CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Cross-Discipline Team Leader Review

Date	7 March 2011
From	Robert B. Shibuya, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-569
Applicant	Archimedes
Date of Submission	30 September 2010
PDUFA Goal Date	23 March 2011
Proprietary Name / Established (USAN) names	Lazanda/fentanyl nasal spray
Dosage forms / Strength	Nasal spray/100mcg per 100mcL & 400 mcg per 100 mcL
Proposed Indication(s)	Management of breakthrough pain in patients with cancer, (b) (4) who are already receiving and who are tolerant to regular opioid therapy (b) (4) (b) (4)
Recommended:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
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CMC: Office of New Drug Quality Assessment
CSS: Controlled Substance Staff
DDMAC: Division of Drug Marketing, Advertising, and Communications
OSE/DRISK: Office of Surveillance and Epidemiology/Division of Risk Management
OSE/DMEPA: Office of Surveillance and Epidemiology/Division of Medication Error Prevention & Analysis

1. Introduction

Lazanda (fentanyl nasal spray) is a formulation of fentanyl citrate intended to be administered via nasal spray. The product belongs to a group of drugs now collectively referred to as Transmucosal Immediate-Release Fentanyls (TIRFs). This group of products is indicated for the management of breakthrough pain in opioid-tolerant patients with pain due to cancer.

While there are four approved TIRFs: Actiq, Fentora, Onsolis, and Abstral, this application would be for the first product to use the nasal mucosa to deliver drug instead of the oral/buccal mucosa. In addition, this would be the first TIRF to be marketed in a multiple-dose container. As will be discussed later in this review, the requirements of a potent opioid that is formulated as a multiple-dose nasal spray pose particular concern because of the challenge of disposal of unwanted drug product necessitated by the drug-delivery device.

2. Background

The original NDA was received on 31 August 2009. During the first cycle, the Pharmacology/Toxicology and Clinical Pharmacology teams recommended approval. However, there were Chemistry/Manufacturing/Controls (CMC) and Clinical Microbiology deficiencies that precluded approval. A Complete Response Action was taken on 30 June 2010. The required actions for the Applicant are transcribed, verbatim, from the Action Letter below.

1. Provide a container closure system that does not result in leakage of fentanyl solution with accidental or minor tampering.
2. Provide a container closure system with a dose counting mechanism that cannot be manipulated and that is always accurate.
3. Reduce the volume of fentanyl solution such that there is either no residual following use of the product or provide a method for disposing of the residual such that it cannot be accidentally accessed.
4. Submit an assay for detecting *Burkholderia cepacia* in the drug product, and include absence of *Burkholderia cepacia* in the drug product specifications.
5. Commit to testing for *Burkholderia cepacia* contamination in the Purified Water, USP, (b) (4)

As will be noted later in this review, the major obstacle to approval for this product has been the issue of safe disposal of priming sprays and residual fentanyl solution. This obstacle is a function of the Applicant's desire to have a device that can deliver multiple doses of a liquid nasal spray and the technical requirements for both priming and having excess solution in the device in order to deliver accurate metered doses associated with such a device.

On several occasions, the Applicant has been strongly advised to address the issues of priming sprays and the residual solution in the bottle after actuation of the metered doses. A review of the regulatory history for NDA 22-569 and IND 70,854, under which Lazanda was developed, shows that Archimedes was advised of the importance of addressing residual fentanyl solution

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on multiple occasions during clinical development. Table 1 summarizes the advice provided (essentially verbatim from the meeting minutes).

Table 1: Excerpts from meeting minutes – issue of waste/residual fentanyl solution

Meeting	Date	Relevant Advice
EOP2	24 August 2006	In terms of abuse, the sponsor will need to clearly instruct patients on how to dispose of the product and will need to devise a way to safely dispose of any remaining product (since the top is locked on). The sponsor indicated that they understood the issue and that the outcome of their attempts to change the bottle and decrease the residual product remaining in it after use will have bearing on the disposal issue and instructions. It will be very important for approval of the product to have data to demonstrate that the product can be used safely. The sponsor should have a Risk Minimization Action Plan (RiskMAP) for the product that addresses how to prevent unintended exposures and pediatric exposures, accidental overdose by the patient, etc
Pre-NDA	22 September 2008	Your REMS must also address proper disposal of the residual fentanyl remaining in the device after use.
End-of-Review	24 August 2010	The large quantity (b) (4) for the high concentration [4 mg/mL] solution) of residual fentanyl solution after maximal use has not been addressed. While your proposal may address concerns about unintentional exposure of patients and household contacts during priming and disposing of unused doses, it does not address the issue of large quantities of residual fentanyl solution in the community. This problem appears to be inherent in the product design. We recommend that you consider redesigning the device to inactivate the residual fentanyl after the 8th dose. The Sponsor proposed that they could remove the current lockout after the 8th dose, and allow a patient to spray the remaining drug product into the pouch. The Division noted that this would not be ideal, since some patients would accidently or intentionally continue to use these diminishing doses. The Sponsor stated that patients could be educated to completely spray out their residual. The Division responded that we would need to be convinced that patients *will* actually do this, rather than patients simply demonstrating that they *can* do this, as would be evidenced in a traditional clinical trial. The Division expressed our concern that having any amount of extra fentanyl in the vial after the 8th use is worrisome. The Division encouraged the Sponsor to continue to investigate the possibilities of chemically inactivating the fentanyl after the last dose. Your REMS must also address proper disposal of residual fentanyl with your product,

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3. CMC/Device

As described in the reviews for the first cycle and in Drs. Julia Pinto's (CMC reviewer) and Luke Yip's (Clinical Reviewer) current reviews, the product is packaged in a glass bottle topped with a plastic spray apparatus (see Figure 1).

Figure 1: Drug product presentation

Source: NDA resubmission of 30 Sep 2010, M3, 32p7, container-closure-system, page 3/29 of pdf

The device requires four priming strokes in order to accurately deliver the intended 100 mcL volume for each spray. The device is designed to deliver eight full sprays (a single dose could be one or two sprays). Following the eighth spray, as much as (b) (4) of fentanyl remain in the bottle. It is possible to express additional sprays after the eight metered sprays. However, the sprays decrease in volume as the residual fentanyl solution in the bottle decreases.

As noted in Section 2, there were three device deficiencies noted in the Complete Response Letter. The deficiencies (paraphrased) and the Applicant's attempts to address the deficiencies are summarized following.

Deficiencies:

1. The container-closure is inadequate because:
    i. The pump can be easily removed from the bottle
    ii. The top of the pump can be easily separated from the bottom of the pump
2. The counter mechanism is inadequate because:
    i. The top of the pump can be easily removed and re-indexed
    ii. It is possible to actuate a dose without causing the dose counter to advance
3. The Applicant did not devise an adequate system to dispose of fentanyl solution from primes and residual after 8 sprays.

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The Applicant attempted to address the deficiencies by:

A. Redesigning how the pump mechanism attaches to the glass bottle (addresses 1i),
B. Strengthening the attachment between the top of the pump and bottom of the pump (addresses 1ii and 2i) while making it easier to advance the dose counter (addresses 2ii), and
C. Designing an activated carbon-lined pouch to dispose of unwanted product (addresses 3).

The device has been modified to address Deficiencies 1 and 2. Briefly, the glass bottle has more lugs and the spray device has additional teeth to engage the lugs. This renders it difficult to separate the plastic spray device and glass bottle. The spray device has been redesigned to make it difficult to separate the top and bottom of the device while making it easier to advance the counter mechanism.

To address the issue of the disposal of waste and residual fentanyl after use, the Applicant has designed an activated carbon-lined pouch, shown in Figure 2. The schematic of the pouch design (Figure 3) shows that it is constructed much like a diaper except that it is lined with activated carbon-cloth, designed to adsorb fentanyl.

Figure 2: Absorbent pouch

a) Absorbent pouch (unsealed) containing inner lining of carbon cloth

b) Illustration of use of pouch to capture sprays

Source: Resubmission dated 9/30/10, 3.2.P.2.4 (Container Closure System), page 40/281 of pdf

Figure 3: Schematic showing layers of pouch

OUTSIDE

(b) (4)

Application of sprays

Source: Resubmission dated 9/30/10, 3.2.P.2.4 (Container Closure System), page 40/281 of pdf

The Applicant conducted extraction studies using simulated saliva, simulated gastric fluid, and simulated intestinal fluid which were included in the 30 September 2010 resubmission. Minimal fentanyl was extracted under those conditions which used an extraction time of two hours.

Upon a request by the Agency, additional extraction studies were conducted to test a wider range of solvents and more rigorous conditions. The extraction conditions were:

- Fentanyl amount: entire contents of 4 mg/mL bottle, left to stand for 20 hours
- Extraction volume: 40 mL
- Temperature: 70˚F
- Time: (up to 24 hours)
- Other: minimal agitation (gentle shake prior to sampling)
- Aliquots were taken at each sampling time and the volume taken replenished

Tables 2 and 3 show summary results from the additional extraction studies.

Table 2: Summary results from expanded extraction studies

Extraction medium	% Fentanyl retained on pouch after extraction				Total amount extracted at 24 hr (mcg)
	1 hr	3 hr	6 hr	24 hr	
Water (intact)	100	99.7	99.2	99.4	33
Water (segmented)	97.7	99.7	100.0	100.0	0
0.1 M HCl (intact)	97.6	100.0	95.6	99.6	21
0.1 M (HCl (segmented)	97.4	97.8	99.2	99.9	7
0.1 M NaOH (intact)	99.3	100	99.0	99.6	22
0.1 M NaOH (segmented)	99.4	99.8	100	100	0
Acetone (intact)	73.7	69.4	70.8	77.0	1201
Acetone (segmented)	71.8	69.1	70.8	76.5	1291
Methanol (intact)	84.9	81.9	84.2	90.8	474
Methanol (segmented)	79.7	84.1	87.6	94.4	275
Ethanol (intact)	98.3	93.4	88.1	85.1	740
Ethanol (segmented)	77.7	77.8	79.5	84.3	801
Ethanol/water (segmented)	94.5	98.0	99.1	99.7	14

*all contents of a 4mg/mL FNS bottle were sprayed into the pouch, which was then left to stand for 20 hours prior to extraction.

Source: Submission to NDA dated 21 February 2011, Attachment 1 to Cover Letter, page 6 of 12 of pdf

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Table 3: Summary results from several ethanol extraction studies

Sample tested	% Fentanyl retained on pouch after extraction				Final amount extracted (mcg)
	1 hr	3 hr	6 hr	24 hr	
Prime + dose + disposal sprays ethanol only	77.7	77.8	79.5	84.3	801
Prime + dose + disposal sprays ethanol only after only 2 h standing	60.1	66.0	71.9	83.6	821
Prime + disposal sprays ethanol only after only 2 h standing	71.7	71.7	70.7	73.6	539
Prime + dose + disposal 50% v/v ethanol:water	94.5	98.0	99.1	99.7	14
Prime + dose + disposal after only 2 h standing 50% v/v ethanol:water	91.1	97.5	99.1	99.9	4
Prime + disposal sprays 50% v/v ethanol:water	96.7	98.7	99.3	99.9	2
Prime + disposal sprays - carbon separated 50% v/v ethanol:water	92.7	94.0	95.0	96.3	55
Prime + dose + disposal sprays - carbon separated 50% v/v ethanol:water	96.3	97.1	97.6	98.3	71

* unless otherwise stated in column 1, all contents of a 4mg/mL FNS bottle were sprayed into the pouch, which was then left to stand for 20 hours prior to extraction,

Source: Submission to NDA dated 21 February 2011, Attachment 1 to Cover Letter, page 7 of 12 of pdf

Table 3 shows that the most effective extraction medium was acetone which resulted in a yield of more than 30% in three hours. On face, the other extraction media were much less effective.

However, when the percent remaining in solid phase (pouch) is assessed over the extraction time, in both tables, some of the conditions show a peculiar trend in that the amount extracted with less time is greater than the amount extracted at 24 hours (maximum extraction time). The Applicant provided no explanation for these results.

The CMC team concluded that the Applicant has successfully addressed Deficiencies 1 (strengthen the bottle to sprayer interface) and 2 (strengthen the interface between the top and bottom of the sprayer and facilitate advancing the dose counter). The CMC team opined that

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the carbon-lined pouch would not be “addict-proof,” in that a determined person could extract 30-40% of the fentanyl in a pouch under certain conditions.

4. Nonclinical Pharmacology/Toxicology

There were no new Pharmacology/Toxicology data submitted in this Complete Response.

5. Clinical Pharmacology/Biopharmaceutics

There were no new Clinical Pharmacology data submitted in this Complete Response.

6. Clinical Microbiology

Items 4 and 5 of the Complete Response Letter pertained to testing for *Burkholderia cepacia* in the drug product and the Purified Water, USP (b) (4). The Applicant submitted a plan for testing for this pathogen. The plan was reviewed by Dr. Stephen Fong and, although his review is pending at this time, at the time of the Wrap Up meeting, Dr. Fong indicated that the Applicant’s response was adequate.

7. Clinical/Statistical- Efficacy

The Applicant met the statutory requirement for efficacy with the initial NDA submission. No new efficacy data were submitted.

8. Safety

There has been little activity in the clinical development program for this product between review cycles. Following the initial submission, the Applicant continued to collect data for Study CP045/06. This is an open-label safety study in opioid-tolerant cancer patients with breakthrough pain. This resubmission contains data on 81 such patients.

Dr. Luke Yip conducted the safety review for these additional data. Given the limitations in interpretability of data from this class of drugs (TIRFs), the additional safety data did not reveal any new or unexpected safety signals.

During the five months between data lock for the first review cycle and data lock for the resubmission (October 2009 to March 2010), of the 81 patients followed, 8 died, 7 experienced non-lethal Serious Adverse Events, and 2 discontinued due to adverse events. Dr. Yip reviewed each case and found that the study drug was unlikely to have contributed to the event. Instead, the major safety findings were typical of patients with advanced cancer and included events such as progression of disease, pulmonary embolism, line sepsis, pneumonia, and intestinal obstruction.

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For this open-label safety data, the incidence and types of common adverse events appeared similar to those reported in the original submission and there were no issues with local irritation reported.

Upon a request from the Agency, the Applicant also submitted a summary of the available postmarketing safety data from non-U.S. countries. As described in Dr. Yip's review, Lazanda is approved and marketed under the tradename "PecFent" in the EU. At the time the postmarketing safety summary was submitted (January 2011), "PecFent" had been marketed in Europe for, at most, three months. The summary states that, at that time, approximately (b) (4) had been sold and there were no new safety signals detected.

9. Advisory Committee Meeting

No Advisory Committee meeting was held for this product.

10. Pediatrics

At the time of the initial NDA review, a safety and pharmacokinetic study in patients age 3 years to 16 years was required. Since that time, this has been modified as data are available that indicate there are too few pediatric patients under the age of 7 years who would meet the requirements for opioid-tolerance to make pediatric studies in patients under age 7 feasible. Thus, during this review cycle, the pediatric requirement to study patients was amended to age 7 years to 16 years. At this time, the Pediatric Review Committee (PeRC) does not object to the change.

11. Other Relevant Regulatory Issues

There are no outstand issues relating to Application Integrity Policy, exclusivity, patent issues, financial disclosures, GCP issues, or DSI audits.

Several organizations within CDER were consulted to assess this resubmission including:

- Controlled Substance Staff (CSS),
- Division of Drug Marketing, Advertisement, and Communications (DDMAC).
- Division of Medication Errors Prevention and Analysis (DMEPA),
- Division of Risk Management (DRISK) for an assessment of the Risk Evaluation Mitigation Strategies (REMS) and of the patient labeling (Medication Guide and Instructions for Use)

<u>Risk Evaluation Mitigation Strategies (REMS)</u>

DRISK was consulted to assess the proposed Lazanda REMS and worked with the Applicant throughout the review cycle via teleconferences and information requests. Please see

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DRISK's interim review for details regarding the specifics of the Lazanda REMS and the negotiations with Archimedes.

CDER's strategy for the TIRF class of products is that, ultimately, the products will fall under a single, shared TIRF REMS to address the key and common safety issues related to these rapidly-absorbed, high-potency opioids. However, the single shared system is likely to require a substantial period of time to develop given the number of products already approved. Thus, for products that are still unapproved, the plan is to have each individual REMS comply to the maximum extent possible with the single, shared REMS, as currently envisioned. The individual REMS must also be forward compatible once the shared system is implemented.

DRISK's interim review, dated 4 March 2011, indicates that the REMS has not been finalized.

Disposal of waste fentanyl/Use of device

DMEPA and the Patient Labeling Review team (PLRt) from DRISK provided consultation regarding the proposed product labeling including the package insert (PI), the medication guide (MG), the instructions for use (IFU), and cartons and containers.

Among lesser concerns such as the direction of travel of the dose counter and minor edits to cartons and containers, collectively, DMEPA and the PLRt had strong concerns regarding the complexity of the tasks required for safe use of this product. DMEPA noted that the Applicant has not submitted any data to suggest that patients will use the child-resistant container to protect household contacts or that patients will use the pouch to dispose of unwanted fentanyl solution. Both DMEPA and the PLRt felt that the MG and IFU contained complex, occasionally conflicting instructions that might lead to confusion or lack of compliance on the part of patients.

Because of the lack of data to support the use of the child-resistant container and the pouch, DMEPA and the PLRt have recommended that a usability study to be conducted prior to approval of this product. While DMEPA and the PLRt have provided very helpful revisions to the PI, MG, and IFU, the use of this product is still very complicated. Thus, DMEPA and the PLRt have recommended that the usability study contain a labeling comprehension component.

CSS indicated that they have concerns about the proposed drug disposal system (pouch) and that the system still presents risks for diversion. CSS also indicated that there is a substantial amount of fentanyl in the used pouch and bottle that is available for misuse and abuse.

12. Labeling

The package insert had been reviewed and revised by the Division during the first review cycle. In the resubmission, the Applicant added some efficacy data and other potentially promotional language that was unacceptable. During this review cycle, the unacceptable efficacy data and promotional language were removed, the label was updated with the current

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REMS language, and comments from our CDER consultants, including DDMAC, were conveyed to clarify and correct the label and to emphasize important safety messages.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response.

- Risk Benefit Assessment

Lazanda generally meets the product quality, pharmacology/toxicology, clinical microbiology, clinical, and statistical requirements for approval of a TIRF for breakthrough pain in opioid-tolerant cancer patients.

However, Lazanda is unique because of its formulation, route of administration, and multiple-dose spray container. On the basis of the pharmacokinetics of the TIRF products alone, Lazanda might have a therapeutic advantage over the oral transmucosal products in that the Tmax appears shorter and the Cmax appears higher than the oral products when adjusted for dose. However, in most cases, this observation is based upon cross-study comparisons.

Whether or not the apparent pharmacokinetic differences between Lazanda and the oral transmucosal fentanyl products translate to clinical advantage has yet to be demonstrated.

However, as explained in Dr. Pinto's CMC review, Archimedes' decision to deliver the product with a multiple-dose nasal spray device has resulted in considerable risk management issues. At this time, the container closure is felt to be adequately rugged. The major obstacle continues to be how to safely dispose of waste fentanyl solution from the priming process as well as the solution remaining in the bottle after eight or fewer sprays are delivered.

As emphasized by DMEPA and the PLRt, the instructions for use are quite complex and some are counterintuitive to patients familiar with nasal sprays. For example, presumably half of the patients will spray once into one nostril, which is very uncommonly done for products administered per the nose. While over 500 patients with cancer were able to successfully use the device in the outpatient setting, those patients were in a clinical trial where they presumably received more instruction in the use of the device and medication compliance was particularly emphasized.

To properly use the proposed disposal system, patients will have to prime the device into the pouch. Then they will have to retain the pouch from the time they prime the device until they complete eight sprays as therapy. While this could be as little as 24 hours (patients are allowed a maximum of four doses per day and each dose could consist of two sprays), it could be substantially longer if patients have infrequent breakthrough pain episodes. Following the use of eight sprays, patients will then have to spray the residual solution into the used pouch until all of the solution is gone. Then, they will have to dispose of the pouch and spent bottle in the household trash.

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The pouch disposal system was never tested in clinical trials. The Applicant has provided no data to support the notion that patients can understand and will execute these relatively complicated procedures that are necessary to protect patients and household contacts and to decrease the amount of readily available fentanyl for nontherapeutic use.

While Archimedes, in a submission to NDA 22-569 dated 10 September 2010, asserted that the Agency agreed that a use study could be completed post-approval, as presented in the regulatory history in Section 2 of this review, the Applicant's assertion is not true. The Agency has consistently advised Archimedes that the issues of residual fentanyl and safe disposal of fentanyl must be addressed and the Agency never agreed that this could be done post-approval.

Thus, given the importance of the correct use of the product and the necessity of safe disposal of waste fentanyl, I agree with DMEPA and the PLRt that the Applicant must conduct a Use Study to include labeling comprehension prior to approval. The study must assess whether:

- Patients will spray the priming sprays into the pouch.
- Patients will retain the pouch over the in use time of the device.
- Patients will properly use the pouch to dispose of residual fentanyl after the bottle is used.

Given that the clinical trials showed that patients can successfully execute tasks such as priming, dose finding, and maintenance dosing, I think the secondary objectives could assess whether patients can follow the dose-finding instructions and whether an unusual dose such as one spray into one nostril is correctly executed. I defer to DMEPA for other key assessments for this study.

While DMEPA correctly noted that use of the child-resistant container has not undergone systematic testing, other applicants have not been held to that standard pre-approval and there is no need for that to be done now. However, it is appropriate to collect this information as a postmarketing requirement.

The last issue to be addressed is whether, if properly executed, the pouch disposal system is adequate to address the risks to patients and household contacts and whether it adequately mitigates the risks of addiction and misuse in the community.

From the data submitted to date, if the pouch system will be reliably used by patients/caregivers, it appears adequate to protect patients and household contacts. The pouch clearly has the ability to retain the full contents of the bottle under normal conditions.

The pouch is liable to extraction under certain conditions, particularly acetone extraction. Furthermore, under the stressed conditions, the test results yielded results that were difficult to interpret, requiring further evaluation of the methods used in the pouch extraction tests.

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- Recommendation for Postmarketing Risk Evaluation and Management Strategies

This product will require a REMS that is as compliant as possible with the single shared TIRF REMS as currently envisioned and can be made compatible with the shared program. DRISK and DAAP continue to work with Archimedes toward this goal.

- Recommendation for other Postmarketing Requirements and Commitments

As outlined in Section 10 of this review, the Applicant will have to fulfill the requirements of the Pediatric Research Equity Act. In addition, the Agency should consider requiring a study to determine whether the child-resistant container is being properly used.

- Recommended Comments to Applicant:

    1. There are no data to support that the proposed method of disposing of unwanted fentanyl solution (primes and residual fentanyl after use of metered sprays) will be comprehended or faithfully executed by patients.
    2. The data supporting that the activated carbon-lined disposal pouch can adequately sequester fentanyl have unexplained results. Specifically, the extracted fentanyl appears to be rebinding to the pouch under some of the extraction conditions. These findings shed doubt upon the reliability of the extraction assays.
    3. Continue work to devise a method to chemically or physically inactivate the waste fentanyl solution

    To address these deficiencies:

    1. Conduct and submit an actual use study, including a labeling comprehension component, to inform whether patients comprehend and can accurately and reliably execute the complex instructions necessary to dispose of priming sprays, retain the pouch over the use of the device, and dispose of residual fentanyl. Submit any proposal for usability testing to the Agency for review prior to initiating a study.
    2. Conduct carefully designed and executed extraction studies to define the ability of the pouch to sequester fentanyl over a wide variety of conditions.

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/s/

ROBERT B SHIBUYA
03/07/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-569
Priority or Standard	Standard
Submit Date(s)	30 September 2010
Received Date(s)	30 September 2010
PDUFA Goal Date	30 March 2011
Division / Office	DAAP
Reviewer Name(s)	Luke Yip, MD
Review Completion Date	2 March 2011
Established Name	Fentanyl citrate nasal spray
(Proposed) Trade Name	Lazanda
Therapeutic Class	Opioid analgesic
Applicant	Archimedes Development Limited
Formulation(s)	Nasal spray solution
Dosing Regimen	PRN, not to exceed (b)(4) doses per 24 hours and not more frequent than 2 hours apart
Indication(s)	Breakthrough cancer pain
Intended Population(s)	Adult cancer patients receiving around the clock opioids with breakthrough pain

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend a Complete Response action for Fentanyl Citrate Nasal Spray (FCNS) for the indication of "management of breakthrough cancer pain in patients who are tolerant and are already receiving opioid therapy."

While the Applicant submitted substantial evidence of efficacy in the initial submission and the safety of the drug appears to be similar to other drugs of this class, the Applicant has not provided adequate data to support approval because there are no data informing to actual use of the disposal system. If disposed of improperly, this product has the potential to make large quantities of fentanyl, up to (b) (4), available in the community.

1.2 Risk Benefit Assessment

In the initial submission, the Applicant submitted data from a single adequate and well-controlled study that supported efficacy. The initial submission contained data from 614 healthy volunteers (91) and patients with cancer (523). The current resubmission contains new safety data from 81 patients (17 rollover from study CP043/06, 6 rollover from study CP044/06, and 58 de novo from study CP045/06) with cancer. Safety data from this class of drugs (immediate-release fentanyl dosed in the setting of around-the-clock opioids) are difficult to interpret as noted in Section 7 of this review. That being said, the safety data from the FCNS development program are representative of the class and there were no signals of nasal toxicity. So, strictly from the perspective of safety and efficacy, this product could be approved.

However, the Applicant has not adequately addressed certain risk management issues; specifically whether a patient can and *will* properly use the dosing device and properly dispose of the priming sprays, unwanted extra sprays, and residual fentanyl. These risk management deficiencies preclude approval until the Applicant conducts an Actual Use study to inform these questions.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As a fentanyl-containing product for breakthrough cancer pain, FCNS is subject to a Risk Evaluation and Mitigation Strategies (REMS) program. On 22 December 2010, the

Applicant submitted a revised REMS for FCNS. The original REMS and supporting documents were revised and updated. The Division of Risk Management (DRISK) in The Office of Safety and Epidemiology (OSE) has been consulted to review the Applicant's proposed REMS with input from the Division of Drug Marketing and Communication (DDMAC) and the Division of Drug Medication Error Prevention and Analysis (DMEPA). Interactions between the Applicant and the Agency are ongoing at this time.

Ultimately, the Agency's goal for Transmucosal Immediate-Release Fentanyl products (TIRFs) is to have a single shared program for all similar products. At this time work is progressing to harmonize the REMS for individual products that are in development while working towards a single shared REMS program.

The Agency has been working with the Applicant on their proposed REMS, and it should be able to meet the Agency's basic TIRF REMS program requirements.

1.4 Recommendations for Postmarket Requirements and Commitments

(b) (4) . The Applicant will need to fulfill the requirements of PREA which, at this time, will consist of a safety and pharmacokinetic study in opioid-tolerant pediatric patients age 7-16 years.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed indication for FCNS is the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Fentanyl nasal spray is comprised of fentanyl in the form of the citrate salt, pectin, a (b) (4) The Applicant has included pectin in the formulation as a gelling agent. The Applicant purports that pectin modulates the delivery and absorption of fentanyl. The solution is delivered using a commercially available, cleared nasal spray pump. The spray droplets are deposited into the nose and the pectin interacts with calcium ions present in mucus in the nasal cavity to form a soft, mildly adherent gel. Fentanyl diffuses from the pectin gel and is absorbed into the

systemic circulation. The median time to maximum plasma concentration for a nasal dose ranges from 15 to 20 minutes.

FCNS is available in two dose strengths: 1 µg/µL and 4 µg/µL fentanyl base. The fentanyl dose is determined by the selection of strength and number of sprays per dose. Each spray delivers 100 µL of solution containing either 100 µg or 400 µg fentanyl base. The concentration of drug substance within the nasal spray is the same for all product strengths. Each FCNS bottle is printed with a product strength identifier on the bottle label, package insert, and carton label, and packaged in an unmarked child-resistant canister (secondary packaging), which is placed in the carton.

The Applicant has submitted a number of proposed tradenames, many of which have been unacceptable. However, the mostly recently submitted tradename, “Lazanda” has been found acceptable. This review will reference the drug as “FCNS.”

2.2 Tables of Currently Available Treatments for Proposed Indications

Historically, the treatment of breakthrough pain in cancer patients has consisted of treatment of the pain episode with a short-acting, immediate-release oral opioid (or opioid/non-opioid combination product) consisting of approximately 15% of the patient’s total baseline opioid dose. Typically, morphine, oxycodone, or hydromorphone have been used in this setting, however none of the IR oral opioids are approved for this indication.

There are currently four products approved for breakthrough pain in opioid-tolerant cancer patients, Actiq, Fentora, Onsolis, and Abstral.

2.3 Availability of Proposed Active Ingredient in the United States

There are currently seven approved drug products (not including generic forms) in the United States containing the fentanyl moiety. Table 1 summarizes the important aspects of regulatory and post-marketing experience with these products. The overall adverse event profiles for all of the products is similar (e.g., typical opioid effects of sedation, constipation, and respiratory depression). The table illustrates safety concerns that have occurred in addition to the expected events.

Table 1: Currently Marketed Fentanyl Containing Products

Trade Name/established name	NDA #	Approval date	Major Labeling Changes	Pre and Postmarketing Safety concerns
Sublimaze® (fentanyl injection)	16-619	February 19, 1968	None	None
Duragesic® (fentanyl transdermal system)	19-813	August 7, 1990	• RiskMAP • Medguide • Use of overlay • Increased warnings regarding use in opioid naïve patients	• Leaking patches resulting in 2 recalls (2004 and 2008) • Lack of adhesion • Overdose, misuse and abuse • Use in opioid naïve patients
Actiq® (Oral transmucosal fentanyl citrate)	20-747	November 4, 1998	• RiskMAP • Medguide • Warnings regarding dental caries	• Dental caries • Accidental pediatric exposures • Off-label use in opioid naïve patients • Abuse, misuse, overdose
IONSYS® (fentanyl iotophoretic transdermal system)	21-338	May 22, 2006	None	Never marketed due to safety issues regarding the device component
Fentora® (fentanyl buccal tablet)	21-947	September 25, 2006	• Increased warnings regarding misprescribing to opioid naïve patients and improper dosing • RiskMAP was part of original approval	• Off label use in opioid naïve patients • Improper dosing stemming from fact that this product is not bioequivalent to Actiq and therefore doses are not interchangeable
Onsolis® (fentanyl buccal soluble film)	22-266	July 16, 2009	• Increased warnings regarding misprescribing to opioid naïve patients and improper dosing • REMS was part of original approval	• Off label use in opioid naïve patients • Improper dosing stemming from fact that this product is not bioequivalent to Actiq and therefore doses are not interchangeable
Abstral® (fentanyl sublingual tablets)	22-510	January 7, 2011	• Increased warnings regarding misprescribing to opioid naïve patients and improper dosing • REMS was part of original approval	• Off label use in opioid naïve patients • Improper dosing stemming from fact that this product is not bioequivalent to Actiq and therefore doses are not interchangeable

2.4 Important Safety Issues With Consideration to Related Drugs

All opioids have well established adverse event profiles that include sedation, nausea, vomiting, pruritis, hypotension and constipation. The most serious adverse reactions associated with all opioids include respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension and shock. Abuse, tolerance and physical dependence are other recognized risks associated with this class of drugs.

Because of the high potential of abuse and misuse of opioids, and experience with products such as OxyContin and methadone, the Agency now requires REMS be part of the approval package for high potency opioids, including extended-release formulations.

All opioid labels have warnings regarding co-ingestion with alcohol, based on the additive effects of the two substances; however stronger warnings and/or non-approval of a drug could result from findings of significant dose dumping.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

FCNS has been developed under IND 70,854.

Prior to the initial NDA submission and the first review cycle, the following meetings were held. Please see my review of the initial NDA submission for details.

1. Pre-IND meeting on 26 April 2005.
2. End-of-Phase 2 meeting on 24 August 2006.
3. Pre-NDA meeting on 22 September 2008.

On 30 August 2009 the Applicant submitted NDA 22-569 for FCNS for the treatment of breakthrough cancer pain (BTCP). On 30 June 2010, Archimedes was issued a COMPLETE RESPONSE Letter. The COMPLETE RESPONSE Letter included the following deficiencies:

<u>Product Quality</u>

1. "The container-closure system is inadequate to prevent accidental exposure to the fentanyl solution by patients, caregivers, and household contacts.
    a. The (b) (4) pump assembly can be removed from the glass bottle with moderate effort and no tools.
    b. The top of the pump assembly can be easily separated from the bottom of the mechanism, allowing fentanyl solution to leak out."

    <u>To address this deficiency</u>: "Provide a container closure system that does not result in leakage of fentanyl solution with accidental or minor tampering."

2. "The container-closure system is inadequate to ensure an accurate accounting of the number of sprays delivered.

a. If the top of the pump was removed and then replaced, it could be indexed at various positions along the dose counter and would no longer accurately reflect the number of sprays delivered.
b. It is possible to actuate a dose without causing the dose counter to advance."

To address this deficiency: "Provide a container closure system with a dose counting mechanism that cannot be manipulated and that is always accurate."

3. "The method of disposing the residual fentanyl solution, discarding the container in the trash, does not adequately protect household contacts from accidental exposure to the fentanyl solution. (b) (4)

To address this deficiency: "Reduce the volume of fentanyl solution such that there is either no residual following use of the product or provide a method for disposing of the residual such that it cannot be accidentally accessed."

4. "An assay for detecting *Burkholderia cepacia* in the drug product, and inclusion of a specification for the absence of *Burkholderia cepacia* in the drug product, were not submitted."

To address this deficiency: "Submit an assay for detecting *Burkholderia cepacia* in the drug product, and include absence of *Burkholderia cepacia* in the drug product specifications."

5. "A commitment to testing for *Burkholderia cepacia* contamination in the Purified Water, USP, (b) (4) was not provided."

To address this deficiency: "Commit to testing for *Burkholderia cepacia* contamination in the Purified Water, USP, (b) (4)

An End-of-Review meeting was held with the Division on 24 August 2010. The key points of agreement follow:

1. The Sponsor will consider additional methods of disposing or inactivating of all residual fentanyl that remains after the final spray. The Sponsor proposed to instruct a patient to spray the residual drug product into a charcoal pouch as a means of disposal, and we want to be assured that patients *will* actually do this rather than patients simply demonstrating that they can do this, as would be evidenced in a traditional clinical trial.

2. [redacted] (b) (4)

3. The Sponsor will submit a complete REMS with their resubmission, and will endeavor to work with the Sponsors of other fentanyl products to see if they can work together to combine some REMS aspects.

4. We will review your drug utilization study data and data generated in your pharmacovigilance program [redacted] (b) (4)

The current submission contains:

1. CMC information regarding the redesigned bottle and disposable activated charcoal pouch.
2. Proposed label that incorporated additional data from study CP043/06, CP044/06, and CP045/06.
3. Updated REMS
4. Safety data from the USA and post-marketing information from the United Kingdom.

From a clinical perspective there are no new efficacy data. However, there is a small amount of new safety data. These data consist of open-label safety data that were collected between the last data lock for the initial NDA submission and 31 March 2010 (data lock for the resubmission). In addition, there is limited post-marketing information from outside the United States.

2.6 Other Relevant Background Information

FCNS was approved in the European Union on 31 August 2010. The product is marketed in three countries: the United Kingdom, Ireland (launch: 18 October 2010, and Germany (launch: 22 November 2010). The FCNS formulation and available strengths are identical to those proposed for approval in the United States. However, the pump assembly and child-resistant container (CRC) are different than those proposed for use in the United States. The post-marketing experience from outside the United States will provide some additional safety information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The resubmission was legible and complete.

3.2 Compliance with Good Clinical Practices

The Applicant stated that clinical studies were conducted in accordance with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), United States (US) 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects), US 21 CFR Part 56 (IRBs), and in accordance with the Declaration of Helsinki, Edinburgh 2000. The studies also conformed to any local Health Authority regulations.

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454. There were no disclosed financial arrangements with clinical investigators that required further consideration.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Julia Pinto, Ph.D. reviewed the Chemistry/Manufacturing/Controls (CMC) section of this resubmission.

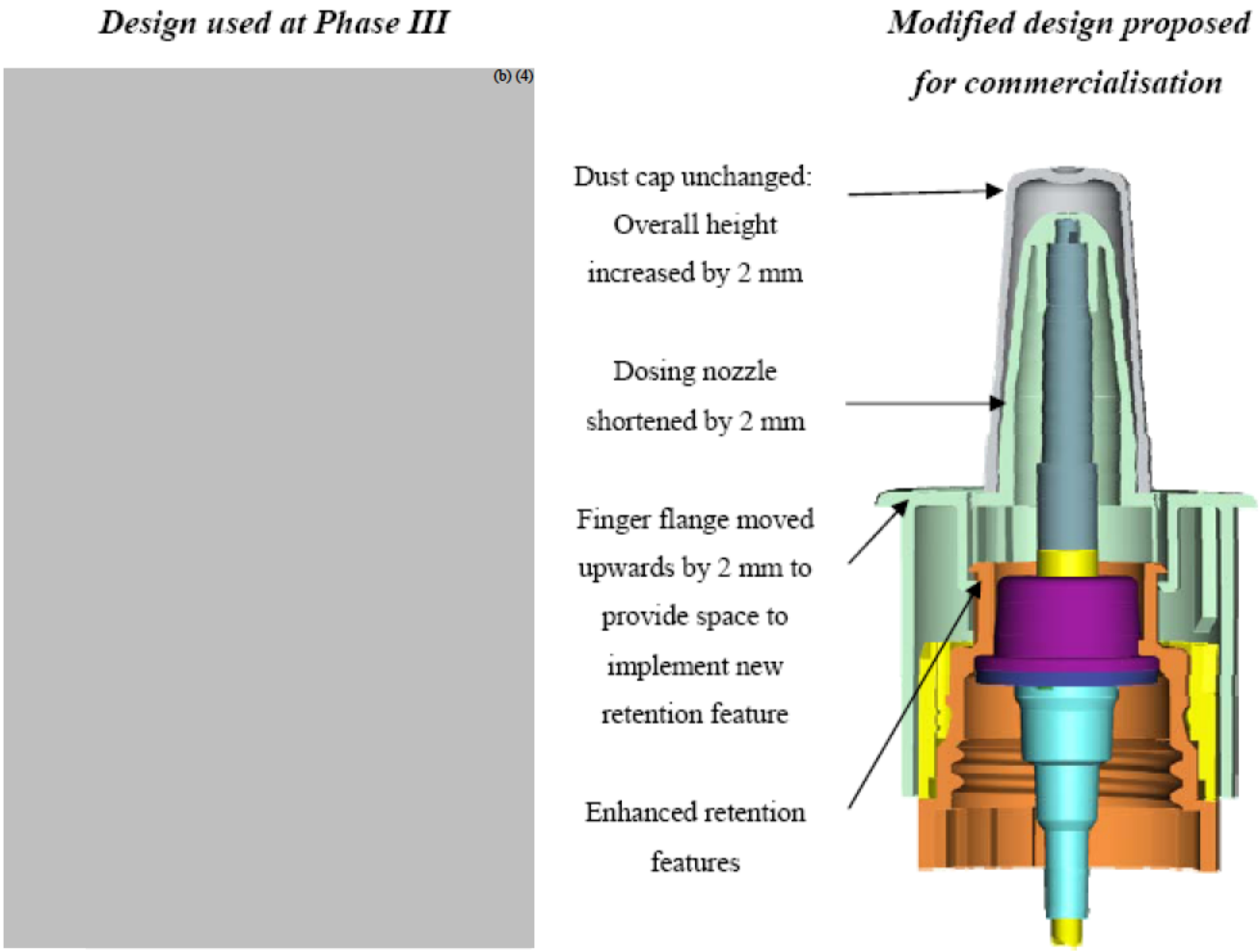
There are three CMC issues cited in the COMPLETE RESPONSE Letter in this regard. Please refer to section **2.5 Summary of Presubmission Regulatory Activity Related to Submission**.

The Applicant addressed these issues by:

1. Modifying to the spray pump screw closure and bottle
    a. A summary of design changes to the (b) (4) nasal spray pump from the design used in Phase 3 studies and the design proposed for commercialization is shown in Figure 1. The pump and glass bottle have been modified such that the plastic teeth on the screw closure have been redesigned with the “saw-tooth” shape (Figure 2) being changed to a flexible design (Figure 3). In addition, the lugs on the glass bottle have been redesigned by the addition of two more lugs. Comparative measurements of the force (Nm) necessary to unscrew the pump from bottle used in Phase 3 studies and the modified container closure system

are shown in Table 2. The force necessary to unscrew the pump from the bottle has been increased [redacted] (b) (4) as a result of these modifications and the Applicant claims it is not possible to unscrew the modified pump from the bottle using bare hands.

Figure 1: Overview of design changes of the [redacted] (b) (4) nasal spray pump

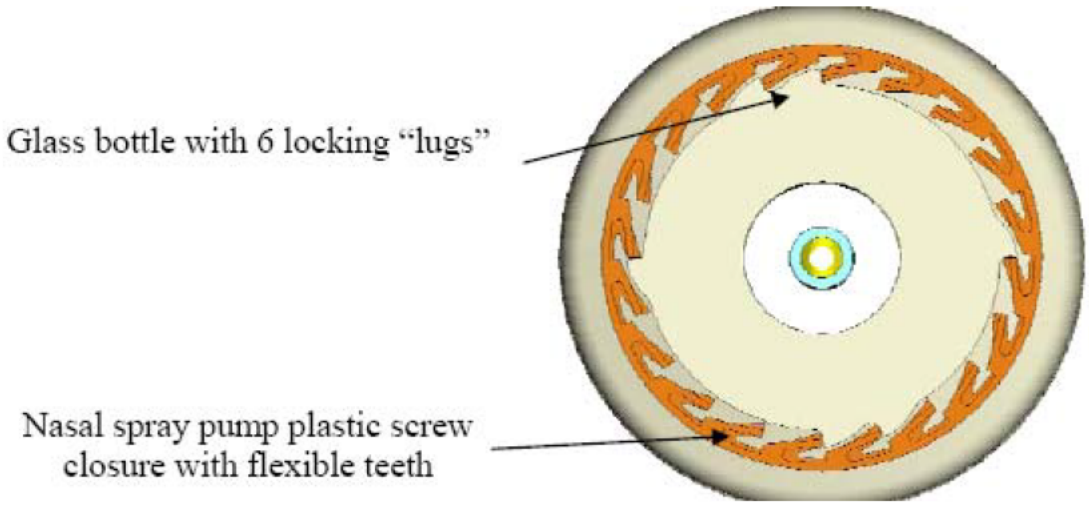


Source: Container Closure System, Sequence 0023, 3.2.P.2.4, page 50/218 of pdf.

Figure 2: Bottle and screw closure teeth design

(b) (4)

Figure 3: Modified bottle and screw closure teeth design



Source: Container Closure System, Sequence 0023, 3.2.P.2.4, page 51/218 of pdf.

Table 2: Torque (Nm) required to unscrew pump form bottle

	Phase 3 studies	Modified container closure system
Mean	(b) (4)	(b) (4)
SD	(b) (4)	(b) (4)

Source: Container Closure System, Sequence 0023, 3.2.P.2.4, page 52/218 of pdf.

The Applicant's modifications appear to have enhanced the robustness of the container closure system. The comparative torque require to unscrew the pump from the bottle in the modified design and our failure to remove the pump from the bottle in the samples of the to-be-marketed product containing only vehicle suggest the pump cannot be separated from the bottle using bare hands.

2. Modifying the actuator component of the spray pump
    a. The connecting parts of the actuator and screw closure components have been modified such that retaining clips which hold the actuator to the screw closure have been enlarged and extended to make them stronger. The modification also reduces the number of positions a displaced actuator could be repositioned. The modifications to the actuator are shown in Figure 4 and the modifications to the screw closure are shown in Figure 5. The Applicant believes these modifications allow the actuator and screw closure components to be more firmly attached and removal of the actuator more difficult. The Applicant also believes it is unlikely that the actuator can be removed without sustaining significant damage. However, in the event that the actuator is removed intact, the potential for repositioning the actuator is reduced by the actual number of positions that a displaced actuator could be repositioned.

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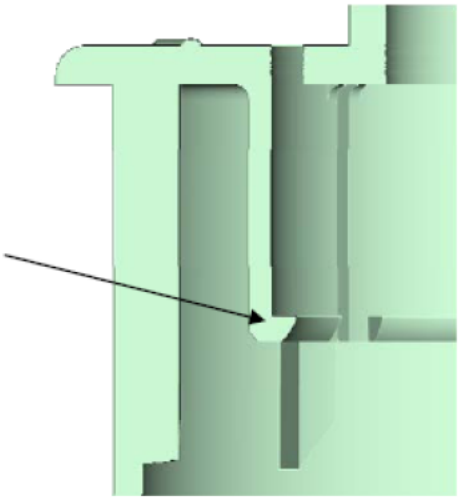
Figure 4: Modification to actuator

(b) (4)

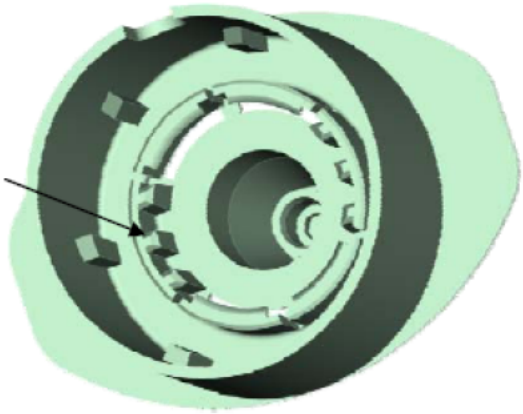
Modified design proposed for commercialisation

New shape of retaining clip



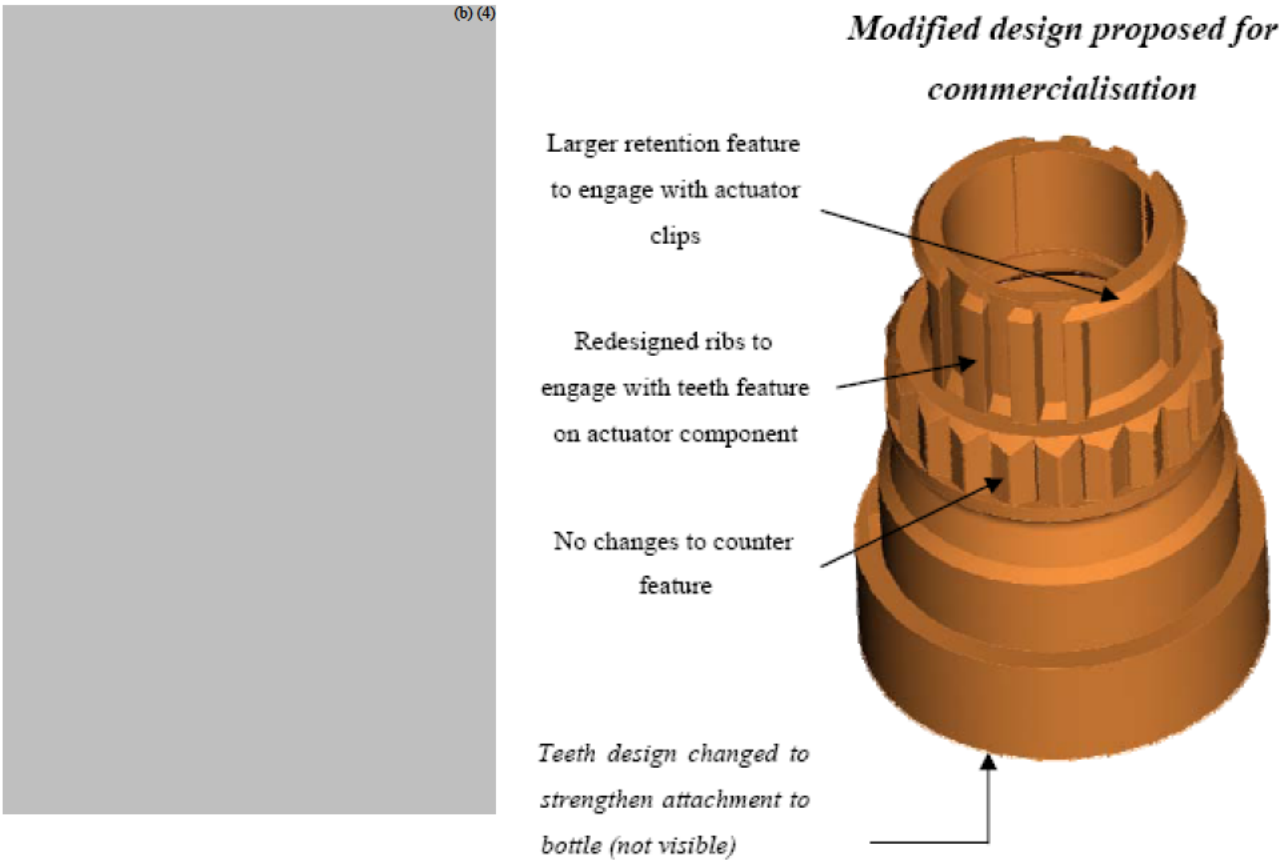
(b) (4)

Teeth which engage with fixture component have been redesigned



Source: Container Closure System, Sequence 0023, 3.2.P.2.4, page 53/218 of pdf.

Figure 5: Modification to screw closure



Source: Container Closure System, Sequence 0023, 3.2.P.2.4, page 54/218 of pdf.

The Applicant's modifications appear to have strengthened the attachment of the actuator. Members of the review team were unable to remove the actuator from the screw closure. On the occasion that the actuator was separated from the screw closure, the separated components were damaged beyond repair and the spray pump was rendered useless.

3. Providing a pouch lined with activated charcoal to absorb the priming, unwanted, and residual fentanyl sprays
    a. In terms of disposing of the priming, unwanted, and residual fentanyl sprays, the Applicant proposed spraying the fentanyl into a pouch lined with an activated charcoal cloth with a 36 cm^2 surface area as shown in Figure 6. The pouch has a flap with a permanent adhesive. The Applicant proposed the pouch will be left unsealed after the priming sprays and when finished using the FCNS bottle and the residual contents have been

sprayed into the pouch, the pouch is then sealed and disposed in the trash. The construction of the activated charcoal-lined pouch is shown in Figure 7.

b. The Applicant reports that the activated charcoal cloth is comprised of 100% activated carbon (b) (4) . The Applicant's *in vitro* experiments demonstrate:
    - The activated charcoal cloth was able to adsorb 4 mg of fentanyl (i.e. approximately equal to priming and all eight dose sprays of FCNS 4 mg/mL). The Applicant purports that the adsorption of fentanyl from aqueous solution was rapid with no drug detected at 5 and 10 minutes.
    - After 4 mg of fentanyl was absorbed onto the activated charcoal cloth, the amount of fentanyl released from the activated charcoal cloth under simulated physiologic fluids (i.e., gastric, intestinal, and saliva) was <0.5% of the applied dose and no fentanyl was detected after 15 minutes in any of the samples.

c. The Applicant reports that *in vitro* experiments with the activated charcoal-lined pouch demonstrate:
    - The absorption efficiency of the activated charcoal-lined pouch following priming sprays, priming sprays plus end-of-use residual sprays, and priming sprays plus 8 dose sprays plus end-of-use residual sprays (FCNS 4 mg/mL) was almost 100%.
    - The percent of absorbed fentanyl that can be eluded, under simulated physiologic fluids (i.e., water, saliva, gastric and intestinal fluid), from the activated charcoal-lined pouch following priming sprays, priming sprays plus end-of-use residual sprays, and priming sprays plus 8 dose sprays plus end-of-use residual sprays (FCNS 4 mg/mL) was less than 3%.

Hypothetically, the Applicant appears to have adequately addressed the fentanyl solution disposal issue. The data presented by the Applicant demonstrate that an activated charcoal-lined pouch appears to be effective at adsorbing and retaining fentanyl. This may be an approach for disposing of FCNS priming and unused dose sprays. However, there may be a problem with the activated charcoal-lined pouch samples provided by the Applicant. The assembly of the activated charcoal-lined pouch may have resulted in a potential physical space between the activated charcoal cloth lining and the pouch. The posterior lining can be separated from the pouch creating an inadvertent second opening where the fentanyl sprays can be deposited. Since only one side of this second opening has an activated charcoal lining, it may be inadequate in absorbing the discarded fentanyl sprays. In addition, the extraction studies presented by the Applicant did not inform about the effects of varying pH or simple solvents. CMC has sent an

information request for the potential inadvertent second opening in the pouch and additional extraction studies (e.g., pH and ethanol) with the pouch.

Dr. Pinto's review has not been finalized at this time. Based on her presentation at the wrap-up meeting, the CMC team believes that the Applicant has adequately addressed the CMC deficiencies. Dr. Pinto reported that the pouch has been redesigned to mitigate the issue of a potential physical space between the activated charcoal cloth lining and the pouch. With regard to the additional extraction studies with organic solvents (i.e., acetone, ethanol, and methanol), only 30% of the fentanyl can be extracted from the activated charcoal-lined pouch following repeated acetone extraction whereas more than 90% of the fentanyl is retained in the pouch following exposure to ethanol and methanol extraction medium. In terms of pH effect on extractability, less than 5% of the fentanyl is extractable in acid pH and ≤ 1% of the fentanyl is extractable in alkaline pH.

Figure 6: Method of disposal

a) Absorbent pouch (unsealed) containing inner lining of carbon cloth

b) Illustration of use of pouch to capture sprays

Source: Container Closure System, Sequence 0023, 3.2.P.2.4, page 40/218 of pdf.

Figure 7: Design schematic of activated charcoal pouch

Source: Container Closure System, Sequence 0023, 3.2.P.2.4, page 40/218 of pdf.

4.2 Clinical Microbiology

Steven Fong, Ph.D. reviewed the resubmission from a product quality microbiology perspective.

There are two issues cited in the COMPLETE RESPONSE Letter in this regard. Please refer to section **2.5 Summary of Presubmission Regulatory Activity Related to Submission**.

The Applicant addressed these issues by submitting:

1. An assay for detecting *B cepacia* in the drug product.
2. A specification for the absence of *B cepacia* in the drug product.
3. A commitment to test for *B cepacia* contamination in the Purified Water, USP, (b) (4)

Dr. Fong's review has not been finalized at this time. Based on his presentation at the wrap-up meeting, the Applicant has adequately addressed the Clinical Microbiology deficiencies.

4.3 Preclinical Pharmacology/Toxicology

Interested readers are referred to Dr. Beth Bolan's review and addendum for a complete discussion of the preclinical development of FCNS.

The Pharmacology/Toxicology team has no approval issues with any of the data from the submitted studies. However, the team was waiting for the (b) (4) genetoxotoxicity qualification studies from the Applicant at the time of my review in the first review cycle.

It was noted that if (b) (4) is positive in those studies, it will likely be an approvability issue. Since that time the Applicant has submitted their completed (b) (4) genetoxotoxicity qualification studies. The Pharmacology/Toxicology team found the impurity (b) (4) has been adequately qualified for genotoxic potential and may be regulated as a standard impurity to levels set in ICH Q3A(R2) and Q3B(R2). There is no approval issue from a nonclinical pharmacology/toxicology perspective.

4.4 Clinical Pharmacology

The Applicant did not submit any new clinical pharmacology study with the current submission. Interested readers are referred to Dr. Sheetal Agarwal's review for a complete discussion of clinical pharmacology aspects of FCNS.

4.4.1 Mechanism of Action

This section is not applicable.

4.4.2 Pharmacodynamics

This section is not applicable.

4.4.3 Pharmacokinetics

This section is not applicable.

4.5 Controlled Substance Staff

Interested readers are referred to the review by Dr. JianPin (John) Gong and Dr. Stephen Sun for a complete Controlled Substance Staff review.

The following represents highlights from the review by Dr. Gong and Dr. Sun. The Controlled Substance Staff (CSS) found that the Applicant's proposal to spray the drug into an activated charcoal-lined pouch is an improvement for disposal of unused fentanyl when compared to the Applicant's original proposal to (b) (4) and dispose of it in the trash. However, CSS expressed the following concerns:

1. The Applicant did not provide sufficient data to show that the pouch can absorb the maximum amount (b) (4) of fentanyl from a full bottle of the highest strength product (i.e., 400 μg/spray; 4 mg/mL, (b) (4)).
2. The residual fentanyl in the pouch may be accessible for misuse or abuse.
3. The data submitted by the Applicant did not adequately address the question of fentanyl extractability from the pouch for purposes of intentional misuse and abuse.

CSS recommended that the Applicant develop a method to inactivate or destroy residual drug, or set up a mail-back program to collect the used pouch and used bottle as a means to prevent diversion.

During the wrap-up meeting, CMC (Dr. Pinto) clarified the absorption efficiency of the activated charcoal-lined pouch for the priming sprays, priming sprays plus end-of-use residual sprays, and priming sprays plus 8 dose sprays plus end-of-use residual sprays was almost 100%. In addition, the Applicant has provided adequate extraction studies (i.e., pH, acetone, ethanol, methanol, water, and simulated physiologic fluids) to address the question of fentanyl extractability from the pouch.

4.6 Division of Medication Error Prevention and Analysis

The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed tradename, “Lazanda” to be acceptable. DMEPA has not finalized their review of the NDA at this time. Based on DMEPA’s information request to the Applicant on 17 February 2011, DMEPA found:

1. “The spray counter counts up rather than down. Post-marketing surveillance has indicated greater patient comprehension occurs when the device counts the number of doses left.”
2. “It is possible to actuate a partial spray without causing the spray counter to advance. Therefore, patients could potentially deliver multiple sprays without advancing the counter.”
3. “The carbon pouch must be kept until the bottle is used up. It is not clear how or where the pouch should be stored while the bottle is in use in order to prevent its exposure to children, pets, etc.”
4. “We recognize the audible “click” and visual advancement of the counter should help inform patients and caregivers that the dose has been delivered, however, this may not be sufficient for patients or caregivers who are impaired in these areas. Additionally, proper disposal of the priming sprays, unwanted extra sprays and residual fentanyl solution is important in order to protect household contacts from accidental exposure to the fentanyl solution. Therefore, we recommend you address the issues outlined above and then conduct a usability/labeling comprehension study with the revised device to determine if patients and caregivers are able to use and dispose of the product correctly using the instructions provided.”

During the wrap-up meeting, the major concern of DMEPA appeared to be that the Applicant conducts an usability/labeling comprehension study, prior to approval, to determine if patients and caregivers are able to correctly use and dispose of the product using the instructions provided.

5 Sources of Clinical Data

The Applicant did not submit any new clinical studies with the current submission. The Applicant did submit new clinical safety data from the on-going, open-label, long-term, safety and tolerability of FCNS in the treatment of breakthrough cancer pain in patients on regular opioid therapy, Study CP045/06. There were no new clinical efficacy data with the current submission.

5.1 Tables of Studies/Clinical Trials

The only new data are from Study CP045/06, an open-label safety study described in the reviews from the initial NDA submission.

5.2 Review Strategy

Interested readers are referred to Dr. Nick Olmos-Lau's review for a complete product safety review. Dr. Olmos-Lau had performed a review of the safety from the entire clinical development program up through the first data lock on 15 October 2009, which includes:

1. Two completed randomized, double-blind, Phase 3 efficacy studies (CP043/06 and CP044/06),
2. An open-label, longer-term study (CP045/06) in patients rolling over from the efficacy studies (CP043/06 and CP044/06) and newly-enrolled patients, and
3. Patients who continued into the Extension Period of study CP045/06.

In the current submission the Applicant provided new safety data from the Extension Period of the ongoing study CP045/06. I will refer to these data as "New Safety Data" from here forward. The reporting period for the New Safety Data is the immediate five months (i.e., 16 October 2009 through 31 March 2010) following the first data lock (i.e., 15 October 2009). The safety data base for the New Safety Data consists of 81 opioid tolerant patients with breakthrough cancer pain. In addition, the Applicant provided a brief narrative summary of the post-marketing experience from the United Kingdom. As indicated below the review of safety is highly confounded for a product of this type. However, the data in the current submission do not change my overall impression of the safety of this drug.

The materials I have reviewed include the major safety findings (i.e., deaths, serious adverse events, and adverse events leading to discontinuation from the study), death narratives, and withdrawal from study for reasons other than death or major adverse events, common adverse events, and case review forms in the New Safety Data as well as the limited post-marketing information from the United Kingdom.

5.3 Discussion of Individual Studies/Clinical Trials

The Applicant did not submit any new clinical studies with the current submission.

6 Review of Efficacy

Efficacy Summary

This section is not applicable.

6.1 Indication

6.1.1 Methods

This section is not applicable.

6.1.2 Demographics

This section is not applicable.

6.1.3 Subject Disposition

This section is not applicable.

6.1.4 Analysis of Primary Endpoint(s)

This section is not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

This section is not applicable.

6.1.6 Other Endpoints

This section is not applicable.

6.1.7 Subpopulations

This section is not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This section is not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

6.1.10 Additional Efficacy Issues/Analyses

This section is not applicable.

7 Review of Safety

Safety Summary

As stated previously, no new studies were conducted. However, there are some additional safety data from an open-label safety study that I reviewed.

Dr. Nick Olmos-Lau conducted the safety review of the original NDA. Interested readers are referred to Dr. Olmos-Lau's review of safety.

In the current submission the Applicant provided new safety data from the Extension Period of the ongoing study CP045/06. The data submitted in the resubmission were collected from 16 October 2009 (last data lock for the initial submission) to 31 March 2010 (data lock for the resubmission).

The safety data base for the New Safety Data consists of 81 opioid tolerant patients with breakthrough cancer pain. In addition, the Applicant provided a brief narrative summary of the post-marketing experience from the United Kingdom. As indicated below the review of safety is highly confounded for a product of this type. In addition, the Extension Period of study CP045/06 differs from the other periods of the study in that patients did not use diaries to record the breakthrough cancer pain episode associated with each FCNS use. As a result, there is no direct link between individual breakthrough cancer pain episodes, the dose of FCNS taken, and adverse events reported. The reported adverse events are assigned to the FCNS dose that was

provided to the patient, whether or not a FCNS dose had been taken at the time of the adverse event.

In the context of the limitations in interpreting data from TIRF trials (see Section 7.1), the data in the current submission do not change my overall impression of the safety of this drug and the adverse event profile appears typical of drugs of this class.

7.1 Methods

The assessment of safety for FCNS is problematic as is the safety of any of the drugs in this class.

