CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209128Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF CLINICAL PHARMACOLOGY

10903 NEW HAMPSHIRE AVENUE, BLDG 51, SILVER SPRING, MARYLAND 20993

Memorandum

Date	October 16, 2018
NDA#	NDA 209128
Brand Name	Dsuvia
Generic Name	Sufentanil Sublingual Tablet 30 mcg (SST 30 mcg)
Submission Date(s)	May 03, 2018
Submission Type	Resubmission (Response to Complete Response Letter)
Dosage Form and Strength	Sublingual tablet; 30 mcg
Proposed Indication	Management of moderate to severe acute pain severe enough to require an opioid agonist in adult patients in a medically supervised setting
Applicant	AcelRx Pharmaceuticals Inc.
Associated IND	IND 113059
Clinical Pharmacology Reviewer	Wei Qiu, Ph.D.
Clinical Pharmacology Team Leader	Yun Xu Ph.D.
Pharmacometrics Reviewer	Gopichand Gottipati Ph.D.
Pharmacometrics Team Leader	Kevin Krudys Ph.D.

Reference ID: 4335931

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1. Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) and Division of Pharmacometrics (DPM) has reviewed NDA 209128 resubmission dated May 3, 2018 and finds it acceptable from clinical pharmacology perspective . As of today (10/16/18) when the review is documented in DARRTS, the labeling negotiation is still ongoing with the applicant. The OCP review team agrees with the applicant's methodology to assess the risk associated with accidental dosing of Dsuvia tablets in a 12 kg child.

1.2 Phase IV Commitments

None

1.3 Background

AcelRx Pharmaceuticals Inc., submitted an original NDA 209128 on December 12, 2016 for sufentanil sublingual tablets 30 mcg [SST 30 mcg] (proposed trade name Dsuvia) via 505(b)(2) regulatory pathway for the management of moderate to severe acute pain severe enough to require an opioid agonist in adult patients in a medically supervised setting. It was for a drug-device combination product containing 30 mcg of a potent opioid agonist, sufentanil, to be administered by a healthcare provider to the patient's sublingual space in a medically supervised setting, using the single-dose applicator (SDA), on an as needed basis with a minimum interval of one hour between doses. The application referenced the agency's previous findings of systemic safety of the identified listed drug Sufenta (sufentanil citrate) injection (NDA 10950) and safety data from a select group of patients receiving Zalviso (Sufentanil Sublingual Tablet 15 mcg) (b) (4) (b) (4) [by establishing a pharmacokinetic bridge in a comparative bioavailability study as discussed below].

The single dose and multiple dose PK of Dsuvia, absolute bioavailability in comparison with Sufenta (sufentanil IV Injection) and comparative bioavailability between Dsuvia and 15 mcg sufentanil sublingual tablet were determined in Study SAP101 in the original submission. A single sublingual administration of Dsuvia has a bioavailability of approximately 53% relative to a one-minute IV sufentanil infusion of 30 mcg. Compared to IV administration, sublingual Cmax values were 17-fold lower. After 12 multiple hourly doses over 11 hours, the geometric mean for the AUC within a dosing interval (AUC0-60min) and Cmax values were increased by 3.7-fold and 2.3-fold greater compared to single-dose administration, respectively. Steady-state plasma

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concentrations were achieved after 7 doses. Both Cmax and AUC0-inf were bioequivalent for a single dose SST 30 mcg and 2 doses of SST 15 mcg (dosed 20 minutes apart).

There were no clinical pharmacology deficiencies identified with the original application and was considered approvable from a clinical pharmacology perspective. However, the application received a Complete Response (CR) letter on October 11, 2017 due to the following deficiencies: (i) inadequate number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of sufentanil sublingual tablets (SST) 30 mcg, and (ii) possibility of misplaced tablets, which pose a risk for accidental exposure and improper dosing.

The current application is a resubmission of the (original) NDA by AcelRx Pharmaceuticals Inc (via 505(b)(2) regulatory pathway) in response to the CR letter issued previously. The applicant did the following to address the deficiencies described in the CR letter:

- Decreased the maximum daily dose to 12 tablets from 24 tablets and submitted new pooled safety analyses to support the safety of the proposed maximum daily dose.
- Performed a new human factors study
- Submitted a risk assessment following accidental exposure to a sufentanil sublingual 30 mcg tablet.

The main focus of this review is to assess the risk associated with accidental dosing of sufentanil sublingual 30 mcg tablet.

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2. Pharmacometrics Assessment: Population PK analyses

2.1 Applicant's Risk Assessment Following Accidental Exposure for Sufentanil Sublingual Tablet(s)

The applicant performed population PK modeling and simulation in the current resubmission to assess the risk of accidental exposure of dropped sufentanil tablets in a pediatric population as it was identified as one of the deficiencies in the previous submission. The purpose of the current analysis is to address the following (i) what are the expected sufentanil exposures following accidental exposures in pediatric population, and (ii) what is the risk associated with these exposures based on comparison with pediatric and adult sufentanil exposures reported in the published literature.

The adult population PK model that was previously submitted under (b) (4) (Zalviso), reviewed by Dr. Naraharisetti (DARRTS 06/14/2014) and considered generally adequate and acceptable was used for simulating sufentanil exposures in a pediatric population. It is worth noting that the Zalviso program included sufentanil sublingual tablets (SST) of 15 mcg strength only, while Dsuvia program includes SST of 30 mcg strength. The applicant performed study SAP101 demonstrating that two 15 mcg SST (Zalviso) were bioequivalent to a single 30 mcg SST (Dsuvia). Since the popPK model from Zalviso included data from adult population alone, the applicant supplemented the analysis with intravenous sufentanil PK data from the literature (Greeley et al[1]) of 19 pediatric patients undergoing cardiovascular procedures. The systemic clearance values in these pediatric patients were reported to be in good agreement with the relationship between systemic clearance and body weight derived from the adult popPK model and is shown in **Figure 1** below.

Subsequently, the applicant utilized the adult popPK model to simulate exposures following accidental doses of 30 and 60 mcg in a 'typical' child weighing 12 kg (shown in **Figure 2** below) using the parameter estimates listed in **Table 1** and under the following assumptions:

i. Sufentanil's absorption characteristics from the sublingual space in the 'typical' child, such as absorption rate (Ka) and lag time (Tlag) are similar to adults.
ii. Doses are administered simultaneously and retained in the sublingual space. The tablet is absorbed through the sublingual space, and not swallowed.
iii. The relationships between apparent clearance (CL/F) and distributional clearance (Q/F) and body weight in the 'typical' child are similar to that described in the adult popPK model.
iv. The PK parameters are independent of the number of tablets (dose-linearity shown in PK studies of sufentanil sublingual tablets)

[1] Greeley WJ, de Bruijn NP, Davis DP. Sufentanil pharmacokinetics in pediatric cardiovascular patients. Anesthesia & Analgesia 1987; 66:1067-1072

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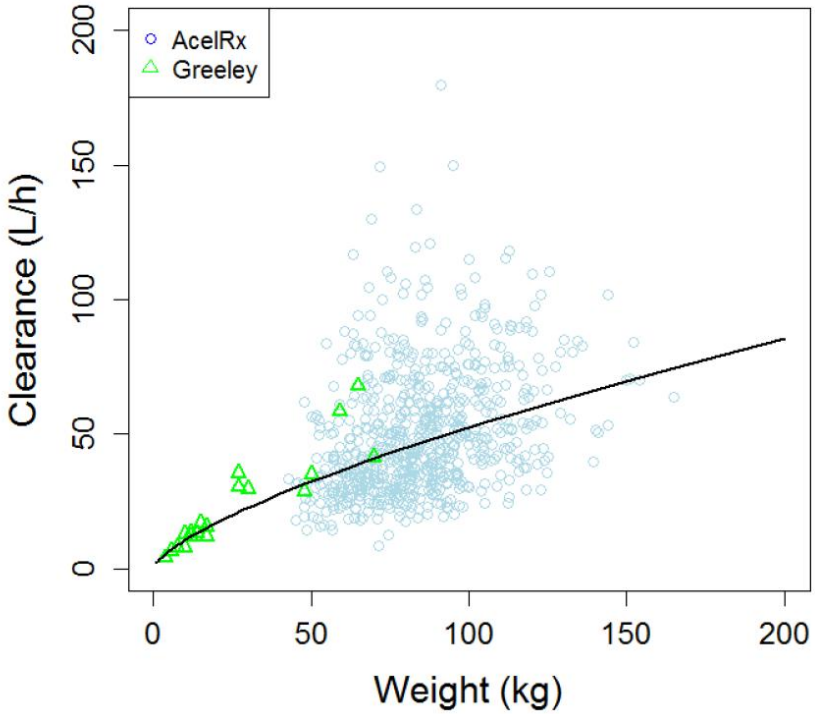
Figure 1 Sufentanil systemic clearance vs. weight based on adult sublingual sufentanil popPK model overlaid with literature reported pediatric systemic clearance values



Source: RSK-7025 Rev. A – Figure on Page 4

Table 1 PK parameters used for simulation of pediatric exposures to sublingual sufentanil tablets

Parameter	Adult (83 kg)	Child (12 kg)	Rationale
Clearance (L/h)	78.1	18.4	Greeley and PopPK CL data
Central volume (L)	67.7	16.2	Greeley shows weight-proportional below 50kg
Distribution Clearance (L/hr)	77.5	24.6	PopPK model has weight effect
Peripheral volume (L)	2200	528	Greeley shows weight-proportional below 50kg
Absorption rate (1/hr)	0.417	0.417	Assume the same
Lag time (hr)	0.134	0.134	Assume the same

Source: RSK-7025 Rev. A – Table 2 on Page 5

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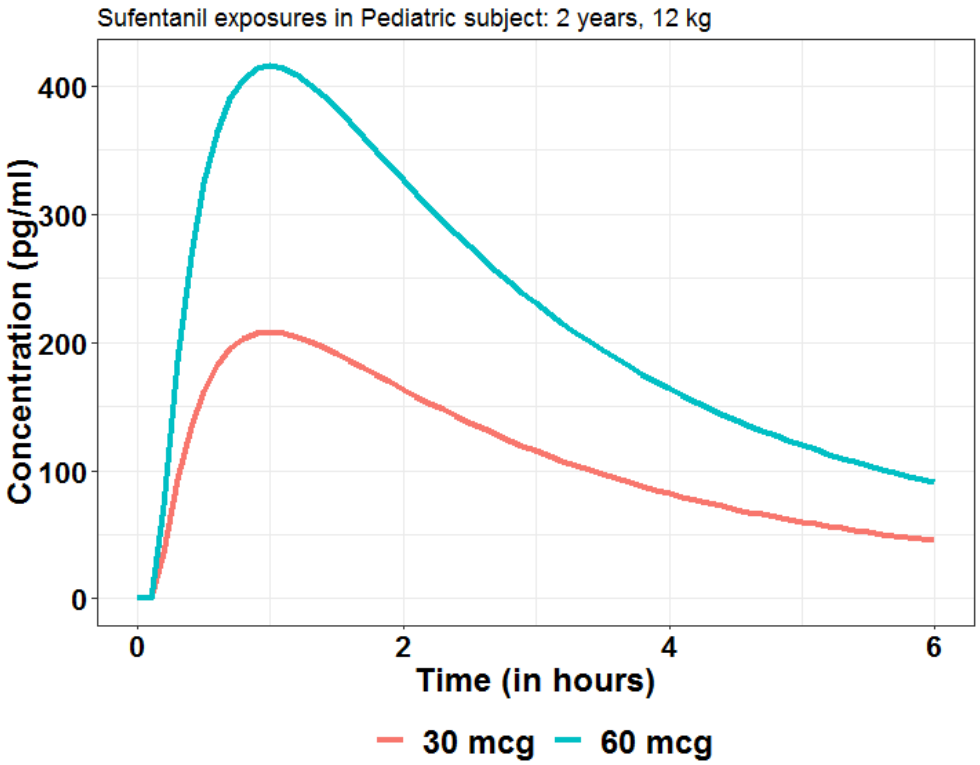
Figure 2 Predicted sufentanil blood levels following accidental doses of Dsuvia tablets (30 and 60 mcg) in a typical 2 year old child weighing 12 kg



The predicted peak plasma concentrations were about 208 pg/ml and 416 ng/ml following accidental doses of 30 and 60 mcg sufentanil sublingual tablets respectively, and occurred approximately 1 hour post-dose. The applicant compared these levels to those reported in the literature:

a) In a correspondence letter to the editor (Haynes et al. 1993)[2], it is reported that intranasal administration of 2 mcg/kg in 15 pediatric outpatients resulted in average peak plasma concentrations of 300 pg/mL and no respiratory depression was reported. It is important to note that the average time to peak sufentanil blood levels occurred at about 15 and 30 min in 8 and 7 subjects respectively, which seems shorter than that predicted following sublingual administration (1 hour).

[2] Haynes G, Brahen NH, Hill HF. Plasma sufentanil concentration after intranasal administration to paediatric outpatients. Canadian Journal of Anaesthesia 1993; 40:286.

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b) In another study conducted by Zedia et al[3], 2 mcg/kg sufentanil was administered intranasally before anesthetic induction in 60 pediatric outpatient surgery patients, aged 0.5 to 6 years old. It was reported that during a period of 15 to 20 minutes of observation before surgery, the vital signs and oxygen saturation did not change significantly before or after surgery.

c) In the study conducted by Greeley et al., 1987 (referenced above), 10-15 mcg/kg of sufentanil was administered as a rapid bolus intravenously in 28 pediatric patients undergoing cardiovascular procedures, age ranging between neonates (0-1 month) to adolescents (12-18 years). It was reported that the average peak sufentanil concentrations in each age group exceeded 14000 pg/ml. However, it is important to note that the pediatric subjects were closely monitored in an inpatient setting.

[3] Zedie N, Amory DW, Wagner BKJ, O'Hara DA. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. Clinical Pharmacology and Therapeutics 1996; 59:341-348.

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Reviewer's Comments

The applicant used the adult popPK model that was previously submitted under (b) (4) *(Zalviso), reviewed by Dr. Naraharisetti (DARRTS 06/14/2014) and considered generally adequate and acceptable to simulate sufentanil exposures in pediatric subjects. This step is considered acceptable because sufentanil sublingual tablet 30 mcg (Dsuvia) was demonstrated to be bioequivalent to two 15 mcg sufentanil sublingual tablets (Zalviso) in PK study SAP101 (please refer to review by Dr. Qiu, DARRTS 09/12/2017 for more details). Furthermore, the systemic clearance values in pediatric patients reported in published literature was in good agreement with the relationship between systemic clearance and bodyweight derived from the adult popPK model, suggesting that this approach is reasonable. It is worth noting that the pediatric patients included from the literature showed a reasonable distribution of pediatric subjects across ages ranging from infants (1-24 months, N=7), children (2-12 years, N=7) and adolescents (N=5). Subsequently, the applicant considered a child weighing 12 kg as 'typical' pediatric subject for the purpose of simulations. This is considered acceptable as 12 kg is the 50th percentile for weight for an 18-24-month child. The assumptions stated by the applicant for simulations in a 'typical' pediatric subject seem reasonable and conservative, as heavier children would have lower plasma concentrations. Additionally, the assumption that the tablet is absorbed through the sublingual space is also conservative, since swallowing results in <10% bioavailability, compared to a bioavailability of approximately 60% following sublingual absorption. Overall, the general methodology and the steps used by the applicant to assess the risk associated with accidental exposures to SST 30 or 60 mcg (Dsuvia) is reasonable and the reviewer considers the applicant's results acceptable.*

The current reviewer also performed independent evaluation of sensitivity of the popPK models from both the current resubmission and the previous submission under NDA 209128 (reviewed by Dr. Kevin Krudys) to explore the impact of the differences in some of the popPK model parameters as noted in section 2.2. It was found that the applicant's predictions of the sufentanil exposures following accidental exposures in 'typical' pediatric subject were conservative estimates compared to the reviewer's predictions based on the other popPK models.

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2.2 Applicant's Population PK Analyses

A population PK analysis was previously submitted by the applicant under NDA 209128 (Dsuvia) and was reviewed by Dr. Kevin Krudys (DARRTS 09/12/2017) and found to be generally adequate and acceptable for the purpose of labeling recommendations. The dataset used for the current analysis is identical to the one used in the previous submission and analysis. The purpose of the current analysis was to evaluate (i) the impact of disease status (i.e., healthy vs. patients) on the PK characteristics of sublingual (SL) sufentanil, (ii) the appropriateness of exponential vs. linear model for explaining the inter-individual variability in the effect of age on the clearance of sufentanil, and (iii) the effect of organ impairment on the apparent clearance while accounting for potential impact of age and/or weight on clearance.

In total, the PK dataset included data from 1,062 healthy subjects and patients from eleven studies with 7452 quantifiable PK samples. Please refer to the previous reviews by Dr. Krudys (NDA 209128, DARRTS 09/12/2017) and Dr. Naraharisetti ((b) (4) DARRTS 06/19/2014) for more details on the key characteristics of the studies included in the PK dataset.

In general, the structural population PK model was similar to those reported previously for Zalviso ((b) (4) and previous submission of Dsuvia (NDA 209128). Details of the modeling approach, including covariate selection can be found in the previous reviews by Dr. Krudys and Dr. Naraharisetti. Briefly, sufentanil pharmacokinetics was described by a two compartment linear model with first-order oral absorption (ka) and a lag time. For this analysis, the fraction absorbed into the systemic circulation (F) was fixed to the estimated value of 0.531 from study SAP101. A common bodyweight effect was estimated on clearance (CL), intercompartmental clearance (Q), and volume of distribution of the central and peripheral compartments (V1, V2), unlike separate bodyweight effects estimated only on CL and Q in previous analyses. Repeat dosing was found to be a significant effect in decreasing in bioavailability (F) (rather than increase in the systemic clearance), accounting for lower systemic exposures at steady-state compared to single dose noted in study SAP101. A linear effect of age was found to be a significant covariate on CL. Patient status (healthy vs. patient) was found to be a significant covariate on F and ka: lower in patients than in healthy subjects.

The final parameter estimates of the popPK model based on bootstrap analysis are provided in **Table *2*** and select goodness of fit plots and prediction corrected visual predictive checks are shown in **Figure *3*** and **Figure *4*** respectively.

