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APPLICATION NUMBER:

209128Orig1s000

CLINICAL REVIEW(S)

Combined Cross-Discipline Team Leader Review And Summary Review for Regulatory Action

Date	(electronic stamp)
Cross-Discipline Team Leader	Joshua Lloyd, MD
Division Director	Sharon Hertz, MD
NDA	209128
Applicant	AcelRx Pharmaceuticals, Inc.
Date of Submission	December 12, 2016
PDUFA Goal Date	October 12, 2017
Proprietary Name / Established (USAN) names	Dsuvia / Sufentanil
Dosage form / Strength	Sublingual tablet / 30 mcg
Proposed Indication(s)	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
Recommended:	Complete Response

1. Introduction

AcelRx Pharmaceuticals, Inc. submitted this 505(b)(2) new drug application (NDA) for Dsuvia, a drug-device combination product containing 30 mcg of the potent opioid agonist, sufentanil, for use as an analgesic in a medically-supervised setting. The product is intended to be administered by a healthcare provider on an as-needed basis with a minimum interval of one hour between doses.

The NDA references the agency's prior finding of safety and efficacy for Sufenta (sufentanil citrate for injection; NDA 19050; Akorn, Inc.), which was approved in 1984 and is indicated for intravenous administration in adults and pediatric patients as an adjunctive and a primary anesthetic and for epidural administration as an analgesic in the setting of labor and vaginal delivery. Sufentanil is currently only approved as a solution for injection. However, the Applicant previously submitted (b) (4) for Zalviso, another sufentanil sublingual tablet drug-device combination product that, in contrast to Dsuvia, contains 15 mcg of sufentanil and was intended to be administered by the patient using a different device. The Zalviso application received a complete response, primarily due to issues surrounding the device and inadvertent loss of dispensed tablets.

The application is supported by data from a Phase 3 placebo-controlled trial, two Phase 3 open-label studies[1], and the Zalviso program, as well as CMC/device, pharmacology/ toxicology, clinical pharmacology, and human factors data.

[1] The clinical development program was conducted under IND 113059.

2. Background

Sufentanil is a Schedule II synthetic opioid agonist that is approximately five to ten times more potent than fentanyl at the mu-opioid receptor and, like fentanyl, has low oral bioavailability. Dsuvia was developed as a healthcare professional (HCP)-administered product designed to deliver sufentanil via the sublingual route using a single dose applicator (SDA) to provide acute onset of analgesia without having to establish intravenous (IV) access. The Applicant states that the product may be useful in situations where IV access may be limited or is otherwise not desirable.

The Division held End-of-Phase 2 and Pre-NDA meetings with the Applicant during clinical development where, among other things, agreement was reached on the amount of safety data that would be required for an NDA. Further, agreement was reached that the safety of Dsuvia may, in part, be supported by patients who were administered two doses of Zalviso 15 mcg, given 20 minutes apart, provided that clinical pharmacology data support that similar exposures to sufentanil are observed compared to a single dose of Dsuvia 30 mcg.

3. CMC/Biopharmaceutics/Device

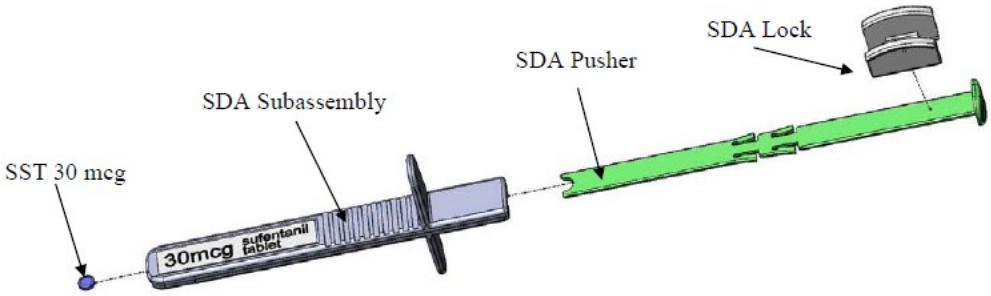
CMC

The drug component of this drug-device combination product consists of an immediate-release sublingual tablet containing 30 mcg of sufentanil. DMF (b) (4) for the drug substance was found to be adequate.

The tablet measures 3 mm in diameter and 0.85 mm in thickness with a nominal tablet weight of 7.40 mg. All of the excipients are compendial and tested to USP requirements. Each disposable single dose applicator (SDA) contains one tablet and is intended for single use. The primary package consists of the SDA co-packaged with an oxygen absorber –StabilOX– in a labeled, (b) (4) laminate foil pouch.

Figure 3.2.P.7.2: 1 Single Dose Applicator

Figure 3.2.P.7.2: 2 SDA Exploded View with Components



A chipped tablet was found during stability at the initial time point. However, the CMC team found this to be acceptable, as the Applicant has sampling plans in place that will reject a defective batch 90% of the time, which CMC deemed to be an appropriate industry standard.

The drug product specifications will include residual (b) (4), at the request of the CMC team, until sufficient data are attained to confirm understanding and control of the process. At that point, the Applicant would be able to submit a prior approval supplement to remove this testing from the specifications.

Biopharmaceutics

The proposed dissolution method and acceptance criterion were found to be adequate.

CMC, based on recommendations from drug substance, drug product, process, facilities, and biopharmaceutics reviewers, recommends approval of this application, and I concur with their conclusions. The manufacturing facilities were deemed acceptable. A (b) (4) month expiry at 20° to 25°C with excursions to 15° to 30°C was granted. The request for a categorical exclusion from the requirement to prepare an environmental assessment was determined to be acceptable. The Applicant included a post-approval stability protocol and commitment testing stability out to 36 months.

Device

The device constituent of this product consists of the SDA, which is intended for storage and to deliver sufentanil to the sublingual space. The HCP is directed to remove the SDA lock, place the SDA tip under the patient's tongue, and depress the green pusher to administer the sufentanil tablet to the sublingual space.

CDRH was consulted, and their evaluation included the following areas:

- Design controls, verification/validation, and risk analysis
- Biocompatibility of the SDA with respect to the sublingual space
- Environment of use

CDRH determined that adequate documentation was provided to support the design control process and found the performance requirements to be adequate. The expiry and shelf-life are (b) (4) However, the CDRH reviewer stated that "[t]he [Applicant] has 18-months chemical stability and functional testing of the finished device, including device performance and has conducted 3 year accelerated aging studies. The real-time 3 year aging studies are ongoing and will be requested as a post approval commitment."

The design validation review consisted of an evaluation of device failures in the clinical study; human factors were evaluated separately.[2] The Applicant evaluated clinical device usability and reliability in the context of the Phase 3 clinical study, SAP303. There were three suspected SDA failures, which consisted of two instances of the tablet missing from the SDA or loose within the pouch and one instance of a dropped tablet by the HCP prior to dosing the patient. In the case of the dropped tablet, the tablet was found and secured. In the case involving a tablet missing from the SDA, the Applicant determined that a manufacturing error had occurred. In the case involving a loose tablet in the pouch, the Applicant determined that the HCP unsuccessfully attempted to open the pouch using scissors and subsequently tore open the package, which resulted in actuation of the SDA. The Applicant also evaluated usability through a questionnaire in this study. However, the questionnaire was administered to nine HCPs only. The CDRH device reviewer determined this to be insufficient to establish usability and deferred to the human factors review. However, the CDRH device reviewer noted that device-specific failures were low across all three Phase 3 clinical studies and were eliminated as development continued.

It is worth noting that the original device iteration was used in the two Phase 3 studies (SAP301 and SAP302), and both the original and revised device iterations were used in the third Phase 3 study (SAP303). The revised device iteration incorporated minor changes to optimize usability and manufacturing, and CDRH determined that these changes do not impact the results of the clinical study and were properly evaluated.

[2] The CDRH device review notes that a separate CDRH human factors consult was performed by Xin Feng in CDRH. However, Carolyn Dorgan, the lead CDRH reviewer confirmed over email on 10/6/2017 that a separate CDRH human factors review was not needed.

The Applicant conducted design verification testing under a variety of conditions. In mouth testing demonstrated that 100% of tablets were delivered to the mouth (acceptance criterion ≥99%); however, only 93.1% were delivered to the sublingual space (acceptance criterion ≥95%) with four tablets landing inside the cheek and one on a tooth. The Applicant found these results acceptable because delivery to the areas of the mouth other than the sublingual space will still result in bioavailability in the range observed with sublingual delivery, none were swallowed (which would result in very low bioavailability), and that this study was intended to be a design verification test rather than a validation test. Design validation will occur in the context of human factors testing. The CDRH reviewer noted that "[t]he [Applicant] has identified the critical performance attribute and design requirements per the design control procedures. The attributes were then verified…All device[s] met the product requirement[s] within the predetermined acceptance criteria."

The biocompatibility reviewer noted cytotoxicity, sensitization, intradermal irritation, and oral irritation assessments conducted by the Applicant and found them to be acceptable.

CDRH notes that "[t]he Sponsor's risk analysis and hazard identification processes have adequately captured the use and design risks associated with the device. The lead reviewer concurs with the mitigations for the use and design related risks. All risks have been reduced to as low a level as possible. Therefore [this] is acceptable." CDRH found the batch release criteria for the SDA to be acceptable. The CDRH device and biocompatibility review teams recommended approval for the device constituent of the product with the following post-marketing commitment:

> Provide real time stability data for the SDA Dispensing Test according to the protocols described in the Post-approval Stability Protocol and Stability Commitment located in Seq 0000/3.2.P.8.2 of NDA 209128.

The CDRH Office of Compliance has recommended post-approval inspections of AcelRx Pharmaceuticals and (b) (4) recommended approval from the perspective of the applicable quality system requirements described under the 21 CFR Part 820 regulations.

I concur with the conclusions reached by the CDRH review team that there are no outstanding CDRH issues that preclude approval.

Human Factors

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors validation study results. The human factors validation study was conducted in 45 untrained participants that included 15 PACU/floor nurses, 15 ER nurses, and 15 paramedics. Participants were provided the directions for use (DFU) and were instructed to read the DFU prior to attempting the tasks. Each participant was asked to administer the medication four times. Three of the scenarios involved administration to three different mock patients, and, in the fourth scenario, participants were given torn packaging and asked to administer the medication to a mock patient to see how this situation may be handled with real-world use. At

the end of the session participants responded to questions regarding important warnings and precautions or critical safety information in the DFU.

DMEPA identified failures related to both essential and critical tasks. DMEPA noted eight failures associated with a critical task to confirm tablet placement in the patient's sublingual space. Failures related to this task are of critical importance because, if an HCP does not confirm accurate placement of the tablet in the sublingual space, a dropped tablet may go undetected. Sufentanil is a highly potent opioid, and dropped tablets pose significant risks to both the patient and others who may knowingly or unknowingly come in contact with the tablet. These risks include overdose and death due to accidental exposure in contacts, improper dosing in patients (i.e., over- or under-dosing and their associated risks), and the risk of diversion and its associated public health consequences. As a result, DMEPA recommended changes to the DFU that will require another human factors validation study to evaluate the effectiveness of the changes to address the observed use-related errors. DMEPA also noted additional failures involving critical and essential tasks for which they did not have any recommendations and found the residual risk to be acceptable.

I concur with the conclusions reached by the DMEPA review team; the outstanding human factors issues preclude approval at this time.

4. Nonclinical Pharmacology/Toxicology

To support a change in route of administration from the reference product, the Applicant conducted repeat-dose buccal irritation/toxicity studies in hamsters. The Applicant also submitted results from genetic toxicity studies for sufentanil impurities.

Dr. Lee notes that:

> The repeat-dose cheek pouch studies in hamsters demonstrated that buccally administered sufentanil showed no local tissue reactions in the cheek pouch. Genetic toxicology studies were conducted for the drug product degradants. Both (b) (4) of sufentanil-N-oxide tested negative in the in vitro bacterial reverse mutation assays and therefore, these impurities may be regulated as non-genotoxic impurities. Additionally, the Applicant has conducted in silico assessments using the DEREK and Leadscope programs on two other degradants (b) (4), and these analyses did not identify any potential mutagenic/genotoxic activity for either compound. CDER Office of Transitional Science evaluation confirmed the results of the Applicant's in silico analyses.
>
> Therefore, the proposed drug substance and drug product specifications are acceptable, the excipients have been adequately qualified for safety, and the nonclinical local tissue toxicity study results do not raise any safety concerns for the proposed indication.

I concur with the nonclinical review team that there are no pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology

The Applicant submitted the results of one clinical pharmacology study—SAP101—using the final to-be-marketed formulation. SAP101 was a randomized, open-label, crossover, comparative bioavailability study conducted in healthy adult volunteers who received naltrexone to block the pharmacodynamics effects of the opioid. The treatment groups consisted of:

- Sufentanil IV (Sufenta; 50 mcg/ml); 30 mcg infused over 1 minute
- Sufentanil sublingual tablet 30 mcg; single dose (Dsuvia)
- Sufentanil sublingual tablet 15 mcg; 2 doses administered 20 minutes apart (Zalviso)
- Sufentanil sublingual tablet 30 mcg; 12 doses administered 1 hour apart (Dsuvia)

SAP101 was conducted to establish a pharmacokinetic (PK) bridge between Dsuvia and the reference product, Sufenta, as the basis for relying on the agency's previous finding of safety and efficacy for Sufenta. The study was also intended to describe the multiple-dose PK for Dsuvia and to serve as the basis for referencing a select group of Zalviso-treated patients in support of the safety of Dsuvia.

The results of SAP101 demonstrated that the systemic exposure to sufentanil was lower with a single dose of Dsuvia than with Sufenta IV and that the absolute bioavailability of Dsuvia was 53%. A single dose of Dsuvia was bioequivalent to two doses of Zalviso administered 20 minutes apart, and the Tmax was comparable. The results are summarized in the table and figures below.

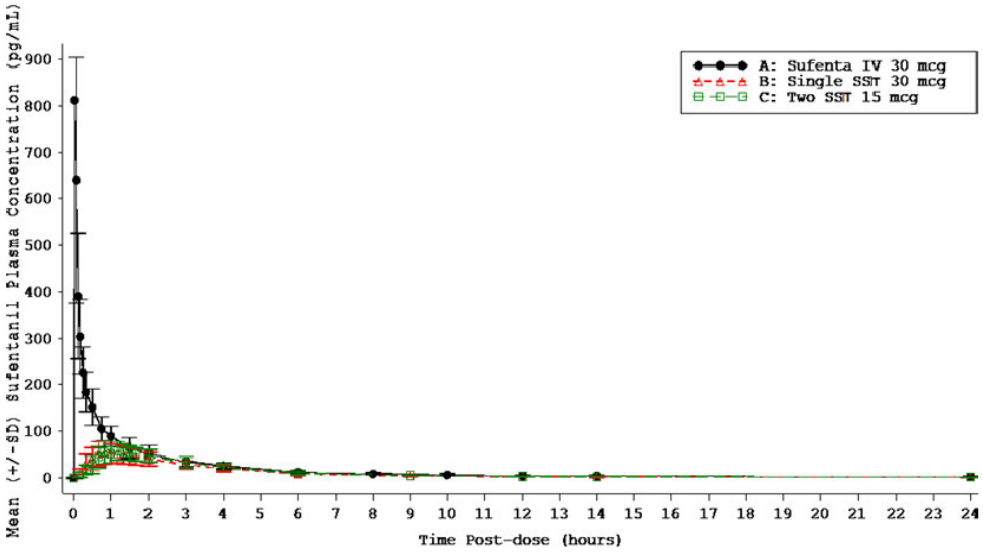
Mean ± SD (%CV) Sufentanil Pharmacokinetic Parameters for a Single Dose of Sufenta IV 30 mcg, a Single Sublingual Dose of Sufentanil Sublingual Tablet (SST) 30 mcg (Dsuvia), and Two Sublingual Doses of SST 15 mcg dosed 20 minutes apart (Zalviso) in Healthy Subjects under Naltrexone Block

PK Parameter	Sufenta IV 30 mcg (n = 35)	Dsuvia 30 mcg (n = 35)	Zalviso 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)

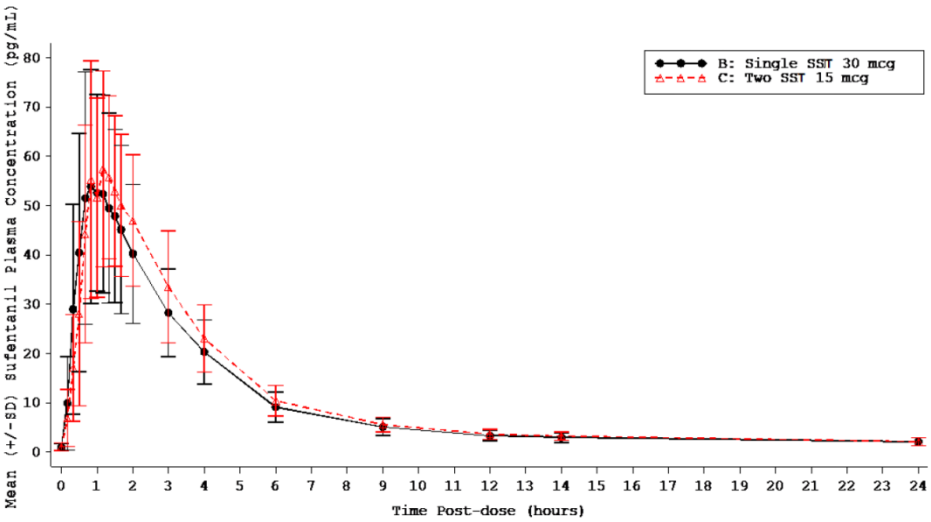
Adapted from Dr. Qiu's review, pg. 3

Mean (± SD) Sufentanil Plasma Concentration Versus Time for Treatments A (Sufenta IV 30 mcg), B (Sufentanil Sublingual Tablet [SST] 30 mcg; Dsuvia), and C (2 doses of SST 15 mcg dosed 20 minutes apart; Zalviso)



Adapted from Dr. Qiu's review, pg. 10

Mean (± SD) Sufentanil Plasma Concentration Versus Time for Treatments B (Sufentanil Sublingual Tablet [SST] 30 mcg; Dsuvia) and C (2 doses of SST 15 mcg dosed 20 minutes apart; Zalviso)

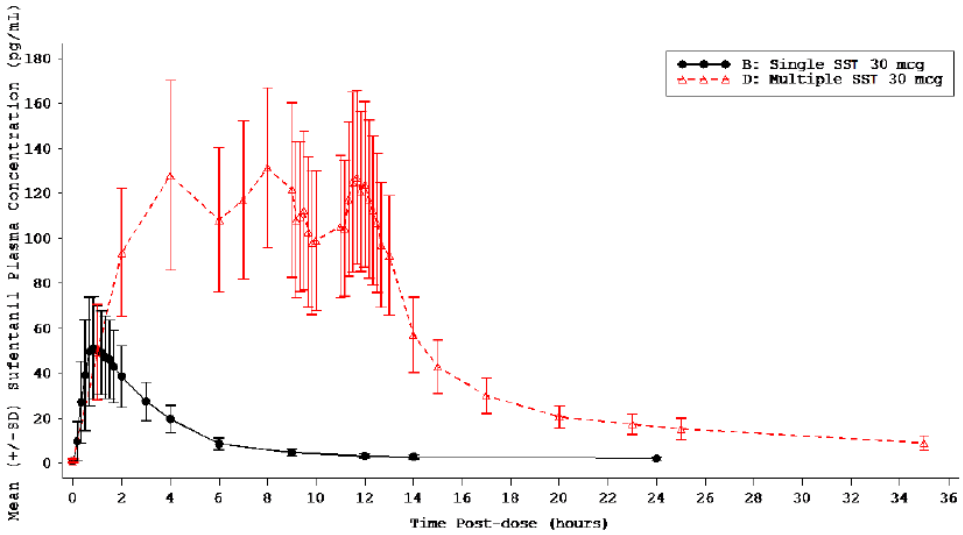


Adapted from Dr. Qiu's review, pg. 10

The Applicant also submitted PK modeling/simulation data, and, taken together with the above PK results, the clinical pharmacology review team concluded that these findings provide support to bridge the systemic safety results for two doses of Zalviso administered 20 to 25 minutes apart to Dsuvia.

Steady state was reached after seven doses of Dsuvia that were administered one hour apart (i.e., after 360 minutes) with the AUC within a dosing interval (i.e., AUC0-60 min) and Cmax values increased by 3.7 and 2.3 fold, respectively, after multiple dosing. Multiple dose PK results are summarized in the table and figure below.

Mean (± SD) Sufentanil Plasma Concentration versus Time for Treatments B (single dose Sufentanil Sublingual Tablet [SST] 30 mcg; Dsuvia) and D (12 x SST 30 mcg administered every hour; Dsuvia)



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.

Adapted from Dr. Qiu's review, pg. 13

Sufentanil Pharmacokinetic Parameters for Single Dose Sufentanil Sublingual Tablet (SST) 30 mcg (Treatment B; Dsuvia) and Multiple Dose SST 30 mcg (Treatment D: 12 x SST 30 mcg administered every hour; Dsuvia)

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)

Adapted from Dr. Qiu's review, pg. 13

The Applicant also submitted a population PK analysis, and the clinical pharmacology review team concluded that no dosage adjustments are required based on age or weight. Insufficient data are available in moderate or severe kidney or hepatic impairment. The Applicant did not evaluate the impact of hot, cold, and various pH liquids or the impact of mucositis on sufentanil PK. The Applicant has proposed to address this (b) (4) (b) (4) and the Division agreed to this approach during clinical development.

I concur with the conclusions reached by the clinical pharmacology review team that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The Applicant submitted the results of one Phase 3, randomized, double-blind, placebo-controlled trial that used the final to-be-marketed sufentanil formulation. Dr. Galati and Dr. Ren conducted a full review of this study, as it is the pivotal trial intended to demonstrate efficacy in acute pain for Dsuvia. I will review the salient study design features and describe the key efficacy results below.

Study SAP301

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil Sublingual Tablet 30 mcg for the Treatment of Post-Operative Pain in Patients after Abdominal Surgery

Primary objective: To compare the analgesic efficacy of Dsuvia to placebo in patients with acute moderate-to-severe pain following outpatient abdominal surgery

Duration of treatment: 48 hours

Population: Adults with moderate-to-severe acute postoperative pain following outpatient abdominal surgery, including abdominoplasty, open tension-free inguinal hernioplasty (Lichenstein repair with mesh), or laparoscopic abdominal surgery

Treatment: Patients were randomized in a 2:1 fashion to receive Dsuvia 30 mcg or placebo administered using the SDA as needed with a minimum of one hour between doses

Rescue medication: Morphine 1 mg IV, no sooner than 10 minutes after study drug administration and as long as the patient was not otherwise eligible to receive another dose of study drug

Design: The study was a multicenter (conducted at four sites in the U.S.), randomized, double-blind, placebo-controlled trial that consisted of a screening visit, an admission for surgery visit, and an up to 48-hour treatment period. Patients were allowed standard-of-care postoperative pain management but needed to have a postoperative pain intensity of ≥4 on an 11-point numeric rating scale (NRS) to be randomized. Patients who did not meet that criterion within 8 hours were discontinued. Patients who remained in the study for 24 or more

hours were considered completers. Patients were required to have a pain intensity of ≥4 on an NRS to continue treatment beyond 24 hours.

Primary efficacy endpoint: Time-weighted summed pain intensity difference (SPID) over 12 hours[3] based on an 11-point NRS (0-10)

Secondary efficacy endpoints: The Applicant included several secondary efficacy endpoints (refer to Dr. Galati's review), including the following:

- SPID24 and SPID48
- Pain intensity and pain intensity difference at each time point
- Proportion of patients requiring rescue
- Time to first use of rescue
- Total number of study medication and rescue medication doses used over the 48-hour study period
- Time to onset of perceptible and meaningful pain relief

Statistical analysis plan: The efficacy analyses were performed on the intent-to-treat (ITT) population, which included all randomized patients who received study drug. The primary efficacy analysis was an analysis of covariance (ANCOVA) model that used treatment, center, and sex as factors and baseline pain intensity score as a covariate. A pre-rescue pain intensity score was carried forward for one hour following the dosing of rescue medication. Regarding missing data, Dr. Ren noted that the Applicant's method was designed to not attribute a favorable pain score to a subject who discontinued early due to an adverse event or lack of efficacy, however, that it was a single imputation method, which is not desirable. Therefore, Dr. Ren performed a sensitivity analysis using a multiple imputation method.

Results: A total of 161 patients were randomized and received study drug. Most of the patients were under 65 and female; however, treatment groups were balanced with respect to baseline characteristics and demographics. Half of the surgeries were abdominoplasty with the remaining 30% laparoscopic abdominal surgery and 21% hernioplasty. Most Dsuvia-treated subjects completed the 12- and 24-hour treatment periods. As expected, fewer placebo-treated subjects completed those same periods due, in large part, to discontinuation due to lack of efficacy. Overall very few patients discontinued due to an adverse event. As the study progressed into the 24 to 48 hour treatment period, the vast majority of discontinuations were due to patients no longer requiring treatment. Patient disposition is summarized in the table below.

[3] Although a SPID24 or SPID48 are more typical for an acute pain setting, the Division agreed to a SPID12 in this particular outpatient surgery acute pain setting provided the Applicant continued to evaluate pain intensity for 48 hours.

Patient Disposition

	Sufentanil 30 mcg	Placebo	Total
Randomized	109	54	163
Did not receive treatment	2	0	2
Included in the ITT population for efficacy analyses	107 (100%)	54 (100%)	161 (100%)
12-Hour Study Period			
Completed the 12-hour study period	104 (97.2%)	43 (79.6%)	147 (91.3%)
Discontinued during the 12 hours	3 (2.8%)	11 (20.4%)	14 (8.7%)
Reason for discontinuation:			
Lack of efficacy	3 (2.8%)	8 (14.8%)	11 (6.8%)
Adverse event	0	2 (3.7%)	2 (1.2%)
Protocol Violation	0	1 (1.9%)	1 (0.6%)
24-Hour Study Period			
Completed the 24-hour study period	102 (95.3%)	41 (75.9%)	143 (88.8%)
Discontinued between 12 and 24 hours	2 (1.9%)	2 (3.7%)	4 (2.4%)
Reason for discontinuation:			
Lack of efficacy	1 (0.9%)	2 (3.7%)	3 (1.8%)
Withdrawal by subject	1 (0.9%)	0	1 (0.6%)
36-Hour Study Period			
Completed the 36-hour study period	22 (20.6%)	9 (16.7%)	31 (19.3%)
Completed 24 hours but did not enter the 36-hour study period	62 (57.9%)	28 (51.9%)	90 (55.9%)
Reason for not entering			
Patient discharged	49 (45.8%)	18 (33.3%)	67 (41.6%)
Recovery	13 (12.1%)	8 (14.8%)	21 (13.0%)
Lack of efficacy	0	2 (3.7%)	2 (1.2%)
Discontinued between 24 and 36 hours	18 (16.8%)	4 (7.4%)	22 (13.7%)
Reason for discontinuation:			
Recovery	15 (14.0%)	4 (7.4%)	19 (11.8%)
Lack of Efficacy	2 (1.9%)	0 (0.0%)	2 (1.2%)
Adverse event	1 (0.9%)	0 (0.0%)	1 (0.6%)
48-Hour Study Period			
Completed the 48-hour study period	10 (9.3%)	8 (14.8%)	18 (11.2%)
Completed 36 hours but did not enter the 48-hour study period	1 (1.9%)	0	1 (0.6%)
Reason for not entering			
Recovery	1 (0.9%)	0 (0.0%)	1 (0.6%)
Discontinued during the 48 hours	11 (10.3%)	1 (1.9%)	12 (7.5%)
Reason for discontinuation:			
Recovery	11 (10.3%)	0	11 (6.8%)
Withdrawal by subject	0	1 (1.9%)	1 (0.6%)

Source: Dr. Ren's Review, pp. 10-11

There was a statistically significant difference ($p < 0.001$) between treatment groups on the primary endpoint, time-weighted SPID12, as shown in the table below.

