



European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

Instanyl

International Nonproprietary Name: **fentanyl**

Procedure No. EMEA/H/C/959

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 Nycomed Danmark ApS submitted on 20 November 2007 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Instanyl, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 1 August 2006. The eligibility to the centralised procedure under Article 3(2) (b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / Known active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The applicant applied for the following indication: the management of breakthrough pain in adults 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.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

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

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

Rapporteur: **Pierre Demolis**

Co-Rapporteur: **Karl Broich**

1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 20 November 2007.
- The procedure started on 26 December 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2008.
- During the meeting on 21-24 April 2008, 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 24 April 2008.
- The summary report of the inspection carried out at sites in Germany, Poland and UK between 13-16 May, 30 June-3 July, 7-11 July 2008 was issued on 10 September 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 August 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 October 2008.
- During the CHMP meeting on 20-23 October 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the list of outstanding issues on 17 January 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues on 29 January. Revised version was circulated on 3 and 4 February 2009.

During the CHMP meeting on 16-19 February 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP on 18 February 2009.

- During the CHMP meeting on 16-19 February 2009, an additional list of outstanding issues to be addressed by the Applicant was adopted.
- The applicant submitted the responses to the additional list of outstanding issues on 19 March 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the additional list of outstanding issues on 6 April 2009. The revised version was circulated on 10 April 2009.
- During the meeting on 20-23 April 2009, 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 Instanyl on 23 April 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 April 2009.
- The CHMP opinions were forwarded in all official languages of the European Union to the European Commission, which adopted the corresponding Decision on 20 July 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Instanyl is a nasal fentanyl formulation, a novel formulation of fentanyl intended to improve the treatment of Breakthrough Pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain.

BTP is a transitory exacerbation of pain that occurs in addition to otherwise stable persistent pain (Mercadante et al. 2002). BTP is usually severe and the median from onset to peak is 3 min (range 1s to 30 min) (Portenoy et al. 1999). Its duration is relatively short, usually no longer than 30 minutes with an average frequency of 3-4 episodes per day. (Portenoy et al. 1999a, Mercadante et al. 2002, Hwang et al. 2003). Although almost 62% of the patients could identify precipitants, almost half (48.2%) also stated that BTP was not predictable.

Currently available BTP treatments are immediate release formulations of the opioids commonly used for treating background cancer pain, i.e. morphine, oxycodone, hydromorphone. In 2001, the first oral transmucosal fentanyl citrate (OTFC) obtained a marketing authorisation through a Mutual Recognition Procedure (Actiq). Since that time, fentanyl buccal tablet (FEBT) was granted a marketing authorisation in the USA on 25th of September 2006 for use in patients with cancer and BTP (Fentora). A positive opinion for Effentora has been given on January 2008 by CHMP.

The development of nasal fentanyl (Instanyl) aims to improve the treatment of BTP in adult cancer patients aged 18 years or more, with stable, chronic opioid treatment of at least 60 mg oral morphine per day, 30 mg oxycodone per day, 8 mg oral hydromorphone per day or 25 micrograms transdermal fentanyl per hour.

A BTP analgesic should provide rapid onset of effect, duration of effect to cover the duration of the episode, no long-active metabolites and availability of a non-invasive formulation. The nasal formulation of fentanyl is expected to provide these features.

Nasal fentanyl bypasses the oral route and, its pharmacokinetic (PK) characteristics and resulting dynamic effects could mimic the course of a BTP episode. Furthermore, it should be convenient for most patients, especially those with nausea or vomiting, dry mouth syndrome, oral mucositis and impaired gastrointestinal function, which are common symptoms in cancer patients.

The nasal fentanyl product developed by Nycomed is self-administered via a mechanical multi-dose nasal spray device. It is proposed for marketing in the final marketed formulation at 3 dose levels, 0.5, 1.0 and 2.0 mg/mL (50, 100 and 200 µg per dose), which are all presented at a pH of 6.5 to 6.6 and an osmolality equivalent to a 0.9% saline solution. Regardless of the concentration (dose strength) of the nasal solution, the nasal spray is designed to deliver a quantity of 100 microliters per dose.

The initial strength should be one dose of 50 micrograms in one nostril, titrating upwards as necessary through the range of available strengths (50, 100, and 200 micrograms). If adequate analgesia is not obtained redosing of the same strength may be administered at the earliest after 10 minutes. Each titration step (dose strength) should be evaluated in several episodes. No more than two doses are to be administered for each BTP episode.

Treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse of fentanyl.

Patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions. Patients must be carefully monitored during the titration process.

Titration to a higher dose necessitates contact with the health care professional.

2.2 Quality aspects

Introduction

Instanyl nasal spray contains fentanyl citrate as active substance. The nasal spray pharmaceutical form is regarded as a novel dosage form in the therapy of break through pain claiming fast absorption of fentanyl through the nasal mucosa. The nasal route of absorption avoids first-pass metabolism of the active substance.

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).

Instanyl is indicated for the management of break through pain in adults who are already receiving maintenance opioid therapy for chronic cancer pain.

It will be marketed in dosage strengths of 0.5 mg/ml, 1.0 mg/ml and 2.0 mg/ml (corresponding to fentanyl) as a multi dose product.

Active Substance

The INN name of the active substance is fentanyl citrate corresponding to the chemical name: *N*-phenyl-*N*-[1-(2-phenylethyl) piperidin-4-yl]propanamide dihydrogen 2-hydroxypropane- 1,2,3-tricarboxylate and to the molecular formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$. The relative molecular mass is: 528.6 (salt), and 336.48 (base). It appears as a white or almost white crystalline powder, soluble in water, freely soluble in methanol, sparingly soluble in alcohol. Its pKa is 8.3.

- Manufacture

Two alternative active ingredient manufacturers are mentioned.

For one of them a CEP is available and has been submitted. Apart from manufacturing the CEP includes supplementary specifications with regard to impurities impurity residual solvents and re-test period.

An ASMF has been submitted for the active substance sourced from the second supplier. Fentanyl is manufactured by several chemical and purification steps all sufficiently described.

- Specification

The active substance release and shelf-life specification complies with the requirements of the European Pharmacopoeia for fentanyl. 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 type III glass with phenolic cap and in double bags placed in HDPE bottles, 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.

Medicinal Product

- Pharmaceutical Development

The medicinal product is a nasal spray solution. It contains a buffered, *non-preserved* aqueous solution of the active substance fentanyl citrate in three strengths; 0.5 mg/ml fentanyl, 1.0 mg/ml fentanyl and 2.0 mg/ml fentanyl.

Fentanyl citrate is listed in Ph. Eur. It is soluble in water, and in solution is most stable at pH between 3.5 and 7.5.

The product's pH of approx. 6.6 falls within the stability optimum for fentanyl citrate solution, which is cited in the literature. The pH of the solution almost approaches the pH of the human nasal mucosa which is cited in the literature.

The osmolality of the solution corresponds to a 0.9 % NaCl solution. Combined with the pH adjustment at a value of pH 6.6 the physiological preconditions for a safe and non-irritating have been considered.

For the respective dosage form the active substance's particle size is therefore no critical parameter regarding the in-vivo performance, since fentanyl citrate is completely dissolved in the aqueous solution.

The excipients used in the formulation are all well known and commonly used in nasal sprays. Both excipients as well as the solvent, purified water are controlled and covered by the requirements of the Ph. Eur.

The container closure system used for the medicinal product is a mechanical multi dose nasal spray device. It consists of a non-vented pump and an actuator mounted on a 10 ml glass v-bottom bottle. Pump delivers a dose of 100 µl. The container closure system is constructed as to form a preservative free system rendering the use of preservative agents unnecessary. The nasal spray will be packaged in a child resistant secondary container, which is not in contact with the medicinal product.

The composition of the pump material and a justification for the suitability of the material for the intended purpose has been provided. Along with a certificate stating the conformity to EU regulations. However the proposed closure system lacks a lock out mechanism to prevent overdosing, a dose counting system to indicate when the solution is exceeding the number of proposed actuations and finally a child resistant pumping device.

With regard to the possible risk of overdose and potential danger of the product for children and family circle because of the primary container closure system, which should include a lock out system and a dose counter, the applicant presented detailed risk evaluation data and risk management plan and committed to continue the development of the multi-dose electronic safety device, with dose counting, lock-out system and built-in child-resistance.

- Adventitious Agents

Not applicable.

- Manufacture of the Product

The manufacturing process comprises the following steps: dissolving the active substance and excipients in the purified water, filtration of solution, filling of bottles, mounting of pump and actuator, and labelling. During the process development a number of process parameters were identified as critical all of which are controlled by in appropriate in process tests.

Based on the provided validation results and keeping in mind that sterility is not defined as quality requirement for nasal non-preserved aqueous nasal spray in multi dose containers in the Ph.Eur.

monograph at the time of assessment of the application, the process should be considered well controlled in regard to microbiological safety aspects.

- **Product Specification**

The specifications of the medicinal product at release and shelf-life include tests for appearance (clarity and colour Ph. Eur.), identification (HPLC and UV), pH (Ph. Eur), assay (HPLC), uniformity of dosage units (Ph. Eur.), mean delivered dose (formula calculation), degradation products (Ph. Eur and HPLC), and microbiological tests (Ph. Eur).

Batch information and batch data for 16 batches of Instanyl nasal spray were provided covering all dosage strengths and package sizes. Fentanyl citrate from both active substance manufacturers has been used for the tested batches. The results comply with the specification, confirm consistency of the product and support the specification acceptance criteria.

- **Stability of the Product**

Stability data is available for a total of 16 batches including all dosage strengths and package sizes (filling volumes) and using fentanyl citrate from both active substance manufacturers. Stability results were presented for up to 5 years under 25°C / 40%RH, for up to one year under 30°C / 65%RH, and for up to six months under 40°C / NMT 25%RH.

All results are in accordance with the specifications and support the proposed shelf life and storage conditions recommendation.

An additional photostability study according to the requirements of the ICH guideline Q1B has been performed on one batch of each package size. No significant changes were seen for samples exposed to light when compared to controls stored in a dark place. It is concluded that the primary packaging protects the product against light.

Extractables and leachables studies

Extractable profile has been established by the manufacturer of the pump and the actuator. Extractables are below the limit of detection (0.01mg/g) and conform to the Ph. Eur. 3.1.3 Polyolefines and 3.1.5 Polyethylene with additives for containers for preparation parenteral use and for ophthalmic preparation.

Leachables have been evaluated by analyzing and comparing placebo product stored at 25°C/40% RH for 12 months, 30°C/65% RH for 12 months and 40°C/25% RH for 12 months, respectively, to Instanyl solution stored at 25°C/40% RH for 12 months and 60 months and 30°C/65% RH for 12 months. LC-MS studies have been performed for identification of potential leachables.

The recommended storage condition for Instanyl is “store below 30°C”. No unspecified impurities are expected to exceed 0.025 µg/100 µl. As eight strokes are the maximum number of strokes allowed per day, they correspond to 0.20 µg per day.

Based on the studies performed and the recommended storage condition to store the product below 30°C it is concluded that leachables are not a concern in Instanyl.

Studies of In-use robustness, temperature cycling and a microbiological In-use test

An In-use study design with three parts (In-use robustness, temperature cycling and a microbiological In-use test) has been performed. For all tests satisfactory results were obtained.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Instanyl nasal spray solution is adequately established. Information on development, manufacture and control of the active 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 medicinal product 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.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant submitted a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

The present marketing authorization application is a complete independent application for marketing authorisation. The submission contains a comprehensive literature overview of the non-clinical safety profile of fentanyl concerning non-clinical pharmacology, pharmacokinetics and toxicology.

With the exception of two local tolerance studies in minipigs, the applicant has not carried out own studies. In substitute for conventional single dose, repeat dose, genotoxicity, reproductive toxicity and cancerogenicity studies, the applicant has provided an overview based on published scientific literature. Since the toxicity profile of fentanyl was extensively studied in various species and different routes of application, the strategy of the company to replace unnecessary animal studies by published scientific literature, where possible, is reasonable.

The studies reported in the literature were not conducted to GLP and therefore the quality with respect to data recording and facilities, environment and investigators cannot be assessed. The data included in the provided review has been judged to be of good scientific quality based on the publications reviewed. No information is available regarding the quality of the active substance used in the publications. In many instances evidence of exposure is available and therefore provides an indication that the active substance contained sufficient fentanyl to achieve the exposure levels cited but does not give an indication of the purity and levels of contaminants.

The pivotal 4-week study of local toxicity following intranasal administration conducted by the applicant in minipigs was GLP compliant.

As the general pharmacodynamic, pharmacokinetic and toxicological properties of fentanyl are well known, only new data or data directly relevant to the nasal formulation itself are more extensively discussed in this report. The main toxicological concern within this marketing authorization application is whether Instanyl administration enhances toxicity due to increased systemic exposure, or causes local toxic effects.

Pharmacology

- Primary pharmacodynamics

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 is around 70 to 100 fold more potent than morphine with a significant shorter duration of action. Fentanyl has been used as an anaesthetic in humans for decades.

However, data on analgesic activity in animals of nasally administered fentanyl is not available, although analgesic activity in humans has been reported. As fentanyl is a substance with well known analgesic activity shown in a variety of animal species and humans it is acceptable to use present published data only and demonstrate the therapeutic effectiveness of the nasal formulation by means of clinical data.

The therapeutic doses of nasal fentanyl are 50, 100 and 200 μg which will be titrated for each individual starting with the lowest dose. Up to two nasal administrations of fentanyl may be made with 10 minutes between administrations to treat an episode of BTP. Data from studies in cancer patients with BTP indicate that mean plasma levels associated with the maximum dose of 200 μg were 1.2 ng/mL, equivalent to around 3.5 nM of compound or where two administrations are made 10

minutes apart plasma peak plasma levels would be around 2.39 ng/mL or 7 nM. Taking into account plasma protein binding, these plasma levels are consistent with the μ -opioid receptor interactions of fentanyl.

- Secondary pharmacodynamics

Fentanyl's analgesic activity is at dose levels that are mostly lower than those associated with secondary or safety pharmacological effects, including

- Bradycardia and decrease in cardiac output in dogs and primates at plasma levels around 80 – 130 nM or 10 – 20 times the levels associated with analgesic activity in these species. Hypotension and an associated reduction in renal blood flow and glomerular filtration rates may explain effects on renal function observed in animals at high dose levels.

- Effects on QT interval with fentanyl where free drug is around 100 nM, equivalent to a total plasma levels of 500 nM, approximately 100 times higher than peak plasma levels of fentanyl found when treating BTP in cancer patients.

- Stimulation of the CNS increasing the level of excitability and arousal and reducing motor coordination at high dose levels achieving plasma concentrations of 126-300 nM: around 50-100 times levels associated with analgesia in rats.