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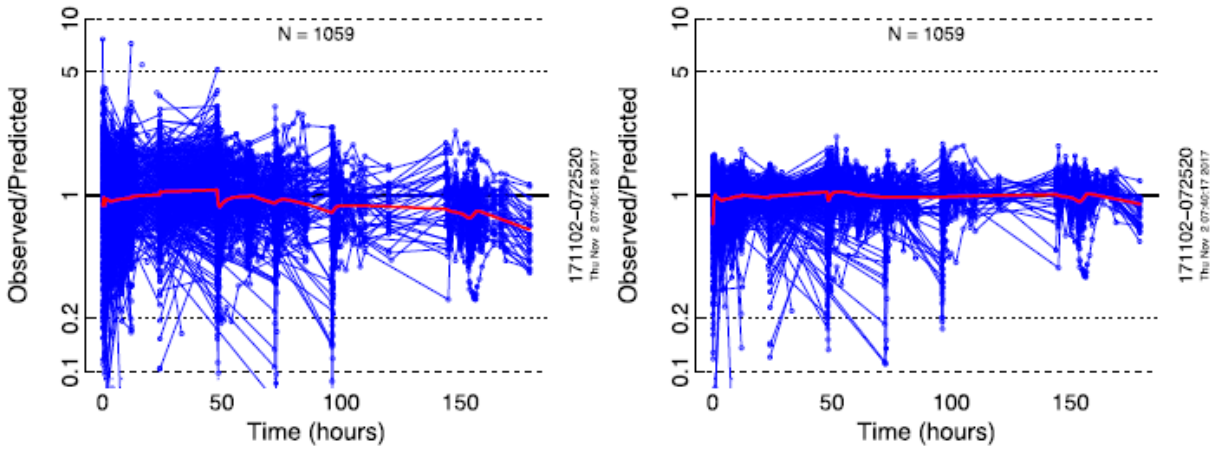
Table 2 Parameter estimates of the final popPK model based on bootstrap analyses

	Estimated			Percentile		
THETA	Value	Mean	SD	5	50	95
All Runs (None were "non reportable"); N = 499						
CL	38.3642	38.5298	2.0184	35.2730	38.8156	41.5111
V_1	47.0466	49.5203	4.2915	42.5122	49.6867	56.5870
CLdist	33.3235	34.4183	1.5854	32.0429	34.3235	36.9043
V_2	670.856	709.351	78.607	615.280	701.031	818.960
k_a	0.5007	0.4967	0.0112	0.4774	0.4968	0.5146
Lag	0.0682	0.0684	0.0021	0.0652	0.0682	0.0721
Repeat dose F	0.6590	0.6601	0.0211	0.6262	0.6600	0.6955
Age/CL	-0.0163	-0.0161	0.0011	-0.0179	-0.0161	-0.0144
Ketoconazole	-0.3701	-0.3721	0.0603	-0.4808	-0.3722	-0.2743
Weight/CL	0.4058	0.4174	0.0513	0.3302	0.4163	0.4957
Relative F: Patients	0.8156	0.8329	0.0365	0.7737	0.8330	0.8891
k_a: Patients	0.7173	0.7165	0.0349	0.6657	0.7158	0.7772

Source: ACX-PPK-259-001 Addendum – Table 8 on Page 35

Figure 3 Goodness of fit plots for the final popPK model



Source: ACX-PPK-259-001 Addendum – Figure 12 on Page 30

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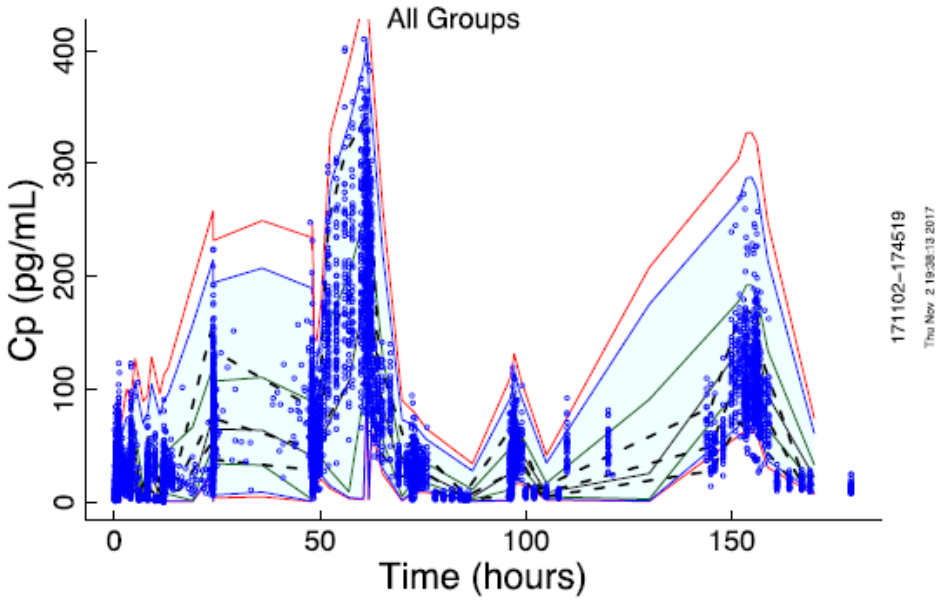
Figure 4 Prediction corrected visual predictive check of the final popPK model



Source: ACX-PPK-259-001 Addendum – Figure 14 (lower panel) on Page 34

The impact of weight and age on the clearance of sufentanil is summarized in **Figure *5*** below. Clearance increased with weight, 0.5% per kg referenced to the median weight of 80 kg and decreased with age, 1.6% per year, referenced to median age of 56 years. Additionally, clearance decreased 35% following administration of ketoconazole, a potent inhibitor of CYP3A4. Repeat dosing resulted in a decrease of bioavailability from 53% to 35%. Lastly, bioavailability and absorption rate was lower in patients compared to healthy subjects.

Hepatic and renal function were assessed in patients in all but two studies (SAP202 and SAP301). Because two studies did not have data, hepatic and renal impairment were assessed with a post-hoc analysis, and were not included in the formal modeling. Hepatic function was evaluated based on composite measures of AST ALT, total bilirubin, and serum creatinine with cut points for each to define “normal”, “mild”, “moderate” and “severe”. For each of AST, ALT, total bilirubin, and serum creatinine, “normal” was defined as a value < the upper limit of normal (ULN) for that test. For ALT and AST, “mild” was defined as a value > ULN but ≤ 3 • ULN; “moderate” was defined as value > 3 • ULN and ≤ 5 • ULN; and “severe” was defined as a value > 5 • ULN. For bilirubin, “mild” was defined as a value > ULN but ≤ 1.5 • ULN; “moderate” was defined as value > 1.5 • ULN and ≤ 3 • ULN; and “severe” was defined as > 3 • ULN.

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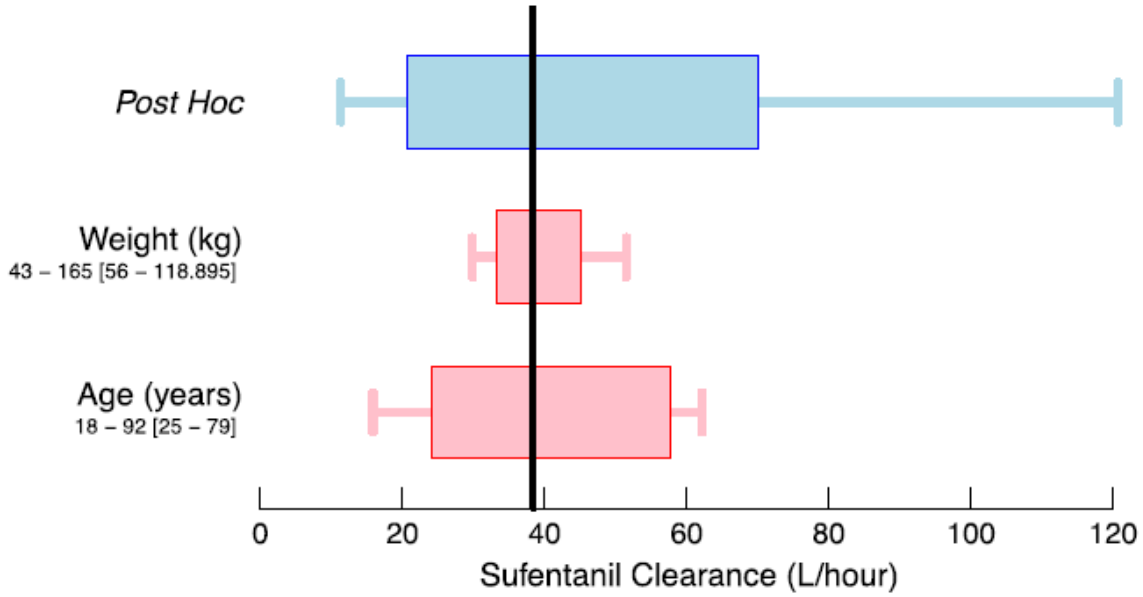
Renal impairment was based on serum creatinine and glomerular filtration rate (GFR) calculated with the Cockcroft-Gault equation ("normal": creatinine < ULN; "mild": creatinine > ULN and GFR > 60 ml/min; "moderate": GFR between 30 and 60 ml/min; and "severe": GFR ≤ 30 ml/min). Based on post-hoc analysis, the post-hoc etas for clearance were plotted against hepatic and renal impairment categories as shown in **Figure *6*** below. A total of 751 and 754 laboratory data on hepatic and renal impairment data were used in the analysis. The normalized clearance (post-hoc clearance divided by the typical value) suggested that there was no evidence that hepatic or renal impairment (or occurrence of both) affected sufentanil clearance.

Figure 5 Tornado plot showing the impact of age and bodyweight on sufentanil clearance for all subjects in the PK analyses



Note: The vertical line is the "typical" value for clearance. For each entry, the rectangle delimits 90% of the values; the line spans the entire range of values. The top entry is based on the post hoc values. The second and third entries are based on the impact of weight and age on sufentanil clearance based on the final popPK model. Values appearing below the covariate text indicate range [5th percentile – 95th percentile] of that covariate.

Source: ACX-PPK-259-001 Addendum – Figure 18 on Page 40

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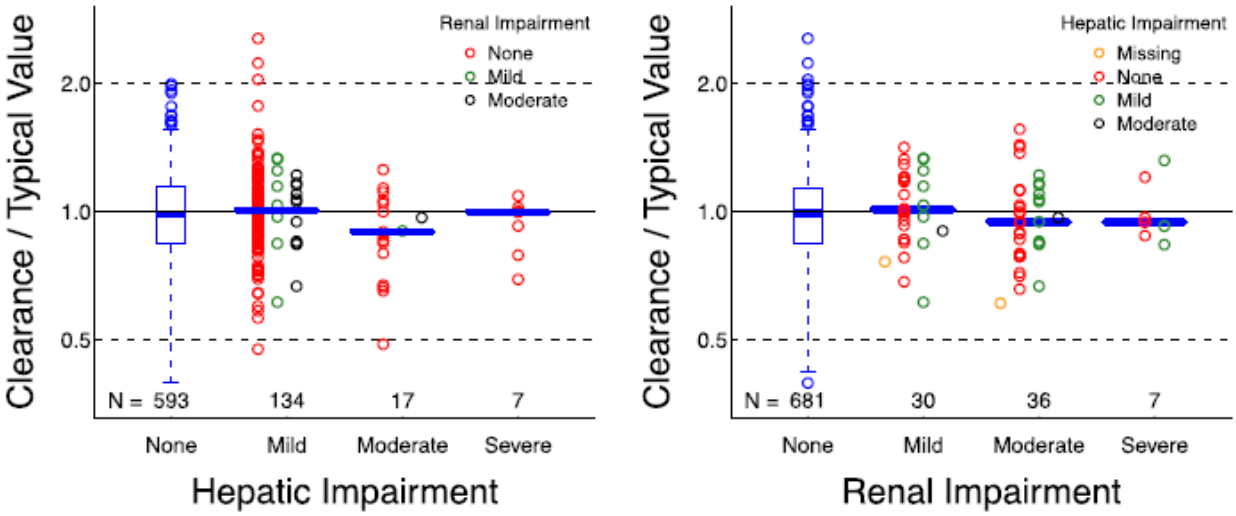
Figure 6 Impact of hepatic and renal impairment on sufentanil clearance



Note: Normalized clearance vs hepatic (left panel) and renal (right panel) impairment. Values are clearance divided by the typical value. A horizontal line appears at the median value. Subjects with no impairment are displayed as a box plot whereas all data are presented for subjects with mild, moderate, or severe impairment. For impaired subjects, the results are stratified by the impairment of the other organ.

Source: ACX-PPK-259-001 Addendum – Figure 16 on Page 38

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Reviewer's Comments:

The structural population PK model was consistent with previous analyses reviewed by Dr. Krudys and Dr. Naraharisetti. However, there were a few differences in parameterization of the covariate effects compared to previous analyses. For example, a single common effect of body weight was retained as a covariate on clearance, intercompartmental clearance, volume of central and peripheral volumes of distribution in this analysis, unlike separate bodyweight effects only on clearance and intercompartmental clearance in the previous analyses. The applicant did not provide a rationale for implementing a single common effect of bodyweight on the aforementioned disposition metrics. The impact of repeat dosing was implemented only on the bioavailability (decreasing from 53% to 35%), unlike the previous analyses where it was implemented on both systemic clearance as well as bioavailability. Impact of age was implemented as a linear effect on clearance, unlike the previous analyses where it was either a dichotomous variable or an exponential model. Patient status (healthy vs. patient) was found to be a statistically significant covariate on the absorption rate constant and bioavailability, which was not evaluated in the previous analyses. Overall, owing to differences in parameterizing the covariates in the current analysis compared to previous analyses, the final popPK parameter estimates were different, most notably the central and peripheral volumes of distribution. The reviewer agrees with the applicant's argument in difficulty in accurate estimation of volume of distribution and terminal half-life due in part to the lack of data collected more than 24 hours post-dose. However, the current reviewer agrees with the prior assessment that, given the on-demand nature of sufentanil dosing, dose adjustment based on different weight and age groups is not needed. Additionally, the current reviewer also agrees with previous reviewer's conclusion "for labeling purposes, we recommend using values from dedicated PK studies that had adequate sampling, if available". The metrics used for evaluating hepatic function do not support labeling the impact of hepatic impairment. The metrics used for evaluating renal function and sample size for patients with mild (N=30) and moderate (N=36) renal impairment are reasonable to support labeling recommendations. Lastly, the reviewer also agrees with previous assessment and labeling of ketoconazole interaction.

3. Detailed Labeling Recommendations

Additions are highlighted and deletions are ~~double strikethrough~~ in Red.

8.6 Hepatic Impairment

Because sufentanil is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension [see Clinical Pharmacology (12.3)]

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8.7 Renal Impairment

Sufentanil and its metabolites are known to be excreted by the kidney. No significant changes have been observed in subjects with mild or moderate renal impairment. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension in patients with severe renal impairment [see Clinical Pharmacology (12.3)]

[*note: to keep them consistent with the list drug product, Sufenta, and as applicable to DSUVIA*]

12.3 Pharmacokinetics

Absorption

A single sublingual administration of DSUVIA has a bioavailability of approximately 53% relative to a one-minute IV sufentanil infusion of 30 mcg (b) (4) (b) (4). Compared to IV administration, sublingual Cmax values were 17-fold lower. The sublingual route of administration of sufentanil (b) (4) (b) (4) both which severely limits bioavailability of swallowed (oral) sufentanil sublingual tablet (b) (4)). Following a single dose of DSUVIA, the mean AUC0-inf is 278 h*pg/mL, the average Cmax of 63.1 pg/mL occurs at a median Tmax of 1.00 hours, (b) (4) (b) (4) (b) (4). After 12 multiple hourly doses over 11 hours (b) (4) the (b) (4) geometric mean for the AUC within a dosing interval (AUC0-60min) and Cmax values were increased by 3.7-fold and 2.3-fold (b) (4) (b) (4) greater compared to single-dose administration, respectively. Steady-state plasma concentrations were achieved after 7 doses (Figure 1).

(b) (4)

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(b) (4)

Figure 1: Sufentanil Concentration-Time Values: Single vs. Consecutive Repeat Doses (12 DSUVIA Doses)

(b) (4)

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Distribution: (b) (4)

(b) (4)

Plasma protein binding of sufentanil, related to the alpha acid glycoprotein concentration, was approximately 93% in healthy males, 91% in mothers and 79% in neonates. (b) (4)

(b) (4)

Elimination:

Following a single dose of DSUVIA, the mean terminal half-life is 13.4 hours, and the mean apparent plasma clearance is 108 L/hour.

Metabolism: The liver and small intestine are the major sites of biotransformation (b) (4)

(b) (4)

Excretion: Approximately 80% of the IV administered dose of sufentanil is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug.

Specific Populations

Clearance is not significantly affected by race, sex, mild or moderate renal impairment based on the population pharmacokinetics.

Drug Interaction Study

Co-administration of a single dose of sufentanil sublingual tablet 15 mcg with a strong CYP3A4 inhibitor, ketoconazole, results in 77% and 19% greater AUCinf and Cmax values of sufentanil, respectively, compared to its administration alone.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WEI QIU
10/16/2018

GOPICHAND GOTTIPATI
10/16/2018

KEVIN M KRUDYS
10/17/2018

YUN XU
10/17/2018

CLINICAL PHARMACOLOGY REVIEW

NDA: 209128	Submission Date(s): December 12, 2016, January 31, 2017
Brand Name	Dsuvia
Generic Name	Sufentanil Sublingual Tablet 30 mcg (aka SST 30 mcg)
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
Pharmacometrics Reviewer	Kevin Krudys, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	AcelRx Pharmaceuticals Inc.
Relevant IND	IND 113059
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Sublingual tablet; 30 mcg
Indication	Management of moderate to severe acute pain severe enough to require an opioid agonist in adult patients in a medically supervised setting
Proposed Dosing Regimen	Administer sublingually a single sufentanil sublingual tablet 30 mcg on an as needed basis, with a minimum of one hour between doses.

