CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209128Orig1s000

STATISTICAL REVIEW(S)

NDA #	209128
Applicant	AcelRx Pharmaceuticals, Inc.
From	Ning Hu (clinical reviewer), Yi Ren (statistical reviewer), David Petullo (statistical team leader), Janet Maynard (clinical team leader)
Subject	Cross-Discipline Team Leader Review; Primary Clinical Review; Primary Statistical Review
Date of Submission	May 3, 2018
PDUFA Goal Date	November 2, 2018
Proprietary Name	Sufentanil sublingual tablet (SST) 30 mcg
Proposed Established or Proper Name	Dsuvia
Dosage Form(s)	Sublingual tablets
Applicant Proposed Indication(s)/Population(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
Applicant Proposed Dosing Regimen(s)	A single sufentanil sublingual tablet 30 micrograms (SST 30 mcg), on an as needed basis, per patient request, with a minimum of 1 hour between doses. Dosing not to exceed 12 tablets in 24 hours.
Recommendation on Regulatory Action	Approval, pending final agreement on REMS
Recommended Indication(s)/Population(s) (if applicable)	DSUVIA is indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

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1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The proposed drug-device combination product contains 30 mcg of the potent opioid agonist, sufentanil, for use in a medically supervised setting for the treatment of adults with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The product is intended to be administered in a medically supervised setting by a healthcare provider to a patient's sublingual space using a single-dose applicator (SDA) on an as needed basis with a minimum interval of one hour between doses.

Adequate control of acute pain is critical and prescription opioids are an important component of modern pain management. However, the treatment of acute pain needs to be balanced with public health considerations related to abuse, misuse, and accidental exposure. While there are multiple drugs approved for treating acute pain, sufentanil sublingual tablet 30 mcg is the first sublingual sufentanil product proposed for acute pain severe enough to require an opioid analgesic. If approved, sufentanil sublingual tablets 30 mcg would add another therapeutic option for the treatment of acute pain.

The application is supported by reference to the Agency's previous findings of efficacy and safety for Sufenta (sufentanil citrate for injection; NDA 19050), cross reference to safety data for sufentanil sublingual tablets 15 mcg (proposed tradename Zalviso; (b) (4)), another drug-device combination product that contains 15 mcg of sufentanil and was intended to be administered by a patient using a different device, a Phase 3 placebo-controlled sufentanil sublingual tablet 30 mcg trial (SAP301), and two Phase 3 open-label sufentanil sublingual tablets 30 mcg studies. Of note, the sufentanil sublingual tablets 15 mcg application received a complete response on July 25, 2014, primarily due to issues surrounding the device and inadvertent loss of dispensed tablets.

The efficacy of sufentanil sublingual tablets 30 mcg was evaluated in one placebo-controlled Phase 3 trial in post-surgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery with acute pain. This trial was adequate and well-controlled and provided evidence of the efficacy of sufentanil sublingual tablets 30 mcg in treating acute pain, based on the time-weighted summed pain intensity difference from baseline over 12 hours (SPID12).

The safety profile of sufentanil sublingual tablets 30 mcg in acute pain was consistent with the typical safety profile of an opioid agonist, however there were two areas of safety concern that required further evaluation: the safety of sufentanil sublingual tablets 30 mcg in patients requiring the maximum dosing proposed for labeling and the risk of misplaced tablets. Given these safety concerns, the application received a complete response and was not approved on October 11, 2017. The focus of this review is the Applicant's resubmission to address these concerns. To address the safety of sufentanil sublingual tablets 30 mcg in patients requiring the maximum dosing proposed for labeling, the Applicant reduced the maximum daily dose from 24 to 12 sufentanil sublingual 30 mcg tablets per day and provided new pooled safety analyses. The Applicant's analyses support the proposed maximum daily dose. To address the concern of misplaced tablets, the Applicant modified the directions for use and performed another human factors validation study. The Agency has determined that the human factors validation study support the safe and effective use of the product.

