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APPLICATION NUMBER:

022569Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-569	Submission Date(s): 08/31/09
Brand Name	(b) (4) (Proposed trade name under review by the Agency at the time of writing this review)
Generic Name	Fentanyl Citrate Nasal Spray (FCNS) or Fentanyl Nasal Spray (FNS)
Reviewer	Sheetal Agarwal, Ph.D.
Clinical Pharmacology Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Analgesia and Anesthesia Products
Sponsor	Archimedes Development Ltd
Submission Type	505 (b) (2) NDA referencing Actiq® (NDA 20-747: oral transmucosal fentanyl in the form of lozenges)
Related IND	70,854
Formulation; Strength(s)	Nasal Spray, each spray delivers 100 mcL of solution containing either 100 mcg or 400 mcg fentanyl base.
Proposed Indication	Management of breakthrough cancer pain in patients who are already receiving and are tolerant to opioid therapy
Proposed Dosage and Administration	• Initial dose for all patients is 100 mcg. • Individually titrate to an effective dose, from 100 mcg to 200 mcg to 400 mcg, and up to a maximum of 800 mcg, that provides adequate analgesia without undue side effects. • Dose is a single spray into one nostril or a single spray into each nostril (2 sprays) • Maximum dose is a single spray into one nostril or single spray into each nostril per episode; no more than (b) (4) doses per 24 h; separate each dose by at least (b) (4) During any episode, if adequate pain relief *is not achieved* within 30 min, the patient may use a rescue medication as directed by their healthcare provider.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

1. Executive Summary

1.1 RECOMMENDATIONS

From the perspective of the Office of Clinical Pharmacology, NDA 22-569 for (b) (4), a nasal spray formulation of fentanyl, is acceptable provided that the Agency and the sponsor come to a mutually satisfactory agreement on the labeling language.

1.2 PHASE 4 COMMITMENTS

None.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

This is a 505 (b) (2) NDA for (b) (4) (proposed brand name) or Fentanyl Citrate Nasal Spray (FCNS) or Fentanyl Nasal Spray (FNS) referencing FDA approved Actiq® (NDA 20-747; (oral transmucosal fentanyl [OTFC] in the form of lozenges approved for the same indication) for its summary of safety and efficacy findings. (b) (4) is to be titrated to effect (similar to other products for this indication) and is indicated for management of breakthrough cancer pain in patients who are already receiving and are tolerant to opioid therapy. The formulation is available in two strengths 100 and 400 mcg per spray (100 µL).

The clinical and clinical pharmacology (CP) database consisted of four Phase 2 and 3 studies and four CP studies. Efficacy was assessed in the pivotal Phase 3 study (CP043) with supportive data from study CP044. The CP package submitted for NDA 22-569 consists of 4 pharmacokinetic (PK) studies in healthy male and female subjects under naltrexone blockade. Naltrexone, an opioid antagonist, was administered to block opioid effects in healthy volunteers. Out of the 4 CP studies submitted, 3 pivotal studies involving assessment of relative bioavailability and dose linearity (CP042/05), changes in absorption on repeated administration to determine an optimal time interval between two consecutive doses of (b) (4) (CP047/07), and absorption in disease condition (allergic rhinitis) and DDI potential with a co-administered nasal decongestant (CP048/07), were reviewed. (b) (4)

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 vasoconstritive 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)

Overall, adequate information has been provided characterizing the clinical pharmacology aspects of the proposed product in this NDA.

2. Question Based Review

2.1 GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

There are currently a number of drug products approved with fentanyl as the active ingredient. Fentanyl is available in a variety of pharmaceutical dosage forms including; parenteral, transdermal patches and oral transmucosal formulations (including oral transmucosal lozenge, buccal and sublingual forms). Three of these oral transmucosal products, Actiq® (the reference drug for this submission), Fentora® and Onsolis® are approved for the same indication as proposed for [(b) (4)] utilizes a new route of administration (intranasal) and pharmaceutical form (nasal spray) for the active ingredient fentanyl (as the citrate salt). The formulation incorporates 'pectin', which interacts with calcium ions present in the nasal mucosa to form a gel. Fentanyl then diffuses from the pectin gel into the systemic circulation.

Pre-IND, End of Phase 2 Meeting and pre-NDA meetings were held between the sponsor and the Agency in April 2005, August 2006, and September 2008 respectively. All CP concerns were adequately addressed at those meetings.

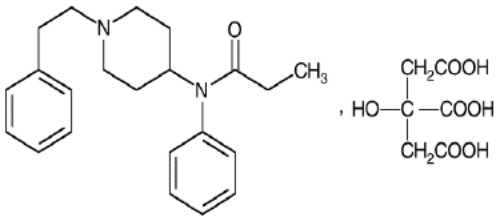
This product was proposed to be marketed under the trade name [(b) (4)] during the pre-NDA stage, then [(b) (4)] when the NDA was submitted and the most recent proposed trade name by the sponsor is [(b) (4)]. The trade name [(b) (4)] is still under review by the Agency at the time of writing this review. Generic names used by the sponsor in their study reports are Fentanyl Citrate Nasal Spray (FCNS) and Fentanyl Nasal Spray (FNS).

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug Substance: fentanyl citrate

Fentanyl, which was first synthesized in 1959, is a lipophilic opioid that may be administered intravenously, or via intramuscular injection to provide pre-operative analgesia, analgesia during surgery and in the post-operative period.

1. Structural formula:



2. Chemical names:
   - N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide, 2-hydroxy-1,2,3-propanetricarboxylate
   - N-(1-Phenethyl-4-piperidyl) propionanilide citrate
3. Molecular formula: C22H28N2O.C6H8O7
4. Molecular weight: 528.59 (336.47 as free base)

Drug Product: [redacted] (Fentanyl Citrate Nasal Spray or FCNS or Fentanyl Nasal Spray or FNS). Note that the proposed trade name [redacted] is still under review by the Agency at the time of writing this review.

[redacted] is a potent opioid analgesic, intended for intranasal administration. The product consists of a practically clear to clear, colorless, aqueous solution of fentanyl citrate in a glass multidose container, to which is attached a metered-dose nasal spray pump with a visual and audible spray counter and end-of-use lock. Each actuation is designed to deliver a spray of 100 mcL of solution containing 100 mcg or 400 mcg fentanyl base, respectively. This enables doses of 100 mcg or 400 mcg to be administered using a single spray into one nostril (1 spray) and 200 mcg or 800 mcg to be administered using a single spray into both nostrils (2 sprays).

Table 1: Composition of Fentanyl Nasal Spray

Component	Reference to Standard	Function	Quantity per mL (mg)	
			FNS 1.0 mg/mL	FNS 4.0 mg/mL
Fentanyl citrate	Ph.Eur./USP	Active	1.570[1]	6.280[2]
[redacted]	In-house [redacted]	[redacted]		
Mannitol	Ph.Eur./USP			
Phenylethyl alcohol	USP			
Propylparaben	Ph.Eur./NF			
Hydrochloric acid or sodium hydroxide	Ph.Eur./NF			
Purified Water	Ph.Eur./USP			

2.1.3 What are the proposed mechanisms of action and therapeutic indications?

Mechanism of Action: The analgesic effects of fentanyl are mediated through interaction with μ-opioid receptors in the CNS. The compound is approximately 100-fold more potent than morphine as an analgesic. Binding studies of fentanyl in rat brain suggest the existence of both high (μ1) and low (μ2) affinity binding sites. The highest level of binding is in the striatum and midbrain. The analgesic effects of fentanyl likely result from suppression of brainstem pain transmission.

Therapeutic Indications: Indicated for management of breakthrough cancer pain in patients who are already receiving and are tolerant to opioid therapy.

2.1.4 What are the proposed dosage and route of administration?

Proposed Dosage and Administration:

- Initial dose for all patients is 100 mcg.
- Individually titrate to an effective dose, from 100 mcg to 200 mcg to 400 mcg, and up to a maximum of 800 mcg, that provides adequate analgesia without undue side effects.
- Dose is a single spray into one nostril or a single spray into each nostril (2 sprays)
- Maximum dose is a single spray into one nostril or single spray into each nostril per episode; no more than [redacted] per 24 h; separate each dose by at least [redacted] During any episode, if adequate pain relief

is not achieved within 30 min, the patient may use a rescue medication as directed by their healthcare provider.

Route of Administration: Intranasal.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Four clinical pharmacology (CP) and four clinical studies were conducted with (b) (4) All studies employed to-be-marketed formulation of (b) (4) All the CP studies were conducted in healthy volunteers under naltrexone blockade to avoid opioid like effects in healthy volunteers.

Clinical studies: Study CP043 provides the primary efficacy data for the product, study CP044 is a supportive trial for efficacy. Please refer to the clinical reviews by Dr's. Luke Yip and Nick Olmos-Lau for a final assessment of the efficacy and safety findings.