1. The patient population that provided the safety data was patients with advanced cancer and they were very ill, primarily due to the malignancy and its treatment but many had other comorbid conditions.
2. Patients were on a wide variety of concomitant medications including treatments specific for their malignancy, other comorbid conditions, and, most importantly, around-the-clock opioids. This makes distinguishing adverse events due to FCNS very difficult because fentanyl, an opioid, has no unique adverse events to distinguish FCNS-related adverse events from those of the around-the-clock opioid.
3. Since the safety data in the current submission is an extension of an open-label, long-term safety and tolerability study, there is no control group for comparison.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

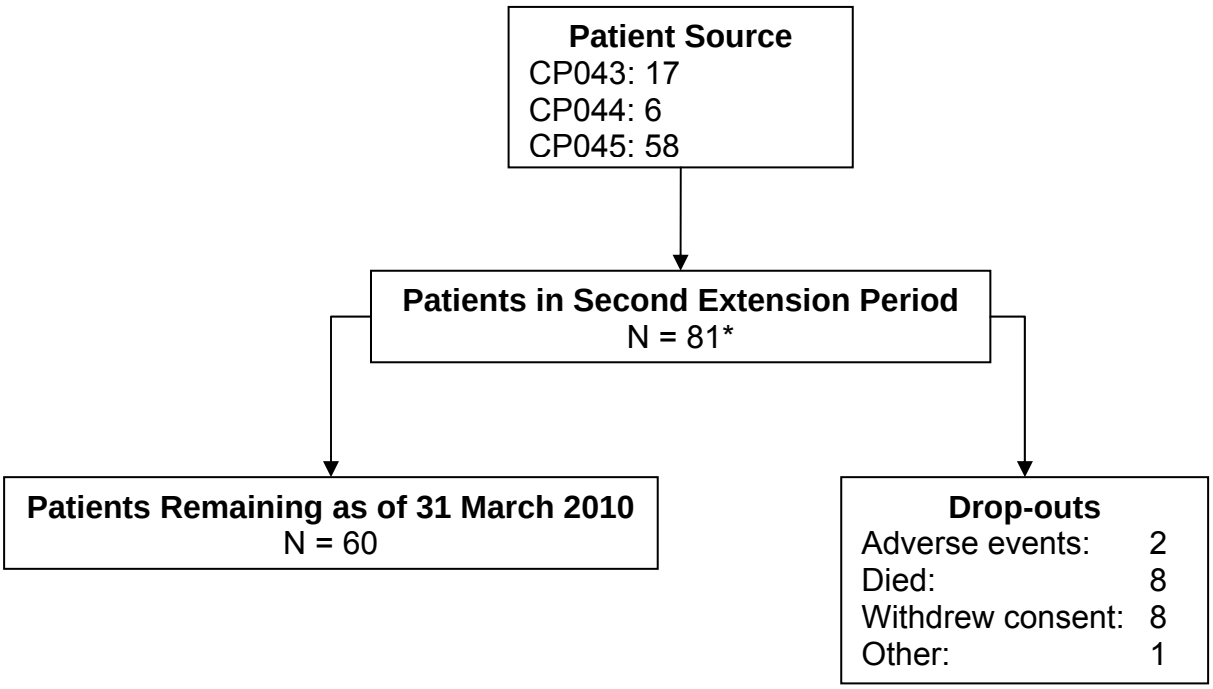
In the current submission the Applicant provided new safety data from the Extension Period of the ongoing study CP045/06. The reporting period for the New Safety Data is the immediate five months following the first data lock (i.e., 15 October 2009). Table 3 shows the number of patients from the different studies making up this database.

Table 3: Clinical Studies Contributing to the New Safety Data

Study	Description	Contribution
CP043/06	Phase 3, multicenter, randomized, placebo-controlled, double-blind, 10-period crossover study to assess the efficacy of FCNS in the treatment of BTCP in opioid tolerant patients on around-the-clock opioid treatment	17 (rollover)
CP044/06	Phase 3, multicenter, randomized, active-controlled, double-blind, double dummy treatment phase, 2-period crossover study to assess the efficacy of efficacy of FCNS compared to immediate-release morphine sulfate in BTCP in opioid experienced subjects	6 (rollover)
CP045/06	An on-going, Phase 3, open-label, safety study designed to determine the long term safety and tolerability on FCNS in the treatment of BTCP in opioid tolerant patients. Patients had to have completed either study CP043/06 or CP044/06 and have persistent episodes of BTCP controlled with FCNS or they could be newly enrolled subjects with malignancies on around-the-clock opioid therapy and BTCP pain. Patients were instructed to treat a maximum of 4 episodes of BTCP per day with a minimum 4 hours dosing interval.	58 (de novo)
TOTAL		**81**

Figure 8, summarizes the disposition of the 81 patients during this second extension period. I note that the Applicant indicated in Figure 2 of the “CLINICAL STUDY REPORT ADDENDUM 2 SECOND EXTENSION PERIOD – 16 OCTOBER 2009 TO 31 MARCH 2010” and Table 7-15 of the “ISS 1 Year Safety Update” (report date 16 August 2010) there were three patients who dropped-out because of adverse events. However, the narratives appear to account for only two patients who dropped-out because of adverse events. It was further noted that one of the three patients reported to have dropped-out because of adverse events was also reported to have died during this extension period. Therefore, the “Drop-outs” box in the figure accounts for this apparent discrepancy.

Figure 8: Patient Disposition in the New Safety Data



*Includes Patient 931/393105 who died during First Extension Period, but had a serious adverse event reported late during this Period.
Source: CP045/06/FCNS, Clinical Study Report Addendum 2, Second extension period – 16 October 2009 to 31 March 3010, page 41/135 of the pdf.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA version 11.0. The appropriateness of the Applicant's coding was evaluated by comparing the preferred terms to the verbatim terms recorded by investigators. The coding was reasonably accurate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant did not submit any new pooled safety data with the current submission.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 4: Summary of Patient Duration of FCNS Exposure in the New Safety Data

	N (%)
Continue in Extension Period[1]	81
No Drug Dispensed or Returned[2]	4 (4.9%)

	Category (Days)					
	1 - 14 Days	15 - 28 Days	29 - 89 Days	90 - 180 Days	> 180 Days	Total
Total[3]	0 (0.0%)	0 (0.0%)	11 (14.3%)	16 (20.8%)	50 (64.9%)	77 (95.1%)
Titrated (Effective) Dose						
All Doses[4]	0 (0.0%)	0 (0.0%)	9 (17.0%)	14 (26.4%)	30 (56.6%)	53 (68.8%)
100 mcg	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)	3 (5.7%)
200 mcg	0 (0.0%)	0 (0.0%)	2 (15.4%)	6 (46.2%)	5 (38.5%)	13 (24.5%)
400 mcg	0 (0.0%)	0 (0.0%)	2 (13.3%)	5 (33.3%)	8 (53.3%)	15 (28.3%)
800 mcg	0 (0.0%)	0 (0.0%)	5 (22.7%)	3 (13.6%)	14 (63.6%)	22 (41.5%)

[1]All subjects that are going to continue to receive study medication during Extension Period (CRF page 103) including subjects that have completed early (ongoing).
[2]Subjects that are ongoing in the Extension Period and have not yet received drug, have not returned drug or information on dosage level has not yet been received and for which total duration in the Extension Period cannot be calculated.
[3]Denominator for percentages is the total number of subjects that have continued in Extension Period and have at least one instance of drug dispensed and returned. Denominator for the total (last column) percentage is the number of subjects that have continued in the Extension Period.
[4]All doses as well as by-dose calculations relate to those subjects that have maintained the same titrated (effective) dose of Nasalfent for the duration of the Extension Period.

Source: CP045/06/FCNS, Clinical Study Report Addendum 2, Second extension period – 16 October 2009 to 31 March 3010, page 76/141 of the pdf.

Table 4 shows that a total of 50 patients were exposed to FCNS ≥ 180 days, and that a substantial proportion of patients (64%) were treated with the highest dose for more than six months.

7.2.2 Explorations for Dose Response

This section is not applicable.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal or in vitro testing performed.

7.2.4 Routine Clinical Testing

No physical examinations or laboratory parameters were required by the protocol for the Extension Period of the ongoing study CP045/06. The Applicant did not submit any laboratory data with the current submission except in some of the patients' narratives pertaining to deaths, serious adverse events, and adverse events leading to discontinuation.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Dr. Sheetal Agarwal's Clinical Pharmacology review for information regarding the metabolic, clearance and interactions of FCNS. The Applicant did not perform specific studies addressing of metabolism or excretion of fentanyl used via intranasal route.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Fentanyl is a potent, short acting analgesic with a well-known pharmacologic profile. As a pure opioid agonist, mediated through high affinity mu-opioid receptor activity, it binds to receptors in the brain, spinal cord, and smooth muscle. Fentanyl also interacts with central and peripheral vascular alpha-adrenergic and muscarinic receptors. The expected adverse events relate to CNS activity, and include sedation, dizziness, somnolence, and headache. In larger doses fentanyl can induce profound analgesia or anesthesia and unconsciousness, leading to respiratory depression and hypotension. Fentanyl has similar effects on gastrointestinal tract as other opioids and can cause nausea, vomiting, or constipation. Observed cardiovascular effects include hypotension, collapse and shock. Compared to other opioids such as meperidine or morphine sulfate, fentanyl seems to cause less histamine release, which is thought to be the cause of hypotension, tachycardia, pruritus, and erythema.

7.3 Major Safety Results

7.3.1 Deaths

There were a total of eight deaths reported in the New Safety Data.

Since patients enrolled in the FCNS trials had advanced cancer with breakthrough pain, a large number of deaths were to be expected. Given that the total number of new patients is 81, the death rate was 10%. This is similar to the death rate (14%) previously reported for all participants during Phase 2/3 studies for this product.

I reviewed the narratives and the corresponding case report forms. The narratives and the case review forms suggest all 8 deaths were due to complications of the underlying disease or disease progression and none of the deaths appeared to be associated with FCNS. The deaths are consistent with those observed in the initial submission and do not change my impression of the safety of this drug. A listing of the new deaths is summarized in Table 5.

Table 5: Deaths in the New Safety Data

Patient Age (Sex)	**Primary**	**FCNS (mcg)**	**Initial AE (Study Day)**	**Clinical Course**	**Reported Cause of Death (Study Day)**
942/594205 78 yr (M)	Bladder with metastases	800	Anemia (138)	Anasarca	Pulmonary embolism (360)
989/598902 70 yr (F)	Breast with metastases	200	Anemia, vomiting (330)	Osetolytic lesion	Disease progression (456)
706/570604 66 yr (F)	Colon with metastases	200	Asthenia, weight loss (123)	Palliative care	Cardiopulmonary arrest (127)
864/586401 48 yr (M)	Multiple myeloma	100	Cancer relapse (288)	Renal failure, encephalopathy	Cardiopulmonary arrest (315)
917/591701 37 yr (F)	Breast with metastases	200	Chest pain (224)	Pulmonary embolism, disease progression and FCNS discontinued (Study Day 249)	Disease progression (255)
938/593807 58 yr (M)	Metastatic melanoma	400	Anxiety (58)	Disease progression, hospice	Disease progression (170)
988/598802 60 yr (F)	Endometrial with metastases	800	Peripheral edema (291)	Disease progression	Disease progression (372)
937/593703 32 yr (F)	Breast with metastases	800	Cancer progression (57)	Disease progression	Disease progression (144)

7.3.2 Nonfatal Serious Adverse Events

There were a total of seven nonfatal serious adverse events reported in the New Safety Data.

I reviewed all the narratives and the corresponding case report forms. The narratives and the case review forms suggest all serious adverse events were consistent with complications of the underlying disease, disease progression or complications of medical procedures and none of the nonfatal serious adverse events appeared to be associated with FCNS. The serious adverse events are consistent with those observed in the initial submission and do not change my impression of the safety of this drug. The seven SAEs are summarized in Table 6.

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Table 6: Nonfatal Serious Adverse Events in the New Safety Data

Patient Age (Sex)	Primary	FCNS (mcg)	SAE (Study Day)	Clinical Course	Outcome
913/391305 53 yr (M)	Bladder with metastases	400	Pulmonary embolism (197)	Medical/surgical treatment, FCNS interrupted for 7 days	FCNS reintroduced
914/391403 50 yr (M)	Chronic lymphatic leukemia	800	Pneumonia (881)	IV antibiotics, FCNS interrupted for 10 days	FCNS reintroduced
914/391407 52 yr (F)	Colorectal	400	Small bowel obstruction (654)	Non-surgical intervention	Discharged after 24 hours
603/460305 56 yr (M)	Gastric	800	Abdominal wall tumor (244)	Tumor excision	Discharged after surgery
506/550601 67 yr (M)	Prostate with metastases	400	Pulmonary embolism and disease progression (152)	Medical treatment of embolism; sepsis; hospice care	FCNS discontinued on study day 152 due to severe disease progression
906/590605 45 yr (M)	Colon with metastases	800	Hepatic catheter infection, biliary drain malfunction (386); sepsis (455); abdominal pain (631); obstructive jaundice (656)	Medical/surgical treatment	Discharged after each hospitalization
942/594204 73 yr (M)	Prostate with metastases	800	Anemia (151)	Transfusion	Discharged after transfusion

7.3.3 Dropouts and/or Discontinuations

Discontinuations for reasons of adverse events

There was a total of two adverse events reported leading to discontinued use of FCNS in the New Safety Data.

I reviewed both narratives and the corresponding case report forms. One of the patients (913/591303) was reported to have experienced sleep apnea syndrome after having been on FCNS 800 mcg for 165 days. He was continued on the same FCNS dose for the next 27 days while having ongoing sleep apnea syndrome. This patient's case report form indicated the adverse event and discontinuation of FCNS occurred prior to the first data lock (i.e., 15 October 2009). The Applicant appeared to have been following up on this case because the patient's ongoing sleep apnea syndrome. Based on this patient's case narrative and case report form, it is highly unlikely that this patient's sleep apnea syndrome is related FCNS.

The second patient (506/550601) was reported to have pulmonary embolism and disease progression after having been on FCNS 400 mcg for 152 days. His embolism was medically treated and he subsequently developed sepsis. It was decided to discontinue FCNS because of the patient's severe disease progression. Incidentally, this patient is also reported under the category of "Nonfatal Serious Adverse Events" (section 7.3.2). Based on this patient's case narrative and case report form, the adverse events are more consistent with complications of the underlying disease or disease progression and none of the adverse events leading to discontinuation of FCNS appear to be associated with adverse events considered to be related to FCNS.

My review of the two adverse events reported leading to discontinued use of FCNS safety do not change my impression of the safety of this drug. A listing of these 2 cases is summarized in Table 7.

Table 7: Adverse Events Leading to Discontinuation in the New Safety Data

Patient Age (Sex)	**Cancer**	**FCNS (mcg)**	**AE (Study Day)**	**Clinical Course**	**Outcome**
913/591303 66 yr (M)	Multiple myeloma	800	Sleep apnea syndrome (165)	FCNS was discontinued on study day 192	Sleep apnea syndrome ongoing
506/550601 67 yr (M)	Prostate with metastases	400	Pulmonary embolism and disease progression (152)	Medical treatment of embolism; sepsis; hospice care	FCNS discontinued on study day 152 due to severe disease progression

<u>Discontinuations for reasons other than death or adverse events</u>

There were a total of nine discontinuations for reasons other than death or adverse events in the new safety data. The resubmission contained limited information so we requested more information.

I have reviewed all the additional information submitted. There were two patients who discontinued from the study because they no longer required FCNS for their breakthrough pain. There were seven patients who discontinued from the study because they withdrew consent after being on FCNS for 70 to 482 days. The narratives did not indicate why these patients withdrew consent. While it would have been preferable to have more information to better understand the patients coded as "withdrew consent," the available data do not indicate any new safety signal. A listing of these nine cases is summarized in Table 8.

Table 8: Withdrawals From Study For Reasons Other Than Death or Adverse Events in the New Safety Data

Patient Age (Sex)	**Cancer**	**FCNS (mcg)**	**Reason for Withdrawal (Study Day)**
603/460301 58 yr (F)	Cervical with metastases	200	Withdrew consent (482)
603/460302 79 yr (F)	Uterine with metastases	200	Withdrew consent (425)
702/570202 40 yr (F)	Breast with metastases	400	Withdrew consent (70)
858/585808 51 yr (F)	Cervical	800	Withdrew consent (264)
858/585818 57 yr (M)	High grade malignant tumor with metastases	400	Withdrew consent (269)
906/590604 53 yr (M)	Lung with metastases	800	No longer require FCNS for breakthrough pain (292)
941/594105 42 yr (F)	Rectal with metastases	400	Withdrew consent (245)
947/594706 61 (M)	Tongue with metastases	800	Withdrew consent (73)
950/595001 33 (F)	Breast	800	No longer require FCNS for breakthrough pain (266)

7.3.4 Significant Adverse Events

The Applicant indicated that subjective and objective nasal assessments were not performed in the Extension Period. However, the Applicant reported "The local tolerability of Nasalfent in longer term treatment continued to be very good – no 'local' /

nasal AEs were reported." and "No subjects experienced nasal adverse events during the Second Extension Period."

7.3.5 Submission Specific Primary Safety Concerns

From purely the clinical perspective, the primary safety concerns for drugs of this class pertain to opioid overdose and addiction. The clinical development plan does not suggest any particular risk for FCNS compared to similar products. However, as noted in other parts of this review, the Applicant has not demonstrated that patients and caregivers can and will carry out the relatively complex priming and disposal instructions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 9 shows the most common adverse events in the New Safety Data. Table 10 shows the most common adverse events from the previous review cycle; Extension Period of Study CP045/06. The most common adverse events reported are consistent with this patient population and the use of opioids. The new data do not change my impression of the safety of this drug.

Table 9: Common Adverse Events Reported for ≥ 2% of Patients in the New Safety Data of Total Incidence (ITT Population)

Preferred Term[b]	100 mcg (N=14)	200 mcg (N=30)	400 mcg (N=31)	800 mcg (N=34)	Total (N=81)
Oedema Peripheral	0	1 (3.3)	0	4 (11.8)	5 (6.2)
Anaemia	0	1 (3.3)	0	3 (8.8)	4 (4.9)
Disease Progression	0	1 (3.3)	1 (3.2)	2 (5.9)	4 (4.9)
Anorexia	0	1 (3.3)	2 (6.5)	1 (2.9)	4 (4.9)
Cancer Pain	0	2 (6.7)	2 (6.5)	0	4 (4.9)
Asthenia	0	1 (3.3)	1 (3.2)	1 (2.9)	3 (3.7)
Chest Pain	0	0	2 (6.5)	1 (2.9)	3 (3.7)
Cystitis	0	1 (3.3)	1 (3.2)	1 (2.9)	3 (3.7)
Decreased Weight	0	2 (6.7)	0	1 (2.9)	3 (3.7)
Insomnia	0	0	0	3 (8.8)	3 (3.7)
Cardio-Respiratory Arrest	1 (7.1)	1 (3.3)	0	0	2 (2.5)
Diarrhoea	1 (7.1)	0	0	1 (2.9)	2 (2.5)
Hematochezia	0	0	2 (6.5)	0	2 (2.5)
Vomiting	1 (7.1)	0	0	1 (2.9)	2 (2.5)
Pneumonia	0	0	1 (3.2)	1 (2.9)	2 (2.5)
Urinary Tract Infection	0	0	1 (3.2)	1 (2.9)	2 (2.5)
Dyspnoea	0	0	1 (3.2)	1 (2.9)	2 (2.5)
Pulmonary Embolism	0	0	2 (6.5)	0	2 (2.5)

Source: ISS 1 Year Safety Update (report date 16 August 2010), page 24/141 of the pdf.

Table 10: Common Adverse Events Reported in the initial NDA submission (ITT Population)

	n (%)				
Preferred Term	**100 mcg (N=25)**	**200 mcg (N=50)**	**400 mcg (N=69)**	**800 mcg (N=61)**	**Total (N=166)**
Subjects with ≥1 AE	9 (36.0)	16 (32.0)	30 (43.5)	23 (37.7)	74 (44.6)
Disease progression	4 (16.0)	4 (8.0)	9 (13.0)	7 (11.5)	24 (14.5)
Anaemia	0 (0.0)	3 (6.0)	2 (2.9)	5 (8.2)	10 (6.0)
Oedema peripheral	0 (0.0)	1 (2.0)	1 (1.4)	7 (11.5)	9 (5.4)
Cancer pain	0 (0.0)	2 (4.0)	5 (7.2)	1 (1.6)	8 (4.8)
Dyspnoea	2 (8.0)	0 (0.0)	3 (4.3)	3 (4.9)	8 (4.8)
Diarrhoea	1 (4.0)	0 (0.0)	3 (4.3)	3 (4.9)	7 (4.2)
Vomiting	1 (4.0)	3 (6.0)	2 (2.9)	1 (1.6)	7 (4.2)
Asthenia	0 (0.0)	2 (4.0)	2 (2.9)	3 (4.9)	7 (4.2)
Constipation	1 (4.0)	2 (4.0)	2 (2.9)	1 (1.6)	6 (3.6)
Chest pain	0 (0.0)	1 (2.0)	3 (4.3)	2 (3.3)	6 (3.6)
Insomnia	0 (0.0)	0 (0.0)	2 (2.9)	4 (6.6)	6 (3.6)
Nausea	1 (4.0)	1 (2.0)	1 (1.4)	2 (3.3)	5 (3.0)
Pyrexia	1 (4.0)	2 (4.0)	1 (1.4)	1 (1.6)	5 (3.0)
Urinary tract infection	0 (0.0)	1 (2.0)	3 (4.3)	1 (1.6)	5 (3.0)
Anorexia	0 (0.0)	1 (2.0)	2 (2.9)	2 (3.3)	5 (3.0)
Weight decreased	0 (0.0)	2 (4.0)	1 (1.4)	1 (1.6)	4 (2.4)
Back pain	1 (4.0)	0 (0.0)	1 (1.4)	2 (3.3)	4 (2.4)
Breast cancer	0 (0.0)	0 (0.0)	3 (4.3)	1 (1.6)	4 (2.4)
Leukopenia	1 (4.0)	0 (0.0)	1 (1.4)	1 (1.6)	3 (1.8)
Cardio-respiratory arrest	1 (4.0)	1 (2.0)	1 (1.4)	0 (0.0)	3 (1.8)
Abdominal pain	0 (0.0)	0 (0.0)	2 (2.9)	1 (1.6)	3 (1.8)
Fatigue	2 (8.0)	0 (0.0)	1 (1.4)	0 (0.0)	3 (1.8)
Cystitis	0 (0.0)	1 (2.0)	1 (1.4)	1 (1.6)	3 (1.8)
Pneumonia	0 (0.0)	0 (0.0)	2 (2.9)	1 (1.6)	3 (1.8)
Sepsis	1 (4.0)	0 (0.0)	0 (0.0)	2 (3.3)	3 (1.8)
Dizziness	0 (0.0)	0 (0.0)	1 (1.4)	2 (3.3)	3 (1.8)
Somnolence	0 (0.0)	1 (2.0)	2 (2.9)	0 (0.0)	3 (1.8)
Anxiety	0 (0.0)	1 (2.0)	2 (2.9)	0 (0.0)	3 (1.8)
Depression	0 (0.0)	1 (2.0)	0 (0.0)	2 (3.3)	3 (1.8)

Source: ISS 1 Year Safety Update (report date 16 August 2010), page 25/141 of the pdf.

7.4.2 Laboratory Findings

No physical examinations or laboratory parameters were required by the protocol for the Extension Period of the ongoing study CP045/06. Because of the limited ability to interpret such data in patients with advanced cancer, this was acceptable.

7.4.3 Vital Signs

The Applicant did not submit any vital signs data with the current submission except in the some patients' narratives pertaining to deaths, serious adverse events, and adverse events leading to discontinuation. Because of the limited ability to interpret such data in patients with advanced cancer, this was acceptable.

7.4.4 Electrocardiograms (ECGs)

The Applicant did not submit any ECG data with the current submission.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant did not submit any special safety study, clinical study or trial data with the current submission.

7.4.6 Immunogenicity

The Applicant did not submit any immunogenicity data with the current submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were only 81 patients who contributed to the New Safety Data. Adverse events by dose are shown in Table 11. There does not appear to be a pattern or clinical significance to the minor differences in rates between doses. There does not appear to be a dose dependency for adverse events.

Table 11: Common Adverse Events Reported for ≥ 2% of Patients in the New Safety Data of Total Incidence (ITT Population)

Preferred Term[b]	100 mcg (N=14)	200 mcg (N=30)	400 mcg (N=31)	800 mcg (N=34)	Total (N=81)
Oedema Peripheral	0	1 (3.3)	0	4 (11.8)	5 (6.2)
Anaemia	0	1 (3.3)	0	3 (8.8)	4 (4.9)
Disease Progression	0	1 (3.3)	1 (3.2)	2 (5.9)	4 (4.9)
Anorexia	0	1 (3.3)	2 (6.5)	1 (2.9)	4 (4.9)
Cancer Pain	0	2 (6.7)	2 (6.5)	0	4 (4.9)
Asthenia	0	1 (3.3)	1 (3.2)	1 (2.9)	3 (3.7)
Chest Pain	0	0	2 (6.5)	1 (2.9)	3 (3.7)
Cystitis	0	1 (3.3)	1 (3.2)	1 (2.9)	3 (3.7)
Decreased Weight	0	2 (6.7)	0	1 (2.9)	3 (3.7)
Insomnia	0	0	0	3 (8.8)	3 (3.7)
Cardio-Respiratory Arrest	1 (7.1)	1 (3.3)	0	0	2 (2.5)
Diarrhoea	1 (7.1)	0	0	1 (2.9)	2 (2.5)
Hematochezia	0	0	2 (6.5)	0	2 (2.5)
Vomiting	1 (7.1)	0	0	1 (2.9)	2 (2.5)
Pneumonia	0	0	1 (3.2)	1 (2.9)	2 (2.5)
Urinary Tract Infection	0	0	1 (3.2)	1 (2.9)	2 (2.5)
Dyspnoea	0	0	1 (3.2)	1 (2.9)	2 (2.5)
Pulmonary Embolism	0	0	2 (6.5)	0	2 (2.5)

Source: ISS 1 Year Safety Update (report date 16 August 2010), page 24/141 of the pdf.

7.5.2 Time Dependency for Adverse Events

7.5.3 Drug-Demographic Interactions

The Applicant did not submit any new drug-demographic interaction data with the current submission.

7.5.4 Drug-Disease Interactions

The Applicant did not submit any new drug-disease interaction studies with the current submission.

7.5.5 Drug-Drug Interactions

The Applicant did not submit any new drug-drug interaction studies with the current submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

For this limited indication in patients with advanced malignancy, an assessment of carcinogenicity was not required.

7.6.2 Human Reproduction and Pregnancy Data

There is no data on human reproduction and pregnancy for this study drug.

7.6.3 Pediatrics and Assessment of Effects on Growth

There was no assessment for the effect of FCNS on growth.

No pediatric exposure was reported in the current submission.

The Applicant requested a partial waiver for children (b) (4) because it would be impractical to conduct an adequate and well-controlled trial based on the following factors:

1. Limited number of children with breakthrough cancer pain in this age group
2. Lack of validated pain assessment instruments in this subpopulation

The Agency had determined that studies in pediatric patients age less than (b) (4) with chronic pain are impractical because there are too few patients in this age group to study. Partially waived studies for selected pediatric subpopulations from birth to 6 years is acceptable considering the necessary studies would be impossible or highly impracticable because there are too few children to meet the requirement for opioid-tolerance.

The Applicant requested a deferral of the Pediatric Assessment required under PREA because the NDA was ready for approval in adults. The Applicant submitted a revised Pediatric Development Plan to the Division on 12 January 2010. The Applicant proposed an open-label safety and pharmacokinetic trial in children and adolescents (b) (4). Since efficacy can be extrapolated from adequate and well-controlled studies in adults, pediatric efficacy studies will not be necessary in this subpopulation. Therefore the required pediatric studies for fentanyl are safety and

pharmacokinetics in pediatric patients ages 7 through 17 years. The Applicant is strongly advised to obtain pharmacokinetic data from an even distribution of age strata (i.e., age 7 to less than 12 years and age 12 to 17 years) and must provide pharmacokinetic data that is evenly distributed across the age range of interest.

At this time, the Pediatric Research Committee agrees with the Division's pediatric study requirements.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no reported incidents of accidental or intentional overdose in the New Safety Data.

7.7 Additional Submissions / Safety Issues

This section is not applicable.

8 Postmarket Experience

FCNS was approved in the European Union on 31 August 2010. The product is marketed in three countries: the United Kingdom, Ireland (launch: 18 October 2010), and Germany (launch: 22 November 2010). The FCNS formulation and available strengths are identical to those proposed for approval in the United States. However, the pump assembly and child-resistant container (CRC) are different than those proposed for use in the United States.

The Applicant reports that since the launch of FCNS in October 2010 until 31 December 2010, there were [redacted] (b) (4) of the 100 mcg strength and [redacted] (b) (4) of the 400 mcg strength sold in the EU [redacted] (b) (4). However, the Applicant does not have information on the number of bottles actually prescribed, as there is at least a 3-month lag in obtaining prescribing information.

The Applicant reports that "To-date, there have been no new safety signals and no reports of accidental exposure, overdose, or misuse/abuse. There has been only one suspect adverse reaction report." Based on the limited information in the CIOMS II report, this case involved a female of an unknown age who "…was very sick (few week to live)…." and was prescribed FCNS for an unreported indication. The patient "…experienced black spots - visual disturbance…." whilst being titrated from to 100 mcg to 400 mcg of FCNS. The patient's concomitant medications included oxycontin for background pain and other non-specified medications for chest infection. This case does not change my impression of the safety of this drug

9 Appendices

9.1 Literature Review/References

Literature is referenced throughout the review as needed.

9.2 Labeling Recommendations

The labeling review is still ongoing in the Division. The labeling will be largely consistent with the other drugs in this class, Actiq, Fentora, and Onsolis. Areas of particular concern in labeling include:

- As described in the summary from the End-Of-Review meeting, the additional information in Section 14 will not be permitted into labeling.
- Inform patients to trust the click of the spray device and the counter and not to rely on the sensation of a spray
- Proper disposal of the priming spray and the residual content of the bottle at the end of use
- Proper use and disposal of the activated charcoal pouch
- A REMS consistent with the recently approved Abstral product

9.3 Advisory Committee Meeting

There was no advisory committee meeting planned for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUKE YIP
03/02/2011

ROBERT B SHIBUYA
03/02/2011
I concur.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Summary Review for Regulatory Action

Date	June 30, 2010
From	Bob A. Rappaport, M.D. Director Division of Anesthesia and Analgesia Products
Subject	Division Director Summary Review
NDA #	22-569
Applicant Name	Archimedes Development Limited
Date of Submission	August 30, 2009
PDUFA Goal Date	June 30, 2010
Proprietary Name / Established (USAN) Name	none/ Fentanyl nasal spray
Dosage Forms / Strength	Nasal spray 100 mcg/spray and 400 mcg/spray
Proposed Indication	For the relief of breakthrough pain in opioid-tolerant cancer patients
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Clinical Review	Luke Yip, M.D. (efficacy) Nick Olmos-Lau, M.D. (safety)
Statistical Review	David Petullo, M.S.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Elizabeth A. Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review	Sheldon Markofsky, Ph.D.; Prasad Peri, Ph.D.
Microbiology Review	Steven Fong, Ph.D.; David Hussong, Ph.D.
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D.; Suresh Doddapaneni, Ph.D.
DSI	Roy Blay, Ph.D.; Tejashri Purohit-Sheth, M.D.
CDTL Review	Robert B. Shibuya, M.D.
OSE/DMEPA	Loretta Holmes, B.S.N., Pharm.D.; Kristina Arnwine, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DRISK	Gita A. Toyserkani, Pharm.D.; Megan Moncur, M.S.; Jeanne Perla, Ph.D.; Claudia Karwoski, Pharm. D.
DDMAC	Mathilda Fienkeng, Pharm.D.; Twyla Thompson, Pharm.D.
Controlled Substance Staff	JianPing Gong, M.D., Ph.D.; Lori A. Love, M.D., Ph.D.; Michael Klein, Ph.D.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DDMAC=Division of Drug Marketing, Advertising and Communications

1. Introduction

Archimedes Development Limited has submitted this application for a fentanyl nasal spray product intended to treat episodes of breakthrough pain in cancer patients who are already being treated with round-the-clock doses of an opioid analgesic for their background cancer pain. There are three transmucosal fentanyl products already approved for this indication: Actiq, a lozenge on a stick approved in 1998; Fentora, a buccal tablet approved in 2006; and Onsolis, a buccal soluble film approved in 2009. As with the Fentora and Onsolis applications, this is a 505(b)(2) application referencing NDA 20-747 for Actiq, and the evidentiary basis for a finding of efficacy for fentanyl nasal spray is a single, adequate and well-controlled clinical trial of a design based on the original studies performed for Actiq. The major regulatory concerns related to this application have been the development of an adequate Risk Evaluation and Mitigation Strategy (REMS) and concerns related to the spray device, including a large quantity of residual fentanyl after maximal use, potentially unsafe priming procedures, ease of access to the fentanyl solution, and the potential for inadvertent excess dosing and surreptitious abuse due to flaws in the dose-counter mechanism.

2. Background

Fentanyl is an extremely potent opioid (approximately 80 times more potent than morphine) that has the potential to cause serious morbidity and death due to respiratory failure if administered to a non-opioid tolerant person. It is also a highly sought after drug of abuse and sells for a high price on the street when either legitimate product is diverted or illicit product, known as China White, becomes available.

This application represents the fourth NDA for a transmucosal fentanyl formulation, but the first intended for nasal mucosal absorption. Actiq was the first oral transmucosal fentanyl product approved and is a lozenge on a stick that is moved between the gum and the buccal mucosa. Actiq was approved under Subpart H, in large part because of the risk for accidental pediatric exposure due to the similarity in its appearance to a lollipop. A Risk Management Plan (later defined as a RiskMAP) was created to attempt to manage some of the risk associated with that product. In addition to identifying the risk for accidental pediatric exposure and providing some methods to try and minimize that risk, other goals described in the RiskMAP included preventing use in opioid non-tolerant patients and other off-label uses. The only clearly unique adverse event associated with Actiq in post-marketing experience has been the occurrence of dental caries, related to the sugar content in the Actiq lozenge.

Fentora was the second oral transmucosal fentanyl formulation approved and is a tablet that is placed between the buccal mucosa and gum where it dissolves with an element of effervescence. The only adverse event associated with Fentora that differed from Actiq in pre- and post-marketing experience was the occurrence of local ulcers in the mouth at the site of drug exposure. Fentora was approved with a RiskMAP comparable to Actiq. Actiq and Fentora were approved for the same indication sought by the applicant, the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The intended population is already on around-the-clock opioids for pain and has episodes of pain that stand out from their background pain. This indication reflects the need for a specific treatment to meet the needs of cancer patients with breakthrough pain, characterized by a relatively early onset of action, relatively short duration of action and high analgesic potency. Fentanyl is a very potent opioid that can cause respiratory depression in microgram quantities. For this reason, the indication also reflects the need for patients to be opioid tolerant, a physiological state in which patients are able to tolerate higher opioid doses without experiencing the CNS and respiratory depression associated with these drugs.

(b) (4)

Based on the post-marketing history of Actiq, it has become clear that prescribers have found Actiq to be useful in patients without cancer pain, both in the settings of chronic non-cancer pain with episodes of breakthrough pain and other chronic painful conditions not generally associated with breakthrough pain episodes. Of note, use of the term

breakthrough pain in non-cancer pain is somewhat controversial. In the Actiq RiskMAP quarterly reports, the use of Actiq in non-cancer pain has exceeded its use in cancer pain, although it is used primarily in opioid tolerant patients with chronic non-cancer pain.

Fentora has greater bioavailability than Actiq and the formulation is less easily removed from the mouth once dosing has begun. Efforts were made to make the difference in bioavailability clear in the Fentora labeling with specific statements that patients should not be converted from Actiq on a mcg for mcg basis and that Fentora is not a generic version of Actiq. However, post-marketing reports have demonstrated a variety of medication errors that include direct conversion on a mcg for mcg basis by prescribers and product substitution at the pharmacy level, in addition to incorrect dosing instructions. The quarterly RiskMAP reports document the very disturbing trend of a steadily increasing frequency of use in patients who are not opioid tolerant. In the first year of marketing there were two deaths reported in patients prescribed Fentora for headache.

As a result of the post-marketing information from Actiq and Fentora, it appeared that the RiskMAP in place for Actiq and Fentora was not effective in mitigating the risks of these products. During a joint meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees on May 6, 2008, the committee members heard presentations from the FDA, SAMHSA and Cephalon, the NDA holder for Actiq and Fentora, about the risks associated with Fentora and the failure of the RiskMAP to mitigate those risks. The committee recommended a more comprehensive program that included patient and physician registration and improved risk communication.

Onsolis was approved with a REMS, as authorized under the Food and Drug Administration Amendments Act passed in September of 2007. The Onsolis REMS, known as FOCUS (Full Ongoing Commitment to User Safety) calls for dispensing Onsolis via specialty pharmacies. The specialty pharmacies ship Onsolis by traceable courier to enrolled patients only after all of the following criteria have been met:

1) the prescription has been written by an enrolled prescriber for an enrolled patient

2) the prescriber has faxed the prescription to a central or regional pharmacy

3) the FOCUS pharmacy has verified that the prescriber and the patient are both enrolled, that the patient has received a FOCUS program counseling call to review the safe use conditions, and that the prescriber has counseled the patient

An additional component of the FOCUS program include a plan to re-counsel and re-enroll prescribers, patients and pharmacies when substantial changes are made to the program or at an interval of at least every two years. If an enrolled patient transfers to another prescriber, the patient and new prescriber must complete a new FOCUS program patient enrollment form. There is also a distribution and prescription data monitoring plan.

Finally, the plan requires that each FOCUS pharmacy keep a record of delays in patients receiving the drug of greater than 72 hours from the time the prescription was received by the pharmacy. The reasons for the delays are to be investigated and reviewed monthly. There has been limited prescribing of Onsolis since its approval, therefore it is not possible at this time to assess the impact of the FOCUS program on safe use of the product.

Archimedes has submitted a REMS as requested in the Pre-NDA meeting that was held on September 22, 2008. The details of their REMS are discussed below in Section 13. However, the spray device used to deliver the fentanyl to the nasal cavity is inadequately designed to protect the patient, caregivers and other family members, and health care providers from inadvertent exposure to or unintended doses of fentanyl. In addition, the device can be easily separated to remove the fentanyl solution by those intent on abuse and/or diversion, and the residual quantity of fentanyl solution after all primings and actuations is unacceptably high.

3. CMC

This product contains fentanyl citrate in an aqueous solution that includes pectin. When the solution is sprayed into the nasal cavities and upon contact with divalent calcium ions in the nasal mucus the pectin forms a soft gel which purportedly modulates the delivery and absorption of fentanyl through the mucosal tissues and into the systemic circulation. The formulation also contains (b) (4) mannitol. (b) (4). The solution is contained in a glass bottle with a locking screw closure, and with a (b) (4) metered-dose nasal spray pump that incorporates a visual and audible spray counter and an end-of-use lock. There are two formulations: 1.0 mg/mL and 4.0 mg/mL fentanyl base. Each actuation of the pump delivers (b) (4) of solution containing 100 mcg or 400 mcg of fentanyl. After priming, the pump delivers up to 8 sprays and then locks. The fill volume is (b) (4) This results in (b) (4) of fentanyl base remaining in the bottles for the low and high concentration products, respectively, after maximal use.

Drs. Markofsky and Peri found the DMF for fentanyl citrate to be adequate to support the NDA. The drug substance specifications were also found to be adequate. While the drug product specifications and the 24-month expiry dating were found to be acceptable, the following concerns led the CMC review team to recommend that the application not be approved at this time:

- The pump system can be unscrewed from the glass container without using any tools, permitting relatively easy access and the potential for inadvertent exposures or frank abuse and diversion.

- There are flaws in the pump assembly that could lead to incorrect priming, dose counting errors, and contact of the fentanyl with the user's hands.

- There is an unacceptably large quantity of residual fentanyl solution remaining after use.

The facilities review and inspection were found to be acceptable. Dr. Fong has concluded that the application should not be approved at this time as the applicant has not provided data to demonstrate that the drug product does not contain Burkholderia cepacia. In addition, they have not provided a validated detection assay. Burkholderia cepacia poses a special threat to individuals with compromised immune systems. It tends to be resistant to preservatives, can survive in nutrient-poor conditions, and has been the cause of several nasal spray recalls.

I concur with the review team that the flaws that are inherent in the current design of this product preclude its approval at this time and that they must complete the microbiological evaluation as per the Agency's prior request.

4. Nonclinical Pharmacology/Toxicology

The applicant submitted 3- and 6-month toxicology studies in rats and a 9-month toxicology study in dogs performed with delivery via the nasal cavity. The histopathological examinations in these studies focused on the nasal cavity, nasopharynx and lung, and found no concerning pathology. The impurity (b) (4) which contained a structural alert for genotoxicity, was adequately qualified and Drs. Bolan and Mellon have concluded that the application could be approved without post-marketing studies.

I concur with the review team that no additional nonclinical pharmacology or toxicology data are necessary for approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the pharmacokinetics of this product (b) (4) was the original trade name proposed by the applicant but it has been found to be unacceptable by DMEPA) has been reproduced from page 3 of Dr. Agarwal's review:

> The relative bioavailability of (b) (4) compared to Actiq® is ~ 120%. Cmax and AUC values for (b) (4) increase with an increase in dose through 100 to 800 mcg and appear dose linear. Median Tmax values range from approximately 15 - 20 min post-dose. A 2 h lapse between two consecutive administrations of (b) (4) is recommended based on lower PK variability (as compared to a 1 h lapse), Tmax range of (b) (4) observed across all the PK studies submitted and frequency of breakthrough pain episodes in the patient population this product is indicated for. (b) (4) absorption in subjects with allergic rhinitis (Active/Untreated) is similar to asymptomatic conditions indicating that presence of rhinitis does not affect absorption of (b) (4) However, (b) (4) absorption in subjects undergoing treatment for allergic rhinitis with oxymetazoline, a vasoconstrictive nasal decongestant, is significantly altered with mean Cmax being significantly lower and mean Tmax being significantly longer as compared to Asymptomatic or Active/Untreated conditions indicating that there exists a possibility of delay in absorption and compromise in efficacy and when a vasoconstrictive nasal agent is co-administered with (b) (4)

The applicant submitted a relative bioavailability study comparing their product to Actiq. That study demonstrated that the fentanyl nasal spray is approximately 20% more bioavailable compared to Actiq at equivalent doses. This will require specific labeling to address the potential for switching from one transmucosal fentanyl product to another. In

general, the nasal spray should always be titrated up from the lowest dose, whether or not the patient is being switched from another transmucosal fentanyl product.

Fentanyl nasal spray is indicated to be used only once per breakthrough cancer pain episode, i.e., it should not be redosed within an episode during either the titration or maintenance phases. The sponsor has recommended a (b) (4) interval between doses during the maintenance phase of treatment. However, based on her review of the pharmacokinetic data, Dr. Agarwal has recommended that a 2-hour dosing interval is acceptable for the maintenance phase. During the titration phase of treatment, if a single dose of fentanyl nasal spray results in inadequate analgesia, patients are to use their customary breakthrough pain therapy (after 30 minutes) as directed by their healthcare provider.

The applicant also studied the effects of allergic rhinitis and concomitant oxymetazoline administration on the absorption of the fentanyl spray. No clinically relevant interactions were noted.

I concur with the review team's conclusion that no additional clinical pharmacology or biopharmaceutics studies are necessary for approval of this application.

6. Clinical Microbiology

There are no clinical microbiology concerns for this application.

7. Clinical/Statistical-Efficacy

Study CP043/06/FCNS enrolled subjects into an open-label, dose-finding period. Dosing was initiated at 100 mcg and increased if an episode of breakthrough pain was inadequately treated. The dose was titrated up from 100 mcg to 200 mcg to 400 mcg to 800 mcg. Subjects were discontinued at any time for intolerable side effects or if they were titrated to 800 mcg without achieving adequate pain control. When a dose level was found to be acceptable, e.g., adequate analgesia and tolerability were achieved, it was repeated for the next episode of pain. If the repeat dose was also successful, that dose was considered to be the subject's titrated dose and the subject was then entered into the double-blind period of the study on that dose.

For the double-blind period, ten doses of study drug were dispensed to each subject; seven were the subject's titrated dose, and three were placebo doses which were randomly assigned to three of the ten breakthrough pain episodes to be treated. Pain intensity was measured on an 11-point numerical rating scale at pre-dose and 5, 10, 15, 30, 25 and 60 minutes post-dose. The primary efficacy endpoint was the SPID30, or summed pain intensity difference from baseline to 30 minutes.

A total of 139 subjects were screened, 114 entered the open-label titration period, and 83 were successfully titrated to a dose of study drug and comprised the intent-to-treat population. Of the 31 subjects who were unable to complete the titration, 6 (5.3%) were unable to tolerate the drug and 7 (6.1%) were unable to achieve an effective level of

analgesia. Other common reasons for discontinuation during the open-label titration period included: did not continue to meet the inclusion/exclusion criteria, 4 (3.5%), and withdrawal of consent, 5 (4.4%). Only 73 subjects completed the study. The explanations for why the 10 subjects discontinued during the double-blind period were varied and did not result in concerns related to the study conduct. The applicant performed their primary efficacy analysis on a modified-ITT population. However, Mr. Petullo performed the analyses on several different populations and found consistent results. The following table, reproduced from page 12 of Dr. Shibuya's review, summarizes Mr. Petullo's analyses:

Table 5: Study 43, FDA's Primary Efficacy Analysis (Applicant's analysis also shown)

Source	Mean $SPID_{30}$ (stdev)			
	Placebo	Fentanyl	Difference	p-value
Applicant, n=73	4.5 (5.5)	6.6 (5.0)	2.1	<0.001
As treated, n=80	4.6 (6.4)	6.0 (6.1)	1.4	<0.001
As randomized, n=80	4.7 (6.2)	6.0 (6.2)	1.3	<0.001

Source: Mr. Petullo's review, page 9/20

The secondary endpoint analyses were supportive of the primary endpoint results. I concur with the clinical and statistical reviewers that the applicant has provided adequate evidence that this product is effective when used according to the proposed labeling.

8. Safety

As with all studies in cancer patients with breakthrough pain, the review of the adverse events for this application was complicated by the fact that the subjects were already quite ill, and many were experiencing significant toxicities related to the treatments for their underlying cancer and the complications associated with the disease. In addition, there were numerous comorbid conditions and, of course, toxicities associated with the subjects' baseline opioid therapy. Finally, since the study design is a 10-period crossover, there is always the potential for some carry-over effect, even with the relatively long dosing intervals. Nevertheless, no unexpected or unusual adverse events were noted in the overall safety database submitted in this application.

There were 88 deaths. Drs. Olmos-Lau and Shibuya concluded that none of these deaths could be clearly attributed to exposure to the study drug. However, it is certainly possible that some of the deaths may have been indirectly related due to the high doses of opioids these patients were being exposed to. Similarly, while many of the non-fatal serious adverse events (which occurred in 70 subjects) and many of the adverse events leading to the discontinuation of 74 subjects may have been exacerbated by exposure to the fentanyl, (e.g., constipation), none appeared to be directly and solely caused by study drug exposure, and the majority appeared to be due to progression of the underlying disease.

The most common adverse events were also, for the most part, those seen with exposure to potent opioids. One exception was pyrexia, which is an event one would nevertheless expect to see in this patient population. Nasal examinations were performed in all of the clinical studies and no significant abnormalities were noted. Adverse events involving the nasal cavities were infrequent and mild.

I concur with the clinical review team that there are no safety concerns specifically related to the proper and labeled use of the product that would preclude approval of this application. However, there are, as noted above, a number of safety concerns related to the design of the product delivery system.

The container-closure system includes a child-resistant outer container for storage when the product is not in use. The drug delivery device itself is, as described above, a spray mechanism that is screwed onto a glass bottle that contains the fentanyl in solution. The plastic spray pump is not glued or crimped to the bottle and the review team found that it could be removed with bare hands by using moderate force. This then permits easy access to a large quantity of fentanyl solution, even after maximal use. On examination of samples provided by the applicant, the review team also found that the device could be easily separated at a point that would allow access to the tubing that accesses the solution, and they observed fluid leaking from the tube when the device was opened in this manner. They also found that the dose-counting mechanism could be easily separated from the spray pump, which could allow for manipulation of the dose counter and then reassembly.

There are additional concerns related to the delivery device as summarized by Dr. Shibuya on page 20 of his review:

> Dr. Olmos-Lau described eleven patients being treated with PecFent who believed that the device either failed to deliver any dose or failed to deliver a full dose. Because of this perception, some patients immediately redosed and one patient suffered a serious adverse event as a consequence. Having seen how the devices work and smelled the product, I believe that adequate patient training and education (to properly actuate the device, to trust the click and counter, and not to redose within two hours) should adequately address the potential for accidental overdose due to confusion about whether the device actuated or not.
>
> While there was a visible plume and an audible click with each actuation, we found that by carefully modulating the force of the actuation, the device could spray without advancing the counter (undercounting). Thus, it is possible for household contacts to use the device undetected by the patient or caretaker.
>
> As noted in Section 2 of this review, the Applicant has been advised on multiple occasions to address the amount of residual remaining in the device after 8 actuations. The Applicant has attempted to optimize the bottle design with a U-shaped cavity to minimize the residual fentanyl solution. According to the Applicant, a fill volume of (b) (4) is optimal to ensure consistent delivery of the desired delivered volume of 100 mcL with a minimal residual volume in the bottle. More than (b) (4) remain in the bottle after full delivery as shown below. In studies of the device, the Applicant found that (b) (4) was recovered.

Activity	Volume dispensed (mL)	Volume remaining (mL)
Full new bottle	(b) (4)	(b) (4)
Priming		
Eight x 100 mcL sprays		

After complete use, each device contains approximately (b) (4) of fentanyl [for the high concentration (4 mg/mL)] solution. Since some patients might use more than one device per day (one device contains as few as 4 doses), a substantial amount of fentanyl could be in the garbage of these patients.

The Applicant proposed to dispose of the fentanyl lost due to priming and any unneeded sprays left in the bottle by (b) (4). This is unacceptable; the chance of transfer of fentanyl to the patient or household contacts is too high. We notified the Applicant of this inadequacy in a 24 March 2010 Discipline Review Letter.

I concur with these concerns. In addition, I think that training and education may not be adequate to assure the safe use of the product by all patients, particularly patients with cognitive impairment and/or mental clouding due to opioid and other drug exposure.

9. Advisory Committee Meeting

The review team determined that an advisory committee meeting was unnecessary for this new formulation of fentanyl as there were no unusual issues related to its safety or efficacy compared to the previously approved products in the class, and there was adequate expertise within the Agency to address the product concerns related to the device and the risk management program.

10. Pediatrics

From page 22 of Dr. Shibuya's review:

> In line with the other "fentanyl for breakthrough cancer pain" products, the ages of birth to 2 years, 11 months may be waived because the numbers of patients available for study are too small. Because the efficacy of opioids may be extrapolated from efficacy in adults, efficacy will not have to be demonstrated in pediatric patients age 3-16 years. However, the Applicant will have to complete a safety and pharmacokinetic study to inform dosing. At the Pediatric Research Committee meeting discussing this NDA, the committee recommended that open-label safety data be collected for a duration of 4-weeks in 30 subjects to adequately address the potential for local irritation.

11. Other Relevant Regulatory Issues

From page 22 of Dr. Shibuya's review:

> The Division of Scientific Investigations (DSI) inspected two sites, both of whom participated in Study 43. While DSI found the data to be acceptable overall, they recommended excluding data from a total of 4 patients because of a lack of documentation of concomitant medications and it was unclear how many doses of study drug one patient administered.

Per their memo dated June 29, 2010, the statistical team reanalyzed the primary endpoint for Study 43, excluding three patients identified by DSI. One of the patients identified by DSI was a screen failure who was not included in the initial analysis. The exclusion of the three patients did not change the interpretation of the study.

12. Labeling

The review team has provided preliminary recommendations regarding changes to the applicant's proposed labeling. However, final labeling discussions will not occur until the applicant addresses the concerns raised during this review cycle in a resubmission.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Complete Response

- Risk Benefit Assessment

  While the applicant has provided adequate evidence to support the efficacy of this product, there are significant design flaws in the delivery device that make its use unsafe for patients, caregivers, family members and health care workers. These flaws include:

  - The device can be opened without an undue amount of effort using only the bare hands, allowing access and possible inadvertent exposure and significant risk for serious adverse consequences.

  - The dose counter can be tampered with allowing for misuse and abuse of the product.

  - An appropriate mechanism for disposal of the residual fentanyl solution after maximal product use has not been delineated.

  The large quantity of residual fentanyl solution after maximal use is particularly concerning due to the high potency of fentanyl and the fact that it is one of the most sought after drugs of abuse. Without the ability to prevent these large quantities of fentanyl solution from gaining access to the community, either inadvertently or by deliberate diversion, the public health risk is considerable. While the applicant's current iteration of their REMS for this product addresses some of the issues related to these risks, it does not adequately address the problems inherent in the product design.

In addition, the applicant has not provided data to assure that the product will not be at risk for contamination with Burkholderia cepacia, a bacterium that could place immune-compromised cancer patients at particularly high risk.

Therefore, the risks associated with the current design of this product and the absence of important data regarding its potential for bacterial contamination outweigh its benefits, particularly in light of the fact that there are three approved OTF products already on the market.

- Required Postmarketing Risk Evaluation and Mitigation Strategy

The applicant did submit a REMS with the NDA, and that REMS included a MedGuide, a Communication Plan, Elements to Assure Safe Use including certification of prescribers and pharmacies, patient registration and documentation of safe use conditions by the pharmacist, and an Implementation System and Timetable for assessments. However, this plan did not include (b) (4) The applicant was advised of this deficiency in a teleconference on April 16, 2010 and the applicant submitted an amended REMS on May 19, 2010.

As the development of REMS for the OTF products has progressed, several different approaches have been pursued by sponsors. Based on our internal discussions, the approach described by the applicant has been found to be acceptable with the modifications provided. This approach includes prescriber enrollment following completion of the program educational materials, counseling of patients, and pharmacy enrollment and pharmacist training. In response to requests from the Agency, the applicant has amended the program to assure that non opioid-tolerant patients will not receive the product, and to assure that prescribers will counsel their patients and attest to having performed that counseling. Based on the use of electronic pharmacy systems, the product will only be dispensed when an enrolled pharmacy can identify that the patient and his or her health care practitioner have both been enrolled as well.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	FENTANYL NASAL SPRAY

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/s/

BOB A RAPPAPORT
06/30/2010

Cross-Discipline Team Leader Review

Date	30 April 2010
From	Robert B. Shibuya, M.D., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-569
Applicant	Archimedes
Date of Submission	31 August 2009
PDUFA Goal Date	30 June 2010
Proprietary Name / Established (USAN) names	None (Fentanyl) Nasal Spray
Dosage forms / Strength	Nasal spray, 100 mcg/100µL or 400 mcg/100µL
Proposed Indication(s)	For the relief of breakthrough pain in opioid-tolerant cancer patients
Recommended:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	
Primary Medical Officer Review	Luke Yip, M.D. (efficacy) Nick Olmos-Lau, M.D. (safety)
Statistical	David Petullo, M.S. Dionne Price, Ph.D.
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D. R. Daniel Mellon, Ph.D.
CMC Review	Sheldon Markofsky, Ph.D. Prasad Peri, Ph.D.
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D. Suresh Doddapaneni, Ph.D.
Microbiology Review	Steven Fong, Ph.D. David Husssong, Ph.D.
OSE/DRISK	Megan Moncur, M.S. Jeanne Perla, Ph.D. Gita Ahkavan-Toyserkani, PharmD Claudia Karwoski, PharmD
DSI	Roy Blay, Ph.D. Tejashri Purohit-Sheth, M.D.
OSE/DMEPA	Loretta Holmes, BSN, PharmD Kristina Arnwine, PharmD Denise Toyer, PharmD Carol Holquist, RPh

1. Introduction

Fentanyl Citrate Nasal Spray (FCNS, also known as (b) (4) or "PecFent") is a reformulation of fentanyl for administration via the nasal mucosa. Archimedes, the Applicant, has formulated fentanyl in an aqueous solution that includes pectin. The drug product is a (b) (4) (b) (4) solution that is capable of being used in a commercially available multiple-use spray device (b) (4). The drug is administered into the nose as a spray. Upon contact with divalent calcium ions in the mucus, the pectin forms a soft gel. Archimedes proposes that the phase change to a gel modulates the delivery and absorption of fentanyl.

The proposed indication is the management of breakthrough pain in opioid-tolerant patients with cancer. Actiq, (fentanyl citrate) oral transmucosal lozenge, approved in 1998, Fentora (fentanyl buccal tablet), approved in 2006, and Onsolis (fentanyl buccal soluble film), approved in 2009, have the same indication.

The products that have followed Actiq have used the 505(b)(2) approval mechanism, referencing Actiq. Using the Agency's previous finding of efficacy and safety for Actiq, the development program for these products is relatively modest. For the oral transmucosal products, one efficacy study is required along with a safety database in the range of 300 patients.

FCNS was tested in a single adequate and well-controlled study using what has become the standard design for these products. Opioid-tolerant cancer patients with breakthrough pain complete an open-label dose-finding period. If a successful dose (adequate balance between analgesia and tolerability) is found, the patient enters a 10-period, double-blind, placebo-controlled period. Sequential doses (7 active and 3 placebo, distributed randomly) are administered upon the start of an episode of breakthrough pain and the pain intensity is graded at close intervals. Episodes treated with FCNS had a statistically significantly larger difference in the summed pain intensity compared to placebo.

The safety database consisted of a total of 614 humans (91 healthy volunteers and 523 patients with cancer). While the safety assessment of this product is confounded (patients were very ill with many concomitant medications and high background opioid use), no unexpected safety signals were observed in the clinical development program. Specifically, there was no evidence of local toxicity to the nose.

As will be described later, the container-closure for the device portion of this combination product is completely inadequate.

<u>RISK MANAGEMENT:</u>

The risks of these products have been recognized and anticipated since the initial approval of Actiq, which was approved under Subpart H. However, the Agency's ability to formally manage those risks has increased over the years.

In 2006, when Fentora was approved, the product was subject to a Risk Minimization Action Plan (RiskMAP). The RiskMAP paradigm employed four strategies to manage risk: labeling, education, surveillance, and intervention. The current paradigm for drug product risk management uses the concept of adding more components as the perceived risks of the product increase. From the current perspective of deciding what Risk Evaluation and Mitigation Strategies (REMS) components are appropriate, the Fentora RiskMAP consisted of the following components: Medication Guide, a educational plan for prescribers and pharmacists, and pharmacovigilance using public health and commercial databases. FDA's options for Sponsor noncompliance with a RiskMAP were very modest: make public statements, hold an Advisory Committee meeting to discuss the safety of the product, or remove the drug from the market.

Unfortunately, the Actiq and Fentora risk management efforts have been less than fully successful as evidenced by documented prescriptions to patients who are not opioid-tolerant which have resulted in patient deaths. We have also observed evidence of inadequate prescriber education such as the use of the drug in patients with headache, improper dose titration and dose regimen, and improper conversion from other products.

In 2007, the Food and Drug Administration Amendments Act (FDAAA) was passed. Among other changes to the law, this statute authorized Risk Evaluation and Mitigation Strategies (REMS). The minimal REMS element is a Timetable for Submission of Assessments. Other components of REMS that may be required include:

- Medication Guide or patient package insert
- Elements to Assure Safe Use (ETASU). Examples of ETASU include:
    - Restricted distribution
    - Certification/attestation of prescribers and pharmacists
    - Mandatory prescriber, pharmacist, or patient education
    - Safe use conditions
    - Required patient monitoring
    - Patient registry
    - Patient counseling
- Communication Plan
- Implementation System

REMS are enforceable under the statute with civil monetary penalties potentially imposed for noncompliance.

Onsolis, approved in 2009, has an approved, implemented REMS. Highlights of the Onsolis REMS follow:

- Medication Guide (MG)
- Communication Plan

    - Prescribers – Dear Prescriber Letter, package insert (PI) and MG, Prescriber Enrollment Form, Patient Enrollment Form (including Health Insurance Portability and Accountability Act (HIPAA) authorization)
    - Pharmacists – Analogous documents to prescribers
- ETASU
    - Education and enrollment of healthcare providers
    - Counseling and enrollment of patients
    - Restricted distribution, Education and enrollment of specialty pharmacies
- Implementation Plan
    - Education and enrollment of the distributor
    - Maintain a database of enrolled parties
    - Monitor distribution
    - Monitor dispensing by selected, specialty pharmacies
    - Monitor and evaluate ETASU
- Timetable for Assessment – every 6 months for 1 year, then annually

To date, the Onsolis REMS appears to be more successful than the Actiq and Fentora RiskMAP programs although this impression is confounded by very low use of the product (<100 patients as of the writing of this review).

Exactly which components in the REMS menu should be required in a REMS for a "fentanyl for breakthough cancer pain" product is under internal discussion at the time of finalization of this review. However, there is consensus within the Agency that patient counseling and a (b) (4) will be necessary components. (b) (4). Thus, FCNS cannot be approved at this time.

2. Background

Fentanyl is a pure mu-opioid agonist and was initially approved in 1968 in an injectable formulation (Sublimaze). The drug substance is highly potent and has a short duration of action. Fentanyl is also highly lipophilic and crosses mucous membranes readily. These features (rapid absorption across the oral mucosa and short duration of action) lend themselves to the treatment of breakthough cancer pain which is defined as a short-duration, crescendo episode of intense, severe pain on top of the underlying chronic pain that many cancer patients develop.

The IND under which FCNS was developed (70,854), was submitted in December 2005. The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) met with the sponsor on three occasions, Pre-IND, End-of-Phase 2, and Pre-NDA, as documented in Dr. Yip's review. Key points related to the clinical development program conveyed over the development history include:

- One efficacy study would suffice to support a NDA.
- Two adequate and well-controlled studies will be required to support any comparative claim.

- The safety database should consist of at least 500 patients, of which at least 150 are treated for at least 3 months. A majority of the patients should be treated with the highest to-be-marketed dose.
- The Sponsor told repeatedly that it must address disposal of the residual drug in the device after use.
- The drug delivery system should be tested under clinical conditions where absorption may be affected such as seasonal allergic rhinitis, upper respiratory infections, and side effects of chemotherapy.
- Evaluate the absorption of fentanyl following eight consecutive doses.
- A RiskMAP will be required. This requirement was updated to a Risk Mitigation and Evaluation Strategy (REMS) at the time of the Pre-NDA Meeting (September 2008). The program must address how inadvertent overdose will be avoided given the ease of administration of multiple doses in quick succession.
- A lock-out and dose-counter are needed on the device.
- Address the safety of dosing frequency.
- Consider the likelihood that the product will be abused and consider methods to minimize the risk of abuse of the product.
- Conduct an in vitro test to assess whether the product will gel if injected.

