

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202788Orig1s000

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

CLINICAL PHARMACOLOGY REVIEW

NDA: 202788	Submission Date(s): March 4, 2011
Proposed Brand Name	SUBSYS™
Generic Name	Fentanyl Sublingual Spray
Reviewer	Wei Qiu, Ph. D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Insys Therapeutics, Inc
Relevant IND(s)	72,411
Submission Type	505(b)(2), original
Formulation; Strength(s)	Sublingual Spray for transmucosal delivery; 100, 200, 400, 600, and 800 mcg
Dosing regimen	Initial dose of 100 mcg; then titrate to a tolerable dose
Indication	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA 202788 submitted on March 4, 2011 and finds it acceptable from clinical pharmacology perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Insys submitted this 505(b)(2) NDA for Fentanyl Sublingual Spray, 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg for the management of breakthrough cancer pain (b) (4) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Sponsor proposed to rely on the Agency's previous finding of the safety and efficacy of Actiq® fentanyl citrate oral transmucosal lozenge (NDA 020747).

Fentanyl is an opioid agonist and available as injectable, transdermal, nasal spray, and transmucosal (oral transmucosal lozenge (Actiq® NDA 20747), buccal tablet (Fentora® NDA 21947), buccal film (Onsolis®, NDA 22266), and sublingual tablet (Abstral® NDA 22510)) formulations. This current submission is for fentanyl sublingual spray.

The clinical and clinical pharmacology database for this NDA consists of one efficacy/safety study (INS-05-001), one open-label safety study (INS-06-007), and four clinical pharmacology studies. These clinical pharmacology studies include (1) pilot ascending single dose PK study in healthy male subjects (FNY-P4-270), (2) single dose

relative bioavailability study in comparison to Actiq® transmucosal lozenge and Fentanyl Citrate Injection in healthy subjects (INS-06-003), (3) a single dose crossover study to evaluate Fentanyl Sublingual Spray dose proportionality and to evaluate the potential effects of temperature and pH on relative bioavailability in healthy subjects (INS-06-004), and (4) a single dose PK study in opioid tolerant cancer patients with and without mucositis (Study INS-09-011). This review focused on Studies INS-06-003, INS-06-004, and INS-09-011. The pilot study FNY-P4-270 was not thoroughly reviewed (b) (4) and the dose levels were further studied in a more comprehensive Study INS-06-004.

Absolute Bioavailability:

The mean absolute bioavailability of Fentanyl Sublingual Spray 400 mcg in comparison to fentanyl citrate intravenous injection 100 mcg was 72.1% and 75.6% based dose normalized AUClast and AUCinf values, respectively.

Relative Bioavailability as Compared to Actiq®:

Single dose of the 1 x 400 mcg fentanyl sublingual spray exhibits 34% and 36% greater Cmax and AUCinf values as compared to Actiq® 1 x 400 mcg under fasting condition. The point estimates of the geometric mean ratio (Fentanyl Sublingual Spray 400 mcg/Actiq® 400 mcg) for Cmax, AUClast, and AUCinf are 133.67%, 133.44% and 136.27%, respectively. The corresponding 90% confidence intervals are 119.67% – 149.31%, 121.47% – 146.58%, and 121.21% – 153.20%, respectively.

Dose Proportionality:

The systemic exposure of fentanyl increased in an approximate dose proportional manner over the 100 mcg – 800 mcg range under fasting condition based on the ANOVA and linear regression of the dose-normalized Cmax, AUClast, and AUCinf values. When each lower strength (100 mcg, 200 mcg, 400 mcg, and 600 mcg) was compared to the highest strength 800 mcg, ANOVA analysis showed that for Cmax/Dose, all the 90% confidence interval fell within the 80-125% range except for the 600 mcg strength (lower bound of the 90% confidence interval was 79.47%). For AUCinf/Dose, all 90% confidence interval fell within the 80-125% limit except for the 100 mcg strength (lower bound of the 90% confidence interval was 77.44%). For AUClast/Dose, the 90% confidence interval for the 400 mcg and 600 mcg fell within the

80-125% while the lower bounds for the 100 mcg and 200 mcg were 67.95% and 76.95%, respectively.

Linear regression results showed that the slopes for C_{max}/Dose and AUC_{inf}/Dose were not significant different from 0. The value of the slope for AUC_{last}/Dose (2.89 E-04) was 2.89 E-04 significant different from zero, however, the value is very close to zero.

Effect of pretreatment of oral cavity with beverages which have different temperatures and pH levels:

The pretreatment of oral cavity with hot water did not affect the PK of fentanyl sublingual spray. The C_{max}, AUC_{last}, AUC_{inf} values after pretreatment with hot water were bioequivalent to the reference (no pretreatment) based on the 90% confidence interval (81.70% – 114.76% for C_{max}; 83.71% – 113.03% for AUC_{last}; 85.87% – 119.38% for AUC_{inf}) falling within the 80-125% limits. The cold water decreased the AUC values of fentanyl by 5 to 8% and had no effect on fentanyl C_{max} values. The point estimate of the geometric mean ratio (cold water/no pretreatment) for C_{max}, AUC_{last} and AUC_{inf} are 100.08%, 94.78%, and 92.23%, respectively. The corresponding 90% confidence interval is 83.07% – 120.58%, 75.95% – 118.29%, and 73.38% – 115.93%, respectively.

The pretreatment of oral cavity with low pH beverage decreased fentanyl C_{max} by 17% but had no effect on the AUC values. The point estimate of the geometric mean ratio (low pH/no pretreatment) for C_{max}, AUC_{last}, and AUC_{inf} are 83.26%, 91.93%, and 95.68%, respectively. The corresponding 90% confidence intervals are 70.81% - 97.90%, 81.70% - 103.44%, and 84.39% - 108.49%, respectively. The pretreatment of oral cavity with high pH beverage increased fentanyl C_{max}, AUC_{last}, and AUC_{inf} by 23%, 19%, and 18%, respectively.

Effect of Mucositis:

In opioid tolerant cancer patients with Grade 1 mucositis, mean fentanyl C_{max} and AUC_{last} values were 73% and 52% greater than the patients without mucositis following the administration of 100 mcg fentanyl sublingual spray. In the two patients with Grade 2 mucositis (subject 804 and 910), fentanyl C_{max} values were 7-fold and 4-fold greater than the mean C_{max} values obtained in patients without mucositis for subject 804 and subject 910, respectively. The corresponding fentanyl AUC_{last} values were 17-fold and

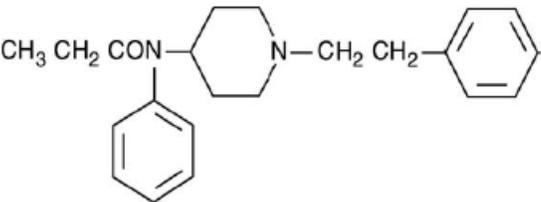
3-fold higher than the values in patients without mucositis. For patients with Grade 2 and more severe mucositis, fentanyl sublingual spray should be avoided. Dose reduction should be done for the patients with Grade 1 mucositis.

2 Question Based Review

2.1 General Attributes of the Drug

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

Table 1 Physical-Chemical Properties of Fentanyl Drug Substance

Drug Name	Fentanyl
Chemical Name	N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide
Structure	
Molecular Formula	C ₂₂ H ₂₈ N ₂ O
Molecular Weight	336.47
Solubility	Aqueous – practically insoluble; non-aqueous – freely soluble in ethanol and methanol; soluble in dilute acids and in methylene chloride

Fentanyl Sublingual Spray is a clear, colorless solution in a clear, colorless glass single-dose stoppered vial assembled into a delivery device to be used as a sublingual spray. The Fentanyl Sublingual Spray is packaged as a unit dose spray device designed to deliver (b) (4) of fentanyl solution containing fentanyl doses 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg. The composition of fentanyl sublingual spray is shown in **Table 2**.

Sponsor stated that throughout clinical development, the composition of the fentanyl solution formulation has remained unchanged. It was also stated that the to-be-marketed formulation is identical to the formulations used in all the clinical studies. (b) (4)

(b) (4). The remaining studies used the unit-dose spray device.

Table 2 Composition of Fentanyl Sublingual Spray, 100, 200, 400, 600, and 800 mcg

Component	Quality Standard	Function	Quantity per 100 µL				
			1 mg/mL (100 µg dose)	2 mg/mL (200 µg dose)	4 mg/mL (400 µg dose)	6 mg/mL (600 µg dose)	8 mg/mL (800 µg dose)
Fentanyl base	In-House	Active Ingredient	100 µg	200 µg	400 µg	600 µg	800 µg
Dehydrated alcohol	USP	(b) (4)					
Propylene glycol	USP						
L-Menthol	USP						
Xylitol	NF						
Purified water	USP						

2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia.

It is indicated for the management of breakthrough cancer pain in patients (b) (4) who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients must remain on around-the-clock opioids when taking fentanyl sublingual spray.

3. What are the proposed dosage(s) and route(s) of administration?

The dosage is sublingual spray for sublingual transmucosal absorption.

2.2 General Clinical Pharmacology

1. *What is known about the PK characteristics of fentanyl in general?*

Fentanyl is highly lipophilic. The plasma protein binding is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4. 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 feces. The metabolites are mainly excreted in the urine.

2. *Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetics?*

The activity is primarily due to the parent compound fentanyl. Fentanyl concentrations were measured in all the clinical pharmacology studies.

3. *Is the Dose Proportionality of Fentanyl Sublingual Spray established?*

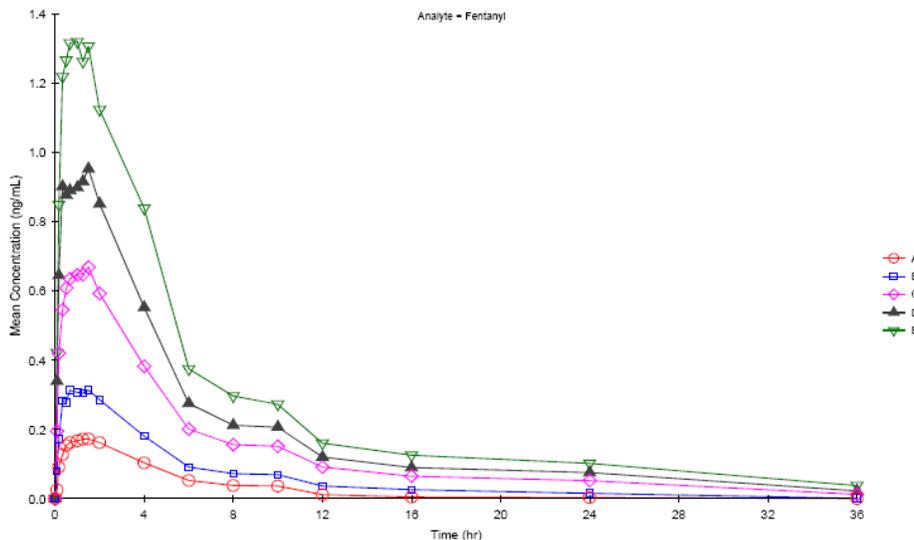
The fentanyl pharmacokinetics of five different strengths including 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg were determined in a single dose crossover study in healthy subjects under fasted conditions (Study INS-06-004 Part A). The fentanyl concentration-time profiles are shown in **Figure 1** and pharmacokinetic parameters along with statistical analysis results are shown in **Table 3**.

Fentanyl plasma concentration-time profiles exhibited similar shape for all strengths. The systemic exposure of fentanyl increased in an approximate dose proportional manner over the 100 mcg – 800 mcg range under fasting condition based on the ANOVA and linear regression of the dose-normalized C_{max}, AUC_{last}, and AUC_{inf} values. When each lower strength (100 mcg, 200 mcg, 400 mcg, and 600 mcg) was compared to the

highest strength 800 mcg, ANOVA analysis showed that for C_{max}/Dose, all the 90% confidence interval fell within the 80-125% range except for the 600 mcg strength (lower bound of the 90% confidence interval was 79.47%). For AUC_{inf}/Dose, all 90% confidence interval fell within the 80-125% limit except for the 100 mcg strength (lower bound of the 90% confidence interval was 77.44%). For AUC_{last}/Dose, the 90% confidence intervals for the 400 mcg and 600 mcg fell within the 80-125% while the lower bounds for the 100 mcg and 200 mcg were 67.95% and 76.95%, respectively.

Linear regression results showed that the slopes for C_{max}/Dose and AUC_{inf}/Dose were not significant different from 0. The value of slope for AUC_{last}/Dose (2.89 E-04) was significant different from zero, however, it is very close to zero. Therefore, the linear regression results confirmed the approximate dose proportionality among different doses from 100 mcg to 800 mcg.

