EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ASSESSMENT REPORT

FOR

PECFENT

International Nonproprietary Name:

fentanyl

Procedure No. EMA/H/C/001164

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Archimedes Development Ltd submitted on 17 April 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for PecFent, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(3).

The chosen reference products are:

▪ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength(s), pharmaceutical form(s): Actiq, 200mcg and 400mcg, lozenge
- Marketing authorisation holder: Cephalon UK Ltd
- Date of authorisation: 2000-10-10
- Marketing authorisation granted by:
    - Member State (EEA): UK
    - Marketing authorisation number(s): PL 16260/0003&4

▪ *Medicinal product authorised in the Community/Member State where the application is made or European reference medicinal product:*

- Product name, strength(s), pharmaceutical form(s): Effentora, 100mcg, 200mcg, 400mcg, 600mcg and 800mcg Buccal tablets
- Marketing authorisation holder: Cephalon (Europe)
- Marketing authorisation number(s): EU/1/08/441/001-010
- Marketing authorisation(s) granted by:
    - Community

▪ *Medicinal Product which is or has been authorised in accordance with Community provisions in force used for the demonstration of bioequivalence (if applicable) and/or in other studies.*

- Study reference number CP042/05
- EudraCT number: 2005-005427-33
- Product name, strength(s), pharmaceutical form(s): Actiq, 200mcg, lozenge
- Marketing authorisation holder: Cephalon
- Marketing authorisation(s) granted by:
    - Member State (EEA): UK
    - Marketing authorisation number(s): PL 16260/0003
    - Member State of source: UK

The applicant applied for the following indication:

Management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.

Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

The legal basis for this application refers to:

Article 10 (3) of Directive 2001/83/EC as amended – relating to applications for hybrid medicinal products.

The application submitted is composed of complete administrative information, complete quality data, and appropriate non-clinical and clinical data for a hybrid medicinal product.

Information on Paediatric requirements

Not applicable.

Scientific Advice

The applicant did not seek scientific advice from the CHMP.

The clinical development programme and the submission plan for PecFent (formerly proposed trade name Nasalfent) in Europe were discussed with several national regulatory agencies in 2006 (Sweden, France, The Netherlands, UK). The minutes of the meetings have been provided.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr. Broich **Co-Rapporteur: Dr. Demolis**

- The application was received by the EMA on 17 April 2009.
- The procedure started on 27 May 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2009 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 August 2009 (Annex 2).
- During the meeting on 21-24 September 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 September 2009 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 November 2009.
- The summary report of the inspection carried out at the drug product manufacturing site between 19-23 October 2009 was issued on 27 November 2009
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 January 2010 (Annex 4).
- During the CHMP meeting on 18-21 January 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding issues on 3 May 2010.
- The summary report of the inspection carried out at the drug product manufacturing site between 19-23 April 2010 was issued on 28 May 2010
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 7 June 2010 (and amended versions on 17 and 21 June 2010) (Annex 6).
- During the meeting on 21-24 June 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to PecFent on 24 June 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 June 2010.

2. Scientific discussion

2.1. Introduction

Fentanyl citrate is a potent opioid analgesic (ATC N02AB). Fentanyl, a pure opioid agonist, acts primarily through interaction with μ receptors located in the brain, spinal cord, and smooth muscle to produce its pharmacologic effect. Its analgesic potency is approximately 80 times that of morphine. The primary site of therapeutic action is the central nervous system (CNS). Fentanyl is a widely approved medicinal active substance with well known pharmacodynamic, pharmacokinetic and toxicological properties, available since 1960s in different formulations, including subcutaneous, intravenous, transdermal and transmucosal dosage forms.

PecFent is indicated for the management of breakthrough pain (BTP), recurrent episodes of acute transitory pain, in patients who are already receiving maintenance opioid therapy for chronic cancer pain. BTP is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.

BTP is severe and achieves peak intensity within a few minutes. The ability to achieve a rapid analgesic effect in this case is essential. Treatment should be part of an overall pain management programme and medication to manage BTP should be titrated individually.

The prevalence of BTP is high, with 64% to 89% of patients with chronic cancer pain experiencing such events. The median duration of an episode is 30 minutes and the median number of episodes is 4 per day. The occurrence of 40% to 50% of episodes is unpredictable.

Opioids are usually administered both for background medication and for BTP management. BTP episodes are usually treated with short-acting or normal-release opioid analgesics. It has been shown that fentanyl is suited for the management of BTP. In recently finalised Centralised Procedures, other fentanyl-containing products (FEBT=fentanyl effervescent buccal tablet, Effentora and fentanyl nasal spray, Instanyl) have been approved for the same indication.

The purpose of Archimedes' nasal fentanyl product PecFent is to deliver fentanyl as a controlled quantity into the nasal cavity and thereby to achieve rapid systemic absorption as well as fast onset of action. Fentanyl is assumed to be suitable for nasal administration due to its low molecular weight, high potency and lipid solubility. Through nasal administration, gastrointestinal and hepatic presystemic elimination is bypassed which is expected to enable high absolute bioavailability of the drug substance.

The PecFent formulation incorporates PecSys, a proprietary pectin-based gelling agent which aims to optimise the profile of fentanyl by modulating absorption; allowing short time to Tmax but controlled Cmax. It comprises fentanyl in the form of the citrate salt, pectin, tonicity adjusting agent and preservatives. The solution has a low viscosity and can be delivered using a conventional nasal spray pump. When the spray droplets are deposited into the nose, the pectin interacts with calcium ions present in the nasal mucosal secretions to form soft, mildly adherent gel droplets on the surface of the nasal mucosa.

2.2. Quality aspects

2.2.1. Introduction

PecFent is an aqueous solution containing the drug substance, fentanyl citrate, which is intended for intranasal use, and which uses a proprietary drug delivery system, based on the gelling properties of LM pectin, which modulates the in-vivo absorption. It is regarded as a novel dosage form in the therapy of breakthrough pain claiming fast absorption of fentanyl through the nasal mucosa. Fentanyl is a well known and characterized potent opioid analgesic with a potency about 100 times that of morphine. The active substance has been first marketed in the early 1960s and meanwhile is available in different pharmaceutical forms (including transdermal, parenteral and transmucosal formulations).

The nasal route of absorption avoids first-pass metabolism of the active substance.

The nasal spray is available in strengths of 1.0 mg/ml and 4.0 mg/ml (corresponding to fentanyl) as a multi dose product.

2.2.2. Active Substance

The chemical name of fentanyl citrate is N-phenyl-N-[1-(2-phenylethyl) piperidin-4-yl]propanamide dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate corresponding to the molecular formula $C_{22}H_{28}N_2O \cdot C_6H_8O_7$ and Relative molecular mass 528.6 (salt) or 336.48 (base). Fentanyl citrate is a well-known drug substance monographed in European Pharmacopoeia. It appears as a white or almost white powder, soluble in water, freely soluble in methanol, sparingly soluble in alcohol.

Manufacture

An ASMF has been submitted for the active substance. Fentanyl is manufactured by several chemical and purification steps all sufficiently described. The materials and reagents used were adequately characterised.

Specification

The quality of the drug substance, fentanyl citrate, complies with the specifications and requirements described in the monograph of the European Pharmacopoeia (Ph. Eur.). Additional in-house testings to the Ph. Eur. monograph are: residue on ignition, heavy metals, fentanyl assay and a number of other impurities by an additional HPLC method and particle sizes for the milled active substance.
Batch analysis data were provided for three batches. All batches met the Ph. Eur. specification.

Stability

Stability data for seven batches, all packaged in two different type of containers, stored at 25°C/60% RH up to 60 months and for two batches stored at 40°C/75% RH up to 6 months were presented.
All parameters tested during the stability studies remained within specifications over the period tested. No real tendency in regard to the active substance's degradation can be concluded from the generated data, neither under long term nor accelerated storage conditions.
Overall, the data submitted support the proposed re-test period when stored in the original packages.
In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of development was to produce a preserved nasal spray formulation for the indication of breakthrough pain, ensuring rapid onset of action by initial rapid absorption of fentanyl, followed by a modulated release across the nasal mucosa due to the gelling concept of the formulation. Based on the pharmacokinetic and tolerability data from the Phase I study, the pectin formulation was selected for further development. All subsequent clinical studies used formulations (1.0 mg/ml and 4.0 mg/ml fentanyl) identical to those currently proposed.

Considering fentanyl citrate's solubility it is obvious that the active substance's particle size is no critical parameter regarding the in-vivo performance, since fentanyl citrate is completely dissolved in the nasal solution. Possible interactions between active substance and excipients are not expected and have not been observed based on the results of the stability studies

LM pectin is included as a gelling agent to provide modulated delivery of fentanyl. When the spray droplets of drug product are deposited in the nose, the LM pectin interacts with calcium ions present in the nasal mucosal fluid to form a gel. The fentanyl then diffuses from the pectin gel and is absorbed. This effect has been demonstrated in vitro using a diffusion cell model. In vivo, the gel formulation modulates the systemic uptake of the fentanyl by maintaining the Tmax whilst reducing the Cmax.

Studies demonstrated the fentanyl release/diffusion properties are expected to remain consistent for different batches of drug product through product shelf life irrespective of changes in pectin gel strength.

A blend of LM pectin with sucrose used in PecFent is considered a novel excipient because it has not previously been used in approved pharmaceutical products intended for the nasal route of administration. The specification for LM pectin is based on the compendial specification for pectin and additionally includes functional tests relevant to the performance of the material in PecFent. Additional tests include pectin content, sucrose content, degree of esterification, gel strength and viscosity.

Pectin and sucrose are both commonly used excipients in pharmaceutical and food products. The specification, information on the analytical test methods and validation of the analytical test methods for LM pectin are fully described.

The LM pectin and sucrose blend physicochemical properties and the optimal concentration have been determined to provide a solution with the desirable physicochemical characteristics which gels on contact with a physiological concentration of calcium and forms a well dispersed spray plume appropriate for nasal delivery when delivered via a metered-dose nasal spray. The effect of excipients and on physicochemical and spray properties were studied. Based on the available data, the diffusion of fentanyl from PecFent seems to be highly consistent when prepared using a range of batches of pectin and sucrose blend if they are in accordance with the quality requirements as laid down in the respective specification.

The safety data generated during both the Phase I/II and pivotal Phase III clinical studies have demonstrated excellent local tolerability of PecFent.

PecFent is preserved with phenylethyl alcohol and propyl parahydroxybenzoate (propylparaben). The preservatives have been selected at concentrations reported to be individually efficacious but are used in combination to provide an appropriate spectrum of action against bacteria, yeasts and moulds.
Preservative effectiveness testing (PET), according to Ph. Eur. 5.1.3, has been conducted as part of the development programme and during stability testing to confirm the efficacy of the chosen combination and support the proposed preservative limits at the end of shelf life.

The manufacturing process comprises preparation of a pH-adjusted bulk solution, which is then filled into bottles and capped with the appropriate nasal spray pump. The process has been developed and scaled-up to the current batch size with little change. An automated filling and capping line will be utilized for the commercial manufacture. In order to minimize residual liquid in the spray bottle at the end of patient use, the fill weight will be reduced from 1.73 grams to 1.57 grams.

The development of the manufacturing process is described in sufficient detail. Additional retrospective process validation data was presented for the pilot scale batches. Critical process parameters and steps were defined as well as other manufacturing process related key parameters. Analytical data relating to a range of batch sizes using different processing conditions and at two different manufacturing sites were provided in the report.

A pre-approval inspection, in order to verify the compliance to EU GMP and related guidelines and to the marketing application for the manufacture of PecFent nasal spray has taken place. The manufacturing site can be considered acceptable for the manufacture of PecFent and in compliance with EU GMP.

PecFent is presented in a 5.3 ml capacity, Ph. Eur. Type I glass bottle sealed with a locking screw closure, metered-dose nasal spray pump containing an integrated visual and audible spray-counter and mechanical end-of-use lock. The bottle has a U-shaped internal chamber to minimise fill volume. Each actuation is designed to deliver 100 µl of solution containing 100 µg or 400 µg fentanyl. When primed, the pump will deliver eight sprays before it locks.

The assembled unit will be placed in a child-resistant outer container. The chosen container will comply with the international standard "ISO 8317:2003, Child-resistant packaging - Requirements and testing procedures for reclosable packages".

Testing has been carried out to establish the likelihood of leaching of substances from the plastic components of the pump. From the results, the only one leachable observed at a meaningful level; the limit of which is controlled in the shelf life specification. Other leachables are at or below quantitation limits.
Appropriate studies assess the effect of dosing orientation on priming and performance of the spray pump in different orientations, defined the maximum non-use period and the appropriateness of the fill volume. It was also demonstrated that wiping the actuator nozzle tip between actuations during routine analysis had an insignificant effect on delivered dose weight.

Results from an in-use study indicate that FNS dose delivery is consistent over the proposed in-use life of the product, with non-use periods up to the recommended maximum non-use period.
The robustness of PecFent drug product units in terms of general product integrity and spray performance (delivered dose and droplet size distribution) is studied in a drop test. The results indicate that the product maintains satisfactory performance when dropped and should perform satisfactorily after events that may arise during normal use.

Adventitious agents

None of the excipients used in PecFent are of human or animal origin.

Manufacture of the product

The manufacturing method is based on standard process for solutions. A flow chart of the manufacturing process including IPCs has been provided.
The entire process comprises the following steps: preparation of solution, filtration of the bulk solution, filling and capping of bottles, labeling and secondary packaging.
The description of the manufacturing process is considered sufficient, including specific information on processing variables.
The IPCs suggested by the applicant are sufficient to control the critical steps during manufacture for a non-sterile nasal spray solution.

Product Specification

The release and shelf life specifications for PecFent include tests and limits for appearance (visual), identification (fentanyl: HPLC, UV, citrate: chemical test), assay (HPLC), delivered dose uniformity and mean delivered dose (Ph. Eur.), number of actuations per unit (counting), quantitative determination of preservatives (HPLC), degradation products (HPLC), microbiological examination (Ph. Eur.), pH (potentiometric), osmolality (freezing point depression), gel strength (texture analysis), particulates (Ph. Eur.), droplet size distribution (laser diffraction).

In the summary of batch analysis data, the results of 6 batches covering three batches for each dosage strength were provided corresponding to 1/3 of the proposed production scale. The batches were used in clinical studies. Results comply with the specifications set.

Stability of the product

Stability data is available for a total of eight batches including both dosage strengths and package sizes (filling volumes). The primary stability lots comprise a 1.7 ml fill volume as used in the clinical program. The fill volume of the commercial pack will be reduced to 1.55 ml. Additional supportive data on two primary batches from a different manufacturer has been provided. All batches were manufactured by the proposed manufacturer and all drug substance batches used in the stability batches have been supplied by the current drug substance manufacturer. The formulation of the batches used in the stability studies is identical to the formulation proposed for marketing.

Results of parameters investigated in the stability program, are within the shelf life specifications and show that PecFent is stable. Stability data, supported by preservative efficacy testing, indicate that the two preservatives remain at efficacious levels up to 24 months, when drug product is stored at long term conditions. No significant changes were observed for all parameters investigated during 6 months testing at accelerated storage conditions (40°C/75%RH).

Additional in-use, temperature cycling and photostability studies have been performed. The information is detailed and comprehensible. The temperature cycling study showed that PecFent should remain in specification following exposure to temperature excursions outside the recommended storage conditions. The proposed fentanyl citrate solution demonstrated better photostability than an equivalent aqueous solution. The spray solution should be considered stable to light. However, as a

precautionary measure and to be in line with the recommendations for the active substance, the product should be protected from light.

Overall the results indicate a good chemical and physical stability of the nasal spray stored under standard ICH conditions and therefore the proposed shelf-life and storage conditions are accepted.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion and Conclusions on chemical, pharmaceutical and biological aspects

The quality of PecFent nasal spray is adequately established. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product and novel excipient has been presented. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3. Non-clinical aspects

2.3.1. Introduction

Fentanyl is a potent opioid that acts primarily through interaction with the μ receptors located in the CNS and smooth muscles to produce its analgesic effect. Fentanyl has been widely marketed since the early 1960s in a variety of different formulations. The intranasal spray formulation of fentanyl citrate (Fentanyl Nasal Spray = FNS) was developed to provide rapid relief from recurrent episodes of acute transitory pain, termed breakthrough pain (BTP) in patients, who are already receiving maintenance opioid therapy for chronic cancer pain.

The pivotal repeat dose toxicology studies in rats (3 and 6 months, Study nos. WFEN/P34/05 and WFEN/P37/05) and dogs (9 months, Study no. WFEN/P36/05) and the accompanying toxicokinetic investigations were performed in compliance to GLP standards.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacodynamic activity of fentanyl has been well characterised and is also documented in the scientific literature, so no additional animal pharmacodynamic studies have been submitted. This application relies on published preclinical data to describe primary, secondary and safety pharmacology of fentanyl (i.e. preclinical studies conducted for the reference products, Effentora and Actiq, data cited from the FDA Summary Basis of Approval (SBA) for Actiq (NDA 20-747) and from the public domain).

Fentanyl is a selective μ-opioid receptor agonist showing selectivity over δ- and κ- opioid receptors of around 200-fold depending on the receptor system studied. It acts primarily through interaction with μ-opioid receptors located in the brain, spinal cord and smooth muscle. Fentanyl is around 80-fold more potent than morphine with a significant shorter duration of action. Fentanyl binding in the central nervous system (CNS) occurs at the following sites in decreasing order of strength: midbrain and striatum, hypothalamus, cerebral cortex, hippocampus, brainstem, spinal cord, and cerebellum. Fentanyl interacts to a lesser extent with central and peripheral (e.g. vascular) α-adrenergic and muscarinic (M_3 subtype) receptors. More recently, it has been postulated that P-glycoprotein ATPase activity may in part be involved in the anti-nociceptive effect of fentanyl and other opiates which are substrates for P-glycoprotein, such as morphine (Hamabe *et al.* 2006). Another study demonstrated that opioid side effects are most easily elicited at anti-nociceptive doses for oxycodone, followed by buprenorphine, hydrocodone, morphine, and codeine, with fentanyl having the lowest overall ratio between ED_{50} for side effects and for analgesic potency (Meert and Vermeirsch, 2005).

Secondary pharmacodynamic studies

The secondary pharmacological effects of fentanyl are all well known consequences of exaggerated pharmacological activity and comprise respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria. These effects are adequately delineated in the proposed SmPC and PL. From a non-clinical perspective, no relevant differences in the primary, secondary and safety pharmacological effects of fentanyl following intranasal application administration compared to conventional routes of administration are expected.

2.3.3. Pharmacokinetics

The overall pharmacokinetic properties of fentanyl have been widely analysed in the literature. Apart from the prominent first-pass effect following oral administration, which can be effectively circumvented by the intranasal route, it is not expected that the pharmacokinetics of FNS will significantly differ from that of other routes. For this reason, the CHMP considered acceptable that the application focuses on absorption aspects and refers to publicly available information regarding all other pharmacokinetic data.
Already known interactions with other medicinal products/drugs as MAO-inhibitors, other opioids, anaesthetics, hypnotics, sedatives, antidepressants, neuroleptics, alcohol or inhibitors or inducers of CYP 3A4 are appropriately included in SmPC and PL.

Fentanyl crosses the placenta in animals and humans, and it is excreted into human breast milk. Therefore, women should only breast-feed while taking fentanyl after a careful benefit-risk evaluation, because of the possibility of sedation and/or respiratory depression in their infants. SmPC and PL have been labelled accordingly.

In order to develop a suitable intranasal formulation for FNS, the applicant performed three pharmacokinetic studies (non-GLP) in sheep to evaluate the absorption of different fentanyl formulations, also in part with or without the presence of pectin.

It can be concluded from these studies that fentanyl is absorbed when administered by the nasal route in sheep. However, the number of animals was low, variability high, and the findings were inconclusive with respect to the effect of pectin concentration on absorption. Furthermore, the test species was different from species used in toxicology studies. These data were considered as supportive by CHMP.