3. CMC/Device

The Chemistry/Manufacturing/Controls (CMC) review was conducted by Sheldon Markofsky, Ph.D. with concurrence by Prasad Peri, Ph.D.

The drug product consists of fentanyl citrate, [redacted] (b) (4) pectin. [redacted] (b) (4) [redacted] (b) (4) (mannitol), [redacted] (b) (4). FCNS is presented in a 5.3 mL capacity glass bottle with a [redacted] (b) (4) metered-dose nasal spray pump. The mechanism includes an integrated visual and audible spray counter and a mechanical end-of-use lock. The Applicant has designed the bottle with a U-shaped cavity for the purpose of minimizing the amount of fentanyl remaining after all 8 sprays are actuated. The fill volume is [redacted] (b) (4) and the Applicant found that approximately [redacted] (b) (4) of drug product remains after complete priming and use of a bottle. The [redacted] (b) (4) of remaining solution contains approximately [redacted] (b) (4) of fentanyl (high concentration product (400 mcg/100 mcL)).

Dr. Markofsky found no deficiencies with the drug substance, excipients, or manufacturing process. The stability program supported the Applicant's proposed 24-month expiry. Dr. Markofsky requested information regarding plume geometry and specifications for droplet size. The Applicant set the specification for droplets [redacted] (b) (4) which is acceptable from a clinical perspective. PecFent is a non-sterile, preserved aqueous solution. The microbiology section of the NDA was reviewed by Dr. Steven Fong who recommended approval provided that the Applicant submit an assay for *Burkholderia cepacia* and demonstrate that the solution is free of this organism.

The Applicant sent samples of the to-be-marketed finished drug product (identical except the samples did not contain fentanyl). Several issues were noted with the device which is described fully in Section 8 of this review.

Over the review period, Dr. Markofsky requested more information from the Applicant including engineering drawings and data regarding spray specifications. Please see Dr. Markofsky's excellent review for further details.

Drs. Markofsky and Peri have recommended against approval, predominantly because the container-closure system is inadequate as will be described in Section 8. The other CMC deficiencies include a. overages (b) (4), b. methods validation on an impurity. The inspection of the drug product manufacturer is pending at the time of finalization of this review.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Elizabeth A. Bolan, Ph.D. with supervisory concurrence by R. Daniel Mellon, Ph.D..

As a 505(b)(2) application, the Applicant was able to adequately address Pharmacology/Toxicology (P/T) requirements with a modest P/T program. The Applicant submitted 3-month and 6-month toxicology studies in the rat and a 9-month toxicology study in the dog with the to-be-marketed formulation of FCNS via the nasal route of administration. The studies adequately addressed the potential for systemic and local toxicity with full histopathologic examinations of the tissues of interest including the nasal cavity, nasopharynx, and lung. The toxicology studies showed typical opioid-related systemic effects. With regard to local toxicity, the dog study showed no changes and the rat studies showed some histopathologic changes to the local tissues. However, these changes were also observed in the control and placebo-treated animals. Thus, Drs. Bolan and Mellon did not consider the changes in the rat to be test article related.

The excipients in the formulation were considered qualified for intranasal administration. The impurities and degradation products in drug substance and drug product were acceptable with one exception, the (b) (4) which contains a structural alert for mutagenicity. The current specification exceeds that allowable NMT 1.5 mcg/day. During the review cycle, the Applicant conducted and submitted a bacterial reverse mutation assay and a chromosomal aberration assay. The P/T team has reviewed those studies and the results are acceptable.

Drs. Bolan and Mellon have recommended approval from the P/T perspective; please see Dr. Bolan's excellent review for details.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by Sheetal Agarwal, Ph.D. with concurrence by Suresh Doddapaneni, Ph.D.

The Applicant conducted four clinical pharmacology studies, all in naltrexone-blocked healthy volunteers (exception, Study CP048/07 which used naltrexone-blocked subjects with allergic rhinitis), summarized in Table 1, following. Following Table 1 are figures and tables providing more detail about some of the key clinical pharmacology findings.

Table 1: Summary of Clinical Pharmacology Studies

Study #	Objective	Treatments	High-level Results
CP037/02	Single-dose formulation study and relative bioavailability to Actiq	3 formulations tested (pectin, chitosan, chitosan/poloxamer 188) at 100 mcg and Actiq, 200 mcg	While the chitosan-containing formulations achieved more rapid and higher Cmax, the pectin-containing formulation was better tolerated.
CP042/05	Single-dose dose-linearity and relative bioavailability to Actiq	100, 200, 400, 800 mcg of FCNS and Actiq, 200 mcg	o Absorption is dose-linear o Tmax = 15-20 minutes o Relative BA to Actiq is 120%
CP047/07	Multiple-dose PK	o Single dose of 100 mcg o Dose of 100 mcg followed by 100 mcg, four hours later o Dose of 100 mcg followed by 100 mcg, four hours later o Dose of 100 mcg followed by 100 mcg, four hours later o Eight consecutive doses of 100 mcg into one nostril	o The Cmax is higher for the second dose of 100 mcg and the magnitude of the difference is inversely related to the dosing interval. o The Cmax and AUC of 8 sprays into one nostril is ~5-fold higher than a single spray.
CP048/07	Drug- and disease-interaction study	o 100 mcg in asymptomatic patients o 100 mcg in patients with untreated symptomatic allergic rhinitis o 100 mcg in patients with symptomatic allergic rhinitis treated with intranasal oxymetazoline	o There were no differences between absorption in the asymptomatic state versus the untreated symptomatic state. o Treatment with oxymetazoline retarded the Tmax, decreased the Cmax, and minimally decreased the AUC.

<u>Single-dose Pharmacokinetics</u>

Table 2 shows the key pharmacokinetic parameters for Study CP042/05, showing that the drug is dose-linear and is absorbed rapidly compared to Actiq.

Table 2: Key Pharmacokinetic Parameters (means and SD), Study CP043/05

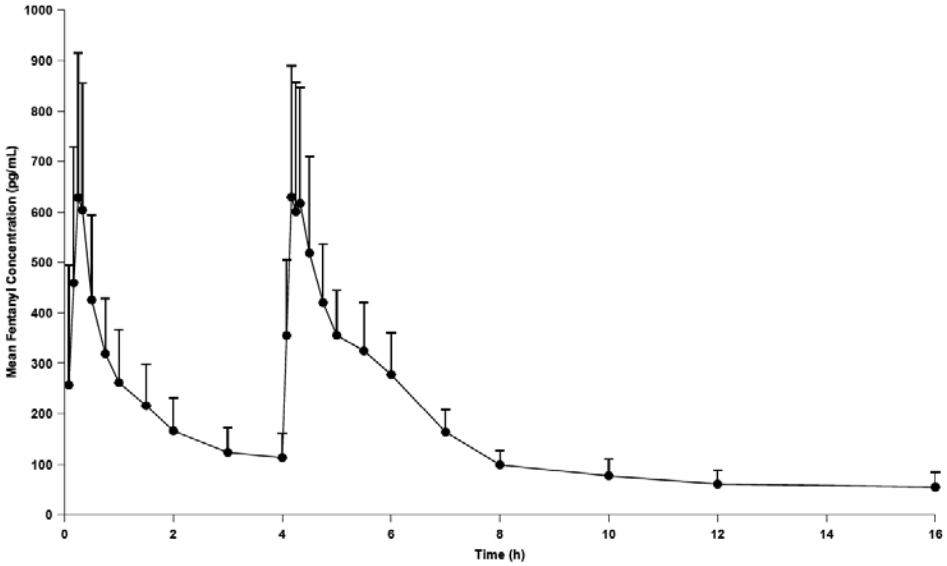
	Mean Cmax (pg/mL)	Mean AUC (pg*h/mL)	Median Tmax (h)	Mean $t_{1/2}$ (h)
100 mcg FCNS	351 (180)	2460 (439)	0.33	22 (3)
200 mcg FCNS	781 (381)	4360 (1299)	0.25	25 (13)
400 mcg FCNS	1552 (407)	7513 (7322)	0.35	15 (4)
800 mcg FCNS	2844 (1592)	17272 (15876)	0.34	25 (23)
200 mcg Actiq	317 (95)	3735 (3581)	1.5	19 (6)

Data extracted from: Table 12; Clinical Study Report CP42/05, page 54/136

Multiple-dose Pharmacokinetics

One of the key questions addressed in Study CP047/07 was what an appropriate, minimum dosing interval would be. To assess this, for three of the treatments, subjects received two doses of FCNS separated by either 1, 2, or 4 hours. The following figure shows "Treatment B" where the second dose occurred 4 hours after the first. Figure 1 shows a concentration-time curve from this study.

Figure 1: Concentration-Time curve for "Treatment B" – one 100 mcg spray followed by another 100 mcg spray, four hours later, Study CP047-07



Source: Figure 5; Clinical Study Report, Study CP047/07, page 58/135

The concentration-time curve shows the expected rise to a maximum concentration that occurs in approximately 30 minutes, followed by a decrease in concentration until the second dose is administered whereupon there is a second spike.

Table 3, following, shows summary data for Study CP047/07, which shows the effect of decreasing the dosing interval on the Cmax for the second dose ($Cmax_2$). All doses were 100 mcg.

Table 3: Summary pharmacokinetic data (means), Study CP047/07

Condition	$Cmax_1$ (pg/mL)	$Cmax_2$ (pg/mL)	% increase [100*(($Cmax_2$-$Cmax_1$)/ $Cmax_1$)]	AUC (pg*h/mL)
Single dose	572	N/A	N/A	1132
Two doses separated by one hour	513	743	45	2776
Two doses separated by two hours	511	687	34	2509
Two doses separated by four hours	642	698	9	2835
Eight consecutive sprays	2955	N/A	N/A	6791

Source: Extracted from Table 3, Clinical Study Report CP047/07, page 18

Three key conclusions can be drawn.

1. Redosing within four hours increases the second Cmax. The shorter the dosing interval, the larger the increase in $Cmax_2$.

2. Even at the minimum dosing interval of one hour, the mean $Cmax_2$ is increased by 45%. NB: Because of the way I calculated the percentage increase in $Cmax_2$, my numbers are higher than Dr. Agarwal's. This represents a worst case scenario.

   Since the use of rescue analgesia in clinical practice (usually 1/6 of the total daily opioid dose administered as an immediate-release dose) usually creates a plasma concentration of approximately twice the steady state levels, redosing once at one hour is probably safe. However, for the sake of safety, it would be prudent to extend the time between doses (after the optimal dose was found) to at least two hours as recommended by the Clinical Pharmacology team.

3. Dosing with 8 times the intended dose results in exposures approximately 5-fold higher than the intended dose, not 8-fold.

Drug/Disease Interactions

Table 4, following, summarizes key data from Study CP047/08, the allergic rhinitis study. Briefly, in this study, patients with allergic rhinitis were treated in a cross-over design under three conditions: asymptomatic, with symptoms induced, and symptomatic/treated with oxymetazoline.

Table 4: Key pharmacokinetic data (means) from Study CP047/08

PK parameter	Asymptomatic	Symptomatic, untreated	Symptomatic, treated	% change from symptomatic/ untreated to treated
Cmax (pg/mL)	420	462	288	-38
Tmax (h)	0.25	0.33	0.75	+100
AUC (pg*h/mL)	1128	1172	936	-20

Extracted from Table 4, Clinical Study Report, Study CP047/08, page 41/225

Study CP047/08 demonstrated that oxymetazoline caused a clinically significant difference in Cmax (approximately 40% lower), Tmax (approximate doubling in length), and a minor difference in overall AUC (20%). There was no effect of allergic rhinitis symptoms on absorption. The oxymetazoline interaction should be reflected in labeling.

Pending labeling negotiations, Drs. Agarwal and Doddapaneni are recommending approval from the clinical pharmacology perspective for this product.

6. Clinical Microbiology

A microbiology quality review was conducted by Steven Fong, Ph.D. Finalization of Dr. Fong's review is pending. However, Dr. Fong has informed me that, at this time, he is not recommending approval because the applicant failed to respond to a request to include absence of *Burkholderia cepacia* in the drug product specifications and to provide an assay for *B. cepacia* detection.

7. Clinical/Statistical- Efficacy

The primary clinical review was conducted by Luke Yip, M.D. and the primary statistical review was conducted by David Petullo, MS with concurrence from Dionne Price, Ph.D.

As a 505(b)(2) application, a single adequate and well-controlled study was required to support efficacy.

The Applicant submitted Study CP043/06/FCNS (Study 43) to support efficacy. As described in Section 1 of this review, Study 43 consisted of two key parts. Eligible patients were opioid-tolerant (requiring ≥60 mg oral morphine equivalents/day) and suffering 1-4 episodes of breakthrough pain per day.

All patients entered into an open-label dose-finding period. They were started with a 100 mcg dose of FCNS. Each breakthrough pain episode was treated. If the test dose resulted in inadequate analgesia, the dose was escalated. Archimedes tested (b) (4) a total of four doses of FCNS: 100, 200, 400, and 800 mcg. Presumably, the reason for this relatively coarse choice of doses pertains to the fact that the Applicant developed two concentrations of drug product, 1 mg/mL and 4 mg/mL and proposes to dose as one or two sprays into one or two nostrils (maximum two sprays per dose). Because of the lack of the ability to fine tune the fentanyl dose, we looked carefully to assess whether the coarse dose adjustment was problematic. In conjunction with the safety findings (see Section 8), we found no evidence that the coarse increments for dose adjustment were problematic.

If intolerable side effects were encountered or the patient did not experience adequate analgesia at 800 mcg, the patient was removed from the study. If the first dose of a dose level was successful (adequate analgesia and tolerable), this dose was repeated. If the repeat dose

was also successful, that was considered to be the patient's titrated dose and the patient entered the double-blind assessment period of the study.

Patients were not allowed to treat episodes at intervals closer than 4 hours and they were instructed to use their pre-existing rescue opioid if the FCNS was ineffective.

In the double-blind period of the study, the patient was dispensed 10 numbered doses. Seven doses were the titrated dose; three were placebo. The placebo doses were randomly scattered throughout the active doses. Upon the onset of an episode of breakthrough pain, patients self-administered the next numbered dose.

Assessments, including pain intensity via an 11-point numerical pain rating scale, were collected pre-dose and 5, 10, 15, 30, 45, and 60 minutes post-dose. The primary efficacy endpoint was the summed pain intensity difference over 30 minutes (SPID30).

A total of 139 patients were screened, 114 entered the open-label titration phase, and 83 successfully titrated to a dose of FCNS between 100 and 800 mcg. A total of 73 patients comprised the intention-to-treat population. The patients that were discontinued during the double-blind assessment period included withdrew consent (3), adverse event (1), death (1), lack of efficacy (1), lost to follow up (1), did not meet mITT criteria such has having at least one post baseline pain intensity measurement (3).

Patients came from the United States (101 enrolled, 70 completed), Costa Rica (10 enrolled, 6 completed), and Argentina (3 enrolled, 0 completed). The enrolled patient population had a slight male predominance (52 vs. 48%) and a mean age of ~53 years (range 21 to 86 years). There was a Caucasian predominance (~70%). Because race is not known to predict the efficacy of opioids, the Caucasian predominance is acceptable. Dr. Yip reviewed the protocol violations and concluded that they were not likely to affect the validity of the results.

The statistics team had some concerns regarding the analysis population because the mITT population included additional qualifiers such as having at least one evaluable placebo-treated and one evaluable FCNS-treated episode. Mr. Petullo analyzed the efficacy data using the Applicant's mITT definition and a less restrictive definition that included seven additional patients and 49 additional episodes that the Applicant had omitted. Mr. Petullo repeated the analysis "as randomized" as opposed to "as treated" (Applicant's method). He found that modifying the analysis population did not change the results.

Study 43 was successful; the Applicant demonstrated a statistically significant treatment difference in the SPID30, favoring FCNS. The summary statistics for the primary efficacy endpoint are shown in Table 5, below.

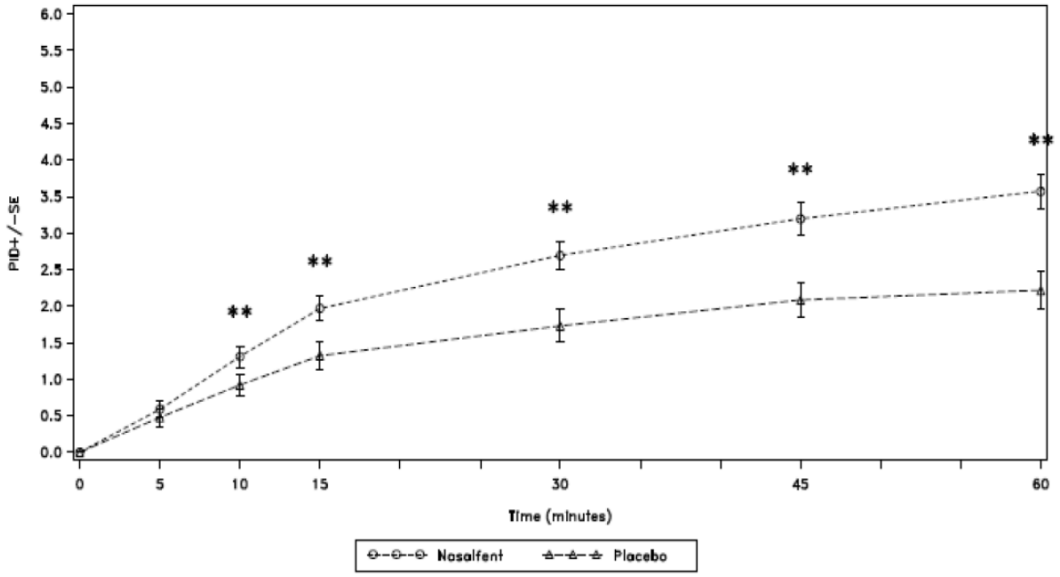
Table 5: Study 43, FDA's Primary Efficacy Analysis (Applicant's analysis also shown)

Source	Mean $SPID_{30}$ (stdev)			
	Placebo	Fentanyl	Difference	p-value
Applicant, n=73	4.5 (5.5)	6.6 (5.0)	2.1	<0.001
As treated, n=80	4.6 (6.4)	6.0 (6.1)	1.4	<0.001
As randomized, n=80	4.7 (6.2)	6.0 (6.2)	1.3	<0.001

Source: Mr. Petullo's review, page 9/20

The pain intensity data, showed as differences from baseline, are shown graphically in Figure 2, following.

Figure 2: Pain intensity difference after dosing, Study 43, mITT population



Source: Dr. Yip's review, page 55/83

Mr. Petullo also analyzed several secondary endpoints including the pain intensity differences and pain relief scores at each time assessed. He found that the analysis of the secondary endpoints supported the primary analysis although there was no correction for multiplicity. The lack of a correction for multiplicity was less concerning since the endpoints were highly correlated and not intended for label claims.

Both Mr. Petullo and Dr. Yip noted a peculiar pattern in the use of rescue. Table 6, following, shows summary data for rescue use (patient's usual oral opioid rescue).

Table 6: Rescue medication use, Study 43

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

[1]P-values from McNemar Test to compare Nasalfent and placebo arms at each timepoint.
Source: End-of-Text Table 14.2.2.15.1

Source: Dr. Yip's review, page 62/83

The rescue medication data indicate that episodes treated with FCNS required more use of rescue soon after dosing although episodes treated with placebo "caught up" at the later timepoints. Mr. Petullo analyzed use of rescue medication as a binary outcome (used or did not use). He found a significant treatment effect, indicating that the FCNS-treated episodes required significantly less rescue medication.

Mr. Petullo's subgroup analysis showed one subgroup, "all others" (race) lacked a significant treatment effect for the primary efficacy endpoint. The "all others" group consisted of 20 patients coded as "Black," "SE Asian," or "Other." Mr. Petullo opined that the lack of treatment effect in this subgroup was due to lack of power. I agree and I would add that there is no recognized difference in the pharmacologic effect of fentanyl associated with race.

The Applicant also submitted CP044/06/FCNS (Study 44), an efficacy study of nearly identical design to Study 43. The objective was to show that FCNS is similar to orally administered immediate-release morphine sulfate tablets over a short evaluation time (15 minutes). As such, Study 43 lacked the placebo-control and used a primary endpoint of the summed pain intensity difference over 15 minutes. The other major difference was that this trial was conducted all outside the US.

The Applicant reported a statistically significant difference for the primary endpoint (SPID15 was 3.02 versus 2.69, $p = 0.0396$). Dr. Yip found no study conduct issues. However, since this study was only supportive, Mr. Petullo did not confirm the Applicant's analysis. While the difference in pain intensity differences qualitatively appeared to persist throughout the 60-minute assessment period, the clinical significance of a small, albeit statistically significant difference at 15 minutes selected by the Applicant is not clear. However, the treatment effect was observed that supports the notion that FCNS has an analgesic effect.

Study 43 supports a finding of efficacy for FCNS. Study 44 supports Study 43 although it is not appropriate for labeling due to lack of replication for a comparative claim (vs. oral morphine) and the question of the clinical significance of the endpoint selected.

8. Safety

My review of the safety of FCNS is divided into three parts as follows:

A. Safety data in the NDA
B. Safety issues related to the dosing device and disposal
C. Risk Evaluation and Mitigation Strategy

A. Safety data in the NDA

The review of clinical safety was conducted by Dr. Nick Olmos-Lau.

As noted by Dr. Olmos-Lau, the assessment of safety for this class of drugs (fentanyl for breakthrough pain) is problematic. First, the patient population that provided a substantial portion of the safety database (patients with advanced cancer) were very ill, primarily due to the malignancy and its treatment but many had other comorbid conditions. Next, patients were on a wide variety of concomitant medications including treatments specific for their malignancy, other comorbid conditions, and around-the-clock opioids. Naturally, this makes distinguishing adverse events due to the study drug very difficult. Third, due to the design of the controlled trial (a 10-period crossover usually finished in a few days), for all intents and purposes, there is no control group for comparison.

A total of 614 patients and subjects were exposed to FCNS in the eight studies that comprise the development program. Of those persons, 91 were healthy volunteers and 523 were patients with cancer. A total of 153 patients were treated for ≥ 90 days. Approximately 39% of the patients were treated with the 400 or 800 mcg doses.

Major Safety Findings

Because of the nature of the patient population for this product, a substantial number of deaths and serious adverse events (SAEs) was to be expected. Across the entire development program, there were a total of 88 deaths and 70 patients who experienced one or more nonfatal SAEs. Two or the SAEs occurred in Phase 1 studies (a subject became pregnant, one subject developed chest pain that was not related to study drug). The deaths and SAEs were largely related to the underlying malignancy or the patient's comorbidities. Some of the SAEs appeared opioid-related (constipation). Again, unfortunately it is not possible to definitively distinguish between adverse events due to the around-the-clock opioid or FCNS. A total of 74 patients discontinued due to adverse events in Phase 2/3. Again, the discontinuations were due to progression of disease or common opioid-related adverse events (nausea, somnolence, vomiting).

Common Adverse Events and Adverse Events of Interest

Again, the assessment of safety for an oral transmucosal fentanyl citrate is highly confounded due to the fact that the study drug is an opioid being dosed on top of to an extended-release opioid in extremely ill patients. In addition, there is no control group for comparison. The Applicant presented the common adverse events in various tables, varying the data presented by part of study (titration vs. stable-dose), whether the Applicant considered them treatment-related, and by thresholds for incidences (≥1% and

≥2.5%). Table 7 shows the adverse events that occurred during titration at a rate ≥ 2.5% and Table 8 shows the most common adverse events in the maintenance phase.

Table 7: Adverse events that occurred during titration at a rate ≥ 2.5%

Preferred Term	n (%)				
	100 mcg (N=483)	200 mcg (N=380)	400 mcg (N=301)	800 mcg (N=161)	Total (N=516)
Subjects with ≥1 AE	124 (25.7)	58 (15.3)	56 (18.6)	29 (18.0)	213 (41.3)
Nausea	19 (3.9)	6 (1.6)	6 (2.0)	5 (3.1)	35 (6.8)
Vomiting	14 (2.9)	10 (2.6)	9 (3.0)	1 (0.6)	33 (6.4)
Dizziness	14 (2.9)	11 (2.9)	6 (2.0)	4 (2.5)	31 (6.0)
Constipation	17 (3.5)	3 (0.8)	3 (1.0)	0 (0.0)	22 (4.3)
Somnolence	8 (1.7)	8 (2.1)	7 (2.3)	1 (0.6)	22 (4.3)

Source: Integrated Summary of Safety, page 65/407 of pdf

Table 8: Most common adverse events that occurred during maintenance therapy

Preferred Term	n (%)				
	100 mcg (N=61)	200 mcg (N=68)	400 mcg (N=109)	800 mcg (N=108)	Total (N=346)
Subjects with ≥1 AE	43 (70.5)	41 (60.3)	75 (68.8)	78 (72.2)	237 (68.5)
Disease progression	11 (18.0)	6 (8.8)	8 (7.3)	19 (17.6)	44 (12.7)
Vomiting	8 (13.1)	5 (7.4)	9 (8.3)	12 (11.1)	34 (9.8)
Nausea	4 (6.6)	6 (8.8)	4 (3.7)	9 (8.3)	23 (6.6)
Pyrexia	3 (4.9)	5 (7.4)	8 (7.3)	6 (5.6)	22 (6.4)
Constipation	6 (9.8)	1 (1.5)	8 (7.3)	5 (4.6)	20 (5.8)

Source: Integrated Summary of Safety, page 68/407 of pdf

The common adverse events were typical for an opioid being dosed in patients with advanced cancer. It is important to note that there was no dose-response for the common adverse events during titration (Table 7) which implies that the relatively coarse dose adjustment was tolerated by patients.

Nasal Safety:

Because of the route of administration, nasal cavity exams were required of the Applicant and nasal complaints are of interest. Briefly, the nose and adjacent structures were specifically examined by an otolaryngologist or specially trained physician throughout clinical development and patients were queried for complaints related to the nose.

Dr. Olmos-Lau notes that that aggregated Phase 1 data does show a high rate of adverse events (rhinnorhea, rhinitis, epistaxis) related to the nose. However, those statistics are driven by Study CP048/07, the allergic rhinitis study, where allergic symptoms were precipitated by deliberate exposure to ragweed and tree pollen.

In the Phase 2/3 studies, the rate of nasal adverse events was low as shown in Table 9, following.

Table 9: Nasal Adverse Events, Phase 2/3

Preferred Term	100 mcg	200 mcg	400 mcg	800 mcg	Total
N	**484**	**389**	**319**	**182**	**516**
Epistaxis	6 (1.2)	3 (0.8)	3 (0.9)	5(2.7)	15(2.9)
Intranasal hypoesthesia	1 (0.2)	1 (0.3)	0	0	2 (0.4)
Nasal Congestion	3 (0.6)	3 (0.8)	0	0	6 (1.2)
Nasal Discomfort	6 (1.2)	2 (0.5)	4 (1.3)	1 (0.5)	11(2.1)
Nasal Dryness	1 (0.2)	0	1 (0.3)	0	2 (0.4)
Nasal Mucosal Disorder	2 (0.4)	0	1 (0.3)	1 (0.5)	4 (0.8)
Nasal Turbinate Hypertrophy	0	0	1 (0.3)	0	1 (0.2)
Postnasal Drip	2 (0.4)	1 (0.3)	2 (0.6)	1 (0.5)	6 (1.2)
Rhinalgia	1 (0.2)	0	0	0	1 (0.2)
Rhinorrhea	5 (1.0)	2 (0.5)	1 (0.3)	5 (2.7)	11 (2.1)
Sneezing	1 (0.2)	0	0	1 (0.5)	2 (0.4)

Source: Extracted from Table 6-2.4.1, ISS Phase 2/3 Statistical Tables ("na-iss-3.pdf"), pages 1335-6

The rates of adverse events related to the nose were low. Reviewing the severity and whether they resolved indicates that the nasal adverse events were mild and self-limited. The objective nasal exam data are summarized in Table 10, following.

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Table 10: Nasal examinations at screening and end-of-treatment, Phase 3 studies

Parameter	Category	Screening (N=500) n (%)	End of Treatment (N=346) n (%)
Obstruction[a]	Absent	481 (96.2)	337 (97.4)
	Mild	17 (3.4)	8 (2.3)
	Moderate	2 (0.4)	1 (0.3)
	Severe	0 (0.0)	0 (0.0)
Inflammation[b]	Absent	485 (97.0)	332 (96.0)
	Mild	15 (3.0)	14 (4.0)
	Moderate	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Discharge present	None	466 (93.2)	334 (96.5)
	Mild	33 (6.6)	12 (3.5)
	Moderate	0 (0.0)	0 (0.0)
	Severe	1 (0.2)	0 (0.0)
Color of mucosa	Normal	465 (93.0)	330 (95.4)
	Pale	14 (2.8)	5 (1.4)
	Red	17 (3.4)	8 (2.3)
	Blue	0 (0.0)	0 (0.0)
	Other	4 (0.8)	3 (0.9)
Side most affected	Left	20 (4.0)	4 (1.2)
	Right	12 (2.4)	7 (2.0)
	Both equally	30 (6.0)	28 (8.1)
	N/A	438 (87.6)	307 (88.7)

N/A=not applicable
[a] Obstruction was recorded as: 0 = absent (No effect observed), 1 = mild (Mild mucosal thickening), 2 = moderate (Edema, narrowing of airways) or 3 = severe (Significant /severe obstruction).
[b] Inflammation was recorded as: 0 = absent (No effect observed), 1 = mild (Some crusting or blood staining), 2 = moderate (Marked crusting, fresh blood, pus or cyanotic mucosa) or 3 = severe (Septal perforation or mucosal ulceration).
Source: Integrated Summary of Safety, Table 11-2, page 112/407 of pdf

The objective findings appear to have improved at end-of-study compared to baseline. While it seems unlikely that FCNS improved the objective nasal examinations, the exams indicate that FCNS does not irritate the nose.

B. Safety issues related to the dosing device and disposal

Per the Agency's request, the Applicant sent us assembled and unassembled samples of the to-be-marketed product that were identical to the commercial product except they did not contain fentanyl; they contained vehicle.

Figure 3 shows the "child-resistant outer container," a white plastic jar that requires the operator to squeeze two tabs while turning the lid to open the container. The Applicant proposed to have patients store FCNS in this container between dosing.

Figure 3: "Child-resistant outer container"

Source: Figure 3.2.P.7.1-2, "container-closure-system," Module 3, page 3 of 13 of pdf

A photograph of the drug delivery device itself follows in Figure 4. The device consists of the (b) (4) spray mechanism that is screwed onto a glass bottle that contains the fentanyl-containing solution. The plastic nasal spay pump is attached to the glass bottle by a threaded mechanism, using an appropriate torque force. The plastic spray pump is not glued or crimped to the bottle and thus we were able to unscrew the spray pump from the bottle using moderate force with bare hands. Removing the plastic spray pump from the bottle allows unfettered access to the entire contents of the bottle.

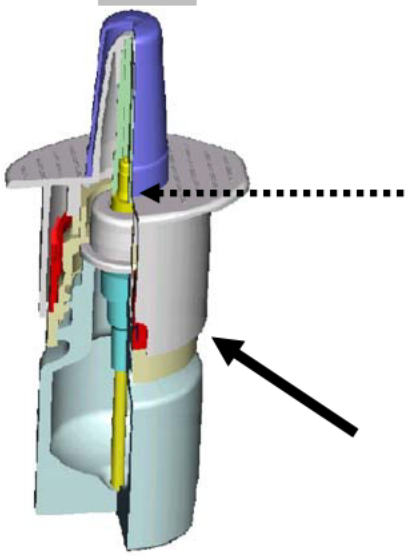
Figure 4: FCNS bottle and pump

Source: Figure 3.2.P.7.1-1, "container-closure-system," Module 3, page 2 of 13 of pdf

Figure 5, following, shows a cutaway drawing of the (b) (4) pump. When we examined the samples, we found that the device could easily be separated at the point indicated by the heavy arrow, exposing the tube (dotted arrow) that accesses the fentanyl. A certain amount of fluid leaking from the tube was observed.

Another issue that was identified is that the parts of the dose counting mechanism and the actual spray pump could be easily separated thus making the counter useless since the device could be reassembled with a different number on the counter although the locking mechanism would still allow the correct number of actuations (eight).

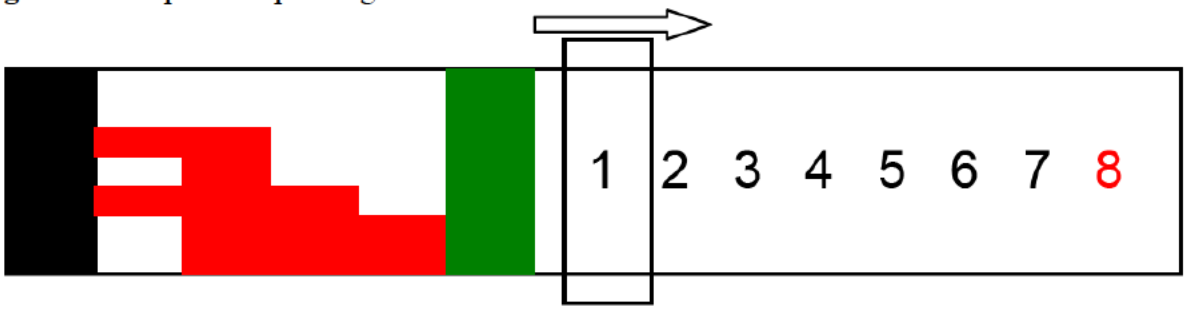
Figure 5: (b) (4) pump system



Source: Figure 3.2.P.7.3-1, "container-closure-system," Module 3, page 5 of 13 of pdf

Figure 6 shows the graphics of the dose counter. Each actuation of the spray device is supposed to move the counter by (presumably) ~25 degrees (1/14 of the circumference). Thus, four actuations will move through the red priming zone and each actuation beyond four will move the counter in an ascending fashion until the device locks out at Spray 8.

Figure 6: Graphics of priming indicator and dose-counter



Source: "container-closure-system," Module 3, page 6 of 13 of pdf

We actuated intact devices through the primes and doses. The phenylethyl alcohol (b) (4) (b) (4) results in a characteristic smell when the product is sprayed. In addition,

when the device is operated correctly, there is a visible plume that emits with a hissing sound and an audible click with each actuation.

Dr. Olmos-Lau described eleven patients being treated with PecFent who believed that the device either failed to deliver any dose or failed to deliver a full dose. Because of this perception, some patients immediately redosed and one patient suffered a serious adverse event as a consequence. Having seen how the devices work and smelled the product, I believe that adequate patient training and education (to properly actuate the device, to trust the click and counter, and not to redose within two hours) should adequately address the potential for accidental overdose due to confusion about whether the device actuated or not.

While there was a visible plume and an audible click with each actuation, we found that by carefully modulating the force of the actuation, the device could spray without advancing the counter (undercounting). Thus, it is possible for household contacts to use the device undetected by the patient or caretaker.

As noted in Section 2 of this review, the Applicant has been advised on multiple occasions to address the amount of residual remaining in the device after 8 actuations. The Applicant has attempted to optimize the bottle design with a U-shaped cavity to minimize the residual fentanyl solution. According to the Applicant, a fill volume of (b) (4) is optimal to ensure consistent delivery of the desired delivered volume of 100 mcL with a minimal residual volume in the bottle. More than (b) (4) remain in the bottle after full delivery as shown below. In studies of the device, the Applicant found that (b) (4) was recovered.

Activity	Volume dispensed (mL)	Volume remaining (mL)
Full new bottle	(b) (4)	(b) (4)
Priming		
Eight x 100 mcL sprays		

After complete use, each device contains approximately (b) (4) of fentanyl [for the high concentration (4 mg/mL)] solution. Since some patients might use more than one device per day (one device contains as few as 4 doses), a substantial amount of fentanyl could be in the garbage of these patients.

The Applicant proposed to dispose of the fentanyl lost due to priming and any unneeded sprays left in the bottle by (b) (4). This is unacceptable; the chance of transfer of fentanyl to the patient or household contacts is too high. We notified the Applicant of this inadequacy in a 24 March 2010 Discipline Review Letter.

C. Risk Mitigation and Evaluation Strategy (REMS)

In the initial submission of this NDA (received 30 August 2009), the Applicant proposed a REMS comprised of:

- Medication Guide
- Communication Plan
    - Healthcare Provider and Pharmacist Letters at launch
    - Website the provides education and facilitates enrollment into the REMS
    - Safety Message Campaign
- Elements to Assure Safe Use
    - Certification of prescribers
    - Certification of pharmacies (using community pharmacies)
    - Patient registration
    - Documentation of Safe Use Conditions. The pharmacist is to verify
        - Prescriber is enrolled.
        - Patient is enrolled.
        - Pharmacy is enrolled.
        - Pharmacist documents dispensing of MedGuide.
        - Pharmacist documents commitment to provide counseling to patients.
- Implementation System
    - Maintain database
    - Monitor prescription data
    - Identify and intervene to address adverse events
- Timetable for assessments (every six months for the first year, then annually)

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology sent information requests on two occasions and two teleconferences were held with the Applicant. While DRISK has not finalized their review at this time, preliminarily, DRISK has identified two key deficiencies in the proposed REMS: 1. There (b) (4) 2. There is no assurance that patients will be counseled on safe use.

At the current time, the final requirements for REMS for fentanyl products for breakthrough cancer pain are still under consideration. However, at this time, it appears that the two deficiencies will be made requirements for these products.

The review of clinical safety showed that, in the clinical development program, FCNS appeared to have a safety profile typical for this class of drug. Specific to this particular product, we saw no safety signals related to the intranasal route of administration nor did the relatively coarse dose adjustment pose any safety concerns.

However, when all of the safety issues are considered, the drug poses substantial safety risks listed below.

1. The (b) (4) spray mechanism readily separates from the glass bottle allowing free access to the fentanyl-containing solution.
2. The top of the spray mechanism separates from the bottom of the mechanism permitting free access to the tube that accesses the solution.

3. The tube accessing the solution appears to leak when the top is removed.
4. Even if the drug delivery system is properly primed and used, between (b) (4) of fentanyl remains left in the device which is to be thrown into the garbage. Patients could use as much as one bottle per day if used per the labeled instructions (four doses/day maximum).
5. When the top is replaced, it can be indexed at various positions along the dose counter rendering the dose counter useless.
6. Partial sprays can be obtained without the counter moving.
7. The proposed disposal of drug from priming or that from partially used bottles (b) (4) (b) (4)) poses excessive risk to household contacts, particularly children.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting held for FCNS.

10. Pediatrics

The Applicant requested a waiver for the Pediatric Research Equity Act for patients (b) (4) years and below for several reasons including concerns about the dose, practicalities of dosing a young patient intranasally, and, more specifically, because the Applicant claimed that the (b) (4). I unofficially consulted the Division of Pulmonary, Allergy, and Rheumatology (DPARP) products who did not agree with the last reason. DPARP requires pediatric studies of intranasal products down to the age of 6 months. In addition to the Applicant's misperception about the requirement to provide an age-appropriate formulation for younger age strata, we do not accept the Applicant's request for (b) (4).

In line with the other "fentanyl for breakthrough cancer pain" products, the ages of birth to 2 years, 11 months may be waived because the numbers of patients available for study are too small. Because the efficacy of opioids may be extrapolated from efficacy in adults, efficacy will not have to be demonstrated in pediatric patients age 3-16 years. However, the Applicant will have to complete a safety and pharmacokinetic study to inform dosing. At the Pediatric Research Committee meeting discussing this NDA, the committee recommended that open-label safety data be collected for a duration of 4-weeks in 30 subjects to adequately address the potential for local irritation.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations (DSI) inspected two sites, both of whom participated in Study 43. While DSI found the data to be acceptable overall, they recommended excluding data from a total of 4 patients because of a lack of documentation of concomitant medications and it was unclear how many doses of study drug one patient administered. Because of the ruggedness of the results of this study, I do not think reanalysis of the data, excluding those patients, will change the conclusion.

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted. The proposed tradenames, (b) (4)" were found to be unacceptable. DMEPA had a number of comments regarding the instructions for use that will be addressed in the labeling meetings and negotiations.

12. Labeling

From the clinical trial data, this product does not appear substantially different from the other fentanyl products for breakthrough cancer pain. Thus, for the most part, labeling should parallel those products, where applicable. In addition to recommendations from other disciplines, key points to be emphasized in labeling include:

1. This product has high bioavailability compared to the approved oral transmucosal fentanyl products and must always be titrated *de novo*. (b) (4)
2. The product must be used exactly as labeled, particularly the proper actuation of the device and the dose-finding procedures.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Complete Response.

- Risk Benefit Assessment

  This risks of this product outweigh the benefits.

  The Applicant has submitted substantial evidence of efficacy when FCNS is compared to placebo. The Applicant has not demonstrated that the drug has any advantages compared to other therapies.

  The Applicant has developed a woefully inadequate drug delivery device. Even if the product is used properly, as much as (b) (4) of fentanyl remain in a used device. Given the public health problem of prescription opioid abuse, this is unconscionable. Even worse than the issue of the residual, is the fact that the spray mechanism readily separates from the bottle which gives access to the entire contents, as much as (b) (4) of fentanyl.

  There are myriad of other deficiencies related to the device itself, REMS deficiencies, drug disposal deficiencies, and CMC and microbiology deficiencies that I summarize at the end of this section.

- Recommendation for Postmarketing Risk Management Activities

  I recommend against approval; consideration of postmarketing risk management activities is premature.

- Recommendation for other Postmarketing Study Commitments

  I recommend against approval; consideration of postmarketing study commitments is premature.

- Recommended Comments to Applicant

  The deficiencies include:

  1. The container-closure is inadequate to mitigate the risks of this product.
     a. The (b) (4) spray mechanism can be removed from the glass bottle with moderate effort and no tools which permits unfettered access to the fentanyl solution.
     b. Even if the drug product is correctly used, as much as (b) (4) of fentanyl remains in the device after all primes and actuations.
     c. The top of the spray mechanism is easily removed from the bottom of the mechanism, giving access to the tube that accesses the fentanyl solution.
     d. When the top is separated, solution leaks from the tube.
     e. Then the top is replaced, it can be indexed at various positions along the dose counter. Thus, the patient may lose count of sprays.
     f. With care, it is possible to actuate a dose without causing the dose counter to advance. Thus, surreptitious use of the product is possible.
  2. The proposed method of disposal for the priming sprays and unwanted extra sprays (b) (4) does not adequately manage the risks to household contacts, particularly children.
  3. The REMS lacks (b) (4)
  4. Submit an assay for detecting *Burkholderia cepacia* in the drug product, and include absence *of Burkholderia cepacia* in the drug product specifications.
  5. Other deficiencies per the CMC team.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

ROBERT B SHIBUYA
04/30/2010

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	NDA 22-569
Priority or Standard	Standard
Submit Date(s)	August 30, 2009
Received Date(s)	August 31, 2009
PDUFA Goal Date	June 30, 2010
Division / Office	Division of Anesthesia and Analgesia Products
Reviewer Name(s)	Nick Olmos-Lau MD
Review Completion Date	April 9, 2010
Established Name	Fentanyl Citrate Nasal Spray
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Opioid Analgesic
Applicant	Archimides Development Ltd
Formulation(s)	Nasal spray solution
Dosing Regimen	PRN not to exceed (b) (4) doses per 24 hours, and not less than 2 hours apart
Indication(s)	Breakthrough cancer pain
Intended Population(s)	Opioid-tolerant patients

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This review is limited to a review of the safety from the entire clinical development program and the Risk Evaluation and Mitigation Strategies (REMS). Dr. Luke Yip has completed a review covering the efficacy of this product and the administrative issues.

From the safety standpoint, I recommend a Complete Response action for Fentanyl Citrate Nasal Spray (FCNS or PecFent) for the indication of "management of breakthrough cancer pain (BTCP) in patients who are tolerant and are already receiving opioid therapy."

Per Dr. Yip's review, substantial evidence of efficacy was provided by the Applicant in the form of an adequate and well- controlled study in patients with BTCP. My review of the safety data did not reveal any unexpected adverse events that could be attributed to the study drug. However, the Applicant has not provided adequate measures to protect public safety. These issues pertain to the disposal of significant doses of unused residual opioid and the use of a container/closure system that is not adequately secure.

As a 505 (b)(2) application the findings rest on the Agency's previous findings of safety and efficacy of Actiq (oral transmucosal fentanyl citrate) which was approved for the same indication in 1998.

Other concerns regarding PecFent are applicable as well to other fentanyl products, used via transdermal and transmucosal routes. Since these products are not bioequivalent or replaceable on microgram basis, it is important that prescribers and patients understand the differences between products. Substitution errors may occur, as they have with the use of Fentora and Actiq. Intense surveillance and prescriber/patient education will be necessary, in order to avoid such medication errors with PecFent.

1.2 Risk Benefit Assessment

The efficacy of PecFent was demonstrated in a single adequate and well-controlled study. Please refer to Dr. Yip's review for details. The review of safety for this product is highly confounded, as described in Section 7.1 of this review. However, given those limitations, the adverse event profile of PecFent appears to be typical for this class. The drug did not appear to adversely affect the nasal cavity, either by objective or subjective measures.

So, from the perspective of the efficacy and safety observed in the clinical development program, the drug could be approved. Unfortunately, the Applicant has failed to address certain risk management issues that the Agency has raised during development, specifically the disposal of fentanyl from priming and unneeded solution as well as the amount of residual after all of the sprays are actuated.

Particularly given that the Applicant has not shown that this product has particular attributes that the three similar approved products lack, these risk management deficiencies preclude approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant submitted a Risk Evaluation and Mitigation Strategy (REMS). This plan consists of a Medication Guide, Communications Plan, Elements To Assure Safe Use (ETASU), and an Implementation Plan. At the time of finalization of this review, the final REMS is under review by the Agency. The Applicant recently reported that it has tested it in a pilot study. At this time, the REMS appears to be inadequate due to (b) (4)

1.4 Recommendations for Postmarket Requirements and Commitments

I do not recommend Approval; therefore, I have no specific recommendations for post-marketing requirements. However, because this product uses a new route of administration, the Applicant will have to meet the requirements of the Pediatric Research Equity Act.

2 Introduction and Regulatory Background

2.1 Product Information

Please see Dr. Yip's review for information on this heading.

2.2 Tables of Currently Available Treatments for Proposed Indications

Please see Dr. Yip's review for information on this heading.

2.3 Availability of Proposed Active Ingredient in the United States

Please see Dr. Yip's review for information on this heading.

2.4 Important Safety Issues with Consideration to Related Drugs

The adverse event profile of opioids is well established and includes: sedation, nausea, vomiting, pruritus, hypotension, and constipation. The most serious AEs associated with all opioids include respiratory depression, potentially leading to apnea or respiratory arrest. This may be accompanied as well by hypotension, and shock. Abuse, tolerance, and physical dependence are well recognized risks in this class of drugs.

Recognizing the high potential for misuse, abuse, and diversion of opioids, the Agency requires a REMS program as part of the approval package for many high-potency opioids.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Please refer to Dr. Yip's review for information regarding presubmission regulatory history.

2.6 Other Relevant Background Information

Please refer to Dr. Yip's review for further background information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was adequate for my review of safety.

3.2 Compliance with Good Clinical Practices

Please see Dr. Yip's review for this information.

3.3 Financial Disclosures

For information regarding certification, financial disclosures and arrangements with clinical investigators please consult Dr. Yip's review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to Dr. Yip's review for information on this section

4.2 Clinical Microbiology

Please refer to Dr. Yip's review for information on this section

4.3 Preclinical Pharmacology/Toxicology

For details on this section please refer to Dr. Yip's review.

4.4 Clinical Pharmacology

For details on this section please refer to Dr. Yip's review.

4.4.1 Mechanism of Action

For details on this section please refer to Dr. Yip's review.

4.4.2 Pharmacodynamics

For details on this section please refer to Dr. Yip's review.

4.4.3 Pharmacokinetics

For details on this section please refer to Dr. Yip's review.

5 Sources of Clinical Data

For details on this section please refer to Dr. Yip's review.

5.1 Tables of Studies/Clinical Trials

Please see Section 7 of this review.

5.2 Review Strategy

I reviewed the major safety findings. I reviewed common adverse event data as pooled by the Applicant (Phase 1, healthy volunteer data comprised one pool; Phase 2/3 data from patients comprised the other pool). I specifically addressed adverse events related to the nose as well as device malfunctions.

5.3 Discussion of Individual Studies/Clinical Trials

For purposes of the safety review each study analyzed is described individually in the safety review section.

6 Review of Efficacy

Efficacy Summary

Please see Dr. Yip's review for this information.

6.1 Indication

Please see Dr. Yip's review for this information.

6.1.1 Methods

Please see Dr. Yip's review for this information.

6.1.2 Demographics

Please see Dr. Yip's review for this information.

6.1.3 Subject Disposition

Please see Dr. Yip's review for this information.

6.1.4 Analysis of Primary Endpoint(s)

Please see Dr. Yip's review for this information.

6.1.5 Analysis of Secondary Endpoints(s)

Please see Dr. Yip's review for this information.

6.1.6 Other Endpoints

Please see Dr. Yip's review for this information.

6.1.7 Subpopulations

Please see Dr. Yip's review for this information.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please see Dr. Yip's review for this information.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please see Dr. Yip's review for this information.

6.1.10 Additional Efficacy Issues/Analyses

Please see Dr. Yip's review for this information.

7 Review of Safety

Safety Summary

The safety database for PecFent consists of 91 healthy volunteers and 523 opioid-tolerant patients with breakthrough cancer pain. As described below, the review of safety is highly confounded for a product of this type. However, my review of safety did not suggest that the adverse event profile was inconsistent with this class of drug in the patient population studied.

7.1 Methods

Over the period of time this drug has been developed, the Applicant has used a variety of names including "Fentanyl Citrate Nasal Spray" (FCNS), (b) (4)" "PecFent" and, most recently, (b) (4) This review will use the name "PecFent" to reference the product. Data from four Phase 1 studies, one Phase 2 study, and three Phase 3 studies was used to evaluate safety.

The assessment of safety for PecFent is problematic as is the safety of any of the drugs in this class.

1. The patient population that provided almost all of the safety data (patients with advanced cancer) was very ill, primarily due to the malignancy and its treatment but many had other comorbid conditions.
2. Patients were on a wide variety of concomitant medications including treatments specific for their malignancy, other comorbid conditions, and, most importantly, around-the-clock opioids. This makes distinguishing adverse events due to PecFent very difficult because fentanyl, an opioid, has no unique adverse events to distinguish PecFent-related adverse events from those of the around-the-clock opioid.
3. Due to the design of the controlled trial (a 10-period crossover conducted in as few as 5 days), for all intents and purposes, there is no control group for comparison. If the exact timing of the onset of the adverse event were known, it may be possible to attribute some adverse events to OVF. However, those detailed data are generally not available.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A total of eight studies contributed to the safety database. Four studies were conducted in healthy volunteers and four were conducted in cancer patients. Table 1 shows the numbers of patients enrolled in the different studies. Because some Phase 3 studies used some patients that rolled over from other studies, the sum of column 3 exceeds the total database (there are duplicate patients).

Table 1: Clinical Studies Contributing to the PecFent safety Database

Type of Study	Phase (# studies)	Total Number (Treated with PecFent)
Pharmacology PK/Special	Phase 1 (4)	91
Open-label	Phase 2 (1)	23
Randomized DB*	Phase 3 (2)	219
Randomized OL** 16 weeks	Phase 3 (1)	364
Prolonged Extension Phase	Phase 3 (1)	130

* Double-blind
** Open-label

Four Phase 1 studies contributed to the safety data base. Four different formulations were used in one of the Phase 1 studies. Based on the findings of this study, the pectin-fentanyl formulation was selected to continue in development. There were 91

subjects receiving one or more doses of PecFent during Phase 1 studies. Table 2 Summarizes the clinical pharmacology studies.

Table 2: Summary of the four Phase 1 studies (from Applicant's table 6-1) Source: Integrated Analysis of Safety: page 16/407, pdf file

CP037/02	Phase 1, single-center, randomized, 4-way crossover study. Subjects received each of the following: nasal fentanyl-chitosan 100 mcg fentanyl, administered into one nostril; nasal fentanyl-pectin 100 mcg fentanyl administered into one nostril; nasal fentanyl-chitosan/poloxamer 188 solution 100 mcg fentanyl administered into one nostril; Actiq 200 mcg, as fentanyl citrate administered orally.
CP042/05	Phase 1, single-center, dose-proportionality, 5-way crossover study. Subjects received each of the following: 100 mcg FNS comprising one 100 mcL administered into one nostril; 200 mcg FNS comprising two 100 mcL administered into each nostril; 400 mcg FNS comprising one 100 mcL administered into one nostril; 800 mcg FNS comprising two 100 mcL administered into each nostril; Actiq 200 mcg administered orally.
CP047/07	Phase 1, single-center, dose-proportionality, 5-way crossover study. Subjects received each of the following doses of FNS: a single dose of 100 mcg; 2 doses of 100 mcg given 4 hours apart; 2 doses of 100 mcg given 2 hours apart; 2 doses of 10 mcg given 1 hour apart; 8 doses of 100 mcg given consecutively.
CP048/07	Phase 1, single-center, randomized, 3-way crossover study for subjects with seasonal allergic rhinitis (SAR) in symptomatic, symptomatic but treated (with oxymetazoline), and asymptomatic states. Subjects were dosed with single doses of FNS 100 mcg into a single nostril on 3 occasions separated by at least 14 days.

The Phase 2/3 pooled dataset includes data from one Phase 2 study, CP041/04, which included 23 subjects, and three Phase 3 studies with 500 subjects receiving treatment with PecFent. Of these 523 total subjects, 516 subjects received at least one dose of the 100, 200, 400, or 800 mcg doses to-be-marketed. Seven subjects received a dose less than 100 mcg. There were 506 subjects dosed with PecFent who kept an e-diary record.

Sample sizes encountered during Safety Analysis

During the course of the review it became apparent that the Applicant calculates the total numbers of patients in slightly different ways:

- 523=Total number of subjects that were treated with any dose of PecFent
- 516=Total number of subjects that were treated at least with one of the to-be-marketed doses (100, 200, 400, or 800 mcg) of PecFent (excludes 7 subjects who received <100 mcg PecFent)
- 506=Total number of subjects who were treated with at least one dose of PecFent that had an eDiary record. This number excludes 3 subjects from CP043, 3 Subjects from CP044, and 4 subjects from CP045 who lack eDiary entries.
- 500=Total number of subjects who were treated with any dose of PecFent in the Phase 3 studies alone. Excludes 23 subjects from Phase 2 studies during Study CP041 that had different assessments.

Study CP041/04 was a Phase 2, open-label multicenter inpatient study to assess the safety, efficacy, and tolerabililty of PecFent for breakthrough pain in cancer patients. There were 23 subjects enrolled in this study. During the first part of this study, subjects were titrated to acceptable levels of analgesia with increasing doses of 25, 50, 100, 200, 400 or 800 mcg. Once identified, the optimal dose was continued during the second part of the study which consisted of 4 different episodes of breakthrough pain (BTCP). There were 8 deaths in this study. The deaths were reported after the conclusion of the study.

Study CP043/06 (Phase 3) was a multicenter, randomized, placebo-controlled, double-blind, 10-period crossover study to assess the efficacy of PecFent in the treatment of BTCP in opioid tolerant subjects on around-the-clock opioid treatment. The study had 4 phases: screening, open-label dose titration starting at 100 mcg increased as needed up to 800 mcg until an effective dose was determined. This was followed by a 3-21 day double-blind phase, using the dose to treat 10 episodes of breakthrough pain. This was followed by an open-label treatment period. Requirements for participation included diagnosed malignancy, and 1-4 episodes of BTCP per day, while taking daily 60 mg of oral morphine daily or the equivalent. Subjects were allowed to treat up to a maximum of 4 episodes daily at 4 hour intervals. The safety evaluation consisted of adverse events, physical examination, vital signs, laboratory tests, nasal symptomatology, and nasal examination. A total of 113 patients received at least one dose. Please see Dr. Yip's review for details about this study.

Study CP044/06 was also a Phase 3, multicenter, randomized, active-controlled, double-blind, double dummy treatment phase, 2-period crossover study to assess the efficacy of efficacy of PecFent compared to immediate-release morphine sulfate (IRMS) in BTCP in opioid experienced subjects. There were 106 subjects receiving at least one dose of PecFent in the open phase of the study. Please see Dr. Yip's review for details about this study.

Study CP045/06 was another Phase 3, open-label, safety study designed to determine the long term safety and tolerability on PecFent in the treatment of BTCP in opioid-tolerant subjects. To be eligible for this study, subjects had to have completed either study CP043 or CP044 and have persistent episodes of BTCP (1-4 episodes daily) controlled with PecFent or they could be newly enrolled subjects with malignancies on around-the-clock opioid therapy and BTCP pain. A maximum of 4 daily episodes of BTCP were allowed to be treated. At the end of the study visit subjects were permitted to remain on the medication and proceed to the Extension Period of the study.

Safety and tolerability were evaluated by AEs, evaluation and examination of the nose, physical examination, vital signs and laboratory tests. For the main portion of the study (16-weeks), there were 281 newly enrolled (not rolled over) subjects receiving at least one dose of study drug. A total of 122 patients rolled over from studies CP043 and

CP044, resulting in a grand total of 403 patients in the study. A total of 130 subjects continued into the extension phase of Study CP045.

The 120-day safety update was submitted by the applicant on December 9, 2009. At the time of the data lock for the results submission, the extension part of Study CP045/06 (beyond the 16-weeks planned) was still ongoing and was not reported in the Integrated Summary of Safety. Subjects in the extension phase did not use diaries so the data available are less detailed for the extension part of this study. For the purposes of the safety update, October 15, 2009 was the cut-off date.

Subjects receiving at least one dose of PecFent were included in the safety analysis. In the phase 1 studies subjects who received naltrexone, fentanyl, or oxymetazoline were included.

All quantitative safety variables were summarized and analyzed by number (N), obtaining mean, and standard deviation, standard error, median, minimum, and maximum. Categorical variables were summarized by frequency, and percentages given by category.

Phase 1 data sets contain safety results presented overall and not separated by dose group. Phase 2-3 studies were presented by subgroups entering the dose titration, double-blind, and open-label phases. Analysis of events is confounded by the changes in dose during titration and open-label phases. To attempt to overcome this, subgroup analysis was also provided in the double-blind phase and open-label effective dose.

The dose-maintained population included subjects that maintained the dose in the double-blind or open-label treatment phases that were rolled over to study CP045 as well as those who were newly entered to the CP045 study. No dose change was permitted in the double-blind treatment segment. Those who did were included in the Titrated dose-changed population.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA version 11.0. The appropriateness of the Applicant's coding was evaluated by comparing the preferred terms to the verbatim terms recorded by investigators. The coding was reasonably accurate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant pooled the Phase 1 and Phase 2/3 safety data separately. This was acceptable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the Integrated Summary of Safety for the initial NDA submission, there were a total of 614 subjects exposed to PecFent in all studies. A total of 91 subjects were healthy volunteers in Phase 1 studies who received at least one dose of PecFent and 523 patients were patients with cancer in Phase 2/3 studies.

Exposure during Phase 2/3 Studies

Table 3, summarizes the exposure to PecFent by dose and duration.

Table 3: Duration of Exposure to PecFent by Dose (Applicant's Table 7-3). Source Integrated Summary of Safety page: 46/407, pdf file

	Number of Subjects Exposed at Any Dose within Specified Duration Range				
All Subjects[a]	**1 - 7 days**	**8 - 14 days**	**15 - 28 days**	**29 - 89 days**	**≥90 days**
Total (N=506)	123	41	57	132	153
	Number (%) of Subjects Exposed at Specific Dose within Duration Range (Subjects could be exposed to more than 1 dose and/or duration)				
100 mcg (N=460)	394 (85.7)	9 (2.0)	14 (3.0)	23 (5.0)	20 (4.3)
200 mcg (N=387)	294 (76.0)	11 (2.8)	22 (5.7)	39 (10.1)	21 (5.4)
400 mcg (N=318)	192 (60.4)	10 (3.1)	22 (6.9)	56 (17.6)	38 (11.9)
800 mcg (N=182)	60 (33.0)	7 (3.8)	22 (12.1)	44 (24.2)	49 (26.9)

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

Source: Table 1-2.14 ISS, Module 5.3.5.3.2

Table 3, shows that a total of 153 subjects were exposed to PecFent ≥ 90 days, and that a substantial proportion of patients (27%), were treated with the highest dose for more than three months.

Demographics of the Study Population

Phase 1 studies

The demographic data for the Phase 1 studies show that the Phase 1 study volunteers were healthy subjects, the majority of which were Caucasian (79%). The mean age was 37.1 years old (19-64 years) and equally divided between male and female. The average BMI was 25.3 kg/m^2. The demographics of patients enrolled in Phase 1 studies, is shown in Table 4 (below).

Table 4: Demographics of Phase 1 Studies (Applicant's Table 2.7.4-9) Source: Integrated Summary of Safety Report, page: 52/407, pdf file

	CP037 (N=18)	CP042 (N=17)	CP047 (N=13)	CP048 (N=52)	Total (N=100)
Age (years)					
Mean (SD)	29.8 (9.38)	37.5 (16.10)	31.8 (14.89)	40.8 (11.49)	37.1 (13.14)
Median	27.5	34.0	25.0	39.5	35.0
Min - Max	20 - 49	19 - 64	20 - 62	22 - 63	19 - 64
Gender, N (%)					
Male	5 (27.8)	8 (47.1)	10 (76.9)	27 (51.9)	50 (50.0)
Female	13 (72.2)	9 (52.9)	3 (23.1)	25 (48.1)	50 (50.0)
Race, N (%)					
White	17 (94.4)	17 (100.0)	11 (84.6)	34 (65.4)	79 (79.0)
Black	0 (0.0)	0 (0.0)	1 (7.7)	12 (23.1)	13 (13.0)
Southeast Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.0)
Other	1 (5.6)	0 (0.0)	1 (7.7)	5 (9.6)	7 (7.0)
BMI (kg/m^2)					
Mean (SD)	23.02 (2.670)	23.94 (2.527)	25.69 (2.323)	26.43 (2.017)	25.30 (2.639)
Median	23.25	23.60	26.00	26.70	25.50
Min - Max	19.4 - 27.5	18.2 - 28.1	22.0 - 29.0	21.6 - 29.4	18.2 - 29.4

Source: Table 2-1.1 ISS, Module 5.3.5.3.2

The most commonly used concomitant medications by the subjects in Phase 1 studies, were those expected in a healthy population. There was 24% use of concomitant prior medications, such as acetaminophen (13%), ibuprofen (5%), oral contraceptives (12%) and, anti-acne preparations (3%).