Pivotal Efficacy Trial CP043 Design:

- Study Design: Phase 3, randomized, double-blind, placebo-controlled, crossover
  - Open label titration to effective dose
    - (b) (4) 100, 200, 400, 800 mcg
  - Randomization
    - 10 BTCP episodes treated 7-active/3-placebo
- N/Population: Screened 139 cancer-related pain patients with frequent acute BTCP
- Duration: ~ 6 wks
- Primary Efficacy Endpoint: Sum of Pain Intensity Difference (SPID) 30
- Efficacy results summarized below:

N=73 mITT Population	Mean (b) (4) (SD)	Mean Placebo (SD)	p-value
SPID 30	6.57 (4.99)	4.45 (5.51)	< 0.0001

Supportive Trial CP044 Design:

- Study Design: Phase 3, randomized, double-blind, double-dummy, active-controlled (morphine), crossover
  - Open label titration to effective dose
    - (b) (4) 100, 200, 400, 800 mcg
  - Randomization (10 BTCP episodes)
    - (b) (4) (5 fentanyl/5 placebo)
    - IRMS (5 IRMS/5 placebo) blisters
      - » Prior effective dose or
      - » 1/6 total daily background MS dose equivalent
- N/Population: 135 cancer-related pain patients with frequent acute BTCP
- Duration: 6 wks

- Primary efficacy endpoint: Pain Intensity Difference (PID) 15
- Efficacy results summarized below:

N=79 mITT Population	Mean [redacted] (SD)	Mean IRMS (SD)	p-value
PID 15	3.02 (1.84)	2.69 (1.69)	0.0396
Baseline PI score	7.76 (1.42)	7.65 (1.37)	0.0270

2.2.2 What is the Sponsor's pediatric plan for [redacted]?

Based on recent pediatric plans for other fentanyl products for this indication, the pediatric data requirements for [redacted] is expected to be as follows: Waiver to study [redacted] for age 0 [redacted] (rationale being small numbers of patients in this population and also small surface area available for absorption through the nose (specific to [redacted]) and Deferral to study [redacted] for age [redacted] to 16 years (rationale being that the product is ready for approval in adults). These deferred study(s) will only include PK and safety objectives as efficacy for this indication for this opioid can be extrapolated from the adult studies.

2.2.3 What are the single dose and multiple dose PK parameters?

Single Dose: Cmax and AUC values for [redacted] increased with an increase in dose through 100 to 800 mcg and appear dose linear.Median Tmax values ranged from approximately 15 to 21 min. 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 h for [redacted] treatments.

Multiple Doses: When 200 mcg [redacted] doses were administered 1 or 2 or 4 h apart, Cmax2 (Cmax after second administration) was greater than Cmax1 (Cmax after first administration) by 30% when [redacted] t was administered 1 h apart, by 25% when [redacted] t was administered 2 h apart and by 10% when [redacted] was administered 4 h apart. The Cmax and AUC values for 800 mcg administered as 8 sprays of 100 mcg were found to be about 5 fold and 6 fold higher respectively compared to the Cmax and AUC values for 100 mcg in this study indicating that the nasal surface area available in each nasal cavity (each nostril) may be a limiting factor for [redacted] absorption.

Single Dose PK: Study **CP042/05** investigated the PK of 100, 200, 400 and 800 mcg single doses of [redacted] for dose linearity. The increase in Cmax and AUC values is linear (**Figure 1** and **Table 2**). For an 8-fold increase in dose, Cmax increased 8.1-fold (352 pg/ml at 100 mcg to 2844 pg/ml at 800 mcg). For an 8-fold increase in dose, AUCt increased 13.6-fold (985 pg·h/ml at 100 mcg to 13383 pg·h/ml at 800 mcg) and AUC increased 7 fold (2460.5 pg·h/ml at 100 mcg to 17272 pg·h/ml at 800 mcg). There was considerable variability in the PK of fentanyl. CV(%) for Cmax ranged from 26 to 56% and for AUCt ranged from 23 to 58% over the dose range 100 to 800 mcg [redacted] Median Tmax values ranged from approximately 15 to 20 min post-dose. 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 h for [redacted] treatments.

Figure 1: Mean (+SD) Plasma Fentanyl Profiles (0-4 h)

Note: Nasalfent = (b) (4)

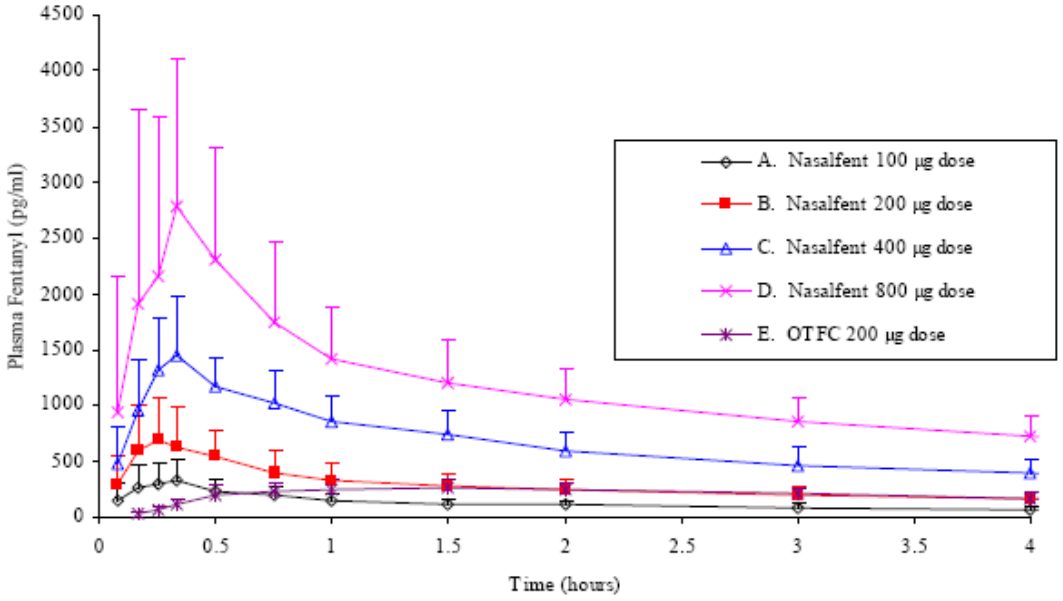


Table 2:Summary of Fentanyl Pharmacokinetic Results in the Dose Linearity Study

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	381.065	406.692	1392.10	94.8889
	Geometric mean	295.378	695.286	1503.68	2458.24	304.301
T_{max} (h)	n	16	14	13	12	13
	Median	0.33	0.25	0.35	0.34	1.50
	Range	0.08 - 1.50	0.17 - 1.60	0.25 - 0.75	0.17 - 3.00	0.50 - 8.00
T_{lag} (h)	n	16	14	13	12	13
	Median	0.00	0.00	0.00	0.00	0.08
	Range	0.00 - 0.10	0.00 - 0.00	0.00 - 0.00	0.00 - 0.00	0.00 - 0.25
λ_z (h^{-1})	n	5	8	12	12	7
	Arithmetic mean	0.03216	0.0337	0.0495	0.03865	0.0405
	SD	0.004521	0.01391	0.0143	0.0156	0.01214
	Geometric mean	0.03191	0.03085	0.04782	0.03436	0.03891
$t_{½}$ (h)	n	5	8	12	12	7
	Arithmetic mean	21.89	24.90	14.95	24.91	18.56
	SD	2.971	12.77	3.688	23.05	5.833
	Geometric mean	21.72	22.47	14.49	20.17	17.81
AUC_t (pg·h/ml)	n	16	14	13	12	13
	Arithmetic mean	984.75	2432.9	6791.5	13383	2147.8
	SD	572.43	1170.1	1531.0	3122.2	1157.4
	Geometric mean	801.90	2192.7	6649.0	13051	1879.9
AUC (pg·h/ml)	n	5	8	12	12	7
	Arithmetic mean	2460.5	4359.9	7513.4	17272	3735.0
	SD	439.27	1298.8	2003.0	8440.5	1223.3
	Geometric mean	2428.0	4205.1	7322.3	15876	3580.6

Multiple Dose PK: Study **CP047/07** investigated the relative BA, PK and safety following a single dose of 100 mcg (b) (4) two doses of 100 mcg (200 mcg) separated by 1, 2 or 4 h and eight immediate consecutive administrations of 100 mcg (8 sprays), each dosing separated by a washout period of at least 3 days to determine a minimum waiting time for two consecutive sprays in the same nostril.

From **Table 3**, as compared to Cmax1, Cmax2 was greater by 30% in Treatment D (200 mcg administered 1 h apart), by 25% in Treatment C (200 mcg administered 2 h apart) and by 10% in Treatment D (200 mcg administered 4 h apart). However, AUC values were similar across all the 3 treatments (**Figure 2** and **Table 3**). (b) (4) a separation period of 2 h seems more appropriate based on the Tmax range of (b) (4) frequency of breakthrough pain episodes in this population and the results of this study. Tmax for (b) (4) is achieved within 2 h in most of the subjects across all the CP studies submitted. The frequency of breakthrough pain episodes in the population this product is indicated for (cancer patients) may be more than once every 4 h. In addition, from the results from this study, it appears that difference in Cmax2 and Cmax1 is more with with a separation period of 1 h as compared to a separation period of 2 h. Therefore, this reviewer recommends that a wait period of 2 h is reasonable before going to a second dose of (b) (4) for additional pain relief.