- A depressed respiratory function by fentanyl, evident at dose levels around the onset of analgesic activity.

- A reduced GI motility at plasma levels of around 24 nM

These effects are well known consequences of exaggerated pharmacological effects of fentanyl and are adequately described in the SPC and PIL.

- Pharmacodynamic drug interactions

No pharmacokinetic studies investigated drug-drug interactions. Data reported from the literature indicate that CYP3A4 inhibitors such as ritonavir and troleandomycin decreased fentanyl clearance and CYP3A4 inducers such as rifampicin increase fentanyl clearance. The available data on fentanyl are adequately reported in section 4.5 of the SmPC.

Pharmacokinetics

No animal or *in vitro* pharmacokinetic studies with Instanyl or other nasal formulations have been submitted. Instead, a comprehensive summary of published kinetic data of various other routes, supplemented with clinical data of Instanyl were presented in the documentation.

There are no reports of the extent of absorption from a nasally administered dose but it has been shown that bioavailability from a trans-membrane dose can be up to 60%. It would be expected that fentanyl absorbed by this route would have the same pharmacokinetics as fentanyl administered by other routes.

Immediately following administration by any route, fentanyl is rapidly taken up by the brain, heart, and lung. Within 30 min, there is redistribution to other organs such as fat, muscle, and glandular tissues. Fentanyl is approximately 80% protein bound. There is no indication of retention of fentanyl or metabolites in the tissues. There is limited transfer at early times post dose across the placenta in pregnant animals, with the rate of disappearance in line with that seen in maternal plasma. There is, however, transfer of fentanyl into milk.

The elimination of fentanyl is via metabolism, mainly to norfentanyl. The metabolism of Fentanyl is dependant on the presence of CYP3A4. Care must, therefore, be taken when concomitantly administering fentanyl with any compounds which also have an effect on or are metabolised by CYP3A4. There is no study of the capacity of fentanyl to inhibit the main drug metabolising Cytochrome P450 enzymes and no study of the capacity of fentanyl to induce the main drug metabolising Cytochrome P450 enzymes in a human in vitro model. Fentanyl has been shown in some studies to be an inhibitor of P-glycoprotein, attention must be given if fentanyl is to be used with other compounds which are P-glycoprotein substrates as their kinetics may be altered by fentanyl.

In all species, excretion occurs via both urine and faeces in rat and dog whereas it is primarily via urine in man.

Toxicology

Taking into account the established clinical use of fentanyl, the main toxicological concerns are focused on whether Instanyl administration enhances toxicity, due to increased systemic exposure, or causes local toxic effects.

Whereas increased systemic exposure could be addressed at the clinical level, the preclinical studies performed by the applicant were limited to local tolerance assessment. The remaining toxicological issues were addressed based on publications and data taken from already marketed fentanyl-containing products.

- **Single dose toxicity**

Systemic toxicity was observed following single dose administration by all routes given, with mild clinical signs associated with pharmacological actions of fentanyl at lower doses and more marked clinical signs such as rigidity and prostration, respiratory depression, cyanosis, and mortality at high doses. Exposures would be significantly above the plasma levels required to achieve analgesia.

- **Repeat dose toxicity (with toxicokinetics)**

The applicant reported repeated dose study data from European Public Assessment Report (EPAR) for IonSyS as well as from FDA submission for Duragesic. Beyond pharmacological related effects, histological changes were observed in the liver and in the kidneys only in the dog at 1 mg/kg following a 4-week daily i.v. administration of fentanyl. Data available to the applicant were incomplete, particularly in term of detailed histopathological finding, to characterize in detail the toxicity of fentanyl following repeated administration. These are however considered sufficient taking into account the long standing clinical experience with fentanyl.

- **Genotoxicity**

Fentanyl was shown as negative in a battery of genotoxicity assays (bacterial mutation, in vitro cytogenetics, mouse lymphoma assay, in vivo cytogenetics and UDS in vitro).

- **Carcinogenicity**

No carcinogenicity data are available. Due to the indication and the lack of signals regarding a carcinogenic potential based on the mode of action, the genotoxicity data and the clinical experience, the lack of carcinogenicity data is considered acceptable.

- **Reproduction Toxicity**

Fentanyl has been shown to cause no adverse effects on fertility or early embryo development in male or female rats following administration by s.c. implanted osmotic minipumps. Fentanyl has been shown not to cause embryo-foetal toxicity or adverse effect on peri- and postnatal development in rats at dose levels up to 500 µg/kg/day. At this dose level, plasma levels were 8.5 ng/mL, compared to C_{max}

of 2.4 ng/mL following clinical i.n. administration of 2x 200 µg fentanyl to patients with cancer for breakthrough pain.

- Local tolerance

Local tolerance of fentanyl intranasally administered was assessed in the Göttingen mini-pig in a program carried out by the applicant under GLP compliance. In the preliminary study, by use of a marker substance (methylene blue), it was demonstrated that the intranasal spray device would deliver fentanyl as far as the middle section of the nasal endoturbinates of the mini-pigs. In the pivotal study, twelve females were exposed. No adverse clinical signs indicative of systemic toxicity or local toxicity at the site of administration at the dose level administered (400 µg/animal, 5x day). The applicant calculated a safety ratio of 2.3 compared to the maximum clinical dose per day based on the FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005. This calculation was not acceptable to CHMP as it is specified page 8 of the guidance that scaling between species based on mg/m² is not recommended for the therapeutics administered by alternative routes such as intranasal. Such therapeutics should be normalized to concentration or amount of drug at application site. In the present case, the concentration of fentanyl is 4 mg/ml, corresponding to 2 times the maximal concentration used at the clinical level. In terms of quantity, 2 mg are administered per day, corresponding to 1.25 times the intended maximum clinical dose per day. These data allowed the HMP to conclude that animals were sufficiently exposed to address the local tolerance in the clinical situation.

The impurities related to fentanyl have a limit specification of less than 0.25% in percentage of area in Fentanyl. The specification is compliant with the monograph of the European Pharmacopoeia. Regarding potential local effects, the pivotal local tolerance study performed by the applicant adequately qualify these impurities.

Ecotoxicity/environmental risk assessment

The predicted environmental concentration in surface waters (PEC_{sw}) for the mentioned maximum dose of active ingredient consumed per inhabitant was determined to be 0.008 µg/L. Fentanyl has a moderate potential for bioaccumulation as indicated by its n-octanol/water partition coefficient, log K_{ow}, of 2.9. It can be assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients, and the submission of ecotoxicological test results was not required.

2.4 Clinical aspects

Introduction

Fentanyl is a well-known µ-opioid receptor agonist which was introduced in the 1960s as an intravenous (IV) anaesthetic and has been used for decades for anaesthesia and analgesia during surgery and intensive care. Fentanyl is 50 to 100 times more potent than morphine on a weight basis.

This application concerns the development of a nasal formulation of fentanyl.

The early (2002) clinical development programme of Instanyl consisted of a pilot study, FT-001-IN, which was a combined phase I/II, placebo-controlled, double blind, cross-over study in opioid-naive non-cancer patients with post operative pain after oral surgery (third molar extraction) evaluating doses of 75, 100, 150 and 200 µg, administered either as one dose (75 and 100 µg) or two doses at 5 minutes interval (150 and 200 µg), and a pivotal study, FT-003-IN, which was a double-blind, double dummy, cross-over, dose ranging study in opioid tolerant cancer patients (doses from 50 to 1200 µg), with an open safety follow-up study, FT-011-IN. The overall objectives of the FT-003-IN and FT-011-IN studies were to demonstrate the efficacy and to evaluate safety and tolerability of nasal fentanyl in the treatment of BTP.

A scientific advice meeting was held with the MHRA/UK on July 29, 2002 to discuss the clinical development programme for Instanyl. At that time study FT-001-IN was completed and the results available. Two indications in two different patient populations were discussed during the meeting i.e.:

- Treatment of episodic or BTP experienced by patients with otherwise controlled chronic background pain
- Treatment of acute and postoperative moderate to severe pain (i.e. acute moderate to severe pain in non-cancer, opioid naïve patients)

The MHRA recommended that an interaction study with a decongestant should be performed (xylometazoline) (this was not done), the kinetic program was considered sufficient (no need of multiple dosing), the use of morphine or Actiq as comparator and evaluation of local tolerance were also discussed. It was also concluded that the design of study FT-003-IN was interesting but that it may be hard to show a difference between the titration dose and half this dose. No further advice was asked by the applicant for studies FT-017-IM and FT-018-IM.

The studies FT-003-IN and FT-011-IN were prematurely terminated and Nycomed decided to terminate the Instanyl development programme in 2003 for the following reasons: the conduct of FT-003-IN had met unforeseen problems including an 8-month delay of initiation, slow recruitment, inclusion of patients in more advanced stages of cancer than expected and therefore in need of higher doses of BTP analgesic than foreseen. Therefore, a new development strategy was decided by Nycomed.

The development was then resumed (2006/2007) and the documentation submitted in this application includes an open, phase Ib study, FT-016-IM, in cancer patients and two phase III, placebo controlled efficacy and safety studies in cancer patients with BTP, FT-017-IM and FT-018-IM.

Overall, the clinical dossier is in compliance, as far as the efficacy endpoints are concerned, with the CHMP Guidelines on 'Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain' (EMEA/CHMP/EWP/612/00 2002),

GCP and inspection issues

All clinical studies in support of this MAA were conducted in Europe. The clinical program for nasal fentanyl was designed in accordance with Good Clinical Practice (GCP) and International Conference on Harmonisation (ICH) guidelines.

On November 30, 2007 observations were reported giving rise to suspicion of misconduct in FT-019-IM (open label, comparative, randomised, balanced crossover trial comparing nasal fentanyl and oral transmucosal fentanyl (Actiq) in breakthrough pain (BTP) in patients with cancer) at site X. This study is not included in the initial Instanyl application, however this investigator did also recruit patients in the trials FT-017-IM and FT-018-IM, which are part of the dossier.

An inspection was conducted following a request from CHMP (May-July 2008). The purpose of the inspection was to verify whether the clinical trials FT-017-IM and FT-018-IM were conducted in compliance with GCP and applicable regulations, in particular where it had impact on the validity of the data or the ethical conduct of the trials. As misconduct in the trials FT-017-IM and FT-018-IM could not be ruled out, the applicant resubmitted the trial data to the EMEA excluding the data of site X.

The site X was inspected, together with site Y, which was the one with the highest number of patients recruited in the trials: 24.5% (46 patients) for FT-017-IM and 29.6% (40 patients) for FT-018-IM.

The inspections identified major and critical findings regarding the quality and validity of the efficacy data (primary and secondary) reported in the two trials. This is three -fold, firstly because of the deficiencies observed for the IMP container design and the subsequent lack of dose compliance monitoring, secondly because of the inaccurate protocol and patient diary design and thirdly because of the insufficient quality measures taken by the sponsor and CRO.

The safety data reported in the clinical trials FT-017-IM and FT-018-IM were not considered reliable by the inspectors for use in the assessment of the marketing authorisation application for nasal fentanyl (Instanyl) at the initial stage of the assessment.

Underreporting of adverse events was observed on three levels:

All sites	It was systematic for all investigational sites involved in terms of the complete absence of space on the diary cards allocated to AE entry.
Both inspected sites	Both investigators of the inspected sites consistently were unaware of the change according to protocol amendment 1 stating that AEs probably related to the progression of the underlying cancer disease were also to be reported as adverse events.
Investigation site Y	At investigation site Y with the highest patient recruitment AE reporting was based on the investigator's subjective judgement but not on the AE definition according to ICH-GCP.

The sponsor started a revisiting of the sites and reassessments of safety data: the results were provided to CHMP.

However, only the adverse events which were actually recorded by the investigators could be collected. Adverse events which occurred but were not noted by the investigator could not be collected retrospectively.

The CHMP considered that the majority of non reported events could not be remedied retrospectively.

The Applicant provided the requested reanalysis. Following the review of the applicant's responses to the Day 180 List of Outstanding Issues the CHMP had still concerns about the quality and reliability of the safety and efficacy data particularly in relation to the following points:

1. Quality Management System

During re-monitoring, 49 additional unreported AEs were discovered in trial FT-017-IM (increase by 70%) and 238 additional AEs in FT-018-IM (increase by 100%, doubled). These high numbers of unreported AEs raised the concern that the underreporting of AEs was not limited to the two inspected investigational sites, and it is the result of inadequate quality management system (monitoring and auditing) in the two trials. The applicant was requested to provide reassurance that the quality management system (monitoring and auditing) was sufficient to ensure the quality and integrity of the safety and efficacy data.

2. Adverse Event Reporting

During the re-monitoring only AEs recorded in the source notes and not reported could be collected retrospectively. The applicant was requested to provide reassurance on the completeness of the safety data.

3. Protocol Design

The fact that according to the protocol instructions, study staff was allowed to enter efficacy data into the patient diary card is an important issue which might have affected the efficacy data of the trial. The applicant was requested to specifically comment on the impact on the reliability of the data collected.

After the Applicant's responses to the 2nd list of Outstanding Issues, and consideration of the the inspectors' report, the CHMP concluded as follows:

1) Quality Management System:

The quality management system for the two trials was not only considered insufficient regarding the aspect of AE reporting, but regarding other aspects, too. An effect of this general deficiency on the efficacy data of the trials could still not be excluded, according to the inspectors.

2) Adverse Event Reporting:

The investigators of both sites which were inspected (site X and Y) were not sufficiently trained in ICH-GCP, which is the essential basis for conducting a clinical trial. Thus even if the investigators have documented according to what is considered by them as "normal clinical practice" relevant safety information might have not been appropriately reported.

The adverse events which occurred but were not recorded by the investigators because they were not aware of the reporting requirements according to the protocols and ICH-GCP or which were not recorded by the patients in the diaries because there was no space allocated, could not be collected retrospectively. Thus, the inspectors notified the CHMP that it still could not be excluded that clinical relevant AE information was lost and to which extent it was lost.

3) Protocol Design:

It was still not clear to which extent the study staff has assisted the outpatients in entering data during visits. Therefore the inspectors notified the CHMP that it was still not assessable whether there was an influence on the efficacy data of the trial.

The inspectors concluded that it appeared that the quality management system was insufficient to ensure the quality and integrity of the efficacy and safety data.

The results obtained are however consistent between the efficacy studies. The CHMP therefore concluded with regard to the whole documentation that the deficiencies found in the quality system of the sponsor are unlikely to invalidate the quality of the efficacy and safety data.

Having reviewed the analysis of the data excluding site X, the CHMP conclusion is that exclusion of site X does not make any substantial changes to the efficacy or safety results as compared to the results for all patients presented in the initial application.