Demographics of Phase 2/3 studies

A total of 523 patients received any dose of PecFent in Phase 2 or 3.

Table 5 (below), shows the demographics of the patients enrolled in Phase 2/3 studies. The ages ranged from 18-86 years, with a mean age of 54.2 years. The majority of the population was Caucasian (55.1%), with a balanced male/female ratio.

Table 5: Demographics of patients in PecFent Phase 2/3 Studies (From Applicant's table 2.7.4-11) Source: Summary of Clinical Safety: page 30 /102, pdf file

	CP041 (N=23)	CP043 (N=113)	CP044 (N=106)	Newly Enrolled CP045 (N=281)	Total (N=523)
Age (years)					
Mean (SD)	56.7 (14.25)	53.8 (11.60)	55.9 (12.29)	53.6 (12.36)	54.2 (12.28)
Min - Max	24 - 84	21 - 86	18 - 82	23 - 84	18 - 86
Age distribution, N (%)					
≤60 years	13 (56.5)	82 (72.6)	69 (65.1)	211 (75.1)	375 (71.7)
>60 years	10 (43.5)	31 (27.4)	37 (34.9)	70 (24.9)	148 (28.3)
Gender, N (%)					
Female	12 (52.2)	53 (46.9)	49 (46.2)	135 (48.0)	249 (47.6)
Male	11 (47.8)	60 (53.1)	57 (53.8)	146 (52.0)	274 (52.4)
Race, N (%)					
Caucasian	20 (87.0)	77 (68.1)	52 (49.1)	139 (49.5)	288 (55.1)
Black	0 (0.0)	13 (11.5)	1 (0.9)	10 (3.6)	24 (4.6)
Chinese/Japanese Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)
Southeast Asian	0 (0.0)	2 (1.8)	0 (0.0)	3 (1.1)	5 (1.0)
Other[a]	3 (13.0)	21 (18.6)	53 (50.0)	128 (45.6)	205 (39.2)

Phase 2/3 Enrollment by Area or Country:

The geographic location of the patients in Phase 2/3 studies was summarized by the Applicant as follows:

- US/Canada 216 (41.3%)
- India 154 (29.4%)
- Europe 106 (20.3%)
- Argentina/Costa Rica 47 (9%)

A large proportion (56%) of the patients had a high functioning Eastern Cooperative Oncology Group (ECOG) score. Most patients were not on chemotherapy (78.6%). Patients graded their BTCP pain as severe (79.8%) with a mean number of daily BTCP episodes of 2.8.

Opioid and other Concomitant Medications

All participating patients were required to take >60 mg of MS or the equivalent in order to qualify for enrollment. The following Table 6, documents the most common opioids used by location, during Phase 3 studies.

Table 6: Opioid Use by Location of Patients in Phase 3. Studies (Applicant's table 2.7.4-13). Source: Summary of Clinical Safety, page: 32/102, pdf file

	n (%)				
Generic Name	US/Canada (N=193)	Europe (N=106)	India (N=154)	Argentina/ Costa Rico (N=47)	Total (N=500)
Morphine sulfate	54 (28.0)	23 (21.7)	86 (55.8)	0 (0.0)	163 (32.6)
Fentanyl	79 (40.9)	58 (54.7)	10 (6.5)	5 (10.6)	152 (30.4)
Morphine	19 (9.8)	7 (6.6)	64 (41.6)	34 (72.3)	124 (24.8)
Oxycodone HCl	33 (17.1)	20 (18.9)	0 (0.0)	0 (0.0)	53 (10.6)
Methadone	35 (18.1)	3 (2.8)	0 (0.0)	9 (19.1)	47 (9.4)

Source: Table 3-2.1 ISS, Module 5.3.5.3.2

7.2.2 Explorations for Dose Response

The Applicant qualitatively explored dose response for the four to-be marketed doses of PecFent: 100, 200, 400, and 800 mcg. There was no dose response for adverse event rate overall nor was there dose effect for the most common adverse events as shown in Tables 7 and 8. The lack of dose response is not surprising; patients were individually titrated to an optimum dose.

Table 7: Summary of Adverse Events Reported by >2.5% of Subjects in any Dose Group During Dose Titration Period- Phase 2/3 Studies (Applicant's Table 14-1). Source: Integrated Summary of Safety Report, page 118/407, pdf file

Preferred Term	n (%)			
	100 mcg (N=483)	**200 mcg** (N=380)	**400 mcg** (N=301)	**800 mcg** (N=161)
Subjects with ≥1 AE	124 (25.7)	58 (15.3)	56 (18.6)	29 (18.0)
Nausea	19 (3.9)	6 (1.6)	6 (2.0)	5 (3.1)
Vomiting	14 (2.9)	10 (2.6)	9 (3.0)	1 (0.6)
Dizziness	14 (2.9)	11 (2.9)	6 (2.0)	4 (2.5)
Constipation	17 (3.5)	3 (0.8)	3 (1.0)	0 (0.0)

Source: Table 6-2.7.2

Table 8: Adverse Events in Double Blind Open-Label, Titration, and Dose Maintained Periods of Phase 2/3 Studies (From Applicant's Table 6-2.7.3) Source: ISS Phase 2/3 Statistical Tables: page 1473/27077, pdf file

Preferred Term	100 mcg N=61	200 mcg N=68	400 mcg N=109	800 mcg N=108	Total N=346
Number (%) of Subjects with at Least One AE	43 (70.5)	41 (60.3)	75 (68.8)	78 (72.2)	237 (68.5)
Disease Progression	11 (18.0)	6 (8.8)	8 (7.3)	19 (17.6)	44 (12.7)
Vomiting	8 (13.1)	5 (7.4)	9 (8.3)	12 (11.1)	34 (9.8)
Nausea	4 (6.6)	6 (8.8)	4 (3.7)	9 (8.3)	23 (6.6)
Pyrexia	3 (4.9)	5 (7.4)	8 (7.3)	6 (5.6)	22 (6.4)
Constipation	6 (9.8)	1 (1.5)	8 (7.3)	5 (4.6)	20 (5.8)
Diarrhoea	5 (8.2)	2 (2.9)	5 (4.6)	5 (4.6)	17 (4.9)
Dyspnoea	3 (4.9)	4 (5.9)	5 (4.6)	5 (4.6)	17 (4.9)
Oedema Peripheral	0 (0.0)	2 (2.9)	7 (6.4)	5 (4.6)	14 (4.0)
Fatigue	2 (3.3)	1 (1.5)	6 (5.5)	4 (3.7)	13 (3.8)
Pain	1 (1.6)	1 (1.5)	5 (4.6)	6 (5.6)	13 (3.8)
Dehydration	1 (1.6)	2 (2.9)	2 (1.8)	7 (6.5)	12 (3.5)
Somnolence	2 (3.3)	0 (0.0)	5 (4.6)	5 (4.6)	12 (3.5)
Asthenia	1 (1.6)	1 (1.5)	7 (6.4)	2 (1.9)	11 (3.2)

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal or in vitro testing performed.

7.2.4 Routine Clinical Testing

The routine clinical testing consisted of hematology, chemistry, and urinalysis. This testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Dr. Sheetal Agarwal's Clinical Pharmacology review for information regarding the metabolic, clearance and interactions of PecFent. The Applicant did not perform specific studies addressing of metabolism or excretion of fentanyl used via intranasal route.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Fentanyl is a potent, short acting analgesic with a well-known pharmacologic profile. As a pure opioid agonist, mediated through high affinity mu-opioid receptor activity, it binds to receptors in the brain, spinal cord, and smooth muscle. Fentanyl also interacts with central and peripheral vascular alpha-adrenergic and muscarinic receptors. The expected adverse events relate to CNS activity, and include sedation, dizziness, somnolence, and headache. In larger doses fentanyl can induce profound analgesia or anesthesia and unconsciousness, leading to respiratory depression and hypotension. Fentanyl has similar effects on gastrointestinal tract as other opioids and can cause nausea, vomiting, or constipation. Observed cardiovascular effects include hypotension, collapse and shock. Compared to other opioids such as meperidine or morphine sulfate, fentanyl seems to cause less histamine release, which is thought to be the cause of hypotension, tachycardia, pruritus, and erythema.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in Phase 1 studies. There were a total of 88 deaths recorded for all participants during Phase 2/3 studies.

Since patients enrolled in the PecFent trials had advanced cancer with breakthrough pain, a large number of fatalities were to be expected. Again, there were 88 deaths reported in the ISS. Given that the total number of patients who participated in all studies was 614, the death rate was 14%. This is not dissimilar from with the mortality rate observed in the Onsolis trials (21%) by Dr. Ellen Fields since the populations were similar and consisted of subjects in advanced stages of cancer with BTCP. A lower rate (7%) was observed in the Fentora trials by Dr. Robert Shibuya. This is most likely due to the fact that Fentora trials were conducted in a substantial number of patients with chronic non-cancer pain.

There were 2 deaths in Study CP041 (Subjects 003 and 008) who were receiving 50 mcg of PecFent. One subject in Study CP043 (391201) had a fatal adverse event associated with placebo. One subject in study CP044 (460306) had a fatal adverse event while on IRMS. One subject had a non-treatment emergent AE (urinary tract infection) in study CP045, and died following withdrawal from that study.
A summary of deaths by Phase of Studies is presented in Table 9:

Table 9: Summary of Deaths by Study Phase (Phase 2-3 Studies). Source: Integrated Summary of Safety Report: page 73/407, pdf file

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

a. Includes 1 subject (510501) with a non-treatment-emergent AE with fatal outcome.
b. Subject 390801 was withdrawn due to death during Study CP045 and also had an AE with fatal outcome reported in Study CP043 after completion of that study.
Source: Table 8-2.1.1

Individual Patient Death Summaries

All available information, including narratives, case report forms and data listings, was reviewed for each death. While it is important to reiterate the substantial confounds in the assessment of safety for this drug, none of the deaths could be conclusively related to the use of PecFent. Table A1, Appendix 9, has a listing of deaths due to malignancy and the timing of the last dose of PecFent (when available).

Because of the limited data collected regarding the exact time of dosing, assessing causality on the basis of the proximity of the time the drug was dosed and the time of death is difficult. There were eight patients that received study drug within 24 hours of their death. The exact relationship to time of last dose to time of death is not generally available. In the majority of cases, (47/88) subjects had their last dose >24-48 hours prior to death, making it extremely unlikely that PecFent directly caused their death. In 26/88 cases, the time of the last dose of study drug was not recorded. In 15/88 the subjects received a study drug dose within 24 hours. Those cases were carefully analyzed.

The narratives following represent cases where PecFent seemed more likely to have contributed to the death. In addition deaths were summarized in the tables included in the Appendix-Section 9.

In PecFent studies, the largest group (50) of deaths was due to malignancy progression. This subgroup includes death due to tissue destruction, expansion, or metastasis. For details please refer to Table AI in the Appendix.

There were 30 deaths due to complications related to the underlying malignancy such as sepsis, leukopenia, anemia, cytopenia, or immunosuppression secondary to chemotherapy, or organ failure. Please refer Table A2 in the Appendix for details.

The group of deaths due to complications due to the underlying malignancy can be subdivided into seven deaths due to cardio-respiratory arrest (not drug related), six deaths due to sepsis or infection as a terminal event, six deaths due to organ failure, three multi-organ failure, two renal failure, one cardiac failure, five deaths were due to hemorrhage (local or external, hemoptysis), four deaths due to CNS invasion with increased intracranial pressure, two (2) deaths due to shock (hypotension and unconsciousness), and one due to pulmonary embolism. Narratives are included and noted in the table.

There were eight deaths that were probably unrelated to the malignancy and were more likely due to an independent or coincidental process, such as a hemorrhagic stroke, MI (myocardial infarction) or pulmonary embolism. Please refer to Table A3 in the Appendix.

The following case narratives are described by subcategory and include:

- Deaths due to a cardiopulmonary process,
- Deaths due to disease progression (sepsis, metastasis, CNS invasion) and
- Other causes (myocardial infarction, hemorrhage, cardiogenic shock, intestinal obstruction)

Cardio-pulmonary deaths

Subject 704-570401 (Study CP045) was an 83 year-old white female with history of pancreatic cancer diagnosed in (b) (6). Other significant medical history included diabetes type II, hypertension, atherosclerosis, and hypercholesterolemia. In 1972 she had a hysterectomy and adnexectomy for ovarian cancer.

Her medications included MS ER100 mg daily, fentanyl citrate transmucosal 400 mcg daily for rescue in addition to ketorolac. She was also on a hydrochlorthiazide-valsartan compound, glybenclamide (glyburide)-metformin compound for diabetes, “Foglia,” digoxin, prednisone, lovastatin, ticlopidine, and lansoprazole.

She was participated in a previous PecFent controlled study on 2/10/2008 and screened for the OL study on 22 September, 2008. Her PE, vital signs, and nasal passages examinations were unremarkable. She described two severe BTCP episodes daily. Her PecFent dose was gradually adjusted to 400 mcg over the course of several weeks.

Several weeks prior to her demise she experienced increasing weakness, fatigue, weight loss, and anorexia. These symptoms were interpreted as indicative as reflective of cancer progression.

On (b) (6) (36 days after entering the study), she had a cardiopulmonary arrest which was the terminal event. The date and time of her last study-medication dose is unknown. The investigator concluded that the cardio-respiratory arrest was unrelated to the study drug.

This elderly woman with carcinoma of the pancreas and a previous history of ovarian cancer, and had significant risk factors for cardiovascular disease such as hypertension, diabetes, atherosclerosis, and hypercholesterolemia. The exact reason for the use of ticlopidine is unknown, though possibly as preventive agent for a cardiovascular or cerebrovascular event. She was also on digitalis for unclear reasons but most likely for a cardiac arrhythmia or heart failure.

Although the terminal event may have been a cardiac (MI or arrhythmia), the possibility of a pulmonary embolism secondary to a hypercoagulable state related to her neoplasm can't be excluded. The role of her carcinoma progression is uncertain but perhaps contributory.

Subject 704-570402 (Study CP045) was a 53 year-old white female with a diagnosis of maxillary cancer, initially resected in 1978. No other medical history was described She suffered a relapse of her maxillary cancer in (b) (6) with metastasis to the soft palate requiring further resection in (b) (6). Her medications were extended-release morphine sulfate, 20-60 mg BID, midazolam, acetaminophen, methylprednisolone, and ranitidine and immediate-release morphine sulfate, 10 mg prn. She was screened for this study on October 18, 2008. Her PecFent dose was optimized at 400 mcg.

On (b) (6), she was seen in the Emergency Department (ED) for difficulty expectorating. There were no signs of respiratory failure at that time.

On (b) (6), she was diagnosed with severe pneumonia and required a prolonged hospitalization. The pneumonia resolved at the time of her hospital discharge on (b) (6). She had several courses of antibiotic and bronchodilatory therapy including: piperacillin, ciprofloxacillin, and tazobactam. She was also given ambroxol, and beclomethasone (aerosol).

Her clinical status continued to deteriorate with the development of weight loss and ptosis. She required oxygen supplementation and increasing analgesics.

Her last dose of PecFent was on (b) (6), 5 days prior to her demise. While in hospice care, she had another episode of respiratory distress on January 16, 2009, for which she was not hospitalized, although a recurrent episode of pneumonitis was suspected. She died on (b) (6). The final diagnosis was pulmonary edema due to progressive disease.

The investigator considered the events of pneumonitis and sputum retention not related to the study drug, and it would be difficult to determine to what extent her respiratory depression might have contributed to by her inability to expectorate properly. It appears unlikely that the cause of death was drug related, but more likely due to disease progression, and perhaps terminal metastatic disease involving the lungs.

Subject 704-570403 (Study CP045) was a 55 year-old Southeast Asian male with a diagnosis of lung adenocarcinoma established in (b) (6). He had a history of lung tuberculosis since 2005, hypertension since 2007, and hepatitis B. He had a thoracentesis and a liver biopsy in (b) (6) that documented liver and bone metastasis. He was treated with radiotherapy. His medications included: oxycodone 40 mg/day and morphine SR 10 mg prn, furosemide, losartan, esomeprazole, enoxaparin, “orbasone,” meropenem (antibiotic) and supplementary O2.

At the time of admission to the trial in October, 2008, he was found to have diminished breath sounds in the right chest and an enlarged liver. He described 3 moderate to severe episodes of BTCP daily. The dose of PecFen was adjusted to 400 mcg daily. Fatigue and dyspnea were noted on November 10. He expired on (b) (6) a cardio-respiratory arrest was noted as the final event apparently while on PecFen 400 mcg q 4hs prn. The time of the last dose was (b) (6) prior to his demise.

The investigator considered the cardio-respiratory arrest unrelated to the study drug. There was evidence of disease progression.

Subject 704-570601 (Study CP045) was a 69 year old WM with metastatic cancer to brain, cerebellum, bone, and adrenal glands diagnosed in (b) (6). The primary lung lesion was found in (b) (6) and the patient received extensive radiotherapy. Other medical history includes hypertension and drug allergies to penicillin and promethazine (1987). His pain was treated with oxycodone ER 40 mg daily, and tramadol 50 mg prn, pregabalin 75 mg bid and paracetamol 1 gm prn for. Other medications included candesartan and furosemide for hypertension, dexamethasone sodium phosphate for brain metastasis, and macrogol (laxative). He had moderate elevation of liver enzymes (AST, ALT and gamma GT) unquantified. On initial

evaluation for study inclusion on July 18, 2008, he had a normal PE including nasal passages. He described four severe BTCP episodes daily and was started on PecFent, adjusted gradually to 400 mcg daily.

The subject developed increasing asthenia, fatigue, and lower extremity edema and was admitted to hospital on (b) (6). He experienced cardio-respiratory arrest on (b) (6) (Study Day 21). The last dose of study drug administered before the event was at 12:22 on (b) (6), two days prior to his demise. Other therapy details are not available. No autopsy was performed. The Investigator considered the cardio-respiratory arrest to be unrelated to study drug.

The final event would appear most likely related to a terminal phase of disease progression. The death was not associated with the use of the study drug.

Subject 706/570602 (Study CP045) was a 70-year-old Caucasian female with lung carcinoma diagnosed in (b) (6). She had extensive metastatic involvement of bone, (b) (6)), left adrenal (b) (6)), liver (b) (6)), and lymph nodes (b) (6) She was enrolled to the study in July 2008. At the time her general physical and nasal passage examinations were normal. She was found to have a rash that was attributed to diclofenac and thiocolchicoside (a muscle relaxant) of undetermined duration. She described 2 severe episodes of BTCP daily and was started on PecFent. The dose was gradually increased to (400 mcg/ 4 h prn) for BTC pain relief. No other medical history was described. Her medications included oxycodone ER 40 mg daily, pregabalin 100 mg bid, and paracetamol 1 gm prn for pain. Other drugs included polyethylene glycol (laxative), and metoclopramide.

The subject started showing signs of clinical progression of anorexia and weakness, fatigue, confusion and stupor. The last dose of study drug was administered on (b) (6) (b) (6), on the same day of her death, however the exact timing was not provided. She experienced a cardiopulmonary arrest on (b) (6) (day 77 of therapy). No autopsy was performed. The Investigator considered the cardio-respiratory arrest not related to study drug.

This subject had extensive metastatic disease from a primary lung carcinoma with terminal progression. It appears unlikely that the final event was secondary to drug effect, although the time lapse between her last dose and terminal event were not documented.

Subject Number: **704/470402** (Study CP045) was a 63-year-old male whose CRF fails to fully document the factual events in this case. It appears that this subject had a pleural mesothelioma diagnosed in (b) (6), with liver metastasis (diagnosed in 2006). Other pertinent medical history was hypertension, a hepatitis B positive titer, history of acute hepatitis in 2004. Since neither the CRF nor the summary mentions that the patient was HIV positive, the hepatitis B positive titer may explain lamivudin

(Epivir) therapy. PE and nasal examination are missing in the CRF. After trial screening in July 2008, the dose of PecFent was gradually adjusted to 200 mcg/ prn daily.

The patient was simultaneously treated with moderately heavy fentanyl doses via 3 routes prior to his demise including: Fentanyl transdermal patch 25 mcg/hr (started on May 5, 2008) total dose of 600 mcg/day, oral transmucosal fentanyl 200 mcg p.o prn (May 5 until (b) (6)) plus trans-nasal fentanyl 200 mcg prn (PecFent).

Concomitant medications included: aldactone, carvedilol, prednisone, “lamivduina": (epivir-HIV antiviral) since 2004, gabapentin, oxygen therapy, furosemide, and ondansetron. The record states the subject suffered from nausea between July and August 2008, and developed fatigue and dyspnea 2 days prior to his demise on (b) (6) (b) (6) (Study Day 38 of the trial), when he experienced a cardio-respiratory arrest while receiving treatment with PecFent (200 mcg/4 h prn) spray for pain relief plus fentanyl transdermal and oral transmucosal. The date of the last dose was not recorded. No autopsy was performed, and no further information was reported on the event.

The Investigator considered the cardio-respiratory arrest not related to study drug. The contributory role of fentanyl accumulation with the concurrent use of fentanyl via 3 routes in a debilitated subject with metastatic liver involvement and on a protease inhibitor is unclear. Drug interaction between lamivudine and fentanyl has not been described, but is probably unlikely since lamivudine does not interfere with the P450-3A4 isoform.

Deaths due to Disease Progression: sepsis, metastasis, CNS invasion

Subject Number: **861/586102** (Study CP045) was a 28-year-old Indian female with breast carcinoma diagnosed in (b) (6). She did not previously participate in Studies 043 or 044.

She was screened for the open-label (OL) PecFent protocol in July 2008, reporting 3 episodes daily of severe BTCP. The dose of PecFent was stabilized at 200 mcg.

At the time of screening she was found to have edema of the left arm. Her nasal passages were normal. Her UA showed 1+ blood.

Her pain medications included MS ER 60 mg/day, (Rumorf) tramadol 50 mg tid, diclofenac, pentazocin, and buprenorphine 0.2 mg prn, since August 19, 2008.

Other medications included torsemide, omeprazole, paracetamol- diclofenac- serration-peptidase combination, diclofenac IV 75 mg prn (diclofenac), (“shabozox”), prophylactic calcium, and multivitamins.

She had several courses of oral and intravenous antibiotics from July to August, 2008, for what may have been for treatment of a mild sepsis of unclear source. The drugs used included amoxicillin, amikacin, cefuroxime, and cefaperazone.

On 26 Aug 2008 (Study Day 44), the last dose of study drug was administered at 22:16. On (b) (6) the subject experienced further progression of her disease with septic shock. Treatment for the events included broad spectrum antibiotics, cardiotonic drugs, and supportive care. She subsequently died at (b) (6) (on Study Day 45). The last dose of PecFent was (b) (6) prior to her death. The investigator considered the septicemia not related to study drug.

This subject had recurrent bouts of septicemia preceding the development of septic shock. The source of sepsis was not clearly identified but it is possible that it relates to immunosuppression due to carcinoma and or her chemotherapy. This death was not associated with the use of the study drug.

Subject 593801 (Study CP045) was a 36 year-old white male with onset of weight loss, and dysphasia in February 2007, who was found to have esophageal cancer with metastasis to the liver in (b) (6), following an EGD (esophago-gastro-duodenoscopy) with biopsy. A jejunostomy with J-tube insertion followed. Several complications ensued including: oral candidiasis, anemia, leukopenia (secondary to chemotherapy), and radiation induced mucositis. He was placed on TPN (total parenteral nutrition) for malnutrition due to severe dysphagia. Other medical problems included varicose veins, hypokalemia secondary to diarrhea, chronic fatigue syndrome and chest pain.

He was enrolled in the open label study on July 19, 2007, reporting 3 bouts of severe, daily BTCP. At the time his PE was unremarkable except for a J-tube in-place. His vital signs were normal. Urinalysis showed glucosuria. The nasal passage examination was unremarkable.

His medications included fentanyl patch 50 mg/hr q 72 hs (total of 1.2 mg/day), since August 26, 2007, hydromorphone 2 mg p.o. for BTCP, ondansetron, prochlorperazine, omeprazole, dyphenoxylate/atropine, octreotide (for diarrhea), epoetin alfa, filgastrin, lidocaine-diphenhydramine-maalox mouth wash, potassium chloride, mannitol, cisplatin, docetaxel (chemotherapy), granisetron, diphenhydramine, cimetidine, magnesium sulfate and dexamethasone. He was started on insulin and glimepiride for hyperglycemia.

He was briefly hospitalized in early (b) (6), for complications related to positioning of the J-tube and was discharged after J-tube removal. He was described as being able to tolerate oral intake, and remained on study drug, PecFent 200 mcg/ q 4 hs prn.

On (b) (6) he was re-hospitalized for dehydration, malnutrition, abdominal wound infection, and poor intake as a result of the J-tube removal. He noted fever, and chills. A positive blood culture revealed gram-positive rods and cocci. He was placed on multiple systemic antibiotics for poly-microbial sepsis.

This treatment included cefazolin, cefepime, and daptomycin. He was also on amikacin (for a draining abdominal fistula) and fluconazol for urogenital candidiasis. The last dose of study drug prior to sepsis was on August 19, 2007. He received another dose on August 24, 2007 prior to being discontinued from the study on his 29th day of participation and (b) (6) prior to his demise.

A chest x-ray revealed bi-basilar atelectasis with pleural effusions and lymphadenopathy. An abdominal abscess with a fistulous tract was suspected on helical CT studies.

On (b) (6) he developed symptoms suggestive of increased intracranial pressure, due to fourth ventricular compression secondary to mass effect. Multifocal hemorrhages involving the posterior fossa, basal ganglia, and right thalamus were documented and thought to be due to hemorrhagic metastasis. A ventriculostomy tube was inserted on (b) (6). Despite all efforts, trans-tentorial herniation and electro-cerebral silence developed. A diagnosis of brain death preceded extubation on (b) (6).

This is a complicated medical case, of an unfortunate subject with of esophageal cancer with metastasis, who suffered the effects of malnutrition and immunosuppression leading to infection and emerging diabetes. There were complications from J tube insertion, fever sepsis and an abdominal abscess, and from his inability to tolerate it. The terminal event was CNS metastatic disease with trans-tentorial herniation leading to brain death. The death of this subject was not related to the study drug.

Deaths due to other causes: MI, hemorrhage, cardiogenic shock, intestinal obstruction.

Subject 857/485701 (Study CP045) was a 57 year-old Indian male with oropharyngeal cancer diagnosed in (b) (6), originating in the tonsil He complained of cervical lymph node tenderness, cough, blocked nose and a nasal drip and had a tongue ulceration. He also had a sore throat with pain and difficulty swallowing. His throat pain radiated to the left ear and temporal region. He had diminished appetite and disturbed sleep. He entered the OL study after participation in study # 044. He was screened on September 29, 2008. Findings on PE included an area of tender, stretched, and pigmented skin on the left side of his neck. There was a red discoloration of his tongue with an area of ulceration on the lateral side. His vital signs were unremarkable, and his

weight was recorded at 50.4 kg. Urinalysis was unremarkable. Nasal passages examination showed a mild discharge and nasal drip, with dryness, and a burning discomfort. He described BTCP twice daily. PecFent was titrated up to 400 mcg daily prn.

Other medications included: MS SR 30-90 mg daily and MS 20 mg short acting for rescue prn. He was also on sodium picosulfate, lactulose syrup, vitamin B complex, lignocaine gargle, and omeprazole-dromperidone, and ibuprofen-paracetamol 400 mg-325 mg tid, lidocaine, diphenhydramine-mylanta mouth washes.

On September 27, 2008 he had unquantified fever for approximately two hours.

On [redacted] (b) (6), (19th day of OL study participation) experienced an episode of severe cough, followed by profuse oral bleeding 15 minutes later (10:15 am). He was taken to hospital where he was pronounced dead at [redacted] (b) (6).

The last dose of PecFent was recorded at 9:02 am (approximately one hour prior to the onset of the oral hemorrhage).

It seems likely that this subject developed an erosive ulcerating lesion of his tonsil and tongue with glossopharyngeal nerve involvement (neuralgia) followed by a massive oropharyngeal hemorrhage causing an upper respiratory pathway obstruction.

Although it is known, that subjects with neck and head cancer may develop life threatening carotid hemorrhages often related to previous surgery or radiation, the exact reason in this case remains unclear. This death was not associated with the use of PecFent but most likely related to cancer progression and or complications related to it.

Subject 859/585908 (study 045) was a 55 year-old Indian male with bronchial carcinoma diagnosed in [redacted] (b) (6), with multiple bone metastases (diagnosed in [redacted] (b) (6)). He complained of right shoulder and back pain.

On PE, the only remarkable findings were decreased breath sounds on the right chest and right acromial tenderness. Examination of nasal passages was normal. Vital signs were unremarkable and his weight was 52 kg. Urinalysis was negative.

Medications included: MS SR 600 mg daily, MS 30 mg IR prn, cipropheptadine 4 mg bid, multivitamins, vitamin C, and tramadol.

The subject was enrolled in the OL study on 7 January, 2009, describing 3 severe episodes of BTCP daily. He had not previously participated in one of the controlled studies. The dose was titrated gradually to 800 mcg prn daily.

On (b) (6)) the subject developed acute chest pain and gasping, lasting for 20 minutes. He expired at (b) (6)

The last study drug dose was administered 1.5 hours prior to the onset of his chest pain.

Subject 859/585908 had a terminal episode preceded by chest pain. We are unable to determine how the diagnosis of myocardial infarction was established (EKG abnormality, enzyme elevation etc). The differential diagnosis includes pulmonary embolism, chest tamponade, or myocardial tumor invasion (diagnosable via Echocardiogram).

The record states that the occurrence of myocardial infarction was “confirmed”; however it isn’t clear if there was an autopsy performed.

Despite the proximity of drug administration to symptom onset it is unlikely there was an immediate relation. This death would not appear to be associated with the study drug.

Subject 114/511403 (study 045) was a 72 year-old white female with stage II B (diffuse large B-cell) lymphoma and extensive nodal lymphoma with vertebral involvement at T11-12 and neural involvement at L1-2 level diagnosed in (b) (6) and a left breast lumpectomy in (b) (6).

Other significant medical history included asthma and hypertension for approximately 10 years, ischemic heart disease, a history of TIA (transient ischemic attack) in July (b) (6) and a coronary artery bypass graft in (b) (6) She also had a thyroidectomy in 1989, GERD (gastro-esophageal reflux disease) for 3 years, knee osteoarthritis since 1993, and left leg skin graft, and cystostomy, bladder incontinence treated with Botox injection, constipation, and a history of diverticular disease since (b) (6). She had campylobacter diarrhea in (b) (6) and bilateral leg edema with right leg cellulitis in (b) (6). IBS (irritable bowel syndrome) was diagnosed in 1972.

Her medications included oxycodone modified release 80-100 mg daily, oxycodone IR 10 mg prn, ASA 75 mg, salbutamol inhaler, beclomethasone inhaler, levothyroxine, atrovastatin 80 mg p.o daily, tibolone, docusate, alendronic acid, co-amilofruse, lansoprazole, calcium carbonate, calciferol, and zopiclone.

She was enrolled in the OL trial on July 1, 2008 without previous participation in the controlled trials. She described one or two episodes of severe BTCP daily. The dose of PecFent was adjusted to 200 mcg daily.

On PE she was found to have a retro-sternal scar. Her abdomen was slightly distended. She had a scar across her lower neck from thyroidectomy. Her ankles were swollen. Vital signs were normal and her weight was 48.7 kg. UA was unremarkable.

Nasal passages were unremarkable. She complained of nasal obstruction intermittently due to chronic rhinitis. She had chronic constipation.

It appears that this subject suffered a perforated bowel on (b) (6) complicated with peritonitis. Having received a dose of study medication 21 minutes before she experienced the onset of severe abdominal pain, the clinic was informed by the husband that the patient was withdrawn from the study. She was taken to the hospital ER where sub-diaphragmatic air was found and was transferred to ICU. Bowel ischemia was thought to have been the underlying cause of the perforation. She received urgent antibiotic therapy with teicoplanin IV, meropenem, and acyclovir and underwent an exploratory laparotomy, including a colectomy and ileostomy. In the post-operative period she developed septic shock and multiorgan failure despite treatment which included sustained antibiotic therapy with gentamycin and tazobactam. She was treated with noradrenalin and adrenaline IV, vasopressin and dobutamine. She also received heparin, and MS, midazolam and alfentanyl, hydrocortisone, amiodarone and pantoprazol, oxygen and nutritional support.

She expired on (b) (6) and was removed from the study on (b) (6) 2008. The record states the investigator considered that the study medication may have possibly contributed to her condition.

Subject 114/511403 had a complicated medical history with significant neoplastic and cardiovascular disease. Since there were known predisposing risk factors for mesenteric thrombosis in this instance, the management of the case and procedures performed indicate that this was a high priority diagnostic consideration in the management of this case. Unfortunately, despite all efforts, this entity carries a high mortality and a poor prognosis. The development of bowel necrosis and infarction often leads to rupture, peritonitis, septic shock, and multiple organ failure. Since the main cause of mesenteric thrombosis is usually thrombo-embolic it seems unlikely that this death was not associated with the use of the study drug.

7.3.2 Nonfatal Serious Adverse Events

There were two subjects during Phase 1 studies that had serious adverse events (SAEs). Both were non-fatal and judged mild by the investigator. One subject had mild chest pain, and another subject became pregnant. A narrative of the subject who became pregnant is provided in Section 7.6.2.

In Phase 2/3, a total of 134 patients experienced a SAE. Of those patients, 66 died. Thus, there were 68 nonfatal serious adverse events. Table 10 below, contains a tabular summary of the nonfatal SAEs by MEDDRA system organ class.

Table 10: Nonfatal Serious Adverse Events in Descending Order in the Safety Population in Phase 2/3 studies. Source: ISS Phase 2/3 Statistical Tables: page 2900/27077, pdf file

System Organ Class	Most Common Preferred Terms Observed	Total
Gastrointestinal	Nausea, vomiting, constipation	15
General and administration site	Pain, pyrexia, chest pain	14
Infections and infestations	Pneumonia, sepsis, gastroenteritis	14
Respiratory, thoracic, mediastinal	Dyspnea, COPD, pulmonary embolism	14
Blood and lymphatic	Anemia, neutropenia, febrile neutropenia	9
Musculoskeletal and connective tissue	Back pain, arthralgia, musculoskeletal pain	5
Renal and urinary	Acute renal failure, anuria, bladder outlet obstruction	5
Nervous system	Cerebrovascular accident, loss of consciousness	5
Psychiatric	Mental status changes, confusional state	4
Neoplasm, benign or malignant	Malignant anorectal, metastasis	3
Investigations	Blood pressure increased, blood urine present, hemoblogin decreased	3
Vascular	Deep vein thrombosis, subclavian vein thrombosis	3
Injury, poisoning, procedural complications	Feeding tube complication, lower limb fracture	2
Metabolism and nutrition	Dehydration, hyponatremia	2
Skin and subcutaneous	Decubitus ulcer, skin necrosis	2

The SAEs observed are typical for a population of patients with advanced malignancy.

The following patient summaries and comments were selected from the data provided by the Applicant and reflect the major SAEs encountered during Phase 2/3 studies: These cases were selected as examples of the complexity and disease burden of the subject population with emphasis on those with some likelihood that opioid treatment may have been contributory.

Individual Serious Adverse Event Summaries

Patient 937/393706 (Study CP043) was a 71 year-old Hispanic male with prostatic cancer. The subject suffered from occasional incontinence, and muscle skeletal pain in his hips and spine and humerus, related to degenerative arthritic changes,

spondylolisthesis, and spinal stenosis. Other medical history includes hypertension anemia, arthritis, and diabetes. There was a history of intestinal obstruction, status-post cholecystectomy, and herniorrhaphy. There is also a history of depression, allergies and asthma, and prior cigarette smoking. The Applicant's narrative states that he had a "gestational trophoblastic tumor." This is a very rare cancer in women and a medical oddity in a male, presenting as a testicular tumor (The American Journal of Surgical Pathology: December 2009 - Volume 33 - Issue 12 - pp 1902-1905) Metastatic Epithelioid Trophoblastic Tumor in a Male Patient With Mixed Germ-cell Tumor of the Testis).

His medications included ramipril, zolpidem, metformin, pamidronate disodium, ciprofloxacin, atrovastatin, ferrous sulfate, APAP, erythropoietin, prochlorperazine, furosemide, glipizide, and rosiglitazone maleate. Other drugs include hydrochlorthiazide, ferrous sulfate, furosemide, pantoprazol, fluoxetine, terazosin, humulin, ondansetron, levofloxacin, promethazine, hydrocodone, hydromorphone.

On day 12 of the study with PecFent for BTCP, at a dose of 400 mcg/ every 4 hours he developed recurrent chest pain. He was hospitalized to rule out angina pain. The vital signs were normal and there were no cardiac arrhythmias. The admitting diagnosis was non-cardiac chest pain. He was treated with isosorbide isonitrate and packed cells. His chest pain resolved in 5 days. The result of the serial ECGs and enzymes is unknown. The CRF states he also had intermittent vomiting, ileus, and disease progression. The investigator considered this a serious event possibly related to the study drug. The subject was removed from the study due to disease progression.

The subject appears to have developed a poorly localized ileus, possibly related to study drug use; however, the etiology of his chest pain is unclear, with angina considered as a leading cause.

Patient 941/394103 Study (CP043) was a 29 year-old white woman with cervical-squamous cell carcinoma treated with chemotherapy and radiation. Her past medical history included a tubal ligation and a kidney stent. She developed severe nausea and vomiting on day 10 of study with PecFent up to 200 mcg several times daily. She also received MS 50 mg daily, methadone 60-80 mg daily, hydromorphone HCL (Dilaudid) 32 mg, and gabapentin 150 mg tid. She took doxepin and trazodone for depression and zolpidem for insomnia. She was on treatment with polyethylene glycol for constipation, ropinirole for restless legs and megestrol 400 mg qid for cachexia. She was on diphenhydramine for itching. When she was hospitalized for severe nausea and vomiting at the time of her week # 4 return visit she was diagnosed to have acute gastroenteritis. She was treated with IV fluids, ondansetron, and prochlorperazine. She was also was suffering from anorexia, anemia, neutropenia and DVT. She was treated with enoxaparin sodium and naloxone HCL. During her hospitalization she withdrew consent for treatment with study drug due to disease progression. The investigator considered this an unrelated event to the study drug.

The clinical picture was recognized as acute gastro-enteritis of such severity that it required hospitalization for IV fluid support and anti-nausea medication. While initially the patient had a slight leukocytosis, but was neutropenic, she had also developed deep vein thrombosis (DVT) perhaps related to hypercoagulability and hemoconcentration. Multiple drug and multi-opioid exposure may have been contributory.

Patient 604/460402 (StudyCP044) was a 69 year-old white male with pancreatic and prostatic carcinoma and bone metastasis. He suffered from carcinomatous cachexia, weakness, and leg edema. He had an episode of respiratory depression on (b) (6) for which he was placed on naloxone.

He experienced hematuria followed by anuria due to an obstructive uropathy on day 12 of the drug study. He underwent a nephrostomy with resolution. The study drug was permanently discontinued on study day #14 of the trial post nephrostomy.
His medications included etamsylate (dicynene- hemostatic), tranexamic acid, furazidin, nystatin, furosemide, prednisone, metoclopramide, docusate sodium, flutamide, and sulfamethoxazole. He was also on a fentanyl transdermal patch, flutamide, nimesulide, docusate, zoldaex, furagin, (MS), haloperidol, midazolam, fentanyl IV, naloxone, cefuroxin, lignocaine, methylprednisolone, propranolol, digoxin, and dexamethasone.

This subject developed an obstructive uropathy related to hemorrhage leading to anuria requiring surgical intervention. The subject was removed from the trial. It is unlikely that the study drug was causative, and the possibility of disease progression or metastasis could be contributory.

Patient 114/411401 (Study CP045) was a 72 year-old white male with metastatic adenocarcinoma of the prostate. He had multiple bone metastases (right femoral head and hemi-pelvis, lower sacrum, spine) with L 2-3 disc protrusion. He was titrated to a dose of 800 mcg. Other significant medical history included hypertension, anemia, pressure sore in the right heel, deafness, renal failure, cellulitis with septicemia, and intermittent palpitation. Physical examination at week 16 (end of treatment); states that he had right facial weakness and minimal right arm weakness. This was attributable to a left dural metastasis visualized on MRI scan. He also had a below knee cast in his right leg, with an ulcer in the right heel that had been present for 4 years with necrosis and proven osteomyelitis changes. He had childhood polio residuals.

Medications listed include oxycodone oral, modified release 300 mg and injectable 100 mg, amoxicillin, metronidazole, floxacillin, phenoxymethyl penicillin, docetaxel, metoclopramide, prednisolone, dexamethasone, loperamide, erythromycin, tinzaparin prophylaxis, gentamycin, glycerol, pregabalin, soluble aspirin. He also received palliative radiotherapy.

He suffered a fall on study drug day #109, and sustained fractures of right tibia and fibula. He was admitted to hospital and treated under anesthesia. His infected right heel ulceration was treated with antibiotics and maggots. He also developed a sacral decubitus ulcer. Because of persistent diarrhea the antibiotics were stopped. He was transfused for severe anemia (Hemoglobin was 7.6 gm). The treatment with PecFent was reviewed by the palliative team and was interrupted on day #111 not to be resumed. The subject was excluded from the study on October 15, 2008, and was given the drug on compassionate basis. It was substituted for oxycontin and oxycodone oral and parenteral. He was discharged from the hospital after his ulcer improved, but the tibial and fibular fractures remained unhealed up to the time of his death. The investigator considered the fracture and skin necrosis unrelated to the study drug.

This subject had brain metastasis, and multiple bone metastases. He may have sustained pathologic bone fractures. In this advanced stage of carcinomatosis with anemia and a malnourished state, he would be a candidate for skin ulcerations and decubitus ulcers. It is unlikely that the study drug was the source of such multiplicity of complications.

Patient 217-521701 (Study CP045) was a 64 year-old white female with chronic myelogenous leukemia who developed a right subclavian vein thrombosis on study day #14 for which she was hospitalized. She was found to be dehydrated approximately 3-4 weeks prior to this event, and started on IV fluids with essential amino-acids. It was discovered during her hospitalization that she had a coagulopathy reflected by high D-dimer levels, indicative of a high level of fibrin degradation products. She was treated with phenprocoumone (a warfarin derivative) and subcutaneous low molecular heparin sodium. She was treated with IV paracetamol for fever for 2 days and was also thought to have a viral gastrointestinal with nausea, for which she was treated with ondansetron and metoclopramide.

Other medical problems included: UTI, hypokalemia, post-menopausal syndrome, heart disease with history of a previous myocardial infarction, right leg thrombosis, depression, reflux esophagitis, and psoriasis vulgaris.

Her medications included: MS SR 10 mg prn, hydromorphone 32-40 mg, buprenorphine 140 mcg/hr, estrogen, duloxetine, risperidone, glycerol, potassium chloride, ibuprofen, nilotinib, pantoprazol, nitrazepam, bisacodyl, sodium picosulfate, etoricoxib, and levofloxacin. This was described as a catheter related complication. She was apparently treated with anticoagulants and IV fluids and improved. The investigator thought this was an unrelated problem to her treatment with PecFent. At discharge she was re-titrated with PecFent 400 mcg, and developed cystitis that resolved in 2 days on treatment with levofloxacin. She had a mild gastritis for which she received oral “carvomin” (a European oral herbal preparation for dyspepsia) for which she was re-hospitalized and discharged 12 days later. Two months later she developed a subcalvian vein port catheter port infection-abscess which was removed at surgery and

received IV and oral antibiotic treatment with moxifloxacin. She completed study participation (95 days) in March, 2009 and continued into the extension phase. The event was considered resolved and she was discharged from hospital. The investigator did not consider these events related to study drug.

This patient had an initial subclavian vein thrombosis, cystitis, and dehydration. This was further complicated by abscess and infection of the venous port in the subclavian vein. These events were most likely related to her neoplasm, coagulopathy, dehydration and depressed immunity, and unlikely study drug related. The subject apparently recovered successfully from this episode.

Patient 304-530401 (Study CP045) was a 56 year-old white male with multiple myeloma, who developed pyrexia and leucopenia, on study day #34 while receiving treatment with 800 mcg of PecFent for pain relief. He had a history of constipation. His concurrent medications were dexamethasone, paracetamol, clonazepam, melphalan, amitriptyline, and pantoprazol. He was hospitalized on study day #34 for fever and leukopenia, and was complaining of dizziness, fatigue, and somnolence. He had neutropenia, thrombocytopenia, and anemia following chemotherapy. He was treated with antibiotics (ceftriaxone, valcyclovir, pristinamycin, and levofloxacin). He received metoclopramide for nausea, platelet transfusion, lenogastrim for leukopenia, and furosemide for hypertension. He also received sucralfate and fluconazole for mucositis.

Other medications included: lactulose, macrogol, transipeg, epoetin, codeine, acetylcysteine, and paracetamol. The fever resolved in 2 days after antibiotics plus symptomatic therapy. The leukopenia improved one day after. He complained of dry eyes on study day #39. The subject was discharged on study day #39. The investigator considered that the subject's fever and cytopenia were unrelated to the study drug.

The subject was re-hospitalized on study day #69 for intractable pain, and was treated with oxycodone hydrochloride, and herbal medication (saw palmetto) for dysuria. On study day #72 he complained of severe neuralgic pain and the study drug was stopped. He withdrew from the study on day #72 due to lack of efficacy. The laboratory parameters showed improvement and he was discharged from hospital. The investigator did not attribute the pain to the study-medication.

The clinical picture is consistent with pancytopenia and sepsis, related to chemotherapy for his myeloma. He responded favorably to treatment unfortunately the study drug was unable to control his BTCP. Neither event appears to have been caused by study-medication.

Patient 809-580901 (Study CP045) was a 52 year-old female who had a complete thyroidectomy for papillary thyroid cancer in 2004. She developed metastasis (site not

specified). She described 3 episodes of daily BTCP at screening. Other significant past medical history includes right ovarian cyst removal, sacrectomy, hysterectomy, urinary incontinence due to bladder prolapse (s/p colposacropexy) and L5-S1 laminectomy. Her medications included gabapentin, MS IR 10 mg prn, pethidine, pantoprazol, I 131 and ciprofloxacin.

Prior to study enrollment on day -32 she experienced intense pain and required hospitalization for one day. Her pain was treated with pethidine. An MRI scan (site unclear) revealed tumor enlargement and disease progression.

After discharge she was enrolled in the PecFent study and titrated to a dose of up to 400 mcg. She complained of itchy throat and mouth ulcers on study day #3 due to mouth ulcers and persistent pain. PecFent was discontinued on study day #6. The investigator thought the mouth ulcers were related to the study drug. She withdrew from the study due to rapid progression and intractable pain**.** It is possible that mouth ulceration and throat discomfort may have been caused by the study drug.

Patient 856-585605 (Study CP045). This is a 42 year-old Indian male with carcinoma of the larynx treated status post chemotherapy and radiotherapy. He enrolled into the study and achieved a stable maintenance dose of 400 mcg on August 8, 2008. His past medical history included bronchospasm and the malignancy that qualified him for the study. His concomitant medications also imply that he had hypertension. At study enrollment, his medications included morphine sulfate, extended-release, morphine sulfate, immediate-release, diclofenac-paracetamol, amitriptyline, bisacodyl, metoclopramide, ibuprofen-paracetamol, doxycycline (for a skin eruption), fexophenadine (itching), salubair (bronchospasm), pregabalin, losartan-hydrochlorthiazide, and cetuximab (monoclonal antibody).

On [redacted] (b) (6)), the patient experienced an episode of breakthrough pain for which he initially said that he self administered one spray (400 mcg). According to the available documents, he initially reported that he immediately because drowsy and lost consciousness with a few minutes. Apparently, he was observed to have stertorous breathing and cyanosis. The episode was reported to have lasted for 45 minutes after which the patient regained consciousness. He was taken to the hospital for observation but, by that time, no treatment was necessary.

He was discharged from the hospital on [redacted] (b) (6) During the hospitalization, he had been queried about his PecFent use. He stated that the device was malfunctioning and that he was not getting the same amount of drug with each spray or the device occasionally failed to deliver any dose. Upon further questioning, it appears that the overdose occurred because he repeatedly redosed himself because he did not sense delivery of the spray. The investigator estimated that the overdose occurred after administration of 800 to 2000 mcg. He was counseled about the safe use of the product. PecFent was reintroduced on August 25 (Study Day 18).

This patient completed the 16-week duration of Study CP045 as well as 126 additional days during the Extension Phase. While he reported an additional 36 incidents of "failure to administer dose," there were no incidents of overdose.

Patient 904-390403 (Study CP045) was a 59 year-old white female with carcinoma of the lung that developed acute gastro-enteritis with dehydration on study day #38 while receiving treatment of PecFent 800 mcg. Approximately 4 days previously, she had stopped taking her prednisone abruptly because she felt it was making her ill. This was manifested by nausea, vomiting, diarrhea, and jerking movements. Two days later she presented for a routine physician appointment and fainted. She was admitted to hospital and treated for dehydration. The study drug was not available during hospital stay. Her calcium was noted to be low, along with an elevated WBC (13.9) count and moderately elevated glucose (150 mg). She developed hypokalemia and metabolic acidosis that resolved in 2 days in hospital care. Steroids were resumed, after she had a noted improvement two days later. The study drug was resumed on day #41.

Significant past medical history included right upper lobe lung resection 9 years previously, seasonal allergies, post-herpetic neuralgia, hypothyroidism, vitamin D deficiency, anemia, osteoarthritis, hypertension, idiopathic peripheral neuropathy, constipation, bleeding peptic ulcer, carotid stenosis, nephrolithiasis, and COPD.

Concomitant medications included: levothyroxine, oxycontin, gabapentin, prednisone, bumetanide, estrogen, ranitidine, furosemide, ASA, and esomeprazol. She was withdrawn from the study on day #59 for lack of efficacy. The investigator did not think this event was related to the study drug. It is unlikely that this picture was related to the use of study drug.

Patient 907/390704 (Study CP045) was a 64 year-old white female with lymphocytic leukemia, and polycythemia vera, who had an episode of acute confusion with slurred speech and ataxia on day #117 of the trial. She was receiving a dose of 400 mcg q 4 hs of PecFent. She was hospitalized and was found to be normotensive, and afebrile, but had a facial droop. Past medical history was significant for diabetes, hypertension, and depression. She had a stable clivus meningioma that appeared unchanged compared to a previous baseline study. She had some white matter changes but no acute infarct was present on neurodiagnostic testing. She was diagnosed as a TIA.

Laboratory findings were significant for an elevated WBC of 16.8, glucose 170 mg with ketones in the urine and mild proteinuria. The next day her speech improved and she saw a hem-oncologist who found no significant hematologic abnormalities in her parameters. The neurologist found a mild left hemiparesis, consistent with a right hemispheric infarct. The EEG was normal. She was started on topiramate (for jerking).

Other medications included: ASA, carbidopa/levodopa, duloxetine, gemfibrozile, heparin, hydrochlorthiazide, insulin, lisinopril, loperamide, paroxetine, KCL, pregabaline, simvastatin, diazepam, acetomorphine, and alprazolam. She received IV fluids to correct her dehydration due to ketosis. She was discharged six days after admission, and the event was deemed resolved. The investigator concluded that this AE was not related to the study drug. This was a reasonable conclusion, in that it is quite likely that the episode of cerebrovascular ischemia more likely attributable to several significant risk factors but not likely study drug related.

Patient 907/394103 (Study CP045) was a 29 year white female with uterine cervical carcinoma, who developed neutropenia, nausea, vomiting on study day #30 while receiving treatment with PecFent 200 mcg every 4 hours prn. Her past medical history was significant for cervical biopsies for diagnosis of squamous cell carcinoma in 2007, a kidney stent, and neurogenic pain. Concurrent medications included: methadone, hydromorphone HCL, pregabalin, diphenhydramine, methylphenidate, cisplatin, topotecan.

She had been treated with cisplatin and topotecan on study day #29 and received radiation but the date of this is unclear. Her symptoms worsened the following day. On study day #36 she was admitted to hospital with intractable pain, nausea, vomiting, dehydration, and possible pyelonephritis. She had neutropenia with a WBC of 600, pyuria (4+ bacteria in urine); the presumed diagnosis was hydronephrosis, pyelonephritis, and hypokalemia, cytopenia due to chemotherapy and B12 deficiency. She was transfused. Her symptoms resolved by study day #46 and she was discharged. She was readmitted to the hospital because of recurrent neutropenia, nausea, and vomiting. She was treated with filgastrin, epoetin and transfused blood and platelets. Her course was uneventful except for restless legs syndrome. She was discharged and the study drug was restarted on day #62, at which point she withdrew consent and was removed from study. Her symptoms had resolved at the time of discharge to hospice care. The investigator did not consider that her nausea, vomiting, and neutropenia were drug related. This appears justified in view of the concurrence with anti-neoplastic therapy. She was discontinued from the study on day #63 due to withdrawn consent. Her neutropenia resolved during hospice care.

Patient 941/594103 (Study CP045) was a 53 year-old white female with endometrial carcinoma who developed left facial weakness, numbness in the right face and tongue and slurred speech on study day #8. She had been treated for her endometrial carcinoma with 6 cycles of chemotherapy. Her concurrent medications included hydromorphone HCL. She was also on diphenhydramine, APAP, magaldrate, timolol, celecoxib, methylprednisolone, enoxaparin sodium, simvastatin, and furosemide.

She was found to have a suspected hemorrhagic infarct on imaging studies (CT and MRI of the brain) and was initially thought to have sustained a stroke while on 400 mcg

of PecFent. There were three lesions of focal contrast enhancement and mass effect suggestive of metastasis. The next day a CT scan showed a hypodense area in the parietal region suspicious of an acute infarct. The lesions in her brain were thought to represent metastasis and she was treated with radiation. She was hospitalized. Her past medical history included glaucoma. On study day #9 she developed deep vein thrombosis in her lower extremities and she was treated with heparin. She improved in two days, and was released from hospital on day #9 of the study on enoxaparin. The investigator did not think that the study drug was contributory or causal in the development of her stroke. Participation in the study was suspended on study day #22 due to brain invasion. From the clinical perspective it appears that the patient suffered from metastatic brain disease and or an infarct, and it is unlikely that the study drug was contributory.

Patient 941/594101 (Study CP045) was a 37 year-old black female with metastatic breast carcinoma who experienced left shoulder pain while receiving treatment with PecFent 800 mcg q4 hs for BTCP on study day #60 that resolved uneventfully. Her past medical history included s/p right mastectomy, muscle spasms, asthma, anemia related to chemotherapy, esophagitis due to radiation. Concomitant medications were: levofloxacin, leuprolide acetate, oxycodone/APAP (Percocet), gabapentin, promethazine, baclofen, amoxicillin, warfarin, and chemotherapy (paclitaxel and bevacizumab). She was admitted to hospital to evaluate a 2 week history of left shoulder pain. An ultrasound, CT scan, x-rays and MRI of the area were unrevealing. She had a fever of 102 F and was treated with IV fluids and antibiotics. She complained that MS was not adequate to control the pain and was then switched to hydromorphone. She was discharged on study day #65 with a resolved complaint. She entered the extension phase of the study on study day #155. She had neutropenia and fever on the study approximately one month after she began the extension phase. Her symptoms resolved in 14 days. The investigator did not think these symptoms were related to study-medication. The nature of her left shoulder pain remained obscure, but thought to be possibly muscle-skeletal in origin, and not related to the study drug.

Patient 941/595111 (Study CP045) was a 52 year white female with metastatic carcinoma with multiple primaries. Her past medical history reveals that in 1982 (at age 26 years) she developed carcinoma of the cervix and had a partial hysterectomy. At age 28 years she developed carcinoma of the ovaries and had bilateral oophorectomy. At the age of 43 years in 1999 she had a thyroidectomy and laryngectomy for cancer in the neck. At the age of 49 years in 2005 she was found to have cancer in her kidneys and liver. During 2008, she had developed bone metastasis to the pelvis, femur and sternum and severe breakthrough pain in her mid-abdomen and constipation. Her concomitant medications were: morphine sulfate, hydromorphone, and levothyroxine, prochlorperazine, and Senna alexandrina.

The patient developed dyspnea on study day #8 shortly after receiving treatment with PecFent 200 mcg. She developed profound dyspnea on study day #11 shortly after taking the third dose of study drug on that day along with a panic reaction she required oxygen use. On study day # 12 she wanted to re-challenge herself with a dose of PecFent and again became dyspneic. The study drug was thereafter discontinued permanently and the subject was removed from the study. The event was considered resolved. She developed pneumonia on study day #23 and she was treated with azithromycin. The investigator regarded the dyspnea severe in intensity and probably related to the study drug. The pneumonia was regarded of moderate intensity and unrelated. The close relation to dosing and the repetitive occurrence of dyspnea shortly after use of PecFent could indicate a cause effect relation. There is not enough information regarding this AE to determine if this was related to bronchospasm, hypoxia, or desaturation.

7.3.3 Dropouts and/or Discontinuations

During Phase 1, four subjects discontinued treatment due to adverse events:

- Subject 6 in Study CP047 due to vomiting after receiving 2 doses of naltrexone prior to dosing with PecFent
- Subject 2 in Study CP047 after a single-dose of 100 mcg of PecFent developed mild chest pain. The event was classified as SAE because of admission to the Clinical Unit. The event was judged unrelated to study-medication and possibly related to naltrexone.
- Subject 8 in Study 048 withdrew due to an allergic reaction (AE) prior to dosing with PecFent. The event was deemed as a substance allergic reaction (SAR) after one dose of 100 mcg PecFent
- Subject 10 in Study CP048 withdrew due to development of palpitations prior to dosing with PecFent after having been administered oxymetazoline. The subject completed the first leg of the study receiving 100 mcg of PecFent.

There were 74 subjects in Phase 2/3 studies that had AEs leading to discontinuation of treatment. Please refer to Table 11 for a tabular summary of the specific causes.

Table 11: Adverse Events Leading to Discontinuation of Treatment in ≥2 Subjects - Phase 2/3 studies. Source: Integrated Summary of Safety Report: page 84/407, pdf file

Preferred Term	n (%)				
	100 mcg (N=484)	200 mcg (N=389)	400 mcg (N=319)	800 mcg (N=182)	Total (N=516)
Subjects with ≥1 AE leading to discontinuation of treatment	19 (3.9)	20 (5.1)	18 (5.6)	18 (9.9)	74 (14.3)
Disease progression	5 (1.0)	5 (1.3)	6 (1.9)	7 (3.8)	23 (4.5)
Cardio-respiratory arrest	0 (0.0)	2 (0.5)	4 (1.3)	0 (0.0)	6 (1.2)
Vomiting	2 (0.4)	3 (0.8)	0 (0.0)	1 (0.5)	6 (1.2)
Nausea	1 (0.2)	0 (0.0)	0 (0.0)	4 (2.2)	5 (1.0)
Dizziness	3 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)	4 (0.8)
Constipation	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.5)	3 (0.6)
General physical health deterioration	1 (0.2)	0 (0.0)	2 (0.6)	0 (0.0)	3 (0.6)
Pulmonary embolism	2 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.6)
Bradycardia	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.4)
Dehydration	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.4)
Breast cancer	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.4)
Headache	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Confusional state	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.4)
Dysuria	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.4)
Hypoxia	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.4)
Deep vein thrombosis	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.4)

Source: Table 6-2.19.1

The most common cause was disease progression which occurred in 23 subjects (4.5%). This was followed by cardio-respiratory arrest and vomiting in 6 subjects (1.2% each).

A total of seven long-term subjects had adverse events leading to discontinuation. None of the events leading to discontinuation were considered by the investigator to be treatment-related. Two subjects had adverse events related to disease progression.

Subjects who discontinued treatment in phase 2/3 trials due to other reasons can be found in the Appendix in table C1. This was predominantly due to non-compliance issues (18/37). The remainder were due to lack of efficacy, protocol violation, disqualification, or titration failure.

7.3.4 Significant Adverse Events

Adverse Events of Special Interest:

Severe Cutaneous Adverse Events

There was one case of (nasal) skin exfoliation at 800 mcg. Subject 603/460305, a 60 year-old subject with gastric carcinoma, cachexia, and pneumonia, was enrolled in Study CP045. He was stabilized at a dose of PecFent of 800 mcg. He developed a mild desquamating skin rash on top of his nose, approximately 37 days after starting on PecFent. His BTCP increased in intensity, requiring additional transdermal fentanyl skin patch 200 mcg/hr. He was hospitalized for worsening pain and started on amoxicillin for pneumonia, fluconazol, and haloperidol (for hiccups). His skin rash gradually resolved. The event was recorded as treatment emergent cutaneous adverse event.

Nasal Adverse Events

Because of the route of administration for PecFent, the Applicant was asked to carefully assess the effects of PecFent on the nose and associated structures in clinical development. Objective nasal examinations were conducted, nasal adverse events were tabulated, and patients were queried for nasal symptoms at screening and at end-of-treatment for all subjects in the ITT population. Table 12 shows the common adverse events in Phase 1 Studies.

Table 12: Adverse Events in Descending Order-Safety Population-Phase 1 Studies (from Applicant's table 6-1.3) Source: Integrated Summary of Safety: Phase 1 Studies: page 19/162, pdf file

Preferred Term	Total N=100
Number (%) of Subjects with at Least One AE	73 (73.0)
Rhinorrhoea	36 (36.0)
Headache	34 (34.0)
Rhinitis	32 (32.0)
Nausea	22 (22.0)
Dizziness	17 (17.0)
Vomiting	15 (15.0)
Fatigue	12 (12.0)
Somnolence	12 (12.0)
Pharyngolaryngeal Pain	10 (10.0)
Epistaxis	8 (8.0)
Nasal Congestion	8 (8.0)
Abdominal Pain Upper	7 (7.0)
Cough	7 (7.0)
Dysgeusia	6 (6.0)
Feeling Hot	6 (6.0)
Malaise	6 (6.0)

Note: Subjects are counted only once at each level of summarization.
Source: Integrated Phase 1 Studies (CP037, CP042, CP047, CP048).