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Reference ID: 4151649

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this submission dated December 12, 2016 and January 31, 2017 and finds it acceptable. This product will not be approved during this review cycle and there is no labeling recommendation at this time.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Clinical pharmacology study supported the dosing regimen used in the clinical trials.
General dosing instructions	Administer sublingually a single sufentanil sublingual tablet 30 mcg on an as needed basis, with a minimum of one hour between doses.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Insufficient data are available in patients with severe and moderate liver or severe kidney impairment. This product should be used with caution in such patients due to the importance of these organs in the metabolism and excretion of sufentanil. Given as-needed dosing of sufentanil tablet, the likely effect of co-administration with a CYP3A4 inhibitor is less dosing frequency of the sufentanil tablet. The observed effect of increased systemic exposure of SL sufentanil tablet with CYP3A4 inhibitor does not warrant an altered dosing recommendation.
Labeling	This product will not be approved during this review cycle and there is no labeling recommendation at this time.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation used in Phase 3 clinical trials was also evaluated in the Phase I clinical pharmacology study.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

AcelRx Pharmaceutical Inc. submitted an original 505(b)(2) NDA 209-128 on December 12, 2016 for Dsuvia (Sufentanil Sublingual Tablet 30 mcg, also known as SST 30 mcg) for the management of moderate to severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting. A single SST 30 mcg is to be administered sublingually on an as needed basis, with a minimum of one hour between doses. Dsuvia is not for home use or for use in children.

The sponsor has conducted four (4) clinical efficacy/safety studies (1 Phase 2 Study SAP202, 3 Phase 3 Studies SAP301, SAP302, and SAP303) with SST 30 mcg. The final

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to-be-marketed 30 mcg formulation was used in all Phase 3 studies. A different formulation was used in the Phase 2 study SAP202.

In this 505(b)(2) application, the sponsor proposed to rely in part on the agency's previous findings of systemic safety of the identified listed drug, Sufenta (sufentanil citrate) Injection (NDA 19-050) and safety data from a select group of patients on Zalviso (Sufentanil Sublingual Tablet 15 mcg, also known as SST 15 mcg) (b) (4) by establishing a pharmacokinetic bridge in the comparative bioavailability Study SAP101. Study SAP101 was conducted in healthy volunteers under naltrexone blockade to establish a pharmacokinetic bridge between a single sublingual dose of SST 30 mcg, a single 30 mcg IV dose (Sufenta) and 2 sublingual doses of SST 15 mcg (dosed 20 minutes apart). The same study also evaluated multiple dose PK of SST 30 mcg given every hour. The final to-be-marketed SST 30 mcg formulation was used in Study SAP101. The sponsor conducted a population PK analysis including data from a population PK analysis previously submitted for SST 15 mcg as part of the Zalviso NDA (b) (4) PK data from Study SAP101, sparse PK data from Phase 2 Study SAP202 and two Phase 3 Studies SAP301 and SAP303 with SST 30 mcg.

Absolute Bioavailability of A Single Sublingual Dose of SST 30 mcg in Comparison to A Single IV Injection of Sufenta IV 30 mcg

Systemic exposure of sufentanil was greater for a single dose of Sufenta IV 30 mcg than a single sublingual dose of SST 30 mcg. The mean absolute bioavailability of a single sublingual dose of SST 30 mcg was approximately 53%. These PK results support for bridging to the systemic safety information of Sufenta IV.

Table 1 Mean ± SD (%CV) Sufentanil Pharmacokinetic Parameters for Single Dose of Sufenta IV 30 mcg, Single Sublingual Dose of SST 30 mcg, and 2 Sublingual Doses of SST 15 mcg (dosed 20 minutes apart) in Healthy Subjects under Naltrexone Block and Statistical Analysis (Study SAP101)

PK Parameter	Sufenta IV 30 mcg (n = 35)	Single SST 30 mcg (n = 35)	2 x SST 15 mcg (n = 35)
AUCinf (pg.h/mL)	539.68 ± 112.12 (20.96%)	277.68 ± 84.36 (30.38%)	307.30 ± 79.08 (25.73%)
Cmax (pg/mL)	1073.94 ± 968.17 (90.15%)	63.14 ± 23.49 (37.21%)	66.00 ± 20.38 (30.88%)
T1/2 (h)	13.72 ± 6.12 (44.6%)	13.37 ± 8.89 (66.5%)	15.66 ± 9.38 (59.9%)
Tmax (h)[a]	0.07 (0.02, 0.17)	1.00 (0.50, 2.00)	1.17 (0.67, 2.00)
CL (mL/h)	57878 ± 11446 (20%)	--	--
Amount Absorbed (mcg)	30 mcg	15.9 ± 5.2 (32.7%)	17.6 ± 5.2 (29.5%)
F (%)	--	52.86 ± 17.22 (32.6%)	58.76 ± 17.50 (29.8%)
Geometric Mean Ratio (1 x SST 30 mcg/2 x SST 15 mcg) % (90% CI)			
AUCinf		0.89 (0.81, 0.97)	
Cmax		0.93 (0.84, 1.03)	

[a] tmax reported as median (min, max)
Source: Tables 10, 11, and 12 of study SAP101 report.

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Comparative Bioavailability between A Single Sublingual Dose of SST 30 mcg and Two Sublingual Doses of SST 15 mcg (dosed 20 minutes apart)
Median Tmax was 1 hour after administration of a single SST 30 mcg dose and 1.17 hours after administration of 2 doses of SST 15 mcg (dosed 20 minutes apart). Both Cmax and AUC0-inf were bioequivalent for a single dose SST 30 mcg and 2 doses of SST 15 mcg (dosed 20 minutes apart). The point estimate of the geometric mean ratio (1 x SST 30 mcg /2 x SST 15 mcg) for sufentanil Cmax and AUCinf were 89% and 93%, respectively. The corresponding 90% confidence intervals (CIs) were 81 – 97% and 84 – 103%, respectively. All these 90% CIs fell within the 80 to 125% BE limit (**Table 1** above).

Based on the PK results for a single SST 30 mcg and 2 doses of SST 15 mcg (dosed 20 minutes apart), similar exposure for a single SST 30 mcg and 2 doses of SST 15 mcg (with 20 to 25 minutes between doses) was demonstrated based on PK modeling/simulation (submitted to IND 113059 SN0027 on September 2, 2015). These PK results support for bridging to the systemic safety information of 2 doses of SST 15 mcg (dosed 20 to 25 minutes apart).

Multiple Dose PK of SST 30 mcg with Q1h Dosing Regimen
Sufentanil concentrations accumulated upon multiple dosing of SST 30 mcg. The analysis on pre-dose concentrations showed that steady state for SST 30 mcg after multiple every hour dosing was achieved by 7 doses (or 360 minutes). At steady state, the AUC within a dosing interval (AUC0-60min) and Cmax values were increased by 3.7-fold and 2.3-fold, respectively.

Effect of Consumption of Hot, Cold and Various pH liquids:
The sponsor proposed to use the same approach of addressing the impact of consumption of hot/cold and various pH liquids by labeling "patients (b) (4) not eat or drink and minimize talking for 10 min after (b) (4)", which was considered acceptable for SST 15 mcg and is acceptable for SST 30 mcg as well.

Effect of Intrinsic and Extrinsic Factors on the PK of SST 30 mcg based on PopPK Analysis:
The population PK analysis included data from a population PK analysis previously submitted for SST 15 mcg as part of the Zalviso NDA (b) (4) PK data from Study SAP101 and sparse PK data from Phase 2 Study SAP202, and two Phase 3 Studies SAP301 and SAP303 with SST 30 mcg. Body weight, repeat dosing, age and ketoconazole were found to be significant covariates on sufentanil clearance. As weight varies from the 5th to 95th percentiles, clearance varies from -19% to +29% of the value in a typical patient. As age varies from the 5th to 95th percentiles, clearance varies from -18% to +37% of the value in a typical patient. Due to the on-demand nature of dosing, however, sufentanil concentrations in clinical trials were largely similar in patients with varying body weight and age and therefore dose adjustment is not needed.

2 Question Based Review

2.1 General Attributes of the Drug

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1. *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug product?*

AcelRx Pharmaceutical Inc. submitted an original 505(b)(2) NDA 209-128 on December 12, 2016 for Dsuvia for the management of moderate to severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting. A single SST 30 mcg is to be administered sublingually on an as needed basis, with a minimum of one hour between doses. Dsuvia is not for home use or for use in children.

The sponsor has conducted four (4) clinical efficacy/safety studies (1 Phase 2 Study SAP202, 3 Phase 3 Studies SAP301, SAP302, and SAP303) with SST 30 mcg. The final to-be-marketed 30 mcg formulation was used in all Phase 3 studies but a different formulation was used in the Phase 2 study SAP202.

In this 505(b)(2) application, the sponsor proposed to rely in part on the agency's previous findings of systemic safety of the identified listed drug, Sufenta (sufentanil citrate) Injection (NDA 19-050) and safety data from a select group of patients on Zalviso (sufentanil sublingual tablet 15 mcg, also known as SST 15 mcg) (b) (4) by establishing pharmacokinetic bridges in comparative bioavailability Study SAP101. The final to-be-marketed SST 30 mcg formulation was used in Study SAP101.

In the EOP2 meeting held on December 18, 2013, the Division stated that, if the Sponsor demonstrated that the exposure with the single dose of SST 30 mcg was lower than that with the two 15 mcg doses of Zalviso given 20 minutes apart (a total dose of 30 mcg), then it might be acceptable to use the same safety exposure data in the Zalviso application. The Sponsor stated that they would conduct a study to demonstrate the comparable Cmax levels. Because patients with mucositis can be prescribed another product, the Sponsor was not planning to conduct PK studies in those patients (b) (4) (b) (4). The Division agreed with the approach (b) (4) (b) (4) (b) (4) The Sponsor proposed to use the same approach as for Zalviso to address the effect of pH and temperature on drug absorption and the Division agreed that this seemed reasonable.

In the Pre-NDA meeting held on December 9, 2015, the Division agreed that patients who received two 15-mcg doses of Zalviso given 20 to 25 minutes apart can supplement the safety database requirements for Dsuvia based on comparable Cmax and AUC between SST 30 mcg and 2 x SST 15 mcg (dosed 20 minutes apart) obtained from Study SAP101 and the comparable PK for 2 doses of SST 15 mcg spaced at 20 through 25 minutes intervals from PK modeling.

Multiple dose PK of Dsuvia was also assessed in Study SAP101. The sponsor conducted a population PK analysis (Report ACX-PPK-259-001) using data from a population PK analysis previously submitted for SST 15 mcg as part of the Zalviso NDA (b) (4) PK data from Study SAP101, and sparse PK data from Phase 2 Study SAP202 and two Phase 3 Studies SAP301 and SAP303 with SST 30 mcg to evaluate the effects of intrinsic and extrinsic factors on the PK of SST 30 mcg.

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

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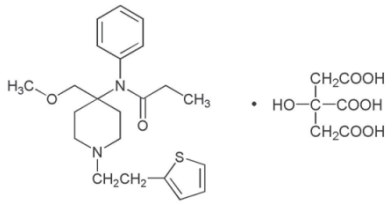
Table 2 Physical-Chemical Properties of Sufentanil

Drug Name	Sufentanil Citrate
Chemical Name	N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide citrate
Structure	
Molecular Formula	$C_{28}H_{38}N_2O_9S$
Molecular Weight	578.7 g/mol (MW of sufentanil free base is 386.55)
Melting Point	136.5°C
Appearance	(b) (4)
Solubility	Sufentanil Citrate is soluble in water, soluble to sparingly soluble in alcohol, sparingly soluble in acetone and chloroform, and freely soluble in methyl alcohol. Solubility of Sufentanil Citrate in water is 46 mg/mL.

Dsuvia contains one 30 mcg sufentanil tablet housed in a disposable single-dose applicator (SDA). The Dsuvia tablet is an immediate release formulation intended for sublingual administration. Each tablet is blue, flat-faced with a diameter of 3 mm. SST 30 mcg is the same formulation with the drug content and colorant in comparison to SST 15 mcg (**Table 3**). The tablet size, shape, weight are identical. The proposed final to-be-marketed formulation was used in the comparative bioavailability study SAP101 and all Phase 3 Studies SAP301, SAP302, and SAP303. The formulation of SST 30 mcg and Zalviso (sufentanil sublingual tablet 15 mcg, also known as SST 15 mcg) (b) (4)) are similar and the only differences are the amounts of active ingredient and color.

Table 3 Components and Composition of SST 30 mcg and SST 15 mcg

Components	Quality Reference	Function	Composition per tablet (mg)	
			SST 15 mcg Proposed Commercial Formulation	SST 30 mcg Phase 3/ proposed Commercial Formulation
Sufentanil Citrate	USP	Active pharmaceutical ingredient	(b) (4)	
Mannitol (b) (4)	USP, EP	(b) (4)		
Dicalcium Phosphate Anhydrous	USP			
Hypromellose (b) (4) (b) (4)	USP, EP, JP			
Croscarmellose Sodium	NF, EP			
FD&C Blue #2 (b) (4) (b) (4)	FD&C			
(b) (4)	FD&C			
Stearic Acid (b) (4) (b) (4)	NF, Ph Eur, BP, JP			
Magnesium Stearate (b) (4)	NF, Ph Eur, BP, JP (b) (4)			
		Total	7.4	7.4

(b) (4)

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

Sufentanil is an opioid analgesic. As an opioid agonist, the principle therapeutic action is analgesia, the precise mechanism of which is not known, but the effects are thought to be mediated through opioid-specific receptors, primarily the mu opioid receptor, in the CNS. Opioid analgesics may also affect the emotional response to pain. There is no intrinsic limit to the analgesic effect of sufentanil. In clinical practice, limitations are imposed by its adverse effects, primarily nausea and vomiting, sedation, and respiratory depression, which can result from high doses. In patients administered IV sufentanil, there was no indication of any histamine release.

Dsuvia is indicated for the management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting.

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

Dsuvia sublingual tablet is to be administered by a healthcare professional in response to pain using the single-dose applicator (SDA). The SDA is used as a placement aid for the healthcare professional to administer sublingually a single sufentanil sublingual tablet 30 microgram (SST 30 mcg), on an as needed basis, with a minimum of 1 hour between doses. The dispensed sublingual tablet dissolves under the tongue and should not be chewed or swallowed. Patients should not eat or drink and should minimize talking for 10 minutes after each dose of Dsuvia.

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of sufentanil for the listed drug Sufenta® (sufentanil citrate) Injection (NDA 19-050) and the cross referenced product Zalviso (sufentanil sublingual tablet 15 mcg) (b) (4)?

According to the Sufenta (sufentanil citrate) Injection labeling:

- Pharmacokinetics of intravenous sufentanil can be described as a three-compartment model, with a distribution time of 1.4 minutes, redistribution of 17.1 minutes and elimination half-life of 164 minutes in adults.
- The elimination half-life of sufentanil is shorter (e.g. 97 +/- 42 minutes) in infants and children, and longer in neonates (e.g. 434 +/- 160 minutes) compared to that of adolescents and adults.
- The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug.
- Plasma protein binding of sufentanil, related to the alpha acid glycoprotein concentration, was approximately 93% in healthy males, 91% in mothers and 79% in neonates.

According to the clinical pharmacology review of (b) (4) for Zalviso (sufentanil sublingual tablet 15 mcg):

- The mean (SD) erosion time of sufentanil tablet from the sublingual space was about 6.4 (3.1) min.

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- Peak sufentanil concentration was reached at a median Tmax of approximately 50 min.
- The absolute bioavailability of SST 15 mcg was 58%. However, the absolute oral bioavailability of SST 15 mcg was 8%, indicating extensive first pass of sufentanil when administered orally.
- The elimination half-life of a single SST 15 mcg by sublingual route was 10 h where after Sufenta IV was 11 h.
- Following multiple dose administration (40 repeated doses every 20 minutes), Cmax was 8-fold higher than a single dose. There was a dose-stacking effect as reflected by the fact that the AUC0-tau after multiple dose within a dosing interval was 40% lower compared to AUCinf after a single dose suggested decreased absorption after multiple dose. It was indicated that the decreased AUC after repeated dosing was maybe due to swallowing of drug or the swallowing of saliva with solubilized drug after certain doses. Steady state was achieved after 13 doses.
- Concurrent administration of SST 15 mcg with ketoconazole increased the AUCinf and Cmax of sufentanil by 77% and 19%, respectively. Although dose reduction was not warranted because of the nature of dosing regimen for SST 15 mcg (i.e., as needed), warning language was needed to inform the drug interaction with CYP3A4 inhibitors.
- Population pharmacokinetic analysis concluded that sufentanil clearance increased with weight increase, decreased with age increase, but not affected by drug-lot, race, gender, or a concomitant CYP3A4 substrate. Due to limited data from moderately and severely hepatically impaired patients and severely renally impaired patients, the effect of moderate or severe hepatic dysfunction and severe renal dysfunction may not have been detected.
- It was acceptable to address the potential impact of consumption of hot/cold and various pH liquids with SST 15 mcg by labeling as "patients (b) (4) not eat or drink and minimize talking for 10 minutes after (b) (4)".

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

The active moiety is sufentanil and its concentrations in plasma were measured for the characterization of pharmacokinetics of SST 30 mcg.

2.3 Intrinsic Factors

1. *What is the pediatric plan?*

The Division agreed with the waiver for (b) (4) years of age and deferral for (b) (4) according to the agreed Pediatric Study Plan (PSP) in a communication dated November 2, 2017.

2. *What are the effects of different covariates on the pharmacokinetics of SST 30 mcg based on population pharmacokinetic analyses?*

The population PK analysis included data from a population PK analysis previously submitted for SST 15 mcg as part of the Zalviso NDA (b) (4) PK data from Study SAP101, and sparse PK data from Phase 2 Study SAP202 and two Phase 3

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Studies SAP301 and SAP303 with SST 30 mcg. Body weight, repeat dosing, age and ketoconazole were found to be significant covariates on sufentanil clearance. As weight varies from the 5th to 95th percentiles, clearance varies from -19% to +29% of the value in a typical patient. As age varies from the 5th to 95th percentiles, clearance varies from -18% to +37% of the value in a typical patient. Sufentanil exposure was also higher after the first dose (relative to repeat doses) and in patients receiving concomitant ketoconazole. Due to the on-demand nature of dosing, however, sufentanil concentrations in clinical trials were largely similar in patients with varying body weight and age.