The application was discussed at an Anesthetic and Analgesic Advisory Committee meeting on October 12, 2018, and the majority of committee members recommended approval (10 yes; 3 no). Sufentanil sublingual tablets 30 mcg offer a benefit for the treatment of acute pain. The risks of sufentanil are consistent with other opioids. The risks associated with the small tablet size specific to SST, such as misplaced tablets and accidental exposure, will be managed with a REMS with ETASU. The overall benefit/risk is favorable in the context of these risk mitigation strategies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain is a serious medical condition which can affect function and quality of life. • Acute pain significantly impacts the lives of patients due to pain and decreased physical function.	Acute pain is a potentially serious condition and is common in a variety of medical and surgical settings. While there is heterogeneity in the types and causes of acute pain, adequate control of acute pain is important regardless of the etiology.
Current Treatment Options	• Prescription medications are often a component of a multimodal analgesic approach, which is standard in many institutions. Pharmacologic options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical agents (e.g., local anesthetics), and opioids. • Opioids are commonly used to control postoperative pain. They can be administered via oral, transdermal, parenteral, neuraxial, and rectal routes. In the postoperative setting, opioids are frequently administered intravenously (IV), either through clinician administered boluses or via PCA. • Parenteral opioids currently approved for acute pain in the United States include morphine, fentanyl, meperidine, and hydromorphone.	There are multiple current pharmacologic treatment options for patients with acute pain.
Benefit	• The efficacy of sufentanil sublingual tablets (SST) 30 mcg was evaluated in one randomized, double-blind, placebo-controlled trial that enrolled 161 patients (age 18 to 69 years) with acute postoperative pain (pain intensity of ≥4 on a 0-10 numeric rating scale [NRS]) after abdominal surgery (studied up to 48 hours) (Study SAP 301) • Patients were dosed with SST 30 mcg or placebo as needed with a minimum of 60 minutes between doses. Morphine sulfate 1 mg IV was available as rescue medication.	The SST 30 mcg clinical trial was adequate and well-controlled. SST 30 mcg was effective in reducing pain. Only one trial was needed to support this formulation change given that the efficacy of sufentanil (Sufenta) has already been established and the Applicant is relying on the Agency's previous finding of Sufenta's efficacy and safety.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The primary efficacy endpoint was the time-weighted sum of pain intensity difference over 12 hours (SPID12). Patients using SST 30 mcg had a statistically significantly lower SPID12 than patients using placebo. • Median time to onset (measured using the double stopwatch method) was 54 minutes for the SST group and 84 minutes for the placebo group. • Approximately 22.4% of patients in the DSUVIA group and 64.8% of patients in the placebo group took rescue medication within the first 12 hours of the treatment phase.	
Risk	• The safety of SST 30 mcg was evaluated in a total of 646 patients with moderate-to-severe acute postoperative pain or pain due to trauma which required opioid analgesia. • The safety profile of sufentanil sublingual tablets 30 mcg in acute pain was consistent with the typical safety profile of an opioid agonist, however there were two areas of safety concern that required further evaluation in this resubmission: the safety of sufentanil sublingual tablets 30 mcg in patients requiring the maximum dosing proposed for labeling and the risk of misplaced tablets. • To address the safety of sufentanil sublingual tablets 30 mcg in patients requiring the maximum dosing proposed for labeling, the Applicant reduced the maximum daily dose from 24 to 12 sufentanil sublingual 30 mcg tablets per day and provided new pooled safety analyses. • To address the concern of misplaced tablets, the Applicant modified the directions for use and performed another human factors validation study.	The size of the safety database for SST 30 mcg is adequate. Its safety profile is well characterized, and the Applicant has provided adequate data to support the proposed maximum dose. The main safety concerns associated with SST 30 mcg are related to opioid-related side effects, such as respiratory depression, and risks associated with the small tablet size, such as accidental exposure, misuse and abuse.
Risk Management	• SST 30 mcg has risks associated with opioids and risks associated with its small tablet size, such as accidental exposure, misuse, and abuse.	• SST 30 mcg will have boxed warnings similar to other opioids including accidental exposure, life-threatening respiratory depression, and addiction, abuse, and misuse, cytochrome P450 3A4 interactions, and risks from concomitant use with benzodiazepines or other CNS depressants. • SST 30 mcg will have Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETASU) and use will be limited to certified medically supervised settings. Use will be limited to certified medically supervised settings

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		to ensure that there is access to equipment and personnel trained to detect and manage acute opioid overdose, including respiratory depression.