The pectin excipient is a well known constituent in foods and medicinal products where it is primarily used as a gelling agent. When the solution is deposited in the nose, the calcium ions within nasal mucosal secretions interact with pectin to form a weak gel. Fentanyl diffuses from the gel and is absorbed through the nasal mucosa resulting in an attenuated C_{max} without compromising t_{max}. Avoidance of high peak plasma concentration could be expected to reduce the risk of adverse effects, while the short t_{max} will still lead to rapid onset of pain relief.

Due to the droplet size characteristics of FNS which favours nasal distribution of fentanyl, potential for exposure of the lung can be regarded as very low.

2.3.4. Toxicology

Single dose toxicity, Repeat dose toxicity and Genotoxicity

With regard to single dose toxicity, reproduction toxicity and genotoxicity potential of FNS, the applicant refers to the reference medicinal products Actiq and Effentora. Moreover, carcinogenicity has not been studied, which is acceptable in the light of the experience gained with other fentanyl-containing products in the same indication and target patient population. In the opinion of the assessors, the submitted results from repeated-dose toxicity studies over three and six months in rats and nine months in dogs represent the first examples of long-term toxicity investigations of fentanyl and hence add to the knowledge on the active substance. Findings in these studies were predominantly restricted to typical pharmacological side effects of fentanyl treatment.

In the 6 months chronic toxicity study in rats, mild anaemia along with minor leukocyte levels and adipose infiltration of the bone marrow was recorded in all FNS-treated groups. In clinical trials with FNS, low haematological values were observed in around 20 % of the patients. The applicant was unable to correlate these signs of anaemia to FNS treatment, because of the progressive or terminal disease status of these patients. From 19 anaemic patients of the phase II/III safety database (N = 506) only one case was potentially attributed to FNS. With respect to adipocyte infiltration of bone marrow subsequent to fentanyl treatment, no clinical information is available. Although these haematological changes are also known for "*Effentora*", it seems noteworthy that effects of FNS were reversible in rats and did not occur in dogs. Moreover, signs of hypercellular bone marrow varied to a comparable extent also among controls. Due to the lack of a clear correlation with FNS administration, the limitation to a single study and the reversibility of the mild effects further non-clinical investigations are not deemed necessary.

Local Tolerance

Local tolerance was analysed as part of the repeated-dose toxicity studies. Both in the three months toxicity study in rats and the nine months chronic toxicity study in dogs, no signs of local intolerability were apparent. In contrast, a higher incidence of minimal to slight goblet cell hypertrophy/hyperplasia in the most anterior and the next following segment of the nasal cavity was found in female rats of the high dose group in the six months toxicity study in rats. No such changes were evident at the end of the recovery period. Hypertrophy/hyperplasia of this cell type is considered to be a reversible regular physiological adaptive response to exposure to a mild irritant. In addition, there is evidence that the rat may be generally more susceptible to toxic effects on nasal cavity than non-rodents due to their thinner nasal mucosa. Although in clinical trials with FNS nasal mucosa related side effects such as sneezing, nasopharyngitis and rhinitis were observed, the overall nasal tolerability was adequately demonstrated in humans. Altogether, the risk that patients who are using FNS will suffer from irreversible nasal toxicity is considered to be highly unlikely.

There were no nasal findings when the vehicle alone, containing propylparaben and phenylethylalcohol, was administered nasally.
Furthermore, higher incidences of alveolar macrophages with foamy/vacuolated cytoplasm were detected in the lungs of both male and female rats administered the high dose and male rats of the intermediate dose group. It is likely that deposition in the lung of the rat might be consequential to the dosing technique (instillation of relatively large dose volumes). Due to interspecies differences in the physiology of the respiratory tract and the droplet size of FNS which rather favours nasal distribution of fentanyl, the possibility for unintentional lung exposure of the target patient population seems to be very low.

Although systemic and local nasal safety factors are absent or marginal in these studies (Systemic SF: rat 0.3-1.6, dog: 4.5-6.3; Intranasal SF: rat < 1, dog < 3) the Rapporteurs believe that further nonclinical studies would not contribute significantly to the benefit/risk evaluation, particularly as FNS was well tolerated when clinically administered.

In the three months repeated-dose toxicity study in rats and in the nine months study in dogs, fentanyl was determined in samples collected from control animals. In the rat study, four animals of the saline control group were concerned, which was explained as sample contaminations since levels were just above the LLOQ. However, in the chronic toxicity study in dogs, one control animal which was supposed to receive pectin obviously received FNS instead. It is agreed that both events did not significantly affect the interpretation of study data, because all other animals of the respective control groups were not contaminated.

Formaldehyde was identified as a leachable in stability tests of FNS and was limited to an appropriate level (max. administration of 800 µl FNS/day). On basis of inhalation limits set by governmental agencies for formaldehyde, adequate safety factors could be derived.

Carcinogenicity

Carcinogenicity studies have not been conducted by the applicant and are not reported in the literature. Due to the indication and the lack of alert regarding a carcinogenic potential based on the mode of action, the genotoxicity data and the clinical experience, the lack of carcinogenicity studies was considered acceptable.

Reproduction Toxicity

The applicant did not conduct any new study and relies on the data detailed in the FDA Summary Basis of Approval for Actiq.
These studies do not fully comply with the current requirements, but this is considered acceptable for fentanyl.

Studies performed in rats with continuous intravenous doses up to 0.5 mg/kg/day via osmotic minipumps implanted subcutaneously did not show adverse effects on embryo-fetal development. In the study published by Fujinaga et al (1986), the plasmatic fentanyl level reached 8.5 ng/ml at the high dose level. This is higher than the Cmax measured in patients following a single 800 µg intranasal dose of PecFent (2.844 ng/ml), but below the Cmax expected in patients receiving the maximal daily dose of 3.2 mg (10.7 ng/ml). In this study, no adverse effect on postnatal development is reported.
In other rat studies, embryonal mortality and pup mortality were enhanced at 0.03 mg/kg IV. The effects on embryo were reproduced in subcutaneous studies, where fertility was impaired.

The proposed wording for reproduction toxicity in SmPC section 5.3 is acceptable.

2.3.5. Ecotoxicity/environmental risk assessment

No experimental environmental risk assessment is required for fentanyl citrate because the predicted concentration in surface water is lower than the action limit, the log Kow is lower than 4.5, and there is no indication that fentanyl might effect the environment at concentrations lower than 10 ng/l.

2.3.6. Discussion on non-clinical aspects

The pharmacodynamic activity of fentanyl has been well characterised and is also documented in the scientific literature, so no additional animal pharmacodynamic studies have been submitted.

This application relies on published preclinical data to describe primary, secondary and safety pharmacology of fentanyl.

2.3.7. Conclusion on the non-clinical aspects

Taking into account all available non-clinical and clinical information, it can be assumed that from a non-clinical point of view nasally administered fentanyl has an acceptable safety profile, if used appropriately.

2.4. Clinical aspects

2.4.1. Introduction

The clinical programme initially submitted for PecFent comprised 2 completed studies: study CP041/04, which was a proof of concept, open-label, multicentre, in-patient phase II study to investigate the efficacy and tolerability of nasal fentanyl solution for the relief of breakthrough pain in cancer patients and study CP043/06, which was a multicentre , placebo-controlled, double-blind, two-phase cross-over phase III study of PecFent in the treatment of breakthrough cancer pain in subjects taking regular opioid therapy and 2 studies ongoing at the time of initial submission: study 044/06 which was a multicentre double-blind double-dummy two-phase cross-over phase III study of PecFent compared to immediate release morphine tablets in the treatment of BTCP in subjects taking regular opioid therapy and study CP045/06 which was an open label phase III study investigating long term safety and tolerability of PecFent in the treatment of breakthrough pain in patients taking regular opioid therapy.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

  (Note: this table reflects the final status of studies CP044/06 and CP045/06 following their completion and submission with Day 120 responses).

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects	Duration of treatment
Efficacy safety phase II	CP041/04 completed	Efficacy, safety and tolerability BTCP	Open, multicentre, in-patients	Intranasal titration phase: FNS 25, 50, 100, 200, 400 up to 800 µg Treatment phase: up to 4 episodes of BTCP	Titration phase: 23 entered, 18 completed Treatment phase: 15 entered, 12 completed	Titration to effective analgesia followed by treatment of up to 4 episodes BTCP
Efficacy safety phase III	CP043/06 completed	Efficacy and safety BTCP	Open, dose-titration phase, followed by double-blind placebo-controlled treatment phase cross-over	Intranasal titration: 100 to 800 µg, up to 4 episodes BTCP/day Double-blind: 10 total doses: 7 doses of 100, 200, 400 or 800 µg FNS. 3 doses of matched placebo. Up to 4 episodes BTCP/day	139 screened 114 open dose titration phase 83 double blind treatment phase 73 completed	Maximum duration approx 8 weeks
Efficacy safety phase III	CP044/06 Ongoing at initial submission	Efficacy and safety BTCP	Open dose titration phase, followed by double-blind double-dummy comparator controlled treatment phase. Cross-over	Intranasal titration: 100 to 800 µg. up to 4 episodes BTCP/day. Double-blind: 10 total doses: 5 doses of 100, 200, 400 or 800 µg FNS plus tablet placebo. 5 doses of IRMS tablets plus spray placebo. Up to 4 episodes BTCP/day	135 patients screened 110 open dose titration phase 84 double blind treatment phase 79 completed.	Maximum duration approx 8 weeks
Safety phase III	CP045/06 Ongoing at initial submission	Long term safety. Patients newly enrolled or enrolled from CP043/06 and CP044/06	Open dose titration phase (newly enrolled patients) followed by open treatment phase	Intranasal titration (newly enrolled patients): 100 to 800 µg up to 4episodes BTCP/day. Open treatment phase: 100, 200, 400 or 800 µg FNS up to 4 episodes BTCP/day	351 screened, 287 open dose titration phase 356 open-label treatment phase: 234 newly enrolled, 66 enrolled from CP043/06, 56 from CP044/06	The maximum main study duration for individual subjects will be 5 months. Continuation in an extension period at the discretion of the subject/clinician

2.4.2. Pharmacokinetics

The pharmacokinetic profile of fentanyl is well known and has been extensively characterized (Mather and Gourlay 1991). Therefore, only studies designed to characterize those aspects of the pharmacokinetics of PecFent that were expected to be unique for this novel dosage form have been conducted for the purpose of this MAA.

Breakthrough cancer pain is characterised by rapid onset (median interval from onset to peak pain intensity is three minutes, range one second to thirty minutes), moderate to severe in intensity, and of relatively short duration (mean 30 minutes). Because of these characteristics, an ideal treatment for breakthrough cancer pain would have a rapid onset and relatively short duration of analgesic effect. It is acknowledged that several advantages may be realized from delivering fentanyl intranasally: (1) avoidance of hepatic first-pass elimination, gut wall metabolism, and/or destruction in gastrointestinal fluids; (2) the rate and extent of absorption and the plasma level-time profile can be made quite comparable to that obtained by i.v. medication; and (3) the rich vasculature and numerous microvilli structure in the nasal cavity offer a feasible and desirable site for absorption of systemically effective drugs (Chien & Chang 1987. Intranasal drug delivery for systemic medications, Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 4, Issue 2, p. 67-194).

Overall, four pharmacokinetic (PK) studies have been carried out:

Study CP037/02
Investigation of Bioavailability, PK, safety and tolerance of 3 novel nasal spray formulations vs OTFC lozenge (Actiq) (clinical phase 2002-05-08 to 2002-06-24)

Study CP042/05
Investigation of Bioavailability, PK (dose proportionality), safety and tolerance of increasing doses vs OTFC lozenge (Actiq) (clinical phase 2006-01-11 to 2006-04-10)

Study CP047/07
Investigation of Bioavailability, PK (dose accumulation), safety and tolerance of repeat doses (single dose vs two doses with 1, 2, and 4 hours in-between vs 8 consecutive doses) (clinical phase 2007-08-01 to 2007-09-20)

Study CP048/07
Investigation of Bioavailability, PK, safety and tolerance in subjects suffering from allergic rhinitis (in symptomatic, symptomatic but oxymetazoline-treated, and asymptomatic states) (clinical phase 2007-11-21 to 2008-06-16)

Absorption

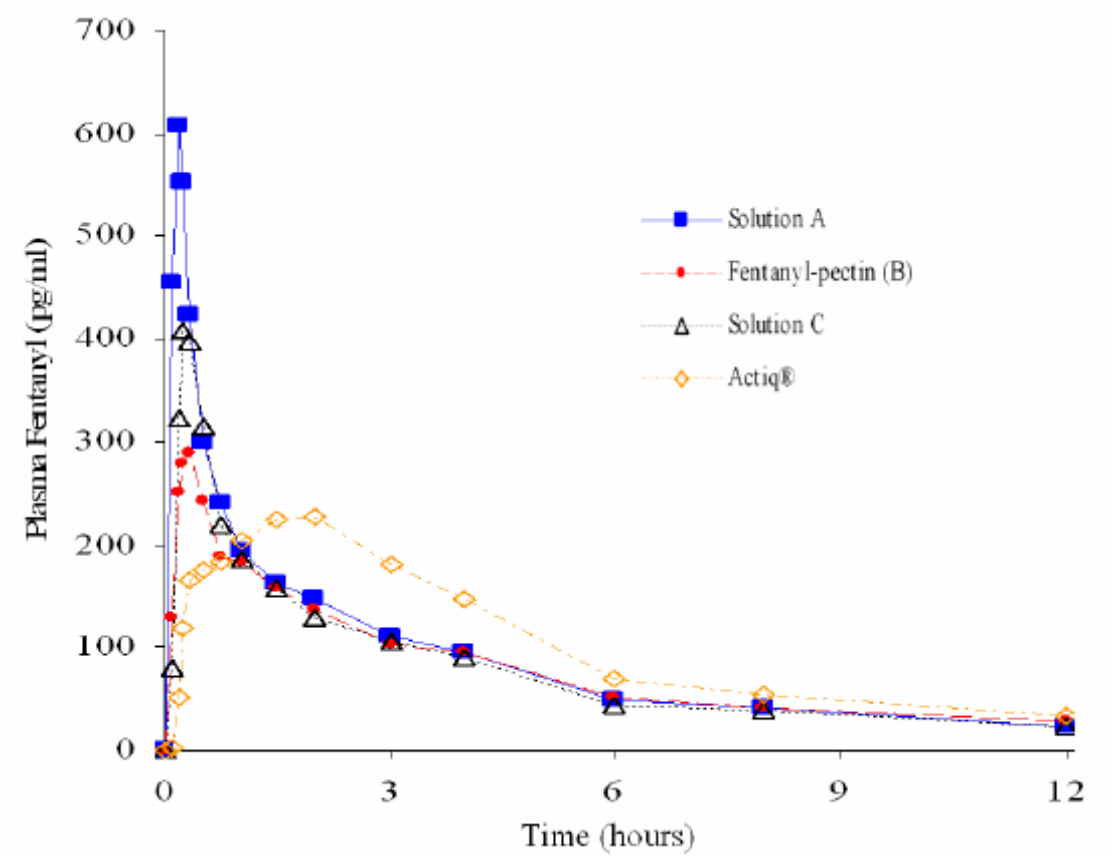
Study CP037/02
A randomised, single centre, four-way complete crossover trial to assess the pharmacokinetics and safety of three novel nasal formulations of fentanyl, including, fentanyl-pectin (Solution B), compared to the oral transmucosal (lozenge) formulation

This study was performed to select a nasal fentanyl formulation that would maintain the early Tmax obtained with nasal administration of fentanyl whilst modulating Cmax, to achieve a fast onset of action without additional side effects compared to existing routes of administration of fentanyl. The primary efficacy measures were the Cmax, Tmax, and AUC of plasma fentanyl following administration of each formulation. The secondary efficacy measure was the bioavailability of the nasal formulations relative to the oral lozenge, Frel. Safety and tolerability were assessed by a reactogenicity (local nasal tolerability) questionnaire, completed after each nasal dose, and by monitoring other adverse events throughout the study.

During the study, 18 healthy male and female subjects (aged ≥ 18 and ≤ 50 years) each received 100 µg fentanyl (1.0 mg/ml fentanyl base, in the form of the citrate salt) in the three different nasal formulations and 200 µg fentanyl as the lozenge formulation, on four separate dosing periods (following a randomised Latin square design). Naltrexone was administered to the subjects before and during each dosing period to block the pharmacological effects of the fentanyl. Blood samples were

collected at regular intervals up to 24 hours after each dose administration. There was a washout period of, at least, three days between each dose.

Plasma concentrations of fentanyl following single dose administration of different formulations to healthy volunteers (Study CP037/02)



Fentanyl (100 µg) appeared to be absorbed more rapidly and with greater relative bioavailability when administered nasally compared to Actiq, the oral transmucosal lozenge treatment (200 µg).

Each of the three different FCNS-formulations displayed rapid increase of plasma concentration with Tmax ranging from approx. 10 min to approx. 19 min. As expected, Tmax of the OTFC oral lozenge was observed considerably slower (approx. 90 min). It is important to note that it is known from previous applications for fentanyl-containing BTP-medications that the onset of efficacy occurs much earlier than attainment of Tmax since analgesia may begin at plasma concentrations well below Cmax. The applicant's decision to proceed the clinical development programme with the formulation that showed the lowest Cmax was considered appropriate by CHMP.

The data presented above were not dose normalised for the Actiq 200 µg dose. As compared to the 100 µg doses of the fentanyl formulations, Actiq displayed lower Cmax values. This finding is explainable by the fact that only a portion of the OTFC dose is absorbed transmucosally. The remaining portion is swallowed and is either later absorbed or presystemically eliminated by first-pass metabolism. The first pass effect observed after oral administration also explains the less than proportional increase in AUC for the 200 µg Actiq dose as compared to the 100 µg FCNS dose.

Standardised methods were employed for assessing product safety in the Phase I studies. Local tolerability was assessed by the subjects using a specifically designed reactogenicity questionnaire and completing an overall assessment of the convenience of nasal dosing at the end of each nasal treatment. A clinical safety assessment by an ear, nose and throat (ENT) specialist was

made using a conventional rating scale at the beginning and end of the study, and nasal assessments were also carried out by the study physician.

Data on local nasal reactogenicity and inconvenience & clinician nasal assessment in study CP037/02 point to the fentanyl-pectin formulation having the lowest incidence rate. The inconveniences reported were mainly related to nasal discharge and occurrence of erythema.

In the formulation chosen for further development pectin is included as a gelling agent. The solution has a low viscosity and can be delivered using a conventional nasal spray. When the spray droplets are deposited into the nose, the pectin interacts with calcium ions present in the nasal mucosal secretions to form soft, mildly adherent gel droplets on the surface of the nasal mucosa. In order to be absorbed into the systemic circulation, fentanyl needs to diffuse from the pectin gel before crossing the nasal mucosa.

It remains unclear for how long the gel prevails in the nasal mucosa and how sensitive this gel is expected to be e.g. in case of blowing the nose by the patient. In study CP042/05 the subjects were advised to refrain from blowing their nose for up to one hour after dosing

Overall, the favourable pharmacokinetic profile together with the apparently higher tolerability of the pectin formulation indicated that this was the preferred formulation for further development. The three further Phase I studies discussed below all used this pectin formulation of fentanyl nasal spray.

- **Influence of food**

As nasal fentanyl is absorbed across the nasal mucosa, its bioavailability is not affected by food intake. The absence of studies is acceptable.

Distribution

Fentanyl is highly lipophilic and is well distributed beyond the vascular system (Mather and Gourlay 1991) with a large apparent volume of distribution (Vz) of approximately 1100 l following an intravenous dose of fentanyl. The nasal route of administration should not impact on the systemic distribution of fentanyl. Animal data have shown that fentanyl undergoes initial rapid distribution that represents an equilibration of fentanyl between plasma and the highly perfused tissues (brain, heart, and lungs). Fentanyl reaches the deep-tissue compartment at a slower rate compared with the highly perfused tissues. Subsequently, fentanyl is redistributed between the deep tissue compartment (muscle and fat) and the plasma.

The plasma protein binding of fentanyl is 80% to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis.