Primary Efficacy Analysis Results for SPID12

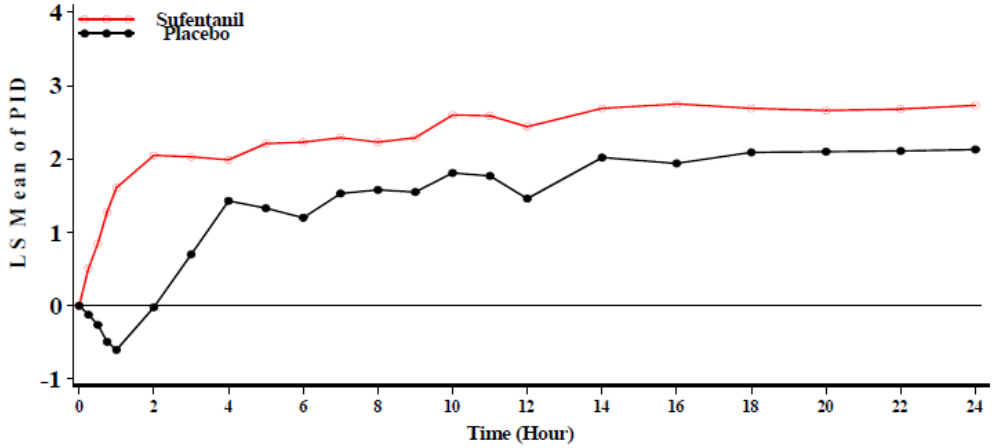
	Sufentanil (n=107)	Placebo (n=54)	P-value
Baseline Pain Intensity			
Mean (SD)	5.79 (1.75)	5.59 (1.56)	
Range	(3.00, 10.00)	(4.00, 9.00)	
LS mean (SEM)	5.87 (0.15)	5.73 (0.20)	
95% CI	(5.58, 6.17)	(5.34, 6.13)	
Difference			
LS mean (SEM)	0.14 (0.23)	NA	0.543
95% CI	(-0.31, 0.59)		
SPID12			
Mean (SD)	25.93 (20.25)	11.88 (19.47)	
Range	(-42.15, 71.87)	(-34.96, 64.37)	
LS mean (SEM)	26.36 (1.83)	13.66 (2.44)	
95% CI	(22.74, 29.98)	(8.83, 18.48)	
Difference			
LS mean (SEM)	12.70 (2.80)	NA	<0.001
95% CI	(7.17, 18.24)		

Source: Dr. Ren's review, pg. 12
SD: standard deviation
SEM: standard error of the LS mean

The results of Dr. Ren's sensitivity analysis to address the lack of a multiple imputation strategy were consistent with the primary analysis.

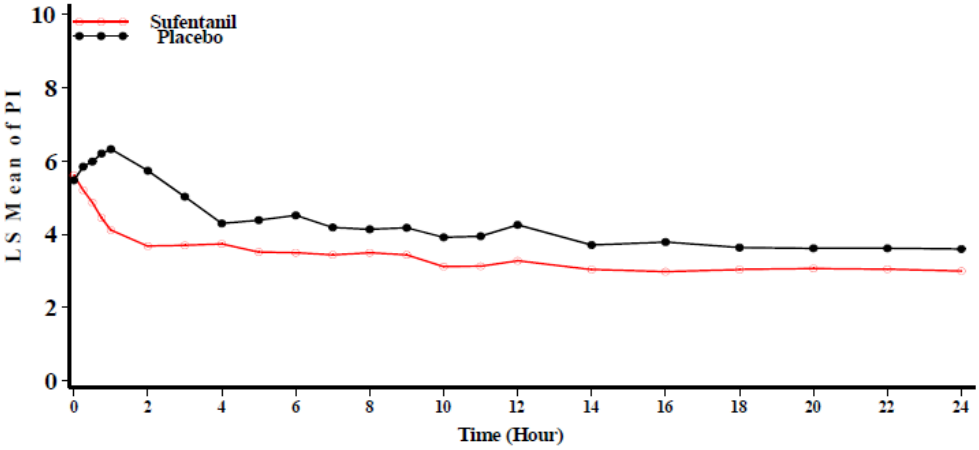
Pain intensity difference and pain intensity over the first 24 hours are summarized in the figures below, respectively.

Least Squares Mean of Pain Intensity Difference by Evaluation Time Point Over the 24-Hour Study Period: ITT Population



ITT: intent-to-treat; LS: least squares; PID: pain intensity difference.
Source: Applicant's Clinical Study Report for SAP301, pg. 67

Least Squares Mean of Pain Intensity by Evaluation Time Point Over the 24-Hour Study Period: ITT Population



ITT: intent-to-treat; LS: least squares; PI: pain intensity.
Source: Applicant's Clinical Study Report for SAP301, pg. 67

Dsuvia-treated patients required less rescue analgesics and had a longer time to first rescue use compared to placebo, which is consistent with a treatment effect favoring Dsuvia. Approximately 27% of patients required rescue medication in the Dsuvia group compared to approximately 65% in the placebo group in the first 24 hours. Dr. Ren performed a Kaplan-Meier analysis for time to first rescue and found that there was a statistically significant difference between Dsuvia and placebo over the first 12 hours and over the entire 48-hour treatment period. Dsuvia-treated patients consistently required less rescue doses over the course of the study compared to placebo, as summarized in the table below.

Number of Rescue Morphine Doses Used by Study Period: ITT Population

Number of Doses Used	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)	p-value [1]
0 - 6 Hours: n (%)			< 0.001
0	89 (83.2%)	21 (38.9%)	
1 – 2	15 (14.0%)	27 (50.0%)	
3 – 4	3 (2.8%)	5 (9.3%)	
> 4	0	1 (1.9%)	
Mean (SD) number of doses used	0.3 (0.7)	1.1 (1.1)	< 0.001
Median	0.0	1.0	
(Min, max)	(0.0, 4.0)	(0.0, 5.0)	
0 - 12 Hours: n (%)			< 0.001
0	83 (77.6%)	19 (35.2%)	
1 – 2	21 (19.6%)	24 (44.4%)	
3 – 4	1 (0.9%)	6 (11.1%)	
> 4	2 (1.9%)	5 (9.3%)	
Mean (SD) number of doses used	0.4 (1.0)	1.6 (1.8)	< 0.001
Median	0.0	1.0	
(Min, max)	(0.0, 7.0)	(0.0, 8.0)	
0 - 24 Hours: n (%)			< 0.001
0	78 (72.9%)	19 (35.2%)	
1 – 2	24 (22.4%)	18 (33.3%)	
3 – 4	2 (1.9%)	8 (14.8%)	
> 4	3 (2.8%)	9 (16.7%)	
Mean (SD) number of doses used	0.5 (1.4)	2.1 (2.9)	< 0.001
Median	0.0	1.0	
(Min, max)	(0.0, 11.0)	(0.0, 14.0)	
Total No. of Doses Used for Entire Study Period: n (%)			< 0.001
0	78 (72.9%)	19 (35.2%)	
1 – 2	23 (21.5%)	18 (33.3%)	
3 – 4	2 (1.9%)	8 (14.8%)	
> 4	4 (3.7%)	9 (16.7%)	
Mean (SD) total number of doses used	0.6 (1.6)	2.4 (3.7)	0.001
Median	0.0	1.0	
(Min, max)	(0.0, 13.0)	(0.0, 19.0)	

ITT: intent-to-treat; SD: standard deviation
Source: Applicant's Clinical Study Report for SAP301, pg. 81

The median time to meaningful pain relief was 54 minutes for the Dsuvia group and 84 minutes for the placebo group. Dr. Ren's Kaplan-Meier analysis revealed that the time to meaningful pain relief was shorter for Dsuvia compared to placebo over the first 12 hours but that the difference was not statistically significant.

In the first 12- and 24-hour study periods, the mean duration between doses was approximately 3 to 3.5 hours for the Dsuvia group, as summarized below.

Mean Duration of the Inter-dosing Interval During the 12-Hour and 24-Hour Study Periods: ITT Population

	Sufentanil 30 mcg (n = 101)	Placebo (n = 52)	p-value [1]
12-Hour Study Period			
Mean (SD)	181.40 (85.24)	143.12 (83.11)	
LS mean (SEM)	185.41 (8.80)	146.55 (11.97)	0.008
95% CI	(168.02, 202.80)	(122.90, 170.19)	
Difference†			
LS mean (SEM)	38.87(14.39)	NA	
95% CI	(10.44, 67.29)		
24-Hour Study Period			
Mean (SD)	217.78 (95.78)	185.85 (120.68)	
LS mean (SEM)	220.81 (10.87)	189.82 (14.78)	0.083
95% CI	(199.33, 242.29)	(160.61, 219.03)	
Difference†			
LS mean (SEM)	30.99 (17.77)	NA	
95% CI	(-4.12, 66.10)		

†Sufentanil minus placebo.
CI: confidence interval; ITT: intent-to-treat; LS: least squares; SD: standard deviation; SEM: standard error of the LS mean.
Source: Applicant's Clinical Study Report for SAP301, pg. 79

Dr. Ren was able to reproduce the results of all primary and secondary analyses and concluded that there is sufficient evidence to support the efficacy of Dsuvia 30 mcg for management of moderate-to-severe acute pain. Dr. Galati also concluded that the primary and supporting secondary efficacy results demonstrated superior efficacy for Dsuvia compared to placebo.

I concur with the conclusions reached by the statistical and primary clinical reviewers that there are no outstanding efficacy issues that preclude approval.

8. Safety

Dr. Galati conducted a review of the safety of Dsuvia, which was based on four clinical studies in the Dsuvia program and selected patients from the Zalviso program that received the first dose of sufentanil sublingual tablet 15 mcg followed by a second dose of sufentanil sublingual tablet 15 mcg within 20 to 25 minutes.[4] Subsequent dosing in the Zalviso-treated patients was on an as needed basis with a 15 mcg dose of sufentanil sublingual tablet and a 20 minute lockout between doses. As stated above in Section 5 of this review, the clinical pharmacology team determined that the Applicant provided sufficient support to allow these Zalviso-treated patients to contribute to the evaluation of safety for Dsuvia.

The Applicant conducted three Phase 3 clinical studies—SAP301 (the pivotal Phase 3 efficacy trial) and SAP302 and SAP303 (open-label safety studies)—and one Phase 1 relative

[4] This included data from six Zalviso studies in patients with postoperative pain after open abdominal surgery, total knee arthroplasty, or total hip arthroplasty; refer to Dr. Galati's review for more details.

bioavailability study (SAP101) using the final to-be-marketed sufentanil formulation. The designs of SAP301 and SAP101 have been discussed previously. SAP302 was a multicenter, open-label study in patients 18 years of age and older who were being treated in the emergency department for moderate-to-severe acute pain due to obvious trauma or injury. Patients could receive up to four doses in the five hour treatment period. SAP303 was a multicenter, open-label study in patients 40 years of age and older who underwent a surgical procedure requiring general anesthesia or spinal anesthesia that did not include intrathecal opioids and who were experiencing acute postoperative pain of at least 4 on an 11-point NRS. The study included a 12-hour treatment period.

The Applicant additionally conducted a Phase 2, randomized, double-blind study in a bunionectomy pain population (SAP202). However, this study was conducted using a different formulation, and the Applicant's submitted in vitro data were not sufficient to bridge the formulation used to the final to-be-marketed formulation. Therefore, the safety data from this study do not support the safety of Dsuvia.

During clinical development, the Division agreed that an overall safety database of at least 500 patients would be required with at least 350 of those treated with Dsuvia and at least 100 patients treated with multiple doses. An assessment of the clinical safety of Dsuvia requires an understanding of the safety of the proposed dosing for sufentanil (i.e., systemic exposure to sufentanil) and the safety of the product as a whole, that is, the safety of sufentanil in combination with the SDA device. Overall, 646 patients were treated with sufentanil sublingual tablets, with 323 of those exposed to Dsuvia and 323 exposed to Zalviso.[5] Very few patients were treated with Dsuvia for 24 hours and beyond, which is expected given the design of the studies and the nature of the patient populations studied. The value of the Zalviso-treated patients is that they provide experience with a duration of exposure to sufentanil of up to 48 hours or more.[6] There were also a greater number of Zalviso-treated patients that were elderly and who underwent major surgery, as compared to Dsuvia.[7] Dr. Galati concluded that the submitted safety database was adequate to inform the safety of Dsuvia, despite the Applicant having not provided 350 overall exposures to Dsuvia. I concur with this assessment given the indication and planned restricted setting of use, the prior findings for Sufenta, and the overall size of the safety database when the Zalviso-treated patients are included.

Deaths and non-fatal Serious Adverse Events (SAEs)

There were no deaths in the Dsuvia program. There was one death in a 69 year-old female with a history of hypertension, hypercholesterolemia, and gout who underwent a unilateral total knee replacement patient and received Zalviso postoperatively. The patient received six doses of sufentanil for postoperative pain in the 24 hours after surgery and was taking OxyContin and ibuprofen at the time of discharge from the study. Six days after her last dose, she was re-hospitalized with pancolitis and acute renal failure and ultimately died of the renal

[5] The Applicant notes that over half of the patients who received two doses of Zalviso 20 to 25 minutes apart also received a third dose within the hour (i.e., 45 mcg/hour), which exceeds the total hourly dose received with Dsuvia.

[6] Refer to Dr. Galati's review, Table 17, pg. 47.

[7] Refer to Dr. Galati's review, Table 23, pg. 52.

failure 30 days after the knee surgery. Dr. Galati determined this case to be unlikely related to study drug, and I concur.

Two patients experienced a nonfatal serious adverse event (SAE)—one case of syncope and one case of hemiparesis—in the placebo-controlled Dsuvia study (SAP301); however, both cases occurred in the placebo group. One SAE occurred in the open-label Dsuvia studies. This was a case of chest pain in a 65 year-old female with a history of coronary artery disease/myocardial infarction, diabetes mellitus, and congestive heart failure who presented to the emergency department with a femur fracture and was treated with Dsuvia for pain. The patient subsequently developed chest pain that responded to nebulized albuterol. The study staff were then informed by the healthcare providers that the patient also experienced similar symptoms prior to having received Dsuvia, and the patient was subsequently diagnosed with a myocardial infarction.

In the Zalviso placebo-controlled group, there were three patients who experienced SAEs. The first case involved a 65 year-old female who developed a decreased oxygen saturation to 40 to 50% with periods of apnea, excess sedation, diaphoresis, and tachycardia in the evening after undergoing a total knee replacement under spinal anesthesia. She had received 14 doses of Zalviso over approximately 7 hours in the postoperative period, along with 11 mg of IV morphine over the same period, fentanyl in the context of her procedure, and oxycodone/acetaminophen. The patient responded to naloxone and study medication was discontinued. This case highlights the very real and all-too-frequent risk of opioid overdose in this setting. The second case involved an 80 year-old female who developed aspiration pneumonia and pulmonary embolism one day after undergoing total knee replacement. Her signs and symptoms related to this event included hypoxia and encephalopathy with confusion/delirium (confusional state) and wide complex paroxysmal tachycardia/atrial fibrillation. The patient had taken five doses of Zalviso in the postoperative period on the same day as the surgery. The third SAE was new onset atrial fibrillation in a 78 year-old male with a history of hypertension who underwent total knee replacement.

In the Zalviso open-label group, a 68 year-old male patient with a history of diverticulitis who underwent an open sigmoid resection experienced an SAE of postoperative ileus associated with hypoxia (oxygen saturation of 84%). He received no additional doses of Zalviso after this event. The patient underwent repeat laparotomy and his postoperative course was subsequently complicated by axillary vein thrombosis and clostridium difficile sepsis.

Discontinuations due to an Adverse Event (AE)

There was 1 (0.9%) patient who discontinued due to an adverse event (AE) in in the placebo-controlled Dsuvia study (SAP301). The AE that led to discontinuation was an oxygen saturation decrease from a baseline of 98% to 93-95%. Two (3.7%) additional patients discontinued due to adverse events in the placebo group (due to the SAEs noted above). In the open-label Dsuvia studies, 4 (1.9%) patients discontinued due to an AE. Two of the patients discontinued due to intermittent oxygen desaturations down to the low 90's that responded to supplemental oxygen. One patient discontinued due to dizziness that was accompanied by a systolic blood pressure that remained in the normal range but was approximately 30 mmHg lower than baseline. The fourth patient discontinued due to pruritus.

In the Zalviso placebo-controlled group, 11 (5.2%) Zalviso-treated patients discontinued due to an AE compared to 4 (3.8%) in the placebo group. The AEs that led to discontinuation in this group are summarized in the table below.

	Treatment Group		
	Sufentanil 15 mcg[a]	Placebo	Tre p-
Number of Patients Enrolled in the Study	211	104	
Number (%) of Patients Who Received Treatment	211 (100%)	104 (100%)	
Number (%) of Patients Without Any Adverse Event Causing the Discontinuation of Study Drug	200 (94.8%)	100 (96.2%)	
Number (%) of Patients With at Least One Adverse Event Causing the Discontinuation of Study Drug	11 (5.2%)	4 (3.8%)	
Number (%) of Patients Who Reported Adverse Events Causing the Discontinuation of Study Drug by System Organ Class			
GASTROINTESTINAL DISORDERS	3 (1.4%)	1 (1.0%)	
Nausea	3 (1.4%)	0	
Abdominal Pain	0	1 (1.0%)	
INVESTIGATIONS	2 (0.9%)	1 (1.0%)	
Respiratory Rate decreased	1 (0.5%)	1 (1.0%)	
Oxygen saturation decreased	1 (0.5%)	0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.5%)	1 (1.0%)	
Back Pain	1 (0.5%)	1 (1.0%)	
NERVOUS SYSTEM DISORDERS	3 (1.4%)	1 (1.0%)	
Sedation	2 (0.9%)	0	
Dizziness	1 (0.5%)	0	
Tremor	0	1 (1.0%)	
PSYCHIATRIC DISORDERS	2 (0.9%)	0	
Anxiety	1 (0.5%)	0	
Confusional State	1 (0.5%)	0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.5%)	0	
Hypoventilation	1 (0.5%)	0	

Source: Dr. Galati's review, Table 34, pg. 65

Dr. Galati compared the discontinuations due to an AE between the open-label Zalviso and Dsuvia groups in the first hour of dosing, as summarized below.

	Treatment Group		
	Sufentanil 15 mcg[a]	Sufentanil 30 mcg	Treatment p-value[b]
Number of Patients Enrolled in the Study	112	216	
Number (%) of Patients Who Received Treatment	112 (100%)	216 (100%)	
Number (%) of Patients Without Any Adverse Event Causing the Discontinuation of Study Drug	104 (92.9%)	212 (98.1%)	
Number (%) of Patients With at Least One Adverse Event Causing the Discontinuation of Study Drug	8 (7.1%)	4 (1.9%)	0.026
Number (%) of Patients Who Reported Adverse Events Causing the Discontinuation of Study Drug by System Organ Class			
GASTROINTESTINAL DISORDERS	2 (1.8%)	0	NS
Nausea	2 (1.8%)	0	NS
INVESTIGATIONS	2 (1.8%)	2 (0.9%)	NS
Oxygen saturation decreased	2 (1.8%)	2 (0.9%)	NS
NERVOUS SYSTEM DISORDERS	2 (1.8%)	1 (0.5%)	NS
Sedation	2 (1.8%)	0	NS
Dizziness	0	1 (0.5%)	NS
PSYCHIATRIC DISORDERS	2 (1.8%)	0	NS
Agitation	1 (0.9%)	0	NS
Anxiety	1 (0.9%)	0	NS
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (1.8%)	0	NS
Bradypnoea	1 (0.9%)	0	NS
Hypoxia	1 (0.9%)	0	NS
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.5%)	NS
Pruritus	0	1 (0.5%)	NS

[a] Patients who received at least 2 SST 15 mcg (Zalviso) tablets dosed within 20-25 minutes of each other in the first hour of dosing. All patients in this group received 30 to 45 mcg of sufentanil in the first hour of Zalviso treatment, followed by prn dosing of 15 mcg/dose (subject to a 20 min lockout) for the duration of the Zalviso study.

Source: Dr. Galati's review, Table 35, pg. 66

Common Adverse Events

The frequency of adverse events that occurred in the placebo-controlled study (SAP301) is summarized in the table below.

		Actual Treatment for Period 01				
		Sufentanil 30 mcg		Placebo		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Gastrointestinal disorders	Nausea	35	32.7%	16	29.6%	51
	Vomiting	8	7.5%	1	1.9%	9
	Flatulence	4	3.7%	4	7.4%	8
	Diarrhoea	1	0.9%	.	.	1
	Dry mouth	1	0.9%	.	.	1
	Dyspepsia	1	0.9%	.	.	1
	Gastritis	1	0.9%	.	.	1
	Hypoaesthesia oral	1	0.9%	.	.	1
	Retching	.	.	1	1.9%	1
Nervous system disorders	Headache	22	20.6%	10	18.5%	32
	Dizziness	6	5.6%	2	3.7%	8
	Somnolence	3	2.8%	2	3.7%	5
	Presyncope	1	0.9%	1	1.9%	2
	Hemiparesis	.	.	1	1.9%	1
	Syncope	.	.	1	1.9%	1
Vascular disorders	Hypotension	6	5.6%	2	3.7%	8
	Hypertension	1	0.9%	1	1.9%	2
	Orthostatic hypotension	1	0.9%	.	.	1
Injury, poisoning and procedural complications	Procedural nausea	3	2.8%	3	5.6%	6
	Procedural vomiting	2	1.9%	.	.	2
Skin and subcutaneous tissue disorders	Pruritus	2	1.9%	2	3.7%	4
	Pruritus generalised	1	0.9%	1	1.9%	2
Cardiac disorders	Tachycardia	3	2.8%	.	.	3
	Sinus tachycardia	.	.	1	1.9%	1
Psychiatric disorders	Anxiety	.	.	1	1.9%	1
	Hallucination	1	0.9%	.	.	1
	Insomnia	.	.	1	1.9%	1
Renal and urinary disorders	Bladder spasm	.	.	1	1.9%	1
	Dysuria	.	.	1	1.9%	1
	Incontinence	.	.	1	1.9%	1
General disorders and administration site conditions	Non-cardiac chest pain	1	0.9%	.	.	1
	Pyrexia	.	.	1	1.9%	1
Musculoskeletal and connective tissue disorders	Muscle spasms	1	0.9%	.	.	1
	Musculoskeletal pain	1	0.9%	.	.	1
Respiratory, thoracic and mediastinal disorders	Haemoptysis	.	.	1	1.9%	1
	Hypoxia	1	0.9%	.	.	1
Investigations	Oxygen saturation decreased	1	0.9%	.	.	1

Source: Dr. Galati's review, Table 38, pg. 71

The most common adverse events occurring in at least 1% of patients while on treatment and within the 12 hour period after discontinuation of dosing in the open-label Dsuvia studies are summarized in the table below.

	Treatment Group
	Sufentanil 30 mcg
Number of Patients Enrolled in the Study	216
Number (%) of Patients Who Received Treatment	216 (100%)
Number (%) of Patients Without Any Adverse Event	148 (68.5%)
Number (%) of Patients With at Least One Adverse Event	68 (31.5%)
Number (%) of Patients Who Reported Adverse Events by System Organ Class	
CARDIAC DISORDERS	3 (1.4%)
Bradycardia	1 (0.5%)
GASTROINTESTINAL DISORDERS	47 (21.8%)
Nausea	45 (20.8%)
Vomiting	4 (1.9%)
INVESTIGATIONS	6 (2.8%)
Oxygen saturation decreased	5 (2.3%)
NERVOUS SYSTEM DISORDERS	19 (8.8%)
Headache	8 (3.7%)
Dizziness	7 (3.2%)
Somnolence	4 (1.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6 (2.8%)
Pruritus	5 (2.3%)
VASCULAR DISORDERS	6 (2.8%)
Hypotension	3 (1.4%)
Hypertension	2 (0.9%)

Source: Applicant's ISS amendment, Table 21, pg. 39

Dr. Galati found that the analysis of common adverse events in the Zalviso-treated patients were consistent with the known safety profile of an opioid. It is worth noting that many of the common AEs in the open-label Zalviso group occurred at a higher frequency than that of the Dsuvia open-label group.[8] The Applicant noted that this finding may, in part, be due to over half of the Zalviso-treated patients having received three doses (i.e., 45 mcg) in the first hour of treatment rather than two (i.e., 30 mcg). However, the Applicant performed an analysis of common AEs between those Zalviso-treated patients that received two doses and those that received three doses in the first hour,[9] and there were no consistent trends to support that the patients who received a higher hourly dose of Zalviso meaningfully contributed to the observed increase in AEs for the Zalviso-treated patients compared to Dsuvia. The Zalviso-treated patients, on average, were older and underwent major surgery, and, therefore, the safety data from the Zalviso-treated patients may actually be a more accurate reflection of the anticipated safety of Dsuvia in older populations or in patients undergoing major surgeries. Therefore, if the Applicant is able to address the deficiencies in the application, this information should be included in labeling along with the relevant safety information from the Dsuvia program.

Additional Respiratory Safety Findings

Dr. Galati evaluated changes in oxygen saturation between treatment arms in the Dsuvia placebo-controlled study. From his review:

[8] Refer to Applicant's Integrated Summary of Safety (ISS), Table 41, pg. 112.
[9] Refer to Applicant's ISS, Table 42, pg. 114.

Oxygen Saturation:

> There were small, but statistically significant differences between treatment groups for mean changes from baseline at 1 hour (-0.88% vs. -0.24%; p = 0.007) and 20 hours (-1.32% vs. -0.71%; p = 0.032), with greater decreases in the sufentanil group than in the control group at these times. For the sufentanil group, the mean decreases from baseline ranged from -0.19% at 15 minutes to -1.47% at 44 hours. For the placebo group, mean decreases from baseline ranged from -0.17% at 30 minutes to -1.22% at 36 hours. The proportions of patients who had SpO2 levels < 93% or < 95% during the study were higher in the sufentanil group than in the placebo group (< 93%: 7.5% vs. 0%; p = 0.052; <95%: 23.4% vs. 7.4%; p = 0.016). Additionally, two sufentanil-treated patients had SpO2 less than 92% during the study. A summary of oxygen saturation is shown in [the table below].

Summary of Oxygen Saturation – SAP301

SPO_2	Sufentanil (n=107)	Control (n=54)
Less than 95%	25 (23.4%)	4 (7.4%)
Less than 93%	8 (7.5%)	0 (0%)
Less than 90%	1 (0.9%)	0 (0%)
Mean (SD)	95.3 (1.7)	96.1 (1.3)

Source: Dr. Galati's review, Table 46, pg. 80.

Additional Safety Concern Associated with Dropped Tablets

The safety profile observed in the clinical development program is typical for an opioid analgesic. However, the small tablet size creates additional risk for accidental exposure associated with dropped tablets. The human factors evaluation noted eight failures associated with a critical task to confirm tablet placement in the patient's sublingual space, and because the tablet is very small, there is potential that an improperly administered tablet will go undetected. The potential risks associated with dropped tablets are of great consequence and include accidental exposure, overdose, death, improper dosing, and diversion for misuse and abuse, as described in the human factors section of this review (Section 3).

The Applicant reported a total of three dropped tablets in the Dsuvia Phase 3 program. In one case, a tablet bounced off the patient's tongue and landed out of the mouth. The HCP located and accounted for this dropped tablet. A second case involved an SDA that was prematurely actuated. The HCP located and secured the tablet. In the last and most worrisome case, the patient was aware that the dose was not properly administered, but the HCP did not follow the Directions for Use and failed to confirm presence of the tablet after dose administration (Directions for Use step #6). The patient subsequently located the tablet and placed it in the trash can. The patient later notified the morning shift HCP of where the tablet had been placed who then properly secured the tablet and documented the event.

