BTCP episode.
- FCNS has been shown to be statistically significantly superior to both placebo and the currently approved treatment, IRMS, in the treatment of BTCP in opioid-tolerant cancer patients.
- The effective dose can be easily titrated in each patient to provide maximum pain relief whilst minimising adverse effects.
- Patient acceptability assessments indicate that patients are generally satisfied or very satisfied with fentanyl nasal spray in treating episodes of BTCP, and this is supported by the low use of rescue medication following use of the product (6% of episodes during maintenance treatment). The assessments of overall acceptability, speed of relief, and the episode-by-episode reliability of the nasal spray used also significantly favoured fentanyl nasal spray over placebo. Patients also considered fentanyl nasal spray was convenient and easy to use.

9.2. First round assessment of risks

The risks of FCNS in the proposed usage are:

- The expected known AEs which are those for a potent opioid.
- The potential for misuse and abuse

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of fentanyl nasal spray, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

On the basis of the clinical data submitted it is recommended that PecFent be approved.

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