2.4 General Biopharmaceutics

1. *What is the absolute bioavailability and relative bioavailability of sufentanil following a single dose administration of the proposed SST 30 mcg in comparison to a single dose of the listed drug Sufenta 30 mcg and two doses of SST 15 mcg dosed 20 minutes apart (Zalviso under (b) (4)), respectively?*

The absolute bioavailability of a single sublingual administration of SST 30 mcg was 53%. A single SST 30 mcg tablet (1 x 30 mg) and 2 doses of SST 15 mcg (dosed 20 minutes apart) showed bioequivalent AUCinf and Cmax, and similar median (min, max) Tmax values (1.00 (0.50, 2.00) h for a single SST 30 mcg and 1.17 (0.67, 2.00) h for two SST 15 mcg (dosed 20 minutes apart).

In the comparative bioavailability study SAP101 conducted in healthy nonsmoking subjects (ages 18 to 45 years), the absolute bioavailability and relative bioavailability of a single sublingual administration of SST 30 mcg was determined by comparing with a single IV administration of 30 mcg Sufenta and sublingual administration of two doses of SST 15 mcg dosed 20 minutes apart, respectively. The same study also evaluated the multiple dose PK of SST 30 mcg following 12 consecutive doses of 30 mcg every 1 hour. Study SAP101 was a randomized, open-label, 2-sequence, 4-treatment, 4-period crossover study in healthy volunteers under naltrexone blockade. The following treatments were administered during the study:

Treatment A: single dose of Sufenta IV (50 mcg/mL) 30 mcg infused over 1 min
Treatment B: single dose of SST 30 mcg
Treatment C: 2 consecutive doses of SST 15 mcg administered 20 minutes apart
Treatment D: 12 consecutive doses SST 30 mcg administered every 1 hour

Subjects were randomized to 1 of the 2 treatment sequences: ABCD or ACBD. Treatment periods were separated by a 48 hour washout period. For treatment B, C, and D, the site staff placed SSTs under each subject's tongue with forceps. The SSTs were allowed to dissolve under the tongue and were not to be crushed, chewed or swallowed. Subjects were not to eat or drink and were to minimize talking for 10 minutes after a SST was administered. Subjects received concomitant dosing of naltrexone 50 mg to clock the opioid effects of sufentanil.

Blood samples for pharmacokinetic determination were collected from each subject at pre-dose, and at 1, 4, 7, 10, 15, 20, 30, 45 min and at 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours post dose for Treatment A; at pre-dose and 10, 20, 30, 40, 50 min and at 1,

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1.17, 1.33, 1.5, 1.67, 2, 3, 4, 6, 9, 12, 14, and 24 hours post dose for Treatment B and C; and at pre-dose and 1, 2, 4, 6, 7, 8, 9, 9.17, 9.33, 9.5, 9.67, 9.83, 10, 11, 11.17, 11.33, 11.5, 11.67, 11.83, 12, 12.17, 12.33, 12.5, 12.67, 13, 14, 15, 17, 20, 23, 25, and 35 hours after the first SST 30 mcg dose for Treatment D.

The mean sufentanil plasma concentration-time profiles after Sufenta IV 30 mcg infused over 1 minute (Treatment A), single dose SST 30 mcg (Treatment B), and 2 doses of SST 15 mcg (Treatment C) are shown in **Figure 1.** Sufentanil plasma concentration-time profiles following administration of single dose SST 30 mcg (Treatment B) and 2 doses of SST 15 mcg (Treatment C) are presented in **Figure 2**.

Figure 1 Mean (± SD) Sufentanil Plasma Concentration Versus Time for Treatments A (Sufenta IV 30 mcg), B (SST 30 mcg), and C (2 doses of SST 15 mcg dosed 20 minutes apart) (Study SAP101)

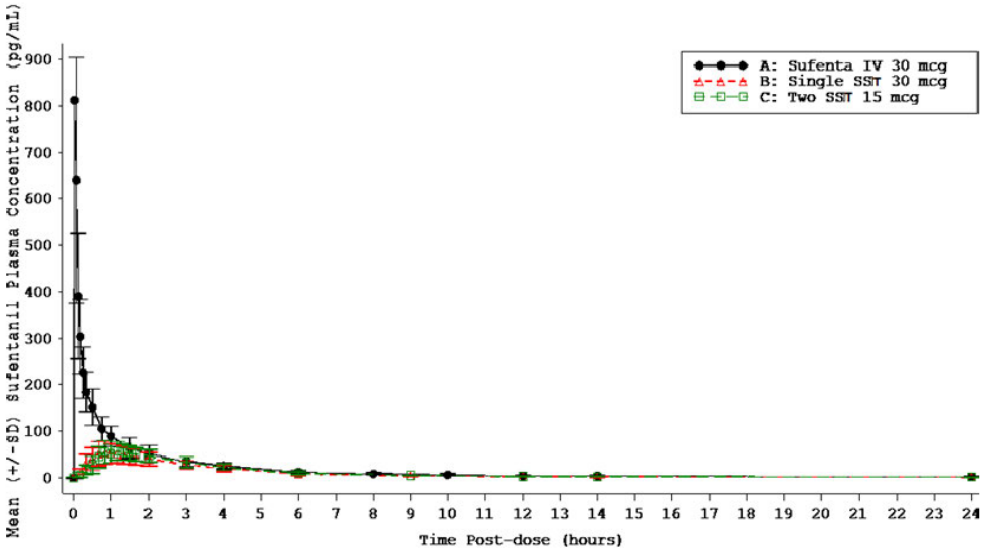
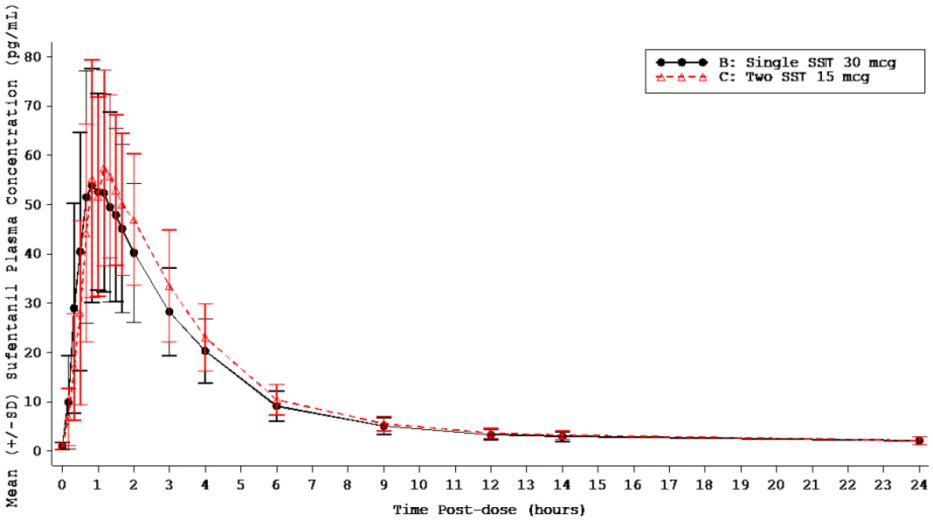


Figure 2 Mean (± SD) Sufentanil Plasma Concentration Versus Time for Treatments B (SST 30 mcg) and C (2 doses of SST 15 mcg dosed 20 minutes apart) (Study SAP101)



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Descriptive statistics of PK parameters for Sufenta IV 30 mcg, SST 30 mcg and two SST 15 mcg are summarized in **Table 1** in **Executive Summary**. Systemic exposure (AUCinf and Cmax) of sufentanil for a single IV dose of Sufenta IV 30 mcg was greater than the systemic exposures for the sublingual administration of a single SST 30 mcg. The mean absolute bioavailability (F) value was approximately 53% for a single dose of SST 30 mcg administered sublingually. The Cmax of a single SST 30 mcg was about 6% of the Cmax for Sufenta IV 30 mcg.

Single dose SST 30 mcg and 2 doses of SST 15 mcg were bioequivalent as the 90% confidence intervals for both Cmax and AUCinf values falling within the BE range of 0.8 to 1.25. The 90% confidence intervals for the geometric mean ratios of Cmax values were from 81% to 97%. The 90% confidence intervals for the geometric mean ratios of AUCinf values were from 84% to 103%. Similar Tmax values were also observed. Median (min, max) Tmax value was 1.00 (0.5, 2.00) h for the SST 30 mcg and 1.17 (0.67, 2.00) h for two doses of SST 15 mcg (dosed 20 minutes apart), respectively.

Reviewer's Comment:
(1) The sponsor's identified list drug product Sufenta is approved for IV doses of up to 8 mcg/kg as an analgesic adjunct to general anesthesia, and at IV does ≥ 8 mcg/kg (8 to 30 mcg/kg) as a primary anesthetic agent for induction and maintenance of anesthesia.

Per the proposed labeling for SST 30 mcg, it is stated (b) (4)

(b) (4)

In Study SAP101, it has been shown that the proposed SST 30 mcg had an absolute bioavailability of 53% in comparison with Sufenta IV 30 mcg. Thus, the systemic exposure of SST 30 mcg administered according to the proposed labeling will be less than the approved dose of Sufenta IV and the PK bridging between SST 30 mcg and Sufenta is established.

(2) The sponsor proposed to include patients from the completed Zalviso studies who were dosed with two doses of 15 mcg tablet administered 20 to 25 minutes apart to supplement the safety database for SST 30 mcg. Study SAP101 has shown bioequivalent exposures of sufentanil (AUCinf and Cmax) and similar Tmax values between a single dose of SST 30 mcg and 2 doses of SST 15 mcg (dosed 20 minutes apart). Based on the PK results from SAP101, similar exposure for a single SST 30 mcg and 2 doses of SST 15 mcg (dosed 20 – 25 minutes apart) was demonstrated based on PK modeling/simulation (submitted to IND 113059 SN0027 on September 2, 2015). The sufentanil concentration time profiles for 2 doses of SST 15 mcg dosed 20 minutes or 25 minutes apart are shown in **Figure 3**. Therefore, the PK bridging between SST 30 mcg and 2 doses of SST 15 mcg dosed within 20 to 25 minutes is established.

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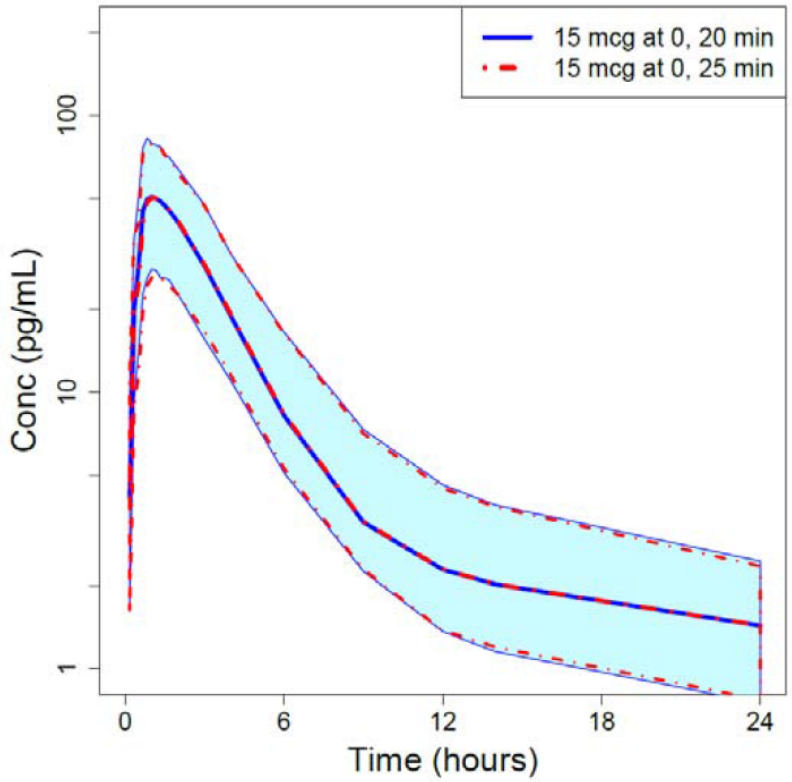
Figure 3 Spread of PK (10th – 90 h prediction range) for the 0, 20 min regimen and 0, 25 min regimen over 24 hours



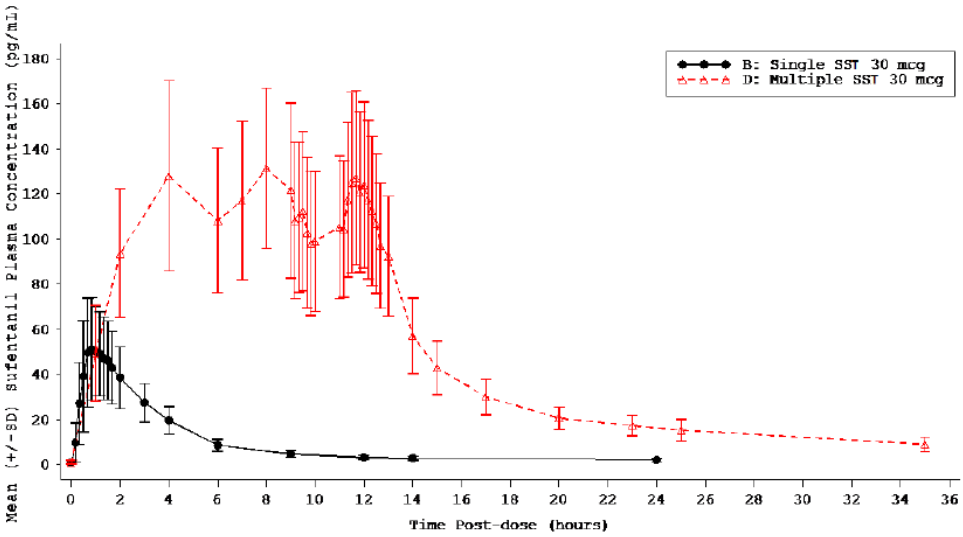
Note: The blue band is the 10th to 90th percentile prediction range for the 0, 20 min regimen, based on 1000 simulated subjects. The blue line is the median. The dashed thin red lines are the 10th to 90th percentile prediction range for the alternate regimen with a dosing interval of 25 min. The dashed thick red line is the median.

2. *What is the multiple dose pharmacokinetics of SST 30 mcg with a dosing regimen of every 1 hour?*

Multiple dose PK of SST 30 mcg was also evaluated in the comparative bioavailability study SAP101. As indicated previously, Study SAP101 was a randomized, open-label, 2-sequence, 4-treatment, 4-period crossover study in healthy volunteers under naltrexone blockade. In Treatment B, subjects received a single SST 30 mcg. In Treatment D, subjects were given 12 consecutive doses of SST 30 mcg every hour and blood samples were collected at pre-dose and 1, 2, 4, 6, 7, 8, 9, 9.17, 9.33, 9.5, 9.67, 9.83, 10, 11, 11.17, 11.33, 11.5, 11.67, 11.83, 12, 12.17, 12.33, 12.5, 12.67, 13, 14, 15, 17, 20, 23, 25, and 35 hours after the first SST 30 mcg dose. The blood samples were collected prior to dose number 1, 2, 3, 5, 7, 8, 9, 10, 11, and 12 to determine the time to steady state.

Sufentanil concentration-time profiles are shown in **Figure 4**. Descriptive statistics of single and multiple dose PK parameters are summarized in **Table 4**.

Figure 4 Mean (± SD) Sufentanil Plasma Concentration versus Time for Treatments B (single dose SST 30 mcg) and D (12 x SST 30 mcg administered every hour) (Study SAP101)



Abbreviations: SD = standard deviation; SST = sufentanil sublingual tablet.
Treatment B: single dose of SST 30 mcg.
Treatment D: multiple (12 consecutive) doses of SST 30 mcg administered 1 hour apart.

Table 4 Sufentanil Pharmacokinetic Parameters for Single Dose SST 30 mcg (Treatments B) and Multiple Dose SST 30 mcg (Treatment D: 12 x SST 30 mcg administered every hour) (Study SAP101)

Parameter	Single SST 30 mcg (n = 32)	12th Dose of SST 30 mcg (n = 32)
AUCinf (pg.h/mL)	269.82 ± 79.51 (29.47%)	--
AUC0-60min (pg.h/mL)	33.71 ± 16.23 (48.15%)	118.25 ± 34.45 (29.13%)
AUC0-720min (pg.h/mL)	196.26 ± 61.76 (31.47%)	--
Cmax (pg/mL)	60.55 ± 22.65 (37.40%)[a]	134.12 ± 39.51 (29.46%)
T1/2 (h)	14.12 ± 9.09 (64.3%)	12.68 ± 4.31 (34.0%)
Tmax (h)[a]	1.00 (0.50, 2.00)	0.67 (0.33, 1.33)
Geometric Mean Ratio (Last Dose (12th) of SST 30 mcg Q1H/Single Dose SST 30 mcg) (90% CI)		
AUC0-60min	3.74 (3.25 – 4.31)	
Cmax	2.27 (2.01 – 2.56)	

[a] tmax reported as median (min, max)
Source: Tables 13 and 14 of Study SAP101 report.

Sufentanil concentrations accumulated with the dosing regimen of every 1 hour. After the last of 12 consecutive doses of SST 30 mcg, AUC0-60min and Cmax were increased by 3.7-fold and 2.3-fold, respectively. Analysis of the pre-dose concentrations to determine the time to steady state for SST 30 mcg after multiple every hour dosing is summarized in **Table 5**. Mean pre-dose concentration prior to each dose was compared to the mean pre-dose concentrations pooled over all remaining doses. This analysis showed that the first nonsignificant comparison was for the dose number of 7 and it suggested that steady state was achieved by the 7th dose (or 360 minutes) of SST 30 mcg.