Pharmacokinetics

The clinical pharmacology documentation is comprised of 2 clinical pharmacokinetic studies (FT-001-IN, FT-016-IM), 14 pivotal publications on pharmacokinetics and metabolism of fentanyl and 19 publications providing supplementary pharmacokinetic information. These latter publications were designated as "non pivotal" by the applicant.

The pharmacokinetic studies consisted of a pilot dose-finding study and a pharmacokinetic study in cancer patients.

- Absorption

In the two pharmacokinetic studies submitted, plasma concentrations were determined using validated methods. The intra assay, inter assay precision and mean accuracy were within the $\pm 15\%$ limits for all concentrations.

Fentanyl formulated as nasal spray is readily absorbed. Mean time to maximum observed plasma concentration (T_{max}) is about 13 minutes. Absolute bioavailability is close to 100%.

Comparatively, the median T_{max} of Actiq varies between 20 to 40 minutes (20-280) and the mean T_{max} of Effentora is 46.8 minutes (20-240).

- Distribution

From the literature, it is known that the volume of distribution is approximately 4 l/kg. There is a rapid redistribution phenomenon characterised by a slow return of the unchanged drug from peripheral compartment containing the well perfused tissues to the central compartment.

The plasma protein binding is about 80%. The main binding protein is alpha – 1 – acid glycoprotein but both albumin and lipoproteins contribute to some extent to the binding.

Mass balance data from the literature indicate that after IV fentanyl administration, 85% of the dose is recovered in urine (76%) and in feces (9%). A small proportion of the dose is recovered unchanged in urine (1.2%) suggesting that fentanyl is extensively metabolised. CYP3A4 was found to be mainly responsible for the dealkylation of fentanyl to norfentanyl. Hydroxynorfentanyl and hydrofentanyl were also identified. Fentanyl metabolites possess no significant activity.

- Elimination

Mass balance data from the literature indicate that after IV fentanyl administration, 85% of the dose is recovered in urine (76%) and in feces (9%). A small proportion of the dose is recovered unchanged in urine (1.2%) suggesting that fentanyl is extensively metabolised. CYP3A4 was found to be mainly responsible for the dealkylation of fentanyl to norfentanyl. Hydroxynorfentanyl and hydrofentanyl were also identified. Fentanyl metabolites possess no significant activity.

The disposition of fentanyl formulated as nasal spray in cancer patients was characterised by a slow elimination phase resulting in a mean T_{1/2} of approximately 200 minutes.

- Dose proportionality and time dependencies

Dose proportionality

Dose proportionality of single 50 to 200 µg nasal doses of fentanyl was evaluated in patients with cancer with breakthrough pain receiving chronic non fentanyl-opioids as an around the clock pain treatment. C_{max} and AUC values of fentanyl following nasal administration were less than dose proportional across the dose range 50 – 200 µg. There was no kinetic information on doses ranging between 200 and 400 µg, whereas the administration of 200 µg x 2 is possible according to the SmPC (and occurred in more than 75% of the patients receiving 200 µg in clinical studies). This lack of data was of concern to the CHMP, who requested the applicant to provide further studies.

In their response, the applicant provided the results of study FT-024-IM, a randomised, single-center, open-label, 2-way crossover study to compare the bioequivalence of single doses (200 µg) of fentanyl nasal spray using single dose (SDS) and multi-dose delivery systems (MDS) followed by a third dosing period (two doses of 200 µg) using a multi-dose delivery system in healthy subjects.

This study was primarily designed to investigate bioequivalence of a single 200 µg dose administered either from a single- or multiple-dose device. It failed in this objective, since the 90.2% CI for the C_{max} ratio (0.90) fell outside the 0.8-1.25 acceptance range (0.74 – 1.09). However, it also provided some data on the fentanyl blood levels after two successive 200 µg doses, either administered as simultaneous doses (one in each nostril) or with a 10 minute interval between the two doses

Unexpectedly C_{max} after simultaneous two doses of 200 µg each (2 x 100 µl) was considerably lower than the maximum concentration achieved with the 10 min interval. It might be related to drainage of parts of the applied solution into the oro-pharynx in case of simultaneous administration. Furthermore, the number of subjects was rather small: parallel group design with 7 or 8 subjects for each group. The applicant proposed as an explanation that these results could be due to the low number of subjects included and consequently to a lack of power for both studies.

Considering the importance of these PK data that have to be seen in the context of the whole 10 min interval concept, a larger study population and a cross-over design for the second phase of the study would have been desirable. Although the second half of the dose was administered after 10 minutes, higher C_{max} was found. The finding gives rise to further questions, e.g. the comparison of 400 µg in 100 µl (one dose) versus 2 doses of 200 µg (100 µl each, 10 min interval) in order to eliminate the oro-pharynx drainage as an influencing factor.

In the answers to the day 180 questions, the applicant have presented modelling data of the PK profile after two administrations of 200 µg with a 10 minutes interval and referenced to the PK US studies. The result for the ratio of mean AUC indicated the plasma drug exposure was comparable between the two treatments. Moderately lower peak plasma concentration was observed following administration of two doses of fentanyl nasal spray 200 µg with the second dose administered immediately after the first compared to the second dose given after a 10-minutes interval. The relative bioavailability of fentanyl nasal spray 200 µg x two doses taken immediately is less than that of the fentanyl nasal spray 200 µg x two doses taken 10 minutes apart (ratio of 0.91).

Although dose proportionality between 200 and 400 µg doses was not studied in cross-over design, the AUC and C_{max} results from study FT-024-IM seem to indicate that fentanyl pharmacokinetics is approximately linear between these 2 doses. The CHMP considered this issue solved.

It was also unclear from the initially submitted documentation whether the bioavailability was modified after long term treatment due either to saturability of absorption with respect to a possible volume effect, the influence of a nasal decongestant in patients with seasonal allergic rhinitis, or the effect of a common cold with upper respiratory symptoms.

The applicant was requested to provide further studies: the data on saturability of absorption with respect to a possible volume effect (study FT-023-IM), the influence of a nasal decongestant in patients with seasonal allergic rhinitis (study FT-025-IM) and the effect of a common cold with upper respiratory symptoms (study FT-026-IM) were provided in the day 180 answers as summaries of each study as the final study report had not yet been signed off.

These three PK-studies used the single-dose nasal spray, whereas the pivotal studies used the multi-dose nasal spray. Bioequivalence data between the single-dose and the multi-dose nasal spray were available from study FT-024-IM.

Study FT-026-IM has shown that following administration of one dose of fentanyl nasal spray 200 µg, an upper respiratory infection does not alter the absorption of fentanyl nasal spray in subjects with a common cold.

In study FT-023-IM, although “dripping” was observed in seven out of twelve subjects with increasing numbers of subsequent actuations into the same nostril, approximate linearity of fentanyl plasma concentration was found. The application of two, three or even four doses in quick succession into the same nostril is, however, an artificial scenario that is not expected to occur based the recommended method of administration according to the SPC. Furthermore, the focus is placed upon observing “dripping out of the nostril”. The question of possible drainage into the oro-pharynx was not addressed. Coming back to the results obtained in study FT-024-IM (C_{max} higher with 10 min interval as compared to two simultaneous doses, one into each nostril), it would have been interesting to evaluate any possible “saturation effects” (drainage) by comparing 1 x 200 µg dose (100 µl) with two simultaneous doses of 100 µg (100 µl into each nostril). This scenario was considered to represent a more realistic clinical setting with regard to “volume effects”.

In their answers the applicant also discussed studies¹ about the influence of head position on nasal administration. Some (uncomfortable) head positions allow for a wider mucosal distribution of the drug. However studies with fentanyl nasal spray using a ‘generic’ instruction on how to administer the drug have shown a rapid absorption and high (close to 100%) bioavailability of fentanyl, hence positional differences were not considered to be of crucial importance from a pharmacokinetic point of view.

Study FT-025-IM assessed the pharmacokinetics of fentanyl nasal spray in subjects with seasonal allergic rhinitis with and without prior administration of oxymetazoline.

The study showed that following administration of a single dose of 200 µg fentanyl nasal spray to the subjects with allergic rhinitis, the prior treatment of the nasal constrictor (oxymetazoline) decreased peak fentanyl plasma concentration by over 50%, and T_{max} was substantially increased by 2-fold (median 21 minutes versus 46 minutes). The CHMP therefore proposed the insertion of appropriate wording in sections 4.5 and 5.2 of the SPC, and considered the issue solved.

(section 4.5)

In a pharmacokinetic interaction study it was found that the maximum plasma concentration of nasally applied fentanyl was reduced about 50% by the concomitant use of oxymetazoline, while the time to reach C_{max} (T_{max}) was doubled. This may reduce the efficacy of Instanyl. It is recommended that concomitant use of nasal decongestants is avoided (see section 5.2)

¹ Bateman et al (2002) and Raghavan & Logan (2000)

(section 5.2)

A drug-drug-interaction study was performed with a nasal vasoconstrictor (oxymetazoline). Subjects with allergic rhinitis received oxymetazoline nasal spray one hour prior to Instanyl. Comparable bioavailability (AUC) of fentanyl was achieved with and without oxymetazoline, while fentanyl C_{max} decreased and T_{max} increased by a factor two when oxymetazoline was administered. The overall extent of fentanyl exposure in subjects with allergic rhinitis without prior treatment with nasal vasoconstrictor is comparable to that in healthy subjects. Concomitant use of nasal vasoconstrictor should be avoided (see section 4.5).

**Fentanyl mean pharmacokinetic parameters for a dose of
and a dose of twice 200 µg with the second dose 10 minutes after the first dose**

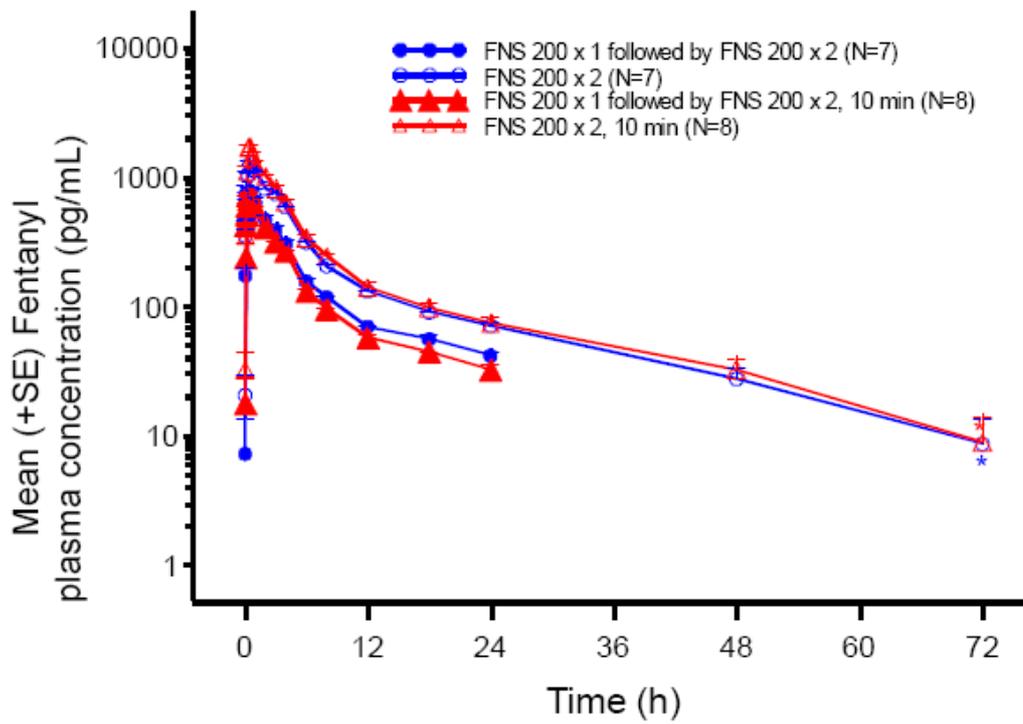
Parameter (units)	FNS 200 µg/100 µl ^a	N	Mean ± SD	Median	Minimum	Maximum
AUC(0-∞) (pg·h/ml)	x 2 MDS	7	8902 ± 1876	9416	5405	10914
	x 2, 10 min MDS	8	10102 ± 3446	9432	5110	15155
C _{max} (pg/ml)	x 2 MDS	7	1316 ± 293	1300	971	1710
	x 2, 10 min MDS	8	2009 ± 444	2160	1280	2500
<hr/>						
AUC(0-last) (pg·h/ml)	x 2 MDS	7	7919 ± 1645	8209	4748	9671
	x 2, 10 min MDS	8	9073 ± 3017	8433	4547	13601
T _{max} (min)	x 2 MDS	7	33 ± 16	30	8	60
	x 2, 10 min MDS	8	29 ± 9	30	20	45
T _½ (h)	x 2 MDS	7	19.2 ± 7.3	21.3	8.7	27.7
	x 2, 10 min MDS	8	18.9 ± 7.4	19.3	7.9	30.0

^a x 2 MDS = 2 doses from multi-dose FNS immediately; x 2, 10 min MDS = 2 doses from multi-dose FNS 10 minutes apart.