Figure 1 Mean Fentanyl Concentration-Time Profiles after Administration of Single Doses of Fentanyl Sublingual Spray 100 mcg (Treatment A), 200 mcg (Treatment B), 400 mcg (Treatment C), 600 mcg (Treatment D), and 800 mcg (Treatment E) from Study INS-06-004



A: fentanyl sublingual spray 100 mcg; **B:** fentanyl sublingual spray 200 mcg; **C:** fentanyl sublingual spray 400 mcg; **D:** fentanyl sublingual spray 600 mcg; **E:** fentanyl sublingual spray 800 mcg

Table 3 Mean (%CV) Pharmacokinetic Parameters of Fentanyl following the administration of single doses of 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg sublingual spray (Study INS-06-004)

Parameter	Treatment A: 100 mcg		Treatment B: 200 mcg		Treatment C: 400 mcg		Treatment D: 600 mcg		Treatment E: 800 mcg	
	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Tmax (hr)*	42	1.25 (0.17, 2.05)	45	1.25 (0.17, 2.03)	42	1 (0.17, 2.03)	46	0.67 (0.083, 2)	44	0.69 (0.17, 4)
Cmax (ng/mL)	42	0.202 (28.35)	45	0.378 (29.69)	42	0.800 (27.66)	46	1.17 (32.48)	44	1.61 (37.22)
AUClast(ng/ mL.hr)	42	0.9776 (49.82)	45	1.985 (40.93)	42	4.643 (44.53)	46	6.682 (32.46)	44	9.450 (36.62)
AUCinf (ng/mL.hr)	38	1.245 (53.82)	42	2.475 (46.48)	42	5.342 (44.16)	45	7.446 (31.54)	44	10.38 (35.60)
T1/2 (hr)	38	5.25 (89.92)	42	8.45 (77.94)	42	11.03 (62.20)	45	10.64 (41.73)	44	11.99 (32.15)
Tlast (hr)*	42	10 (2, 36)	45	16 (8, 36)	42	24 (12, 36)	46	36 (24, 36)	44	36 (24, 36)
Statistical Analysis: Geometric Mean Ratio % (Test/Reference) (90% CI)										
Ln (Cmax/D)	100.9 (92.03, 110.62)		98.27 (90.59, 106.60)		99.26 (88.15, 111.78)		92.70 (79.47, 108.14)		Reference	
Ln (AUClast/D)	76.49 (67.95, 86.10)		83.74 (76.95, 91.13)		94.82 (83.93, 107.12)		100.28 (87.95, 114.33)		Reference	
Ln (AUCinf/D)	86.12 (77.44, 95.77)		92.31 (85.58, 99.57)		100.33 (88.39, 113.87)		100.58 (88.58, 114.21)		Reference	

*median (min, max)

2.3 Intrinsic Factors

1. What is the pediatric plan?

[Redacted text block containing multiple lines of information, likely a clinical plan or protocol details.]

(b) (4)

2. How do oral mucositis affect the pharmacokinetics of fentanyl sublingual spray?

The effect of oral mucositis was assessed by comparing fentanyl pharmacokinetics of a single 100 mcg dose of fentanyl sublingual spray in opioid tolerant cancer patients with or without oral mucositis (Study INS-09-011). Fentanyl plasma concentration-time profiles are shown in **Figure 2** and fentanyl pharmacokinetics and statistical analysis results are summarized in **Table 4**.

In opioid tolerant cancer patients with Grade 1 mucositis (N = 7), mean fentanyl C_{max} and AUC_{last} values were 73% and 52% greater than the patients without mucositis (N = 8) following the administration of 100 mcg fentanyl sublingual spray. In the two patients with Grade 2 mucositis (subjects 804 and 910), fentanyl C_{max} values were 7-fold and 4-fold greater than the mean C_{max} values obtained in patients without mucositis for subject 804 and subject 910, respectively. The corresponding fentanyl AUC_{last} values were 17-fold and 3-fold higher than the values in patients without mucositis. For patients with Grade 2 and more severe mucositis, fentanyl sublingual spray should be avoided. Dose reduction should be done for the patients with Grade 1 mucositis.

Figure 2. Fentanyl plasma concentration-time profiles in subjects without mucositis (left panel) and subjects with mucositis Grade 1 or 2 (right panel) from Study INS-09-011

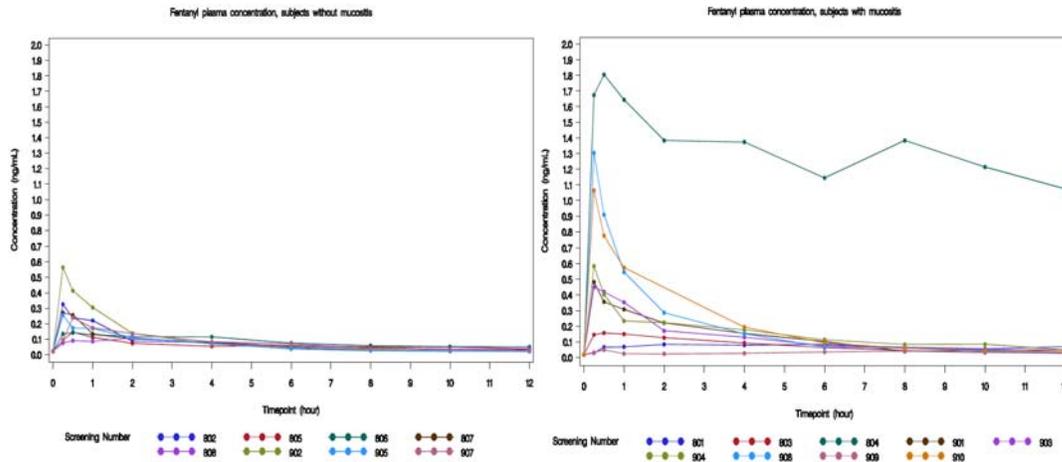


Table 4 Mean (%CV) PK parameters of fentanyl in cancer patients with mucositis and without mucositis following the administration of a single 100 mcg dose of Fentanyl Sublingual Spray (Study INS-09-011)

PK Parameter	Non-mucositis (n=8)	Mucositis Grade 1 (n=7)	Mucositis Grade 2 (N = 2)	
			Subject 804	Subject 910
Tmax*(hr)	0.38 (0.25, 2.00)	0.25 (0.25, 2.00)	0.5	0.25
Cmax (ng/mL)	0.26 (55.94)	0.45 (96.26)	1.81	1.07
AUClast (ng/mL.hr)	0.91 (14.67)	1.38 (44.80)	15.78	2.56

*: median (min, max)

Reviewer's Comments:

Fentanyl is mainly metabolized by CYP3A4 and inhibition of CYP3A4 will result in an increase in the systemic exposure of fentanyl. In Study INS-09-011, concomitant medications (prescription, over-the-counter, vitamin, or herbal substances) were prohibited for the duration of the study. As was expected for this patient population, all patients were taking one or more concomitant medications/supplements. For example, subject 804 (with Grade 2 mucositis) was taking calcium, ensure, erbitux, morphine, vitamin D and carboplatin taxotere. However, these medications/supplements are not known CYP3A4 inhibitors. Therefore, available data did not suggest that the increased exposure of fentanyl in this patient was due to the inhibition of CYP3A4. The only reported adverse events were mild burning sensation in the oral mucosa in two subjects (subject 904 with Grade 1 mucositis and subject 910 with grade 2 mucositis).

2.4 Extrinsic Factors

1. Does the pretreatment of oral cavity with hot or cold water affect the absorption of fentanyl from sublingual spray?

The effects of temperature of the oral cavity on the pharmacokinetics of fentanyl sublingual spray 200 mcg was analyzed by comparing the fentanyl PK parameters obtained following pretreatment with a cold or hot water to the fentanyl PK parameters for the reference treatment (sublingual dosing following no pretreatment) (Study INS-06-004 Part B). The cold water was cooled to the temperature of refrigerated ice water. The

hot water was heated to the temperature of hot coffee or tea. Fentanyl pharmacokinetic parameters and statistical analysis results are summarized in **Table 5**.

The pretreatment of oral cavity with hot water did not affect the PK of fentanyl sublingual spray. The C_{max}, AUC_{last}, AUC_{inf} values after pretreatment with hot water were bioequivalent to the reference (no pretreatment) based on the 90% confidence interval (81.70% – 114.76% for C_{max}; 83.71% – 113.03% for AUC_{last}; 85.87% – 119.38% for AUC_{inf}) falling within the 80-125% limits. The cold water decreased the AUC values of fentanyl by 5 to 8% and had no effect on fentanyl C_{max} values. The point estimate of the geometric mean ratio (cold water/no pretreatment) for C_{max}, AUC_{last} and AUC_{inf} are 100.08%, 94.78%, and 92.23%, respectively. The corresponding 90% confidence intervals are 83.07% – 120.58%, 75.95% – 118.29%, and 73.38% – 115.93%, respectively.

Table 5 Mean (%CV) Pharmacokinetic Parameters of Fentanyl after Administration of 200 mcg of Fentanyl Sublingual Spray after Pretreatment of the Oral Cavity with Cold Water (Test), Hot Water (Test), and no Pretreatment (Reference) (Study INS-06-004)

PK Parameter	Fentanyl Sublingual Spray 200 mcg (pretreatment with cold water)		Fentanyl Sublingual Spray 200 mcg (pretreatment with hot water)		Fentanyl Sublingual Spray 200 mcg (no pretreatment)	
	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
T _{max} (hr)*	11	1.22 (0.17, 1.5)	11	1.5 (0.33, 4)	12	1.375 (0.33, 2)
C _{max} (ng/mL)	11	0.325 (30.00)	11	0.324 (39.50)	12	0.336 (26.24)
AUC _{last} (ng/mL.hr)	11	1.983 (33.14)	11	2.005 (34.36)	12	1.997 (35.20)
AUC _{inf} (ng/mL.hr)	9	2.468 (43.60)	11	2.459 (37.11)	10	2.427 (40.49)
T _{1/2} (hr)	9	9.90 (72.84)	11	8.43 (58.76)	10	8.00 (65.21)
Statistical Analysis: Geometric Mean Ratio (Test/Reference) (90% CI)						
Ln (C _{max})	100.08 [83.07, 120.58]		96.88 [81.79, 114.76]		Reference	

Ln (AUClast)	94.78 [75.95, 118.29]	97.27 [83.71, 113.03]	Reference
Ln (AUCinf)	92.23 [73.38, 115.93]	101.25 [85.87, 119.38]	Reference

*median (min, max)

Statistical analysis based on n=11 for Cmax and AUClast for both cold and hot beverage and n = 9 for AUCinf for cold beverage and n = 10 for AUCinf for hot beverage

2. Does the pretreatment of oral cavity with low and high pH beverages affect the absorption of fentanyl from sublingual spray?

The effects of pH of the oral cavity on the pharmacokinetics of fentanyl sublingual spray 200 mcg was analyzed by comparing the fentanyl PK parameters obtained following pretreatment with low or high pH beverages to the fentanyl PK parameters for the reference treatment (sublingual dosing following no pretreatment) (Study INS-06-004 Part B). The low pH beverage was a commercially available carbonated drink i.e., Coca-Cola or Sprite. The high pH beverage was from a solution of ½ tsp of sodium bicarbonate dissolved in 4 ounces of room temperature water. Fentanyl pharmacokinetic parameters and statistical analysis results are summarized in **Table 6**.

The pretreatment of oral cavity with low pH beverage decreased fentanyl Cmax by 17% but had no effect on the AUC values. The point estimate of the geometric mean ratio (low pH/no pretreatment) for Cmax, AUClast, and AUCinf are 83.26%, 91.93%, and 95.68%, respectively. The corresponding 90% confidence intervals are 70.81% - 97.90%, 81.70% - 103.44%, and 84.39% - 108.49%, respectively. The pretreatment of oral cavity with high pH beverage increased fentanyl Cmax, AUClast, and AUCinf by 23%, 19%, and 18%, respectively.