Elimination

Excretion

Disposition of fentanyl after administration as PecFent has not specifically been characterized in a mass-balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the faeces.

Despite its long t½, fentanyl is known to exhibit a short duration of action that is consistent with rapid and extensive uptake of fentanyl in highly perfused tissues (brain, heart, and lungs) (Mather and Gourlay 1991). This rapid uptake, as well as the redistribution of fentanyl between a deep tissue compartment and the plasma, results in plasma concentrations that decrease rapidly to below a clinically relevant threshold.

Metabolism

The metabolism of fentanyl has been extensively described in the literature, and there is no reason to believe that administration by the intranasal route would alter the metabolic pathways; therefore, the

metabolic profile of fentanyl after administration as PecFent has not specifically been characterized in clinical studies. However, the progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver.

Fentanyl is primarily metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome CYP3A4 isoforms. Other metabolites represent only a minor portion of the fentanyl dose. In animal studies, norfentanyl and minor metabolites were not found to have significant pharmacological activity (Goromaru et al 1982, Hug and Murphy 1981, Mather 1983).

Pharmacokinetics of metabolites

The metabolites are mainly excreted in the urine, while faecal excretion is less important (Mather and Gourlay 1991, Murphy et al 1979).

Consequences of possible genetic polymorphism

Not examined.

Dose proportionality and time dependencies

Dose proportionality

Study CP042/05
Study CP042/05 was a single centre, dose-proportionality, five-way trial to assess the relative bioavailability, pharmacokinetics and safety of four escalating doses of Fentanyl Citrate Nasal Spray (FCNS, 100, 200, 400, 800 µg) compared to the oral transmucosal (OTFC, lozenge) formulation.

Primary Objectives were:

1. To determine the pharmacokinetics of different single doses of FCNS in healthy subjects and compare these to the pharmacokinetics of the commercially available OTFC lozenge.
2. To determine the relative bioavailability of FCNS compared to the commercially available OTFC lozenge.
3. To assess the dose proportionality of different single doses of FCNS.

Safety
4. To determine local and systemic safety and tolerability of different single doses of FCNS.
5. To compare the local and systemic safety and tolerability of FNCS with the commercially available OTFC lozenge.

The FCNS doses were administered in an escalating dose order and the OTFC dose was administered at any point in the FCNS sequence, according to a randomisation code. There were at least three days of washout between dose periods. For doses of 200 µg and 800 µg two sprays of 100 µg respectively two sprays of 400 µg (one in each nostril) were administered.

An overall of 17 blood samples (5 ml) for fentanyl analysis were taken up to 48 hours post-dose.

As known from study CP037/02, Tmax is expected to occur after about 19 minutes. Five blood samples were taken within the first 30 min post-administration, which is believed to adequately cover the time of maximum plasma concentration. Terminal elimination of fentanyl is known to take long due to redistribution from peripheral tissues. Hence, the overall sampling period of 48 hours was considered adequate.

17 subjects were enrolled, of which 12 (8 males, 4 females) completed the study successfully and comprised the PK population.

Although the test products were administered under naltrexone block, high doses (up to 800 µg) were applied to healthy volunteers in study CP042/05. Accordingly, it does not surprise that five out of 17 enrolled subjects dropped out. 4 subjects were withdrawn from the study (1 due to AEs [vomiting after

naltrexone], 2 due to opiate intolerance, 1 due to positive drugs of abuse urine testing) and 1 subject withdrew consent.
Safety assessment in PK study CP042/05 conducted in healthy volunteers is to focus on local tolerability and application site disorders.

Cmax increased in a dose-proportional manner for the fentanyl nasal spray treatments over the dose range used. Dose proportionality was established for AUC, but was only indicated for AUCt.

The summary pharmacokinetic parameters are given in the following Table:

Table 12: Summary of Fentanyl Pharmacokinetic Results: PK Population

Parameter	Summary Statistic	100 µg FCNS	200 µg FCNS	400 µg FCNS	800 µg FCNS	200 µg OTFC
Number of subjects receiving treatment		16	14	13	12	13
C_{max} (pg/ml)	n	16	14	13	12	13
	Arithmetic mean	351.511	780.820	1552.07	2844.01	317.394
	SD	180.356	381.063	406.692	1592.10	94.8889
	Geometric mean	295.378	695.286	1503.68	2458.24	304.301
T_{max} (h)	n	16	14	13	12	13
	Median	0.33	0.25	0.35	0.34	1.50
	Range	0.08 - 1.50	0.17 - 1.60	0.25 - 0.75	0.17 - 3.00	0.50 - 8.00
T_{lag} (h)	n	16	14	13	12	13
	Median	0.00	0.00	0.00	0.00	0.08
	Range	0.00 - 0.10	0.00 - 0.00	0.00 - 0.00	0.00 - 0.00	0.00 - 0.25
λ_z (h^{-1})	n	5	8	12	12	7
	Arithmetic mean	0.03216	0.0337	0.0495	0.03865	0.0405
	SD	0.004521	0.01391	0.0143	0.0156	0.01214
	Geometric mean	0.03191	0.03085	0.04782	0.03436	0.03891
$t_{½}$ (h)	n	5	8	12	12	7
	Arithmetic mean	21.89	24.90	14.95	24.91	18.56
	SD	2.971	12.77	3.688	23.05	5.833
	Geometric mean	21.72	22.47	14.49	20.17	17.81
AUC_t (pg·h/ml)	n	16	14	13	12	13
	Arithmetic mean	984.75	2432.9	6791.5	13383	2147.8
	SD	572.43	1170.1	1531.0	3122.2	1157.4
	Geometric mean	801.90	2192.7	6649.0	13051	1879.9
AUC (pg·h/ml)	n	5	8	12	12	7
	Arithmetic mean	2460.5	4359.9	7513.4	17272	3735.0
	SD	439.27	1298.8	2003.0	8440.3	1223.3
	Geometric mean	2428.0	4205.1	7322.3	15876	3580.6
F_{rel} (%)[1]	n	4	5	6	7	-
	Arithmetic mean	116.742	122.715	122.606	110.805	-
	SD	17.191	21.741	29.653	21.261	-
	Geometric mean	115.821	121.087	119.240	108.903	-
F_{rel} (%)[2]	n	13	12	12	12	-
	Arithmetic mean	121.014	134.313	179.617	177.447	-
	SD	64.515	69.751	87.810	89.947	-
	Geometric mean	102.546	119.491	163.215	160.776	-

Data source: Section 14.3.4
[1] = Based on AUC [2] = Based on AUC_t

Statistical demonstration of dose proportionality was been provided for Cmax and AUC. More than dose proportional increases in plasma concentration have been observed for the extent of absorption from time zero to the last quantifiable timepoint post-dose (AUCt).
The applicant argued that this may be related to the low number of subjects on the one side and plasma concentrations below LLOQ for the lower doses on the other side, and was considered acceptable by CHMP. In any case, for this kind of on-demand medication, Tmax and Cmax are considered the more relevant PK parameters since they characterize the rapid increase in fentanyl's plasma concentrations.
Overall, dose proportionality over the proposed dose range of 100 to 800 µg per puff was shown to an acceptable degree.

Safety results

Local tolerability was monitored objectively (ENT specialist assessment) and subjectively by the volunteers (reactogenicity questionnaire). The most often reported clinical finding was erythema of mild intensity. In one case local findings are considered to be related to an ongoing upper respiratory tract infection. However, occurrence of local findings appears to be related to the number of nasal spray actuations as well (accumulation in the right nostril). Overall, the PecFent formulation did not demonstrate particular local tolerability problems and the majority of subjects rated FCNS administration as not inconvenient.

Time dependency

Study CP047/07
This was a single centre, five-way open trial to assess the relative bioavailability, pharmacokinetics and safety of multiple doses of PecFent (Fentanyl Citrate Nasal Spray [FCNS]) compared to a single NasalFent dose.

It was conducted in 13 healthy male and female volunteers (10 completed) that received fentanyl intranasally as a single 100 µg dose, as two 100 µg doses (administered one, two and four hours apart) and as eight 100 µg doses administered consecutively. Five treatments regimens were administered to each subject in the order listed below ('dose escalation'), with a washout period of at least three days between each regimen:

- Treatment A: Single dose of 100 µg PecFent (100 mcl) into the right nostril
- Treatment B: Two doses of 100 µg PecFent (2 x 100 mcl) 4 hours apart into the right nostril
- Treatment C: Two doses of 100 µg PecFent (2 x 100 mcl) 2 hours apart into the right nostril
- Treatment D: Two doses of 100 µg PecFent (2 x 100 mcl) 1 hour apart into the right nostril
- Treatment E: Eight doses of 100 µg PecFent (8 x 100 mcl) consecutively into the right nostril

The primary objective was to evaluate the pharmacokinetics (PK) of PecFent following eight immediate consecutive administrations of 100 µg (8 x 100 µl) and after various time periods between two 100 µg (2 x 100 µl) doses. The safety objective was to determine and compare the local and systemic safety and tolerability profiles of single and multiple doses of PecFent.

Subjects received two doses of 100 µg of PecFent 1, 2 or 4 h apart in order to gain insight into the length of time a patient should wait before taking a second dose of PecFent for pain relief. Eight doses of 100 µg of PecFent were administered to the same nostril to determine what happens if the contents of one device (8 x 100 µl) is taken at once. The PK data obtained following a single dose of 100 µg of PecFent were used as reference.

The proposed PecFent labelling specifies that PecFent is to be used for treatment of BTP episodes with an interval of at least 4 hours in-between. The design of study CP047/07 (two sprays of FCNS 1, 2 and 4 hours apart) is suitable to provide data on possible dose accumulation and thus to justify the proposed dosing recommendation.

The intranasal fentanyl doses were administered in an ascending total dose manner as a safety precaution. Each treatment was administered under a naltrexone block to prevent the development of the unwanted effects of opiate administration in naïve subjects.

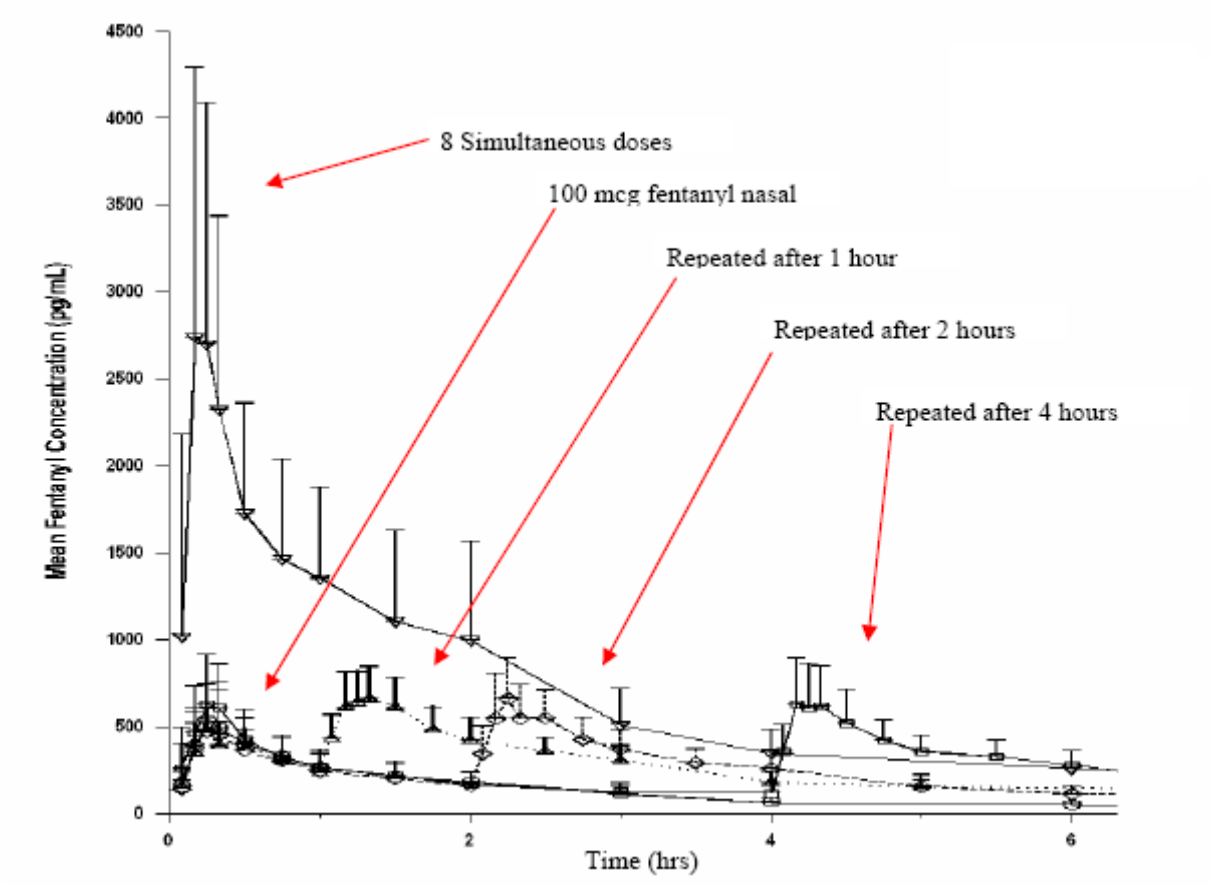
AEs were monitored for the duration of the study. Nasal examinations (performed by an ENT specialist or a suitably trained clinician) and reactogenicity questioning were performed.

Based on the fentanyl plasma concentrations, the following parameters were determined:

• Cmax and Tmax (after each single dose in Treatments A, B, C and D and after eight consecutive doses in Treatment E)

• AUCt, AUC0-24 and AUC (for each treatment overall)

Mean (+SD) Plasma Fentanyl Concentration-time Profiles after five fentanyl nasal spray treatment regimens (for the first 6 hours post-administration)



Mean (SD) PK parameters for fentanyl: PK Population

Table 10: Summary of Fentanyl Pharmacokinetic Results: PK Population

		Treatment				
Parameter	Summary Statistic	A	B	C	D	E
Number of subjects receiving treatment		12	11	10	10	10
C_{max1} (pg/mL)*	n	12	11	10	10	10
	Arithmetic mean	572.098	642.506	511.463	513.324	2955.323
	SD	230.297	263.887	245.872	124.966	1501.465
	Geometric mean	520.562	582.201	468.315	499.305	2603.741
C_{max2} (pg/mL)*	n	NA	11	10	10	NA
	Arithmetic mean		698.905	687.458	742.671	
	SD		245.973	217.247	177.795	
	Geometric mean		657.834	658.640	724.242	
T_{max1} (h)*	n	12	11	10	10	10
	Median	0.300	0.267	0.333	0.250	0.250
	Range	0.18 – 0.50	0.17 – 0.78	0.25 – 0.75	0.08 – 0.50	0.17 – 0.33
T_{max2} (h)*	n	NA	11	10	10	NA
	Median		0.250	0.250	0.333	
	Range		0.17 – 0.75	0.17 – 0.53	0.17 – 0.62	
λ_z (h^{-1})	n	11	11	10	10	10
	Arithmetic mean	0.21646	0.10619	0.11856	0.10893	0.10196
	SD	0.12248	0.05056	0.04260	0.03740	0.07198
	Geometric mean	0.18913	0.09814	0.11105	0.10427	0.08905
$t_{½z}$ (h)	n	11	11	10	10	10
	Arithmetic mean	4.134	7.524	6.701	6.886	8.466
	SD	1.993	2.592	2.708	1.713	3.012
	Geometric mean	3.665	7.063	6.242	6.648	7.784
AUC_t (pg·h/mL)	n	12	11	10	10	10
	Arithmetic mean	1132.4	2835.4	2509.9	2776.0	6791.4
	SD	453.5	1061.1	821.3	794.6	2902.9
	Geometric mean	1046.6	2685.0	2385.2	2672.3	6151.8
$AUC_{0\text{-}24}$ (pg·h/mL)	n	12	11	10	10	10
	Arithmetic mean	1264.8	2847.4	2596.6	2823.2	6857.6
	SD	466.1	942.0	731.1	698.3	2847.5
	Geometric mean	1179.7	2730.5	2500.2	2747.9	6239.8
AUC (pg·h/mL)	n	11	11	10	10	10
	Arithmetic mean	1319.8	3160.6	2833.9	3103.8	7859.5
	SD	548.5	1100.7	910.1	799.5	3536.3
	Geometric mean	1211.1	3012.3	2699.1	3009.3	7104.0

Data source: Section 14.3.3
Treatment Codes: A = 100 µg NasalFent; B = 2 x 100 µg NasalFent given 4 h apart; C = 2 x 100 µg NasalFent given 2 h apart; D = 2 x 100 µg NasalFent given 1 h apart; E = 8 x 100 µg NasalFent given consecutively.
* For the two dose treatment regimens (Treatments B, C & D) C_{max1} and T_{max1} are following first dose and C_{max2} and T_{max2} are following the second dose.

For each of the two-dose regimens, the maximal fentanyl concentration was higher after the second dose of PecFent than after the first dose. When the two doses of PecFent were administered one and two hours apart the difference in Cmax was statistically significant. Conversely, there was no statistically significant increase in Cmax after the 2nd dose when the proposed 4 hours interval was observed between two administrations. Hence, the proposed dosing recommendations do not lead to dose accumulation.

Following eight consecutive 100 µg PecFent administrations, there was an approx. 5.2 fold increase in Cmax and an approx. 5.4 fold increase in AUC0-24. Statistical comparison following dose normalisation found that AUC, AUC0-24 and AUCt were not equivalent between a single administration and eight consecutive administrations and hence the increase in exposure after administration of eight consecutive doses of 100 µg PecFent (8 x 100 µl) was not dose-proportional.

The applicant concludes that this lack of proportionality supports the assumption that the gel-forming characteristics of the PecFent formulation are impaired following repeated immediate administrations and thus its ability to deliver additional fentanyl and considers that this may represent an additional safety feature of the formulation following intentional or unintentional over-administration. Indeed, there were less than dose-proportional increases after repetitive consecutive actuations. It is unclear whether the deviation from dose-proportionality seen following the eight-dose regimen is due to the limited capacity of the nasal cavity, or whether it reflects an overwhelming of the gel-forming properties of the formulation, which would facilitate early run-off (and non-absorption) of un-gelled product. However, with an ordinary aqueous nasal solution drainage into the oropharynx is expected to be even more pronounced (and, in consequence, even lower increases in fentanyl plasma levels). Therefore, the about 5-fold increase in bioavailability (instead of 8-fold) is not regarded as a particular safety feature as compared to other BTP medications. In any way, there are no regulatory requirements to demonstrate the safety of a medicinal product after intentional overdose.

Safety

Of the 35 subjects screened for this study, 13 subjects (10 male and 3 female) were enrolled into the study and received study medication and 10 subjects successfully completed the study according to the protocol. Three male subjects were withdrawn from the study; one due to withdrawal of consent and two as a result of AEs, which were assessed as not related to the study drug.

There was a total of 106 AEs reported by 100% of subjects (13/13), of which 9.4% (10/106) from 5 subjects were assigned to pre-dose and the remaining 90.6% (96/106) from 12 subjects were study drug treatment-emergent.

Despite the administration of naltrexone to block or reduce the occurrence of AEs associated with the administration of fentanyl, the majority of the most common treatment-related AEs were characteristic of the side effects of opioid administration. These included headache (9 instances in 6 subjects), vomiting (9 instances in 3 subjects), dizziness (7 instances in 3 subjects) and nausea (5 instances in 4 subjects). In addition, treatment-related AEs related to the nasal route of drug administration were observed, including nasal mucosal erythema (6 instances in 4 subjects), rhinorrhoea (6 instances in 3 subjects), nasal congestion (4 instances in 3 subjects) and nasal discomfort (2 instances in 1 subject).

Like already observed in the previous PK studies, PecFent does not appear to cause undue local tolerability problems and seems to be well tolerated.