FNS: Fentanyl nasal spray

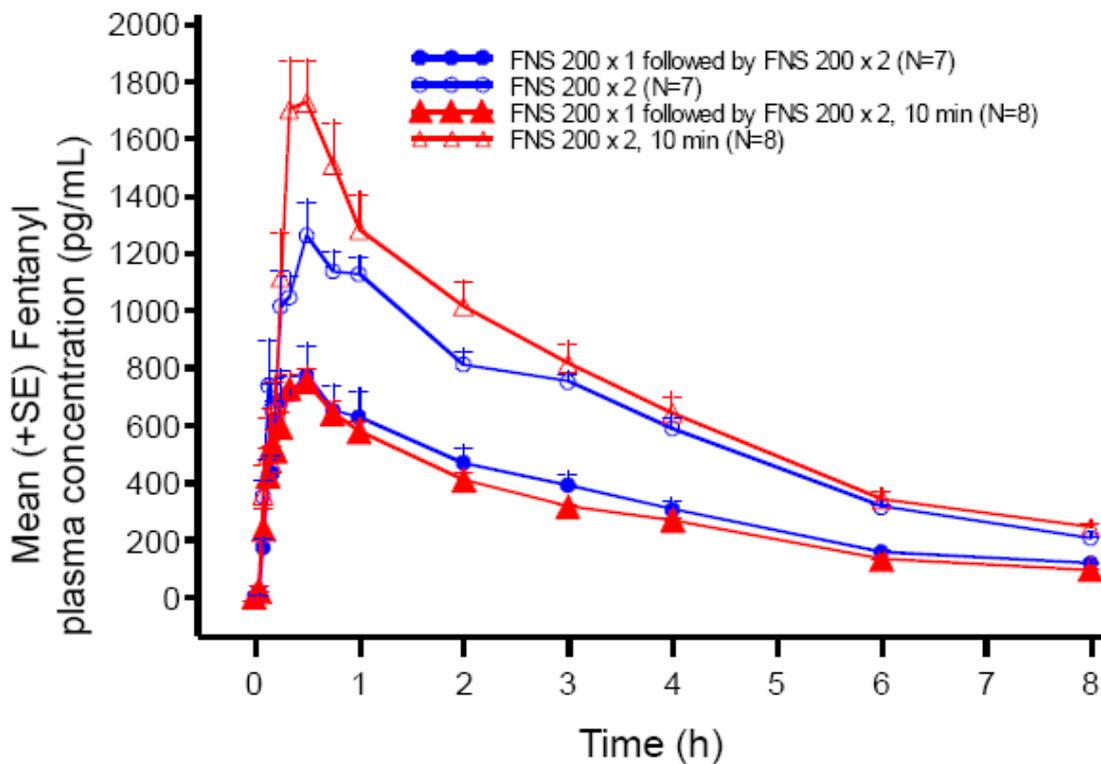
Source: Summary FT-024-IM, Table 5

Mean fentanyl plasma concentration-time curves following administration of single-dose or 2 doses of fentanyl nasal spray 200 µg using MDS: (top, log scale, 0 to 72 hours; bottom, linear scale 0 to 8 hours)



* = Mean is calculated based on all values including those set to zero (less than LLOQ). For the 2 time points of the eliminal phase marked in the figure, fewer than 3 values are above the LLOQ.

Source: Summary FT-024-IM, Figure 5a



Source: Summary FT-024-IM, Figure 6b

Interindividual variability

In patients, the interindividual variability expressed as coefficients of interindividual variation for AUC and Cmax are of 40-50%, and are in the same order of magnitude as shown for other fentanyl

formulations intended for the treatment of breakthrough pain. The estimation of the intraindividual variability shows that the intraindividual variability is likely to be high, i.e; higher than 30%. This intra individual variability was calculated in a study performed in standardised conditions. However, the safety data derived from the clinical studies did not show any particular concern. The CHMP therefore considered the issue solved.

- Special populations

No formal clinical pharmacology studies were specifically conducted in special populations. Data from the literature are scarce. Published experience with fentanyl in elderly subjects shows discrepancies in the data. Accordingly, as with other marketed fentanyl formulations, a special warning for the use in patients with impaired hepatic or renal functions and in elderly patients was included in the SmPC.

- Pharmacokinetic interaction studies

No pharmacokinetic studies investigated drug-drug interactions, other than oxymethazoline. Data reported from the literature indicate that CYP3A4 inhibitors such as ritonavir and troleandomycin decreased fentanyl clearance and CYP3A4 inducers such as rifampicin increase fentanyl clearance. The available data on fentanyl interactions were considered adequately reported in section 4.5 of the SmPC.

- Pharmacokinetics using human biomaterials

No studies were submitted and this was considered acceptable by CHMP.

Pharmacodynamics

No specific pharmacodynamic studies were performed for the nasal fentanyl formulation. Fentanyl is a well known analgesic which acts as an opioid agonist. It has been used for years as an analgesic either in intravenous or transdermal administration and its major effect and side-effect profiles are well known and well documented.

Clinical efficacy

The efficacy documentation comprises a pilot dose finding study (FT-001-IN), 2 clinical studies aimed to investigate the efficacy and safety of Instanyl, which were terminated prematurely (FT-003-IN and FT-011-IN) and two main pivotal studies (FT-017-IM and FT-018-IM).

Please refer to the discussion above under GCP/inspections for the deficiencies identified during the inspection of these studies.

- Dose response study(ies)

Study FT-001-IN: pilot, cross-over study to evaluate the tolerability, pharmacokinetic profile as well as onset, duration and extend of pain relief of nasal administration of fentanyl with i.v. administration at four different doses (75, 100, 150 and 200 microgrammes) in patients undergoing third molar surgical extraction. The dose schedule used in this trial was based on the recommendations for i.v./i.m. fentanyl for post-operative pain: 50 to 100 µg repeated every 5 to 10 minutes to achieve the desired level of analgesia and on the published pharmacokinetics of nasal fentanyl with a bioavailability of 71% as compared to i.v. fentanyl.

Each patient had two nasal applications, one in each nostril, with an interval of five minutes. Simultaneously, the patient had two i.v. injections of 2.0 ml with an interval of five minutes. Depending on randomisation the first dose of test treatment was either nasal or i.v; fentanyl. Nasal and i.v. placebo formulations were used as the second dose for the two lowest dose groups (75 and 100 µg). 24 subjects were randomised and 23 completed the study.

The results of this study showed that nasal fentanyl presents a short onset of action (7 minutes) and a median duration of action of 56 minutes. These clinical characteristics fit well with the treatment of

BTP. The studied doses of nasal fentanyl allowed to achieve a decrease of pain intensity of the same magnitude to the one observed after i.v. administration. In addition, there is a dose-response relationship (exploratory population) with a mean duration of action of 47 minutes for 75 micrograms and 89 minutes for 200 micrograms ($p=0.04$).

However, the chosen dose and the proposed administration schedule were not justified. The fact that patients with the lowest dose (75 and 100 μg) received single administration whereas patients with the highest dose (150 and 200 μg) received two administrations at 5 minutes interval made the interpretation of the results difficult. The applicant was requested to explain the choice of this design.

At day 180, the applicant submitted new kinetic data regarding dose linearity between 200 and 400 μg , effect of volume on saturability and data on nasal congestion, allergic rhinitis with or without the administration of vasoconstrictor and common cold and patient intra-variability (see discussion under Pharmacokinetics). Thus these major objections were considered solved, and the corresponding information, when needed, has been included in the SPC.

The clinical efficacy of the second dose is confirmed by the re-analysis provided for study FT-018-IM, even if the question of the choice of dose interval (50 to 200 μg) and the mode of administration (one dose followed, in case of inefficacy, by a second one 10 minutes after) were not convincingly demonstrated in this trial.

- Main study(ies)

The two main studies (pivotal study FT-017-IM and confirmatory study FT-018-IM) were performed to evaluate the efficacy of nasal fentanyl in the treatment of BTP in adult cancer patients already receiving maintenance opioid therapy for chronic cancer pain., The patients included in study FT-018-IM should have received at least one dose of Instanyl as part of studies FT-016-IM or FT-017-IM (see below).

Study FT-017-IM

Intranasal fentanyl for the treatment of breakthrough pain in cancer patients: A randomised, double-blind, placebo-controlled, cross-over confirmatory trial testing the doses 50, 100 and 200 μg fentanyl and placebo in eight breakthrough pain episodes.

METHODS

Study Participants

The main inclusion criteria for both studies were as follows:

- adult cancer patients aged 18 or more, with stable chronic opioid treatment equivalent to 60-500 mg oral morphine/day or to transdermal fentanyl 25-200 $\mu\text{g}/\text{hour}$,
- background pain controlled to a mild level (defined as ≤ 4 on an 11 point NRS),
- at least three episodes of BTP per week but not more than 4 episodes per day

Facial radiotherapy was an exclusion criterion due to potential effects on the uptake of nasally administered fentanyl caused by damage to the epithelial cells of the nose.

The current opioid background dose was defined as being equivalent to 60-500 mg morphine/day or to transdermal fentanyl 25-200 $\mu\text{g}/\text{h}$.

Treatments

Doses of 0, 50, 100 and 200 μg fentanyl were given twice following a randomised order for the treatment of eight BTP episodes. The Investigational Medicinal Product (IMP) was administered as one dose in one nostril. In case of insufficient pain relief, a second dose (of the same dose) was taken after 10 min. Rescue analgesics were allowed after further 10 min.

During the trial, patients received their stable background pain opioid(s) and were allowed to take their usual analgesic for any type of pain. Administration of rescue analgesic for BTP in case of IMP failure

was recorded in the diary. Analgesics other than IMP taken outside the time interval of 0-60 min after IMP administration – apart from the background pain opioid(s) - were regarded as concomitant medication.

For patients who took rescue analgesic before 60 min, the last value prior to taking rescue analgesics was carried forward (LOCF) and imputed for all time points after administration of rescue analgesic. Rescue analgesics included any analgesic taken between time=0 min and time=60 min as a supplement to the IMP. A second dose of IMP was allowed if required and was not considered rescue medication.

Instanyl was supplied in a glass container with a standard nasal spray pump and actuator, containing 40 doses. The containers were labelled in local language. The Instanyl was available as a phosphate buffered solution of fentanyl citrate in three strengths: 0.5 mg/ml, 1.0 mg/ml and 2.0 mg/ml fentanyl in multiple-dose containers. The corresponding doses were 50, 100 and 200 µg fentanyl/dose as to be administered as one dose in one nostril. One dose defined and equalled one dose (100 µl). During their baseline visit, each patient was given instructions on how to use the Instanyl spray bottle and practiced with the test bottle. Placebo for nasal use was supplied in identical spray bottles containing sodium citrate in a phosphate buffered solution.

To ensure safety of patients, a 200 µg test dose was given in-hospital prior to randomisation. If clinically significant intolerable reactions occurred, the patient was not randomised.

Objectives

The objective of study 017 was to demonstrate efficacy of nasal fentanyl (Instanyl) in the treatment of breakthrough pain in cancer patients, and to explore the relationship between the response to the Instanyl dose and the stable background pain opioid dose.

Endpoints

The main efficacy variables for this study were:

- Pain Intensity (PI) evaluated on an 11 point Numerical Rating Scale (NRS), at 0, 10, 20, 40 and 60 minutes,
- Pain Intensity Difference (PID) and Sum of Pain Intensity Difference (SPID), which were derived from PI.
- Global Impression (GI) measured with a five-point Verbal Rating Scale (VRS) at 1 hour,
- Rescue medication.

The primary efficacy variables were PID10 (PID at 10 minutes) and average responder rates: average responder rates were computed by dose. A positive response to treatment of a BTP episode for each patient for each dose was defined as $PID_{10} > 2$, where PID10 was calculated as an average score for the two episodes within a patient.

Sample size

184 patients were enrolled.

Randomisation

The patients first received a test dose of 200 µg nasal fentanyl (Instanyl) and were randomised if they did not develop clinically substantial respiratory depression or other clinically meaningful intolerable reactions (e.g. sedation, vertigo, nausea). Then they received a Instanyl kit containing 8 bottles, 2 of each dose (placebo, 50, 100 and 200 µg fentanyl/dose) in a random order.

Eight BTP episodes per patient (within the treatment phase of up to three weeks) were treated with the following doses: 2 x placebo, 2 x 50 µg Instanyl, 2 x 100 µg Instanyl and 2 x 200 µg Instanyl. Patients were randomised to dosing sequences in which each of the four doses (including placebo) was received twice. The randomisation was restricted such that the first four and last four episodes were

treated with four different doses. The eight episodes of BTP were to be treated with IMP in the order the spray bottles were numbered (1 to 8).

The intended purpose of this trial design was questioned by CHMP as assignment of fixed doses (instead of individual titration) inevitably led to under- and overdosed BTP periods in each patient. The applicant justified their choice of design stating that their primary aim was to demonstrate efficacy and dose response of nasal fentanyl of each of the three fixed strengths. This was accepted by CHMP but the study was still considered methodologically flawed.

Statistical Methods

The PID10 for each patient for each dose was calculated as an average score for the two episodes. Individual as well as mean dose response curves were presented graphically.

The PID10 was analysed by successive F-tests of the contrasts of 200 µg vs placebo, 100 µg vs placebo and 50 µg vs placebo. To ensure protection of the significance level, the tests were performed sequentially, only proceeding to the next test if the current test was statistically significant so it was not possible to conclude that 100 µg was effective if 200 µg was not. For each test, the hypothesis was that of no difference between mean response on active dose and mean response on placebo with the alternative that they differ. The trial followed a cross-over design with each of the four doses taken twice. The corresponding mixed linear model included the following fixed effects:

- Treatment (0, 50, 100, 200 µg IMP) (categorical)
- Centre (categorical)
- Average baseline PI (over all episodes for a patient) (continuous)
- Deviation of baseline PI for each episode from average baseline PI (continuous)

RESULTS

Recruitment

This study was conducted from May 2006 to May 2007.

Conduct of the study

The inspections identified major and critical findings regarding the quality and validity of the efficacy and safety data (primary and secondary) reported in the trial, particularly with reference to site X. This is three -fold, firstly because of the deficiencies observed for the IMP container design and the subsequent lack of dose compliance monitoring, secondly because of the inaccurate protocol and patient diary design and thirdly because of the insufficient quality measures taken by the sponsor and CRO.

For a detailed discussion refer to the GCP section.

Baseline data

The relationship between the IMP dose and the baseline dose of the background pain opioid was evaluated for PID10 and for responders (PID10 >2). For this purpose, the background pain opioid dose was standardised to morphine equivalent doses (Breitbart et al, 2000). Based on the acceptable range of background pain opioid dose which was equivalent to 60 to 500 mg oral morphine/day (inclusion criterion 5) the cut-off points were defined as increments of 180 mg/day: low (≤ 180 mg/d), medium ($>180 - \leq 360$ mg/d), and high dose (>360 mg/d) of background pain opioid. Summary statistics for PID10 and for responders by dose were presented by category of baseline background pain opioid dose (low, medium, high).

The most frequently reported background pain opioid medications were fentanyl (89 patients, 58.6%) and morphine (65 patients, 42.8%).

The mean standardised morphine equivalent dose of background opioid pain medication at baseline was 191.7 mg/d. The majority of patients (100 patients, 65.1%) were considered to be in the 'low' dose category (≤ 180 mg/d); 25.7% were in the 'medium' dose category ($>180 - \leq 360$ mg/d), and

9.2% were in the ‘high’ dose category (>360 mg/d). Six patients had baseline background opioid daily doses that slightly exceeded the protocol-specified limit of 500 mg (maximum dose used was 600 mg/d) but were included in the ITT and PP analysis sets.

Numbers analysed

Of the 184 enrolled patients, 19 patients were enrolled at site X and were excluded from the re-analysis of the trial data, as shown in Table 1. Of the six patients who did not tolerate the test dose, and were therefore excluded from randomisation, none were enrolled at site X, resulting in a total of 159 randomised patients in the re-analysed population. Additionally, none of the seven patients excluded from the ITT analysis set, none of the 16 patients excluded from the PP analysis set, and none of the 14 patients who discontinued prematurely were at site X.