Although no specific adverse events were associated with these instances of dropped tablets, these are serious errors with potentially grave consequences. These safety concerns preclude approval and must be addressed prior to approval.

9. Advisory Committee Meeting

An Advisory Committee (AC) meeting was not held for this application, as the issues that preclude approval did not require additional input. However, if the Applicant addresses these issues in a resubmission and the application may otherwise be approved, an AC meeting will likely be necessary to get additional input on the potential impact of any regulatory decision given the current public health crisis surrounding opioids.

10. Pediatrics

Data from the pediatric population were not included in this application. The agency agreed with the Applicant's pediatric study plan (PSP) on November 2, 2016. The agreed PSP includes a request for waiver in patients birth to <6 years of age because children in this age group would not be able to consistently comply with the dosing instruction to keep the tablet in the sublingual space for approximately ten minutes after administration. Sufentanil has a very low oral bioavailability, and swallowing the tablet would result in subtherapeutic concentrations. The agreed PSP includes a deferral for studies in the remaining pediatric age ranges. If the Applicant is able to address the deficiencies, the following deferred studies will be required:

- An open-label, multiple-dose, pharmacokinetic and safety study in pediatric patients 6 to <12 years of age with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
- An open-label, multiple-dose, pharmacokinetic and safety study in pediatric patients 12 to <17 years of age with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate

Efficacy may be extrapolated from adults to the required pediatric age groups provided that the exposures between adults and those pediatric age groups are similar.

11. Other Relevant Regulatory Issues

Risk Evaluation and Mitigation Strategy (REMS)
A REMS is required to mitigate the serious risk of life-threatening or fatal respiratory depression resulting from accidental exposure by requiring that Dsuvia is only dispensed by and administered in inpatient or similarly-resourced healthcare settings that are certified. Although serious, life-threatening or fatal respiratory depression has been observed with all opioids, Dsuvia carries additional risk because sufentanil is a highly potent opioid and the tablet is very small (3 mm by 0.85 mm). Errors involving the critical task of confirming tablet placement in the sublingual space were identified in the human factors study and dropped tablets were noted in the clinical studies. The tablet must be delivered by an HCP, and the HCP must confirm the tablet is in place. Lost tablets will be hard to locate given their size, posing risk to those who may accidentally come in contact with the lost tablet, including children. To ensure the benefits continue to outweigh the risks, the agency is requesting a

REMS by requiring that Dsuvia is only dispensed by hospitals and surgery centers that are specially certified (ETASU B) and that Dsuvia is only administered in the certified hospitals and surgery centers (ETASU C).

Controlled Substances Staff
CSS concluded that Dsuvia "contains one sublingual tablet which contains 45 mcg of sufentanil citrate equivalent to 30 mcg sufentanil base, a potent, Schedule II, μ-opioid agonist with a high abuse potential" and that the major risks associated with Dsuvia are opioid overdose and unauthorized access to the product for purposes of misuse and abuse. CSS noted that unauthorized access could occur in the medical setting; however, "there is no reason to believe the risk of occurrence would be greater or different from other Schedule II opiates also being dispensed at the facility."

Clinical Site Inspections
Navid Homayouni, MD, from the Office of Scientific Investigations (OSI) completed the Clinical Inspection Summary for this application. Study SAP301 is the pivotal efficacy study submitted in support of this application. Two clinical investigator sites were selected for audit by the agency. Two additional clinical investigator sites and the contract research organization (CRO), (b) (4), for the pivotal study were inspected by the European Medicines Agency (EMA) between August 7 and 5, 2017.

OSI found that "[t]he data for Study SAP301 submitted by the [Applicant] to the agency in support of NDA 209128 appear reliable based on available information from the inspection of two clinical sites. There were no significant inspectional observations for clinical investigator, Dr. David Leiman, M.D., and final inspection classification is No Action Indicated (NAI). Although regulatory violations were observed during the inspection of Dr. Harold Minkowitz, M.D., these violations are unlikely to significantly impact the determination of efficacy and safety and the final classification for the inspection is Voluntary Action Indicated (VAI).

There were no major inspectional findings for Drs. Lakshman and Melson. There were no critical findings for (b) (4) during the EMA inspection. While there were inspectional findings at the CRO, they are unlikely to substantially impact the determination of efficacy and safety of the clinical trial. If indicated, an Inspection Summary addendum will be following receipt and review of the EMA Integrated Inspection Report."

I concur with the OSI reviewers that the inspectional findings at the four clinical investigator sites and the CRO are unlikely to impact the interpretation of the pivotal study results.

Financial Disclosures
The Applicant provided certification that there were no financial interests or arrangements to disclose.

505(b)(2) Committee
This application was presented at a meeting of the 505(b)(2) committee on September 25, 2017, and it was cleared for action from their perspective.

12. Labeling

DMEPA found the proposed proprietary name, Dsuvia, to be acceptable. DMEPA also provided comments on the prescribing information, as well as on the directions for use, device labeling, and carton and container labeling. Additionally, the Division of Pediatric and Maternal Health (DPMH) and the Controlled Substances Staff (CSS) provided recommendations on relevant sections of the labeling.

Some of the DMEPA labeling comments were related to deficiencies in the application and will be communicated in the complete response letter. Otherwise, labeling comments will not be provided to the Applicant, and labeling will be addressed in a resubmission because these comments may change as the deficiencies are addressed.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Complete Response

- Risk Benefit Assessment

  CDTL
  The Applicant submitted this application for Dsuvia, a drug-device combination product containing 30 mcg of sufentanil that is intended to be delivered to the sublingual space by a healthcare professional no more than once an hour for the management of acute pain that requires opioid-level analgesia in an inpatient or similarly-resourced healthcare setting. Although the dose and dosing regimen for sufentanil 30 mcg appear effective in the proposed patient population and reasonably safe in the context of existing opioid therapy, there are safety concerns that must be addressed before this application can be approved.

  An adequate and well-controlled clinical trial in a postoperative pain population demonstrated a statistically superior treatment effect in favor of Dsuvia on the prespecified primary endpoint, SPID12, which was supported by multiple secondary analyses, including rescue analgesic use. The safety evaluation did not identify a risk for the drug component that would not be expected for an opioid analgesic. Additionally, the availability of this product in this particular setting would not be expected to further add to the ongoing opioid epidemic that we are currently experiencing in the U.S. provided that adequate restrictions are in place to confine its use to an appropriate healthcare setting.

  However, the human factors evaluation identified serious concerns regarding the use of the device. Specifically, there were numerous errors related to study participants not being able to correctly confirm the placement of the tablet in the

sublingual space. A dropped tablet poses significant risks, including life-threatening or fatal respiratory depression due to accidental exposure, improper dosing, and diversion. Furthermore, due to the size of the tablet, a dropped tablet may go undetected by the patient and the HCP. The Applicant must address this concern prior to approval. DMEPA recommended modifications to the directions for use to ensure that the risks associated with not confirming placement of the tablet are minimized and that the adequacy of those changes be confirmed through additional human factors evaluation.

Division Director
Dr. Lloyd has provided a thorough summary and review of the individual discipline reviews, and I concur with most of his conclusions.

The efficacy data from Study 301 demonstrate that a 30-mcg sublingual sufentanil tablet is able to provide more analgesia than placebo in postoperative patients. The Applicant has made no attempt to demonstrate that Dsuvia has a role that is superior to traditional oral analgesics in the postoperative period, nor that it is even equivalent.

The patients in Study 301 did not use a lot of postoperative analgesic medication, even in the placebo group. The number of rescue morphine doses used by placebo patients averaged 1.1 doses in the first 6 hours (median 1.0), 1.6 doses (median 1.0) in the 0 to 12 hour interval, and 2.1 doses (median 1.0) in the 0 to 24 hour interval. In the 0 to 12 hour interval, only 15% of placebo patients used 3 to 4 doses of rescue morphine and just 16.7% of placebo patients used more than four doses of rescue morphine. There were some patients with difficult to control pain; the maximum use of rescue doses was 11 in the Dsuvia group and 14 in the placebo group. In the assessment of whether there was sufficient exposure to Dsuvia and Zalviso for a safety assessment, the total number of patients treated with sublingual sufentanil tablets was 646, with 323 of those exposed to Dsuvia and 323 exposed to Zalviso. So while I agree that the number could have been sufficient, the experience with repeated dosing is not. Table 18 of Dr. Galati's review provides the number of doses of sublingual sufentanil used. Of the 323 patients exposed to Dsuvia, 86% used fewer than six doses in the first 12 hours of the study, and the remaining 14% used from 6 to 12 doses. It takes seven doses of Dsuvia, administered one hour apart to reach steady state. With multiple dosing, the exposure to sufentanil accumulates with increases in AUC (AUC0-60 min) and Cmax of 3.7-fold and 2.3-fold, respectively. This means that most of the safety database from Dsuvia clinical trials represents the adverse event profile of a less than steady-state exposure to sufentanil from Dsuvia. The adverse effects of the maximum exposure of sufentanil following multiple dosing have not been adequately evaluated.

The concern about misplaced tablets cannot be understated. The experience with Zalviso demonstrated that patients who self-administered the small sublingual fentanyl tablet were not always aware that the dose was not properly administered

and several were found in bed sheets. In the limited evaluation of Dsuvia, administration errors were made, the nature of which could result in misplaced tablets without the awareness of either the patient or healthcare provider. The risk of unaccounted sufentanil is unacceptable.

Overall, although efficacy was demonstrated, Dsuvia offers no apparent advantage to currently available therapies. There are two areas of safety concern with this product that require further evaluation: the safety of Dsuvia in patients requiring the maximum dosing proposed for labeling because of the accumulation of sufentanil and the risk of misplaced tablets due to the small tablet size, use of an applicator, and inadequate directions for use. These concerns outweigh the possible benefit at this time.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  If the deficiencies can be adequately addressed, a REMS restricting use of Dsuvia to an appropriate healthcare setting will be required.

- Recommendation for other Postmarketing Requirements and Commitments

  If the deficiencies can be adequately addressed, pediatric studies based on the requirements of the Pediatric Research Equity Act will be required

- Recommended Comments to Applicant

  SAFETY
  The safety database, while suitable in number of patients, did not contain a sufficient number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of Dsuvia. This is particularly important as there is a nearly 4-fold increase in the exposure and a more than 2-fold the maximum concentration when Dsuvia is dosed at steady state.

  To address this deficiency:
  Collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety of Dsuvia for a period following the maximum dosing proposed.

  HUMAN FACTORS

  We have determined that the human factors (HF) validation study data did not demonstrate that the user interface supports safe and effective use of the product by intended users for intended uses and environments. Failures that result in dropped sufentanil tablets pose a risk for accidental exposure, improper dosing, and diversion. Overall, we do not find the risk acceptable and note that you did not propose any additional measures to further mitigate the risk.

To address this deficiency:
We recommend you make the following changes to the user interface and conduct another HF validation study to demonstrate the effectiveness of the recommended mitigation strategies in addressing the use-related errors that were observed in your validation study and to ensure that the changes do not introduce new risks:
A. Directions for Use (DFU)

1. Revise step 6 of the DFU: "Depress the green Pusher to deliver the tablet to the patient's sublingual space and confirm tablet placement" into two separate steps such as the following:

"Step 6: Depress the green Pusher to deliver the tablet to the patient's sublingual space."

"Step 7: Visually confirm tablet placement in the sublingual space."

2. Modify the figures that depict the patient's mouth by labeling parts of the mouth so they represent a more accurate representation of human anatomy. Labeling parts of the mouth within the graphics will help guide users in the proper administration technique.

3. Label each figure (e.g., Figure 1, Figure 2) in the DFU and refer to the figures within the written instructions (e.g. "see Figure 1").

B. Pouch Package
1. Consider replacing the simplified graphics on the back of the foil pouch with the complete DFU (written instruction with revised and labeled graphics) such that complete DFU cannot be easily separated from the foil packet prior to use or discarded along with the carton.

Additional comments:

CONTAINER LABEL AND CARTON LABELING COMMENTS
We reserve final comment on the proposed container label and carton labeling until the application is otherwise adequate. The following comments are being shared at this time for your consideration:

A. Single Dose Applicator Container Label

In accordance with the requirements of 21 CFR 201.10(i), the label must include the following information, at a minimum:

1. Proprietary name
2. Established name
3. Lot or control number
4. Name of manufacturer, packer or distributer of the drug

Include all of the above information on this container label. In addition, we recommend including the expiration date[10].

B. Pouch Labeling- Front

1. To improve readability, consider an alternative presentation for the proprietary name. We recommend the proprietary name "DSUVIA" is presented in all the same color without any intervening matter.
2. (b) (6)
3. If room permits, consider adding the statements, "Instruct the patient to not chew or swallow the tablet. Instruct the patient to not eat or drink and minimize talking for 10 minutes after receiving the tablet."

C. Pouch Labeling - Back

1. Revise the statement, (b) (4) to read, "Administration Information" so that it more accurately reflects the information that follows.
2. Modify the figures that depict the patient's mouth by labeling parts of the mouth so they represent a more accurate illustration of human anatomy. Labeling parts of the mouth within the graphics may help guide users in the proper administration technique.

D. Carton Labeling

To improve readability, consider an alternative presentation of the proprietary name on the carton labeling. We recommend the proprietary name "DSUVIA" is presented in all the same color without any intervening matter.

[10] United States Pharmacopoeia (USP) General Chapter <7> Labeling

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

/s/

JOSHUA M LLOYD
10/11/2017

SHARON H HERTZ
10/11/2017

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209128
Priority or Standard	Standard
Submit Date(s)	12/12/16
Received Date(s)	12/12/16
PDUFA Goal Date	10/12/17
Division / Office	DAAAP/ODE II
Reviewer Name(s)	Steven Galati M.D.
Review Completion Date	9/6/17
Established Name	Sufentanil Tablet
(Proposed) Trade Name	Dsuvia
Therapeutic Class	Opioid
Applicant	ACERX
Formulation(s)	Sublingual Tablet/Device
Dosing Regimen	30 mcg
Indication(s)	Management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting.
Intended Population(s)	Acute Pain

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Complete Response

1.2 Risk Benefit Assessment

To support the efficacy and safety of their product, the Applicant submitted the results of a pivotal Phase 3 trial (SAP301) using the to-be-marketed formulation, in conjunction with the Agency's previous findings of safety and efficacy for the reference drug Sufenta (NDA 19050), for the proposed indication of management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting. The trial was designed and conducted in a reasonably adequate and well-controlled fashion that is sufficient to rely upon for a determination of efficacy. The data reviewed in the pivotal controlled clinical trial, in patients with acute post-surgical pain due to outpatient abdominal surgery, support the effectiveness of Dsuvia for the treatment of acute pain in this population as evidence by the statistical significance of the primary endpoint compared to placebo and the clinically meaningful benefit of this finding.

Additional safety information was included in the form of two open-label, Phase three studies conducted in patients with acute pain from a surgical procedure or acute injury in an emergency room setting and additional safety data that were bridged via the pharmacokinetic study SAP101 to the Applicant's other sufentanil tablet program Zalviso (b) (4). Details of the pharmacokinetic bridge data and interpretation are described in the clinical pharmacology section as well as the section on safety. The totality of the safety data did not demonstrate any new safety signals beyond what is already known for sufentanil or other opioid products.

In addition to the clinical studies, human factor studies were completed as part of the NDA. Nasim Roosta, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) completed a review of the human factors (HF) validation study results, device label, pouch label, carton labeling, Directions For Use (DFU), and Prescribing Information (PI) submitted by the Applicant. Dr. Roosta describes DMEPA's concerns with the HF study and how critical failures that were noted in the study may result in dropped tablets and accidental exposure to sufentanil in clinical use of Dsuvia. Dr. Roosta also concluded "the human factors validation study data did not demonstrate that the user interface supports safe and effective use of the product by intended users for intended uses and environments." The failed HF validation study, coupled with the

potency of Dsuvia, small size of the tablets, and potential consequences of these failures identified in the HF study, is the primary reason for the Complete Response.

Benefits:

- Evidence of effectiveness was established in a single, adequate and well-controlled trial based on analysis of the primary endpoint (see Section 6 for details)
- The primary efficacy analysis is further supported by results in favor of Dsuvia compared to placebo on various secondary endpoints
- The sublingual route of administration may serve as an alternate, non-invasive route of administration for analgesia if intravenous route not available and a patient prefers oral administration compared to intramuscular
- No active metabolites, and therefore may reduce delayed adverse events

Risks:

- No new safety signal was identified in review of this application
- As described, numerous HF failures resulting in concerns over dropped and lost tablets which may result in accidental exposure, overdosing (more than 1 dose per hour), under dosing the patient, and diversion.
- Small tablet size and high potency opioid results in concerns for serious adverse events including death if accidental exposure occurs
- User interface requires changes as detailed in DMEPA's review

Overall, the risk-benefit profile of Dsuvia in this patient population is not acceptable. Although no new safety signal was detected in the clinical studies, the HF study results demonstrated a concern for the functionality of the device, as well as deficiencies observed in the DFU, carton and pouch labeling to allow consistently safe administration of the drug. Based on the deficiencies of the device delivery system cited by DMEPA, especially given the potency and small size of the sufentanil tablet, dropped and/or lost tablets may have significantly adverse clinical outcomes (i.e., accidental exposure, overdose, diversion). Therefore, I recommend a Complete Response. If this product is approved at a later date after resolution of the HF deficiencies, I recommend that all patients receiving Dsuvia be monitored using oxygen saturation to detect potential hypoxia.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The NDA was presented to the REMS Oversight Committee (ROC) on July 27, 2017. The purpose of the presentation to the ROC, was to clarify whether the product would require a REMS if the HF study was repeated successfully and appropriate changes were made to the user interface.

The committee agreed that a REMS would be necessary for the approval of Dsuvia. The REMS would limit the use of DSUVIA to certified hospital and surgical center locations.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend a Complete Response, and therefore, any postmarket evaluation recommendations are not relevant.

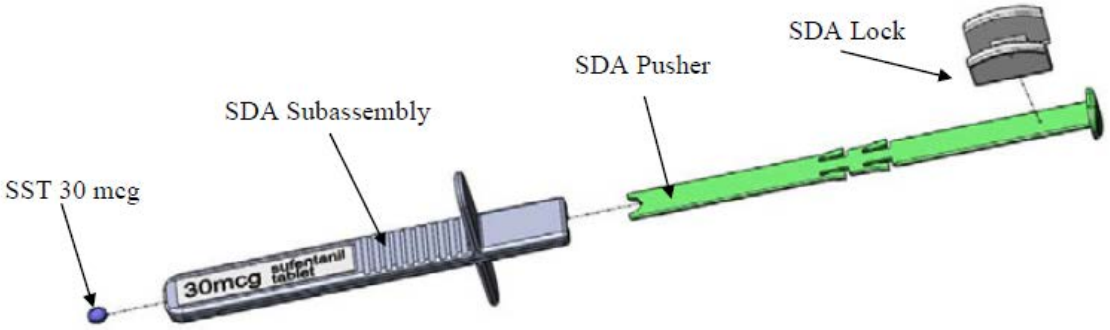
2 Introduction and Regulatory Background

2.1 Product Information

Sufentanil (NDA 19050) was approved in 1984 as tradename Sufenta and is a potent synthetic opioid agonist approved as an analgesic and as an anesthetic agent. Sufenta is approved for intravenous and epidural use. Dsuvia is a drug-device combination product designed to deliver a 30 mcg sufentanil tablet to the patient's sublingual space in an acute pain setting. A healthcare provider must administer Dsuvia. The Applicant designed the tablet to be very small (3 mm in diameter and 0.85 mm thick) to minimize a salivary response and reduced possibility of swallowing which would reduce the bioavailability.

The product consists of a tablet which is individually packaged in and dispensed from a single-dose applicator (SDA) composed of five main components: Top, Base, Pusher, Lock and Label (Figure 1). The SDA tip goes under the patient's tongue, green pusher depressed by a healthcare profession (HCP) to administer to sublingual space.

Figure 1: Device Components



Source: Applicant's Direction for Use Document

The Applicant's rationale for development of Dsuvia is to provide a non-invasive alternative for the management of moderate-to-severe acute pain in opioid-naïve adult patients[1] who require opioid therapy in a medically supervised setting.

2.2 Tables of Currently Available Treatments for Proposed Indications

Alternative treatment options include other immediate-release opioid analgesics.

2.3 Availability of Proposed Active Ingredient in the United States

1 Defined as equivalent of 15 mg oral morphine or less per day

Table 1: Brand Name for Sufentanil NDAs

Drug Product Name	NDA	Action Date	Dose Form	Indications
Sufenta (sufentanil citrate)	19050	May 4, 1984	Injectable; Injection	• as an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated. • as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. • for epidural administration as an analgesic combined with low dose (usually 12.5 mg per administration) bupivacaine usually during labor and vaginal delivery.

Source: Sufenta product labeling and the FDA Orange Book

2.4 Important Safety Issues With Consideration to Related Drugs

Opioid drug products have numerous safety concerns. Opioid products have a risk of the development of addiction, abuse, as well as misuse. Opioids may also lead to respiratory depression, central nervous system depression, hypotension and gastrointestinal events (e.g., obstruction), especially at higher doses or in opioid naïve patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant previously submitted an application for their sufentanil sublingual product Zalviso (b) (4) Zalviso, a drug-device combination product intended for patient-administration for the management of acute pain in hospitalized patients, consisted of 15 mcg tablets of sufentanil and a controller device. The product received a Complete Response (CR) due to higher than acceptable error rates of delivery (up to 8%) and finding dispensed tablets in the bed linens and on the floor, as well as two reports of patients accidentally dispensing tablets that they did not take. The Applicant developed Dsuvia to be administered only by a healthcare provider to limit potential patient error in delivery.

Table 2: Key Presubmission Regulatory Activities

Date	Meeting	Comments
12/18/2013	End-of-Phase 2	• If PK study SAP101 showed exposure with 30 mcg single-dose of ARX-04 comparable exposures to two 15 mcg doses of Zalviso given 20 min apart, then selected Zalviso subjects may be included in safety database
6/13/2014	Advice Letter	• Division agreed on SPID12 as the primary efficacy endpoint
12/9/2015	Pre-NDA	• Safety database was revised to include at least 350 subjects exposed to at least one dose of SST 30 mcg and 100 of these subjects exposed to multiple doses • ISS should have multiple pools including and excluding the Zlaviso clinical program • Safety information included in the labeling will be based on the totality of the data included in the submission

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All data and documents in this application were electronically submitted following the guidances for electronic submission. The documents were organized in electronic Common Technical Document (eCTD) format. The datasets were in Study Data Tabulation Model (SDTM) format, however, the ISS was submitted in Analysis Data Model (ADaM). The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable.

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

The Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI) performed an inspection of two clinical sites. One of the sites, inspection of Dr. Harold Minkowitz, M.D., showed several regulatory violations but were determined to be unlikely to have significant impact on the determination of efficacy and safety. The final classification for the inspection is Voluntary Action Indicated (VAI). For further details, please refer to the review by Navid Homayouni, M.D., Medical Officer OSI.

3.3 Financial Disclosures

The Applicant submitted a form 3454 “Certification: Financial Interests and Arrangements of Clinical Investigators” attached with a list of the investigators listed in the study reports, certifying that they had no financial interests or arrangements to disclose (see Appendix for Clinical Investigator Financial Disclosure).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Dsuvia tablet is an immediate-release sublingual tablet containing 30 mcg of sufentanil. The Dsuvia tablet is a blue-colored flat-faced tablet with rounded edges. It is 3 mm in diameter and 0.85 mm thick with a nominal tablet weight of 7.40 mg. The quality reviewer, Dr. Valerie Amspacher, noted "all of the excipients are listed in the FDA Inactive Ingredient Query at or below levels listed in the FDA Inactive Ingredient Query for buccal/sublingual formulations. Dicalcium phosphate anhydrous is listed in the FDA Inactive Ingredient Query as anhydrous dibasic calcium phosphate." In addition, Dr. Amspacher noted the key elements of the quality review appeared adequate. For a detailed review of chemistry, please refer to Dr. Amspacher's review.

4.2 Clinical Microbiology

This is not an antimicrobial, therefore there is no clinical microbiology review.

4.3 Preclinical Pharmacology/Toxicology

The final toxicology review had not been completed at the time of this clinical review. However a preliminary assessment, from a nonclinical pharmacology toxicology perspective, concludes this NDA may be approved with no post-marketing requirements. Of note, FD&C Blue No. 2 (b) (4) has not been used in FDA-approved sublingual drug products. Although FD&C Blue No. 2 (b) (4) is not listed in the FDA's Inactive Ingredient Database (IID) for sublingual dosage forms, it is listed for oral products and a buccal product with a maximum potency for the buccal product of 0.008 mg (one Dsuvia tablet contains (b) (4) mg). FD&C Blue No. 2 (b) (4) is acceptable for use in foods, drugs, and cosmetics. There was no evidence of any obvious safety concern from the clinical data presented as part of this NDA. The nonclinical reviewer, Dr. Grace Lee, noted in her preliminary review "Based on the fact that color additive FD&C Blue No. 2 is provisionally listed under 21 CFR §74.1102 for use in ingested drugs and FD&C Blue No. 2 (b) (4) is used in the FDA-approved oral drug products, along with available clinical data of the sublingual use of FD&C Blue No. 2 (b) (4), the Reviewer considers that there is adequate safety information for the sublingual use of FD&C Blue No. 2." For further details of the nonclinical review please refer to Dr. Lee's final review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Dsuvia is an immediate-release mu opioid agonist.

4.4.3 Pharmacokinetics

The final clinical pharmacology review had not been completed at the time of this clinical review. However, the clinical pharmacology reviewer, Dr. Wei Qiu, has noted that the NDA appears acceptable based on the data submitted pending any agreed upon language to be included in the package insert. This is a 505(b)(2) application, and the Applicant 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 in the Zalviso (Sufentanil Sublingual Tablet 15 mcg, also known as SST 15 mcg) (b) (4) clinical studies, by establishing a pharmacokinetic (PK) bridge in the comparative bioavailability Study SAP101. The final to-be-marketed SST 30 mcg formulation was used in Study SAP101, a PK study conducted in healthy volunteers under naltrexone blockade. SAP101 served to establish a PK 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.

Dr. Qiu's preliminary review states "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." The data from the study is shown below (Table 3). The data from this study also supported the bridge from the Zalviso program by showing 2 doses of 15 mcg SST dosed 20 minutes apart were bioequivalent to a single dose of SST 30 mcg.

Table 3: 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: Dr. Wei Qiu's review and Tables 10, 11, and 12 of study SAP101 report.

For further details of the clinical pharmacology data and interpretation, please refer to the final review by Dr. Qiu.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical studies conducted in support of this NDA are listed in below in Table 4. As described in Section 5.2, the Phase 2 study SAP202 is not included in the efficacy or safety analyses due to a lack of an appropriate scientific pharmacokinetic bridge to the to-be-marketed formulation.

Table 4: Overview of Phase 3 Studies - Dsuvia Clinical Program

Study	Design	Treatment/Duration	Number of Subjects	Rescue	Population
SAP301 (pivotal efficacy study)	Multicenter, randomized, double-blind, placebo-controlled	Dsuvia 30 mcg; PRN; sublingual Placebo; PRN; sublingual Up to 48 hours	Dsuvia: treated 107; completed 102 Placebo: treated 54 completed 41	Morphine IV	Post-surgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery
SAP302	Multicenter, open-label	Dsuvia 30 mcg; PRN; sublingual Up to 5 hours	Treated 76; completed 65 (2-hour period)	Morphine IV or oral oxycodone	Emergency room setting – adult patients with pain due to trauma or injury
SAP303	Multicenter, open-label in subjects 40	Dsuvia 30 mcg; PRN; sublingual	Treated 140; completed	Morphine IV	Post-surgical patients 40 years or older following

	years and over	Up to 12 hours	132		any type of surgery

Source: Adapted from Applicant's Summary of Clinical Safety and Clinical Overview

The Applicant included select subjects from a previous clinical program studying sufentanil sublingual tablets which utilized a different delivery device (Zalviso (b) (4) (b) (4) Study SAP101 served as the pharmacokinetic (PK) study comparing Dsuvia to the Zalviso 15 mcg doses set 20 minutes apart (described in Section 5.2). An overview of this study is provided in Table 2. An overview of the Zalviso clinical studies included in the pooled analyses of safety are summarized in Table 6.