Table 5 Analysis of Time to Steady State Based on Pre-Dose Concentrations

Dose Number	Time point (minutes)	N	Geometric LS means	Ratio of Geometric LS Means	90% CI of Ratio (%)	p-value[a]
2	60	34	44.27	0.419	(0.381, 0.460)	<0.001
3	120	34	87.96	0.811	(0.737, 0.891)	<0.001
5	240	34	119.71	1.121	(1.019, 1.234)	0.050
7	360	34	102.31	0.950	(0.862, 1.047)	0.386[b]
8	420	34	110.20	1.029	(0.932, 1.137)	0.629
9	480	34	124.99	1.230	(1.110, 1.362)	<0.001
10	540	34	114.47	1.195	(1.072, 1.332)	0.007
11	600	34	92.81	0.939	(0.828, 1.064)	0.405
12	660	34	98.89			

CI = confidence interval; LS = least squares; N = number of subjects
a p-value was for testing if the corresponding ratio of geometric LS means was 1.
b The first nonsignificant comparison at the 0.1 level.
An analysis of variance was performed with the natural log-transformed predose concentrations as the dependent variable and time point as fixed effect. Ratio was for comparing the geometric mean concentration of the corresponding time point to the geometric mean concentrations pooled over all remaining time points.

3. *How were the potential impacts of the consumption of hot, cold and various pH liquids on SST 30 mcg absorption addressed?*

The sponsor has not conducted PK studies with either SST 15 mcg (Zalviso) or SST 30 mcg (Dsuvia) to evaluate the effects of consumption of hot, cold and various pH liquids on sufentanil absorption. The sponsor proposed to use the same approach of addressing the impact of consumption of hot/cold and various pH liquids by labeling "patients (b) (4) not eat or drink and minimize talking for 10 min after (b) (4)". The Division agreed with the approach at the EOP2 meeting.

4. *How was the potential impact of mucositis on SST absorption addressed?*

As discussed at the EOP2 meeting, the sponsor stated that because patients with mucositis can be prescribed another product, the sponsor is not planning to conduct PK studies in those patients (b) (4). The Division agreed with the approach (b) (4) (b) (4).

5. *Was the proposed final to-be-marketed formulation used in clinical studies?*

The final to-be-marketed SST 30 mcg product was used in the comparative bioavailability study SAP101 and all of the Phase 3 studies (SAP301, SAP302, and SAP303) except the Phase 2 Study SAP202.

The formulation used in the SAP202 differed from the proposed to-be-marketed formulation (**Table 6**). The major difference is in the use of (b) (4), which is

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completely absent in the Phase 2 formulation and present in the to-be-marked formulation. According to the CMC/Biopharm review team, this would be considered a 100% change per SUPAC IR guidance, however, there is no direct comparison in PK between the SAP202 formulation and the to-be-marketed formulation.

Table 6 Summary of Formulation Composition for SST 30 mcg Used in An Earlier Phase 2 Study (Study SAP202) and the To-be-marked Product (Used in the Comparative Bioavailability Study SAP101 and All Phase 3 Studies)

Purpose		Phase 2 Study			Phase 1 Definitive PK Study, Phase 3 Studies and Primary Stability Studies	
Dosage Strength (mcg)		20	30	Placebo	30	Placebo
Tablet Weight (mg)		(b) (4)			7.40	7.40
Bulk Lot #		110621 [a]	110623 [a]	081101	3120301R 3120302R 3120303R	3119898R
Components	Function	Composition (% w/w)				
Sufentanil Citrate	(b) (4)					
(b) (4)						
Mannitol (b) (4)						
(b) (4)						
Dicalcium Phosphate Anhydrous						
Hypromellose (b) (4)						
(b) (4)						
Croscarmellose Sodium						
FD&C Blue #2, (b) (4)						
(b) (4)						
Stearic Acid, (b) (4)						
Magnesium Stearate, (b) (4)						
(b) (4)						
	TOTAL	100	100	100	100	100

n/a = not applicable
[a] Bulk tablets were manufactured at (b) (4) and packaged at (b) (4)

2.5 Analytical Section

1. *Are the bioanalytical methods adequately validated for determining plasma concentrations of sufentanil?*

A validated LC-MS/MS method (as described in report (b) (4) 116587-B) was used for the determination of sufentanil in human plasma samples in Studies SAP101, SAP202, SAP301, and SAP303. The accuracy and precision are summarized in **Table 7**.

Table 7 Summary of Accuracy and Precision Data for Determination of Plasma Concentrations of Sufentanil

Study	LLOQ Calibration Range	QC	QC Precision (%CV)	QC % Accuracy
Study SAP101 (Bioanalytical Report ACX009UF-140092-A)	LLOQ: 1 pg/mL Calibration Range: 1.00, 2.00, 5.00, 20.0, 50.0, 200, 500, 800, and 1000 pg/mL	3.00, 50.0, 500, and 800 pg/mL	2.6 – 3.9%	1.4 – 2.6%
Study SAP202 (Bioanalytical Report	LLOQ: 1 pg/mL Calibration Range: 1.00, 2.00, 5.00, 20.0,	3.00, 50.0, 500, and 800 pg/mL	3.5 – 4.8%	-2.3 – 0.4%

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ACZ335UL-113917-A)	50.0, 200, 500, 800, and 1000 pg/mL			
Study SAP301 (Bioanalytical Report ACX203UL-142037-A)	LLOQ: 1 pg/mL Calibration Range: 1.00, 2.00, 5.00, 20.0, 50.0, 200, 500, 800, and 1000 pg/mL	3.00, 50.0, 500, and 800 pg/mL	2.4 – 3.3%	-0.2 – 1.8%
Study SAP303 (Bioanalytical Report ACX017UL-160177-A)	LLOQ: 1 pg/mL Calibration Range: 1.00, 2.00, 5.00, 20.0, 50.0, 200, 500, 800, and 1000 pg/mL	3.00, 50.0, 500, and 800 pg/mL	3.8 – 4.5%	-1.6 – 1.3%

Note: The bioanalytical reports are in the following locations in the NDA:
Study SAP101: 5.3.3.1 sap101 Study Report Body Bioanalytical Report ACX009UF-140092-A
Study SAP202: 5.3.5.1 sap202 Study Report Body Bioanalytical Report – ACX335UL-113917-A
Study SAP301: 5.3.5.1 sap301 Study Report Body Bioanalytical Report – ACX203UL-142037-A
Study SAP303: 5.3.5.2 sap303 Study Report Body Bioanalytical Report – ACX017UL-160177-A

3 Detailed Labeling Recommendations

This product will not be approved during this review cycle and there is no labeling recommendation at this time.

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4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA/BLA Number	209128	Brand Name	Dsuvia
OCP Division (I, II, III, IV, V)	II	Generic Name	Sufentanil sublingual tablet, 30 mcg
Medical Division	DAAAP	Drug Class	Opioid analgesic
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Management of moderate to severe acute pain severe enough to require an opioid agonist in adult patients in a medically supervised setting
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	Sublingual tablet
Pharmacometrics Reviewer	Kevin Krudys	Dosing Regimen	
Date of Submission	12/12/16	Route of Administration	sublingual
Estimated Due Date of OCP Review	8/21/17	Sponsor	AcelRx
Primary Review Due	9/7/17	Priority Classification	standard
PDUFA Due Date	10/12/17		

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	1		SAP101
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
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:				
Phase 3:				
PK/PD -				

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Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	x	1		**Poppk report ACX-PPK-259-001**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	(1)		**SAP101**
alternate formulation as reference:	x	(1)		**See 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		2		

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	Sponsor stated that the final to-be-marketed formulation was used in the PK study (SAP101) and all of the Phase 3 studies for SST30 mcg (SAP301, SAP302, and SAP303)
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
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	x			

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	begin?				
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			Sponsor submitted PK dataset for SAP101 as well as datasets for PopPK analysis in SAS transport format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
	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	Sponsor requested waiver for (b) (4) and deferral for (b) (4) (b) (4) (b) (4) according to the agreed Pediatric Study Plan (PSP).
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			

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19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____YES___

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

This NDA submission is fillable from clinical pharmacology perspective.

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

There is no potential review issue to be included in the 74-day letter. On 1/26/17, an IR was issued to request population PK model codes and output listings for all major model building steps.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

AcelRx submitted a 505(b) (2) NDA for Dsuvia (sufentanil sublingual tablet 30 mcg) for the management of moderate-to-severe acute pain severe enough to require an opioid agonist in adult patients in a medically supervised setting. SST 30 mcg has been used thorough out the drug development process. The proposed dosing regimen is to administer sublingually a single SST 30 mcg on an as needed basis, with a minimum of 1 hour between doses.

Sponsor proposed to rely on the agency's finding of Sufenta® (sufentanil citrate solution) (NDA 19-050). In addition, sponsor proposed to use some safety data from the Zalviso (sufentanil sublingual tablet 15 mcg) application to support Dsuvia. Zalviso is also known as SST 15 mcg.

The PK studies supporting this NDA include a comparative BA/BE study SAP101 and a population PK analysis. Study SAP101 is used to build up the "bridge" between SST 30 mcg and Sufenta, and between SST 30 mcg and SST 15 mcg and to characterize multiple dose PK of SST 30 mcg. Sponsor concluded that the mean absolute bioavailability of SST 30 mcg was approximately 53%. Both sufentanil Cmax and AUC0-inf values were equivalent for single dose SST 30 mcg and 2 doses of SST 15 mcg (with 20 minutes between doses). PK modeling/simulation was conducted to support the use of safety data from Zalviso patients who dosed the second tablet within 20 to 25 min of the first tablet (the PK modeling/simulation was submitted to IND (b) (4)SN0027). Sufentanil concentrations accumulated upon multiple dosing. After the last of 12 consecutive doses of SST 30 mcg, AUC0-60min and Cmax increased by 3.7-fold and 2.3-fold, respectively, compared to after the first dose.

The population PK analysis was conducted using data from Zalviso application with additional data from three efficacy/safety studies conducted with SST 30 mcg. The sponsor concluded that SST 15 mcg and

SST 30 mcg sublingual PK are well described by a 2-compartment PK model with first-order absorption. Patient weight and age are key covariates on clearance. Ketoconazole reduced clearance by 40%. Hepatic impairment and renal impairment had minimal effect on clearance in the SST 30 mcg population, clearance being reduced by no more than 25% in severe impairment.

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4.2 Pharmacometrics Assessment: Population PK Analyses

A population PK analysis was previously submitted by the Applicant under (b) (4) (Zalviso) and was reviewed by Dr. Naraharisetti (DARRTS 06/19/2014) and found to be generally adequate and acceptable for the purpose of labeling recommendations. This analysis included PK data from 700 subjects from three Phase 1 studies, one dose-finding study (ARX-C-001) and three Phase 3 studies (IAP309, IAP310 and IAP311). Most patients received the 15 mcg dose. The purpose of the current analysis is to update the previous analysis by including data from studies which used the sufentanil sublingual 30 mcg tablet.

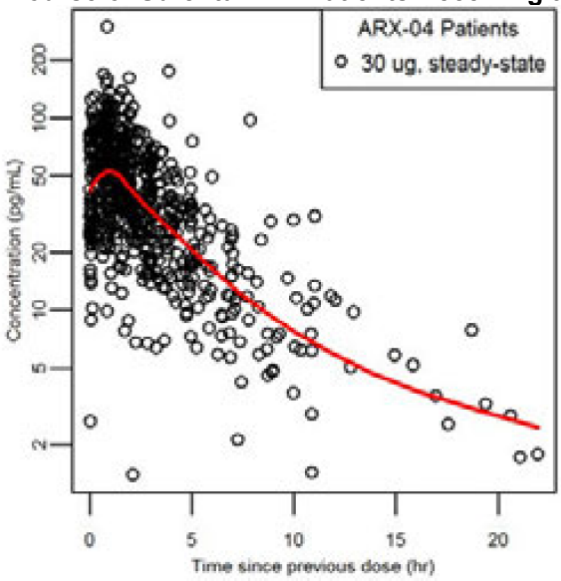
The key attributes of the new studies (SAP101, SAP202, SAP301 and SAP303) added to the database are listed in Table 1. In total, the PK database included 1,066 subjects with 8,436 quantifiable samples. Approximately 40% of the PK samples were from SAP101. Figure 1 shows the PK data in patients dosed on-demand with the 30 mcg sublingual tablet.

Table 1: Summary of Studies Added to Population PK Analysis

Protocol	Population	N	Regimen	PK sampling schedule	Samples per subject
SAP101	Healthy subjects	39	30 mcg IV	0, 1, 4, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 600, 720, 840 minutes, and 24 hours after dose	20.1
			Two 15 mcg dosed 20 minutes apart	0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 180, 240, 360, 540, 720, 840, 840 minutes, and 24 hours after dose	18.1
			30 mcg	0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 180, 240, 360, 540, 720, 840, 840 minutes, and 24 hours after dose	18.1
			12 consecutive 30 mcg doses every hour	0, 60, 120, 240, 360, 420, 480, 540, 550, 560, 570, 580, 590, 600, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 780, 840, 900, 1020, 1200, 1380, 1500 minutes, and 35 hours after the first dose	32.0
SAP202	Bunionectomy alone or with hammertoe repair	80	20 mcg or 30 mcg dosed at most every hour for up to 12 hours	1, 4, 8, and 12 hours and/or at time of early termination	3.9
SAP301	Abdominal surgery	107	30 mcg dosed at most every hour for up to 48 hours	1, 12, and 24 hours and/or at time of early termination	2.9
SAP303	Surgery in patients aged 40 years or older	140	30 mcg dosed at most once every hour for up to 12 hours	1, 4, 8, and 12 hours and/or at time of early termination	3.8

Source: ACX-PPK-259-001, Table 1, Page 18.

Figure 1: Time-Course of Sufentanil in Patients Receiving the 30 mcg Tablet



Source: ACX-PPK-259-001, Figure 1, Page 31.

The population PK model was similar to the one reported previously for Zalviso. Details of the modeling approach, including covariate selection can be found in the previous review by Dr. Naraharisetti. Briefly, sufentanil pharmacokinetics was described with a two-compartment linear model with first-order oral absorption and lag time. For this analysis, the fraction absorbed (F) was fixed to the estimated value of 0.531 from SAP101 to account for the IV dosing regimen in the first period of the study. Similar to the previous analysis, repeat dosing, body weight, age and ketoconazole were found to be significant covariates on clearance and weight was found to be a covariate on inter-compartment clearance. The final parameter estimates are provided in Table 2 and selected goodness-of-fit plots are displayed in Figure 2.

Table 2: Parameter Estimates of the Final PK Model

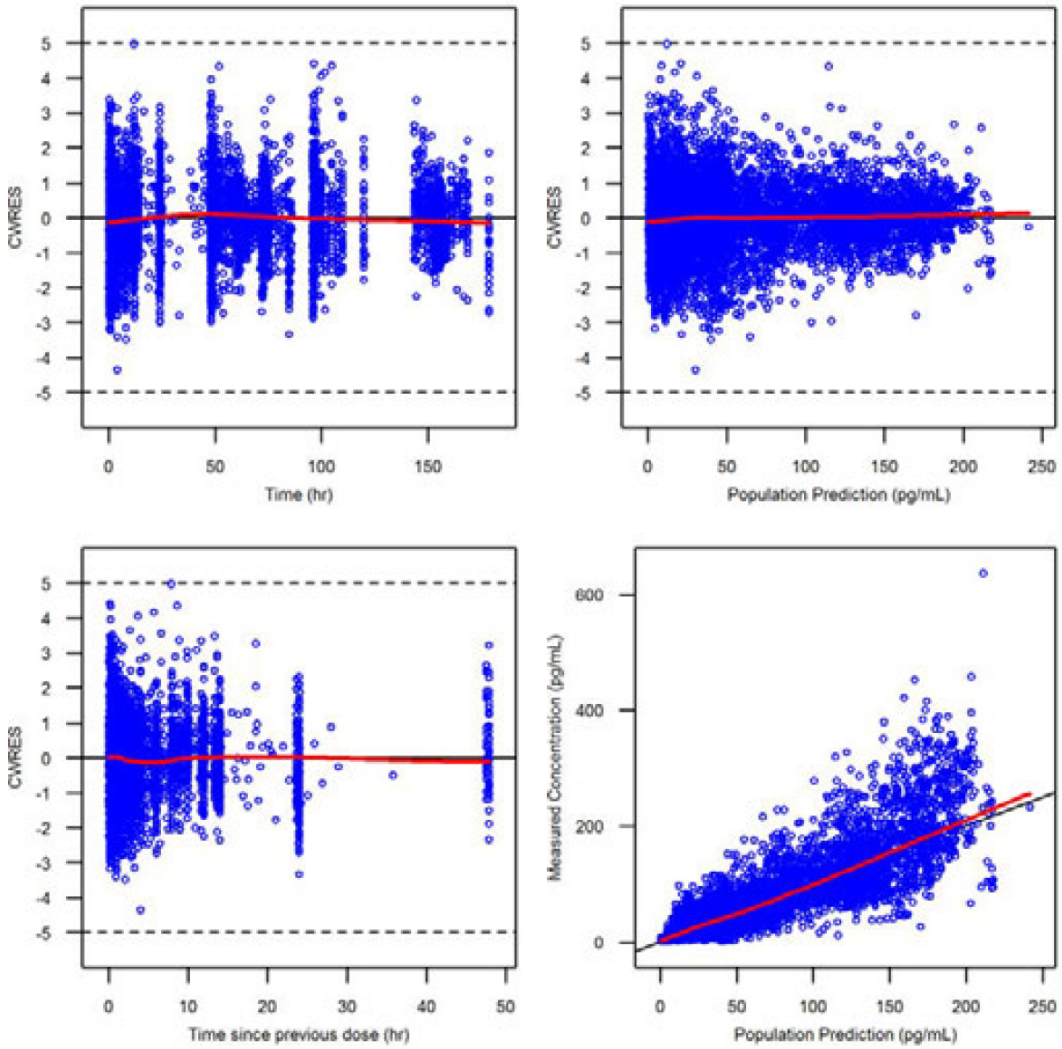
Parameter	Variable	Estimate	SE (%)	95% CI	Variability	Shrinkage (%)
First Dose Clearance (L/hr)	CL/F	78.0	4.8	70.6, 85.4	45%	16
First Dose Clearance (L/hr)*		84.2				
Repeat Dose Clearance (L/hr)		120				
Repeat Dose Clearance (L/hr)*		129				
Central Volume (L)	V_c/F	120	20.3	72.3, 168.0	80%	34
Dist Clearance (L/hr)	Q/F	70.4	4.3	64.5,76.4		
Dist Volume (L)	V_p/F	1712	9.5	1392, 2032	49%	59
Absorption Rate Constant (1/hr)	ka	0.405	7.7	0.344, 0.466	19%	43
Lag Time (hr)	Tlag	0.0683	2.9	0.0644, 0.0722		
Bioavailability	F	0.531				
Repeated dose on relative F	Frel	0.651	3.2	0.611, 0.692		
Age on CL		-0.572	9.6	-0.679, -0.464		
Ketoconazole on CL		-0.398	19.6	-0.550, -0.245		
Weight on CL		0.633	11.1	0.496, 0.770		
Weight on Q		0.443	29.8	0.184, 0.702		
Covariance CL and Vc		0.125				
Covariance CL and ka		-0.0306				
Covariance Vc and ka		-0.0888				
Intrasubject Residual Variance		0.0714				

Note: All values are for an 80 kg, 56 year old patient not taking ketoconazole (typical patient from combined ARX-01 and ARX-04 studies), except where indicated.

