

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-947

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-947
Brand Name (proposed by the Sponsor): _____
Generic Name: Fentanyl Citrate
Dosage Form: Effervescent Buccal Tablet
Dose Strengths: 100, 200, 400, 600 and 800 mcg
Indication: / / /

Dosage and Administration: Physicians should individualize treatment using a progressive plan of pain management.

NDA Type: 505(b)(2); New Formulation; Standard Review
Relevant INDs: IND 65,447
Submission Date(s): 08/31/2005, 09/09/2005, 01/05/2006, 01/06/2006, 01/20/2006, 02/22/2006 and 02/24/2006

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1. EXECUTIVE SUMMARY

Fentanyl citrate is a potent opioid analgesic. Actiq® (oral transmucosal fentanyl citrate) is currently the only opioid analgesic approved in the United States for breakthrough pain in patients with cancer receiving opioids as their around the clock therapy for persistent pain.

Orally administered fentanyl undergoes considerable first-pass metabolism. Thus, the rate and extent of absorption of fentanyl vary according to the formulation used. The Actiq formulation is a lozenge that has a handle, and is used by the patient to continuously move around the mouth in order to maximize transmucosal absorption of fentanyl. The absolute bioavailability of fentanyl from Actiq is ~50%, with ~25% of the dose being absorbed via the oral mucosa. A significant fraction of drug entering the body via intestinal absorption is immediately subject to inactivation in the intestinal mucosa and the liver by CYP-450 enzymes.

The drug product subject to this NDA (21-947) fentanyl effervescent buccal tablets (OraVescent fentanyl citrate or OVF) is a similar formulation that utilizes proprietary technology to facilitate delivery and enhance the absorption of fentanyl through the oral mucosa. The NDA includes 5 dosage strengths (100, 200, 400, 600 and 800 mcg) as part of a 505(b)(2) submission to support the safety and efficacy of OVF for the management of breakthrough pain in patient with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain.

The drug product is designed for placement and retention within the oral cavity for a period sufficient to allow disintegration of the tablet. Effervescent disintegration enhances absorption of fentanyl across the oral mucosa to maximize absorption, minimize first-pass metabolism, and allow rapid delivery of therapeutically effective plasma fentanyl concentrations to be attained with lower fentanyl doses compared to Actiq.

The clinical pharmacology program in this NDA focuses on the dose-proportionality, and relative bioavailability studies to obtain appropriate dose strength of OVF while relying on the clinical pharmacology aspects of the approved transmucosal fentanyl product Actiq. The approved dose strengths of Actiq are 200 mcg, 400 mcg, 600 mcg, 800 mcg and 1600 mcg.

Six Phase 1 clinical pharmacology studies investigated absolute and relative bioavailability, bioequivalence, dose proportionality, and single and multiple dose pharmacokinetic characteristics of OVF. Across these 6 studies, 177 healthy men and women received 1 or more single doses of OVF, and 21 of these subjects additionally received multiple doses of OVF.

Findings from the BA study (#1028) suggested that the fraction of the OVF dose absorbed transmucosally is approximately 50% of the total dose compared to that of approximately 25% from Actiq resulting in a higher absolute bioavailability (65%±20%) when compared with Actiq (47%±11%). Based on these comparisons, an approximately 30% smaller dose of OVF has been suggested to achieve systemic exposures comparable with those following administration of Actiq. It is noted that absolute bioavailability of OVF taken orally is only 31% ±13% and any unintentional swallowing of the OVF tablets would provide far lower exposure than that from the same dose administered through the intended buccal route. Additionally, findings from dose proportionality studies indicate an approximately dose-proportional increase for AUC and C_{max} over the dose range of 100 through 800 mcg, supporting the linear pharmacokinetic profile of effervescent fentanyl over the proposed dose strengths. Inter-individual variability for both C_{max} and AUC_{0-inf} was approximately 37% and intra-individual variability for C_{max} and AUC_{0-inf} were approximately 31% and 25%, respectively following administration of OVF.

Finding from the single dose PK study (#1026) showed that 4x100 mcg OVF tablets were not bioequivalent, and resulted in 12% and 13% higher C_{max} and AUC levels, respectively compared to 1x400 mcg dosing. This finding has been included in the Sponsor's proposed label to support the dose titration with the starting dosing regimen of 100 mcg to be titrated to a dose that provides adequate analgesia with minimal side effect.

The ongoing study 099-16 is evaluating the safety and tolerability, and to characterize the absorption/distribution of a single 200 mcg dose of OVF fentanyl in opioid-tolerant patients with cancer and oral mucositis compared to patients without oral mucositis. This report presents preliminary interim results of this ongoing, open-label study in 8 patients – 4 mucositis and 4 non-mucositis. Plasma fentanyl concentrations increased rapidly to peak concentration, with a median t_{max} of 30 minutes (range 15-45 min) in patients with mucositis and 27 minutes (range 20-34 min) in patients without mucositis. The mean C_{max} and AUC₀₋₈ values were approximately 26% (cv 49-63%) and 40% (cv 45-48%) higher, respectively for patients with oral mucositis compared to those without oral mucositis.

The following dissolution method was used for the clinical trial formulation:

Apparatus:	Small volume dissolution apparatus, paddle, speed 100 rpm
Medium:	pH 7.0 phosphate buffered saline solution; 37 °C±0.5 °C 100 mL for 100 mcg and 400 mcg strengths 200 mL for 200 mcg, 600 mcg and 800 mcg strengths
Proposed Specification:	NLT (Q) in 10 minutes

Dissolution of fentanyl effervescent buccal tablets occurs in less than 10 min. The release data for the pivotal clinical and registration stability batches ranged from 96% to 102% (average) with a low individual value of — . Thus, the specification NLT — (Q) in 10 minutes is acceptable.

1.1. Recommendation:

From a Clinical Pharmacology and Biopharmaceutics perspective, NDA 21-947 is acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Cephalon regarding the language in the package insert.

1.2. Phase IV Commitments:

None from Clinical Pharmacology and Biopharmaceutics perspective.

2. QUESTION-BASED REVIEW

2.1. General Attributes

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

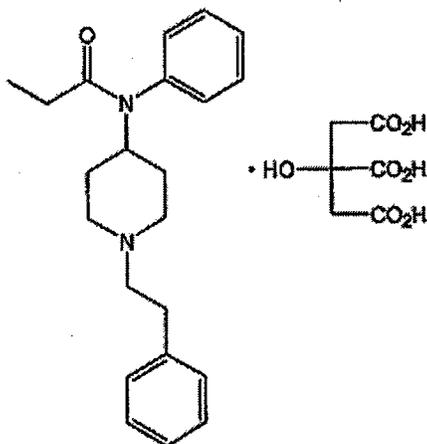
Actiq (Oral Transmucosal Fentanyl Citrate (OTFC, NDA 20-747)), a Troche/Lozenge formulation was approved in November of 1998 for the management of breakthrough cancer pain in patients tolerant to opioid therapy. Actiq is marketed by Cephalon in 200, 400, 600, 800, 1200 and 1600 mcg (free base) strengths.

The drug product subject to this NDA (21-947), fentanyl effervescent buccal tablets (also referred as effervescent fentanyl/OraVescent or OVF), is another formulation that utilizes proprietary technology to facilitate the absorption of fentanyl through the oral mucosa. The relevant IND application (IND 65,447) on OVF was originally submitted by CIMA Labs, Inc. On August 12, 2004, CIMA became a wholly owned subsidiary of Cephalon. Cephalon has filed this NDA 21-947 as a 505(b)(2) application to support the safety and efficacy of OVF for the management of breakthrough pain in patient with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the product?

Chemical Name: N-(1-Phenethyl-4-piperidyl) propionanilide citrate.

Structural formula



Molecular Weight of the Free Base: 336.5

Physicochemical Properties: Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The pKa of the tertiary nitrogens are 7.3 and 8.4.

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, magnesium stearate, and

2.1.2 What are the proposed mechanism of action and therapeutic indication of fentanyl?

Mechanism of Action: Fentanyl, a pure opioid agonist, acts primarily through interaction with opioid mu-receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system.

Indications: OraVescent is indicated for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain.

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, OraVescent is contraindicated in the management of acute or postoperative pain. Because OraVescent has not been studied in opioid non-tolerant patients, this product must not be used in opioid non-tolerant patients.

2.1.3 What is the proposed dosage and route of administration?

The proposed initial starting dose is 100 mcg. Patients should be titrated to a dose that provides adequate analgesia with minimal side effects. Patients should remove the tablet from the blister unit and immediately place the entire OraVescent tablet in the buccal cavity (above a rear molar between the upper cheek and gum). Patients should not attempt to split the tablet. The OraVescent tablet should not be sucked, chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed. The OraVescent tablet should be left between the cheek and gum until disintegrated, which usually takes approximately 14-25 minutes. After 30 minutes, if remnants from the OraVescent tablet remain, they may be swallowed with a glass of water.

2.2. General Clinical Pharmacology

2.2.1. What are the known key clinical pharmacology attributes of fentanyl citrate related to this NDA?

Clinical pharmacology of fentanyl citrate from the approved oral transmucosal lozenge formulation, Actiq is summarized below:

Following oral transmucosal administration, the pharmacokinetics of fentanyl are characterized by an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract.

Normally, approximately 25% of the total dose of Actiq is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of Actiq is divided equally between rapid transmucosal and slower GI absorption.

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%. Fentanyl undergoes extensive first-pass metabolism, and is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies.

Fentanyl is primarily (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). The terminal elimination half-life of fentanyl is about 7 hours.

Dose proportionality among four of the available strengths of Actiq (200, 400, 800, and 1600 mcg) has been demonstrated in a crossover design in adult subjects with both the C_{max} and AUC_{0-∞} showing a dose-dependent increase in a manner that is approximately proportional to the dose administered. The mean C_{max} ranged from 0.39-2.51 ng/mL. The median T_{max} across these four doses of Actiq varied from 20-40 minutes (range of 20-480 minutes) as measured after the start of administration.

2.2. What are the Basis of Clinical Pharmacology of OraVescent Fentanyl (OVF) Citrate?

The clinical pharmacology program in this NDA focuses on the dose-proportionality, and relative bioavailability studies to obtain appropriate dose strength of OVF while relying on the clinical pharmacology aspects of the approved transmucosal fentanyl product Actiq.

Six Phase 1 clinical pharmacology studies investigated absolute and relative bioavailability, bioequivalence, dose proportionality, and single and multiple dose pharmacokinetic characteristics of OVF. Across these 6 studies, 177 healthy men and women received 1 or more single doses of OVF, and 21 of these subjects additionally received multiple doses of OVF.

Two supportive Phase 1 studies were conducted in healthy Japanese subjects. An additional study is ongoing in a population of opioid-tolerant patients with cancer with or without oral mucositis to evaluate safety and PK exposure due to mucositis. Results of interim report from this study are included in the submission.

The efficacy and safety of OVF at doses of 100, 200, 400, 600, and 800 mcg is supported through the pivotal Phase 3 randomized, double-blind, placebo-controlled trial (study 099-14) in opioid-tolerant patients (N=123) with break-through-pain (BTP) conducted in the United States. In addition, the clinical program includes also interim safety data from double-blind efficacy/safety study (study 3039) in opioid-tolerant patients with BTP, and two 12-month, open-label safety/efficacy studies, 1 in patients with cancer and BTP (study 099-15) and the other in patients with chronic non-cancer pain and BTP (study C25608/3040). At the time of this submission, effervescent fentanyl has been evaluated in a total of 360 patients (266 with cancer and 94 with non cancer pain).

2.2.1. What is the rationale for the proposed effervescent transmucosal formulation?

Buccal administration of effervescent OVF tablet minimizes first-pass metabolism and enhances bioavailability compared to Actiq.

Fentanyl citrate is a potent opioid analgesic. The analgesic effects of fentanyl are related to the concentrations of the drug in the blood. Actiq (oral transmucosal fentanyl citrate) is currently the only opioid analgesic approved in the US for break through pain (BTP) in patients with cancer receiving opioids as their around the clock therapy for persistent pain.

Orally administered fentanyl undergoes considerable first-pass metabolism. Thus, the rate and extent of absorption of fentanyl vary according to the formulation used. The Actiq formulation is a lozenge with a handle and is used by the patient to continuously move around the mouth in order to maximize transmucosal absorption of fentanyl. The absolute bioavailability of fentanyl from Actiq is ~50%, with ~25% of the dose being absorbed via the oral mucosa. While much of the swallowed portion is eventually absorbed in the intestine, the time from ingestion to absorption across the gut mucosa can vary. Furthermore, a significant fraction of drug entering the body via this route is immediately subject to inactivation in the intestinal mucosa and the liver by CYP-450 enzymes. OraVescent Fentanyl Citrate is an effervescent fentanyl buccal tablet designed for placement and retention within the oral cavity for a period sufficient to allow disintegration of the tablet. Effervescent disintegration is theorized to enhance absorption of fentanyl across the oral mucosa to maximize absorption, minimize first-pass metabolism, and allow delivery of therapeutically effective plasma fentanyl concentrations to be attained with lower fentanyl doses compared to Actiq formulation.

2.2.2. What is the rationale for the proposed dose and dosing regimen?

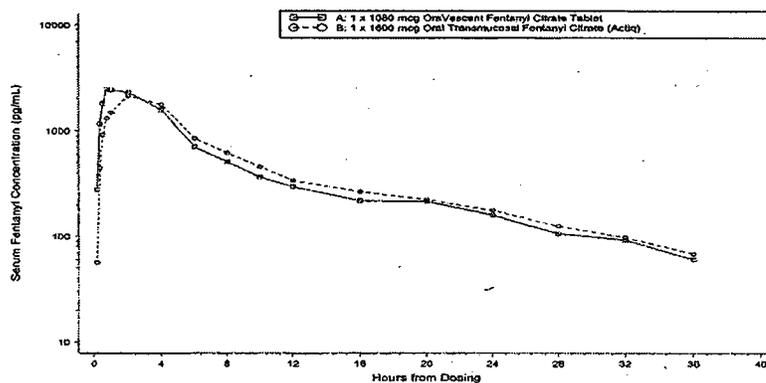
The dose selection was based on the absolute and relative bioavailability profiles of OVF in relation to Actiq, while the dosing regimens were supported by the dose proportionality study across the proposed strengths.

Bioavailability Study:

OVF demonstrates a higher absolute bioavailability (0.65%) when compared with ACTIQ (47%).

Dose selection in Phase 3 studies of effervescent fentanyl was made on the basis of findings for the relative bioavailability of the effervescent fentanyl formulation (1080 mcg) and ACTIQ (1600 mcg) from study 099-11 in conjunction with absolute bioavailability of OVF. Findings of this study showed that the ratios of means of fentanyl C_{max}, AUC_{0-t}, and AUC_{0-inf} for OVF 1080 mcg/Actiq 1600 mcg were 123.4%, 101.4%, and 101.1%, respectively, while the respective 90% CI values were 111.8% – 136.2%, 94.4% – 108.9%, and 93.6% – 109.2%. These data indicate that the peak exposure was approximately 23% higher for OVF 1080 mcg compared to Actiq 1600 mcg. Also the AUC of OVF 1080 mcg is bioequivalent to Actiq 1600 mcg indicating similar average exposure for both (Figure 1). The median T_{max} for OVF was 1 hr occurred an hour earlier than that for Actiq at 2.0 hour indicating that the rate of fentanyl absorption was significantly faster for the effervescent formulation (median T_{max} = 1hr) compared to the Actiq formulation (median T_{max} = 2hr).

Figure 1. Mean Serum Fentanyl Concentrations Versus Time Treatments A (OVF 1080 mcg) and B (Actiq 1600 mcg)



To further support the therapeutic doses in relation to the approved Actiq dosing, study 1028 was conducted to assess the absolute and relative bioavailability of OVF. . The study compared bioavailability of single dose of 400 mcg OVF by the proposed buccal administration against 800 mcg OVF given orally, 800 mcg Actiq given vial transmucosal route and 400 mcg of fentanyl given by IV route. Results of this study (Table 1 below) suggested that the fraction of the OVF dose absorbed transmucosally is approximately 50% of the total dose (f_{TM}=0.48), and the fraction of the Actiq dose absorbed transmucosally is approximately 25% of the total dose (f_{TM}=0.22). As a result, OVF demonstrates a higher absolute bioavailability (FOVF=0.65) when compared with ACTIQ (FACTIQ=0.47). Dose normalization to equal doses (400 mcg), effervescent fentanyl demonstrated higher exposure compared with ACTIQ (as measured by C_{max}, AUC_{0-∞}, and AUC_{0-tmax}) (Figure 2 below).

