CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022510Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
NDA	22-510
Submission Date:	August 5, 2009
Brand Name:	Abstral®
Generic Name:	Fentanyl citrate
Formulation/Strength:	(b) (4) tablet; 100, 200, 300, 400, 600, and 800 mcg
OCP Reviewer:	Zhihong Li, Ph.D.
OCP Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	Division of Clinical Pharmacology 2
OND Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Sponsor:	ProStrakan Inc.
Submission Type; Code:	New formulation; Standard review
Dosing regimen:	Initial dose of 100 mcg, individually titrate to a tolerable dose that provides adequate analgesia
Indication:	Breakthrough cancer pain

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

From the viewpoint of the Office of Clinical Pharmacology, NDA 22-510 submitted on August

5, 2009 is acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling for Abstral.

1.2 PHASE IV COMMITMENTS

None.

Labeling Recommendations

Please see Section 3 Detailed Labeling recommendations.

1.3 CLINICAL PHARMACOLOGY SUMMARY

The current submission is an original NDA submission of Abstral® (b) (4) (b) (4) for the treatment of breakthrough pain in opioid-tolerant cancer patients. This is a 505(b)(2) application and the Reference Listed Drug (RLD) is Actiq® (NDA 20747). The route of administration of this product is sublingual. Abstral (b) (4) contains the active substance fentanyl citrate, an opioid analgesic, in strengths of 100, 200, 300, 400, 600 and 800 µg. The initial dose is 100 µg, patients will be individually titrated to a tolerable dose that provides adequate analgesia. In addition to Actiq, the two other approved products for this indication in the U.S. are Fentora (fentanyl citrate buccal tablet- NDA 21947) and Onsolis (fentanyl citrate buccal film- NDA 22266).

The clinical pharmacology/clinical program for this product consisted of one pivotal Phase III study (EN3267-005), one Phase II study (SuF-002), and 13 Phase I Clinical Pharmacology studies.

Within the clinical pharmacology studies, single and multiple dose pharmacokinetics of fentanyl after Abstral (b) (4) dosing were studied. Pharmacokinetic studies have confirmed dose proportional pharmacokinetics of fentanyl across the available dose range. Adequate data were provided to compare (a) PK and BA of Abstral (b) (4) and the RLD Actiq, (b) to bridge the commercial formulation and a formulation used in development, (c) commercial formulation manufactured at different sites, and (d) to demonstrate dosage form bioequivalence of different tablet strengths at a dose of 800 mcg. Orally administered fentanyl undergoes pronounced hepatic and intestinal first pass effects. Sublingual fentanyl absorption avoids this first pass metabolism and therefore an increased bioavailability is expected. The absolute bioavailability of Abstral sublingual tablets has been estimated to be 54% (study EN3267-012). The median time to maximum plasma concentration (Tmax) across a dose range of 100 to 800 µg varied from 30 to 60 minutes (range of 19 – 240 minutes). Study EN3267-012 demonstrated that the absolute bioavailability of 1600 µg Actiq and 800 µg Abstral (b) (4) is similar (52% and 54%, respectively) and that they were bioequivalent (after dose-normalization). Absolute bioavailability of Fentora was higher (about 68%) compared to Abstral (b) (4) and Actiq. Study EN3267-013 further demonstrated that 800 µg and 1600 µg doses of Abstral (b) (4) were bioequivalent to the corresponding doses of Actiq. Study SuF-003 demonstrated that the commercial formulation (formulation A) and a formulation used in development (formulation 1) are bioequivalent. Dose proportionality across the 100 µg to 800 µg Abstral dose range (given as 100 µg, 200 µg, 400 µg, or 2 x400 µg units) has been demonstrated in study 2246-EU-005. In study EN3267-013, dose-proportionality between 800 µg and 1600 µg was demonstrated. Study EN3267-003

demonstrated that Abstral (b) (4) administered as 2 × 400 µg tablets and as 4 × 200 µg tablets is bioequivalent with Abstral (b) (4) administered as 1 × 800 µg tablet in healthy subjects administered a single sublingual dose of each treatment. Study EN3267-010 demonstrated that Abstral (b) (4) 400 µg sublingual tablet formulation manufactured in the United States (Novartis) was bioequivalent to the formulation manufactured in Sweden (Orexo).

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

2 QUESTION BASED REVIEW

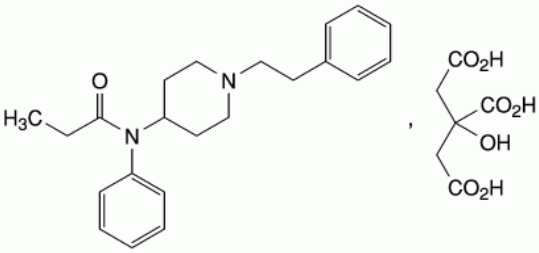
2.1 GENERAL ATTRIBUTES

2.1.1 What 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. It has been also been used for the treatment of breakthrough cancer pain by transmucosal (and under special circumstances by epidural) administration and for chronic pain through transdermal administration.

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)

Fentanyl citrate active pharmaceutical ingredient is manufactured by the following drug substance manufacturers' DMFs:

• Type II DMF (b) (4)
• Type II DMF (b) (4)

Drug product: Abstral®

The drug product, Abstral® [redacted] is a sublingual tablet containing the active ingredient, fentanyl citrate. Abstra [redacted] is administered by placing the tablet under the tongue where it disintegrates followed by dissolution and absorption through the oral mucosa.

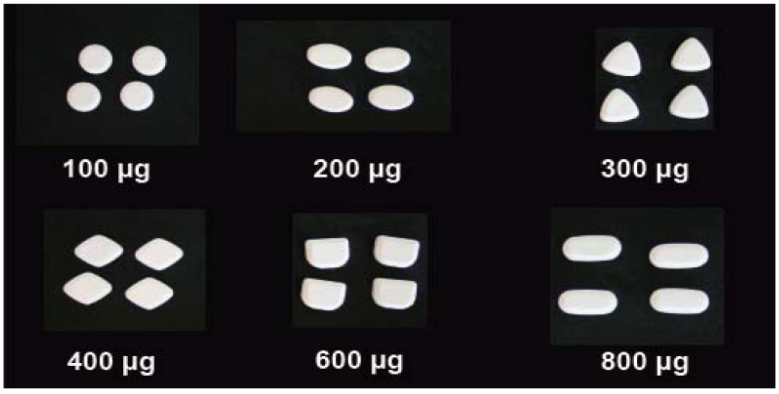
Abstral [redacted] will be supplied in six different tablet strengths: 100 µg, 200 µg, 300 µg, 400 µg, 600 µg, and 800 µg. The tablets are white and differentiated by a unique shape and debossing on one side of the tablet (see Table 1-1). In addition, Abstral [redacted] are packaged in individually sealed child resistant [redacted] foil/foil aluminum blister packaging which are color-coded to readily distinguish between strengths.

A summary of the differentiating parameters are presented in Table 1-1. A photograph showing tablet shapes is presented in Figure 1-1.

Table 1–1 Abstral [redacted] Description and Differentiation

Dosage Strength (µg)	Debossing (Side 1)	Tablet Shape	Carton/Blister Package Color
100	1	Round	[redacted]
200	2	Oval	
300	3	Triangle	
400	4	Diamond	
600	6	D-shaped	
800	8	Capsule	

Figure 1–1 Tablet Shape Differentiation Abstral [redacted]



The composition per tablet is given in Table 1-2 below.

Table 1–2 Composition of Abstral (b) (4) (100 µg, 200 µg, 300 µg, 400 µg, 600 µg and 800 µg) for Commercial Supply

Components	Quality Std	Function	100 µg Strength (mg/tablet)	200 µg Strength (mg/tablet)	300 µg Strength (mg/tablet)	400 µg Strength (mg/tablet)	600 µg Strength (mg/tablet)	800 µg Strength (mg/tablet)
Fentanyl Citrate, (b) (4) (b) (4)	USP	Active drug substance						(b) (4)
Mannitol (b) (4)	USP							(b) (4)
Silicified Microcrystalline Cellulose[3] (b) (4)	NF							
Croscarmellose Sodium (b) (4)	NF							
Magnesium Stearate, (b) (4) (b) (4)	NF							
Tablet weight (mg)			**70.0**	**70.0**	**70.0**	**70.0**	**105.0**	**140.0**

(b) (4)

2.1.2 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

Abstral is indicated only for the management of breakthrough cancer pain in patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

2.1.3 What are the proposed dosage and route of administration?

Initial dose of Abstral: 100 µg. Individually titrate to a tolerable dose that provides adequate analgesia.

Administer on the floor of the mouth directly under the tongue and allow to completely dissolve.

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?

NDA 22-510 is a 505(b)(2) application and the Reference Listed Drug (RLD) is Actiq®. The sponsor conducted a single pivotal Phase III study, a long term safety study, as well as Clinical pharmacology and biopharmaceutis studies to support dosing and claims. The key design features of these studies were summarized in the Table 1.

Table 1. Design features of studies to support dosing and/or claims

Type of Study [a]	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 [b,c]	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy Safety	EN3267-005	5.3.5.1	To compare the efficacy of Abstral (b) (4) with placebo in treating BTcP in opioid-tolerant cancer patients who were using stable doses of opioid medication as measured by: 1) The SPID from Baseline to 30 min after dosing; and 2) Ratings of pain intensity, pain relief, patient global evaluation of study medication, and use of rescue medication. To evaluate the safety and tolerability of Abstral (b) (4) in treating BTcP as measured by the occurrence of AEs and withdrawals due to AEs.	Double-blind, randomized, placebo-controlled, multicenter study with an open-label titration phase followed by a non-randomized, open-label, long-term extension period	Abstral (b) (4) or placebo tablets; 100, 200, 300, 400, 600, or 800 µg; sublingual	131 Enrolled Open-label Titration: 131 Treated 78 Completed Double-blind, Randomized Period [e]: 66 Treated 60 Completed Open-label Extension Period [f]: 72 Treated 25 Completed	Opioid-tolerant cancer patients	Open-label Titration: Titrate from 100 µg to stable dose in 2-week period Double-blind, randomized Period: Receive 7 doses of stable dose and 3 matching placebo doses Open-label Extension Period: Remain on stable dose for up to 12 months	Complete; full

Type of Study [a]	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 [b,c]	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Long-term Effectiveness / Safety	EN3267-007	5.3.5.2	To evaluate the long-term safety and effectiveness of Abstral (b) (4) in treating BTcP episodes in opioid-tolerant cancer patients who were using stable doses of opioid medication.	Multiple-dose, non-randomized, open-label, multicenter study with an open-label titration phase.	Abstral (b) (4) 100, 200, 300, 400, 600, or 800 µg; sublingual	139 Enrolled Open-label Titration: 139 Treated 96 Completed Maintenance Period: 96 Treated 19 Completed	Opioid-tolerant cancer patients	Open-label Titration: Titrate from 100 µg to stable dose in 2-week period Maintenance Period: Remain on stable dose for up to 12 months	Complete; full

Type of Study [a]	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 [b,c]	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PD	SuF-002	5.3.5.1	1) To evaluate pharmacodynamics (ie, effect) of sublingual fentanyl with regard to pain intensity difference (PID), with primary comparison of Abstral (b) (4) 400 µg versus placebo. 2) To evaluate global assessment of treatment, need for rescue medication and dose-effect relationships upon sublingual administration of Abstral (b) (4) 00, 200, and 400 µg. To compare tolerability with regard to doses (placebo, 100, 200, and 400 µg) and time of doses.	Randomized, multicenter, double-blind, four-period crossover study	Abstral (b) (4) or placebo tablets; four single doses of placebo, 100, 200, or 400 µg; sublingual	38 Enrolled 27 Treated 23 Completed	Opioid-tolerant patients with locally advanced or generalized cancer	Three single doses (Abstral (b) (4) 100, 200, and 400 µg) and placebo (given in random order at consecutive pain episodes) with a washout period of at least 1 day	Complete; full

Clinical Study and Country	Study Design/Objectives	Dosage and Formulation
Key Studies		
SuF-003, Sweden	Open-label, single centre, single dose, randomized 4-treatment, 4-period crossover study in 16 opioid-naïve healthy male Caucasian subjects/bioequivalence Formulation 1 versus A-C	400 µg Abstral (b) (4) (sublingual) Formulations A - C and 1
EN3267-001, Sweden	Open-label, randomized, 2 centre, single dose, 4-treatment, 4-period crossover PK study in 42 opioid-naïve healthy male and female subjects/bioavailability	100 µg Abstral (b) (4) (Formulation A - C) vs. 200 µg Actiq (oral transmucosal lozenge) & 800 µg Abstral (b) (4) vs. 1600 µg Actiq
EN3267-010, US	Open-label, randomized, single-dose study in 34 opioid-naïve healthy adults/bioequivalence Formulation A from different manufacturing sites (Orexo vs. Novartis)	400 µg Abstral (b) (4) (sublingual) Formulation A
EN3267-003, US	Open-label, randomized, single-dose study in 30 opioid-naïve healthy adults/bioavailability	800 µg Abstral (b) (4) (either 2 x 400 µg, 4 x 200 µg or 1 x 800 µg Abstral (b) (4) [sublingual] Formulation A)
EN3267-012, US	Open-label, randomized, study in 35 opioid-naïve healthy adults/comparison of absolute and relative bioavailability of four fentanyl formulations	800 µg Abstral (b) (4) (sublingual) Formulation A, 800 µg Fentora (buccal tablet), 1600 µg Actiq (oral transmucosal lozenge), and 600 µg fentanyl citrate (injection IV)
EN3267-013, US	An open-label, randomized, four-period crossover study in 30 healthy males and females/to compare the relative bioavailability and dose proportionality of Fentanyl and Actiq	800 µg and 1600 µg (2x800 µg) Abstral (b) (4) (sublingual) Formulation A or Actiq (transmucosal lozenge)
Supportive Studies		
2246-EU-003, Sweden	Open-label, single centre, single dose, 2-treatment, 2-period randomized crossover study in 51 opioid- naïve healthy Caucasian male subjects/bioequivalence	100, 200, 400 µg as single or as two dose units of Abstral (b) (4) (sublingual) Formulation 2
EN3267-004, US	Open-label, randomized, single-dose study in 24 opioid-naïve healthy adults/bioequivalence Formulation A from different manufacturing sites (Orexo vs. Novartis)	400 µg Abstral (b) (4) (sublingual) Formulation A

Study Code/ Country	Study Design	Patient Population	Number of Subjects	Dosage / Formulation
2246-EU-001, UK	Open-label, single centre, ascending single dose, 4-period PK study	Opioid-naïve healthy Japanese & Caucasian male subjects	21 Enrolled 21 Treated (10 Japanese, 11 Caucasian) 20 Completed	50, 100, 150*, 200 µg Formulation 1
SuF-001, Sweden	Double-blind, single centre, randomised 2-period, crossover single dose PK study	Opioid-tolerant, male and female Caucasian cancer patients	15 Enrolled 14 Treated (9 males, 5 females) 8 Completed	100, 200, 400 µg Formulation 1
2246-EU-002, UK	Open-label, single centre, repeated dose PK study	Opioid-naïve healthy Japanese male and female subjects	10 Enrolled 10 Treated 10 Completed (5 males, 5 females)	50 µg every 4 hours for 44 h (ie, 12 doses) Formulation 1
2246-EU-004, Germany	Open-label, single centre, repeated dose PK study	Opioid-naïve healthy Japanese male subjects	24 Enrolled 24 Treated 17 Completed	100, 200, 300*, 400 µg single and repeated dose every 4 h for 72 h (ie, 19 doses) Formulation 2
2246-EU-005, UK	Open-label, single centre, repeated dose PK study	Opioid-naïve healthy Japanese males and female subjects	48 Enrolled 48 Treated 48 Completed (24 males, 24 females)	100, 200, 400, 800* µg single and repeated dose every 6 h for 72 h (i.e. 13 doses) Formulation A

* 150, 300 and 800 µg doses given as 2 x Abstral (b) (4)

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint for the pivotal Study EN3267-005 in the Abstral (b) (4) clinical program is the SPID from Baseline to 30 minutes after treating BTcP episodes with study medication (SPID 30). Baseline for each episode was defined as the pain score recorded prior to taking study medication for that episode. For phase II Study SuF-002, the primary efficacy endpoint was the ID, which was defined as pre-dose pain intensity minus pain intensity 5, 10, 15, 20, and 30 minutes after study drug administration. No primary efficacy endpoint was defined for the open-label safety Study EN3267-007.

In addition to the SPID at 30 minutes, a series of secondary endpoints have been assessed across the three studies to provide support of the primary endpoint. See clinical review by Dr. Frank Pucino for final assessment of the safety and efficacy data from the clinical studies.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Fentanyl, the active moiety, and the metabolite norfentanyl were appropriately measured using validated LC-MS/MS methods in the plasma and urine for the pharmacokinetic parameters.

2.2.4 Exposure-response

No Exposure-response relationship was assessed in this program.

No information regarding the potential of Abstral to prolong the QT or QTc interval was submitted.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

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

Single dose

Single dose pharmacokinetic data were available from several studies. Parameters from two studies are shown below.