Table 6 Mean (%CV) Pharmacokinetic Parameters of Fentanyl after Administration of 200 mcg of Fentanyl Sublingual Spray after Pretreatment of the Oral Cavity with Low pH Beverage (Test), High pH Beverage (Test), and no Pretreatment (Reference) (Study INS-06-004)

PK Parameter	Fentanyl Sublingual Spray 200 mcg	Fentanyl Sublingual 200 mcg	Fentanyl Sublingual Spray 200 mcg
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	(Pretreatment with Low pH Beverage)		(Pretreatment with High pH Beverage)		(no pretreatment)	
	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Tmax (hr)*	13	2 (1, 2.07)	13	1 (0.33, 2)	12	1.375 (0.33, 2)
Cmax (ng/mL)	13	0.291 (36.99)	13	0.409 (39.25)	12	0.336 (26.24)
AUClast (ng/mL.hr)	13	1.833 (54.79)	13	2.316 (44.08)	12	1.997 (35.20)
AUCinf (ng/mL.hr)	12	2.368 (56.62)	12	2.746 (46.40)	10	2.427 (40.49)
T1/2 (hr)	12	8.19 (72.01)	12	8.60 (63.61)	10	8.00 (65.21)
Statistical Analysis: Geometric Mean Ratio % (Test/Reference) (90% CI)						
Ln (Cmax)	83.26 [70.81, 97.90]		123.08 [107.98, 140.29]		Reference	
Ln (AUClast)	91.93 [81.70, 103.44]		119.08 [101.60, 139.58]		Reference	
Ln (AUCinf)	95.68 [84.39, 108.49]		118.56 [104.16, 134.95]		Reference	

*median (min, max)

Statistical analysis based on n=12 for Cmax and AUClast for both low and high pH beverages and n=10 for AUCinf for low pH beverage and n=9 for AUCinf for high pH beverage

2.5 General Biopharmaceutics

1. Is the proposed to-be-marketed formulation the same as the clinical formulation?

Throughout clinical development, the composition of the fentanyl solution formulation has remained unchanged. (b) (4)

The proposed product is single-dose spray device with five strengths, 100, 200, 400, 600, and 800 mcg. All five strengths were used in the clinical studies.

2. What is the absolute bioavailability of fentanyl sublingual spray? Is the proposed fentanyl sublingual spray bioequivalent to the reference product, Actiq® transmucosal lozenge?

The absolute bioavailability fentanyl sublingual spray 400 mcg to fentanyl citrate intravenous injection 100 mcg and the relative bioavailability to Actiq® 400 mcg were determined in a single dose crossover study in healthy subjects under fasted condition

(Study INS-06-003). Fentanyl pharmacokinetic parameters and statistical analysis results are shown in **Table 7**.

The mean absolute bioavailability of Fentanyl Sublingual Spray 400 mcg was 72.1% and 75.6% based dose normalized AUClast and AUCinf values, respectively. For the reference product Actiq®, the absolute bioavailability was 54.0% and 51.1% based on dose normalized AUClast and AUCinf, respectively.

Single dose of the 1 x 400 mcg fentanyl sublingual spray exhibits 34% and 36% greater Cmax and AUCinf values as compared to Actiq® 1 x 400 mcg under fasting condition. The point estimates of the geometric mean ratio (Fentanyl Sublingual Spray 400 mcg/Actiq® 400 mcg) for Cmax, AUClast, and AUCinf are 133.67%, 133.44% and 136.27%, respectively. The corresponding 90% confidence intervals are 119.67 – 149.31%, 121.47 – 146.58%, and 121.21 – 153.20%, respectively. Therefore, fentanyl sublingual spray is not bioequivalent to the reference product, Actiq®.

Table 7 Mean (%CV) Pharmacokinetic Parameters of Fentanyl and Statistical Analysis (Study INS-06-003)

PK Parameter	400 mcg Fentanyl Sublingual Spray		400 mcg Actiq® (fentanyl citrate) oral transmucosal lozenge		100 mcg Fentanyl Citrate Injection	
	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
Tmax (hr)*	21	1.5 (0.17, 2.00)	21	2 (0.5, 2.12)		--
Cmax (ng/mL)	21	0.813 (31.01)	21	0.607 (30.55)		--
AUClast (ng/mL.hr)	21	4.863 (35.12)	21	3.677 (39.17)	21	1.688 (24.38)
AUCinf (ng/mL.hr)	16	5.761 (33.26)	18	4.182 (39.93)	16	1.758 (21.74)
T1/2 (hr)	16	9.98 (44.14)	18	7.89 (47.15)	16	4.50 (43.02)
Statistical Analysis: Geometric Mean Ratio (Fentanyl Sublingual spray/Actiq®) (90% CI)						
Cmax	133.67 [119.67, 149.31]					

AUClast	133.44 [121.47, 146.58]
AUCinf	136.27 [121.21, 153.20]

* median (min, max)

2.6 Analytical Section

1. How is fentanyl measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

A validated LC-MS/MS method was used for the determination of fentanyl in human plasma. The established lower limit of quantitation (LLOQ) was 0.025 ng/mL.

Table 8 Summary of the bioanalytical method for determination of plasma fentanyl concentration

Study	Method	LLOQ	QCs	Accuracy	Precision
INS-06-003	LC-MS/MS	0.025 ng/mL	0.075, 0.300, 0.750, 1.50, and 3.75 ng/mL	-4.3% to 0.3%	2.1% to 8.3%
INS-06-004	LC/MS-MS	0.025 ng/mL	0.075, 0.249, 0.498, 1.50, and 3.75 ng/mL	-4.0% to 8.8%	1.7% to 8.3%
INS-09-011	LC/MS-MS	0.025 ng/mL	0.075 ng/mL, 0.300, 0.750, 1.50, and 3.75 ng/mL	-1.1% to 3.3%	2.2% to 4.6%

3 Detailed Labeling Recommendations

(~~RED Strikeout~~ text should be removed from labeling; Blue double underlined text should be added to labeling)

The following labeling recommendations are preliminary. As of today (November 30, 2011), labeling negotiation with sponsor is still ongoing.

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page



4 Appendix

4.1 Filing memo

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA/BLA Number	202788	Proposed Brand Name	SUBSYS™	
OCP Division (I, II, III, IV, V)	II	Generic Name	Fentanyl Sublingual Spray	
Medical Division	DAAP	Drug Class	Opioid	
OCP Reviewer	Wei Qiu	Indication(s)	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer	
OCP Team Leader	Yun Xu	Dosage Form	Sublingual spray 100, 200, 400, 600, and 800 mcg	
Pharmacometrics Reviewer		Dosing Regimen	Initial dose of 100 mcg; titrate to a tolerable dose	
Date of Submission	March 4, 2011	Route of Administration	Sublingual spray for transmucosal delivery	
Estimated Due Date of OCP Review	Nov 30, 2011	Sponsor	Insys Therapeutics, Inc.	
Medical Division Due Date		Priority Classification	Standard	
PDUFA Due Date	Jan 4, 2012			
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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		FNY-P4-270, INS-06-003, INS-06-004
multiple dose:				
Patients-				
single dose:	X	1		INS-09-011
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

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			INS-06-003
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			Same as above
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4	3	(b) (4)

4.2 Individual Study Synopsis

**2. SYNOPSIS**

Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: Fentanyl		
Title of Study: A Single-Dose Crossover Study of Fentanyl Sublingual Spray 400 mcg versus Actiq [®] 400 mcg versus Fentanyl Citrate Injection (IV) 100 mcg Under Fasted Conditions		
Investigators: Frederick A. Bieberdorf, M.D., CPI; James P. Doherty, D.O.; Ronald C. Only, D.O.; Daniel V. Freeland, D.O., CCI; Joe H. Juren, M.D.; Thomas Stanciu, M.D.; Sherilyn Adcock, R.Ph., Ph.D., Shelly Spencer, MSN, APRN, BC; John M. Thompson, M.D.; Joel T. Davidson, M.D.; Rey Ximes, M.D.; Larry W. Magnuson, M.D.		
Study Center(s): CEDRA Clinical Research, LLC, 8501 North MoPac Expressway, Suite 200, Austin, Texas 78759		
Publication (reference): None		
Study Period (days): 57	Phase of Development: I	
Objectives: The objective of this study was to compare the rate of absorption and bioavailability of Fentanyl Sublingual Spray 400 mcg to Actiq [®] 400 mcg and to Fentanyl Citrate Injection (IV) 100 mcg under fasting conditions.		
Study Design (Methodology): This was a Phase I, single-dose, open-label, randomized, three-period, three-treatment crossover study in which up to 40 healthy subjects were scheduled to receive a single dose of Fentanyl Sublingual Spray 400 mcg, Actiq [®] 400 mcg and a single dose of Fentanyl Citrate Injection (IV) 100 mcg after a 10-hour overnight fast.		
Number of Subjects: 40	Planned: up to 40	Analyzed: 21
Diagnosis and Main Criteria for Inclusion: Healthy adult male or non-pregnant, non-breast-feeding female volunteers, between 18 – 55 years of age, inclusive, with BMI between 18 – 30 kg/m ² , inclusive, and body weight of at least 60 kg (132 lbs).		
Test Product (Treatment A) Dose and Mode of Administration, Lot Number: Fentanyl Sublingual Spray (1 x 400 mcg sublingual spray) Lot # 06MM-017		
Duration of Treatment: Three single dose treatments were administered with a 7-day washout period between doses.		
Reference Product (Treatment B) Dose and Mode of Administration, Lot Number: Actiq [®] (1 x 400 mcg oral transmucosal unit) Lot # P63968		



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: Fentanyl		
Reference Product (Treatment C), Dose and Mode of Administration, Lot Number: Fentanyl Citrate Injection (1 x 100 mcg IV) Lot # 44-474-DK		
Criteria for Evaluation: <u>Efficacy:</u> No efficacy evaluations were performed in this study. <u>Safety:</u> Safety variables included physical examinations, vital signs, pulse-oximetry tests, clinical laboratory tests, pregnancy screens, electrocardiogram (ECG), concomitant medications, and adverse event (AE) assessments. An opioid antagonist, naltrexone, was also administered before product dosing to reduce the incidence and severity of AEs known to be associated with fentanyl administration. Subjects were monitored for any adverse events from the time of consent through the end of the study.		
Statistical Methods: Data from 21 subjects who completed the study were included in the pharmacokinetic and statistical analyses. The concentration-time data were transferred from Watson LIMS directly to WinNonlin Enterprise Edition (Version 4.0, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses. The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}). Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.		



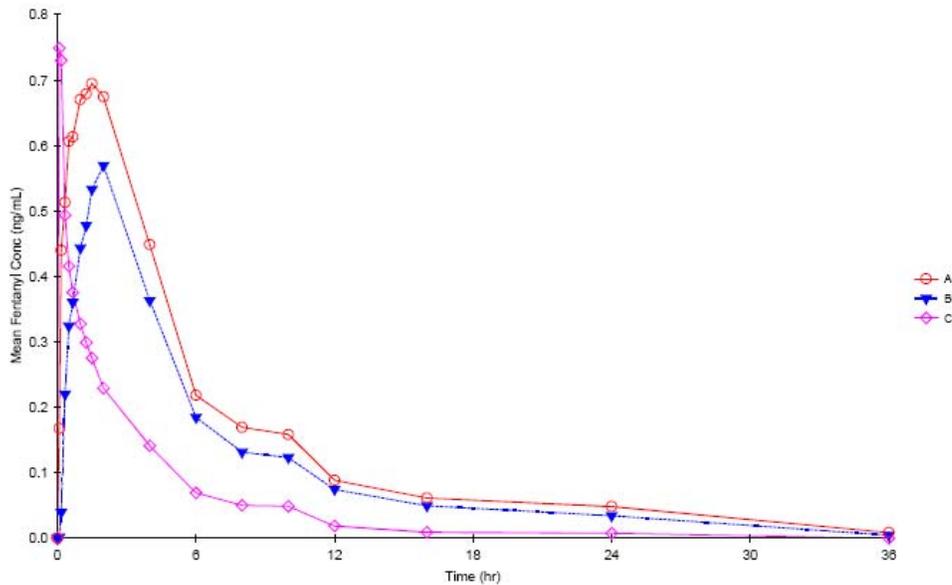
Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray	Volume: Page:	
Name of Active Ingredient: Fentanyl		

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Mean concentration-time data are shown in Synopsis Figure 1. Results of the pharmacokinetic and statistical analyses are shown below in Synopsis Tables 1 and 2.