Table 5: Phase 1 Study Overview – Dsuvia Clinical Program

Study	Design	Treatment/Duration	Number of Subjects	Population
SAP101	Single-center, randomized, open-label; 4-period, crossover Single dose and multi-dose up to 12 hours	A: Sufental 30 mcg; infused over 1 minute; IV B: SST 30 mcg; single dose; sublingual C: SST 15 mcg; 2 doses 20 minutes apart; sublingual D: SST 30 mcg; 12 doses 1 hour apart; sublingual	treated 40; completed 34	Naltrexone-blocked healthy subjects aged 18 – 45 years

Abbreviations: IV = intravenous; SST = sufentanil sublingual tablet
Source: Adapted from Summary of Clinical Safety, p. 8

Table 6: Summary of Supporting Studies for Safety (Zalviso Program)

Study	Design	Treatment/Duration	Number of Subjects	Rescue
IAP310 Phase 3	Multicenter, randomized, double-blind trial; placebo control Open abdominal surgery	Sufental 15 mcg tab; placebo Up to 72 hours	Sufental: treated 114; completed 78 Placebo: treated 58 completed 27 Included in pool: Sufentanil - 51 Placebo -27	Morphine IV
IAP311	Multicenter, randomized,	Sufental 15 mcg tab; placebo	Sufental: treated 315; completed	Morphine IV

Phase 3	double-blind trial; placebo control Total knee or hip replacement	Up to 72 hours	215 Placebo: treated 104, completed43 Included in pool: Sufentanil -142 Placebo -54	
IAP309 Phase 3	Multicenter, randomized, open-label trial; active control (AC) Open abdominal surgery or knee or hip replacement	Sufental 15 mcg tab; AC -sublingual Morphine 1 mg Up to 72 hours	Sufental: treated 177; completed 146 Morphine: treated 180, completed 136 Included in pool: Sufentanil -94	Morphine IV
ARX-COO1 Phase 2	Multicenter, randomized, double-blind trial; placebo control Total knee replacement	Sufentanil 5 mcg, 10 mcg, and 15 mcg tab; placebo Up to 12 hours	Sufental 15 mcg: treated 20; completed 13 Placebo: treated 24, completed 7 Included in pool: Sufentanil -12 Placebo -15	No rescue
ARX-COO5 Phase 2	Multicenter, randomized, double-blind trial; placebo control Open abdominal surgery	Sufentanil 10 and 15 mcg; Placebo Up to 12 hours	Sufentanil 15 mcg: treated 29; completed 25 Placebo: treated 30; completed 9 Included in pool: Sufentanil -6 Placebo -8	No rescue
ARX-COO4 Phase 2	Multicenter, open-label trial; no control Knee replacement	Sufentanil 15 mcg Up to 12 hours	Sufentanil 15 mcg: 18	No rescue

Source: Adapted from Summary of Clinical Safety Table 2.7.4:3

5.2 Review Strategy

Trial SAP301 is the pivotal, placebo-controlled study reviewed for efficacy as well as a significant contributor to the safety analysis. The primary efficacy analyses of trial SAP301 was confirmed by Dr. Yi Ren, statistical reviewer. With regard to safety,

several studies contributed to the entire safety database (see Section 5.1). The pivotal trial will serve as the most relevant safety analysis due to the comparison to a placebo control. The additional open-label studies (SAP302 and SAP303) will be assessed as well for supportive safety information. However, given the different study designs (i.e., duration, dosing intervals) the combined pooled analysis is for the purpose of detecting a safety signal as opposed to a direct comparison to a placebo control.

As discussed in the Pre-NDA meeting with the Applicant, the safety database must include at least 350 subjects exposed to at least one dose of Dsuvia 30 mcg and 100 of these subjects exposed to multiple doses of Dsuvia 30 mcg over the anticipated duration of use.

The Division previously discussed and agreed (Pre-NDA meeting) with the Applicant's proposal to include a portion of the safety database from their previous sufentanil clinical program for Zalviso (b) (4) The sufentanil product Zalviso had been bridged to the current sufentanil product Dsuvia through a PK study SAP101 with PK modeling supporting bioequivalence to Dsuivia 30mcg in subjects where a Zalviso patient dosed the second tablet (2 x 15 mcg) within 25 minutes. The safety data from 323 Zalviso patients who were dosed with a second tablet within 20 to 25 minutes of the first tablet could be submitted as supportive and included in the safety database for Dsuvia.

Study SAP202 used a formulation that was not bridged to the to-be-marketed formulation and therefore was not included in the safety database. The dissolution data provided by the Applicant was reviewed by our chemists and determined inadequate to bridge to the to-be-marketed formulation due to major differences in formulations. The major difference in the formulations is the use of (b) (4), which is completely absent in phase 2 formulation (SAP202) and present in the to-be-marketed formulation. This would be considered a 100% change per the Immediate Release Scale-up and Post Approval Change guidance. Therefore, the Applicant would be required to perform adequate bridging with an in vivo bioequivalence study to include SAP202. The safety database appears to still be adequate even in the absence of SAP202 and the bridging study is not required, but SAP202 was removed from the total safety database. The Applicant was informed of our findings in the 74-day letter and updated safety pools within the Integrated Summary of Safety (ISS) were requested as follows:

- All DSUVIA Phase 3 studies (placebo-controlled study SAP301 and open-label studies SAP302 and SAP 303)
- Placebo-controlled selected ZALVISO exposures
- Phase 3 DSUVIA open-label studies (SAP302 and SAP303) and open-label selected ZALVISO exposures

- Phase 3 DSUVIA open-label studies (SAP302 and SAP303)
- Open-label selected ZALVISO exposures

Because the safety evaluation of Dsuvia will be based on the overall safety of the drug and device in combination, and not just the safety of the systemic drug levels that are achieved, the main focus will be on the Dsuvia program (SAP301, SAP302 and SAP303). The exposures from the Zalviso clinical program are only for additional supportive data for systemic safety of sufentanil sublingual tablets.

The results of the studies are discussed in the relevant sections below.

5.3 Discussion of Individual Studies/Clinical Trials

Trial SAP301

"A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of the Sufentanil Sublingual Tablet 30 mcg for the Treatment of Post-Operative Pain in Patients after Abdominal Surgery"

The study was conducted at four clinical sites within the United States

Date of Report: March 7, 2016

Protocol

Objective/Rationale
The primary objective of this study is to compare the efficacy and safety of sufentanil sublingual tablet (30 mcg) to the placebo control sublingual tablet for management of acute moderate-to-severe pain following outpatient abdominal surgeries[2].

The secondary objectives are the following:
- Patient ratings of pain intensity (PI)
- Patient ratings of pain relief (PR)
- Time to perceptible and meaningful pain relief
- Percentage of patients requiring rescue due to inadequate analgesia
- Global assessments
- Use of rescue medication

2 Abdominoplasty, open tension-free inguinal hernioplasty (Lichenstein repair with mesh), or laparoscopic abdominal surgery

Of note, the Applicant did not note any as key and there was no adjustment for multiplicity.

Overall Design

This was to have been a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in patients 18 years and older who had undergone an outpatient abdominal surgery intended to demonstrate the efficacy, safety and tolerability of sufentanil sublingual tablets compared to a placebo control for up to 48 hours. Patients were to be randomly assigned (2:1 sufentanil to placebo, respectively) and were to have a minimal PI of ≥ 4 just prior to the first dose of study drug (baseline PI) to be administered by a healthcare professional (HCP). The first dose was to be the beginning of the 48-hour study period. Additional doses were to be administered by an HCP when requested by the patient with a minimum re-doing interval of 60 minutes. Rescue opioid medication was to be administered if the patient reported pain scores that allowed administration but the study drug/placebo was not eligible (i.e., within the 60 minute interval after study drug administered). A patient was to be considered a completer if they remained in the study for ≥ 24 hours after the first dose. To remain in the study beyond 24 hours the PI score was to be ≥ 4 for an additional dose. This concept was to be applied at the 36-hour time-point as well.

Treatment

- Sufentanil tablet 30 mcg
  - Comes in single-dose applicator (SDA) individually packaged and sealed to be administered by HCP only
- Placebo tablet – matched to study drug in appearance
- Opioid rescue[3]
  - 1 mg IV morphine was to be given no sooner than 10 minutes after study drug and no more frequently than every 60 minutes
  - PI and PR scores were to be recorded prior to all doses of rescue in addition to required measures the specified time-points
- If pain continued after rescue and not controlled by study drug or rescue medication, then the patient was to be discontinued and an alternate form of analgesia per the standard of care was to be given

Population and Procedures

Inclusion/Exclusion Criteria

The Applicant planned to enroll approximately 180 patients (120 sufentanil-treated patients, 60 placebo patients) to ensure at least 159 patients (106 sufentanil-treated patients, 53 placebo patients) received study drug. The randomized population was to

3 IV morphine, hydromorphone or fentanyl

consist of 163 patients (109 sufentanil, 54 placebo). The analyzed population was to consist of 161 patients (107 sufentanil, 54 placebo).

Key Inclusion Criteria at Screening

- Male or female patients 18 years of age or older
- Scheduled to undergo outpatient abdominal surgery under general or spinal anesthesia that did not include intrathecal opioids
- Effective method of birth control, if appropriate, at the time of screening visit and for 30 days following the end of the study period[4]
- Expected to have moderate-to-severe post-operative pain for at least 24 hours

Key Exclusion Criteria at Screening

- Patients who had taken an opioid for more than 30 consecutive days, at a daily dose of more than 15 mg of morphine (or equivalent), within the past 3 months
- Positive drug of abuse screen
- History of opioid dependence within 2 years defined by the DSM-IV-TR
- Had used any illicit drugs of abuse within 5 years
- Abused any prescription medication or alcohol within 1 year
- Allergy or hypersensitivity to opioids
- Taking monoamine oxidase inhibitors (MAOIs) or had taken MAOIs within 14 days
- Current, documented sleep apnea diagnosis
- Pregnant (positive pregnancy test at screening or on the day of surgery), breastfeeding, or planning to breastfeed within 30 days of the last dose of the study drug
- Medical condition that could adversely impact the patient's participation or safety, conduct of the study, or interfere with the pain assessments, including chronic pain or active infection
- Previously had abdominoplasty or had an inguinal hernia repair on the same side
- Had cancer and were receiving radiation/chemotherapy and were expecting to receive radiation/chemotherapy within 48 hours after surgery
- Additional scheduled surgical procedure within 48 hours of the surgery
- Received perioperative regional anesthetic techniques including epidural, intra-articular, peripheral nerve block, and local anesthetic wound infiltration
- Expected to have post-operative analgesia supplied by a long-acting or continuous regional technique
- Received surgical premedication with long-acting opioid analgesics
- Receiving oxygen therapy at the time of screening

4 Oral or transdermal contraceptives, condom, spermicidal foam, intrauterine device, progestin implant or injection, abstinence, vaginal ring, or sterilization of partner. The reason for non-child bearing potential, such as bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or postmenopausal for > 1 year. Hormonal forms of contraception must also have been willing to use a barrier method of contraception from screening through 30 days following the study

Exclusion Criteria at Randomization

- Not awake, not breathing spontaneously, or had a respiratory rate less than 8 breaths per minute (bpm) or greater than 24 bpm
- Arterial oxygen saturation by pulse oximetry (SpO2) that could not be maintained at ≥ 95% with or without supplemental oxygen
- Not able to answer questions and follow commands
- Vomiting and not responsive to standard treatment
- Any deviation from the surgical or anesthetic protocols

The inclusion/exclusion and entry criteria appear appropriate for safety and efficacy study in an acute pain population.

Procedures

The study was to consist of a screening visit, admission for surgery visit (Day 1), and the study period (up to 48 hours). At screening, the patients were to have a physical examination, vital sign assessment, medical history review, drug abuse screen, pregnancy test (if applicable), inclusion/exclusion criteria review and sign the informed consent. On admission for surgery, eligibility requirements were to be reviewed and then randomized if appropriate. Patients were to be allowed opioids for pain according to standard of practice for post-operative care before the start of the study, but must still have reported a PI score of 4 or more just prior to dosing with the study drug. If a patient did not meet entry criteria by 8 hours after surgery, they were not to be randomized and were discontinued. During the study period, the patient must report a PI score ≥ 4 on an 11-point rating scale just prior to the first dose of study drug. Patients who were withdrawn from the study for any reason prior to 24 hours were to be considered early terminations. To remain in the study after 24 hour, the patient was to require a PI≥ 4 to continue. The same requirements for PI were to be applied at 36 hours. Details of the procedures for SAP301 are in the table below (Table 7).

Table 7: Schedule of Assessments and Procedures - Study SAP301

Procedures	Hospital Admission	PACU or Research Unit	0 - 12hr Treatment Period	12 - 24hr Treatment Period	24–36 hr Treatment Period[F]	36–48 hr Treatment Period	Study Completion or Early Termination
Pregnancy test	✓						
Exclusion Criteria at Randomization		✓					
Randomize Patient/Dispense Study Drug to HCP		✓					
Baseline Pain Intensity (just prior to 1st dose)		✓					
First dose of study drug		✓					
Study drug administration (record time and date of each dose)			✓	✓	✓	✓	
Double stop-watch of "perceptible" and "meaningful" pain relief after first dose only			✓				
Pain intensity and pain relief assessments		✓[A]	✓[A]	✓[A]	✓[A]	✓[A]	✓[A]
Blood pressure and heart rate		✓[A]	✓[A]	✓[A]	✓[A]	✓[A]	
Respiratory rate, oxygen saturation		✓	✓[B]	✓[B]	✓[B]	✓[B]	
Blood sampling for PK analysis			✓[C]	✓[C]			✓[C]
PGA and HPGA Questionnaires				✓[D]		✓[D]	✓[D]
Study Drug Administration Questionnaire							✓[E]
Study drug accountability							✓
Record concomitant medications	✓	✓	✓	✓	✓		✓
Record adverse events			✓	✓	✓	✓	✓[G]

[A]Blood pressure, heart rate, pain intensity, pain relief: collected just prior to first dose of study medication (PI, BP, and HR only at baseline) then at 15 min, 30 min, 45 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after the first dose of study drug is taken, then every 2 hours during 12-24 hours, and every 4 hours during 24-48 hours. PI/PR collected just prior to all doses of rescue medication. Vital signs collected first followed by pain intensity and then pain relief at each of the time points.
[B]Respiratory rate, oxygen saturation recorded at 15 min, 30 min, 45 min, and 1 hour after first dose, then every 30 min through the remainder of 48 hour study period.
[C]Blood sampling for PK performed at 1, 12 and 24hours after the first dose of study drug, or at early termination.
[D]PGA and HPGA to be completed 24 and 48 hours after first dose of study drug or at termination.
[E]Every HCP who dosed at least 3 patients was to complete the Study Drug Administration Questionnaire at the completion of the study.
[F]Prior to continuing in the study at 24 and 36 hours, when the patient requests another dose of study drug, the patient's pain intensity score must have been ≥4. If the pain intensity score was < 4 and did not increase to ≥ 4 within one hour, or the patient was unwilling to wait up to one hour, the patient was to be discontinued from the study and given a standard analgesic medication.
[G]Adverse events were monitored for12 hours after last dose of study drug.

Source: Applicants CSR for SAP301, p. 33-34

The safety assessments appear to be appropriate to capture the safety signals in this population exposed to this class of drug.

Screening Visit

- Physical examination was to include vital signs, height, and weight, drug abuse screen and an examination of the oral mucosa
- Female patients were to have a pregnancy test

Subject Withdrawal

Subjects in this clinical study were to be discontinued for any of the following reasons:

- Investigator and/or the Medical Monitor could exercise judgment to terminate a patient's participation in the study if it was in the best interest of the patient (e.g., adverse event)
- Oxygen saturation levels that could not be maintained at ≥ 95% with or without the use of supplemental oxygen
- Respiratory rate less than 8 bpm
- Excessive sedation
- Death
- Withdrawal of consent
- Protocol violation
- Lack of efficacy
    - If a patient was unable to obtain satisfactory analgesia using the study drug along with rescue medication, he/she was withdrawn from the study

Evaluations/Endpoints

Primary Endpoint:

The pre-specified primary efficacy variable was the time-weighted summed pain intensity difference (SPID) over the12-hour study period (SPID12). PI was measured using an 11-point NRS with 0 (no pain) and 10 (worst possible pain). The pain intensity difference (PID) at each evaluation time point after the initiation of the first dose is the difference in pain intensity at the specific evaluation time point and baseline pain intensity [PID (evaluation time after the first dose) = PI (baseline) – PI (evaluation time after the first dose)]. The time-weighted SPID12 is the time-weighted summed PID over the 12-hour study period. Pain intensity was to be measured at baseline and at 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 44, and 48 hours following the first dose of study drug. If rescue medication was to be used, the PI-NRS score recorded just prior to taking rescue medication.

The pre-specified primary endpoint is acceptable for the measure of efficacy in an acute pain population.

Secondary Efficacy Endpoints:

- Time-weighted SPID over the first hour of the study period (SPID1)
- Time-weighted SPID over the 24 and 48 hours of the study period (SPID24 and SPID48)
- Total pain relief (TOTPAR) over the12, 24, and 48 hours of the study period (TOTPAR12, TOTPAR24, and TOTPAR48)
- Time-weighted summed pain relief intensity difference (SPRID) over the 12, 24, and 48 hours of the study period (SPRID12, SPRID24, and SPRID48)
- Proportion of patients who terminated from the study due to inadequate analgesia

- Proportion of patients who required rescue medication due to inadequate analgesia
- Proportion of patients and healthcare professionals who responded to the global assessments as "excellent" or "good"
- Proportion of patients and healthcare professionals who responded in each category of the global assessments
- Pain intensity (PI) at each evaluation time point
- Pain intensity difference (PID) at each evaluation time point
- Pain relief (PR) at each evaluation time point
- Pain relief intensity difference (PRID) at each evaluation time point
    - PRID is the sum of PR and PID
- Proportion of patients who completed 24 hours in the study and did not require study medication beyond the 24-hour study period
- Time to first use of rescue medication
- Total number of study medication and rescue medication doses used over the 48-hour study period
- Mean duration of inter-dosing interval over the 12, 24, and 48 hours
- Time to onset of perceptible and meaningful pain relief

Safety Assessments

- Patient was to be continuously monitored for first hour after dose of study drug
- Vital signs[5] were to be measured just prior to being dosed with PI and P measures
- Respiratory rate and oxygen saturation were to be measured at baseline and at 15 min, 30 min, 45 min, and 60 minutes after the first dose of study drug, and then 30 minutes for the remainder of the study(Table 4)
- Incidence of AE/SAEs
- Physical examinations
- Laboratory parameters
    - Drug screen - screening
    - Pregnancy test - screening and admission
    - No laboratory data available to perform an analysis.

The safety assessments appear reasonable for an acute pain study using an opioid medication in the clinical setting described above.

Statistical Plan

Primary Analysis

- The primary efficacy endpoint was to be the time-weighted summed pain intensity difference (SPID) over the 12-hour study period (SPID12) on NRS

5 Heart rate, BP, respiratory rate and oxygen saturation

- The primary null hypothesis tested was to be the difference in the least squares (LS) mean of the time-weighted SPID12, between the sufentanil 30 mcg treatment and placebo treatment groups equals zero
    - Performed at the $\alpha = 0.05$ significance level
- A parallel lines analysis of covariance (ANCOVA) model was to be used for the analysis of the primary efficacy endpoint, time-weighted SPID12
    - Model was to include treatment, center, and sex (male and female) factors, and baseline pain intensity as a covariate

Baseline Comparability

- Demographics and baseline characteristics were to be compared for all randomized patients
- A two-sample t-test was to analyze the numeric variables and variances was to be measured through an F-test
- Similar summaries were to be performed for the ITT population, completers population and safety population

Analysis Population and Handling of Dropouts

- The main analysis of the primary and secondary efficacy endpoints was to include the intent-to-treat (ITT) population. The ITT population was to include all randomized patients who received study medication.
- A patient was to be considered a completer if they completed the study through 24 hours, otherwise they were to be an early termination

Missing data for PI or PR:

- First imputed on a patient-by-patient basis using the linear interpolation method between two observed pain scale values
- For patients who used any rescue medication during the study period, the last observed pain data (PI or PR) prior to taking each dose of rescue medication was to be carried throughout a one-hour time interval following the dosing of rescue medication
- Missing pain data at follow-up time points post-termination up to the end of the study period were to be imputed on a patient-by-patient basis
- A model was to be used for imputing missing data in clinical studies: a modified method for imputing the post-termination missing pain PI and PR data (terminated from the study prior to the 48-hour time point)
    - This same method was to be applied to impute missing PI data at all scheduled pain evaluation time points for all dropouts

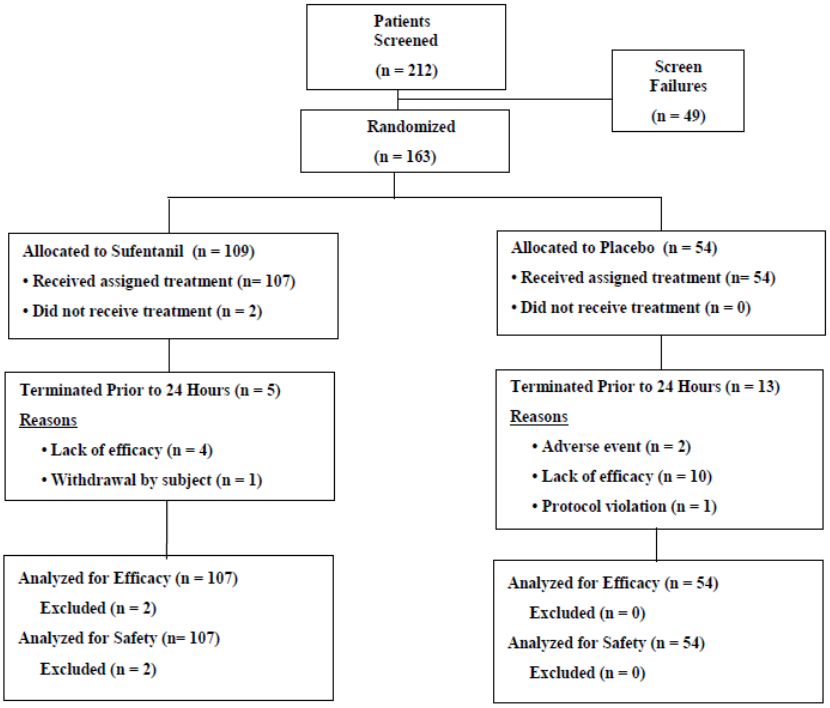
For detailed description of the statistical methods please refer to the review by Dr. Yin Ren.

Results

Subject Disposition

A total of 163 patients (109 sufentanil, 54 placebo) were enrolled and randomized in this study. Two subjects (both sufentanil) did not receive study drug. Therefore, 161 subjects were included in the ITT and safety populations. The main analysis of the efficacy data used the ITT population, which included all randomized patients who received study drug. A total 143 patients (88.8%; 102 sufentanil, 41 placebo) completed the 24-hour study period and were included in the completer efficacy analysis. Eighteen patients (5 sufentanil, 13 placebo) terminated the study during the 24-hour study period and the most frequent reason was lack of efficacy (4 sufentanil, 10 placebo patients). Figure 2 displays an overview of the disposition of subjects. The size of the study population further decreased after 24 hours. A total of 31 subjects completed the 36-hour period and 18 completed the 48-hour period. This decrease in number of subjects is not surprising given this is an outpatient procedure and most patients may not require prolonged management. The primary endpoint is the SPID-12, and the number of subjects who completed the first 12 hours is adequate to assess efficacy in acute pain. The safety should also be adequately assessed given this is a rapid acting opioid and most adverse events will be observed relatively quickly after dosing. Majority of reasons for leaving the study before the 24-hour, 36-hour and 48-hour periods are due to recovery or patient discharged from the unit (Table 8).

Figure 2: Subject Disposition – Study SAP301



Source: CSR, p. 53

Table 8: Subject Disposition and Reason for Termination- Study SAP301

Number of Patients	Sufentanil 30 mcg (n = 109)	Placebo (n = 54)	Total (n = 163)
Randomized	109	54	163
Did not receive treatment	2	0	2
Included in safety analyses	107 (100%)	54 (100%)	161 (100%)
Included in efficacy analyses for the ITT population	107 (100%)	54 (100%)	161 (100%)
24-Hour Study Period			
Completed the 24-hour study period and included in the efficacy analyses for study Completers	102 (95.3%)	41 (75.9%)	143 (88.8%)
Terminated study during the24-hour study period	5 (4.7%)	13 (24.1%)	18 (11.2%)
Reason for termination before 24 hours:			
Adverse event	0	2 (3.7%)	2 (1.2%)
Lack of efficacy	4 (3.7%)	10 (18.5%)	14 (8.7%)
Protocol violation	0 (0.0%)	1 (1.9%)	1 (0.6%)
Withdrawal by subject	1 (0.9%)	0 (0.0%)	1 (0.6%)
Completed 24-hour study period but did not enter 36-hour study period	62 (57.9%)	28 (51.9%)	90 (55.9%)
Reason for not entering 36-hour study period			
Lack of efficacy	0	2 (3.7%)	2 (1.2%)
Recovery	13 (12.1%)	8 (14.8%)	21 (13.0%)
Patient discharged	49 (45.8%)	18 (33.3%)	67 (41.6%)
36-Hour Study Period			
Entered 36-hour study period	40 (37.4%)	13 (24.1%)	53 (32.9%)
Completed 36-hour study period	22 (20.6%)	9 (16.7%)	31 (19.3%)
Terminated between 24 and 36 hours	18 (16.8%)	4 (7.4%)	22 (13.7%)
Reason for termination between 24 and 36 hours:			
Adverse event	1 (0.9%)	0 (0.0%)	1 (0.6%)
Lack of efficacy	2 (1.9%)	0 (0.0%)	2 (1.2%)
Recovery	15 (14.0%)	4 (7.4%)	19 (11.8%)
Completed 36-hour study period but did not enter 48-hour study period	1 (0.9%)	0	1 (0.6%)
Reason for not entering 48-hour study period			
Recovery	1 (0.9%)	0	1 (0.6%)
48-Hour Study Period			
Entered 48-hour study period	21 (19.6%)	9 (16.7%)	30 (18.6%)
Completed 48-hour study period	10 (9.3%)	8 (14.8%)	18 (11.2%)
Discontinued between 36 and 48 hours	11 (10.3%)	1 (1.9%)	12 (7.5%)

Number of Patients	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)	Total (n = 163)
Reason for discontinuation between 36 and 48 hours:			
Recovery	11 (10.3%)	0	11 (6.8%)
Withdrawal by subject	0	1 (1.9%)	1 (0.6%)

Source: CSR, p.54-55

Demographics

The main analysis of efficacy data is based on the ITT population (all randomized who received study drug). For the ITT population (Table 9), the mean (SD) age was 40.9 (11.1) years and 2 (1.2%) patients were at least 65 years old. The majority of subjects were white and female, 109 (67.7%) and 113 (70.2%) respectively. A total of 80 (49.7%) patients underwent abdominoplasty, 33 (20.5%) underwent hernioplasty, and 48 (29.8%) patients had laparoscopic abdominal surgery. No statistically significant differences between treatment groups for demographic or baseline variables were observed. The demographic information appears consistent for the population being studied and is not expected to have any bias in favor of treatment for efficacy or safety analyses.