Table 1: Mean (+/- SD) Pharmacokinetic Parameters of Fentanyl in Healthy Volunteers (N= 26) Administered a Single Dose of 400 mcg OVF or 800 mcg ACTIQ Transmucosally, 400 mcg Fentanyl Intravenously, or 800 mcg OVF Orally

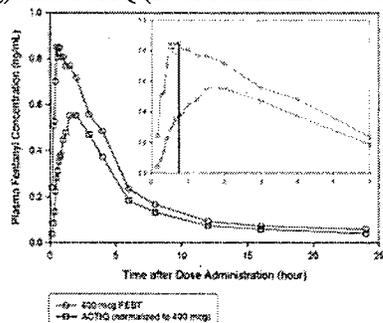
Parameter	400 OVF	400 IV	800 OVF (po)	800 ACTIQ
C _{max} (ng/mL)	1.020 ± 0.424	3.000 ± 1.112	0.984 ± 0.542	1.257 ± 0.414
t _{max} (hr) ^a	0.78 [0.33-4.00]	0.17 [0.08-0.75]	1.50 [0.68-4.00]	1.51 [0.58-4.00]
AUC _{0-∞} ^a (ng·hr/mL)	0.398 ± 0.178	1.43 ± 0.39	0.110 ± 0.136	0.280 ± 0.101
AUC ₀₋₂₄ (ng·hr/mL)	5.00 ± 1.74	7.79 ± 1.95	4.87 ± 3.01	7.31 ± 2.57
AUC ₀₋₄ (ng·hr/mL)	5.52 ± 2.43	9.01 ± 2.79	5.52 ± 4.15	8.47 ± 3.73
AUC ₀₋₇₂ (ng·hr/mL)	5.79 ± 2.50	9.31 ± 2.76	5.76 ± 4.15	8.79 ± 3.69
AUC _{0-∞} (ng·hr/mL)	6.48 ± 2.98	10.29 ± 2.88	6.60 ± 4.47	9.58 ± 3.91
λ _z (hr ⁻¹)	0.0568 ± 0.0364	0.0411 ± 0.0153	0.0703 ± 0.0527	0.0438 ± 0.0195
t _{1/2} (hr) ^b	12.2	16.9	9.87	15.8
CL or CL/F (L/hr)	77.0 ± 42.8	41.7 ± 11.3	174 ± 108	95.0 ± 31.7
V _d or V _d /F (L)	1481 ± 493	1102 ± 332	2696 ± 769	2345 ± 780
AUC Extrap. (%)	13.2 ± 4.9	11.5 ± 5.3	13.5 ± 6.7	12.5 ± 5.5
F _{ORAL}	NA	NA	0.311 ± 0.131	NA
F _{OVF}	0.648 ± 0.200	NA	NA	NA
F _{ACTIQ}	NA	NA	NA	0.465 ± 0.105
f _{TM}	0.477 ± 0.318	NA	NA	0.224 ± 0.173
f _G	0.523 ± 0.318	NA	NA	0.776 ± 0.173
F _{OVF:AC}	1.34 ± 0.39	NA	NA	NA
F _{OVF:po}	2.32 ± 1.07	NA	NA	NA
F _{ACTIQ:po}	NA	NA	NA	1.80 ± 0.75

^a Median [range]; ^b Harmonic mean; NA = Not Applicable.

F_{OVF:AC}, F_{OVF:po}, F_{ACTIQ:po} = Relative bioavailability of OVF to ACTIQ, OVF to oral OVF, and ACTIQ to oral OVF, respectively.

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Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single Doses of Effervescent Fentanyl (400 mcg) and ACTIQ (Dose Normalized to 400 mcg) in Healthy Subjects



NOTE: Data are from the 1028 study.

Inset shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the T_{max} .

FEFT=effervescent fentanyl (OVF)= t_{max} for the reference treatment.

These data indicate that the differences between effervescent fentanyl and Actiq in absolute bioavailability, and in the fractions absorbed transmucosally, must be taken into consideration when selecting dose regimens or switching treatment regimens. Based on these comparisons, an approximately 30% smaller dose of OVF will achieve systemic exposures comparable with those following administration of Actiq.

Dose Proportionality:

Single-dose pharmacokinetics of fentanyl were characterized by a linear pharmacokinetic profile of effervescent fentanyl over this dose range of 100 to 800 mcg.

Dose proportionality between the proposed strengths (i.e., 100, 200, 400, 600, and 800 mcg) is a key element in the selection of dosing regimen for OVF when compared to the marketed fentanyl product Actiq. Actiq has been shown to have dose proportionality between the approved dosing range of 100 mcg to 1600 mcg fentanyl lozenges.

Study 1027 was conducted to establish dose proportionality for OVF based on the single dose pharmacokinetics of the four doses 100, 200, 400, and 800 mcg in 32 adult healthy male and female subjects.

The results of this study showed that the single-dose pharmacokinetics of fentanyl were characterized by a rapid absorption phase, with dose-independent median t_{max} values of 35 through 45 minutes across dose groups (Fig 1 and Tab 1). AUCs and C_{max} increased in an approximately dose-proportional manner over the dose range of 100 through 800 mcg, supporting the linear pharmacokinetic profile of effervescent fentanyl over this dose range (Figures 3-4, and Table 2 below).

Figure 3. Mean Plasma Concentration Versus Time Profiles Following Single 100-, 200-, 400-, and 800-mcg Doses of Effervescent Fentanyl in Healthy Subjects (Study #1027)

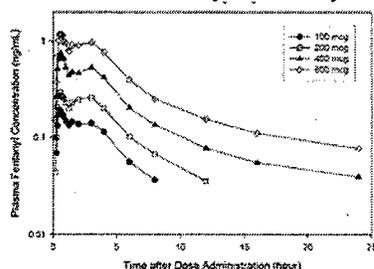


Figure 4. Mean (SEM) C_{max} and AUC_{0-inf} as a Function of Dose Following Single 100-, 200-, 400-, and 800-mcg Doses of Effervescent Fentanyl in Healthy Subjects

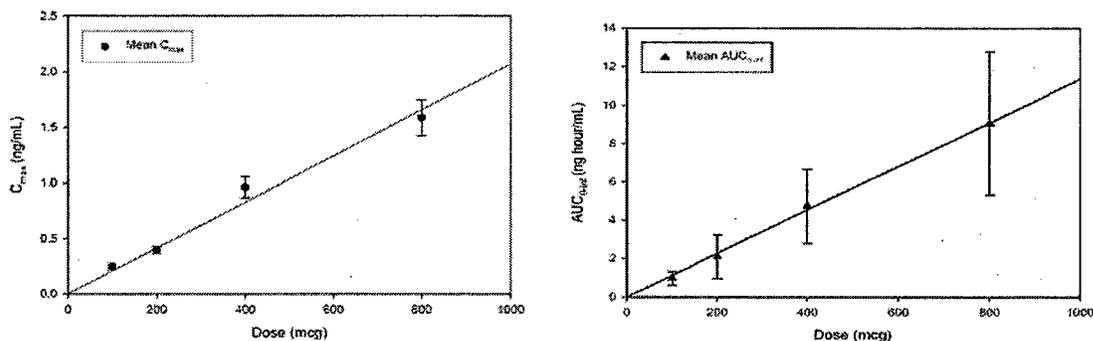


Table 2. Summary of Single Dose Pharmacokinetics from Dose-Proportionality Study 1027

Variable	ORAVESCENT fentanyl			
	100 mcg (N=31)	200 mcg (N=31)	400 mcg (N=31)	800 mcg (N=31)
AUC _{0-inf} ^a (ng hr/mL)	0.98±0.37	2.11±1.13	4.72±1.95	9.05±3.72
AUC _{0-t} ^c (ng hr/mL)	0.80±0.26	1.39±0.46	2.90±0.92	5.27±1.85
AUC ₀₋₂₄ (ng hr/mL)	0.96±0.41	1.85±0.80	3.98±1.37	7.38±2.71
AUC ₀₋₇₂ (ng hr/mL)	0.99±0.46	1.93±0.90	4.39±1.80	8.39±3.59
AUC _{0-max} ^c (ng hr/mL)	0.09±0.06	0.13±0.09	0.34±0.23	0.52±0.38
AUC _{0-t} ^c (ng hr/mL)	0.91±0.42	1.79±0.82	4.17±1.72	8.11±3.63
C _{max} (ng/mL)	0.25±0.14	0.40±0.18	0.97±0.53	1.59±0.90
t _{max} ^b (min)	45.0 (25.0, 181.0)	40.0 (20.0, 180.0)	35.0 (20.0, 180.0)	40.0 (25.0, 180.0)
t _{1/2} ^{a,b} (hr)	2.63 (1.47, 13.57)	4.43 (1.85, 20.76)	11.09 (3.44, 20.59)	11.70 (4.63, 28.63)

^a Not all subjects' data were extrapolated. For 100 mcg, n=25; for 200 mcg, n=27; for 400 mcg, n=29; and for 800 mcg, n=30.

^b Median (range) is presented for these variables. Mean±SD is presented for all other variables.

AUC_{0-t}^c = AUC from time zero to the last time point at which at least 75% of the subjects within all dose groups had a measurable plasma concentration.

Related supportive dose proportionality studies included several other strengths of OVF doses in the range of 270 mcg, 810 mcg, 1080 mcg and 1300 mcg (study #099-11), and 200 mcg, 500 mcg, 810 mcg, and 1080 mcg (study# 1018). These strengths are not sought for approval. The studies were crossover design conducted in healthy male and female volunteers. The findings from these studies were similar to those observed in study 1027 above. Fentanyl AUC increased proportionally to the dose in the range of 270 to 1300 mcg (study #099-11) and 200 to 1080 mcg (study #1018) for the OVF tablet formulations. There were no significant differences in dose-normalized AUC(0-t) or AUC(0-inf) among the OraVescent doses in both studies, while a slightly less than proportional increases in C_{max} were observed with the higher fentanyl doses 810 mcg, 1080 mcg and 1300 mcg in these studies.

2.2.3. What are single and multiple dose PK characteristics of OVF?

2.2.3.1. Single Dose PK Characteristics

Single-dose pharmacokinetic data for fentanyl following administration of effervescent fentanyl from the buccal position were obtained in studies 099-11, 099-18, 1026, 1027, 1028, and 1029. Single dose fentanyl PK characteristics obtained from these studies have been summarized above under section 2.2.2.

In each of the above single dose study group, pharmacokinetics of fentanyl were characterized by a rapid absorption phase, with the dose-independent median t_{max} values of 35 through 45. The median T_{max} (0.998 hr) for the OVF was significantly earlier ($p=0.001$) compared to Actiq (1.999 hr). Both formulations were well tolerated by the oral mucosa as indicated by the oral irritation assessment. However, the t_{max} showed a wide variation ranging from 25 to 180 minutes (Table 2 above) across dose groups. For the majority of subjects, the absorption phase was followed by a biexponential decline from peak concentration at the lower doses of 100 and 200 mcg, and a triexponential decline from peak concentration at the highest dose at 800 mcg (Fig 3 above).

The median estimated $t_{1/2}$ values increased with increasing dose (ranged from ~ 3 through 12 hours) which may have been largely due to incomplete characterization of the terminal elimination phase where plasma concentrations at sampling times later in the profiles were not quantifiable for many subjects.

As mentioned above, there was a wide variation in the individual T_{max} value at each dose. At the lower doses (100 mcg and 200 mcg) about 60% of the subjects exhibited T_{max} between 20 to 60 minutes, while a significant number of subjects (26% with 100 mcg, and 44% with 200 mcg) attained T_{max} at a later time between 90-180 minutes. With higher doses (400 mcg and 800 mcg), 70-78% of subjects had T_{max} in the range of 20-60 minutes, while one-fourth (25%) exhibited T_{max} between 90-180 minutes. The large inter subject variations in T_{max} values are presumably due to variation in buccal absorption. The clinical significance of the variation in T_{max} is that the onset of pain relief may also vary among patients.

Table 3. Median T_{max} and Inter subject Variation for 4 doses in Study 1027

Dose	Median	T_{max} (hr) n/%/(range hr)				
		0.33- 0.50	0.51-1.0	1.1-1.5	1.51-2.0	2.1-3.0
100 mcg (N=31)	0.75	10/32% (0.42-0.50)	10/32% (0.58- 0.83)	3/9.7% (1.1- 1.50)	2/7% (2.00)	6/19.3% (3.00- 3.01)
200 mcg (N=32)	0.67	9/28% (0.33- 0.50)	9/28% (0.58- 1.00)	0	6/19% (2.00)	8/25% (3.00)
400 mcg (N=32)	0.58	12/38% (0.33-0.50)	11/34% (0.58- 1.0)	0	3/9% (1.00)	6/19% (3.00)
800 mcg (N=32)	0.67	10/31% (0.42-0.50)	13/40% (0.58- 1.0)	1/3% (1.50)	4/13% (1.51-2.0)	4/13% (3.00)

The single dose PK study #1026 was conducted to assess the bioequivalency between the 4x100 mcg OVF tablets compared to 1x400 mcg OVF tablet. The study was conducted to support the proposed starting dosing regimen of 100 mcg to be titrated to a dose that provides adequate analgesia with minimal side effect. Thus, patients needing to titrate above 100 mcg can be instructed to use two 100 mcg (one on each side of the mouth in the buccal cavity). If this dose is not successful in controlling the breakthrough pain episode, the patient could be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets).

The 90% CI for C_{max} and AUC_{0-inf} did not meet the C_{max} criteria of bioequivalence (Table 4 below). The point estimates for the mean ratios suggest approximately 12% and 13% higher values for C_{max} and AUC_{0-inf} , respectively for 4x100 mcg tablets compared to the 1x400 mcg tablet. The relatively higher rate of absorption with the 4x100 mcg tablets may be attributable to the larger surface area present when 4 tablets are administered at once.

Table 4: Bioequivalence Assessment between One 400- mcg Tablet (A) and Four 100-mcg Tablets (B) of OVF (Study #1026)

PK Measures	Ratio (B/A)	90%CI
Cmax (ng/mL)	1.121	0.995-1.262
AUC0-inf (ng•hr/mL)	1.128	1.016-1.251
AUC0-t (ng•hr/mL)	1.111	1.028-1.201
AUC0-24 (ng•hr/mL)	1.091	1.020-1.168

2.2.3.1.1. What is the Effect of Dwell Time on the Pharmacokinetics of Effervescent Fentanyl?

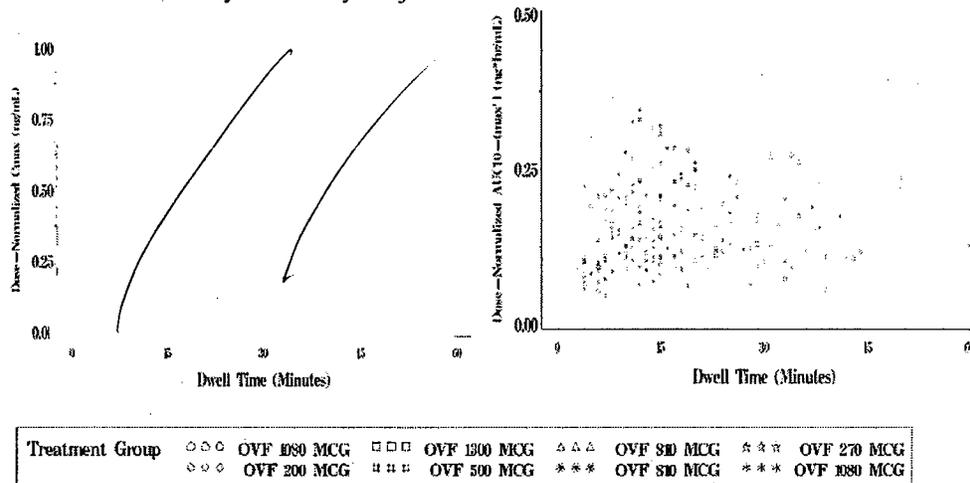
Dwell time was defined as the time between tablet placement and the complete disappearance of tablet residue from the oral cavity, determined by visual inspection.

In order to identify and describe potential trends in the pharmacokinetic parameters of effervescent fentanyl relative to dwell time, an exploratory analysis of tmax and dose-normalized AUC0-tmax' and Cmax values versus dwell time was performed for individual subject data obtained in studies 099-11 and 099-18. The dwell time data are summarized in the table below. Figure 5 depicts the relationship between the individual PK parameters (AUC and Cmax) and dwell time:

Table 5. Mean Dwell Time for OVF (Study # 099-11 and 099-18)

	Dwell Time (minute)				
	Study # 099-11				
Treatment	270 mcg (N=14)	810 mcg (N=13)	1080 mcg (N=40)	1300 mcg (N=12)	1600 mcg (Actiq)(N=42)
Mean±SD (range)	22±17 (4-62)	25±14 (4-50)	21±12 (3-48)	19±11 (4-33)	34±15 (9-77)
	Study # 099-18				
Treatment	200 mcg (N=25)	500 mcg (N=26)	810 mcg (N=27)	1080 mcg (N=27)	-
Mean±SD (range)	14±8 (4-37)	14±6 (6-33)	17±10 (5-41)	15±11 (4-60)	-

Figure 5 : Individual Dose-normalized (100 mcg) Cmax and AUC0-tmax' by Dwell Time Following Single Doses of Effervescent Fentanyl in Healthy Subjects



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Despite a relatively large intersubject variability in dwell time, visual inspection of these plots does not show a dramatic difference in Cmax or AUC. Comparing the dwell time vs non dose-normalized PK parameters (Tmax, Cmax and AUC0-inf) from individual subjects randomly selected to represent dwell time ranging from 4 to 48 minutes did not show a dramatic difference either. As shown in the Table below, there is not a conclusive pattern in the relationship between dwell time and PK measures of individual subjects.

Relationship between Dwell Time and PK Parameters (Study 099-11)
Treatment 1080 mcg

Subjects	Dwell Time	Tmax (hr)	Cmax (pg/mL)	AUC0-inf (pg.hr/mL)
1	12	0.75	2241	18354
2	4	1.00	1513	12009
4	5	0.50	2827	20278
6	38	0.75	3936	22587
9	15	0.74	2486	15048
12	12	1.00	2582	18309
15	7	2.00	1784	11750
16	25	0.75	13648	13648
17	18	0.75	2592	20217
18	39	2.00	2118	15778
19	7	0.75	3114	16699
22	11	1.00	2184	14709
23	21	2.00	3027	24452
29	15	2.00	2533	3974
30	20	2.00	4201	-
31	48	0.99	2755	-

2.2.3.2. What are multiple dose PK characteristics of the test product?

Study 1029 was conducted to characterize the multiple dose pharmacokinetics of effervescent fentanyl tablets. This was an open-label, in 24 healthy young men and women. Each subject received a single 400-mcg dose of effervescent fentanyl on day 1, followed by multiple 400-mcg doses of effervescent fentanyl administered every 6 hours from days 4 through 9. Twenty-one subjects received 400 mcg of OVF as a single dose on day 1 and as multiple doses on days 4 through 9. It is noted that the q6h dosing regimen used in this multiple dose study is not applicable for the proposed indication of break through pain. The purpose of this study may be considered to evaluate any undue accumulation of the drug at best.

Plasma samples for pharmacokinetic profiling of fentanyl were obtained over 72-hour periods following the dose on day 1 and the final dose on day 9. The PK results are shown in Tables 6 and 7 below. The mean plasma concentration versus time profiles of fentanyl are presented in Figure 6.