Table 1 Summary of Patient Disposition

Number of Patients		
	All Patients	Site X Excluded
Enrolled (received NAF test dose)	184	165
Randomised	178	159
Intent-to-treat analysis set (ITT)	171 (100.0%)	152 (100.0%)
Per-protocol analysis set (PP)	155 (90.6%)	136 (89.5%)
Completed double-blind treatment phase	157 (91.8%)	138 (90.8%)
Discontinued prematurely	14 (8.2%)	14 (9.2%)
Adverse events	8 (4.7%)	8 (5.3%)
Non-compliance with protocol	3 (1.8%)	3 (2.0%)
Other	3 (1.8%)	3 (2.0%)

NAF = nasal fentanyl

Exclusion of study center X did not alter the demographic proportions of the study population: 52.6% male and 47.4% female, mean age (61.6 years), mean BMI (23.7 kg/m²), mean weight (67.3 kg for males and 64.9 kg for females), and mean height (171.3 cm for males and 162.5 cm for females). All patients for whom race was reported were Caucasian (data collected for 145 patients, 95.4%).

The six patients who did not tolerate the test dose experienced nausea (3 patients), vertigo (3 patients), vomiting (1 patient), hypertension (1 patient), sedation (1 patient), and syncope (1 patient). The ITT analysis set comprised all randomised patients who took at least one dose of double-blind trial drug for treatment of BTP. Of the 159 patients who tolerated the test dose and were randomised, seven patients were excluded from the ITT analysis set: six received no trial treatment whereas one patient received medication kit from trial FT-018-IM by mistake. Sixteen patients were excluded from the PP analysis set for the following reasons: 3 patients violated various inclusion criteria, 2 patients did not follow the randomisation schedule, and 11 patients did not have at least one per-protocol episode for each dose of the trial drug.

Outcomes and estimation

Patients were instructed to treat only one episode per day with IMP. The trial design conditions that allowed to treat at the most one BTP episode per day with the test product, do not reflect the typical needs of cancer patients suffering an average of 1-5 breakthrough pain episodes per day (Bennett D et al. 2005. Consensus Panel Recommendations for the Assessment and Management of Breakthrough Pain. Part I Assessment). Furthermore, the dosing instructions given in the SPC point out that,

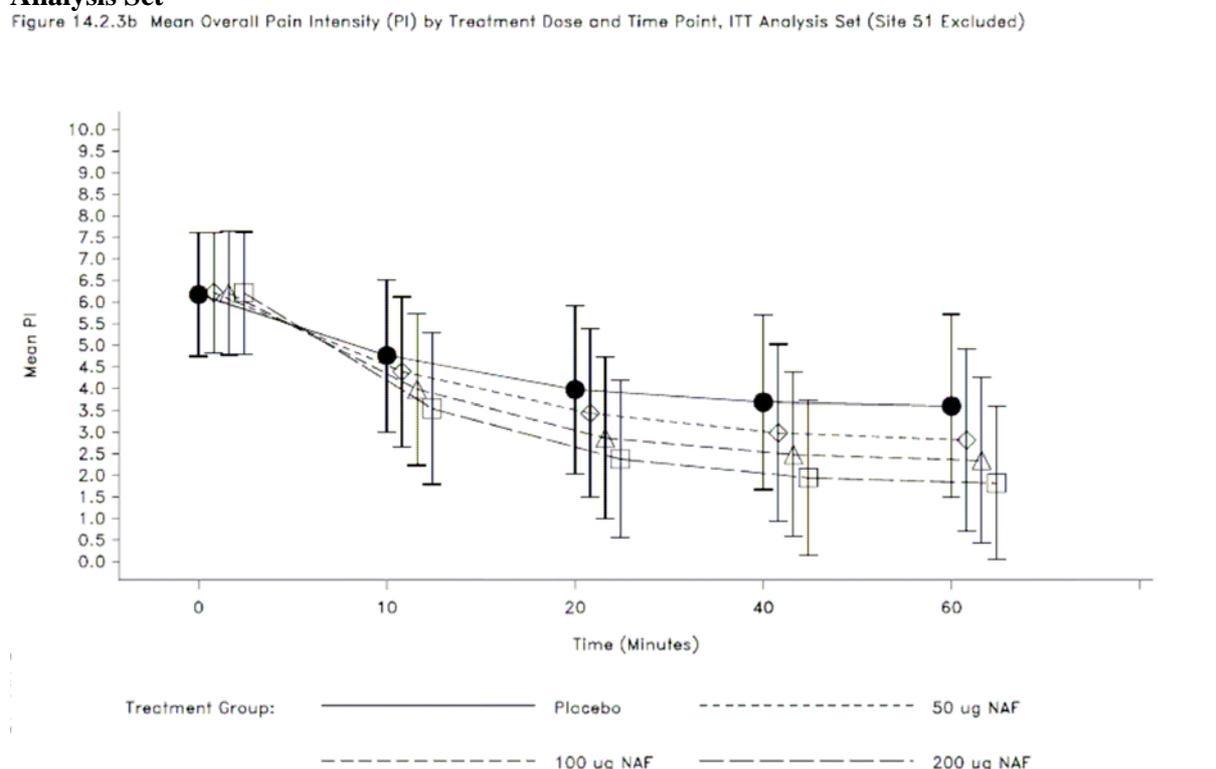
typically, no more than four breakthrough pain episodes should be treated per day. This discrepancy between the trial design and the need of the average patient that requires to cover 1-5 episodes per day arises even more concerns when considering that no PK-data have been generated for multiple dosing either. The applicant justified this choice with the argument that in order to minimise the risk of carryover effect in the FT-017-IM dose-response crossover study between each BTP treatment with intranasal fentanyl, only one BTP per day was treated with intranasal fentanyl. In the FT-018-IM confirmatory efficacy study four BTP episodes per day were treated. This was accepted by CHMP.

Furthermore, the concerns about the design of study FT-017-IM which was conducted following a fixed-dose design which contradicts the principle of individual dose titration and thus does not reflect the dosing instructions proposed in the SPC have been mentioned. The fixed-dose design inevitably leads to under- and over-dosed patients which hampers both interpretation of efficacy data in terms of PID and assessment of adverse events.

These methodological flaws notwithstanding, the results of study FT-017-IM were as follows:

Study FT-017-IM: Mean Overall Pain Intensity by Treatment Dose and Time Point – ITT Analysis Set

Figure 14.2.3b Mean Overall Pain Intensity (PI) by Treatment Dose and Time Point, ITT Analysis Set (Site 51 Excluded)



The mean PID10 were 1.41, 1.82, 2.23 and 2.65 for placebo and Instanyl 50, 100 and 200 µg respectively. The corresponding LS mean (versus placebo) were 0.41, 0.81 and 1.24 for 50, 100 and 200 µg respectively (p value versus placebo <0.001 for all doses).

The PID at 20 minutes and thereafter (possibly after another dose of the same dose) continued to increase.

The results in term of responder rates are presented in the table below.

FT-017-IM Responder Rate at 10 minutes-ITT analysis set

Responder Rate at 10 Minutes, ITT Analysis Set	Placebo		Fentanyl 50 µg NAF		Fentanyl 100 µg NAF		Fentanyl 200 µg NAF	
	All Patients	Site X Excluded	All Patients	Site X Excluded	All Patients	Site X Excluded	All Patients	Site X Excluded
N	164	145	167	148	167	148	166	147
Mean	23.48	22.07	29.94	29.05	45.51	41.55	53.92	49.66
Standard Deviation	34.331	33.269	37.649	37.350	42.094	41.399	44.035	43.987
Median	0	0.0	0	0.0	50.0	50.0	50.0	50.0
Minimum	0	0.0	0	0.0	0	0.0	0	0.0
Maximum	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

A responder for a treated break through pain (BTP) episode has pain intensity difference at 10 min (PID₁₀) >2 for that episode. Overall responder rate is equal to: (1) 100% if patient is a responder in both treated BTP episodes within a dose. (2) 50% if patient is a responder in one treated BTP episode and non-responder in the other treated BTP episode within a dose. (3) 0% if patient is a non-responder in both treated BTP episodes.

ITT= intent-to-treat; NAF = nasal fentanyl

The responder rate after one dose at 10 minutes varies from 31% to 49% depending on the dose received, whether in the placebo group, the responder rates varies from 20% to 22%.

For study FT-017-IM, the analysis of each BTP treatment in terms of number of Instanyl doses, shows that 78.1%, 75.7%, 68.8% and 61.5% of patients required two doses for the first BTP episode and 79.0%, 75.0%, 71.9% and 54.7% required two doses for the second BTP episode, in placebo and Instanyl 50, 100, 200 µg groups respectively.

Due to high proportion of patients requiring a second dose 10 minutes after the first actuation, the dose chosen was not considered justified. Particularly the range proposed 50 to 200 µg and the mode of administration have not been adequately determined by dose ranging studies. The fact that more than ¾ of the patients needed two doses to treat BTP episode with the 200 µg dose suggest that the administration of highest dose could be useful to treat BTP episodes.

This was addressed by the applicant with the submission of further studies during the procedure (see below)

Study FT-018-IM

Study 018 was conducted as a double-blind, randomised, placebo-controlled trial confirming the efficacy of nasal fentanyl titrated to 50, 100 or 200 µg with an open long-term safety follow-up in cancer patients with breakthrough pain. The trial was initiated on 13 June 2006, data obtained from the open-label long-term safety follow-up period were reported as 4-month data until 13 September 2007. The study report was last modified on 15 February 2008 after exclusion of study center X (see above).

METHODS

Study Participants

Inclusion criteria in study 018 correspond to those already described for study 017.

In study FT-018-IM, patients included should have already received nasal fentanyl as part of the study FT-016-IM or FT-017-IM. After randomisation, they entered a first phase of dose titration then the dose identified as successful during this phase was used to treat six BTP episodes, and placebo was used to treat two BTP episodes, in a randomised double-blind sequence. A safety follow-up phase followed this double-blind phase, during which patients received open-label Instanyl treatment for BTP episodes.

As a consequence of this design, the population included in study Ft-018-IM is the same as the ones already included in studies FT-016-IM and FT-017-IM. Moreover, as these patients have already

received Instanyl, they may be considered as responders and tolerant (in terms of safety) to Instanyl. This biased the results of this study.

Moreover, these patients know well the treatment and its effects: the blinding of such a study could be questionable. However, as these studies were fixed dose studies, without titration of the patients to an effective dose, it is not so clear that these patients could be considered as responders to nasally administered fentanyl.

Treatments

During dose titration, the following efficacy variable was assessed by the patient and recorded in the patient diary:

- The GI of efficacy in the treatment of BTP(s) was assessed 60 min after the first Instanyl dose using a categorical 5-point VRS: 0=poor, 1=fair, 2=good, 3=very good; 4=excellent (Collins et al, 2001). For each IMP-treated BTP episode, the patients had to enter a GI score as a means of rating the efficacy of the BTP treatment at 60 min after the first dose. A summary of the activities that were to be performed by the patient for each IMP-treated BTP episode is provided in Table 2.

Table 2 Dose Administration and Assessment of BTP Episodes in Phase 1

Time (min)	0	10	20	60
Administration of IMP				
First IMP puff	X			
One additional IMP puff, if needed		(X)		
Rescue analgesic, if needed			(X).....(X)	
Assessment				
General Impression (GI)				X

X = mandatory activity or assessment; (X) = activity if applicable

Source: Appendix 1.1

The titration should always be started on the 50 µg dose. For an Instanyl dose (50, 100 or 200 µg) to be considered successful, treatment of at least three of four BTP episodes had to be considered successful by the patient according to the following definition: The definition of successful Instanyl treatment (one or two doses) was:

- 1) No need of rescue analgesic within the first 60 min;
- 2) A score of ≥ 2 on the GI scale by the patient at 60 min after the first Instanyl dose; and
- 3) No severe undesirable effects such as pronounced hypoventilation, unacceptable sedation or drowsiness.

If two treatments with a dose were unsuccessful, the patient was to proceed to the next dose (one step up or down). If in three of four episodes, pain relief was obtained only after a second Instanyl dose, the investigator was to consider increasing the dose. This consideration had to be based on a balance between efficacy and safety (as indicated by AEs experienced by the patient as a result of Instanyl treatment). The algorithm for determining adjustments in a patient's Instanyl dose is summarised in Table 3.

Table 3 Algorithm for Dose Adjustment

BTP treatment	Successful		Unsuccessful	
	No	Yes	No	Yes
Undesirable effects				
Decision	Go to Phase 2	One strength down For 50 µg: withdrawal	One strength up For 200 µg: withdrawal	Withdrawal

Pain relief
Yes: Three of four BTP episodes with GI \geq 2, no use of rescue analgesic
No: At least two episodes with GI $<$ 2 and/or use of rescue analgesic

Undesirable effects
Yes: One or more undesirable effects
No: No severe undesirable effects

Source: Appendix 1.1

If after up to four titration steps (all three doses and possibly one down-titration) a successful dose was not identified, the patient was withdrawn.

Once the successful dose was established, the patient entered the efficacy phase of the trial (Phase 2), in which the Instanyl dose identified in Phase 1 was used to treat six BTP episodes and placebo was used to treat two episodes in a randomised, double-blinded sequence. Pain intensity (PI, using the 11-pt NRS) and General Impression (GI) scores were assessed for each BTP episode as shown below.

Table 4 Dose Administration and Assessment of BTP Episodes in Phase 2

Time (min)	0	10	20	40	60
Administration of IMP					
First IMP puff	X				
One additional IMP puff, if needed		(X)			
Rescue analgesic, if needed			(X).....(X)		
Assessments					
Pain intensity (PI)*	X	X	X	X	X
General Impression (GI)					X

X = mandatory activity or assessment; (X) = activity if applicable
*Assessments had to be recorded before administration of IMP and any rescue analgesics.
Source: Appendix 1.1

Following assessment of the double-blinded treatment of the eight BTP episodes, patients continued participation in the trial in a safety follow-up phase (Phase 3) during which they received open-label Instanyl treatment for BTP episodes.

Objectives

The aim was to confirm the efficacy of Instanyl titrated to doses of 50, 100 or 200 µg for treatment of BTP in cancer patients tolerant to opioids, to establish the long-term safety of treatment with Instanyl and to explore the relationship between the dose of background pain opioid treatment and the titrated Instanyl dose.

Endpoints

The primary efficacy variable was the PI difference at 10 min (PID10) after the first actuation. Responder rate was computed from the number of patients with a PID10 $>$ 2. The secondary efficacy variables were the sum of the PIDs over the time interval 0-60 min (SPID0-60) and the GI score.

Sample size

135 patients were enrolled.

Randomisation

Patients were randomised to treatment sequences in which six treatments were the successful Instanyl dose identified in the titration phase and two were placebo. The eight episodes of BTP were to be treated with Instanyl in the order the spray bottles were numbered (1 to 8).