After eight consecutive 100 mcg doses of fentanyl nasal spray (eight x 100 µL), the Cmax was 5.2 fold greater than Cmax after a single 100 mcg dose of fentanyl nasal spray (100 µL). Similarly, AUC was approximately 6 fold greater than AUC after a single 100 mcg dose (100 µL) (**Table 3**). This result indicates that the nasal surface area available in each nasal cavity (each nostril) may be a limiting factor for (b) (4) absorption. However, there is no data to indicate how many number of sprays (i.e, fewer than eight sprays) is the threshold that will result in decreased absorption.

Figure 2: Plasma profiles for treatments B (200 mcg dose administered 4 h apart), C (200 mcg dose 2 h apart) and D (200 mcg dose 1 h apart)

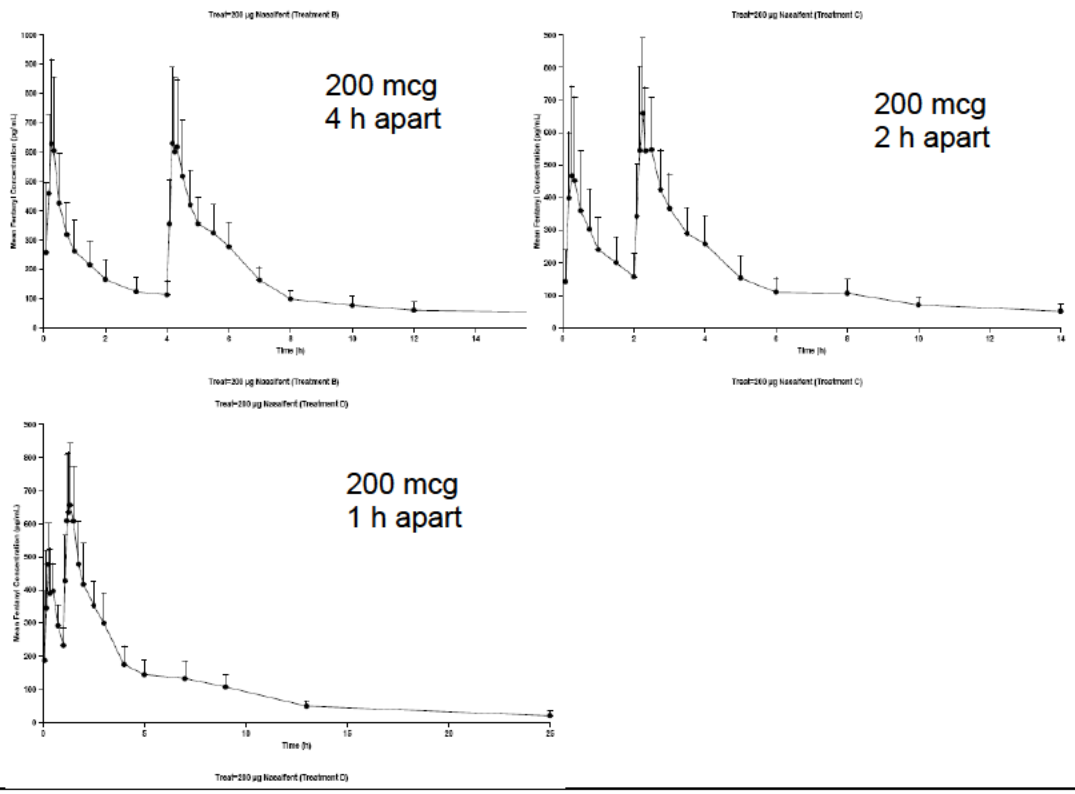


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Table 3: Summary of Fentanyl Pharmacokinetic Results from a Multiple Dose Study

Treatment A = 100 mcg (1 spray of 100 µL); Treatment B = 200 mcg (2 sprays of 100 µL each) administered 4 h apart; Treatment C = 200 mcg (2 sprays of 100 µL each) administered 2 h apart; Treatment D = 200 mcg (2 sprays of 100 µL each) administered 1 h apart; Treatment E = 800 mcg (8 sprays of 100 µL each), all treatment administered in the same nostril

	Treatment				
	A (n = 12)	B (n = 11)	C (n = 10)	D (n = 10)	E (n = 10)
C_{max1} (pg/mL)[1]	572.098 (230.297)	642.506 (263.887)	511.463 (245.872)	513.324 (124.966)	2955.323 (1501.465)
C_{max2} (pg/mL)[1]	NA	698.905 (245.973)	687.458 (217.247)	742.671 (177.795)	NA
T_{max1} (h)[1,2]	0.300 (0.18 - 0.50)	0.267 (0.17 - 0.78)	0.333 (0.25 - 0.75)	0.250 (0.08 - 0.50)	0.250 (0.17 - 0.33)
T_{max2} (h)[1,2]	NA	0.250 (0.17 - 0.75)	0.250 (0.17 - 0.53)	0.333 (0.17 - 0.62)	NA
λ_z (h^{-1})	0.21646 (0.12248)[3]	0.10619 (0.05056)	0.11856 (0.04260)	0.10893 (0.03740)	0.10196 (0.07198)
$t_{½z}$ (h)	4.134 (1.993)[3]	7.524 (2.592)	6.701 (2.708)	6.886 (1.713)	8.466 (3.012)
AUC_t (pg·h/mL)	1132.4 (453.5)	2835.4 (1061.1)	2509.9 (821.3)	2776.0 (794.6)	6791.4 (2902.9)
AUC_{0-24} (pg·h/mL)	1264.8 (466.1)	2847.4 (942.0)	2596.6 (731.1)	2823.2 (698.3)	6857.6 (2847.5)
AUC (pg·h/mL)	1319.8 (548.5)[3]	3160.6 (1100.7)	2833.9 (910.1)	3103.8 (799.5)	7859.5 (3536.3)

2.2.4 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose linearity across the 100 µg to 800 µg dose range of [(b) (4)] has been shown in study **CP042/05.** Mean plasma fentanyl levels following single doses of [(b) (4)] are shown in **Figure 1** and **Table 2**.

2.3 GENERAL BIOPHARMACEUTICS

2.3.1 What is the relative bioavailability of the two formulations (reference and test)?

The bioavailability of fentanyl from [(b) (4)] was approximately 20% higher compared with Actiq®. Cmax and AUCt were 2.3-fold and 1.2-fold greater for [(b) (4)] 200 mcg compared to Actiq® at the 200 mcg dose level.

Relative BA: In addition to dose linearity, a second objective of study **CP042/05** was to assess the relative BA of 100, 200, 400 and 800 mcg of [(b) (4)] with the RLD, Actiq® (200 mcg). From **Figure 1** and **Table 2**, Cmax and AUCt were 2.3-fold and 1.2-fold greater for [(b) (4)] 200 mcg compared to Actiq® at the 200 mcg dose level. At the same dose level (200 mcg) the Frel of [(b) (4)] was 123% compared to Actiq® based on AUC values. Cmax for 100 mcg [(b) (4)] (351.5 pg/ml) was comparable with 200 mcg Actiq® (317 pg/ml). However, AUCt values differ significantly between 100 mcg [(b) (4)] (984.75 pg.h/ml) and 200 mcg Actiq® (2147.8 pg.h/ml). For the primary endpoints of fentanyl Cmax and AUCt, the 90% CIs for the dose-normalized treatment differences were not within the range of 80 to 125%. Therefore none of the [(b) (4)] treatments were equivalent with Actiq®.

2.3.2 What are the general ADME characteristics of the drug?

Extracted from the label:

Absorption**:** Fentanyl is absorbed from the nasal mucosa following intranasal administration of (b) (4) with a median Tmax value of 15-21 min (b) (4) after administration of a single dose.

Distribution**:** Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80% to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean volume of distribution at steady state (Vss) was 4 L/kg.

Metabolism**:** The metabolic pathways following intranasal administration of (b) (4) have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active.

Elimination: Disposition of fentanyl following intranasal administration of (b) (4) has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

2.4 INTRINSIC FACTORS

2.4.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

As a 505 (b) (2) application, most of this information was borrowed from the approved label for the RLD Actiq®. One PK study (CP048/07) was conducted in subjects with allergic rhinitis (induced in the laboratory) to determine differences in (b) (4) absorption, if any, in this population. This study is discussed in Section 2.5.2 under Drug Interactions.

2.5 EXTRINSIC FACTORS

2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of extrinsic factors such as herbal products, diet, smoking or alcohol use on the PK or PD of (b) (4). Most of the drug class (opioid) information was borrowed from the RLD Actiq® label.