*These clearance values are for the typical ARX-04 patient only (78.5 kg, 47 year old patient not taking ketoconazole).

Source: ACX-PPK-259-001, Table 6, Page 34.

Figure 2: Goodness-of-Fit Plots for the Final PK Model



The upper left plot shows CWRES versus time from initial dose. The horizontal black line is the zero line. The solid red line is a smooth to the data. The dashed black lines are at CWRES of ±5, which were the cutoffs used to identify outliers. The upper right plot shows CWRES versus population prediction, the lower left shows CWRES versus time since previous dose, and the lower right shows measured concentrations versus population predictions.

Source: ACX-PPK-259-001, Figure 4, Page 35.

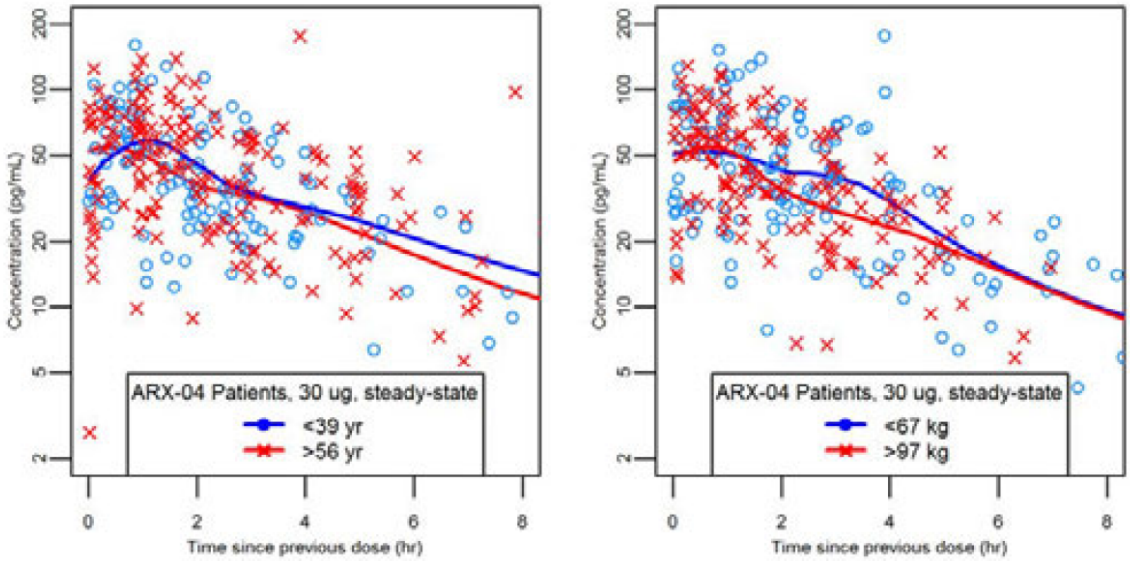
The impact of significant covariates on the clearance of sufentanil is summarized in Table 3. As weight varies from the 5th to 95th percentiles, clearance varies from -19% to +29% of the value in a typical patient. As age varies from the 5th to 95th percentiles, clearance varies from -18% to +37% of the value in a typical patient. Due to the on-demand nature of dosing, however, sufentanil concentrations were largely similar in patients with varying body weight and age (Figure 3).

Table 3: Factors Explaining Variability in Apparent Clearance

Covariate values			Estimate	Change from Typical (%)
Typical patient, with median body weight of 78.5 kg and age of 47 yr			**84.2**	—
5th Percentile clearance			52.8	-37.3
95th Percentile clearance			223.4	+165.2
Weight (kg)	5th Percentile	56	68.2	-19.0
	95th Percentile	117	108.4	+28.7
Age	5th Percentile	27 yr	115.6	+37.3
	95th Percentile	67 yr	68.8	-18.3
Ketoconazole	Absent		84.2	—
	Present		50.7	-39.8
Dose Status	First Dose		84.2	—
	Repeat Dose		129.3	+53.0

Source: ACX-PPK-259-001, Table 7, Page 40.

Figure 3: Concentrations of Sufentanil in Weight and Age Extremes



Graph of sufentanil concentrations below the 25th or above the 75th percentile for age (left) or weight (right). The red and blue lines are smoothed curves through the data.

Source: ACX-PPK-259-001, Figure 2, Page 32.

Reviewer's Comments: The current analysis is largely in agreement with the previous analysis reviewed by Dr. Naraharisetti and the current reviewer agrees with the prior assessment that the " population PK analysis is generally adequate and acceptable for the purpose of labeling." The magnitude of covariate effects (i.e., weight, age, ketoconazole, and dose status) on clearance in this analysis is consistent with previous findings. Importantly, the observed sufentanil concentrations in patients were similar in different weight and age groups due to the on-demand nature of dosing, and therefore dose adjustment is not needed. The parameter estimates from the current analysis were similar to the previous analysis with the exception of central and peripheral volumes of distribution (120 L and 1712 L in the current analysis, respectively vs. 68 L and 2200 L in the previous analysis). We agree with the Sponsor, who noted in the previous population PK report that "accurate estimation of the volume of distribution and terminal half-life is difficult to achieve…" due in part to the lack of data collected more than 24 hours post-dose. For labeling purposes, we recommend using values from dedicated PK studies that had adequate sampling, if available. The reviewer also agrees with the previous review regarding issues related to hepatic and renal impairment and labeling of the ketoconazole interaction.

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4.3 Individual Study Synopsis

4.3.1 Study SAP101

2 SYNOPSIS

Name of Sponsor/Company: **AcelRx Pharmaceuticals, Inc.**	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	**Volume:**	
Name of Active Ingredients: Sufentanil Citrate	**Page:**	

Title of Study: Pharmacokinetics of Sufentanil Sublingual Microtablet 30 mcg and 15 mcg in Healthy Subjects	
Investigator: Sandra K. Willsie, DO, MA	
Study Center: (b) (4)	
Publication (reference): None	
Study Period: Date first subject treated: 06 May 2014 Date last subject completed: 14 May 2014	**Phase of Development:** 1

Study Objective:
To establish the single-dose and multiple-dose pharmacokinetics (PK) of sublingual administration of the Sufentanil Sublingual Tablet (SST) 30 mcg and compare the PK of a single dose of SST 30 mcg to 2 doses of SST 15 mcg administered 20 minutes apart.

Trial Design:
This was a single-center, randomized, open-label, 2-sequence, 4-treatment, 4-period, crossover study in healthy male and female adult subjects.

The following treatments were administered during the study:
Treatment A: Sufenta® intravenous (IV) (50 mcg/mL) 30 mcg infused over 1 minute
Treatment B: single-dose SST 30 mcg
Treatment C: 2 consecutive doses SST 15 mcg administered 20 minutes apart
Treatment D: 12 consecutive doses of SST 30 mcg administered 1 hour apart

Forty subjects were enrolled and randomized to 1 of the 2 treatment sequences as follows: ABCD or ACBD. Each subject was administered Treatment A in Period 1. After completing Treatment A, subjects received Treatment B or Treatment C in Period 2 or Period 3 in a 2-sequence, 2-treatment, 2-period, crossover design. All subjects were administered Treatment D in Period 4. Treatment periods were separated by a 48-hour washout period.

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Name of Sponsor/Company: AcelRx Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	**Volume:**	
Name of Active Ingredients: Sufentanil Citrate	**Page:**	

Subjects received a total of 11 concomitant doses of 50 mg naltrexone orally to block the opioid effects of sufentanil at prespecified times predose and post dose for each treatment. The total duration of the study for each subject (including the 28-day screening period) was approximately 38 days.

Number of Subjects (planned and analyzed):
A sample size of 40 subjects was planned for this study to ensure 36 subjects completed all 4 treatments. A total of 40 subjects were enrolled and included in the analysis of safety data. Of the 40 enrolled subjects, 35 subjects (87.5%) were included in the PK analyses for Treatments A, B, and C, and 32 subjects (80%) were included in the PK analyses for Treatments B and D.

Diagnosis and Criteria for Inclusion:
Healthy, nonsmoking male and female subjects aged 18 to 45 years, inclusive. Subjects had a body mass index (BMI) between 18 and 30 kg/m^2, inclusive.

Test Product, Dose, Lot Number, Mode of Administration:
Sufentanil Sublingual Tablet 15 mcg (Lot number 3103832) and 30 mcg (Lot number 3120690), sublingual. Sufenta, 30 mcg (6 mL of 5 mcg/mL) (Lot Number 101243), IV infusion over 1 minute.

Study Procedures:
All subjects were screened for participation within 28 days prior to admission to the clinical facility on Day -1. Following informed consent, the screening visit consisted of the following procedures: collection of medical history; physical examination (PE); vital signs, including blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature, and oxygen saturation; orthostatic hypotension assessment; clinical laboratory tests, including blood chemistry, hematology, urinalysis, and serology; 12-lead electrocardiogram (ECG); pregnancy test (females only); serum follicle stimulating hormone screen (postmenopausal females only); and a urine drug screen for drugs of abuse, alcohol, and cotinine.

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Subjects who satisfied inclusion and exclusion criteria and were deemed eligible based on screening tests returned to the clinical facility for Check-in on Day -1. Upon being admitted to the clinical facility, subjects underwent an abbreviated PE; clinical laboratory tests (chemistry, hematology, and urinalysis); ECG; vital signs measurements; serum pregnancy test (females only); naloxone challenge; and a urine drug screen for drugs of abuse, alcohol, and cotinine.

Subjects were randomized to 1 of the 2 following treatment sequences: ABCD or ACBD. On Day 1 in Period 1, subjects received 50 mg naltrexone orally approximately 14 hours and 2 hours before and 10 hours after administration of Sufenta IV 30 mcg. For Treatments B and C, subjects received naltrexone doses approximately 2 hours before and 10 hours after administration of the first dose of SST on Days 3 and 5 in Periods 2 and 3, respectively. For Treatment D, subjects received naltrexone doses approximately 2 hours before and 10, 22, and 34 hours after the first administration of SST on Day 7.

For Treatment A, serial blood samples were collected at predose and 1, 4, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 600, 720, 840, and 1440 minutes (24 hours) post dose.

For Treatments B and C, serial blood samples were collected at predose and 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 180, 240, 360, 540, 720, 840, and 1440 minutes (24 hours) post dose.

For Treatment D, serial blood samples were collected at predose and 60, 120, 240, 360, 420, 480, 540, 550, 560, 570, 580, 590, 600, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 780, 840, 900, 1020, 1200, 1380, 1500, and 2100 minutes (35 hours) after the first SST dose. The blood samples from predose to 660 minutes were collected prior to each subsequent administration of SST (ie, prior to dose number 1, 2, 3, 5, 7, 8, 9, 10, 11, and 12).

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Subjects remained at the clinical facility from Check-in on Day -1 through Day 9. On Day 9 or at early termination, subjects underwent a PE, including vital signs collection; ECG; and clinical laboratory tests, including blood chemistry, hematology, and urinalysis.

Safety Monitoring:

Subjects had screening and end-of-study PEs, clinical laboratory tests (chemistry, hematology, and urinalysis), and ECGs. Safety was monitored via measurement of vital signs (including BP, HR, RR, temperature, and oxygen saturation) as well as assessment of adverse events (AEs) at periodic and predetermined time points throughout the study.

Blood Pressure and Heart Rate

BP and HR were measured at predose and 2, 4, 6, 8, 10, and 12 hours after the start of Treatments A, B, and C. BP and HR were measured predose and 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26 hours after the start of Treatment D.

Respiratory Rate

RR was measured every 30 minutes from predose to 4 hours after the start of dosing, then every hour until 12 hours after the start of dosing, and then every 4 hours until 24 hours after the start of dosing for Treatments A, B, and C. For Treatment D, RR was measured every 30 minutes from predose to 4 hours after the completion of dosing, then every hour until 12 hours after the final dose, and then every 4 hours until 24 hours after the final dose.

Temperature

Temperature was measured predose for each treatments on dosing days. On nondosing days, temperature was measured daily on along with BP, HR, RR, and oxygen saturation.

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Oxygen Saturation

For all 4 treatments, oxygen saturation was measured continuously from predose to 4 hours after the final dose. The oxygen saturation value was recorded when respiratory rate value was measured and recorded.

Pharmacokinetic and Safety Variables:

Pharmacokinetic Variables

Based on the plasma concentration data of sufentanil, the following noncompartmental, model-independent PK parameters were calculated using the trapezoidal rule:

AUC_{0-60} (h*pg/mL):	Area under the plasma concentration-time curve from time zero to 60 minutes post dose, calculated using the trapezoidal rule.
AUC_{0-720} (h*pg/mL):	Area under the plasma concentration-time curve from time zero to 720 minutes post dose, calculated using the trapezoidal rule.
AUC_{0-inf} (h*pg/mL):	Area under the plasma concentration-time curve from time zero to time infinity.
C_{max} (pg/mL):	Maximum observed plasma concentration either over the entire sampling period or the specified time interval, directly obtained from the experimental data of plasma concentration versus time curves without interpolation.
C_{min} (pg/mL):	Minimum observed plasma concentration within the 60-minute interval after the last dose of Treatment D directly obtained from the experimental data of plasma concentration versus time curves without interpolation.
T_{max} (h):	Time to reach the maximum plasma concentration.
K_{el} (1/h):	Apparent terminal elimination rate constant.
$t_{1/2}$ (h):	Apparent terminal elimination half-life, calculated as $\ln(2)/K_{el}$, where K_{el} is the apparent terminal elimination rate constant estimated by log-linear regression of the last portion of the serum concentration profile. This log-linear regression was fitted according to the least-squares approach without weighting.

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Starting with the last 3 quantifiable measurements and stepping back, the best fit was determined by minimizing the residual sums of squares; the time interval and the number of time points used for this optimal fit were provided.

CL (mL/min): Clearance value; calculated as Dose/$AUC_{0\text{-}inf}$ (Treatment A).

Bioavailability value (F value) (%):

The absolute amount of sufentanil absorbed was calculated by multiplying each treatment's $AUC_{0\text{-}inf}$ values and the clearance value derived from the reference IV treatment (Treatment A). The bioavailability value (F) for each treatment was calculated as the ratio of the amount of sufentanil absorbed divided by the nominal dose administered.

$CST_{1/2}$ (h): Context-sensitive half-time measured as the time from T_{max} to time for plasma concentration to reach half of C_{max} following discontinuation of drug administration.

Steady-state: Analysis of steady-state performed using Helmert's Method.

Safety Variables

Safety assessments included the incidence and severity of AEs during treatment; clinical laboratory tests, including blood chemistry, hematology, and urinalysis; vital signs; 12-lead ECGs; physical examinations; and concomitant medications.

Primary Efficacy Variables:

The following primary plasma PK parameters were estimated as follows: $AUC_{0\text{-}60}$, $t_{1/2}$, K_{el}, and $CST_{1/2}$ for Treatment B and the last dose in Treatment D; C_{max} and T_{max} for Treatment B, Treatment C, Treatment D, and the last dose in Treatment D; $AUC_{0\text{-}720}$ for Treatment B only; and $AUC_{0\text{-}inf}$ for Treatments B, C, and D.

Reference ID: 4151649

Name of Sponsor/Company: AcelRx Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	Volume:	
Name of Active Ingredients: Sufentanil Citrate	Page:	

Analysis Populations:
The analysis of the PK parameters included all enrolled subjects who received all study drugs and had available data. Subjects who had predose concentration >5% of C_{max} for a specific treatment period of Treatment B or C were excluded from the analysis of PK parameters. All enrolled subjects who received at least 1 dose of study drug were included in the summary of safety data.

Analysis of PK Parameters:
Individual subject's PK parameters for each treatment, as well as summary descriptive statistics (eg, group averages, standard deviations [SD], geometric mean, geometric SD, coefficients of variation [CVs], 90% confidence intervals [CIs], and ratio of means) of all PK parameters, were presented. The T_{max}, K_{el}, $t_{1/2}$, and $CST_{1/2}$ were analyzed without log transformation, and differences rather than ratios between 2 treatments were calculated.

Analysis of PK Parameters obtained from Treatments A, B, and C:
An analysis of variance (ANOVA) model for crossover design was performed on natural log-transformed AUC_{0-60}, AUC_{0-inf}, and C_{max}. This ANOVA model included sequence, subject within sequence, period, and treatment factors. An estimate of the ratio of geometric means (GMs) and its 90% CI was calculated with the log-transformed data. The calculation of these estimates was based on the estimate of the difference between the least squares (LS) mean of the test treatment minus the LS mean of the reference treatment and the standard error (SE) of the estimate provided by the ANOVA model. The reference treatments of Sufenta IV 30 mcg and 2 doses of SST 15 mcg administered 20 minutes apart were used for these calculations.

The following ratios were calculated: ratio of C_{max} for Treatment B over Treatment C; and ratio of AUC_{0-inf} for Treatment B over Treatment C.

An ANOVA model for crossover design was performed on T_{max}, K_{el}, $t_{1/2}$, and $CST_{1/2}$.

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This ANOVA model included sequence, subject within sequence, period, and treatment factors. The LS mean of each treatment and its 90% CI was presented. A pairwise difference between each test treatment and reference treatment (test treatment minus reference treatment) in the treatment LS mean and its 90% CI were constructed. There were 2 sets of analysis of PK parameters obtained from Treatments B and C. One set of analysis using ANOVA model included data from Treatments A, B, and C. Another set of analysis using ANOVA model only included data from Treatments B and C.