Blinding (masking)

In the efficacy phase, the treatment sequence was double-blinded and randomised such that one placebo treatment occurred in episodes 1-4 and one in episodes 5-8.

Statistical methods

The variation in PID10 between treated BTP episodes within patient was calculated by treatment (Instanyl or placebo) and expressed as SD and coefficient of variation (CV). The statistical analysis was performed with a mixed linear model including the following fixed effects: treatment, centre, average baseline PI (over all episodes for a patient), deviation of baseline PI for each episode from average baseline PI). Patient was included in the model as a random effect. There was no imputation for missing episodes. If rescue medication was taken within the first 10 min, the PI scores were set to missing for all consecutive time points, i.e. the PID10 was missing as well. The primary endpoint was analysed for the ITT and the PP datasets.

RESULTS

Conduct of the study

This was an efficacy and safety study, recruiting patients from studies FT-016-IM and FT-017-IM. Patients were enrolled in 23 centres in five European countries (Austria, Germany, Denmark, France, Poland).

Baseline data

The numbers of male and female patients were equal (63 of each). Mean age was 60.9 years and ranged from 33 to 83 years. Mean body mass index (BMI) was 24.1 kg/m² (range 15.4-50.2). Mean weight was 71.7 kg for the male patients (range 48.0-106.0), and 65.8 kg (range 40.0-130.0) for the females. Mean height was 173.7 cm for the male patients (range 158-192), and 163.7 cm (range 150-178) for the females. All patients for whom race was reported were Caucasian. The demographic profile of the ITT analysis set excluding site X was not different from the total population.

The majority of patients (105 patients, 83.3%) reported a past or concomitant illness, including previous neoplasms (Table 14.1.05). The most frequently reported were vascular disorders in 59 patients (46.8%). The mean number of concomitant illnesses was 3.4 (median = 3). The maximum number of concomitant illnesses per patient was 16 (for one patient) and the minimum was one (21 patients).

The most frequently reported concomitant medications were ketoprofen (41 patients, 32.5%), omeprazole (35 patients, 27.8%), megestrol acetate (31 patients, 24.6%), lactulose (27 patients, 21.4%), dexamethasone (26 patients, 20.6%), and furosemide (26 patients, 20.6%) (Table 14.1.10). The majority of concomitant medications taken during this trial were related to treatment of the patient's primary diagnosis as well as palliative treatments for sequelae of radiation or chemotherapy. The most frequently reported primary tumour sites were lung/ respiratory system (22 patients, 17.5%); breast (19 patients, 15.1%), colon/rectal (16 patients, 12.7%); and female genital (13 patients, 10.3%)

Background pain opioid medication at baseline: The most frequently reported were fentanyl (62 patients, 49.2%) and morphine (58 patients, 46.0%).

The mean standardised morphine equivalent dose of background opioid pain medication at the end of titration was 209.6 mg/d. The majority of patients (76 patients, 60.3%) were in the 'low' dose category

(≤ 180 mg/d); 23.8% were in the ‘medium’ dose category ($>180 - \leq 360$ mg/d), and 15.9% were in the ‘high’ dose category (>360 mg/d).

A total of 127 patients completed titration (112 when patients for centre X are excluded). One hundred and nine patients were titrated to either 100 or 200 μg doses. The remaining 18 patients were titrated to the 50 μg dose. In general, patients with low level background opioid pain treatment tend to achieve effective pain relief with a correspondingly lower Instanyl dose compared to the patients taking the higher levels of background pain opioids.

Numbers analysed

Of the 135 enrolled patients, 15 were enrolled at site X and were excluded from the re-analysis of the trial data. All remaining 120 patients were included in the Safety Analysis set. Of these, 113 patients were randomised to double-blind efficacy treatment; 111 of the patients who entered the efficacy phase were included in the ITT analysis set and 101 were included in the PP analysis set.

Summary of Patient Disposition

Number of Patients		
	All Patients	Site X Excluded
Enrolled	135	120
Safety Analysis Set	135 (100.0%)	120 (100.0%)
Randomised	128 (94.8%)	113 (94.2%)
Intent-to-treat analysis set (ITT)	126 (93.3%)	111 (92.5%)
Per-protocol analysis set (PP)	114 (84.4%)	101 (84.2%)

Of the 119 patients who entered the titration phase (patient 0202 entered the titration phase but the titration dose was not reached – patient was put on the 200 μg dose for phase 2 and 3), 112 completed the titration phase. Of these, 111 patients entered the double-blind efficacy phase (ITT). During titration, 5 withdrew due to adverse events and 2 patients withdrew consent.

The demographic profile of the ITT analysis set excluding site X was not different from the total population. Mean age was 60.6 years and ranged from 35 to 79 years. Mean body mass index (BMI) was 24.0 kg/m². Mean weight was 70.3 kg for the male patients, and 63.0 kg for the females. All patients for whom race was reported were Caucasian (data collected for 107 patients, 96.4%).

Protocol violations occurred led to the exclusion of 12 patients from the PP analysis set .

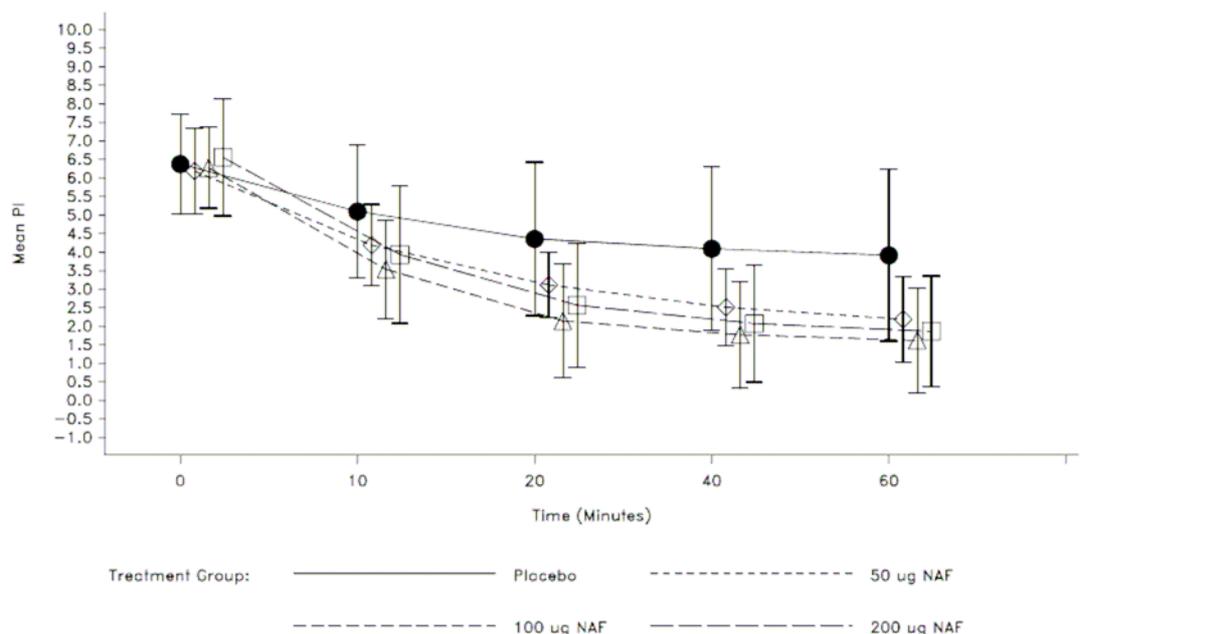
Outcomes and estimation

With site X excluded, a total of 95 patients were titrated to either 100 (51/112, 45.5%) or 200 μg (44/112, 39.3%) doses. The remaining 17 (15.2%) patients were titrated to the 50 μg dose.

In preceding MA procedures dealing with rapidly absorbed fentanyl preparations, a rate of about 65% subjects finding a successful dose during titration was found. However, it is to be taken into consideration that in these studies patients were recruited that were naïve to this type of breakthrough pain treatment. In study FT-018-IM, 112 out of 119 (94.1%) patients are able to define their individual successful dose. This figure is to be explained by the fact that only patients that previously participated in studies 016 and/or 017 were recruited in study 018, thereby constituting a known responder collective.

A responder was defined as having a PID10 > 2 for a given episode.

FT-018-IM: Mean overall pain intensity by treatment dose and time point- efficacy phase, ITT analysis set (site X excluded)



In study FT-018-IM, pain intensity that amounts to about 6.5 on average on NRS scale before administration, is reduced to a score of about 4.0-4.5 ten minutes after the first actuation of Instanyl. Highly significant superiority in PID10 scores over placebo could be shown for all three dose strengths (Placebo: 1.28, 50 µg: 2.0, 100 µg: 2.74, 200 µg: 2.60). Therefore, based on the PID10 results obtained in study FT-018-IM, it is acknowledged that breakthrough pain occurring in cancer patients receiving opioid maintenance therapy can be successfully treated with nasally administered fentanyl.

Also for this study, the PID at 20 minutes and thereafter (possibly after another dose of the same dose) continued to increase.

The results of this study in term of responder rates are presented in the table below.

FT-018-IM: Responder Rate -ITT analysis set

Responder Rate at 10 Minutes, ITT Analysis Set	Placebo		Fentanyl 50 µg Instanyl		Fentanyl 100 µg Instanyl		Fentanyl 200 µg Instanyl		Total Fentanyl Instanyl	
	All Patients	Site X Excluded	All Patients	Site X Excluded	All Patients	Site X Excluded	All Patients	Site X Excluded	All Patients	Site X Excluded
N	125	110	19	18	55	48	52	45	126	111
Mean	19.20	20.91	33.33	31.48	64.55	60.42	54.54	48.95	55.71	51.08
Standard Deviation	32.863	34.122	31.914	31.772	37.823	38.535	37.681	37.383	38.145	38.108
Median	0.0	0.0	16.7	16.7	83.3	66.7	66.7	66.7	66.7	66.7
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	100.0	100.0	83.3	83.3	100.0	100.0	100.0	100.0	100.0	100.0

responder for a treated break through pain (BTP) episode has pain intensity difference at 10 min (PID₁₀) >2 for that episode. Overall responder rate is defined as the percentage of BTP episodes with a positive response to treatment (Instanyl or placebo) within a patient. ITT= intent-to-treat; Instanyl = nasal fentanyl

The responder rate after one dose at 10 minutes varies from 31% to 49% depending on the dose received, whether in the placebo group, the responder rates varies from 20% to 22%.

For study FT-018-IM, the majority of all BTP episodes were treated with two doses of Instanyl. The proportions were highest for the placebo group (85.1%) compared to all Instanyl doses combined (63.6%). The numbers of BTP episodes necessitating 2 doses were 84%, 68.5%, 61.5% and 76.4% in the placebo and fentanyl 50, 100 and 200 µg groups respectively.

Coming back to the issue of missing dose-finding data, it appears evident that for a good portion of patients breakthrough pain might have been more effectively treated if higher doses were applied straight away.

Overall, it can be concluded that early onset analgesia with significantly superior pain reduction after ten minutes is achievable by means of nasally applied fentanyl when compared to placebo. With regard to maturity of clinical development, however, the studies submitted in support of the Instanyl application, demonstrate major methodological drawbacks and leave essential questions in relation to dose finding and the appropriateness of the applied dosing regimen unanswered.

Study FT-019-IM

This study report was submitted during the procedure as part of the answers to address the clinical objections regarding the chosen dose and the proposed administration schedule. The pivotal phase III trials were started with a dose range that was not tested before in the target population. These doses taken as one dose seem to be insufficient to treat BTP as more than 50% of patients needed a second dose. The possibility to take a second dose in case of inefficacy of the first one after 10 minutes was also derived from results obtained in opioid naïve patients, difficult to extrapolate to patient with BTP.

Study FT-019-IM was an open label, comparative, randomised, balanced crossover trial comparing nasal fentanyl and oral transmucosal fentanyl (Actiq) in breakthrough pain in patients with cancer. The aim was to compare the efficacy of Instanyl titrated to one or two doses of 50, 100, 200 µg to Actiq titrated to one or two doses of 200, 400, 600, 800, 1200 or 1600 µg for the treatment of BTP. During the titration and efficacy phase, all BTP episodes, up to four per day were to be treated with Instanyl or Actiq.

Instanyl was to be administered as one dose in one nostril. If the patient had insufficient pain relief, an extra dose was to be taken after 10 minutes, preferably in the other nostril. The maximum dose was 2x200 µg taken 10 minutes apart.

Actiq was to be applied to the oral cavity in doses of 200, 400, 600, 800, 1200 and 1600 µg fentanyl per lozenge. If the patient had insufficient pain relief, a second lozenge could be taken 30 minutes after the start of the administration of the first one.

A total of 196 patients were enrolled, 139 were randomised (71 to nasal fentanyl/Actiq, 68 to Actiq/nasal fentanyl) and 86 patients completed the study. Mean age of the patients was 62.0 years (22 to 94).

The majority of patients reached successful doses during titration in both treatment sequence (98.3% for Instanyl and 64.7% for Actiq).

The primary endpoint of the study was the time to onset of meaningful pain relief, recorded by stopwatch, and was defined as the time at which the patient experienced meaningful pain relief.

The results show that the median total difference between treatments was 5.0 minutes in favour of nasal fentanyl. The proportion of patients with a fastest time to onset of pain relief was higher for nasal fentanyl and the differences were statistically significant. All nasal fentanyl doses provided higher mean PID10 scores (from 1.64 to 3.00) compared with all Actiq doses (from 0.51 to 1.46). Higher mean PID scores were obtained for nasal fentanyl compared to Actiq at 20 minutes with the LS mean difference of the PID20 being statistically significant (1.20; CI: 1.05, 1.35; p<0.001).

- Clinical studies in special populations

No specific studies were performed by the applicant using nasal fentanyl in elderly patients or in patients with severe hepatic or renal impairment. However, elderly patients were not excluded from

the clinical programme. Since elderly patients may experience a higher exposure to fentanyl for a given dose, caution should be taken in treatment of elderly patients. Due to the fact that fentanyl is metabolised in the liver by the cytochrome P (CYP) 3A4 isoform, caution should be taken in treatment of patients with severe hepatic impairment or receiving concomitant medication that may alter CYP3A4 activity.

- Supportive study(ies)

Studies FT-003-IN/FT-011-IN

These studies were designed to investigate the efficacy and safety of nasal fentanyl administered at doses between 50 and 1200 micrograms per episode in the treatment of BTP in patients with cancer related pain (study FT-003-IN) and to evaluate safety and tolerability of nasal fentanyl in the treatment of BTP (FT-011-IN).