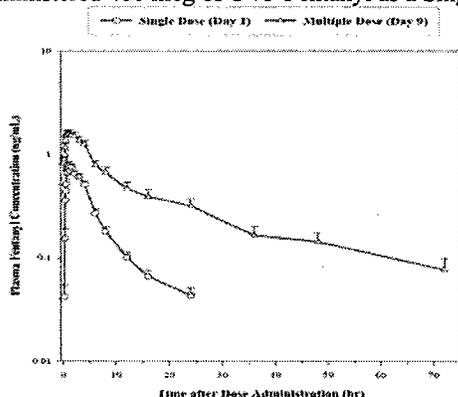
Table 6. Pharmacokinetic Parameters Determined After Single and Multiple 400-mcg Doses of OVF

PK Measures	OVF Fentanyl Mean SD	
	Single Dose	Multiple Dose
Cmax (ng/mL)	0.88±0.30	1.77±0.63
AUC0-6 (ng• hr/mL)	3.11±0.94	-
AUC0-24 (ng• hr/mL)	4.90±1.75	15.8±8.20
AUC0-72 (ng• hr/mL)	5.80±2.46	23.2±15.01
AUC0-t (ng• hr/mL)	5.33±2.52	22.9±15.21
AUC0-inf (ng• hr/mL)	6.07±2.80	7.59±3.00
Tmax (min)	52.2 (37.8-180.0)*	49.8 (25.2-240.0)*
T1/2 (hr)	12.3 (2.7-35.8)*	21.7 (10.8-44.7)*
Ke (1/hr)	0.08±0.06	0.04±0.01

Table 7: Trough Plasma Concentrations (ng/mL) of Fentanyl

Day (time point)	ORAVESCENT fentanyl Mean±SD (N=21)
8 (1400)	0.60±0.30
8 (2000)	0.65±0.33
9 (0200)	0.75±0.34
9 (0800)	0.85±0.38
9 (1400)	0.78±0.37

Figure 6 : Mean Plasma Concentration Versus Time Profiles of Fentanyl in Healthy Subjects Administered 400 mcg of OV Fentanyl as a Single Dose (Day 1) and as Multiple Doses (Day 9)



As evident by the single-dose data, OV F the mean C_{max} of 0.88 ng/mL was attained rapidly (median t_{max} of approximately 50 minutes) following administration of a 400-mcg dose. As observed in other single dose studies, fentanyl exhibited a biexponential or triexponential decline from the peak plasma concentration. The median estimated $t_{1/2}$ was approximately 12 hours.

Following the multiple-dose administration of 400 mcg of effervescent fentanyl (q6hx5 days starting on Day 5) the median t_{max} was achieved in about 50 minutes, same as observed with single dose profile, and the fentanyl C_{max} value was 1.77 ng/mL. Fentanyl exhibited a triexponential decline from peak plasma concentration (consistent with a very rapid distribution to the highly perfused tissues, followed by an elimination/gastrointestinal absorption phase and a terminal elimination/redistribution phase between plasma and a deep-tissue compartment). The median estimated $t_{1/2}$ (approximately 22 hours) was longer than the median estimated $t_{1/2}$ after single-dose administration, partially due to the higher plasma concentrations following multiple-dose administration, which allowed for a more adequate characterization of the terminal portion of the curve.

The 90% CIs for the ratio of mean trough plasma concentrations following the final 3 doses of fentanyl on day 9 were within the confidence interval limits (0.8, 1.25). The C_{max} and t_{max} after administration of multiple doses were consistent with those after administration of a single dose. Based upon the similarity in trough plasma concentrations of fentanyl, subjects appeared to be at or near pharmacokinetic steady state on day 5 of multiple-dose administration which is consistent with the $t_{1/2}$.

2.3. Intrinsic Factors

2.3.1. Clinical Pharmacology in Cancer Mucositis Patients

Preliminary data from the on going study 099-16 in cancer patients are indicative of about 25-40% higher exposure (for both the C_{max} and AUC in mucositis patients compared to non-mucositis.

Oral mucositis is a common side effect in patients with cancer undergoing chemotherapy or radiotherapy. Besides being painful, mucositis can result in changes in the epithelium of the oral mucosa. Since OVF is administered buccally and absorbed through the oral mucosa, the tolerability and absorption of OVF could be different in cancer patients with mucositis compared to patients without mucositis.

The ongoing study 099-16 is being conducted in order to evaluate the safety and tolerability, and to characterize the absorption/distribution of a single 200 mcg dose of OVF fentanyl in opioid-tolerant patients with cancer and oral mucositis compared to patients without oral mucositis. This report presents preliminary interim results of this ongoing, open-label study.

The 200-mcg dose of OVF fentanyl was selected for evaluation in this single-dose study in patients with cancer because it is currently the lowest dose that has demonstrated acceptable plasma concentrations of fentanyl in healthy subjects. Patients took study drug in the morning and were not required to have fasted prior to that.

Plasma pharmacokinetic data obtained for 8 patients (4 with mucositis and 4 without mucositis) for this interim data report are given in Table 8 and the plasma-fentanyl time concentration plot depicted in Figure 7 below.

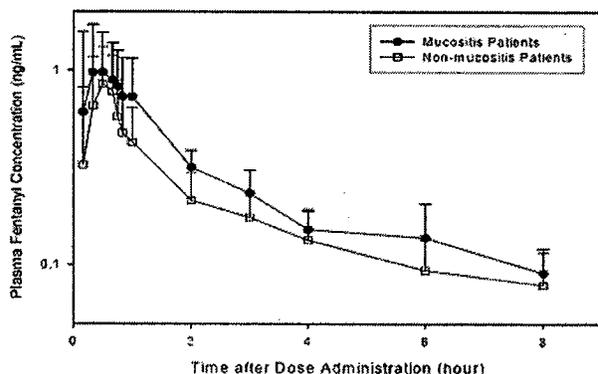
Table 8: Mean (SD) Pharmacokinetic Parameters of Fentanyl in Patients With Cancer With (n=4) or Without (n=4) Mucositis Administered a Single Dose of 200 mcg of OVF Fentanyl

Patient status	C_{max} (ng/mL)	t_{max}^a (min)	$AUC_{0-t_{max}}$ (ng·hr/mL)	AUC_{0-8} (ng·hr/mL)
Mucositis	1.147±0.732	30.0 (15.0–45.0)	0.263±0.264	2.278±1.035
No mucositis	0.911±0.447	27.0 (19.8–34.2)	0.181±0.164	1.624±0.791

^a Median (range).

SD=standard deviation; C_{max} =maximum observed plasma concentration; t_{max} =time to maximum observed plasma concentration; $AUC_{0-t_{max}}$ =area under the plasma concentration-time curve up to t_{max} , whereby t_{max} is the median t_{max} derived from patients without mucositis after study drug administration; AUC_{0-8} =AUC over the time period 0-8 hours.

Figure 7: Mean Plasma Concentration versus Time Profiles of Fentanyl in Patients with Cancer with (n=4) or without (n=4) Mucositis



Plasma fentanyl concentrations increased rapidly to peak concentration, with a median t_{max} of 30 minutes in patients with mucositis and 27 minutes in patients without mucositis. The mean C_{max} AUC_{0-8} values were approximately 26% and 40% higher, respectively for patients with oral

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mucositis compared to those without oral mucositis. However, as indicated in the Table above, these results exhibit large interpatient variability in both groups.

No deaths, other serious adverse events, or withdrawals due to adverse events occurred in this study. Two patients had adverse events: Patient 6007 (mucositis) had mild dizziness (about 14 minutes after tablet placement) that was possibly related to study drug (but not to oral mucositis or tablet placement), and resolved with no residual effect. Patient 6002 (no mucositis) had mild dizziness (about 27 minutes after tablet placement) that was probably related to study drug (but not to oral mucositis or tablet placement), and resolved with no residual effect.

No patient had a clinically significant abnormal vital signs measurement including pulse, systolic and diastolic blood pressure, and respiratory rate.

Oral mucosal examinations to evaluate mucosal irritation were performed for all patients by the investigator just before the administration of OVF fentanyl at baseline (time 0), at the end of dwell time, and 1, 2, 3, 4, and 8 hours following the administration of OVF fentanyl. No patient with normal oral mucosa (no mucositis) before treatment was found to have abnormal mucosa findings after treatment. For those with mucositis, no changes in grade of mucositis were observed after treatment with OVF fentanyl.

Although the sample size in this study precludes making any inference, the preliminary data may be indicative of higher exposure (by about 25-40%) for both the C_{max} and AUC in mucositis patients compared to non-mucositis.

2.3.2. Are there any Gender Effects on the Pharmacokinetics of OVF?

No formal clinical pharmacology studies were specifically conducted to study the effect of sex on the pharmacokinetics of OVF. Summary of available data showed ~22-29% higher exposure in women compared to men largely attributable to differences in weight.

The single-dose pharmacokinetic parameters of effervescent fentanyl from pooled database from studies 099-11, 099-18, 1026, 1027, 1028, and 1029 were used to characterize the single-dose pharmacokinetic parameters (normalized to the lowest dose, i.e., 100 mcg) and analyzed for gender effect. The results are summarized in the Table below. Systemic exposure was higher for women than men: the mean dose-normalized C_{max} and AUC_{0-∞} values were approximately 29% and 22% higher, respectively, in women. When the single-dose pharmacokinetic parameters of effervescent fentanyl were summarized by weight and sex, the results showed that the observed differences between men and women were largely attributable to differences in weight.

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Table 9. Pharmacokinetic Parameters for Fentanyl Following a Single Dose of OraVescent Fentanyl by Sex

Parameter Statistic	Men (N=112)	Women (N=64)	All Subjects (N=176)
Dose-Normalized AUC_[0-inf] (ng·hr/mL)			
n	105	59	164
Mean	1.46	1.78	1.57
SD	0.611	0.697	0.660
Median	1.40	1.73	1.56
Min, max	0.400, 3.46	0.500, 4.30	0.400, 4.30
Dose-Normalized C_{max} (ng/mL)			
n	112	64	176
Mean	0.225	0.290	0.248
SD	0.0882	0.1001	0.0976
Median	0.203	0.287	0.227
Min, max	0.090, 0.461	0.124, 0.567	0.090, 0.567
t_{max} (hr)			
n	112	64	176
Mean	1.26	1.05	1.14
SD	0.709	0.580	0.667
Median	1.00	0.81	0.91
Min, max	0.430, 4.00	0.330, 3.01	0.330, 4.00
t_{max} (min)			
n	112	64	176
Mean	71.8	63.3	66.7
SD	42.55	34.77	40.00
Median	60.0	48.5	54.7
Min, max	25.8, 240.0	19.8, 180.6	19.8, 240.0

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2.4. Extrinsic Factors

2.4.1. Pharmacokinetic Profile in Healthy Japanese Subjects

The Sponsor has conducted two studies to characterize PK parameters and to evaluate the safety and tolerability of OVF in adult healthy Japanese population.

Study #099-19 was conducted to characterize pharmacokinetic parameters and evaluate the dose proportionality of single doses of fentanyl citrate OVF tablets over a 100 mcg through 800 mcg dose range in 23 healthy Japanese volunteers. Results of this study are summarized in the Table below:

Table 10 Pharmacokinetic Parameters Following a Single Buccal Administration of 100, 200, 400, and 800 mcg Doses of OVF Citrate (Population: Pharmacokinetic, Study 011-19).

Parameter	Statistic	ORAVESCENT fentanyl citrate dose			
		100 mcg	200 mcg	400 mcg	800 mcg
C _{max} (pg/mL)	n	21	21	22	21
	Mean	452.67	905.14	1623.91	2992.38
	SD	165.77	218.91	434.30	804.1
AUC _{0-inf} (pg·hr/mL)	n	16	19	18	20
	Mean	1862.3	4214.1	9182.7	17444.8
	SD	466.80	950.54	2241.3	3876.8
AUC _{0-last} (pg·hr/mL)	n	21	21	22	21
	Mean	1707.4	3844.9	8069.8	16599.8
	SD	447.31	811.80	1927.7	3798.1
t _{max} (hr)	n	21	21	22	21
	Median	1.50	1.50	1.50	1.50
	Min, Max	0.50, 3.00	0.50, 3.00	0.50, 2.00	0.50, 3.00
t _{1/2} (hr)	n	16	19	18	20
	Mean	2.60	5.56	10.44	10.06
	SD	0.940	3.236	3.576	2.954

C_{max} values increased with increasing dose. With a 2-fold increase in dose from 100 to 200 mcg, the observed C_{max} values increased 2-fold. However, as the dose was increased to 400 and 800 mcg, the increases were less than expected. A slightly greater than proportional increase in

AUC_{0-inf} was observed as the administered dose of OVF increased from 100 mcg to 200 mcg and then to 400 mcg. An approximately proportional increase (1.9-fold) in AUC_{0-inf} was observed as the administered dose increased from 400 to 800 mcg. AUC_{0-last} values tended to increase in a slightly greater than proportional manner across the entire dose range. Dose proportionality was not established for AUC_{0-last} and C_{max}, and was marginal for AUC_{0-inf}. The median T_{max} was 90 minutes and remained dose independent across the doses. The mean half-life of fentanyl tended to increase with dose up to 400 mcg, due presumably to non-quantifiable serum concentrations much earlier at the lower doses. The mean dwell times of the OVF tablets were 49, 59, 59, and 68 minutes for the 100-mcg, 200-mcg, 400-mcg, and 800-mcg doses, respectively.

Oral Mucosa Irritation: There were no subjects who had any reported changes in the oral mucosa evaluation after dosing with OVF.

Study #099-20 was conducted to characterize pharmacokinetic parameters of multiple dosing of fentanyl citrate OVF tablets in 14 healthy Japanese volunteers. Subjects received a single dose of OVF 400 mcg Q6H for a total of 10 doses. One subject withdrew from the study due to treatment-related nausea and vomiting. The tolerability of the OVF citrate tablets was evaluated by performing oral mucosa examinations after each dose and by monitoring adverse events for any association with the oral mucosa.

Results of this study are summarized in the Table 11, and the mean serum fentanyl concentration versus time profiles are illustrated in Figure 8 below.

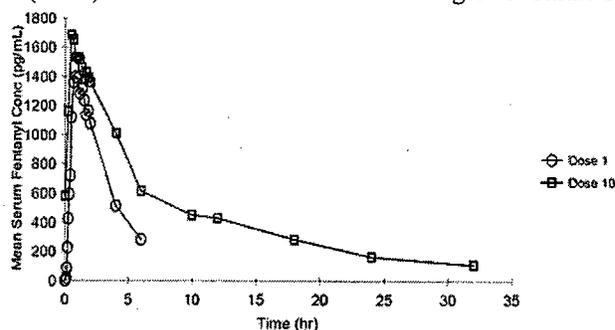
Table 11: Fentanyl Serum Pharmacokinetics (Mean, %CV) Following 1 and 10 Buccal Administrations of 400-mcg ORAVESCENT Fentanyl Citrate Tablets in Healthy Japanese Subjects

Parameter	1 st dose (n=14)	Last (10 th) dose (n=13)
C _{max} (pg/mL)	1702.4 (28.7)	1972.3 (21.2)
t _{max} (hr) ^a	0.833 (0.500, 1.833)	0.500 (0.250, 2.000)
AUC ₀₋₆ (pg·hr/mL)	4458.4 (25.5)	6805.4 (13.3)
AR-C _{max}	NA	1.23 (43.3)
AR-AUC ₀₋₆	NA	1.55 (22.6)
Accumulation Factor (R)	NA	2.05 (21.1)
AUC _{0-∞} (pg·hr/mL)	NA	16085.48 (14.1)
AUC _{0-last} (pg·hr/mL)	NA	14410.85 (12.7)
C _{min} (pg/mL)	NA	577.31 (19.7)
λ _z (1/hr)	NA	0.07 (17.1)
t _{1/2} (hr)	NA	10.29 (14.8)

^at_{max} is presented as the median (minimum, maximum).

AR=accumulation ratios for multiple compared to single dosing calculated as the ratio of AUC₀₋₆ Dose 10/AUC₀₋₆ Dose 1 and as the ratio of C_{max} Dose 10/C_{max} Dose 1

Figure 10: Mean Serum Fentanyl Concentrations in Healthy Japanese Subjects Following 1 (N=14) or 10 (N=13) Buccal Administrations of 400-mcg OVF Citrate Tablets



The fentanyl t1/2 (~10 hr) of the multiple 400 mcg of dose was similar to that in single 400 mcg dose, and the Cmax value observed in study single dose 400 mcg study was similar to that observed after the first dose in this study. Accumulation of fentanyl in serum was observed following administration of 10 successive 400-mcg doses of OVF.

OVF citrate tablets were generally well tolerated at the site of tablet placement for the initial 4 doses when administered as 10 successive 400-mcg doses at 6-hour intervals. At doses 5 through 10 there was an indication of mucosa changes at the application site associated with the use of the tablets, which has led to a recommendation to routinely vary the site of tablet placement (eg, using alternate sides of the mouth).

The adverse events of nausea and vomiting that led to the withdrawal of one subject (#207) appeared to be related to study drug and are consistent with adverse events that have been reported for both fentanyl and naltrexone.

2.5. General Biopharmaceutics

2.5.1. Are the OVF Formulations used in PK trials same as that used in the clinical efficacy studies, and in the proposed marketing product?

As reported in the NDA submission, all the clinical pharmacology studies and clinical efficacy and safety trials used the to-be-marketed formulation (the Generation III formulations).

2.5.2. What are the components and composition of the to-be-marketed formulation?

The components and compositions of a 100 mcg to-be-marketed formulation are provided in the Table below. *The 200 mcg – 800 mcg tablets have a size of 5/16 in and the total weight of 200 mg/tablet in each case.*

200 mcg – 800 mcg tablets size 5/16 in., total weight = 200 mg/tablet

Table 1: 100 mcg Fentanyl 1/4 in. Tablet

Component	Reference to quality standard	mg/tablet	Qty/Batch (kg)
Fentanyl Citrate	USP/Ph.Eur.		
Mannitol	USP/Ph.Eur.		
Sodium Bicarbonate	USP/ Ph.Eur.		
Citric Acid,	USP/Ph.Eur.		
Sodium Carbonate,	NF/Ph.Eur.		
Sodium Starch Glycolate	NF/Ph.Eur.		
Magnesium Stearate, Non-Bovine	NF/Ph.Eur.		
Total		100.000	

2.5.3. What are the Dissolution Characteristics of the proposed marketing product?

Dissolution of fentanyl effervescent buccal tablets occurs in less than 10 min, with average release rate ranging from 96% to 102%.