2.5.2. Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes. A study was conducted to assess differences in (b) (4) absorption, if any, when co-administered with oxymetazoline, a nasal decongestant in subjects undergoing treatment for seasonal allergic rhinitis Mean Cmax values for Treated arm (Rhinitis treated with oxymetazoline, a decongestant) were about 32% and

40% lower and mean AUCt values were about 10% and 17% lower for Ragweed and Tree pollen induced cohorts respectively as compared to the Asymptomatic arm in each cohort indicating that there may be compromise in efficacy if (b) (4) *is co-administered with a nasal decongestant such as oxymetazoline. Mean Tmax for Treated arm was 0.75 h (range 0.08-3 h) for the Ragweed pollen induced cohort and 1.25 h (range 0.08-3 h) for Tree pollen induced cohort as compared to 0.25 h (0.17-1 h) and 0.33 h (0.17-2 h) for the Asymptomatic arm in each cohort respectively indicating that there may be delay in absorption when a vasoconstrictive agent such as oxymetazoline is co-administered with* (b) (4)*.*

In addition this study also assessed differences in (b) (4) *absorption, if any, in subjects with allergic rhinitis as compared to asymptomatic condition. Fentanyl absorption was similar in asymptomatic vs. allergic rhinitis condition indicating that presence of rhinitis may not affect absorption of* (b) (4)

DDI: Since efficacy and/or safety of a nasally-administered medication might be impacted by differences in nasal pathology (for example when suffering from rhinitis) and/or co-administration of a decongestant (for example: oxymetazoline) to treat the rhinitis, it is important to study differences in absorption of fentanyl (if any) in those conditions. Study (**CP048/07**) was conducted to assess relative BA, PK, safety and tolerability of (b) (4) in subjects with known seasonal allergic rhinitis and undergoing treatment with oxymetazoline (vasoconstrictive agent) for change in (b) (4) exposure. The following treatments were administered in a cross-over fashion.

• Treatment A: Active Leg: Suffering from seasonal allergic rhinitis (SAR) acutely induced under laboratory conditions
• Treatment C: Treated Leg: Suffering from SAR acutely induced under laboratory conditions following treatment with oxymetazoline, a nasal decongestant
• Treatment B: Asymptomatic Leg: Asymptomatic for SAR.

Figure 3, Figure 4, Table 4 and Table 5 show the pertinent data from the study.

Fentanyl absorption was similar in the Asymptomatic and the Active/Untreated arms in both the Ragweed and Tree pollen induced cohorts indicating that presence of rhinitis may not affect PK absorption of (b) (4).

Cmax for Treated arm (Rhinitic state treated with oxymetazoline) was about 32% less as compared to the Asymptomatic arm in the Ragweed pollen induced cohort, AUCt for Treated arm was about 10% lower as compared to the Asymptomatic arm and mean Tmax for Treated arm was 0.75 h (range 0.08-3 h) as compared to 0.25 h (0.17-1 h) for the Asymptomatic arm. From Figure 4 and Table 5, Cmax for Treated arm (Rhinitis treated with oxymetazoline) was about 40% less as compared to the Asymptomatic arm in the Tree pollen induced cohort and AUCt for Treated arm was about 17% lower as compared to the Aymptomatic arm. In addition, mean Tmax for Treated arm was 1.25 h (range 0.08-3 h) as compared to 0.33 h (0.17-2 h) for the Asymptomatic arm. These results indicate that there was a PK interaction when both agents are nasally administered.

This reviewer concurs with the sponsor that "the efficacy of (b) (4) appears unlikely to be affected by the onset of untreated allergic rhinitis in patients established on a given dose. However, it, may be somewhat less effective in a patient with active rhinitis when administered concomitantly with a decongestant (such as oxymetazoline), thus potentially impairing pain management." "Additionally, in view of the possibility that the titration of a patient while they are experiencing an acute episode of rhinitis could lead to incorrect dose identification (particularly if they are using a vasoconstrictive decongestant), titration under these circumstances should probably be avoided."

Figure 3: Mean Graph of Fentanyl Plasma Concentration (Ragweed Cohort) up to 24 h

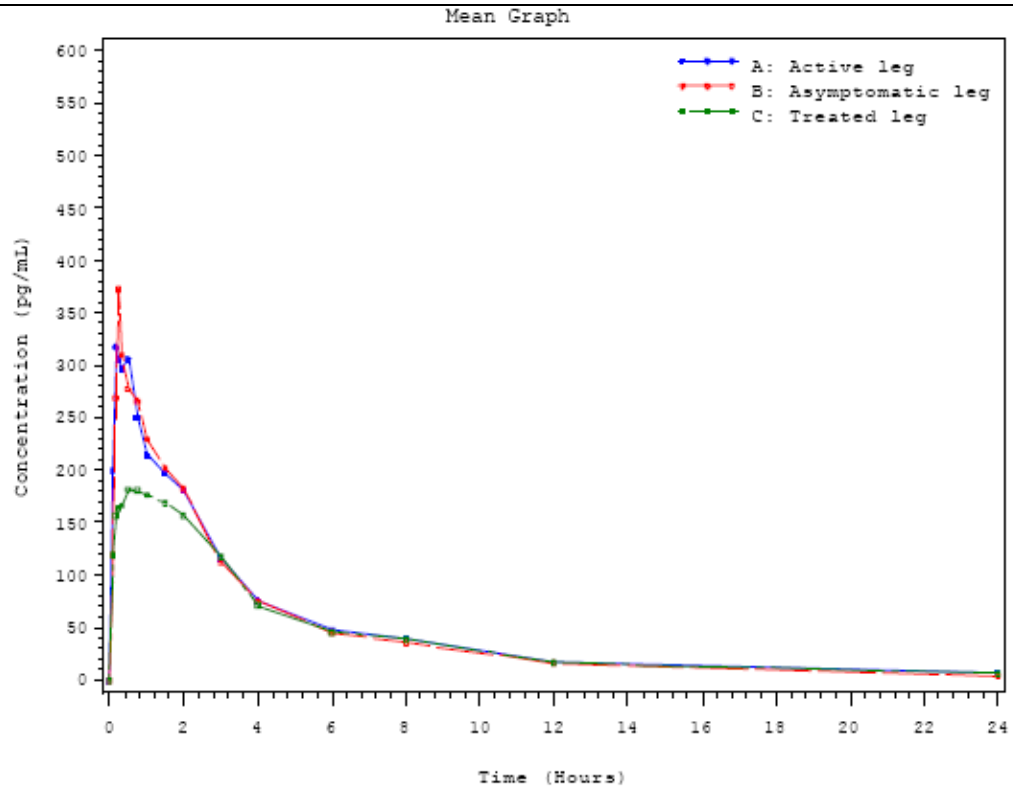


Table 4: Summary of Fentanyl PK Parameters for Reference and Ragweed Pollen Exposed Conditions.

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

Figure 4: Mean Graph of Fentanyl Plasma Concentration (Tree Pollen Cohort) up to 24 h

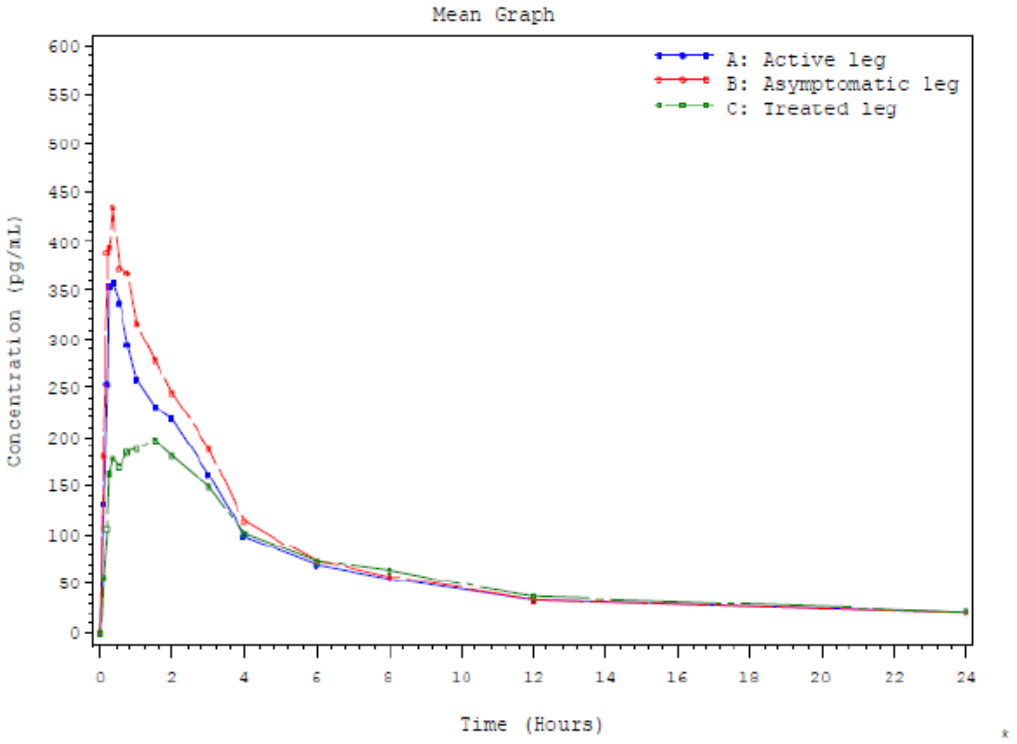


Table 5: Summary of Fentanyl PK Parameters for Reference and Tree Pollen Exposed Conditions.