Table 9: Demographics and Baseline Characteristics for SAP301- ITT Population

	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)	Total (n = 161)
Age (years): n (%)			
< 65	106 (99.1%)	53 (98.1%)	159 (98.8%)
≥ 65	1 (0.9%)	1 (1.9%)	2 (1.2%)
Mean (SD)	41.2 (10.6)	40.4 (12.1)	40.9 (11.1)
Min, max	18.0, 69.0	20.0, 68.0	18.0, 69.0
Sex: n (%)			
Male	34 (31.8%)	18 (33.3%)	52 (32.3%)
Female	73 (68.2%)	36 (66.7%)	109 (67.7%)
Race: n (%)			
White	76 (71.0%)	37 (68.5%)	113 (70.2%)
Black or African American	21 (19.6%)	10 (18.5%)	31 (19.3%)
Asian	3 (2.8%)	1 (1.9%)	4 (2.5%)
Other	7 (6.5%)	6 (11.1%)	13 (8.1%)
Ethnicity: n (%)			
Hispanic or Latino	42 (39.3%)	19 (35.2%)	61 (37.9%)
Not Hispanic or Latino	65 (60.7%)	35 (64.8%)	100 (62.1%)
Body Mass Index (kg/m^2) : n (%)			
< 30	77 (72.0%)	35 (64.8%)	112 (69.6%)
≥ 30	30 (28.0%)	19 (35.2%)	49 (30.4%)
Mean (SD)	27.5 (4.8)	27.6 (4.9)	27.5 (4.8)
Min, max	18.0, 42.0	15.8, 39.2	15.8, 42.0
Surgery: n (%)			
Abdominoplasty	52 (48.6%)	28 (51.9%)	80 (49.7%)
Hernioplasty	23 (21.5%)	10 (18.5%)	33 (20.5%)
Laparoscopic abdominal surgery	32 (29.9%)	16 (29.6%)	48 (29.8%)

Source: CSR, p.58

Prior and Concomitant Drug Treatments

The majority of subjects (97%) took one or more concomitant medications. The percentages for different medications were similar between groups with the expected exception of morphine use in the placebo group (Table 10).

Table 10: Concomitant Medications – SAP301

Medication Class Medication	Sufentanil 30 mcg (n=107)	Placebo (n=54)	Total (n=161)
Any Concomitant Medication	**102 (95.3%)**	**54 (100%)**	**156 (96.9%)**
Anilides	**20 (18.7%)**	**8 (14.8%)**	**28 (17.4%)**
Paracetamol	20 (18.7%)	8 (14.8%)	28 (17.4%)
Electrolyte Solutions	**23 (21.5%)**	**12 (22.2%)**	**35 (21.7%)**
Sodium chloride	23 (21.5%)	12 (22.2%)	35 (21.7%)
Medical Gases	**61 (57.0%)**	**29 (53.7%)**	**90 (55.9%)**
Oxygen	61 (57.0%)	29 (53.7%)	90 (55.9%)
Natural Opium Alkaloids	**29 (27.1%)**	**35 (64.8%)**	**64 (39.8%)**
Morphine or morphine sulfate	29 (27.1%)	35 (64.8%)	64 (39.8%)
Serotonin (5-HT_3) Antagonists	**47 (43.9%)**	**20 (37.0%)**	**67 (41.6%)**
Ondansetron	47 (43.9%)	20 (37.0%)	67 (41.6%)
Solutions Affecting the Electrolyte Balance	**42 (39.3%)**	**20 (37.0%)**	**62 (38.5%)**
Flebobag Ring lact	42 (39.3%)	20 (37.0%)	62 (38.5%)

Source: CSR, p.109

Protocol Deviations

There were a number of protocol deviations reported by the Applicant and the data analyses were adjusted as follows:

- Patients randomized but not dosed (2 sufentanil). Patients were excluded from the analysis of efficacy and safety data.
- Patient randomized according to wrong stratification factor as female instead of male (1 sufentanil). Patient was excluded from the analysis of efficacy and safety data because he did not receive study drug.
- Missing pain intensity (PI) data prior to the first dose for the 24-36 hour study period (7 sufentanil, 1 placebo). Data were adjusted for the derivation of efficacy outcome variables.
- Missing PI data prior to the first dose for the 36-48 hour continuation period (1 sufentanil, 1 placebo). Data were adjusted for the derivation of efficacy outcome variables.
- Missing PI and/or Pain relief (PR) data prior to rescue medication (1 sufentanil, 5 placebo). Data were adjusted for the derivation of efficacy outcome variables.

- Missing scheduled PI and/or PR data (16 sufentanil, 7 placebo). Data were adjusted for the derivation of efficacy outcome variables.
- Patient Global (PGA) not collected at early termination (6 sufentanil, 5 placebo). Data were adjusted for the derivation of efficacy outcome variables.
- HPGA not completed at 24 hours, 48 hours, and/or early termination time points (13 sufentanil, 10 placebo). Data were adjusted for the derivation of efficacy outcome variables.
- Missing baseline SpO2 data (3 sufentanil). Excluded from by-visit summary of SpO2 data.

These deviations were discussed with the statistician and did not appear to cause a significant impact on the efficacy analyses. The majority of missing data were outside of the primary endpoint assessment period (i.e., 12 hours).

Additional results are discussed in the relevant sections below.

6 Review of Efficacy

Efficacy Summary

The pivotal, placebo-controlled, randomized, double-blind, Phase 3 study (SAP301) was conducted in 161 patients who had undergone outpatient abdominal surgeries (abdominoplasty, inguinal hernioplasty, laparoscopic abdominal surgery), with a primary endpoint of the time-weighted summed pain intensity difference over 12 hours (SPID12). The Phase 2 study (SAP302) is not included in the efficacy assessment due to different formulation administered.

SAP301 showed a statistically significant difference for the primary efficacy endpoint of SPID12. Treatment differences between subgroups were mostly consistent across age, sex, race, and investigational site. Secondary endpoints, such as time to first use of rescue medication over the first 12 hours and number of rescue medication used over the first 12 hours, showed statistical evidence of benefit for Dsuvia when compared to placebo. Time to onset of a meaningful measure of pain relief was numerically shorter for the Dsuvia group compared to placebo. The secondary measures are supportive of the primary endpoint measure. However, there was no control for multiplicity of these endpoints.

In summary, Dsuvia showed superior analgesic efficacy compared to placebo based on the primary endpoints and supporting secondary endpoints. The Applicant's findings were confirmed by our statistical reviewer, Dr. Yi Ren. Dr. Ren also ran an additional sensitivity analysis which confirmed the efficacy findings. For details of the statistical methods, please refer to Dr. Ren's review.

6.1 Indication

Management of moderate-to-severe acute pain severe enough to require an opioid agonist, in adult patients in a medically supervised setting.

- Not for home use or for use in children

6.1.1 Methods

See Section 5.2

6.1.2 Demographics

See Section 5.2

6.1.3 Subject Disposition

See Section 5.2

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the time-weighted summed pain intensity difference (SPID-12). Pain intensity was measured using an 11-point NRS. Pain intensity was recorded at baseline, and then pain intensity assessed at the following time points: 15 min, 30 min, 45 min, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after the first dose of study drug and then every 2 hours between 12 and 24 hours. Of note, only 14 patients (8.7%) prematurely discontinued the study within the first 12-hour study period would not lead to a large impact on the data analyses.

The ITT population analysis (Table 11) showed the Dsuvia (sufentanil) group showed statistical significance compared to placebo with respect to the SPID-12 with an estimated mean difference of 12.70 (LS mean [SEM]: 25.8 [1.71] vs. 13.1 [2.35]; LS mean difference [95% CI]: 12.7 [7.2, 18.2]).

Table 11: Analysis of time-weighted SPID12: ITT population (SAP301)

	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)	P-value[a]
Baseline Pain Intensity			
Mean (SD)	5.79 (1.75)	5.59 (1.56)	
LS mean (SEM)	5.61 (0.13)	5.48 (0.18)	0.547
95% CI	(5.36, 5.87)	(5.13, 5.84)	
Time-weighted SPID12			
Mean (SD)	25.93 (20.25)	11.88 (19.47)	
LS mean (SEM)	25.84 (1.71)	13.14 (2.35)	< 0.001
95% CI	(22.46, 29.22)	(8.50, 17.79)	
Difference[b]			
LS mean (SEM)	12.70 (2.80)	NA	
95% CI	(7.16, 18.23)		

Abbreviations: CI = confidence interval; ITT = intent-to-treat; LS = least squares; NA = not applicable; SD = standard deviation; SEM = standard error of the LS mean; SPID12 = summed pain intensity difference over the 12-hour study period.

[a]P-value for the test of treatment effect is based on Type III analysis.

[b]Sufentanil minus placebo.

Note: For the baseline pain intensity, the LS mean and SEM were estimated from the ANOVA model that included treatment, center, and sex factors. For the time-weighted SPID12, the LS mean and SEM were estimated from the ANCOVA model that included treatment, center, and sex factors, and baseline pain intensity as a covariate.

Source: Study SAP301 CSR, Table-5

FDA statistical reviewer, Dr. Yi Ren, confirmed the results of the primary analysis (Table 12). Dr. Ren's analysis also showed a statistically significant difference ($p < 0.001$) between treatment groups for time-weighted SPID-12, with a higher mean SPID-12 score in the Dsuvia group (LS mean [SE]: 26.36 [1.83]) than in the placebo group (LS mean [SE]: 13.66 [2.44]). There was not a significant difference in the baseline pain scores.

Table 12: Primary Efficacy Analysis Results for SPID-12

	Dsuvia (Sufentanil) (n=107)	Placebo (n=54)	P-value
Baseline Pain Intensity			
Mean (SD)	5.79 (1.75)	5.59 (1.56)	
Range	(3.00, 10.00)	(4.00, 9.00)	
LS mean (SEM)	5.87 (0.15)	5.73 (0.20)	
95% CI	(5.58, 6.17)	(5.34, 6.13)	
Difference			
LS mean (SEM)	0.14 (0.23)	NA	0.543
95% CI	(-0.31, 0.59)		

SPID12			
Mean (SD)	25.93 (20.25)	11.88 (19.47)	
Range	(-42.15, 71.87)	(-34.96, 64.37)	
LS mean (SEM)	26.36 (1.83)	13.66 (2.44)	
95% CI	(22.74, 29.98)	(8.83, 18.48)	
Difference			
LS mean (SEM)	12.70 (2.80)	NA	<0.0001
95% CI	(7.17, 18.24)		

SD: standard deviation
SEM: standard error of the LS mean

Source: Dr. Yi Ren's review, Table-3

The applicant did not conduct any sensitivity analyses, however, Dr. Ren conducted a sensitivity analysis which examined the impact of missing data on the primary efficacy analysis. Dr. Ren used a multiple imputation method based on baseline distribution for all patients were used to replace the monotone missing PI values for early dropouts. The combined results of the sensitivity analysis were consistent with the primary results and showed a statistically significant difference between treatment groups in the first 12 hours (Table 13).

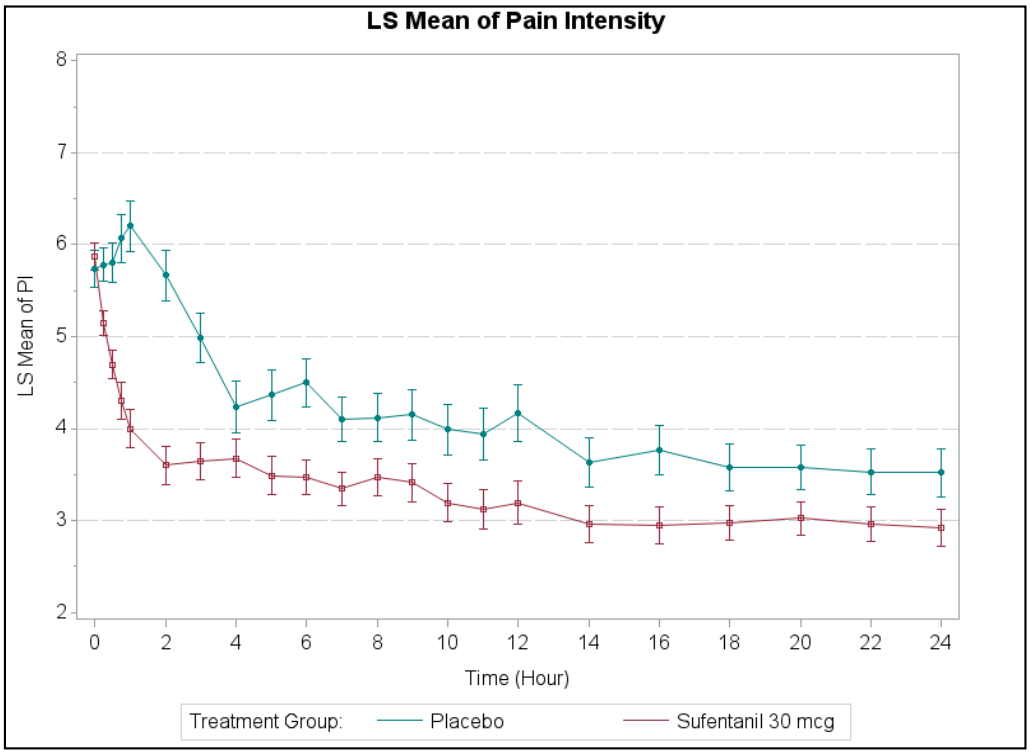
Table 13: Sensitivity Analysis Results for SPID-12

	Dsuvia (Sufentanil) 30 mcg (n=107)	Placebo (n=54)	P-value
SPID12			
Mean (SD)	25.74 (20.21)	11.10 (19.87)	
Range	(-41.93, 71.75)	(-36.09, 64.25)	
LS mean (SEM)	25.74 (1.75)	12.43 (2.42)	
95% CI	(22.29, 29.18)	(7.66, 17.20)	
Difference			
LS mean (SEM)	13.30 (2.87)	NA	<0.0001
95% CI	(7.63, 18.98)		

Source: Dr. Yi Ren's review, Table-4

Although the Division agreed the SPID-12 was a reasonable primary endpoint to determine efficacy, we requested pain assessments be measure beyond the 12 hour point (i.e., at least 24 hours). Dr. Ren analyzed the pain curves for the first 24 hours showing a difference between Dsuvia and placebo (Figure 3). As shown there is a sharp contrast between pain score differences early in treatment. The LS mean PI scores were significantly lower in the Dsuvia group than in the placebo group at all evaluation time points except for 4 hours ($p = 0.082$) and after 20 hours (p-values equal to 0.051, 0.051, and 0.049 for 20 hours, 22 hours, and 24 hours, respectively).

Figure 3: Least Squares Mean of Pain Intensity over the 24-Hour Study Period



Source: Dr. Yi Ren's review, Figure 1

6.1.5 Analysis of Secondary Endpoints(s)

No secondary endpoints were identified as key. Also, the Applicant did not adjust for multiplicity for any of the secondary endpoints. However, I discussed several clinical endpoints that were most relevant for the proposed indication with Dr. Ren who subsequently analyzed the raw data for the endpoints below. The p-values are for descriptive purposes only since there was no control for multiplicity. The most relevant secondary endpoints are:

- Time to first use of rescue medication
- Total number of doses of study drug and rescue medication used over 12-hour study period (this has been changed from the pre-specified secondary endpoint that used 48-hour study period)
- Time to onset of meaningful pain relief

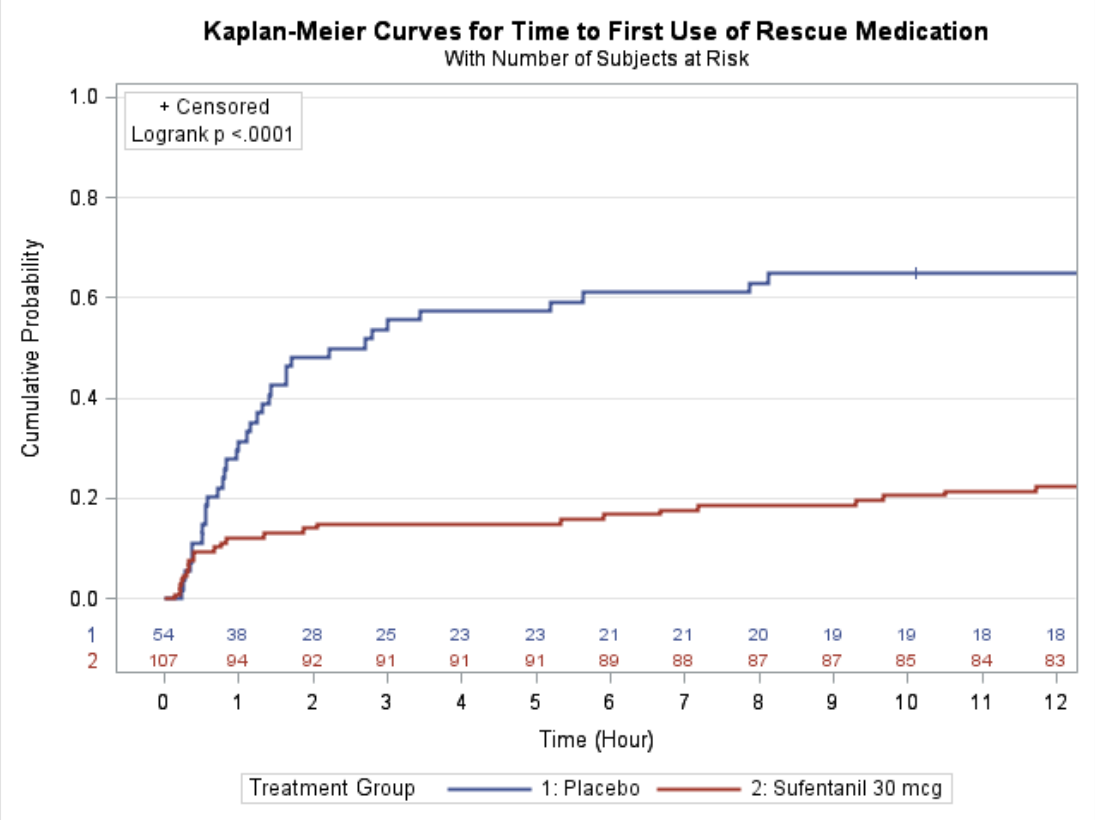
In assessment of acute pain after a surgical procedure, comparing use of rescue is important. If the treatment group showed an improvement in pain score difference but also used considerably more rescue, then whether the primary outcome is clinically

meaningful would come into question. Also, the time to onset of meaningful pain relief is very important for an acute pain drug. An acute pain medication should have a meaningful onset within a reasonably short period of time to be useful in clinical practice. Given these results are supportive of the primary endpoint, the 12-hour period is the most relevant to analyze.

Time to first use of rescue medication

There was a statistically significant difference ($p < 0.001$) between Dsuvia and placebo with respect to time-to-first use of rescue medication over the first 12-hours of the study (Figure 4). The Kaplan-Meier curves in the figure below show the clear separation between the two groups.

Figure 4: Kaplan-Meier Curves for Time to First Use of Rescue Medication over the 12-Hour Study Period



Source: Dr. Yi Ren's review, Figure-3

Total number of study drug and rescue medication doses used over the 12-hour study period

There were statistically significant differences between Dsuvia and placebo groups for the LS mean total number of rescue medication doses used during the 12-hour study period showing a higher proportion of rescue usage in the placebo group (Table 14).

Table 14: Number of Rescue Medication Doses Used over the 12-Hour Study Period

Number of Doses Used over 12 Hours	Dsuvia (Sufentanil) 30 mcg (n = 107)	Placebo (n = 54)	P-value
Mean (SD)	0.4 (1.0)	1.6 (1.8)	
Median	0	1	
Range	(0, 7)	(0, 8)	
LS mean difference	-1.2 (-1.6, -0.8)		<0.001
Number (%) by category			
0	83 (77.6)	19 (35.2)	<0.001
1-2	21 (19.6)	23 (42.6)	
3-4	1 (0.9)	8 (14.8)	
>4	2 (1.9)	4 (7.4)	

P-value for total number of doses is based on the ANOVA model including treatment, center, and gender; P-value for number by category is based on Fisher's exact test.

Source: Dr. Yi Ren's review, Table-6

There was no significant difference between usage of Dsuvia and placebo groups. This result is likely due to the placebo groups showing some efficacy with usage of rescue and therefore no difference between groups could be detected. However, the Applicant noted in their analysis that the LS mean dosing interval was longer in the Dsuvia group for the 12-hour study period (185.41 vs. 146.55 minutes; p = 0.008).

Time to meaningful pain relief over the 12-hour study period

The time to onset of meaningful pain relief was also shorter in the Dsuvia group than in the placebo group (54 vs. 84 minutes). Over half of the Dsuvia group has a meaningful pain relief within 1 hour, compared to 1.5 hours for the placebo group. Although numerically this shows an advantage for the Dsuvia-treated patients, no statistical significance was shown (p=0.156). This lack of statistical significance does not necessarily mean the differences were not clinically important. The analysis may be confounded by use of rescue, also the time period was relatively short and therefore a statistical difference may be hard to achieve.

6.1.6 Other Endpoints

Other notable secondary endpoints analyzed by the Applicant only are described below.

Rescue medication use due to inadequate analgesia

Dsuvia was superior to placebo for the proportion of patients who took rescue medication due to inadequate analgesia ($p < 0.001$), with a higher proportion of patients in the placebo group (35/54, 64.8%) requiring rescue medication due to inadequate analgesia than in the Dsuvia group (29/107, 27.1%).

Proportion of patients who terminated from the study due to inadequate analgesia

Dsuvia was superior to placebo for the proportion of patients who terminated the study due to inadequate analgesia during the 24-hour study period ($p = 0.002$). Dsuvia also had a longer time to termination due to inadequate analgesia over the 24-hour study period and over the entire study period ($p = 0.001$ for both).

6.1.7 Subpopulations

Both the Applicant and Dr. Ren conducted analyses by age, sex, race, BMI and type of surgery (Table 15). Statistically significant differences were noted for most subgroups.

Table 15: Analysis of time-weighted SPID12 by demographic variables, BMI, and type of surgery: ITT population (SAP301)

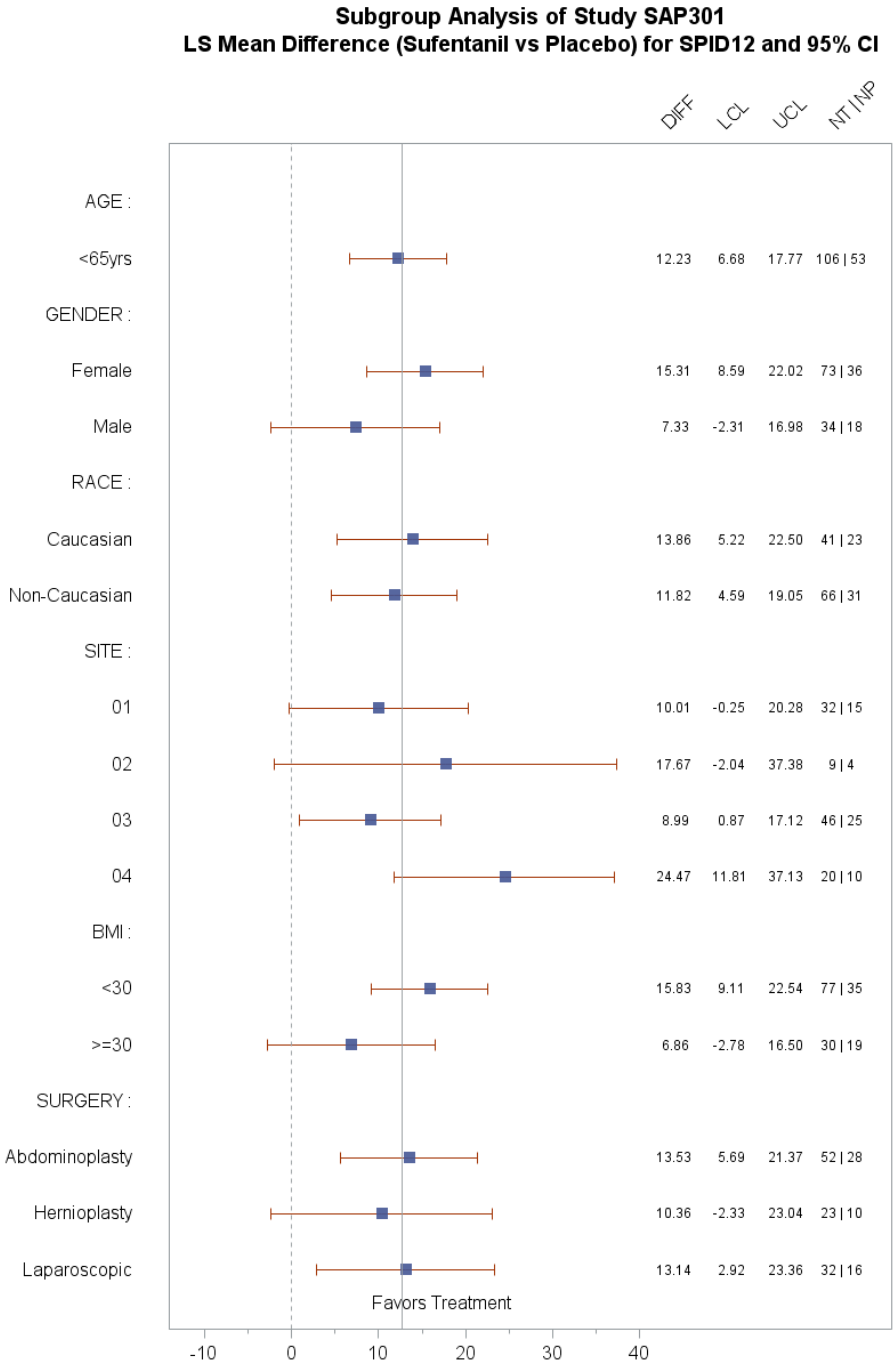
Time-weighted SPID12	Sufentanil 30 mcg	Placebo	Difference[a]	P-value[b]
Age < 65 Years: n	106	53		
LS mean (SEM)	25.15 (1.62)	12.92 (2.29)	12.23 (2.81)	< 0.001
95% CI	(21.96, 28.35)	(8.40, 17.45	(6.68, 17.77)	
Male patients: n	34	18		
LS mean (SEM)	18.55 (2.73)	10.31 (3.77)	8.24 (4.69)	0.085
95% CI	(13.07, 24.03)	(2.73, 17.89)	(-1.19, 17.68)	
Female patients: n	73	36		
LS mean (SEM)	28.90 (2.00)	13.60 (2.84)	15.30 (3.48)	< 0.001
95% CI	(24.94, 32.86)	(7.97, 19.24)	(8.41, 22.19)	
Caucasian patients: n	41	23		
LS mean (SEM)	23.31 (2.35)	9.37 (3.14)	13.95 (3.92)	0.001
95% CI	(18.61, 28.02)	(3.08, 15.65)	(6.10, 21.80)	
Non-Caucasian patients: n	66	31		
LS mean (SEM)	26.86 (2.19)	15.21 (3.20)	11.65 (3.88)	0.003
95% CI	(22.51, 31.21)	(8.86, 21.57)	(3.94, 19.36)	
BMI < 30 kg/m^2: n	77	35		
LS mean (SEM)	26.54 (1.99)	10.95 (2.95)	15.60 (3.56)	< 0.001
95% CI	(22.60, 30.48)	(5.10, 16.79)	(8.54, 22.66)	
BMI ≥ 30 kg/m^2: n	30	19		
LS mean (SEM)	22.87 (2.54)	15.93 (3.20)	6.94 (4.09)	0.096
95% CI	(17.75, 27.99)	(9.49, 22.36)	(-1.28, 15.17)	
Abdominoplasty: n	52	28		
LS mean (SEM)	30.82 (2.28)	17.62 (3.11)	13.19 (3.87)	0.001
95% CI	(26.27, 35.36)	(11.42, 23.83)	(5.49, 20.89)	
Hernioplasty: n	23	10		
LS mean (SEM)	18.55 (3.45)	7.70 (5.29)	10.86 (6.38)	0.099
95% CI	(11.51, 25.59)	(-3.10, 18.49)	(-2.18, 23.89)	
Laparoscopic abdominal surgery: n	32	16		
LS mean (SEM)	21.38 (3.12)	8.24 (4.41)	13.14 (5.40)	0.019
95% CI	(15.09, 27.66)	(-0.65, 17.13)	(2.25, 24.03)	

Abbreviations: BMI = body mass index; CI = confidence interval; ITT = intent-to-treat; LS = least squares; SD = standard deviation; SEM = standard error of the LS mean; SPID12 = summed pain intensity difference over 12 hours.
[a]Sufentanil minus placebo.
[b]P-value for the comparison between treatment groups is based on Type III analysis from the model described in the Study SAP301 CSR.
Note: LS mean and SEM were estimated from the ANCOVA that included treatment factor and baseline pain intensity as a covariate.