Dissolution profiles were obtained using various phosphate- or acetate-buffered media over a pH of 4.5 to 8.0, as well as in water. No significant effect on dissolution profile was observed. Varying rotation speeds over 50 to 100 rpm were also tried, the 100 rpm was found to be most suitable in terms of eliminating a trend of decreasing amount of fentanyl dissolved with increased dosage strength.

The following dissolution method was used for the clinical trial formulation (intended to-be-marketed batch) of the OVF tablets:

Apparatus: Small volume dissolution apparatus, paddle, speed 100 rpm
 Medium: pH 7.0 phosphate buffered saline solution; 37 °C±0.5 °C
 Volume: 100 mL for 100 mcg and 400 mcg strengths
 200 mL for 200 mcg, 600 mcg and 800 mcg strengths
 Specification: NLT — Q) in 10 minutes

The results of the dissolution testing are summarized in the Table below

Table12: Fentanyl Effervescent Buccal Tablets Dissolution Release Data

Batch Number	Strength	Dissolution (% dissolved)			
		mean % (10 minutes)	range % (10 minutes)	mean % (15 minutes)	range % (15 minutes)
Method:		ATM-339, 390, 391, 450			
Acceptance Criteria:		Meets current USP criteria where Q = 100% in 10 minutes. ^{a,b}			
730963	100	100		100	
730964	100	99		99	
730965	200	98		98	
730966	200	100		100	
730969	400	97		98	
730970	400	96		97	
730971	600	98		97	
730972	600	99		99	
730973	800	97		97	
730974	800	98		99	
740697	200	101		101	
740684	100	100		101	
740685	200	102	102		
740686	400	99	100		

Dissolution of fentanyl effervescent buccal tablets occurs in less than 10 min. Because of the rapid dissolution, a single dissolution time point specification is appropriate. The release data for the pivotal clinical and registration stability batches ranged from 96% to 102% (average) with a low individual value of — . Thus, the specification NLT — Q) in 10 minutes meets the current USP <711> criteria, and is acceptable.

2.6. Analytical Section

Concentrations of fentanyl were determined in human plasma samples by a validated high-performance LC-MS/MS method.

The analytical analyses were done at either of the following two sites:

_____, for Study # 099-16, C25608/1026, C25608/1027, C25608/1028, C25068/1029;
The method included _____

/ / / /

_____ for Study # 099-11, 099-18, 099-19, 099-20. The

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4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Review

4.2.1. Study Protocol C25608/1027

Title: *An Open-Label, Randomized, Crossover Study to Assess the Dose Proportionality and Pharmacokinetics of 4 Doses (100, 200, 400, and 800 mcg) of ORAVESCENT® Fentanyl Citrate in Healthy Subjects.*

Study Site: _____

Principal Investigator: _____

Objectives:

The objectives of the study were to evaluate the dose proportionality of 4 single doses (100, 200, 400, and 800 mcg) of ORAVESCENT fentanyl citrate (OVF), and to determine various pharmacokinetic measures of OVF.

Study Design: This was a Phase 1, open-label, randomized, crossover study to assess the dose proportionality and pharmacokinetics of 4 single doses (100, 200, 400, and 800 mcg) of OVF. Subjects received all 4 doses of study drug over the study period (minimum of 25 days following screening period). Subjects were randomized to 1 of 4 treatment sequences (ABDC, BCAD, CDDBA, or DACB), where A, B, C, and D denoted the dose groups from lowest to highest (100, 200, 400, and 800 mcg). Successive treatments were separated by a minimum 7-day washout period.

Treatments:

OVF tablets were administered as single doses of 100, 200, 400, and 800 mcg. Each subject received 1 tablet during each treatment period. Subjects received all 4 doses of study drug. Study drug was orally administered to subjects, at approximately 0800 on study days 1, 8, 15, and 22 (relative to first study drug administration [day 1]). All treatments were in a fasted state following a 10-hour overnight fast.

Subjects placed the tablet into a buccal position (between the upper gum and cheek, above a molar tooth) and allowed the tablet to disintegrate undisturbed for 10 minutes. If subjects felt that after 10 minutes a portion of the tablet still remained, they gently and continuously massaged the cheek in the area corresponding to the location of the tablet for the next 5 minutes. At 30 minutes after tablet administration, subjects were asked to swallow, with approximately 125 mL of water, any portion of the tablet that had not disintegrated.

Subjects received one 50-mg tablet of naltrexone hydrochloride for blockade of opioid effects, approximately 15 hours and 3 hours before study drug administration and approximately 9 hours after study drug administration.

A total of 32 subjects (26 males and 6 females, 22 Caucasians, 3 African American, 4 Asian, and 3 Others) were enrolled in the study. Thirty-one subjects completed the study. One subject withdrew from the study and did not receive the last treatment (100 mcg). The mean age of the subjects was 29.3 years (range 19-44 years), the mean height and weight were 175.4 cm (range 160.0-190.5 cm), and 74.7kg (range 54.4-94.5 kg).

Blood samples (7 mL) were collected at the following times for: predose (Hour 0), and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50., 60, 75 and 90 minutes; and 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 36, 48, and 72 hours postdose.

Human serum samples were analyzed for fentanyl concentrations by _____ using a validated LC-MS/MS method, _____

PK Measures and Methods: Pharmacokinetic parameters e.g., C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, and t_{1/2} for fentanyl were evaluated. The dose proportionality across the range of 100 to 800 mcg was evaluated using a 90% confidence interval for AUC. Treatments B (200 mcg), C (400 mcg), and D (800 mcg) were compared to treatment A (100 mcg, reference). A mixed model with a compound covariance was used to calculate the slope and the confidence intervals (CIs) for the ln(AUC) versus ln(dose) to account for intra- and inter-subject variability.

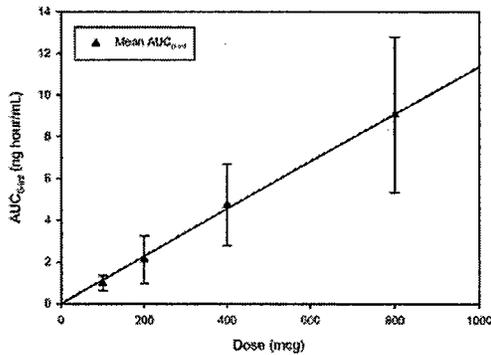
Results of Pharmacokinetic and Statistical Analyses:

The extent of exposure parameters AUC_{0-t} and AUC_{0-inf} are presented by treatment with dose proportionality slopes in Table 1 below. In addition, AUC_{0-inf} is plotted versus dose in Figure 1. Both AUC_{0-t} and AUC_{0-inf} appeared to increase in a dose proportional manner.

Table 1: Pharmacokinetic Parameters (AUC_{0-t} and AUC_{0-inf}) by Treatment With Dose Proportionality Slopes

Variable Statistic	ORAVESCENT fentanyl				Slope	90% CI
	100 mcg (N=31)	200 mcg (N=31)	400 mcg (N=31)	800 mcg (N=31)		
AUC _{0-t} (ng·hr/mL)						
N	31	31	31	31		
Mean±SD	0.80±0.26	1.39±0.46	2.90±0.92	5.27±1.85	0.9226	(0.8832, 0.9620)
AUC _{0-inf} (ng·hr/mL)						
N	25	27	29	30		
Mean±SD	0.98±0.37	2.11±1.13	4.72±1.95	9.05±3.72	1.0490	(0.9954, 1.1025)

Figure 1: Mean (SE) AUC_{0-inf} as a Function of Dose Following a Single Dose of 100, 200, 400, or 800 mcg of ORAVESCENT Fentanyl



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Table 2: Summary of Single Dose Pharmacokinetics from Dose-Proportionality Study 1027

Variable	ORAVESCENT fentanyl			
	100 mcg (N=31)	200 mcg (N=31)	400 mcg (N=31)	800 mcg (N=31)
AUC _{0-inf} ^a (ng hr/mL)	0.98±0.37	2.11±1.13	4.72±1.95	9.05±3.72
AUC _{0-t} (ng hr/ml)	0.80±0.26	1.39±0.46	2.90±0.92	5.27±1.85
AUC ₀₋₂₄ (ng hr/ml)	0.96±0.41	1.85±0.80	3.98±1.37	7.38±2.71
AUC ₀₋₇₂ (ng hr/ml)	0.99±0.46	1.93±0.90	4.39±1.80	8.39±3.59
AUC _{0-max'} (ng hr/ml)	0.09±0.06	0.13±0.09	0.34±0.23	0.52±0.38
AUC _{0-t} (ng hr/ml)	0.91±0.42	1.79±0.82	4.17±1.72	8.11±3.63
C _{max} (ng/mL)	0.25±0.14	0.40±0.18	0.97±0.53	1.59±0.90
t _{max} ^b (min)	45.0 (25.0, 181.0)	40.0 (20.0, 180.0)	35.0 (20.0, 180.0)	40.0 (25.0, 180.0)
t _{1/2} ^{a,b} (hr)	2.63 (1.47, 13.57)	4.43 (1.85, 20.76)	11.09 (3.44, 20.59)	11.70 (4.63, 28.63)

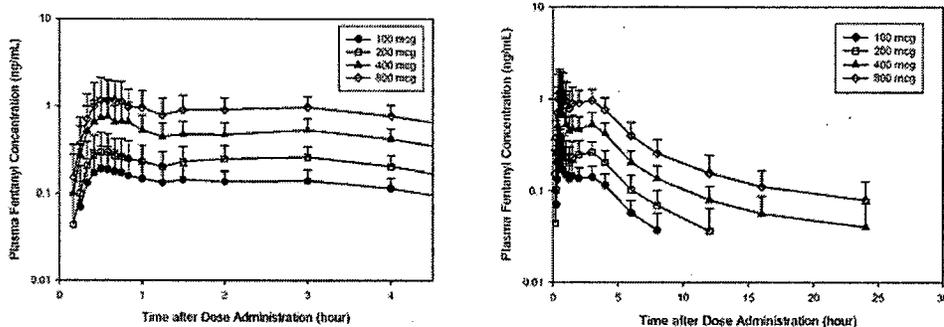
^a Not all subjects' data were extrapolated. For 100 mcg, n=25; for 200 mcg, n=27; for 400 mcg, n=29; and for 800 mcg, n=30.

^b Median (range) is presented for these variables. Mean±SD is presented for all other variables.

AUC_{0-t}' = AUC from time zero to the last time point at which at least 75% of the subjects within all dose groups had a measurable plasma concentration.

The mean serum fentanyl concentration versus time curves for each treatment are presented in Figures 2 (0-4 hr) and 3.

Figure 2: Mean (SE) Plasma Concentration Versus Time (Up to 4 Hours, Top Panel) Profiles of Fentanyl in Healthy Subjects Administered Single Doses of 100, 200, 400, or 800 mcg of OVF



Interindividual variability for both C_{max} and AUC_{0-inf} was approximately 37% and intraindividual variability for C_{max} and AUC_{0-inf} were approximately 31% and 25%, respectively following administration of ORAVESCENT fentanyl.

The median estimated t_{1/2} values increased with increasing dose (ranged from approximately 3 through 12 hours) which may have been largely due to incomplete characterization of the terminal elimination phase where plasma concentrations at sampling times later in the profile were not quantifiable for many subjects.

For the majority of subjects, the absorption phase was followed by a biexponential decline from peak concentration at the lower doses (100 and 200 mcg) and a triexponential decline from peak concentration at the highest dose (800 mcg) (Figures 2 and 3).

While the mean pharmacokinetic profile following 400-mcg dose depicts a triexponential decline, approximately half of the individual subject profiles show a biexponential decline. The initial portion of decline represents a very rapid distribution followed by an elimination/gastrointestinal absorption phase and a final phase of redistribution between plasma and tissue.

At the lower doses (100 mcg and 200 mcg) of OVF about 60% of the subjects exhibited Tmax between 20 to 60 minutes, while a significant number of subjects (26% with 100 mcg, and 44% with 200 mcg) attained Tmax at a later time between 90-180 minutes. With higher doses (400 mcg and 800 mcg) 70-78% of subjects had Tmax in the range of 20-60 minutes, while one-fourth (25%) exhibited Tmax between 90-180 minutes. The large inter subject variations in Tmax values are presumably due to variation in buccal absorption. The clinical significance of the variation in Tmax is that the onset of pain relief may also vary among patients.

Table 3. Median Tmax and Inter subject Variation for 4 doses in Study 1027

Dose	Median	Tmax (hr) n%/(range hr)				
		0.33- 0.50	0.51-1.0	1.1-1.5	1.51-2.0	2.1-3.0
100 mcg (N=31)	0.75	10/32% (0.42-0.50)	10/32% (0.58- 0.83)	3/9.7% (1.1- 1.50)	2/7% (2.00)	6/19.3% (3.00- 3.01)
200 mcg (N=32)	0.67	9/28% (0.33- 0.50)	9/28% (0.58- 1.00)	0	6/19% (2.00)	8/25% (3.00)
400 mcg (N=32)	0.58	12/38% (0.33-0.50)	11/34% (0.58- 1.0)	0	3/9% (1.00)	6/19% (3.00)
800 mcg (N=32)	0.67	10/31% (0.42-0.50)	13/40% (0.58- 1.0)	1/3% (1.50)	4/13% (1.51-2.0)	4/13% (3.00)

Safety Results: All subjects were treated with naltrexone (50 mg) prior to and following each study drug administration, thereby blocking opioid receptor-mediated adverse events. There were no deaths or other serious adverse events reported in this study. One subject withdrew prior to study completion due to an adverse event (tooth abscess) unrelated to study drug. The most common adverse events (occurring in more than 5% of the subjects) were nausea, somnolence, application site erythema, headache, application site ulcer, oxygen saturation decreased, upper abdominal pain, fatigue, dizziness, pharyngolaryngeal pain, vomiting, application site pain, and stomach discomfort. Gastrointestinal disorders, general disorders, fatigue, and application site ulceration but not erythema appeared to be dose related. The majority of adverse events were reported as mild in severity and none were reported as severe. Six subjects experienced the adverse event of decreased oxygen saturation; all events were considered to be related to OraVescent fentanyl, but not to dose, and all events resolved with no residual effects. Administration of oxygen was not deemed necessary by the investigator.

Conclusions:

- The pharmacokinetics of fentanyl were characterized by a rapid absorption phase with median t_{max} being independent of dose and ranging from 35 to 45 minutes. The individual T_{max} values across the strengths ranged from 20 to 181 minutes. For the majority of subjects, the absorption phase was followed by a biexponential decline from peak concentration at the lower doses (100 and 200 mcg) and a triexponential decline from peak concentration at the highest dose (800 mcg).
- The estimated median $t_{1/2}$ ranged from approximately 3 hours for the 100-mcg dose to approximately 12 hours at the 800-mcg dose.
- The 4 doses (100, 200, 400, and 800 mcg) of ORAVESCENT fentanyl, as assessed by $AUC_{0-\infty}$ and AUC_{0-t} , appeared to be dose proportional. While the CIs for some parameter, e.g. C_{max} did not fall entirely within dose proportionality limits, exceptions showed no trend toward deviation from linearity.
- There was no clear effect of dose on overall incidence of adverse events, although dose-related increases in gastrointestinal disorders, general disorders, fatigue, and administration site conditions were observed.

4.2.2. Study Protocol 099-18

Title: A Pharmacokinetic Study in Healthy Subjects to Evaluate the Dose Proportionality of Fentanyl Citrate Formulated as ORAVESCENT Tablets When Administered in Doses of 200 mcg, 500 mcg, 810 mcg, and 1080 mcg.

Study Site: _____

Principal Investigator: _____

Objectives:

This study was conducted to more fully evaluate the dose proportionality (AUC and C_{max}) of fentanyl citrate formulated in OraVescent tablets over the range that may be used therapeutically, and to confirm the C_{max} observations already made following administration of 810 mcg and 1080 mcg doses of OraVescent.

Study Design: This was a single-dose, randomized, open-label, 4-treatment, 4-period, crossover study. Subjects received all 4 doses of study drug over the study period. Successive treatments were separated by a minimum 7-day washout period.

Treatments: The subjects were randomized to receive the following treatments:

Treatment A: OraVescent Fentanyl Citrate 200 mcg tablets

Treatment B: OraVescent Fentanyl Citrate 500 mcg tablets

Treatment C: OraVescent Fentanyl Citrate 810 mcg tablets

Treatment D: OraVescent Fentanyl Citrate 1080 mcg tablets

OraVescent (OVF) tablets were administered as single doses of 200, 500, 810, and 1080 mcg tablets placed between the upper gum and cheek, above a molar tooth, and allowed to disintegrate for 10 minutes. All treatments were in a fasted state following a 10-hour overnight fast.

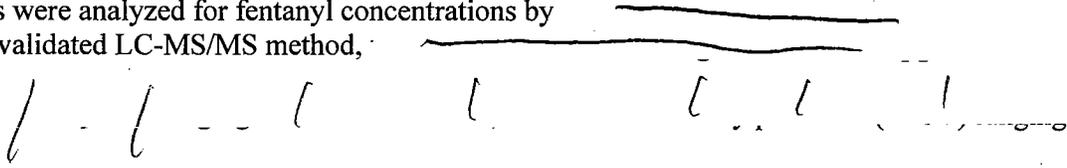
Subjects received one 50-mg tablet of naltrexone hydrochloride for blockade of opioid effects, approximately 15 hours and 3 hours before study drug administration for Treatment A, and

approximately 15 hours and 3 hours prior to dosing, and 12 hours post-dose for Treatments B,C, and D.

A total of 28 subjects (16 males and 12 females, 22 Caucasians, 3 African American, 4 Asian, and 3 Others) were enrolled in the study. Twenty-five subjects completed the study. Two subjects voluntarily dropped from the study prior to Period 3, and one subject was dropped following dosing on Period 2 because of AE. The mean age, height and weight of the subjects were 33 years (range 19 – 55 years), 68.6 inches (range 60 – 76 inches), and 160.9 pounds (range 110 – 215 pounds), respectively.