Parameter (unit)	REFERENCE		TREE EXPOSED			
	Asymptomatic (B)	n	Active (A)	n	Treated (C)	n
C_{max} (pg/mL)	553.37 ± 291.31	10	435.74 ± 235.00	11	246.77 ± 125.63	12
T_{max}[a] (h)	0.33[a] [0.17-2.00][b]	10	0.33[a] [0.17-3.00][b]	11	1.25[a] [0.08 -3.00][b]	12
AUC_t (pg.h/mL)	1805.68 ± 591.74	10	1609.84 ± 591.08	11	1498.28 ± 559.15	12

2.6 ANALYTICAL SECTION

2.5.1 What bioanalytical methods are used to assess drug concentrations?

The plasma samples were analyzed by a validated HPLC method with MS/MS detection for total fentanyl in the Bioanalytical Department at [redacted] (b) (4) The analytical procedure involved extraction from human plasma by a [redacted] (b) (4) method using heptane. The internal standard was fentanyl-d5. The lower limit of quantification (LLOQ) of the assay was 19.87 pg/ml. Precision and accuracy at the LLOQ were 9.70% and 0.23%, respectively. From the quality control samples, inter-assay precision ranged from 2.65 to 9.36% and inter-assay accuracy ranged from 0.80 to 4.25%.

3. Detailed Labeling Recommendations

Following are the highlights of the labeling comments at the time of the writing this review. (Reviewer suggested changes: ~~Strikeout text~~ is suggested for deletion and underlined text is suggested for addition). Please note that the label still has the originally proposed trade name by the sponsor 'Pecfent' and not (b) (4) which was proposed by the sponsor at a later stage in the review cycle.

(b) (4)

(b) (4)

(b) (4)

4 PAGES OF DRAFT LABELING HAS BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

4. Appendices

4.1 Sponsor's Proposed Package Insert

38 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

4.2 Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA 22-569**	**Brand Name**	**(b) (4))**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Fentanyl nasal spray**
Medical Division	**DAARP**	**Drug Class**	**Opioid Analgesic**
OCP Reviewer	**Sheetal Agarwal**	**Indication(s)**	**Management of breakthrough cancer pain who are already receiving and who are tolerant to regular opioid therapy**
OCP Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Nasal spray solution 100 and 400 mcg contained in each spray**
Pharmacometrics Reviewer		**Dosing Regimen**	**Initial dose for all patients: 100 mcg to be titrated to an effective dose**
Date of Submission	**09/17/09**	**Route of Administration**	**Nasal**
Estimated Due Date of OCP Review		**Sponsor**	**Archimedes Development, Inc.**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE		**5**	**5**	**4 Clin Pharm studies and 1 bioanalytical method**
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	**X**			
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods		**1**	**1**	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:	**X**	**1**	**1**	**(b) (4))**

multiple dose:	**X**	**1**	**1**	A single (100 mcg) and repeat dose study in healthy volunteers under naltrexone blockade (CP047/07): - 1 x 100 mcg h apart in the same nostril - 2 x 100 mcg 2 h apart in the same nostril - 2 x 100 mcg 4 h apart in the same nostril - 8 x 100 mcg doses administered consecutively in the same nostril
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**	**1**	A single, escalating dose (100 mcg, 200 mcg, 400 mcg, 800 mcg) study in healthy volunteers under naltrexone blockade (CP042/05)
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**1**	**1**	A single dose study in subjects with allergic rhinitis (CP048/07) in: -Unchallenged state (Asymptomatic, reference) -Untreated challenged state (Active) - Oxymetazoline-treated challenged state (Treated) is a DDI study (absorption related)
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	**X**	**1**	**1**	(b) (4) were administered (100 mcg) under naltrexone blockade, as was the RLD, oral-transmucosal fentanyl citrate (OTFC) lozenge (Actiq®, 200 mcg), as comparator.
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				

BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan		**1**	**1**	
Literature References				
Total Number of Studies	**5**	**6**	**6**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			RLD Actiq label
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Efficacy studies with suggested doses have been submitted
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to			X	

	demonstrate effectiveness, if the drug is indeed effective?				
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

SHEETAL AGARWAL	09/26/09
Reviewing Clinical Pharmacologist	Date
SURESH DODDAPANENI	09/26/09
Team Leader/Supervisor	Date

4.3 Individual Study Reviews

4.3.1 Study CP042/05: A single centre, dose-proportionality, five-way trial to assess the relative bioavailability, pharmacokinetics and safety of four escalating doses of Fentanyl Citrate Nasal Spray (FCNS) compared to the oral transmucosal (OTFC, lozenge) formulation

Study Design:	Five way dose escalation, Naltrexone blockade. OTFC as reference
Objectives:	Investigation of Bioavailability, PK, safety and tolerance of increasing doses vs OTFC lozenge (Actiq®)
Protocol Number:	Study CP042/05 (Medeval Study No. ME0947)
Study Center(s):	CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217
Subjects:	12 healthy volunteers completed (16 dosed)
Formulations:	FCNS solution 1.57 mg/ml (fentanyl citrate), 1 or 2 intranasal sprays, 100 or 200 mcg (fentanyl base), Batch No.: WFEN/018/F, Expiry Date: 07 June 2006 FCNS solution 6.28 mg/ml (fentanyl citrate), 1 or 2 intranasal sprays, 400 and 800 mcg (fentanyl base), Batch No.: WFEN/019/F, Expiry Date: 08 June 2006 OTFC (Actiq® lozenge), 200 mcg (fentanyl base), oral lozenge, Batch No.: P67054, Expiry Date: 31 January 2008
Study Initiation Date:	11 January 2006
Study Completion Date:	10 April 2006
Principal Investigator:	Dr Cyril Clarke, Medeval Limited Medeval Limited Skelton House Manchester Science Park Lloyd Street North Manchester M15 6SH, UK Tel: +44 161 226 6525 Fax: +44 161 226 8936

Treatments: Each subject was to receive the following five treatments:

Treatment A: 100 mcg fentanyl, from a FCNS solution of 1.57 mg/ml, comprising one 100 mcl dose (1 spray), administered into one nostril.

Treatment B: 200 mcg fentanyl, from a FCNS solution of 1.57 mg/ml, comprising two 100 mcl doses, administered as one dose (1 spray) into each nostril (total of 2 sprays) giving a 200 mcg dose.

Treatment C: 400 mcg fentanyl, from a FCNS solution of 6.28 mg/ml, comprising one 100 mcl dose (1 spray), administered into one nostril.

Treatment D: 800 mcg fentanyl, from a FCNS solution of 6.28 mg/ml, comprising two 100 mcl doses, administered as one dose (1 spray) into each nostril (total of 2 sprays) giving a 800 mcg dose.

Treatment E: 200 mcg OTFC lozenge (Actiq®), administered orally with an integral oromucosal applicator.

Treatments A to D were administered in ascending dose order and Treatment E was administered at any part of the treatment sequence, according to the randomization code.

Drug Concentration Measurements: Blood samples (5 ml) for fentanyl analysis were taken at the following time points: Pre-dose and 5, 10, 15, 20, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 h post-dose.

Adverse Events: No relationship of treatment emergent AEs to dose of FCNS was observed. It should be noted that subjects were administered naltrexone to block opioid effects.

Table A: Overall Summary of Treatment-emergent Adverse Events by Treatment: Safety Population

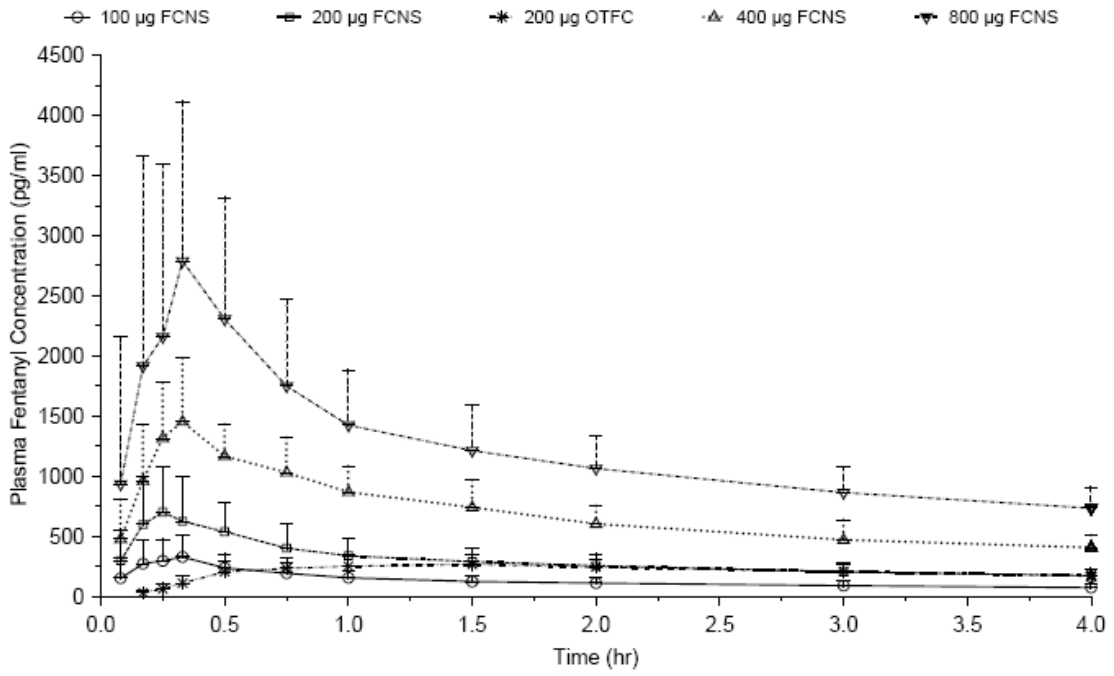
	100 µg FCNS	200 µg FCNS	400 µg FCNS	800 µg FCNS	200 µg OTFC
Number of subjects treated	16	14	13	12	13
Subjects with at least one treatment-emergent AE	15 (93.8%)	12 (85.7%)	11 (84.6%)	10 (83.3%)	9 (69.2%)
Subjects with treatment-related AEs	13 (81.3%)	11 (78.6%)	9 (69.2%)	6 (50.0%)	9 (69.2%)
Subjects with SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total number of treatment-emergent AEs	87	80	48	28	36
Total number of treatment-related AEs	58	54	30	15	18
Total number of SAEs	0	0	0	0	0