Study FT-003-IN comprised a blinded dose-finding phase in which for each patient a successful Instanyl dose for treatment of the target BTP was established (phase 2), then a randomised, cross-over, double-blind treatment phase in which the successful dose of Instanyl was compared with half this dose (phase 3). During the dose-finding phase, patients treated each episode of BTP with 2 doses at the same time (one in each nostril) and with a third dose in case of insufficient pain relief after 15 minutes. So the dose to be administered may vary from 50 to 1200 µg.

Study FT-011-IN was an open, multi-centre study, planned as a follow-up for two protocols. Only patients that completed FT-003-IN were enrolled since the other study was never initiated.

At the termination of the studies, data from only 17 patients were available for study FT-003-IN which did not allow any statistical testing to be performed. The 14 patients that completed the dose finding phase were titrated to various successful Instanyl doses (50 µg for 2 patients, 100 µg for 4 patients, 400 µg for 3 patients and 800 µg for 4 patients) . In phase 3, these doses were tested against half the dose in 12 BTP episodes. When the successful doses were compared to half the doses (6 BTP episodes each, randomly), the effects of the low and the high doses (mean SPID, mean TOTPAR, PID and PAR by time point) were similar.

The 14 patients who completed study FT-003-IN entered the study FT-011-IN. None of these patients completed the 6-month follow-up period.

Out of the 17 patients included in study FT-003-IN, 14 completed the dose-finding phase, thus achieving a successful dose of nasal fentanyl between 50 and 800 µg.

- Discussion on clinical efficacy

The applicant acknowledges that no clear dose-effect relationship have been established in patients presenting BTP with a background opioid treatment for cancer pain. The chosen dose for pivotal studies and the mode of administration (one dose then another one 10 minutes after in case of inefficacy) are based on a study in healthy volunteers, undergoing third molar extraction, and not treated with opioids as a background therapy. Thus the conditions of the dose finding study are very different from the conditions of cancer patients presenting with BTP. The fact that the results of this kind of study could be extrapolated to the target population were considered questionable.

Considering the patient with BTP, The CHMP recognised that BTP episodes may vary for the same patient, depending on the conditions in which it occurs. This variability in BTP justifies the fact that a titration is individually needed for a given BTP episode.

In the FT-018-IM study, more than 50% of the patients needed two doses to treat their BTP. When looking at the results, it can be seen that patients taking a second dose presented PID lower than patients taking only one dose. The administration of a second dose allows these patients to attain the same level of PID than patients responding to only one dose.

All of the PID achieved with Instanyl, either with one or two doses, are significantly different from the one obtained with placebo.

Even if the questions of the dose-effect relationship and the choice of mode of administration were not fully elucidated, the CHMP considered that, as Instanyl is effective in about 50% of patients who take one dose, and as the patients who took a second dose achieved a clinical and significant additional benefit, the doses and mode of administration proposed by the applicant were acceptable.

Clinical safety

- Patient exposure

Safety information presented into this document is derived from:

- 6 clinical studies conducted by Nycomed: FT-001-IN, FT-003-IN, FT-011-IN, FT-016-IM, FT-017-IM and FT-018-IM. Moreover 9 publications report the efficacy and/or pharmacokinetic and safety results of prospective, controlled studies in which nasal fentanyl was administered to adults (patients or healthy volunteers). These publications have been designated ‘pivotal’ by the applicant for the purposes of this submission, but were not considered as such by the CHMP.
- 15 publications providing information on the safety of fentanyl administered nasally (uncontrolled studies or studies in children), or via other routes. These publications have been designated ‘non-pivotal’ by the applicant.

The table below summarises the clinical trial exposure

Study	Indication	Underlying condition	Brief study design	N analysed for safety
FT-001-IN	Post-op pain	Molar extraction	Pharmacokinetics + efficacy	24 patients
FT-003/011-IN	BTP	Cancer	Dose-finding Efficacy	17 patients
FT-016-IM	BTP	Cancer	Pharmacokinetics	19 patients
FT-017-IM	BTP	Cancer	Efficacy + safety	152 patients
FT-018-IM	BTP	Cancer	Dose titration Efficacy Safety follow-up	119 patients 111 patients 108 patients
FT-019-IM	BTP	Cancer	Comparison with Actiq+ efficacy + safety follow-up	139 patients
FT-021-IM	PK	Healthy	Pharmacokinetics + comparison with Actiq	24 healthy subjects
FT-022-IM	PK	Healthy	Pharmacokinetics + dose linearity	12 healthy subjects
FT-023-IM	PK	Healthy	Pharmacokinetics + volume effect	12 healthy subjects
FT-024-IM	PK	Healthy	Pharmacokinetics + bioequivalence	16 healthy subjects
FT-025-IM	PK	Healthy (allergic rhinitis)	Pharmacokinetics in seasonal allergic rhinitis + drug interaction (oxymetazoline)	12 subjects with allergic rhinitis
FT-026-IM	PK	Healthy (common cold)	Pharmacokinetics in common cold	8 subjects with common cold
FT-1305-028-SP	PK	Healthy	Pharmacokinetics + bioequivalence	24 healthy subjects (including elderly)

A total of 207 patients treated with a total of 3351 episodes of BTP with nasal fentanyl were included in the Instanyl development programme submitted with the initial application. The studies were performed in different adult populations of patients with chronic cancer pain. The mean age and the gender are summarised below.

	FT-003/011-IN (N=17)	FT-016-IM (N=19)	FT-017-IM¹ (N=171)	FT-018-IM² (N=126)
Age, years				
Mean	52.5	57.8	61.8	60.9
Range	25 to 75	39 to 68	32 to 86	33 to 83
Gender, n (%)				
Male	12 (71%)	7 (37%)	90 (53%)	63 (50%)
Female	5 (29%)	12 (63%)	81 (47%)	63 (50%)

¹ In study FT-017-IM, demographics are presented for the intent-to-treat population which was the basis for safety analyses.

² In study FT-018-IM, demographics are presented for the intent-to-treat population (n=126); demography was not summarised for the safety population (n=135).

Dose levels ranged from 50 µg to 800 µg. Duration of treatment ranged from single dose (study FT-016-IM) to 8 days for controlled phase of the studies. In the follow-up of FT-018-IM, patients were treated up to 4 months. The frequency of administration also varied from single dose to a maximum of four BTP episodes per day. Fentanyl was administered as a pre-specified dose (studies FT-016-IM and FT-017-IM) or was individually titrated (studies FT-003-IN, FT-011-IN and FT-018-IM). Four studies permitted an additional dose of nasal fentanyl if pain relief was inadequate (studies FT-003-IN, FT-011-IN, FT-017-IM and FT-018-IM).

The number of patients (207) is rather small. Fentanyl has a well-known risk profile for i.v. or transdermal administration.

- Adverse events

The following assessment pertains to the evaluation of the initially submitted data:

The proportion of patients presenting with at least one AE was 62.2% for study FT-018-IN, 52.9 and 100% for both studies 003/011-IN, 31.6% for study FT-016-IM and 21.6% for study FT-017-IM. The nature of the AE reported corresponds to the known safety profile of fentanyl.

Overall, the percentage of patients who experienced at least one AE was low in these studies, compared to more than 80% patients experiencing at least one AE in Effentora pivotal studies. This fact is surprising in a population of patients with severe illness and with a chronic opioid treatment and other concomitant drugs. One possible reason could be the noted deficiency in the reporting of the AEs.

SAEs were reported for 42% of patients in study FT-018-IM, 17.6% and 100% for both studies 003/011 respectively, 5.3% of patients in study Ft-016-IM and 6.4% of patients of study FT-017-IM. The percentage of SAE reported is unusually low in studies FT-016-IM and FT-017-IM. (for comparison, 34% of patients reported at least 1 SAE for Effentora). If this low reporting can be explained for study FT-016-IM by the short duration of the study, this is not the case for study FT-017-IM. It is unclear whether this low reporting is related to the mode of collection of AE or the analytical method.

Of note, a severe respiratory depression occurred in a patient 80 minutes after the administration of Instanyl (study FT-017-IM). When considering the delay of occurrence of this adverse event, a relationship with the administration of Instanyl was considered unlikely. Moreover, as the titration and administration of Instanyl should be performed under the supervision of a healthcare professional, the monitoring of the patients was considered adequate.

Further to the results of the inspection, the safety data for studies FT-017-IM and FT-018-IM were re-monitored. A summary report of this re-monitoring was provided by the applicant, and is assessed below:

In study FT-017-IM, a total of 49 additional AEs in 23 patients were identified during re-monitoring. That have not been previously reported. These AEs were allocated to nasal fentanyl as follows: 14 AEs in 10 patients (6.8% for 50 µg, 9 AEs in 6 patients (4.0%) for 100 µg, 12 AEs in 8 patients (5.4%) for 200 µg, and 14 AEs in 10 patients (6.8%) for placebo. Of these, none were severe, serious, or resulted in death or withdrawal. One patient experienced three AEs (two occurrences of malignant neoplasm progression and one of paraesthesia) that were considered possibly or probably related to treatment. These were the only newly identified events that were considered to have a possible or probable relationship to treatment.

In study FT-018-IM, a total of 238 additional AEs in 65 patients were identified during re-monitoring of sites that had not been previously reported. Of these, 4 patients (3.3%) experienced severe AEs; 3 patients (2.5%) experienced AEs that were considered related to treatment; 5 patients (4.2%) experienced serious AEs (SAEs); 1 patient (0.8%) died; and 1 patient (0.8%) was withdrawn due to AEs.

The AEs identified during re-monitoring were attributed to the phases of the trial as follows: 33 AEs in 19 patients (16.0%) in the titration phase; 7 AEs in 6 patients (5.4%) in the efficacy phase, and 198 AEs in 59 patients (54.6%) in the safety follow-up phase.

None of the newly identified severe (5 events in 4 patients) or serious (8 events in 5 patients) AEs were considered related to treatment

Among the three patients with newly identified AEs with a possible or probable relationship to nasal fentanyl treatment, all were mild in severity and non-serious; none resulted in withdrawal or death.

The key results of study FT-019-IM were also provided. Overall, 79 patients (56.8%) had AEs during the trial: 56 patients (45.9%) following nasal fentanyl treatment and 41 patients (34.7%) following Actiq treatment. Most of the AEs (160 of 228) were reported during titration, and most (160 of 228) were not considered related to treatment.

Serious AEs (SAEs) were reported for a total of 19 patients (13.7%): 13 patients (10.7%) had SAEs allocated to nasal fentanyl treatment and 6 patients (5.1%) to Actiq treatment, though none were considered related to either trial medication. A total of five patients who took at least one dose of IMP in the trial (3.6%) died due to causes unrelated to study treatment: four patients (2.9%) during the titration phase and one patient (0.7%) during the efficacy phase died of malignant neoplasm progression; these were allocated to the nasal fentanyl portion of the crossover treatment. One additional patient experienced disease progression on the day of randomisation to Actiq and died seven days later. The patient had not completed any entries in the patient diary.

Severe AEs were reported for a total of 25 patients (18.0%):

16 patients (13.1%) following nasal fentanyl treatment and 9 patients (7.6%) following Actiq treatment. No SAE was considered related to a trial medication.

A total of 16 patients (11.5%) were discontinued from the trial due to AEs. Of these, 10 patients (8.2%) experienced AEs following nasal fentanyl treatment and 8 patients (6.8%) experienced AEs following Actiq treatment.

Severe nasal ulcer related to nasal fentanyl was reported for one patient. This patient (number 092) had a medical history of chronic hepatitis and prostate cancer with bone metastases. Seven days after initiation of nasal fentanyl treatment, two small ulcers of the nasal mucosa (one in each nostril) developed. The patient was concomitantly treated with chemotherapy. The patient had no prior history of nasal ulcers (e.g. herpes infection). No further examinations were performed in relation to the ulcers. Nasal fentanyl spray was discontinued and the patient recovered nine days later. This is the only reported instance of nasal ulcers in any nasal fentanyl trial to date.

The most frequently occurring AEs overall were nausea, vomiting, and constipation, reported in 16 patients (11.5%), 10 patients (7.2%), and 9 patients (6.5%), respectively. Nausea was the most

frequently reported AE for both treatments: 10 patients following nasal fentanyl, and 9 patients following Actiq (three patients experienced nausea following both treatments). Nausea was considered related to treatment in all cases, and was considered severe for three patients (two patients following nasal fentanyl and one patient following Actiq; Vomiting was considered related to treatment for three patients following nasal fentanyl and two patients following Actiq and was considered severe for one patient in each treatment group.

Constipation was considered related to treatment for two patients in each group, and was considered severe for one patient following treatment with Actiq.

System organ class	Common	Uncommon
Psychiatric disorders		Dependence, insomnia
Nervous system disorders	Somnolence, dizziness, headache	Sedation, myoclonus, paraesthesia, dysaesthesia, dysgeusia
Ear and Labyrinth disorders	Vertigo	Motion sickness
Cardiac disorders		Hypotension
Vascular disorders	Flushing, hot flush	
Respiratory, thoracic and mediastinal disorders	Throat irritation	Respiratory depression, epistaxis, nasal ulcer, rhinorrhea
Gastrointestinal disorders	Nausea, vomiting	Constipation, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pain of skin, pruritus
General disorders and administration site conditions		Pyrexia

The following points were particularly considered during the inspection:

Translation error (Rescue medication)

During re-monitoring all investigators confirmed to have understood and communicated the instruction for rescue medication correctly despite of this formally unacceptable translation error. The applicant therefore considered that the original results and conclusions in the study reports from FT-017-IM and FT-018-IM are not invalidated by the translation error. Retrospective re-evaluation of the actual timepoint of rescue medication usage and its bearings on efficacy parameters like e.g. PID60 was thought to be difficult. However, the CHMP conceded that it is rather improbable that the inconsistencies arising from the translation error entirely invalidate the efficacy results.

Dose titration

In line with the translation error finding described above, the protocol deviations regarding the dose titration procedure are thought to be reflective of suboptimal GCP compliance. In the case of leaving the patient on the same dose despite four consecutively unsuccessfully treated episodes is not only of ethical concerns but may also have to do with the general shortcoming of the whole clinical development, i.e. missing dose-finding and, in consequence, offering a dose range to the patients in phase III that potentially is too narrow.

Recording and reporting of AEs

The applicant reassures that in future trials, Nycomed will ensure that diary cards will have allocated space for entering information about AEs. During re-monitoring the newly identified events were almost entirely AEs associated with the underlying diseases of the patient population of adults with cancer, and did not reveal any new severe, serious or other important events considered related to the study drug. Additional safety data are reported from recently conducted study FT-019-IM, an open-label comparison of Instanyl with Actiq. For the purpose of study FT-019-IM, new patients (without pre-knowledge of Instanyl) have been recruited. Similar safety profiles of Instanyl were observed

across all studies. Re-monitoring of AEs – although difficult to accomplish retrospectively – did not change the overall safety evaluation of nasally applied fentanyl. Nonetheless, the responses of the Applicant did not change the GCP inspectors' major concerns about the quality and reliability of the safety and efficacy data of the trials.