Special populations

- **Impaired renal or hepatic function**

No data are available on the use of nasal fentanyl in patients with severe hepatic or renal disease. After IV administration, the PK of fentanyl is unaffected in patients with compensated liver cirrhosis, whereas high dosages result in a markedly prolonged elimination half-life (Scholz et al. 1996). As fentanyl is metabolised to inactive metabolites in the liver, patients with severe hepatic disease may have a decreased metabolism and should therefore be observed carefully. Approximately 75-80% of a fentanyl dose is excreted into the urine, mostly as metabolites with less than 6% as unchanged drug (McClain & Hug 1980). Thus, patients with renal impairment might have a delayed elimination. However, renal insufficiency does not appear to alter PK properties significant after fentanyl bolus administration.

The lack of specific data on the influence of hepatic and renal impairment on the pharmacokinetics of Instanyl has been appropriately addressed in the product particulars. Although fentanyl kinetics are known to be altered as a result of hepatic and renal disease due to alterations in metabolic clearance and plasma protein binding, the duration of effect for the initial dose of fentanyl is largely determined by the rate of distribution of the drug (Hug and Murphy 1981, Mather 1983, Mather and Gourlay 1991). Diminished metabolic clearance may therefore become significant, primarily with repeated dosing or at very high single doses.

In the current SmPC proposal the following statement is given under section 4.2:

Hepatic or renal impairment. PecFent should be administered with caution to patients with moderate or severe hepatic or renal impairment (see section 4.4)

And In Section 4.4:

In addition, PecFent should be administered with caution to patients with hepatic or renal impairment. The influence of hepatic and renal impairment on the pharmacokinetics of the medicinal product has not been evaluated; however, when administered intravenously the clearance of fentanyl has been shown to be altered in hepatic and renal impairment due to alterations in metabolic clearance and plasma proteins. Therefore, special care should be taken during the titration process in patients with moderate or severe hepatic or renal impairment.

- **Gender, Weight**

No formal clinical pharmacology studies were specifically conducted to study the effect of gender or weight on the pharmacokinetics of fentanyl formulated as PecFent.

Each PecFent patient is to be titrated to the successful dose individually. The applicant was requested to examine whether trends towards changes of bioavailability of PecFent were discernable by pooling data according to gender and/or weight across the entire PK database generated for PecFent: no effect of these parameters was apparent.

- **Race**

PK studies were conducted in the UK, the phase II study was conducted in Canada, and the pivotal phase III trial (CP043/06) was conducted at 36 active sites in the US, Costa Rica and Argentina. The active comparator phase III study CP044/06 was conducted at 35 active sites in India and seven EU Members States, while the open-label safety study CP045/06 was conducted in 91 active sites in Argentina, Costa Rica, Canada, the US, India and eight EU Member States.

With regard to ethnicity, the database is acceptable for a medicinal product intended for the European market.

- **Elderly, Children**

No specific PK studies have been conducted on the use of PecFent in either the elderly (older than 65 years) or children and adolescents less than 18 years old.

Due to the lack of data on safety and efficacy, PecFent is not recommended for use in children and adolescents.

Differences in the PK profile as a function of age have been reported in the literature. In individuals aged >60 years the apparent elimination half-life of nasal administered fentanyl may be significantly longer. In a study by Bentley et al (1982) higher serum concentrations of fentanyl in elderly patients than in younger adult patients (< 50 years) were seen, despite equivalent dosing. The prolonged fentanyl elimination in elderly patients results mainly from reduced drug clearance. In a postoperative study of five younger (age 30-65 years) and 6 elderly (age 78-88 years) the elimination half-life of fentanyl was 23 hours longer in the elderly compared to the younger patients (Esteve et al. 1991). These data suggest that a given dose of fentanyl will last longer in elderly patients than in younger

adult patients. Hence, elderly patients should be observed carefully for signs of fentanyl toxicity.

The Applicant was requested to pool data from the pivotal trials by age, and examine whether any trends (successful dose, PK etc) were discernible for elderly patients.

Table 8.1: Proportions of patients titrating to each dose during PecFent clinical studies, by age group (ISS population)

Patient Group	Successful titrated dose				All n=399
	100 mcg n=70	200 mcg n=87	400 mcg n=129	800 mcg n=113	
Age					
≤ 60 years	67.1	78.2	71.3	77.9	73.9
> 60 years	32.9	21.8	28.7	22.1	26.1
≤ 65 years	78.6	86.2	82.9	84.1	83.2
> 65 years	21.4	13.8	17.1	15.9	16.8
≤ 75 years	94.3	97.7	96.1	96.5	96.2
> 75 years	5.7	2.3	3.9	3.5	3.8

Source: ISS Post hoc analysis; Post Hoc 21-2.6

For none of the examined age groups (60, 65, 75 years) there was a clear tendency to titrate to either higher or lower PecFent doses.

The SmPC section "use in the elderly" therefore reads as follows:

In the PecFent clinical trial programme, 26.1% of patients were over 60 years of age, 16.8% over 65 years and 3.8% over 75 years. There was no indication that older patients tended to titrate to lower doses or experience more adverse reactions. Nevertheless, in view of the importance of renal and hepatic function in the metabolism and clearance of fentanyl, additional care should be exercised in the use of PecFent in the elderly. No data on the pharmacokinetics of PecFent in elderly patients are available.

Pharmacokinetic interaction studies

- ***In vitro***

No in-vitro studies have been performed to assess the impact of potential metabolic interactions on the administration of PecFent.

- ***In vivo***

Fentanyl is primarily metabolized in the liver and intestinal mucosa by the cytochrome CYP3A4/5 isoforms to norfentanyl. Drugs that inhibit CYP3A4/5 activity may decrease the systemic clearance of fentanyl.

Itraconazole, a potent CYP3A4 inhibitor, at 200 mg per day orally for 4 days had no significant effect on the pharmacokinetics of intravenous fentanyl (Palkama et al 1998). However, oral ritonavir, one of the most potent CYP3A4 inhibitors, has been shown to reduce the clearance of intravenous fentanyl by two-thirds. The interaction between ritonavir and fentanyl was investigated in 11 healthy volunteers in a randomized crossover study (Olkkola et al 1999). Subjects received oral ritonavir or placebo for 3 days.

The results suggested that ritonavir may decrease the clearance of fentanyl by 67%, resulting in a nearly 3-fold increase in fentanyl AUC0-∞. Coadministration of ritonavir in patients receiving PecFent has not been studied; however, the concomitant use of potent CYP3A4 inhibitors, such as ritonavir, with PecFent may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic effect and adverse events, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of ritonavir

or other CYP3A4 inhibitors and PecFent is not recommended unless the patient is closely monitored. Drugs that induce CYP3A4/5 activity may decrease the bioavailability and increase the systemic clearance of fentanyl. Thus, patients who begin or end therapy with potent inducers of CYP3A4/5 (e.g. rifampicin, carbamazepine, phenytoin) while receiving PecFent should be monitored for a change in opioid effects and, if warranted, the dose of PecFent should be adjusted accordingly.

The proposed SmPC section 4.5 is fully in line with the recently approved SmPC for Effentora (wording of the CYP 3A4 paragraph, MAO inhibitor paragraph and additional pharmacological interaction regarding the concomitant use of fentanyl with partial opioid agonsists/antagonists, e.g. buprenorphine, nalbuphine, pentazosine).

Study CP048/07

To investigate whether the PecFent PK profile could be influenced by co-existing acute rhinitis and/or co-administration of nasal decongestants like e.g. oxymetazoline, PK study CP048/07 was performed.

It was a single centre, three-way cross-over trial to assess the relative bioavailability, pharmacokinetics, safety and tolerability of single doses of PecFent (Fentanyl Citrate Nasal Spray [FCNS]) when administered to subjects with seasonal allergic rhinitis in symptomatic, symptomatic but treated (with oxymetazoline) and asymptomatic states.
The primary objective was to determine and compare the pharmacokinetic profiles of single doses of PecFent during symptomatic rhinitis when untreated (Active), symptomatic rhinitis when treated (Treated) and asymptomatic (Asymptomatic, Reference) conditions. The order of exposure to each of these conditions was randomized for each subject and separated by a 14 day wash-out period. 132 male and female subjects, aged 18 to 65 years (91 ragweed and 41 tree pollen), were enrolled. Of these 54 volunteers were randomized and 28 subjects completed the study. PecFent 100µg administered to subjects while asymptomatic was used as reference.

The safety objective was to determine and compare the local and systemic safety and tolerability of single doses of PecFent in subjects with seasonal allergic rhinitis, whilst they were in the above states.

All eligible subjects who volunteered for the study had documented evidence of seasonal allergic rhinitis due to either ragweed or tree pollen. If they passed the screening visit, they were enrolled and their allergy induced through exposure in an Environmental Exposure Chamber (EEC).

Given the rapid absorption of fentanyl after intranasal application, it is evident that the rate and degree of absorption of fentanyl is highly dependent upon the perfusion properties of nasal vasculature.

The results of this study showed that by administration of vasoconstrictive agents like oxymetazoline two hours before PecFent administration Cmax was about halved while time to maximum concentration was more than doubled. Co-existing seasonal allergic rhinitis did not deteriorate local tolerability of PecFent. Similar results have been obtained in another application for a fentanyl-containing nasal spray.

The issue is adequately reflected in section 4.5 of the proposed SmPC.

Concomitant use of nasally administered oxymetazoline has been shown to decrease the absorption of PecFent (see section 5.2). The concomitant use of nasally administered vasoconstrictive decongestants during titration is therefore not recommended as this may lead to patients titrating to a dose that is higher than required. PecFent maintenance treatment may also be less effective in patients with rhinitis when administered concomitantly with a nasal vasoconstrictive decongestant. If this occurs, patients should be advised to discontinue their decongestant.

2.4.3. Pharmacodynamics

Mechanism of action

Fentanyl citrate (ATC code N02AB) is a potent opioid analgesic with an analgesic potency approximately 80 times that of morphine. Fentanyl, a pure opioid agonist, acts primarily through

interaction with μ-opioid receptors located in the brain, spinal cord, and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS).

Primary and Secondary pharmacology

Three different oral transmucosal application forms of fentanyl citrate (Actiq, as lozenges with integral oromucosal applicator, OTFC; Effentora, as effervescence buccal tablet, FEBT; Abstral, as sublingual tablet) have already been developed and marketed for the same indication. The differences in the pharmacokinetic profile between these products and intranasally applied fentanyl are explained in terms of differences regarding the rate and extent of absorption of fentanyl. Therefore, dose inferences from one product to the other are virtually impossible as reflected by the need for individual dosing if the patient is switched from one product to another. To define the clinically relevant dose range for FCNS, study CP041/04 was performed.

Study CP041/04
Phase II study CP041/04 was an open-label, multi-centre, in-patient study to investigate the efficacy and tolerability of nasal fentanyl solution for the relief of breakthrough pain in cancer patients.

The primary objective of this study was to determine the efficacy of Archimedes' nasal fentanyl-pectin solution for the relief of breakthrough pain in cancer patients. The secondary objective was to establish the acceptability of FCNS by patients for the relief of breakthrough pain and as an additional objective the study also aimed to evaluate the safety and tolerability of the nasal fentanyl-pectin solution.

After PK characterisation the clinical development of the product was continued by initiating a proof-of-principle Phase II trial, Study CP041/04, that was conducted as an open-label, multi-centre, in-patient study, carried out in Canada, using a single dose disposable spray device, delivering 25 μg, 100 μg or 400 μg fentanyl. The study population comprised hospital in-patients with cancer over the age of 18 requiring background opioid therapy on a regular basis, and as required to relieve episodes of breakthrough pain. Their breakthrough pain had to be of at least moderate severity (pain score ≥2 on a five-point pain scale) and opioid responsive.

Study CP041/04 was subdivided into two parts. Part 1 investigated the efficacious dose of nasal fentanyl required to alleviate BTP in patients requiring medication of acute pain. During period 1, patients received incremental doses of 25 μg, 50 μg, 100 μg, 200 μg, 400 μg and 800 μg fentanyl (maximum of 3 episodes of BTP) in an attempt to ascertain the efficacious dose.

Using a 5 point pain scale, pain intensity was evaluated. The dose which achieved meaningful reduction in pain intensity was selected as the efficacious dose. Meaningful pain relief is defined as a reduction of 2 or more points in the pain intensity score.

Part 1 - 1st Episode of BTP
The staff administered the required dose of nasal fentanyl (25μg). Pain intensity scores were obtained pre-dose and at 5 and 10 minutes after the initial dose. If the PI decreases by 2 points from 'baseline' then the clinic staff continued to monitor the patient at the intervals defined in the protocol. 25μg was chosen as the effective dose.

If the pain score did not decrease by 2 points, the staff administered additional nasal fentanyl (25μg). The cumulative dose was then 50μg. Again the pain intensity score was assessed with comparison to the original 'baseline' score. If the pain score decreased by 2 points from 'baseline', then the clinic staff continued to monitor the subject at the intervals defined in the protocol. 50μg was chosen as the effective dose.

If the pain score did not decrease by 2 points, the patients was dosed with an additional 2 sprays of the required study medication (25μg x 2 = 50μg). The cumulative dose at this point was 100μg. The subject was then assessed again at 5 and 10 minutes. If the pain score decreased by 2 points from 'baseline', then the clinic staff continued to monitor the subject at the intervals defined in the protocol. Note: The next episode of BTP was to be dosed in Part 1 – 2nd Episode of BTP at 100 μg.

If the pain score did not decrease by 2 points (from 'baseline'), the patient was administered rescue medication and moved to the next drug strength.

Part 1 – 2nd Episode of BTP
All of the above mentioned procedures were followed using a 1.0mg/ml device (i.e. starting dose 100 µg)

Part 1 – 3rd Episode of BTP
Upon continuing to the 3rd episode of BTP in Part 1, the above mentioned procedures were followed using a 4.0mg/ml device (i.e. starting dose of 400 µg). The patient could receive a maximum of 2 sprays (cumulative dose of 800µg). If the patient did respond to this strength of medication, the patient was withdrawn and did not enter Part 2 of the study.

The protocol required that patients in Part 1 who responded successfully to 100 or 400µg of fentanyl from 4 separate spray administrations of the 0.25 or 1.0mg/ml strength, repeated that dose as a single spray at the next episode of BTP continuing in Part 1.

The 5-point PI (Pain Intensity) scale used was a simplified version of the more established 11-point scale, and asked the patient to rate their current pain intensity according to the following definitions:
0 = no, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe pain

This scale has the disadvantage of being less sensitive to minor changes in pain intensity, but had the advantage (in the context of a proof-of-concept study) of reducing the risk of false positive conclusions being reached. The use of varying pain intensity scales does not compromise overall data interpretability since the essential demonstration of efficacy and safety is provided by study CP043/06.

PI scores were collected at baseline, then at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes post-dosing with study medication. The resultant data were analysed in the fashion established by the earlier BTCP studies, by calculating and plotting pain intensity difference (PID) from baseline.

PR (Pain Relief) was assessed using the well-established 5-point PR scale, according to the following definitions:
0 = no, 1 = slight, 2 = moderate, 3 = good, 4 = total relief (i.e., no pain)

Meaningful pain relief was defined as a change in pain score of 2, or more, points. The time to meaningful pain relief was derived for each patient for each episode of BTP evaluated in Part 2 (55 episodes). Duration of meaningful pain relief was calculated as the time interval over which the reduction in the pain intensity score was equal or larger than 2 points.

There were 75 potential patients considered for this study. Twenty-nine (29) patients were consented and 23 started Part 1. Fifteen (15) patients began Part 2 and 12 patients completed the entire study and were considered in the efficacy data set (mean age 59 years ranging from 43 to 75, 13 Caucasian – 2 Native American, 8 female - 7 male).

The efficacy population was based on 55 episodes of BTP treated with nasal fentanyl-pectin solution in 15 patients. Of the 55 episodes of BTP in 53 episodes, patients expressed some degree of pain relief with nasal fentanyl-pectin solution, and in 40 episodes, patients experienced meaningful pain relief. All patients experienced meaningful pain relief for at least one episode of BTP. All doses of nasal fentanyl were effective in at least one patient.

At their individual selected dose, all 15 patients analyzed for efficacy experienced meaningful pain relief. However, three subjects (002, 101 and 208) received up to 800µg of nasal fentanyl in Part 1 of the study without experiencing meaningful pain relief. These subjects are considered to have left the study prematurely.

Low doses of 25 µg or 50 µg were possible in this study by offering an additional 0.25 mg/ml solution which is not proposed for marketing. Six (6) out of 15 patients defined 25 µg or 50 µg as their individually effective doses.

These doses were not carried forward to the subsequent phase III trial CP043/06. However, the efficacy dataset comprises 15 subjects only and is thus regarded as rather small. Furthermore, during subsequent efficacy assessment the low doses did not prove consistently effective in terms of a higher incidence of both non-responding episodes of breakthrough pain (18.2% vs 6.1%) and even consecutive worsening of the pain score during the 60 min post-administration period (22.7% vs

9.1%). Hence, in the respective six subjects definition of 25 and 50 µg as the individually effective dose during titration, was regarded by CHMP as premature and mistaken.

With regard to efficacy it could be concluded that the data obtained in this proof-of-principle study CP041/04 justified to pursue further phase III trails with the test product in order to demonstrate a positive efficacy-safety balance.

2.4.4. Discussion on clinical pharmacology

Four PK studies have been submitted. Results show that a single dose of PecFent has reproducible pharmacokinetics across the four studies. Tmax values following a single dose of PecFent ranged from 15 to 21 minutes, demonstrating that a clinically significant plasma concentration was quickly reached. It is evident that a rapid rise in plasma levels constitutes a prerequisite for rapid onset of pain relief in a clinical situation. However, it has been demonstrated in previous applications that the analgesic effect may well start earlier than at the calculated Tmax (at plasma levels lower than Cmax).

In study CP037/02, fentanyl appeared to be absorbed more rapidly and gave greater Cmax values at a dose of 100 µg compared to the oral transmucosal lozenge, Actiq, at a dose of 200 µg; this, together with the finding that the relative bioavailability of PecFent was approx. 146% compared to Actiq, indicates nasal bioavailability to be greater than oral/transmucosal.

In study CP042/05, dose proportionality was observed for Cmax and AUC over the dose range employed, but could not be established for AUCt. Since, rapid rise in plasma levels (best characterized by Tmax, Cmax) is an essential feature for this kind of medication, dose proportionality of PecFent over the 100-800 µg dose range is regarded as adequately demonstrated. PecFent is proposed for marketing in two different concentrations (1 mg/ml and 4 mg/ml), i.e. that the intermediate dose (200 µg) and the maximum dose (800 µg) is enabled by two actuations of half the dose (one in each nostril). By demonstrating dose linearity across the entire dose range of 100 to 800 µg it is shown at the same time that the method of administration (one or two successive puffs, one in each nostril) does not interfere with the bioavailability of the PecFent formulation.

In Phase I study CP047/07, multiple doses of PecFent were evaluated. Increases in Cmax values seen following a second dose given one, two, and four hours after the initial were statistically significant for the one- and two-hour intervals. PecFent is labelled to be used in BTP episodes with a minimum time interval of 4 hours between the episodes. Hence, no dose accumulation is to be expected when the proposed 4 hour time span is observed.

Dose proportionality was not observed following eight consecutive doses in the same nostril, indicating reduced exposure following repeated, immediate dosing. Instead, there was a 5.2 fold increase in Cmax and an approx. 5.4 fold increase in AUC0-24, only. Based on this finding the applicant suggests the existence of an additional safety feature of the gel-forming mode of action of fentanyl nasal spray. However, this conclusion is questioned since drainage into the oropharynx is expected to be even more pronounced in case of ordinary aqueous fentanyl nasal spray solutions.

Study CP048/07 investigated the pharmacokinetics of single doses of PecFent in healthy subjects suffering from seasonal allergic rhinitis, due to either ragweed or tree pollen. It was found that the clinical efficacy of PecFent is unlikely to be significantly affected by untreated allergic rhinitis occurring in a patient already established on a given dose, but may be impaired in a patient with rhinitis using a vasoconstrictive nasal decongestant such as oxymetazoline. The issue is adequately reflected in section 4.5 of the SmPC.