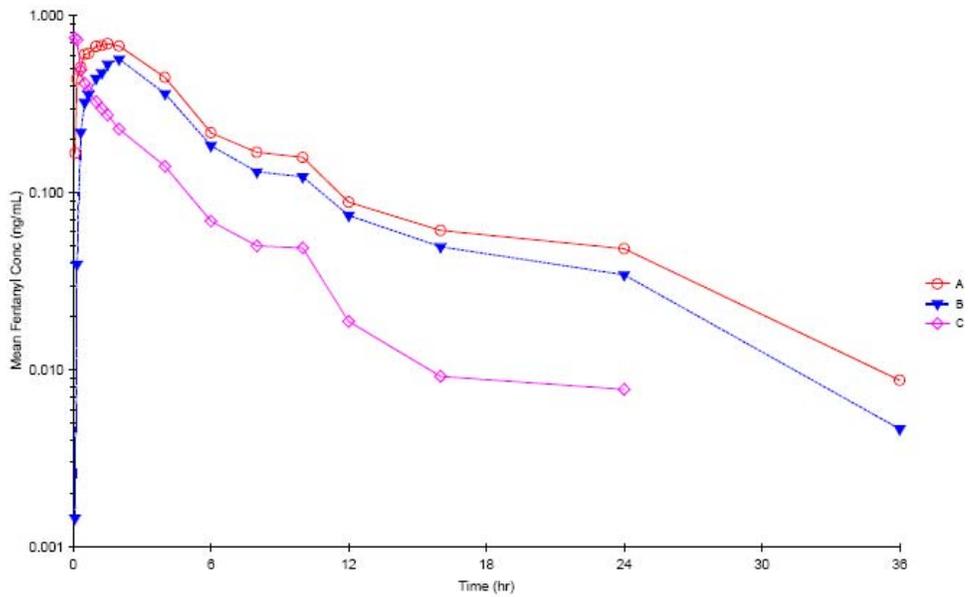
Synopsis Figure 1: Mean Fentanyl Concentration-Time Profiles for Fentanyl Sublingual Spray 400 mcg (Treatment A), Actiq 400 mcg (Treatment B), and Fentanyl Citrate Injection 100 mcg (Treatment C)





Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: Fentanyl		

Mean Fentanyl Concentration-Time Profiles for Fentanyl Sublingual Spray 400 mcg (Treatment A), Actiq 400 mcg (Treatment B), and Fentanyl Citrate Injection 100 mcg (Treatment C) (continued)



Source Data: Tables 14.2.1-14.2.3



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: Fentanyl		

Synopsis Table 1: Pharmacokinetic Parameters of Fentanyl

Parameter	Treatment A: Fentanyl Sublingual Spray 400 mcg				Treatment B: Actiq 400 mcg			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	21	1.28	0.60	47.18	21	1.70	0.42	25.04
C _{max} (ng/mL)	21	0.813	0.252	31.01	21	0.607	0.185	30.55
AUC _{0-t} (hr*ng/mL)	21	4.863	1.708	35.12	21	3.677	1.440	39.17
AUC _{inf} (hr*ng/mL)	16	5.761	1.916	33.26	18	4.182	1.670	39.93
AUC _{Extrap} (%)	16	10.26	5.66	55.19	18	10.64	5.68	53.38
λ _z (hr ⁻¹)	16	0.0904	0.0571	63.16	18	0.1097	0.0532	48.51
T _{1/2} (hr)	16	9.98	4.41	44.14	18	7.89	3.72	47.15
T _{last} (hr)	21	25.15	7.17	28.50	21	22.86	6.83	29.87
C _{last} (ng/mL)	21	0.0408	0.0117	28.74	21	0.0363	0.00953	26.23

Parameter	Treatment C: Fentanyl Citrate Injection 100 mcg			
	n	Mean	SD	CV%
T _{max} (hr)	21	0.16	0.08	50.52
C _{max} (ng/mL)	21	0.929	0.515	55.48
AUC _{0-t} (hr*ng/mL)	21	1.688	0.4114	24.38
AUC _{inf} (hr*ng/mL)	16	1.758	0.3822	21.74
AUC _{Extrap} (%)	16	11.14	3.44	30.92
λ _z (hr ⁻¹)	16	0.1775	0.0662	37.30
T _{1/2} (hr)	16	4.50	1.94	43.02
T _{last} (hr)	21	13.81	5.51	39.90
C _{last} (ng/mL)	21	0.0352	0.0117	33.08

Note: Full precision data used in pharmacokinetic analysis
Source data: Tables 14.2.4-14.2.6



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>																																											
Name of Finished Product: Fentanyl Sublingual Spray																																													
Name of Active Ingredient: Fentanyl																																													
<p>Synopsis Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Fentanyl Comparing Fentanyl Sublingual Spray 400 mcg (Treatment A) to Actiq 400 mcg (Treatment B)</p> <table border="1"> <thead> <tr> <th rowspan="2">Dependent Variable</th> <th colspan="2">Geometric Mean^a</th> <th rowspan="2">Ratio (%)^b (Test/Ref)</th> <th colspan="2">90% CI^c</th> <th colspan="2">ANOVA</th> </tr> <tr> <th>Test</th> <th>Ref</th> <th>Lower</th> <th>Upper</th> <th>Power</th> <th>CV%</th> </tr> </thead> <tbody> <tr> <td>ln(C_{max})</td> <td>0.7865</td> <td>0.5884</td> <td>133.67</td> <td>119.67</td> <td>149.31</td> <td>0.9527</td> <td>20.85</td> </tr> <tr> <td>ln(AUC_{0-t})</td> <td>4.6392</td> <td>3.4767</td> <td>133.44</td> <td>121.47</td> <td>146.58</td> <td>0.9859</td> <td>17.65</td> </tr> <tr> <td>ln(AUC_{inf})</td> <td>5.5080</td> <td>4.0420</td> <td>136.27</td> <td>121.21</td> <td>153.20</td> <td>0.9341</td> <td>17.06</td> </tr> </tbody> </table> <p>^a Geometric Mean for Treatment A (Test) and Treatment B (Ref) based on Least Squares Mean of log-transformed parameter values ^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref) ^c 90% Confidence Interval Source data: Listing 16.4.3.1 – 16.4.3.2</p> <p>Fentanyl Sublingual Spray 400 mcg (Test) vs. Actiq 400 mcg (Reference): The 90% confidence intervals for comparing the maximum exposure, based on ln(C_{max}), and total systemic exposure, based on ln(AUC_{last}) and ln(AUC_{inf}), under fasted conditions were not within the 80% to 125% limits. The ratios of geometric means of C_{max}, AUC_{last} and AUC_{inf} in this study were 133.67%, 133.44% and 136.27%, respectively. The mean absolute bioavailability, F, of the test formulation (A) and Actiq (B) were 0.721 and 0.540, respectively, based on the AUC_{last} parameter and were 0.756 and 0.511, respectively, based on the AUC_{inf} parameter.</p> <p>SAFETY RESULTS:</p> <p>Subjects were monitored for any adverse events from the beginning of confinement until study discharge. A total of 26 treatment emergent AEs were reported by 15 of the 40 subjects over the course of the study. All of the AEs were mild. Two of the AEs were probably related to the study drug. Three of the AEs were possibly related to the study treatment; the remaining 21 were not related to study treatment. In total, 31 AEs were reported over the course of the study. No clinically significant abnormalities in vital signs, ECGs, or physical exams were observed. Please refer to Tables 14.3.1 and 14.3.2 for more detailed data regarding AE/study treatment relationship.</p> <p>CONCLUSION:</p> <p>Therefore, the test formulation, Fentanyl Sublingual Spray 400 mcg was not bioequivalent to the reference formulation, Actiq 400 mcg. It, however, had a greater mean absolute bioavailability (0.721) than Actiq 400 mcg (0.540).</p> <p>Date of Report: 22 August 2007</p>								Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		ANOVA		Test	Ref	Lower	Upper	Power	CV%	ln(C _{max})	0.7865	0.5884	133.67	119.67	149.31	0.9527	20.85	ln(AUC _{0-t})	4.6392	3.4767	133.44	121.47	146.58	0.9859	17.65	ln(AUC _{inf})	5.5080	4.0420	136.27	121.21	153.20	0.9341	17.06
Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		ANOVA																																							
	Test	Ref		Lower	Upper	Power	CV%																																						
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ln(AUC _{0-t})	4.6392	3.4767	133.44	121.47	146.58	0.9859	17.65																																						
ln(AUC _{inf})	5.5080	4.0420	136.27	121.21	153.20	0.9341	17.06																																						



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>	
Name of Finished Product: Fentanyl Sublingual Spray	Volume:		
Name of Active Ingredient: fentanyl	Page:		
Title of Study: A Five-Treatment, Five Sequence, Five-Period, Crossover Study of Fentanyl Sublingual Spray Under Fasted Conditions			
Investigators: Jolene K. Berg, M.D.; James P. Doherty, D.O.; Frederick A. Bieberdorf, M.D.; Rey Ximenes, M.D.; Mary Nelson-Wade, APRN, BC			
Study Center(s): CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217			
Publication (reference): None			
Study Period (days): 39	Phase of Development: I		
Objectives: The primary objective of this clinical trial was to determine the pharmacokinetics of five different doses of Insys Therapeutics' Fentanyl Sublingual Spray in healthy subjects under fasted conditions (Part A). The secondary objective of this study was to assess the impact of temperature and pH in the oral cavity on the relative bioavailability of Fentanyl Sublingual Spray (Part B).			
Study Design (Methodology): Part A of this was a single dose, five-treatment, five-sequence, five-period crossover study. Part B was a single-dose, five-treatment, two sequence, five-period crossover study. Up to 70 healthy subjects could be dosed in order to obtain 40 evaluable subjects for dose proportionality (Part A) and 8 subjects for the effects of temperature and pH (Part B). Subjects were randomly assigned to one of the five treatments sequences according to the randomization schedule. Dosing days were separated by a washout period of at least 7 days.			
Number of Subjects: 67	Planned: 45 (A) 14 (B)	Analyzed: 38 (A) 11 (B)	
Diagnosis and Main Criteria for Inclusion: Healthy male or non-pregnant, non-breast-feeding female subjects between the ages of 18-55 inclusive, with BMI between 18 and 30 kg/m ² , inclusive, and body weight of at least 60 kg (132 lbs).			
Duration of Treatment: Five single dose treatments were administered with a 7-day washout period between doses.			
Test Product, Dose and Mode of Administration, Lot Number: Treatment A Fentanyl Sublingual Spray (1 × 100 µg) Lot 06MM-015 Mfg Date 12/8/2006			



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray	Volume:	
Name of Active Ingredient: fentanyl	Page:	
Test Product, Dose and Mode of Administration, Lot Number: Treatment B Fentanyl Sublingual Spray (1 × 200 µg) Lot 06MM-016 Mfg Date 12/12/2006		
Test Product, Dose and Mode of Administration, Lot Number: Treatment C Fentanyl Sublingual Spray (1 × 400 µg) Lot 06MM-017 Mfg Date 12/14/2006		
Test Product, Dose and Mode of Administration, Lot Number: Treatment D Fentanyl Sublingual Spray (1 × 600 µg) Lot 06MM-018 Mfg Date 12/15/2006		
Test Product, Dose and Mode of Administration, Lot Number: Treatment E Fentanyl Sublingual Spray (1 × 800 µg) Lot 06MM-019 Mfg Date 12/18/2006		
Criteria for Evaluation: <u>Efficacy:</u> Efficacy was not assessed in this study. <u>Safety:</u> Safety was assessed by physical examinations, vital signs, pulse-oximetry tests, clinical laboratory tests, pregnancy screens, electrocardiograms (ECGs), concomitant medications, and adverse event (AE) assessments. Subjects were monitored for any adverse events throughout the study.		



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: fentanyl		
Statistical Methods: In Part A of this study, data from subjects who completed at least one study period were included in the pharmacokinetic and statistical analyses. Concentration-time data were transferred from Watson LIMS directly to WinNonlin Enterprise Edition (Version 4.0, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses. The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}). Dose-normalized C_{max} , AUC_{last} , and AUC_{inf} were calculated by dividing the parameter values for individual subjects by the administered dose. Pharmacokinetic parameters were summarized by treatment using descriptive statistics. The effect of dose on the pharmacokinetic parameters of fentanyl was assessed by comparing each treatment to the lowest dose (100 mcg, Treatment A) and the highest dose (800 mcg, Treatment E). Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed, dose-normalized pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence intervals for the ratio of the geometric means (Test/Reference) were calculated in two separate analyses where the lowest strength (100 mcg) was used as the reference in one set of comparisons and then highest strength (800 mcg) was used as the reference in the other set of comparisons, yielding a total of 8 comparisons. Bioequivalence between dose strengths was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%. In addition to the ANOVAs, dose-proportionality was assessed using linear regression of the dose-normalized parameters C_{max} , AUC_{last} , and AUC_{inf} . The slope, y-intercept, 95% confidence intervals, and p-values were reported; a significant difference in the dose-normalized parameters across treatments groups was defined <i>a priori</i> as $p < 0.05$.		