It is interesting to note that some of the most common AEs observed in Phase 1 were attributable to the nose and include rhinorrhea (36%), headache (34%), and rhinitis (32%).

The Applicant suggests that the high rate of nasal adverse events in Phase 1 is driven by Study CP048. This was a pharmacokinetic study in normal subjects and subjects with allergic rhinitis to determine whether absorption of fentanyl was affected by the

state of the rhinitis or treatment with oxymetazoline. Thus, the incidence of rhinorrhea and similar symptoms was high in this study.

In addition, Study CP037/02 tested several formulations including: nasal fentanyl-chitosan, nasal fentanyl-pectin, and fentanyl chitosan-poloxamer. While 30.4% of fentanyl-chitosan poloxamer and 29.5 % of fentanyl chitosan subjects experienced nasal AEs, only 2% of fentanyl-pectin reported symptoms of discomfort or runny nose. This also contributed to the high aggregate incidence of nasal complaints in Phase 1 and led the Applicant to continue development of the pectin-containing formulation.

The high rates of nasal findings appear to be due to the nature of the Phase 1 studies, not consequent to the to-be-marketed formulation.

Phase 3 Data:

Again, nasal exams and adverse event solicitation were included in Studies CP043, CP044, and CP045. Nasal and other symptom scores (nausea, level of sedation) for study CP041 were not performed and were not included in the safety data base.

A total of 45,599 of BTCP episodes were treated with PecFent during Phase 2/3 studies. According to the Applicant, 43 subjects developed one or more nasal AEs that were felt to be treatment-related by the investigator.

Table 13 has a breakdown by dose and type, of the most common nasal AEs in Phase 3 studies These included nasal discomfort in 10 cases (1.9%), followed by epistaxis in 7 cases (1.4%), and rhinorrhea in 6 (1.2%).

Table 13: Treatment-Related Nasal Adverse Events – Phase 2/3 Studies (from Applicant's Table 9-25). Source: Integrated Summary of Safety Report: page 94/407, pdf file

Preferred Term	n (%)				
	100 mcg (N=484)	200 mcg (N=389)	400 mcg (N=319)	800 mcg (N=182)	Total (N=516)
Subjects with ≥1 treatment-related nasal event	19 (3.9)	8 (2.1)	7 (2.2)	10 (5.5)	44 (8.5)
Nasal discomfort	6 (1.2)	2 (0.5)	4 (1.3)	0 (0.0)	10 (1.9)
Epistaxis	2 (0.4)	1 (0.3)	2 (0.6)	4 (2.2)	7 (1.4)
Rhinorrhoea	5 (1.0)	0 (0.0)	1 (0.3)	2 (1.1)	6 (1.2)
Nasal congestion	2 (0.4)	2 (0.5)	0 (0.0)	0 (0.0)	4 (0.8)
Postnasal drip	2 (0.4)	1 (0.3)	0 (0.0)	1 (0.5)	4 (0.8)
Rhinitis	1 (0.2)	1 (0.3)	0 (0.0)	1 (0.5)	3 (0.6)
Nasal mucosal disorder	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.5)	3 (0.6)
Nasal dryness	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.4)
Intranasal hypoaesthesia	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.4)
Sneezing	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.4)
Nasopharyngitis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Rhinalgia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Source: Table 7-2.4.1

Results of the nasal exams are summarized in Table 14 and Table 15. Mild mucosal thickening that was reported as mild obstruction was present in 17 subjects before treatment and in 8 subjects after treatment. Moderate edema or narrowing of the airway was present in 2 subjects before treatment and one after treatment. No subject had severe nasal obstruction either before or after treatment. While it seems unlikely that the mild obstruction was alleviated by PecFent, the data support the conclusion that PecFent is not irritating to the nasal mucosa.

Table 14: Findings of Nasal Examination at Screening and End-of-Treatment in Phase 2/3 Studies (from Applicant's Table 18-2-2). Source: Integrated Summary of Safety Phase 2/3 Statistical Tables: page 4503/27077, pdf file

Parameter: Obstruction

N(%) Subjects (N=500)	Visit1 (Screening[1])				
	Absent	Mild	Moderate	Severe	Missing
End of Treatment[2]					
Absent	328 (65.6)	9 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Mild	6 (1.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Moderate	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing[2]	147 (29.4)	7 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)

[1]Screening data for subjects enrolled in both CP043/06/FCNS or CP044/06/FCNS and CP045/06/FCNS is the Visit 1 (screening) data available from earlier studies. End of treatment data for these subjects is data available in CP045/06/FCNS.
[2]The missing category includes subjects that may not have reached end of treatment.
Source: Integrated ISS database: Phase 3 Studies (CP043/06/FCNS, CP044/06/FCNS, CP045/06/FCNS).

Table 15: Nasal Examination Results from Screening to End of Treatment in Phase 2/3 Studies (from Applicant's Table 18-2-3). Source: Integrated Summary of Safety Phase 2/3 Statistical Tables: page 4523/27077, pdf file

Location: Other - Parameter: Inflammation

Study Time Point[1]	Categories	Total
Screening (N=47)	Absent	46 (97.9%)
	Mild	1 (2.1%)
	Moderate	0 (0.0%)
	Severe	0 (0.0%)
End of Treatment (N=29)	Absent	27 (93.1%)
	Mild	2 (6.9%)
	Moderate	0 (0.0%)
	Severe	0 (0.0%)

[1]Screening data for subjects enrolled in both CP043/06/FCNS or CP044/06/FCNS and CP045/06/FCNS is the Visit 1 (screening) data available from earlier studies. End of treatment data for these subjects is data available in CP045/06/FCNS.
Source: Integrated ISS database: Phase 3 Studies (CP043/06/FCNS, CP044/06/FCNS, CP045/06/FCNS).

Of the subjects that presented at screening with no evidence of obstruction, inflammation or discharge, only 6 subjects (1.8%) developed mild mucosal thickening (obstruction), 8 (2.4%) had mild inflammation and 8 subjects had mild discharge. Of

those subjects with normal color mucosa at screening, there were 9 subjects (2.8%) that developed some pallor or redness at end of treatment.

Table 16, Table 17, and Table 18, represent the objective comparative findings at screening and end of treatment, regarding presence and degree of obstruction, inflammation, color of the mucosa, as well as symptoms such as bleeding, cough, and crusting.

Table 16: Objective Nasal Examination at Screening and End of Treatment Phase (Phase 3 Studies). Source: Table 2.7.4-48, Summary of Clinical Safety, page: 82/106, pdf File

		Screening	End of Treatment
		(N=500)	(N=346)
Parameter	Category	n (%)	n (%)
Obstruction[a]	Absent	481 (96.2)	337 (97.4)
	Mild	17 (3.4)	8 (2.3)
	Moderate	2 (0.4)	1 (0.3)
	Severe	0 (0.0)	0 (0.0)
Inflammation[b]	Absent	485 (97.0)	332 (96.0)
	Mild	15 (3.0)	14 (4.0)
	Moderate	0 (0.0)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Discharge present	None	466 (93.2)	334 (96.5)
	Mild	33 (6.6)	12 (3.5)
	Moderate	0 (0.0)	0 (0.0)
	Severe	1 (0.2)	0 (0.0)
Color of mucosa	Normal	465 (93.0)	330 (95.4)
	Pale	14 (2.8)	5 (1.4)
	Red	17 (3.4)	8 (2.3)
	Blue	0 (0.0)	0 (0.0)
	Other	4 (0.8)	3 (0.9)
Side most affected	Left	20 (4.0)	4 (1.2)
	Right	12 (2.4)	7 (2.0)
	Both equally	30 (6.0)	28 (8.1)
	N/A	438 (87.6)	307 (88.7)

N/A=not applicable

[a] Obstruction was recorded as: 0 = absent (No effect observed), 1 = mild (Mild mucosal thickening), 2 = moderate (Edema, narrowing of airways) or 3 = severe (Significant /severe obstruction).

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

Source: Table 18-2.1 ISS, Module 5.3.5.3.2

Table 17: Nasal Signs and Symptoms at Screening and End of Treatment in Phase 3 Studies (from Applicant's Table 2.7.4-49) (Part A) Source: Table 2.7.4-49, Summary of Clinical Safety, page: 84/106, pdf file

Parameter	Category	Screening (N=475) n (%)	End of Treatment (N=287) n (%)
Bleeding (nose)	Absent	470 (98.9)	283 (98.6)
	Mild	4 (0.8)	4 (1.4)
	Moderate	1 (0.2)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Burning or discomfort (nose)	Absent	459 (96.6)	278 (96.9)
	Mild	15 (3.2)	6 (2.1)
	Moderate	0 (0.0)	3 (1.0)
	Severe	1 (0.2)	0 (0.0)
Cough	Absent	424 (89.3)	253 (88.2)
	Mild	40 (8.4)	31 (10.8)
	Moderate	9 (1.9)	3 (1.0)
	Severe	2 (0.4)	0 (0.0)
Crusting or dryness (nose)	Absent	426 (89.7)	258 (89.9)
	Mild	41 (8.6)	25 (8.7)
	Moderate	8 (1.7)	3 (1.0)
	Severe	0 (0.0)	1 (0.3)

Source: Table 19-2.1 ISS, Module 5.3.5.3.2

Table 18: Nasal Signs and Symptoms at Screening and End of Treatment in Phase 3 Studies (from Applicant's Table 2.7.4-49) (Part B) Source: Table 2.7.4-49, Summary of Clinical Safety, page: 85/106 pdf file

Itching or sneezing	Absent	458 (96.4)	277 (96.5)
	Mild	14 (2.9)	10 (3.5)
	Moderate	2 (0.4)	0 (0.0)
	Severe	1 (0.2)	0 (0.0)
Postnasal drip	Absent	432 (90.9)	260 (90.6)
	Mild	38 (8.0)	24 (8.4)
	Moderate	4 (0.8)	2 (0.7)
	Severe	1 (0.2)	1 (0.3)
Runny nose	Absent	430 (90.5)	258 (89.9)
	Mild	38 (8.0)	25 (8.7)
	Moderate	6 (1.3)	2 (0.7)
	Severe	1 (0.2)	2 (0.7)
Sore throat	Absent	427 (89.9)	268 (93.4)
	Mild	37 (7.8)	14 (4.9)
	Moderate	7 (1.5)	4 (1.4)
	Severe	4 (0.8)	1 (0.3)
Stuffy nose	Absent	400 (84.2)	267 (93.0)
	Mild	49 (10.3)	16 (5.6)
	Moderate	25 (5.3)	4 (1.4)
	Severe	1 (0.2)	0 (0.0)
Taste disturbance	Absent	390 (82.1)	250 (87.1)
	Mild	57 (12.0)	30 (10.5)
	Moderate	23 (4.8)	5 (1.7)
	Severe	5 (1.1)	2 (0.7)

Source: Table 19-2.1 ISS, Module 5.3.5.3.2

Nasal tolerability was also assessed subjectively during Phase 3 studies in subjects, before and after treatment, by assessing symptoms of stuffy/blocked nose, runny nose, itching, sneezing, crusting and dryness, burning discomfort, bleeding, cough, post-nasal drip, sore throat, and taste alteration. These symptoms were scored on a 4-point scale

(0-3) (0=none and 3=severe). Data was collected before the first dose of PecFent, then at weeks 4, 8 and 12 of the open-label treatment and then at end of treatment.

A second set of data was collected 60 minutes after dosing for each episode of dose titration, double-blind treatment, and open-label. There were no clinically significant changes found.

After the administration of the study drug, taste disturbances were reported by 9.1%, runny nose, runny nose in 8.6%, cough in 8.2%, and crusting and dryness in 8.1%.

In the long term subjects (>90 days exposure), there were no significant changes related to obstruction, inflammation, discharge, color of the mucosa. There was also no evidence of increasing incidence of severe nasal symptoms or changes with increasing dose.

Conclusion:

The Applicant conducted a thorough assessment of the effects of PecFent on the nose and associated structures in Phase 3. The analyses used as many as 516 patients, many of whom were treated for more than 90 days. The evaluation was objective and subjective. The data show that the administration of PecFent was associated with rare, mild, self-limited nasal complaints. Because of the lack of an effective comparator, the incidence of the nasal adverse events cannot be placed into context. However, the drug appeared to not cause any clinically relevant nasal complaints.

7.3.5 Submission Specific Primary Safety Concerns

PecFent Formulation Safety Concerns

PecFent is an intranasal formulation of fentanyl that was developed with the goal of increasing the speed of absorption of fentanyl and subsequent faster onset of pain relief in patients.

PecFent includes (b) (4) pectin, a biopolymer. Once deposited on the mucosa the calcium ions interact with the pectin to form a gel. According to the Applicant, this gel optimizes the absorption of fentanyl.

Pectin is a polysaccharide rich in galactosyluronic acid. It is used commercially in the production of jams and jellies and has been used as an excipient in medicinal products.

Pectin has a low immunoreactivity. Hypersensitivity reactions appear to be extremely rare. Inhalation and ingestion of pectin may produce hypersensitivity reactions. A review of the medical literature revealed only a single report of anaphylaxis in one

patient that was thought to be related to oral ingestion of a smoothie with pectin contents (Ferdman, RM, Ong, PY, Church, JA: Pectin anaphylaxis and possible association with cashew allergy. Annals of Allergy, Asthma, and Immunology, V 97, No 6, Dec 2006 pp 759-60. My literature search revealed one case of occupational asthma developed in a mixer, exposed to powdered pectin in a manufacturing plant of jam products after repeated long term exposure (Cohen AJ, Forse, MS, Tarlo SM: Occupational asthma caused by pectin inhalation during manufacture of jam. Chest Jan; 103 (1):309-11, 1993

For more information about the PecFent formulation, please refer to the Chemistry/Manufacturing/Controls review by Dr. Sheldon Markofsky.

Droplet size

PecFent droplet parameters were assessed by the Applicant using laser diffraction and plume geometry. In testing, approximately (b) (4) of the particles were less than (b) (4) microns in size. The Applicant proposes a specification that not more than (b) (4) of the droplets will be less than (b) (4).

A literature search conducted by the Applicant in support of their proposed standard for drop diameter size shows that particles larger than (b) (4) are not inhaled to the lungs. Sprays tested with (b) (4) of the droplets smaller than (b) (4) show no evidence of significant lung deposition.

Nine-month toxicology studies in dogs performed by the Applicant, using a (b) (4) spray pump with similar size droplet spray size to the commercial product using 3 sprays per nostril 4 times daily revealed no lung changes

Pulmonary safety studies during the development of Sprix (intranasal ketorolac) included lung scintigraphy to determine lung deposition, laryngeal endoscopy, spirometry, and laser scattering. Ninety percent of the average particle size of the droplets generated by the IN ketorolac device were greater than (b) (4). The data spectrum provided by the Applicant indicates that PecFent falls within or below those parameters.

The droplet size specification for PecFent appears acceptable from a clinical perspective.

Container and Closure System

PecFent will be marketed in a 5.3 ml capacity container with a glass bottle sealed with a locking screw closure. A metered-dose nasal spray pump contains a visual and audible spray counter. A mechanical end-of use lock activates after 8 sprays are used. The Applicant has used a U-shaped bottle to minimize fill volume.

Each spray is (b) (4). The bottle will be filled with (b) (4) of product. When not in use, the assembly is to be kept in a child resistant outer canister that has a child resistant closure.

Recoverable Residual

The Applicant reports that, of the initial (b) (4) in the bottle, approximately (b) (4) mL will remain at end-of-use. The Applicant determined the residual by conducting a study where six drug product units with a (b) (4) fill were weighed, primed and 8 sprays actuated. The pump was removed and the amount of product recovered by inverting the bottle or by using a Pasteur pipette to recover the remains in the bottle. The results provided by the Applicant are shown in Tables 22 and 23, which show the mean recovery range of PecFen fill volume from units with pump removed from bottle.

Table 19: Mean Recovery Range of PecFent from Units with Pump Removed (from Applicant's Table 3.2.P.2.4-27) Source: Container Closure System: Section 3.2.P2 Vol #3, Quality page 36/197, pdf file

Prime (mL)	Dose sprays (mL)	Recoverable residual volume (mL)			Unrecoverable residual volume (mL)
		Bottle inversion (n=3)	Pipette (n=3)	Average	
(b) (4)					

Table 20: Mean Recovery Range of PecFent from Units with Pump Lock Broken (from Applicant's Table 3.2.P.2.4-28)

Prime (mL)	Dose sprays (mL)	Recoverable residual volume (mL)	Unrecoverable residual volume (mL)
(b) (4)			

Safety Issues derived from bottle residual and tamper protection issues

The amount of recoverable residual PecFent represents a significant health hazard because of the amount of fentanyl that will be introduced into the community in the form of used bottles.

The issue of excessive residual must be addressed by improving the bottle design in order to reduce the amount of drug residual drug. The bottle design should also be redesigned to strengthen the join of the glass bottle and the spray device.

Intravenous Administration of PecFent

This was an issue discussed during the development process. The Applicant has not assessed the risks of the IV administration of PecFent by potential abusers. The potential for emboli, due to intravascular gel formation when PecFent is exposed to divalent calcium ions when administered intravenously, is unknown.

While this assessment was recommended, current Division policy does not require a safety assessment via unlabeled routes of administration for an analgesic product. In comparison, a product indicated for addiction must have an assessment of administration by likely, unlabeled routes.

Instructions for Disposal of PecFent Residual

(b) (4)

Disposal of unopened bottles of PecFent no longer needed

(b) (4)

Comment:

The proposed disposal of residual PecFent by (b) (4) is potentially hazardous for the individual and household contacts. The potential risks of substantial fentanyl exposure and morbidity (particularly for a child) are high given that fentanyl readily is absorbed across the skin. The guidelines for the disposal of unused PecFent by patients need to be improved.

Safe product disposal is a priority in order to improve the public safety. A safer and better constructed container would also help to decrease the risks of diversion and misuse.

Overuse due to unperceived sprays or suspicion of device malfunction

The Applicant reports that, during Phase 3 studies, 17,182 doses were dispensed to 516 subjects. There were 325 cases of potential malfunction reported (1.9%). Please also see Section 7.6.4 for additional information related to device malfunction.

Key information and comments regarding device malfunctioning follows:

- Half of the reports indicate that the device did not appear to administer the dose adequately
- Bottle appeared empty before it reached counter of spray #8
- Counter was already advanced when bottle was received
- Doses were lost during priming
- Device did not prime appropriately
- Medication was dried out in the bottle
- Bottle top came off and leaked

:
Table 21 is a summary of the malfunctions reported in Phase 3 trials.

Table 21: Summary of Potential Medical Device Malfunctions-Phase 3 Studies. Source: Table 2.7.4-51: Summary of Clinical Safety, page 100/106, pdf file

	45,599 Treated Episodes	515 Total Subjects
Potential Device Malfunction	Number of Events (N=325 Overall)	Number of Subjects (N=106 Overall)
Unable to operate device	5	5
Device did not prime	10	9
Device didn't appear to administer the dose	156	55
Counter did not advance	32	22
Other	122	46

Source: Table 20-2.1

Device malfunctions have the ability to result in overdose if the patient does not realize that s/he was dosed and redoses. In some cases of overdose, there were instances where the device was perceived by the subject as having malfunctioned. Following are examples of statements by patients regarding unperceived sprays. This is the language used by the subjects; the subject ID is in parentheses.

- “Unaware that the dose was delivered to the nose” (390404),

- "Did not feel the spray entering the nostril" (391402),
- "Felt drug was not delivered" (460305),
- "Uneven puffs, fail to deliver study-medication, episode of cyanosis and unconsciousness" (585605),
- "Missed nose" (585903),
- "Felt there was a mismatch between the number of doses and the administrations" (520401)

The Applicant states that a low volume and speed of spray delivery may account for the failure to perceive a dose.

In conclusion, some subjects described that they do not perceive that spray has been delivered to their nose, while dosing may have occurred. A clear explanation for this is not evident.

The Applicant recommends that subjects or patients rely on the click generated by the device and by the number advance on the counter device to determine if a dose has been delivered. The Applicant will be providing detailed information regarding how to use this product in the medication guide.

Device Tampering

There were two instances of device tampering reported.

Subject 391403 was a 50 year-old male who completed Study CP403 and was enrolled in study CP 045 stabilized on a dose of 80 mcg of PecFent. He retuned to kits with each showing one bottle that had the appearance of dismantling, with incorrect reassembly. One bottle had pliers marks. The subject, who was an engineer, said he was curious about the functioning of the device. After counseling there was no further evidence of tampering. The subject had a couple of bottles misplaced. The medication use was below expected.

Subject 594402 was a 28 year-old Caucasian male was able to titrate successfully to 800 mcg of PecFent and entered the Open-label treatment phase of study CP045. On study day 30 when he returned the first 4 bottles, one of the kits appeared to have been tampered. The other 6 bottles were not returned. The 10 bottles in the second kit were unopened. The subject withdrew consent to participation. His diary showed a mismatch of the number of doses dispensed, and the number of BTCP episodes recorded of (-12.5%) and indicates a protocol deviation.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common AEs observed during Phase 1 were discussed in section 7.3.5 under the section of AEs of special interest in relation to nasal AEs.

During Phase 2/3 studies, 389 subjects experienced 1 or more AEs. A higher proportion of AEs were reported in subjects receiving higher doses of PecFent (400 and 800 mcg). The Applicant suggests that this may be a reflection of the high numbers of episodes treated at higher doses of PecFent. Most adverse events were mild or moderate in intensity: 142 (27.5%) subjects had severe AEs at some point during the studies. Seventy-four (14.3%) had AEs leading to drug discontinuation.

The safety assessment program (SAP) analyzed the adverse event data in 3 populations; the overall safety population, dose titration and dose-maintained population. The last two populations are most important in clinical practice.

During dose titration, 213 subjects (41.3%) subjects reported mild or moderate intensity AEs. Twenty-seven (5.2%) reported severe adverse events. Such AEs led to drug discontinuation in 21 (4.2%). There were no notable differences observed across different doses in the titration phase.

The most common AEs in phase 2/3 studies (516 subjects) were as documented in Table 22 below, that included: vomiting in 71 patients (13.8%), nausea in 63 patients (12.2%), disease progression in 62 patients (12%), constipation in 50 patients (9.7%), dizziness in 42 patients (8.1%), somnolence in 36 patients (7%), pyrexia in 28 patients (5.4%) and pain in 24 patients (4.7%).

Table 22: Adverse Events by Preferred Term in the Safety Population in Phase 2/3 studies arranged by dose of PecFent (from Applicant's table 6-2.7.1). Source: ISS Phase 2/3 Statistical Tables, page: 1431/27077, pdf file

Preferred Term	100 mcg N=484	200 mcg N=389	400 mcg N=319	800 mcg N=182	Total N=516
Number (%) of Subjects with at Least One AE	150 (31.0)	109 (28.0)	139 (43.6)	113 (62.1)	389 (75.4)
Vomiting	20 (4.1)	20 (5.1)	21 (6.6)	14 (7.7)	71 (13.8)
Nausea	23 (4.8)	15 (3.9)	12 (3.8)	14 (7.7)	63 (12.2)
Disease Progression	16 (3.3)	8 (2.1)	16 (5.0)	26 (14.3)	62 (12.0)
Constipation	23 (4.8)	6 (1.5)	14 (4.4)	8 (4.4)	50 (9.7)
Dizziness	16 (3.3)	14 (3.6)	8 (2.5)	9 (4.9)	42 (8.1)
Somnolence	10 (2.1)	8 (2.1)	14 (4.4)	7 (3.8)	36 (7.0)
Pyrexia	7 (1.4)	6 (1.5)	9 (2.8)	7 (3.8)	28 (5.4)
Pain	5 (1.0)	4 (1.0)	8 (2.5)	8 (4.4)	24 (4.7)
Dyspnoea	9 (1.9)	4 (1.0)	5 (1.6)	5 (2.7)	23 (4.5)
Diarrhoea	7 (1.4)	4 (1.0)	6 (1.9)	6 (3.3)	22 (4.3)
Headache	9 (1.9)	7 (1.8)	2 (0.6)	2 (1.1)	20 (3.9)
Anaemia	1 (0.2)	8 (2.1)	4 (1.3)	6 (3.3)	19 (3.7)
Fatigue	3 (0.6)	3 (0.8)	9 (2.8)	5 (2.7)	19 (3.7)

Note: Subjects are counted only once at each level of summarization.
Source: Integrated ISS database: Phase 2/3 Studies (CP041, CP043/06/FCNS, CP044/06/FCNS, CP045/06/FCNS).

The adverse event data was subdivided into dose-titrated and dose-maintained populations by the Applicant.

Of the 516 subjects who entered the dose-titration phase, 240 subjects (41.3%) had one or more AEs. The incidence across all 4 doses was quite similar as illustrated in Table 23. Common AEs (≥5%) included: nausea, vomiting 33, and dizziness 31. Constipation and somnolence were in the 4% range. Six adverse effects were reported in >1% <2.5% of the subjects including: headache, pain and pyrexia (both 1.6%), dyspnea and epistaxis (both 1.2%). There was no dose response seen during titration.

Table 23: Adverse Events in Titration Phase in Descending Order- Phase 2/3 Studies (from Applicant's Table 6-2.7.2). Source: ISS Phase 2/3 Statistical Tables: page 1431/27077, pdf file

Preferred Term	100 mcg N=483	200 mcg N=380	400 mcg N=301	800 mcg N=161	Total N=516
Number (%) of Subjects with at Least One AE	124 (25.7)	58 (15.3)	56 (18.6)	29 (18.0)	213 (41.3)
Nausea	19 (3.9)	6 (1.6)	6 (2.0)	5 (3.1)	35 (6.8)
Vomiting	14 (2.9)	10 (2.6)	9 (3.0)	1 (0.6)	33 (6.4)
Dizziness	14 (2.9)	11 (2.9)	6 (2.0)	4 (2.5)	31 (6.0)
Constipation	17 (3.5)	3 (0.8)	3 (1.0)	0 (0.0)	22 (4.3)
Somnolence	8 (1.7)	8 (2.1)	7 (2.3)	1 (0.6)	22 (4.3)
Headache	7 (1.4)	4 (1.1)	1 (0.3)	0 (0.0)	12 (2.3)
Disease Progression	3 (0.6)	1 (0.3)	3 (1.0)	2 (1.2)	9 (1.7)
Pain	4 (0.8)	2 (0.5)	1 (0.3)	1 (0.6)	8 (1.6)
Pyrexia	5 (1.0)	1 (0.3)	2 (0.7)	1 (0.6)	8 (1.6)
Dyspnoea	6 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.2)
Epistaxis	3 (0.6)	2 (0.5)	2 (0.7)	0 (0.0)	6 (1.2)
Anxiety	2 (0.4)	1 (0.3)	2 (0.7)	0 (0.0)	5 (1.0)
Cough	3 (0.6)	0 (0.0)	2 (0.7)	0 (0.0)	5 (1.0)

Note: Subjects are counted only once at each level of summarization.
Source: Integrated ISS database: Phase 2/3 Studies (CP041, CP043/06/FCNS, CP044/06/FCNS, CP045/06/FCNS).

During the dose titration phase, there were 27 (5.2%) subjects who had severe AEs, and 21(4.1%) patients experienced adverse events that led to discontinuation.

There were 346 subjects who entered the dose-maintained treatment phase of the double-blind and open-label (OL) studies. Of those 237 (68.5%) reported one or more AE's. No notable difference in incidence is noted among different groups, with increasing dose. The most common AEs reported in the dose-maintained population in descending order were: disease progression 12.7%, vomiting 9.8%, nausea 6.6%, pyrexia 6.4%, constipation 5.8%, diarrhea 4.9%, and dyspnea 4.9%.

7.4.2 Laboratory Findings

The Applicant reported changes in hematology, chemistry, and urinalysis, with summaries of mean changes from screening to end of treatment. None of the laboratory shifts observed in subjects during Phase 1 trials were clinically significant.

Patients enrolled in the Phase 2/3 studies have end-stage cancer. As such, the interpretation of laboratory abnormalities is confounded due to the underlying tumor plus various other medical treatments used, including chemotherapy and/or radiation.

Summaries of mean and shift changes from beginning to end of treatment were provided and showed changes in neutrophils and leukocytes with values within those expected in subjects with terminal disease.

The changes in serum chemistry also reflected changes consistent with disease progression. The albumin levels were consistent with the declining clinical status of the patients. One subject with diabetes developed hyperglycemia. The assessment of laboratory values in this population was difficult due to the high incidence of life threatening metabolic and hepato-renal complications. However, in the context of fentanyl not be associated with changes in chemistry, urinalysis, or hematology, the laboratory data appear do not suggest that PecFent adversely affects laboratory data.

7.4.3 Vital Signs

Vital signs were recorded during Phase 1 and 3 studies, including systolic/diastolic BP, heart rate, respiratory rate and weight in kg. No clinically significant changes were found from screening to end of treatment during Phase 1 studies. Findings were summarized separately using descriptive statistics (N, mean, median, SD, SE, minimum and maximum) at screening and end of treatment.

Collection of Vital Signs was not required for study CP041 (Phase 2 study)

During Phase 3, the changes observed from screening to end of treatment were small and clinically insignificant. The Applicant reported no statistically significant changes by

geographic location or race. Table 24 shows the mean changes from screening to end of treatment in vital signs of Phase 3 studies.

Table 24: Changes in Vital Signs from Screening to End of Treatment- Phase 2/3 Studies (from Applicant's Table 11-1). Source: Integrated Summary of Safety Report, page: 110/407, pdf file

	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Weight (kg)
Screening	(N=499)	(N=499)	(N=498)	(N=491)	(N=499)
Mean (SD)	122.5 (16.05)	76.2 (10.04)	80.1 (12.15)	17.2 (3.07)	67.2 (20.15)
End of Treatment	(N=349)	(N=349)	(N=352)	(N=349)	(N=339)
Mean (SD)	121.5 (16.61)	75.5 (10.45)	81.7 (12.86)	17.0 (3.09)	67.6 (20.55)
Change from Screening	(N=349)	(N=349)	(N=352)	(N=346)	(N=339)
Mean (SD)	-1.2 (17.21)	-0.5 (11.44)	1.8 (13.13)	0.1 (2.64)	-0.8 (5.30)
Median	0.0	0.0	0.0	0.0	0.00
Min - Max	-73 – 63	-50 – 38	-82 – 52	-10 – 10	-24.3 – 49.4

Source: Table 17-2.1

Fentanyl is associated with certain changes in vital signs including blood pressure and respiratory rate. However, due to the confounded nature of the safety data, the lack of detail in adverse event data, and lack of a comparator group, this is difficult to interpret. Given these limitations, no unexpected safety signals were observed.

7.4.4 Electrocardiograms (ECGs)

The Applicant obtained routine ECGs during Phase 1 studies CP037/02 and CP042/05. No ECG abnormalities were detected during the PK studies.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical studies or trials conducted outside of the study CP048 for allergic rhinitis described earlier.

7.4.6 Immunogenicity

The literature supports the conclusion that PecFent poses little risk of immunogenicity. PecFent contains (b) (4) pectin (b) (4) Pectin). (b) (4) that form gels on contact with multivalent ions. In the nasal cavity (b) (4) Pectin gels mainly by interaction with divalent calcium. The Applicant has conducted studies on the gelling properties of (b) (4) pectin in the rat nasal cavity. In the nasal cavity the gel tends to form plaques rather than a mass after gelling. Pectin has not been reported in the medical literature as a highly immunoreactive product.

Local intranasal toxicity of aqueous fentanyl was investigated by Ranklove, LB, Thorhauge, MMK, Eriksen CS, Glerup, and P: The use of minipigs for testing the local intranasal toxicity of fentanyl. Scand J Lab. Anim. Sci: V 33, No 1, (2006). In 4 minipigs, the distribution was studied by applying methylene blue. No relevant microscopic or macroscopic findings in the nasal mucosa were found in minipigs that received 5 x 400 mcg daily for 4 weeks.

There is evidence in the medical literature on the successful use of liquid pectin to emulsify or thicken gastric feedings with the purpose of diminishing respiratory symptoms in handicapped impaired children with GERD (Miyazawa R, Haneko H, Tomomasa T, Shimizu N, Morikawa A: Effects of pectin liquid on respiratory symptoms in neurologically impaired children with gastroesophageal reflux disease:, Pediatric Respiratory Reviews, Vol 7 Suppl 1 2006) pp S295

The Applicant conducted a 9-month dog and 6-month rat toxicology study, both with intranasal administration of the pectin/fentanyl formulation. There were no alterations referable to the immune system in the dog. In the rat, some goblet cell hypertrophy/hyperplasia in the nasal cavities was seen in females at the high dose. Alveolar macrophage infiltration in the lung was seen at the high dose in both sexes

For details please refer to the Pharmacology/Toxicology review by Dr. Bolan.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the titration phase, the incidence of common adverse events did not appear to correlate with dose. Actually, the AEs reported in ≥5% of the subjects appeared to have an inverse relationship with dose. These data are summarized in Table 25.

The incidence of AEs in dose-maintained subjects appeared evenly distributed in all groups. Certain AEs are marginally higher at 800 mcg; some are lower. There is no pattern or clinical significance to the minor differences in rates between doses. The dose response data are shown in Table 26.

Table 25: Summary of AEs reported in >5% of Subject in Phase 2/3 Studies, titration phase (from Applicant's table 12-2.1.2). Source: ISS Phase 2/3 Statistical Tables: page: 3467/27077, pdf file

System Organ Class Preferred Term	100 mcg N=483	200 mcg N=380	400 mcg N=301	800 mcg N=161	Total N=516
Number (%) of Subjects with at Least One AE	40 (8.3)	25 (6.6)	16 (5.3)	8 (5.0)	81 (15.7)
Gastrointestinal Disorders					
Nausea	19 (3.9)	6 (1.6)	6 (2.0)	5 (3.1)	35 (6.8)
Vomiting	14 (2.9)	10 (2.6)	9 (3.0)	1 (0.6)	33 (6.4)
Nervous System Disorders					
Dizziness	14 (2.9)	11 (2.9)	6 (2.0)	4 (2.5)	31 (6.0)

Note: Subjects are counted only once at each level of summarization.
This table is sorted by alphabetic order of System Organ Class and by descending frequency of Preferred Term for the total column.
Source: Integrated ISS database: Phase 2/3 Studies (CP041, CP043/06/FCNS, CP044/06/FCNS, CP045/06/FCNS).

Table 26: Summary of AEs reported by >2.5%of all Subjects in Descending Order-Overall Incidence, Phase 2/3 Studies in Dose Maintained Population. Source: Table 9-9 Integrated Summary of Safety Report: page 68/407, pdf file

	n (%)				
Preferred Term	**100 mcg (N=61)**	**200 mcg (N=68)**	**400 mcg (N=109)**	**800 mcg (N=108)**	**Total (N=346)**
Subjects with ≥1 AE	43 (70.5)	41 (60.3)	75 (68.8)	78 (72.2)	237 (68.5)
Disease progression	11 (18.0)	6 (8.8)	8 (7.3)	19 (17.6)	44 (12.7)
Vomiting	8 (13.1)	5 (7.4)	9 (8.3)	12 (11.1)	34 (9.8)
Nausea	4 (6.6)	6 (8.8)	4 (3.7)	9 (8.3)	23 (6.6)
Pyrexia	3 (4.9)	5 (7.4)	8 (7.3)	6 (5.6)	22 (6.4)
Constipation	6 (9.8)	1 (1.5)	8 (7.3)	5 (4.6)	20 (5.8)
Diarrhoea	5 (8.2)	2 (2.9)	5 (4.6)	5 (4.6)	17 (4.9)
Dyspnoea	3 (4.9)	4 (5.9)	5 (4.6)	5 (4.6)	17 (4.9)
Oedema peripheral	0 (0.0)	2 (2.9)	7 (6.4)	5 (4.6)	14 (4.0)
Fatigue	2 (3.3)	1 (1.5)	6 (5.5)	4 (3.7)	13 (3.8)
Pain	1 (1.6)	1 (1.5)	5 (4.6)	6 (5.6)	13 (3.8)
Dehydration	1 (1.6)	2 (2.9)	2 (1.8)	7 (6.5)	12 (3.5)
Somnolence	2 (3.3)	0 (0.0)	5 (4.6)	5 (4.6)	12 (3.5)
Asthenia	1 (1.6)	1 (1.5)	7 (6.4)	2 (1.9)	11 (3.2)
Anaemia	1 (1.6)	3 (4.4)	2 (1.8)	4 (3.7)	10 (2.9)
Pharyngolaryngeal pain	3 (4.9)	3 (4.4)	1 (0.9)	3 (2.8)	10 (2.9)
Anxiety	2 (3.3)	1 (1.5)	5 (4.6)	1 (0.9)	9 (2.6)
Cough	1 (1.6)	0 (0.0)	5 (4.6)	3 (2.8)	9 (2.6)
Insomnia	2 (3.3)	2 (2.9)	3 (2.8)	2 (1.9)	9 (2.6)
Urinary tract infection	2 (3.3)	0 (0.0)	4 (3.7)	3 (2.8)	9 (2.6)

Source: Table 6-2.7.3, Table 11-2.1.3 and Table 12-2.1.3

7.5.2 Time Dependency for Adverse Events

There was no relationship between dose at onset and incidence for the most common AEs.

7.5.3 Drug-Demographic Interactions

Age: Subjects older than 60 years old represented a smaller proportion (27%) of the population sample (143/516). Differences of >5% in the incidence of AEs were noted only in 2 instances. The findings show a higher incidence constipation in the older group, and a lower occurrence of pyrexia in those less than 60 years old. These differences do not appear to be clinically significant. The adverse events by age are summarized in Table 27.

Table 27: Common Reported >2.5% in Subjects with Treatment Emergent AEs by Age Groups in Phase 2/3 Studies (from Applicant's Table 16-1). Source: Integrated Summary of Safety Report, page: 123/407, pdf file

Preferred Term	Age Group	
	≤60 years (N=373)	>60 years (N=143)
Number (%) of subjects with ≥1 AE	282 (75.6)	107 (74.8)
Vomiting	52 (13.9)	19 (13.3)
Nausea	48 (12.9)	15 (10.5)
Disease progression	49 (13.1)	13 (9.1)
Constipation	30 (8.0)	20 (14.0)
Dizziness	30 (8.0)	12 (8.4)
Somnolence	24 (6.4)	12 (8.4)
Pyrexia	26 (7.0)	2 (1.4)
Pain	18 (4.8)	6 (4.2)
Dyspnoea	17 (4.6)	6 (4.2)
Diarrhoea	14 (3.8)	8 (5.6)
Headache	16 (4.3)	4 (2.8)
Anaemia	13 (3.5)	6 (4.2)
Fatigue	11 (2.9)	8 (5.6)
Oedema peripheral	14 (3.8)	5 (3.5)
Dehydration	13 (3.5)	5 (3.5)
Anxiety	10 (2.7)	7 (4.9)
Insomnia	11 (2.9)	6 (4.2)
Asthenia	12 (3.2)	4 (2.8)
Epistaxis	10 (2.7)	5 (3.5)
Cough	11 (2.9)	3 (2.1)
Pharyngolaryngeal pain	10 (2.7)	4 (2.8)

Source: Table 6-2.8

Differences in treatment-related AEs by age group between 1-3% were also listed but this marginal difference is not clinically significant.

Gender: The number of subjects with ≥1 AE was slightly higher in females (73.5% vs 77.5%). Treatment-emergent AEs reported for more than 2.5% of all subjects in Phase 2/3 studies are documented in Table 28 and Table 29.

There was a slightly higher incidence of vomiting in females (17.2% vs 10.7%), and a higher incidence of pyrexia in males (8.1 vs. 2%). The relatively high rate of vomiting observed in women is usually observed in clinical trials. The excess rate of pyrexia is of uncertain significance. Fentanyl is not known to affect body temperature.

Table 28: Common Reported >2.5% of Subjects Overall Treatment Emergent Adverse Events by Gender in Phase 2/3 Studies. Source: Integrated Summary of Safety Report: page 125/407, pdf file

	Gender	
Preferred Term	**Female (N=244)**	**Male (N=272)**
Number (%) of subjects with ≥1 AE	189 (77.5)	200 (73.5)
Vomiting	42 (17.2)	29 (10.7)
Disease progression	32 (13.1)	30 (11.0)
Nausea	32 (13.1)	31 (11.4)
Constipation	22 (9.0)	28 (10.3)
Dizziness	25 (10.2)	17 (6.3)
Somnolence	15 (6.1)	21 (7.7)
Pyrexia	6 (2.5)	22 (8.1)
Pain	11 (4.5)	13 (4.8)
Dyspnoea	12 (4.9)	11 (4.0)
Diarrhoea	8 (3.3)	14 (5.1)
Headache	12 (4.9)	8 (2.9)
Anaemia	6 (2.5)	13 (4.8)
Fatigue	5 (2.0)	14 (5.1)
Oedema peripheral	7 (2.9)	12 (4.4)
Dehydration	6 (2.5)	12 (4.4)
Anxiety	6 (2.5)	11 (4.0)
Insomnia	7 (2.9)	10 (3.7)
Asthenia	6 (2.5)	10 (3.7)
Epistaxis	8 (3.3)	7 (2.6)
Cough	2 (0.8)	12 (4.4)
Pharyngolaryngeal pain	6 (2.5)	8 (2.9)

Source: Table 6-2.9

Table 29: Common Reported >1.0 % Treatment-Related Adverse Events by Gender in Phase 2/3 Studies. Source: Integrated Summary of Safety Report, page 126/407, pdf file

Preferred Term	Gender	
	Female (N=244)	Male (N=272)
Number (%) of subjects with ≥1 treatment-related AE	79 (32.4)	70 (25.7)
Dizziness	19 (7.8)	13 (4.8)
Somnolence	12 (4.9)	13 (4.8)
Vomiting	19 (7.8)	6 (2.2)
Nausea	16 (6.6)	7 (2.6)
Constipation	6 (2.5)	9 (3.3)
Headache	6 (2.5)	6 (2.2)
Nasal discomfort	5 (2.0)	5 (1.8)
Epistaxis	4 (1.6)	3 (1.1)
Dysgeusia	2 (0.8)	4 (1.5)
Pruritus	4 (1.6)	2 (0.7)
Rhinorrhoea	3 (1.2)	3 (1.1)
Disorientation	3 (1.2)	2 (0.7)

Source: Table 7-2.6

Race:
The Applicant grouped adverse events into the following three groups: Caucasian, N=281 (55 %); Black, N=24 (5 %) and Other, N=205 (40%). The group coded as "other" were predominantly patients from India. The Applicant states that the low percentage of Black subjects precludes from meaningful conclusions. Table 30 shows a comparison of common treatment emergent AEs that occurred in ≥2.5% subjects, by race. The significance of higher or lower incidences of vomiting, disease progression, nausea, somnolence, pyrexia, anxiety, and insomnia are of uncertain significance.

Table 30: Common >2.5% Treatment emergent AEs by Race in Phase 2/3 Studies. Source: Integrated Summary of Safety Report: page 127/407, pdf file.

Preferred Term	Race		
	Caucasian (N=281)	Black (N=24)	Other (N=205)
Number (%) of subjects with ≥1 AE	217 (77.2)	20 (83.3)	149 (72.7)
Vomiting	30 (10.7)	7 (29.2)	34 (16.6)
Disease progression	33 (11.7)	6 (25.0)	23 (11.2)
Nausea	50 (17.8)	5 (20.8)	8 (3.9)
Constipation	29 (10.3)	2 (8.3)	19 (9.3)
Dizziness	29 (10.3)	2 (8.3)	10 (4.9)
Somnolence	26 (9.3)	1 (4.2)	8 (3.9)
Pyrexia	7 (2.5)	1 (4.2)	20 (9.8)
Pain	20 (7.1)	1 (4.2)	3 (1.5)
Dyspnoea	13 (4.6)	2 (8.3)	7 (3.4)
Diarrhoea	11 (3.9)	0 (0.0)	11 (5.4)
Headache	11 (3.9)	1 (4.2)	7 (3.4)
Anaemia	15 (5.3)	0 (0.0)	4 (2.0)
Fatigue	16 (5.7)	0 (0.0)	2 (1.0)
Oedema peripheral	13 (4.6)	0 (0.0)	6 (2.9)
Dehydration	9 (3.2)	1 (4.2)	8 (3.9)
Anxiety	8 (2.8)	2 (8.3)	7 (3.4)
Insomnia	10 (3.6)	3 (12.5)	4 (2.0)
Asthenia	9 (3.2)	0 (0.0)	7 (3.4)
Epistaxis	10 (3.6)	1 (4.2)	3 (1.5)
Cough	6 (2.1)	0 (0.0)	8 (3.9)
Pharyngolaryngeal pain	9 (3.2)	1 (4.2)	4 (2.0)

Location:

Phase 2/3 studies were conducted in several countries and continents and were summarized by the Applicant in **Table 31 .** The data is sorted by participant population in the US/Canada N=209 (41%), Europe N=106 (21%), India N=154 (30%), Other N=47 (9%). Commonly reported AEs >2.5% as treatment-emergent by location are also provided in the same table**.** While certain differences in adverse event incidence are observed, the significance of these differences is unclear. It is possible that some of the differences in reporting rates may be due to cultural differences.

Table 31: Common >2.5% Treatment-Related AEs by Location in Phase 2/3 Studies. Source: Integrated Summary of Safety Report, page: 129/407, pdf file

Preferred Term	Location			
	US/Canada (N=209)	Europe (N=106)	India (N=154)	Other (N=47)
Number (%) of subjects with ≥1 AE	160 (76.6)	83 (78.3)	107 (69.5)	39 (83.0)
Vomiting	25 (12.0)	14 (13.2)	21 (13.6)	11 (23.4)
Disease progression	32 (15.3)	8 (7.5)	15 (9.7)	7 (14.9)
Nausea	42 (20.1)	17 (16.0)	1 (0.6)	3 (6.4)
Constipation	20 (9.6)	14 (13.2)	14 (9.1)	2 (4.3)
Dizziness	18 (8.6)	14 (13.2)	4 (2.6)	6 (12.8)
Somnolence	12 (5.7)	14 (13.2)	4 (2.6)	6 (12.8)
Pyrexia	5 (2.4)	3 (2.8)	19 (12.3)	1 (2.1)
Pain	6 (2.9)	15 (14.2)	3 (1.9)	0 (0.0)
Dyspnoea	6 (2.9)	9 (8.5)	7 (4.5)	1 (2.1)
Diarrhoea	9 (4.3)	3 (2.8)	4 (2.6)	6 (12.8)
Headache	9 (4.3)	4 (3.8)	4 (2.6)	3 (6.4)
Anaemia	7 (3.3)	10 (9.4)	2 (1.3)	0 (0.0)
Fatigue	6 (2.9)	12 (11.3)	1 (0.6)	0 (0.0)
Oedema peripheral	5 (2.4)	8 (7.5)	6 (3.9)	0 (0.0)
Dehydration	8 (3.8)	2 (1.9)	7 (4.5)	1 (2.1)
Anxiety	9 (4.3)	1 (0.9)	5 (3.2)	2 (4.3)
Insomnia	7 (3.3)	6 (5.7)	4 (2.6)	0 (0.0)
Asthenia	4 (1.9)	5 (4.7)	6 (3.9)	1 (2.1)
Epistaxis	9 (4.3)	3 (2.8)	1 (0.6)	2 (4.3)
Cough	5 (2.4)	1 (0.9)	8 (5.2)	0 (0.0)
Pharyngolaryngeal pain	4 (1.9)	5 (4.7)	4 (2.6)	1 (2.1)

Source: Table 6-2.11

7.5.4 Drug-Disease Interactions

The Applicant compared asymptomatic otherwise healthy subjects, with subjects with symptomatic allergic rhinitis. The subjects with rhinitis were treated with oxymetazoline (Study CP048). No clinically significant effect on Cmax, Tmax, or overall exposure was noted by comparing challenged and unchallenged conditions. This would indicate that the clinical efficacy of one dose of PecFent would be unaffected in untreated rhinitis.

The Applicant presented the adverse events reported for more than 2.4% of subjects in Phase 2/3 studies and summarized the subpopulations by history, symptoms, treatment of allergic disorders. No differences of ≥5% were observed between those with or without allergic symptoms.

7.5.5 Drug-Drug Interactions

A pharmacokinetic study evaluating the absorption and tolerability of PecFent in subjects with allergic rhinitis in Phase 1 Study CP048 was performed as mentioned above. In the third crossover period, patients with allergic rhinitis were treated with oxymetazoline. The Cmax for subjects treated with oxymetazoline was approximately 25% lower than the untreated subjects and the Tmax lengthened to 45 minutes compared to 15-20 minutes in the untreated state.

There were no formal PecFent drug-drug interaction studies conducted by the Applicant. Fentanyl is a known CYP3A4 substrate. Thus, there are known interactions with CYP3A4 inhibitors or inducers.

Interpretation of outcomes and AEs in these studies is confounded by the effect of background use of opioids and the large variety of other medications used in this patient population. Given those limitations, no drug-drug interactions were apparent.

A summary of the opioid use for background pain among long term subjects in the Phase 3 studies is presented in Table 32.

Table 32: Opioid Use for Background Pain >5% overall use by Location for Long Term Subjects. Source: Integrated Summary of Safety Report, page 152/407, pdf file

Generic Name	US/Canada (N=74)	Europe (N=28)	India (N=37)	Argentina/Costa Rica (N=14)	Total (N=153)
Morphine sulfate	28 (37.8)	7 (25.0)	16 (43.2)	0 (0.0)	51 (33.3)
Fentanyl	28 (37.8)	17 (60.7)	2 (5.4)	1 (7.1)	48 (31.4)
Morphine	7 (9.5)	0 (0.0)	24 (64.9)	9 (64.3)	40 (26.1)
Methadone	11 (14.9)	2 (7.1)	0 (0.0)	5 (35.7)	18 (11.8)
Oxycodone HCl	8 (10.8)	3 (10.7)	0 (0.0)	0 (0.0)	11 (7.2)

Note: Opioid use data from CP041 were not available.
Source: Table 3-2.4

An analysis of the most common concomitant medications used by long term subjects is presented in Table 33. Rescue medication use was reported by 12.3% during the Open-label and Dose-titration phases and by 5.1-6.6% during other study phases.

Table 33: Concomitant Medication Use (>10%) by Location in Long term Subjects Source: Integrated Summary of Safety Report page 153/407, pdf file

Generic Name	US/Canada (N=74)	Europe (N=28)	India (N=37)	Argentina/Costa Rica (N=14)	Total (N=153)
Morphine sulfate	16 (21.6)	17 (60.7)	10 (27.0)	0 (0.0)	43 (28.1)
Dexamethasone	11 (14.9)	9 (32.1)	8 (21.6)	3 (21.4)	31 (20.3)
Gabapentin	20 (20.7)	3 (10.7)	5 (13.5)	2 (14.3)	30 (19.6)
Metoclopramide	9 (12.2)	3 (10.7)	11 (29.7)	5 (35.7)	28 (18.3)
Paracetamol	9 (12.2)	8 (28.6)	3 (8.1)	6 (42.9)	26 (17.0)
Morphine	3 (4.1)	2 (7.1)	16 (43.2)	5 (35.7)	26 (17.0)
Ondansetron	13 (17.6)	2 (7.1)	9 (24.3)	1 (7.1)	25 (16.3)
Bisacodyl	5 (6.8)	2 (7.1)	16 (43.2)	0 (0.0)	23 (15.0)
Omeprazole	8 (10.8)	8 (28.6)	4 (10.8)	3 (21.4)	23 (15.0)
Ibuprofen	15 (20.3)	3 (10.7)	0 (0.0)	1 (7.1)	19 (12.4)
Multivitamins	11 (14.9)	0 (0.0)	8 (21.6)	0 (0.0)	19 (12.4)
Pregabalin	11 (4.9)	5 (17.9)	2 (5.4)	0 (0.0)	18 (11.8)
Oxycodone	15 (20.3)	0 (0.0)	0 (0.0)	2 (14.3)	17 (11.1)
Zolpidem tartrate	12 (6.2)	4 (14.3)	0 (0.0)	0 (0.0)	16 (10.5)

Source: Table 4-2.4

7.6 Additional Safety Evaluations

There were no additional safety evaluations performed.

7.6.1 Human Carcinogenicity

Carcinogenicity studies were not conducted.

7.6.2 Human Reproduction and Pregnancy Data

There were no specific studies conducted by the Applicant to assess the reproductive toxicity of PecFent. Fentanyl would be expected to affect the fetus and the newborn. Caution must be exercised during labor and delivery because fentanyl crosses the placenta and will cause pharmacodynamic effects in the fetus. Drug withdrawal may be precipitated in newborns born to mothers chronically using opioids.

Two subjects developed a positive pregnancy test while in studies using PecFent.

Subject 225 is a 37 year-old female randomized to treatment in Study CP048 (was a Phase 1, crossover study for subjects with seasonal allergic rhinitis). The subject completed the first 2 legs of the study (active and asymptomatic periods). When she

presented for the third leg of the study (oxymetazoline treatment leg), she was found to have a positive routine pregnancy test. The results were confirmed and she was withdrawn from the study. The subjected indicated that she was using an ethinyl estradiol contraceptive patch and her partner was using a condom. The date of her last normal menstrual period and anticipated delivery dates were unknown. She was a cigarette smoker and used < 7 units of alcohol weekly.

She decided to terminate the pregnancy by induced abortion. The pregnancy termination was not considered drug related. Following the abortion she was placed on doxycycline hyclate 100 mg.

Subject 853/585301, in study CP045, was found to have a positive urine and serum pregnancy test during screening, despite have a "normal" menstrual period 1 week earlier. The serum Beta hCG test was elevated (436 mIU/mL) corresponding approximately to a 4 week pregnancy. A gynecologist found no evidence of a fetus on utrasonography and determined she was not pregnant. The findings were attributed to her tumor. She had pancreatic carcinoma. She was allowed to enroll, and participated in the study until her death from disease progression within a month.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric exposure was reported in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant defined overdose as an incident that occurs when more study drug is administered than prescribed and is associated with adverse clinical effects. Over-administration was defined as the administration of more study drug than prescribed but without adverse effects.

The Applicant reports 11 cases of potential overdose instances (as defined above). The cases are summarized as follows:

Subject 390404 was a 63 year-old African-American male with progressive obstructive jaundice and cholangitis from unknown source of primary carcinoma. This patient experienced severe bouts of BTCP. He was titrated to 800 mcg of PecFent as a participant in Study CP043. His other medications included MS ER and IR, hydromorphone, zolpidem, methylphenidate, prednisone, warfarin, and pregabalin, The CRF does not provide cancer type.

He reported being unaware of the spray delivery into his nostrils and he took 2 extra sprays. The total dose he received was 1600 mcg of PecFent in the active arm. He

reported no adverse effect and continued on to the open label phase study CP045, completing the 16-week OL (open-label) phase uneventfully. He died of disease progression on study day #140.

Subject 390504 was a 59 year-old African-American woman. Initially, she described difficulties adjusting during the titration phase, but gradually advanced to a daily dose of 400 mcg of PecFent. There were significant errors in her e-diary keeping. She used PecFent 400 mcg twice without efficacy in two subsequent days and was given instructions on study day 5, to use 800 mcg at her next episode of BTCP. She left the nozzle cap on and missed a dose of 400 mcg. On study day 6 she administered 400 mcg without relief, and was told to advance to 800 mcg at the next episode. On day 7 she administered 1600 mcg (2 sprays to each nostril). She developed sweating and vomiting after dose administration. This was assessed by the investigator as drug related and she was withdrawn from the study for protocol violation on study day # 11. No intervention was deemed necessary

Subject 391201 was a 46-year-old white male who was enrolled and successfully titrated to 800 mcg dose and started the double-blind phase of Study CP043. He completed the study. Twenty three days after completing the trial, he received Naloxone for mild accidental opioid overdose. This occurred 22 days after his last dose of active drug. He was withdrawn from the study when he expired of hepato-renal failure.

Subject 391402 was a 53 year white female who was successfully titrated to a dose of 400 mcg of PecFent and entered the double-blind treatment phase of Study CP043. Two days later, while using a bottle of PecFent to treat an episode of BTCP, she did not feel that the spray entered her nostril repeating the dose. There were no AEs reported and she completed the open label phase of 16 weeks of study CP045 and entered the extension phase. She was withdrawn from the study on study day #422 at the discretion of the investigator.

Subject 460305 was a 56 year-old male who was titrated and commenced the double-blind phase of Study CP044 on 400 mcg. He also described that no drug was delivered to his nose by the spray bottle, so he administered another spray. However, this was a placebo bottle. He was rolled over to study CP045 and completed the 16-week course and extended trials uneventfully.

Subject 520401, a 61 year-old white woman, who while commencing titration with a dose of 100 mcg took a second dose shortly after without precise interval described, because her pain had not subsided. She reported only one episode while conflicting data from the bottle suggested she had administered 3. She reported one episode of dyspnea but was assessed as possibly related. She withdrew consent at the time.

Subject 520703 a 49 year-old white woman who commenced titration. She reported errors twice of mistaking a 400 mcg dose instead of 200 mcg. There were no AEs reported and she successfully titrated to 200 mcg and completed the entire study.

Subject 560302 was a 35 year-old white male who titrated to 200 mcg. On study day 48 he reported to the investigator that he had increased to 400 mcg while not reporting it in the diary. Although there were no overdose signs he was removed from the study on study day # 50 for protocol violation; he expired the next day from disease progression (study day #51)

Subject 570801 a 28 year-old white woman who was started on titration and reported that on one instance when mistakenly gave herself 800 mcg instead of 400 mcg. She experienced no AEs, and was able to enter the OL phase. While her dose was increased to 800 mcg, she withdrew consent due to lack of efficacy on SD #47.

Subject 585605 (This case was already described in the Section pertaining to Individual SAEs 7.3.2). A 42 year-old Indian male, with carcinoma of the larynx, and status post radical neck dissection. This patient overdosed, with an estimated total dose of 800 to 2000 mcg because he repeatedly sprayed himself. He had not sensed delivery of the drug.

Subject 585903 a 58 year-old Indian male titrated up to 400 mcg and entered the OL treatment phase. The subject reported missing his nose once and repeating the dose administration. He completed the trial without further incidents.

According to the Applicant's definition of abuse/overuse, there were only 3 cases in the previous narratives where the subject clearly self-administered more study drug than prescribed and was associated with adverse effects. The Applicant explains this issue by the fact that the fine low-volume spray delivered at low speed is often not felt by the user. Clear and specific instructions, as well as warnings of this issue are essential in order to prevent inadvertent dosing and adverse outcomes in the general population. Relying on the click noise and the advancing number should be other reliable indicators of dose delivery, other than from the nasal sensation.

The Applicant is fully aware of these occurrences and their significance is discussed in the section of device malfunction. The Applicant attempts to clarify and prevent the occurrence of improper re-dosing, by providing adequate instructions to the patients and instructing them to rely on device click, rather than the puff or spray perception.

Abuse Liability Narratives

The staff participating in the PecFent trials was trained to detect signs of abuse of the drug product. Such behaviors included:

- Acute overdose or over-administration,
- Chronic overuse or misuse
- Inability to account for medication (inconsistent diary reporting)
- Premature discontinuation due to violation,
- Non-compliance,
- Lack of efficacy or
- Loss to follow-up.

The following subjects exhibited potentially aberrant behavior during Phase 3 studies.

Subject 393701 was a 65 year-old Hispanic subject in Study CP043 who was titrated to 400 mcg. After completing the double-blind phase of treatment he was rolled over to study CP045 and continued treatment. During this phase it was noted that his medication use was higher than the number of episodes reported in his diary. In one instance he reported treating 5 episodes in one day. On day #81 he was found to have intentionally abused/misused medication and he was withdrawn from the study, returning a considerable amount of unused study-medication. There was no previous history of drug abuse at enrollment

Subject 390703 was a 50 year-old Caucasian subject in Study CP043 who titrated up to 800 mcg of PecFent. After successful completion of the double-blind phase was rolled into Study CP045. During the open-label treatment phase persistently continued to treat 4 BTCP episodes daily, without recording them in the e-diary. The subject was withdrawn from the study on day #98 for non-compliance. There was no previous history of drug abuse.

Subject 410704 was a 39 year-old Caucasian subject that started the titration process. This subject returned 3 days later complaining that the e-diary would not upload and was unable to record any pain episodes. The subject returned empty bottles of study drug and was withdrawn from the study from lack of efficacy. There was no previous history of medication abuse.

Subject 393703 was a 59 year-old Caucasian subject in Study CP043 who titrated up to 800 mcg. The subject successfully completed the double-blind phase, and was rolled over to Study CP045. During the double-blind phase his medication use was noted to be higher than the number of episodes reported on the e-diary (+43%). In other words, there was a mismatch between the number of doses used and the number of episodes of BTCP recorded in the e-Diary. There was an average occurrence of 2.9 episodes daily, and not exceeding 4 episodes daily. On study day #36 he was reported to have been abused medication. This apparently started previously and was detected during a telephone call where he admitted consuming all 80 doses available. The subject

returned to site 7 days later (study day #41) and was withdrawn from the study for nausea and diarrhea. The subject returned all containers empty. He admitted to having experienced a previous episode of Oxycontin withdrawal syndrome 8 months prior to enrollment.

Drug Addiction

The Applicant states cautiously that there have been no such reported instances of addiction, compulsion, or craving during the program thus far.

While there was no overt evidence of addiction during the trials, fentanyl is a schedule II opioid. This product delivers a relatively high Cmax rapidly which predicts a high very high potential risk for abuse and addiction. Because of this risk, it is very important that a comprehensive REMS program be established.

Drug Diversion

During the course of the Phase 3 program 17,182 spray bottles of PecFent were distributed to 516 subjects. One percent of the bottles (179) were not returned. The Applicant purports that the patients not returning bottles had acceptable behavior and explanations. The Controlled Substance Staff is reviewing the diversion events in detail. Their review is not final at this time.

Withdrawal and Rebound

There were no reports or incidents of withdrawal or rebound during the development program of PecFent. The subjects used background opioids for pain control at substantial doses, such as the discontinuation of PecFent would not be expected to induce significant withdrawal reaction.

7.7 Additional Submissions / Safety Issues

7.7.1 120 day Safety Update

The 120 Safety Update was received and reviewed. The Update contains data from the extension phase of Study CP045/06. To reiterate, Study CP045/06 was an open-label safety study in patients with breakthrough cancer pain. The main part of the study consisted of 3 parts: Screening, Open-label dose titration, and a 16 week Open-label maintenance period where the optimum dose is used to treat a maximum of 4 episodes of BTCP episodes per day.

In order to provide access to PecFent treatment to patients who may have found it beneficial, those who participated in previous studies were offered participation to the CP045 Extension Period, until the drug becomes commercially available. Newly enrolled patients were also allowed to participate, if they had BTCP and took regularly 24 hour opioids, and had 1-4 episodes of BTCP per day.