2.7.2.6.1 Overall Pharmacokinetic Parameters After Single Dose Abstral (b) (4)

Study N°/ Location	Study objectives	Study design	Treatment (Dose, route, formulation)	Subjects (Entered, completed, Race, M/F, age [range])*		Abstral (b) (4) pharmacokinetic parameters: mean (CV%)					
						C_{max} (ng/mL)	T_{max} (min)[a]	$AUC_{(0\text{-last})}$ (ng.h/mL)	$T_{1/2}$ (h)[a]	$AUC_{0\text{-inf}}$ (ng.h/mL)[a]	T_{first} (min)[a]
2246-EU-001 / United Kingdom	Safety, tolerability and PK of Abstral (b) (4) sublingual tablets in healthy subjects	Open-label, single center, ascending single dose, 4 periods study in Caucasian (C) and Japanese (J) healthy male subjects	50, 100, 150, 200 µg fentanyl citrate sublingual tablet Formulation 1	21 20 10 C / 11 J M 26 [20-45]	Caucasian: 50 µg – n=10 (1 tablet) 100 µg – n=10 (1 tablet) 150 µg – n=10 (2 tablets) 200 µg – n=10 (1 tablet) Japanese: 50 µg – n=10 (1 tablet) 100 µg – n=10 (1 tablet) 150 µg – n=10 (2 tablets) 200 µg – n=10 (1 tablet)	0.097 (32) 0.219 (28) 0.292 (33) 0.452 (32) 0.110 (35) 0.219 (30) 0.301 (24) 0.412 (36)	60 [20-120] 30 [20-240] 45 [20-120] 38 [20-75] 38 [20-90] 30 [15-120] 30 [15-120] 53 [20-120]	0.372 (37) 0.915 (36)[7] 1.47 (40) 2.32 (41) 0.321 (58) 0.932 (60) 1.43 (60) 2.20 (57)	3.46 (38)[7] 3.05 (32)[8] 4.71 (53)[7] 7.61 (50)[8] 3.33 (28)[6] 4.13 (87)[9] 4.86 (78)[9] 5.79 (58)[7]	0.544 (12)[5] 1.03 (22)[8] 1.66 (37)[7] 2.80 (47)[8] 0.672 (33)[3] 1.06 (70)[9] 1.77 (64)[9] 1.97 (51)[7]	20 [10-30] 10 [5-30] 10 [5-15] 10 [5-10] 13 [10-20] 10 [5-15] 8 [5-15] 10 [5-15]
SuF-001 / Sweden	Safety, tolerability and PK of Abstral (b) sublingual tablets in cancer patients	Double-blind, single center, randomised 2-period, crossover single dose study in male and female Caucasian cancer patients	100, 200, 400 µg fentanyl citrate sublingual tablet Formulation 1	15 8 C 10 M / 5 F 62 [34-75]	100 µg 200 µg 400 µg	0.243 (58) 0.471 (34) 0.956 (46)	30 [17-60] 60 [18-90] 60 [10-90]	nd nd nd	6.08 (34) 6.28 (25) 5.37 (32)	1.24 (42) 2.65 (25) 4.85 (32)	10 [5-15] 9 [3-10] 10 [3-15]

a: median [range] PE: point estimate of the ratio of the test treatment over the reference, determined by ANOVA methods
*: C: Caucasian, B: Black or African American, A: Asian, I American Indian or Alaska Native, J: Japanese
nd: not determined
n: number of subjects

Multiple dose

It should be noted there is no fixed multiple dose regimen for this indication. Generally speaking BTP episodes occur three to four times a day and patients are not required to be on Abstral around the clock but rather use it as needed to treat the pain from BTP episodes. Multiple dose pharmacokinetics of Abstral (b) (4) were studied in Studies 2246-EU-002, 2246-EU-004 and 2246-EU-005. In Studies 2246-EU-002 and 2246-EU-004, Abstral (b) (4) was given at 4-hour intervals for three days at doses ranged from 50 to 400 µg. Steady state conditions were reached

after approximately 24 hours, and accumulation to steady-state levels was approximately 3-fold for this dose regimen, irrespective of the dose level. In Study 2246-EU-005 Abstral (b) (4) was dosed at 6-hour intervals for three days at doses ranged from 100 to 800 µg. Accumulation ratios of 2 to 2.5 were obtained across the tested dose range. Steady-state conditions were reached after 24 to 48 hours. The following are the PK parameters;

2.7.2.6.2 Overall Pharmacokinetic Parameters After Repeated Dose Abstral (b) (4)

Study N°/ Location	Study objectives	Study design	Treatment (Dose, route, formulation)	Subjects (Entered, completed, Race, M/F, age [range])*		Abstral (b) (4) pharmacokinetic parameters: mean (CV%)					
						C_{max} (ng/mL)	T_{max} (min)[a]	$AUC_{(0-t)}$ (ng.h/mL)	$T_{1/2}$ (h)	AUC_{0-inf} (ng.h/mL)	Rac
2246-EU-002 / Sweden	Safety, tolerability and PK of repeated Abstral (b) sublingual tablets in healthy subjects	Open-label, single centre, repeated dose study in male and female Japanese healthy subjects	50 µg every 4h for 3 days fentanyl citrate sublingual tablet Formulation 1	10 10 J 5M/ 5F 27.7 [23-38]	Male - n=5 Day 1 Day 3 Female – n=5 Day 1 Day 3	 0.084 (21) 0.230 (24) 0.105 (28) 0.235 (26)	 60 [30-60] 30 [30-65] 30 [30-60] 30 [30-60]	 0.235 (24) 0.719 (33) 0.251 (22) 0.737 (43)	 nd 24.9 (69) nd 11.9 (48)	 nd 2.47[2] nd 1.08[2]	 - 3.1 (25) - 3.0 (33)
2246-EU-005 / Sweden	Safety, tolerability and PK of repeated Abstral (b) sublingual tablets in healthy subjects	Open-label, single centre, repeated dose, study in male and female Japanese healthy subjects	Single dose 100, 200, 400, 800 µg (Period 1) 100, 200, 400, 800 µg every 6h for 3 days (Period 2) fentanyl citrate sublingual tablet Formulation A	48 48 J 24M/24F 26.9 [20-38]	Males 100 µg - n=6 Day 1, Period 1 Day 3, Period 2 200 µg – n=6 Day 1, Period 1 Day 3, Period 2 400 µg - n=6 Day 1, Period 1 Day 3, Period 2 800 µg - n=6 Day 1, Period 1 Day 3, Period 2 Females 100 µg - n=6 Day 1, Period 1 Day 3, Period 2 200 µg – n=6 Day 1, Period 1 Day 3, Period 2	 0.221 (30) 0.270 (22) 0.250 (24) 0.477 (25) 0.737 (25) 1.25 (28) 1.38 (37) 2.04 (26) 0.153 (20) 0.271 (27) 0.355 (26) 0.703 (23)	 30 [30-60] 30 [5-120] 90 [45-240] 120 [30-120] 60 [30-60] 120 [30-240] 22 [15-60] 45 [30-240] 30 [19-120] 38 [30-240] 37 [16-120] 52 [30-240]	 0.658 (26)[b] 1.20 (23) 1.01 (21)[b] 2.31 (31) 2.77 (28)[b] 5.95 (28) 4.28 (38)[b] 9.49 (30) 0.541 (16)[b] 1.25 (33) 1.12 (16)[b] 2.94 (17)	 4.38 (44) 14.2 (56) 5.89 (31) 21.9 (18) 11.6 (20) 17.4 (24) 8.33 (25) 15.2 (15) 5.67 (56) 22.5 (32) 7.45 (27) 25.9 (23)	 1.01 (38) nd 1.89 (38) nd 5.90 (33) nd 8.02 (42) nd 0.941 (32) nd 1.95 (16) nd	 - 1.9 (18) - 2.3 (11) - 2.2 (17) - 2.3 (20) - 2.3 (31) - 2.7 (24)

2246-EU-005 / Sweden	Safety, tolerability and PK of repeated Abstral (b) (4) sublingual tablets in healthy subjects	Open-label, single centre, repeated dose, study in male and female Japanese healthy subjects	Single dose 100, 200, 400, 800 µg (Period 1) 100, 200, 400, 800 µg every 6h for 3 days (Period 2) fentanyl citrate sublingual tablet Formulation A	48 48 J 24M/24F 26.9 [20-38]	400 µg - n=6 Day 1, Period 1 Day 3, Period 2 800 µg - n=6 Day 1, Period 1 Day 3, Period 2	0.793 (48) 1.19 (33) 1.45 (32) 2.03 (30)	60 [30-120] 120 [30-240] 30 [30-60] 240 [45-240]	2.43 (37)[b] 5.17 (27) 4.69 (29)[b] 9.85 (35)	15.4 (42) 24.7 (14) 11.8 (32) 26.2 (18)	5.09 (39) nd 9.87 (25) nd	- 2.3 (30) - 2.1 (26)
2246-EU-004 / Sweden	Safety, tolerability and PK of repeated Abstral (b) sublingual tablets in healthy subjects	Open-label, single centre, repeated dose, study in male Japanese healthy subjects	Single dose 100, 200, 300, 400 µg (Period 1) 100, 200, 300, 400 µg every 4h for 3 days (Period 2) fentanyl citrate sublingual tablet Formulation 2	24 17 J M 28.3 [20-43] [1 subject completed at 400 µg but not included in PK analysis]	100 µg - n=6 Day 1, Period 1 Day 3, Period 2 200 µg – n=5 Day 1, Period 1 Day 3, Period 2 300 µg - n=5 Day 1, Period 1 Day 3, Period 2	0.139 (32) 0.343 (38) 0.245 (20) 0.713 (47) 0.321 (17) 0.869 (11)	120 [120-240] 45 [30-240] 120 [30-120] 30 [15-60] 120 [30-240] 120 [60-240]	0.427 (30)[b] 1.24 (38) 0.746 (20)[b] 2.32 (41) 0.924 (18)[b] 3.11 (12)	4.75 (27) 15.9 (29) 6.31 (34) 19.9 (31) 7.54 (14) 13.5 (23)	1.04 (36) nd 1.63 (30) nd 2.63 (19) nd	- 2.9 (27) - 3.2 (38) - 3.5 (23)

a: median [range] PE: point estimate of the ratio of the test treatment over the reference, determined by ANOVA methods

[b] $AUC_{0\text{-last}}$ for Day 1, Period 1 as in this study a single dose was given followed by washout, before multiple dosing was started

*: C: Caucasian, B: Black or African American, A: Asian, I American Indian or Alaska Native, J: Japanese

nd: not determined

n: number of subjects

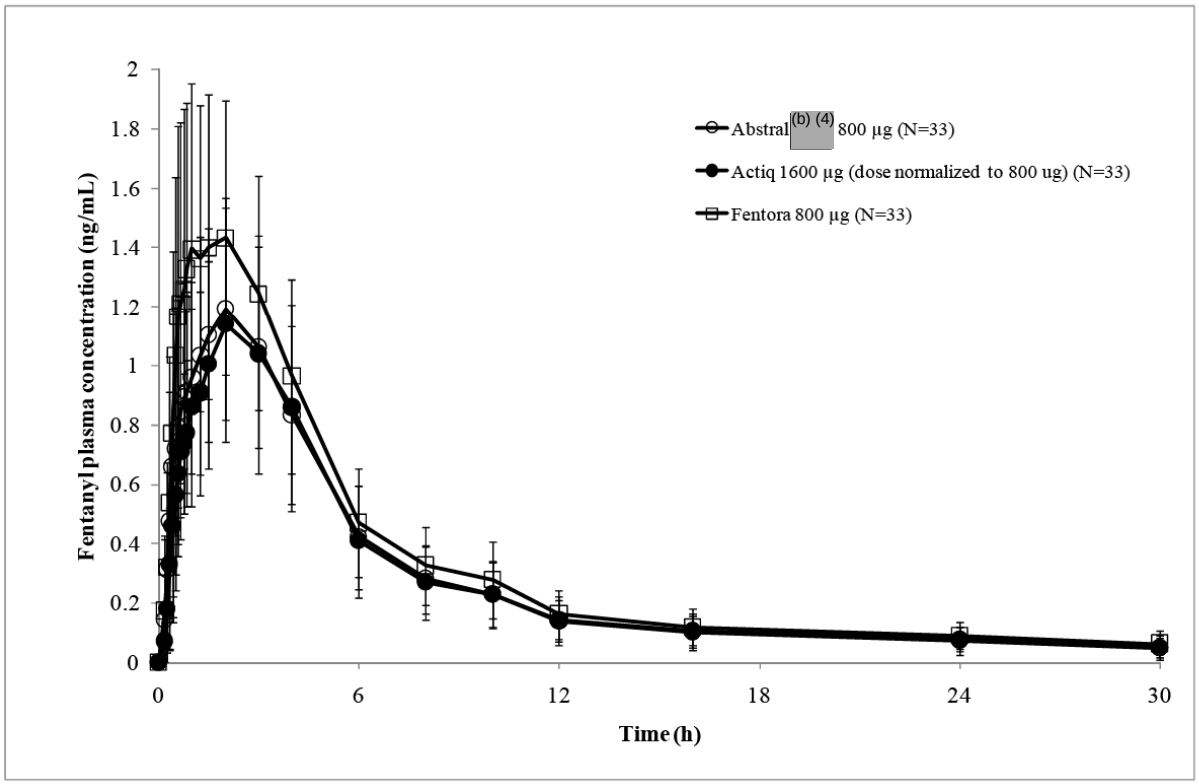
2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Among the thirteen Phase I PK studies, twelve were done in healthy volunteers and only one single dose study (SuF-001) was done in cancer patients. The available PK parameters were similar between healthy volunteers and cancer patients (see section 2.2.5.1).

2.2.5.3 What are the characteristics of drug absorption?

Abstral (b) (4) is a sublingual tablet designed specifically for oral transmucosal delivery. Orally administered fentanyl undergoes pronounced hepatic and intestinal first pass effects. Sublingual fentanyl absorption avoids this first pass metabolism therefore an increased bioavailability is expected. Study EN3267-012 assessed the absolute bioavailability and relative bioavailability of Abstral (b) (4) Actiq, and Fentora formulations. The absolute bioavailability of Abstral sublingual tablets and Actiq has been estimated to be 54% and 52%, respectively. The absolute bioavailability of Fentora is higher (about 68%). After dose-normalization, this study also demonstrated that Abstral (b) (4) is bioequivalent to Actiq. Mean fentanyl plasma concentration-time curves for Abstral (b) (4), Fentora and Actiq are shown in Figure 2–7. The median time to maximum plasma concentration (Tmax) across a dose range of 100 to 800 µg varied from 30 to 60 minutes (range of 19 – 240 minutes).

Figure 2–7 **Mean (± SD) Plasma Concentration of Fentanyl Versus Time After Administration of a Single Dose of 800 µg Abstral (b) (4) 800 µg Fentora or 1600 µg Actiq (Dose-Normalized to 800 µg) to Healthy Subjects; Study EN3267-012**



Study EN3267-013 further demonstrated that 800 µg and 1600 µg doses of Abstral (b) (4) were bioequivalent to the corresponding doses of Actiq. Mean fentanyl plasma concentration-time curves are shown in Figure 2–8. For both dose levels, the mean plasma concentration versus time profiles were similar for Abstral (b) (4) and Actiq. When the Actiq lozenge is used up completely, bioequivalence was shown for Abstral (b) (4) and Actiq. For the 800 µg dose level, the Abstral (b) (4) /Actiq geometric mean ratios for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and Cmax were 97% (90% CI of 91% - 103%), 102% (90% CI of 95% - 109%), and 97% (90% CI of 89% - 106%) respectively (Table 2–12). For the 1600 µg dose level similar results were obtained. The Abstral (b) (4) /Actiq geometric mean ratios for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and Cmax were 95% (90% CI of 89% - 101%), 100% (90% CI of 94% - 107%), and 95% (90% CI of 87% - 103%), respectively.

Figure 2–8 **Mean (± SD) Plasma Concentration of Fentanyl Versus Time by Treatment; Study EN3267-013**

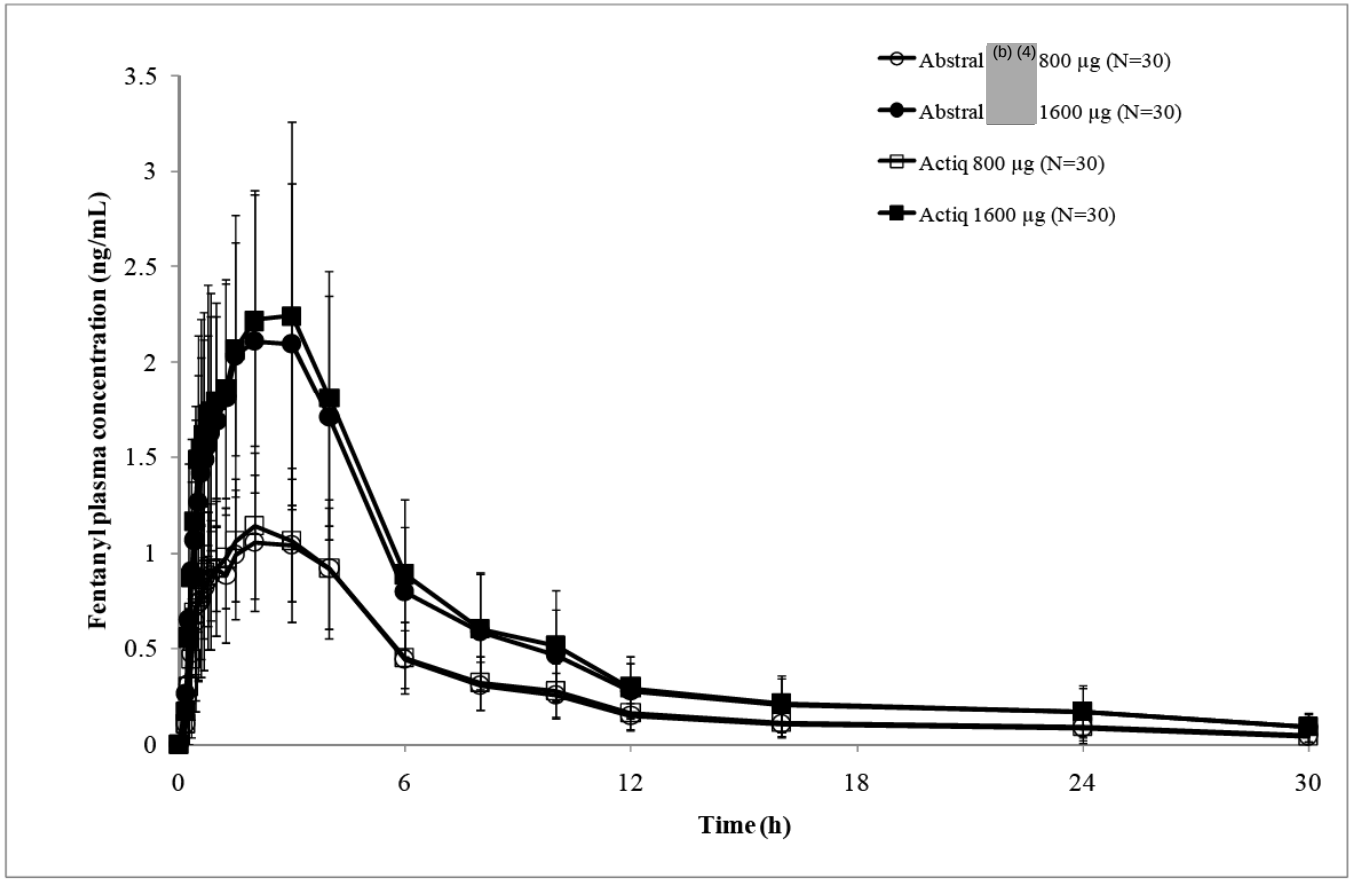


Table 2–12 Statistical Analysis of Plasma Pharmacokinetic Parameters of Fentanyl: Study EN3267-013

Parameter	Treatment[a]	n	Geometric Means	PE (90% CI): [A/C]	PE (90% CI): [B/D]
$AUC_{0\text{-last}}$ (ng.h/mL)	A	30	7.894	0.9651 (0.9085, 1.0253)	0.9468 (0.8912, 1.0058)
	B	30	14.986	-	-
	C	30	8.180	-	-
	D	30	15.828	-	-
$AUC_{0\text{-}15}$ (ng.h/mL)	A	30	0.011	0.7040 (0.5005, 0.9902)	0.8887 (0.6315, 1.2506)
	B	29	0.032	-	-
	C	30	0.015	-	-
	D	30	0.036	-	-
$AUC_{0\text{-}30}$ (ng.h/mL)	A	30	0.121	0.9195 (0.7706, 1.0971)	0.9261 (0.7745, 1.1074)
	B	29	0.245	-	-
	C	30	0.131	-	-
	D	30	0.265	-	-
$AUC_{0\text{-inf}}$ (ng.h/mL)	A	21	8.926	1.0223 (0.9548, 1.0946)	1.0006 (0.9376, 1.0678)
	B	22	16.281	-	-
	C	22	8.731	-	-
	D	25	16.271	-	-
C_{max} (ng/mL)	A	30	1.277	0.9705 (0.8912, 1.0568)	0.9465 (0.8692, 1.0307)
	B	30	2.395	-	-
	C	30	1.316	-	-
	D	30	2.531	-	-

a Treatment A = Abstral (b) (4) (1 x 800 µg sublingual tablet), Treatment B = Abstral (b) (4) (2 x 800 µg sublingual tablet), Treatment C = Actiq (1 x 800 µg oral transmucosal lozenge), Treatment D = Actiq (1 x 1600 µg oral transmucosal lozenge)

2.2.5.4 What are the characteristics of drug distribution?

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (Vss) was 4 L/kg.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

As a 505(b)(2) submission, mass balance study was not done in this program.