Blood samples (7 mL) were collected at the following times for subjects assigned to Treatment A: Predose (Hour 0), 10, 20, 30, and 45 minutes; and 1, 2, 4, 6, 8, 9, 10, 11, 12, 14, 16, 20, and 24 hours postdose. Blood samples (7 mL) were collected at the following times for subjects assigned to Treatments B, C and D: Predose (Hour 0), 10, 20, 30, and 45 minutes; and 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, and 36 hours postdose.

Samples were analyzed for fentanyl concentrations by using a validated LC-MS/MS method,



PK Measures and Methods: The pharmacokinetic parameters C_{max}, T_{max}, AUC(0-t), AUC(0-inf), AUCR, AUC(0-t_{max}), K_{el}, and T_{1/2} were calculated using noncompartmental methods. Log-transformed parameters were analyzed using a mixed effects model including the log-transformation of dose as well as fixed and random effects for intercept. A 90% confidence interval (CI) about the fixed effect for slope was calculated and compared to the range (0.8677, 1.1323), which is the appropriate critical range given the range of doses investigated in this study. Dose proportionality was concluded if the 90 %CI were within the critical range. The PK profile is summarized in Tables 4-5, and depicted in Figure 3 below:

The dwell time values (length of time the formulation was present in the oral cavity) were calculated by subtracting the medication administration time from the time of perceived and documented disappearance of the formulation. These values summarized in the table below

Table 4. Mean Dwell Time for OVF (Study # 099-18)

Dwell Time (Minutes)				
	Treat A (N=40)	Treat B (N=42)	Treat C (N=12)	Treat D (N=13)
Mean	14	14	17	15
SD	8	6	10	11
CV	59	45	57	72
Minimum	4	6	5	4
Maximum	37	33	41	60

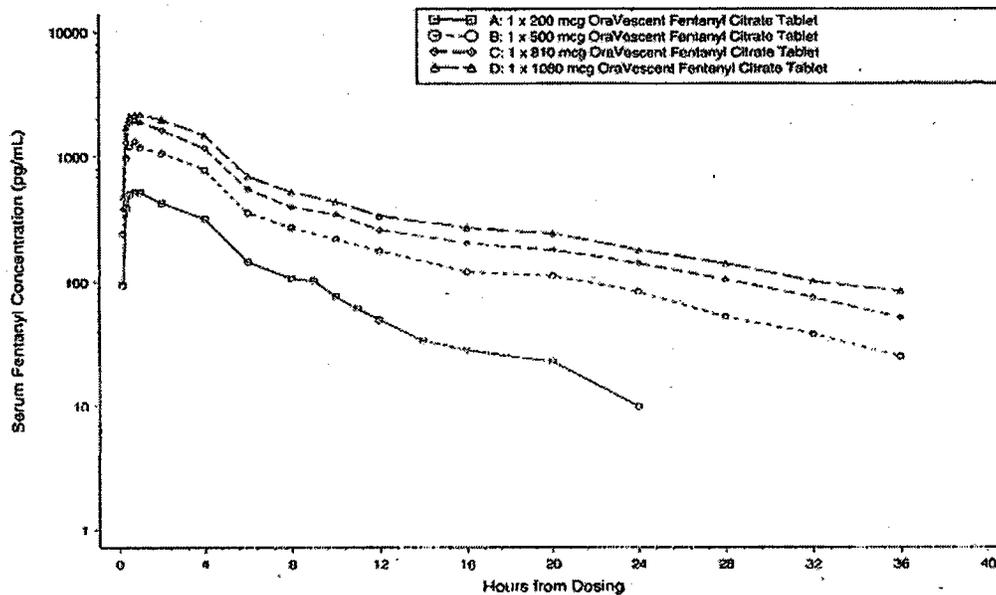
Treat A = 200 mcg, Treat B = 500 mcg, Treat C = 810 mcg, Treat D = 1080 mcg

Table 5. Summary the Pharmacokinetic Parameters of Serum Fentanyl

Pharmacokinetic Parameters	Serum Fentanyl											
	Treatment A			Treatment B			Treatment C			Treatment D		
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD
C _{max} (pg/mL)	25	617.8	236.7	26	1546.2	621.4	27	2280.1	968.9	27	2682.3	1106.0
*t _{max} (hr)	25	0.76	0.33-4.0	26	0.75	0.33-4.0	27	0.99	0.33-4.0	27	0.75	0.33-4.0
AUC(0-t) (pg*hr/mL)	25	2876.3	1107.7	26	8501.2	3346.2	27	13301	4069.1	27	16813	5232.2
AUC(0-inf) (pg*hr/mL)	24	3543.9	1304.5	26	9701.9	3651.5	27	14962	4709.6	27	18664	6266.0
TL/2 (hr)	24	6.48	3.69	26	12.0	8.18	27	12.8	4.08	27	11.4	4.34
Ke ₁ (1/hr)	24	0.143	0.0802	26	0.0746	0.0377	27	0.0592	0.0167	27	0.0679	0.0216
AUC _R	24	0.843	0.0604	26	0.875	0.0929	27	0.893	0.0589	27	0.909	0.0602
C _{max} /dose (pg/mL/mcg)	25	3.09	1.18	26	3.09	1.24	27	2.81	1.20	27	2.48	1.02
AUC(0-t)/dose (pg*hr/mL/mcg)	25	14.4	5.54	26	17.0	6.69	27	16.4	5.02	27	15.6	4.84
AUC(0-inf)/dose (pg*hr/mL/mcg)	24	17.7	6.52	26	19.4	7.30	27	18.5	5.81	27	17.3	5.80
ln(C _{max} /dose)	25	1.06	0.383	26	1.05	0.426	27	0.945	0.439	27	0.836	0.386
ln(AUC(0-t)/dose)	25	2.59	0.424	26	2.75	0.441	27	2.75	0.324	27	2.69	0.356
ln(AUC(0-inf)/dose)	24	2.81	0.369	26	2.89	0.413	27	2.87	0.329	27	2.79	0.372

*Median and min-max are reported for t_{max}.
 Treatment A = 1 x 200 mcg OraVescent Fentanyl Citrate Tablet
 Treatment B = 1 x 500 mcg OraVescent Fentanyl Citrate Tablet
 Treatment C = 1 x 810 mcg OraVescent Fentanyl Citrate Tablet
 Treatment D = 1 x 1080 mcg OraVescent Fentanyl Citrate Tablet

Figure 3 Mean Serum Fentanyl Concentrations Versus Time (Semi-Log Scale)



The oral irritation assessments were conducted at 4 hours postdose. Two subjects (Subjects 6 and 23) reported slight oral irritation (2 and 3 on a scale of 1 to 10) that occurred following Treatment A. The irritation was on the left side of the mouth following test product administration during Period 2 for both subjects; one of these subjects (Subject 23) also exhibited redness upon visual inspection of the area by study personnel. One additional subject (Subject 25) reported pain in the upper left buccal area at the gum line 11 minutes following Treatment C

CONCLUSIONS:

- Fentanyl AUC increased proportionally with increasing dose in the range of 200 mcg to 1080 mcg.
- Slightly less than proportional increases in C_{max} were observed with the highest fentanyl doses (810 mcg, and 1080 mcg).
- The mean dwell time for the 200 mcg, 500 mcg, 810 mcg and 1080 mcg OraVescent^o Fentanyl Citrate tablets were similar, at 14 minutes, 14 minutes, 17 minutes, and 15 minutes, respectively.
- As reported by the Sponsor, there were no serious or unexpected adverse events during the study. All formulations were well tolerated by the oral mucosa. However, it is noted that the Medical Officer will conduct an overall assessment of safety in the NDA.

4.4.3. Study Protocol 099-11

Title: *A Pharmacokinetic study in healthy subjects to compare the bioavailability of fentanyl when administered as 4 OraVescent Fentanyl Citrate doses manufactured by CIMA Lab Inc. and the marketed 1600 µg Fentanyl Citrate Oral Transmucosal Formulation, Actiq®, manufactured by Cephalon, Inc.*

Study Site:

Principal Investigator:

Objectives: The primary objective was to determine the bioequivalence of single dose of fentanyl citrate when administered as OraVescent Fentanyl Citrate 1080 µg and as a marketed 1600 µg oral transmucosal formulation, Actiq.

The secondary objective was to assess the dose proportionality of the OVF formulation in the dose strengths of 270 µg, 810 µg, 1080 µg, and 1300 µg

Study Design: For the first two periods the study utilized a single-dose, randomized, open-label, 2-way crossover design of the designated test OVF 1080 µg (Treat A) and reference (Treat B) products Actiq 1600 µg. Subjects were then randomized to receive one of three additional test formulations (OVF 270 µg, 810 µg, and 1300 µg) during Period 3. All subjects randomized were in a fasted state following a 10-hour overnight fast. There was a 7-day washout interval between the three dose administrations. The subjects were confined to the clinic through 36 hours post fentanyl administration.

Treatments:

Subjects received one of the following fentanyl treatments at each of 3 periods:

- Treatment A: Single oral dose of one 1080 µg OVF tablet placed between the upper gum and cheek above a molar tooth and allowed to disintegrate for 10 minutes.
- Treatment B: Single oral dose of one 1600 µg Actiq unit placed in the mouth between the cheek and lower gum. The unit was to be moved from side to side using the handle and allowed to dissolve for 15 minutes.
- Treatment C: Single oral dose of one 1300 µg OVF tablet administered as in Treat A.
- Treatment D: Single oral dose of one 810 µg OVF tablet administered as in Treat A.

- Treatment E: Single oral dose of one 270 µg OVF tablet administered as in Treat A.

All treatments were in a fasted state following a 10-hour overnight fast. There was a 7-day washout interval between the three dose administrations. The subjects were confined to the clinic through 36 hours post fentanyl administration.

Subjects received 50 mg naltrexone hydrochloride tablets at each period as detailed below:

- Subjects assigned to Treatments A, B, C, and D received an oral dose of one 50 mg naltrexone tablet at 15 hours and 3 hours prior to, and 12 hours following the fentanyl dose.
- Subjects assigned to Treatment E received an oral dose of one 50 mg naltrexone tablet at 15 hours and 3 hours prior to the fentanyl dose.

A total of 42 subjects (17 males and 25 females, 33 Caucasians, 1 American Indian, 4 Asians, 2 European and 2 Hispanic) were enrolled in the study. Thirty-nine subjects, 17 males and 22 females, completed the study. Three subjects (#10, 15 and 42) were discontinued/withdrawn from the study. The mean age, height and weight of the subjects were 27 years (range 19-55 years), 68 inches (range 62 - 74 in), and 152.1 pounds (range 109.0 - 197.0 lb), respectively.

Blood samples (7 mL) were collected at the following times for Treatments A-D: predose (Hour 0), and 10, 20, 30, and 45 minutes; and 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, and 36 hours postdose. For Treat E samples were collected at predose (Hour 0), and at 10, 20, 30, and 45 minutes; and 1, 2, 4, 6, 8, 9, 10, 11, 12, 14, 16, 20, and 24 hours postdose.

Human serum samples were analyzed for fentanyl concentrations by _____ using a validated LC-MS/MS method as summarized above for study 099-18.

Oral Irritation

An assessment for oral irritation was done 4 hours following the start of administration for each treatment. One subject reported slight oral irritation (2 on a scale of 1 to 10) that occurred following Treat C. The irritation was on the right side of the mouth following test product administration during Period 3. There was one report of redness upon visual inspection of the area on the right upper cheek by study personnel that occurred following Treat E.

PK Measures and Methods:

The pharmacokinetics of fentanyl were assessed by measuring serial serum concentrations following single dose administration of 1080 pg OraVescent Fentanyl Citrate tablet (Treatment A, test) and a marketed 1600 mg oral transmucosal fentanyl citrate, Actiq (Treatment B, reference).

The pharmacokinetic parameters of C_{max}, T_{max}, AUC(0-t_{max}), AUC(0-t), AUC(0-inf), AUCR, Kel, and t_{1/2} were calculated using noncompartmental methods. The 90% confidence interval of the ratio of the geometric least squares means (test/reference) was determined for each parameter.

Serum fentanyl concentrations and pharmacokinetic parameters were also determined for 1300 µg, 810 µg, and 270 µg OVF Tablets (Treatments C, D, and E, respectively). To evaluate dose

proportionality, a mixed linear model was applied to the dose-normalized Cmax and AUC parameters from Treatments A, C, D, and E.

Results of Pharmacokinetic and Statistical Analyses:

The arithmetic means of serum fentanyl PK parameters and statistical comparisons following Treatments A and B are summarized in Table 1 below. The mean serum fentanyl concentration versus time curves for Treatments A and B are presented in Figure 4 (semi-log scale).

Table 7 summarizes the arithmetic means of the serum fentanyl pharmacokinetic parameters following Treatments C, D, and E. The mean serum fentanyl concentration versus time curves for Treatments A, C, D, and E are presented in Figure 5 (a semi-log scale).

Table 6. Summary of the Pharmacokinetic Parameters of Serum Fentanyl for Treat A and B

Pharmacokinetic Parameters	Serum Fentanyl						90% CI*	% Mean Ratio*
	Treatment A			Treatment B				
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD		
Cmax (pg/mL)	40	2704.3	877.6	40	2191.6	693.5	-	-
AUC (0-tmax) (pg*hr/mL)	40	3840.1	1266.2	40	2566.2	911.82	-	-
AUC (0-t) (pg*hr/mL)	40	16537	5464.6	40	16701	6530.1	-	-
AUC (0-inf) (pg*hr/mL)	35	17736	5424.3	39	18319	7118.5	-	-
T1/2 (hr)	35	11.7	5.04	39	11.2	4.37	-	-
Ke1 (1/hr)	35	0.0701	0.0310	39	0.0695	0.0227	-	-
AUCR	35	0.918	0.0458	39	0.917	0.0335	-	-
ln(Cmax)	40	7.854	0.3132	40	7.640	0.3349	111.82-136.20	123.4
ln[AUC (0-t)]	40	9.662	0.3226	40	9.649	0.3945	94.42-108.86	101.4
ln[AUC (0-inf)]	35	9.739	0.3027	39	9.742	0.3941	93.60-109.23	101.1

* = Based on LS Means

Treatment A = 1 x 1080 mcg OraVescent Fentanyl Citrate Tablet: test

Treatment B = 1 x 1600 mcg Oral Transmucosal Fentanyl Citrate (Actiq): reference

Figure 4. Mean Serum Fentanyl Concentrations Versus Time Treatments A and B

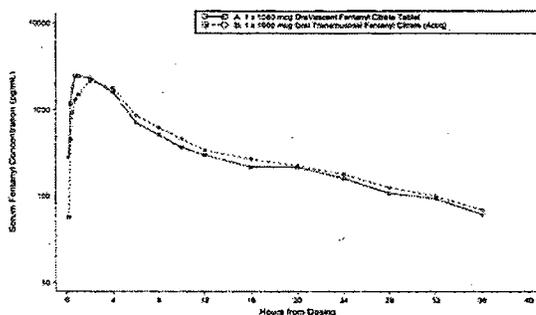
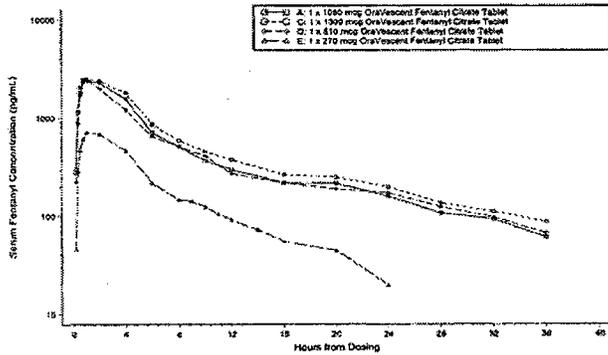


Table 7. Summary of the Pharmacokinetic Parameters of Serum Fentanyl for Treatments C, D and E

Pharmacokinetic Parameters	Serum Fentanyl								
	Treatment C			Treatment D			Treatment E		
	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD
Cmax (pg/mL)	12	2791.4	874.3	13	2646.9	778.7	14	797.9	312.9
AUC (0-tmax) (pg*hr/mL)	12	4008.3	1259.1	13	3694.8	971.89	14	1095.6	433.92
AUC (0-t) (pg*hr/mL)	12	18921	6470.2	13	15339	4260.4	14	4333.5	1597.9
AUC (0-inf) (pg*hr/mL)	12	21033	7346.3	13	16831	4449.8	9	4221.9	1747.8
T1/2 (hr)	12	13.2	7.67	13	11.7	4.66	9	6.62	3.17
Ke1 (1/hr)	12	0.0687	0.0354	13	0.0703	0.0352	9	0.126	0.0538
AUCR	12	0.907	0.0683	13	0.909	0.0376	9	0.865	0.0381

Treat C = 1 x 1300 mcg, Treat D = 1 x 810 mcg, and Treat E = 1 x 270 mcg OraVescent Fentanyl Citrate Tablet

Figure 5. Mean Serum Fentanyl Concentrations Versus Time Treatments A,C,D and E



The dose-normalized pharmacokinetic parameters for Treatments A, C, D, and E and the p-values for the differences between the treatments are summarized in the following table.