The data gathered in the extension was restricted to safety (AE) reporting, concomitant medication and drug reconciliation. PecFent could be used to treat up to 4 episodes of breakthrough pain per day no more frequently than every four hours. If patients were not able to obtain relief they could use their usual rescue drug. During this phase, patients were allowed to titrate their PecFent dose as needed. E-diary data was not collected, and thus full reconciliation of dose administration with each episode was not available.

Mean Drug Exposure

Patients in the Extended Period have had a variable exposure between 6- 672 days. Most were exposed to the higher doses of 400-800 mcg, as outlined in Table 34. Patients were treated with PecFent for up to 672 days at 100 mcg, and 634 days with 800 mcg.

Table 34: Subject Mean Exposure in Days –Extension Period ITT Population. Source: Addendum 1 Study Report, page 60/225, pdf file

	N	Mean	SD	SE	Median	Minimum	Maximum
Extension Period							
Total[1]	130	180.8	156.00	13.68	138.0	6	672
100 mcg	9	204.2	134.79	44.93	181.0	11	399
200 mcg	22	121.6	79.91	17.04	105.5	26	327
400 mcg	39	199.9	188.51	30.19	137.0	6	672
800 mcg	36	186.8	151.14	25.19	147.5	28	634

[1]Total includes all subjects in Extension Period that have at least one instance of drug dispensed and returned regardless of effective dose.
By dose calculations relate to those subjects that maintained the same titrated (effective) dose of Nasalfent for the duration of the Extension Period.
Reference: Listings 16.2.15.1, 16.2.15.5.

Date of Reporting Dataset Creation: 16NOV2009.

Safety Population

- 146 patients entered the extension period; there were 97 newly enrolled subjects
- 130 patients received at least one instance of drug dispensed
- 106 patients were titrated previously, and maintained their dose throughout

Subject Disposition

- There were 85 patients that withdrew from the Extension Phase. The most common cause for discontinuation/withdrawal was death (42 patients). Other reasons include: withdrawal of consent (16), adverse events (6), inability to return (2), lack of efficacy (2), lost to follow up (4), and"other" (13).

- There are 61 patients who continue to participate in the Extension Period. There are 39 newly enrolled patients and 16 who rolled over from Study CP043 and 6 patients from Study CP044.

Major Safety Findings

Narratives for the major safety findings were provided and were reviewed.

Deaths

A total of 42 patients died in the extension phase of Study 45. The distribution by dose was as follows:

- 100 mcg 6 subjects
- 200 mcg 8 subjects
- 400 mcg 14 subjects
- 800 mcg 13 subjects
- Unknown 1 subject

With regard to the cause of death, a total of 24 patients died of disease progression. Other causes of death during the extension phase included sepsis, respiratory failure, cardiac failure, infection, hemorrhage, and multi-organ failure. The deaths did not appear to be related to the use of PecFent.

Serious AEs

There were 12 patients with nonfatal SAEs. Key information regarding these cases is summarized following in Table 35.

Table 35: Nonfatal SAEs that occurred during the Extension Phase of Study CP 045: Source ISS, 120 Safety Update, Dec 9, 2009

Site/ Subject #	Age/Sex/Race	Onset Day/ Resolution Day	Preferred Term	Relationship	Outcome
917/591701	37/F/Caucasian	224 / ongoing	Chest pain	Not related	Resolved

869/586907	61/M/Indian	79 / 81 81 / 81	Diarrhoea Hypotension	Not related Not related	Resolved Died
901/590103	69/M/Caucasian	109 / 138	Oesophageal cancer	Not related	Resolved
991/599102	51/F/Caucasian	199 / 202 196 / 264	Neurotoxicity Disease progression	Possible Not related	Resolved Died
991/599104	68/F/Caucasian	137 / 147	Intestinal obstruction	Not related	Resolved
941/594105	42/F/Caucasian	60 / 72	Rectal abscess	Not related	Resolved
901/390102	42/M/Caucasian	120 / 127 122 / ongoing 151 / 155 212 / 262	Sepsis Renal failure acute Sepsis Disease progression	Not related Not related Not related Not related	Resolved Not resolved yet Resolved Died
903/390306	74/M/Caucasian	399 / 403 418 / 443	Dental caries Oedema peripheral	Not related Remote	Resolved Resolved
905/390501	57/F/Caucasian	286 / 288 286 / 288 476 / 479	Face oedema Urticaria Respiratory failure	Not related Not related Not related	Resolved Resolved Died
913/391301	46/M/Caucasian	594 / ongoing	Coronary artery disease	Not related	Not resolved yet
914/391403	50/M/Caucasian	349 / 382 349 / 382	Disease progression Chronic lymphocytic leukaemia	Not related Not related	Resolved Resolved
941/594101	37/F/Black	321 / 329 551 / 565 587 / 605	Chest pain Febrile neutropenia Catheter related infection	Not related Not related Not related	Resolved Resolved Died

Source: 120-Day Safety Update, page 27/39 of the pdf

The Serious Adverse Events did not appear to be related to the use of PecFent.

Adverse events leading to discontinuation

Four patients who discontinued due to adverse events did not experience a fatal event. These four patients discontinued due to progression of disease.

Common Adverse events

In Table 36, truncated from the Applicant's submission, the most common adverse events observed during the Extension Phase were progression of disease, anemia, constipation, dyspnea, and vomiting. These are consistent with this patient population and the use of opioids.

Table 36: Common Adverse Events, Study CP045, Extension Phase

Preferred Term	n (%)				
	100 mcg (N=23)	200 mcg (N=41)	400 mcg (N=61)	800 mcg (N=45)	Total (N=146)
Subjects with ≥1 AE	9 (39.1)	13 (31.7)	27 (44.3)	22 (48.9)	69 (47.3)
Disease progression	5 (21.7)	6 (14.6)	10 (16.4)	8 (17.8)	29 (19.9)
Anaemia	0 (0.0)	2 (4.9)	2 (3.3)	2 (4.4)	6 (4.1)
Constipation	1 (4.3)	2 (4.9)	2 (3.3)	1 (2.2)	6 (4.1)
Dyspnoea	2 (8.7)	0 (0.0)	2 (3.3)	2 (4.4)	6 (4.1)
Vomiting	0 (0.0)	3 (7.3)	2 (3.3)	0 (0.0)	5 (3.4)

Source: 120-Day Safety Update, page 21/39 of the pdf

Overdose

One incident of unintentional overdose was reported. Subject 991/599102 administered 4 consecutive sprays of 400 mcg instead of using rescue doses of clonazepam and oxycodone. The subject developed visual and tactile hallucinations lasting for 48 hours. This was treated by interrupting treatment with PecFent. The patient was treated with haloperidol, gabapentin, and clonazepam. The subject recovered in 3 days but eventually died as a result of disease progression. Interestingly there was no respiratory depression in this case. The investigator appropriately assigned the event as study drug related.

Drug Abuse

During the Extension Period, five patients were withdrawn for noncompliance with correct use of PecFent.

Conclusions from the 120 day Safety Update:

Data from the 120-Day Safety Update do not change my impression of the safety of the drug.

8 Postmarket Experience

PecFent is not marketed anywhere in the world.

9 Appendices

Table A1

Deaths due to Malignancy-Tissue destruction, expansion or metastasis

Pt ID	Study #	Comment
390601	CP043	Study drug d/c prior to death timing unknown
398003	CP043	Study drug d/c prior to death protocol violation
420210	CP044	Study drug d/c 3 days prior to death
460306	CP044	Study drug d/c 2 days prior to death
390404	CP045	Study drug d/c 28 days prior to death
390801	CP045	Study drug d/c not recorded
391004	CP045	Study drug d/c not recorded (withdrawn)
393706	CP045	Study drug d/c 6 days prior to death
394105	CP045	Study drug d/c 15 days prior to death
394107	CP045	Study drug d/c 15 days prior to death
394201	CP045	Study drug d/c not recorded
421003	CP045	Study drug d/c 23 days prior to death (withdrawn)
460404	CP045	Study drug d/c not recorded
470101	CP045	Study drug d/c not recorded
485403	CP045	Study drug d/c not recorded
510501	CP045	69 year-old female with multiple myeloma and melanoma. Was withdrawn from the study due to lack of efficacy despite reaching dose of 800 mcg. She died as a result of a UTI. Study drug was d/c 45 days prior to death
520702	CP045	Pancreatic cancer with liver metastasis, candida esophagitis. Last dose of study drug not recorded
560302	CP045	Sarcoma of pelvis on chemotherapy. Withdrawn from study due to protocol deviation not recording all doses. Last dose 1 day prior to death
585201	CP045	Study drug d/c 3 days prior to death
585301	CP045	Study drug d/c 11 days prior to death
585302	CP045	Study drug d/c 1 day prior to death
585303	CP045	Study drug d/c 7 days prior to death
585304	CP045	Study drug d/c 2 days prior to death
585403	CP045	Study drug d/c 3 days prior to death
585405	CP045	Study drug d/c 8 days prior to death
585705	CP045	Study drug d/c 15 days prior to death
585901	CP045	Study drug d/c 36 hours prior to death
585903	CP045	Study drug d/c not recorded
585906	CP045	Study drug d/c 17 hours prior to death
586103	CP045	Study drug d/c 2 days prior to death
586403	CP045	Study drug d/c not recorded
586406	CP045	Study drug d/c not recorded
586904	CP045	Study drug d/c 2 days prior to death
590603	CP045	Study drug d/c 8 days prior to death
590607	CP045	Study drug d/c same day as death, time not

		recorded
591003	CP045	Study drug d/c 9 days prior to death
591301	CP045	Study drug d/c 19 hours prior to death
591502	CP045	Study drug d/c 3 days prior to death
593501	CP045	Study drug d/c 4 days prior to death
594202	CP045	Study drug d/c 3 days prior to death
595004	CP045	Study drug d/c 26 days prior to death
595005	CP045	Study drug d/c 45 days prior to death
595102	CP045	Study drug d/c was not recorded
595103	CP045	Study drug d/c 2 days prior to death
595106	CP045	Study drug d/c was on the day of death
598001	CP045	Study drug d/c was on the day of death
598101	CP045	Study drug d/c 2 days prior to death
598302	CP045	Study drug d/c was not recorded
598606	CP045	Study drug d/c 1 days prior to death
599102	CP045	Study drug d/c was not recorded

Table A2-Deaths due to Complication of underlying malignancy (sepsis, leukopenia, anemia secondary to chemotherapy, organ failure)

Pt ID	Study #	Comment	Narrative
460403	CP044	Renal failure drug d/c 1 day prior to death	
486906	CP045	Multiorgan failure Study drug d/c 5 days prior to death	
470402	CP045	Pleural mesothelioma with liver metastasis and hepatitis B titer (2004) on transdermal and transmucosal fentanyl. Had a cardio-respiratory arrest on day 38 of trial. Date of last study drug not recorded	**X**
480101	CP045	Colon-rectal carcinoma with skin metastasis, hypercalcemia, uncontrolled pain and renal. Withdrawn from study 15 days prior to death. Hospitalized with renal failure with delirium on terminal palliative sedation. Terminal Anuria.	
485701	CP045	Oropharyngeal carcinoma with paroxysmal cough followed by profuse oral bleeding and death. Last study drug dose 1 hour prior to death	**X**
485902	CP045	67-year-old female with breast carcinoma experienced hypotension and loss of consciousness on day 94 of the OL trial. She died 5.5 hours later. Last study drug dose occurred 4 days previously. Probably an acute cardiovascular or massive cerebrovascular event (intracerebral hemorrhage?)	
485903	CP045	48 woman with breast carcinoma (ulcerated	

		lesion) and hypertension developed right arm edema and fever on day 49 of the study. Placed on antibiotics and died 3 days later. The last study-medication dose was administered 8 hours prior to death. Would suspect septic thrombophlebitis or septicemia as terminal events	
485904	CP045	54 year-old woman with breast carcinoma of the right breast, post right mastectomy, developed right arm pain and weakness. Had right lymphedema. She developed hypotension and loss of consciousness 3 hours before her death. The last dose of study-medication was 8.5 hours prior to death. Cause of death listed as "progression"	
485905	CP045	37 year woman with breast cancer on Coumadin for lymphedema, Treated with diazepam for a convulsion 17 days prior to her demise. She apparently developed right arm pain, followed by gasping in 24 hs and death. Her last dose of study drug was 2 days prior to death. Suspect thrombophlebitis and pulmonary embolism as terminal events.	
485906	CP045	54 year-old man with unknown cancer had hemoptysis. No summary or CRF available	
485909	CP045	65 year woman with carcinoma of the cervix, post hysterectomy, and recurrence. Developed a recto-vaginal with bleeding and vesico-vaginal fistula and a UTI and increased vomiting. She had an episode of unconsciousness and hypotension followed by death. The last dose of study-medication was 4 days prior to death	
486905	CP045	70 year-old man with oral mucosal carcinoma with dysphagia. Developed neck swelling with invasion of cervical blood vessels. He had severe hemorrhage with exsanguination leading to death. Last study drug dose was 3 days prior to death	
486906	CP045	57 female with carcinoma of pancreas developed dyspnea weakness and dysphasia. Became unconscious and died at home from multi-organ failure. Last study drug dose was 5 days prior to death	
486907	CP045	69 year-old female with carcinoma of the tongue developed dysphagia vomiting and	

		pain in the right ear. She developed acute cardiac failure and died. The last dose of study drug was given on the same she died. The time was not recorded.	
486909	CP045	38 year male with chondrosarcoma and oral cavity tumor, left facial pain, dysphagia, EOM limitation, intracranial invasion, brain stem compression and respiratory failure. Last study drug dose 22 days prior to death	
486910	CP045	59 year man with stomach carcinoma with abdominal and lung metastasis, resulting in starvation, ketoacidosis and multiple organ failure. Last study drug dose was 1 day prior to death	
511403	CP045	72 year female B cell and nodal lymphoma with vertebral and neural involvement. HTN, TIA, CABG, diverticulosis, cellulitis, s/p thyroidectomy. Death resulted from a perforated bowel, septic shock, and probable mesenteric thrombosis. Last study drug dose 8 days prior to death	**X**
511405	CP045	60 year male with right gluteus spindle cell sarcoma, gastric ulcer, and anemia. Post-operative scar abscess grew MRSA, required drain under anesthesia and severe anemia (Hb 8.3) resulted in death. Last study drug dose not recorded.	
570401	CP045	83 year female with carcinoma of pancreas and previous adnexectomy for ovarian cancer. On ticlopidine and digitalis for undocumented events. She had a cardiorespiratory arrest that was labeled as disease progression. Last dose of study drug was not recorded.	**X**
570402	CP045	53 year female with maxillary cancer resection, relapse of maxillary cancer with soft palate metastasis, treated with radiation. Developed severe pneumonitis and sputum retention. Respiratory distress and disease progression. Withdrawn from study. Last dose of study-medication 5 days prior to death.	**X**
570403	CP045	55 male with adenocarcinoma of the lung, pleural effusion dyspnea, liver and bone metastasis, lung tuberculosis, hepatitis B positive markers. Died as a result of a cardio-respiratory arrest at home. Last dose of study drug was 2 days prior to death	**X**

570601	CP045	69 male with lung carcinoma metastatic to adrenal, bone, and brain. He experienced a cardiorespiratory arrest as a terminal event. Last dose of study drug was 2 days prior to death	**X**
570602	CP045	70 year female with metastatic lung carcinoma to liver, adrenal, and lymph nodes. She experienced a terminal cardio-respiratory arrest after experiencing weakness and anorexia. Last dose of study drug was on same day as death. Time was not recorded.	**X**
585611	CP045	49 year male with squamous cell carcinoma of the larynx and lung metastasis, developed fever, dyspnea, pneumonitis and septic shock with death. The last dose of study drug was 2 days prior to death	
586102	CP045	28 year female with breast carcinoma and left arm edema. She had several courses of antibiotics for mild septicemia. On the day prior to her death she developed septic shock probably related to immunosuppression. The last dose of study drug was administered 7 hours prior to death	**X**
586908	CP045	45 year-old male with carcinoma of the tongue with sudden onset of uncontrolled bleeding from the mouth that was uncontrollable and lasted for 4 hours. He went into cardiogenic shock and died. The last dose of study drug was administered 9 hours prior to death	
593801	CP045	36 year male with esophageal cancer with liver metastasis. He had a J tube inserted for nutrition but was not tolerated. Developed complications from chemotherapy, inanition, and immunosuppression including sepsis and an abdominal abscess. He developed terminal CNS metastasis with transtentorial herniation. The last dose of study drug was 12 days prior to death	**X**
593801	CP045	36 year male with esophageal cancer with	**X**

		liver metastasis. He had a J tube inserted for nutrition but was not tolerated. Developed complications from chemotherapy, inanition, and immunosuppression including sepsis and an abdominal abscess. He developed terminal CNS metastasis with transtentorial herniation. The last dose of study drug was 12 days prior to death	
594203	CP045	49 year-old male with metastatic prostate cancer experienced severe anemia (hemoglobin 5 gm). He was transfused but was unable to recover and expired from cardio-respiratory failure. His last dose of study drug was not recorded	
598306	CP045	56 year-old female with malignant melanoma and severe immunosuppression secondary to radiotherapy. She died of septic shock. Her last dose of study drug was 7 days prior to death	
598604	CP045	50 year-old female with breast cancer, metastatic to bone and brain. She died from increased intracranial pressure due to brain metastasis. Her last dose of study drug was 3 days prior to her death	

Table A3-Deaths due to other than underlying malignancy (hemorrhage, Stroke, MI, PE)

Pt ID	Study #	Comment	Narrative
510501	CP045	69 year WF Multiple Myeloma and Melanoma died on SD #49 due to UTI. Withdrew from study on SD#4 due to lack of efficacy.	
480101	CP045	Renal insufficiency Study drug d/c 5 days prior to death	
585607	CP045	57 male with carcinoma of the tongue. Hospitalized for mouth bleeding which became uncontrollable with **hemorrhagic shock and cardiorespiratory arrest**. Last dose of study drug 2 days prior to death	
585908	CP045	55 year-old male with right bronchial cancer, multiple skeletal metastasis, and right shoulder pain. He developed intense chest pain, followed by gasping that lasted 20 minutes prior to his death attributed to a myocardial infarction. Last study drug dose was given 1 hour and 50 minutes before the onset of chest pain.	**X**
585909	CP045	35 year female with breast carcinoma. She experienced convulsions, loss of consciousness and tachypnea and was declared dead as a result of a **pulmonary embolism**. No relevant studies or autopsy was carried out. Last study drug dose was 8 hours prior to death	
586905	CP045	60 year-old male with adenocarcinoma of the stomach experienced an event at home that was attributed to sudden cardiac death due to a **myocardial infarction.** There were no studies and no autopsy was performed. The last dose of study drug was administered 12 hours prior to death	
591501	CP045	56 year-old male with metastatic carcinoma of pancreas to liver. He developed deep venous thrombosis with multiple pulmonary emboli. He was treated with anticoagulants and an inferior vena cava filter was inserted. He developed severe hypoxia and new PE was found and became unresponsive. The last dose of study drug was administered 17 days prior to his death.	
599001	CP045	75 year-old male with renal carcinoma with nephrectomy. He developed **hyperglycemia** and was hospitalized and treated with insulin. He was removed from the study on day 42 of the OL study. He remained hospitalized and expired due to a **cardio-respiratory arrest.** The last dose of study drug he received was 6 days prior to death	

Table: B1/ Serious Adverse Events due to Underling Malignancy or Comorbid States

		Related to PecFent					
Pt ID	Study	Definitely	Possibly	Not	Description	Comments	Narrative
937/393706	CP043 DB phase		X (invest)		71 yr MO prostate cancer with Chest pain	Non cardiac, on study day 12, anemia	X
941/394103	CP043 DB phase			X	29FW with cervical CA with N/V day10	Acute GE	
941/394108	CP043 DB phase			X	58BFPancreatic/pelvic cancer ChestpainSDay19	Placebo arm Non cardiac	
991/399901	CP043 DB phase				51WF Lung CA cough sputum&fever SD#10	Community acq pneumonia resolved c/AB	
110/411002	CP044 DB phase				63WM prostate CA, vomiting SD#4 weakness and leg pain SD#7	Chest infection, bone mets. recovered	
604/460402	CP044 DB phase				69 WM pancreatic/prostatic CA, anuria,obstr uropathy, hematuriaSD#12,13,14	Nephrostomy SD#14 resolved Drug d/c	X
104/510403	CP405 OL Phase			X	69WF with MM developed sepsis on SD#2	Favorable response ot AB	
110/511001	CP405 OL Phase			X	50WM colo-rectal carcinoma bladder obstruction SD#134	Catheterized, clot vs tumor invasion	
110/511002	CP405 OL Phase			X	47WF Ovarian CA, anemia, neutropenia hypotension, syncope SD#131	Anemia profound, transfused had 2 subsequent episodes	
114/411401	CP405 OL Phase			X	72WMProstatic CA with multiple bone mets fall SD#109 fracture right tibia/fibula	Skin necrosis right heel SD#112 discharged	X
207/520703	CP405 OL			X	49WF Lung CA non-Small cell metastatic	Transfused	

	Phase				Anemia SD#-1, decubitus ulcer SD#56		
210/521001	CP405 OL Phase			X	54 WF Breast CA hematuria & pain SD#107 Bladder irrigation and urethral splint Subsequent UTO SD#114	Disease progression with multiorgan collapse SD#147	
217/521701	CP405 OL Phase			X	64WF CML subclavian vein thrombosis SD#14, catheter related complication	Treated with anticoagulants and antibiotics, improved	X
304/530401	CP405 OL Phase			X	56 WM Myeloma, prexia & leucopenia SD#34, thrombocytompenia and anemia	Severe pain unresponsive to PecFent and Oxycodone withdrew study day #72 lack of efficacy	X
404/540401	CP405 OL Phase			X	47WF Pancreatic CA with pneumothorax SD#19 subclavian area.	Treated with thoracic drain. Subject withdrew consent. .Resolved	
601/460305	CP405 OL Phase			X	56 WM Gastric CA Increased background pain SD#132 Treated withsucralfate. Resolved	Possible gastro-dudoenitis?	
Pt ID	Study	Definitely	Possibly	Not	Description	Comments	Narrative
604/460408	CP405 OL Phase			X	52 WM Pancreatic CA post Whipple procedure. Increasing pain SD#85	Resolved	
809/580901	CP405 OL Phase			X	52WF papillary thyroid cancer Uncontrolled pain SD#-32(screening) Mouth ulcers on SD#3	Withdrawn due to rapid progression	X
708/570801	CP405 OL Phase			X	28WF colon adenoCA on SD#9 LS pain. Sibject withdrew due to lack of efficacy SD#46	Resolution prior to hospital discharge	
856/585605	CP405 OL		X		42 MO Larynx CA BTCP SD#13	Post hospital d/c c/o malfunctioning	X

	Phase				Drowsy/unconscious following dose, cyanosis and stertorous breathing lasted 45 min Drug stopped. Reintroduced SD 18	device Investigator attributed to OD 2nd malfunction device	
857/585704	CP405 OL Phase			X	71 MO Prostatic CA with hyponatremia, severe knee & back pain SD#57, Drug stopped SD#59. Treated with IV fluids and parenteral fentanyl. Resolved on SD#63		
861/586101	CP405 OL Phase			X	60 MO renal cell CA had hypertension, dyspnea on SD#35. Last dose same day became breathless, had increased neutrophil count, pleural effusion	Withdrawn from study on SD #38	
01/390102	CP405 OL Phase			X	42 WM rectal cancer, chills sepsisSD#120 infected port, treated AB SD#122 ARF, hypercalcemia Resolved day SD#127. Extension phase SD#151 sepsis x 5 days.	Disease progression day 212, expiredSD # 262 with ARD Completed study	
901/390103	CP405 OL Phase			X	50WF Breast CA, COPD, DM, COPD exacerbation SD#74	Withdrawn from study day #98 for non-compliance	
904/390403	CP405 OL Phase			X	59WF Lung CA with acute GE and dehydration on SD# 38, hypokalemia, and metabolic acidosis resolved in 2 days when Study drug resumed	Withdrawn from study on day 59 for lack of efficacy	X
907/3 90704	CP405 OL Phase				64 WF Lymphocytic leukemia, P vera, on SD#117 had acute confusion (poss TIA) slurred speech & ataxia date of last SD unknown, stable mass	Subject was not removed from study.	X

					in anterior pons (meningioma) Findings suggestive of right frontal infarct. Resolved SD #120.		
908/590803	CP405 OL Phase			X	50 WF Lung CA with asthenia-dyspnea on SD#1 resolved. On SD#37 intractable pain and disease progression	Withdrawn from study SD#37	
910/391006	CP405 OL Phase			X	39 MO Anorectal CA recurrence SD#62 and splenomegaly, anemia. Hospitalized SD#128 rectal hemorrhage, LUL infiltrate effusion SD#97	SD#110 completd trial. Discharged to hospice SD#258 prostate CA progression	
914/391408	CP405 OL Phase			X	49 MO Liver CA with pancreatitis SD#105 bile duct stenosis-stricture. SD#127 surgical repair. Resolved SD #138		
914/591401	CP405 OL Phase			X	77WM Pancreatic CA developed PE on SD#1. Study drug was stopped for 1 day	Resolved	
917/591702	CP405 OL Phase			X	54 FO Breast CA with Pneumonia, bronchospasm SD#8 Lung metastasis found SD#14	Lost to f/u on SD#83 last visit	
931593105	CP405 OL Phase			X	70 MO oral/tongue carcinoma with mouth hemorrhage SD#66. Transfused,	Lingual remobilization attempt. Expired SD#77 2nd progression	
935/593503	CP405 OL Phase			X	54FW Lung CA, tamponade pleural effusions developed empyema SD#18 received AB, chest tube and O2 Culture +Peptostreptococcus	Resolved SD#30 on AB Withdrawn from study due to non-compliance SD#63	
35/593505	CP405			X	75 WM non-small cell	Pneumonia	

	OL Phase				Lung CA with wheezing on SD#7, diagnosed pneumonia on SD#14 unimproved by SD#19 Hospice care	resolved SD#23 study drug re-introduced. Progression and stopped SD#56	
937/393704	CP405 OL Phase			X	53 WM rectal cancer on SD #114, had CR arrest on SD#234	Drug stopped for surgery on SD 113 and resumed 6 days later	
941/394103	CP405 OL Phase			X	29 WF Cervical CA with neutropenia N/V SD#30 following dosing with cisplatin. Recurrent cytopenia	Discontinued from study on Day 62 due to withdrawn consent. Neutropenia resolved to hospice care	X
941/394113	CP405 O Phase		X		53 WM M. Myeloma. Rolled over from study 043 on SD#25 developed N/V	Symptoms improved after 24 hs IV fluid and anti-nausea meds.	
941/394115	CP405 OL Phase		X		50 BF uterine leiomyosarcoma and endometrial CA. Had N/V SD#27 and day 42 post chemotherapy (2 episodes)		
941/594101	CP405 OL Phase			X	37 BF Breast CA Lt shoulder pain SD#60 Resolved	Neutropenic fever recorded day#551	X
Pt ID	Study	Definitely	Possibly	Not	Description	Comments	Narrative
941/594103	CP405 OL Phase			X	53WF Endometrial CA, on SD#8 (facial weakness-slurred speech) found brain mets on CT/MRI ?hemorragic infarct treated with radiotherapy	SD#9 developed DVT treated with heparin. SD#11 resolved Withdrawn from studySD#22 due to brain mets	X
941/594105	CP405 OL Phase			X	42 WF with rectal CA developed altered MS SD#11 2nd Pneumonia/UTI	rectal abscess on SD#60 resolved on SD#72	
948/394803	CP405 OL Phase		X		60 WF Breast CA developed severe constipation and LBP SD#19		
951/595111	CP405 OL Phase	Very likely			52 WF Metastatic CA-multiple primaries, with dyspnea SD#8	Profound dyspnea on repeat SD# 11 &12. Study Drug d/c Pneumonia SD#23	X
951/595116	CP405			X	47 BF metastatic Lung	SD resumed SD#9	

	OL Phase				CA with angina, PE and DVT SD#6	to be d/c on SD#36 for consent w/d	
983/598301	CP405 OL Phase			X	60FO Breast CA had DVT on SD#97 with mild diarrhea		
986/598607	CP405 OL Phase			X	51 WF with malignant melanoma developed vomiting on SD#32 due to chemotherapy	ON SD#35 withdrawn for protocol non-compliance	
991/599101	CP405 OL Phase			X	51 WM scalp skin cancer, oat cell CA lung. On SD#8 spinal cord compression, while hospitalized febrile neutropenia, COPD exacerbation and dyspnea, delirium	Withdrawn from study on SD#93 for poor condition.	
991/599104	CP405 OL Phase			X	68 WF metastatic colon cancer on SD#119 developed chest pain non cardiac, chest wall	Completed study on day# 126	

Table C-1 (ISS Source: Integrated Summary of Safety p:173)

Appendix Table 22-1: Listing of Subjects Who Discontinued Treatment due to Other Reasons

Study	Subject	Other reason
Dose-Titration		
CP041	005	Subject condition deteriorating – unable to verbally answer pain assessments.
CP041	101	After 2 doses of 400 mcg with no pain relief, remove subject from study.
CP041	208	Did not obtain efficacious dose. Did not proceed to Part 2.
CP043	390303	Noncompliance with titration.
CP043	391306	Inability to maintain study diary.
CP043	393301	Subject removed from study due to noncompliance; did not understand how to properly self-titrate.
CP043	394505	Per request of medical director. (b) (4)
CP043	399101	Did not complete Titration Phase because <1 episode of BTCP/day.
CP044	460407	Failure of FNS titration. Subject was not compliant; did not titrate appropriately.
CP044	470601	Titration failure.
CP044	486302	Titration failure for subject's safety.
CP044	486904	Noncompliance.
CP045	585305	Noncompliance to study medication.
CP045	591702	Subject was lost to follow-up; taken off the study then returned for late final visit.
CP045	594103	Brain metastasis.
CP045	598903	The subject did not present on average 1 – 4 episodes of BTCP/day for 14 days.
Double-Blind Phase		
CP044	470201	Site decision (suspected rapid disease progression).
Open-Label Phase		
CP041	019	Condition worsening/cognitive deterioration.
CP043	390103	Noncompliance with diary completion and study medication.
CP043	390304	Noncompliance.
CP043	390505	Subject's noncompliance.
CP043	390704	Subject chose to end study treatment.
CP043	394105	Disease progression.
CP043	394113	Subject non-compliant with protocol; tampered with *e*-diary.
CP044	410702	Major surgery unable to use nasal fentanyl medication.
CP044	485802	*E*-diary noncompliance.
CP045	585404	Due to noncompliance with the use of *e*-diary.
CP045	585606	Non-compliant with study drug and *e*-diary.
CP045	590606	Disease progression; noncompliance.
CP045	591403	Noncompliance.
CP045	593503	Noncompliance with study medication.
CP045	594104	Noncompliance with study medication.
CP045	595112	Subject discharged from hospice.
CP045	598607	Non-protocol compliance.
CP045	599101	Bad general condition. No pain without opioids.

9.1 Literature Review/References

The Applicant provided 51 references with the original NDA submission and five additional references in the submission of February 10, 2010. There were ten publications pertinent to trans-mucosal fentanyl or transdermal fentanyl, in cancer pain treatment or for use in post-operative pain. Another twelve publications pertained to use or observations on the use of intranasal fentanyl; there were two poster presentations. Two intranasal fentanyl articles pertained specifically to studies of intranasal fentanyl use in pediatric populations (ages 7-15 years). A review of the abstracts revealed no new safety data. The remainder of the references involved use of opioids in BTCP and interaction of fentanyl with other drugs, particularly tricyclic drugs. Additional literature is referenced throughout the review as needed.

9.2 Labeling Recommendations

The labeling review is still ongoing in the Division. The proprietary name is being reviewed by DMEPA. The labeling will be largely consistent with the other drugs in this class, Actiq, Fentora, and Onsolis. As discussed in this review, particular attention will be paid to the pharmacokinetics of this product and the attendant safety risks. It will be important to inform patients to trust the click of the spray device and the counter and not to rely on the sensation of a spray.

9.3 Advisory Committee Meeting

There was no advisory committee meeting for this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

NICK OLMOS-LAU
04/12/2010

ROBERT B SHIBUYA
04/12/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-569
Priority or Standard	Standard
Submit Date(s)	30 August 2009
Received Date(s)	31 August 2009
PDUFA Goal Date	30 June 2010
Division / Office	DAAP
Reviewer Name(s)	Luke Yip, MD
Review Completion Date	
Established Name	Fentanyl citrate nasal spray
(Proposed) Trade Name	None
Therapeutic Class	Opioid analgesic
Applicant	Archimedes Development Limited
Formulation(s)	Nasal spray solution
Dosing Regimen	PRN, not to exceed (b)(4) doses per 24 hours and not more frequent than 2 hours apart
Indication(s)	Breakthrough cancer pain
Intended Population(s)	Adult cancer patients receiving around-the clock opioids with breakthrough pain

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the perspective of efficacy alone, I recommend an Approval action for Fentanyl Citrate Nasal Spray (FCNS) for the indication "the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy (b) (4) (b) (4)

Substantial evidence of efficacy was provided by a single adequate and well-controlled efficacy study in cancer patients with breakthrough pain. The Applicant also submitted an active-controlled trial that provides additional support for the efficacy finding. Dr. Nick Olmos-Lau conducted the review of the safety of this product and found that the safety profile is typical for this type of product.

As a 505(b)(2) application, the above findings also rest in part on the Agency's previous findings of safety and efficacy for Actiq (oral transmucosal fentanyl citrate) which was approved for the same indication in 1998.

1.2 Risk Benefit Assessment

Based on the efficacy and safety data presented by the Applicant from their clinical development program, as well as the known chemistry, pharmacology and toxicology profiles of this and other fentanyl products, the benefits of FCNS appear to outweigh the risks for the intended use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As a fentanyl-containing product for breakthrough cancer pain, FCNS is subject to a Risk Evaluation and Mitigation Strategies (REMS) program. Please see Dr. Olmos-Lau's review for further details regarding the REMS for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant requested a deferral of the Pediatric Assessment required under the Pediatric Research Equity Act (PREA), discussed in Section 7.6.3. As described in this section, the Applicant will need to fulfill the requirements of PREA.

Studies in patients age birth to 2 years may be acceptable because the necessary studies would be impossible or highly impracticable because there are too few children with breakthrough pain who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain to study.

Pediatric studies should be feasible in pediatric patients age 3 years through 16 years. Pediatric efficacy studies are not necessary in this pediatric subpopulations because efficacy can be extrapolated from adequate and well-controlled studies in adults. Thus, the pediatric studies can be limited to safety and pharmacokinetics.

Other Phase 4 Requests: There are no additional Phase 4 requests.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed indication for FCNS is the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to opioid therapy (b) (4) (b) (4)

Fentanyl nasal spray is comprised of fentanyl in the form of the citrate salt, pectin, (b) (4) (b) (4). The Applicant has included pectin in the formulation as a gelling agent. The Applicant purports that pectin modulates the delivery and absorption of fentanyl. The solution is delivered using a commercially available, cleared nasal spray pump. The spray droplets are deposited into the nose and the pectin interacts with calcium ions present in mucus in the nasal cavity to form a soft, mildly adherent gel. Fentanyl diffuses from the pectin gel and is absorbed into the systemic circulation. The median time to maximum plasma concentration for a nasal dose ranges from15 to 20 minutes.

FCNS is available in two dose strengths: 1 µg/µL and 4 µg/µL fentanyl base. The fentanyl dose is determined by the selection of strength and number of sprays per dose. Each spray delivers 100 µL of solution containing either 100 µg or 400 µg fentanyl base. The concentration of drug substance within the nasal spray is the same for all product strengths. Each FCNS bottle is printed with a product strength identifier on the bottle label, package insert, and carton label, and packaged in an unmarked child-resistant canister (secondary packaging), which is placed in the carton.

There is no acceptable tradename at this time. The Division of Medication Errors and Technical Support found the proposed names (b) (4)" unacceptable. This review will reference the drug as "FCNS."

2.2 Tables of Currently Available Treatments for Proposed Indications

Historically, the treatment of breakthrough pain in cancer patients has consisted of treatment of the pain episode with a short-acting, immediate-release oral opioid (or opioid/non-opioid combination product) consisting of approximately 15% of the patient's total baseline opioid

dose. Typically, morphine, oxycodone, or hydromorphone have been used in this setting, however none of the IR oral opioids are approved for this indication.

There are currently three products approved for BTP in opioid-tolerant cancer patients, Actiq, Fentora, and Onsolis.

2.3 Availability of Proposed Active Ingredient in the United States

There are currently five approved drug products (not including generic forms) in the United States containing the fentanyl moiety. Table 1 summarizes the important aspects of regulatory and post-marketing experience with these products. The overall adverse event profiles for all of the products is similar (e.g., typical opioid effects of sedation, constipation, and respiratory depression). Table 1. also illustrates safety concerns that have occurred in addition to the expected events.

Table 1: Currently Marketed Fentanyl Containing Products

Trade Name/established name	NDA #	Approval date	Major Labeling Changes	Pre and Postmarketing Safety concerns
Sublimaze® (fentanyl injection)	16-619	February 19, 1968	None	None
Duragesic® (fentanyl transdermal system)	19-813	August 7, 1990	-RiskMAP -Medguide -Use of overlay -Increased warnings re: use in opioid naïve patients	-Leaking patches resulting in 2 recalls (2004 and 2008) -Lack of adhesion -Overdose, misuse and abuse -Use in opioid naïve patients
Actiq® (Oral transmucosal fentanyl citrate)	20-747	November 4, 1998	-RiskMAP -Medguide -Warnings re: dental caries	-Dental caries -Accidental pediatric exposures -Off-label use in opioid naïve patients -Abuse, misuse, overdose
IONSYS® (fentanyl iotophoretic transdermal system)	21-338	May 22, 2006	None	Never marketed due to safety issues regarding the device component
Fentora® (fentanyl buccal tablet)	21-947	September 25, 2006	-Increased warnings re: mis-prescribing to opioid naïve patients and improper dosing -RiskMAP was part of original approval	-off label use in opioid naïve patients -Improper dosing stemming from fact that this product is not bioequivalent to Actiq and therefore doses are not interchangeable
Onsolis® (fentanyl buccal soluble film)	22-266	July 16, 2009	-Increased warnings Regarding misprescribing to opioid naïve patients and improper dosing -REMS was part of original approval	-Off label use in opioid naïve patients -Improper dosing stemming from fact that this product is not bioequivalent to Actiq and therefore doses are not interchangeable

2.4 Important Safety Issues With Consideration to Related Drugs

All opioids have well established adverse event profiles that include sedation, nausea, vomiting, pruritis, hypotension and constipation. The most serious adverse reactions associated with all opioids include respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension and shock. Abuse, tolerance and physical dependence are other recognized risks associated with this class of drugs.

Because of the high potential of abuse and misuse of opioids, and experience with products such as OxyContin and methadone, the Agency now requires REMS be part of the approval package for high potency opioids, including extended-release formulations.

All opioid labels have warnings regarding co-ingestion with alcohol, based on the additive effects of the two substances; however stronger warnings and/or non-approval of a drug could result from findings of significant dose dumping.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

FCNS has been developed under IND 70,854.

A **Pre-IND meeting** was held with the Division on 26 April 2005. The proposed indication for FCNS was management of breakthrough cancer pain in patients (b) (4) who are already receiving and who are tolerant to opioid therapy (b) (4) (b) (4) The advice provided by the Division regarding the clinical development plan included the following:

- With respect to efficacy, one adequate and well-controlled clinical trial would be sufficient.
- A safety database of 500 patients is required and 150 patients treated for at least 3 months.
- A majority of the patients should be treated at the highest-to-be-marketed dose.
- A lock-out and dose-counter are needed on the product.
- Use the multi-dose, to-be-marketed device in the pivotal trial.
- The nasal drug delivery system should be tested under clinical conditions that may potentially alter the absorption of the product such as seasonal/allergic rhinitis, upper respiratory infections, side effects of chemotherapy.
- A human abuse liability study will not be required, but an Abuse Liability section will be required in the NDA submission.
- A RiskMAP will be required for this product.

An **End-of-Phase 2 meeting** was held on 24 August 2006. The advice provided by the Division regarding the clinical development plan included the following:

- The lock-out after the eighth (last) dose does not prevent patient overdose and you should address the safety of dosing frequency. Provide a description of the lock-out and clarify if it involves a timer, electronic circuit.
- Consider the likelihood the product will be abused and to begin to consider methods to minimize the risk of misuse of this high-potency opioid product.
- Conduct an *in vitro* test to support the assumption that the pectin would not gel if the product were given intravenously (intentionally misused).
- Sponsor was reminded to collect pharmacokinetic information in patients with rhinitis and rhinitis treated with oxymetazoline.
- One controlled cross-over Phase 3 clinical trial where FCNS is tested against placebo, (similar in design to Actiq® as a 505(b)(2)), with approximately 80 patients to complete would appear adequate to evaluate efficacy.
- To support any comparative claims, two adequate and well-controlled studies are required.
- The dosing instructions in the package insert must be based on successful (safe and effective) use of the same dosing instructions during clinical studies.
- Strongly recommended that the Sponsor evaluate the pharmacokinetics of eight consecutive doses to determine the bioavailability of fentanyl when dosed in this manner.
- Collect enough data to support that the product can be used safely at home without healthcare oversight.
- At the time of NDA submission, have a RiskMAP that includes how to prevent unintended exposures and pediatric exposures, accidental overdose by the patient, and a final RiskMAP to include the tools, surveillance, educational materials, that will be utilized in the plan.
- Risk minimization for this product that must be addressed is how inadvertent overdose as well as intentional misuse and diversion will be avoided given the ease of multiple doses in rapid succession.
- Design the device to limit the number of sprays available in a given time.

A **Pre-NDA meeting** was held on 22 September 2008. The advice provided by the Division regarding the clinical development plan included the following:

- Provide an accurate estimate of the residual fentanyl for the (b) (4) fills. Include the estimated loss of fentanyl due to priming.
- Clinical trials are the best validation of the performance of the to-be marketed device.
- Agency concurred that the four single- and repeat-dose pharmacokinetic studies will provide sufficient information on the pharmacokinetics of FCNS in patients, including those with conditions which might potentially alter the absorption of the product to support the NDA.
- One positive, adequate and well-controlled efficacy study will support a 505 (b)(2) application for FCNS for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain.

- The Sponsor was reminded that in the 26 April 2005 Pre-IND meeting, "you were told that the total safety database should consist of at least 500 patients, of which at least 150 should be treated for at least 3 months. The majority of the patients should be treated with the highest- to- be- marketed dose."
- Regarding a waiver of PREA in patients age less than 7 years, provide a strong rationale to support the contention that the proposed indication does not exist in this population. The NDA must contain a pediatric plan at the time of submission.
- The Sponsor will be required to submit a complete Risk Evaluation and Mitigation Strategy (REMS) for this product at the time of initial NDA submission.
- The REMS will also need to address proper product storage in the home.
- With regard to specific risk management strategies, refer to the Anesthetic and Life Support Drugs Advisory Committee Meeting convened on 6 May 2008 during which the risk management of a similar product was discussed.
- Any proposal including a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use should be submitted as a proposed Risk Evaluation and Mitigation Strategy (REMS).
- Submit the proprietary name and all associated labels and labeling for review as soon as available.
- Provide overall education, in addition to statements on the labels and labeling and child resistant container CRC to inform patients, caregivers and providers that the device must be primed.
- Recommend that the dose counter track the number left by counting down.
- Office of Surveillance and Epidemiology (OSE) found the blank child resistant container (CRC) proposal acceptable; however, if the blank CRC is pursued, the two bottles will need to be easily and readily distinguishable from on another.
- Provide the complete description intended to instruct patients how to prime the device, including where the primed spray is to be directed and how much active ingredient is released with each prime.

2.6 Other Relevant Background Information

FCNS is not approved in any other country; therefore there is no additional relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted to inspect two study sites in the United States. The selection of sites was based on the numbers of patients enrolled. DSI found that, although minor regulatory violations were noted at both sites, these findings are unlikely to impact overall data integrity and the study appears to have been conducted adequately. The data

generated by the clinical sites appear acceptable. It is noted that DSI suggested excluding data from Patient 08 at Dr. Wallace's site because of inconsistencies in documenting intake of the study drug and excluding data from Patients 102, 109, and 113 at Dr. Galan's site because of omissions in documenting the use of concomitant medications.

Please see Dr. Roy Blay's clinical inspection summary for details.

3.2 Compliance with Good Clinical Practices

The Applicant purports clinical studies were conducted in accordance with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), United States (US) 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects), US 21 CFR Part 56 (IRBs), and in accordance with the Declaration of Helsinki, Edinburgh 2000. The studies also conformed to any local Health Authority regulations.

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454. There were no disclosed financial arrangements with clinical investigators that required further consideration.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Interested readers are referred to Dr. Sheldon Markofsky's review for a complete discussion of CMC issues.

FCNS is a nasal spray form of the potent opioid analgesic, fentanyl citrate, intended for application to the nasal mucosa. Fentanyl nasal spray is comprised of fentanyl in the form of the citrate salt, pectin, (b) (4). Pectin is a gelling agent that, the Applicant purports, modulates the delivery and absorption of fentanyl. The solution is delivered using a conventional nasal spray pump. The spray droplets are deposited into the nose and the pectin interacts with calcium ions present in the nasal mucosal liquid to form a soft, mildly adherent gel. Fentanyl diffuses from the pectin gel and is absorbed into the systemic circulation.

4.2 Clinical Microbiology

Interested readers are referred to Dr. Steven Fong's review for a complete product quality microbiology review.

The drug product is to be provided as a [redacted] (b) (4) solution. The formulation includes phenylethyl alcohol and propylparaben [redacted] (b) (4). Microbial limits testing demonstrated that the product has a total aerobic microbial count of < 10^2 CFU/mL, a total combined yeast and molds count of < 10^1 CFU/mL, and is free of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Dr. Fong recommended approval from a microbiology quality standpoint with provision that the Applicant submit an assay for *Bukholderia cepacia* and to demonstrate the solution is free of this bacterium.

4.3 Preclinical Pharmacology/Toxicology

Interested readers are referred to Dr. Beth Bolan's review for a complete discussion of the preclinical development of FCNS.

The Applicant submitted:

- Pharmacokinetic studies following intranasal absorption of fentanyl with and without pectin (non-GLP) in rat and sheep;
- Repeat dose toxicology studies with evaluation of local toxicity of nasal passages in rat and in dog;
- 28-day toxicology study with pectin vehicle;
- *in vivo* study to assess the gelling properties of pectin in the rat nasal cavity
- Literature review of pectin excipient; and
- SAR evaluation with DEREK of fentanyl metabolite/synthesis impurity/degradation product [redacted] (b) (4)

The Pharmacology/Toxicology team has no approval issues with any of the data from the submitted studies. However, the team is waiting for the [redacted] (b) (4) genetoxotoxicity qualification studies from the Applicant. If [redacted] (b) (4) is positive in those studies, it will likely be an approvability issue.

4.4 Clinical Pharmacology

Interested readers are referred to Dr. Sheetal Agarwal's review for a complete discussion of clinical pharmacology aspects of FCNS.

4.4.1 Mechanism of Action

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, hydrocodone and oxymorphone.

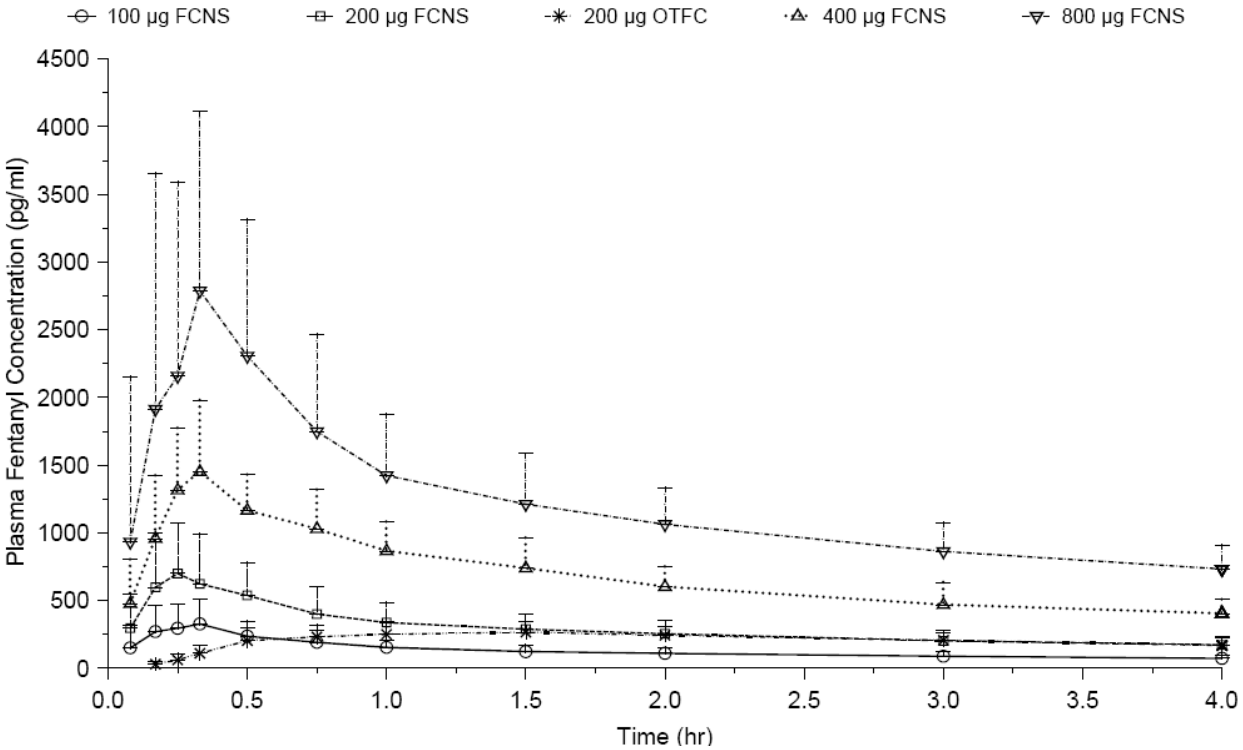
4.4.2 Pharmacodynamics

Pharmacological effects of opioid agonists are well-known and include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

4.4.3 Pharmacokinetics

Absorption of fentanyl from FCNS is mainly through the nasal mucosa. Figure 1 and Table 2 show summary data from a pharmacokinetic and relative bioavailability study (CP04205) of FCNS. Single doses of 100 mcg, 200 mcg, 400 mcg, and 800 mcg were compared with an oral transmucosal fentanyl citrate lozenge (Actiq®, 200 mcg). This study showed that the Cmax and AUC values were dose linear but not dose proportional. The median Tmax values ranged from 15 to 21 minutes. Following Cmax, plasma fentanyl concentrations declined in an apparent bi-exponential manner, with geometric mean apparent terminal half-life values ranging from 14.5 to 22.5 hours.

Figure 1: Mean plasma fentanyl concentrations following single doses of FCNS and Actiq® in healthy subjects, Study CP04205



Source: CP04205-report-body, page 51/132 of the pdf

Table 2: Summary of fentanyl pharmacokinetic results, Study CP04205

Parameter	Summary Statistic	100 µg FCNS	200 µg FCNS	400 µg FCNS	800 µg FCNS	200 µg OTFC
Number of subjects receiving treatment		16	14	13	12	13
C_{max} (pg/ml)	n	16	14	13	12	13
	Arithmetic mean	351.511	780.820	1552.07	2844.01	317.394
	SD	180.356	381.063	406.692	1592.10	94.8889
	Geometric mean	295.378	695.286	1503.68	2458.24	304.301
AUC (pg·h/ml)	n	5	8	12	12	7
	Arithmetic mean	2460.5	4359.9	7513.4	17272	3735.0
	SD	439.27	1298.8	2003.0	8440.3	1223.3
	Geometric mean	2428.0	4205.1	7322.3	15876	3580.6
$t_{½}$ (h)	n	5	8	12	12	7
	Arithmetic mean	21.89	24.90	14.95	24.91	18.56
	SD	2.971	12.77	3.688	23.05	5.833
	Geometric mean	21.72	22.47	14.49	20.17	17.81

Source: CP04205-report-body, page 50/132 of the pdf

In a multiple-dose pharmacokinetic study, Study CP04707, FCNS was administered as a single 100 mcg dose (one spray) or two 100 mcg doses (two sprays). In the instance where two sprays were administered, the sprays were separated by one, two, and four hours. The study also assessed the pharmacokinetics following 8 consecutive sprays (800 mcg total). As shown in Table 3, when compared to Cmax1, Cmax2 was higher by 30% in Treatment D (200 mcg administered 1 hour apart), by 25% in Treatment C (200 mcg administered 2 hours apart) and by 10% in Treatment B (200 mcg administered 4 hours apart). However, the AUC values were similar between one, two, and four hour dosing intervals (Table 3 and Figure 2).

The Applicant has proposed a (b) (4) dosing period. However, a 2-hour separation between two consecutive FCNS doses may be more appropriate based the median time to maximum plasma concentration for a nasal dose (15 to 20 minutes) and on the results of this study (i.e., 5% difference between Cmax2 and Cmax1 when FCNS is dosed 1 and 2 hours apart).

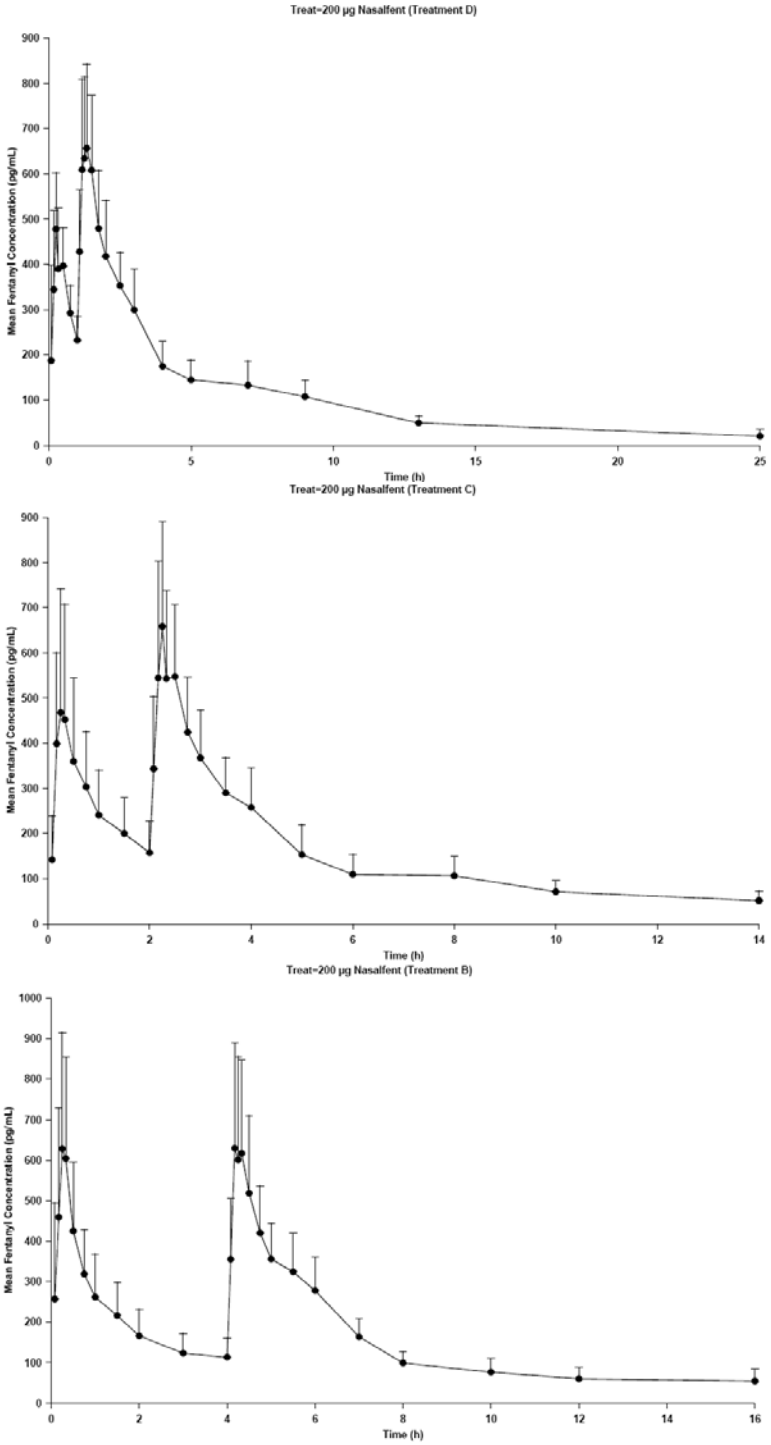
The Cmax for the 800 mcg dose (2955 pg/mL) administered as 8 sprays of 100 mcg was about 5 fold higher than the Cmax after a single 100 mcg dose (572 pg/mL). Similarly, the AUC was about 6 fold higher for the 800 mcg dose than the AUC after a single 100 mcg dose (Table 3). This result suggests the nasal surface area in each nostril may be a limiting factor for FCNS absorption.

Table 3: Summary of fentanyl pharmacokinetic results

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

Data source: Section 14.3.3
Treatment Codes: A = 100 µg NasalFent; B = 2 x 100 µg NasalFent given 4 h apart; C = 2 x 100 µg NasalFent given 2 h apart; D = 2 x 100 µg NasalFent given 1 h apart; E = 8 x 100 µg NasalFent given consecutively.
* For the two dose treatment regimens (Treatments B, C & D) C_{max1} and T_{max1} are following first dose and C_{max2} and T_{max2} are following the second dose.
Source: CP04707-report-body, page 54/135 of the pdf

Figure 2: Mean plasma fentanyl concentration-time profiles (D=200 mcg 1 h apart; C=200 mcg 2 h apart; B=200 mcg 4 h apart)



Source: CP04707-report-body, page 58-60/135 of the pdf

Study CP04807 was conducted to assess the relative bioavailability, pharmacokinetics, safety and tolerability of FNS in subjects with seasonal allergic rhinitis. This study compared the absorption of fentanyl delivered by FCNS in the asymptomatic patient, with the acutely challenged rhinitic state, and the acutely challenged and oxymetazoline-treated state (Figure 3 and Table 4). There were no clinically meaningful pharmacokinetic differences in asymptomatic patients and the active/untreated arms indicating that rhinitis may not affect pharmacokinetic absorption of FCNS. The Cmax for the rhinitic state treated with oxymetazoline was about 32% less as compared to the asymptomatic arm. AUCt for active/treated arm was only 10% lower as compared to the asymptomatic arm indicating that although statistically significant, the extent of exposure is not significantly affected. Mean Tmax for the treated arm was 0.75 h as compared to 0.25 h for the asymptomatic arm indicating that there might be a delay in absorption when oxymetazoline is co-administered with FCNS.

Figure 3: Fentanyl plasma concentration – ragweed cohort

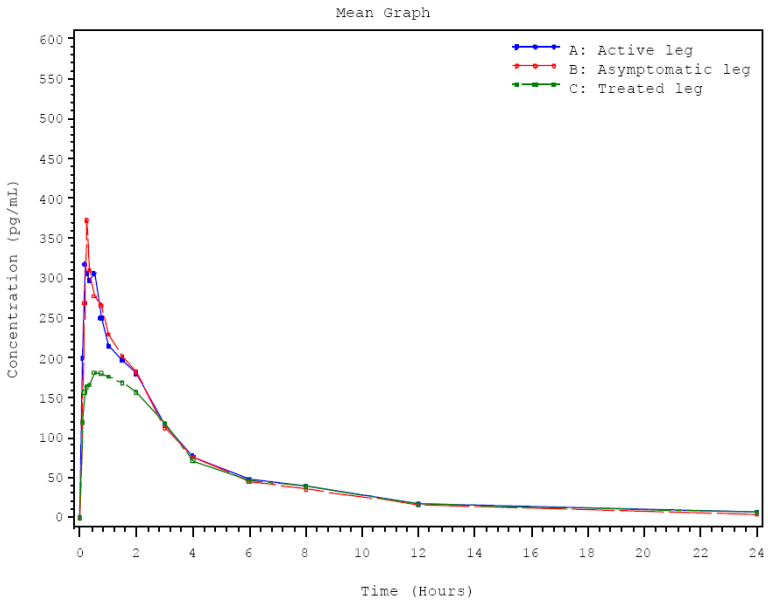


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Table 4: Fentanyl pharmacokinetic for reference, ragweed pollen exposure, and treatment

Parameter (unit)	REFERENCE		RAGWEED EXPOSED			
	Asymptomatic (B)	n	Active (A)	n	Treated (C)	n
C_{max} (pg/mL)	420.23 ± 213.50	18	462.96 ± 222.93	19	288.00 ± 288.93	18
T_{max}[a] (h)	0.25[a] [0.17-1.00][b]	18	0.33[a] [0.08 – 2.00][b]	19	0.75[a] [0.08-3.00][b]	18
AUC_t (pg.h/mL)	1058.57 ± 415.36	18	1108.40 ± 411.72	19	954.85 ± 425.92	18
AUC_{inf} (pg.h/mL)	1128.11 ± 428.72	17	1171.97 ± 425.51	15	936.22 ± 355.61	13
$t_{1/2}$[a] (h)	4.48 ± 3.17	17	4.73 ± 3.28	15	3.91 ± 1.99	13

[a] Median
[b] Range
[c] AUC_{inf} relative to the Asymptomatic (Reference) Leg
n = Number of subjects

Source: CP04807-report-body, page 41/225 of the pdf

The metabolism of fentanyl is well understood. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by CYP3A4 isoform. The concomitant use with strong CYP3A4 inhibitors or the weak CYP3A4 inhibitor cimetidine may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. The concomitant use of FCNS with potent CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of FCNS.

5 Sources of Clinical Data

The sources of clinical data for this review include the clinical study reports submitted by the Applicant and information from the labeling of related products.