Dosing compliance

Dose accountability was not provided – neither during the clinical trials nor in clinical practice.

- Serious adverse event/deaths/other significant events

The following relates to the initially reported adverse events:

In study FT-018-IM, 46 patients (34%) died during the study. In study FT-003/011-IN three patients (18%) died in dose-finding study FT-003-IN and 11 patients (79%) during follow-up study FT-011-IN, giving a total of 14 out of 17 patients (82%). In study FT-017-IM, eight patients (5%) died during the double-blind phase. 6 deaths were due to disease progression, 1 dyspnoea, and 1 cachexia.

The majority of the deaths reported were related to disease progression. None of the death was related to treatment administration. The high number of deaths in studies 003/011 is explained by the applicant by the fact that patients included in this study presented more advanced stage of disease than expected, which was one of the reason of the early termination of these studies.

Upon re-evaluation of the data following the inspection, only a few additional serious adverse events were identified (see paragraph above), and these were considered not related to treatment. Even with the proven deficiencies of the quality management system, it can be assumed that serious AEs were collected.

In conclusion, the newly reported AEs identified for both studies did not alter the safety profile initially assessed for fentanyl nasal spray at doses of 50 to 200 µg, administered as one dose or two doses 10 minutes apart.

- Laboratory findings

Laboratory parameters were not assessed in studies FT-017-IM or FT-018-IM. Laboratory tests were performed at screening only in pharmacokinetic study FT-016-IM. In study FT-003-IN, laboratory parameters were to be assessed at baseline and the end-of-study visit. However, laboratory samples were not analysed because the majority of end-of-study samples were missing.

This was considered acceptable by CHMP in light of the known profile of Fentanyl.

- Safety in special populations

Elderly

The applicant did not provide any assessment of AEs related to age. The mean age of included patients was around 60 years, with a maximum of 83. An integrated safety report regarding elderly patients (>75 years) should be provided and has been requested as part of the follow up measures.

Hepatic and renal impairment

No particular evaluation was made in patient with renal and hepatic insufficiency. However, the information proposed in the SPC is in agreement with the one included in the SPC of other fentanyl containing products. This was considered acceptable by CHMP.

Overdose, drug abuse, withdrawal and rebound

One patient in the titration phase of study FT-018-IM had an AE of accidental overdose (patient received one dose of 100 µg and was described by the investigator as “cerebrally affected”); the subject was withdrawn from the study. No other cases of fentanyl overdose were reported in any of the clinical studies.

In study FT-011-IN, three patients (21.4%) had AEs of dependence during the 6-month safety follow-up. There were no other reports of dependence in any studies.

No evidence of rebound or withdrawal effects was seen in these patients

The applicant was requested to propose how to evaluate by the patient the number of self administration and the time between two administrations. In the response to the LoI the applicant proposed to provide patients with a dosing scheme in the educational material. However, the only way to really evaluate the number of self administrations would be the implementation of a counting system, and this was requested in the follow-up measures.

- Safety related to drug-drug interactions and other interactions

No interaction studies have been performed with nasal fentanyl. One study with oxymethazoline was submitted during the procedure and is discussed in the pharmacokinetics section.

The absence of the other studies was acceptable to CHMP due to the fact that fentanyl is a well known active substance.

- Discontinuation due to adverse events

In study FT-018-IM, a total of 51 patients (37.8%) were withdrawn due to AEs during the study; six patients (4.5%) during the titration phase, one patient (0.8%) during the efficacy phase and 44 patients (35.8%) during the safety phase.

In study FT-003-IN, one patient (6%) was withdrawn due to a fatal AE (malignant neoplasm progression). In study FT-011-IN, 13 patients (93%) were withdrawn due to an AE; 11 of these patients died. AEs leading to withdrawal were not summarised for study FT-011-IN

In study FT-017-IM six patients were withdrawn due to AEs after the 200 µg nasal fentanyl test dose; nausea and vertigo were reported for two patients; vertigo, vomiting and hypertension in one patient; nausea in one patient; sedation in one patient, and syncope in one patient. A total of eight patients (4.7%) were withdrawn due to AEs during the double-blind phase of this study. The most common AE leading to withdrawal was malignant neoplasm progression (two patients)

In long term studies a very high percentage of patients were withdrawn, mostly due to malignant neoplasm progression. However, during the safety phase of study FT-018-IM, 33 (27%) patients withdrawn their consent and 11 (9%) for other reasons. It is surprising that in patients with a severe pathology and a credible increasing pain, the Instanyl treatment was withdrawn. This can be explained either by a lack of efficacy (or a decrease of efficacy with time) or AEs. The applicant was requested to provide more in details the reason for the withdrawal of these patients. The answers of the applicant and the inspection report confirm that underreporting and incorrect recording took place.

However, due to the fact that no unexpected toxicity was evidenced for this well known active substance, the CHMP considered this point resolved.

- Discussion on clinical safety

The safety profile of Instanyl seems comparable to the one of the other fentanyl containing products.

After the inspection and reassessment of the data, the CHMP concluded that the newly reported AEs identified for both studies did not alter the safety profile initially assessed for fentanyl nasal spray at doses of 50 to 200 µg, administered as one dose or two doses 10 minutes apart.

Nonetheless, the responses of the Applicant did not change the GCP inspectors' major concerns about the quality and reliability of the safety and efficacy data of the trials.

However, even with the proven deficiencies of the quality management system, it can be assumed that the serious AEs were collected. Furthermore, Instanyl safety profile does not seem to differ from the safety profile of other fentanyl containing products indicated in the treatment of BTP. However, the non serious AEs were probably under reported. This is not considered as a public health concern, and the AE profile of Instanyl will be further defined with the RMP. Also the applicant should provide the CHMP with an integrated safety reports of all the safety data (including the FT-019-IM study versus Actiq), and particularly regarding the elderly (>75 years old) as a follow-up measure.

Potential risk of overdose and danger for children and family circle remains with the proposed device due the proposed container closure system. The Applicant has undertaken to develop an improved device.

Additionally, section 4.2 of the SPC states that:

Treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse of fentanyl.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

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

Summary of the EU Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Propose risk minimisation activities (routine and additional)
Device	Targeted pharmacovigilance surveillance	Special and restricted prescription: Treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse of fentanyl. Educational material Child-resistant secondary container Different colour of labelling material for different strengths Dose-counting scheme Systematic return of used and unused nasal spray solutions Development of a secure multi-dose device with dose counting and lock-out system
Off-label use	Targeted pharmacovigilance surveillance Drug utilisation study	Special and restricted prescription: Treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse

		of fentanyl. Educational material
Abuse	Targeted pharmacovigilance surveillance Post-authorisation surveillance study	Special and restricted prescription Warning in Summary of Product Characteristic: Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is rare in the treatment of cancer related pain. Educational material
Misuse, diversion	Targeted pharmacovigilance surveillance Post-authorisation surveillance study	Special and restricted prescription Warning in Summary of Product Characteristic: Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is rare in the treatment of cancer related pain. Educational material
Accidental overdose	Targeted pharmacovigilance surveillance Post-authorisation surveillance study	Educational material Child-resistant secondary container Different colour of labelling material for different strengths Dose-counting scheme Development of a single dose fentanyl nasal spray as a line-extension to the multi dose product
Local tolerability symptoms	Routine pharmacovigilance Local tolerability sub-trial	None

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. With regard to the possible risk of overdose and potential danger of the product for children and family circle because of the primary container closure system, which should include a lock out system and a dose counter, the applicant presented detailed risk evaluation data and risk management plan and committed to continue the development of the multi-dose safety device, with dose counting, lock-out system. There are a number of other quality issues that will be resolved as Follow-up Measures within an agreed timeframe. None of the above issues is expected to have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

As the general pharmacodynamic, pharmacokinetic and toxicological properties of fentanyl are well known, the main toxicological concerns within this authorization application is whether Instanyl administration enhances toxicity due to increased systemic exposure, or causes local toxic effects.

The data related to the specific toxicological issues raised for Instanyl compared to the already marketed fentanyl-containing products indicated that Instanyl is expected to be well tolerated locally, provided qualification of the impurities and did not indicate special hazard for the environment.

Efficacy

The applicant acknowledges that no clear dose-effect relationship have been established in patients for nasally administered fentanyl. Fentanyl is a highly potent opioid agonist which has been in clinical use for decades and its major effect and side-effect profiles are well known and well documented.

This new fentanyl formulation was intended to improve the treatment of BTP in adults, by providing a rapid onset of effect, duration of effect to cover the duration of the episode, no long-active metabolites and availability of a non invasive formulation.

Instanyl has a fast onset of efficacy (10 minutes), which is supported by kinetic data and is an advantage as compared to the other available treatments indicated in the treatment of BTP.

Kinetic data were provided for doses between 50 and 400 mg, corresponding to the doses allowed in the clinical program.

Despite the lack of justification for the proposed dosage regimen, in both pivotal studies nasal fentanyl led to a statistically significant and clinically relevant decrease of PID10 (at 10 minutes) compared to placebo with a dose-effect relationship evidenced in study FT-017-IM. The efficacy of nasal fentanyl was confirmed on the other important criteria such as responder rates, patient general impression and SPID0-60.

In study FT-018-IM, pain intensity that amounts to about 6.5 on average on NRS scale before administration, is reduced to a score of about 4.0-4.5 ten minutes after the first actuation of Instanyl. Highly significant superiority in PID10 scores over placebo could be shown for all three dose strengths (Placebo: 1.28, 50 µg: 2.0, 100 µg: 2.74, 200 µg: 2.60). Therefore, based on the PID10 results obtained in study FT-018-IM, it is acknowledged that breakthrough pain occurring in cancer patients receiving opioid maintenance therapy can be successfully treated with nasally administered fentanyl. A responder was defined as having a PID10 > 2 for a given episode.

The responder rate after one dose at 10 minutes varies from 31% to 49% depending on the dose received, whether in the placebo group, the responder rates varies from 20% to 22%.

Even if the questions of the dose-effect relationship and the choice of mode of administration were not fully elucidated, the CHMP considered that, as Instanyl is effective in about 50% of patients who take one dose, and as the patients who took a second dose achieved a clinical and significant additional benefit, the doses and mode of administration proposed by the applicant were acceptable.

The inspection conducted in May-July, at the request from CHMP for studies FT-017-IM and FT-018-IM led to the conclusion that there were major deficiencies in the conduct of the studies and in the quality management system. After the applicant has conducted a remonitoring of all the centres, there were still concern on the quality management system, the adverse event reporting and the protocol device.

Following the applicant response, it appears that the quality management system was insufficient to ensure the quality and integrity of the efficacy and safety data.

However, the results obtained are consistent between the efficacy studies. The CHMP therefore concluded with regard to the whole documentation that the deficiencies found in the quality system of the sponsor are unlikely to invalidate the quality of the efficacy and safety data.

In conclusion, Instanyl has shown clinical efficacy in the treatment of BTP in patients with chronic cancer pain treated by opioids.

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

Even with the proven deficiencies of the quality management system, it can be assumed that the serious AEs were collected. Instanyl safety profile does not seem to differ from the safety profile of other fentanyl containing products indicated in the treatment of BTP. However, the non serious AEs were probably under reported. This is not considered as a public health concern, and the AE profile of Instanyl will be further defined with the RMP. Also the applicant should provide the CHMP with an integrated safety reports of all the safety data (including the FT-019-IM study versus Actiq), and particularly regarding elderly patients (>75 years old) as a follow-up measure.

Potential risk of overdose and danger for children and family circle remains with the proposed device due the proposed container closure system. The Applicant has undertaken to develop an improved device. The follow-up measures proposed by the applicant are acceptable.

- User consultation

The methodology is acceptable. The test is satisfactory in terms of Guideline requirements, but the report presents several insufficiencies and isn't detailed enough, especially in terms of specifying the criteria of inclusion and exclusion, the verbatim of the answers of the participants, the description of the modifications made to the PIL and the data processing.

The test is however considered as acceptable.

Risk-benefit assessment

Fentanyl is a highly potent opioid agonist which has been in clinical use for decades and its major effect and side-effect profiles are well known and well documented.

This new fentanyl formulation was intended to improve the treatment of BTP in adults, by providing a rapid onset of effect, duration of effect to cover the duration of the episode, no long-active metabolites and availability of a non invasive formulation.

Nasally administered fentanyl was shown to have a fast onset of efficacy (10 minutes), which is supported by kinetic data, which were provided for doses between 50 and 400 mg, corresponding to the doses allowed in the clinical program.

In both pivotal studies nasal fentanyl led to a statistically significant and clinically relevant decrease of PID10 (at 10 minutes) compared to placebo with a dose-effect relationship evidenced in study FT-017-IM. The efficacy of nasal fentanyl was confirmed on the other important criteria such as responder rates, patient general impression and SPID0-60.

The responder rate after one dose at 10 minutes varies from 31% to 49% depending on the dose received, whether in the placebo group, the responder rates varies from 20% to 22%. A responder was defined as having a PID10 > 2 for a given episode.

Even if the questions of the dose-effect relationship and the choice of mode of administration were not fully elucidated, the CHMP considered that, as Instanyl is effective in about 50% of patients who take one dose, and as the patients who took a second dose achieved a clinical and significant additional benefit, the doses and mode of administration proposed by the applicant were acceptable.

GCP Inspections concluded that quality management system was insufficient to ensure the quality and integrity of the efficacy and safety data.

However, the results obtained are consistent between the efficacy studies. The CHMP therefore concluded with regard to the whole documentation that the deficiencies found in the quality system of the sponsor are unlikely to invalidate the quality of the efficacy and safety data.

In conclusion, Instanyl has shown clinical efficacy in the treatment of BTP in patients with chronic cancer pain treated by opioids.

Even with the proven deficiencies of the quality management system, the CHMP concluded that the serious AEs were adequately collected. Instanyl safety profile does not seem to differ from the safety profile of other fentanyl containing products indicated in the treatment of BTP. However, the non serious AEs were probably under reported. This is not considered as a public health concern, and the AE profile of Instanyl will be further defined with the RMP.

However, potential risk of overdose and danger for children and family circle still remains due to the device design. The Applicant has undertaken to develop an improved device.

Additionally, section 4.2 of the SPC states that:

Treatment should be initiated by and remain under the supervision of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse of fentanyl.

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: see as detailed in section 2.3

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Instanyl in the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain was favourable and therefore recommended the granting of the marketing authorisation.