Table 8. Summary of the Dose-Normalized Pharmacokinetic Parameters of Serum Fentanyl for Treatments A, C, D, and E

Summary of the Dose-Normalized Pharmacokinetic Parameters of Serum Fentanyl for Treatments A, C, D, and E

Pharmacokinetic Parameters	P-Value	Serum Fentanyl							
		Treatment A		Treatment C		Treatment D		Treatment E	
		Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD	Arithmetic Mean	SD
C _{max} /dose (pg/mL/mcg)	.	2.5	0.8	2.1	0.7	3.3	1.0	3.0	1.2
AUC(0-t)/dose (pg*hr/mL/mcg)	.	15.4743	5.01901	14.555	4.9771	18.937	5.2597	16.050	5.9180
AUC(0-inf)/dose (pg*hr/mL/mcg)	.	16.5851	5.00318	16.179	5.6510	20.779	5.4935	15.637	6.4732
ln(C _{max} /dose)	0.0127	0.8788	0.3115	0.7190	0.3151	1.137	0.3356	1.011	0.3974
ln[AUC(0-t)/dose]	0.1727	2.690	0.3170	2.625	0.3409	2.901	0.3032	2.706	0.4002
ln[AUC(0-inf)/dose]	0.0783	2.765	0.3003	2.725	0.3633	2.998	0.2894	2.681	0.3892

The dwell time data from different treatments are summarized in the table below:

	Dwell Time (minute)				
	Treat A (N=40)	Treat B (N=42)	Treat C (N=12)	Treat D (N=13)	Treat E (N=14)
Mean	21	34	19	25	22
SD	12	15	11	14	17
CV	58	44	56	57	75
Minimum	3	9	4	4	4
Maximum	48	77	33	50	62

Treat A, C, D, and E = 1 x 1080 mcg, 1 x 1300 mcg, 1 x 810 mcg, and 1 x 270 mcg OraVescent Fentanyl tablets, respectively. Treat B = 1 x 1600 mcg Actiq

CONCLUSIONS:

- The primary objective of this study was to assess the bioequivalence of a 1080 µg dose of OraVescent Fentanyl Citrate tablet (Treat A, test) compared to the marketed 1600 µg oral transmucosal fentanyl citrate, Actiq (Treat B, ref) under fasted conditions. The ratios of geometric least square means (test/ref) for fentanyl C_{max}, AUC(0-t), and AUC(0-inf) were 123.4%, 101.4%, and 101.1%, respectively. These data indicate that the average fentanyl

exposure was similar but the peak exposure was higher for Treat A compared to Treat B. The Tmax for Treat A (1.0 hour) occurred an hour earlier than Treat B (2.0 hour) and Cmax was 23% higher, indicating that the rate of fentanyl absorption was significantly faster for Treat A compared to Treat B.

- The 90% confidence intervals for Cmax at 111.82% – 136.20%, AUC(0-t) at 94.42% – 108.86%, and AUC(0-inf) at 93.60% – 109.23% indicated that Treat A and Treat B met the requirements for bioequivalence with respect to AUC but not with respect to Cmax.
- Fentanyl AUC increased proportionally to the dose in the range of 270 to 1300 µg for the OVF tablet formulations. There were no significant differences in dose-normalized AUC(0-t) or AUC(0-inf) among the 4 OraVescent doses. A significant overall treatment effect was found for the comparison of dose-normalized Cmax between Treat D (810 µg) and Treat A (1080 µg). However, there was no difference in dose-normalized Cmax between Treat C (1300 µg) and Treat A or between Treat E (270 µg) and Treat A. Therefore, the finding may be due to higher intrasubject variability in Cmax.
- There were no serious or unexpected adverse events during the study. Both formulations were well tolerated by the oral mucosa.

4.2.4. Study Protocol C25608/1026

Title: A Randomized, Open- Label, Crossover Study to Evaluate the Bioequivalence of ORAVESCENT® Fentanyl Citrate (Four 100- mcg Tablets Versus One 400- mcg Tablet) and the Pharmacokinetics (From Arterial and Venous Blood Samples) of ORAVESCENT® Fentanyl Citrate (One 400- mcg Tablet) in Healthy Subjects.

Study Site: _____

Principal Investigator: _____

Study Dates: 02/24/05-93/21/05

Objectives:

The primary objective of the study was to assess BE of four 100-mcg tablets of ORAVESCENT fentanyl to one 400-mcg tablet of ORAVESCENT fentanyl. The secondary objective of the study was to compare the pharmacokinetic profile of ORAVESCENT fentanyl (400 mcg) following arterial and venous blood sampling from before study drug administration through 4 hours after study drug administration.

Study Design: Open-label, 3-way crossover design, Subjects were randomized to 1 of the following 2 treatment sequences: AB and BA where A was treatment with one 400-mcg tablet of OVF, and B was treatment with four 100-mcg tablets of OVF for treatment periods 1 and 2 (bioequivalence). In treatment period 3 (pharmacokinetics, arterial and venous blood sampling), all subjects were administered one 400-mcg tablet of ORAVESCENT fentanyl.

Study Drug Administration:

All eligible subjects received a single dose of each of the 2 treatments of ORAVESCENT fentanyl (one 400-mcg ORAVESCENT fentanyl tablet and four 100-mcg tablets). Subjects received 1 treatment on the first day of treatment periods 1 and 2 (days 1 and 8), according to randomization. Subjects received one 400-mcg tablet of ORAVESCENT fentanyl on the first

day of treatment period 3 (day 15). Treatment periods were separated by a 7-day washout period.

For treatment A, subjects placed the tablet between the upper gum and cheek, above a molar tooth, and allowed the tablet to disintegrate undisturbed for 10 minutes. For treatment B, subjects placed 2x1000 mcg tablets on each side of the mouth. The tablets could not partly cover or touch each other. If subjects felt that after 10 minutes a portion of the tablet(s) still remained, they gently and continuously massaged the cheek in the area corresponding to the location of the tablet(s) for the next 5 minutes. Thirty minutes after tablet administration, subjects were asked to swallow any portion of the tablet(s) that had not disintegrated with approximately 125 mL of water.

Naltrexone hydrochloride 50 mg tablets were administered at approximately 15 hours and 3 hours before and approximately 9 hours after study drug administration.

Exclusion Criteria (among others):

- The subject had received any investigational drug within 30 days or 5 half-lives (whichever was longer) before screening visit or in the case of a new chemical entity, 3 months or 5 half-lives (whichever was longer) before screening visit.
- The subject had used any systemic, topical prescription or nonprescription (over-the-counter medication (except acetaminophen, ibuprofen, and permitted contraceptives) or herbal supplements within 2 weeks before the screening visit or 5 half lives (whichever was longer).

A total of 27 subjects (21 males and 6 females, 25 Caucasians, 1 Asians, and 1 Other participated in the study. The mean age of the subjects was 24.1 years (range 19-45 years), the mean height and weight were 174.8 cm (range 149.9-195.6 cm), and 77 kg (range 53.5-99.8 kg). All 27 subjects completed the treatments 1 and 2, whereas only 17 subjects completed treatment period 3 as 9 subjects had difficulties inserting the arterial line, and 1 subject was dropped due to a positive urine test.

Blood samples (4 mL each) were collected at the following times for Treatments A-B: predose (Hour 0), and at 5, 10, 15, 20, 25, 30, 40, 45, 50, 75, and 90 minutes; and 2, 4, 6, 8, 12, 16, 24, 36, 48, 72 hours postdose. For treatment period 3, samples were collected at the above time points up to and including 4 hours following study drug administration.

Plasma samples were analyzed for fentanyl concentrations by 

- The analytical method validation has been reported above under study 1027.

Pharmacokinetic Results and Analysis:

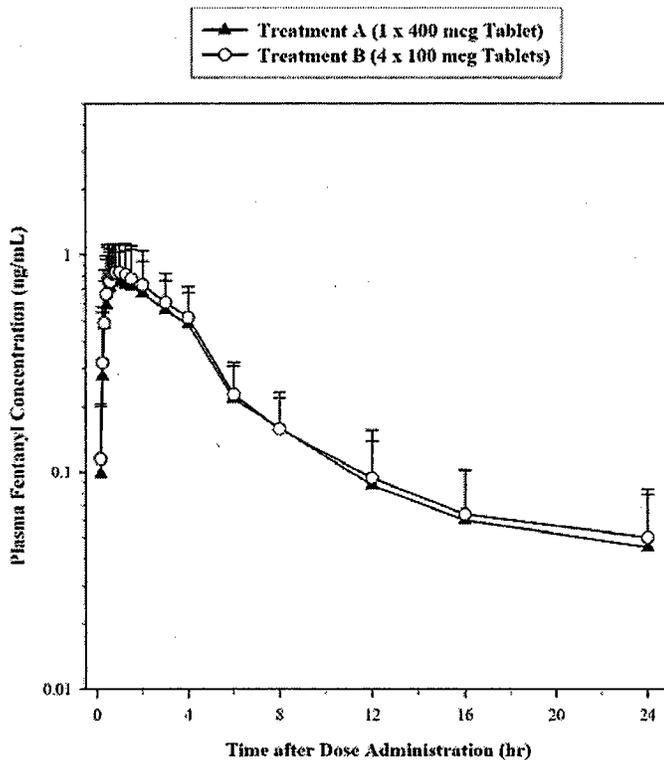
Summary statistics for the pharmacokinetic parameters are presented in Table 9 and mean plasma concentration time profile is depicted in Fig 6. Similar pharmacokinetic profiles were observed following administration of treatment A and treatment B. Mean PK profiles exhibit a rapid absorption phase with median t_{max} being reached at approximately 45 minutes, followed by a triexponential decline from peak concentration (Fig 6). There was no statistically significant difference in $t_{1/2}$ ($p=0.89$) or t_{max} ($p=0.48$) between one 400-mcg tablet and four 100-mcg tablets

Table 9: Plasma Fentanyl Pharmacokinetic Parameters (\pm SD*) for Treatments A and B.

PK Measures	Treat A (1x400 mcg OVF), N=27	Treat B (4x100 mcg OVF), N=27
Cmax (ng/mL)	0.94 \pm 0.42	1.03 \pm 0.37
AUC0-inf (ng•hr/mL)	6.15 \pm 3.31	6.30 \pm 3.06
AUC0-t (ng•hr/mL)	4.96 \pm 2.73	5.37 \pm 2.70
AUC0-24 (ng•hr/mL)	4.65 \pm 2.03	4.98 \pm 1.96
Tmax (min)	45 (25.2-126.0)	45 (19.8-127.2)
T1/2 (hr)	13.5 (2.50-32.1)	14.3 (2.90-25.10)
Ke (1/hr)	0.08 \pm 0.07	0.06 \pm 0.05

*Median (range) is presented for Tmax and t1/2

Figure 6: Mean Plasma Concentration Versus Time Profiles of Fentanyl in Healthy Subjects Administered a Single Dose of Treatment A (One 400- mcg OVF Tablet) or Treatment B (Four 100- mcg OVF Tablets).



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The 90% CI for Cmax and AUC0-inf between one 400-mcg tablet of ORAVESCENT fentanyl and four 100-mcg tablets of ORAVESCENT fentanyl did not meet the criteria for bioequivalence (Table 10). The point estimates for the mean ratios suggest approximately 12% and 13% higher values for Cmax and AUC0-inf, respectively, for Treat B (4x100 mcg tablets) to Treat A (1x400 mcg tablet). The 90% CIs for the mean ratios for AUC0-t and AUC0-24hr were within the acceptable limits of 80%-125%, however the point estimate still indicate 9-11% higher values for Treat B compared to that of Treat A.

Table 10: Bioequivalence Assessed between One 400- mcg Tablet and Four 100- mcg Tablets of ORAVESCENT Fentanyl During Treatment Periods 1 and 2

PK Measures	Ratio (B/A)	90%CI
Cmax (ng/mL)	1.121	0.995-1.262
AUC0-inf (ng•hr/mL)	1.128	1.016-1.251
AUC0-t (ng•hr/mL)	1.111	1.028-1.201
AUC0-24 (ng•hr/mL)	1.091	1.020-1.168

Comparison of Pharmacokinetic Parameters as Measured Through Arterial and Venous Sampling

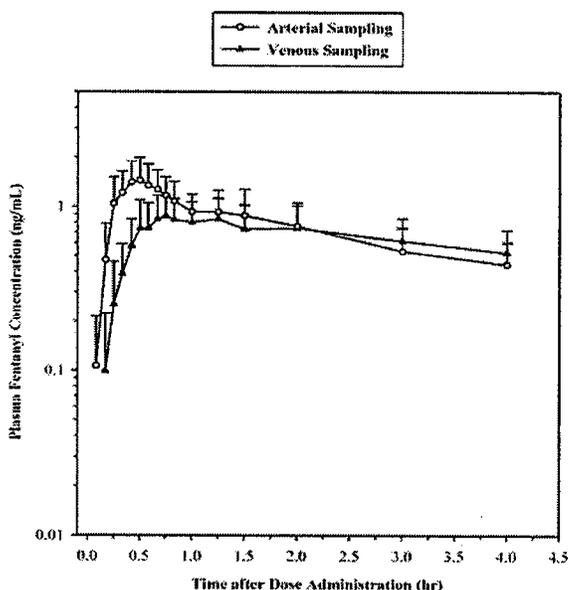
Following buccal administration of a single 400-mcg dose of ORAVESCENT fentanyl, early exposure (AUC0-tmax) measured in arterial circulation was significantly (more than 2-fold) higher than that in venous circulation. The mean peak plasma concentration of fentanyl in arterial circulation was significantly (approximately 60%) higher and occurred 15 minutes earlier (based on median tmax) than that measured from venous circulation (Table 11 and Figure 7).

Table 11: Pharmacokinetic Parameters* for Treatment Period 3 Arterial vs. Venous Sampling

PK Measures	Arterial Sampling (N=17)	Venous Sampling (N=17)
Cmax (ng/mL)	1.62 ± 0.56	1.03 ± 0.37
AUC0-t (ng•hr/mL)	3.00 ± 0.93	2.56 ± 0.85
AUC0-24 (ng•hr/mL)	0.72 ± 0.23	0.32 ± 0.15
Tmax (min)	28.8 (15.0-88.8)	43.8 (28.8-118.8)

*Mean SD presented for Cmax and AUC and Median (range) is presented for tmax

Figure 7: Mean Arterial and Venous Plasma Concentration Versus Time Profiles of Fentanyl in Healthy Subjects Administered a Single 400- mcg Dose of OVF



Safety Results

A total of 23 (85%) subjects experienced treatment-emergent adverse events during the study. Of the 27 subjects in treatment periods 1 and 2, 15 subjects had adverse events after treatment A (one 400-mcg tablet of ORAVESCENT fentanyl) and 16 subjects had adverse events after

treatment B (four 100-mcg tablets of ORAVESCENT fentanyl). Of the 17 subjects in treatment period 3 (one 400-mcg tablet of ORAVESCENT fentanyl), 9 subjects had adverse events. Adverse events reported included dizziness, nausea, pallor, decreased systolic blood pressure, headache, nasal congestion, and rhinorrhea. All adverse events were mild to moderate in severity. Five subjects had abnormal oral mucosal examination findings. All events resolved with no residual effect.

It is noted that the Medical Officer will conduct an overall assessment of safety in the NDA.

Pharmacokinetic Conclusions

The comparisons for C_{max} and AUC_{0-inf} between one 400-mcg tablet of ORAVESCENT fentanyl and four 100-mcg tablets of ORAVESCENT fentanyl did not meet the 90% CI criteria for bioequivalence, while that for AUC_{0-t} and AUC₀₋₂₄ values fall within the acceptable limits. The relatively higher rate of absorption with the 4x100 mcg tablets may be attributable to the larger surface area present when 4 tablets are administered at once.

After a single buccal dose of ORAVESCENT fentanyl, mean peak plasma concentration of fentanyl in the arterial circulation was approximately 60% higher and occurred 15 minutes earlier than that in the venous circulation.

4.2.5. Study Protocol C25608/1028

Title: An Open- Label, Randomized, Crossover Study to Assess the Relative and Absolute Bioavailability of ORAVESCENT ® Fentanyl Citrate (400 mcg) in Healthy Subjects.

Study Site: _____

Principal Investigator: _____

Study Dates: 02/21/05-03/18/05

Objective: The objective of the study was to evaluate the relative bioavailability of a single 400-mcg transmucosal dose of ORAVESCENT fentanyl when compared to a single 800-mcg oral dose of ORAVESCENT fentanyl and a single 800-mcg transmucosal dose of ACTIQ; and the absolute bioavailability of these formulations compared with an intravenous infusion of 400-mcg fentanyl.

Study Design: Open label, 4-treatment, 4-period crossover study. Subjects were randomized to 1 of the following 4 treatment sequences: ABDC, BCAD, CDBA, or DACB, whereby A was the 400-mcg transmucosal dose of ORAVESCENT fentanyl, B was the 400-mcg iv dose of fentanyl, C was the 800-mcg oral dose of ORAVESCENT fentanyl, and D was the 800-mcg transmucosal dose of ACTIQ. Subjects received 1 formulation on the first day of each treatment period (days 1, 8, 15, and 22), according to randomization. Each treatment was separated by a minimum 7-day washout period. Each subject received one 50-mg tablet of naltrexone hydrochloride for blockade of opioid effects approximately 15 hours and 3 hours before study drug administration and approximately 9 hours after study drug administration. Subjects were permitted to leave the study center on completion of the 72-hour pharmacokinetic profiling after each treatment period.

Exclusion Criteria (among others):

Table 11: Mean (+/- SD) Pharmacokinetic Parameters of Fentanyl in Healthy Volunteers (N= 26) Administered a Single Dose of 400 mcg OVF or 800 mcg ACTIQ Transmucosally, 400 mcg Fentanyl Intravenously, or 800 mcg OVF Orally

Parameter	400 OVF	400 IV	800 OVF (po)	800 ACTIQ
C _{max} (ng/mL)	1.020 ± 0.424	3.000 ± 1.112	0.984 ± 0.542	1.257 ± 0.414
t _{max} (hr) ^a	0.78 [0.33-4.00]	0.17 [0.08-0.75]	1.50 [0.68-4.00]	1.51 [0.58-4.00]
AUC _{0-max'} (ng·hr/mL)	0.398 ± 0.178	1.43 ± 0.39	0.110 ± 0.136	0.280 ± 0.101
AUC ₀₋₂₄ (ng·hr/mL)	5.00 ± 1.74	7.79 ± 1.95	4.87 ± 3.01	7.31 ± 2.57
AUC ₀₋₁ (ng·hr/mL)	5.52 ± 2.43	9.01 ± 2.79	5.52 ± 4.15	8.47 ± 3.73
AUC ₀₋₇₂ (ng·hr/mL)	5.79 ± 2.50	9.31 ± 2.76	5.76 ± 4.15	8.79 ± 3.69
AUC _{0-∞} (ng·hr/mL)	6.48 ± 2.98	10.29 ± 2.88	6.60 ± 4.47	9.58 ± 3.91
λ _z (hr ⁻¹)	0.0568 ± 0.0364	0.0411 ± 0.0153	0.0703 ± 0.0527	0.0438 ± 0.0195
t _{1/2} (hr) ^b	12.2	16.9	9.87	15.8
CL or CL/F (L/hr)	77.0 ± 42.8	41.7 ± 11.3	174 ± 108	95.0 ± 31.7
V _z or V _z /F (L)	1481 ± 493	1102 ± 332	2696 ± 769	2345 ± 780
AUC Extrap. (%)	13.2 ± 4.9	11.5 ± 5.3	13.5 ± 6.7	12.5 ± 5.5
F _{ORAL}	NA	NA	0.311 ± 0.131	NA
F _{OVF}	0.648 ± 0.200	NA	NA	NA
F _{ACTIQ}	NA	NA	NA	0.465 ± 0.105
f _{TM}	0.477 ± 0.318	NA	NA	0.224 ± 0.173
f _G	0.523 ± 0.318	NA	NA	0.776 ± 0.173
F _{OVF/AC}	1.34 ± 0.39	NA	NA	NA
F _{OVF/po}	2.32 ± 1.07	NA	NA	NA
F _{AC/po}	NA	NA	NA	1.80 ± 0.75

^a Median [range]; ^b Harmonic mean; NA = Not Applicable.