A review of results from the local nasal reactogenicity questionnaire for studies CP042/05, CP047/07 and CP048/07 using the final (pH-adjusted) PecFent formulation did not indicate any trends towards increased nasal symptoms following treatment and the scores were generally low indicating that the formulation was well tolerated.

During the evaluation, the CHMP raised a concern on why pectin was included in the PecFent formulation as a gelling agent, since the gel formation could in principle cause lower Cmax and later Tmax values as compared to simple aqueous solutions. Since the pectin formulation and simple aqueous solution have not directly been compared in a PK study, the Applicant addressed this issue by overlaying the PecFent plasma concentration curve with the one of Instanyl (data taken from a

publication of Christrup et al., 2008). Christrup and co-workers compared the PK profile after intranasal and intravenous administration of fentanyl and calculated a Tmax value of about 11 min for the intranasal route. In the PecFent dose proportionality study CP042/05 Tmax values ranged from approx. 15 to 19 min over the entire 100-800 µg dose range. Therefore the inclusion of pectin does not fundamentally alter the time to maximum plasma concentration.

As already mentioned, the analgesic effect occurs at lower than maximum plasma concentrations and earlier than formal attainment of Tmax. This is reflected by early pain assessment time points for PecFent (from 5 min onwards) and was previously observed in preceding MAA for fentanyl-containing breakthrough pain medications.

On the other side, it is obvious that Cmax achieved with the aqueous solution is about three times higher than the one achieved with PecFent (across study comparison). The Applicant points out that the lower Cmax values are intended to cause fewer adverse events. This line of reasoning was not fully endorsed by CHMP as neither for the aqueous fentanyl solution nor for PecFent a clear relationship between rapid attainment of high plasma levels and increased occurrence of typical AEs (somnolence, respiratory depression) was observed. This might be explainable by the fact that only opioid tolerant patients were included in the clinical studies.

About 80% of Cmax is maintained for 30 min post-administration for the pectin formulation, thus the kinetic profile of PecFent adequately matches the average time course of a breakthrough pain episode. In more than 90% of PecFent-treated episodes, patients did not need further medication.

2.4.5. Conclusions on clinical pharmacology

The pharmacological profile of fentanyl is well established. The rationale for using fentanyl in the management of BTP is based on its high analgesic potency, the rapid onset and the short duration of effect. In the proof-of-principle study CP041/04 a dose range of 25 to 800 µg was tested in cancer patients. This study demonstrates that patients dose-titrated to an effective BTP relief dose of nasal fentanyl-pectin solution (25 - 800µg) obtain pain relief within 10 min of dosing and gain maximal benefit within 60 min. As discussed, the low doses did not prove consistently effective during the subsequent efficacy assessment and were not further developed.

In pain therapy, it is generally difficult to establish a relationship between the plasma concentration of the active substance and the clinical effect. This may be explained by the fact that response to an analgesic is largely individual and varies from patient to patient. Initially, PecFent is to be titrated individually to a successful dose for each patient, and this is adequately reflected in the SmPC.

2.5. Clinical efficacy

Demonstration of efficacy of the novel PecFent formulation is mainly based on the phase II dose-finding, proof-of-principle study CP041/04 and the pivotal phase III trial CP043/06.

2.5.1. Dose response study(ies)

Following generation of Phase I data, which demonstrated the pharmacokinetic profile of fentanyl delivered by the PecSys intranasal delivery system, an open-label, multi-centre, in-patient Phase II trial, Study CP041/04, already described, was conducted in order to confirm the efficacy, safety, tolerability and acceptability of fentanyl nasal spray in opioid-tolerant patients with breakthrough cancer pain.

The study was conducted using unit dose presentations delivering 25, 100 or 400 µg fentanyl per spray, allowing doses of 25, 50, 100, 200, 400 and 800 µg to be administered by using one or two sprays per dose. This study produced first efficacy and tolerability data, which were used as the basis for choosing the 100 and 400 µg strengths as most suitable for further development. The 100 and 400 µg strengths

enabled doses of 100, 200, 400 and 800 µg to be delivered, achieved by administering either one or two sprays from each strength respectively.

A multi-dose presentation was developed for the Phase III trials, incorporating risk minimisation features like a visual numerical dose counter, also an audible click after each actuation to help prevent accidental over-administration. The spray pump also locks after the eighth spray has been administered to confirm to the patient that the last dose has been delivered.

The formulation tested in the clinical trials had been optimized, in particular in terms of gelling agent, isotonicity agent and preservatives to both provide good local tolerability and to deliver the most appropriate absorption properties, pharmacokinetic profile and thus optimise efficacy and safety. The formulation and presentation proposed for commercialisation is identical to that used in the Phase III programme.

2.5.2. Main studies

Two phase III trials that provide the pivotal clinical data are presented in this application:

Study CP043/06
Phase III multi-centre, placebo-controlled, randomised, double-blind, two-phase, cross-over study of fentanyl nasal spray. Subjects were dosed with 100 µg, 200 µg, 400 µg, 800 µg fentanyl nasal spray or placebo.

Study CP045/06
Phase III multi-centre, open-label study of fentanyl nasal spray assessing safety. This study was submitted as an interim analysis in the initial submission and in full at day 120. Subjects were dosed with 100 µg, 200 µg, 400 µg or 800 µg fentanyl nasal spray. Subjects were newly enrolled or may have entered after completing Study CP043/06 or Study CP044/06.

Additionally, a further comparator study was underway (Study CP044/06) and was submitted at day 120 of the procedure, to compare the efficacy and safety of fentanyl nasal spray at the same doses with those of immediate release morphine sulphate.

Study CP043/06

Methods

Study Participants

Study CP043/06 was a multi-centre, placebo-controlled, double-blind, two-phase crossover study of PecFent (at the time: Nasalfent, Fentanyl Citrate Nasal Spray) in the treatment of breakthrough cancer pain (BTCP) in subjects taking regular opioid therapy.

Patients (≥18 years) who were taking at least 60 mg oral morphine or equivalent for at least 1 week for cancer-related pain as regular, 24-hour medication for their underlying persistent cancer pain were eligible to enrol into an initial open-label, dose-titration phase.

Eligible patients were experiencing, on average, but not necessarily every day, 1 to 4 episodes of BTCP (Breakthrough Cancer Pain) per day that were adequately controlled with a stable dose of standard rescue medication, typically a fast-acting opioid, of which the patient was to have an adequate supply throughout the study. Breakthrough pain was defined as a transitory flare of moderate to severe pain (on a 4-point scale from 0 to 3 [none, mild, moderate, severe]) that occurred on a background of persistent pain controlled to moderate intensity or less by the opioid regimen. If the patient had more than 1 type of breakthrough pain, or had breakthrough pain in more than 1 location, only 1 of the pains was identified as a "target" breakthrough pain.

Patients who successfully completed the dose-titration phase were then to continue into a double-blind treatment phase, where up to 10 episodes of breakthrough pain were treated with the study drug.

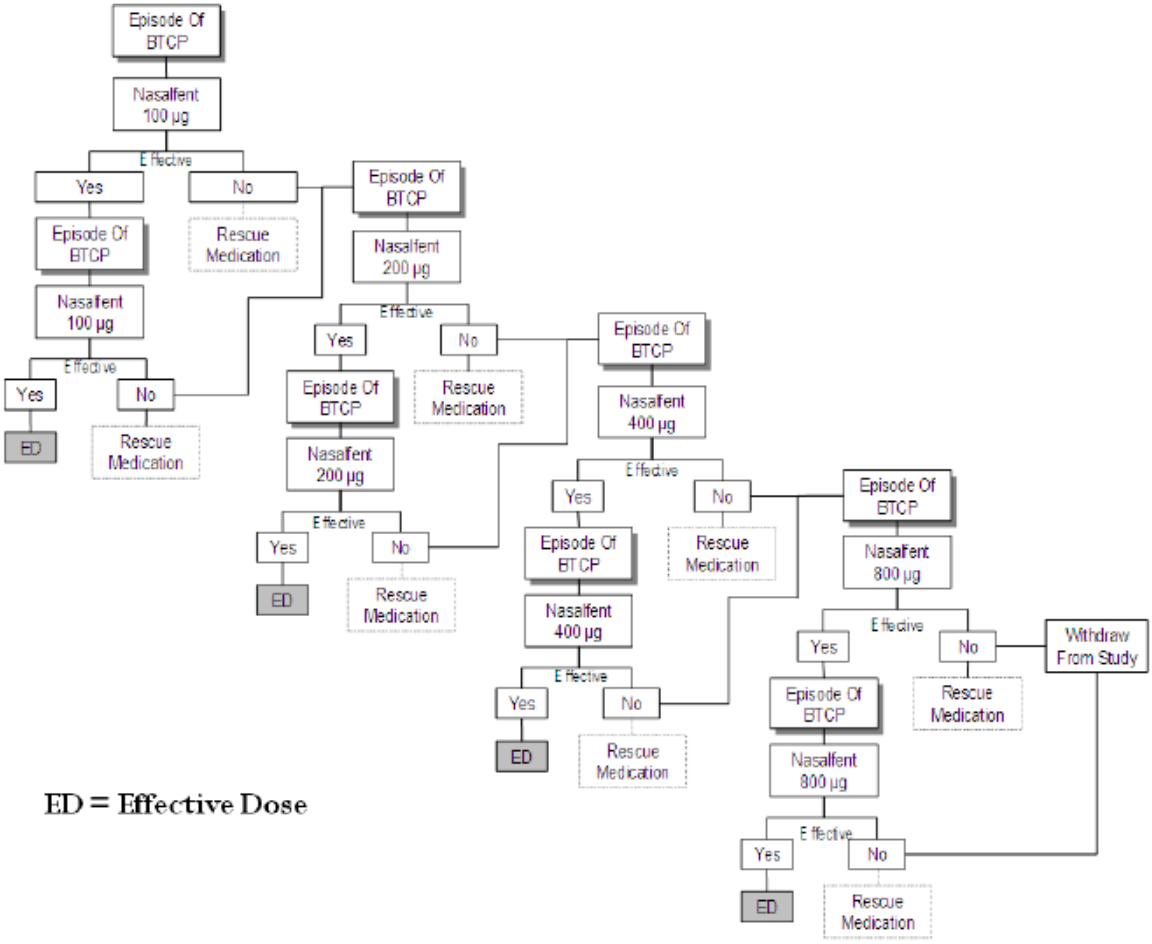
Treatments

The study consisted of 4 phases: screening phase (up to 10 days), open dose-titration phase (up to a maximum of 14 days), double-blind randomised placebo controlled crossover phase (3 days minimum to 21 days maximum), and end of treatment phase (between 1 and 14 days after the last dose). Patients were required to come to the study centre for up to 4 visits. The total duration of individual patient participation was approximately 6 to 8 weeks.

The objective of the open dose titration phase was to titrate each patient to the dose of PecFent that treat 2 consecutive episodes of target BTCP (acceptable pain relief within 30 minutes on 1 type and 1 location of BTCP) without unacceptable AEs. The first dose (100 µg) was taken at study site and observed for a minimum of 1 hour by medically trained personnel. Subsequent titration doses could have been taken in the home environment but under close (daily telephonic) supervision of study site personnel.
The titration steps were as follows: the patient received 100 µg as the initial dose. If this first dose was considered effective (acceptable pain relief within 30 minutes without unacceptable AEs) the next episode was treated with the same dose. PecFent doses were titrated sequentially up to 200, 400 or 800 µg until an effective dose was obtained. Once the same dose of PecFent was deemed to have effectively treated 2 consecutive episodes of target BTCP, titration was complete and an effective dose determined. Following this titration phase, the patient returned to the study site to enter the double-blind period. He was then supplied with a drug pack containing 10 blinded bottles containing either the PecFent at the efficacious dose (7 bottles) or placebo (3 bottles) and returned to home to treat 10 subsequent episodes of the target BTCP.

The dose-titration schedule is presented in the Figure below.

Figure 2 Dose-Titration Schedule



ED = Effective Dose

It is acknowledged that the study design described above represents a kind of enrichment paradigm but this design feature was not considered by CHMP likely to compromise overall data validity since it reflects clinical practice.

Objectives

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

Outcomes/endpoints

All primary and secondary efficacy data were recorded by each patient using a e-diary after training. The primary efficacy variable was the patient-averaged summed pain intensity difference (SPID) from 5 to 30 minutes post-dose.

The key secondary patient-level efficacy variables were as follows:

- SPID at 10, 15, 45, and 60 minutes post-dose.
- Pain Intensity (PI) score at 5, 10, 15, 30, 45, and 60 minutes post-dose.
- 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.

Among other secondary efficacy endpoints a responder and rescue medication usage analysis was undertaken:

- 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 post-dose.
- Rescue medication usage.

Pain intensity was assessed using an 11-point scale (0=no pain to 10=worst possible pain) and PR was assessed using a 5-point scale (0=none to 4=complete).

Information on whether or not the patient decided to take additional medication for the relief of pain for each episode (yes or no) together with the type, amount, and timing was collected.

The patient's global assessment, including overall satisfaction, ease of use, and convenience, was assessed using a 4-point scale: 1 (not satisfied); 2 (neither satisfied nor dissatisfied); 3 (satisfied); 4 (very satisfied).

Sample size

Sample size: based on data for Actiq, with a difference of 2.25 with a SD of 4.35 for mean SPID values, with a power of 90% at a significant level of 0.05, a sample size of 80 patients was required for a cross over study. In order to achieve that 80 patients completed the study, 180 patients were needed to enter the open phase.

Randomisation

In view of the multiple crossover nature of the study design, patients were not assigned to separate treatment groups, but received both treatments (active:placebo in a 7:3 ratio) according to the randomization schedule provided by an un-blinded statistician not otherwise working on the study. This multi-crossover design permits the comparison of two treatment modalities across multiple episodes in the same patient thereby avoiding the impact of between-patient differences in response to the treatments being compared, increasing the statistical power of the study to demonstrate any differences between the treatments, and the CHMP considered it suitable for this kind of on-demand medication.

Statistical methods

The modified intent-to-treat (mITT) and per-protocol (PP) pain intensity analyses utilized the LOCF method to impute missing PI values due to omission, prior to calculating the average values for each patient.

Data were summarized 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 α = 0.05 (2-sided). Confidence intervals (CIs), where detailed, had 95% coverage probability, were 2-sided and were based on the normal approximation.

Analysis population: the primary statistical analyses were performed on the mITT population and the supportive analyses on the PP population, defined as follows.
mITT population: all patients in the randomised population that treated at least one mITT evaluable episode with PecFent and 1 with placebo defined as follows: episode treated with the study drug, with baseline and at least 1 post baseline PI measurement.
PP population: all patients included in the mITT population in whom at least 2 PP episodes had been treated (1 with each of the 2 treatments), all PP episodes were those

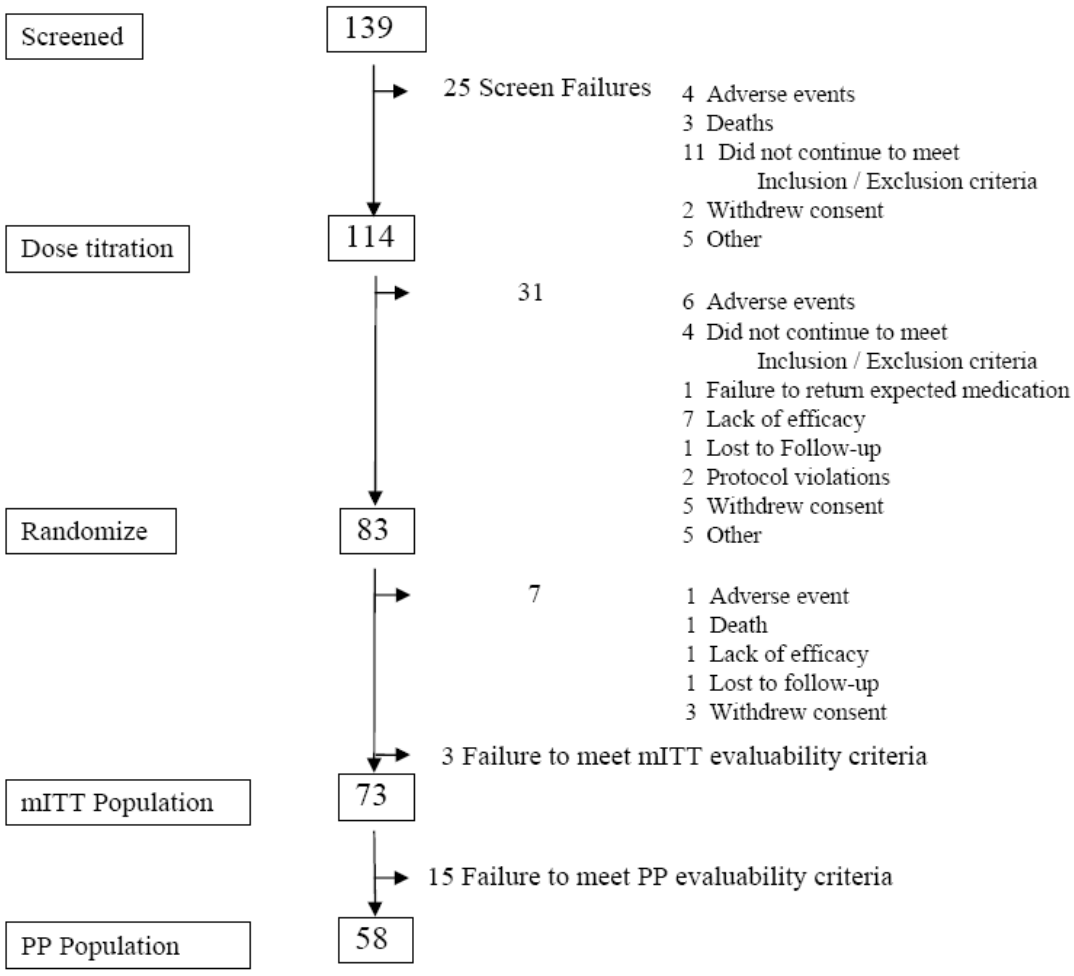
- Treated in patients who met all the study entry criteria and had no major protocol violations
- With PI scores for baseline, 5, 10, 15 and 30 minutes postdose
- That had not been treated with additional 'rescue' medication prior to 30 minutes postdose
- Treated as part of an ascending sequence of bottle numbers, with the correct number of sprays / actuations used, according to the post-study compliance check.

Efficacy analyses were performed using analysis of covariance (ANCOVA).

Results

Participant flow

Disposition of patients: a total of 139 patients were screened and 114 (82%) entered the open phase. 113 patients received at least one dose of PecFent. 83 patients (72.8% of those entering the open phase) identified an effective dose of PecFent and were randomised to the double-blind treatment. 76 patients (91.6%)completed the double-blind phase. The disposition of patients is summarised below.



Recruitment

The clinical period lasted from 2006-12-13 till 2008-07-28. The clinical study report was released on 2009-03-29.

The study was conducted at 58 sites (36 active) in the United States, Costa Rica, and Argentina.

Baseline data

The demographic characteristics of the population are summarised below.

Summary of patients' demographic characteristics: open, dose-titration phase (safety population)

Parameter	Summary Statistics
Age (years)	
N	113
Mean (SD)	53.8 (11.60)
Standard Error	1.09
Median	53.0
Min – Max	21 - 86
Age (years)	
<= 60 years	82 (72.6)
> 60 years	31 (27.4)
Race [N (%)]	
Caucasian	77 (68.1)
Black	13 (11.5)
Chinese/Japanese Asian	0 (0.0)
Southeast Asian	2 (1.8)
Other	21 (18.6)
Gender [N (%)]	
Male	60 (53.1)
Female	53 (46.9)
Weight (kg)	
N	113
Mean (SD)	78.8 (18.52)
Standard Error	1.74
Median	78.1
Min – Max	45.0 - 147.7
ECOG score [1]	
0	18 (15.9)
1	59 (52.2)
2	36 (31.9)

[1] ECOG = Eastern Cooperative Oncology group (ECOG) scores
SD = standard deviation; Min = minimum; Max = maximum

Concomitant medications: 111 (98.2%) patients reported use of concomitant medication. The most commonly used (by more than 10% of patients) were gabapentin(22.1%), zolpidem tartrate (15.9%), hydromorphone hydrochloride (14.2%), pregabalin (12.4%) oxycocet (11.5%), oxycodone (10.6%) and ibuprofen (10.6%).
All patients used opioids, the most commonly used being morphine sulphate (25.7%), fentanyl (23.9%), oxycodone hydrochloride (18.6%) and methadone (17.7%). Opioid use did not change during the study for more than 92% patients. The total dose of opioids use was within the protocol specified morphine equivalent criteria.
The pain at baseline for the BTCP was comparable between groups: 6.89 for PecFent and 6.96 for placebo.