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray	Volume: Page:	
Name of Active Ingredient: fentanyl		
<p>In Part B of this study, data from subjects who completed at least one study period were included in the pharmacokinetic and statistical analyses. Concentration-time data were transferred from Watson LIMS directly to WinNonlin Enterprise Edition (Version 4.0, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses.</p> <p>The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}).</p> <p>Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated, where the Reference treatment was Fentanyl Sublingual Spray 200 mcg administered without any pretreatment of the oral cavity. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.</p> <p>The effects of temperature of the oral cavity on fentanyl absorption was analyzed by comparing the pharmacokinetic parameters obtained following pretreatment with a cold beverage to the pharmacokinetic parameters for the reference treatment (sublingual dosing following no pretreatment) and by comparing the pharmacokinetic parameters obtained following pretreatment with a hot beverage to the pharmacokinetic parameters for the reference treatment (sublingual dosing following no pretreatment).</p> <p>The effects of pH of the oral cavity on fentanyl absorption was analyzed by comparing the pharmacokinetic parameters obtained following pretreatment with a carbonated beverage to the pharmacokinetic parameters for the reference treatment (sublingual dosing following no pretreatment) and by comparing the pharmacokinetic parameters obtained following pretreatment with an aqueous solution of sodium bicarbonate solution to the pharmacokinetic parameters for the reference treatment (sublingual dosing following no pretreatment).</p>		

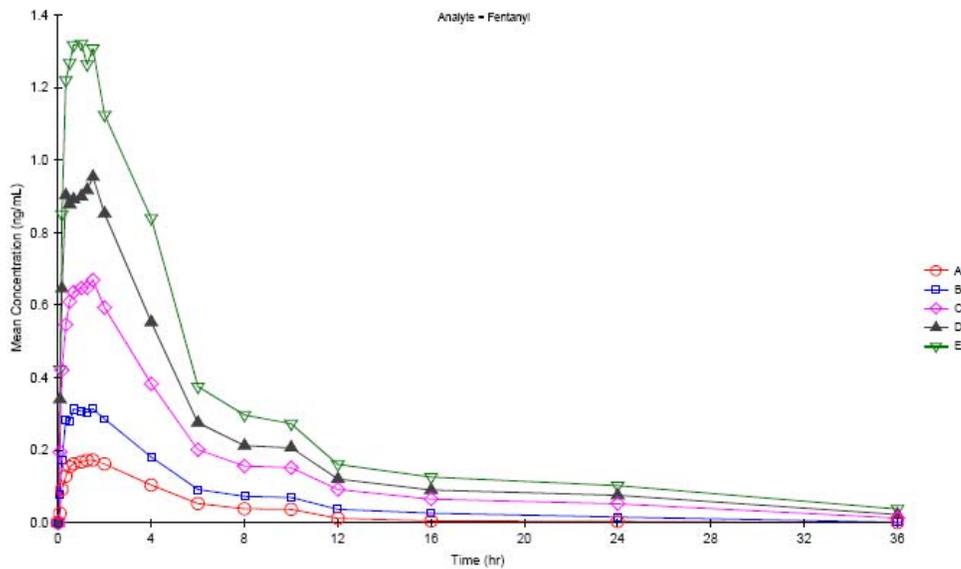
Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: fentanyl		

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

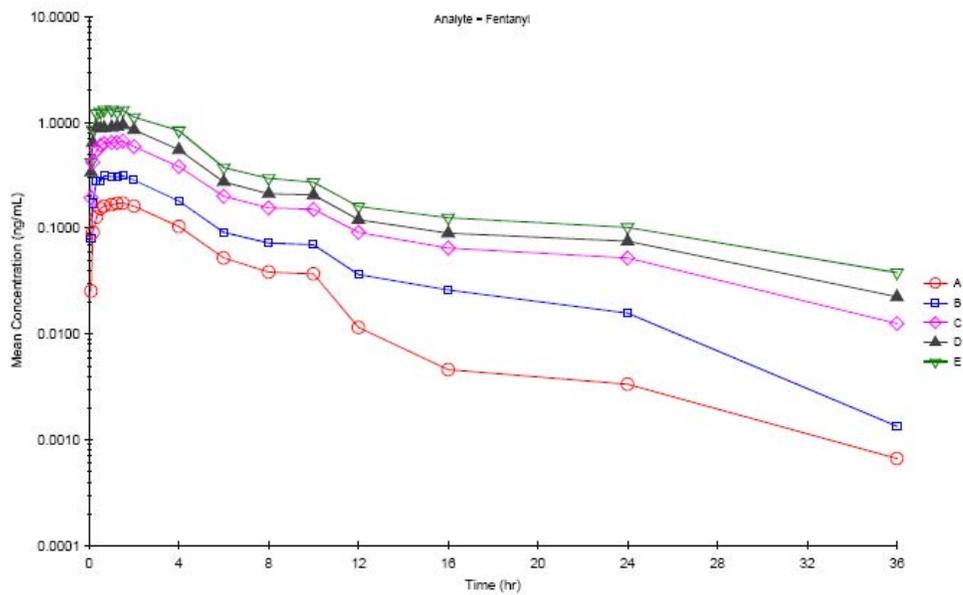
Mean concentration-time data are shown in Synopsis Figures 1 (Part A) and 2 (Part B). Results of the pharmacokinetic and statistical analyses are shown below in Synopsis Tables 1 (Part A) and 2 (Part B).

Synopsis Figure 1: Mean Fentanyl Concentration-Time Profiles (36 hours) after Administration of Fentanyl Sublingual Spray 100 mcg (Treatment A), 200 mcg (Treatment B), 400 mcg (Treatment C), 600 mcg (Treatment D), and 800 mcg (Treatment E)



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: fentanyl		

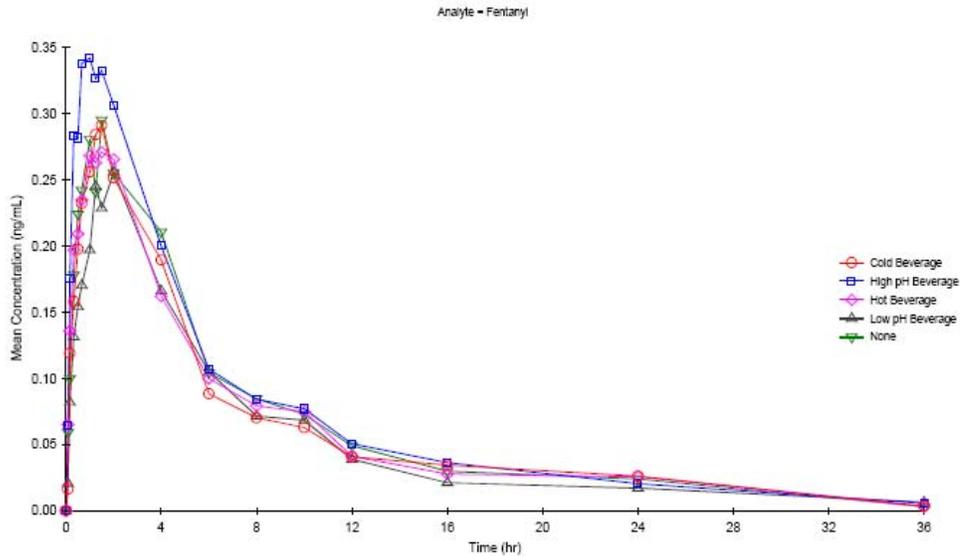
Synopsis Figure 1: Mean Fentanyl Concentration-Time Profiles (36 hours) after Administration of Fentanyl Sublingual Spray 100 mcg (Treatment A), 200 mcg (Treatment B), 400 mcg (Treatment C), 600 mcg (Treatment D), and 800 mcg (Treatment E) (continued)



Source data: Tables 14.2.1 - 14.2.5

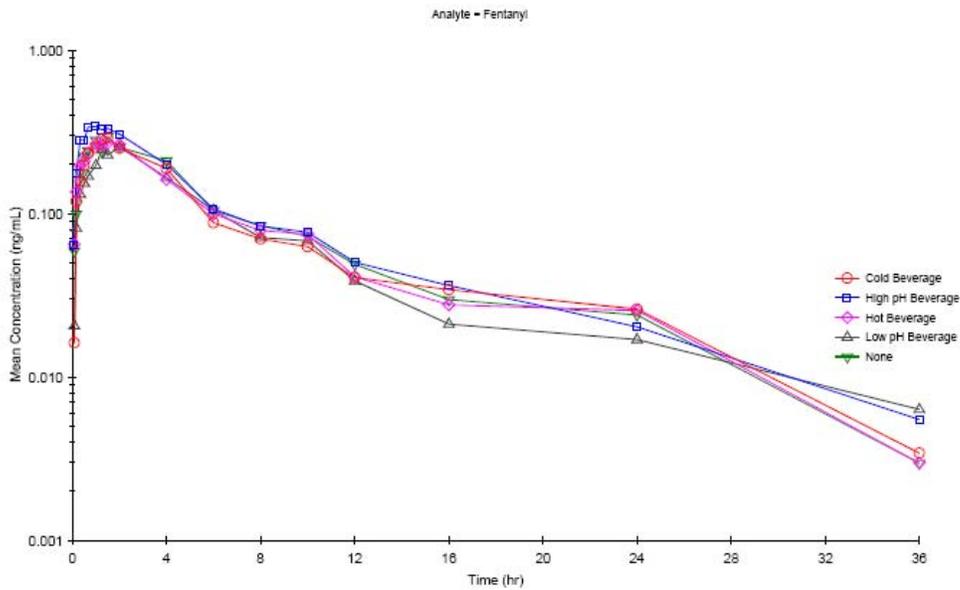
Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: fentanyl		

Synopsis Figure 2: Mean Fentanyl Concentration-Time Profiles after Administration of 200 mcg of Fentanyl Sublingual Spray after Pretreatment of the Oral Cavity with Cold Beverage (Treatment 1), Hot Beverage (Treatment 2), None/No Pretreatment (Treatment 3), Low pH Beverage (Treatment 4), and High pH Beverage (Treatment 5)



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: fentanyl		

Synopsis Figure 2: Mean Fentanyl Concentration-Time Profiles after Administration of 200 mcg of Fentanyl Sublingual Spray after Pretreatment of the Oral Cavity with Cold Beverage (Treatment 1), Hot Beverage (Treatment 2), None/No Pretreatment (Treatment 3), Low pH Beverage (Treatment 4), and High pH Beverage (Treatment 5)



Source data: Tables 14.2.11 - 14.2.15



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: fentanyl		

Synopsis Table 1: Parameters of Fentanyl

Parameter	Treatment A: Fentanyl Sublingual Spray 100 mcg				Treatment B: Fentanyl Sublingual Spray 200 mcg			
	n	Mean	SD	CV	n	Mean	SD	CV
				(%)				(%)
T _{max} (hr)	42	1.12	0.56	50.19	45	1.06	0.53	50.22
C _{max} (ng/mL)	42	0.202	0.0573	28.35	45	0.378	0.112	29.69
C _{max} /Dose	42	0.00202	0.000573	28.35	45	0.00189	0.000561	29.69
AUC _{last} (hr*ng/mL)	42	0.9776	0.4870	49.82	45	1.985	0.8122	40.93
AUC _{last} /Dose	42	0.009776	0.004870	49.82	45	0.009923	0.004061	40.93
AUC _{inf} (hr*ng/mL)	38	1.245	0.6700	53.82	42	2.475	1.150	46.48
AUC _{inf} /Dose	38	0.01245	0.006700	53.82	42	0.01237	0.005752	46.48
AUC _{Extrap} (%)	38	19.45	7.64	39.30	42	16.12	8.65	53.69
λ _z (hr ⁻¹)	38	0.1871	0.0921	49.20	42	0.1254	0.0689	54.90
T _{1/2} (hr)	38	5.25	4.72	89.92	42	8.45	6.58	77.94
T _{last} (hr)	42	11.38	6.00	52.70	45	17.78	7.01	39.43
C _{last} (ng/mL)	42	0.0341	0.00720	21.10	45	0.0361	0.0128	35.31

Note: Full precision data used in pharmacokinetic analysis; parameters were dose-normalized by dividing the parameter value (C_{max}, AUC_{last}, AUC_{inf}) by the administered dose



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: fentanyl		

Synopsis Table 1: Parameters of Fentanyl (continued)

Parameter	Treatment C: Fentanyl Sublingual Spray 400 mcg			
	n	Mean	SD	CV (%)
T _{max} (hr)	42	0.98	0.60	61.00
C _{max} (ng/mL)	42	0.800	0.221	27.66
C _{max} /Dose	42	0.00200	0.000553	27.66
AUC _{last} (hr*ng/mL)	42	4.643	2.068	44.53
AUC _{last} /Dose	42	0.01161	0.005169	44.53
AUC _{inf} (hr*ng/mL)	42	5.342	2.359	44.16
AUC _{inf} /Dose	42	0.01335	0.005897	44.16
AUC _{Extrap} (%)	42	12.63	6.14	48.60
λ _z (hr ⁻¹)	42	0.0905	0.0547	60.45
T _{1/2} (hr)	42	11.03	6.86	62.20
T _{last} (hr)	42	26.10	7.30	27.96
C _{last} (ng/mL)	42	0.0437	0.0138	31.52

Note: Full precision data used in pharmacokinetic analysis; parameters were dose-normalized by dividing the parameter value (C_{max}, AUC_{last}, AUC_{inf}) by the administered dose



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray		
Name of Active Ingredient: fentanyl		

Synopsis Table 1: Parameters of Fentanyl (continued)