PK results: Mean plasma fentanyl levels following (b) (4) administration are shown in Table B and plasma profiles are shown in Figure A.

Table B: Summary of Fentanyl Pharmacokinetic Results

Parameter	Summary Statistic	100 µg FCNS	200 µg FCNS	400 µg FCNS	800 µg FCNS	200 µg OTFC
Number of subjects receiving treatment		16	14	13	12	13
C_{max} (pg/ml)	n	16	14	13	12	13
	Arithmetic mean	351.511	780.820	1552.07	2844.01	317.394
	SD	180.356	381.063	406.692	1592.10	94.8889
	Geometric mean	295.378	695.286	1503.68	2458.24	304.301
T_{max} (h)	n	16	14	13	12	13
	Median	0.33	0.25	0.35	0.34	1.50
	Range	0.08 - 1.50	0.17 - 1.60	0.25 - 0.75	0.17 - 3.00	0.50 - 8.00
AUC_t (pg·h/ml)	n	16	14	13	12	13
	Arithmetic mean	984.75	2432.9	6791.5	13383	2147.8
	SD	572.43	1170.1	1531.0	3122.2	1157.4
	Geometric mean	801.90	2192.7	6649.0	13051	1879.9
AUC (pg·h/ml)	n	5	8	12	12	7
	Arithmetic mean	2460.5	4359.9	7513.4	17272	3735.0
	SD	439.27	1298.8	2003.0	8440.3	1223.3
	Geometric mean	2428.0	4205.1	7322.3	15876	3580.6

Figure A: Mean (+SD) Plasma Fentanyl Profiles (0-4 h)



Reviewer's comments:

1. Although extent of exposure (AUC values) differ significantly between 100 mcg FCNS (2460.5 pg.h/ml) and 200 mcg OTFC (3735 pg/h/ml); peak concentration (Cmax) values for 100 mcg FCNS (351.5 pg/ml) are comparable with 200 mcg OTFC (317 pg/ml).
2. The relative bioavailability of FCNS seems about 20% higher than OTFC based on AUC comparisons for 200 mcg FCNS (2460.5 pg.h/ml) and 200 mcg OTFC (3735 pg/h/ml).
3. Cmax and AUC values for FCNS increase with an increase in dose through 100 to 800 mcg and appear dose linear. For an 8-fold increase in dose, Cmax increased 8.1-fold (352 pg/ml at 100 mcg to 2844 pg/ml at 800 mcg). For an 8-fold increase in dose, AUCt increased 13.6-fold (985 pg·h/ml at 100 mcg to 13383 pg·h/ml at 800 mcg) and AUC increased 7 fold (2460.5 pg·h/ml at 100 mcg to 17272 pg·h/ml at 800 mcg). There was considerable variability in the PK of fentanyl. CV(%) for Cmax ranged from 26 to 56% and for AUCt ranged from 23 to 58% over the dose range 100 to 800 mcg (b) (4)
4. Median Tmax values ranged from approximately 15 to 20 min post-dose.
5. 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 h for the FCNS treatments and 17.8 h for the OTFC treatment.

4.1.2 Study CP047/07: A Single Centre, Five-Way Open Trial to Assess the Relative Bioavailability, Pharmacokinetics and Safety of Multiple Doses of NasalFent (Fentanyl Citrate Nasal Spray [FCNS]) Compared to a Single NasalFent Dose

Study Design:	Single-centre, five-period, open label study. Naltrexone blockade.
Objectives:	Evaluate the pharmacokinetics (PK) of NasalFent following eight immediate consecutive administrations of 100 µg (8 x 100 µL) and after various time periods between two 100 µg (2 x 100 µL) doses.
Protocol Number:	Study CP047/057
Study Center(s):	CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217
Subjects:	13 subjects were enrolled into the study and 10 subjects completed the study.
Formulations:	NasalFent (100 µL, 100 µg fentanyl). Batch number: 700354; Expiry date: 22 August 2008.
Study Initiation Date:	01 August 2007
Study Completion Date:	20 September 2007
Principal Investigator:	Dr Cyril Clarke, ICON Development Solutions ICON Development Solutions Skelton House Manchester Science Park Lloyd Street North Manchester M15 6SH, UK Tel: +44 161 226 6525 Fax: +44 161 226 8936

Treatments: Five treatments were administered to each subject in the order listed below (dose escalation), with a washout period of at least three days between each treatment:

• Treatment A: Single dose of 100 µg NasalFent (100 µL) into the right nostril.
• Treatment B: Two doses of 100 µg NasalFent (2 x 100 µL) 4 h (h) apart into the right nostril.
• Treatment C: Two doses of 100 µg NasalFent (2 x 100 µL) 2 h apart into the right nostril.
• Treatment D: Two doses of 100 µg NasalFent (2 x 100 µL) 1 h apart into the right nostril.
• Treatment E: Eight doses of 100 µg NasalFent (8 x 100 µL) consecutively into the right nostril.

Drug Concentration Measurements: Blood samples for analysis of plasma fentanyl concentrations were collected at the following time-points:
• Treatment A and Treatment E: pre-dose and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720 and 1440 min after administration of the single dose of NasalFent (Treatment A) or after administration of the eighth dose of NasalFent (Treatment E).
• Treatment B: pre-dose and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180 and 240 min after the first dose and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720 and 1440 min after the second dose.
• Treatment C: pre-dose and 5, 10, 15, 20, 30, 45, 60, 90 and 120 min after the first dose and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720 and 1440 min after the second dose.
• Treatment D: pre-dose and 5, 10, 15, 20, 30, 45 and 60 min after the first dose and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720 and 1440 min after the second dose.

Adverse events: No relationship of treatment emergent AEs to dose of FCNS was observed. It should be noted subjects were provided naltrexone blockade to block opioid related effects.

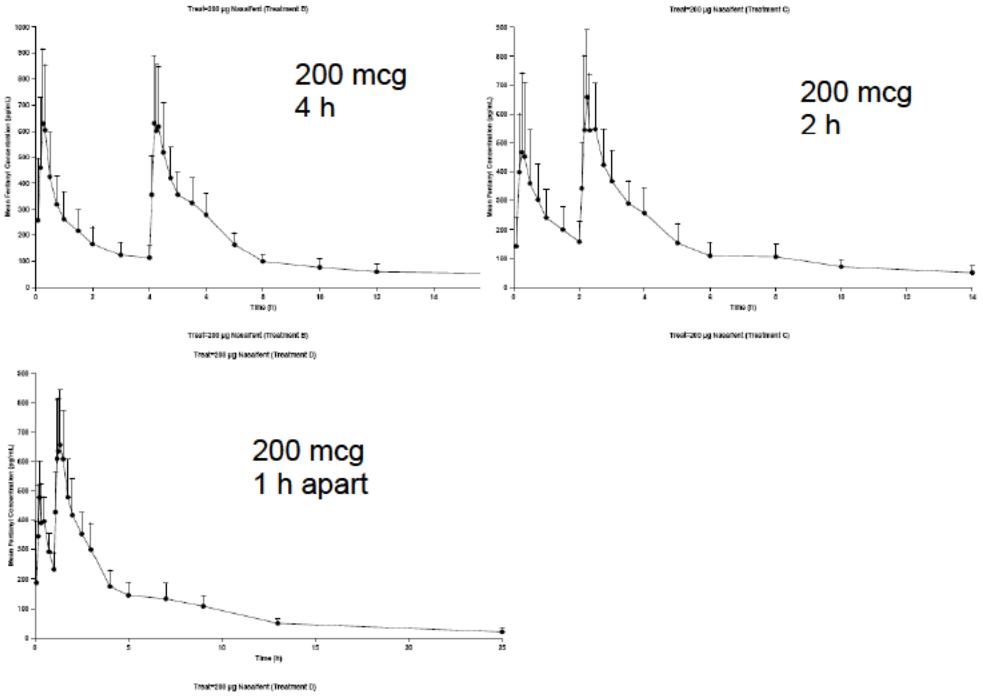
PK results:

Table C: Summary of Fentanyl Pharmacokinetic Results

	Treatment				
	A (n = 12)	B (n = 11)	C (n = 10)	D (n = 10)	E (n = 10)
C_{max1} (pg/mL)[1]	572.098 (230.297)	642.506 (263.887)	511.463 (245.872)	513.324 (124.966)	2955.323 (1501.465)
C_{max2} (pg/mL)[1]	NA	698.905 (245.973)	687.458 (217.247)	742.671 (177.795)	NA
T_{max1} (h)[1,2]	0.300 (0.18 - 0.50)	0.267 (0.17 - 0.78)	0.333 (0.25 - 0.75)	0.250 (0.08 - 0.50)	0.250 (0.17 - 0.33)
T_{max2} (h)[1,2]	NA	0.250 (0.17 - 0.75)	0.250 (0.17 - 0.53)	0.333 (0.17 - 0.62)	NA
λ_z (h^{-1})	0.21646 (0.12248)[3]	0.10619 (0.05056)	0.11856 (0.04260)	0.10893 (0.03740)	0.10196 (0.07198)
$t_{½z}$ (h)	4.134 (1.993)[3]	7.524 (2.592)	6.701 (2.708)	6.886 (1.713)	8.466 (3.012)
AUC_t (pg·h/mL)	1132.4 (453.5)	2835.4 (1061.1)	2509.9 (821.3)	2776.0 (794.6)	6791.4 (2902.9)
AUC_{0-24} (pg·h/mL)	1264.8 (466.1)	2847.4 (942.0)	2596.6 (731.1)	2823.2 (698.3)	6857.6 (2847.5)
AUC (pg·h/mL)	1319.8 (548.5)[3]	3160.6 (1100.7)	2833.9 (910.1)	3103.8 (799.5)	7859.5 (3536.3)

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.
[1] 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.
[2] Median (range) for T_{max1} and T_{max2}
[3] n = 11
NA = Not applicable.

Figure B: Plasma profiles for treatments B (200 mcg dose administered 4 h apart), C (200 mcg dose 2 h apart) and D (200 mcg dose 1 h apart)



Reviewer's comments:

1. From Table C and Figure B, Cmax2 was greater by 30% in Treatment D (200 mcg administered 1 h apart), by 25% in Treatment C (200 mcg administered 2 h apart) and by 10% in Treatment B (200 mcg administered 4 h apart) as compared to Cmax1. However, AUC values were similar across all the 3 treatments.
2. [redacted] However, a waiting period of 2 h between two consecutive doses of [redacted] seems more appropriate based on:
    a. Results of this study: Although Cmax2 is higher than Cmax1 when [redacted] is administered 2 h apart, the difference is smaller vs. when administered 1 h apart.
    b. Tmax range of [redacted]: Tmax for [redacted] is achieved within 2 h in most of the subjects across all the PK studies submitted.
    c. Frequency of breakthrough pain episodes in this population: The frequency of acute pain episodes in a cancer population may be less than once every 4 h.
3. After eight consecutive 100 mcg doses of fentanyl nasal spray (eight x 100 µL), the Cmax was 5.2 fold greater than Cmax after a single 100 mcg dose of fentanyl nasal spray (100 µL). Similarly, AUC was approximately 6 fold greater than AUC after a single 100 mcg dose (100 µL) (table C). This result indicates that the nasal surface area available in each nasal cavity (each nostril) can be a limiting factor for [redacted] absorption although data is not available to say how many sprays (i.e, fewer than eight sprays) is the threshold to result in decreased absorption.

4.1.3 Study CP048/07: A single centre, three-way cross-over trial to assess the relative bioavailability, pharmacokinetics, safety and tolerability of single doses of NasalFent (Fentanyl Citrate Nasal Spray [FCNS]) when administered to subjects with seasonal allergic rhinitis in symptomatic, symptomatic but treated (with oxymetazoline) and asymptomatic states

Study Design:	Five way dose escalation, Naltrexone blockade. OTFC as reference
Objectives:	The objectives of this study were to determine and compare the PK profiles, local and systemic safety and tolerability of single doses of FCNS in subjects who suffer from seasonal allergic rhinitis, whilst they were in the symptomatic (Active Leg), symptomatic but treated (with oxymetazoline (Treated Leg) and asymptomatic states (Asymptomatic (Reference) Leg).
Protocol Number:	Study CP048/07 (Cetero Research Number: P2FK07001)
Study Center(s):	Cetero Research 4520 Dixie Road Mississauga, Ontario, Canada L4W 1N2
Subjects:	Two cohorts (ragweed: 37 randomized, 11 completed and tree pollen: 17 randomized, 11 completed) each consisting of healthy male and female subjects, aged 18 to 65 years inclusive, with a clinical history of seasonal allergic rhinitis and with a positive skin prick test to ragweed or tree pollen allergen within the 12 months prior to Visit 1. Subjects were mostly Caucasian (~60%); with ~20% Africans and ~20% Hispanic.
Formulations:	NasalFent (Fentanyl Citrate Nasal Spray [FCNS]) 100 mcg For the tree pollen cohort, the batch number for the FCNS was 606086, with an expiry date of 17-Feb-2008. For the ragweed pollen cohort, the batch number for the FCNS was 700354, with an expiry date of 22-Aug-2008.
Study Initiation Date:	21Nov07
Study Completion Date:	16Jun08
Principal Investigator:	Dr. Deepen Patel, MD, CCFP Cetero Research

Treatments: All doses were to be administered into the same nostril (the subject's right nostril). Each subject was to receive each treatment. Subjects were to be dosed under each of the following conditions:
• Treatment A: Active Leg: Suffering from seasonal allergic rhinitis (SAR) acutely induced under laboratory conditions
• Treatment C: Treated Leg: Suffering from SAR acutely induced under laboratory conditions following treatment with oxymetazoline, a nasal decongestant
• Treatment B: Asymptomatic Leg: Asymptomatic for SAR.
On dose administration days, subjects who participated in the Active and Treated Legs were to be exposed to ragweed or tree pollen in the Environmental Exposure Chamber (EEC). Following an initial 30-minute exposure, subjects were to record their NSS (Nasal Symptom Score) at 30-minute intervals until at least moderate rhinitis symptoms developed (minimum TNSS (Total Nasal Symptom Score) of 6 out of 12 including a score of at least 2 for nasal congestion on two consecutive diary cards). Following this, subjects in the Active Leg were to receive the FCNS dose. Subjects in the Treated Leg were to receive oxymetazoline first following development of at least moderate rhinitis symptoms, followed by the FCNS dose two hours later. Subjects who participated in the Asymptomatic (Reference) Leg were to be assessed for rhinitis symptoms on the dose administration day. If no rhinitis symptoms were present (rated on the diary card as TNSS $\leq$3 out of 12 with a score for nasal congestion $\leq$1), they were to be dosed with FCNS without exposure to allergen in the EEC.

Drug Concentration Measurements: Blood samples (5 ml) for fentanyl analysis were taken at the following time points: before dose administration (pre-dose, within 10 min prior to dosing); and at

approximately 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720 and 1440 min after dosing (16 samples).

Adverse events: No relationship of treatment emergent AEs to treatment arm was observed in either the ragweed or the tree pollen cohorts.

Table D: Summary of Post-Treatment Adverse Event(s) by Severity (Ragweed Cohort)

Severity	Asymptomatic Leg N=23	Active Leg N=23	Treated Leg N=21
Mild	6 (26.1 %)	3 (13.0 %)	8 (38.1 %)
Moderate	2 (8.7 %)	1 (4.3 %)	0 (0.0 %)
Severe	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)

Table E: Summary of Post-Treatment Adverse Event(s) by Severity (Tree Pollen Cohort)

Severity	Asymptomatic Leg N=13	Active Leg N=13	Treated Leg N=13
Mild	2 (15.4 %)	3 (23.1 %)	3 (23.1 %)
Moderate	2 (15.4 %)	1 (7.7 %)	1 (7.7 %)
Severe	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)

PK results:

Since efficacy and/or safety of a nasally-administered medication might be impacted by differences in nasal pathology (for example when suffering from rhinitis) and/or co-administration of a decongestant (for example: oxymetazoline) to treat the rhinitis, it is important to study differences in absorption of fentanyl (if any) in those conditions. A summary of PK parameters obtained for all the three treatment legs in ragweed and tree pollen induced cohorts is shown in tables F and H respectively. Tables G and I show means determined by ANOVA and figures C and D show the plasma profiles for all the three treatment arms in the ragweed and tree pollen induced cohorts respectively.

Table F: Summary of fentanyl pharmacokinetic parameters for reference and ragweed pollen exposed conditions. Mean ± SD unless otherwise stated.

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

Table G: Summary of fentanyl pharmacokinetic parameters for reference and ragweed pollen exposed conditions. Means determined by ANOVA.