5.1 Tables of Studies/Clinical Trials

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA PK	CP037/02	5.3.3.1.1	Investigation of Bioavailability, PK, safety and tolerance of 3 novel nasal spray formulations vs OTFC lozenge (Actiq®)	Four-way randomised cross over Naltrexone blockade OTFC as reference	Three novel nasal formulations (including FNS) Intranasal 100 mcg OTFC lozenge 200 mcg, oral	18	Healthy subjects	Single dose of FNS	Complete; full
BA PK	CP042/05	5.3.3.1.2	Investigation of Bioavailability, PK, safety and tolerance of increasing doses vs OTFC lozenge (Actiq®)	Five way dose escalation, Naltrexone blockade. OTFC as reference	FNS Intranasal 100, 200, 400 and 800mcg OTFC lozenge, 200mcg, oral	16 (12 completed)	Healthy subjects	Four single doses of FNS	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA PK	CP047/07	5.3.3.1.3	Investigation of Bioavailability, PK, safety and tolerance of repeat doses	Five way crossover Naltrexone blockade	Intranasal A: 100 mcg FNS single dose B: 2 x 100 mcg FNS 4 hours apart C: 2 x 100 mcg FNS 2 hours apart D: 2 x 100 mcg FNS 1 hour apart E: 8 x 100 mcg FNS consecutively	12 (10 completed)	Healthy subjects	Five dosing days, variable dose regimen in each day	Complete; full
Type of Study	**Study Identifier**	**Location of Study Report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
BA PK	CP048/07	5.3.3.3.1	Investigation of Bioavailability, PK, safety and tolerance in subjects suffering from allergic rhinitis	Three way crossover, open Naltrexone blockade. Allergic rhinitis induced in an exposure chamber	Intranasal A. single dose 100mcg FNS in subjects with active rhinitis B. single dose 100mcg fentanyl nasal spray 2 hrs after dosing with oxymetazoline in subjects with active rhinitis C. single dose 100mcg FNS in subjects not exposed to the antigen and not suffering from rhinitis	36 28 completed (17 ragweed, 11 tree pollen)	Subjects with seasonal allergic rhinitis	Three single doses of FNS	Complete; full
Efficacy Safety Phase II	CP041/04	5.3.5.2.1	Efficacy, safety and tolerability BTCP	Open, multi-centre, in-patient	Intranasal Titration phase: FNS 25, 50, 100, 200, 400 up to 800 mcg Treatment phase: Up to 4 episodes of BTCP	Titration phase; 23 entered, 18 completed Treatment phase: 15 entered 12 completed	Cancer patients; opioid tolerant receiving regular opioid therapy	Titration to effective analgesia followed by treatment of up to 4 episodes BTCP	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy Safety Phase III	CP043/06	5.3.5.1.1	Efficacy and safety BTCP	Open, Dose-Titration Phase , followed by Double-Blind, Placebo-controlled Treatment Phase Crossover	Intranasal Titration: 100 to 800 mcg Up to 4 episodes BTCP/day. Double-blind: 10 total doses: 7 doses of 100, 200, 400, or 800 mcg FNS. 3 doses of matched placebo. Up to 4 episodes BTCP/day.	139 screened 114 Open Dose Titration Phase 83 to Double Blind Treatment Phase; 73 completed	Cancer patients with BTCP; opioid tolerant receiving regular opioid therapy	Max duration approx 8 weeks	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy Safety Phase III	CP044/06	5.3.5.1.2	Efficacy and safety BTCP	Open, Dose-Titration Phase, followed by Double-Blind, Double-Dummy Comparator-controlled Treatment Phase. Cross over	Intranasal Titration: 100 to 800 mcg Up to 4 episodes BTCP/day. Double-blind: 10 total doses: 5 doses of 100, 200, 400, or 800 mcg FNS. Plus tablet placebo. 5 doses of IRMS tablets plus spray placebo. Up to 4 episodes BTCP/day.	135 patients entered, 79 completed	Cancer patients with BTCP; opioid tolerant receiving regular opioid therapy	Maximum duration 6 weeks	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety Phase III	CP045/06	5.3.5.2.2	Long term safety. Patients newly enrolled or enrolled from CP043/06 and CP044/06	Open Dose Titration Phase (newly enrolled patients) followed by Open Treatment Phase	Intranasal Titration (newly enrolled patients): 100 to 800mcg Up to 4 episodes BTCP/day. Open Treatment phase: 100 mcg, 200 mcg, 400 mcg or 800 mcg FNS Up to 4 episodes BTCP/day	287 newly enrolled patients entered the Open Dose Titration phase: of the 356 patients who entered the Open Treatment Phase, 234 were newly enrolled, 66 rolled over from CP043/06 and 56 rolled over from CP044/06	Cancer patients with BTCP: opioid tolerant receiving regular opioid therapy.	The maximum Main Study duration for individual subjects will be 5 months. Continuation in an Extension Period at the discretion of the subject/ clinician.	Complete (extension ongoing); Full

Key: BA Bioavailability; BTCP Break Through Cancer Pain; FNS Fentanyl Nasal Spray; IRMS Immediate Release Morphine Sulphate tablets; OTFC Oral-transmucosal fentanyl citrate; PK Pharmacokinetics

Source: Tabular listing of all clinical studies, page 74-79/79 of the pdf

5.2 Review Strategy

For this 505(b)(2) application, the Applicant submitted a single adequate and well-controlled efficacy study (CPO43/06/FCNS).

Mr. David Petullo of the Division of Biometrics reanalyzed and confirmed the Applicant's analysis of efficacy for the primary endpoint. The interested reader is referred to his review for a detailed description of the analysis and findings.

The primary electronic datasets used for the efficacy analyses were those containing data for Study CPO43/06/FCNS.

5.3 Discussion of Individual Studies/Clinical Trials

1. NDA 22-569 is supported by a single adequate and well-controlled clinical trial, protocol CP043/06/FCNS.

2. Study CP044/06/FCNS (randomized, double-blind, double-dummy, crossover study) provides support for the efficacy findings demonstrated in CP043/06/FCNS.

CP043/06/FCNS

Title
"A Multicenter, Placebo-Controlled, Double-Blind, Two-Phase Crossover Study of Nasalfent (Fentanyl Citrate Nasal Spray) in the Treatment of Breakthrough Cancer Pain (BTCP) in Subjects Taking Regular Opioid Therapy"

Objectives

- Primary objective: "…to demonstrate the efficacy of Nasalfent in the treatment of BTCP in opioid-tolerant patients who were receiving regular opioid therapy."

- Secondary objective: "… to demonstrate the speed of action, safety, tolerability, and acceptability of Nasalfent in the treatment of BTCP in opioid-tolerant patients who were receiving regular opioid therapy."

Study Design
This was to have been a multicenter, randomized, placebo-controlled, double-blind, crossover efficacy and safety trial to take in approximately 43 centers across the United States and Canada.

Duration
The study was to have consisted of a screening period of up to 10 days before enrollment, an Open, Dose-Titration Period of up to 14 days, a Double-Blind, Placebo-Controlled Crossover Period of up to 21 days, and an End-of-Treatment Period was to have been 1 to 14 days following the last dose of treatment. The total study duration for individual patients was to have been approximately 6 weeks.

Sample Size
180 patients with cancer-related pain and frequent episodes of acute BTCP superimposed on their chronic pain were to have been enrolled into the titration portion of the study in order that approximately 80 patients were to have been ensured to complete the double-blind portion of the study.

Inclusion Criteria
Patients were to be included in the study if they met all of the following criteria:

1. Able and willing to provide written informed consent
2. Male or non-pregnant, non-lactating female age 18 years and older; female of childbearing potential (not surgically sterile or ≤ 1 year after the onset of amenorrhea due to menopause) must agree to practice a reliable form of contraception or abstinence during the study
3. A histological diagnosis of a malignant solid tumor or a hematological malignancy causing cancer-related pain
4. Taking at least 60 mg oral morphine or equivalent for at least one week for cancer-related pain as regular, 24-hour medication for their underlying persistent cancer pain

5. Experiencing, on average, but not necessarily every day, 1 to 4 episodes of BTCP per day (i.e., a transitory flare of moderate to severe pain that occurs on a background of persistent pain controlled to moderate intensity or less by the opioid regimen) that are adequately controlled with a stable dose of standard rescue medication, typically a fast-acting opioid, of which the subject should have an adequate supply throughout the study. If the patient has more than one type of BTCP, or has BTCP in more than one location, only one of the pains will be identified as a "target" BTCP.
6. Willing and able (personally or with the help of a caregiver) to
    a. Evaluate and record pain intensity and pain relief
    b. Assess medication performance at specific times after dosing
    c. Record adverse events
    d. Record each instance of the use of study drug and standard rescue medication in a diary for the duration of the study
7. An Eastern Cooperative Oncology Group (ECOG) score of ≤ 2 and a life expectancy which, in the opinion of the investigator, will allow them to participate for the duration of the study

Exclusion Criteria
Patients were to be excluded from participating in the study if they meet any of the following criteria:

1. Opioid or fentanyl intolerant
2. Uncontrolled or rapidly escalating pain
3. On intrathecal or epidural opioids
4. Unstable or rapidly deteriorating condition such that the effective dose found during the Open, Dose-Titration Period is unlikely to remain so for the duration of the study
5. Sleep apnea or active brain metastases with increased intracranial pressure
6. Respiratory or cardiac condition that, in the opinion of the investigator, may be worsened by opioids
7. Medical condition that, in the judgment of the investigator, would confound the objectives of the study
8. Recent history of alcohol or substance abuse that would compromise data collection
9. History of or current neurological or psychiatric impairment, or cognitive dysfunction that, in the opinion of the investigator, would compromise data collection
10. Clinically significant renal and hepatic dysfunction test results at Screening outside the following limits:
    a. Serum creatinine must be ≤ 2.0 mg/dL, or creatinine clearance calculated by Cockcroft-Gault formula must be ≥ 50 mL/min
    b. Serum total bilirubin must be ≤ 2.0 mg/dL
    c. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase must be ≤ 3 times the upper limit of normal (≤ 5 times the upper limit of normal if due to liver metastases)
11. Medication likely to affect the physiology of the nasal mucosa
12. Abnormal nasal physiology and/or pathology which, in the opinion of the investigator, would not allow the objectives of the study to be accomplished

13. Known intolerance to nasal sprays and/or pharmaceutical materials found in the investigational products
14. Taking monoamine oxidase inhibitors (MAOIs) within 14 days of the Screening or with an anticipated need for MAOIs during the study.
15. Subjects taking analgesics, if the dose has changed during the 21 days prior to the Screening (this "no change" criterion does not apply to medication for their underlying, persistent cancer pain or for BTCP)
16. Taking antiepileptic medication (e.g., gabapentin, topiramate, lamotrigine) for neuropathic pain, if the dose has changed during the 14 days prior to Screening
17. Uncontrolled infection
18. Received treatment with an investigational drug within 4 weeks of Screening
19. Treatment with any form of radiotherapy within 30 days prior to study entry or who have had any therapy that could alter pain or response to pain medication
20. Planning to undergo chemotherapy (unless it has been demonstrated in that subject to have no effect on the BTCP), radiotherapy, or surgery during the treatment period
21. Primary source of breakthrough pain is not cancer related

Treatments
FCNS were to have been dispensed in a multidose vial and dosed as 1 or 2 sprays.

Titration period: All patients were to have received open-label FCNS supplied as one bottle of 100 mcg per spray and one bottle of 400 mcg per spray. After each dose, the subject was to have been instructed to record the dosing details and the time and date the dose was taken on the appropriate screen in the electronic diary.

Double-blind period:
Eligible patients were to have been supplied with FCNS as a 10-dose drug pack containing 10 separate blinded bottles, marked 1 through 10, containing either the "effective" dose (total 7) or placebo (total 3), randomly allocated in each pack. After each dose, the patient was to have been instructed to record the bottle number and the time and date the dose was taken on the appropriate screen in the electronic diary.

For FCNS, there was to have been two possible drug packs: one containing bottles with 100 mcg of FCNS for patients receiving low doses (100 mcg or 200 mcg) and one containing bottles with 400 mcg of FCNS for subjects receiving high doses (400 mcg or 800 mcg).

Study Schedule of Events

Table 5: Schedule of Events

Phase	Screening	Dose Titration Phase	Double-Blind Phase	End of Treatment
Length	Up to 10 days	Up to 14 days	3 to 21 days	1 day
Visit	*V1*	*V2*	*V3*	*V4*[a]
Informed consent	X			
Inclusion/exclusion criteria	X	X	X	
Medical history	X			
Concomitant medications	X	X	X	X
Physical examination	X			X
Objective nasal examination	X			X
Vital signs[b]	X			X
Routine clinical laboratory tests	X			X
Urine pregnancy[c]	X			X
Breakthrough Pain Questionnaire	X			X
ECOG	X			
Observation of first dose		X		
Practice with e-diary		X		
Daily phone calls to subject[d]		X		
Adverse events[e]		X	X	X
Dispense/instruct on pain diary		X	X	
Subject daily diary assessments[f]		X	X	
Subjective nasal assessment		X	X	X
Review diary			X	X
Collect diary				X
Assess medication compliance			X	X
Collect used and unused study medication			X	X
Dispense study medication		X	X	

[a] Or early discontinuation.
[b] All vital signs will be obtained after the subject has been in the supine position for at least 5 minutes.
[c] For all women of childbearing potential.
[d] Daily telephone contact to discuss and review treatment; implement titration of dose, if needed; review diary information; record AEs; record concomitant and rescue medications; and assess medication and diary compliance.
[e] Recorded by the clinician at scheduled visits and via telephone calls.
[f] For each episode of target BTCP treated with Nasalfent (up to 4 episodes on any particular day), subjects will record pain relief, pain intensity, subjective nasal assessments, subject acceptability assessments, information about study medication, and information about rescue medication. Details of other episodes not treated with Nasalfent will also be recorded.

ECOG=Eastern Cooperative Oncology Group

Source: CP043/06/FCNS Appendix 16.1.1 Protocol and Protocol Amendments, page 32/105 of the pdf

Study Conduct

Screening: Day -10 to 0 (Visit 1)

All patients were to have signed an informed consent prior to conduct of any study procedures. Key procedures that were to have been conducted at screening included:

- Verification of eligibility on the basis of the inclusion and exclusion criteria
- Medical history

- Review of concomitant medications
- Physical examination
- Nasal examination
- Vital signs
- Clinical laboratory tests (i.e., hematology, chemistry, urine pregnancy test for females of childbearing potential, urinalysis)
- Urine pregnancy test for women of childbearing potential
- Breakthrough Pain Questionnaire
- ECOG

Open-Label, Dose-Titration period: Day 1-14 (Visit 2)
Patients were to have eligibility verified base on inclusion and exclusion criteria and the following assessments and procedures

- Review concomitant medications
- Assess adverse events
- Subjective nasal assessment before first dose of study medication

Study medication and a diary were then to have been dispensed to the patients. Following an episode of pain, the first dose of FCNS was to be taken and was to be observed by medically trained personnel (i.e., clinician or nurse). Patients were to remain under observation for at least one hour, during which time the patient was to practice filling out the e-diary. The following information was to be collected:

- Use of study medication
- Pain intensity at 0, 5, 10, 15, 30, 45, 60 minutes post-dose
- Pain relief at 5, 10, 15, 30, 45, 60 minutes post-dose
- Patient acceptability assessments at 30 and 60 minutes post-dose
- Subjective nasal symptom score at 60 minutes post-dose
- Use of rescue medication (if applicable)

At the end of an hour, if the patient had not experienced unacceptable adverse events, they were to have been provided with bottles of study medication and allowed to go home, or return to their ward if inpatients.

When a patient experienced their first episode of target BTCP, they were to have received their first titration dose of FCNS, 1 spray of 100 mcg into 1 nostril. If this first dose was to be considered "effective" (i.e., pain relief within 30 minutes without unacceptable adverse events) the next episode of target BTCP was to be treated with the same dose of FCNS, 1 spray of 100 mcg into 1 nostril. However, if pain relief was to have been inadequate after 30 minutes then the patient may take their usual BTCP analgesia as rescue medication; there must have been at least 4 hours between the rescue medication use and the next FCNS dose. Similarly, if another BTCP episode was to have occurred before the next FCNS dose can be taken (i.e., within 4 hours of the previous dose of analgesia) then the new episode was to have been treated with the patient's

usual BTCP analgesia, and another 4 hour period must have been elapsed before the next FCNS dose can be taken.

For the next episode of target BTCP treated, the patient was to have increased the dose of FCNS to 200 mcg (1 spray of 100 mcg per spray administered into both nostrils; 2 sprays). As before, if that dose was considered to be "effective" the next episode of target BTCP will be treated with the same dose. If this dose is not effective the patient was to have increased the dose to 400 mcg for the next episode of target BTCP. This was to have been achieved by selecting the higher strength bottle and using one spray (i.e., 1 spray of 400 mcg per spray administered into 1 nostril; 1 spray). If this new dose was to have been considered "effective" the next episode of target BTCP will be treated with the same FCNS dose, 1 spray of 400 mcg. However, if pain relief was to have been inadequate after 30 minutes then the patient may take their usual BTCP analgesia as rescue medication; there must have been at least 4 hours between the rescue medication use and the next FCNS dose. For the next episode of target BTCP treated, the patient was to have increased the FCNS dose to 800 mcg (1 spray of 400 mcg per spray administered into both nostrils; 2 sprays). As before, if that dose was to have been considered "effective" the next episode of target BTCP will be treated with the same dose. If this dose was to have been ineffective the patient will be withdrawn from the study.

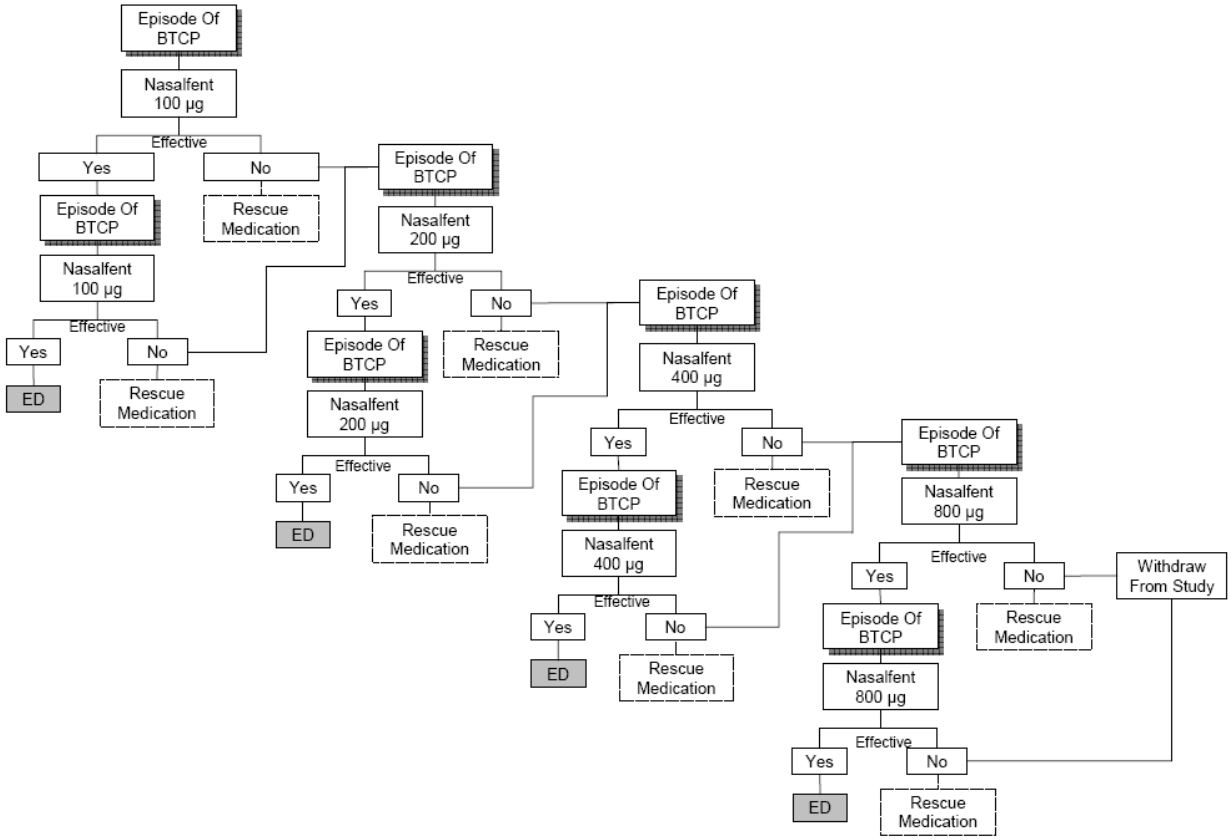
For each episode of BTCP that was to have been treated with FCNS (up to 4 episodes on any particular day), and there must have been at least four hours between each use of FCNS; episodes of target BTCP occurring before fours hours were to have been treated with the patients' usual pain relief medication, patients were to have been instructed to record the following in the diary after each dose:

- Use of study medication
- Pain intensity at 0, 5, 10, 15, 30, 45, 60 minutes post-dose
- Pain relief at 5, 10, 15, 30, 45, 60 minutes post-dose
- Subject acceptability assessments at 30 and 60 minutes post-dose
- Subjective nasal symptom score at 60 minutes post-dose.
- Use of rescue medication (if applicable).

Details of other episodes of BTCP not treated with blinded study medication were to have been recorded in the diary after each dose. Each day, study site personnel was to have made a telephone call to the patient to assist patients in determining their individual effective doses, and to review diary information, concomitant medications, and compliance with completing the diary.

Once the same FCNS dose was to have been "effective" in treating 2 consecutive episodes of target BTCP without unacceptable adverse events, titration was to have been complete and an effective dose was to have been determined.

Figure 4: Titration Dosing Schedule



BTCP=Breakthrough cancer pain; ED=effective dose
Source: CP043/06/FCNS Appendix 16.1.1 Protocol and Protocol Amendments, page 26/105 of the pdf

The Double-Blind, Placebo-Controlled Crossover Phase of the study was to have begun once all of the following have occurred:

- An effective dose has been determined without any unacceptable adverse events
- Study data, including pain relief and adverse events, have been accurately recorded
- The patient is comfortable with the use of the nasal spray, as assessed by study site staff in conjunction with the patient
- The patient is skilled and compliant with the use of the diary, as assessed by study site staff

<u>Double-Blind, Placebo-Controlled Crossover period</u>: Minimum 3 days to maximum 21 days (Visit 3)

- Verification of continued eligibility on the basis of the inclusion and exclusion criteria
- Review of concomitant medications
- Assess adverse events
- Review diary data
- Assess medication compliance

- Collect used and unused study medication
- Dispense study medication and re-issue diary
- Assess suitability to continue

Patients were to have been supplied with a 10-dose drug pack containing 10 separate blinded bottles, marked 1 to 10. Patients were to have been instructed to self-administer each dose, according to the correct technique, starting at bottle 1 and working through to bottle 10 for each of 10 individual episodes of target BTCP (maximum of 4 episodes treated in any single day). The blinded doses were to have contained either the "effective" dose found during the Open, Dose-Titration Period (total 7) or placebo (total 3), randomly allocated in each pack.

Blinded study medication was to have been used to treat up to a maximum of 4 episodes of target BTCP per day and there must be at least 4 hours between each use of blinded study medication; episodes of target BTCP that occur before 4 hours were to have been treated with the patient's usual pain relief medication. If, at any time after 30 minutes, pain relief with blinded study medication was to have been inadequate during any individual episode, patients were suppose to have taken their usual breakthrough pain medication and there must be at least 4 hours between the use of rescue medication and the next dose of blinded study medication. If the patient was to experience more than 4 episodes of target BTCP in 1 day, then they should revert to their usual pain medication for those additional episodes. Patients who were to have experienced more than 4 episodes of target BTCP per day should, in any case, discuss their analgesic medication needs with the investigator and/or study staff.

For each episode of target BTCP that was to have been treated with blinded study medication (up to 4 episodes on any particular day), patients were to have been instructed to record the following in the diary after each dose:

- Bottle number
- Pain intensity at 0, 5, 10, 15, 30, 45, 60 minutes post-dose
- Pain relief at 5, 10, 15, 30, 45, 60 minutes post-dose
- Patient acceptability assessments at 30 and 60 minutes post-dose
- Subjective nasal assessment at 60 minutes post-dose
- Use of rescue medication (if applicable).

Details of other episodes of BTCP not treated with blinded study medication were to have been recorded in the diary after each dose.

If any nasal pathology (e.g., due to an upper respiratory tract infection, chemotherapy, and allergy) was to have appeared during this phase of the study, this condition was to have been noted in the CRF. However, the double-blind treatment was to have continued unless the investigator believes it is not in the best interests of the patient to do so. Details of the condition should have included diagnosis, time and date of onset, time and date of cessation, and treatment necessary. The Double-Blind Treatment Period was to have been completed when the 10 doses in the drug pack have been used, or more than 21 days have elapsed.

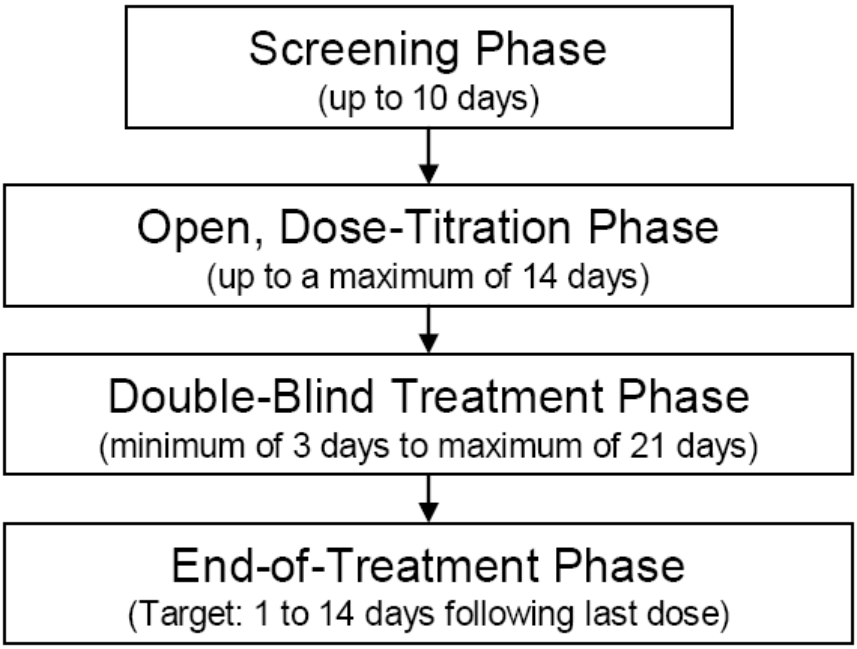
The double-blind phase was to have been completed when the 10 doses in the drug pack have been used, or more than 21 days have elapsed.

End of Treatment: 1 to 14 days following last treatment dose (Visit 4)
At the end of the double-blind treatment phase, patients were to have returned for final assessments. Patients who discontinued early or did not enter the Double-Blind Treatment Period were also to have returned for a final assessment. The following assessments and procedures were to have been performed:

- Review of concomitant medications
- Physical examination
- Vital signs
- Clinical laboratory tests
- Urine pregnancy test
- Assess adverse events
- Objective nasal examination
- Subjective nasal assessment
- Breakthrough Pain Questionnaire
- Assess medication compliance
- Collect used and unused study medication
- Collect diary and review diary data

Study Flow Chart

Figure 5: Study flow chart



Source: CP043/06/FCNS Appendix 16.1.1 Protocol and Protocol Amendments, page 16/105 of the pdf

Removal of Subjects from Therapy or Assessment
Each patient was to have been free to withdraw from the trial at any time without prejudice to further treatment. A patient's participation in the trail may be discontinued at any time at the discretion of the Investigator. Justifiable reasons for the Investigator to discontinue a patient from the trail may include the following:

- Adverse Event (AE): Clinical or laboratory events occur that, in the medical judgment of the investigator, are grounds for discontinuation, for the best interest of the patient. This includes serious and non-serious AEs regardless of relation to study drug.
- Withdrawal of consent: The patient requests withdrawal from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gives a reason for his or her withdrawal, it must be recorded in the CRF.
- Lost to Follow-Up: The patient stops coming for visits and study personnel are unable to contact the patient.
- Pregnancy: Women who become pregnant during the study will be withdrawn from treatment at the earliest opportunity. Any pregnancy will be followed to its conclusion and the neonate will be evaluated, as appropriate.
- Concomitant therapy: The patient receives any therapy that would possibly alter pain or reaction to pain medication (e.g., chemotherapy, radiotherapy, surgery).
- Lack of Efficacy: A patient who has not found an effective dose after 14 days of treatment in the Open, Dose-Titration Period.
- Other: The patient is terminated for a reason other than those listed above, such as theft or loss of study drugs or termination of the study by the Applicant. The reason, if provided, must be recorded on the CRF.

Should a patient decide to withdraw after administration of the investigational product(s), or should the investigators decide to withdraw the patient, all efforts were to have been made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal was to have been made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason, date, and time for withdrawal was to have been noted in the CRF. If the reason for withdrawal is a clinical AE or an abnormal laboratory test result, monitoring was to have continued until the outcome is evident. The specific event or test result(s) was to have been recorded in the CRF.

The sponsor reserved the right to terminate the trial at any time.

Concurrent therapy

- Concomitant use of other central nervous system depressants, including opioids used to treat pain other than the underlying cancer pain, sedatives, or hypnotics; general anesthetics; phenothiazines; tranquilizers; skeletal muscle relaxants; and sedating

antihistamines were to have been avoided or, if the medication was to have been taken for 2 or more weeks, the dose must remain stable during the study.

- No monoamine oxidase inhibitors (MAOIs) within 14 days of the screening visit or with an anticipated need for MAOIs during the study were to have been permitted.
- No antiepileptic medication (e.g., gabapentin, topiramate, or lamotrigine) for neuropathic pain, if the dose had changed during the 14 days prior to the screening visit were to have been permitted.
- No treatment with any form of radiotherapy within 30 days prior to study entry or who had any therapy that could alter pain or response to pain medication was to have been permitted.
- No planned chemotherapy (unless it had been demonstrated in that patient to have no effect on the BTCP), radiotherapy, or surgery during the treatment period was to have been permitted..
- Any prior and concurrent medication, including over-the-counter and prescription drugs, vitamins, minerals, and dietary supplements disclosed by the patient at any time period from 10 days before study drug administration through completion of the study procedures were to be documented on the Medication CRF page. Wherever possible, the generic name, indication for use, date of last dose prior to the administration of study drug, and whether the medication was taken after administration of study drug were to be recorded on these CRF pages. For combination products, the trade names were to be used.

Rescue Medication

Patients were to have been allowed their usual BTCP analgesia as rescue medication 30 minutes after study drug administration if adequate pain relief had not occurred; there must have been at least 4 hours between the rescue medication use and the next FCNS dose. This was to have been permitted during the titration and double-blind periods of the study.

Outcome Measures

Efficacy

For each episode of target BTP that was to have been treated with study medication, patients were to have recorded on their electronic diary the date of the episode, time of study drug application, and pain intensity at that time. Response information was to have been recorded using the pain scales at 5, 10, 15, 30, 45, and 60 minutes after taking study drug.

1. Pain intensity: Patients were to have rated their pain intensity on an 11-point scale ranging from 0 = no pain to 10 = worse possible pain.
2. Pain relief: Patients were to have rated their pain relief on a 5-point scale ranging from 0 = none to 4 = complete.
3. Rescue mediation: Information on whether the patient decided to take additional medication for pain relief for each episode (yes or no) together with the type, amount, and timing was to have been recorded.
4. Global assessments: The patient's global assessment, including overall satisfaction, ease of use, and convenience, were to have been assessed using a 4-point scale (1 = not satisfied, 2 = not satisfied or dissatisfied, 3 = satisfied, 4 = very satisfied).

- Patients were to have been asked "How satisfied are you overall with the nasal spray you have used to treat this episode of BTCP?" and "How satisfied are you with the speed of relief you gained with the nasal spray in the treatment of this episode of BTCP?" at 30 and 60 minutes after each treated episode of target BTCP.
- At 60 minutes after each treated episode of target BTCP patients were to have been asked "How satisfied are you with the reliability of the nasal spray in the treatment of this episode of BTCP?"
- After the last (i.e., 10th) episode of target BTCP treated during the Double-Blind Treatment Period, patients were to have been asked "How satisfied are you overall with the ease of use of the nasal spray?" and "How satisfied are you overall with the convenience of the nasal spray?"

Primary Efficacy Endpoint
The primary outcome variable was to have been the sum of pain intensity differences 30 minutes (SPID30) after dosing for FCNS versus placebo during the double-blind period of the Study. The SPID30 was to have been defined as the cumulative sum of the recorded difference between pain intensity and baseline. Pain intensity was to have been recorded on an 11-point scale (0 = no pain and 10 = worst possible pain) immediately before dosing and at 5, 10, 15, 30, 45, and 60 minutes after dosing.

Secondary Efficacy Endpoints
There were a number of secondary efficacy endpoints to have been related to PI, PR, and patient global. These endpoints were to have been expressed as average values for each patient for the FCNS and placebo exposure:

- $SPID_{10, 15, 45, 60 \text{ min.}}$
- $TOTPAR_{10, 15, 30, 45, 60 \text{ min.}}$
- Pain Intensity $score_{0, 5, 10, 15, 30, 45, 60 \text{ min.}}$
- Pain Intensity Difference to $baseline_{5, 10, 15, 30, 45, 60 \text{ min.}}$
- Pain Relief $score_{5, 10, 15, 30, 45, 60 \text{ min.}}$
- Patient acceptability assessments.

<u>Safety</u>
Safety endpoints were to have included AEs and serious AEs (SAEs), and other examinations.

Statistical Analysis

Three datasets were to have been used for analysis: safety, intent-to-treat, and per-protocol. The definitions of these datasets follow:

- <u>Safety Population</u>: All subjects who received at least one dose of study medication.

- Intent-to-Treat (ITT) Population: All patients who entered the double-blind phase of the trial and who took at least one dose of study medication and have at least one post-baseline pain intensity measurement.
- Per-protocol Population: Supportive analyses of efficacy were to have been conducted in the "Per Protocol" (PP) dataset. The PP dataset was to have contained all patients in the double-blind phase that substantially met study entry criteria and had no major protocol violations. The criteria for the major protocol violations were to have been defined in the statistical analysis plan (SAP). Decisions regarding patients to be included in the PP dataset were to have been made prior to any unblinding of the treatment allocations.

Any subgroup analyses concerning the primary efficacy endpoint must be planned and documented in the SAP. Also, after the blinded data review, decisions were to have been taken about grouping together centers that have recruited only small numbers of subjects.

Primary efficacy analysis
The primary outcome variable was to have been the SPID30 after dosing for FCNS versus placebo during the double-blind period of the Study.

- The mean value of each variable for each patient was to have been assessed (up to 7 target BTCP episodes per patient treated with FCNS and up to 3 target BTCP episodes per patient treated with placebo), giving 2 numbers per variable per patient. An analysis of covariance was to have been undertaken. The SPID30 score was to have been the dependent variable and the model was to have contained terms for treatment, center, dose level following the titration, sequence, patient nested within sequence, and dose number. Dose number was to have been 1 if the patient was dosed the first time with the specific drug, 2 if it is the second dose, and so forth. Dose number was to be equivalent to the place of treatment in the sequence. Incorporating dose number into the model may make one or more other effects non-estimable, in which case it was to have been dropped from the model. Interactions were also to have been investigated (such as the treatment-by center) and were to have been removed from the model if not significant at a 10% level. A covariate for age category (≤ 60, > 60) was also to have been included in the model and retained only if its significance level is below 0.05. The sequence effect was to have been tested using the subject within sequence effect; all other effects were to have been tested using the residual error term.
- From the final model, a least square mean estimate of the difference between treatments, with associated 95% confidence interval (CI), was to have been calculated.
- An additional model was to have been fit to explore the effect of rescue medication on the efficacy results. An indicator to whether a subject had received rescue medication was to have been added to the above ANCOVA model as a covariate.
- The ITT and PP analyses were to have utilized the Last Observation Carried Forward (LOCF) method to input missing values due to omission or use of rescue medication, prior to calculating the average values for each patient. An additional sensitivity analysis was to have used the LOCF imputation method for any missing data with the exception of those episodes where rescue medication was taken.

The ITT and PP analyses was to have utilized the Last Observation Carried Forward (LOCF) method to input missing values due to omission or use of rescue medication, prior to calculating the average values for each patient. An additional sensitivity analysis was to have used the LOCF imputation method for any missing data with the exception of those episodes where rescue medication was taken.

Secondary analyses
Data for these secondary endpoints was to have been handled in a similar way to the primary endpoint if interactions are established. Alternatively paired-comparison t-tests will be performed.

For the following secondary endpoints, all episodes were to have been considered for analyses (up to 7 during FCNS exposure and up to 3 during placebo exposure). Incidences were to have been based on total number of episodes regardless of how many episodes were experienced by each patient:

- Time to achieve total pain relief (< 5, 5 to < 10, 10 to < 15, 15 to < 30, 30 to < 45, 45 to < 60 min).
- Time to rescue medication (< 5, 5 to < 10, 10 to < 15, 15 to < 30, 30 to < 45, 45 to < 60 min).
- Quantity and type of rescue medication.

Safety data during the double-blind phase were to have been summarized by treatment. The results from the subjective nasal assessment were to have been summed and the means compared with placebo by t-test. No statistical testing was to have been planned for other safety parameters. Descriptive statistics including mean, median, range, SD, and frequency counts, as appropriate to the structure of the data, were to have been used.

Adverse events were to have been assessed from the start of study drug administration through the final follow-up visit.

Adverse events were to have been summarized in terms of the number of events and the percentage of subjects that experienced at least 1 AE by System Organ Class, Preferred Term, and treatment group. Adverse events were to have also been presented by severity, relationship to drug, and seriousness. All patients who experienced SAEs or discontinued because of AEs were to have been summarized. A listing was to have been provided for all subjects who discontinued because of an AE. In addition, those AEs that resulted in death or were classified as serious or as “other significant AEs” were to have been presented in a separate listing. Other significant AEs were to have included discontinuations due to AEs as well as potentially important abnormalities not meeting the definition of serious and not leading to death. These may have included marked abnormalities, presumably not enough to be considered serious, and AEs that were to have been led to the addition of significant additional concomitant therapy. Patient narratives for discontinuations due to AEs, SAEs, and other significant AEs were also to have been provided.

Clinical Laboratory Tests: The hematology and serum chemistry laboratory parameters were to have been summarized using descriptive statistics (mean, standard error, SD, median, range); these summaries were also to have been produced for the change from screening at follow-up. Shift tables were also to have been provided. The central laboratory was to have specified normal ranges. Clinically significant abnormal laboratory results were to have been flagged in the data listings. Patients missing a value at any time point were to have been excluded from the summary statistics for that time point and its corresponding change from baseline evaluation. If a patient was to have more than 1 value at any time point, then the latest non-missing value was to have been used.

Physical Examination: Each body system was to have been summarized by frequency tables (Done, Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) at screening and follow-up.

Vital Signs: Vital sign data including blood pressure and pulse rate were to have been summarized using descriptive statistics at screening and follow-up. In addition, the change from baseline in vital sign data was to have been calculated for each patient and summarized.

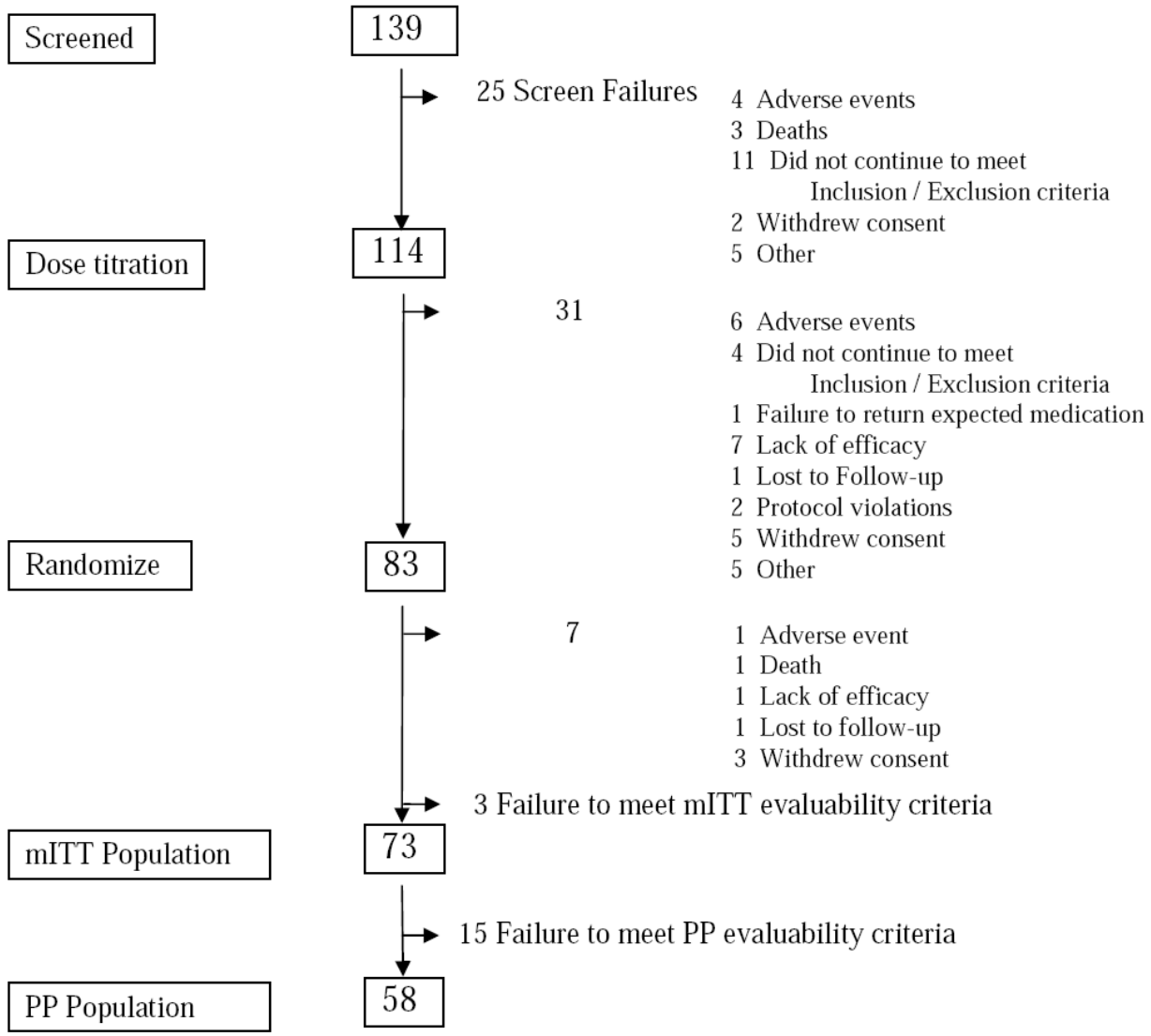
Objective Nasal Examinations: Nasal examinations were to have been summarized using descriptive statistics at each visit. In addition, the change from baseline was to have been calculated for each patient and summarized at each visit.

Subjective Nasal Assessments: Nasal examinations were to have been summarized using descriptive statistics at each visit. In addition, the change from baseline was to have been calculated for each patient and summarized at each visit.

Protocol Amendments
One amendment (Amendment #1) was submitted to the NDA on 08 January 2007, three months and 13 days after the initial protocol was submitted. The amendment described administrative changes to the reporting procedures for adverse events.

Results
Disposition of Patients
The figure below illustrates patient disposition in study CP043.

Figure 6: Patient Disposition



mITT=modified intent-to-treat; PP=per-protocol
Source: End-of-Text Table 14.1.1.1 and 14.1.1.2

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 62/1548 of the pdf

Although patients were enrolled across 58 (36 active) sites in the United States, Costa Rica, and Argentina, the trial was conducted predominantly (89% of patients) in the United States. A total of 139 patients were screened and enrolled for participation in the trial. Of the 139 enrolled patients, 114 (82.0%) entered the titration period, and 113 (81.3%) received at least one dose of FCNS and were included in the Safety Population; Patient 910/391002 met all inclusion criteria and formally entered the Open, Dose-Titration Phase but withdrew consent before receiving any study drug.

A total of 25 patients (18.0%) were excluded at screening, 31 patients (22.3%) discontinued during the titration period, and 7 patients (5.0%) discontinued during the double-blind period. The reasons for screening failure, discontinuation during the titration and double-blind portions of the study are as indicated in Figure 6 above. The most common reason for screening failure (11/25, 7.9%) was inability to meet the inclusion criteria. The most common reasons for discontinuation from the Open, Dose-Titration Phase were lack of efficacy (7 [6.1%] patients) and AEs (6 [5.3%] patients). There were five patients who were excluded during the Screening and five patients from the Titration Period who did not continue onto the Double-Blind Period for unspecified "other" reasons. The Applicant was queried with regard to actual reason(s) for discontinuation and the response follows in Table 6.

Table 6: Reasons for discontinuation between titration and double-blind periods

CP043 (from Listing 16.2.1)	
Patient number	**Reason for discontinuation**
Screening	
907/390703	Patient transferred care
914/391405	Lost to follow-up
917/391702	Non-compliant
928/392801	Unable to dose with study drug due to technical problems with diary
931/393103	Leucopenia (immunity problem)
Titration	
903/390303	Non-compliance with titration
913/391306	Inability to maintain study diary
933/393301	Pt removed from study due to non-compliance; did not understand how to properly self-titrate
945/394505	Per request of Medical Director, (b) (4)
991/399101	Did not complete titration phase because less than 1 episode of Btcp per day

Source: Appendix 2 – Clinical Response document FDA Clinical Questions – 2 Feb 2010, page 1/8 of the pdf

There were 83 patients who completed the titration period by achieving an effective and tolerable FCNS dose. All these patients entered the Double-Blind Period and received 10 separate

"blinded" bottles, marked 1 through 10, containing either the FCNS strength needed for their effective dose (total 7 bottles) or placebo (total 3 bottles), in a randomly designated order. Patients were to use a single dose of medication (either 1 or 2 sprays) for each BTCP episode. A total of 76 (91.6%) patients completed this part of the trial, but not all had treated 10 episodes. Among the 7 (8.4%) patients who discontinued, 3 (3.6%) withdrew consent and 4 discontinued for the following reasons (1 each): an AE, death, lack of efficacy, and lost to follow-up.

Of the 83 randomized patients in the Double-Blind Treatment Period, 73 (88%) were included in the mITT Population and 58 (69.9%) were included in the PP Population, as summarized overall and by dose group in Table 7 below. The reasons for excluding 10 randomized patients from the mITT Population are as indicated in Table 8 below. The reason for excluding 15 mITT patients from the PP Population is because of failure to meet PP evaluability criteria (i.e., all patients who were part of the mITT Population and in whom at least 2 episodes identified as evaluable PP episodes had been treated, 1 with each of the 2 treatments (FCNS or placebo) and all episodes identified as evaluable PP episodes were treated using part of an ascending sequence of bottle numbers). An evaluable PP episode was defined as an mITT evaluable episode, the episode was treated in patients who met all the main study entry criteria and had no major protocol violations, the episode had a baseline pain score, all postbaseline scores for baseline, 5, 10, 15 and 30 minutes time points, rescue medication was not taken prior to or at 30 minutes posttreatment, and the correct number of sprays/actuations (consistent with the patient's titrated effective dose of FCNS) was used as confirmed by the poststudy compliance check (the counter on each individual bottle).

Table 7: Summary of all randomized patient disposition

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

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

[1] Patients who have a completion date on CRF

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

Source: End-of-Text Table 14.1.1.2

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 60/1548 of the pdf

Table 8: Patients excluded from mITT

Patient Number	Primary Reason for Exclusion	Details
910/391005	Only Nasalfent data	2 episodes (Nasalfent), only 1 was evaluable
913/391304	No evaluable data	20 episodes (Nasalfent and placebo), all bottles had been used more than once
931/393101	Only Nasalfent data	2 episodes (Nasalfent and placebo) but only Nasalfent episode was evaluable
940/394003	Lost to follow-up	Medication dispensed, but patient failed to return and supplied no e-diary data
941/394107	No evaluable data	Episodes were recorded in the e-diary, but bottle numbers were missing
941/394109	Only Placebo data	8 episodes (Nasalfent and placebo). The 1 Nasalfent evaluable episode was excluded because the bottle was used more than once
945/394501	No evaluable data	Episodes were recorded in the e-diary, but bottle numbers were missing
980/398001	Only Nasalfent data	3 episodes (Nasalfent and placebo), but only 2 Nasalfent episodes were evaluable; placebo episode was not evaluable
980/398005	Only Nasalfent data	3 episodes (Nasalfent and placebo), but only 1 Nasalfent episode evaluable
980/398006	Only Nasalfent data	24 episodes (Nasalfent and placebo), but only 1 Nasalfent bottle used once, all others were used more than once

mITT=modified intent-to-treat
Source: Listing 16.2.2.4

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 61/1548 of the pdf

There were a total of 11 patients who discontinued from the trial due to an AE: 4 patients (2.9%) during Screening, 6 patients (4.3%) during the titration period, and one (0.07%) during the double-blind period.

Protocol Deviations

A total of two patients (1.8%) were discontinued from the trial because of protocol violations. Both discontinuations occurred during the titration period.

Protocol deviations were identified prior to unblinding the data. The most frequent protocol deviations were:

- Returned drug did not match the episode data entered in e-diary.
- Spray count discrepancies. This was usually noted as underuse or overuses of medication. Overuses of medication were frequently associated with treatment of additional episodes of BTCP, and missed assessments for certain visits.

These violations did not appear to confound study results as demonstrated by the consistency in efficacy outcomes for the mITT and PP Populations. The details of each deviation appear in the Applicant's Protocol Deviation Listing, Listing 16.2.2.3, and this has been summarized in Table 9 below.

Table 9: Summary of Protocol Deviations

Protocol Deviations	**N = 47**
Multiple deviations*	13
Improper canister use/dosing**	10
Missing scheduled data (e.g., exam, weight, labs, follow-up)	5
Improper sequential canister use***	4
Logistics with signing ICF/HIPAA forms	4
Missing episode data	3
Inclusion/exclusion criteria violation	3
Improper questionnaire distribution	2
Improper e-diary documentation	1
Distribution of study medications	1
Late follow up	1

*Multiple deviations include combinations of deviations listed.
**Improper canister use/dosing includes improper priming of the canister, more than expected number of clicks per canister, and more than intended dose was taken.
***Improper sequential canister use includes not using the specified number of canisters.

Demographics and Other Baseline Characteristics

Table 10 below presents a summary of subject demographics for the titration (safety) and double-blind (mITT) periods.

Table 10: Summary of subject demographics

Characteristic	Titration N=113	Double-Blind (mITT) N=73
Age (yrs)		
Mean (SD)	53.8 (11.6)	51.8 (11.9)
Median	53.0	52.0
Min, Max	21, 86	21, 76
≤ 60	82 (72.6)	58 (79.5)
> 60	31 (27.4)	15 (20.5)
Gender, n (%)		
Male	60 (53.1)	38 (52.1)
Female	53 (46.9)	35 (47.9)
Race, n (%)		
Caucasian	77 (68.1)	53 (72.6)
Black	13 (11.5)	7 (9.6)
Asian	2 (1.8)	2 (2.7)
Other	21 (18.6)	11 (15.1)
Weight (pounds)		
Mean (SD)	78.8 (18.5)	79.9 (19.5)
Median	78.1	79.0
Min, Max	45.0, 147.7	46.0, 147.7
Eastern Cooperative Oncology Group score, n (%)		
0	18 (15.9)	10 (13.7)
1	59 (52.2)	42 (57.5)
2	36 (31.9)	21 (28.8)
Location, n (%)		
Unite States	100 (88.5)	
Argentina/Costa Rica	13 (11.5)	
Allergic disorder, n (%)		
Yes	57 (50.4)	
No	56 (49.6)	
Upper respiratory infection, n (%)		
Yes	21 (18.6)	
No	92 (81.4)	
Chemotherapy, n (%)		
Yes	22 (19.5)	
No	91 (80.5)	

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 344-347/1548 of the pdf

Of the 113 patients in the safety population, 60 (53.1%) were men, the median age was 53 years (range, 21 to 86 years), the majority of patients (72.6%) were 60 years and younger and they were Caucasian (68.1%). There were no important differences in the demographic characteristics between the safety and the mITT and PP populations.

In both populations, the most common cancer diagnoses were breast, lung, reticulo-endothelial, and bowel (53.9% of Titration and 54.5% of Double-Blind). The remaining cancer types were prostate, musculoskeletal including primary bone and sarcoma), primary not specified or known, upper gastrointestinal including gastric and esophageal, pancreatic, renal, throat, CNS, ovarian,

uterine, liver, cervical, testicular, melanoma, neuroendocrine, and bladder cancer as shown in Table 11 below.

Table 11: Summary of primary tumor types in patients at Screening and Titration Period

Primary tumour type / location	Screened (n=139)		Entered titration (n=114)	
	Number	%	Number	%
Breast	24	17.3	18	15.8
Lung	18	12.9	15	13.2
Reticulo-endothelia (incl. lymphoma, myeloma)	17	12.2	14	12.3
Bowel	16	11.5	15	13.2
Prostate	9	6.5	8	7.0
Musculoskeletal (incl. primary bone, sarcoma)	7	5.0	6	5.3
Primary not specified / known	7	5.0	4	3.5
Upper gastrointestinal (incl. gastric, esophageal)	5	3.6	3	2.6
Pancreas	4	2.9	4	3.5
Renal	4	2.9	4	3.5
Throat	4	2.9	3	2.6
CNS	4	2.9	4	3.5
Ovary	4	2.9	1	0.9
Uterus	3	2.6	3	2.6
Primary hepatic	3	2.6	3	2.6
Cervix	2	1.4	2	1.8
Testicular	2	1.4	2	1.8
Melanoma	2	1.4	1	0.9
Neuroendocrine	2	1.4	2	1.8
Bladder	2	1.4	2	1.8

Source: Study CP043/06/FCNS Listing 16.2.4.1
Source: CP043/06/FCNS Study Report Body-2 Post-Hoc Analysis Table, page 1/1 of the pdf

The Applicant was queried (2 February 2010) with regard to classification for the pain pathophysiology (e.g. neuropathic, nociceptive, or mixed) for the patients studied. The Applicant responded: "As a result of this relatively large body of data that demonstrate a lack of correlation between the pathophysiology of the BTCP pain and the dose and/or efficacy of

fentanyl in its treatment, in particular the studies conducted for the reference product, Actiq, Archimedes considered that the collection of such data in the (b) (4) Phase III studies was unnecessary, and would not assist the risk/benefit assessment of the product. These data cannot therefore be provided." While, for the purposes of completeness, it would have been preferable to have a classification of the pain physiology, it is not necessary for the evaluation of efficacy.

A total of 111 (98.2%) patients reported use of concomitant medication during the study. The most commonly used concomitant medications (used by more than 10% of patients in the Safety Population) were gabapentin (22.1%), zolpidem tartarate (15.9%), hydromorphone hydrochloride (14.2%), pregabalin (12.4%), oxycodone/actetaminophen (11.5%), oxycodone (10.6%), and ibuprofen (10.6%).

All 113 patients in the Safety Population used opioids, as specified in the protocol's inclusion criteria. The most commonly used opioids were morphine (45 [39.9%] patients), fentanyl (27 [23.9%] patients), oxycodone (21 [18.6%] patients), and methadone (23 [20.4%] patients). Summary of opioid use is summarized in Table 12 below.

Table 12: Summary of opioid use in Safety Population

	Total (N=113) Number (%) of Subjects
Subjects with Opioid Use	113 (100.0)
DIPHENYLPROPYLAMINE DERIVATIVES	1 (0.9)
DEXTROPROPOXYPHENE NAPSILATE	1 (0.9)
PROPACET	1 (0.9)
DRUGS USED IN OPIOID DEPENDENCE	23 (20.4)
METHADONE	20 (17.7)
METHADONE HYDROCHLORIDE	3 (2.7)
NATURAL OPIUM ALKALOIDS	79 (69.9)
HYDROMORPHONE	4 (3.5)
HYDROMORPHONE HYDROCHLORIDE	3 (2.7)
MORPHINE	14 (12.4)
MORPHINE HYDROCHLORIDE	2 (1.8)
MORPHINE SULFATE	29 (25.7)
OXYCOCET	9 (8.0)
OXYCODONE	5 (4.4)
Reference: Listing 16.2.4.5	
NATURAL OPIUM ALKALOIDS	
OXYCODONE HYDROCHLORIDE	21 (18.6)
VICODIN	7 (6.2)
OPIUM ALKALOIDS AND DERIVATIVES	5 (4.4)
HYDROCODONE	5 (4.4)
OTHER OPIOIDS	1 (0.9)
TRAMADOL	1 (0.9)
(b) (4)	27 (23.9)
FENTANYL	27 (23.9)

Reference: Listing 16.2.4.5
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 351-352/1548 of the pdf

Treatment Compliance

Dosing compliance during the double-blind period showed a mean of 89% of doses taken as instructed. Three subjects were withdrawn from the study during the titration period because of noncompliance with study drug administration.

All 113 (100%) patients who received FCNS took their first dose under observation. For 109 (96.5%) patients, the first-dose observation was done in the clinic, for 3 (2.7%) patients it was done outside the clinic, and for 1 (0.9%) patient the location was not recorded.

Study drug was dispensed to all 113 (100%) randomized patients in the Open, Dose-Titration Period. A total of 88 (77.9%) patients were administered the first dose for BTCP, 23 (20.4%) patients were administered the first dose for pain not defined as BTCP, and for 2 (1.8%) patients the reason for administration was not recorded.

Analysis of Efficacy

Primary Efficacy Endpoint: Sum of Pain Intensity Differences at 30 Minutes (SPID30)

The statistical review was conducted by David Petullo, M.S. Please see Mr. Petullo's review for further details.

The SPID was analyzed using a mixed model of repeated measures with fixed effects for treatment, pooled site, treatment-pooled center interaction, age category (≤ 60 and > 60 years), Sequence and Indicator for rescue medication for any mITT evaluable episode within 30 minutes, and a random effect for subjects. The analysis was conducted on 73 patients who met the definition of mITT Population, which was defined as all patients in the randomized population that treated at least one episode with FCNS and one with placebo, had a baseline and at least one postbaseline PI measurement.

The mean SPID at 30 minutes was greater for FCNS-treated episodes (6.57) compared to the placebo-treated episodes (4.45) and the difference in treatments was statistically significant ($p < 0.0001$). This indicated the overall degree of pain relief experienced by patients over that 30 minutes was significantly greater following FCNS treatment. When included in the model in addition to treatment, pooled centreer was not significant ($p = 0.5891$). Treatment-Pooled center interaction, Age category (≤ 60 and > 60 years), Sequence and Indicator for rescue medication for any mITT evaluable episode within 30 minutes variables were also investigated (in addition to treatment) in an overall model, and none were significant at the 0.05 level. The Applicant's Table 13 below illustrates this analysis.

Table 13: Summary of SPID30 mITT population

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

SD = standard deviation; mITT=modified intent-to-treat
Note: Pain Intensity Scores were recorded in an e-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'. The Last Observation Carried Forward (LOCF) method was used to input missing scores for evaluable episodes due to omission or use of rescue medication, prior to calculating the average value for each patient/treatment group. The higher the SPID score the better.
[1] P-values from the analysis of covariance (ANCOVA) model.
[2] Indicator whether the patient has taken any rescue medication within 30 minutes for any mITT evaluable episode
Source: End-of-Text Table 14.2.1.1.1
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 69/1548 of the pdf

The Applicant also provided a sensitivity analysis; the SPID at 30 minutes was calculated for the mITT Population "as randomized" instead of "as-treated." A similar statistically significant treatment difference (p = 0.0001) was observed between FCNS- and placebo-treated episodes in this population (Table 14). The results were also similar in the PP Population (p = 0.0009) (Table 15). These data indicate that the finding of significantly superior efficacy for FCNS compared with placebo on the primary efficacy endpoint is highly robust.

Table 14: Sensitivity analysis summary of SPID30 mITT Population "as randomized"

Treatment Group (N = 72)	
Nasalfent	
Mean	6.44
SD	5.12
Standard Error	0.60
Median	5.07
Minimum	0.00
Maximum	25.43
Placebo	
Mean	4.58
SD	5.29
Standard Error	0.62
Median	3.00
Minimum	-1.00
Maximum	27.67
P-values [1]	
Treatment	0.0001
Pooled Center	0.5770

Note: Pain Intensity Scores are recorded in an electronic diary on a rating scale of 0 to 10, where 0 represents 'no pain' and 10 represents 'worst possible pain'. The Last Observation Carried Forward (LOCF) method is used to input missing scores for evaluable episodes due to omission or use of rescue medication, prior to calculating the average value for each subject/treatment group.
The higher the SPID score the better.
[1] P-values from the analysis of covariance model.
Reference: Listing 16.2.6.2.2

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 406/1548 of the pdf

Table 15: Sensitivity analysis summary of SPID30 PP Population

Treatment Group (N = 58)	
Nasalfent	
Mean	6.49
SD	4.94
Standard Error	0.65
Median	5.17
Minimum	0.00
Maximum	25.43
Placebo	
Mean	4.89
SD	5.67
Standard Error	0.74
Median	3.00
Minimum	-1.00
Maximum	27.67
P-values [1]	
Treatment	0.0009
Pooled Center	0.1383

Note: Pain Intensity Scores are recorded in an electronic diary on a rating scale of 0 to 10, where 0 represents 'no pain' and 10 represents 'worst possible pain'.
The Last Observation Carried Forward (LOCF) method is used to input missing scores for evaluable episodes due to omission or use of rescue medication, prior to calculating the average value for each subject/treatment group.
The higher the SPID score the better.
[1] P-values from the analysis of covariance model.
Reference: Listing 16.2.6.2.2

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 412/1548 of the pdf

Secondary Efficacy Analysis

The following Tables and Figures summarize the descriptive statistics and p-values for the following secondary endpoints:

- Table 16: Mean SPID by Time Point (mITT population)
- Figure 7 : SPID (mean ± SE) after FCNS and Placebo Administration (mITT Population)
- Table 17: Mean PI Score by Treatment and Time Point (mITT population)
- Figure 8: PI Score (mean ± SE) after FCNS and Placebo Administration (mITT Population)
- Table 18: Mean PID[1] by Treatment and Time Point (mITT population)

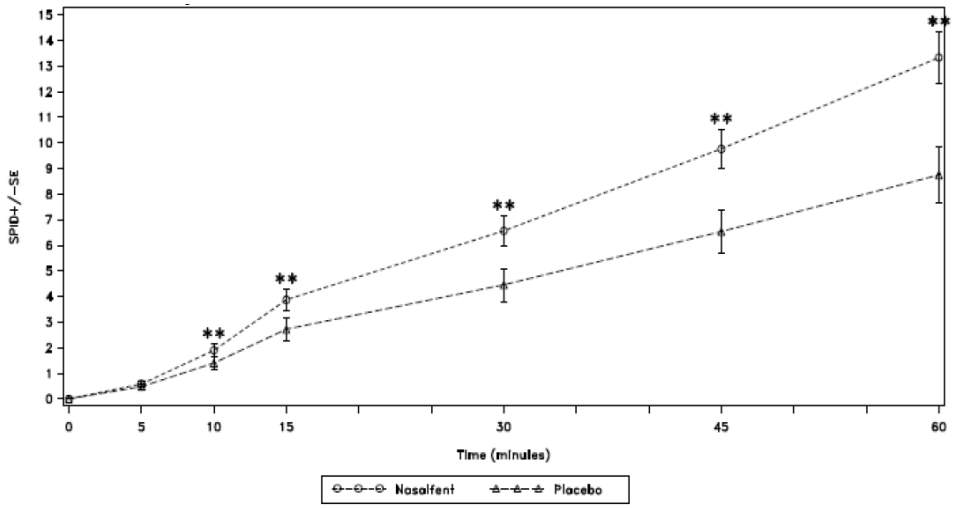
- Figure 9: PID (mean ± SE) after FCNS and Placebo Administration (mITT Population)
- Table 19: Mean Pain Relief[1] by Treatment and Time Point (mITT population)
- Figure 10: Pain Relief Scores (mean ± SE) after FCNS and Placebo Administration (mITT Population)
- Table 20: Mean Total Pain Relief[1] by Time Point (mITT population)
- Figure 11: Total Pain Relief Scores (mean ± SE) after FCNS and Placebo Administration (mITT Population)

PI Scores were recorded in an e-diary on a rating scale of 0 to 10, where 0 represented "no pain" and 10 represented "worse possible pain." P-values were obtained from an ANCOVA model performed separately at each time point. While the Applicant's p-values are shown, there was no correction for multiple comparisons done.