2.2.5.6 What are the characteristics of drug metabolism?

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by CYP3A4. Norfentanyl was not found to be pharmacologically active in animal studies. Avoidance of first-

pass metabolism by the liver accounts for the increased bioavailability of Abstral fentanyl compared to oral formulations of fentanyl.

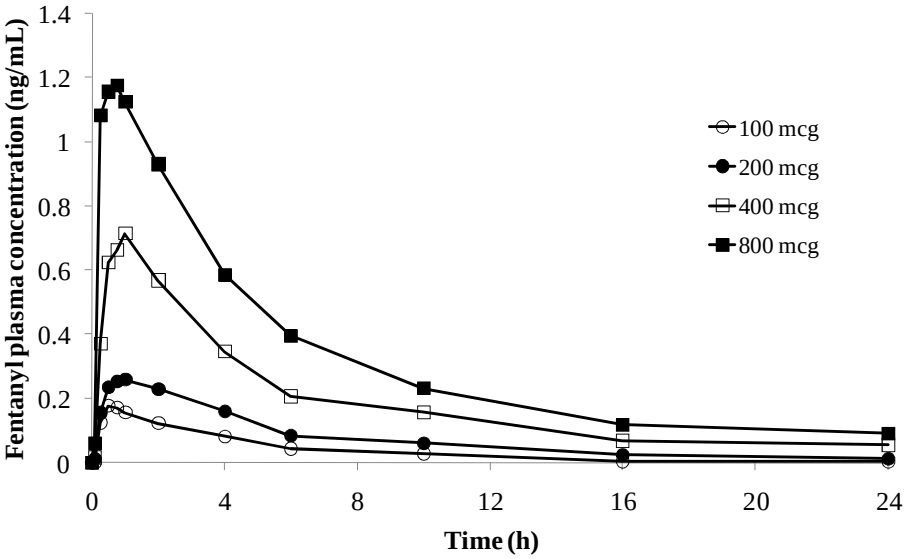
2.2.5.7 What are the characteristics of drug excretion?

Fentanyl is more than 90% eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the 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 was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg).

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Dose proportionality across the 100 µg to 800 µg Abstral dose range has been demonstrated in one study (2246-EU-005). Mean plasma fentanyl levels following single doses of Abstral are shown in Figure 1. Furthermore, Tmax was independent of the dose.

Figure 1: Mean (+/- SD) Plasma Fentanyl Concentration versus Time after Administration of Single Doses of 100 mcg, 200 mcg, 400 mcg and 800 mcg ABSTRAL to Healthy Subjects



Pharmacokinetic parameters are presented in Table 3.

Table 3. Mean (CV%) Fentanyl Pharmacokinetic Parameters after Single-Dose Administration of 100, 200, 400 and 800 mcg Doses of ABSTRAL to Healthy Subjects (n=12 per Dose Level)

Parameter	Unit	Abstral dose			
		100 mcg	200 mcg	400 mcg	800 mcg
C_{max}	(ng/mL)	0.187 (33)	0.302 (31)	0.765 (38)	1.42 (33)
T_{max} [a]	(min)	30 [19-120]	52 [16-240]	60 [30-120]	30 [15-60]
AUC_{0-inf}	(ng.h/mL)	0.974 (34)	1.92 (27)	5.49 (35)	8.95 (33)
$T_{1/2}$	(h)	5.02 (51)	6.67 (30)	13.5 (37)	10.1 (34)

a: median (range)

In another study (EN3267-013), dose proportionality between 800 mcg and 1600 mcg in C_{max} and AUC has also been demonstrated and median Tmax values were the same for both dose levels.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Multiple dose pharmacokinetics of Abstral (b) (4) were studied in Studies 2246-EU-002, 2246-EU-004 and 2246-EU-005. In Studies 2246-EU-002 and 2246-EU-004, Abstral (b) (4) was given at 4-hour intervals for three days at doses ranged from 50 to 400 mcg. Steady state conditions were reached after approximately 24 hours, and accumulation to steady-state levels was approximately 3-fold for this dose regimen, irrespective of the dose level. In Study 2246-EU-005 Abstral (b) (4) was dosed at 6-hour intervals for three days at doses ranged from 100 to 800 mcg. Accumulation ratios of 2 to 2.5 were obtained across the tested dose range. Steady-state conditions were reached after 24 to 48 hours.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-individual variability in fentanyl PK parameters after Abstral dosing was moderate. CV% for Cmax and AUC was in the range of 16% to 50% across all studies. The inter-individual variability in PK parameters in cancer patients has a similar 25-40% range.

2.3 INTRINSIC FACTORS

Abstral dose will be individually titrated to a tolerable dose that provides adequate analgesia.

2.3.1 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?

Both male and female opioid-tolerant cancer patients were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were noted either in efficacy or in observed adverse reactions.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

The safety and efficacy of Abstral have not been established in patients below 18 years of age. No pediatric data has been submitted in this application. Sponsor will be granted waiver in the age group of 0 to 2 years as there are fewer patients in this age group and data in the age range of 3 years to 16 years will be deferred as the adult studies are ready for approval. Sponsor will be required to obtain PK and safety data as a post marketing requirement in this age group. Efficacy for this product will be extrapolated down to pediatrics from adults.

2.3.2.2 Body Size

The effect of body size on dosage regimen was not evaluated.

2.3.2.3 Elderly

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger adult population. Therefore, caution should be exercised when individually titrating Abstral in elderly patients to provide adequate efficacy while minimizing risk.

2.3.2.4 Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of Abstral in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and the inactive metabolite is mostly eliminated in urine. If the drug is used in these patients, use the drug with caution because of the reduced hepatic metabolism and renal excretion capacity in such patients.

2.3.2.5 Renal Impairment

See section 2.3.2.4.

2.3.2.6 Race/Ethnicity

The potential effects of race/ethnicity on the pharmacokinetics of Abstral were not investigated.

2.3.2.7 What pregnancy and lactation use information is there in the application?

Following information is stated in the package insert of Actiq and the sponsor is proposing to add the same information in this package insert as well. Abstral is a pregnancy category C drug. There are no adequate and well-controlled studies in pregnant women. Use ABSTRAL during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated

with intravenous fentanyl.

Fentanyl readily crosses the placenta. Therefore do not use ABSTRAL during labor and delivery (including caesarean section) since it may cause respiratory depression in the fetus or in the newborn infant.

Fentanyl is excreted in human milk; therefore, do not use ABSTRAL in women who are nursing because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using ABSTRAL.

2.4 EXTRINSIC FACTORS

2.4.1 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 factors such as herbal products, diet, smoking or alcohol use on the PK or PD of Abstral.

The concomitant use of Abstral with alcoholic beverages may produce increased depressant effects.

2.4.2 Drug-drug interactions

No drug-drug interaction studies were conducted for Abstral.

2.4.2.1 Is there an *in vitro* basis to suspect *in-vivo* drug-drug interactions?

No *in vitro* metabolic profiling was done in this program. However, it is well established that fentanyl is metabolized mainly via the CYP3A4, so there is a high potential for *in vivo* DDI.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Fentanyl is metabolized mainly via the CYP3A4. Potential interactions may occur when Abstral is given concomitantly with agents that affect CYP3A4 activity.

The concomitant use of Abstral with CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of Abstral. Patients receiving Abstral with CYP3A4 inducers should be monitored for signs of decreased Abstral activity and the dose of Abstral should be titrated accordingly. The genetic polymorphisms of CYP3A4 are not expected to influence the metabolism of fentanyl in humans.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

It is unknown if fentanyl is an inhibitor or inducer of CYP enzymes.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Definitive information is not available to address this aspect.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Not known.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

None indicated.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Since this is for the treatment of pain associated with BTP, patients will be on an around the clock opioid for the treatment of background pain and possibly on other drugs to treat the underlying disease causing the background pain

2.4.2.8 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?

No dedicated studies have been conducted in humans to evaluate the effect of co-administration CYP3A4 inhibitors, inducers on the PK of Abstral. However, based on theoretical expectations and other available data, the following labeling language is included in the proposed package insert:

Monitor patients who begin therapy with, or increase the dose of, inhibitors of CYP450 3A4 for signs of opioid toxicity.

Monitor patients who stop therapy with, or decrease the dose of, inducers of CYP3A4 for signs of opioid toxicity.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. So, it is conceivable that drugs that cause CNS depression may result in pharmacodynamic drug interactions, if coadministered with this product. Proposed package insert has appropriate class labeling language related to this.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The sponsor did not submit these data for this 505(b)(2) submission.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-market formulation was used in the pivotal clinical trial.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Abstral is a sublingual tablet for trans-mucosal delivery. Therefore, an evaluation of food effect is not necessary.

2.5.4 Are the commercial and clinical formulations used during development adequately linked?

Study SuF-003 demonstrated that the commercial formulation (formulation A) and a formulation used in development (formulation 1) are bioequivalent with 90% CIs of the geometric mean of individual test/reference ratios for both Cmax and AUC inside the 0.80 to 1.25 bioequivalence limits. Mean fentanyl plasma concentration-time curves and pharmacokinetic parameters are depicted in Figure 2–1 and Table 2–1 respectively. The fentanyl plasma concentration profiles obtained after administration of Formulation A and reference Formulation 1 (Treatment D) were super-imposable.

Figure 2–1 **Mean Fentanyl Plasma Concentration After a Single Sublingual Dose of 400 µg Abstral ((b) (4) Given as Four Different Formulations (A, B, C and D) (n=16); Study SuF-003**

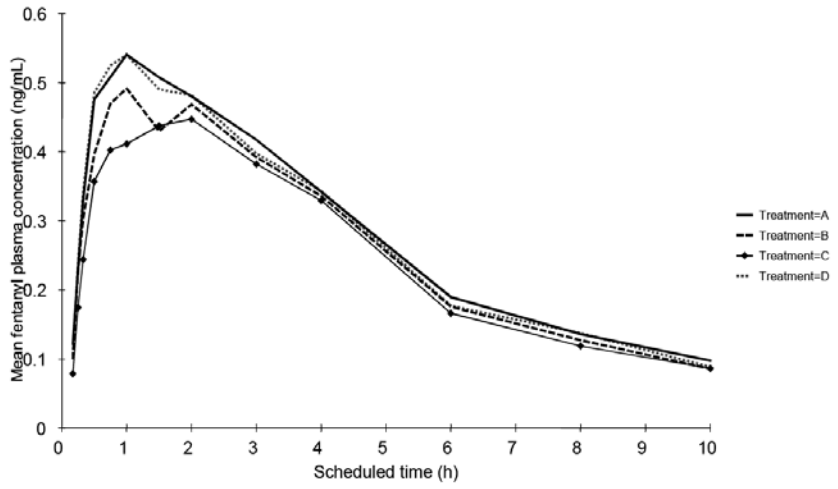


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Table 2–1 **Mean Fentanyl Pharmacokinetic Parameters After Administration of Single Doses of 400 µg Abstral (b) (4) Given as Four Different Formulations to Healthy Male Subjects (n = 16); Study SuF-003**

Mean (CV) Parameters	Abstral (b) (4) Formulations			
	A	B	C	1 (Treatment D) reference
C_{max} (ng/mL)	0.63 (30)	0.61 (31)	0.55 (29)	0.62 (23)
PE	101.2	97.7	87.5	-
(90%CI)[a]	(89.2- 114.7)	(86.1-110.8)	(77.1-99.3)	
$AUC_{(0\text{-}10h)}$ (ng.h/mL)	2.79 (25)	2.61 (22)	2.47 (27)	2.75 (25)
PE	101.5	95.7	89.5	-
(90%CI)[a]	(94.6-109.0)	(89.2-102.7)	(83.4-96.1)	-
$AUC_{0\text{-}inf}$ (ng.h/mL)	3.40 (38)	3.13 (24)	3.03 (33)	3.31 (30)
PE	102.9	96.0	91.2	-
(90%CI)[a]	(95.8-110 .5)	(89.4-103.2)	(84.9-98.0)	-
T_{max} (min)[b]	52.5 [20-121]	60 [20-121]	75 [15-182]	54 [20-180]

a: PE: geometric mean of the individual ratios of C_{max} and AUC of the test formulations (A, B and C) vs. reference (formulation 1)

b: median (range)

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Study EN3267-010 demonstrated that Abstral (b) (4) 400 µg sublingual tablet formulation manufactured in the United States (Novartis) was bioequivalent to the formulation manufactured in Sweden (Orexo). Mean fentanyl plasma concentration-time curves and pharmacokinetic parameters are depicted in Figure 2–5 and Table 2–5, respectively. The mean plasma concentration versus time profiles of both treatments were generally superimposable.

Based on the geometric mean ratio for $AUC_{0\text{-}inf}$, Abstral (b) (4) manufactured in the United States achieved a relative bioavailability of 98.4% compared with the same formulation manufactured in Sweden (Table 2–6). The 90% CIs of the geometric mean ratio were of 92% and 105%, which is contained within the interval of 80% to 125% required to establish bioequivalence. The 90% CIs of the geometric mean ratio for $AUC_{0\text{-}last}$ and Cmax were also within the 80% to 125% limits. Differences in median Tmax values were not statistically significant as measured by the Wilcoxon signed rank test.

Figure 2–5 **Mean (± SD) Plasma Concentration of Fentanyl Versus Time After Administration of a Single Dose of 400 µg Abstral (b) (4) Manufactured in the US and Sweden to Healthy Subjects; Study EN3267-010**

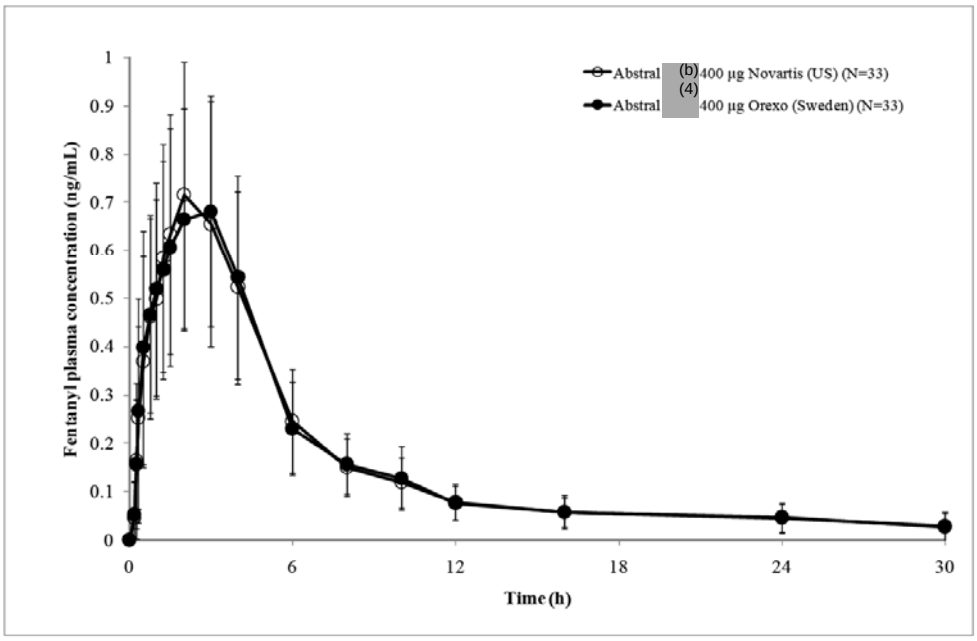

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Table 2–6 **Statistical Analysis of Plasma Pharmacokinetic Parameters of Fentanyl – Pharmacokinetic Population; Study EN3267-010**

Parameter	Treatment[a]	n	Geometric Least-Square Means	PE[b] (A/B)	90% CI of PE[b] (A/B)
$AUC_{0\text{-}inf}$ (ng.h/mL)	A	24	5.038	0.984	(0.92,1.05)
	B	23	5.120	-	-
$AUC_{0\text{-}\tau}$ (ng.h/mL)	A	33	4.390	0.995	(0.94,1.06)
	B	33	4.413	-	-
C_{max} (ng/mL)	A	33	0.764	1.047	(0.98,1.12)
	B	33	0.729	-	-

a Treatment A = Abstral (b) (4) 400 µg sublingual tablets manufactured in the US
Treatment B = Abstral 400 µg sublingual tablets manufactured in Sweden

b PE: geometric mean of the individual ratios

Study EN3267-003 demonstrated that Abstral (b) (4) administered as 2 × 400 µg tablets and as 4 × 200 µg tablets is bioequivalent with Abstral (b) (4) administered as 1 × 800 µg tablet in healthy subjects administered a single sublingual dose of each treatment.