Numbers analysed

Summary of patients disposition: double-blind treatment phase (all randomised patients)

Number (%) of Patients	N (%)
Randomized	83
Included in mITT Population	73 (88.0)
100 mcg	8 (9.6)
200 mcg	7 (8.4)
400 mcg	24 (28.9)
800 mcg	34 (41.0)
Included in PP Population	58 (69.9)
100 mcg	7 (8.4)
200 mcg	5 (6.0)
400 mcg	20 (24.1)
800 mcg	26 (31.3)
Completed the Study[1]	76 (91.6)
100 mcg	10 (12.0)
200 mcg	7 (8.4)
400 mcg	24 (28.9)
800 mcg	35 (42.2)
Discontinued Early	7 (8.4)
Primary Reasons for Early Discontinuation	
Adverse Event	1 (1.2)
Concomitant Therapy	0 (0.0)
Did not continue to meet inclusion/exclusion criteria	0 (0.0)
Inability to evaluate and record patient assessment data (Inc #7 was not met)	0 (0.0)
Death	1 (1.2)
Inability to Explain Return of Less Than Predicted Study Drug	0 (0.0)
Lack of Efficacy	1 (1.2)
Lost to Follow-up[2]	1 (1.2)
Pregnancy	0 (0.0)
Protocol Violation	0 (0.0)
Withdrawal of Consent	3 (3.6)
Other	0 (0.0)

mITT=modified intent-to-treat; PP=per protocol

[1] Patients who have a completion date on CRF

[2] The patient who was lost to follow-up was contacted by phone calls and by sending letters to get the status

Outcomes and estimation

The primary efficacy endpoint was the SPID at 30 minutes. The mean SPID 30 post dose was greater and statistically significant for PecFent treated episodes (6.57) compared with placebo treated episodes (4.45), $p<0.0001$.
A summary of SPID at 30 minutes for the mITT Population is presented in the table below.

Treatment (N = 73)	
Nasalfent	
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 Center	0.5891
P-values [1]	Additional covariates
Treatment	<.0001
Pooled Center	0.7568
Treatment Pooled Center	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 in an e-diary on 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.

[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

The CHMP considered that it would have been more appropriate to choose pain intensity difference (PID) at 10 or 15 minutes after administration as the primary endpoint, especially with respect to the intended purpose –rapid onset of action- of this formulation. The applicant was requested to comment on the clinical meaning of the summed pain intensity difference (SPID) outcome at 30 minutes.

In their answer, the applicant argued that SPID30min has been the preferred primary end point term for cross-over placebo-controlled studies with the EU approved oral mucosa formulations (Actiq and Effentora) (Farrar 1998; Portenoy 2006; Slatkin 2007; Effentora EPAR: EMA H/C/833)). The benefit of the SPID30min term is that it provides a cumulative summation of pain difference over a time period rather than at a specific time point. In addition to the need to demonstrate speed of onset, there is a need to demonstrate that pain relief persists appropriately, without the frequent need for further dosing or additional medication. The CHMP, considering the results obtained with the secondary criteria (PID at different times, percentage of responders, need for rescue medication) concluded that these supported a statistical and clinical difference in favour of PecFent versus placebo.

The mean PI score for PecFent treated episodes was statistically different from that of placebo treated episodes at the 5 minute time point ($p=0.0298$) and decreased over the subsequent time points (10 to 60 minutes) ($p \leq 0.0014$).

The mean PID was statistically significantly greater for PecFent treated episodes than for the placebo treated episodes at each time point from 10 to 60 minutes post dose.

Similar results were observed for PR and TOTPAR. The overall mean patient-averaged acceptability assessment score was significantly greater for PecFent as compared with placebo at 30 minutes postdose (2.63 vs. 2.01, $p<0.0001$) and at 60 minutes postdose (2.73 vs. 2.02, $p<0.0001$).

Responder rate: the number of patients with a ≥ 33%, ≥ 50% and a ≥ 60% in PI score from baseline is summarised below.

Treatment (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 (4.1%)	8 (11.0%)	28 (38.4%)	41 (56.2%)	54 (74.0%)	55 (75.3%)
Placebo	4 (5.5%)	8 (11.0%)	14 (19.2%)	20 (27.4%)	25 (34.2%)	32 (43.8%)
P-values[1]	0.3173	1.0000	0.0017	<.0001	<.0001	<.0001
	Number (%) of Patients with Reduction in PI Score ≥50%					
Nasalfent	2 (2.7%)	7 (9.6%)	9 (12.3%)	25 (34.2%)	35 (47.9%)	39 (53.4%)
Placebo	2 (2.7%)	6 (8.2%)	7 (9.6%)	12 (16.4%)	15 (20.5%)	15 (20.5%)
P-values[1]	1.0000	0.6547	0.4142	0.0029	<.0001	<.0001
	Number (%) of Patients with Reduction in PI Score ≥66%					
Nasalfent	1 (1.4%)	1 (1.4%)	6 (8.2%)	8 (11.0%)	16 (21.9%)	23 (31.5%)
Placebo	1 (1.4%)	3 (4.1%)	5 (6.8%)	6 (8.2%)	9 (12.3%)	10 (13.7%)
P-values[1]	1.0000	0.1573	0.6547	0.4142	0.0348	0.0008

mITT=modified intent-to-treat; PI=pain intensity; min=minute

[1]P-values from McNemar Test to compare Nasalfent and placebo at each timepoint.

Rescue medication: rescue medication was evaluated by patients and by episodes. The results are presented below.

Rescue medication usage (mITT population)

Treatment (N=73)	0-5 min	0-10 min	0-15 min	0-30 min	0-45 min	0-60 min
	Number (%) of Patients Who Used Rescue Medication					
Nasalfent	3 (4.1%)	4 (5.5%)	4 (5.5%)	6 (8.2%)	13 (17.8%)	26 (35.6%)
Placebo	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	12 (16.4%)	27 (37.0%)
P-values[1]	0.0833	0.0455	0.0455	0.1025	0.8084	0.8185

[1]P-values from McNemar Test to compare Nasalfent and placebo arms at each timepoint.

Episode rescue medication usage up to 4 hours (mITT population)

Treatment (N=659)	0-30 min	30-60 min	60 min-4 hrs
	Number (%) of Episodes Where Rescue Medication was Used		
Nasalfent	9/459 (2.0%)	34/459 (7.4%)	0/459 (0.0%)
Placebo	2/200 (1.0%)	38/200 (19.0%)	0/200 (0.0%)
P-values[1]	0.3845	<.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.

Even if rescue medication was not allowed before 30 minutes, more patients with PecFent used rescue medication during the first 30 minutes than placebo patients. When evaluating rescue medication by episodes, no difference was found during the first 30 minutes between PecFent and placebo. This could be explained by the fact that more episodes were treated with PecFent than with placebo for each patient (7 compared to 3). After 30 minutes, the use of rescue medication is statistically significantly higher for patients with placebo than with PecFent.

Efficacy conclusion

The primary efficacy endpoint of this study was the SPID from 5 to 30 minutes post-dose. BTCP episodes treated with PecFent showed a mean SPID score that was significantly higher than that for episodes treated with placebo (6.57 vs. 4.45, respectively, $p<0.0001$).

The mean PI score was significantly lower following PecFent treatment than following placebo treatment at each observed time-point from 5 to 60 minutes post-dose, indicating that the onset of

pain relief was evident from 5 minutes and was sustained throughout the first hour. All secondary efficacy analyses, across both the mITT and PP populations, supported these findings, and confirmed the efficacy of PecFent in this patient group. The use of rescue medication was significantly lower in PecFent-treated episodes compared with placebo-treated episodes up to 60 minutes after treatment.

Study CP045/06

This study was initially submitted as an interim report. The final report was submitted with the answers to Day 120 List of Questions.

Methods

Study Participants

Study CP045/06 was an open-label study investigating long-term safety and tolerability of Nasalfent (Fentanyl Citrate Nasal Spray, now: PecFent) in the treatment of breakthrough cancer pain (BTCP) in patients taking regular opioid therapy.

Patients with cancer who experienced on average one to four episodes of BTCP over 2 weeks, but not necessarily every day, while taking at least 60 mg per day of oral morphine (or equivalent opioid) for their underlying cancer pain were eligible to enrol into the study. Only results from the planned Interim Analysis are presented in this report. The Interim Analysis was performed upon enrolment of 132 patients in the study. Patients were newly enrolled (N = 73) or were enrolled after successfully completing studies CP043/06 or CP044/06 (N = 59).

Treatments

The open-dose titration phase for newly enrolled patients was identical to that described in study CP043/06.

The objective of the titration phase of the study was to titrate for each patient the dose of PecFent needed to treat breakthrough pain episodes until 2 consecutive episodes of target BTCP were successfully treated (defined as acceptable pain relief within 30 minutes) with the same dose without unacceptable AEs. Study site personnel assisted patients in determining their individual effective doses using daily telephone contact. The maximum duration of the titration phase was 14 days.

For the open-label treatment phase (up to 16 weeks) each patient was supplied with up to a 4-week supply of fentanyl nasal spray. Patients were instructed to self-administer the effective dose of fentanyl nasal spray established during the open, dose-titration phase. Fentanyl nasal spray was to be used to treat a maximum of 4 episodes of BTCP per day. At least four hours between each use of fentanyl nasal spray were mandated. If pain relief was inadequate after 30 minutes or if a separate episode of BTCP occurred before the next dose of fentanyl nasal spray was permitted (i.e., within 4 hours), patients were allowed to take their usual BTCP analgesia as rescue medication (at least 4 hours was also to elapse between the use of rescue medication and the next dose of fentanyl nasal spray).

Collection of data for each episode and the recording of data in the e-diary were similar to study CP043/06.
For the first 4 weeks, telephone visits were scheduled weekly to review safety and adjust dose levels, if needed. Clinic visits were to subsequently occur at weeks 4, 8, and 12 to assess safety and tolerance, to review e-diary data, and to collect old medication and dispense new study medication. Extra clinic visits occurred where necessary to dispense additional study drug, according to the patient's needs.

In order to provide patients who were gaining clinical benefit from the use of PecFent with access to the treatment following their participation in the main study, they were allowed to enter the CP045/06/FCNS extension period, at their discretion and that of their physician. Following completion of the End-of-Treatment Phase of the Main Study, patients were provided with further supplies of trial medication for as long as necessary, according to their clinical need, up until the time that PecFent becomes commercially available in their country. No e-diary (efficacy) data were collected during the extension period, only safety and drug accountability data.

Objectives

The primary objective of this study was to investigate the long-term safety, tolerability, and acceptability of fentanyl nasal spray in the treatment of patients with BTCP.
Variables to be included in the interim analyses were AEs, objective nasal examination, subjective nasal assessment, withdrawals due to AEs, physical examinations, vital signs, laboratory assessments, and patient acceptability assessments.
This was primarily a safety study; the main results from CP045/06 are discussed in the safety section of this assessment report. However the results from the study that relate to efficacy are presented in this section.

Outcomes/endpoints

Acceptability
The following acceptability endpoints were assessed in the study:

- Per episode
  - Overall satisfaction
  - Speed of relief
- Per treatment period (global assessment)
  - Ease of use
  - Convenience
  - Reliability

Each parameter was assessed using a 4-point scale: 1 (not satisfied), 2 (not satisfied or dissatisfied), 3 (satisfied), and/or 4 (very satisfied). The 'per episode' assessments were made at 60 minutes post study drug administration for each episode during the 16 week treatment period. The 'per treatment period' (global) assessments were made by patients at Weeks 1, 4, 8, and 12.

If at any time after 30 minutes, pain relief with study medication was inadequate during any individual episode, patients were allowed to take their usual breakthrough pain medication, provided there was at least four hours between the use of rescue medication and the next dose of study medication. A patient was defined as taking rescue medication, if he/she took rescue medication for any episode treated. Where patients had taken rescue medication within 60 minutes of study drug administration, an additional sensitivity analysis was performed on the data at 60 minutes, excluding those episodes where rescue medication had been taken at any time point during the assessment period.

Sample size

The applicant stated that a sufficient number of subjects would be enrolled to ensure that 500 subjects had been exposed to PecFent across the three Phase III studies and that 150 of these had been dosed for 3 or more months.

Results

Participant flow

In the initially submitted interim report, a total of 132 patients were included in the ITT Population; 73 (55.3%) were newly enrolled and 59 (44.7%) were rolled over from study CP043/06/FCNS. No patient was included from study CP044/06/FCNS because very limited amounts of data were available from this study. Furthermore, as this study had yet to be un-blinded, no causality assessment of AEs was possible, so the data were not included in the interim analysis.

In the final report, 351 patients were screened for the entry into the study, of which 64 patients failed screening. Subsequently, 287 patients entered the Open, Dose-Titration Phase. Of these, 51 patients withdrew (including 6 patients who did not take any doses of Nasalfent). A total of 236 patients of the 287 were successfully titrated (82.2%). Two of these patients entered directly into the Extension

Period rather than the Open-Label Treatment Phase, as recruitment to that Phase had closed by the time they completed titration. Consequently, 234 new patients entered the Open-Label Treatment Phase. These patients were joined by 66 patients 'rolling-over' from study CP043/06/FCNS and 56 patients from study CP044/06/FCNS. These roll-over patients had previously been titrated to an effective dose and had completed a double-blind phase of treatment. A total of 356 patients thus entered the Open-Label Treatment Phase of the study.

The ITT Population consisted of 403 patients.

Recruitment

The study was conducted at 62 centres in Argentina, Canada, Costa Rica, Czech Republic, Germany, United Kingdom, India, Italy, Poland, and the United States (US).

Baseline data

A majority of patients in the ITT 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.

Numbers analysed

The ITT Population (N=403) consisted of all 356 patients who were entered into the Open-Label Treatment Phase, plus the 2 patients who were entered directly into the Extension Period from the Open-Dose Titration Phase, plus the 45 withdrawn patients exposed during the Open-Dose Titration Phase (51 patients minus the 6 patients who were dispensed Nasalfent treatment but did not take any).

Outcomes and estimation

It has to be kept in mind that study CP045/06 was an open-label trial conducted primarily to generate long-term safety data. Any efficacy results are therefore to be interpreted with caution.

The acceptability analyses were based on 2 populations; the overall dataset (including all patients for whom acceptability data were available from the Open-Label Treatment Phase) and the "Acceptability Assessment Population" dataset. This latter population included all patients in the Open-Label Treatment Phase who had completed at least 12 weeks (3 months) of Nasalfent therapy.

A total of 24012 episodes (at different maximum dose levels; 100 mcg: 2847 episodes, at 200 mcg: 3259 episodes, at 400 mcg: 7723 episodes, and at 800 mcg: 10187 episodes) were assessed for acceptability at 60 minutes after Nasalfent administration.

Overall, patients reported being 'satisfied' or 'very satisfied' following the use of Nasalfent spray for the treatment of 15770 (65.7%) and 5762 (24.0%) BTCP episodes, respectively.
For speed of relief, patients reported being 'satisfied' or 'very satisfied' following the use of Nasalfent spray for the treatment of 15550 (64.8%) and 6072 (25.3%) BTCP episodes, respectively.

Usage of rescue medication during dose titration is an expected phenomenon in case the tested dose proves to be insufficient. In only about 6% of episodes rescue medication was used during the treatment period. This figure points to good efficacy and acceptability of the individual FCNS dose on the one side, and considerable stability of this dose over time on the other side.

The portions of patients requiring rescue medication within 60 min post-dose were evenly spread across the entire dose range of 100 to 800 µg, which is indicative of the appropriateness of the dose range tested in this patient population.

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

No formal sub-group analyses were performed and none were required by CHMP. 29% of the patients who participated in the clinical trail programme with PecFent were over 60 years of age. No significant interaction was found when age was assessed as covariate in the ANCOVA analysis. PecFent is intended to be titrated to an individual successful dose in each patient. Section 4.2 of the SmPC contains a recommendation to conduct dose titration with particular caution in the elderly.

Supportive study

During the assessment period (Day 120), the final study report of a further phase III trial (CP044/06, n=110 entering dose titration) was submitted. Study CP044/06 was a double-blind, double-dummy crossover comparison between PecFent and Immediate-release Morphine sulphate tablets (IRMS) in the treatment of BTP in subjects taking regular opioid therapy. The primary endpoint of this study was the PID at 15 minutes post-dose. At 15 min post-dose, the mean PID score for PecFent-treated episodes was significantly higher than the mean PID score for IRMS-treated episodes (3.02 vs 2.69, respectively; p=0.0396). At 10 minutes, however, the difference between the groups was not yet statistically significant (secondary endpoint PID 10 min: PecFent 2.02, IRMS 1.80; p=0.0844).

However, in principle, active comparator data are not compulsory for demonstration of efficacy and safety of this pectin-based fentanyl nasal spray. Essential data for evaluation of PecFent's risk-benefit balance are derived from the double-blind, multiple (within patient) crossover, placebo-controlled phase III trial CP043/06.

2.5.3. Discussion on clinical efficacy

The studies conducted in proof of efficacy of PecFent use well-established designs and validated endpoints very similar to those used in studies conducted in support of formulations of fentanyl that are already licensed for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain (Portenoy et al 2006). These studies and endpoints have demonstrated to high degrees of statistical significance the efficacy of fentanyl nasal spray in a demographically homogeneous population.

The primary endpoint of the pivotal efficacy Study CP043/06 was met, demonstrating that at 30 minutes post-dose, the mean SPID score for fentanyl nasal spray-treated episodes was significantly higher than that for placebo-treated episodes (6.57 vs. 4.45, respectively, p<0.0001).

Due to high vasculature of the nasal mucosa fentanyl is expected to be absorbed rapidly and provide fast onset of action when applied as nasal spray. Therefore, the choice of SPID30 as primary efficacy endpoint is considered to be rather cautious or conservative. With regard to earlier time-points of pain assessment as secondary endpoints, however, study CP043/06 demonstrated significant improvements of PI and PR at all time points from 10 minutes after dosing (and for some endpoints, from 5 minutes after dosing) that persisted throughout the 60 minute study period, strongly suggesting that patients had titrated appropriately and identified effective yet well-tolerated doses.

During the initial dose escalation period of study CP043/06 patients were titrated to their individual successful dose. The successful dose was reached when the patient achieved adequate pain relief over two consecutive episodes with the same dose and without experiencing undue adverse events. The protocol of the titration procedure was straightforward and delivered unambiguous information on adequacy of the chosen dose. Patients did not have the option of a "second puff" of PecFent. Pain relief was subjectively assessed by the patient after 30 min. In case of insufficient pain relief the patient was free to use his usual rescue medication and the patient used a higher dose for the next episode. A dose range of 100 to 800 µg per single dose was tested in phase III. In study CP043/06, 72.85% of patients were able to find their successful dose during titration (6.1% withdrawn due to lack of efficacy, 5.3%

withdrawn due to AE). The portion of patients able to define their successful dose is thus well in accordance with the portions known from preceding MAA for similar products.

During the preceding phase II dose-finding, proof-of-principle study CP041/04 a wider array of doses was tested in cancer patients ranging from 25 to 800 µg fentanyl. The overall number of subjects was low, however, 6 out of 15 study completers defined 25 or 50 µg as their successful dose. These doses were not carried forward into phase III as they did not show consistent effectiveness in subsequent investigations. On the other hand, adequacy of the chosen dose range of 100 to 800 µg was clearly demonstrated by consistent and favourable efficacy results (PI, PR, responder analyses) in phase III and an evenly spread usage of rescue medication across the entire dose range.