Parameter	Treatment D: Fentanyl Sublingual Spray 600 mcg				Treatment E: Fentanyl Sublingual Spray 800 mcg			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	46	0.95	0.64	67.84	44	1.00	0.70	70.00
C _{max} (ng/mL)	46	1.17	0.378	32.48	44	1.61	0.601	37.22
C _{max} /Dose	46	0.00194	0.000631	32.48	44	0.00202	0.000751	37.22
AUC _{last} (hr*ng/mL)	46	6.682	2.169	32.46	44	9.450	3.460	36.62
AUC _{last} /Dose	46	0.01114	0.003615	32.46	44	0.01181	0.004325	36.62
AUC _{inf} (hr*ng/mL)	45	7.446	2.348	31.54	44	10.38	3.697	35.60
AUC _{inf} /Dose	45	0.01241	0.003913	31.54	44	0.01298	0.004621	35.60
AUC _{Extrap} (%)	45	9.47	4.80	50.71	44	9.26	4.56	49.18
λ _z (hr ⁻¹)	45	0.0780	0.0338	43.31	44	0.0647	0.0240	37.12
T _{1/2} (hr)	45	10.64	4.44	41.73	44	11.99	3.86	32.15
T _{last} (hr)	46	30.27	6.06	20.03	44	32.73	5.41	16.52
C _{last} (ng/mL)	46	0.0469	0.0170	36.18	44	0.0530	0.0220	41.49

Note: Full precision data used in pharmacokinetic analysis

Source data: Tables 14.2.16 - 14.2.20



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray	Volume: Page:	
Name of Active Ingredient: fentanyl		

Synopsis Table 2: Parameters of Fentanyl

Parameter	Treatment 1: Fentanyl Sublingual Spray 200 mcg (Cold Beverage)				Treatment 2: Fentanyl Sublingual Spray 200 mcg (Hot Beverage)			
	n	Mean	SD	CV (%)	n	Mean	SD	CV (%)
T _{max} (hr)	11	1.10	0.40	36.82	11	1.58	0.99	62.80
C _{max} (ng/mL)	11	0.325	0.0976	30.00	11	0.324	0.128	39.50
AUC _{last} (hr*ng/mL)	11	1.983	0.6574	33.14	11	2.005	0.6889	34.36
AUC _{inf} (hr*ng/mL)	9	2.468	1.076	43.60	11	2.459	0.9124	37.11
AUC _{Extrap} (%)	9	17.98	7.39	41.10	11	17.33	5.89	33.98
λ _z (hr ⁻¹)	9	0.1110	0.0874	78.71	11	0.1243	0.0948	76.24
T _{1/2} (hr)	9	9.90	7.21	72.84	11	8.43	4.95	58.76
T _{last} (hr)	11	22.00	7.43	33.77	11	20.55	8.20	39.92
C _{last} (ng/mL)	11	0.0326	0.00410	12.58	11	0.0381	0.0109	28.71

Note: Full precision data used in pharmacokinetic analysis

Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	<i>(For National Authority Use Only)</i>		
Name of Finished Product: Fentanyl Sublingual Spray				
Name of Active Ingredient: fentanyl				
Synopsis Table 2: Parameters of Fentanyl (continued)				
Parameter	Treatment 3: Fentanyl Sublingual Spray 200 mcg (None)			
	n	Mean	SD	CV (%)
T _{max} (hr)	12	1.26	0.60	48.10
C _{max} (ng/mL)	12	0.336	0.0882	26.24
AUC _{last} (hr*ng/mL)	12	1.997	0.7030	35.20
AUC _{inf} (hr*ng/mL)	10	2.427	0.9828	40.49
AUC _{Extrap} (%)	10	15.17	5.04	33.19
λ ₂ (hr ⁻¹)	10	0.1206	0.0669	55.50
T _{1/2} (hr)	10	8.00	5.22	65.21
T _{last} (hr)	12	19.17	9.00	46.97
C _{last} (ng/mL)	12	0.0587	0.0846	144.19
Note: Full precision data used in pharmacokinetic analysis				



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray	Volume:	
Name of Active Ingredient: fentanyl	Page:	

Synopsis Table 2: Parameters of Fentanyl (continued)

Parameter	Treatment 4: Fentanyl Sublingual Spray 200 mcg (Low pH Beverage)				Treatment 5: Fentanyl Sublingual Spray 200 mcg (High pH Beverage)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	13	1.72	0.40	23.13	13	0.99	0.51	51.68
C_{max} (ng/mL)	13	0.291	0.108	36.99	13	0.409	0.161	39.25
AUC_{last} (hr*ng/mL)	13	1.833	1.004	54.79	13	2.316	1.021	44.08
AUC_{inf} (hr*ng/mL)	12	2.368	1.341	56.62	12	2.746	1.274	46.40
AUC_{Extrap} (%)	12	17.76	7.28	40.98	12	15.85	6.34	40.01
λ_z (hr⁻¹)	12	0.1243	0.0682	54.86	12	0.1167	0.0676	57.96
T_{1/2} (hr)	12	8.19	5.90	72.01	12	8.60	5.47	63.61
T_{last} (hr)	13	18.62	9.39	50.47	13	20.46	8.49	41.50
C_{last} (ng/mL)	13	0.0381	0.00905	23.74	13	0.0364	0.0102	27.96

Note: Full precision data used in pharmacokinetic analysis
Source data: Tables 14.2.21 - 14.2.25



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray	Volume: Page:	
Name of Active Ingredient: fentanyl		

SAFETY RESULTS:

Subjects were monitored for any adverse events from the beginning of confinement until study completion.

During Part A, a total of 100 treatment emergent AEs were reported by 31 of the 53 subjects over the course of the study. Seventy-five of the 100 AEs were mild and 25 were moderate. Forty-six of the AEs were probably related to the study treatment, 29 of the AEs were possibly related, and the remaining 25 were not related to the study treatment.

During Part B, a total of 29 treatment emergent AEs were reported by 9 of the 14 subjects over the course of the study. Six of the 29 AEs were moderate and the remaining 23 were mild. Seven of the AEs were probably related to the study treatment. Seventeen of the AEs were possibly related to the study treatment and the remaining five were unrelated to study treatment.

No clinically significant abnormalities in vital signs, ECGs, or physical exams were observed. Please refer to Table 14.3.1 and Table 14.3.2 for more detailed data regarding AE/study treatment relationship.

CONCLUSION:

Part A:

The pharmacokinetic data from Part A of this study, from both the bioequivalence analysis and linear regression of the dose-normalized pharmacokinetic parameters (C_{max} , AUC_{last} , AUC_{inf}), indicate that administration of fentanyl using a sublingual spray (b) (4) of spray per dose administered) is dose-proportional over the 100 mcg to 800 mcg range. Deviations from strict linearity in the dose proportionality assessments using AUC_{last} are quantitatively small and may be attributable to the shorter duration of obtaining quantifiable fentanyl concentrations after administration of the lowest dose.

Sublingual dosing resulted in sustained fentanyl concentrations at near the maximal level, producing a concentration plateau that is maintained for 60 to 90 minutes. Fentanyl concentrations increase rapidly following administration of the sublingual spray, reaching approximately 60.6% of the peak plateau by 10 minutes post-dose and 86.6% of the peak plateau by 20 minutes post dose.

Part B:

- Temperature Effect

The C_{max} after pretreatment with cold and hot beverages were bioequivalent to the reference (no pretreatment) based on the 90% confidence interval falling within the traditional limits of 80% to 125%.

The AUC_{last} and AUC_{inf} after pretreatment with hot beverage were bioequivalent to the reference (no pretreatment) based on the 90% confidence intervals falling within the traditional limits of 80% to 125%. However, the AUC_{last} and AUC_{inf} after pretreatment with cold beverage were not bioequivalent to the reference (no pretreatment); the lower bounds of the 90% confidence interval for the cold beverage pretreatment were outside the traditional 80% to



Name of Sponsor/Company: Insys Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Fentanyl Sublingual Spray	Volume: Page:	
Name of Active Ingredient: fentanyl		
<p>125% bioequivalence limits, 75.95% for AUC_{last} and 73.38% AUC_{inf}. Unity (100%) was included within the 90% confidence interval for these comparisons.</p> <ul style="list-style-type: none">• pH Effect <p>The C_{max} after pretreatment with Low pH and High pH beverages were not bioequivalent to the reference (no pretreatment); the lower bounds of the 90% confidence interval for the low pH beverage pretreatment was outside the traditional 80% to 125% bioequivalence limits (70.81%) and the upper bound of the 90% confidence interval for the high pH beverage pretreatment was outside the traditional 80% to 125% bioequivalence limits (140.29%). Unity (100%) was included within the 90% confidence interval for only the high pH beverage comparison.</p> <p>The AUC_{last} after pretreatment with low pH beverage was bioequivalent to the reference (no pretreatment) based on the 90% confidence interval falling within the traditional limits of 80% to 125%. However, the AUC_{last} after pretreatment with high pH beverage was not bioequivalent to the reference (no pretreatment); the upper bound of the 90% confidence interval for the high pH beverage pretreatment was outside the traditional 80% to 125% bioequivalence limits (139.58%). Unity (100%) was included within the 90% confidence intervals for these comparisons.</p> <p>The AUC_{inf} after pretreatment with low pH beverage was bioequivalent to the reference (no pretreatment) based on the 90% confidence interval falling within the traditional limits of 80% to 125%. However, the AUC_{inf} after pretreatment with high pH beverage was not bioequivalent to the reference (no pretreatment); the upper bound of the 90% confidence interval for the high pH beverage pretreatment was outside the traditional 80% to 125% bioequivalence limits (134.95%). Unity (100%) was included within the 90% confidence interval for these comparisons.</p>		
Date of Report: 01 October 2007		

2. SYNOPSIS

Name of Sponsor	Insys Therapeutics, Inc.	
Name of Product	Fentanyl sublingual spray (Fentanyl SL Spray)	
Name of Active Ingredient	Active ingredient: Fentanyl base Unit strengths: 100 mcg Fentanyl per actuation (unit dose spray device) Administered dose: 100 mcg Fentanyl	
Indication (phase)	Breakthrough cancer pain (Phase III)	
Title of Study	Evaluate Safety and Tolerability and Compare Absorption/Distribution Kinetics of a Single 100 mcg Dose of Fentanyl Sublingual Spray (Fentanyl SL Spray) in Cancer Subjects with or without Oral Mucositis	
Publications	None to date	
REPORT PARTICULARS		
Report date	16 November 2010	
Period of study	05 October 2009 (first subject dosed) to 28 October 2010 (database lock)	
Principal Investigators	Lisa Jo Stearns, MD Center for Pain and Supportive Care 10460 N. 92nd Street, Suite 300 Scottsdale, AZ 85258	Sarah D. Atkinson, MD Finger Lakes Clinical Research 885 South Winton Road Rochester, NY 14618-0218
OBJECTIVES		
Study Objective	The primary objective was to evaluate the safety, tolerability, and absorption/distribution kinetics of a single 100 mcg dose of Fentanyl SL Spray in subjects with cancer, with or without mucositis.	
METHODOLOGY		
Study Design	<p>This was an open-label, single dose study to assess the safety, tolerability and absorption/distribution kinetics of a single 100 mcg dose of Fentanyl SL Spray in opioid-tolerant cancer subjects, with or without oral mucositis.</p> <p>It was conducted at two centers in the United States. This study was to enroll up to 20 subjects with cancer pain: 10 subjects with mild mucositis (Grade 1 or 2) and 10 subjects without mucositis.</p> <p>The pharmacokinetic profile of Fentanyl SL spray was evaluated based on C_{max}, T_{max} and AUC_{0-last}. Safety was assessed using multiple variables including physical examination, oral cavity examination, vital signs, clinical laboratory tests, electrocardiograms, concomitant medications assessments, and adverse events.</p>	
Treatments	Subjects received a single 100 mcg dose of Fentanyl SL Spray. Each dose of Fentanyl SL Spray was administered by the study staff as a sublingual spray. No water was given for a period of 1 hour prior and 1 hour post study drug administration. All doses were administered following an overnight fast of at	

	least 8 hours and subjects continued fasting for at least 4 hour post-dose.
Treatment Duration	This was a single dose study. Subjects were released from the clinic after the 12-hour post-dose assessments were completed.
Study Drug	Fentanyl sublingual spray (Fentanyl SL Spray). A single Fentanyl SL Spray dose strength of 100 mcg was provided for the treatment.
Batch Numbers	The lot used for packaging Fentanyl SL Spray, 100 mcg was Lot # 709673. Each spray device was individually blister packaged under packaging Lot # 9054665.
SUBJECT POPULATION	
Number Planned	This study was to enroll up to 20 subjects with cancer pain: 10 subjects with mild mucositis (Grade 1 or 2) and 10 subjects without mucositis.
Inclusion Criteria	<p>Subjects were to meet the following criteria to be included in the trial:</p> <ol style="list-style-type: none"> 1. Male or female subjects at least 18 years of age. 2. Diagnosis of cancer. 3. Opioid-tolerant. Subjects who were treated with opioids were defined as those subjects who were taking at least 60 mg of oral morphine/day, at least 30 mg of oxycodone/day, at least 8 mg of oral hydromorphone/day, or an equianalgesic dose of another opioid for at least seven days for cancer related pain. 4. Experiencing persistent pain related to the cancer or its treatment during the 7 days preceding the treatment. 5. Subjects had to be able to provide written informed consent after risks and benefits had been explained and must have been willing to comply with study procedures. 6. Female subjects of child bearing potential were to have a negative urine pregnancy test at screening and prior to drug administration. 7. Mucositis subjects were to have Grade 1 or Grade 2 mucositis on the day of study drug administration. Subjects without mucositis were to have a normal oral cavity upon examination on the day of study drug administration.
Exclusion Criteria	<p>Subjects who met any of the following criteria were ineligible for participation in the study:</p> <ol style="list-style-type: none"> 1. Intolerable side effects to opioids or fentanyl. 2. Current use of any fentanyl product. Subjects previously on Actiq[®], Fentora[®], or Duragesic[®] were able to be enrolled after a seven day washout. 3. A history of major organ system impairment or disease that, in the Investigator's or his/her designee's opinion could have increased the risk associated with the use of opioids. 4. Uncontrolled hypertension despite anti-hypertensive therapy, or a history of hypertensive crisis within the preceding two years. 5. A recent history (within the preceding two years) of transient ischemic attacks, neural vascular disease, stroke, or cerebral aneurysms. 6. Brain metastases with signs or symptoms of increased intracranial pressure. 7. Received an investigational study product(s) within 30 days of the Screening Visit. 8. Use of monoamine oxidase (MAO) inhibitors within 14 days of the Screening