2.5.5 Is there dosage form bioequivalence between 200 µg, 400 µg, and 800 µg tablets ?

The mean plasma fentanyl concentration-time curves were similar for the three Abstral (b) (4) treatments used in this study (1 × 800 µg vs. 2 × 400 µg vs. 4 × 200 µg) (Figure 2–6). Based on the PE for AUC0-inf, Abstral (b) (4) administered as 2 × 400 µg tablets (Treatment B) achieved a relative bioavailability of 106.9% compared with Abstral (b) (4) administered as a single 800 µg tablet (Treatment A)(Table 2–8). The 90% CI for the geometric mean ratio was 98% to 116%, which is contained within the interval of 80% to 125%, and indicates equivalent bioavailability. Bioequivalence was also demonstrated for AUC0-last and Cmax.

Figure 2–6 **Mean (± SD) Plasma Concentration of Fentanyl Versus Time After Administration of a Single Dose of 800 µg Abstral (b) (4) Given as 1 x 800µg, 2 x 400 µg or 4 x 200 µg Tablets to Healthy Subjects: Study EN3267-003**

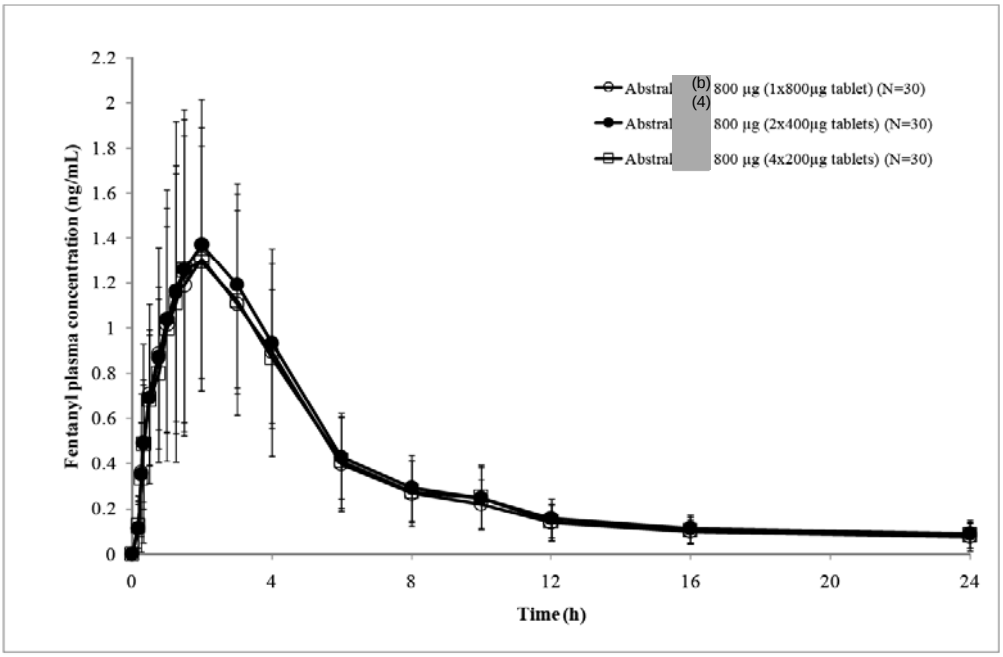


Table 2–8 **Statistical Analysis of Plasma Pharmacokinetic Parameters of Fentanyl; Study EN3267-003**

Parameter	Treatment[a]	n	Geometric Means	PE[b] [(B or C)/A]	90% CI of PE[b] [(B or C)/A]
$AUC_{0\text{-inf}}$ (ng.h/mL)	B	22	8.457	1.069	(0.98,1.16)
	C	19	8.387	1.060	(0.97,1.16)
	A	19	7.913	-	-
$AUC_{0\text{-last}}$ (ng.h/mL)	B	30	8.169	1.086	(1.01,1.16)
	C	30	7.769	10.33	(0.96,1.11)
	A	30	7.525	-	-
C_{max} (ng/mL)	B	30	1.364	1.002	(0.92,1.10)
	C	30	1.357	0.997	(0.91,1.09)
	A	30	1.361	-	-

a A = Abstral (b) (4) 1 x 800 µg tablet
B = Abstral 2 x 400 µg tablets
C = Abstral 4 x 200 µg tablets

b PE: ratio of geometric means

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Two bioanalytical methods were developed and validated during the drug development of

Abstral. A summary of the analytical methods used in each study is listed in Table 1-4:

Table 1 – 4 Overview of Bioanalytical Methods

Method	Bioanalytical Laboratory	Validation Report / Method Number	Study Number
HPLC with MS/MS detection	(b) (4)		EN3267-003 EN3267-004 EN3267-010 EN3267-012 EN3267-013
HPLC with MS/MS detection	Quintiles AB, Uppsala, Sweden	Q99032/AS M-054	2246-EU-001 2246-EU-002 2246-EU-004 2246-EU-005 EN3267-001 SUF-001 SUF-003

The bioanalytical method "Quantitation of Fentanyl in Human Plasma via HPLC with MS/MS Detection" was developed and validated (b) (4) . This method is applicable to the quantitation of fentanyl within a nominal range of (b) (4)

Fentanyl and norfentanyl in human plasma was also determined by LC-MS/MS as described in validation report Q990323. The quality of the determination of fentanyl and its metabolite norfentanyl was satisfactory and within the quality control (QC) acceptance criteria of ± 15%. The lower limit of quantification was 20 pg/mL for fentanyl in human plasma. The mean accuracy to the assay as determined from the analysis of QC samples was within ± 4.5% of the respective nominal value for fentanyl and norfentanyl, respectively.

The parent drug, fentanyl, and the metabolite, norfentanyl, were determined in urine samples from studies 2246-EU-001, 2246-EU-004, and 2246-EU-005.

2.6.2 Which metabolites have been selected for analysis and why?

Norfentanyl as the major metabolite was analyzed in plasma and urine.

3 DETAILED LABELING RECOMMENDATIONS

Changes by this reviewer are indicated by strikethrough for deleted text and additions by underlined text, as follows:

The following recommendations are proposed:

Use of rapidly to describe the formulation is not adequate.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------DOSAGE AND ADMINISTRATION----------

- Initial dose of ABSTRAL: 100 mcg. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia. (2.1)
- <u>No more than one dose can be taken per breakthough pain episode. (2.1)</u>
- <u>Wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL. (2.1)</u>
- Administer on the floor of the mouth directly under the tongue and allow to completely dissolve. (2.4)

1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

4 APPENDICES

4.1 PROPOSED PACKAGE INSERT (ORIGINAL AND ANNOTATED)

See attached draft annotated label at the end of this document.

4.2 INDIVIDUAL STUDY REVIEW

1. SuF-003, Bioequivalence of Abstral (b) (4) Formulations A-C vs. Formulation 1

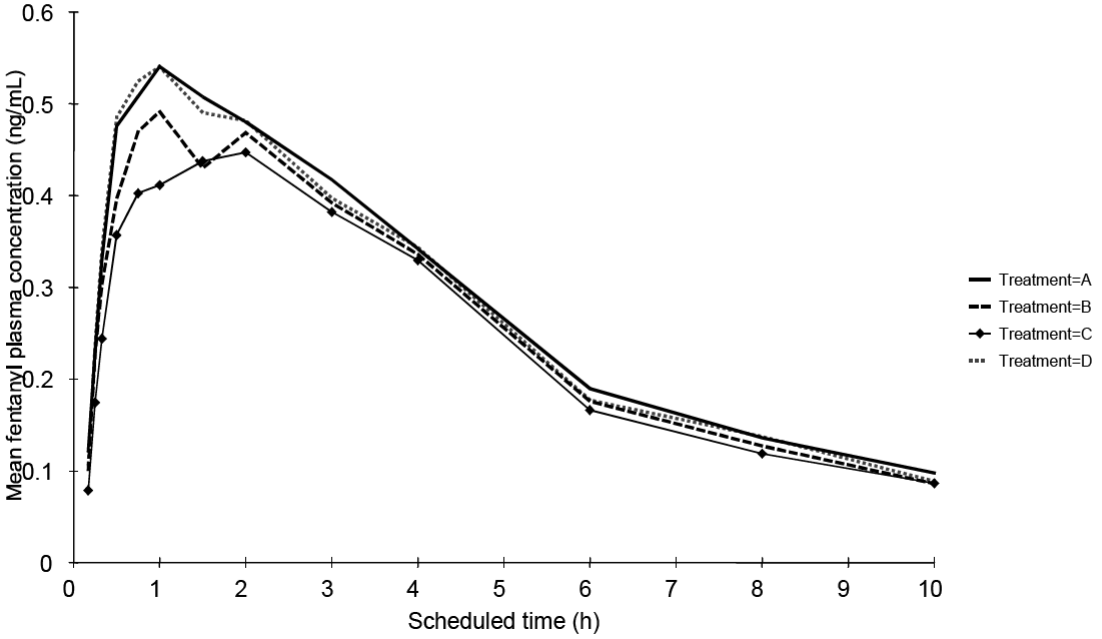
Title of Study: An open randomized four-period crossover study to assess the bioavailability of sublingual fentanyl for the treatment of acute pain

Methodology:
This was a single-centre, open, randomized, four-period crossover trial to evaluate and compare the bioavailability of three new pharmaceutical compositions of sublingual fentanyl 400 µg and a previously developed sublingual fentanyl composition 400 µg. The administrations of the four investigational products were given to the subjects in random order. The administrations were separated by a washout period of at least two days. To protect subjects from opioid-related adverse effects, the opioid antagonist naltrexone hydrochloride was administered 12 hours before each study drug administration.

Results:
Summary: Abstral (b) (4) (fentanyl) Formulations A and B were shown to be bioequivalent to the reference Formulation 1, with 90% CIs for both Cmax and AUC inside 0.80 to 1.25. Formulation A was selected for commercialization.

Mean fentanyl plasma concentration-time curves and pharmacokinetic parameters are depicted in Figure 2–1 and Table 2–1 respectively. The fentanyl plasma concentration profiles obtained after administration of Formulation A and reference Formulation 1 (Treatment D) were super-imposable. Maximal plasma concentrations for Formulations B and C appeared to be lower than for the two other formulations. Fentanyl elimination was similar for all four formulations. Time to reach maximal plasma concentrations was longer for Formulation C, compared to the other formulations.

Figure 2–1 **Mean Fentanyl Plasma Concentration After a Single Sublingual Dose of 400 µg Abstral [(b) (4)] Given as Four Different Formulations (A, B, C and D) (n=16); Study SuF-003**



Formulations A and B were shown to be bioequivalent to the reference Formulation 1 with 90% CIs of the geometric mean of individual test/reference ratios for both Cmax and AUC inside the 0.80 to 1.25 bioequivalence limits. Formulation C was not strictly bioequivalent to the reference formulation, as for Cmax, the lower limit of the 90% CI of the geometric mean of individual test/reference ratios was below 80%. Formulation A was selected for further development.

Table 2–1 **Mean Fentanyl Pharmacokinetic Parameters After Administration of Single Doses of 400 µg Abstral (b) (4) Given as Four Different Formulations to Healthy Male Subjects (n = 16); Study SuF-003**

Mean (CV) Parameters	Abstral (b) (4) Formulations			
	A	B	C	1 (Treatment D) reference
C_{max} (ng/mL)	0.63 (30)	0.61 (31)	0.55 (29)	0.62 (23)
PE	101.2	97.7	87.5	-
(90%CI)[a]	(89.2- 114.7)	(86.1-110.8)	(77.1-99.3)	
$AUC_{(0-10h)}$ (ng.h/mL)	2.79 (25)	2.61 (22)	2.47 (27)	2.75 (25)
PE	101.5	95.7	89.5	-
(90%CI)[a]	(94.6-109.0)	(89.2-102.7)	(83.4-96.1)	-
AUC_{0-inf} (ng.h/mL)	3.40 (38)	3.13 (24)	3.03 (33)	3.31 (30)
PE	102.9	96.0	91.2	-
(90%CI)[a]	(95.8-110 .5)	(89.4-103.2)	(84.9-98.0)	-
T_{max} (min)[b]	52.5 [20-121]	60 [20-121]	75 [15-182]	54 [20-180]

a: PE: geometric mean of the individual ratios of C_{max} and AUC of the test formulations (A, B and C) vs. reference (formulation 1)

b: median (range)

2. EN3267-001, Comparative Bioavailability of Abstral (b) (4) and Actiq

Title of Study: A Randomized, Single-Dose, Four-Period Crossover Study to Compare the Bioavailability of Fentanyl Citrate Sublingual Tablets in Healthy Adult Subjects

Methodology

This study utilized a randomized, single-dose, four-period, open-label, crossover design. Each subject was randomized to one of two dose groups (low or high dose) and one of four treatment sequences. In each of the four treatment periods, subjects received a single oral dose of the assigned treatment (three formulations of EN3267 and Actiq®) in the order and at the dose level specified by the randomization schedule. Treatment periods were separated by a washout period of at least 4 days. During each treatment period, subjects received a total of two oral doses of naltrexone 50 mg at the following time points: in the evening of Day –1 (approximately 12 hours before study medication administration) and on the morning of Day 1 (approximately 2 hours before study medication administration). All study medication was administered by the study nurse. Study participants were housed in the clinical research facility during each treatment period beginning on the evening prior to administration of study medication (Day –1) and extending until collection of the 24-hour blood sample following administration of study medication (Day 2). At each site, the low and high dose groups were to be administered study medication at least 1 hour apart, ensuring that subjects assigned to these respective groups received the assigned dose. Alternatively, the low and high dose groups were to be dosed on different days. All subjects were to return to the clinic between 5 and 7 days after completing the last treatment period for final safety assessments.

Results:

Summary: Abstral (b) (4) Formulations A (sublingual tablets, the proposed commercial product) and B had twice the bioavailability of Actiq (lozenges) with the particular Actiq dosing instructions applied in this study. Abstral (b) (4) Formulations A and B were bioequivalent to Actiq at one-half the dose of Actiq, based on 90% CIs for AUC and Cmax of the combined low and high dose groups, that were contained within the 80 to 125% limits.

Mean fentanyl concentration versus time curves of Abstral (b) (4) Formulation A and Actiq are presented in Figure 2–2 and Figure 2–3.

Figure 2–2 **Mean Plasma Fentanyl Concentrations (0 – 24 Hours Post Dose) After Administration of Single 100 and 800 µg Doses of Abstral (b) (4) Formulation A, and After Single 200 and 1600 µg Dose of Actiq to Healthy Subjects; Study EN3267-001**