The CL and absolute amount of sufentanil absorbed were summarized descriptively. An ANOVA model for crossover design was performed on the bioavailability value (F value). The analysis of the F value only included Treatments B and C. This ANOVA model included sequence, subject within sequence, period, and treatment factors. The LS mean of each treatment and its 90% CI was presented. A 90% CI of the difference in the mean F value between Treatment B and C was calculated.

Analysis of PK Parameters Obtained from Treatments B and D:

Individual subject treatment-specific PK parameters (AUC_{0-60}, AUC_{0-720}, AUC_{0-inf}, and C_{max}) were natural log-transformed prior to analysis. AUC_{0-60} and C_{max} from Treatment B and from the last dose of Treatment D were analyzed with a paired t-test. An estimate of geometric mean ratio (GMR) and its 90% CI were calculated with the log-transformed data. For the purpose of determining whether the PK was time invariant, AUC_{0-720}, for Treatment B, and AUC_{0-60}, for the last dose of Treatment D, were compared using a paired t-test. Again, the estimate of GMR and its 90% CI were calculated with the log-transformed data.

The following ratios were calculated:

- ratio of AUC_{0-60} for the last dose of Treatment D over AUC_{0-60} for Treatment B
- ratio of AUC_{0-60} for the last dose of Treatment D over AUC_{0-720} for Treatment B
- ratio of dose-normalized AUC_{0-inf} for Treatment D over AUC_{0-inf} for Treatment B
- ratio of C_{max} for Treatment D over C_{max} for Treatment B

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- ratio of C_{max} for the last dose of Treatment D over C_{max} for Treatment B

T_{max}, K_{el}, $t_{1/2}$, and $CST_{1/2}$ were not log-transformed. A paired t-test was used to test the significance of the mean difference against zero. The differences, rather than ratios, between Treatments B and D were calculated.

The C_{min} derived from the 60-minute interval after the last dose of Treatment D was summarized descriptively.

Analysis of Safety Data:
All 40 enrolled subjects received at least 1 study treatment and were included in the analysis and summary of safety data. AEs were summarized for all enrolled subjects by treatment at onset. Other safety data, such as clinical laboratory tests, vital signs measurements, ECG data, and concomitant medications, were tabulated or listed.

RESULTS AND CONCLUSIONS:

Demographics:
Forty subjects (17 male and 23 female) were enrolled in the study, including 19 African American subjects, 15 white subjects, 4 subjects identified as "Other," and 2 Asian subjects. The mean age was 30.5 years (range: 19-46 years). All subjects met age inclusion criteria at the time of consent; Subject (b) (6) was 45 years old at the time of study consent and turned 46 the following day. The mean BMI was 24.7 kg/m^2 (range: 18.7-29.6 kg/m^2).

Pharmacokinetic Results:
PK parameters and their analyses are summarized in the following tables:

Reference ID: 4151649

Name of Sponsor/Company: AcelRx Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	**Volume:**	
Name of Active Ingredients: Sufentanil Citrate	**Page:**	

Analysis of Sufentanil $AUC_{0\text{-}inf}$, C_{max}, T_{max}, K_{el}, $t_{1/2}$, and $CST_{1/2}$ for Treatments A, B, and C

Pharmacokinetic Parameter	Treatment		
	Sufenta IV[a] 30 mcg (n = 35)	Single SST[b] 30 mcg (n = 35)	Two SST[c] 15 mcg (n = 35)
$AUC_{0\text{-}inf}$ (h*pg/mL)			
Mean (SD)	539.68 (113.12)	277.68 (84.36)	307.30 (79.08)
Median	519.73	282.52	300.24
(Min, Max)	(386.99, 787.77)	(90.00, 451.20)	(151.06, 440.74)
Geometric Mean (CV%)	528.5 (20.96)	262.4 (30.38)	295.9 (25.73)
LS Geometric Mean	518.0	257.2	292.9
(90% CI of LS Geometric Mean)	(478.2, 561.2)	(237.5, 281.5)	(267.7, 317.3)
Reference Treatment: Sufenta IV 30 mcg			
Ratio of LS Geometric Mean	NA	0.50	0.56
90% CI of Ratio	NA	(0.45, 0.55)	(0.51, 0.62)
p-value (versus Reference)[d]	NA	<0.001	<0.001
Reference Treatment: Two SST 15 mcg			
Ratio of LS Geometric Mean	1.79	0.89	NA
90% CI of Ratio	(1.62, 1.95)	(0.80, 0.97)	
p-value (versus Reference)[d]	<0.001	0.037	
C_{max} (pg/mL)			
Mean (SD)	1073.94 (968.17)	63.14 (23.49)	66.00 (20.38)
Median	745.00	61.50	64.80
(Min, Max)	(201.00, 4510.00)	(21.00, 118.00)	(37.40, 115.00)
Geometric Mean (CV%)	796.3 (90.15)	59.1 (37.21)	62.8 (30.88)
LS Geometric Mean	788.4	58.0	62.2
(90% CI of LS Geometric Mean)	(671.8, 916.0)	(49.4, 67.4)	(53.5, 72.2)
Reference Treatment: Sufenta IV 30 mcg			
Ratio of LS Geometric Mean	NA	0.07	0.08
90% CI of Ratio	NA	(0.06, 0.09)	(0.07, 0.10)
p-value (versus Reference)[d]	NA	<0.001	<0.001
Reference Treatment: Two SST 15 mcg			
Ratio of LS Geometric Mean	12.68	0.93	NA
90% CI of Ratio	(10.49, 15.33)	(0.77, 1.13)	
p-value (versus Reference)[d]	<0.001	0.532	
T_{max} (hour)			
Mean (SD)	0.05 (0.03)	0.95 (0.33)	1.19 (0.36)
Median	0.07	1.00	1.17
(Min, Max)	(0.02, 0.17)	(0.50, 2.00)	(0.67, 2.00)

Reference ID: 4151649

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Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	**Volume:**	
Name of Active Ingredients: Sufentanil Citrate	**Page:**	

LS Mean (SEM)	0.06 (0.05)	0.96 (0.05)	1.20 (0.05)
(90% CI of LS Mean)	(-0.02, 0.14)	(0.88, 1.04)	(1.11, 1.28)
Reference Treatment: Sufenta IV 30 mcg			
LS Mean Difference (SEM)	NA	0.90 (0.06)	1.14 (0.06)
90% CI of Difference	NA	(0.80, 1.00)	(1.04, 1.24)
p-value (versus Reference)[d]	NA	<0.001	<0.001
Reference Treatment: Two SST 15 mcg			
LS Mean Difference (SEM)	-1.14 (0.06)	-0.24 (0.06)	NA
90% CI of Difference	(-1.24, -1.04)	(-0.33, -0.14)	
p-value (versus Reference)[d]	<0.001	<0.001	
K_{el} (1/hour)			
Mean (SD)	0.064 (0.040)	0.090 (0.069)	0.071 (0.065)
Median	0.056	0.049	0.051
(Min, Max)	(0.023, 0.207)	(0.020, 0.276)	(0.016, 0.294)
LS Mean (SEM)	0.063 (0.010)	0.088 (0.010)	0.070 (0.010)
(90% CI of LS Mean)	(0.045, 0.080)	(0.071, 0.106)	(0.052, 0.087)
Reference Treatment: Sufenta IV 30 mcg			
LS Mean Difference (SEM)	NA	0.026 (0.013)	0.007 (0.013)
90% CI of Difference	NA	(0.004, 0.047)	(-0.015, 0.029)
p-value (versus Reference)[d]	NA	0.053	0.598
Reference Treatment: Two SST 15 mcg			
LS Mean Difference (SEM)	-0.007 (0.013)	0.019 (0.013)	NA
90% CI of Difference	(-0.029, 0.015)	(-0.003, 0.041)	
p-value (versus Reference)[d]	0.598	0.155	
$t_{1/2}$ (hour)			
Mean (SD)	13.72 (6.12)	13.37 (8.89)	15.66 (9.38)
Median	12.48	14.22	13.66
(Min, Max)	(3.34, 29.38)	(2.52, 34.39)	(2.36, 42.69)
LS Mean (SEM)	14.13 (1.44)	13.75 (1.44)	16.10 (1.44)
(90% CI of LS Mean)	(11.73, 16.52)	(11.36, 16.15)	(13.70, 18.49)
Reference Treatment: Sufenta IV 30 mcg			
LS Mean Difference (SEM)	NA	-0.38 (1.88)	1.97 (1.88)
90% CI of Difference	NA	(-3.51, 2.75)	(-1.16, 5.10)
p-value (versus Reference)[d]	NA	0.841	0.297
Reference Treatment: Two SST 15 mcg			
LS Mean Difference (SEM)	-1.97 (1.88)	-2.35 (1.88)	NA
90% CI of Difference	(-5.10, 1.16)	(-5.48, 0.78)	
p-value (versus Reference)[d]	0.297	0.215	
$CST_{1/2}$ (hour)			
Mean (SD)	0.20 (0.21)	2.49 (0.85)	2.49 (0.88)

Reference ID: 4151649

Median	0.10	2.33	2.33
(Min, Max)	(0.03, 0.72)	(0.83, 4.83)	(0.83, 4.83)
LS Mean (SEM)	0.20 (0.13)	2.49 (0.13)	2.49 (0.13)
(90% CI of LS Mean)	(-0.01, 0.41)	(2.28, 2.71)	(2.28, 2.70)
Reference Treatment: Sufenta IV 30 mcg			
LS Mean Difference (SEM)	NA	2.29 (0.15)	2.29 (0.15)
90% CI of Difference	NA	(2.04, 2.54)	(2.04, 2.54)
p-value (versus Reference)[d]	NA	<0.001	<0.001
Reference Treatment: Two SST 15 mcg			
LS Mean Difference (SEM)	-2.29 (0.15)	0.01 (0.15)	NA
90% CI of Difference	(-2.54, -2.04)	(-0.24, 0.26)	
p-value (versus Reference)[d]	<0.001	0.966	

Note: Both Sufenta IV 30 mcg and two SST 15 mcg were used as the reference treatments for comparisons. CI = confidence interval; CV% = coefficient of variation; IV = intravenous; LS = least squares; Max = maximum; Min = minimum; n = number of subjects in subset; NA = not applicable; SD = standard deviation; SEM = standard error of mean; SST = sufentanil sublingual tablet

These estimates were obtained from the ANOVA model that included sequence, period, and treatment fixed factors and subject within sequence random factor.

a Treatment A: Sufenta IV (50mcg/mL) 30 mcg infused over 1 minute

b Treatment B: Single dose of SST 30 mcg

c Treatment C: 2 consecutive doses of SST 15 mcg administered 20 minutes apart

d The p-value (versus Reference) for the pairwise test of difference of the LS mean between each treatment and reference treatment was based on the t-test of Type III analysis from the model described above.

Analysis of Sufentanil $AUC_{0\text{-}inf}$, C_{max}, T_{max}, K_{el}, $t_{1/2}$, and $CST_{1/2}$ for Treatments B and C

Pharmacokinetic Parameter	Treatment		
	Single SST[a] 30 mcg (n = 35)	Two SST[b] 15 mcg (n = 35)	Overall Treatment p-value[c]
$AUC_{0\text{-}inf}$ (h*pg/mL)			
Mean (SD)	277.68 (84.36)	307.30 (79.08)	
Median	282.52	300.24	
(Min, Max)	(90.00, 451.20)	(151.06, 440.74)	
Geometric Mean (CV%)	262.4 (30.38)	295.9 (25.73)	
LS Geometric Mean	257.2	290.0	0.035
(90% CI of LS Geometric Mean)	(235.1, 281.5)	(265.1, 317.3)	
Reference Treatment: Two SST 15 mcg			
Ratio of LS Geometric Mean	0.89	NA	
90% CI of Ratio	(0.81, 0.97)		

Reference ID: 4151649

Name of Sponsor/Company: AcelRx Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	**Volume:**	
Name of Active Ingredients: Sufentanil Citrate	**Page:**	

C_{max} (pg/mL) Mean (SD) Median (Min, Max) Geometric Mean (CV%) LS Geometric Mean (90% CI of LS Geometric Mean) **Reference Treatment: Two SST 15 mcg** Ratio of LS Geometric Mean 90% CI of Ratio	63.14 (23.49) 61.50 (21.00, 118.00) 59.1 (37.21) 56.8 (51.4, 63.4) 0.93 (0.84, 1.03)	66.00 (20.38) 64.80 (37.40, 115.00) 62.8 (30.88) 60.9 (55.1, 68.0) NA	0.238
T_{max} (hour) Mean (SD) Median (Min, Max) LS Mean (SEM) (90% CI of LS Mean) **Reference Treatment: Two SST 15 mcg** LS Mean Difference (SEM) 90% CI of Difference	0.95 (0.33) 1 (0.50, 2.00) 0.97 (0.06) (0.86, 1.07) -0.24 (0.06) (-0.34, -0.14)	1.19 (0.36) 1.17 (0.67, 2.00) 1.20 (0.06) (1.10, 1.31) NA	<0.001
K_{el} (1/hour) Mean (SD) Median (Min, Max) LS Mean (SEM) (90% CI of LS Mean) **Reference Treatment: Two SST 15 mcg** LS Mean Difference (SEM) 90% CI of Difference	0.090 (0.069) 0.049 (0.020, 0.276) 0.087 (0.012) (0.067, 0.107) 0.019 (0.013) (-0.003, 0.040)	0.071 (0.065) 0.051 (0.016, 0.294) 0.069 (0.012) (0.049, 0.088) NA	0.151
$t_{1/2}$ (hour) Mean (SD) Median (Min, Max) LS Mean (SEM) (90% CI of LS Mean) **Reference Treatment: Two SST 15 mcg** LS Mean Difference (SEM) 90% CI of Difference	13.37 (8.89) 14.22 (2.52, 34.39) 13.89 (1.59) (11.20, 16.59) -2.35 (2.17) (-6.03, 1.33)	15.66 (9.38) 13.66 (2.36, 42.69) 16.24 (1.59) (13.55, 18.94) NA	0.288

Reference ID: 4151649

$CST_{1/2}$ (hour)			
Mean (SD)	2.49 (0.85)	2.49 (0.88)	
Median	2.33	2.33	
(Min, Max)	(0.83, 4.83)	(0.83, 4.83)	
LS Mean (SEM)	2.50 (0.16)	2.49 (0.16)	0.969
(90% CI of LS Mean)	(2.23, 2.76)	(2.23, 2.76)	
Reference Treatment: Two SST 15 mcg			
LS Mean Difference (SEM)	0.01 (0.17)	NA	
90% CI of Difference	(-0.27, 0.29)		

Note: Two SST 15 mcg was used as the reference treatment for comparison.
ANOVA = analysis of variance; CI = confidence interval; CV% = coefficient of variation; IV = intravenous; LS = least squares; Max = maximum; Min = minimum; n = number of subjects in subset; NA = not applicable; SD = standard deviation; SEM = standard error of mean; SST = sufentanil sublingual tablet
These estimates were obtained from the ANOVA model that included sequence, period, and treatment fixed factors and subject within sequence random factor.
a Treatment B: Single dose of SST 30 mcg
b Treatment C: 2 consecutive doses of SST 15 mcg administered 20 minutes apart
c The p-value (overall) for the comparison between two treatments was based on Type III analysis from the model described above.

Summary of CL of Sufenta IV 30 mcg (Treatment A), Absolute Amount of Sufentanil Absorbed, and Bioavailability of Treatments B and C

Pharmacokinetic Parameter	Treatment			
	Sufenta IV[a] 30 mcg	Single SST[b] 30 mcg	Two SST[c] 15 mcg	p-value
Clearance (mL/hour)				
n	35	0	0	NA
Mean (SD)	57878 (11446)			
Median	57723			
(Min, Max)	(38082, 77521)			
Absolute Amount Absorbed (mcg)				
n	35	35	35	<0.001[d]
Mean (SD)	30.0 (0.0)	15.9 (5.2)	17.6 (5.2)	
Median	30	15.9	17.7	
(Min, Max)	(30.0, 30.0)	(6.1, 28.5)	(7.7, 29.5)	
F (%)[e]				
n		35	35	

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Mean (SD) Median (Min, Max) LS Mean (SEM) (90% CI of LS Mean) **Reference Treatment: Two SST 15 mcg** LS Mean Difference (SEM) 90% CI of Difference		52.86 (17.22) 53.10 (20.30, 94.90) 52.25 (3.14) (46.93, 57.57) -6.00 (2.59) (-10.39, -1.62)	58.76 (17.50) 58.90 (25.60, 98.20) 58.26 (3.14) (52.94, 63.58) NA	0.027[f]

ANOVA = analysis of variance; CI = confidence interval; F = bioavailability; LS = least squares; Max = maximum; Min = minimum; n = number of subjects in subset; NA = not applicable; SD = standard deviation; SEM = standard error of the mean; SST = sufentanil sublingual tablet
a Treatment A: Sufenta IV (50mcg/mL) 30 mcg infused over 1 minute
b Treatment B: Single dose of SST 30 mcg
c Treatment C: 2 consecutive doses of SST 15 mcg administered 20 minutes apart
d The p-value for the overall comparison among treatment groups was based on the F-test of Type III treatment factor from the ANOVA model including only the treatment factor for numeric data.
e Two SST 15 mcg treatment was used as the reference treatment for comparison.
f The p-value (overall) for the comparison between 2 treatments was based on Type III analysis from the ANOVA model that included sequence, period, and treatment fixed factors, and subject within sequence random factor.