2. Introduction

This is a review of AcelRx's Pharmaceuticals, Inc (AcelRx's) response to the Complete Response (CR) letter issued on October 11, 2017, for new drug application (NDA) 209128 for sufentanil sublingual tablets (proposed trade name Dsuvia). The application was originally submitted on December 12, 2016, as a 505(b)(2) new drug application (NDA) for sufentanil sublingual tablets (SST), a drug-device combination product containing 30 mcg of the potent opioid agonist, sufentanil. The product is intended to be administered by a healthcare provider to the patient's sublingual space in a medically supervised setting, using the single-dose applicator (SDA), on an as needed basis with a minimum interval of one hour between doses.

AcelRx's proposed indication is for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting.

The NDA references the Agency's previous findings of efficacy and safety 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. Sufenta is currently only approved as a solution for injection. The Applicant also cross references their previously submitted (b) (4) for sufentanil sublingual tablet 15 mcg, another sufentanil sublingual tablet drug-device combination product that, in contrast to sufentanil sublingual tablet 30 mcg, contains 15 mcg of sufentanil and was intended to be administered by the patient using a different device. The sufentanil sublingual tablet 15 mcg application received a complete response on July 25, 2014 primarily due to issues surrounding the device and inadvertent loss of dispensed tablets. The inclusion of selected safety data from the sufentanil sublingual tablet 15 mcg program was determined to be reasonable as the Applicant established a pharmacokinetic bridge between two doses of sufentanil 15 mcg sublingual tablets within 20 to 25 minutes and a single dose of sufentanil sublingual tablet 30 mcg.

The original sufentanil sublingual tablet 30 mcg application was supported by the Agency's previous findings for Sufenta (NDA 19050), a Phase 3 placebo-controlled sufentanil sublingual tablet 30 mcg trial (SAP301), two Phase 3 open-label sufentanil sublingual tablet 30 mcg studies, and selected safety data from the sufentanil sublingual tablet 15 mcg program, as well as CMC/device, pharmacology/toxicology, clinical pharmacology, and human factors data.

There were two deficiencies outlined in the complete response letter. The first deficiency was an inadequate number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of sufentanil sublingual tablet 30 mcg. To address this deficiency, the Applicant was asked to collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety of sufentanil sublingual tablet 30 mcg for a period following the maximum proposed dosing. The second deficiency was the possibility of misplaced tablets, which pose a risk for accidental exposure and improper dosing. To address this deficiency, the Applicant was asked to develop mitigation strategies to address the risk of dropped sufentanil

tablets and to conduct another human factors validation study. See the cross-discipline team leader (CDTL)/Division Director review from the first cycle. Of note, in this previous review, the names "Dsuvia" and "Zalviso" are used, while sufentanil sublingual tablets, 30 mcg and 15 mcg, respectively, are used in the current review.

In this complete response submission, the Applicant did the following to address the deficiencies described in the complete response letter:

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

This review will be focus on the Applicant's complete response submission. Background Sufentanil is a synthetic opioid analgesic that is five to ten times more potent than its analog, fentanyl.

Sufenta (NDA 19050) is the only listed sufentanil product and is for intravenous and epidural use. If approved, sufentanil sublingual tablet 30 mcg would be the first sufentanil analgesic product for sublingual use.

The proposed indication is the management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. A variety of immediate-release opioid analgesics and combination opioid/non-opioid products are approved for management of acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate. Available opioid products include meperidine, tramadol, codeine, hydrocodone, oxycodone, morphine, oxymorphone, hydromorphone, and fentanyl. The available products can be given via various routes of administration, such as oral, transdermal, intramuscular, subcutaneous, intravenous, transmucosal, and epidural/intrathecal.

Key regulatory interactions since the original NDA was submitted on December 12, 2016, are listed below by date. Points of discussion or Agency recommendations are provided as a bulleted list for each meeting or interaction. The development program for sufentanil sublingual tablet 30 mcg occurred under IND 113059.

October 11, 2017 – Complete Response letter issued

January 26, 2018 – Post-action meeting

- The Applicant proposed a revised maximum daily dose from 24 tablets in 24 hours to 12 tablets in 24 hours. In addition, the Applicant proposed pooled analyses from the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg programs. The Agency agreed on this approach, but noted that the adequacy of the data would be a review issue.