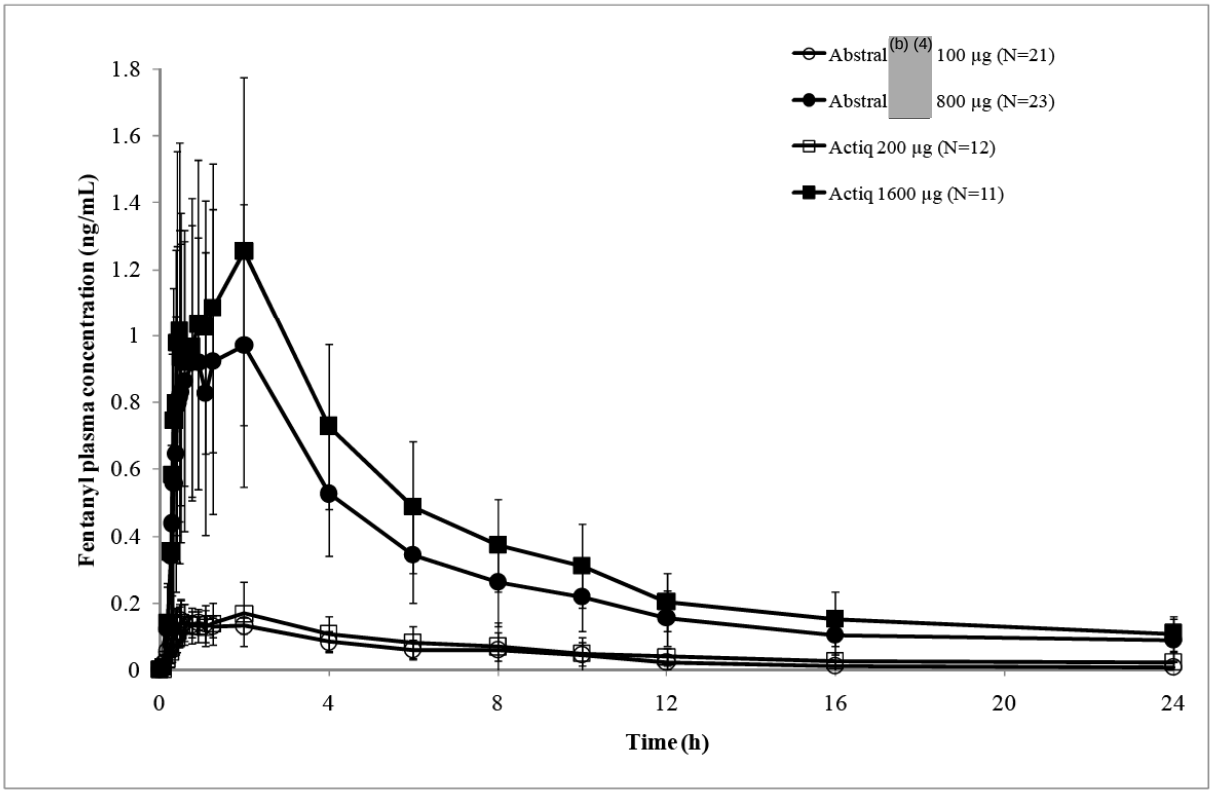
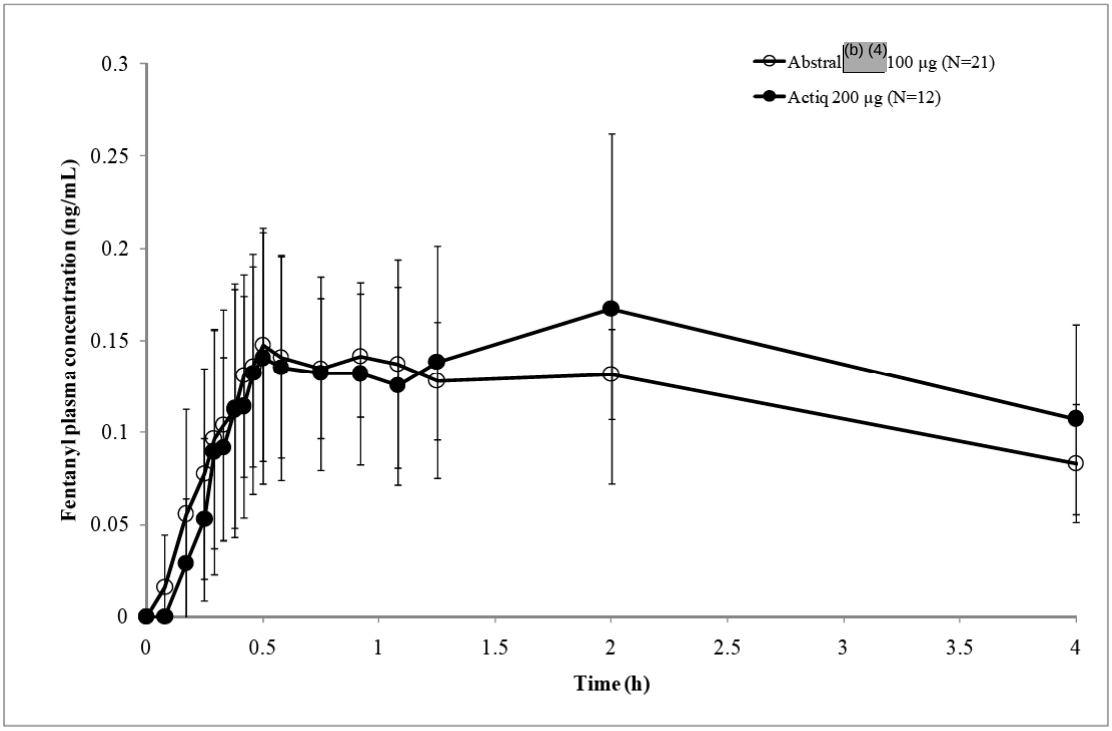
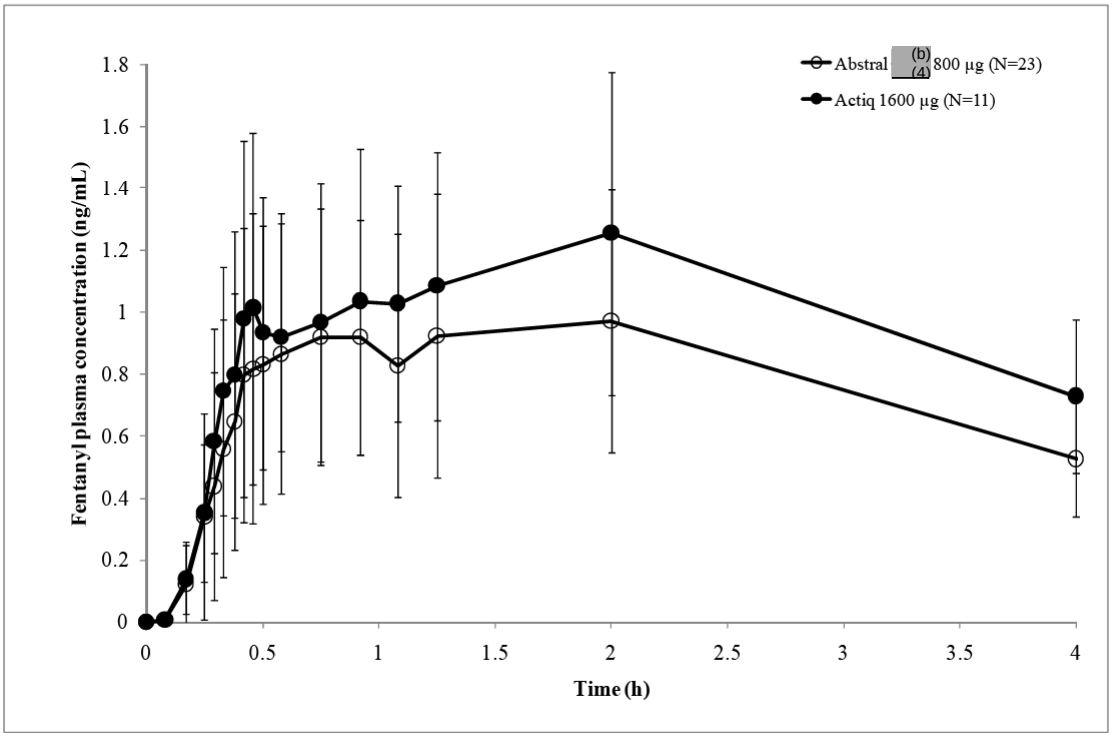


Figure 2–3 **Mean Plasma Fentanyl Concentrations (0 – 4 Hours Post Dose) After Administration of: A) a Single 100 µg Dose of Abstral (b) (4) Formulation A, and a Single 200 µg Dose of Actiq and B) a Single 800 µg Dose of Abstral (b) (4) Formulation A, and a Single 1600 µg Dose of Actiq to Healthy Subjects; Study EN3267-001**





Abstral [(b) (4)] Formulations A (the proposed commercial product) and B had twice the bioavailability of Actiq. The 90% CI of the geometric mean ratios were within the 80.0% to 125.0% limits for both Cmax and AUC, at one-half the dose of Actiq. This indicates that 100 and 800 µg doses of Abstral [(b) (4)] Formulations A and B were bioequivalent to 200 and 1600 µg dose of Actiq, respectively, with the Actiq dosing instructions applied in this study, which were consistent with the approved US label.

3. EN3267-010, Bioequivalence of Abstral [(b) (4)] Manufactured in the United States or Sweden

Study title: An open-label, randomized, single-dose, two-period crossover study to determine the bioequivalence of an EN3267 formulation manufactured in the United States (Novartis) with the same formulation manufactured in Sweden (Orexo) in healthy adult subjects

Study Design:
This study utilized an open-label, randomized, single dose, two-period crossover design in 33 opioid-naïve healthy adults to compare the bioequivalence of 400 µg Abstral [(b) (4)] manufactured by Novartis, United States (Treatment A) with 400 µg Abstral [(b) (4)] manufactured at Orexo, Sweden (Treatment B). Each subject received Treatment A or B in a randomized fashion. The two study periods were separated by a 7-day washout.

Results:
Summary: Abstral [(b) (4)] 400 µg sublingual tablet formulation manufactured in the United States (Novartis) was demonstrated to be bioequivalent to the formulation manufactured in Sweden (Orexo).

Mean fentanyl plasma concentration-time curves and pharmacokinetic parameters are depicted in Figure 2–5 and Table 2–5, respectively.

The mean plasma concentration versus time profiles of both treatments were generally superimposable (Figure 2–5).

Figure 2–5 **Mean (± SD) Plasma Concentration of Fentanyl Versus Time After Administration of a Single Dose of 400 µg Abstral (b) (4) Manufactured in the US and Sweden to Healthy Subjects; Study EN3267-010**

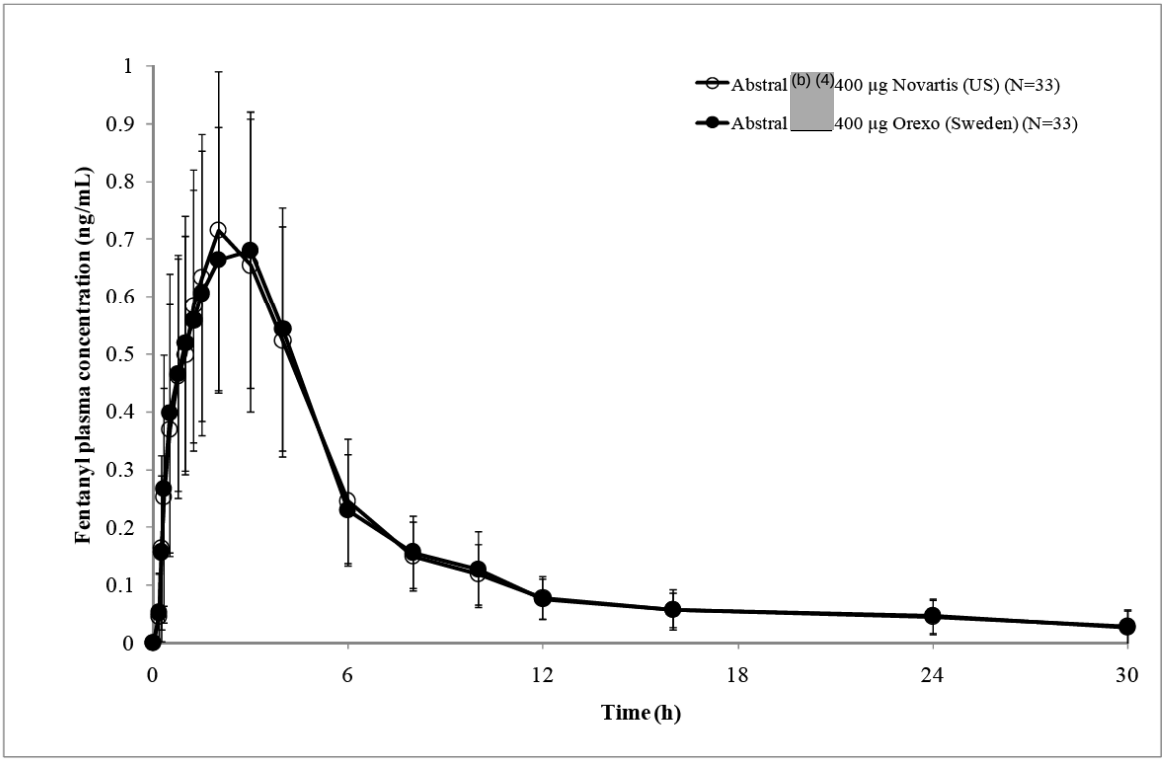


Table 2–5 **Pharmacokinetic Parameters [Mean (%CV)] of Fentanyl (n = 33); Study EN3267-010**

Parameter	Treatment A Novartis (US)	Treatment B Orexo (Sweden)
$AUC_{0\text{-last}}$ (ng.h/mL)	4.689 (36)	4.707 (35)
$AUC_{0\text{-inf}}$ (ng.h/mL)	5.533 (45)[b]	5.312 (39)[c]
C_{max} (ng/mL)	0.807 (34)	0.771 (32)
T_{max} (h)[a]	2.0 [0.50 – 6.00]	2.0 [0.75 – 4.00]
$T_{1/2}$ (h)	11.9 (54)[b]	9.3 (44)[c]

a Median [Min – Max]
b n = 24
c n = 23
Note: Treatment A = Abstral (b) (4) 400 µg sublingual tablets manufactured in the United States.
Treatment B = Abstral (b) (4) 400 µg sublingual tablets manufactured in Sweden

Based on the geometric mean ratio for AUC0-inf, Abstral (b) (4) manufactured in the United States achieved a relative bioavailability of 98.4% compared with the same formulation manufactured in Sweden (Table 2–6). The 90% CIs of the geometric mean ratio were 92% and 105%, which is contained within the interval of 80% to 125% required to establish bioequivalence. The 90% CIs of the geometric mean ratio for AUC0-last and Cmax were also

within the 80% to 125% limits. Differences in median Tmax values were not statistically significant as measured by the Wilcoxon signed rank test.

Table 2–6 Statistical Analysis of Plasma Pharmacokinetic Parameters of Fentanyl – Pharmacokinetic Population; Study EN3267-010

Parameter	Treatment[a]	n	Geometric Least-Square Means	PE[b] (A/B)	90% CI of PE[b] (A/B)
$AUC_{0\text{-inf}}$ (ng.h/mL)	A	24	5.038	0.984	(0.92,1.05)
	B	23	5.120	-	-
$AUC_{0\text{-}\tau}$ (ng.h/mL)	A	33	4.390	0.995	(0.94,1.06)
	B	33	4.413	-	-
C_{max} (ng/mL)	A	33	0.764	1.047	(0.98,1.12)
	B	33	0.729	-	-

a Treatment A = Abstral (b) (4) 400 µg sublingual tablets manufactured in the US
Treatment B = Abstral 400 µg sublingual tablets manufactured in Sweden

b PE: geometric mean of the individual ratios

Note: An ANOVA model was performed on the natural logarithms of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. The model included fixed factors for sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect. Point estimates and 90% CI for differences on the log scale were exponentiated to obtain estimates for the ratios of geometric means on the original scale.

The Abstral (b) (4) 400 µg sublingual tablet formulation manufactured by Novartis, United States (b) (4) used in this study was demonstrated to be bioequivalent with the drug product manufactured at Orexo, Sweden ((b) (4)) with respect to the pharmacokinetic parameters for AUC0-inf (90% CI of 92 - 105%), AUC0-last (90% CI of 94 - 106%) and Cmax (90% CI of 98 - 112%) in healthy subjects administered a single sublingual dose of each formulation. The safety profiles of the two drug products are similar (based on the nature and frequency of adverse events (AEs), clinical laboratory test results, and vital sign measurements). The two single dose administrations of Abstral (b) (4) were well tolerated in these healthy subjects.

4. EN3267-003, Comparison of Bioavailability for a Single Dose of Abstral (b) (4) Given as One, Two, or Four Sublingual Tablets

Study title: An open-label, randomized, single-dose, three-period crossover study to compare the relative bioavailability of EN3267 administered as 1 × 800 µg tablet versus 2 × 400 µg tablets and 4 × 200 µg tablets in healthy adult subjects

Study Design and Objectives:
This study utilized an open-label, randomized, single-dose, three-treatment, three-period crossover design in 30 opioid-naïve healthy adults. The study objective was to compare the bioavailability for Abstral (b) (4) administered as a single 800 µg tablet (Treatment A) with Abstral (b) (4) administered as 2 × 400 µg tablets (Treatment B) and with Abstral (b) (4)

administered as 4 × 200 µg tablets (Treatment C). Each subject was randomized to one of six possible sequences. Each study period was separated by a minimum 7-day washout.

Results:

Summary: Abstral (b) (4) (Formulation A) administered as 2 × 400 µg tablets and as 4 × 200 µg tablets were demonstrated to be bioequivalent to Abstral (b) (4) (Formulation A) administered as 1 × 800 µg tablet.

The mean plasma fentanyl concentration-time curves (0 - 30 hours post dose) (linear and semi logarithmic scale) were similar for the three Abstral (b) (4) treatments used in this study (1 × 800 µg vs. 2 × 400 µg vs. 4 × 200 µg) (Figure 2–6). Pharmacokinetic parameters are given in Table 2–7.

The mean plasma concentration versus time profiles of the three treatments were generally superimposable (Figure 2–6).

Figure 2–6 **Mean (± SD) Plasma Concentration of Fentanyl Versus Time After Administration of a Single Dose of 800 µg Abstral (b) (4) Given as 1 x 800µg, 2 x 400 µg or 4 x 200 µg Tablets to Healthy Subjects: Study EN3267-003**

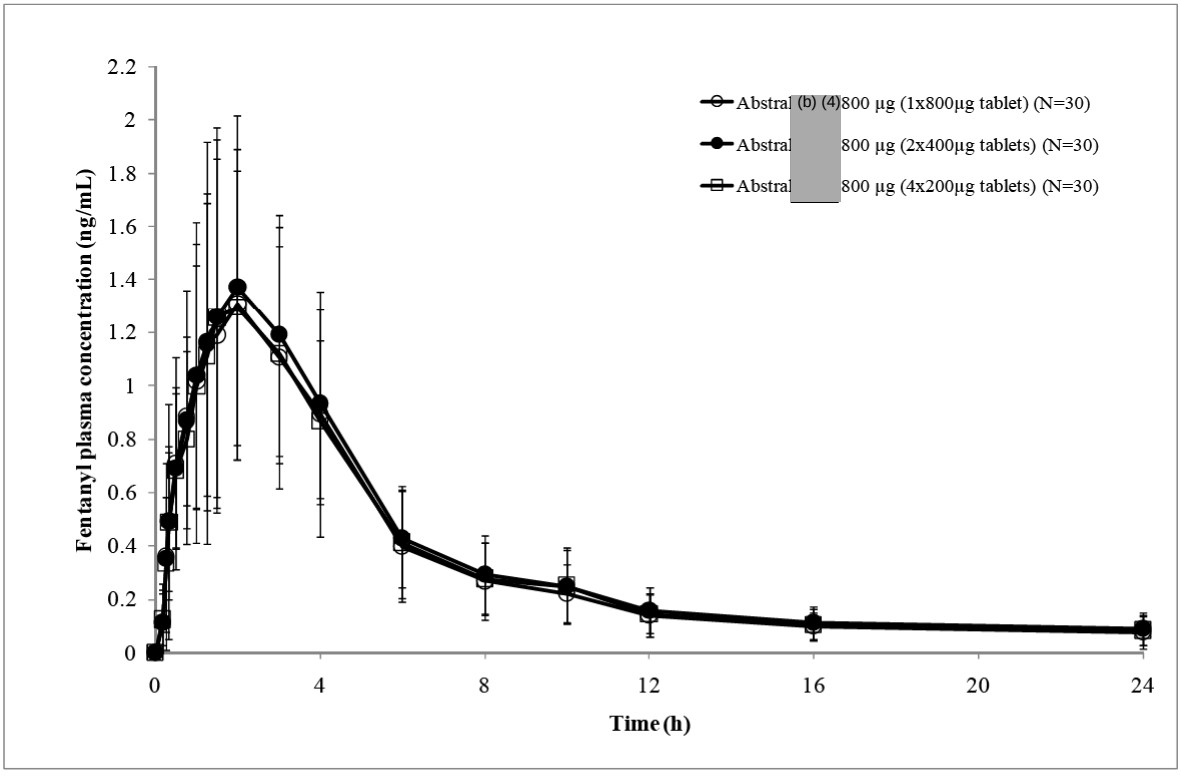


Table 2–7 Pharmacokinetic Parameters [Mean (%CV)] of Fentanyl – Pharmacokinetic Population (n = 30); Study EN3267-003

Parameter	Treatment A Abstral (b) (4) 1 x 800 µg	Treatment B Abstral (b) (4) 2 x 400 µg	Treatment C Abstral (b) (4) 4 x 200 µg
$AUC_{0\text{-last}}$ (ng.h/mL)	8.359 (45)	8.971 (41)	8.482 (39)
$AUC_{0\text{-inf}}$ (ng.h/mL)	8.128 (33)[a]	9.118 (39)	9.218 (40)[a]
C_{max} (ng/mL)	1.533 (50)	1.515 (46)	1.485 (40)
T_{max} (h)[c]	2.0 [0.33 – 4.00]	2.0 [0.33 – 3.03]	2.0 [0.25 – 4.00]
$T_{1/2}$ (h)	10.8 (27)[a]	11.6 (21)[b]	11.2 (32)[a]

a n = 19

b n = 22

c Median [Min – Max]

Treatment: A = Abstral (b) (4) 1 x 800 µg tablet; B = Abstral (b) (4) 2 x 400 µg tablets; C = Abstral (b) (4) 4 x 200 µg tablets

Based on the PE for AUC0-inf, Abstral (b) (4) administered as 2 × 400 µg tablets (Treatment B) achieved a relative bioavailability of 106.9% compared with Abstral (b) (4) administered as a single 800 µg tablet (Treatment A)(Table 2–8). The 90% CI for the geometric mean ratio was 98% to 116%, which is contained within the interval of 80% to 125%, and indicates equivalent bioavailability. Bioequivalence was also demonstrated for AUC0-last and Cmax.