Pharmacokinetic Analysis of Sufentanil $AUC_{0\text{-}inf}$, C_{max}, and T_{max} for Treatments B and D

Pharmacokinetic Parameter	Treatment	
	Single SST[a] 30 mcg (n = 32)	**Multiple SST[b] 30 mcg (n = 32)**
$AUC_{0\text{-}inf}$ (h*pg/mL) Mean (SD) Median (Min, Max) Geometric Mean (CV%) (90% CI of Geometric Mean)	269.82 (79.51) 280.37 (90.00, 451.20) 257.24 (29.47) (232.76, 284.29)	2022.81 (532.80) 1915.44 (1400.71, 3877.52) 1958.63 (26.34) (1826.21, 2100.65)
Normalized to Single SST[a] 30mcg **$AUC_{0\text{-}inf}$ (h*pg/mL)** Mean (SD) Median (Min, Max) Geometric Mean (CV%)	269.82 (79.51) 280.37 (90.00, 451.20) 257.24 (29.47)	168.57 (44.40) 159.62 (116.73, 323.13) 164.02 (26.34)

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(90% CI of Geometric Mean)	(232.76, 284.29)	(152.93, 175.91)
Reference Treatment: Single SST 30 mcg		
Ratio of Geometric Mean	NA	0.64
90% CI of Ratio		(0.58, 0.70)
p-value[c]		<0.001
C_{max} (pg/mL)		
Mean (SD)	60.55 (22.65)	150.78 (36.40)
Median	58.60	153.50
(Min, Max)	(21.00, 118.00)	(98.90, 278.00)
Geometric Mean (CV%)	56.26 (37.40)	146.94 (24.14)
(90% CI of Geometric Mean)	(50.40, 63.43)	(137.00, 157.59)
Reference Treatment: Single SST 30 mcg		
Ratio of Geometric Mean	NA	2.61
90% CI of Ratio		(2.32, 2.92)
p-value[c]		<0.001
T_{max} (hour)		
Mean (SEM)	0.98 (0.06)	8.82 (0.51)
SD	0.36	2.87
Median	1.00	8.92
(Min, Max)	(0.50, 2.00)	(3.92, 12.33)
(90% CI of Mean)	(0.87, 1.09)	(7.96, 9.68)
Reference Treatment: Single SST 30 mcg		
Mean Difference (SEM)	NA	7.84 (0.51)
90% CI of Difference		(6.97, 8.70)
p-value[c]		<0.001

Note: Single SST 30 mcg treatment was used as the reference treatment for comparison.
CI = confidence interval; CV% = coefficient of variation in percent; Max = maximum; Min = minimum; n = number of subjects in subset; NA = not applicable; SD = standard deviation; SEM = standard error of the mean; SST = sufentanil sublingual tablet
a Treatment B: Single dose of SST 30 mcg
b Treatment D: Multiple (12 consecutive) doses of SST 30 mcg administered 1 hour apart
c The p-value for the test of mean change from single SST 30 mcg to multiple SST 30 mcg was based on the paired t-test.

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Name of Sponsor/Company: AcelRx Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	**Volume:**	
Name of Active Ingredients: Sufentanil Citrate	**Page:**	

Pharmacokinetic Analysis of Sufentanil AUC_{0-60}, AUC_{0-720}, C_{max}, C_{min}, T_{max}, K_{el}, $t_{1/2}$, and $CST_{1/2}$ for Treatment B and Last Dose of Treatment D

Pharmacokinetic Parameter	Treatment	
	Single SST[a] 30 mcg (n = 32)	Last Multiple SST[b] 30 mcg (n = 32)
AUC_{0-60} (h*pg/mL)		
Mean (SD)	33.71 (16.23)	118.25 (34.45)
Median	31.89	115.47
(Min, Max)	(9.22, 79.27)	(46.52, 223.30)
Geometric Mean (CV%)	30.27 (48.15)	113.30 (29.13)
(90% CI of Geometric Mean)	(26.31, 34.81)	(103.54, 123.97)
Reference Treatment: Single SST 30 mcg		
Ratio of Geometric Mean	NA	3.74
90% CI of Ratio		(3.25, 4.31)
p-value[c]		<0.001
AUC_{0-720} (h*pg/mL) of Treatment B versus AUC_{0-60} (h*pg/mL) of Last Treatment D		
Mean (SD)	196.26 (61.76)	118.25 (34.45)
Median	185.70	115.47
(Min, Max)	(60.15, 380.73)	(46.52, 223.30)
Geometric Mean (CV%)	186.79 (31.47)	113.30 (29.13)
(90% CI of Geometric Mean)	(169.02, 206.44)	(103.54, 123.97)
Reference Treatment: Single SST 30 mcg		
Ratio of Geometric Mean	NA	0.61
90% CI of Ratio		(0.55, 0.68)
p-value[c]		<0.001
C_{max} (pg/mL)		
Mean (SD)	60.55 (22.65)	134.12 (39.51)
Median	58.60	135.00
(Min, Max)	(21.00, 118.00)	(48.90, 244.00)
Geometric Mean (CV%)	56.26 (37.40)	127.74 (29.46)
(90% CI of Geometric Mean)	(50.40, 63.43)	(116.75, 141.17)
Reference Treatment: Single SST 30 mcg		
Ratio of Geometric Mean	NA	2.27
90% CI of Ratio		(2.01, 2.56)
p-value[c]		<0.001
C_{min} (pg/mL)		
Mean (SD)	NA	103.38 (30.78)
Median		103.00
(Min, Max)		(44.20, 207.00)

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Name of Sponsor/Company: AcelRx Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	**Volume:**	
Name of Active Ingredients: Sufentanil Citrate	**Page:**	

Geometric Mean (CV%) (90% CI of Geometric Mean)		99.48 (29.77) (90.92, 108.85)
T_{max} (hour) Mean (SEM) SD Median (Min, Max) (90% CI of Mean) **Reference Treatment: Single SST 30 mcg** Mean Difference (SEM) 90% CI of Difference p-value[c]	 0.98 (0.06) 0.36 1.00 (0.50, 2.00) (0.87, 1.09) NA	 0.72 (0.05) 0.28 0.67 (0.33, 1.33) (0.64, 0.80) -0.26 (0.07) (-0.38, -0.14) <0.001
K_{el} (1/hour) Mean (SEM) SD Median (Min, Max) (90% CI of Mean) **Reference Treatment: Single SST 30 mcg** Mean Difference (SEM) 90% CI of Difference p-value[c]	 0.085 (0.012) 0.068 0.048 (0.020, 0.276) (0.065, 0.106) NA	 0.060 (0.004) 0.020 0.058 (0.026, 0.131) (0.054, 0.066) -0.025 (0.012) (-0.046, -0.004) 0.052
$t_{1/2}$ (hour) Mean (SEM) SD Median (Min, Max) (90% CI of Mean) **Reference Treatment: Single SST 30 mcg** Mean Difference (SEM) 90% CI of Difference p-value[c]	 14.12 (1.61) 9.09 14.50 (2.52, 34.39) (11.40, 16.85) NA	 12.68 (0.76) 4.31 12.01 (5.30, 26.91) (11.38, 13.97) -1.45 (1.60) (-4.16, 1.27) 0.373
$CST_{1/2}$(hour) Mean (SEM) SD Median (Min, Max) (90% CI of Mean) **Reference Treatment: Single SST 30 mcg** Mean Difference (SEM) 90% CI of Difference	 2.50 (0.15) 0.85 2.33 (0.83, 4.83) (2.25, 2.76) NA	 2.50 (0.13) 0.72 2.33 (1.67, 5.67) (2.28, 2.71) 0.00 (0.20) (-0.34, 0.33)

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p-value[c]		0.988

Note: Single SST 30 mcg treatment was used as the reference treatment for comparison.
CI = confidence interval; CV% = coefficient of variation in percent; LS = least squares; Max = maximum; Min = minimum; n = number of subjects in subset; NA = not applicable; SD = standard deviation; SEM = standard error of the mean; SST = sufentanil sublingual tablet
a Treatment B: Single dose of SST 30 mcg
b Treatment D: Multiple (12 consecutive) doses of SST 30 mcg administered 1 hour apart
c The p-value for the test of mean change from single SST 30 mcg to multiple SST 30 mcg was based on the paired t-test.

Analysis of Steady State

Dose Number	Time point (minutes)	N	Geometric LS means	Ratio of Geometric LS Means	90% CI of Ratio (%)	p-value[a]
2	60	34	44.27	0.419	(0.381, 0.460)	<0.001
3	120	34	87.96	0.811	(0.737, 0.891)	<0.001
5	240	34	119.71	1.121	(1.019, 1.234)	0.050
7	360	34	102.31	0.950	(0.862, 1.047)	0.386[b]
8	420	34	110.20	1.029	(0.932, 1.137)	0.629
9	480	34	124.99	1.230	(1.110, 1.362)	<0.001
10	540	34	114.47	1.195	(1.072, 1.332)	0.007
11	600	34	92.81	0.939	(0.828, 1.064)	0.405
12	660	34	98.89			

CI = confidence interval; LS = least squares; N = number of subjects;
a p-value was for testing if the corresponding ratio of geometric LS means was 1.
b The first nonsignificant comparison at the 0.1 level.
An analysis of variance was performed with the natural log-transformed predose concentrations as the dependent variable and time point as fixed effect. Ratio was for comparing the geometric mean concentration of the corresponding time point to the geometric mean concentrations pooled over all remaining time points.

After administration of either single-dose SST 30 mcg or 2 doses of SST 15 mcg, T_{max} was approximately 1 hour post dose, and C_{max} were similar. Upon reaching a peak concentration, sufentanil declined in a multiphasic manner until 24-hours post dose, the last time point. Following administration of single-dose SST 30 mcg or 2 doses of SST 15 mcg, the concentration-time profile of sufentanil were similar. Following

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administration of Sufenta IV 30 mcg, sufentanil concentrations were higher than after administration of single-dose SST 30 mcg or 2 doses of SST 15 mcg for the first 2-3 hours post dose, and following the first 2-3 hours, concentrations were approximately the same among all treatment groups.

T_{max} was similar following administration of either single-dose SST 30 mcg or 2 doses of SST 15 mcg. Median T_{max} following administration of single-dose SST 30 mcg was 1 hour compared to 1.17 hours after administration of 2 doses of SST 15 mcg. After 2 doses of SST 15 mcg, sufentanil reached a maximum concentration and then declined in a multiphasic manner until 24 hours post dose, the last time point.

After administration of single-dose SST 30 mcg and after the final dose of 12 consecutive doses of SST 30 mcg, a median T_{max} of 1 hour and 0.67 hour, respectively was observed. After reaching a maximum concentration, sufentanil declined in a multiphasic manner until 24 hours post dose after administration of multiple-dose SST 30 mcg and declined until 24 hours post dose after single-dose SST 30 mcg. Concentrations after administration of the final dose of multiple-doses SST 30 mcg were higher than after administration of single-dose SST 30 mcg.

<u>Treatment A versus Treatment B or Treatment C</u>

Systemic exposure for sufentanil, as $AUC_{0\text{-}inf}$ and C_{max}, was higher following administration of Sufenta IV 30 mcg compared to the systemic exposure following administration of either single-dose SST 30 mcg or 2 consecutive doses of SST 15 mcg.

Median $t_{1/2}$ after administration of Sufenta IV 30 mcg (12.48 hours) was shorter than after administration of SST 30 mcg (14.22 hours) or 2 consecutive doses of SST 15 mcg (13.66 hours). Median $CST_{1/2}$ after IV administration was 0.10 hours compared to 2.33 hours after administration of SST 30 mcg or 2 consecutive doses of SST 15 mcg.

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Treatment B versus Treatment C

There were no relevant differences between any PK parameter ($AUC_{0\text{-}inf}$, C_{max}, T_{max}, K_{el}, $t_{1/2}$, and $CST_{1/2}$) after administration of single-dose SST 30 mcg when compared to that of 2 consecutive doses of SST 15 mcg. $AUC_{0\text{-}inf}$ and C_{max} both had 90% CIs of the GMR that fell within the 0.8 to 1.25 range, supporting bioequivalence.

Mean F values were 52.86% and 58.76% after administration of single-dose SST 30 mcg and 2 doses of SST 15 mcg, respectively.

Treatment B versus Treatment D

$AUC_{0\text{-}inf}$ and C_{max} were higher after administration of multiple-dose (12 consecutive) SST 30 mcg compared after administration of single-dose SST 30 mcg.

Dose-normalized $AUC_{0\text{-}inf}$ was 57% lower after administration of multiple-dose SST 30 mcg compared to after single-dose SST 30 mcg.

Median T_{max} was 8.92 hours after administration of multiple-dose SST 30 mg compared to 1.00 hour after administration of single dose SST 30 mcg.

Treatments B versus the Last Dose of Treatment D

Geometric mean $AUC_{0\text{-}60}$ of the last dose for multiple-dose SST 30 (113.30 h*pg/mL) was greater compared to single-dose SST 30 mcg (30.27 h*pg/mL) and lower compared to $AUC_{0\text{-}720}$ for single-dose SST 30 mcg (186.79 h*pg/mL).

Geometric mean C_{max} of the last dose administered for multiple-dose SST 30 mcg (127.74 pg/mL) was higher compared to single-dose SST 30 mcg (56.26 pg/mL). Median T_{max} after the last dose for multiple-dose SST 30 mcg was 0.67 hours compared to 1.0 hour for single-dose SST 30 mcg. Median $t_{1/2}$ after the last of 12 oral doses of SST 30 mcg was approximately 12 hours compared to approximately 14 hours for single-dose SST 30 mcg. Median $CST_{1/2}$ was 2.33 hours regardless of whether observed after a

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single-dose or multiple-dose SST 30 mcg.

Steady-State Analysis

Analysis using Helmert's method, for subjects who received Treatment D, indicated that steady state was achieved by 7 doses (or 360 minutes) of SST 30 mcg.

Safety Results:

Since study drug was administered under a naltrexone block, potential AEs associated with naltrexone could have contributed to the overall AE profile, and AEs potentially due to sufentanil effects at the mu opioid receptor would be reduced due to the naltrexone block.

In general, SST 30 mcg was safe and well tolerated when administered as single or multiple doses.

There were no deaths or serious AEs reported during the study. Two subjects discontinued from the study due to treatment-related AEs. Subject (b) (6) experienced an AE of nausea that was mild in severity and considered probably related to study drug. Subject (b) (6) experienced an AE of lip swelling that was moderate in severity and considered possibly related to Treatment C.

All treatment-emergent AEs were mild in severity, with the exception of 1 subject who experienced a moderate AE of lip swelling after administration of Treatment C.

Twelve of 40 subjects (30.0%) reported a total of 23 AEs after administration of Sufenta IV. The most frequently reported AEs after Sufenta IV administration were gastrointestinal disorders (9 subjects [22.5%]), including nausea (5 subjects [12.5%]), and nervous system disorders (5 subjects [12.5%]), including dizziness (5 subjects [12.5%]).

Nine of 39 subjects (23.1%) reported a total of 10 AEs after administration of single-dose SST 30 mcg. The most frequently reported AEs after single-dose SST 30 mcg administration were gastrointestinal disorders (7 subjects [17.9%]), including dyspepsia (3 subjects [7.7%]), and psychiatric disorders (2 subjects [5.1%]), including euphoric mood (2 subjects [5.1%]).

Seven of 39 subjects (17.9%) reported a total of 9 AEs after administration of 2 doses of SST 15 mcg. The most frequently reported AEs after 2 doses of SST 15 mcg were nervous system disorders (3 subjects [7.7%]), including dizziness (2 subjects [5.1%]), and gastrointestinal disorders (3 subjects [7.7%]).

Twelve of 34 subjects (35.3%) reported a total of 14 AEs while receiving multiple-dose SST 30 mcg. The most frequently reported AEs after multiple-dose SST 30 mcg were nervous system disorders (6 subjects [17.6%]), including headache (4 subjects [11.8%]), and gastrointestinal disorders (4 subjects [11.8%]), including constipation (2 subjects [5.9%]).

Concomitant medications were administered to 7 subjects for treatment of AEs. These included 5 reports of headache, 2 reports of nausea, 1 report of lip swelling, and 1 report of limb discomfort. All other events resolved with no additional treatment.

There were no clinically significant findings in clinical laboratory tests, vital signs measurements, or ECGs that were considered related to study drug.

Conclusions:

SST Administration versus Sufenta IV Administration

- Systemic exposure of sufentanil after Sufenta IV 30 mcg was greater than after single-dose SST 30 mcg. The mean F value was approximately 53% for a single dose of SST 30 mcg.

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- Median $t_{1/2}$ was 14.22 hours after single-dose SST 30 mcg compared to 12.48 hours after administration of Sufenta IV 30 mcg ($p = 0.841$).
- Median $CST_{1/2}$ was 2.33 hours after administration of either single-dose SST 30 mcg or 2 consecutive doses of SST 15 mcg compared to 0.10 hours following Sufenta IV 30 mcg ($p < 0.001$).

Single–dose SST 30 mcg versus 2 Doses of SST 15 mcg

- PK parameters were similar after administration of single-dose SST 30 mcg dose compared to after administration of 2 doses of SST 15 mcg (with 20 minutes between doses). Both C_{max} and $AUC_{0\text{-}inf}$ were bioequivalent for single-dose SST 30 mcg and 2 doses of SST 15 mcg (with 20 minutes between doses).
- Systemic availability after administration of single-dose SST 30 mcg dose was approximately the same as after administration of 2 doses of SST 15 mcg. Mean bioavailability was approximately 53% after single-dose SST 30 mcg and 59% after 2 doses of SST 15 mcg ($p = 0.027$).
- Median T_{max} was 1 hour after administration of single-dose SST 30 mcg and 1.17 hours after administration of 2 doses of SST 15 mcg ($p<0.001$).
- Median $t_{1/2}$ and $CST_{1/2}$ after administration of single-dose SST 30 mcg were 14.22 hours and 2.33 hours, which were similar to the corresponding values after administration of 2 doses of SST 15 mcg (13.66 hours and 2.33 hours, respectively).

Single-dose versus Multiple-dose SST 30 mcg

- Sufentanil concentrations accumulated upon multiple dosing. After the last of 12 consecutive doses of SST 30 mcg, $AUC_{0\text{-}60}$ and C_{max} increased by 3.7 fold and 2.3 fold, respectively, compared to after the first dose. These increases were statistically significant ($p < 0.001$).
- $AUC_{0\text{-}60}$ of the last dose after administration of multiple-dose SST 30 mcg doses was lower by approximately 40% compared to $AUC_{0\text{-}720}$ after administration of single-dose SST 30 mcg, and this decrease was statistically significant ($p < 0.001$).

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Name of Sponsor/Company: AcelRx Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Products: Sufentanil Sublingual Tablet (15 mcg and 30 mcg)	**Volume:**	
Name of Active Ingredients: Sufentanil Citrate	**Page:**	
• Upon multiple dosing, steady state was achieved by 7 doses (or 360 minutes) of SST 30 mcg based on the predose plasma concentration data analyzed according to Helmert's method. • In general, SST 30 mcg was safe and well tolerated when administered as single or multiple sublingual doses.		
Date of Report: 1 December 2014		

Reference ID: 4151649

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/s/

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