- The Applicant stated that they incorporated the Agency's recommendations for the Directions for Use (DFU) and planned an additional human factors study to evaluate the effectiveness of the changes to the DFU in addressing the risk of dropped tablets. The Agency reiterated its concern regarding sufentanil sublingual tablet 30 mcg's small tablet size.

3. Product Quality

See the CDTL/Division Director review from the original NDA submission for details regarding the product quality considerations.

In summary, the drug component of this drug-device combination product consists of an immediate-release sublingual tablet containing 30 mcg of sufentanil. The tablet measures 3 mm in diameter and 0.85 mm in thickness with a nominal tablet weight of 7.40 mg. The tablet is blue. Each disposable single dose applicator (SDA) contains one tablet and is intended for single use.

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 health care provider 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.

Figure 1: Single Dose Applicator Container Label – Front

Source: 3.2.P, page 1, submitted on 05/03/2018

Human Factors
The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors (HF) validation study results from the original NDA and the human factors study in the resubmission. See Section 8 for a discussion of the HF validation studies.

The OPQ recommendation for this application at the end of the original review cycle was that the application could be approved, from a CMC perspective. Although there were no CMC-related comments included in the CR letter, the new submission includes new stability data. The CMC review concludes that "the new stability data submitted with the resubmission justifies a shelf-life of 36 months." There are no approvability issues from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

See the CDTL/Division Director review from the original NDA submission for details regarding the nonclinical pharmacology/toxicology considerations. No new nonclinical data were included in the complete response submission.

5. Clinical Pharmacology

See the CDTL/Division Director review from the original NDA submission for details regarding the clinical pharmacology considerations.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP-DCP-2) and the Division of Pharmacometrics reviewed the resubmission and found it acceptable from a clinical pharmacology perspective. See Section 8.2.b for a discussion of OCP's assessment of the Applicant's methodology to assess the risk associated with accidental dosing of Dsuvia in a 12-kg child.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Efficacy of this product was based on the results from a single Phase 3 clinical trial, SAP301. See the CDTL/Division Director review from the original submission for a detailed discussion of this study.

The following is a summary of the efficacy review of SAP301 that was previously reviewed in the initial NDA. Study SAP301 was a multicenter, randomized, double-blind, and placebo-controlled study. Randomization was stratified by sex and investigational site. Patients were randomly assigned to treatment with sufentanil sublingual tablets 30 mcg or placebo at a 2:1 ratio within each stratum. Study medication was administered by a health care professional using the single-dose applicator on an as needed basis with a minimum of one hour between doses. The study period was up to 48 hours. Efficacy was assessed by patient-reported pain intensity (PI) on an 11-point numerical rating scale. Prior to randomization, a patient was required to have a minimum postoperative PI score of 4 (baseline PI) and a minimum PI score of 4 to continue treatment beyond 24 hours. Rescue medication, 1 mg IV morphine, was allowed if the patient requested additional medication for pain beyond the use of the study medication.