On the other hand, it has to be acknowledged that the analgesic properties of fentanyl are well established and that clearly positive efficacy results have been obtained.

Overall, it can be concluded that study CP043/06 has demonstrated that the dose range chosen was suitable to provide effective pain relief in the short-term in a large number of patients, and study CP045/06 has confirmed that this dose range remains efficacious in this patient population over a period of up to 4 months, with no evidence of a loss of efficacy or the development of tolerance in the vast majority of patients.

There was a statistically significant difference in acceptability scores as measured on a 4-point scale between fentanyl-treated episodes and those treated by placebo at both 30 and 60 minutes post dose ($p<0.0001$) in study CP043/06. Mean assessment scores for speed of relief and reliability of nasal spray also favoured fentanyl nasal spray over placebo at both the 30 and 60 minute time points ($p<0.0001$).

2.5.4. Conclusions on the clinical efficacy

The design and conduct of the overall clinical development is straightforward and acceptable, using validated endpoints which have supported other applications for similar products.

The overall clinical development programme is considered adequate to address the relevant efficacy issues of PecFent.

2.6. Clinical safety

The substance-specific adverse event profile of the strong µ-receptor agonist is well established after decades of widespread clinical use. The major safety issue associated with this novel nasal fentanyl dosage form is the question whether the observed rapid increase in plasma levels after nasal application causes particular safety concerns (e.g. in terms of respiratory depression, sedation etc.) and whether particular local tolerability problems have been observed during the clinical trials.

Patient exposure

Safety information has been collected from eight studies, four Phase I studies and four Phase II/III studies. Of these, three Phase III studies (CP043/06, CP044/06 and CP45/06) have been performed with the multi-dose device that is proposed for marketing: CP043 and an interim report for CP045/06 were submitted with the original MAA; CP044 and the final report for CP045 were submitted with the response to the list of questions (LOQ) at Day 120 and considerably increased the size of the Phase III database (506 patients were included in the integrated Phase II/III safety population compared to 209 submitted with the original application)

All patients treated with fentanyl nasal spray in the Phase III studies were administered one of the following doses: 100mc g, 200mcg, 400mcg, or 800mcg fentanyl. The fentanyl-pectin nasal spray formulation utilising the PecSys nasal drug delivery system to modulate the delivery and absorption of fentanyl has been used throughout the Phase I and Phase II/III studies.

A total of 102 subjects were enrolled in the Phase I studies, and were exposed to both single and repeat doses of PecFent. Single doses were predominantly 100 mcg fentanyl. Repeat doses varied between 100 mcg and 800 mcg.

A total of 648 patients were screened for enrolment in the Phase II/III studies, 110 of whom were withdrawn at the end of screening. Reasons for withdrawal at the end of screening included not meeting the inclusion/exclusion criteria (58 patients), withdrawal of consent (16 patients), adverse event (11 patients), death (5 patients), lost to follow-up (1 patient), and other reasons (19 patients). An additional four patients did not withdraw at screening and did not have PecFent dispensed. A total of 534 patients were enrolled in the Phase II/III studies, 11 of whom did not take PecFent.

In the Phase II/III studies, each patient first went through a titration period. A total of 523 patients entered titration, took study drug, and comprised the Safety Population.
A total of 506 patients were treated with 1 or more of the 4 doses of PecFent that are the basis of the safety database (100 mcg, 200 mcg, 400 mcg, and 800 mcg). Of these patients, 36.0% were treated with the highest dose of 800 mcg and 62.8% were treated with 400 mcg at least once. It should be noted that patients could receive multiple dose levels of PecFent because of the titration process. Of the 74 patient-years of exposure to PecFent, almost two-thirds (64%) of the years were exposure at one of the two highest doses. Of the 506 patients, 123 were treated for one to seven days, 41 were treated for 8 to 14 days, 57 were treated for 15 to 28 days, and 132 were treated for 29 to 89 days; a total of 153 patients were treated with PecFentfor ≥90 days.

For the Phase II/III studies, each patient first went through a titration period of up to 14 days. A total of 346 patients maintained treatment at the same dose following dose-titration; the majority of these patients were treated at 400 mcg or 800 mcg.

The mean duration of treatment was 73.14 days. A total of 153 patients were treated with PecFent for between 90 and 159 days. A total of 45,599 BTCP episodes were treated with PecFentduring the Phase II/III studies. Of these episodes, 6,243 (13.7%) were treated with 100 mcg, 7,479 (16.4%) were treated with 200 mcg, 14,937 (32.8%) were treated with 400 mcg, and 16,940 (37.1%) were treated with 800 mcg.

The mean BTCP episodes/week/patient treated with PecFent increased as time progressed, probably due to worsening pain in view of the progressive character of the underlying cancer disease.
On the other hand, the BTP episode frequency may well depend upon adequacy of the maintenance opioid dose for the treatment of persistent pain. The reported figure of initially 9.1 episodes/week/patient points to generally adequate management of persistent pain. The relation between maintenance dose and BTP episode frequency is adequately reflected in the SmPC:

Patient Demographics and Disease Stage
The healthy population exposed to fentanyl nasal spray in the phase I studies was mainly white (78.8%), aged 19-64 years, with approximately equal proportions of males and females, average height, weight and other physical characteristics. There do not appear to be any differences between the study groups that would have any bearing on the safety assessments.

Demographics for cancer patients treated with PecFent in the Phase II/III studies show that patient mean ages and ranges were very similar across the three studies. A mean of 29.2% of patients included in the safety analysis were above the age of 60 years, 16.8% over 65 years and 3.8% over 75 years. Overall, the mean proportions of females and males were similar (45.5% female: 54.5% male). Regarding race overall, the greatest proportion of patients was Caucasian (69.4%), with Black, Southeast Asian and Hispanics also represented. The proportions were similar in Study CP043/06 and CP045/06, but there was a higher proportion of Caucasians (87%) in Study CP041/04 than in the other studies. Mean weight was very similar across the three studies (78.8 kg in CP043/06, 72.0 kg in CP045/06 with a range of 39-150 kg).

Disease stage in patients included in Study CP043/06 and CP045/06 was standardised as a diagnosed solid tumour or haematological tumour requiring regular, 24-hour medication (60 mg oral morphine or equivalent opioid) for underlying persistent cancer pain and typically having one to four episodes of BTCP per day to be eligible for participation.

In the Phase II/III Studies, the most common concomitant medications were gabapentin (22.5% of patients), fentanyl (21%), dexamethasone (20.1%), morphine (other) (17.7%), morphine sulphate (16.7%), hydromorphone hydrochloride, lorazepam, granisetron hydrochloride (15.3%), paracetamol

(14.8%), metoclopramide hydrochloride, docusate sodium (13.4%), omeprazole (12%), sennoside A and B, zolpidem tartrate, pregabalin (11.5%), lactulose, furosemide (11%), acetyl salicylic acid, ibuprofen (10%).

Gabapentin was the most often used concomitant medication in the phase II/III patient population. Thus it may be inferred that a considerable portion of participants presented with neuropathic pain or cancer pain of mixed neuropathic / nociceptive origin. There was no subgroup-analysis of the efficacy/safety of PecFent undertaken with regard to origin of cancer pain (predominantly nociceptive / neuropathic or mixed state).

Overall, the safety population is considered to be a relatively homogeneous group with respect to demographics for the phase II/III trials. The target population appears well represented.

Methods for Assessing Product Safety

Standardised methods were employed for assessing product safety in the phase I studies. Local tolerability was assessed by the subjects using a specifically designed reactogenicity questionnaire and completing an overall assessment of the convenience of nasal dosing at the end of each nasal treatment. A clinical safety assessment by an ear, nose and throat (ENT) specialist was made using a conventional rating scale at the beginning and end of the study, and nasal assessments were also carried out by the study physician.

In Phase II Study CP041/04, adverse events and patient well-being were monitored throughout the study. Safety and tolerability were assessed by observation, questionnaire and recording of AEs.

In Phase III Studies CP043/06, CP044/06 and CP045/06, safety was assessed by recording of AEs, general physical examination, vital signs, clinical laboratory parameters, objective nasal examination, and subjective nasal symptomatology.

The main phase III trials were conducted principally in out-patients. All efficacy-relevant data were collected on an e-diary reporting system. The patient self-initiated the diary in case an episode occurred and was alerted six times afterwards to make pain intensity- and pain relief entries. Rescue medication was to be reported for 60 min post-dose.

Adverse events

Nasal clinical examination and local tolerability

As already discussed in the efficacy section, PecFent did not appear to cause any local tolerability problems. Information on epistaxis has been adequately treated in the SmPC.

Treatment-emergent adverse events (TEAE)

As already mentioned, it is possible that a proportion of the TEAEs ascribed to fentanyl nasal spray may in fact be due, at least in part, to the patients' regular background opioid medication. In addition the background rate of AEs is particularly high in this patient population.

The expected treatment-related AE profile of a strong opioid was observed with dizziness and gastrointestinal disorders ranking first. The CHMP thought it remarkable that not a single case of respiratory depression was reported in the initially submitted data, and requested clarifications.
With the answers at day 121, the availability of data on a substantial number of additional patients, and over longer periods of time, has increased the number of treatment-emergent adverse events of dyspnoea to 27, occurring in 23 patients. Only two of these were assessed by the investigator as being possibly (1) or probably (1) related to study medication (PecFent). The CHMP endorsed this conclusion.

Of the 523 subjects in the safety population, 7 subjects from CP041 did not receive 1 of the 4 doses of FNS that comprise the basis of this summary of safety. Thus, for displays that present data by dose, 516 subjects comprise the safety population.

During the Phase I studies, 62.0% of the subjects experienced one or more adverse events that were assessed by the investigator as treatment-related. The most frequently reported treatment-related adverse events were rhinitis, headache, rhinorrhoea, and nausea. The majority of treatment-related adverse events were mild or moderate in intensity. Severe adverse events included one event each of vomiting, rhinitis, balance disorder, headache, and rhinorrhoea.

The majority (75.4%) of patients in the Phase II/III studies experienced one or more adverse events.

During the Phase II/III studies, 28.9% of patients experienced adverse events assessed by the investigator as possibly, probably, or definitely treatment-related. The most common treatment-related adverse events included dizziness (6.2%), vomiting (4.8%), somnolence (4.8%), nausea (4.5%), and constipation (2.9%). Patients treated a total of 45,599 episodes of BTCP during the Phase III longer-term study (CP045); 343 (0.75%) of these episodes had adverse events that were considered by the investigator to be possibly or probably related to treatment.

The incidence of the most commonly reported TEAEs, with the exception of disease progression, was greatest in the 100 and 800mcg dosage groups as might be expected for patients entering the Titration Phase (100mcg) or treating most episodes (800mcg). Disease progression was most commonly reported in the 800mcg dosage group. The TEAEs are as expected for fentanyl, and disease progression is to be expected in this group of patients.

Among application site disorders, epistaxis (n=8, 3.8%) and nasopharyngitis (n=7, 3.3%) were observed most often.

Treatment related TEAEs have been analysed with respect to age group, gender, race, location and long-term treatment. Regarding age, in the group aged over 60 years, the incidence of treatment related TEAEs was higher in the 800mcg group, whereas there was very little difference between dose levels in the 60 years or under group. All the events of epistaxis were observed in the 60 years and younger age group. With respect to gender, overall the incidence of treatment related TEAEs was lower in males than females (29.8% in males vs. 40.0% in females), with the incidence being greater at the 100mcg dose level. No differences were observed when the results were analysed according to race, location or in patients on long-term treatment.

Regarding the intensities of TEAEs, gastrointestinal TEAEs were mainly mild or moderate, general disorders were mainly severe, due principally to the natural severity of disease progression.

Common adverse events

Treatment related TEAEs reported in ≥ 1% of the overall safety population are presented in the Table below.

	Common	**Uncommon**
Infections and infestations		Pneumonia Nasopharyngitis Pharyngitis Rhinitis
Blood and lymphatic system disorders		Neutropenia
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders		Dehydration Hyperglycaemia Decreased appetite Increased appetite
Psychiatric disorders	Disorientation	Drug abuse Delirium Hallucination Confusional state Depression Attention deficit/ hyperactivity disorder Anxiety Euphoric mood Nervousness

	Common	**Uncommon**
Nervous system disorders	Dysgeusia Dizziness Somnolence Headache	Loss of consciousness Depressed level of consciousness Convulsion Ageusia Anosmia Memory impairment Parosmia Speech disorder Sedation Lethargy Tremor
Cardiac disorders		Cyanosis
Ear and Labyrinth Disorders		Vertigo
Vascular disorders		Cardiovascular insufficiency Lymphoedema Hypotension Hot flush
Respiratory, thoracic and mediastinal disorders	Epistaxis Rhinorrhoea Nasal discomfort	Upper airway obstruction Intranasal hypoaesthesia Pharyngolaryngeal pain Rhinalgia Nasal mucosal disorder Cough Dyspnoea Sneezing Upper respiratory tract congestion Nasal congestion Throat irritiation Postnasal drip Nasal dryness
Reproductive System and Breast Disorders		Vaginal haemorrhage
Gastrointestinal disorders	Vomiting Nausea Constipation	Intestinal perforation Peritonitis Oral hypoaesthesia Oral paraesthesia DiarrhoeaRetching Abdominal pain Tongue disorder Mouth ulceration Dyspepsia Dry mouth
Skin and subcutaneous tissue disorders	Pruritus	Hyperhydrosis Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia Muscle twitching
Renal and urinary disorders		Anuria Dysuria Proteinuria Urinary hesitation

	Common	Uncommon
General disorders and administration site conditions		Non-cardiac chest pain Asthenia Chills Face oedema Peripheral oedema Gait distrurbance Pyrexia Fatigue Malaise Thirst
Investigations		Platelet count decreased Weight increased
Injury, poisoning and procedural complications		Fall Intentional drug misuse Medication error

All common adverse events tabulated above are adequately reflected in section 4.8 of the SmPC.

With regard to epistaxis the applicant was requested to implement a warning note in section 4.4 of the SmPC.

Drug abuse

In view of the Controlled Drug classification of the study medication, the highest possible standards of drug reconciliation were maintained for all Phase III studies, with double- (2 person) checking of dispensing and returning of study medication, and recording of the number of sprays administered, as indicated by the counter on each bottle for all the phase III studies. All such data were recorded on the CRF/ Drug Reconciliation Log as appropriate.

Investigators and study staff impressed upon patients at all appropriate points in the studies, the need to supervise and safeguard carefully their study medication supplies (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.

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.

For CP043/06 the median discrepancy for the Titration Phase was +1 sprays (lower and upper quartiles +0 and +2, minimum and maximum -9 and +15). The median discrepancy for the Double-Blind Treatment Phase was +0 sprays (lower and upper quartiles +0 and +3.5, minimum and maximum -10 and +60). Out of the 113 patients, the circumstances associated with the discrepancies were 24 (21%) with no recorded discrepancy, 50 (44%) with e-diary/protocol deviations (such as additional treated episodes recorded in the e-diary), 5 (4%) with additional episodes treated but not recorded in the e-diary, 9 (8%) with priming errors, 16 (14%) with errors in bottle use, 15 (13%) with reported device malfunctions, 4 (4%) who did not return medication, 27 (24%) with minor unexplained errors and 13 (12%) with larger unexplained errors. A significant number of patients fell into more than 1 category, and therefore the percentages add up to more than 100%.

No investigator reported any specific concerns over abuse or diversion for any of the patients within trial CP043/06 – however, the possibility cannot be completely excluded for the small number of patients with large unexplained discrepancies. However, it is more likely in this population that any use of doses outside the protocol was for extra episodes of breakthrough pain that were not recorded in the e-diary.

For study CP045/06 the median discrepancy for the Titration phase was +0 sprays (lower and upper quartiles +0 and +1, minimum and maximum -6 and +7). The median discrepancy for the Open Label phase was +12 sprays (lower and upper quartiles +2 and +50, minimum and maximum -74 and +293).

One patient was withdrawn from the trial for the adverse event of intentional drug misuse (patient 937/393701). This patient had completed trial CP043/06/FCNS, during which there was no evidence of

drug misuse (and the patient's total spray discrepancy was 2 sprays). The total spray discrepancy during Study CP045/06 was 86 sprays (145.3% of the expected spray use).

Another Patient 937/393703 had the AE of drug abuse recorded at a routine visit on 05 Sep 2007, but was permitted to continue in the study – a reported action of 'discontinuation of study medication' ticked on the AE report form for that visit appears not to have been the case. The patient was dispensed further drug supply and continued to use and record the use of fentanyl nasal spray for episodes of BTCP. On 26 Sep 2007, a telephone contact between the site and the patient recorded in the CRF reported "subject admitted taking/abusing all 80 doses". The patient returned to the site on 01 Oct 2007, and was withdrawn from the trial, albeit with the AE of nausea and diarrhoea cited as the reason. The patient's overall positive spray discrepancy for this trial was 46 sprays (143.4% of the expected spray use).

No other investigator reported any specific concerns over abuse or diversion for any of patients within the trial programme – once again, however, this cannot be completely excluded for the patients with larger positive discrepancies. As for Study CP043/06 it is more likely in this population that any use of doses outside the protocol was for extra episodes of breakthrough pain that were not recorded in the e-diary.

Overall, the CHMP concluded that for PecFent the long known issue of abuse/overuse of strong opioids is reasonably addressed by the inherent safety devices of the multiple dose container (audible click for each successful actuation, drug counting system, lock-out after eight administrations) within the legal framework of Controlled Drug prescription regulations.

Device malfunction

Device malfunctions (overall causes) was 16.9% of the number of patients in trial CP043/06 and 8.9% in trial CP045/06. This showed that malfunction is nearly halved when the studies progress from titration to the double-blind treatment phase. The reported malfunctions are thus likely to reflect patient inexperience in the use of the device, such as not recognising spray delivery, rather than true device malfunction. The overall technical reliability of the dosage form appears acceptable.

Serious adverse event/deaths/other significant events

Non-fatal serious TEAEs have been analysed for patients in the phase II/III studies. An overall incidence in 13.2% of patients was reported, with infections in 2.7% (including pneumonia), gastrointestinal disorders in 2.9% (nausea and vomiting) and general disorders in 2.7%, (including disease progression). A similar pattern was observed when the results were analysed by race or location. Long-term treatment did not appear to affect the incidence of non-fatal serious TEAEs.

Serious TEAEs have been analysed by preferred term. A total of 26.0% of patients reported at least one serious TEAE. The most commonly reported were disease progression (7.0%); nausea, vomiting (1.2%); constipation, pneumonia (1.0%). Long-term treatment did not affect the serious TEAE profile of fentanyl.

Most adverse events classified as serious were attributable to progression of the underlying cancer disease in this patient collective (brain neoplasm, colon cancer metastatic, pancreatic carcinoma, breast cancer etc.). Overall, the frequency of severe or serious probably treatment-related adverse events does not seem to be unduly increased by the rapid rise in fentanyl plasma level achieved after nasal application. In all cases of treatment-related serious TEAEs (constipation, intestinal perforation, non-cardiac chest pain, peritonitis) a great deal of overlap with either maintenance opioid medication or the underlying cancer disease is assumed. Not a single case of serious, probably treatment-related respiratory depression was observed.

Deaths

In total, 88 deaths were reported in all studies. Five of these (all occurring in Study CP45/06) were associated with adverse events considered possibly (4) or remotely (1) related to fentanyl nasal spray:

Patient 910/391004 died due to disease progression, but also reported anxiety that was considered remotely related to study drug.

Patient 904/390404 died secondary to cholestatic jaundice in the setting of progressive metastatic liver disease, but also had pruritus that was considered possibly related to study drug.
Patient 114/511403 died secondary to constipation, intestinal perforation, and peritonitis that were considered possibly related to study drug.
Patient 859/585903 died secondary to disease progression and pneumonia that was considered possibly related to study drug; this patient also had cough that was considered possibly related to study drug.
Patient 859/585901 died due to cachexia secondary to disease progression, but also had ageusia that was considered possibly related to study drug.