Treatment Leg	In-Transformed Parameter	Ragweed Pollen	
		Ratio of Means[a] (%)	90% Confidence Interval (%)
Active/Asymptomatic	AUC_t (pg.h/mL)	102.4	91.7 – 114.3
	AUC_{inf} (pg.h/mL)	105.1	91.2 – 121.1
	C_{max} (pg/mL)	109.4	87.1 – 137.4
Treated/Asymptomatic	AUC_t (pg.h/mL)	84.8	75.8 – 94.8
	AUC_{inf} (pg.h/mL)	83.1	72.0 – 96.0
	C_{max} (pg/mL)	60.0	47.6 – 75.6
Active/Treated	AUC_t (pg.h/mL)	120.8	108.2 – 134.7
	AUC_{inf} (pg.h/mL)	126.4	108.5 – 147.2
	C_{max} (pg/mL)	182.3	145.3 – 228.7

Figure C: Mean Graph of Fentanyl Plasma Concentration (Ragweed Pollen Cohort) up to 24 h

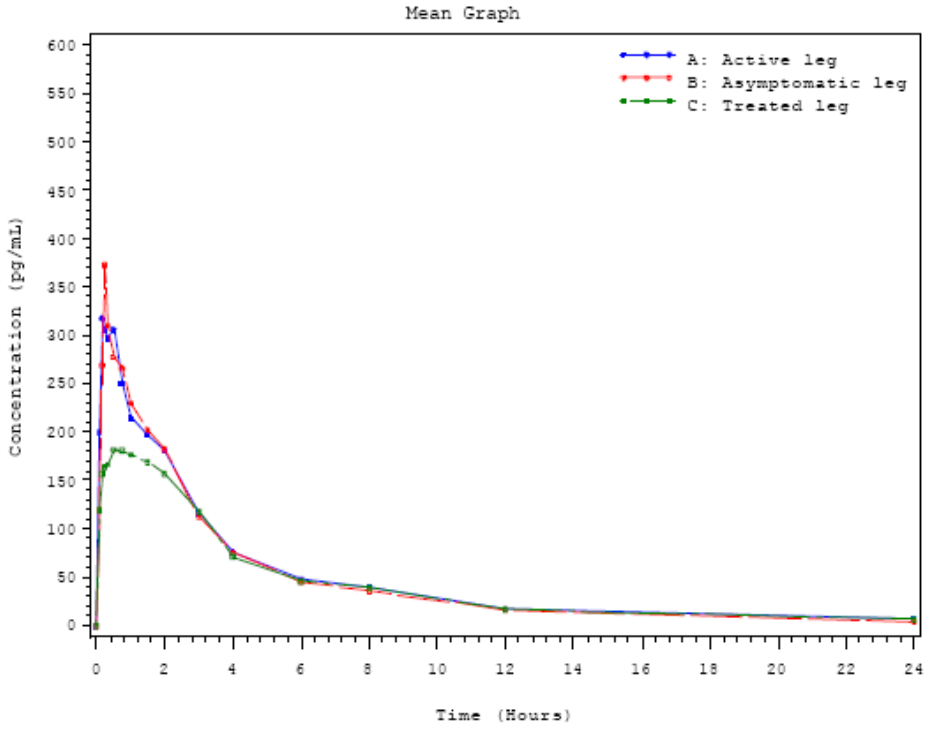


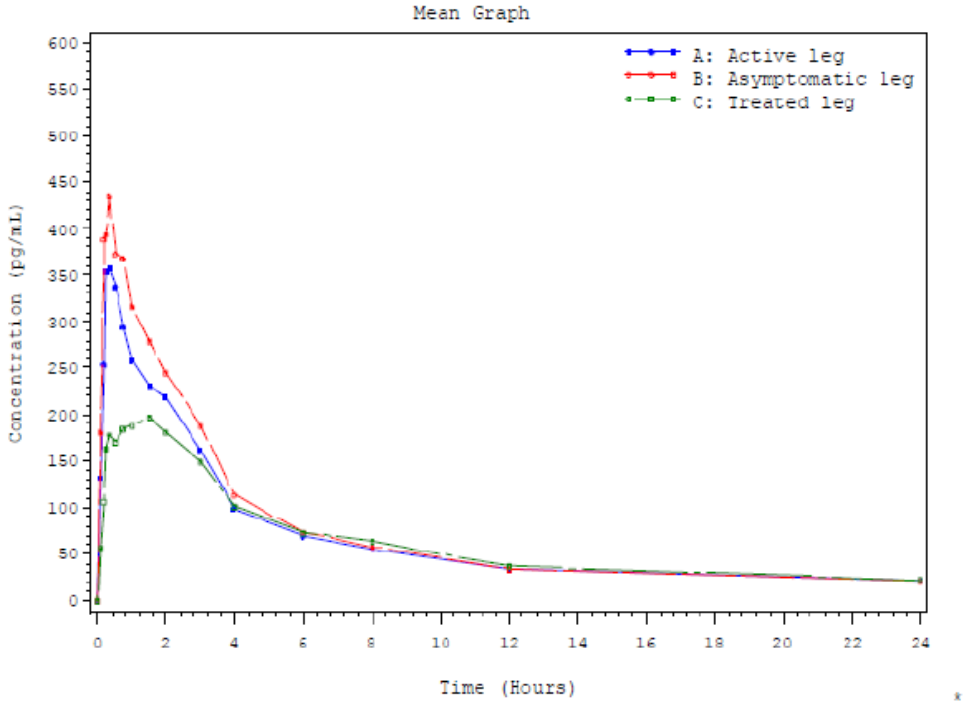
Table H: Summary of fentanyl pharmacokinetic parameters for reference and tree pollen exposed conditions. Mean ± SD unless otherwise stated.

Parameter (unit)	REFERENCE		TREE EXPOSED			
	Asymptomatic (B)	n	Active (A)	n	Treated (C)	n
C_{max} (pg/mL)	553.37 ± 291.31	10	435.74 ± 235.00	11	246.77 ± 125.63	12
T_{max}[a] (h)	0.33[a] [0.17-2.00][b]	10	0.33[a] [0.17-3.00][b]	11	1.25[a] [0.08 -3.00][b]	12
AUC_t (pg.h/mL)	1805.68 ± 591.74	10	1609.84 ± 591.08	11	1498.28 ± 559.15	12

Table I: Summary of fentanyl pharmacokinetic parameters for reference and tree pollen exposed conditions. Means determined by ANOVA.

Treatment Leg	In-Transformed Parameter	Tree Pollen	
		Ratio of Means (%)	90% Confidence Interval (%)
Active/Asymptomatic	AUC_t (pg.h/mL)	81.5	69.4 – 95.8
	AUC_{inf} (pg.h/mL)	72.2	60.6 – 86.1
	C_{max} (pg/mL)	75.6	56.6 – 101.1
Treated/ Asymptomatic	AUC_t (pg.h/mL)	76.8	89.9 – 65.6
	AUC_{inf} (pg.h/mL)	71.3	83.9 – 60.6
	C_{max} (pg/mL)	44.5	59.2 – 33.5
Active/Treated	AUC_t (pg.h/mL)	106.2	91.2 – 123-6
	AUC_{inf} (pg.h/mL)	101.3	86.6 – 118.6
	C_{max} (pg/mL)	169.8	129.0 – 223.6

Figure D: Mean Graph of Fentanyl Plasma Concentration (Tree Pollen Cohort) up to 24 h



Reviewer's comments:

1. From Figures C and D and Tables F, G, H and I, (b) (4) absorption was similar in the Asymptomatic and the Active/Untreated arms in both the Ragweed and Tree pollen induced cohorts indicating that presence of rhinitis may not affect PK absorption of (b) (4)
2. From Figure C and tables F and G, Cmax for Treated arm (Rhinitis treated with oxymetazoline) was about 32% less as compared to the Asymptomatic arm in the Ragweed pollen induced cohort, AUCt for Treated arm was about 10% lower as compared to the Aymptomatic arm and mean Tmax for Treated arm was 0.75 h (range 0.08-3 h) as compared to 0.25 h (0.17-1 h) for the Asymptomatic arm.

3. From Figure D and tables H and I, Cmax for Treated arm (Rhinitis treated with oxymetazoline) was about 40% less as compared to the Asymptomatic arm in the Tree pollen induced cohort and AUCt for Treated arm was about 17% lower as compared to the Aymptomatic arm. In addition, mean Tmax for Treated arm was 1.25 h (range 0.08-3 h) as compared to 0.33 h (0.17-2 h) for the Asymptomatic arm.
4. These results indicate that oxymetazoline affects the PK of intranasal fentanyl when both agents are nasally administered.
5. This reviewer concurs with the sponsor that "the efficacy of FCNS appears unlikely to be affected by the onset of untreated allergic rhinitis in patients established on a given dose. However, it, may be somewhat less effective in a patient with active rhinitis when administered concomitantly with a decongestant (such as oxymetazoline), thus potentially impairing pain management. Additionally, in view of the possibility that the titration of a patient while they are experiencing an acute episode of rhinitis could lead to incorrect dose identification (particularly if they are using a vasoconstrictive decongestant), titration under these circumstances should be avoided."

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/

SHEETAL S AGARWAL
04/09/2010

SURESH DODDAPANENI
04/09/2010