F_{OVF/AC}, F_{OVF/po}, F_{AC/po} = Relative bioavailability of OVF to ACTIQ, OVF to oral OVF, and ACTIQ to oral OVF, respectively.

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Figure 8: Mean Plasma Concentration versus Time Profiles of Fentanyl in Healthy Volunteers (N= 26) Administered a Single Dose of 400 mcg OVF or 800 mcg ACTIQ Transmucosally, 400 mcg Fentanyl Intravenously, or 800 mcg OVF Orally

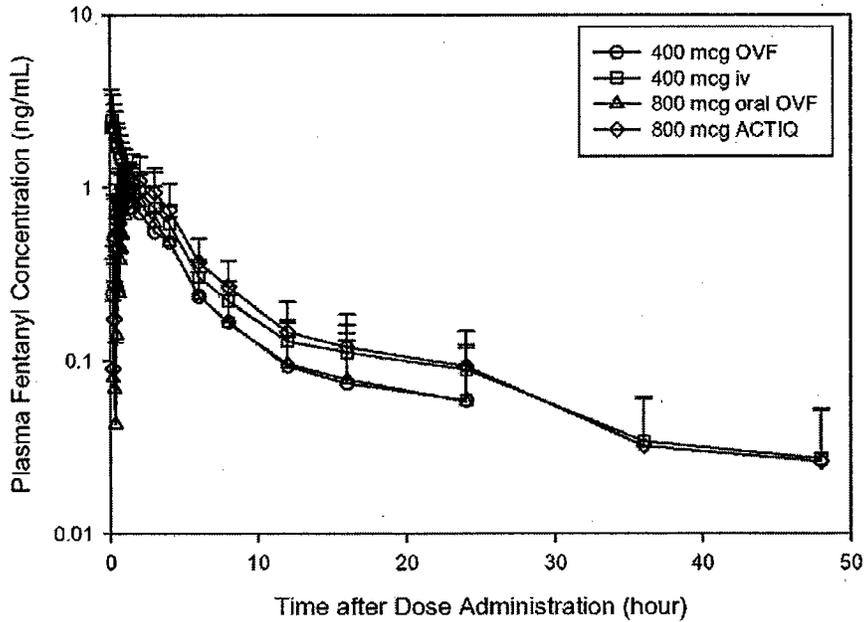


Figure 9: Mean Plasma Concentration versus Time Profiles of Fentanyl (Truncated at 4 hours) in Healthy Volunteers (n= 26) Administered a Single Dose of 400 mcg OVF or 800 mcg ACTIQ Transmucosally, 400 mcg Fentanyl Intravenously, or 800 mcg OVF Orally

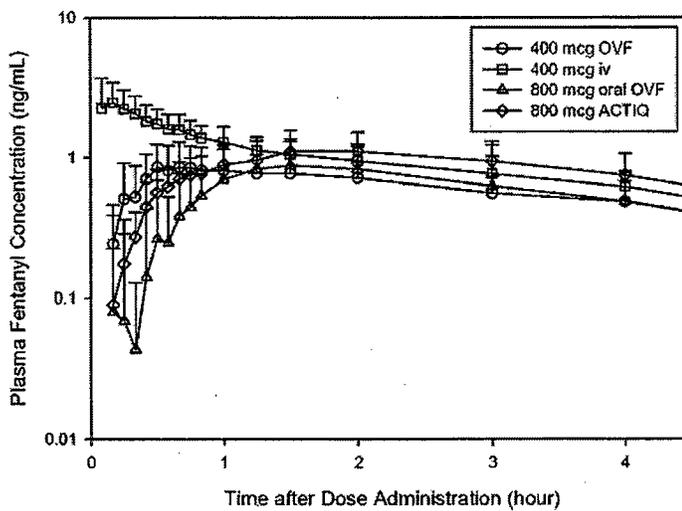
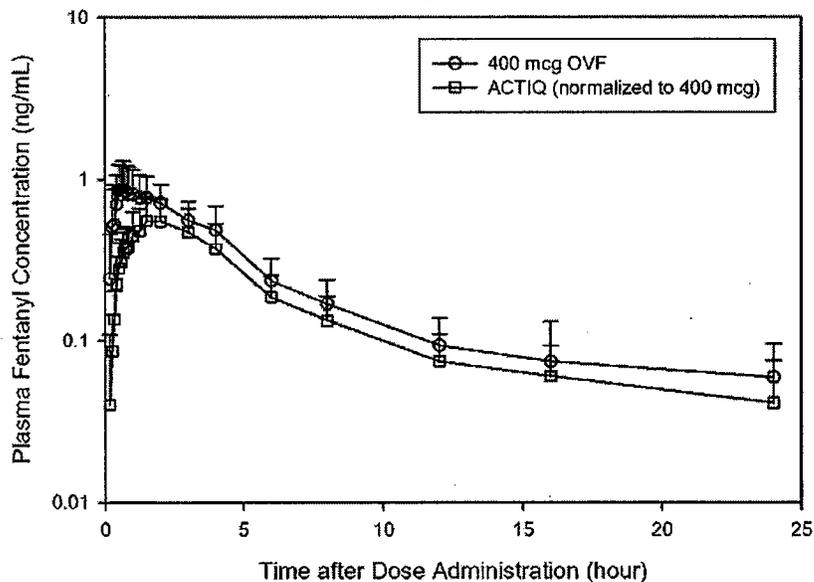


Figure 10: Mean Plasma Concentration versus Time Profiles of Fentanyl in Healthy Volunteers (N= 26) Administered a Single Dose of 400 mcg OVF or 800 mcg ACTIQ Transmucosally (ACTIQ Data Normalized to 400 mcg)



Adverse Events:

There were no deaths or other serious adverse events in this study. There were no adverse events of respiratory depression reported during the study.

Overall, the incidence of adverse events was lower following transmucosal ORAVESCENT fentanyl administration (42%) than following oral ORAVESCENT fentanyl, ACTIQ, or intravenous fentanyl administration 16 (all 59%).

Treatment-related adverse events were reported for 35% of subjects following transmucosal ORAVESCENT fentanyl administration, 41% following oral ORAVESCENT fentanyl, 52% following transmucosal ACTIQ, and 48% following intravenous fentanyl. The most common treatment-related adverse events were nausea (52%), headache (48%), dizziness (38%), somnolence (24%), abdominal pain upper and dysgeusia (17% each), vomiting (14%), and euphoric mood and fatigue, (7% each). The majority of treatment-related events were considered mild in severity, none was considered severe, and all events resolved with no residual effects.

Comments:

The purpose of the study was to evaluate the relative bioavailability of a single 400-mcg transmucosal dose of ORAVESCENT fentanyl when compared to a single 800-mcg oral dose of ORAVESCENT fentanyl and a single 800-mcg transmucosal dose of ACTIQ; and the absolute bioavailability of these formulations compared with an intravenous infusion of 400-mcg fentanyl.

Fentanyl was rapidly absorbed following administration of the 400-mcg OVF tablet (transmucosal), with a median t_{max} of 0.78 hours; whereas, the median t_{max} values for 800-mcg ACTIQ and 800-mcg OVF (oral) were approximately 1.5 hours. The disposition of fentanyl in plasma was multiphasic and was characterized by an initial rapid distribution phase followed by a somewhat slower elimination phase.

Plasma levels of fentanyl were quantifiable through 24 to 36 hours in the majority of subjects for all treatments. There were very few subjects with quantifiable fentanyl concentrations beyond 48 hours postdose.

The transmucosal dose of ORAVESCENT fentanyl demonstrated the highest absolute bioavailability (FOVF=0.65) when compared with ACTIQ (FACTIQ=0.47) or the oral dose of ORAVESCENT fentanyl (FORAL=0.31) (where FOVF, FACTIQ, and FORAL represent the dose-normalized ratios of the AUC from time zero to infinity [AUC_{0-inf}] for each of the 3 formulations to the AUC_{0-inf} of intravenous fentanyl).

Compared to ACTIQ, the OVF formulation used in the current study resulted in a larger fraction of the dose being absorbed transmucosally (OVM f_{TM} 0.48 vs Actiq f_{TM} 0.22), thus a smaller fraction was subject to first-pass metabolism by the gut and liver, resulting in greater fentanyl bioavailability.

Regarding safety considerations, it is again pointed out that the Medical Officer will conduct an overall assessment of safety in the NDA.

4.2.6. Study Protocol C25608/1029

Title: An Open-Label Study to Assess the Pharmacokinetics of Single and Multiple Doses of ORAVESCENT® fentanyl citrate (400 mcg) in Healthy Subjects.

Study Site: _____

Principal Investigator: _____

Study Dates: 01/24/05-02/18/05

Objective: The objective of the study was to characterize the pharmacokinetic profiles following single and multiple doses of 400 mcg of ORAVESCENT fentanyl in healthy subjects.

Study Design: Open label, nonrandomized study to assess the pharmacokinetics of a single dose and multiple doses of OVF fentanyl (400 mcg) in healthy subjects. Subjects remained in the study center throughout the study. Subjects received a single dose of 400 mcg of ORAVESCENT fentanyl on day 1. Subjects received one 50-mg tablet of naltrexone hydrochloride approximately 15 hours and 3 hours before and 9 hours after study drug administration.

Blood samples were collected just before and over a 72-hour period after study drug administration to determine the pharmacokinetics after single-dose administration

Pharmacokinetic Results and Analysis:

The mean pharmacokinetic parameters of fentanyl from OVF fentanyl as the single dose and multiple dose administration of OVF transmucosal are shown in the Tables below. The corresponding mean plasma concentration versus time profiles are shown in Figure 1.

Table 12. Pharmacokinetic Parameters Determined After Single and Multiple 400-mcg Doses of OVF

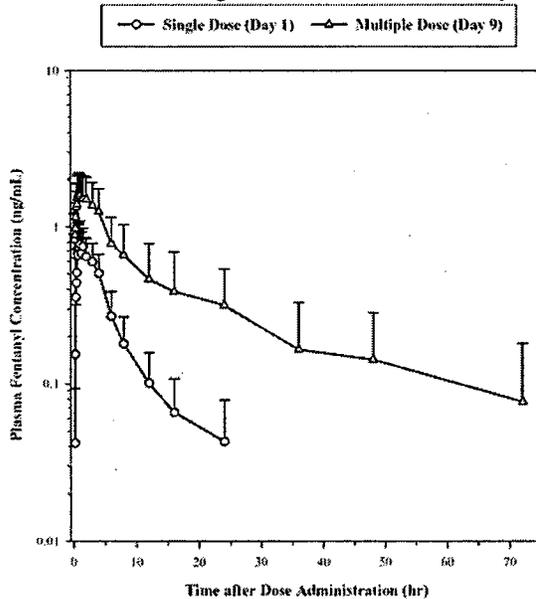
PK Measures	OVF Fentanyl Mean SD	
	Single Dose	Multiple Dose
Cmax (ng/mL)	0.88±0.30	1.77±0.63
AUC0-6 (ng• hr/mL)	3.11±0.94	-
AUC0-24 (ng• hr/mL)	4.90±1.75	15.8±8.20
AUC0-72 (ng• hr/mL)	5.80±2.46	23.2±15.01
AUC0-t (ng• hr/mL)	5.33±2.52	22.9±15.21
AUC0-inf (ng• hr/mL)	6.07±2.80	7.59±3.00
Tmax (min)	52.2 (37.8-180.0)*	49.8 (25.2-240.0)*
T1/2 (hr)	12.3 (2.7-35.8)*	21.7 (10.8-44.7)*
Ke (1/hr)	0.08±0.06	0.04±0.01

*median (range) is presented for Tmax and t1/2

Table 13: Trough Plasma Concentrations (ng/mL) of Fentanyl

Day (time point)	ORAVESCENT fentanyl Mean±SD (N=21)
8 (1400)	0.60±0.30
8 (2000)	0.65±0.33
9 (0200)	0.75±0.34
9 (0800)	0.85±0.38
9 (1400)	0.78±0.37

Figure 11: Mean Plasma Concentration Versus Time Profiles of Fentanyl in Healthy Volunteers (= 21) Administered 400 mcg of ORAVESCENT Fentanyl as a Single Dose (Day 1) and as Multiple Doses (Day 9)



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After buccal administration of a single 400-mcg dose of OVF, maximum plasma concentration was attained rapidly (median t_{max} of approximately 50 minutes). While the mean pharmacokinetic profile depicted a biexponential decline from peak concentration, individual profiles for approximately half of the subjects showed a triexponential decline. The median estimated t_{1/2} was approximately 12 hours.

Following the multiple-dose administration of 400 mcg of effervescent fentanyl (q6hx5 days starting on Day 5) the median t_{max} was achieved in about 50 minutes, same as observed with single dose profile, and the fentanyl C_{max} value was 1.77 ng/mL. Fentanyl exhibited a triexponential decline from peak plasma concentration (consistent with a very rapid distribution to the highly perfused tissues, followed by an elimination/gastrointestinal absorption phase and a terminal elimination/redistribution phase between plasma and a deep-tissue compartment). The median estimated t_{1/2} (approximately 22 hours) was longer than the median estimated t_{1/2} after single-dose administration, partially due to the higher plasma concentrations following multiple-dose administration, which allowed for a more adequate characterization of the terminal portion of the curve.

The 90% CIs for the ratio of mean trough plasma concentrations following the final 3 doses of fentanyl on day 9 were within the confidence interval limits (0.8, 1.25). The C_{max} and t_{max} after administration of multiple doses were consistent with those after administration of a single dose. Based upon the similarity in trough plasma concentrations of fentanyl, subjects appeared to be at or near pharmacokinetic steady state on day 5 of multiple-dose administration which is consistent with the t_{1/2}.

Safety Results: There were no deaths, serious adverse events, or withdrawals due to adverse events reported in this study. The most common adverse events (occurring in more than 10% of the subjects) were application site erythema, application site inflammation, stomatitis, dizziness, and headache. The majority of adverse events were mild in severity and none were reported as severe. Half of all subjects experienced application site erythema and/or inflammation that was mild and transient. There were no clinically meaningful trends in changes from baseline to final assessment in serum chemistry or hematology variables. Five subjects had clinically significant changes in vital signs (pulse [2 subjects, ≥ 120 bpm and increase of ≥ 15] and diastolic blood pressure [2 subjects, ≤ 50 bpm and decrease of ≥ 15 ; and 1 subject ≥ 105 and increase ≥ 15]). A modest elevation in pulse was observed, though not clinically significant, at several later time points starting 6 hours after study drug administration. No trends were noted for systolic or diastolic blood pressure. There were no clinically meaningful ECG or physical examination findings.

Again as noted earlier, the Medical Officer will conduct an overall assessment of safety in the NDA.

4.2.7. Study Protocol 099-19

Only a brief synopsis of this study is provided.

Title of Study: Evaluation of the Dose Proportionality of 100 µg, 200 µg, 400 µg and 800 µg Single Doses of ORAVESCENT® Fentanyl Citrate Administered Buccally to Healthy Japanese Volunteers.

Investigators and Study Centers:

Study Period: 29 June 2004 to 5 September 2004

Objectives: The objectives of the study were: To characterize certain pharmacokinetic parameters and evaluate the dose proportionality of single doses of fentanyl citrate formulated in ORAVESCENT tablets over a 100 mcg through 800 mcg dose range in healthy Japanese volunteers.

Subjects: Twenty-five subjects were enrolled, 23 subjects (2 males and 21 females) received ORAVESCENT fentanyl citrate and 19 subjects completed the study. The mean age, weight and height of the subjects were 23 years (20-51 yrs), 57.4 kg (44.5-83.7 kg) and 162.2 cm (151.0-194.7 cm).

Diagnosis and Main Criteria for Inclusion: Subjects were included in the study if all of the following criteria were met:

- healthy adult male or female Japanese volunteers 20 through 55 years of age
- lived less than 10 years outside Japan, had a valid visa or, alternatively, showed proof of enrollment prior to the date of recruitment for this study in a local school near the clinical site, and had no plans to leave the country until 1 week after the end of the study
- a body mass index (BMI) within the range of 17.6 through 29 kg/m²

Main Criteria for Exclusion:

- use of prescription medications (including monoamine oxidase inhibitors [MAOI]) within 14 days prior to the first dose of ORAVESCENT fentanyl citrate or during the study. This prohibition did not include hormonal contraceptives for females
- use of over-the-counter medication (including herbal supplements) within 7 days prior to the first dose of ORAVESCENT fentanyl citrate or during the study
- use of any drugs or substances known to be strong inhibitors of cytochrome P450 enzymes within 10 days prior to the first dose or during the study
- use of any drugs or substances known to be strong inducers of cytochrome P450 enzymes within 30 days prior to the first dose or during the study.

General Design and Methodology: This was a single-dose, open-label, 4-period, crossover dose-proportionality and safety and tolerability study. Subjects were randomized to treatment sequence.