Table 2–8 Statistical Analysis of Plasma Pharmacokinetic Parameters of Fentanyl; Study EN3267-003

Parameter	Treatment[a]	n	Geometric Means	PE[b] [(B or C)/A]	90% CI of PE[b] [(B or C)/A]
$AUC_{0\text{-inf}}$ (ng.h/mL)	B	22	8.457	1.069	(0.98,1.16)
	C	19	8.387	1.060	(0.97,1.16)
	A	19	7.913	-	-
$AUC_{0\text{-last}}$ (ng.h/mL)	B	30	8.169	1.086	(1.01,1.16)
	C	30	7.769	10.33	(0.96,1.11)
	A	30	7.525	-	-
C_{max} (ng/mL)	B	30	1.364	1.002	(0.92,1.10)
	C	30	1.357	0.997	(0.91,1.09)
	A	30	1.361	-	-

a A = Abstral (b) (4) 1 x 800 µg tablet

B = Abstral (b) (4) 2 x 400 µg tablets

C = Abstral (b) (4) 4 x 200 µg tablets

b PE: ratio of geometric means

Note: An ANOVA model was performed on the natural logarithms of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. The model included fixed factors for sequence, period, and treatment, and subject nested within sequence as a random factor. Point estimates and 90% CI for differences on the log scale were exponentiated to obtain estimates for the ratios of geometric means on the original scale.

Similar pharmacokinetic results were obtained when Abstral (b) (4) administered as 4 × 200 µg tablets (Treatment C) was compared with Abstral (b) (4) administered as a single 800 µg tablet (Treatment A). The 90% CIs of the geometric mean ratios for AUC0-inf, AUC0-last and Cmax were all within the 80% to 125% limits, indicating bioequivalence. The relative bioavailability compared to the single 800 µg tablet was 106.0% based on the geometric mean ratio.

There were no significant differences in median Tmax values (2.0 hours for all treatments). The ranges of individual values were also similar.

Based on these results Abstral (b) (4) administered as 2 × 400 µg tablets and as 4 × 200 µg tablets is bioequivalent with Abstral (b) (4) administered as 1 × 800 µg tablet in healthy subjects administered a single sublingual dose of each treatment. The safety profiles of the three drug products are similar (based on the nature and frequency of AEs, clinical laboratory test results, and vital sign measurements). The three single dose administrations of Abstral (b) (4), given with a naltrexone blockade, were well tolerated in these healthy subjects.

5. EN3267-012, Absolute and Relative Bioavailability of Four Different Fentanyl Formulations

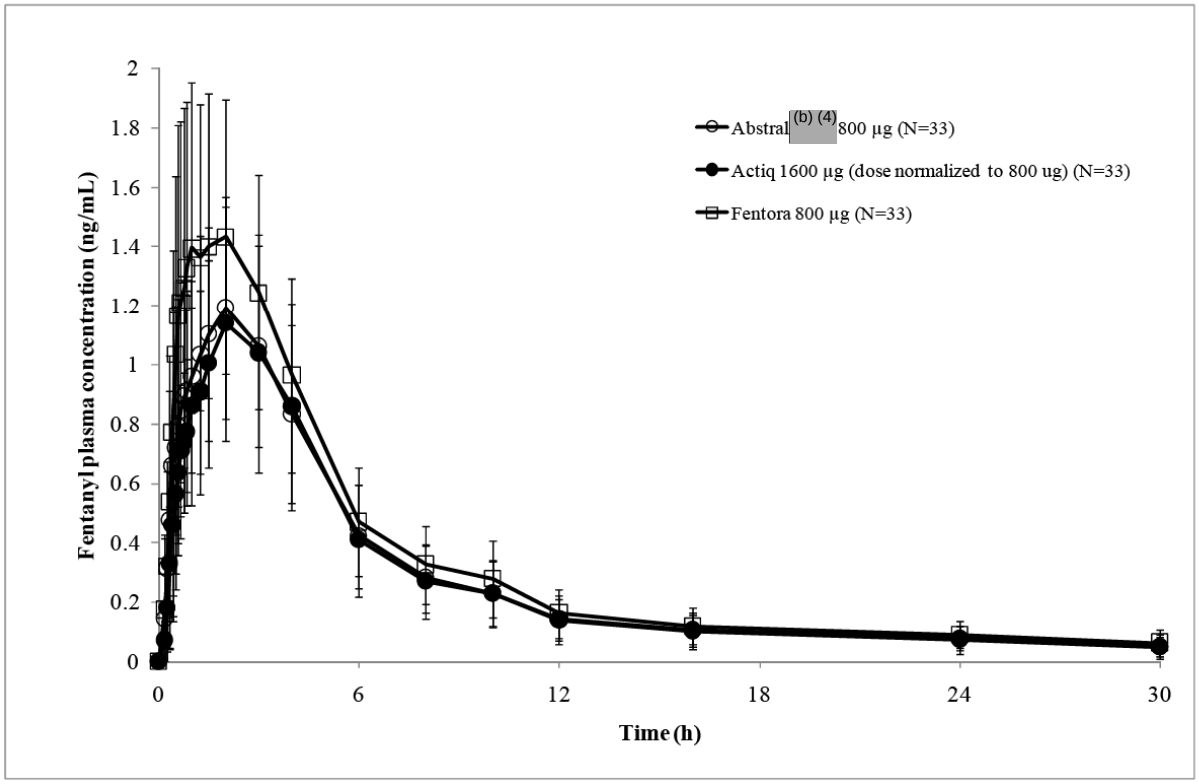
Study title: An open-label, randomized, four-period crossover study to compare the single-dose absolute and relative bioavailability of four formulations of fentanyl (EN3267, fentora®, actiq® and fentanyl citrate injection) in healthy adult subjects

Study Design:
This study utilized an open-label, randomized, single-dose, 4-treatment, 4-period crossover design. Based on the treatment sequence, each subject received either Treatment A (EN3267, 1 × 800 µg fentanyl citrate sublingual tablet), Treatment B (Fentora, 1 × 800 µg fentanyl buccal tablet), Treatment C (Actiq, 1 × 1600 µg oral transmucosal fentanyl citrate) or Treatment D (fentanyl citrate injection, 600 µg infused over 30 minutes) in Period 1 and the alternate 3 treatments in Period 2, Period 3 and Period 4, respectively. Each study period was separated by a minimum 4-day washout.

Results:
Summary: Absolute bioavailability is similar for Abstral (b) (4) and Actiq (54% and 52%, respectively), when the Actiq lozenge is used up completely, and higher for Fentora (68%). Bioequivalence was demonstrated for Abstral (b) (4) and Actiq, based on dose normalized AUC and Cmax.

Mean fentanyl plasma concentration-time curves (for Abstral (b) (4), Fentora and Actiq only) and dose-normalized pharmacokinetic parameters are depicted in Figure 2–7 and Table 2–9, respectively.

Figure 2–7 **Mean (± SD) Plasma Concentration of Fentanyl Versus Time After Administration of a Single Dose of 800 µg Abstral (b) (4), 800 µg Fentora or 1600 µg Actiq (Dose-Normalized to 800 µg) to Healthy Subjects; Study EN3267-012**



After dose normalization, the mean plasma concentration versus time profiles of Abstral (b) (4) and Actiq were generally superimposable (Figure 2–7).

Table 2–9 Mean (%CV) of Dose-Normalized Plasma Pharmacokinetic Parameters of Fentanyl; Study EN3267-012

Parameter	Treatment A Abstral (b) (4) 800 µg sublingual	Treatment B Fentora 800 µg buccal tablet	Treatment C Actiq 1600 µg oral trans-mucosal lozenge	Treatment D Fentanyl citrate 600 µg iv
$AUC_{0\text{-}last}$ (ng.h/mL/µg)	0.010 (32)	0.012 (33)	0.010 (38)	0.019 (19)
$AUC_{0\text{-}inf}$ (ng.h/mL/µg)	0.011 (33)[a]	0.014 (37)[a]	0.011 (36)[b]	0.020 (24)[c]
C_{max} (ng/mL/µg)	0.002 (35)	0.002 (35)	0.002 (35)	0.006 (30)
T_{max} (h)[d,e]	2.0 [0.42 – 4.00]	1.5 [0.25 – 3.10]	2.0 [0.50 – 4.12]	0.6 [0.33 – 0.83]
$T_{1/2}$ (h)[d]	11.7 (16)[a]	12.6 (22)[a]	11.5 (22)[b]	12.2 (17)[c]

a n = 23
b n = 26
c n = 24
d Values were not dose-normalized
e Median [Min – Max]

Treatment: A = Abstral (b) (4) fentanyl citrate (1 x 800 µg sublingual tablet); B =Fentora (1 x 800 µg buccal tablet); C =Actiq (1x1600 µg oral transmucosal lozenge); D = Fentanyl citrate injection (600 µg infused over 30 minutes)

Based on the statistical analysis results, the absolute bioavailability as measured by the geometric mean ratio for dose-normalized AUC0-inf and AUC0-t were approximately 54% (90% CI of 50% - 59%) and 53% (90% CI of 49% - 56%), respectively for Abstral (b) (4) (Treatment A); 68% (90% CI of 62% - 73%) and 64% (90% CI of 60% - 68%), respectively for Fentora (Treatment B); and 52% (90% CI of 48% - 56%) and 50% (90% CI of 47% - 54%), respectively for Actiq (Treatment C) each compared with IV fentanyl (Treatment D).

For Abstral (b) (4) compared with Actiq, the relative bioavailability as measured by the geometric mean ratio for dose-normalized AUC0-inf, AUC0-last, and Cmax were approximately 105% (90% CI of 97% - 113%), 105% (90% CI of 98% - 112%), and 107% (90% CI of 96% - 118%), respectively (Table 2–10). The 90% CIs for the Abstral (b) (4)/Actiq geometric mean ratios were contained within the interval of 80% to 125% typically used to establish bioequivalence.
For Abstral (b) (4) compared with Fentora, the relative bioavailability as measured by the geometric mean ratio for dose-normalized AUC0-inf, AUC0-last, and Cmax were approximately 80% (90% CI of 74% - 87%), 82% (90% CI of 77% - 88%), and 77% (90% CI of 70% - 86%), respectively. The 90% CIs were not contained within the interval of 80% to 125%.

For Fentora compared with Actiq, the relative extent and rate of absorption as measured by the geometric mean ratio for dose-normalized AUC0-inf, AUC0-last, and Cmax were approximately 130% (90% CI of 120% - 141%), 127% (90% CI of 119% - 136%), and 138% (90% CI of 124% - 153%). The 90% CIs for the B/C point estimates for the relative extent and rate of absorption values were not contained within the interval of 80% to 125%. Differences in median Tmax values for Abstral (b) (4), Fentora and Actiq (2.0, 1.5, and 2.0 hours, respectively) each compared

with IV fentanyl citrate (0.6 hours) were statistically significant as measured by the Hodge-Lehmann method, which is to be expected when comparing transmucosal formulations to IV dosing. No statistically significant differences in median Tmax were observed between Abstral (b) (4) and either Fentora or Actiq.

The safety profiles of the four fentanyl treatments were similar (based on the nature and frequency of AEs, clinical laboratory test results, and vital signs measurements). The four single-dose administrations of fentanyl were well tolerated in these healthy subjects.

Table 2–10 Statistical analysis of Dose-Normalized Plasma Pharmacokinetics Parameters of Fentanyl; Study EN3267-012

Parameter	Treatment[a]	N	Geometric means	PE (90% CI): [(A, B or C)/D]	PE (90% CI): [(A or B)/C]	PE (90% CI): [A/B]
$AUC_{0\text{-last}}$ (ng.h/mL/µg)	A	33	0.010	0.5270 (0.4927, 0.5637)	1.0488 (0.9798, 1.1226)	0.8234 (0.7693, 0.8813)
	B	33	0.012	0.6400 (0.5983, 0.6847)	1.2737 (1.1904, 1.3629)	-
	C	33	0.009	0.5025 (0.4697, 0.5375)	-	-
	D	34	0.018	-	-	-
$AUC_{0\text{-inf}}$ (ng.h/mL/µg)	A	23	0.011	0.5423 (0.5007, 0.5873)	1.0467 (0.9669, 1.1330)	0.8034 (0.7403, 0.8718)
	B	23	0.014	0.6750 (0.6238, 0.7304)	1.3028 (1.2029, 1.4111)	-
	C	26	0.011	0.5181 (0.4794, 0.5600)	-	-
	D	25	0.020	-	-	-
C_{max} (ng/mL/µg)	A	33	0.002	0.2814(0.2543, 0.3114)	1.0655 (0.9619, 1.1803)	0.7734 (0.6982, 0.8566)
	B	33	0.002	0.3639 (0.3288, 0.4028)	1.3777 (1.2443, 1.5254)	-
	C	33	0.002	0.2641 (0.2387, 0.2923)	-	-
	D	34	0.006	-	-	-

a A = Abstral (b) (4) (1 x 800 µg sublingual tablet)
B = Fentora (1 x 800 µg buccal tablet)
C = Actiq (1x1600 µg oral transmucosal lozenge)
D = Fentanyl citrate injection (600 µg infused over 30 minutes)

Note: An ANOVA model was performed on the natural logarithms of $AUC_{0\text{-last}}$, dose-normalized $AUC_{0\text{-inf}}$, and dose-normalized C_{max}. The model included fixed factors for sequence, period, and treatment, and subject nested within sequence as a random effect. Point estimates and 90% CI for differences on the log scale were exponentiated to obtain estimates for the ratios of geometric means on the original scale.

6. EN3267-013, Comparison of the Relative Bioavailability and Dose Proportionality of 800 µg and 1600 µg Doses of Abstral (b) (4) and Actiq (OTFC)

Study title: An open-label, randomized, four-period crossover study to compare the relative bioavailability and dose proportionality of 800 µg and 1600 µg doses of en3267 (fentanyl citrate) sublingual tablets and actiq® (oral transmucosal fentanyl citrate) lozenges in healthy adult subjects

Methodology:
This study utilized an open-label, randomized, single-dose, 4-treatment, 4-period crossover design. Based on the treatment sequence, each subject received either Treatment A (EN3267 fentanyl citrate, 1 × 800-µg sublingual tablet), Treatment B (EN3267 fentanyl citrate, 2 × 800-µg sublingual tablet), Treatment C (Actiq, 1 × 800-µg oral transmucosal lozenge), or Treatment D (Actiq, 1 × 1600-µg oral transmucosal lozenge) in Period 1 and the alternate three treatments in Period 2, Period 3, and Period 4, respectively. Each study period was separated by a minimum 4-day washout. Study participants were housed in a clinical research facility during each study period, beginning on the evening prior to administration of fentanyl (Day -1) and extending until

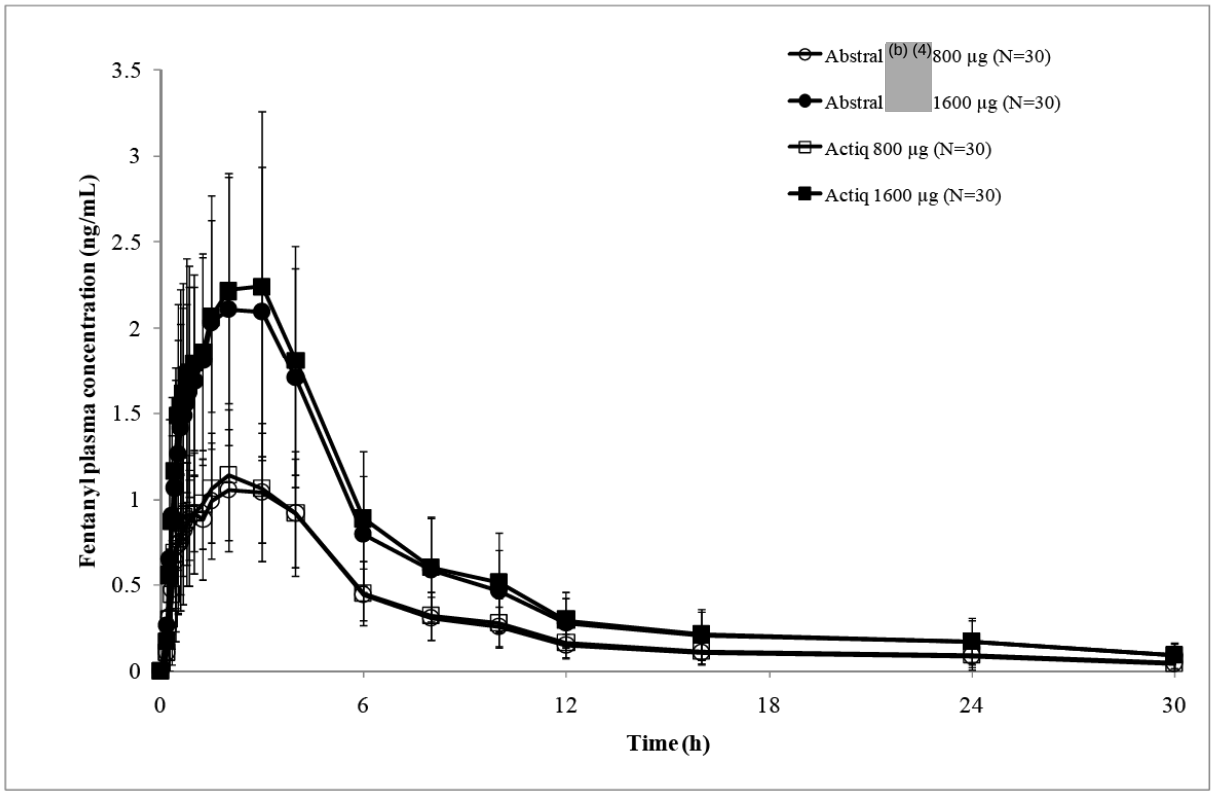
completion of all study evaluations and collection of the 30-hour post-dose blood sample (Day 2). To lessen the potential for opioidrelated adverse events (AEs), the opioid antagonist naltrexone hydrochloride (HCl) was administered orally 12 hours before and 2 hours before each fentanyl dose administration.