	<p>Visit.</p> <p>9. Prior participation in either Insys Fentanyl Sublingual Spray Phase III protocol INS-05-001 or INS-06-007</p>																																																																																				
ASSESSMENTS																																																																																					
Pharmacokinetics	<p>A total of 10 blood samples were collected over a 12 hour period from each subject for the determination of Fentanyl concentration. Blood samples were collected before dosing, and at 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr and 12 hr post dose. Fentanyl concentration assays were performed using a fully validated and sensitive LC MS/MS method, documentation for which is provided in the bioanalytical report.</p> <p>These concentrations were used to estimate C_{max}, T_{max} and AUC_{0-last}.</p>																																																																																				
Safety	<p>Safety assessments included physical examinations, oral cavity examinations, vital signs, clinical laboratory tests, electrocardiograms, concomitant medications assessments, and adverse event assessments.</p>																																																																																				
STATISTICAL METHODS AND ANALYSIS																																																																																					
Pharmacokinetics	<p>The absorption/distribution profiles obtained in cancer subjects with or without oral mucositis were evaluated for differences between the study groups in C_{max}, T_{max} and AUC_{0-last} via 90% confidence intervals.</p>																																																																																				
Safety	<p>All safety parameters were evaluated descriptively and as data listings.</p>																																																																																				
STUDY POPULATION																																																																																					
Populations Analyzed	<p>All dosed subjects were included in the Safety Analyses. A total of 18 subjects were dosed (mucositis group N = 9; Non-mucositis group N = 9).</p> <p>For the analysis of pharmacokinetics, one subject was excluded (subject 809, non-mucositis group) due to a self-administered dose of a Fentanyl product prior to the study drug dose (violation of Exclusion Criterion 2). This subject has been excluded from all summaries of pharmacokinetic parameters. The resulting numbers for the two groups were: mucositis group N = 9; non-mucositis group N = 8.</p>																																																																																				
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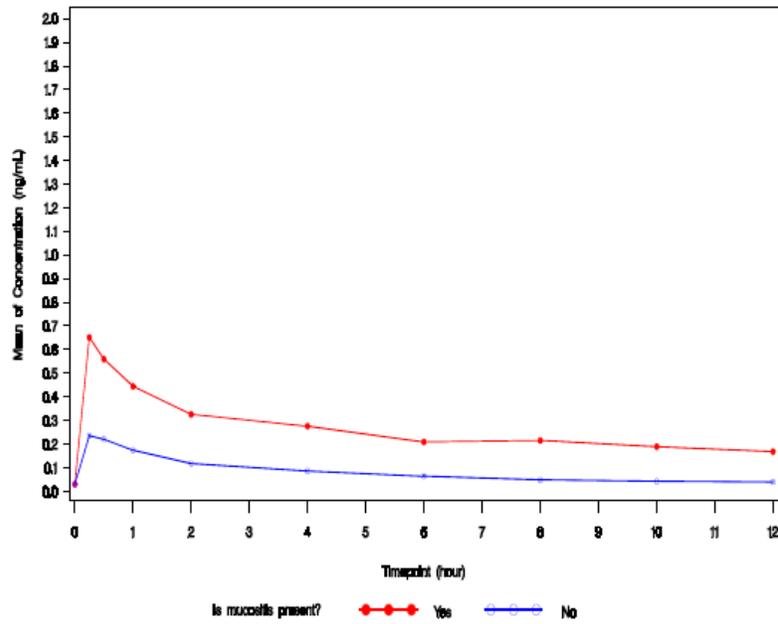
	baseline parameters (physical examinations, medical history, concomitant medications, laboratory parameters, electrocardiograms, vital signs) or demographic characteristics, with the exception of weight. Within the mucositis group, seven of the nine subjects (78%) had a mucositis grade of 1 and two of nine subjects (22%) had a mucositis grade of 2.																																																						
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<p>All Adverse Events</p>	<p>Two of the nine subjects (22%) in the mucositis group reported a mild burning sensation in the oral mucosa. Both of these events were considered, by the investigator, as “probably related” to treatment. These were the only reported adverse events in the study. No adverse events were reported for the non-mucositis group.</p>																																																						
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CONCLUSIONS

No statistically significant differences were observed between the mucositis subjects and the non-mucositis subjects for any of the tested pharmacokinetic parameters in this trial that was designed to compare the absorption/distribution kinetics of a single 100 mcg dose of Fentanyl Sublingual Spray between these two groups.

Mucositis Subjects vs. Non-Mucositis Subjects, Mean Fentanyl Concentration-Time Curve



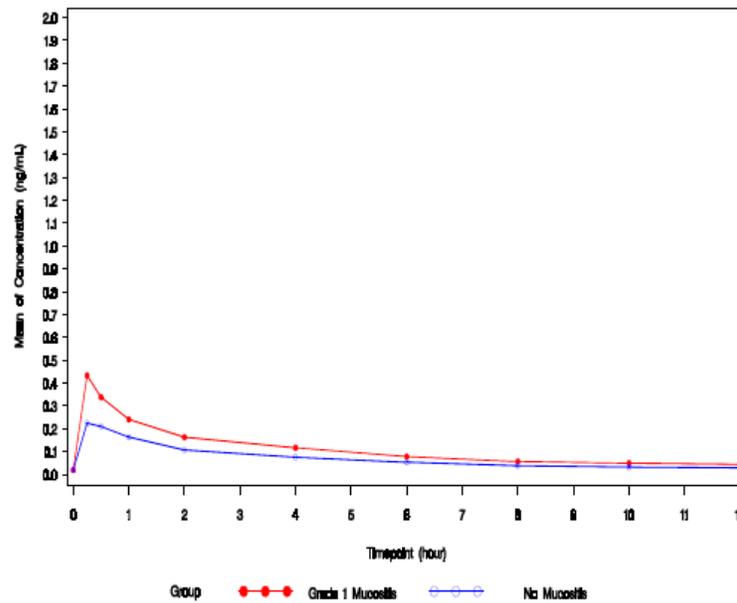
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C_{max}	0.2296 – 0.7024	0.1268 – 0.4150
T_{max}	0.1896 – 0.8660	0.2038 – 0.9212
AUC_{0-12h}	1.1654 – 2.7020	0.5793 – 1.4135

-Source: Section 14, Table 14.2.2; Section 16.2, Listing 16.2.6.1

CONCLUSIONS (continued)

No statistically significant differences were observed between the grade 1 mucositis subjects and the non-mucositis subjects for any of the tested pharmacokinetic parameters in this trial.

Grade 1 Mucositis Subjects vs. Non-Mucositis Subjects, Mean Fentanyl Concentration-Time Curve



90% Confidence Intervals, All PK Parameters, Grade 1 Mucositis vs. Non-Mucositis		
	Grade 1 Mucositis N = 7	Non-Mucositis N = 8
C_{max}	0.1583 – 0.5007	0.1339 – 0.3930
T_{max}	0.1591 – 0.9838	0.1768 – 0.9482
AUC_{0-12h}	0.9525 – 1.5942	0.7112 – 1.1514

-Source: Section 14, [Table 14.2.4](#); Section 16.2, [Listing 16.2.6.1](#)

2. SYNOPSIS

Title of Study:

A Single Site, Ascending Dose Study to Determine the Pharmacokinetics, Safety and Tolerability of a New Formulation of Fentanyl Sublingual Spray in Healthy Male Volunteers

Protocol No.: FNY-P4-270

Qualified Investigator:

Eric Sicard, M.D., Clinical Investigator.

Study Center:

Algorithme Pharma Inc., 9000 L'Acadie Blvd., Montreal, Quebec, Canada, H4N 2Y8.

Publication (reference):

None

Time of Clinical Part:

2005/04/13 to 2005/05/13

Phase of Development:

Phase I

Objectives:

The main objective of this study was to determine the pharmacokinetics of a new formulation of Fentanyl SL after increasing sublingual dose administration in healthy volunteers under fasting conditions. The secondary objective was to determine the safety and tolerability of Fentanyl sublingual spray in humans.

Methodology:

Single center, single-dose, single-blinded, sequential ascending dose and repeated design.

Number of Subjects (Planned and Analyzed):

Planned for inclusion: 9

Enrolled: 9

Included: 9

Drop-outs: 4

Analyzed and considered in the statistical analysis: 6

Diagnosis and Main Criteria of Inclusion:

Male subjects, non- or ex-smokers, of at least 18 but no more than 55 years of age with a body mass index (BMI) greater than or equal to 19 and below 30 kg/m². Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (ECG) and the usual clinical laboratory tests (hematology, biochemistry, urinalysis) including negative HIV, Hepatitis B and Hepatitis C tests as well as negative screening of ethyl alcohol and drugs of abuse in urine. Seated diastolic blood pressure was to be equal to or over 60 mm Hg, at screening. The respiratory rate and the oxygen saturation of blood were to be monitored.

Test Product, Dose and Mode of Administration, Batch Number:

Test 1 (A)

Name: Fentanyl 1 mg/mL

Mode/route: sublingual spray /oral

Regimen: single dose of 1 x 100 µg

Batch no.: F-34

Test Product, Dose and Mode of Administration, Batch Number:

Test 2 (B)

Name: Fentanyl 4 mg/mL

Mode/route: sublingual spray /oral

Regimen: single dose of 1 x 400 µg

Batch no.: F-35

Test Product, Dose and Mode of Administration, Batch Number:

Test 2 (C)

Name: Fentanyl 4 mg/mL

Mode/route: sublingual spray /oral

Regimen: single dose of 800 µg (2 x 400 µg)

Batch no.: F-35

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo-Test 1 (D)

Name: Placebo 1 mg/mL (contains the non-medicinal ingredients of the active drug)

Mode/route: sublingual spray /oral

Regimen: single dose of 1 x 100 µg

Batch no.: F-32PL

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo-Test 2 (E)

Name: Placebo 4 mg/mL (contains the non-medicinal ingredients of the active drug)

Mode/route: sublingual spray /oral

Regimen: single dose of 1 x 400 µg

Batch no.: F-33PL

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo-Test 2 (F)

Name: Placebo 4 mg/mL (contains the non-medicinal ingredients of the active drug)

Mode/route: sublingual spray /oral

Regimen: single dose of 1 x 800 µg (2 x 400 µg)

Batch no.: F-33PL

Treatment Periods:

Period 1: 2005/04/14

Period 2: 2005/04/29

Period 3: 2005/05/12

Duration of Treatment:

A single oral dose was administered under fasting conditions in each study period. Periods 1 and 2 were separated by a wash-out of 15 days while periods 2 and 3 were separated by a wash-out of 13 days.

Blood Sampling Points:

Blood samples were collected prior to and 0.08, 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours after drug administration.

Criteria for Evaluation**Analytical Method:**

Analyte: Fentanyl in plasma

Method: LC with MS/MS detection

Assay range: 50.0 pg/mL to 20000.0 pg/mL

Pharmacokinetics:

Main absorption and disposition parameters using non-compartmental approach (C_{max} , T_{max} , AUC_T , AUC_{∞} , $AUC_{T/\infty}$, K_{el} and $T_{1/2el}$).

Safety:

Adverse events, standard laboratory evaluation, vital signs, respiratory rate, oxygen saturation of blood by finger pulse oximetry and ECG.