Source; Summary of Clinical Efficacy, p. 18

Dr. Ren's analysis is shown in the figure below (Figure 5). Dr. Ren's findings are consistent with the Applicant's. For subgroups that did not show a statistical difference in treatment effect, there was a numerically higher LS mean SPID-12 score favoring the Dsuvia-treated patients. Overall, the treatment effect appears generally consistent across groups.

Figure 5: Subgroup Analyses for Primary Endpoint SPID-12



Source: Dr. Yi Ren's review, Figure-6

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed dose is 30 mcg, there is not additional dosing options for Dsuvia.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This medication is intended for acute treatment of pain. The concepts of tolerance and persistence of efficacy beyond the short treatment period are not relevant in this application.

7 Review of Safety

Safety Summary

The clinical safety database for this NDA comprises four clinical studies in the Dsuvia program (all phases) and six clinical studies from the Zalviso clinical program. The Zalviso clinical studies provide supportive safety data from select subjects based on the pharmacokinetic bridging data. These subjects were exposed to at least two doses of sufentanil 15 mcg sublingual tablets within 25 minutes. The main focus of the safety analysis is on the Dsuvia clinical program (most notably the placebo-controlled pivotal study SAP301), because the safety evaluation is based on the overall safety of the drug and device in combination, and not just the safety of the systemic drug levels that are achieved. However, relevant Zalviso safety data was reviewed in case there was important safety information deemed necessary to communicate to prescribers which cannot be fully captured by the safety results from the Dsuvia program. As stated above, SAP202 is not included in the safety database due to a difference in the formulation used in the study.

The Applicant submitted their application as a 505(b)(2) NDA referencing the approved drug Sufenta (sufentanil citrate injection; NDA 19050). The Applicant is relying in part on the Agency's previous findings of safety and efficacy of the active drug moiety covered under NDA 19050 in addition to safety findings from their clinical program. The entire safety database consists of 646 exposures from the Dsuvia and Zalviso clinical programs and 323 total exposures from the Dsuvia program. As described in Section 5.2 of this review, the safety analyses will be based on a review of the pivotal trial SAP301 as well as numerous pools of data which may include selected subjects from the Zalviso clinical program. Additional pools of interest include the Dsuivia open-label pooled studies (SAP302 and SAP302), the placebo-controlled pooled Zalviso studies and the open-label Zalviso studies. As stated above, the Zalviso data will be analyzed to detect any potential safety signal but not as the primary safety data for this analysis.

My analysis of the clinical program, based on adverse events (AE), suggests that the Dsuvia product has the typical safety profile of an opioid agonist. When compared to a placebo control, there were more AEs, most notably gastrointestinal and respiratory, but no signal was detected beyond the expected level of an opioid drug product. The majority of AEs were mild to moderate in intensity and no opioid reversal agents (e.g.,

naloxone) were required for any patient receiving Dsuvia throughout all Phase 2 or Phase 3 studies. Review of the additional Zalviso subjects did not identify any additional safety concerns.

Summary of Dropped Tablets:
A main concern for the Dsuvia program relates to dropped tablets and the subsequent potential for accidental exposure. The Applicant reported a total of three dropped/misdosed tablets (2 sufentanil and 1 placebo) or 0.15% of the total 1782 single-dose applications (SAP301 = 1,223, SAP302 = 88, and SAP303 = 471) in the Phase 3 studies. The Phase 1 and Phase 2 studies used forceps and therefore these applications were not relevant. All three of the dropped tablets were located and no accidental exposure took place.

SAP301:

- Patient (b) (6) (placebo):
  - The first patient to be dosed at the clinical site. It was determined by the Applicant that the SDA tip was being aimed at the underside of the patient's tongue (instead of the floor of the patient's mouth) as they were lying down, resulting in the tip of the SDA being pointed upwards. The tablet had bounced off the tongue and out of the patient's mouth and was sequestered appropriately by the HCP. No further misplaced doses at the site.
- Patient (b) (6) (sufentanil):
  - The patient was aware that the dose was not properly administered into the sublingual space. The HCP did not follow the Directions for Use and failed to confirm presence of the tablet after dose administration (Directions for Use step #6). The patient had located the tablet and placed in the room's trash can and told the morning shift HCP who then properly sequestered the tablet and documented the event.

SAP303:

- Patient (b) (6) (sufentanil):
  - The HCP prematurely actuated the SDA prior to placing the SDA tip under the patient's tongue. This was a user error of not placing the tip in the correct location prior to actuation. The HCP was aware of the error, and picked up the dropped tablet and properly secured it for accountability.

Overview of Pivotal Study SAP301:
Overall, 96 (59.6%) subjects had at least 1 AE during the study (sufentanil, 62 [57.9%]; placebo, 34 [63.0%]). The number of AEs were similar between treatment groups and no significant differences were noted (Table 16).

Table 16: Summary of Adverse Events - SAP301

Number (%) of Patients	Sufentanil 30 mcg	Placebo	Total
Received treatment	107 (100%)	54 (100%)	161 (100%)
With at least one AE	62 (57.9%)	34 (63.0%)	96 (59.6%)
With at least one AE related to study drug	49 (45.8%)	21 (38.9%)	70 (43.5%)
With serious AE	0	2 (3.7%)	2 (1.2%)
With serious AE related to study drug	0	2 (3.7%)	2 (1.2%)
With AE causing discontinuation of study drug	1 (0.9%)	2 (3.7%)	3 (1.9%)
With severe AE	5 (4.7%)	2 (3.7%)	7 (4.3%)
With severe AE related to study drug	5(4.7%)	1 (1.9%)	6 (3.7%)
No. of Incidents of AEs	107	56	163

Source: Applicants CSR, p.99

Deleted Sections:

The following sections were deleted because no data was submitted or was not relevant to the safety analysis of this product:

7.2.3 Special Animal and/or In Vitro Testing

7.2.5 Metabolic, Clearance, and Interaction Workup

7.4.6 Immunogenicity

7.5.4 Drug-Disease Interactions

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

7.6.3 Pediatrics and Assessment of Effects on Growth

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.7 Additional Submissions / Safety Issues

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Trial SAP301 is the primary placebo-controlled study used for the safety analysis and is described in detail in Section 5.3. However, the safety database consists of a number of pools, as well as an individual review of Trial SAP301. As stated above, although the focus is on the Dsuvia program, most notably the placebo-controlled trial SAP301, the overall safety conclusions are based on the totality of the data submitted in the application in order to examine any potential safety signals that may be present. Additional focus will be placed on the Dsuvia open-label pool, which may provide additional safety information appropriate for labeling. The Zalviso program (select subjects that were bridged to the Dsuvia dose) will also be reviewed to broaden the safety population.

7.1.2 Categorization of Adverse Events

All treatment emergent adverse events (TEAEs) were coded by using the Medical Dictionary for Regulatory Activities (MedDRA), Version 11.0. Adverse events occurring while patients were on study drug, or within 12 hours after the discontinuation of study drug, were to be summarized by treatment group. All randomized patients who received at least one dose of study drug were included in the analyses and summaries of safety data.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As stated in Section 5.2, safety data was pooled from a number of clinical studies in the Dsuvia program and the Zalviso program. The safety analyses are combined in these separate pools in order to capture any potential safety signal.

7.2 Adequacy of Safety Assessments

Overall, the safety assessments appeared adequate for the population, clinical setting and know safety profile of the drug.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

Entire safety pool
The entire safety pool included the Dsuvia clinical program (SAP301, SAP302 and SAP303) as well as select Zalviso exposures for a total of 646 subjects (Table 17). The design of the Zalviso program's studies allowed for a greater duration of exposure to the

study drug. Given the product is an immediate-release opioid product intended for acute pain, the duration of these exposures is adequate to characterize the safety for the intended indication.

Table 17: Entire Safety Population Drug Exposure (SAP301, SAP302, SAP303 and Bridged Zalviso Exposures)

	Treatment Group			
	Sufentanil 15 mcg	Zalviso Placebo	Sufentanil 30 mcg	ARX-04 Placebo
Number of Patients Who Received Treatment - n (%)	323	104	323	54
>= 1 Minute	323 (100.00%)	104 (100.00%)	323 (100.00%)	54 (100.00%)
>= 30 Minutes	321 (99.38%)	104 (100.00%)	225 (69.66%)	52 (96.30%)
>= 1 Hour	317 (98.14%)	92 (88.46%)	225 (69.66%)	52 (96.30%)
>= 2 Hours	307 (95.05%)	75 (72.12%)	211 (65.33%)	49 (90.74%)
>= 4 Hours	297 (91.95%)	65 (62.50%)	190 (58.82%)	47 (87.04%)
>= 6 Hours	292 (90.40%)	58 (55.77%)	178 (55.11%)	42 (77.78%)
>= 8 Hours	291 (90.09%)	52 (50.00%)	154 (47.68%)	39 (72.22%)
>= 12 Hours	255 (78.95%)	47 (45.19%)	93 (28.79%)	32 (59.26%)
>= 16 Hours	247 (76.47%)	44 (42.31%)	83 (25.70%)	27 (50.00%)
>= 20 Hours	240 (74.30%)	42 (40.38%)	75 (23.22%)	24 (44.44%)
>= 24 Hours	226 (69.97%)	41 (39.42%)	25 (7.74%)	9 (16.67%)
>= 32 Hours	206 (63.78%)	38 (36.54%)	15 (4.64%)	5 (9.26%)
>= 40 Hours	196 (60.68%)	33 (31.73%)	10 (3.10%)	4 (7.41%)
>= 48 Hours	101 (31.27%)	19 (18.27%)	1 (0.31%)	0 (0.00%)

Source: ISS Table 14.2.235

Source: Applicant's submission in response to Division's information request on 5/18/17

The number of doses administered in the Zalviso clinical program showed more dosing beyond the 12-hour time-point (Table 18). This is consistent with the design and populations of the studies. The number of doses and duration appear adequate for an acute pain product.

Table 18: Total Number of Doses Administered in Entire Safety Database

	Treatment Group					
	Sufentanil 15 mcg (n = 323)	Zalviso Placebo (n = 104)	Sufentanil 30 mcg (n = 323)	ARX-04 Placebo (n = 54)	Total (n = 804)	p-value[1]
Number of Doses Used (0 - 12 Hours) - n (%)	323 (100%)	104 (100%)	323 (100%)	54 (100%)	804 (100%)	<0.001
< 6	31 (9.6%)	32 (30.8%)	277 (85.8%)	37 (68.5%)	377 (46.9%)	
6 - 12	121 (37.5%)	23 (22.1%)	46 (14.2%)	17 (31.5%)	207 (25.7%)	
13 - 24	145 (44.9%)	38 (36.5%)	0 (0%)	0 (0%)	183 (22.8%)	
> 24	26 (8.0%)	11 (10.6%)	0 (0%)	0 (0%)	37 (4.6%)	
Mean (SD)	14.1 (6.9)	12.6 (8.3)	3.2 (2.1)	4.7 (2.3)	8.9 (7.6)	<0.001
Median	13.0	11.5	3.0	4.0	6.0	
(Min, Max)	(2, 33)	(3, 34)	(1, 9)	(1, 11)	(1, 34)	
Number of Doses Used (0 - 24 Hours) - n (%)	287 (100%)	81 (100%)	107 (100%)	54 (100%)	529 (100%)	<0.001
< 6	16 (5.6%)	20 (24.7%)	42 (39.3%)	25 (46.3%)	103 (19.5%)	
6 - 12	40 (13.9%)	10 (12.3%)	56 (52.3%)	25 (46.3%)	131 (24.8%)	
13 - 24	84 (29.3%)	14 (17.3%)	9 (8.4%)	4 (7.4%)	111 (21.0%)	
> 24	147 (51.2%)	37 (45.7%)	0 (0%)	0 (0%)	184 (34.8%)	
Mean (SD)	25.1 (12.9)	22.1 (15.8)	7.0 (3.6)	6.4 (3.8)	19.0 (14.1)	<0.001
Median	25.0	19.0	7.0	6.0	15.0	
(Min, Max)	(2, 55)	(3, 55)	(1, 15)	(1, 18)	(1, 55)	

Source: Applicant's submission in response to Division's information request on 5/18/17

Study SAP301:

The description of the demographics and disposition is detailed in Section 5.3. A total of 161 subjects were included in the safety population. In the sufentanil group, 82.2% of subjects received study drug for at least 12 hours and 23.4% received study drug for at least 24 hours. In the placebo group, 59.3% of subjects received study drug for at least 12 hours and 16.7% received study drug for at least 24 hours (Table 19). Although the percentage of subjects who received treatments is lower in the placebo group, there was no statistically significant differences between treatment groups for the mean number of study drug doses from 0 to 12 hours (sufentanil 4.4, placebo 4.7), 0 to 24 hours (sufentanil 7.0, placebo 6.4), or for the total number of doses administered (sufentanil 7.8, placebo 7.1). The study drug dosing data for the safety population was exactly the same as for the ITT population (see Section 5.3).

Table 19: Study Drug Dosing: Safety Population – SAP301

Number (%) of Patients who Received Treatment	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)
≥1 minute	107 (100%)	54 (100%)
≥ 1 hour	101 (94.4%)	52 (96.3%)
≥ 2 hours	101 (94.4%)	49 (90.7%)
≥ 4 hours	96 (89.7%)	47 (87.0%)
≥ 6 hours	93 (86.9%)	42 (77.8%)
≥ 8 hours	91 (85.1%)	39 (72.2%)
≥ 12 hours	88 (82.2%)	32 (59.3%)
≥ 16 hours	83 (77.6%)	27 (50.0%)
≥ 20 hours	75 (70.1%)	24 (44.4%)
≥ 24 hours	25 (23.4%)	9 (16.7%)
≥ 28 hours	17 (15.9%)	5 (9.3%)
≥ 32 hours	15 (14.0%)	5 (9.3%)
≥36 hours	14 (13.1%)	4 (7.4%)
≥ 40 hours	10 (9.4%)	4 (7.4%)
≥ 44 hours	8 (7.5%)	3 (5.6%)
≥48 hours	1 (0.9%)	0

Source: CSR, p.98

Open-Label Dsuvia studies (SAP302 and SAP303)

A total of 216 subjects were included in the Dsuvia open-label safety population with a mean number of doses being 2.6 with a SD of 1.8. The exposure is similar to the pivotal study SAP301 showing a trend to have a significant decline in doses and subjects as time progressed (Table 20). This is expected from the nature of the design and populations chosen. However, the exposure is shorter in the open-label population compared to SAP301. This is not unexpected since SAP302 only treated up to 5 hours (as opposed to up to 48 hours in SAP301), and the population was located in the emergency department presenting for an acute injury. SAP303 was also a different population and design from SAP301. SAP303 dosed up to 12 hours and was an older population following any type of surgery. Although there were differences in the exposure duration, given this is a drug for acute pain, the duration is adequate for the purposes of an open-label safety review.

Table 20: Extent of Exposure to Study Drug: Patients Enrolled in Dsuvia Open Label Studies (SAP302 and SAP303)

	Treatment Group 30 mcg
Number of Patients Who Received Treatment - n (%)	216
≥ 1 Minute	216 (100.00%)
≥ 30 Minutes	124 (57.41%)
≥ 1 Hour	124 (57.41%)
≥ 2 Hours	110 (50.93%)
≥ 4 Hours	94 (43.52%)
≥ 6 Hours	85 (39.35%)
≥ 8 Hours	63 (29.17%)
≥ 12 Hours	5 (2.31%)
≥ 16 Hours	0 (0.00%)
≥ 20 Hours	0 (0.00%)
≥ 24 Hours	0 (0.00%)
≥ 32 Hours	0 (0.00%)
≥ 40 Hours	0 (0.00%)
≥ 48 Hours	0 (0.00%)

Source: Applicant's Response to an information request from 5/18/17, source ISS Table 14.2.6

Open-Label Zalviso studies (ARX-C-004 and IAP309)

A total of 112 subjects were included in the Zalviso open-label safety population. The extent of exposure had a similar trend to the open-label Dsuvia studies, however, the Zalviso open-label studies have a greater percentage of subjects being treated beyond the 30 minute time-point Table 21).

Table 21: Extent of Exposure to Study Drug: Patients Enrolled in Dsuvia (SAP302 and SAP303) and Zalviso Open-Label Studies (ARX-C-004 and IAP309)

	Treatment Group	
	Sufentanil 15 mcg	Sufentanil 30 mcg
Number of Patients Who Received Treatment - n (%)	112	216
≥ 1 Minute	112 (100.00%)	216 (100.00%)
≥ 30 Minutes	112 (100.00%)	124 (57.41%)
≥ 1 Hour	112 (100.00%)	124 (57.41%)
≥ 2 Hours	111 (99.11%)	110 (50.93%)
≥ 4 Hours	108 (96.43%)	94 (43.52%)
≥ 6 Hours	106 (94.64%)	85 (39.35%)
≥ 8 Hours	106 (94.64%)	63 (29.17%)
≥ 12 Hours	92 (82.14%)	5 (2.31%)
≥ 16 Hours	87 (77.68%)	0 (0.00%)
≥ 20 Hours	84 (75.00%)	0 (0.00%)
≥ 24 Hours	80 (71.43%)	0 (0.00%)
≥ 32 Hours	74 (66.07%)	0 (0.00%)
≥ 40 Hours	70 (62.50%)	0 (0.00%)
≥ 48 Hours	26 (23.21%)	0 (0.00%)

Source: ISS Table 14.2.6

The Zalviso open-label studies also had a much larger number of doses compared to the Dsuvia studies (Table 22). This larger number of doses is due to the prolonged dosing periods (e.g., IAP309 dosed up to 72 hours) and a different population (i.e., both Zalviso studies were post-operative). This increased exposure provides additional patient exposure for the supportive safety results.

Table 22: Summary of Number of Doses Used in Patients Enrolled in Dsuvia Open- Label Studies (30 mcg) and Zalviso (15 mcg) Open-Label Studies

	SST 15 mcg Doses		SST 30 mcg Doses	
	Mean (SD)	Highest Number	Mean (SD)	Highest Number
Open-label Study Pool	41.2 (29.1)	153	2.6 (1.8)	8

Source: ISS Table 14.2.12

Demographics

Entire safety pool
The Table below describes the complete safety database demographics for both the Dsuvia (sufentanil 30 mcg) and bridged Zalviso (sufentanil 15 mcg) subjects. The Zalviso program included older subjects whereas the Dsuvia program included mostly subjects under 55 years of age (69%). Both programs included mostly white and female subjects.

Table 23: Demographics and Baseline Characteristics of Safety Population (SAP301, SAP302, and SAP303) and Zalviso Studies

	Treatment Group					
	Sufentanil 15 mcg (n = 323)	Zalviso Placebo (n = 104)	Sufentanil 30 mcg (n = 323)	ARX-04 Placebo (n = 54)	Total (n = 804)	p-value[1]
Age (years) - n (%)	323 (100%)	104 (100%)	323 (100%)	54 (100%)	804 (100%)	<0.001
< 55	57 (17.6%)	31 (29.8%)	223 (69.0%)	47 (87.0%)	358 (44.5%)	
55 - < 65	102 (31.6%)	33 (31.7%)	66 (20.4%)	6 (11.1%)	207 (25.7%)	
65 - < 75	100 (31.0%)	24 (23.1%)	26 (8.0%)	1 (1.9%)	151 (18.8%)	
>= 75	64 (19.8%)	16 (15.4%)	8 (2.5%)	0 (0%)	88 (10.9%)	
Mean (SD)	64.0 (12.1)	60.3 (13.0)	47.2 (13.2)	40.4 (12.1)	55.2 (15.4)	<0.001
Median	65.0	61.0	48.0	42.0	56.0	
(Min, Max)	(19.0, 86.0)	(32.0, 87.0)	(18.0, 84.0)	(20.0, 68.0)	(18.0, 87.0)	
Sex - n (%)	323 (100%)	104 (100%)	323 (100%)	54 (100%)	804 (100%)	0.050
Male	114 (35.3%)	37 (35.6%)	145 (44.9%)	18 (33.3%)	314 (39.1%)	
Female	209 (64.7%)	67 (64.4%)	178 (55.1%)	36 (66.7%)	490 (60.9%)	
Race - n (%)	323 (100%)	104 (100%)	323 (100%)	54 (100%)	804 (100%)	<0.001
American Indian or Alaska Native	0 (0%)	1 (1.0%)	6 (1.9%)	0 (0%)	7 (0.9%)	
Asian	1 (0.3%)	1 (1.0%)	5 (1.5%)	1 (1.9%)	8 (1.0%)	
Black or African American	39 (12.1%)	16 (15.4%)	67 (20.7%)	10 (18.5%)	132 (16.4%)	
Native Hawaiian or Other Pacific Islander	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	
White	279 (86.4%)	84 (80.8%)	238 (73.7%)	37 (68.5%)	638 (79.4%)	
Other	3 (0.9%)	2 (1.9%)	7 (2.2%)	6 (11.1%)	18 (2.2%)	

Source: Applicant's Response to an information request from 5/18/17

Study SAP301:
The description of the demographics (107 subjects in Sufentanil group and 54 subjects in placebo group) and disposition is further detailed in Section 5.3.

I evaluated the demographics by sex, age, and race using JMP Clinical 6.1 software. The mean age was about 41 years-old and no difference detected between groups. As shown in the tables below, the percentages were very similar between treatment groups.

Table 24: Safety Population Breakdown by Sex – SAP301

	Actual Treatment for Period 01					
	Placebo		Sufentanil 30 mcg			
Sex	Count	Column %	Count	Column %	Count	% of Total
F	36	66.7%	73	68.2%	109	67.70%
M	18	33.3%	34	31.8%	52	32.30%
All	54	100.0%	107	100.0%	161	100.00%

Source: Clinical Reviewer's Safety Analysis - JMP Clinical 6.1

Table 25: Safety Population Breakdown by Age – SAP301

	Actual Treatment for Period 01					
	Placebo		Sufentanil 30 mcg			
Age Group	Count	Column %	Count	Column %	Count	% of Total
Age 39 or younger	26	48.1%	53	49.5%	79	49.07%
Age between 40 and 64	27	50.0%	53	49.5%	80	49.69%
Age 65 and older	1	1.9%	1	0.9%	2	1.24%
All	54	100.0%	107	100.0%	161	100.00%

Source: Clinical Reviewer's Safety Analysis - JMP Clinical 6.1

Table 26: Safety Population Breakdown by Race – SAP301

	Actual Treatment for Period 01					
	Placebo		Sufentanil 30 mcg			
Race	Count	Column %	Count	Column %	Count	% of Total
ASIAN	1	1.9%	3	2.8%	4	2.48%
BLACK OR AFRICAN AMERICAN	10	18.5%	21	19.6%	31	19.25%
OTHER	6	11.1%	7	6.5%	13	8.07%
WHITE	37	68.5%	76	71.0%	113	70.19%
All	54	100.0%	107	100.0%	161	100.00%

Source: Clinical Reviewer's Safety Analysis - JMP Clinical 6.1

Open-Label Dsuvia studies (SAP302 and SAP303)

The open-label studies consisted of a higher percentage of subjects over age 65 and male compared to the pivotal study SAP301 (Table 27). Also, the open-label studies had a broader range of surgical procedures and non-surgical pain. However, the demographics of this pool are adequate for the purposes of this safety review.

Table 27: Demographics and Baseline Characteristics of Safety Population: Patients Enrolled in Dsuvia (30 mcg) and Zalviso (15 mcg) Open-Label Studies

	Treatment Group		Total	
	Sufentanil 15 mcg (n = 112)	Sufentanil 30 mcg (n = 216)	(n = 328)	p-value*
Age (years) - n (%)	112 (100%)	216 (100%)	328 (100%)	<0.001
< 55	15 (13.4%)	128 (59.3%)	143 (43.6%)	
55 - < 65	38 (33.9%)	55 (25.5%)	93 (28.4%)	
65 - < 75	39 (34.8%)	25 (11.6%)	64 (19.5%)	
≥ 75	20 (17.9%)	8 (3.7%)	28 (8.5%)	
Mean (SD)	64.8 (11.4)	50.1 (13.5)	55.1 (14.6)	<0.001
Median	65.5	51.5	57.0	
(Min, Max)	(19.0, 85.0)	(21.0, 84.0)	(19.0, 85.0)	
Sex - n (%)	112 (100%)	216 (100%)	328 (100%)	0.004
Male	39 (34.8%)	111 (51.4%)	150 (45.7%)	
Female	73 (65.2%)	105 (48.6%)	178 (54.3%)	
Race - n (%)	112 (100%)	216 (100%)	328 (100%)	0.004
American Indian or Alaska Native	0 (0%)	6 (2.8%)	6 (1.8%)	
Asian	0 (0%)	2 (0.9%)	2 (0.6%)	
Black or African American	10 (8.9%)	46 (21.3%)	56 (17.1%)	
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	
White	102 (91.1%)	162 (75.0%)	264 (80.5%)	
Other	0 (0%)	0 (0%)	0 (0%)	
Ethnicity - n (%)	112 (100%)	216 (100%)	328 (100%)	<0.001
Hispanic or Latino	1 (0.9%)	34 (15.7%)	35 (10.7%)	
Not Hispanic or Latino	111 (99.1%)	182 (84.3%)	293 (89.3%)	
Caucasian - n (%)	112 (100%)	216 (100%)	328 (100%)	<0.001
Yes	101 (90.2%)	130 (60.2%)	231 (70.4%)	
No	11 (9.8%)	86 (39.8%)	97 (29.6%)	
Surgery Type - n (%)	112 (100%)	216 (100%)	328 (100%)	<0.001
Orthopedic	93 (83.0%)	28 (13.0%)	121 (36.9%)	
Abdominal	19 (17.0%)	83 (38.4%)	102 (31.1%)	
Other Surgery	0 (0%)	29 (13.4%)	29 (8.8%)	
Non-Surgical	0 (0%)	76 (35.2%)	76 (23.2%)	

Source: Applicant's Response to an information request, source ISS Table 14.1.24

Placebo-Controlled Zalviso Studies (ARX-C-001, ARX-C-005, IAP310 and IAP311)
Compared to the pivotal Dsuvia placebo-controlled study (SAP301), the Zalviso studies included orthopedic procedures (73%) and more subjects over the age of 55 (Table 28).