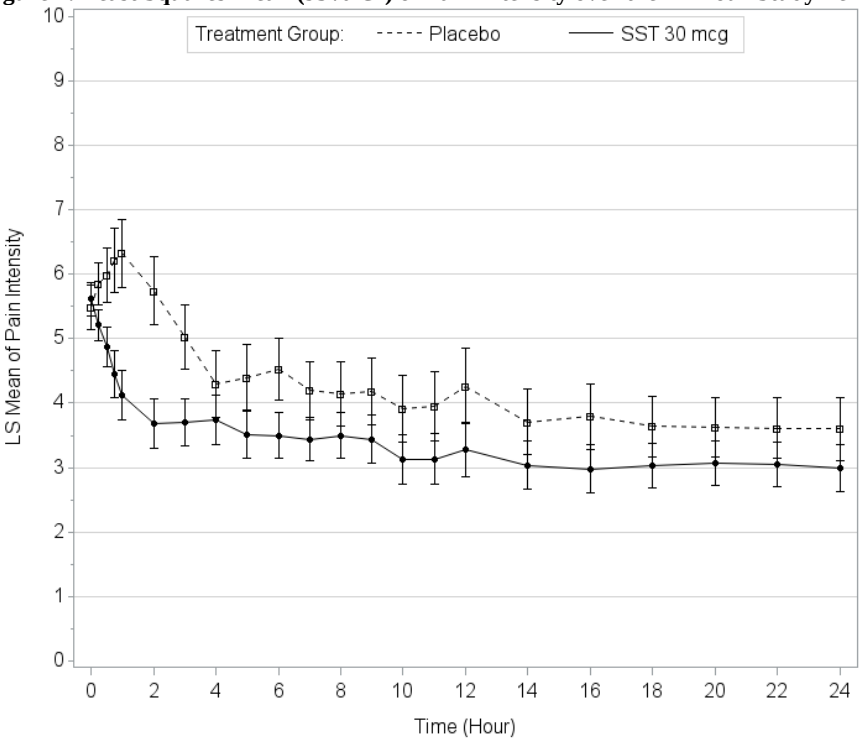
The primary efficacy endpoint was time-weighted summed pain intensity difference from baseline over 12 hours (SPID12). As supportive evidence, the following secondary efficacy endpoints were also examined:
• Time to first use of rescue medication

• Total number of study medication and rescue medication doses used over 12-hour study period
• Time to onset of meaningful pain relief

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 PI score as a covariate. A pre-rescue PI score was carried forward for one hour following the dosing of rescue medication. For intermittent missing data, a linear interpolation method was used to impute the missing values between two observed pain scores. A modified Brown's method was adopted by the Applicant to impute post-dropout missing values. Since it was a single imputation method, a sensitivity analysis using multiple imputation with baseline distribution was performed to evaluate the impact of missing data. Time to first use of rescue medication and time to onset of meaningful pain relief were summarized using Kaplan-Meier product-limit estimates and were compared between treatment groups using a log-rank test. The number of study medication and rescue medication doses used was analyzed using an ANCOVA model that included treatment, center, and sex as factors. Since there was no adjustment for multiplicity for any of the secondary endpoints, these endpoints were considered supportive of the primary efficacy endpoint and would not be suitable for inclusion in section 14 of the product label.

A total of 161 patients were randomized and received study medication. There was a statistically significant difference ($p < 0.001$) between treatment groups with respect to the primary efficacy endpoint SPID12 (mean difference of 12.7, 95% CI of [7.2, 18.2]). The estimated mean of PI and its 95% confidence interval (CI) at each analysis time point were plotted in Figure 2. There was a separation between curves over the 24-hour study period. Given the results of sensitivity analysis and the small number of early dropouts, the impact of missing data was minimal. The efficacy noted with the primary endpoint SPID12 was supported by the results from clinically relevant secondary endpoints, time to first use of rescue mediation and amount of rescue medication used over the first 12 hours.

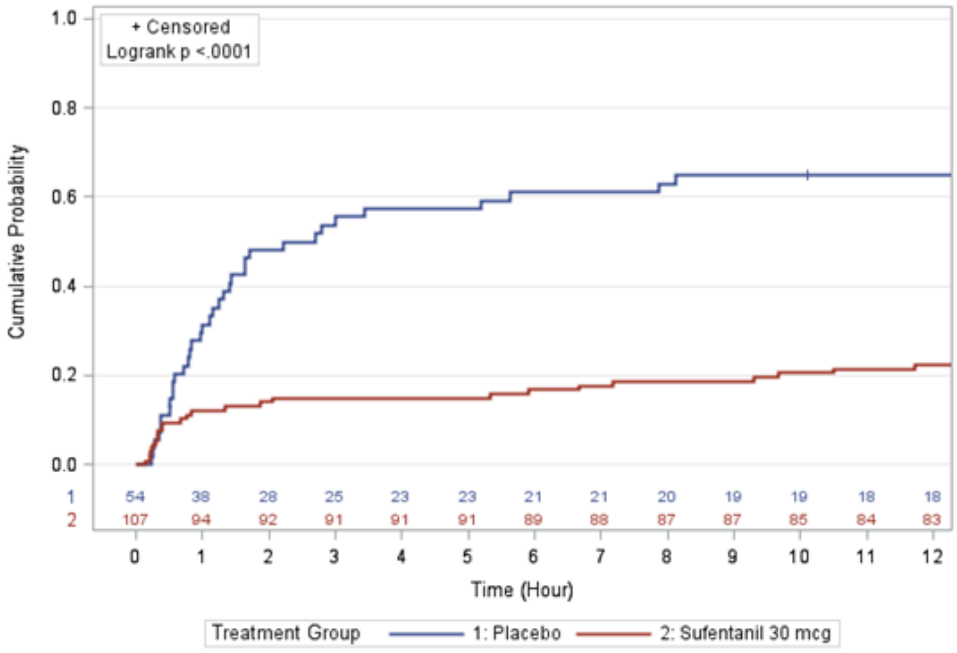
Figure 2: Least Squares Mean (95% CI) of Pain Intensity over the 24-Hour Study Period