Although it is not possible to rule out a contribution of fentanyl nasal spray or the regular background opioids to the cause of death, there are clear reasons in each case to ascribe the major contributor to the cause as the patient's underlying disease.

Laboratory findings

Haematology laboratory, serum chemistry and urinalysis parameters as well as vital signs were assessed in the phase I and II/III studies.

The pharmacological profile of fentanyl is well established after decades of widespread clinical use. As expected, no significant effects of treatment on haematology laboratory, serum chemistry, urinalysis or vital signs were observed.

Safety in special populations

Age
All PecFent clinical studies were conducted in adults aged at least 18 years of age. Nasal fentanyl is not recommended for use in children below 18 years of age. Overall, 29% of the patients who participated in the clinical trial programme with PecFent were over 60 years of age.
Data from IV studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life and they may be more sensitive to fentanyl than younger patients. Caution should be taken in treatment of elderly patients.

In clinical studies with Effentora patients older than 65 years tended to titrate to a lower effective dose than younger patients (SmPC Effentora, 2008). It is recommended that increased caution should be exercised in titrating the dose of fentanyl nasal spray in elderly patients.

Impaired liver or renal function
In the PecFent Phase III studies, patients were excluded with clinically significant renal and hepatic dysfunction test results at screening outside the following limits:

- Serum creatinine had to be ≤ 2.0 mg/dl, or creatinine clearance calculated by Cockcroft-Gault formula had to be ≥ 50 ml/minutes.
- Serum total bilirubin had to be ≤ 2.0 mg/dl.
- Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase had to be ≤ 3 times the upper limit of normal (≤ 5 times the upper limit of normal if due to liver metastases).

Fentanyl nasal spray should be administered with caution to patients with moderate or severe hepatic or renal impairment.
The influence of hepatic and renal impairment on the pharmacokinetics of the medicinal product has not been evaluated, however, when administered intravenously the clearance of fentanyl has been shown to be altered in hepatic and renal impairment due to alterations in metabolic clearance and plasma proteins. After administration of fentanyl nasal spray, impaired hepatic and renal function may both increase the bioavailability of fentanyl and decrease its systemic clearance, which could lead to increased and prolonged opioid effects.

Therefore, special care should be taken during the titration process in patients with moderate or severe hepatic or renal impairment. (SmPC Effentora, 2008).

Safety related to drug-drug interactions and other interactions

Concomitant use of nasally administered oxymetazoline decreased the absorption of fentanyl with PecFent. The concomitant use of nasally administered vasoconstrictive decongestants during titration is therefore not recommended as this may lead to patients titrating to a dose that is higher than required. PecFent maintenance treatment may also be less effective in patients with rhinitis when administered concomitantly with a nasal vasoconstrictive decongestant.

No specific drug interactions were observed in the clinical trials. No other specific safety data are presented on drug interactions.

The issue of metabolic interaction (CYP3A4, MAO) and pharmacokinetic interaction is adequately reflected under section 4.5 of the SmPC and is in line with the SmPC approved for Effentora. No further interaction studies for PecFent were required in the opinion of CHMP.

Discontinuation due to adverse events

TEAEs leading to discontinuation occurred in 14.3% of patients – 6.1% with general disorders, principally disease progression; 2.9% with cardiac disorders, principally cardiorespiratory arrest; 2.0% with respiratory, thoracic and mediastinal disorders; 1.7% with neoplasms; 1.4% of patients with gastrointestinal disorders, principally nausea and vomiting; 1.4% with psychiatric disorders. The percentage of discontinuations was higher in the 800mcg group.

Treatment related TEAEs leading to discontinuation occurred in 4.5% of patients – 2.3% with gastrointestinal disorders, principally nausea and vomiting; 1.2% with nervous system disorders and 0.8% of patients with psychiatric disorders. The AE profile is as expected for fentanyl in this group of patients. The percentage of discontinuations tended to be higher in the 100mcg and 800mcg groups. No treatment related TEAEs led to discontinuation in the long-term treatment group.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The substance-specific adverse event profile of this strong μ-receptor agonist is well established after decades of widespread clinical use. The major safety issue associated with this novel nasal fentanyl dosage form is the question whether the observed rapid increase in plasma levels after nasal application causes particular safety concerns (e.g. in terms of respiratory depression, sedation etc.) and whether particular local tolerability problems have been observed during the clinical trials. It is considered that the total number of episodes that were treated by each of the strengths (a total of 45,599 episodes was treated, with 16,940 of these treated with the 800mcg dose) is adequate to address these questions.

PecFent has been shown to be generally well tolerated in Phase I and Phase II/III clinical trials. While efficacy data and active monitoring of nasal tolerability were recorded using an e-diary system, safety data (AEs) were recorded using standard methodology of prompted recall/questioning of patients at all contacts between themselves and site staff, i.e. at each study visit, during planned telephone contacts (occurring during the titration phase of each study) and upon any informal / unplanned contacts during other phases. All reported events were recorded on the appropriate CRF page for that study. Increasing time spans elapsed between patient-study staff contacts, reflective of the risk involved at the particular study phase: daily contacts during first exposure (titration). Thereafter, spans extended to contacts at least once a week during the treatment periods once the individually effective and tolerable dose has been established. The rationale behind this approach was that entry of AEs by means of the electronic recording device would have added considerably to the complexity / burden of the e-diary system and would have been hardly feasible in this frail study population.

The reported portion of 75.4% of patients reporting at least one AE is in the expected order of magnitude in this patient population and does not point to systematic AE under-reporting.

It should be noted that PecFent has been administered concomitantly with the patients' regular opioid medication in all cases and it is therefore difficult to absolutely attribute causality for adverse events to fentanyl. The high background rate of adverse events in this population of patients also makes assessment of causality difficult. However, overall the pattern of adverse events that can be attributed to PecFent is similar to that reported from the use of other fentanyl-based formulations, both in clinical trials and in clinical practice.

Objective (ear-nose-throat-trained clinician) and subjective nasal tolerance assessments have systematically been undertaken and did not reveal any clinically significant effects of PecFent that would limit its use. Regarding local effects due to administration of the spray, epistaxis and the other nasal adverse events were considered most likely to be caused by local trauma related to administration of the nasal spray. It should be noted that only two of these events led to discontinuation of the nasal spray.

In the PecFent clinical trial programme, 26.1% of patients were over 60 years of age, 16.8% over 65 years and 3.8% over 75 years. There was no indication that older patients tended to titrate to lower doses or experience more adverse reactions.

The multiple dose container proposed for marketing of PecFent contains additional safety features like an audible click in case of successful actuation, dose counting, and a lock-out mechanism after eight actuations (each spray bottle is designed for eight applications).

The question of inclusion of pectin as gelling agent was raised as it was thought it might have an unfavourable impact on rapid drug delivery.
The Applicant demonstrated, however, that PecFent does not unfavourably compare with already approved (non-gelling) BTP medications.
The combined PecFent dataset submitted from the Phase III programme comprises 511 patients exposed to the product for periods of up to 159 days, with 153 patients for over 90 days. This represents the largest clinical trial programme ever undertaken for a rapid onset fentanyl product in BTCP.
According to literature reports (Christrup et al. 2008), the Tmax value of an ordinary aqueous solution of fentanyl was about 11 min after intranasal administration. In the PecFent dose proportionality study CP042/05 Tmax values ranged from approx. 15 to 19 min over the entire 100-800mcg dose range. It is therefore noted that inclusion of pectin does not fundamentally alter the time to maximum plasma concentration. When considering the clinical implication of different Tmax values, it is to be taken into consideration that the analgesic effect occurs at lower than maximum plasma concentrations and earlier than formal attainment of Tmax. This is reflected by early pain assessment time points for PecFent (from 5 min onwards) and was previously observed in preceding MAA for fentanyl-containing breakthrough pain medications.

Cmax achieved with the ordinary aqueous nasal solution is about three times higher than the one achieved with PecFent (across study comparison). However, while plasma levels for the aqueous solution decline rapidly after attainment of Cmax, about 80% of Cmax are maintained for 30 min post-administration for the pectin formulation. The Applicant thus demonstrated that the kinetic profile of PecFent adequately matches the average time course of a breakthrough episode.

A number of other fentanyl-containing dosage forms with rapid increase of plasma concentrations (Actiq, Abstral, Effentora, Instanyl) have been authorised in the past. Apart from the concern described above regarding possible time spans between occurrence and report of AEs, there are no further major concerns with regard to the safety profile of the novel pectin-based gel-forming PecFent nasal spray.

2.6.2. Conclusions on the clinical safety

The risk profile of nasally applied fentanyl in elderly, hepatic or renal impairment is considered to correspond to the risk profile of intravenously applied fentanyl. The respective warning notes and dosing recommendations in the proposed SmPC are in line with those approved for Effentora. However, the CHMP decided that the PSUR cycle will be independent from the one of the reference products, to allow identification of any issues related to the new formulation and novel mode of administration.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirement.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Respiratory depression or insufficiency	• Routine pharmacovigilance • Six-monthly PSURs • Ongoing monitoring to identify any specific safety signals that require immediate action	• SmPC section 4.3 provides a contraindication and section 4.4 provides warnings regarding respiratory depression • Training of field representatives to alert healthcare professionals to the risks of respiratory depression or insufficiency
Circulatory depression, including severe bradycardia, hypotension, and shock	• Routine pharmacovigilance • Six-monthly PSURs • Ongoing monitoring to identify any specific safety signals that require immediate action	• SmPC section 4.4 provides warnings regarding circulatory insufficiency • Training of field representatives to alert healthcare professionals to the risks of circulatory depression
Local tolerability	• Routine pharmacovigilance • Six-monthly PSURs • Ongoing monitoring to identify any specific safety signals that require immediate action	• Nasal adverse events are listed in SmPC section 4.8, Undesirable effects
Misuse, abuse, or diversion	• Routine pharmacovigilance • Six-monthly PSURs • Ongoing monitoring to identify any specific safety signals that require immediate action • Drug Utilisation Study • Physician Surveys	• Section.4.2 of the SmPC states that *"Physicians should keep in mind the potential for abuse of fentanyl."* • In section 6.6 of the SmPC and in the PIL advice is given on appropriate storage and disposal in order to minimise diversion. • Education for prescribing physicians about the risks of abuse and the importance of secure medication storage

		• Training of field representatives to alert healthcare professionals to the risks of misuse, abuse and diversion • Use of a tamper-evident container-closure system
Off-label use	• Routine pharmacovigilance • Six-monthly PSURs • Ongoing monitoring to identify any specific safety signals that require immediate action • Drug Utilisation Study • Physician Surveys	• Education for prescribing physicians • Training of field representatives to alert healthcare professionals to the risks of off-label use in opioid non-tolerant patients • SmPC section 4.3 contraindicates use in non-opioid-tolerant patients and section 4.4 provides an additional warning
Accidental exposure	• Routine pharmacovigilance • Six-monthly PSURs • Ongoing monitoring to identify any specific safety signals that require immediate action • Drug Utilisation Study • Physician Surveys	• Packaging within a child-resistant container • Training of field representatives to alert healthcare professionals to the risks accidental exposure in patients and non-patients • SmPC section 4.4 warns that PecFent should be kept out of the reach and sight of children • SmPC section 6.4 states that the bottle should be stored in the child-resistant container

As mentioned, the outstanding issues concerning the RMP are addressed as follow-up measures .

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

Prior to launch in each member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, at launch, all physicians, pharmacists and patients expected to prescribe/use PecFent are provided with educational material informing about the correct and safe use of the product.

Educational material for patients should highlight the following:
- Instructions for use of the nasal spray device
- Instructions for opening and closing of the child-resistant box
- Information on the correct indication
- Only use PecFent nasal spray if you are using other opioid pain medicine on a daily basis
- Only use PecFent nasal spray if you have been experiencing breakthrough cancer pain episodes
- Do not use PecFent nasal spray to treat any other short-term pain or pain status
- Do not use PecFent nasal spray for treatment of more than four breakthrough cancer pain episodes a day

- Only use PecFent nasal spray if you have received the proper information regarding the use of the device and the safety precautions from the prescriber and/or the pharmacist
- All unused devices or empty containers should be returned systematically according to the local regulation

Educational material for physicians should highlight the following:

- PecFent nasal spray should be prescribed only by physicians experienced in the management of opioid therapy in cancer patients.
- The prescribers of PecFent nasal spray must critically select the patients and closely follow
    - Instructions for use of the nasal spray device
    - Instructions for opening and closing of the child-resistant box
    - Information on the correct indication
- PecFent nasal spray should not be used to treat any other short-term pain or pain status.
- All unused devices or empty containers should be returned systematically according to the local regulation.
- The prescriber must make use of the checklist for prescribers

Educational material for pharmacists should highlight the following:

- PecFent nasal spray is only indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain
- PecFent nasal spray should not be used to treat any other short-term pain or pain status
- The pharmacist must be familiar with the educational material of PecFent nasal spray before using it in his/her organization
- The PecFent nasal spray dose strengths can not be compared with other PecFent products
- Instructions for use of the nasal spray device
- Instructions for opening and closing of the child-resistant box
- The pharmacist must inform the patients that in order to prevent theft and misuse of PecFent nasal spray they have to keep it in a safe place to avoid misuse and diversion
- All unused devices or empty containers should be returned systematically according to the local regulation
- The pharmacist must make use of the checklist for pharmacist

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

At least 90% of participants were able to find each item of information and of these, at least 90% understood it correctly. It is concluded that the PIL for PecFent 100 mcg and 400 mcg / nasal spray solution provides the necessary information in a way that is accessible and understandable to the patient.

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

There is a recognised clinical need for analgesics with rapid onset of action in cancer patients with breakthrough pain. Due to its pharmacokinetic profile the fentanyl-containing PecFent nasal spray is suitable to meet this clinical need. Efficacy of PecFent in the proposed dose ranging from 100 to 800 mcg per administration has been shown in adequately designed, placebo- and active- controlled phase III studies.

Efficacy of the PecFent formulation was mainly demonstrated by the phase II dose-finding, proof-of-principle study CP041/04, the pivotal phase III trial CP043/06 and the supportive phase III trial

CP044/06. In general, the studies conducted in proof of efficacy of PecFent use well-established designs and validated endpoints very similar to those used in studies conducted in support of formulations of fentanyl that are already licensed for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain (Portenoy et al 2006). These studies and endpoints have demonstrated to high degrees of statistical significance the efficacy of PecFent in a demographically homogeneous population. The primary endpoint of the pivotal efficacy Study CP043/06 was met, demonstrating that at 30 minutes post-dose, the mean SPID score for fentanyl nasal spray-treated episodes was significantly higher than that for placebo-treated episodes (6.57 vs. 4.45, respectively, $p<0.0001$).

- Uncertainty in the knowledge about the beneficial effects.

Not applicable. Fentanyl has a long use and established efficacy in the treatment of breakthrough pain.

Risks

- Unfavourable effects

The adverse effect profile exhibits the known common effects of an analgesic opioid: gastrointestinal effects and dizziness, somnolence, headache. Nasal effects (epistaxis, rhinorrhoea) and information on the concomitant use of nasal decongestants are adequately addressed in the SmPC.

The potential for overdose and abuse is known and has been adequately covered in the product literature.

- Uncertainty in the knowledge about the unfavourable effects.

The CHMP was concerned by the possible risk of abuse and misuse and potential danger with the product for children and family circle due to the lack of a lock out mechanism that is adapted to the posology and mode of administration. The applicant has adequately recognized the regulatory concern and incorporated the following features:

Only 8 sprays per pack, use of a bottle design that minimises residual liquid at the end of use, visual spray counter with audible click, end of use lock out mechanism, child resistant secondary packaging along with a pump attached to the bottle which impedes access to bottle content.
As additional measure the applicant declared to improve the application device with the initial aim of establishing a lock out system between doses within a certain time frame. This issue has been addressed in a follow up measure.

An aspect of product safety arising from inclusion of pectin, is the possible implication of intravenous misuse of the intranasal solution. The gel is formed when the solution interacts with calcium ions. On the one side, pectin inclusion may be regarded as an additional deterrent against intravenous misuse. Section 4.4 of the SmPC alerts against intravenous misuse of the PecFent solution.

Risk Management Plan
Several issues regarding the RMP need to be addressed as follow-up measures. In particular the applicant is requested to provide educational material as additional risk minimisation activities.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The CHMP acknowledges that the one-dose concept of PecFent suitably meets the requirements of providing rapid pain relief in breakthrough pain episodes.

The issues pertaining to a dosage form with rapid increase of plasma concentrations are known and common to other authorised products (Actiq, Abstral, Effentora, Instanyl) and do not raise any specific concern in this case.

In a long-term, open-label, safety study (Study 045), 355 patients entered the 16-week treatment phase, during which 42,227 episodes of breakthrough cancer pain (BTP) were treated with PecFent. One hundred of these patients continued treatment for up to 26 months in an extension phase. Of the 355 patients treated in the open-label treatment phase, 90% required no increase in dose. It is considered that the total number of episodes that were treated by each of the strengths as well as the duration of treatment are adequate to evaluate overall safety.

Objective (ear-nose-throat-trained clinician) and subjective nasal tolerance assessments have systematically been undertaken and did not reveal any clinically significant effects of fentanyl nasal spray that would limit its use.

- Benefit-risk balance

After assessment of the data on Quality, Pharmacokinetics, Safety and Efficacy, the CHMP considers that the application for PecFent, in the treatment of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain is approvable, provided that the applicant undertakes the required follow-up measures.

2.8.1. Discussion on the benefit-risk balance

Overall, the conclusion is drawn that for the pectin-containing formulation, phase III data have been provided that point to a positive benefit-risk balance with regard to efficacy (early significant pain relief, maintained over the 60 min observation period) and safety (good, actively monitored, local tolerability).

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

The following additional risk minimisation activities were required:

Prior to launch in each member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, at launch, all physicians, pharmacists and patients expected to prescribe/use PecFent are provided with educational material informing about the correct and safe use of the product.

Educational material for patients should highlight the following:

- Instructions for use of the nasal spray device
- Instructions for opening and closing of the child-resistant box
- Information on the correct indication
- Only use PecFent nasal spray if you are using other opioid pain medicine on a daily basis
- Only use PecFent nasal spray if you have been experiencing breakthrough cancer pain episodes

- Do not use PecFent nasal spray to treat any other short-term pain or pain status
- Do not use PecFent nasal spray for treatment of more than four breakthrough cancer pain episodes a day
- Only use PecFent nasal spray if you have received the proper information regarding the use of the device and the safety precautions from the prescriber and/or the pharmacist
- All unused devices or empty containers should be returned systematically according to the local regulation

Educational material for physicians should highlight the following:

- PecFent nasal spray should be prescribed only by physicians experienced in the management of opioid therapy in cancer patients.
- The prescribers of PecFent nasal spray must critically select the patients and closely follow
    - Instructions for use of the nasal spray device
    - Instructions for opening and closing of the child-resistant box
    - Information on the correct indication
- PecFent nasal spray should not be used to treat any other short-term pain or pain status.
- All unused devices or empty containers should be returned systematically according to the local regulation.
- The prescriber must make use of the checklist for prescribers

Educational material for pharmacists should highlight the following:

- PecFent nasal spray is only indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain
- PecFent nasal spray should not be used to treat any other short-term pain or pain status
- The pharmacist must be familiar with the educational material of PecFent nasal spray before using it in his/her organization
- The PecFent nasal spray dose strengths can not be compared with other PecFent products
- Instructions for use of the nasal spray device
- Instructions for opening and closing of the child-resistant box
- The pharmacist must inform the patients that in order to prevent theft and misuse of PecFent nasal spray they have to keep it in a safe place to avoid misuse and diversion
- All unused devices or empty containers should be returned systematically according to the local regulation
- The pharmacist must make use of the checklist for pharmacist

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of PecFent in the management of:

> *breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.*
> *Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.*

was favourable and therefore recommended the granting of the marketing authorisation.