Table 28: Demographics and Baseline Characteristics of Safety Population: Patients Enrolled in Zalviso Placebo-Controlled Studies

	Treatment Group			
	Sufentanil 15 mcg (n = 211)	Placebo (n = 104)	Total (n = 315)	p-value*
Age (years) - n (%)	211 (100%)	104 (100%)	315 (100%)	0.174
< 55	42 (19.9%)	31 (29.8%)	73 (23.2%)	
55 - < 65	64 (30.3%)	33 (31.7%)	97 (30.8%)	
65 - < 75	61 (28.9%)	24 (23.1%)	85 (27.0%)	
≥ 75	44 (20.9%)	16 (15.4%)	60 (19.0%)	
Mean (SD)	63.6 (12.5)	60.3 (13.0)	62.5 (12.7)	0.030
Median	64.0	61.0	63.0	
(Min, Max)	(24.0, 86.0)	(32.0, 87.0)	(24.0, 87.0)	
Sex - n (%)	211 (100%)	104 (100%)	315 (100%)	0.996
Male	75 (35.5%)	37 (35.6%)	112 (35.6%)	
Female	136 (64.5%)	67 (64.4%)	203 (64.4%)	
Race - n (%)	211 (100%)	104 (100%)	315 (100%)	0.684
American Indian or Alaska Native	0 (0%)	1 (1.0%)	1 (0.3%)	
Asian	1 (0.5%)	1 (1.0%)	2 (0.6%)	
Black or African American	29 (13.7%)	16 (15.4%)	45 (14.3%)	
Native Hawaiian or Other Pacific Islander	1 (0.5%)	0 (0%)	1 (0.3%)	
White	177 (83.9%)	84 (80.8%)	261 (82.9%)	
Other	3 (1.4%)	2 (1.9%)	5 (1.6%)	
Ethnicity - n (%)	211 (100%)	104 (100%)	315 (100%)	0.287
Hispanic or Latino	9 (4.3%)	2 (1.9%)	11 (3.5%)	
Not Hispanic or Latino	202 (95.7%)	102 (98.1%)	304 (96.5%)	
Caucasian - n (%)	211 (100%)	104 (100%)	315 (100%)	0.954
Yes	171 (81.0%)	84 (80.8%)	255 (81.0%)	
No	40(19.0%)	20 (19.2%)	60 (19.0%)	
Surgery Type - n (%)	211 (100%)	104 (100%)	315 (100%)	0.416
Orthopedic	154 (73.0%)	69 (66.3%)	223 (70.8%)	
Abdominal	55 (26.1%)	33 (31.7%)	88 (27.9%)	
Other Surgery	2 (0.9%)	2 (1.9%)	4 (1.3%)	
Body Mass Index (kg/m^2) - n (%)	211 (100%)	104 (100%)	315 (100%)	0.527
< 30	113 (53.6%)	54 (51.9%)	167 (53.0%)	
30 - 40	77 (36.5%)	43 (41.3%)	120 (38.1%)	
> 40	21 (10.0%)	7 (6.7%)	28 (8.9%)	
Mean (SD)	30.7 (7.2)	31.2 (5.8)	30.9 (6.8)	0.476
Median	29.4	29.8	29.7	
(Min, Max)	(17.5, 62.0)	(21.0, 52.0)	(17.5, 62.0)	

Source: Applicant's Response to an information request from 5/18/17

Open-Label Zalviso Studies (ARX-C-004 and IAP309)

Compared to the Dsuvia open-label studies, the Zalviso studies had a smaller number of subjects but have a larger proportion of older subjects (Table 27). The Zalviso studies also have a lower proportion of non-white subjects. The Zalviso studies are strictly a post-operative patient pool consisting of mostly orthopedic procedures. Although there are some differences, this pool is adequate for the purposes of exploring the additional supportive safety results.

7.2.2 Explorations for Dose Response

There was no formal exploration for a dose-response relationship in any of the studies. The pivotal, placebo controlled study, SAP301, only used the 30 mcg dose.

7.2.4 Routine Clinical Testing

The safety monitoring plan is outlined for the pivotal trial in Section 5.3, which appears adequate for this population.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant collected and evaluated adverse event reports and assessed vital signs throughout all trials. This would be expected to capture adverse events related to the opioid class of medications.

7.3 Major Safety Results

7.3.1 Deaths

Study SAP301:

- There were no deaths in this study

Open-Label Dsuvia studies (SAP302 and SAP303)

- There were no deaths in these studies

Placebo-Controlled Zalviso studies (ARX-C-001, ARX-C-005, IAP310 and IAP311)

- There was one death in study ARX-C001

Narrative:

Subject (b) (6) – 69-year-old female died of acute renal failure 30 days after unilateral total knee replacement surgery. Medical history was significant for hypertension, hypercholesterolemia, and gout. The record shows she received 6 doses of sufentanil within approximately 24 hours after surgery. Six days after her last dose, she was hospitalized and diagnosed with acute renal failure and pancolitis. The patient died 30 days after the surgery/initiation of sufentanil and about 29 days after sufentanil discontinuation. The patient was taking ibuprofen, and OxyContin at

discharge from the study. This event does not appear to be related to the study drug.

Open-Label Zalviso studies (ARX-C004 and IAP309)

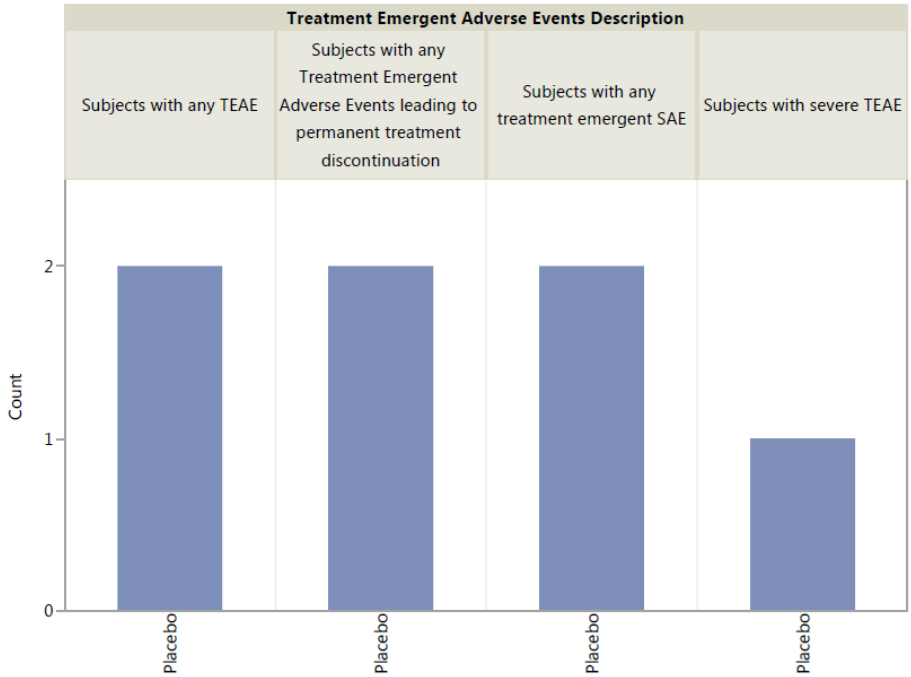
- There was one death in ARX-C004 in a subject randomized to active-comparator treatment IV morphine died of severe sepsis. There were no deaths in any exposures to Zalviso.

7.3.2 Nonfatal Serious Adverse Events

Study SAP301:

There were two serious adverse events (SAE) (syncope and left-sided hemiparesis), both in the placebo group (Figure 6). Also, there was one severe AE (same subject in SAE group with left-sided hemiparesis – USUBJID SAP301-(b) (6)). Given the SAEs occurred only in the placebo group, there is no negative impact of these findings on the safety profile.

Figure 6: Serious and Severe Adverse Events – SAP301



Source: Clinical Reviewer's Analysis Using JMP Clinical 6.1

Open-Label Dsuvia studies (SAP302 and SAP303)

There was one SAE, and the event occurred in patient 3906 in study SAP302 (Table 29).

Table 29: Serious Adverse Events During the 24-hour period after dosing in Dsuvia (30 mcg) and Zalviso (15 mcg) Open-Label Studies

	Treatment Group	
	Sufentanil 15 mcg[a]	Sufentanil 30 mcg
Number of Patients Enrolled in the Study	112	216
Number (%) of Patients Who Received Treatment	112 (100%)	216 (100%)
Number (%) of Patients Without Any Serious Adverse Event	111 (99.1%)	215 (99.5%)
Number (%) of Patients With at Least One Serious Adverse Event	1 (0.9%)	1 (0.5%)
Number (%) of Patients Who Reported Serious Adverse Events by System Organ Class		
CARDIAC DISORDERS	0	1 (0.5%)
Angina pectoris	0	1 (0.5%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.9%)	0
Postoperative ileus	1 (0.9%)	0

Source: ISS Table 14.2.36

Narrative:

Subject (b) (6) SAP302 (Angina pectoris with myocardial infarction, moderate severity)

The patient was a 65-year-old Hispanic woman with a history of coronary artery disease/myocardial infarction (MI), squamous cell carcinoma of anus status post resection, chemotherapy, presyncope, diabetes mellitus, congestive heart failure and a right distal femur fracture who presented to the emergency department with a right femur subtrochanteric fracture. She was dosed with hydromorphone about three hours after presentation and then sufentanil 30 mcg about six hours after presentation. She developed an AE of chest pain that was rated as moderate and possibly related about one and a half hours after sufentanil administered that was treated successfully with an albuterol nebulizer until the event subsided. The staff nurse informed the research nurse that the subject had previously experienced the same chest pain symptoms prior to administration of study drug and had used albuterol with complete relief of chest pain. A 12-lead EKG showed sinus rhythm with occasional supraventricular premature complexes, ST-segment deviation and moderate T-wave abnormality, and diagnosed with a MI. The patient recovered after hospitalization and was discharged. Given the patient's history of heart disease and previous MI, in addition to having chest pain prior to drug administration, I do not believe the test drug was related to the event.

Placebo-Controlled Zalviso studies (ARX-C-001, ARX-C-005, IAP310 and IAP311)
There were a total of two SAEs in the placebo-controlled Zalviso pool within 24 hours of exposure (Table 30). I reviewed the case narratives and agreed with the Applicant's assessment that the events were either consistent with the side-effect profile of an opioid medication or likely not related. In the cases, additional conditions (e.g., infection) or medications (e.g., fentanyl) also were confounding factors.

Table 30: Serious Adverse Events During the 24-hour Period After the 1st Dose: Patients Enrolled in Zalviso Placebo-Controlled Studies (ARX-C-001, ARX-C-005, IAP310 and IAP311

	Treatment Group	
	Sufentanil 15 mcg[a]	Placebo
Number of Patients Enrolled in the Study	211	104
Number (%) of Patients Who Received Treatment	211 (100%)	104 (100%)
Number (%) of Patients Without Any Serious Adverse Event	209 (99.1%)	104 (100%)
Number (%) of Patients With at Least One Serious Adverse Event	2 (0.9%)	0
Number (%) of Patients Who Reported Serious Adverse Events by System Organ Class		
INVESTIGATIONS	1 (0.5%)	0
Oxygen saturation decreased	1 (0.5%)	0
PSYCHIATRIC DISORDERS	1 (0.5%)	0
Confusional state	1 (0.5%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.5%)	0
Hypoxia	1 (0.5%)	0
Pulmonary embolism	1 (0.5%)	0

[a] Patients who received the first 2 SST 15 mcg tablets dosed within 20-25 minutes of each other. All patients in this pool received 30 to 45 mcg of sufentanil in 1 hour.

Source: ISS Table 14.2.34

Other SAEs did occur in the placebo-controlled studies (e.g., IAP311) but these subjects were not part of the bridged subject pool or occurred greater than 24-hours after exposure. For completeness, I did review the narratives provided by the Applicant and the events were either consistent with an opioid medication or likely not related to the treatment.

Open-Label Zalviso studies (ARX-C004 and IAP309)
There was one SAE that occurred within the 24 hour period after dosing (Table 29). Given this is a short-acting opioid used in an acute setting, the 24-hour period is reasonable for safety assessments. However, I ran a separate analysis and detected a

total of three SAEs in the Zalviso population for any time-point (Table 31). I reviewed the case narrative for each of the SAEs and concur with the Applicant's conclusion that they were unlikely related. All three of the SAEs occurred in patient (b) (6).

Table 31: Serious Adverse Events for the Open-Label Zalviso Studies

	Actual Treatment for Period 01	
	Sufentanil 15 mcg	Total
	Count (%)	Count (%)
Total	N=112	N=112
Infections and infestations	1(0.9%)	1(0.9%)
Clostridium difficile sepsis	1 (0.9)	1 (0.9)
Injury, poisoning and procedural complications	1(0.9%)	1(0.9%)
Postoperative ileus	1 (0.9)	1 (0.9)
Vascular disorders	1(0.9%)	1(0.9%)
Axillary vein thrombosis	1 (0.9)	1 (0.9)

Source: Clinical reviewer's analysis using JMP Clinical 6.1

The clinical study report also noted five other SAEs, but none were in the selected Zalviso population[6] and therefore not formally part of the safety analysis. One case narrative (subject (b) (6)) of interest developed respiratory depression that required naloxone reversal. However, the patient received 14 doses of Zalviso prior to the event, and then received 69 doses after without an event. It is possible the Zalviso may have acted concomitantly with other medications or clinical disorders during the transient desaturation. If related to the Zalviso, this is not an uncommon AE based on the profile of an opioid agonist.

7.3.3 Dropouts and/or Discontinuations

Study SAP301:

Three subjects (1 sufentanil) had a total of five adverse events leading to discontinuations (Table 32). All subjects were reported to recover/resolve fully. One of

6 Only subjects dosed at least twice with 15 mcg during a 25 minute time period

these subjects was in the sufentanil group and due to a decrease in oxygen saturation (USUBJID - SAP301 (b) (6)) and is discussed in the description below.

Table 32: Drug Withdrawn from Subjects – SAP301

		Actual Treatment for Period 01						
		Placebo				Sufentanil 30 mcg		
		Serious Event				Serious Event		
		N		Y		N		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Count	%	Total
Nervous system disorders	Dizziness	1	1.9%	.	.	.	.	1
	Hemiparesis	.	.	1	1.9%	.	.	1
	Somnolence	1	1.9%	.	.	.	.	1
	Syncope	.	.	1	1.9%	.	.	1
Investigations	Oxygen saturation decreased	.	.	.	.	1	0.9%	1

Where(Action Taken with Study Treatment = DRUG WITHDRAWN)
Source: Clinical Reviewer's Analysis Using JMP Clinical 6.1

Narratives:

Subject SAP301 (b) (6) (oxygen desaturation, rated as mild and resolved):

Subject is a 47-year-old black male with a medical history significant for hypertension, left and right hernia repair, and arthroscopic knee surgery who underwent laparoscopic abdominal surgery for a cholecystectomy on (b) (6). He had been dosed with 11 doses of sufentanil sublingual 30 mcg with the first dose at 1015h, (b) (6), and the last dose at 1330h on (b) (6) with a mean interdosing interval of 163.50 minutes with a baseline oxygen saturation of 98%. His first episode of oxygen desaturation measured at 94% and occurred at the 13 hour assessment point after a total of seven doses of sufentanil administered. He had several other measures that were slightly below the predetermined threshold of 95%, all of which were transient and resolved quickly. His lowest measure was 93% and occurred at 28 and 30 hours assessment points which led to his discontinuation. I reviewed through all the oxygen desaturation measures and the majority measured at or above 95%. It was noted in the case narrative that the subject refused oxygen supplementation. My determination of this event is the oxygen desaturation was mild, transient and possibly related. However, the patient refused oxygen supplementation and was in a post-operative state where mild decreases are not uncommon. Typically patients accept oxygen supplementation. Therefore, it is not clearly related to the study drug, and if related is mild and not unexpected for an opioid medication.

Open-Label Dsuvia studies (SAP302 and SAP303)

There were a total of four patients who discontinued the test drug due to an adverse event (Table 33). These findings did not significantly alter the safety profile of this drug product.

Table 33: Adverse Events Causing the Discontinuation of Study Drug During the 24-hour Period After the 1st Dose: Patients Enrolled in Dsuvia Open-Label Studies (SAP302 and SAP303)

	Treatment Group
	Sufentanil 30 mcg
Number of Patients Enrolled in the Study	216
Number (%) of Patients Who Received Treatment	216 (100%)
Number (%) of Patients Without Any Adverse Event Causing the Discontinuation of Study Drug	212 (98.1%)
Number (%) of Patients With at Least One Adverse Event Causing the Discontinuation of Study Drug	4 (1.9%)
Number (%) of Patients Who Reported Adverse Events Causing the Discontinuation of Study Drug by System Organ Class	
INVESTIGATIONS	2 (0.9%)
Oxygen saturation decreased	2 (0.9%)
NERVOUS SYSTEM DISORDERS	1 (0.5%)
Dizziness	1 (0.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.5%)
Pruritus	1 (0.5%)

Source: Applicant's response to information request, based on ISS Table 14.2.42

Narratives:

Subject SAP303 (b) (6) (Pruritus, mild severity)

52 y/o black woman with a history of mal-positioned right breast implant, ruptured left breast implant, allergy to IV contrast and vancomycin, seasonal allergies, hypertension, stress headache and anxiety who had bilateral breast implant exchange who experienced mild pruritis about one hour after the first dose of sufentanil (two doses given total). She had also been given fentanyl intraoperatively and a rescue dose of morphine prior to the event. Pruritis resolved about two hours after the first dose of sufentanil. The patient terminated from the study prematurely due to this adverse event. It is possible the pruritis was related to the test drug, however, the patient did received several other opioid drugs which also may cause pruritis.

Subject SAP303 (b) (6) (Oxygen saturation decreased, mild severity)

The patient was a 56 year-old black woman with history of obesity (113 kg), hypertension and hypercholesterolemia underwent an abdominal laparoscopic surgery (gastric sleeve) and experienced an adverse event of oxygen saturation decreased postoperatively. She developed oxygen desaturation (93%) 56 minutes after dosing of Dsuvia. Approximately 40 minutes later she desaturated again for approximately 6 minutes to 90-92% but later increased to 97%. However, she was terminated from the study 2.5 hours after dosing. No opioid reversal agents were utilized. Concomitant analgesic medications included hydromorphone 1 mg IV and fentanyl 250 mcg IV for intraoperative surgical pain.

The oxygen desaturation is possibly related to the study drug, however, the patient had numerous reasons for a transient oxygen desaturation as well (i.e., concomitant medications, post-operative state with obesity). Also, transient desaturation is not unexpected after surgery and with the use of an opioid drug. I do not believe this case alters the risk to benefit analysis.

Subject SAP303 (b) (6) (Oxygen saturation decreased, mild severity)

The patient is a 66 year-old white woman with a history of obesity (119 kg), hypertension, hyperlipidemia, hypothyroidism, osteoarthritis, spine surgery x 2, and hysterectomy who underwent a knee replacement surgery and experienced an adverse event of oxygen saturation decreased postoperatively 15 minutes after dosing with Dsuvia down to 91-93% (baseline 95%). Her oxygen saturation dropped 3 different times to 91-93% over the 2 hour period but resolved with nasal cannula. No opioid reversal agents were required. Concomitant analgesic medications included fentanyl 300 mcg IV intraoperatively.

Similar to subject (b) (6), oxygen desaturation is possibly related to the study drug, however, the patient had numerous reasons for a transient oxygen desaturation as well (i.e., concomitant medications, post-operative state with obesity). Also, transient desaturation is not unexpected after surgery and with the use of an opioid drug. I do not believe this case alters the risk to benefit analysis.

Subject SAP303 (b) (6) (Dizziness, mild severity)

55 year-old white woman with history of obesity (107 kg), dyslipidemia, gastroesophageal reflux disease, bronchitis, hysterectomy, kidney stones, degenerative joint disease, left knee joint pain, anxiety and depression who underwent knee replacement and developed dizziness about 3 hours after dosing of Dsuvia. Her vital signs at the time demonstrated a drop in systolic blood pressure (SBP) to 115 mmHg from a baseline SBP of 146 mmHg. Her diastolic blood pressure remained at 71 mmHg, similar to baseline. Her heart rate also decreased from a baseline of 107 beats per min

to 82. Her oxygen saturation remained 95% or above. Concomitant medications included fentanyl 200 mcg IV at 7:30 and morphine 7 mg IV total. The patient was discontinued from the study due to the AE of dizziness.

The AE is possibly related however she had numerous other factors which may have been contributory or causative as well (e.g., concomitant opioids, post-operative state). The drop in blood pressure may have caused the dizziness and may have been related to the same factors. Regardless, this AE is not uncommon in this clinical scenario and does not significantly alter the risk to benefit analysis.

Placebo-Controlled Zalviso studies (ARX-C-001, ARX-C-005, IAP310 and IAP311)
The number of patients who discontinued due to adverse events were greater in the Zalviso group compared to placebo, 5.2% vs. 3.8%, respectively (Table 34). However, the difference was numerically small and it is not unexpected that the placebo group would have less AEs. Additionally, the AEs noted as the cause of discontinuation are within the expected adverse event profile of an opioid analgesic.

Table 34: Adverse Events Causing the Discontinuation of Study Drug: Select Patients Enrolled in Zalviso Placebo-Controlled Studies (ARX-C-001, ARX-C-005, IAP310 and IAP311)

	Treatment Group		
	Sufentanil 15 mcg[a]	Placebo	Treatment p-value[b]
Number of Patients Enrolled in the Study	211	104	
Number (%) of Patients Who Received Treatment	211 (100%)	104 (100%)	
Number (%) of Patients Without Any Adverse Event Causing the Discontinuation of Study Drug	200 (94.8%)	100 (96.2%)	
Number (%) of Patients With at Least One Adverse Event Causing the Discontinuation of Study Drug	11 (5.2%)	4 (3.8%)	NS
Number (%) of Patients Who Reported Adverse Events Causing the Discontinuation of Study Drug by System Organ Class			
GASTROINTESTINAL DISORDERS	3 (1.4%)	1 (1.0%)	NS
Nausea	3 (1.4%)	0	NS
Abdominal Pain	0	1 (1.0%)	NS
INVESTIGATIONS	2 (0.9%)	1 (1.0%)	NS
Respiratory Rate decreased	1 (0.5%)	1 (1.0%)	NS
Oxygen saturation decreased	1 (0.5%)	0	NS
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.5%)	1 (1.0%)	NS
Back Pain	1 (0.5%)	1 (1.0%)	NS
NERVOUS SYSTEM DISORDERS	3 (1.4%)	1 (1.0%)	NS
Sedation	2 (0.9%)	0	NS
Dizziness	1 (0.5%)	0	NS
Tremor	0	1 (1.0%)	NS
PSYCHIATRIC DISORDERS	2 (0.9%)	0	NS
Anxiety	1 (0.5%)	0	NS
Confusional State	1 (0.5%)	0	NS
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.5%)	0	NS
Hypoventilation	1 (0.5%)	0	NS

Abbreviation: NS = not statistically significant at 0.10 level.

Source: ISS Table 14.2.40

Open-Label Zalviso studies (ARX-C004 and IAP309)

There were more discontinuations in the bridged Zalviso open-label exposures compared to the Dsuvia open-label exposures (Table 35). This difference is likely due to the difference in designs of the open-label studies. The Zalviso open-label studies extended to as far as 72 hours, whereas the Dsuvia open-label studies were 5 hour and 12 hour studies. The AEs seen are within the expected the safety profile of an opioid analgesic medication.

Table 35: Adverse Events Causing the Discontinuation of Study Drug During the 24-hour Period After the 1st Dose: Patients Enrolled in Dsuvia Open-Label Studies (Sufentanil 30mcg) and Zalviso Open-Label Studies (Sufentanil 15 mcg)

	Treatment Group		Treatment p-value[b]
	Sufentanil 15 mcg[a]	Sufentanil 30 mcg	
Number of Patients Enrolled in the Study	112	216	
Number (%) of Patients Who Received Treatment	112 (100%)	216 (100%)	
Number (%) of Patients Without Any Adverse Event Causing the Discontinuation of Study Drug	104 (92.9%)	212 (98.1%)	
Number (%) of Patients With at Least One Adverse Event Causing the Discontinuation of Study Drug	8 (7.1%)	4 (1.9%)	0.026
Number (%) of Patients Who Reported Adverse Events Causing the Discontinuation of Study Drug by System Organ Class			
GASTROINTESTINAL DISORDERS	2 (1.8%)	0	NS
Nausea	2 (1.8%)	0	NS
INVESTIGATIONS	2 (1.8%)	2 (0.9%)	NS
Oxygen saturation decreased	2 (1.8%)	2 (0.9%)	NS
NERVOUS SYSTEM DISORDERS	2 (1.8%)	1 (0.5%)	NS
Sedation	2 (1.8%)	0	NS
Dizziness	0	1 (0.5%)	NS
PSYCHIATRIC DISORDERS	2 (1.8%)	0	NS
Agitation	1 (0.9%)	0	NS
Anxiety	1 (0.9%)	0	NS
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (1.8%)	0	NS
Bradypnoea	1 (0.9%)	0	NS
Hypoxia	1 (0.9%)	0	NS
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.5%)	NS
Pruritus	0	1 (0.5%)	NS

[a] Patients who received at least 2 SST 15 mcg (Zalviso) tablets dosed within 20-25 minutes of each other in the first hour of dosing. All patients in this group received 30 to 45 mcg of sufentanil in the first hour of Zalviso treatment, followed by prn dosing of 15 mcg/dose (subject to a 20 min lockout) for the duration of the Zalviso study.

Source: ISS Table 14.2.42

7.3.4 Significant Adverse Events

Adverse events of special interest for an opioid product include respiratory, neuropsychiatric, and gastrointestinal events. Study SAP301 is the only placebo-controlled trial in the Dsuvia program and is the main contributor for the safety analysis of this drug product. The events are described in the relevant sections above. Given

the short-term use and acute indication, oxygen desaturation is the most significant AE and is briefly discussed further below.

SAP301:

Oxygen desaturation and hypoxia (both mild in severity) were slightly higher in the sufentanil group versus placebo (1.8% vs 0%, respectively). This is an expected AE for an opioid and the difference between the two groups is not impressive. Also, one of the subjects (described in narrative above) refused oxygen supplementation after surgery. Therefore, the oxygen desaturation may not have been due to the medication. As stated in Section 7.3.2, there were no severe AEs in the Dsuvia group. The severe adverse events are discussed under Section 7.3.2.

There were no laboratory measures to analyze.

Open-Label Dsuvia studies (SAP302 and SAP303)

In addition to the four cases described in the narratives of the section 7.3.3 (discontinuations), there were three other oxygen desaturation AEs considered to be clinically significant. I reviewed the case narratives and the AEs are possibly related although there were other concomitant factors (e.g., other opioids administered, medical condition). Given this is a pool of open-label studies, there is no comparison to a placebo group. However the mild severity of these AEs, coupled with the number of events, did not raise any additional safety concern beyond a typical opioid product.

Severe AEs were also analyzed and displayed below (Table 36). There were few events categorized as severe. The AEs shown are consistent with the safety profile of an opioid product.

Table 36: Severe Adverse Events During the 24-hour Period After the 1st Dose: Patients Enrolled in Dsuvia Open-Label Studies (SAP302 and SAP303)

	Treatment Group
	Sufentanil 30 mcg
Number of Patients Enrolled in the Study	216
Number (%) of Patients Who Received Treatment	216 (100%)
Number (%) of Patients Without Any Severe Adverse Event	213 (98.6%)
Number (%) of Patients With at Least One Severe Adverse Event	3 (1.4%)
Number (%) of Patients Who Reported Severe Adverse Events by System Organ Class	
GASTROINTESTINAL DISORDERS	2 (0.9%)
Nausea	2 (0.9%)
Dry mouth	1 (0.5%)
NERVOUS SYSTEM DISORDERS	1 (0.5%)
Dizziness	1 (0.5%)
Headache	1 (0.5%)
PSYCHIATRIC DISORDERS	2 (0.9%)
Confusional state	1 (0.5%)
Euphoric mood	1 (0.5%)

Source: ISS Table 14.2.233

Placebo-Controlled Zalviso studies (ARX-C-001, ARX-C-005, IAP310 and IAP311)
The number of severe adverse events reported in the bridged Zalviso placebo-controlled population were small in number (Table 37). The severe AEs in this population does not alter the risk to benefit analysis for this product.