Results:

Summary: The relative bioavailability, as measured by the geometric mean ratio of AUC0-t, AUC0-inf, and Cmax for Abstral (b) (4) *given as 1 x 800 µg and 2 x 800 µg sublingual tablets is similar to the corresponding measures for Actiq given as 1 x 800 µg and 1 x 1600 µg oral transmucosal lozenge, when the Actiq lozenge was completely used up.*

Mean fentanyl plasma concentration-time curves and pharmacokinetic parameters are depicted in Figure 2–8 and Table 2–11, respectively.

Figure 2–8 Mean (± SD) Plasma Concentration of Fentanyl Versus Time by Treatment; Study EN3267-013



For both dose levels, the mean plasma concentration versus time profiles were similar for Abstral (b) (4) and Actiq (Figure 2–8).

Table 2–11 Mean (%CV) of Plasma Pharmacokinetic Parameters of Fentanyl (n = 30); Study EN3267-013

Parameter	Treatment A Abstral (b) (4) 1 x 800 µg	Treatment B Abstral (b) (4) 2 x 800 µg	Treatment C Actiq 1 x 800 µg	Treatment D Actiq 1 x 1600 µg
$AUC_{0\text{-last}}$ (ng.h/mL)	8.366 (36)	16.021 (38)	8.705 (37)	16.918 (39)
$AUC_{0\text{-30}}$ (ng.h/mL)	0.162 (84)	0.303 (79)[a]	0.158 (69)	0.292 (47)
$AUC_{0\text{-inf}}$ (ng.h/mL)	9.407 (25)[b]	16.356 (32)[c]	9.696 (32)[c]	16.573 (32)[d]
C_{max} (ng/mL)	1.332 (29)	2.537 (35)	1.365 (28)	2.661 (33)
T_{max} (h)[e]	1.98 [0.33, 4.00]	2.00 [0.25, 4.00]	2.00 [0.43, 4.00]	2.00 [0.50, 3.07]
$T_{1/2}$ (h)	11.27 (24)[b]	10.51 (24)[c]	10.80 (23)[c]	11.15 (18)[d]

a n = 29
b n = 21
c n = 22
d n = 25
e Median [minimum, maximum]
Treatment A = Abstral (b) (4) (1 x 800 µg sublingual tablet), Treatment B = Abstral (b) (4) (2 x 800 µg sublingual tablets), Treatment C = Actiq (1 x 800 µg oral transmucosal lozenge), Treatment D = Actiq (1 x 1600 µg oral transmucosal lozenge)

When the Actiq lozenge is used up completely, bioequivalence was shown for Abstral (b) (4) and Actiq. For the 800 µg dose level, the Abstral (b) (4) /Actiq geometric mean ratios for AUC0-last, AUC0-inf, and Cmax were 97% (90% CI of 91% - 103%), 102% (90% CI of 95% - 109%), and 97% (90% CI of 89% - 106%) respectively (Table 2–12). For the 1600 µg dose level similar results were obtained. The Abstral (b) (4) /Actiq geometric mean ratios for AUC0-last, AUC0-inf, and Cmax were 95% (90% CI of 89% - 101%), 100% (90% CI of 94% - 107%), and 95% (90% CI of 87% - 103%), respectively.

Median Tmax values, as well as the ranges of individual values, were similar for Abstral (b) (4) and Actiq.

Table 2–12 Statistical Analysis of Plasma Pharmacokinetic Parameters of Fentanyl: Study EN3267-013

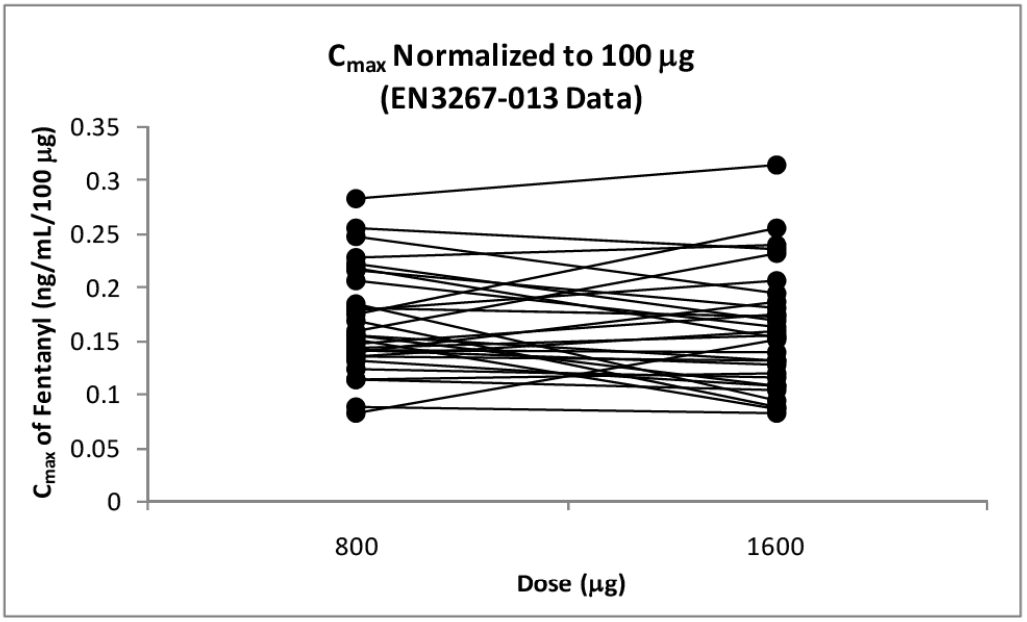
Parameter	Treatment[a]	n	Geometric Means	PE (90% CI): [A/C]	PE (90% CI): [B/D]
$AUC_{0\text{-last}}$ (ng.h/mL)	A	30	7.894	0.9651 (0.9085, 1.0253)	0.9468 (0.8912, 1.0058)
	B	30	14.986	-	-
	C	30	8.180	-	-
	D	30	15.828	-	-
$AUC_{0\text{-}15}$ (ng.h/mL)	A	30	0.011	0.7040 (0.5005, 0.9902)	0.8887 (0.6315, 1.2506)
	B	29	0.032	-	-
	C	30	0.015	-	-
	D	30	0.036	-	-
$AUC_{0\text{-}30}$ (ng.h/mL)	A	30	0.121	0.9195 (0.7706, 1.0971)	0.9261 (0.7745, 1.1074)
	B	29	0.245	-	-
	C	30	0.131	-	-
	D	30	0.265	-	-
$AUC_{0\text{-inf}}$ (ng.h/mL)	A	21	8.926	1.0223 (0.9548, 1.0946)	1.0006 (0.9376, 1.0678)
	B	22	16.281	-	-
	C	22	8.731	-	-
	D	25	16.271	-	-
C_{max} (ng/mL)	A	30	1.277	0.9705 (0.8912, 1.0568)	0.9465 (0.8692, 1.0307)
	B	30	2.395	-	-
	C	30	1.316	-	-
	D	30	2.531	-	-

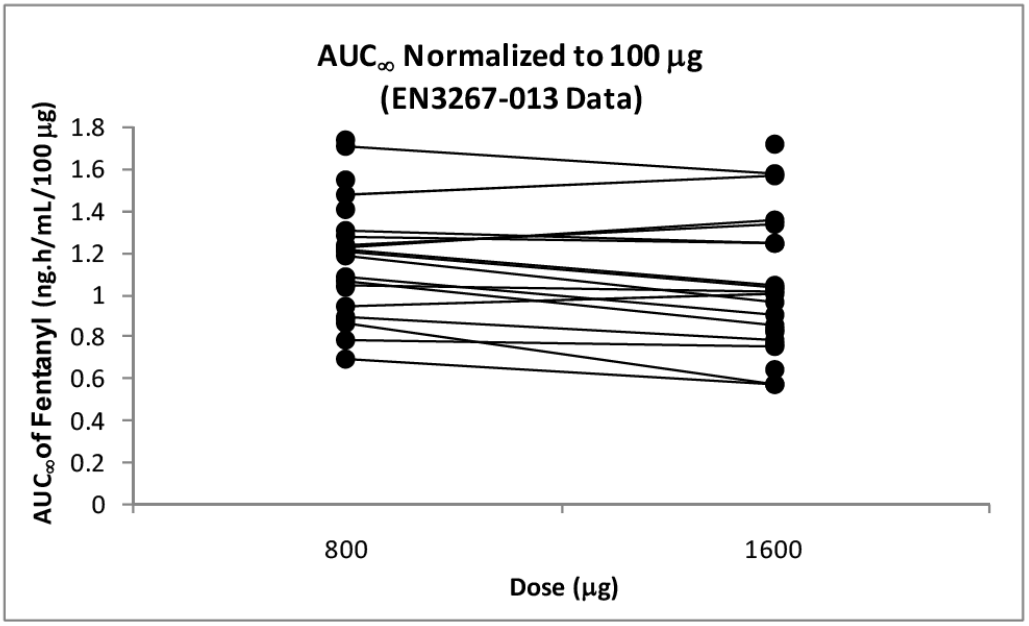
a Treatment A = Abstral (b) (4) (1 x 800 µg sublingual tablet), Treatment B = Abstral (b) (4) (2 x 800 µg sublingual tablet), Treatment C = Actiq (1 x 800 µg oral transmucosal lozenge), Treatment D = Actiq (1 x 1600 µg oral transmucosal lozenge)

Note: An ANOVA model was performed on the natural logarithms of $AUC_{0\text{-last}}$, $AUC_{0\text{-}15}$, $AUC_{0\text{-}30}$ $AUC_{0\text{-inf}}$, and C_{max}. The model included fixed factors for sequence, period, and treatment, and subject nested within sequence as a random factor. Point estimates and 90% CI for differences on the log scale were exponentiated to obtain estimates for the ratios of geometric means on the original scale

Dose normalized individual Cmax and AUC values for Abstral (b) (4) are shown per dose level in Figure 2–9. The individual dose normalized Cmax and AUC values were in the same range for the 800 and 1600 µg dose levels, indicating dose proportionality. Actiq is recognized as having dose proportional pharmacokinetics and the equivalency of Abstral (b) (4) and Actiq Cmax, AUC0-last, and AUC0-inf, also demonstrates that Abstral (b) (4) has dose proportional pharmacokinetics.

Figure 2–9 **Individual Dose Normalized C_{max} and $AUC_{0\text{-}inf}$ Values per Dose Level after Administration of a Single Dose of Abstral (b) (4); Study EN3267-013**





The pharmacokinetic results in healthy adult subjects show that, when the Actiq lozenge is used up completely, the relative bioavailability, as measured by the geometric mean ratio of AUC0-last, AUC0-inf, and Cmax for Abstral (b) (4) fentanyl citrate given as 1 × 800 µg sublingual tablet is similar to the corresponding measures for Actiq given as 1 × 800 µg oral transmucosal lozenge, and that for Abstral (b) (4) fentanyl citrate given as 2 × 800 µg sublingual tablets is similar to the corresponding measures for Actiq given as 1 × 1600 µg oral transmucosal

lozenge. The pharmacokinetics of Abstral [redacted] at single doses of 1 × 800 µg and 2 × 800 µg are dose proportional.

The safety profiles of the four fentanyl treatments are similar (based on the nature and frequency of AEs, clinical laboratory test results, and vital signs measurements). The four single-dose administrations of fentanyl were well tolerated in these healthy subjects.

7. EN3267-004, Bioequivalence of Abstral [redacted] Manufactured in the United States or Sweden

Study title: An open-label, randomized, single-dose, two-period crossover study to determine the bioequivalence of an EN3267 formulation manufactured in the United States with the same formulation manufactured in Sweden in healthy adult subjects

Methodology:
This study utilized an open-label, randomized, single-dose, two-period crossover design. Each subject was randomized to one of two sequences (AB or BA). Based on treatment sequence, each subject received Treatment A or B in Period 1 and the alternative treatment in Period 2. The two study periods were separated by a 7-day washout. Study participants were housed in a clinical research facility during each study period, beginning on the evening prior to administration of EN3267 study medication (Day –1) and extending until completion of all study evaluations and the collection of the 24-hour blood sample following administration of EN3267 study medication (Day 2). To protect subjects from potential opioid-related adverse events (AEs), the opioid antagonist naltrexone hydrochloride (HCl) was administered orally 12 hours before and again 2 hours before each EN3267 dose administration.

Results:
Summary: Abstral [redacted] 400 µg sublingual tablet formulation manufactured by Novartis in the United States [redacted] was not quantitatively identical to the formulation manufactured by Orexo in Sweden [redacted] The difference [redacted] between the two sites explains the lack of bioequivalence. The product manufactured by Novartis [redacted] used in this study was not used in further studies.

Bioequivalence could not be shown for the Novartis and Orexo product as 90% CIs of AUC0-inf and Cmax were not contained within the 80% to 125% interval required to establish bioequivalence. Differences in median Tmax values were not statistically significant.

Comparative quantitative assessment of the Abstral [redacted] drug products used in this study revealed that the fentanyl content of the Novartis drug product was [redacted] than that of the Orexo drug product, which may be explained by the differences [redacted] used at the manufacturing sites. This in turn may explain the lack of bioequivalence demonstrated in this study.

8. Study 2246-EU-001; Safety, Tolerability and Pharmacokinetics of a Single Sublingual Dose of Abstral [redacted] in Healthy Male Japanese and Caucasian Subjects

Title of Study:
A Phase I, Single-Centre, Ascending Single Dose Study to Determine the Safety And Tolerability Of Sublingual KW-2246 Tablets And To Investigate The Pharmacokinetic Profiles In Japanese And Caucasian Volunteers

To investigate the pharmacokinetic profiles of fentanyl citrate and its metabolite, norfentanyl, when given as a sublingual KW-2246 tablet in healthy male Japanese and Caucasian volunteers.

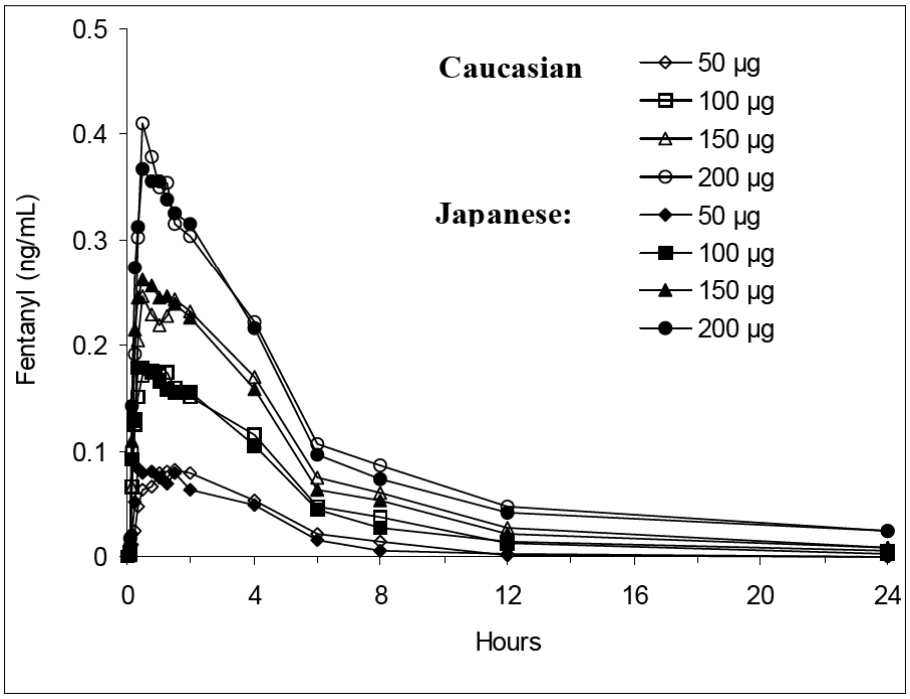
Methodology:
This was a single centre study conducted in an open label, ascending single dose manner. Each subject received a single dose of the investigational product under fasting conditions on the morning of Day 1 of each of four study periods.

Results:
Summary: Fentanyl C_{max} and AUC increased proportional to the dose. No statistically significant differences in fentanyl pharmacokinetic parameters after single Abstral (b) (4) *dosing were observed between healthy Caucasian and Japanese male subjects were observed.*

Mean fentanyl concentration versus time curves are presented in Figure 2–1 and Figure 2–2 and pharmacokinetic parameters are given in Table 2–1 for all 20 healthy male subjects combined.