Statistical Methods**Pharmacokinetics:**

Parametric ANOVA on C_{max} , T_{max} , AUC_T , AUC_{∞} , $AUC_{T/\infty}$, K_{el} , $T_{1/2el}$, Cl/F and V_Z ; geometric confidence interval for C_{max} , AUC_T and AUC_{∞} based on ln-transformed data; T_{max} rank transformed.

ANOVA model:

-fixed factors: treatment

-random factor: subject effect

Criteria for Bioequivalence:

Not applicable.

Safety:

Descriptive statistics.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

The pharmacokinetic parameters were well defined for the three doses (100 µg, 400 µg and 800 µg) administered in this study. The three doses were mainly proportional. The pharmacokinetic parameters derived from the fentanyl plasma concentrations versus time profiles are presented in the following summary tables (see subsequent pages).

Safety Results:

All nine subjects experienced a total of hundred-twenty-seven (127) adverse events during the study. No serious adverse events were recorded in this study. Twenty adverse events (8 different types) were reported after the single dose administration of the Test 1 (A) product, fifty-six adverse events (26 different types) were reported after the single dose administration of the Test 2 (B) product, twenty-two adverse events (19 different types) were reported after the single dose administration of the Test 2 (C) product, ten adverse events (8 different types) were reported after the single dose administration of the Placebo-Test 1 (D) product, eleven adverse events (9 different types) were reported after the single dose administration of the Placebo-Test 2 (E) product and twelve adverse events (8 different types) were reported after the single dose administration of the Placebo-Test 2 (F) product. Two (2) adverse events associated with post-study laboratory test results were imputed to the three formulations.

The events abdominal distension, abdominal pain, abdominal pain upper, anxiety, depressed mood, diarrhoea, disturbance in attention, dizziness (10 episodes out of 11), dry mouth, dry skin, dysgeusia, headache, fatigue (6 episodes out of 7), feeling cold, feeling drunk, feeling hot, feeling of relaxation, hot flush, hyperhidrosis, hypoaesthesia oral, hypoaesthesia, nasal congestion, nausea, oral discomfort, pallor, paresthesia oral, pruritus, sensation of heaviness, somnolence, speech disorder, tongue coated and vomiting were assessed to be possibly related to the drugs. The other events cough, dizziness (1 episode out of 11), fatigue (1 episode out of 7), musculoskeletal pain, rhinorrhoea and throat irritation were assessed to be not related to the study drugs. The other event nasopharyngitis was assessed to be unlikely related to the study drugs.

At the post-study evaluation, alanine aminotransferase increased and aspartate aminotransferase increased were observed in one subject. These changes in biological parameters were assessed to be possibly related to the study drugs.

Conclusion:

The objective of this study was to determine the pharmacokinetics of a new formulation of Fentanyl SL (Fentanyl 100 µg, 400 µg and 800 µg manufactured by (b) (4) for Insys Therapeutics Inc., USA) after increasing sublingual dose administration in healthy volunteers under fasting conditions and to determine the safety and tolerability of Fentanyl sublingual spray in humans. The pharmacokinetic parameters were well defined for the three doses (100 µg, 400 µg and 800 µg) administered in this study. C_{max} and AUC_{∞} seem to be proportional, AUC_T is consistent with dose-proportionality between the 400 µg and 800 µg, but the relationship between the 100 µg dose and the other doses is less clear, possibly because of the earlier decrease in concentrations below the LOQ associated with the lowest dose. Once

normalized, the only parameters for which a statistically significant difference was observed between the 100 µg dose and the 400 µg dose were AUC_T , $\ln(AUC_T)$ and $AUC_{T/\infty}$, and the only parameter for which a statistically significant difference was observed between the 100 µg dose and the 800 µg dose was $AUC_{T/\infty}$. Furthermore, the two formulations of fentanyl (b) (4) sublingual spray in doses of 100 µg, 400 µg and 800 µg administered during the study were well tolerated in most of the subjects. No subject participating in the trial reported serious adverse events during the course of this study.

Pharmacokinetic Parameters

Fentanyl (n=6)

Non-normalized Data

PARAMETER	TEST 1 (100 µg) n=6		TEST 2 (400 µg) n=6		TEST 2 (800 µg) n=2	
	MEAN	C.V. (%)	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	172.0	27.1	708.0	50.2	1270.4	37.7
$\ln(C_{max})$ (pg/mL)	5.1207	4.8	6.4509	8.2	7.1102	5.4
T_{max} (hours)	0.50	29.7	0.50	61.3	0.75	0.0
AUC_T (pg·h/mL)	472.6	66.2	3556.1	63.0	5417.3	30.6
$\ln(AUC_T)$ (pg·h/mL)	6.0271	8.6	8.0208	7.5	8.5734	3.6
AUC_{∞} (pg·h/mL)	817.9	36.1	4242.6	57.6	5726.8	28.8
$\ln(AUC_{\infty})$ (pg·h/mL)	6.6607	4.8	8.2303	6.4	8.6317	3.4
$AUC_{T/\infty}$ (%)	54.90	28.7	81.48	10.6	94.35	1.8
K_{el} (hour ⁻¹)	0.2008	27.4	0.1593	44.9	0.1782	0.9
$T_{1/2el}$ (hours)	3.70	30.4	5.20	45.8	3.89	0.9
Cl/F (mL/h/kg)	1718.8	27.7	1532.2	49.7	1837.3	13.1
V_Z/F (mL/kg)	9070.2	34.7	10470.4	47.1	10307.7	12.2

For T_{max} , the median is presented and the statistical analysis is based on ranks.

Data Normalized to the 100 µg dose

PARAMETER	TEST 1 (100 µg) n=6		TEST 2 (400 µg) n=6		TEST 2 (800 µg) n=2	
	MEAN	C.V. (%)	MEAN	C.V. (%)	MEAN	C.V. (%)
C _{max} (pg/mL)	172.0	27.1	177.0	50.2	158.8	37.7
ln (C _{max}) (pg/mL)	5.1207	4.8	5.0646	10.4	5.0307	7.7
T _{max} (hours)	0.50	29.7	0.50	61.3	0.75	0.0
AUC _T (pg·h/mL)	472.6	66.2	889.0 ¹	63.0	677.2	30.6
ln (AUC _T) (pg·h/mL)	6.0271	8.6	6.6346 ¹	9.1	6.4940	4.8
AUC _∞ (pg·h/mL)	817.9	36.1	1060.7	57.6	715.9	28.8
ln (AUC _∞) (pg·h/mL)	6.6607	4.8	6.8440	7.7	6.5523	4.5
AUC _{T/∞} (%)	54.90	28.7	81.48 ²	10.6	94.35 ²	1.8
K _{el} (hour ⁻¹)	0.2008	27.4	0.1593	44.9	0.1782	0.9
T _{½el} (hours)	3.70	30.4	5.20	45.8	3.89	0.9
Cl/F (mL/h/kg)	1718.8	27.7	1532.2	49.7	1837.3	13.1
V _Z /F (mL/kg)	9070.2	34.7	10470.4	47.1	10307.7	12.2

For T_{max}, the median is presented and the statistical analysis is based on ranks.

¹= Different than Test-1 (p< 0.05)

²= Different than Test-1 (p< 0.01)

N.S.= Not Significant (p> 0.05)

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/s/

WEI QIU
11/30/2011

YUN XU
11/30/2011

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Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA/BLA Number	202788	Proposed Brand Name	SUBSYS™	
OCP Division (I, II, III, IV, V)	II	Generic Name	Fentanyl Sublingual Spray	
Medical Division	DAAP	Drug Class	Opioid	
OCP Reviewer	Wei Qiu	Indication(s)	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer	
OCP Team Leader	Yun Xu	Dosage Form	Sublingual spray 100, 200, 400, 600, and 800 mcg	
Pharmacometrics Reviewer		Dosing Regimen	Initial dose of 100 mcg; titrate to a tolerable dose	
Date of Submission	March 4, 2011	Route of Administration	Sublingual spray for transmucosal delivery	
Estimated Due Date of OCP Review	Nov 30, 2011	Sponsor	Insys Therapeutics, Inc.	
Medical Division Due Date		Priority Classification	Standard	
PDUFA Due Date	Jan 4, 2012			
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			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3		FNY-P4-270, INS-06-003, INS-06-004
multiple dose:				
Patients-				
single dose:	X	1		INS-09-011
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				

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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			INS-06-003
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			Same as above
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		To-be-marketed formulation and clinical formulation are the same.
2	Has the applicant provided metabolism and drug-drug interaction information?		X		Rely on reference product's label
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			

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8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			SAS transport files
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	(b) (4)
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES _____

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

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

We noticed that in your study INS-09-011, subject #804 with Grade 2 mucositis has a Cmax value of fentanyl of 1.81 ng/mL and AUClast value of 15.7844 ng/mL.hr, which are significantly greater than those in patients without mucositis and with Grade 1 mucositis. Pending on our review, this information may be included in the product label and used to provide warning for patients with mucositis. Otherwise, you may further investigate the effects of more severe mucositis on the pharmacokinetic of fentanyl following administration of your product.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Insys submitted the Fentanyl Sublingual Spray as a 505(b)(2) application with reference listed drug of Actiq®, fentanyl citrate oral transmucosal lozenge (NDA 020747). Fentanyl Sublingual Spray is indicated only for the management of breakthrough cancer pain in patients (b) (4) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. (b) (4)

Fentanyl is available as oral (fentanyl citrate salt), injectable (fentanyl citrate salt), transdermal (fentanyl base or fentanyl hydrochloride for delivery via iontophoresis), and transmucosal (fentanyl citrate salt in oral transmucosal lozenge (Actiq® 200-1600 mcg), buccal tablet (Fentora® 100-800 mcg) and buccal film (Onsolis®, 200-1200 mcg doses)) formulations.

Fentanyl Sublingual Spray is a clear, colorless solution in a clear, colorless glass single-dose stoppered vial assembled into a delivery device to be used as a sublingual spray. The Fentanyl Sublingual Spray is packaged as a unit dose spray device designed to deliver (b) (4) of fentanyl solution containing fentanyl doses between 100 mcg and 800 mcg. The composition of fentanyl sublingual spray is shown in Table 1.

Sponsor stated that throughout clinical development, the composition of the fentanyl solution formulation has remained unchanged. It was also stated that the to-be-marketed formulation is identical to the formulations used in all the clinical studies. (b) (4)

The remaining studies used the unit-dose spray device.

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Table 1 Composition of Fentanyl Sublingual Spray

Component	Quality Standard	Function	Quantity per 100 µL				
			1 mg/mL (100 µg dose)	2 mg/mL (200 µg dose)	4 mg/mL (400 µg dose)	6 mg/mL (600 µg dose)	8 mg/mL (800 µg dose)
Fentanyl base	In-House	Active Ingredient	100 µg	200 µg	400 µg	600 µg	800 µg
Dehydrated alcohol	USP	(b) (4)					
Propylene glycol	USP						
L-Menthol	USP						
Xylitol	NF						
Purified water	USP						

Clinical database include one efficacy/safety trial (INS-05-001), one open-label safety study (INS-06-007), and four clinical pharmacology studies. These clinical pharmacology studies include a pilot ascending dose PK (FNY-P4-270); relative bioavailability in comparison to Actiq® transmucosal lozenge (RLD) and Fentanyl Citrate Injection (INS-06-003); a single dose crossover study to evaluate Fentanyl Sublingual Spray dose proportionality and to evaluate the potential effects of temperature and pH on relative bioavailability (INS-06-004); and a single dose PK study in cancer patients with and without mucositis (Study INS-09-011).

Pharmacokinetics summary:

- Under fasting condition, there is an approximate dose proportional increase over the 100 mcg – 800 mcg range (Study INS-06-004).
- Under fasting condition, as compared to the reference listed drug Actiq®, Fentanyl Sublingual Spray exhibited greater exposure (34% greater in C_{max} and 36% greater for AUC_{inf}). Thus, these two products were not bioequivalent (Study INS-06-003).
- Under fasting condition, absolute bioavailability of Fentanyl Sublingual Spray, as determined by area under the concentration-time curve of 400 mcg compared to 100 mcg intravenous fentanyl, was 75.6% based on AUC_{inf} (Study INS-06-003). The absolute bioavailability of the reference product (Actiq®) is 51%.
- Temperature and pH of the oral cavity has little effect on Fentanyl SL Spray bioavailability (Study INS-06-004).

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- Mean C_{max} and AUC_{last} values of fentanyl are 2.58-fold and 3.42-fold greater in cancer patients with mucositis as compared to patients without mucositis. Within the mucositis group, seven out of the 9 subjects (78%) had a mucositis grade of 1 and two of 9 subjects had a mucositis grade of 2. Mean C_{max} and AUC_{last} values in patients with grade 1 mucositis are 73% and 52% greater than the patients without mucositis (Study INS-09-011).

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/s/

WEI QIU
04/18/2011

YUN XU
04/18/2011