Table 37: Severe Adverse Events During the 24-hour Period After the 1st Dose: Patients Enrolled in Zalviso Placebo-Controlled Studies (ARX-C-001, ARX-C-005, IAP310 and IAP311)

	Treatment Group			
	Sufentanil 15 mcg[a]	Placebo	Total	Treatment p-value[b]
Number of Patients Enrolled in the Study	211	104	315	
Number (%) of Patients Who Received Treatment	211 (100%)	104 (100%)	315 (100%)	
Number (%) of Patients Without Any Severe Adverse Event	209 (99.1%)	103 (99.0%)	312 (99.0%)	
Number (%) of Patients With at Least One Severe Adverse Event	2 (0.9%)	1 (1.0%)	3 (1.0%)	NS
Number (%) of Patients Who Reported Severe Adverse Events by System Organ Class				
GASTROINTESTINAL DISORDERS	1 (0.5%)	1 (1.0%)	2 (0.6%)	NS
Abdominal pain	0	1 (1.0%)	1 (0.3%)	NS
Nausea	1 (0.5%)	0	1 (0.3%)	NS
INVESTIGATIONS	1 (0.5%)	0	1 (0.3%)	NS
Oxygen saturation decreased	1 (0.5%)	0	1 (0.3%)	NS

Abbreviation: NS = Not statistically significant at 0.10 level.
Notes: Adverse event mapping was based on the MedDRA Version 11.0 thesaurus.
Severity: Severe = Severe or missing severity
A patient may be reported in more than 1 category. Adverse events occurring while patients are on study medication during the study treatment period or within 12 hours after the discontinuation of study medication were included in this data analysis.
[a] Patients who received the first 2 SST 15 mcg tablets dosed within 20-25 minutes of each other. All patients in this pool received 30 to 45 mcg of sufentanil in 1 hour.
[b] The p-values for the comparison between 2 treatment groups are based on a two-sided Fisher's exact test and presented if they are less than 0.10. NS = Not statistically significant at 0.10 level.

Source: ISS Table 14.2.231

Open-Label Zalviso studies (ARX-C004 and IAP309)

There was only one subject reported to have a severe AE in the Zalvsio open-label population. The subject developed a post-operative ileus and oxygen desaturation as discussed under the serious AE subsection (7.3.2).

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

SAP301:

The most frequently reported AEs by organ system were gastrointestinal disorders (sufentanil 40 [37.4%]; placebo, 18 [33.3%]) and nervous system events (sufentanil 28 [26.2%]; placebo, 12 [22.2%]). The most frequently reported AEs were nausea (sufentanil, 35 [32.7%]; placebo, 16 [29.6%]) and headache (sufentanil, 22 [20.6%]; placebo, 10 [18.5%]). I analyzed the safety population and the findings were generally consistent with the Applicant's analysis. Most AEs were comparable to between the two groups. However, there was slights higher frequency of vomiting in the sufentanil group versus placebo (7.5% vs 1.9%, respectively). Additionally, oxygen desaturation and hypoxia (both mild in severity) were slightly higher in the sufentanil group versus placebo (1.8% vs 0%, respectively). These adverse events are expected for an opioid medication and the small difference in the relative frequencies may be due to the increased potency of sufentanil compared to the placebo group's as needed treatment (1 mg IV morphine), or simply due to randomness from the small sample size of 161 subjects. Pooling of the available safety data may provide further information on any potential safety signals. A summary of my analysis is shown in Table 38. Overall, my analysis is consistent with the Applicant's review of safety.

Table 38: Summary of Common Adverse Events – SAP301

		Actual Treatment for Period 01				
		Sufentanil 30 mcg		Placebo		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Gastrointestinal disorders	Nausea	35	32.7%	16	29.6%	51
	Vomiting	8	7.5%	1	1.9%	9
	Flatulence	4	3.7%	4	7.4%	8
	Diarrhoea	1	0.9%	.	.	1
	Dry mouth	1	0.9%	.	.	1
	Dyspepsia	1	0.9%	.	.	1
	Gastritis	1	0.9%	.	.	1
	Hypoaesthesia oral	1	0.9%	.	.	1
	Retching	.	.	1	1.9%	1
Nervous system disorders	Headache	22	20.6%	10	18.5%	32
	Dizziness	6	5.6%	2	3.7%	8
	Somnolence	3	2.8%	2	3.7%	5
	Presyncope	1	0.9%	1	1.9%	2
	Hemiparesis	.	.	1	1.9%	1
	Syncope	.	.	1	1.9%	1
Vascular disorders	Hypotension	6	5.6%	2	3.7%	8
	Hypertension	1	0.9%	1	1.9%	2
	Orthostatic hypotension	1	0.9%	.	.	1
Injury, poisoning and procedural complications	Procedural nausea	3	2.8%	3	5.6%	6
	Procedural vomiting	2	1.9%	.	.	2
Skin and subcutaneous tissue disorders	Pruritus	2	1.9%	2	3.7%	4
	Pruritus generalised	1	0.9%	1	1.9%	2
Cardiac disorders	Tachycardia	3	2.8%	.	.	3
	Sinus tachycardia	.	.	1	1.9%	1
Psychiatric disorders	Anxiety	.	.	1	1.9%	1
	Hallucination	1	0.9%	.	.	1
	Insomnia	.	.	1	1.9%	1
Renal and urinary disorders	Bladder spasm	.	.	1	1.9%	1
	Dysuria	.	.	1	1.9%	1
	Incontinence	.	.	1	1.9%	1
General disorders and administration site conditions	Non-cardiac chest pain	1	0.9%	.	.	1
	Pyrexia	.	.	1	1.9%	1
Musculoskeletal and connective tissue disorders	Muscle spasms	1	0.9%	.	.	1
	Musculoskeletal pain	1	0.9%	.	.	1
Respiratory, thoracic and mediastinal disorders	Haemoptysis	.	.	1	1.9%	1
	Hypoxia	1	0.9%	.	.	1
Investigations	Oxygen saturation decreased	1	0.9%	.	.	1

Source: Clinical Reviewer's Safety Analysis using JMP Clinical 6.1

I performed a separate analysis of AEs occurrence and proportion by sex and race (Table 39 and Table 40). There was a greater percentage of AEs in females, most notably gastrointestinal, nervous system and vascular events. This disparity may be attributable to the different populations (i.e., underlying disorders and procedures). With

regard to race, there were a greater number of white subjects enrolled but no notable differences were detected in this analysis.

Table 39: Most Common Adverse Events Event Occurrence & Proportion Report for Sex
Reporting Events with at least Overall 2% Occurrence – SAP301

	Sex		
	F	M	Total
	Count (%)	Count (%)	Count (%)
Total	N=109	N=52	N=161
Gastrointestinal disorders	42(38.5%)	15(28.8%)	57(35.4%)
Flatulence	7 (6.4)	1 (1.9)	8 (5)
Nausea	37 (33.9)	14 (26.9)	51 (31.7)
Vomiting	7 (6.4)	2 (3.8)	9 (5.6)
Injury, poisoning and procedural complication	6(5.5%)		6(3.7%)
Procedural nausea	6 (5.5)		6 (3.7)
Nervous system disorders	33(30.3%)	6(11.5%)	39(24.2%)
Dizziness	8 (7.3)		8 (5)
Somnolence	5 (4.6)		5 (3.1)
Headache	26 (23.9)	6 (11.5)	32 (19.9)
Skin and subcutaneous tissue disorders	4(3.7%)		4(2.5%)
Pruritus	4 (3.7)		4 (2.5)
Vascular disorders	8(7.3%)		8(5%)
Hypotension	8 (7.3)		8 (5)

Source: Clinical Reviewer's Safety Analysis using JMP Clinical 6.1

Table 40: Most Common Adverse Events Event Occurrence & Proportion Report for Race
Reporting Events with at least Overall 2% Occurrence – SAP301

	Race				
	ASIAN	BLACK OR AFRICAN AMERICAN	OTHER	WHITE	Total
	Count (%)	Count (%)	Count (%)	Count (%)	Count (%)
Total	N=4	N=31	N=13	N=113	N=161
Gastrointestinal disorders	3(75%)	10(32.3%)	3(23.1%)	41(36.3%)	57(35.4%)
Flatulence				8 (7.1)	8 (5)
Nausea	3 (75)	10 (32.3)	3 (23.1)	35 (31)	51 (31.7)
Vomiting		1 (3.2)		8 (7.1)	9 (5.6)
Injury, poisoning and procedural complication		1(3.2%)		5(4.4%)	6(3.7%)
Procedural nausea		1 (3.2)		5 (4.4)	6 (3.7)
Nervous system disorders		8(25.8%)	2(15.4%)	29(25.7%)	39(24.2%)
Dizziness		2 (6.5)		6 (5.3)	8 (5)
Headache		7 (22.6)	2 (15.4)	23 (20.4)	32 (19.9)
Somnolence		1 (3.2)		4 (3.5)	5 (3.1)
Skin and subcutaneous tissue disorders		1(3.2%)		3(2.7%)	4(2.5%)
Pruritus		1 (3.2)		3 (2.7)	4 (2.5)
Vascular disorders				8(7.1%)	8(5%)
Hypotension				8 (7.1)	8 (5)

Source: Clinical Reviewer's Safety Analysis using JMP Clinical 6.1

Open-Label Dsuvia studies (SAP302 and SAP303)

I performed my own analysis of the common AEs in the open-label pool and my findings were consistent with the Applicant's analysis. As expected for an opioid medication, the most common AEs were in the gastrointestinal and nervous system organ classes (Table 41).

Table 41: Most Common Adverse Events with at least 2% Occurrence Dsuvia Open-Label Studies

	Actual Treatment for Period 01	
	Sufentanil 30 mcg	Total
	Count (%)	Count (%)
Total	N=216	N=216
Any Adverse Event	68 (31.5%)	68 (31.5%)
Gastrointestinal disorders	45(20.8%)	45(20.8%)
Nausea	45 (20.8)	45 (20.8)
Investigations	5(2.3%)	5(2.3%)
Oxygen saturation decreased	5 (2.3)	5 (2.3)
Nervous system disorders	13(6%)	13(6%)
Dizziness	7 (3.2)	7 (3.2)
Headache	8 (3.7)	8 (3.7)
Skin and subcutaneous tissue disorders	5(2.3%)	5(2.3%)
Pruritus	5 (2.3)	5 (2.3)

Source: Clinical reviewer's analysis using JMP Clinical 6.1

I also performed an analysis of AEs by sex and race for the open-label Dsuvia studies (Table 42 and Table 43). Similar to SAP301, the pooled Dsuvia open-label analysis showed a greater percentage of AEs in the female population. The analysis by race did not detect any notable differences.

Table 42: Most Common Adverse Events Occurrence (at least 2 %) and Proportion by Sex

	Sex		
	F	M	Total
	Count (%)	Count (%)	Count (%)
Total	N=105	N=111	N=216
Gastrointestinal disorders	28(26.7%)	17(15.3%)	45(20.8%)
Nausea	28 (26.7)	17 (15.3)	45 (20.8)
Investigations	3(2.9%)	2(1.8%)	5(2.3%)

	Sex		
	F	M	Total
	Count (%)	Count (%)	Count (%)
Oxygen saturation decreased	3 (2.9)	2 (1.8)	5 (2.3)
Nervous system disorders	13(12.4%)		13(6%)
Dizziness	7 (6.7)		7 (3.2)
Headache	8 (7.6)		8 (3.7)
Skin and subcutaneous tissue disorders	5(4.8%)		5(2.3%)
Pruritus	5 (4.8)		5 (2.3)

Source: Clinical reviewer's analysis using JMP Clinical 6.1

Table 43: Most Common Adverse Events Occurrence (at least 2 %) and Proportion by Race

	Race			
	AMERICAN INDIAN OR ALASKA NATIVE	BLACK OR AFRICAN AMERICAN	WHITE	Total
	Count (%)	Count (%)	Count (%)	Count (%)
Total	N=6	N=46	N=162	N=216
Gastrointestinal disorders		9(19.6%)	36(22.2%)	45(20.8%)
Nausea		9 (19.6)	36 (22.2)	45 (20.8)
Investigations	1(16.7%)	2(4.3%)	2(1.2%)	5(2.3%)
Oxygen saturation decreased	1 (16.7)	2 (4.3)	2 (1.2)	5 (2.3)
Nervous system disorders			13(8%)	13(6%)
Dizziness			7 (4.3)	7 (3.2)
Headache			8 (4.9)	8 (3.7)
Skin and subcutaneous tissue disorders		2(4.3%)	3(1.9%)	5(2.3%)
Pruritus		2 (4.3)	3 (1.9)	5 (2.3)

Source: Clinical reviewer's analysis using JMP Clinical 6.1

Placebo-Controlled Zalviso studies (ARX-C-001, ARX-C-005, IAP310 and IAP311)
The most common adverse events in the Zalviso placebo-controlled clinical program show an adverse event profile generally consistent with the profile of an immediate-

release opioid product (Table 44). Anemia was seen slightly more in the Zalviso group compared to placebo, 6.6% vs. 1.9%, respectively. None of the anemia events were serious or severe. This difference may simply be due to chance. Otherwise, the AEs were consistent with the Dsuvia program and other opioid products.

Table 44: Most Common (Occurring in at Least 2% of Patients and Greater than Placebo) Adverse Events: Patients Enrolled in Zalviso Placebo-Controlled Studies (ARX-C-001, ARX-C-005, IAP310, and IAP311)

	Treatment			
Adverse Events	**Sufentanil 15 mcg**	**Placebo**	**Total**	**p-value**
SOC/PT	**Count (%)**	**Count (%)**	**Count (%)**	**Count (%)**
Total	N=211	N=104	N=315	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	15 (7.1%)	4 (3.8%)	19 (6%)	NS
Anemia	14 (6.6%)	2 (1.9%)	16 (5.1%)	NS
CARDIAC DISORDERS	10 (4.7%)	3 (2.9%)	13 (4.1%)	NS
Tachycardia	7 (3.3%)	1 (1%)	8 (2.5%)	NS
GASTROINTESTINAL DISORDERS	104 (49.3%)	34 (32.7%)	138(43.8%)	0.006
Nausea	97 (46.0%)	33 (31.7%)	130 (41.3%)	0.021
Vomiting	23 (10.9%)	4 (3.8%)	27 (8.6%)	0.051
PSYCHIATRIC DISORDERS	15 (7.1%)	4 (3.8%)	19 (6.0%)	NS
Insomnia	8 (3.8%)	1 (1.0%)	9 (2.9%)	NS
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	17 (8.1%)	2 (1.9%)	19 (6.0%)	0.041
Pruritus	13 (6.2%)	2 (1.9%)	15 (4.8%)	NS
VASCULAR DISORDERS	15 (7.1%)	7 (6.7%)	22 (7.0%)	NS
Hypotension	7 (3.3%)	3 (2.9%)	10 (3.2%)	NS
INVESTIGATIONS	12 (5.7%)	3 (2.9%)	15 (4.8%)	NS
Oxygen saturation decreased	7 (3.3%)	0	7 (2.2%)	NS
NERVOUS SYSTEM DISORDERS	28 (13.3%)	8 (7.7%)	36 (11.4%)	NS
Headache	12 (5.7%)	5 (4.8%)	17 (5.4%)	NS
Dizziness	10 (4.7%)	2 (1.9%)	12 (3.8%)	NS

Adverse events occurring while patients were on study medication during the study treatment period or within 12 hours after the discontinuation of study medication were included in this data analysis.
a) Patients who received either: 1) SST 30 mcg or 2) the first 2 SST 15 mcg tablets dosed within 20-25 minutes of each other. Inclusion of these patients in pooled analyses with SST 30 mcg is based on the establishment of bioequivalence of

1 SST 30 mcg tablet with 2 SST 15 mcg tablets dosed within 20 minutes of each other and PK modeling. All patients in this pool received 30 to 45 mcg of sufentanil in 1 hour.
b) The p-values for the comparison between 2 treatment groups are based on a two-sided Fisher's exact test and presented if they are less than 0.1 – used for descriptive purposes only

Source: Adapted from ISS Table 14.2.16

Open-Label Zalviso studies (ARX-C004 and IAP309)

The Applicant provided a comparison of the pooled Zalviso and Dsuvia open-label common adverse events (Table 45). The Dsuvia and Zalviso studies had some difference in design and populations, therefore a direct comparison should be viewed cautiously. The most common events were gastrointestinal in both groups. Anemia occurred more frequently in the Zalviso group, but that may be a result of the type of procedures performed as well as the presentation of patients in the Zalviso studies. Overall, I believe the AEs are consistent with an immediate-release opioid product.

Table 45: Most Common (Occurring in at Least 1% of Patients in any Treatment Group) Adverse Events: Dsuvia and Zalviso Open-Label Studies

	Treatment Group			
	Sufentanil 15 mcg	Sufentanil 30 mcg	Total	Treatment p-value[1]
Number of Patients Enrolled in the Study	112	216	328	
Number (%) of Patients Who Received Treatment	112 (100%)	216 (100%)	328 (100%)	
Number (%) of Patients Without Any Adverse Event	23 (20.5%)	148 (68.5%)	171 (52.1%)	
Number (%) of Patients With at Least One Adverse Event	89 (79.5%)	68 (31.5%)	157 (47.9%)	<0.001
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
BLOOD AND LYMPHATIC SYSTEM DISORDERS	17 (15.2%)	0	17 (5.2%)	<0.001
Anaemia	13 (11.6%)	0	13 (4.0%)	<0.001
Leukocytosis	5 (4.5%)	0	5 (1.5%)	0.004
CARDIAC DISORDERS	11 (9.8%)	3 (1.4%)	14 (4.3%)	<0.001
Sinus tachycardia	7 (6.3%)	0	7 (2.1%)	<0.001
Bradycardia	3 (2.7%)	1 (0.5%)	4 (1.2%)	NS
GASTROINTESTINAL DISORDERS	51 (45.5%)	47 (21.8%)	98 (29.9%)	<0.001
Nausea	43 (38.4%)	45 (20.8%)	88 (26.8%)	<0.001
Vomiting	15 (13.4%)	4 (1.9%)	19 (5.8%)	<0.001
Dyspepsia	5 (4.5%)	0	5 (1.5%)	0.004
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9 (8.0%)	2 (0.9%)	11 (3.4%)	0.001
Pyrexia	9 (8.0%)	0	9 (2.7%)	<0.001
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	7 (6.3%)	1 (0.5%)	8 (2.4%)	0.003
Anaemia postoperative	5 (4.5%)	0	5 (1.5%)	0.004
INVESTIGATIONS	16 (14.3%)	6 (2.8%)	22 (6.7%)	<0.001
Oxygen saturation decreased	8 (7.1%)	5 (2.3%)	13 (4.0%)	0.068

	Treatment Group			
	Sufentanil 15 mcg	Sufentanil 30 mcg	Total	Treatment p-value[1]
METABOLISM AND NUTRITION DISORDERS	16 (14.3%)	0	16 (4.9%)	<0.001
Hypocalcaemia	8 (7.1%)	0	8 (2.4%)	<0.001
Hypoalbuminaemia	5 (4.5%)	0	5 (1.5%)	0.004
Hypokalaemia	4 (3.6%)	0	4 (1.2%)	0.013
NERVOUS SYSTEM DISORDERS	21 (18.8%)	19 (8.8%)	40 (12.2%)	0.012
Headache	11 (9.8%)	8 (3.7%)	19 (5.8%)	0.043
Dizziness	5 (4.5%)	7 (3.2%)	12 (3.7%)	NS
Somnolence	0	4 (1.9%)	4 (1.2%)	NS
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6 (5.4%)	6 (2.8%)	12 (3.7%)	NS
Pruritus	4 (3.6%)	5 (2.3%)	9 (2.7%)	NS
VASCULAR DISORDERS	9 (8.0%)	6 (2.8%)	15 (4.6%)	0.048
Hypotension	3 (2.7%)	3 (1.4%)	6 (1.8%)	NS
Hypertension	3 (2.7%)	2 (0.9%)	5 (1.5%)	NS

Note: Most frequent adverse events are those events which were reported by at least 1% of all patients. Adverse event mapping was based on the MedDRA Version 11.0 thesaurus. A patient may be reported in more than one category. Adverse events occurring while patients are on study medication during the study treatment period or within 12 hours after the discontinuation of study medication are included in this data analysis.

[1] The p-values for the comparison between two treatment groups are based on a two-sided Fisher's exact test and presented if they are less than 0.1; NS = Not statistically significant at 0.10 level.

Source: ISS Table 14.2.30

7.4.2 Laboratory Findings

There were no laboratory assessments available for review.

7.4.3 Vital Signs

The vital sign assessments will only contain the data from the placebo-controlled studies given a relative comparison to a placebo group provides context for interpretation of this data. The main focus of this section is on the Dsuvia pivotal placebo-controlled study SAP301. Oxygen saturation is a key vital sign analyzed due to the expected AE profile of an opioid analgesic.

SAP301:

Systolic Blood Pressure (SBP):

There was a consistent trend of a greater decrease in SBP in the sufentanil group compared to the control group. The greatest difference was at 36-hours of -19 compared to - 8 in the sufentanil and control group, respectively. Both groups had statistically significant mean decreases from baseline in SBP with the sufentanil group starting at 30 minutes and the control group starting at 2 hours after study initiation. The range in SBP decrease was mean decreases from baseline ranged from -0.59 mmHg at 15 minutes to -19.14 mmHg at 36 hours in sufentanil group and -1.23 mmHg at 4 hours to -10.36 mmHg at 16 hours in the control group.

Diastolic Blood Pressure (DBP):

There was also a consistent difference between groups for DBP throughout the study. There was a greater mean decrease in the sufentanil group compared to the control group at 12 and 24 hours and a mean decrease in the sufentanil group compared with a mean increase in the control group at 30 minutes. The mean decreases from baseline ranged from -0.43 mmHg at 15 minutes to -10.4 mmHg at 44 hours in the sufentanil group and from -1.37 mmHg at 45 minutes to -11.56 mmHg at 40 hours in the control group.

Overall, both the sufentanil and placebo (prn morphine) groups showed a decrease in blood pressure measures from baseline. There were greater decreases in the sufentanil groups, and this is likely due to the higher dose and or potency of the sufentanil group. However, these differences were fairly small and did not appear to translate into clinically detectable adverse events.

Heart Rate:

There were no statistically significant differences between treatment groups for mean changes from baseline at any time point.

Respiratory Rate:

For sufentanil, mean changes from baseline ranged from -0.19 breaths per minute (bpm) at 1 hour to +1.42 bpm at 28 hours. For control group, the mean changes from baseline ranged from -0.31 bpm at 30 minutes to +2.20 bpm at 32 hours. No patients had any respiratory rate less than 8 bpm. These changes did not appear clinically significant.

Oxygen Saturation:

There were small, but statistically significant differences between treatment groups for mean changes from baseline at 1 hour (-0.88% vs. -0.24%; $p = 0.007$) and 20 hours (-1.32% vs. -0.71%; $p = 0.032$), with greater decreases in the sufentanil group than in the control group at these times. For the sufentanil group, the mean decreases from baseline ranged from -0.19% at 15 minutes to -1.47% at 44 hours. For the placebo group, mean decreases from baseline ranged from -0.17% at 30 minutes to -1.22% at 36 hours. The proportions of patients who had SpO2 levels < 93% or < 95% during the study were higher in the sufentanil group than in the placebo group (< 93%: 7.5% vs. 0%; $p = 0.052$; < 95%: 23.4% vs. 7.4%; $p = 0.016$). Additionally, two sufentanil-treated patients had SpO2 less than 92% during the study. A summary of oxygen saturation is shown in Table 46.

Table 46: Summary of Oxygen Saturation – SAP301

SPO_2	Sufentanil (n=107)	Control (n=54)
Less than 95%	25 (23.4%)	4 (7.4%)
Less than 93%	8 (7.5%)	0 (0%)
Less than 90%	1 (0.9%)	0 (0%)
Mean (SD)	95.3 (1.7)	96.1 (1.3)

Source: Adapted from Table 14.3.24 of Applicant's CSR

Although there is evidence of greater amount and number of oxygen desaturation events, the vast majority were not of clinical consequence. Some transient oxygen desaturation is not uncommon with opioid medications and sufentanil is more potent than the morphine rescue used in the control group. Therefore, it is not unexpected for a small increase in oxygen desaturation. Although it is worth noting this difference, the clinical implications are not impressive in this study.

A summary of all the placebo-controlled studies, including SAP202, was performed by the Applicant (Table 47). This analysis shows similar results to the findings in SAP301.

Table 47: Summary of Lowest Oxygen Saturation that Occurred During the 24-hour Period: Patients Enrolled in Placebo-Controlled Studies from Dsuvia and Zalviso Programs

	Treatment Group		
	Combined Sufentanil[a] (n = 358)	Combined Placebo (n = 178)	p-value[b]
SpO2 < 93% - n (%)	358 (100%)	178 (100%)	0.086
Yes	28 (7.8%)	7 (3.9%)	
No	330 (92.2%)	171 (96.1%)	
SpO2 < 95% - n (%)	358 (100%)	178 (100%)	0.188
Yes	71 (19.8%)	27 (15.2%)	
No	287 (80.2%)	151 (84.8%)	
SpO2 (%) - n (%)	358 (100%)	178 (100%)	0.267
≥ 95	287 (80.2%)	151 (84.8%)	
93 to 94	43 (12.0%)	20 (11.2%)	
90 to 92	24 (6.7%)	7 (3.9%)	
< 90	4 (1.1%)	0 (0%)	
Mean (SD)	95.0 (3.4)	95.7 (1.6)	0.001
Median	95.0	96.0	
(Min, Max)	(40, 100)	(90, 100)	

Source: Applicant's ISS, p.98

7.4.4 Electrocardiograms (ECGs)

ECGs were not analyzed.

7.4.5 Special Safety Studies/Clinical Trials

There were no additional special safety studies

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no analysis for dose dependency. Only the 30 mg dose (or Zalviso bridged dose) was assessed for safety.

7.5.2 Time Dependency for Adverse Events

There was no formal analysis performed on time dependency for AEs. Given this is an immediate-release opioid drug, AEs are expected to occur within several hours of exposure.

7.5.3 Drug-Demographic Interactions

Refer to Section 7.4.1 for details. No significant disparities in AEs were detected between any common demographic.

7.5.5 Drug-Drug Interactions

There was no formal analysis performed in the clinical studies on drug-drug interactions. However, refer to Dr. Qiu's clinical pharmacology review for details about any potential drug-drug interactions.

8 Postmarket Experience

There is no post-market experience with Dsuvia.

9 Appendices

9.1 Literature Review/References

The Applicant submitted 11 references. These references were mostly historical studies citing the efficacy and safety of sufentanil product in clinical practice through intravenous/intrathecal routes. These routes have previously been approved by the FDA.

9.2 Labeling Recommendations

I recommend a Complete Response, therefore no labeling recommendations are indicated at this time.

9.3 Advisory Committee Meeting

No advisory committee meeting scheduled.

Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: 209128

Submission Date(s): 12/12/16

Applicant: ACErx

Product: Dsuvia

Reviewer: Steven Galati

Date of Review: 9/6/17

Covered Clinical Study (Name and/or Number): SAP301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 38		
Number of investigators who are sponsor employees (including both full-time and part-time		

employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 38		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The Applicant submitted the required financial certification and disclosure form (FDA 3454) which certified there was no financial agreement with any of the investigators. A list of 38 investigators was provided attached to the form. The Applicant also certified the investigators were required to disclose any proprietary interest defined in 21 CFR 54.2(b). The Applicant also certified that the investigators did not receive any payments defined in 21 CFR 54.2(f).

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/s/

STEVEN A GALATI
09/08/2017

ELLEN W FIELDS on behalf of JOSHUA M LLOYD
09/08/2017