Table 16: Mean SPID by Time Point (mITT population)

Secondary Endpoint	FCNS (SD)	Placebo (SD)	p-value
SPID 5	0.59 (0.88)	0.48 (1.01)	0.0709
SPID 10	1.90 (2.08)	1.40 (2.29)	0.0042
SPID 15	3.87 (3.49)	2.72 (3.79)	0.0003
SPID 30	6.57 (4.99)	4.45 (5.51)	< 0.0001
SPID 45	9.77 (6.65)	6.54 (7.39)	< 0.0001
SPID 60	13.34 (8.43)	8.75 (9.36)	< 0.0001

Figure 7: SPID (mean ± SE) after FCNS and Placebo Administration (mITT Population)



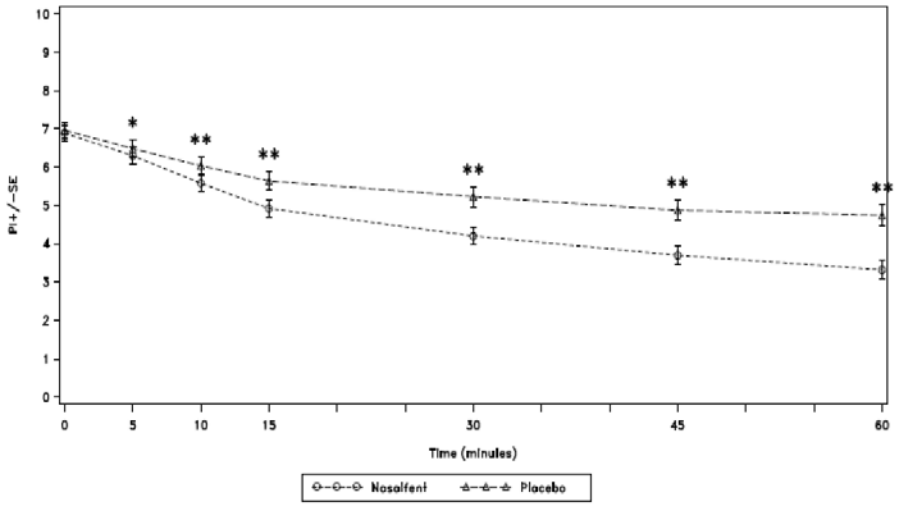
mITT=modified intent-to-treat; SE=standard error; SPID=summed pain intensity difference
Summed Pain Intensity Difference scores compared to baseline (mean of patient means) after Nasalfent and placebo administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and placebo at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and placebo at that time point.
Source: Figure 14.3.8.3.1.1

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 71/1548 of the pdf

Table 17: Mean PI Score by Treatment and Time Point (mITT population)

Secondary Endpoint	FCNS (SD)	Placebo (SD)	p-value
Baseline Pain Intensity	6.89 (1.79)	6.96 (1.83)	0.3176
PI Score 5	6.30 (1.83)	6.48 (1.96)	0.0298
PI Score 10	5.58 (1.91)	6.04 (2.07)	0.0014
PI Score 15	4.92 (1.97)	5.64 (2.16)	< 0.0001
PI Score 30	4.20 (1.96)	5.23 (2.26)	< 0.0001
PI Score 45	3.70 (1.98)	4.88 (2.27)	< 0.0001
PI Score 60	3.32 (2.04)	4.74 (2.36)	< 0.0001

Figure 8: PI Score (mean ± SE) after FCNS and Placebo Administration (mITT Population)



mITT=modified intent-to-treat; SE=standard error; PI=pain intensity
Pain Intensity scores compared to baseline (mean of patient means) after Nasalfent and placebo administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and placebo at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and placebo at that time point.
Source: Figure 14.3.8.3.1.1

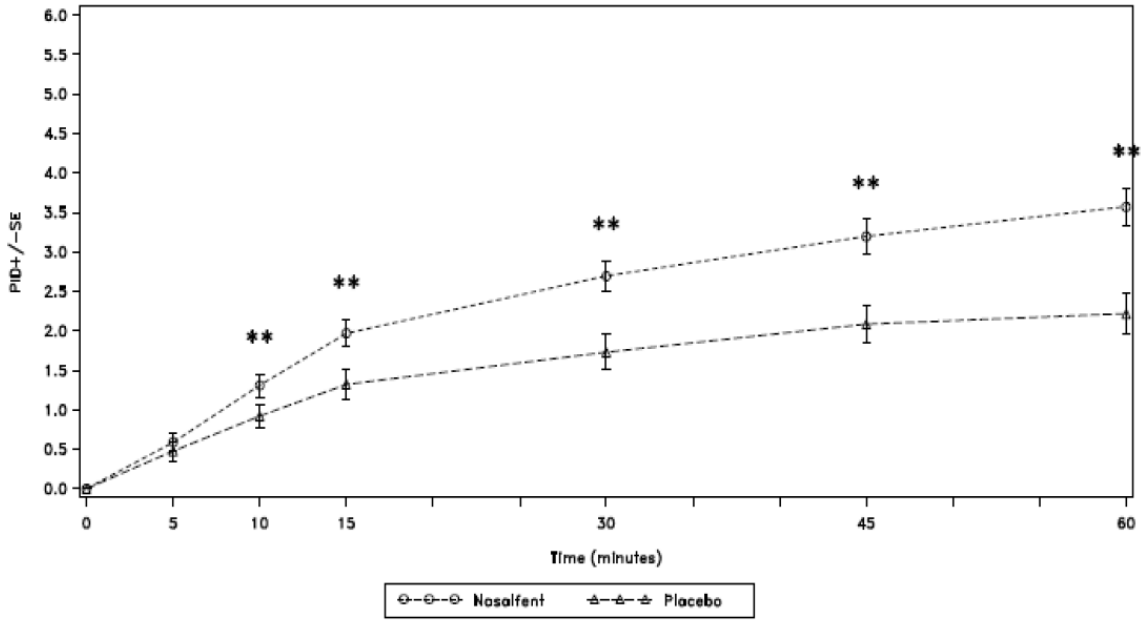
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 71/1548 of the pdf

Table 18: Mean PID[1] by Treatment and Time Point (mITT population)

Secondary Endpoint	FCNS (SD)	Placebo (SD)	p-value
Baseline Pain Intensity	6.89 (1.79)	6.96 (1.83)	0.3176
PID 5	0.59 (0.88)	0.48 (1.01)	0.0709
PID 10	1.31 (1.27)	0.92 (1.32)	0.0023
PID 15	1.97 (1.51)	1.32 (1.57)	< 0.0001
PID 30	2.69 (1.65)	1.73 (1.90)	< 0.0001
PID 45	3.20 (1.85)	2.08 (2.03)	< 0.0001
PID 60	3.57 (1.97)	2.22 (2.14)	< 0.0001

[1]Pain intensity difference was calculated as the baseline pain score minus the pain score at the specified time point. LOCF was used to impute missing data or data after rescue medication usage.

Figure 9: PID (mean ± SE) after FCNS and Placebo Administration (mITT Population)



mITT=modified intent-to-treat; SE=standard error; PID=pain intensity difference
Pain Intensity Difference scores compared to baseline (mean of patient means) after Nasalfent and placebo administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and placebo at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and placebo at that time point.
Source: Figure 14.3.8.3.2.1

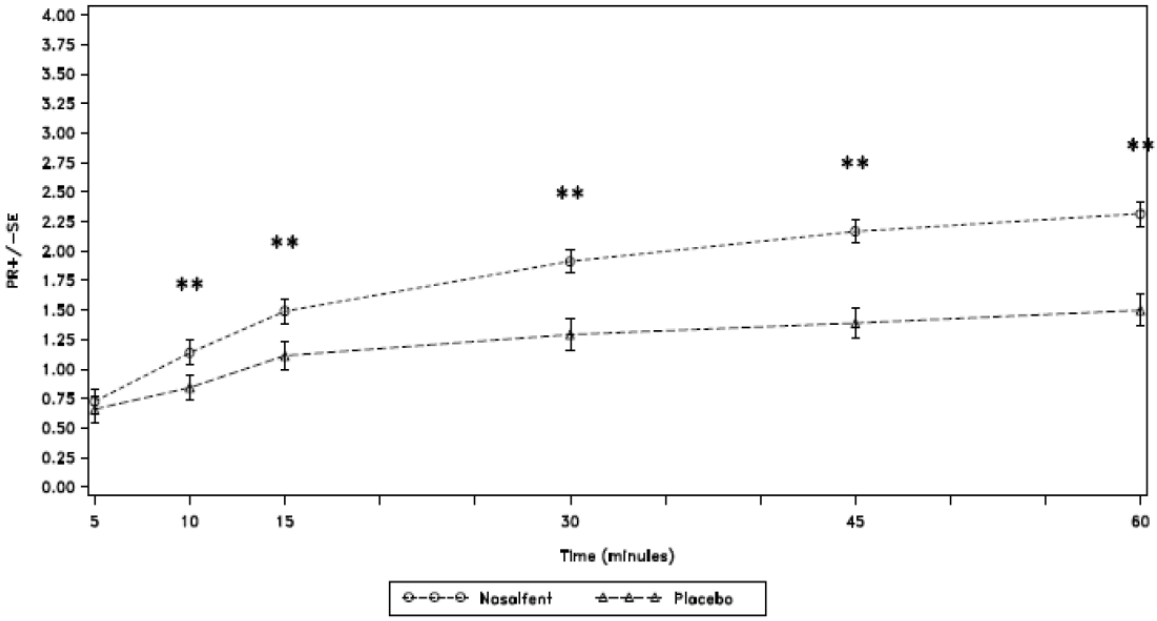
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 76/1548 of the pdf

Table 19: Mean Pain Relief[1] by Treatment and Time Point (mITT population)

Secondary Endpoint	FCNS (SD)	Placebo (SD)	p-value
PR 5	0.73 (0.87)	0.66 (0.93)	0.2149
PR 10	1.14 (0.89)	0.84 (0.93)	0.0002
PR 15	1.49 (0.89)	1.11 (1.01)	0.0004
PR 30	1.91 (0.85)	1.29 (1.16)	< 0.0001
PR 45	2.17 (0.88)	1.39 (1.13)	< 0.0001
PR 60	2.32(0.89)	1.50 (1.19)	< 0.0001

[1] Pain Relief was measured using a 5-point categorical scale (0 = no relief to 4 = complete relief). LOCF was used to impute missing data or data after rescue medication usage.

Figure 10: Pain Relief Scores (mean ± SE) after FCNS and Placebo Administration (mITT Population)



mITT=modified intent-to-treat; SE=standard error; PR=pain relief
Pain Relief scores compared to baseline (mean of patient means) after Nasalfent and placebo administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and placebo at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and placebo at that time point.
Source: Figure 14.3.8.3.4.1

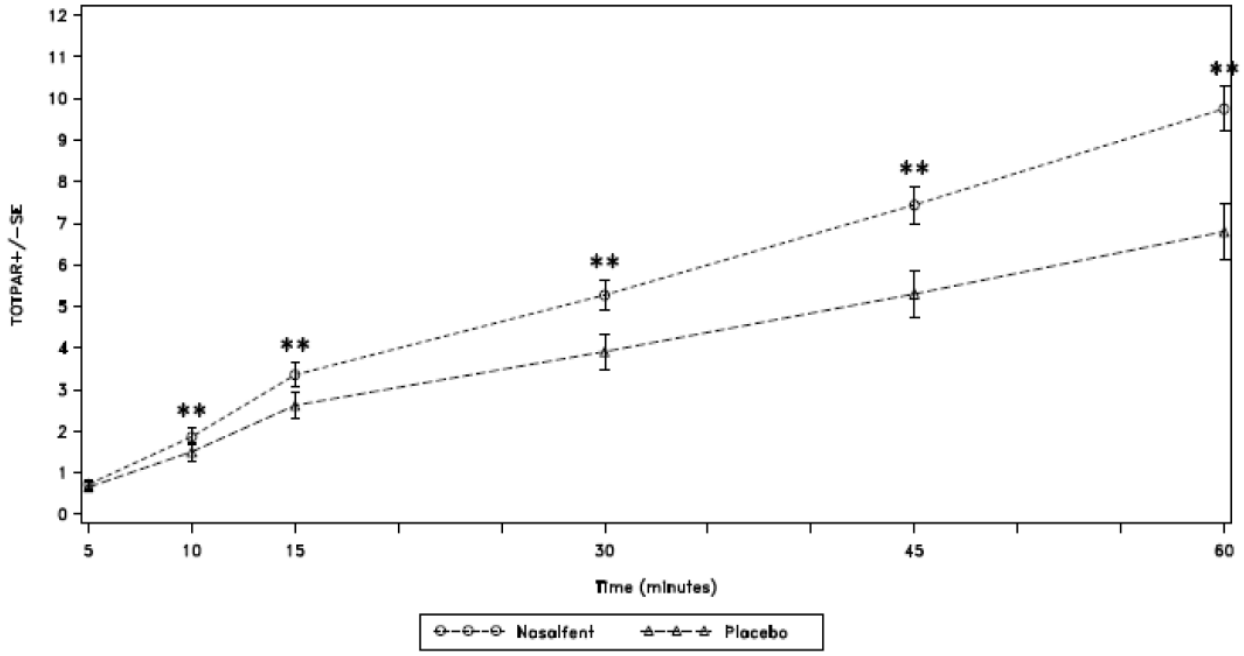
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 78/1548 of the pdf

Table 20: Mean Total Pain Relief[1] by Time Point (mITT population)

Secondary Endpoint	FCNS (SD)	Placebo (SD)	p-value
TOTPAR 5	0.73 (0.87)	0.66 (0.93)	0.2149
TOTPAR 10	1.87 (1.71)	1.50 (1.82)	0.0031
TOTPAR 15	3.36 (2.51)	2.62 (2.75)	0.0007
TOTPAR 30	5.27 (3.21)	3.91 (3.74)	< 0.0001
TOTPAR 45	7.44 (3.90)	5.30 (4.73)	< 0.0001
TOTPAR 60	9.76 (4.56)	6.80 (5.75)	< 0.0001

[1] Total pain relief was calculated as the weighted sum of the pain relief of all time points at or before the time point of interest. LOCF was used to impute missing data or data after rescue medication usage.

Figure 11: Total Pain Relief Scores (mean ± SE) after FCNS and Placebo Administration (mITT Population)



mITT=modified intent-to-treat; SE=standard error; TOTPAR=total pain relief
Total Pain Relief scores compared to baseline (mean of patient means) after Nasalfent and placebo administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and placebo at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and placebo at that time point.
Source: Figure 14.3.8.3.5.1
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 80/1548 of the pdf

Analyses of all of the above secondary endpoints support the primary efficacy finding for FCNS. The mean SPID by time point showed positive results at 10, 15, 30, 45, and 60 minutes. The mean PID, PR, and TOTPAR all showed significant differences between placebo and study drug at 10, 15, 30, 45, and 60 minutes.

Overall satisfaction

Patients evaluated their overall satisfaction with study drug at the 30 minutes and the 60-minutes time points using a 4-point categorical scale (1 = not satisfied to 4 = very satisfied). The overall mean patient-averaged acceptability assessment score was greater for FCNS compared with placebo at 30 minutes postdose (2.63 vs. 2.01, $p < 0.0001$) and at 60 minutes postdose (2.73 vs. 2.02, $p < 0.0001$).

Overall, patients rated 65.1% of the 459 episodes of breakthrough pain treated with FCNS at 30 minutes (67.7% at 60 minutes) as satisfied or very satisfied compared with 37.0 % of 200 breakthrough pain episodes treated with placebo at 30 minutes (37.5% at 60 minutes).

Responder analyses

Five types of responder analyses were performed:

- Mean reduction in PI score ≥ 1 and ≥ 2 at 5, 10, 15, 30, 45, and 60 minutes postdose.
- Mean reduction in SPID Score of ≥ 2, ≥ 3, and ≥ 4 at 10, 15, 30, 45, and 60 minutes postdose.
- Reduction of PI scores from baseline by ≥ 33%, ≥ 50%, and ≥ 66% at 5, 10, 15, 30, 45 and 60 minutes postdose.
- PR scores ≥ 1 and ≥ 2 at 5, 10, 15, 30, 45, and 60 minutes postdose.
- Achievement of percent maxTOTPAR of ≥ 33%, ≥ 50%, and ≥ 66% at 10, 15, 30, 45, 60 minutes postdose.

The tables below illustrate the results of these analyses. P-values from McNemar Test to compare FCNS and placebo treatments at each time point.

Table 21: Mean reduction in PI score ≥ 1 and ≥ 2 mITT Population

Time post dose (min)	**PI ≥ 1**		**p-value**	**PI ≥ 2**		**p-value**
	FCNS (%)	**Placebo (%)**		**FCNS (%)**	**Placebo (%)**	
5	15 (20.5)	16 (21.9)	0.7389	5 (6.8)	5 (6.8)	1.0000
10	41 (56.2)	28 (38.4)	0.0067	18 (24.7)	12 (16.4)	0.0833
15	53 (72.6)	38 (52.1)	0.0011	36 (49.3)	19 (26.0)	0.0002
30	62 (84.9)	44 (60.3)	0.0001	46 (63.0)	26 (35.6)	< 0.0001
45	66 (90.4)	47 (64.4)	< 0.0001	52 (71.2)	32 (43.8)	0.0002
60	70 (95.9)	47 (64.4)	< 0.0001	55 (75.3)	33 (45.2)	< 0.0001

Table 21 shows the reductions in the mean percent PI score ≥ 1 were noted at each time point from 10 minutes through 60 minutes. Differences in PI scores ≥ 2 favoring FCNS over placebo were observed from 15 through 60 minutes.

Table 22: Mean reduction in SPID score of ≥ 2, 3, and 4 by Treatment and Time Point (mITT Population)

Time post dose (min)	SPID ≥ 2		p-value
	FCNS (%)	Placebo (%)	
10	28 (38.4)	17 (23.3)	0.0116
15	47 (64.4)	33 (45.2)	0.0028
30	60 (82.2)	44 (60.3)	< 0.0001
45	65 (89.0)	51 (69.9)	< 0.0001
60	70 (95.9)	54 (74.0)	< 0.0001
	SPID ≥ 3		
10	15 (20.5)	12 (16.4)	0.3173
15	38 (52.1)	22 (30.1)	0.0006
30	54 (74.0)	35 (47.9)	< 0.0001
45	62 (84.9)	44 (60.3)	< 0.0001
60	67 (91.8)	49 (67.1)	< 0.0001
	SPID ≥ 4		
10	8 (11.0)	8 (11.0)	1.0000
15	31 (42.5)	17 (23.3)	0.0010
30	44 (60.3)	28 (38.4)	0.0003
45	58 (79.5)	39 (53.4)	< 0.0001
60	23 (31.5)	10 (13.7)	< 0.0001

Table 22 summarizes the differences in the mean percent SPID score ≥ 2 favoring FCNS over placebo were observed at each time point from 10 minutes through 60 minutes. For SPID score ≥ 3 and ≥ 4, differences favoring FCNS over placebo were noted from 15 minutes through 60 minutes.

Table 23: Mean reduction in PI score by ≥ 33%, 50%, and 66% by Treatment and Time Point (mITT Population)

Time post dose (min)	PI ≥ 33%		p-value
	FCNS (%)	Placebo (%)	
5	3 (4.1)	4 (5.5)	0.3137
10	8 (11.0)	8 (11.0)	1.0000
15	28 (38.4)	14 (19.2)	0.0017
30	41 (56.2)	44 (27.4)	< 0.0001
45	54 (74.0)	47 (34.2)	< 0.0001
60	55 (75.3)	47 (43.8)	< 0.0001
	PI ≥ 50%		
5	2 (2.7)	2 (2.7)	1.0000
10	7 (9.6)	6 (8.2)	0.6547
15	9 (12.3)	7 (9.6)	0.4142
30	25 (34.2)	12 (16.4)	0.0029
45	35 (47.9)	15 (20.5)	< 0.0001
60	39 (53.4)	15 (20.5)	< 0.0001
	PI ≥ 66%		
5	1 (1.4)	1 (1.4)	1.0000
10	1 (1.4)	3 (4.1)	0.1573
15	6 (8.2)	5 (6.8)	0.6547
30	8 (11.0)	6 (8.2)	0.4142
45	16 (21.9)	9 (12.3)	0.0348
60	23 (31.5)	10 (13.7)	0.0008

Table 23 summarizes the percentage of episodes with meaningful (defined as ≥ 33%) decreases in pain scores at protocol-specified postdose time points for the mITT population by treatment. The mean percentage of episodes with at least a 33% reduction in pain scores was higher for FCNS than for placebo at 15, 30, 45, and 60 minutes after dosing. The mean percentage of episodes with at least a 50% reduction in pain scores was higher for FCNS than for placebo at 30, 45, and 60 minutes after dosing. The mean percentage of episodes with at least a 66% reduction in pain scores was higher for FCNS than for placebo at 45, and 60 minutes after dosing.

Table 24: Achieving a PR score by ≥ 1 and 2 by Treatment and Time Point (mITT Population)

Time post dose (min)	PR ≥ 1		p-value	PR ≥ 2		p-value
	FCNS (%)	Placebo (%)		FCNS (%)	Placebo (%)	
5	22 (30.1)	21 (28.8)	0.7389	9 (12.3)	10 (13.7)	0.5637
10	42 (57.5)	32 (43.8)	0.0184	14 (19.2)	11 (15.1)	0.3137
15	54 (74.0)	40 (54.8)	0.0010	23 (31.5)	18 (24.7)	0.1967
30	64 (87.7)	45 (61.6)	< 0.0001	38 (52.1)	21 (28.8)	0.0004
45	66 (90.4)	46 (63.0)	< 0.0001	43 (58.9)	27 (37.0)	0.0035
60	70 (95.9)	49 (67.1)	< 0.0001	48 (65.8)	30 (41.1)	0.0002

There was more number of patients achieving a PR score ≥ 1 following administration of FCNS than following administration of placebo at each observed timepoint from 10 to 60 minutes postdose (Table 24). There were more patients achieving a PR score ≥ 2 following administration of FCNS than following administration of placebo at 30, 45 and 60 minutes postdose.

These PR scores support the superior perceived PI changes for FCNS compared with placebo.

Table 25: Percent of Patients Achieving Percent maxTOTPAR ≥ 33%, ≥ 50% and ≥ 66% by Treatment and Time Point (mITT Population)

Time post dose (min)	TOTPAR ≥ 33%		p-value
	FCNS (%)	Placebo (%)	
10	18 (24.7)	16 (21.9)	0.4142
15	26 (35.6)	21 (28.8)	0.1967
30	31 (42.5)	23 (31.5)	0.0736
45	40 (54.8)	25 (34.2)	0.0018
60	46 (63.0)	27 (37.0)	< 0.0001
	TOTPAR ≥ 50%		
10	10 (13.7)	10 (13.7)	1.0000
15	12 (16.4)	11 (15.1)	0.7055
30	13 (17.8)	13 (17.8)	1.0000
45	19 (26.0)	14 (19.2)	0.1967
60	24 (32.9)	15 (20.5)	0.0290
	TOTPAR ≥ 66%		
10	4 (5.5)	3 (4.1)	0.3137
15	5 (6.8)	4 (5.5)	0.3137
30	4 (5.5)	6 (8.2)	0.1573
45	5 (6.8)	6 (8.2)	0.5637
60	6 (8.2)	6 (8.2)	1.0000

There was more number of patients achieved %maxTOTPAR of ≥ 33% following FCNS administration than following placebo administration at 45 minutes and 60 minutes postdose (Table 25). A higher number of patients achieved %maxTOTPAR of ≥ 50% at 60 minutes following FCNS administration than following placebo administration. No difference was observed in the number of patients achieving %maxTOTPAR of ≥ 66% after use of either FCNS or placebo treatment.

Cumulative responder analysis
There was no cumulative or continuous responder analysis.

Use of rescue medication
A summary of the percentage of patients requiring rescue medication, by treatment, in the mITT Population at various time intervals is presented in Table XXX-XXX below.

Table 26: Rescue Medication Usage (mITT Population)

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

[1]P-values from McNemar Test to compare Nasalfent and placebo arms at each timepoint.
Source: End-of-Text Table 14.2.2.15.1
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 90/1548 of the pdf

Proportionally, more patients used rescue medication following FCNS administration than following placebo administration during the first 45 minutes postdose. However, the clinical relevance of this finding is unclear.

Table 27: Rescue Medication Usage up to 4 Hours mITT Population

Treatment Group (N=73)	Number (%) of subjects that use rescue medication		
	0-30min	30-60min	60min-4hrs
Nasalfent	6 (8.2%)	20 (27.4%)	0 (0.0%)
Placebo	2 (2.7%)	25 (34.2%)	0 (0.0%)
P-values[1]	0.1025	0.2253	1.0000

[1]P-values from a McNemar test to compare Nasalfent versus Placebo at each time point.
Reference: Listing 16.2.6.8
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 503/1548 of the pdf

Proportionally, more patients used rescue medication following FCNS administration than following placebo administration during the first 30 minutes postdose and this observation is reversed from 30 to 60 minutes postdose. There was no difference in rescue medication use between the two groups between 1 and 4 hours postdose. The clinical relevance of these observations is unclear.

Table 28: Episode Rescue Medication Usage mITT Population

Treatment Group (N=659)	Number (%) of episodes where rescue medication is used					
	0-5min N=659	0-10min N=659	0-15min N=659	0-30min N=659	0-45min N=659	0-60min N=659
Nasalfent	5 / 459 (1.1%)	6 / 459 (1.3%)	6 / 459 (1.3%)	9 / 459 (2.0%)	22 / 459 (4.8%)	43 / 459 (9.4%)
Placebo	0 / 200 (0.0%)	0 / 200 (0.0%)	0 / 200 (0.0%)	2 / 200 (1.0%)	16 / 200 (8.0%)	40 / 200 (20.0%)
P-values[1]	---	---	---	0.3845	0.0932	0.0002

[1]P-values from a multilevel model with random effects to compare Nasalfent versus Placebo for each time point category. Due to the low number of episodes where rescue medication was used, fit of the statistical models used is questionable and care must be taken when interpreting inferential statistical results.
Reference: Listing 16.2.6.8

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 504/1548 of the pdf

Proportionally, there was more rescue medication used following FCNS administration than following placebo administration during the first 30 minutes postdose, at which time this observation is reversed. Again, the clinical relevance of this observation is unclear.

Table 29: Episode Rescue Medication Usage up to 4 Hours mITT Population

Treatment Group (N=659)	Number (%) of episodes where rescue medication is used		
	0-30min N=659	30-60min N=659	60min-4hrs N=659
Nasalfent	9 / 459 (2.0%)	34 / 459 (7.4%)	0 / 459 (0.0%)
Placebo	2 / 200 (1.0%)	38 / 200 (19.0%)	0 / 200 (0.0%)
P-values[1]	0.3845	<.0001	---

[1]P-values from a multilevel model for binary data with random effects to compare Nasalfent versus Placebo.
Reference: Listing 16.2.6.8

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 505/1548 of the pdf

Proportionally, there was more episode rescue medication used following FCNS administration than following placebo administration during the first 30 minutes postdose and this observation is reversed from 30 to 60 minutes postdose. There was no difference in the episode rescue medication use between the two groups between 1 and 4 hours postdose.

Discussion of Efficacy Findings

1. The Applicant's analysis of the primary endpoint (SPID30) for Study CP043/06/FCNS, as confirmed by David Petullo, the FDA statistician, supports the finding of efficacy for FCNS compared to placebo ($p < 0.0001$) for the treatment of breakthrough pain in patients with malignancies receiving around-the-clock opioid therapy for cancer pain. In addition, although the analyses of secondary endpoints were not adjusted for multiplicity, due to their consistent trends in favor of FCNS compared to placebo, they support the conclusion that patients receiving FNCS experienced greater pain relief and less pain intensity than those who received placebo.
2. One of the Applicant's efficacy conclusions was that the onset of effect of FCNS occurred as early as 5 minutes after dosing and was sustained throughout the 60-minute period studied. In actuality, the data show that the mean PI score was lower following FCNS treatment than following placebo treatment at each observed time point from 5 to 60 minutes postdose.
3. The secondary endpoints, while not adjusted for multiplicity, support the conclusion that the drug is efficacious.
4. One of the secondary efficacy endpoints was SPID by time point, which showed separation starting at 15 minutes. It is interesting to note that proportionally more rescue medication use occurred within the first 45 minutes following FCNS than placebo treatment. The clinical relevance of this observation is unclear. However, the higher use of rescue in episodes treated with FCNS does shed doubt on the meaning of the early curve separation between FCNS and placebo.
5. One of the most common protocol deviations was improper canister use or dosing, which included improper priming of the canister, more than expected number of clicks per canister, and more than the intended dose was used. These protocol deviations did not appear to confound the results of this crossover design study as demonstrated by the consistency in efficacy outcomes for the mITT and PP Populations.
6. There appears to be a discrepancy between the Applicant's statements that the proportion of rescue medication need was significantly lower in FCNS-treated episodes up to 60 minutes following treatment and the associated data sets that proportionally more rescue medication use following FCNS treatment up to 30 to 45 minutes postdose. (Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 100 and 105/1548 and page 90 and 503/1548 of the pdf.) As noted in this review, rescue was used more often, early after dosing, in episodes treated with FCNS than those treated with placebo.

CP044/06/FCNS

CP044 was to have been a supportive clinical trial for the pivotal clinical trial CP043. The primary objective of CP044 was to demonstrate that FCNS is superior to immediate-release oral morphine sulfate (IRMS) in the treatment of BTCP in opioid-tolerant patients who were receiving regular opioid therapy. The secondary objective of CP044 was to demonstrate the safety, tolerability, and acceptability of FCNS. The trial design was to have been a Phase 3, randomized, double-blind, double-dummy, active-controlled, crossover study across 35 sites in Europe and India. The trial protocol was similar to CP043 with the following notable differences:

- This trial was not to have been conducted in the United States.
- IRMS was the active control.

Only FCNS was titrated to an effective dose during the Open, Dose-Titration Period. For morphine, the effective dose was defined as either one-sixth the total daily dose equivalent of background opioid medication or a previously identified effective dose prior to study entry during the Double-Blind, Double-Dummy Treatment Period.

- The allocation of blinded comparators was 5 FCNS and 5 placebo or 5 IRMS and 5 placebo.
- The primary efficacy endpoint was the pain intensity difference 15 minutes post-dose (PID15).

Protocol Amendments
One amendment (Amendment #1) was submitted to the NDA on 06 December 2006, one month and 16 days after initial protocol was submitted. The amendment described administrative changes to the reporting procedures for adverse events.

Results

Disposition of Patients
A total of 135 patients were screened and enrolled for participation in the trial. Of the 135 enrolled patients, 110 (81.5%) entered the Open, Dose-Titration Period. A total of 106 patients (96.4%) received at least one dose of FCNS and were included in the Safety Population; Patients 705/470501, 806/480601, 854/485402, and 840/48406 had neither diary data nor telephone call records indicating FCNS use and were not included in the Safety Population.

A total of 25 patients (18.5%) were excluded at screening, 26 patients (23.6%) discontinued during the titration period, and 5 patients (6.0%) discontinued during the Double-Blind period. The most common reason for screening failure (18/25, 13.3%) was inability to meet the entry criteria. The most common reasons for discontinuation from the Open, Dose-Titration Phase were withdrawal of consent (7 [6.4%] patients) and lack of efficacy (6 [5.5%] patients). There were four patients who were excluded during the Screening and one patient from the Titration Period who did not continue onto the Double-Blind Period for unspecified “other” reasons. The

Applicant was queried with regard to actual reason(s) for discontinuation and the response follows (Table 30).

Table 30: "Other" reason(s) for discontinuation from the Study

CP044 (from Listing 16.2.1)	
Patient number	**Reason for discontinuation**
Screening	
706/470602	Site lab-value (bilirubin) misinterpretation
Titration	
604/460407	Failure of Nasalfent titration. Patient was not compliant. He did not titrated in
706/470601	Titration failure (no BTCP episodes, according to Listing 16.2.13.1)
863/486302	Titration failure for subjects safety (Listing 16.2.7.1 lists injury to 2 toes on left foot and pruritis as AEs on day prior to withdrawal, but not that they led to withdrawal.)
869/486904	Non-compliance
Double-blind	
702/470201	Site decision (suspected rapid disease progression)

Source: Appendix 2 – Clinical Response document FDA Clinical Questions – 2 Feb 2010, page 6/8 of the pdf

There were 84 patients who completed the titration period by achieving an effective and tolerable FCNS dose. All these patients entered the Double-Blind Period. A total of 79 (94.0%) patients completed this part of the trial, but not all had treated 10 BTCP episodes. Among the 5 (6.0%) patients who discontinued, 2 (2.4%) discontinued due to AE and 3 discontinued due to the following reasons (1 each): inability to meet entry criteria, withdrawal of consent, and suspected rapid disease progression. Of the 84 randomized patients in the Double-Blind Treatment Period, 79 (94.0%) were included in the mITT Population and 72 (85.7%) were included in the PP Population.

Of the 79 patients in the Double-Blind, Double-Dummy Treatment Period, 22 (27.8%) were maintained on a previously identified IRMS dose, and 57 (72.2%) were allocated an IRMS dose equal to one-sixth of the patient's total daily background oral morphine dose equivalent medication.

Protocol Deviations
Protocol deviations were identified prior to unblinding the data; inappropriate use of study drug or inappropriate way of recording in e-diary (21 patients), missed or delayed assessments for scheduled visits (10 patients), missed entries or inappropriate way of filling BTCP questionnaire (9 patients), inappropriately filled ICF or use of wrong ICF version (6 patients), missed visits or visits outside the window period (5 patients), entry into study despite not satisfying inclusion/exclusion criteria (4 patients), missed telephone calls (3 patients), and returned drug did not match the episode data entered in e-diary, delay in SAE report (1 patient each). Some patients reported more than 1 protocol deviation. These deviations did not appear to confound trial results as demonstrated by the consistency in efficacy outcomes between the mITT and PP Populations. The details of each deviation are provided by patient in Listing 16.2.2.3.

Analysis of Efficacy
Primary Efficacy Endpoint: Pain Intensity Differences at 15 Minutes (PID15)

The mean PID 15 was higher in FCNS (3.02) compared with IRMS (2.69) treated BTCP episodes and the difference in treatments was statistically significant (p = 0.0396) as summarized in Table 31 below.

Table 31: Summary of PID15 mITT population

N=79 (mITT)	Mean FCNS (SD)	Mean IRMS (SD)	p-value
Baseline PI score	7.76 (1.42)	7.56 (1.37)	0.0270
PID 15	3.02 (1.84)	2.69 (1.69)	0.0396

Source: CP044/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 79/1590 of the pdf

The mean baseline PI score was similar in the treatment groups (FCNS 7.76, IRMS 7.56).

All secondary efficacy endpoints supported the primary except rescue medication usage that showed proportionally more rescue medication use following FCNS treatment. However, the clinical relevance of this finding is unclear. A summary of the percentage of patients using rescue medication, by treatment, in the mITT Population at various time intervals is presented in Table 32, below. Similarly, there was proportionally more rescue medication used following FCNS administration than following placebo administration during the first 30 minutes postdose, after which, the pattern is reversed. The clinical relevance of this observation is also unclear.

Table 32: Rescue Medication Usage (mITT Population)

Treatment (N=79)	Number (%) of Patients Who Used Rescue Medication					
	0-5 min	0-10 min	0-15 min	0-30 min	0-45 min	0-60 min
Nasalfent	3 (3.8%)	3 (3.8%)	3 (3.8%)	5 (6.3%)	7 (8.9%)	9 (11.4%)
IRMS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (7.6%)	8 (10.1%)
P-values[1]	0.0833	0.0833	0.0833	0.0253	0.7389	0.7815

mITT=modified intent-to-treat; min=minute; IRMS=immediate-release morphine sulphate
[1]P-values from McNemar Test to compare Nasalfent and IRMS arms at each timepoint.
Source: End-of-Text Table 14.2.2.15.1

Source: CP044/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 99/1590 of the pdf

Although the primary efficacy endpoint (PID 15) showed a statistically significant difference between epidodes treated with FCNS and IRMS, this study will not support any labeling. If the Applicant wished to claim earlier onset of action compared to IRMS, the study would have to be replicated. Furthermore, the preferred method for assessing onset of analgesia is with a two-stopwatch method, not a difference in pain intensity at an arbitrarily specified time after dosing.

Discussion of Efficacy Findings

Study CP044 supports the notion that FCNS is effective in that pain scores were generally lower than the active control, immediate-release morphine. However, as discussed earlier, this study will not support any comparative claims versus morphine.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy (b) (4) (b) (4) This is the same indication as that of Actiq, the approved oral transmucosal fentanyl citrate product, to which FCNS is referenced.

6.1.1 Methods

Evidence to support the efficacy of FCNS comes from a single study, CP043/06/FCNS; a double-blind, placebo-controlled, two-phase crossover evaluation of the efficacy, safety, and tolerability of FCNS in the treatment of BTP in cancer subjects who are receiving regular opioid therapy. The Division considered submission of a single adequate and well-controlled efficacy

study in the context of previous Agency findings for fentanyl acceptable for this NDA submission.

6.1.2 Demographics

Overall, there were no important differences between the Open, Dose-Titration population and the Double-Blind population related to demographics and baseline characteristics.

Table 33 below presents a summary of subject demographics for the titration (safety) and double-blind (mITT) periods of study CP043/06/FCNS.

Table 33: Summary of subject demographics

Characteristic	Titration N=113	Double-Blind (mITT) N=73
Age (yrs)		
Mean (SD)	53.8 (11.6)	51.8 (11.9)
Median	53.0	52.0
Min, Max	21, 86	21, 76
≤ 60	82 (72.6)	58 (79.5)
> 60	31 (27.4)	15 (20.5)
Gender, n (%)		
Male	60 (53.1)	38 (52.1)
Female	53 (46.9)	35 (47.9)
Race, n (%)		
Caucasian	77 (6 8.1)	53 (72.6)
Black	13 (11.5)	7 (9.6)
Asian	2 (1.8)	2 (2.7)
Other	21 (18.6)	11 (15.1)
Weight (pounds)		
Mean (SD)	78.8 (18.5)	79.9 (19.5)
Median	78.1	79.0
Min, Max	45.0, 147.7	46.0, 147.7
Eastern Cooperative Oncology Group score, n (%)		
0	18 (15.9)	10 (13.7)
1	59 (52.2)	42 (57.5)
2	36 (31.9)	21 (28.8)
Location, n (%)		
United States	100 (88.5)	
Argentina/Costa Rica	13 (11.5)	
Allergic disorder, n (%)		
Yes	57 (50.4)	
No	56 (49.6)	
Upper respiratory infection, n (%)		
Yes	21 (18.6)	
No	92 (81.4)	
Chemotherapy, n (%)		
Yes	22 (19.5)	
No	91 (80.5)	

In both populations, the most common cancer diagnoses were breast, lung, reticulo-endothelial, and bowel (53.9% of Titration and 54.5% of Double-Blind). The remaining cancer types were prostate, musculoskeletal including primary bone and sarcoma), primary not specified or known, upper gastrointestinal including gastric and esophageal, pancreatic, renal, throat, CNS, ovarian, uterine, liver, cervical, testicular, melanoma, neuroendocrine, and bladder cancer.

A total of 111 (98.2%) patients reported use of concomitant medication during the study. The most commonly used concomitant medications (used by more than 10% of patients in the Safety Population) were gabapentin (22.1%), zolpidem tartarate (15.9%), hydromorphone hydrochloride (14.2%), pregabalin (12.4%), oxycodone/acetaminophen (11.5%), oxycodone (10.6%), and ibuprofen (10.6%).

All 113 patients in the Safety Population used opioids, as specified in the protocol's inclusion criteria. The most commonly used opioids were morphine (45 [39.9%] patients), fentanyl (27 [23.9%] patients), oxycodone (21 [18.6%] patients), and methadone (23 [20.4%] patients). Summary of opioid use is summarized in Table 34 below.

Table 34: Summary of opioid use in Titration (Safety) Population

	Total (N=113) Number (%) of Subjects
Subjects with Opioid Use	113 (100.0)
DIPHENYLPROPYLAMINE DERIVATIVES	1 (0.9)
DEXTROPROPOXYPHENE NAPSILATE	1 (0.9)
PROPACET	1 (0.9)
DRUGS USED IN OPIOID DEPENDENCE	23 (20.4)
METHADONE	20 (17.7)
METHADONE HYDROCHLORIDE	3 (2.7)
NATURAL OPIUM ALKALOIDS	79 (69.9)
HYDROMORPHONE	4 (3.5)
HYDROMORPHONE HYDROCHLORIDE	3 (2.7)
MORPHINE	14 (12.4)
MORPHINE HYDROCHLORIDE	2 (1.8)
MORPHINE SULFATE	29 (25.7)
OXYCOCET	9 (8.0)
OXYCODONE	5 (4.4)

Reference: Listing 16.2.4.5

6.1.3 Subject Disposition

A total of 139 patients were screened and 114 (82.0%) patients were enrolled across 58 opened (36 active) sites in the Open, Dose-Titration Phase. Of the 114 patients, 113 (99.1%) received at least one dose of FCNS and were included in the Safety Population; one patient withdrew consent before taking any study drug.

An an effective and tolerable dose was identified in a total of 83 (72.8%) patients during the Open, Dose-Titration Period. These patients were randomized to the Double-Blind Treatment Phase. Of the 83 patients, 76 (91.6%) completed the Double-Blind Treatment Phase. However, not all of the patients received the full 10 treatment episodes.

The following Tables summarize the rates and reasons for dropout for the Screening, Titration, and Double-blind treatment periods of the study. A total of 66.7% (76/114) of the patients entering the study completed it.

Table 35: Subject Disposition: Open, Dose-Titration Phase (All Enrolled Patients)

Number (%) of Patients	N (%)
Screened	139
Withdrew at End of Visit 1 (Screen Failures)[1]	25 (18.0)
Reasons for Withdrawal at End of Visit 1[1]	
Adverse Event	4 (2.9)
Concomitant Therapy	0 (0.0)
Did Not Continue to Meet Inclusion/Exclusion Criteria	11 (7.9)
Death	3 (2.2)
Withdrawal of Consent	2 (1.4)
Other	5 (3.6)
Enrolled (Entered the Open, Dose-Titration Phase)[1]	114 (82.0)
Included in Safety Population[2]	113 (99.1)
Withdrew from the Open, Dose-Titration Phase[2]	31 (27.2)
Reasons for Withdrawal from the Open, Dose-Titration Phase[2]	
Adverse Event	6 (5.3)
Concomitant Therapy	0 (0.0)
Did Not Continue to Meet Inclusion/Exclusion Criteria	4 (3.5)
Inability to Evaluate and Record Patient Assessment Data (Inc #7 was not met)	0 (0.0)
Death	0 (0.0)
Inability to Explain Return of Less Than Predicted Study Drug	1 (0.9)
Lack of Efficacy	7 (6.1)
Lost to Follow-up	1 (0.9)
Pregnancy	0 (0.0)
Protocol Violation	2 (1.8)
Withdrawal of Consent	5 (4.4)
Other	5 (4.4)
Completed the Open, Dose-Titration Phase[2]	83 (72.8)
Randomized[2]	83 (72.8)

[1] Denominator for percentage calculation is number of patients screened (N=139).
[2] Denominator for percentage calculation is number of patients enrolled (N=114).
Source: End-of-Text Table 14.1.1.1
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 59/1548 of the pdf

The "other" reasons for withdrawing from the Screening Phase included patient transferred care (n=1); lost to follow-up (n=1); non-compliant (n=1); unable to dose with study drug due to technical problems with diary (n=1), and leucopenia. "Other" reasons for withdrawing from the Titration Phase include non-compliance with titration (n=1); request of Medical Director (n=1), and did not complete Titration Phase because less than one episode of breakthrough cancer pain per day (n=1). A full analysis of Dropouts and/or Discontinuations may be found in Section 7.3.3. Please refer to Dr. Nick Olmos-Lau's review.

Table 36: Subject Disposition: Double-Blind Treatment Phase (All Enrolled Patients)

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

mITT=modified intent-to-treat; PP=per protocol
[1] Patients who have a completion date on CRF
[2] The patient who was lost to follow-up was contacted by phone calls and by sending letters to get the status
Source: End-of-Text Table 14.1.1.2
Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 60/1548 of the pdf

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy outcome variable was the sum of pain intensity differences at 30 minutes after dosing (SPID30) for FCNS versus placebo during the double-blind period of the study. The analysis was conducted on 73 patients who met the definition of mITT Population, which was defined as all patients in the randomized population that treated at least one episode with FCNS and one with placebo, had a baseline and at least one postbaseline PI measurement.

The mean SPID30 for FCNS-treated episodes was statistically significantly greater ($p < 0.0001$) than the mean SPID30 for placebo-treated episodes. The mean SPID30 was 6.57 for FCNS and 4.45 for placebo. The Applicant's Table 37 below illustrates this analysis.

Table 37: Summary of SPID30 mITT population

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

SD = standard deviation; mITT=modified intent-to-treat
Note: Pain Intensity Scores were recorded in an e-diary on a rating scale of 0 to 10, where 0 represented 'no pain' and 10 represented 'worst possible pain'. The Last Observation Carried Forward (LOCF) method was used to input missing scores for evaluable episodes due to omission or use of rescue medication, prior to calculating the average value for each patient/treatment group. The higher the SPID score the better.
[1] P-values from the analysis of covariance (ANCOVA) model.
[2] Indicator whether the patient has taken any rescue medication within 30 minutes for any mITT evaluable episode
Source: End-of-Text Table 14.2.1.1.1

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 69/1548 of the pdf

6.1.5 Analysis of Secondary Endpoints(s)

Although several secondary endpoints were studied and analyzed, the Applicant did not apply multiplicity adjustments, and they are therefore considered only supportive and not suitable to support any additional claims. However, analyses of all the secondary endpoints are supportive of the primary endpoint and the finding of efficacy FCNS compared to placebo. A more detailed discussion of the secondary endpoints may be found in section 5.3.

6.1.6 Other Endpoints

Other endpoints included patient acceptability assessments, responder analyses, and rescue medication use. Patients evaluated their overall satisfaction with study drug and the overall mean patient-averaged acceptability assessment score was greater for FCNS compared with placebo at 30 minutes postdose and at 60 minutes postdose.

Reductions in the mean percent PI score ≥ 1 were noted at each time point from 10 minutes through 60 minutes. Differences in PI scores ≥ 2 favoring FCNS over placebo were observed from 15 through 60 minutes. Differences in the mean percent SPID score ≥ 2 favoring FCNS over placebo were observed at each time point from 10 minutes through 60 minutes. For SPID score ≥ 3 and ≥ 4, differences favoring FCNS over placebo were noted from 15 minutes through 60 minutes. The mean percentage of episodes with at least a 33% reduction in pain scores was higher for FCNS than for placebo at 15, 30, 45, and 60 minutes after dosing. Pain relief scores support the superior perceived PI changes for FCNS compared with placebo.

Proportionally, more patients used rescue medication following FCNS administration than following placebo administration during the first 45 minutes postdose. The clinical relevance of this observation is unclear. However, the higher use of rescue in episodes treated with FCNS does shed doubt on the meaning of the early curve separation between FCNS and placebo.

6.1.7 Subpopulations

The effects of gender and age on the primary efficacy endpoint were not statistically significant. Responses to treatment with FCNS and placebo adjusted for gender and age were comparable with the overall population. Treatment effect within the subpopulation (i.e., non-Caucasians) appeared to show a difference. However, the study was not powered to detect a treatment difference within the subpopulation.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Patients were titrated to a successful dose of FCNS to treat their breakthrough cancer pain within the dose range offered (100, 200, 400, and 800 mcg). A summary of doses used by subjects in the double-blind period of the study is provided in Table 38 below.

Table 38: Doses Used in Double-Blind Study

FCNS (mcg)	Double-blind period n (%); N=73
100	8 (9.6)
200	7 (8.4)
400	24 (28.9)
800	34 (41.0)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Chronic opioid therapy leads to tolerance and physical dependence.

Study CP045, an open-label, long-term safety and tolerability study of FCNS in the treatment of BTCP in patients already on opioid therapy informed the persistence of efficacy and tolerance effects.

In the main part of Study CP045 (16-weeks), a total of 300 patients maintained the dose they were first titrated to throughout their participation in the study. Forty-one patients required a dose modification. The available data do not indicate whether the dose change was an increase or decrease.

The 120-Day Safety Update provided information for patients who continued in Study CP045 past the 16 weeks initially planned. The 120-Day Safety Update indicated that 106 patients maintained their titrated effective FCNS dose throughout the Open-Label treatment phase and the Extension Period and 9 patients required a increase in dose.

These data suggest that, once an effective FCNS dose was identified, a substantial proportion of the patients maintained their titrated FCNS dose.

<u>Reviewer's Comments Regarding Efficacy Findings</u>

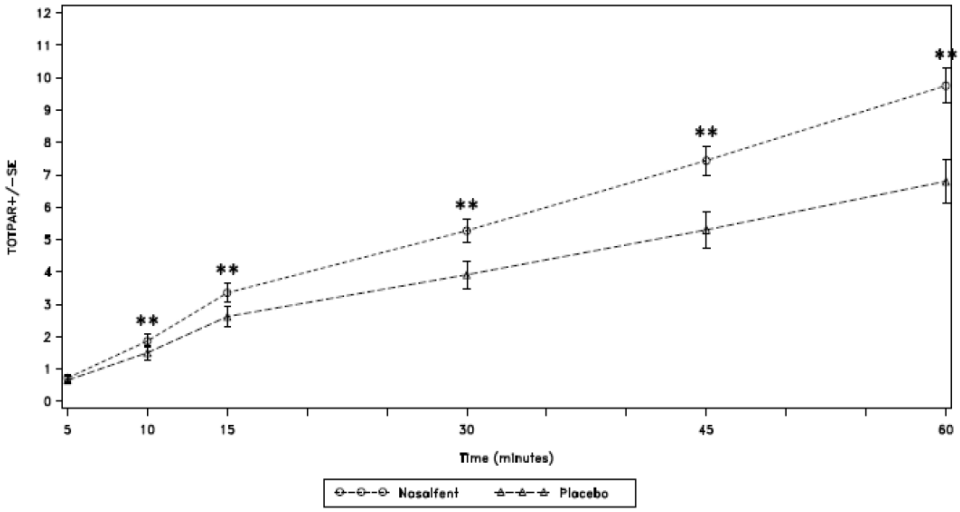
- The Applicant provided substantial evidence of efficacy. The Applicant's statistical analysis was confirmed by Mr. David Petullo of the Division of Biometrics. Details of the statistical analyses may be found in Mr. Petullo's review.

The efficacy findings for FCNS appear consistent with those for Actiq and Fentora. The primary endpoint used for the Actiq Phase 3 trial was pain relief, in contrast to Fentora and FCNS, which used SPID30. Since pain relief data were collected as secondary

endpoints for both Fentora and FCNS, that information can be used to compare the pain relief curves for each drug. Although comparison of inter-trial data has limitations, Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 80/1548 of the pdf

- and Figure 13 below illustrate the similarity between the active drug and placebo curves for each product.

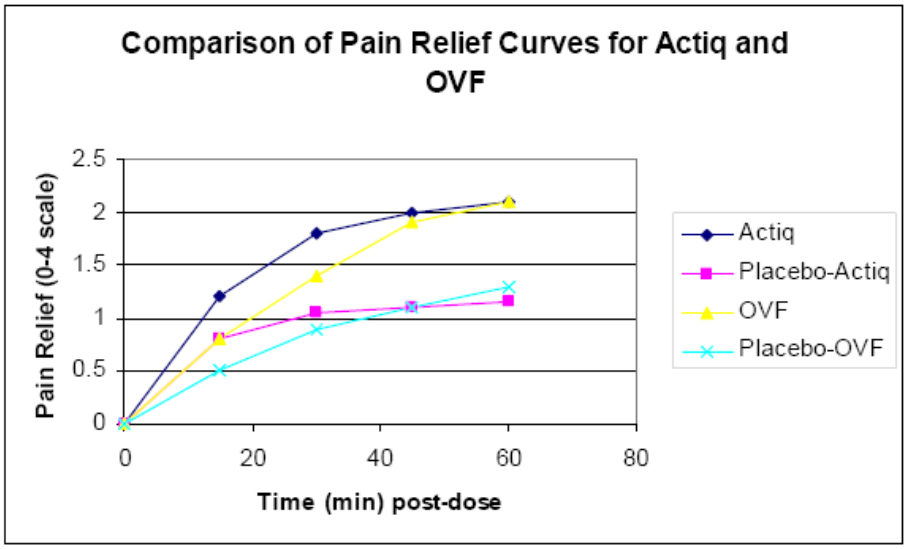
Figure 12: FCNS pain relief vs Placebo



mITT=modified intent-to-treat; SE=standard error; TOTPAR=total pain relief
Total Pain Relief scores compared to baseline (mean of patient means) after Nasalfent and placebo administration.
* Significant difference detected at the alpha ≤0.05 level between Nasalfent and placebo at that time point.
** Significant difference detected at the alpha ≤0.01 level between Nasalfent and placebo at that time point.
Source: Figure 14.3.8.3.5.1

Source: CP043/06/FCNS Study Report Body FINAL CLINICAL STUDY REPORT, page 80/1548 of the pdf

Figure 13: Pain relief curves Actiq and Fentora



Source: Shibuya R: NDA 21-947 Clinical Review 30 August 2006, 7/10 of the pdf; OVF=Fentora

- Although the SPID for FCNS appear to differ from placebo starting with SPID10, the onset of action cannot be accurately determined from this information. Pain relief was not assessed during the trial using the double stop-watch method (measuring time to "perceptible" pain relief and "meaningful" pain relief), so that the true onset of action of the drug was not measured during Study CP043/06/FCNS, and no claims may be made regarding time to onset of pain relief.

6.1.10 Additional Efficacy Issues/Analyses

A supportive study for the efficacy findings demonstrated in CP043/06/FCNS comes from a single study, CP044/06/FCNS; a double-blind, double-dummy, crossover evaluation of the efficacy, safety, and tolerability of FCNS compared with immediate release morphine sulfate (IRMS) in the treatment of breakthrough pain in cancer subjects who are receiving regular opioid therapy. The primary efficacy endpoint was PID15. The mean PID15 was higher in FCNS compared with IRMS treated BTCP episodes and the difference in treatments was statistically significant, although the treatment effect size was small. Study CP044/06/FCNS supports the notion that FCNS is effective in that pain scores were generally lower than IRMS. However, this study will not support any comparative claims versus morphine. If the Applicant wished to claim earlier onset of action compared to IRMS, the study would have to be replicated. Furthermore, the preferred method for assessing onset of analgesia is with a two-stopwatch method, not a difference in pain intensity at an arbitrarily specified time after dosing.

7 Review of Safety

Safety Summary

The review of safety was conducted by Nick Olmos-Lau, M.D. Dr. Olmos-Lau found that the safety profile of FCNS is typical for a product of this type. Please see Dr. Olmos-Lau's review for further detail.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Please see Dr. Olmos-Lau's review.

7.1.2 Categorization of Adverse Events

Please see Dr. Olmos-Lau's review.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Please see Dr. Olmos-Lau's review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Please see Dr. Olmos-Lau's review.

7.2.2 Explorations for Dose Response

Please see Dr. Olmos-Lau's review.

7.2.3 Special Animal and/or In Vitro Testing

Please see Dr. Olmos-Lau's review.

7.2.4 Routine Clinical Testing

Please see Dr. Olmos-Lau's review.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see Dr. Olmos-Lau's review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please see Dr. Olmos-Lau's review.

7.3 Major Safety Results

7.3.1 Deaths

Please see Dr. Olmos-Lau's review.

7.3.2 Nonfatal Serious Adverse Events

Please see Dr. Olmos-Lau's review.

7.3.3 Dropouts and/or Discontinuations

Please see Dr. Olmos-Lau's review.

7.3.4 Significant Adverse Events

Please see Dr. Olmos-Lau's review.

7.3.5 Submission Specific Primary Safety Concerns

Please see Dr. Olmos-Lau's review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Please see Dr. Olmos-Lau's review.

7.4.2 Laboratory Findings

Please see Dr. Olmos-Lau's review.

7.4.3 Vital Signs

Please see Dr. Olmos-Lau's review.

7.4.4 Electrocardiograms (ECGs)

Please see Dr. Olmos-Lau's review.

7.4.5 Special Safety Studies/Clinical Trials

Please see Dr. Olmos-Lau's review.

7.4.6 Immunogenicity

Please see Dr. Olmos-Lau's review.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please see Dr. Olmos-Lau's review.

7.5.2 Time Dependency for Adverse Events

Please see Dr. Olmos-Lau's review.

7.5.3 Drug-Demographic Interactions

Please see Dr. Olmos-Lau's review.

7.5.4 Drug-Disease Interactions

Please see Dr. Olmos-Lau's review.

7.5.5 Drug-Drug Interactions

Please see Dr. Olmos-Lau's review.

7.6 Additional Safety Evaluations

Please see Dr. Olmos-Lau's review.

7.6.1 Human Carcinogenicity

Please see Dr. Olmos-Lau's review.

7.6.2 Human Reproduction and Pregnancy Data

Please see Dr. Olmos-Lau's review.

7.6.3 Pediatrics and Assessment of Effects on Growth

Please see Dr. Olmos-Lau's review.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please see Dr. Olmos-Lau's review.

7.7 Additional Submissions / Safety Issues

Please see Dr. Olmos-Lau's review.

8 Postmarket Experience

There is no post-marketing experience for this product as it is not approved in any country.

9 Appendices

9.1 Literature Review/References

The Applicant provided 56 references which were used as needed in my review. A systematic review of the Applicant's references was not conducted.

9.2 Labeling Recommendations

There are three previously approved oral transmucosal fentanyls for breakthrough cancer pain. The proposed labeling was based on those labels. The FCNS label should closely conform to the most recently approved fentanyl product for breakthrough cancer pain, Onsolis.

Important issues regarding the product label include:

1. The Applicant's proposed tradenames [redacted] (b) (4)" have been deemed unacceptable by DMETS and the Division.
2. Patients are to separate each dose by at least 2 hours. [redacted] (b) (4) [redacted] (b) (4)
3. Applicant to create and include a FCNS titration Figure that is similar Actiq titration Figure.
4. Overdosage section revised to reflect FCNS formulation.
5. Concerns regarding Applicant's proposed disposition for primed FCNS, partially used or unused FCNS; [redacted] (b) (4)

9.3 Advisory Committee Meeting

There is no advisory committee meeting planned for this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

LUKE YIP
04/09/2010

ROBERT B SHIBUYA
04/09/2010
I concur with Dr. Yip's review

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, Building 22, 10903 New Hampshire Ave. Silver Spring MD 20993
Tel:(301)796-2280

Memo to File

DATE: **March 24, 2010**

TO: **NDA 22-569, Nasal Fentanyl Spray**

FROM: **Sharon Hertz, M.D., Deputy Division Director**

RE: **Proposed Disposal Method**

The current NDA under reivew is for a nasal spray formulation of fentanyl intended for the managemeent of breakthrough cancer pain in patients who are already receiving and who are tolerant to regular opioid therapy [redacted] (b) (4). Other products approved for this application are three transmucosal fentanyl formulations, Actiq, Fentora and Onsolis. This product is the first to proposal a nasal route. It is composed of a bottle of fentanyl solution with either 100 mcg or 400 mcg per 100 mcL of solution. Each spray is 100 mcL.

During our August 24, 2006, and September 22, 2008, meetings, the Division instructed the applicant to address the proper and safe disposal of the excess fentanyl from your product. The current methods of disposal proposed in the NDA are inadequate to assure the safety of patients, caregivers and household contacts.

The current design calls for four priming sprays and eight sprays intended to deliver the drug to the patient, and each spray is [redacted] (b) (4) volume. The current fill in this design is [redacted] (b) (4) mL. After the 12 sprays are delivered, there will be a residual [redacted] (b) (4) of fentanyl solution in the bottle. As the product is intended to be marketed with either 100 mcg or 400 mcg of fentanyl per [redacted] (b) (4) the amount of residual fentanyl will be [redacted] (b) (4) fentanyl, respectively. After delivery of all 12 sprays, the bottle is intended to be disposed of by placing into the child proof container and placing in the trash.

For the purpose of priming and for partially-used devices, the instructions are for patients to [redacted] (b) (4)
The proposed disposal methods for the residual fentanyl in the bottle and the fentanyl

(b) (4) is not adequate to protect patients and household contacts from unintentional exposure. The proposed package insert provides the following directions:

(b) (4)

(b) (4)

(b) (4)

The Applicant must propose a method of priming and disposing of partially used and unused bottles that assures the safety of patients, caregivers and household contacts.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22569	ORIG-1	ARCHIMEDES DEVELOPMENT LTD	(b) (4) (fentanyl nasal spray)

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/s/

SHARON H HERTZ
03/24/2010