Study Drug Dose, and Administration: During each of 4 study periods, the subjects were randomly assigned to receive a single dose of 1 of the following ORAVESCENT fentanyl citrate formulations: 100 mcg (treatment A), 200 mcg (treatment B), 400 mcg (treatment C), or 800 mcg (treatment D). Subjects also received 50 mg naltrexone HCl blockade (treatments A and B - 50 mg at 15 hours and 3 hours prior to ORAVESCENT fentanyl citrate administration and

treatments C and D - 50 mg at 15 hours and 3 hours prior to and 12 hours post ORAVESCENT fentanyl citrate administration).

Pharmacokinetics: Blood samples were collected for serum fentanyl pharmacokinetic analysis just before tablet placement (0), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, and 36 hours after tablet placement. Pharmacokinetic parameters included C_{max}, t_{max}, t_{1/2}, AUC_{0-t}, and AUC_{0-inf}. These data were compared with similar data generated in other studies utilizing non-Japanese subjects. Analyses of variance (ANOVA) were performed on the dose-normalized and ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, and C_{max}.

Summary of Results

Pharmacokinetics Results: The primary serum pharmacokinetic parameters and associated statistics are presented below.

Parameter	Dose of ORAVESCENT fentanyl citrate			
	100 mcg	200 mcg	400 mcg	800 mcg
C _{max} (pg/mL)	452.67±165.77	905.14±218.91	1623.91±434.30	2992.38±804.10
		Slope= 0.9118; 90% CI=86.01, 96.35%		
AUC _{0-inf} (pg·hr/mL)	1862.3±466.80	4214.1±950.54	9182.7±2241.3	17444.8±3876.8
		Slope=1.0756; 90% CI=103.77, 111.36%		
AUC _{0-last} (pg·hr/mL)	1707.4±447.31	3844.9±811.80	8069.8±1927.7	16599.8±3798.1
		Slope=1.0992; 90% CI=106.77, 113.07%		

Statistically, dose proportionality for ORAVESCENT fentanyl citrate over the dose range of 100 to 800 mcg was not established for C_{max} and AUC_{0-last} and was marginal for AUC_{0-inf}. The 0% confidence interval for the slope of AUC_{0-inf} was only marginally outside the predetermined range of 89.27% to 110.73%. The 90% confidence interval for the slope of C_{max} and AUC_{0-last} were partially outside this range. The deviation from dose proportionality was small. Statistical analysis results for all of the partial area values tested (AUC₀₋₈, AUC₀₋₁₂, AUC₀₋₁₈, and AUC₀₋₂₄) showed dose proportionality within the 100 to 800 mcg dose range.

The mean dwell time in the buccal position, before complete disappearance of the ORAVESCENT fentanyl citrate tablets, was 48.95, 59.24, 59.27, and 68.14 minutes for the 100-mcg, 200-mcg, 400-mcg, and 800-mcg doses respectively.

Safety Results: Overall 78.3% of subjects experienced adverse events with an incidence of 28.6%, 2.9%, 40.9%, and 38.1% at the 100-mcg, 200-mcg, 400-mcg, and 800-mcg doses, respectively. The individual adverse events with the highest incidence were nausea (39.1%) and dizziness (34.8%). There was only 1 adverse event reported to be associated with the oral mucosa (gingival pain, 200-mcg dose) and only 1 adverse event possibly associated with vital sign abnormalities (syncope vasovagal, 400-mcg dose). There were no serious adverse events and no subjects in the safety population withdrew from the study due to adverse events. There were no clinically significant laboratory abnormalities reported and no clinically significant changes in the mean vital sign measurements (blood pressure, pulse rate, and respiration rate) at 2 or 4 hours after dosing (t_{max} was about 1.5 hours). No clinically meaningful differences were

seen between screening and the end of study visit for physical examination findings, mean heart rate, PR, QRS, QT, or QTc measurements.

Conclusions: Dose proportionality was marginal for AUC_{0-inf}. Dose proportionality was not established for AUC_{0-last} and C_{max}. Post hoc analysis indicated conclusive dose proportionality for all partial areas, namely AUC₀₋₈, AUC₀₋₁₂, AUC₀₋₁₈, and AUC₀₋₂₄. ORAVESCENT fentanyl citrate tablets were well tolerated at the site of tablet placement when delivered via the buccal route, at doses from 100 mcg through 800 mcg, in healthy Japanese subjects. ORAVESCENT fentanyl citrate tablets were generally well tolerated when administered at doses from 100 mcg through 800 mcg to healthy Japanese subjects receiving naltrexone to block the opioid effects of fentanyl.

4.2.8. Study Protocol 099-20

Title of Study: The Accumulation and Pharmacokinetics of Fentanyl During and Following a Multiple Buccal Administration Regimen of 400 µg ORAVESCENT® Tablets (Fentanyl Citrate) to Healthy Japanese Volunteers.

Investigators and Study Centers: _____

Study Period: 26 Jan 2005 to 16 Feb 2005 Phase of Development: Phase 1

Objectives: The objectives of the study were:

- to characterize the accumulation and certain pharmacokinetic parameters of fentanyl during and following a multiple buccal administration regimen (10 doses, 6 hours apart) of 400 mcg ORAVESCENT fentanyl citrate tablets, to healthy Japanese subjects.
- to characterize the safety and tolerability of 400 mcg of ORAVESCENT fentanyl citrate tablets administered as 10 doses, 6 hours apart, to healthy Japanese subjects.

Subjects: Fourteen subjects were enrolled into the study and 13 subjects completed the study.

Main Criteria for Exclusion:

- use of prescription medications (including monoamine oxidase inhibitors [MAOI]) within 14 days prior to the first dose of ORAVESCENT fentanyl citrate or during the study. This prohibition did not include hormonal contraceptives for females
- use of over-the-counter medication (including herbal supplements) within 7 days prior to the first dose of ORAVESCENT fentanyl citrate or during the study
- use of any drugs or substances known to be strong inhibitors of cytochrome P450 enzymes within 10 days prior to the first dose or during the study
- use of any drugs or substances known to be strong inducers of cytochrome P450 enzymes within 30 days prior to the first dose or during the study.

Study Drug Dose, Mode of Administration: During the study, the subjects were assigned to receive a total of 10 doses of the 400-mcg ORAVESCENT fentanyl citrate tablet administered at 6-hour intervals. The ORAVESCENT fentanyl citrate tablets were placed at the same buccal site unless, for a medical reason, the investigator determined otherwise for any given subject.

Subjects also received naltrexone hydrochloride for blockade, one 50-mg tablet at 15 hours and 3 hours (total 2 doses) prior to and every 12 hours (total 5 doses) after the first ORAVESCENT fentanyl citrate tablet administration.

Pharmacokinetics: Venous blood samples (5 mL each) were collected for serum fentanyl pharmacokinetic analysis just before the placement of each tablet and 3, 6, 9, 12, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 240 and 360 minutes after the 1st tablet placement (the 360-minute blood collection was just before placement of the 2nd dose) and 15, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 minutes and 4, 6, 10, 12, 18, 24, and 32 hours after the last (10th) tablet placement (total of 46 samples).

The pharmacokinetic parameters included maximum and minimum serum concentrations and time of maximum serum concentration (C_{max} , C_{min} and t_{max}); the terminal elimination rate constant and half-life (λ_z and $t_{1/2}$); and area under the concentration-time curve from predose to 6 hours postdose (AUC_{0-6}) for the first and last dose, to last quantifiable concentration (AUC_{0-last}), and to infinity ($AUC_{0-\infty}$) for the last dose. Serum concentrations (obtained by sampling immediately preceding each dose and the 6-hour postdose concentration following the last dose administration) were used to calculate any accumulation and assess the extent to which the concentration of fentanyl reached the steady state. Accumulation ratio (AR) and accumulation factor (R) were calculated. The pharmacokinetic parameters were summarized using descriptive statistics.

Summary of Results

Pharmacokinetics Results: Fentanyl serum concentrations versus time data were analyzed using noncompartmental pharmacokinetic analysis in order to estimate the pharmacokinetic parameters. The extent of accumulation was empirically determined from the ratios of AUC_{0-6} (AR-AUC), C_{max} (AR- C_{max}), and R (predose 10/predose 2). The accumulation values were 1.23, 1.55, and 2.05 for C_{max} , AUC_{0-6} , and R, respectively. The pertinent pharmacokinetics parameter estimates and the accumulation values are illustrated in the table below:

Parameter	1 st dose mean (%CV) (n=14)	Last (10 th) dose mean (%CV) (n=13)
C_{max} (pg/mL)	1702.4 (28.7)	1972.3 (21.2)
AUC_{0-6} (pg•hr/mL)	4458.4 (25.5)	6805.4 (13.3)
AR- C_{max}	NA	1.23 (43.3)
AR- AUC_{0-6}	NA	1.55 (22.6)
Accumulation factor (R)	NA	2.05 (21.1)

C_{max} =maximum observed serum concentration.; AUC_{0-6} =area under the serum fentanyl concentration-time curve calculated using linear trapezoidal summation from nominal time 0 to 6 hours after the first and the last doses of ORAVESCENT fentanyl citrate administration; AR=accumulation ratios for multiple compared to single dosing calculated as the ratio of $AUC_{0-6 \text{ Dose } 10}/AUC_{0-6 \text{ Dose } 1}$ and as the ratio of $C_{max \text{ Dose } 10}/C_{max \text{ Dose } 1}$; CV=coefficient of variation (the standard deviation divided by the mean); NA: not applicable.

The statistical analysis for achievement of serum fentanyl steady state was not statistically conclusive; however, a visual review of the serum fentanyl concentrations indicated steady state had already been achieved prior to collection of samples preceding doses 8, 9, and 10 and the 6-hour postdose sample following dose 10.

The recorded dwell times ranged from 9 to 60 minutes with approximately 18% of the

dwelling times being 15 minutes or less.

Safety Results: All 14 subjects in this study experienced 1 or more adverse events. There were no serious or severe adverse events and 9 (64.3%) subjects reported adverse events that were considered to be of moderate severity. The individual adverse events with the highest incidence were somnolence (64.3%), application site pain (57.1%), application site erythema (42.9%), application site reaction (35.7%), and oxygen saturation decreased (28.6%). There was 1 subject (subject 207) withdrawn from the study due to adverse events of nausea and vomiting. There were no clinically significant laboratory abnormalities reported and no clinically significant changes in the mean vital sign measurements blood pressure, pulse, and respiration rate) 1 hour after the first dose (tmax ranged from 0.8-0.5 hours) or just before administration of the last dose. No clinically meaningful differences were seen between screening and the end-of-study visit for physical examination findings, mean heart rate, PR, QRS, QT, or QTc measurements.

Conclusions: Accumulation of fentanyl in serum was observed following administration of 10 successive 400-mcg doses of ORAVESCENT fentanyl citrate. The accumulation ratios of Cmax and AUC0-6 (mean, %CV) were 1.23 (43.2%) and 1.55 (22.6%), respectively. The mean accumulation factor (R) was 2.05 with a %CV of 21.1%. Steady state was visually observed to occur prior to collection of samples prior to administration of dose 8. ORAVESCENT fentanyl citrate tablets were generally well tolerated at the site of tablet placement for the initial 4 doses when administered as 10 successive 400-mcg doses at 6-hour intervals. At doses 5 through 10 there was an indication of mucosal changes at the application site associated with the use of the tablets, which has led to a recommendation to routinely vary the site of tablet placement (eg, using alternate sides of the mouth). ORAVESCENT fentanyl citrate tablets were generally well tolerated when administered as 10 successive 400-mcg doses at 6-hour intervals to healthy Japanese subjects receiving naltrexone to block the opioid effects of fentanyl.

4.4. Cover Sheet and OCPB Filing Review Form

OCPB filing Memo:

Office of Clinical Pharmacology and Biopharmaceutics <i>New Drug Application Filing and Review Form</i>			
General Information About the Submission			
	Information		Information
NDA Number	21-947	Brand Name/ Established Name	TBD/ OraVescent Fentanyl Citrate
OCPB Division (I, II, III)	DPE II	Generic Name	Fentanyl Citrate
Medical Division	DAARP	Drug Class	Opioid analgesic
OCPB Reviewer	Chandra S. Chaurasia, Ph.D.	Indication(s)	Management of breakthrough pain in opioid tolerant patients with cancer
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form/Strengths	Effervescent buccal tablets/ 100, 200, 400, 600, and 800 mcg
Date of Submission	08/31/2005	Dosing Regimen	The proposed initial starting dose is 100 mcg. Patients should be titrated to a dose that provides adequate analgesia with minimal side effects.
Estimated Due Date of OCPB Review	04/30/2006	Route of Administration	Oral transmucosal
PDUFA Due Date	06/30/2006	Sponsor	Cephalon Inc. c/o CIMA Labs 41 Moores Rd. Frazer, PA 19355
Division Due Date	05/30/2006	Priority Classification	Standard

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			<p>HPLC MS/MS</p> <ul style="list-style-type: none"> By [redacted] for Study # 099-16, C25608/1026, C25608/1027, C25608/1028, C25608/1029: [redacted] By [redacted] for Study # 099-11, 099-18, 099-19, 099-20; [redacted]
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers- single dose:	X	8	8	
multiple dose:	X	2	2	<p>1. Study #099-20, Phase 1</p> <ul style="list-style-type: none"> Multiple dose safety, tolerability and PK in Japanese healthy adults following OVF 400 mcg doses. Single-period, N=13 (7 males, 7 females). Study center(s) [redacted] <p>2. Study #C25068/1029, Phase 1</p> <ul style="list-style-type: none"> Single and multiple dose, OVS 400 mcg dose in US healthy subjects. N=24 (20 males and 4 females – 11 White and 13 Black) Study center: [redacted]
Patients- single dose:	X	1	1	<p>Study #099-16, Phase 3</p> <ul style="list-style-type: none"> Single dose (200 mcg OVF) safety, tolerability and pharmacokinetic study in opioid-tolerant cancer patients with and without oral mucositis. US Study. Note: Study on going (interim cut off date June 9, 2005), planned N =20, data from N=8 (4 mucositis and 4 non mucositis - 5 female and 3 male, 5 white and 3 black). May request if the Sponsor plans to submit data from rest of the patients.
multiple dose:				
Dose proportionality -	X			

fasting / non-fasting single dose:	X	4	4	<p>1. Study #099-11</p> <ul style="list-style-type: none"> Dose proportionality of OVF doses 270, 810, 1080 and 1300 mcg BE study (1080 mcg OVF vs. 1600 mcg Actiq). Healthy adult subjects, N=39, (17 males, 22 females), fasted condition. Study center(s): USA <p>2. Study #099-18, Phase 1</p> <ul style="list-style-type: none"> Dose proportionality in healthy US subjects of OVF doses 200, 500, 810, and 1080 mcg. Single dose, 4-period, crossover design. Healthy adult subjects, N=25 (14 males, 11 females). Study center(s): USA <p>3. Study #099-19, Phase 1</p> <ul style="list-style-type: none"> Dose proportionality in healthy Japanese Subjects of OVF doses 100, 200, 400 and 800 mcg. Single dose, 4-period, crossover design. Healthy adult subjects, N=23 (2 males, 21 females). Study center: _____ <p>4. Study #C25608/1027, Phase 1</p> <ul style="list-style-type: none"> Dose proportionality in healthy US subjects. OVF 100, 200, 400 and 800 mcg. Single dose, 4-period, crossover design, N=32 (26 males, 6 females – 22 White, 3 Black and 4 Asian and 3 other). Study center: _____
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:	X	2	2	Study # 099-19 and 099-20
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				

Absolute bioavailability:	X	1	1	<p>Study #C25608/1028, Phase 1</p> <ul style="list-style-type: none"> RELATIVE BA of OVF 400 mcg <u>transmucosal</u> administration compared to OVF 800 mcg <u>oral</u> administration, and 800 mcg of Actiq transmucosal <u>administration</u>; and ABSOLUTE BA of these formulation with 400 mcg of fentanyl IV in healthy subjects. US study, single dose, 4-Period crossover, N=29 (16 males 13 females, 7 Whites, 1 Asian, 21 (Other).
Relative bioavailability -	X	2	2	<p>1. Study # 099-11</p> <ul style="list-style-type: none"> BE Study (<i>see above under dose proportionality</i>). Cmax not bioequiv. but AUC is. <p>2. Study #C25608/1026, Phase 1</p> <ul style="list-style-type: none"> BE study in healthy subjects comparing single doses of 4x100 mcg OVF with 1x400 mcg OVF. Also, PK comparison from arterial and venous blood samples for 400 mcg dose. US study, single dose 3-Period crossover, N=27 (21 males 21, 6 females, 25 Whites, 1 Asian, 1 (Other). Both Cmax and AUC not BE
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X			Study # 099-11 and C2508/1026 (please see above)
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		9	9	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?		Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		

QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. How does the relative bioavailability of the proposed effervescent buccal tablets compare to that of the marketed transmucosal fentanyl citrate, Actiq? 2. Is there a dose proportionality between the proposed strengths (i.e., 100, 200, 400, 600, and 800 mcg) of the test product? 3. What are the relative bioavailability and exposure of the different strengths of the test products? 4. Are the single dose pharmacokinetic characteristics of the proposed effervescent oral tablets similar to those of the approved product Actiq? 5. What are multiple dose PK characteristics of the test product? 6. Are the pharmacokinetic characteristics of the Japanese subjects similar to those in US subjects? 7. What are the dissolution characteristics of the proposed effervescent oral tablets?
Other comments or information not included above	<ol style="list-style-type: none"> 1. As reported in the submission, for all the studies described above, OVF was administered as the formulation used in the clinical safety and efficacy trials, and intended for marketing (the Generation III formulation). 2. There are five additional biopharm. studies (#099-06, 099-07, 099-08, 099-09, and 099-010) that utilized investigational formulations (Generations I and II). These formulations were not used in the clinical safety and efficacy trials. 3. Two additional studies (#099-12 and 099-13) evaluated the oral tolerability of effervescent buccal placebo tablets. 4. The 7 studies (in #2 and 3 above) may not be reviewed unless found relevant during the review process.
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

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this page is the manifestation of the electronic signature.**

/s/

Chandra S. Chaurasia
3/16/2006 09:10:42 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
3/16/2006 09:44:23 AM
BIOPHARMACEUTICS