No difference was observed in plasma fentanyl profiles between Caucasian and Japanese healthy male subjects.

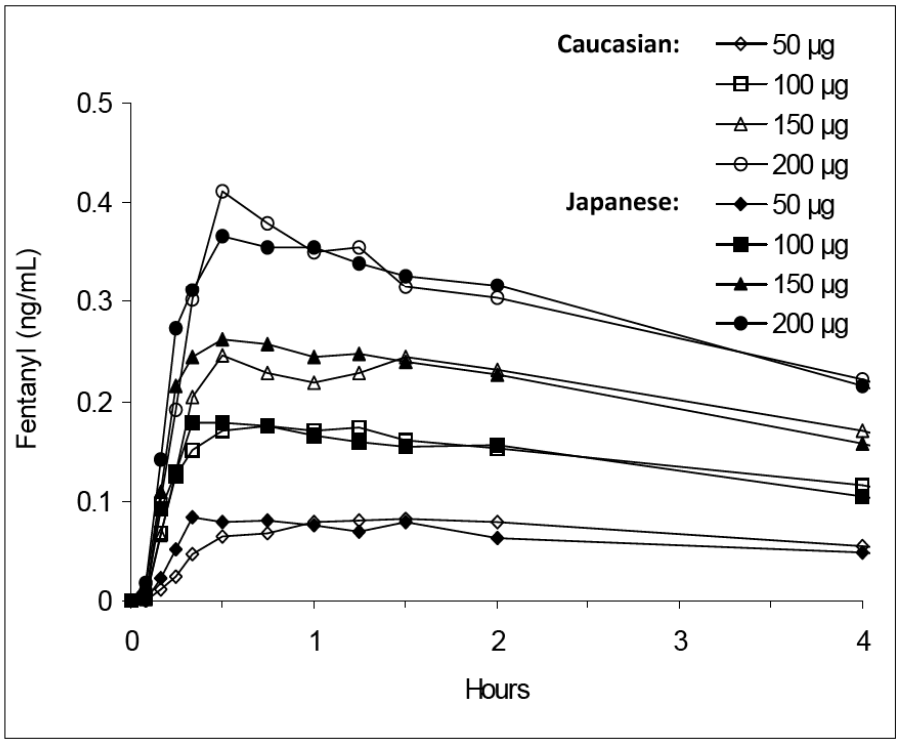
Figure 2–1 **Plasma Fentanyl Concentration Versus Time After Administration of Single Doses of 50 µg, 100 µg, 150 µg and 200 µg Abstral (b) (4) to Healthy Caucasian and Japanese Male Subjects (n = 10 for Each Ethnic Group) (Study 2246-EU-001)**



After a single Abstral (b) (4) dose, quantifiable fentanyl concentrations were obtained as early as 5 minutes after dosing. Mean fentanyl plasma concentrations reached a maximum 30 minutes post-dose and remained close to maximum levels up to 120 minutes (Figure 2–2). Plasma fentanyl concentrations decreased according to a bi-exponential decay.

Overall mean pharmacokinetic parameters are given in Table 2–1.

Figure 2–2 **Mean Plasma Fentanyl Concentration Over 4 Hours After Administration of Single Doses of 50 µg, 100 µg, 150 µg and 200 µg Abstral (b) (4) to Healthy Male Subjects (n = 10 for Each Ethnic Group) (Study 2246-EU-001)**



Median Tmax was independent of the dose. For Cmax and AUC0-inf % CV was in the range of 30% and 50% respectively. Mean T1/2 values increased with dose, most likely due to underestimation at the lower dose levels. At higher dose levels plasma concentrations above the limit of quantification (LOQ) can be obtained for a longer period of time, allowing a more accurate determination of T1/2. Fentanyl pharmacokinetic parameters after single Abstral (b) (4) dosing in healthy Caucasian and Japanese male subjects were not statistically different.

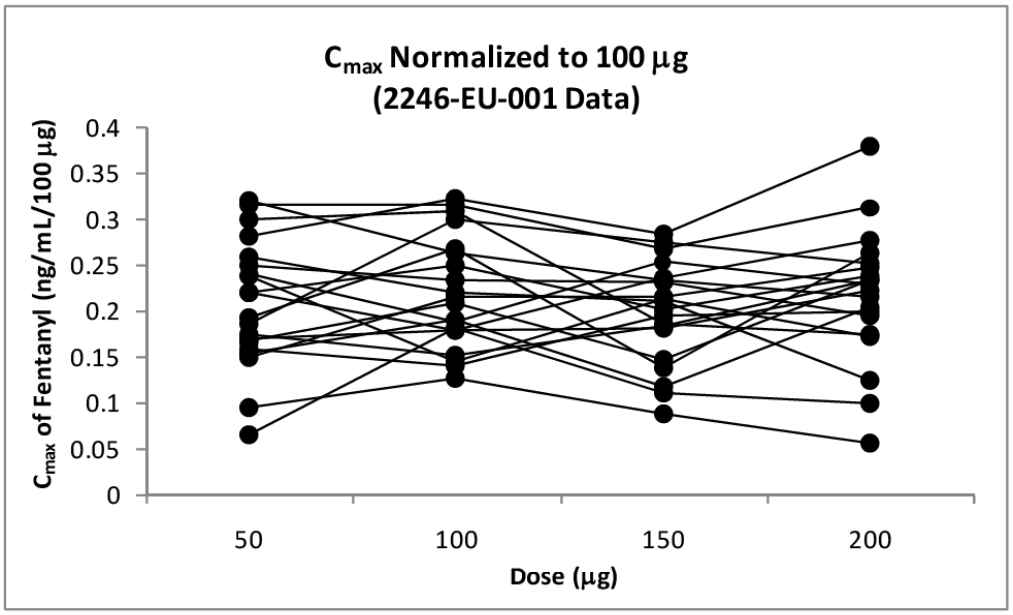
Table 2–1 Fentanyl Pharmacokinetic Parameters After Single Doses of Abstral [redacted] in Healthy Male Subjects (Mean (CV%) – n = 10 for Each Ethnic Group) (Study 2246-EU-001)

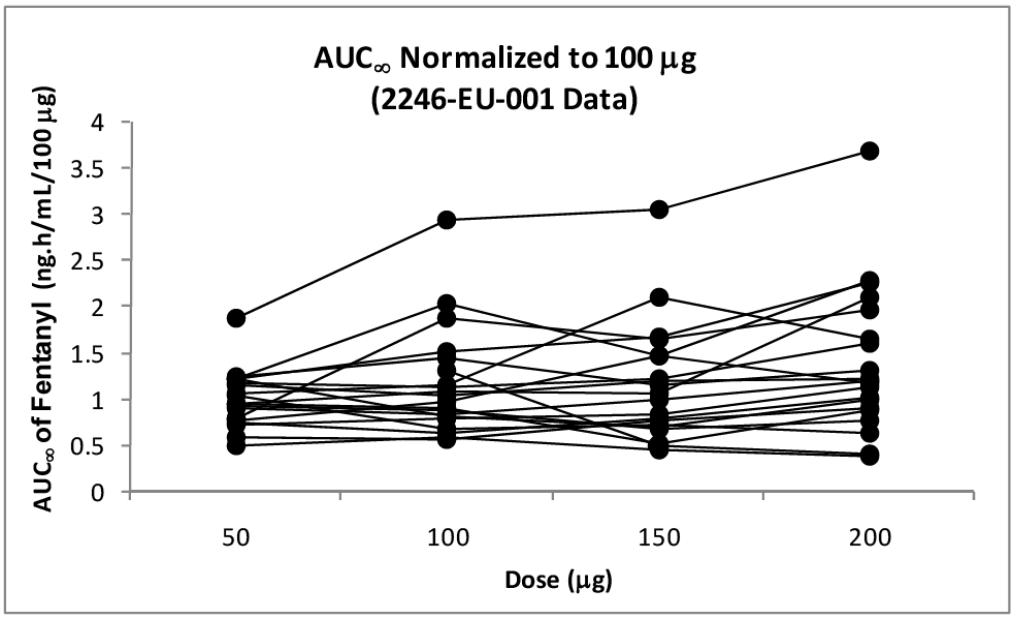
Parameter	Unit	Abstral [redacted] dose			
		50 µg	100 µg	150 µg	200 µg
T_{first} [a]	(min)	15 [10-30]	10 [5-30]	10 [5-15]	10 [5-15]
C_{max}	(ng/mL)	0.104 (33)	0.219 (28)	0.297 (28)	0.432 (33)
T_{max} [a]	(min)	45 [20-120]	30 [15-240]	30 [15-120]	45 [20-120]
AUC_{0-last}	(ng.h/mL)	0.347 (46)	0.923 (48)	1.45 (49)	2.26 (48)
AUC_{0-inf}	(ng.h/mL)	0.592 (24)[b]	1.05 (52) [d]	1.72 (53) [e]	2.42 (50) [f]
$T_{1/2}$	(h)	3.40 (33) [c]	3.62 (74) [d]	4.79 (66) [e]	6.76 (53) [f]

a : median [range]
b: n=8
c: n=13
d: n=17
e: n=16
f: n=15

In Figure 2–3 individual, dose normalized Cmax and AUC values are shown per dose level. Individual dose normalized Cmax values were all in the same range, indicating dose-proportionality. For AUC0-inf values this was also the case. At the 50 µg dose level, dose normalized AUC0-inf values tended to be somewhat lower compared to the other dose groups, most likely related to the underestimation of T1/2 described above.

Figure 2–3 **Fentanyl Dose Normalized C_{max} and AUC_{0-inf} Values After Single Doses of Abstral (b) (4) in Healthy Male Subjects (Study 2246-EU-001)**





9. Study SuF-001; Pharmacokinetics of Abstral (b) (4) in Opioid-tolerant Cancer Patients

Title of Study:
Pharmacokinetics of sublingual fentanyl

Methodology:

The study was conducted as a randomised double-blind two-period crossover trial comparing fentanyl 100 µg and 200 µg, followed by a third open treatment period of fentanyl 400 µg.

Results:
Summary: Approximate dose proportionality was shown across the tested dose range.

The fentanyl pharmacokinetic parameters are presented in Table 2–2.

Table 2–2 Fentanyl Pharmacokinetic Parameters After Single Doses of Abstral (b) (4) in Patients (Mean (CV%) – n = 8) (Study SuF-001)

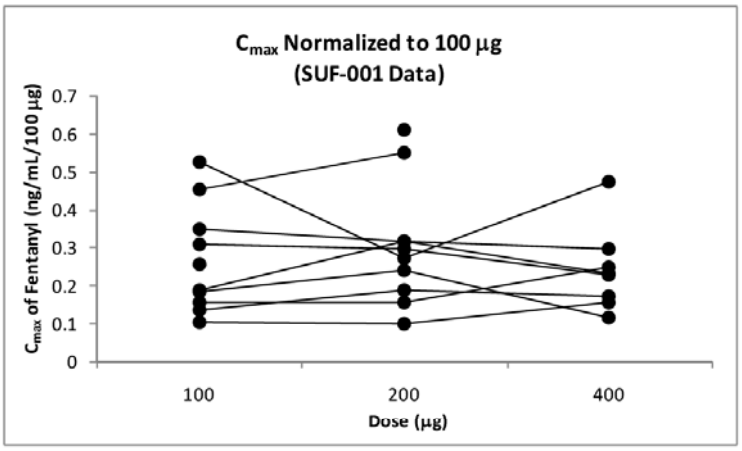
Parameter	Unit	Abstral (b) (4) dose		
		100 µg	200 µg	400 µg
C_{max}	(ng/mL)	0.243 (58)	0.471 (34)	0.956 (46)
T_{max} [a]	(min)	30 [17-60]	60 [18-90]	60 [10-90]
T_{first} [a]	(min)	10 [5-15]	9.0 [3-10]	10 [3-15]
AUC_{0-inf}	(ng.h/mL)	1.24 (42)	2.65 (25)	4.85 (32)
$T_{1/2}$	(h)	6.1 (34)	6.3 (25)	5.4 (32)

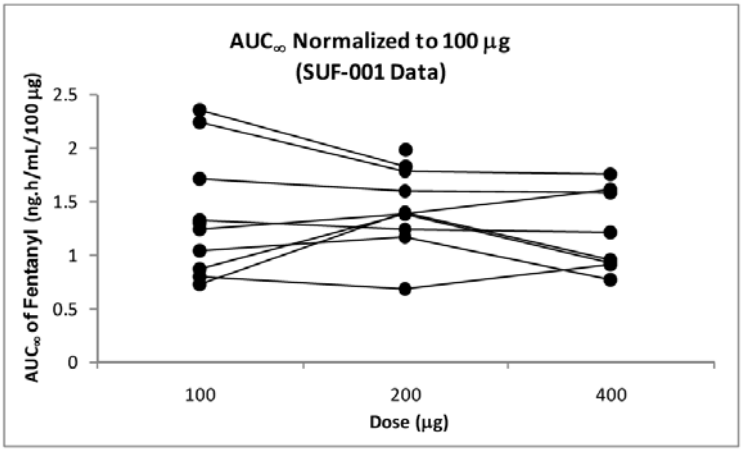
a: median (range)

The median Tmax values were 30 to 60 minutes and the ranges of individual values were similar between dose groups. Inter-subject variability in Cmax and AUC values was in the range of 25% to 58%.

The AUC increased approximately four times when the dose was increased from 100 µg to 400 µg (Table 2–2), indicating dose proportionality. In Figure 2–4 individual dose normalized Cmax and AUC0-inf values have been shown by dose level.

Figure 2–4 **Fentanyl Dose Normalized C_{max} and $AUC_{0\text{-}inf}$ Values After Single Doses of Abstral (b) (4) in Opioid-tolerant Cancer Patients (Study SuF-001)**





Individual dose normalized Cmax and AUC0-inf values were all in the same range across the tested dose levels. Dose proportionality was also shown statistically.

10. Study EN3267-PH001; Pilot study to determine the effect of acidic and basic beverages on oral pH.

Study title: A pilot study to determine the effect of acidic and basic beverages on oral pH

Objectives:
The primary objectives were to determine the effect and time course of effect on oral pH following swish/hold and spit of an acidic or basic beverage.

Methodology:
This study utilized a randomized, three-period crossover design and was conducted in two parts. In Part 1, baseline measurements of oral pH were obtained from each subject prior to receiving each of three beverages: A (black coffee), B (pulp-free orange juice), or C (whole milk). Each subject received 30 mL of the beverage with the order determined by random assignment. After subjects swished (for 2 minutes) and spat a beverage, oral pH measurements were taken at two

sites (buccal, sublingual) in the mouth at specified time points over 1 hour to determine the effect and time course of the effect that the beverage had on oral pH. This procedure was repeated for each beverage.

Part 2 was conducted only if one or more beverages administered in Part 1 resulted in a mean change from baseline of greater than ±0.3 pH units at 5 minutes after swishing and spitting. If only one beverage administered during Part 1 met this criterion, all subjects received this beverage in Part 2. If two or three beverages met the criterion, subjects were randomly assigned to receive the beverages in the order predetermined by a randomization schedule. Oral pH measurements were obtained prior to a 2-minute swish and spit of the beverage. Immediately after spitting the beverage, subjects swished and held 30 mL of water in the mouth for 30 seconds and then spat. Oral pH measurements were then taken at specified time points over 30 minutes after subjects spat the water.

Results:

Summary: There was minimal or no effect on sublingual and buccal pH when beverages were held in the mouth for two minutes. When a small effect was present, it was transitory and oral pH returned to baseline levels within 10 minutes.

The pH values of the beverages were: coffee=4.8, orange juice=3.8, and milk=6.7. Except for the sublingual values after the administration of orange juice, the various beverages had little effect on sublingual and buccal pH measurements 5 minutes after the swish-and-spit. Although the orange juice was acidic, it did not reduce the pH; rather, it increased the mean pH at the sublingual site 5 minutes after the swish-and-spit. The increase was at its largest at this time (mean change of +0.53). Twelve minutes after the swish-and-spit, mean pH had returned to near its baseline level (mean of 7.06). A similar effect was observed when the orange juice swish-and-spit was followed by a water rinse. Five minutes after the orange juice administration, the increase from baseline in mean sublingual pH was 0.68. Twelve minutes after the orange juice administration, mean pH was only slightly higher than the baseline mean pH (mean of 7.31) Conclusions: The results of this study show that when beverages are held in the mouth for a period of 2 minutes, there is minimal or no effect on sublingual and buccal pH. When a small effect is present, it is transitory and the pH returns to baseline levels within approximately 10 minutes. These data suggest that the effect of beverages with different pH values on the absorption of EN3267 is not expected to be significant.

4.3 CLINICAL PHARMACOLOGY FILING MEMO

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA 22-510**	**Brand Name**	**ABSTRAL®**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**N/A**
Medical Division	**DAARP**	**Drug Class**	**Opioid Analgesic**
OCP Reviewer	**Zhihong Li**	**Indication(s)**	**Breakthrough Cancer Pain**
OCP Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**(b) (4) Tablets**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**Titration**
Date of Submission	**08/05/2009**	**Route of Administration**	**Oral, sublingual**
Estimated Due Date of OCP Review	**03/22/2010**	**Sponsor**	**ProStrakan Inc.**
Medical Division Due Date	**04/05/2010**	**Priority Classification**	**Standard**
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				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**5**		
Healthy Volunteers-		**12**		
single dose:	**X**			
multiple dose:	**X**			
Patients-		1		
single dose:	**X**			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**2**		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**1**		
Phase 3:	**X**	**2**		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		
Relative bioavailability -	**X**			
solution as reference:	**X**	**1**		
alternate formulation as reference:	**X**	**5**		
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**3**		
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**		
Literature References				
Total Number of Studies		**15**	**15**	

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			Literature
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			
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 demonstrate effectiveness, if the drug is indeed effective?			X	
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.

None.

Zhihong Li, Ph.D. 10/15/2009
Reviewing Clinical Pharmacologist Date

Suresh Doddapaneni, Ph.D. 10/15/2009
Team Leader/Supervisor Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22510	ORIG-1	PROSTRAKAN INC	Abstral (fentanyl citrate) (b) (4) tablets

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

/s/

ZHIHONG LI
03/10/2010

SURESH DODDAPANENI
03/11/2010