Source: Reviewer

Even though there was very little use of rescue medication on average, subjects who received sufentanil used less doses than subjects who received placebo (Table 1). Additionally, the time to first use of rescue medication was significantly shorter for patients who received sufentanil compared to those who received placebo over the first 12 hours (Figure 3).

Figure 3: Kaplan-Meier Curves for Time to First Use of Rescue Medication over the 12-Hour Study Period



Source: Reviewer
Numbers of subjects at risk are listed at the bottom.

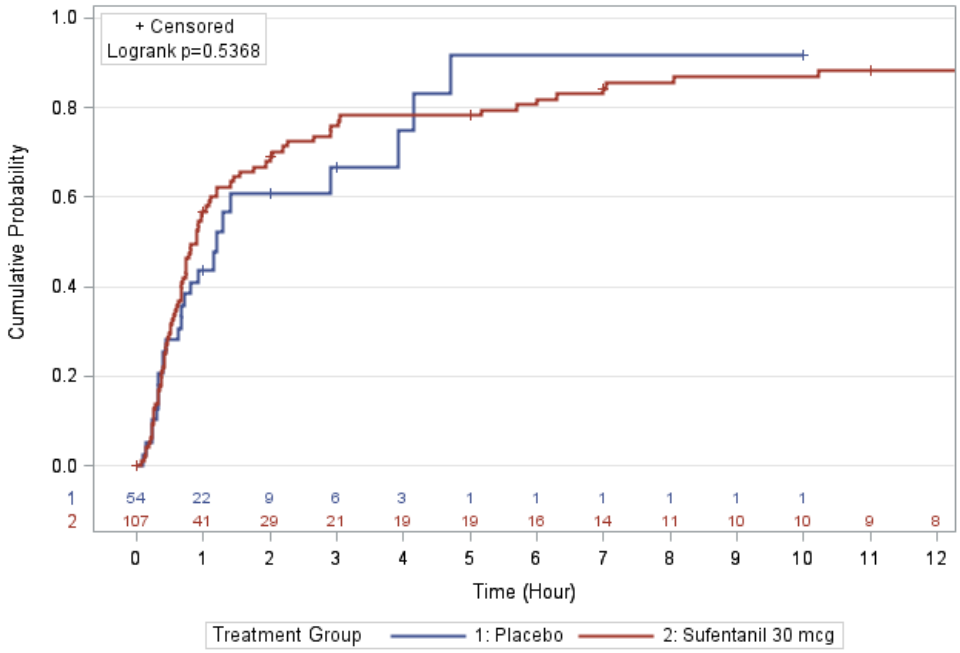
Table 1: Number of Rescue Medication Doses Used over the 12-Hour Study Period

Number of Doses Used over 12 Hours	SST 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)	

Source: Reviewer
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.
Abbreviations: SST: sufentanil sublingual tablet; SD: standard deviation

Although there was no statistically significant difference between sufentanil and placebo groups for the total number of study medication doses used (Figure 4) and the time to onset of meaningful pain relief (Table 2), numerically, sufentanil was better than placebo.

Figure 4. Kaplan-Meier Curves for Time to Meaningful Pain Relief over the 12-Hour Study Period



Source: Reviewer
Numbers of subjects at risk are listed at the bottom.

Table 2. Number of Study Drug Doses Used over the 12-Hour Study Period

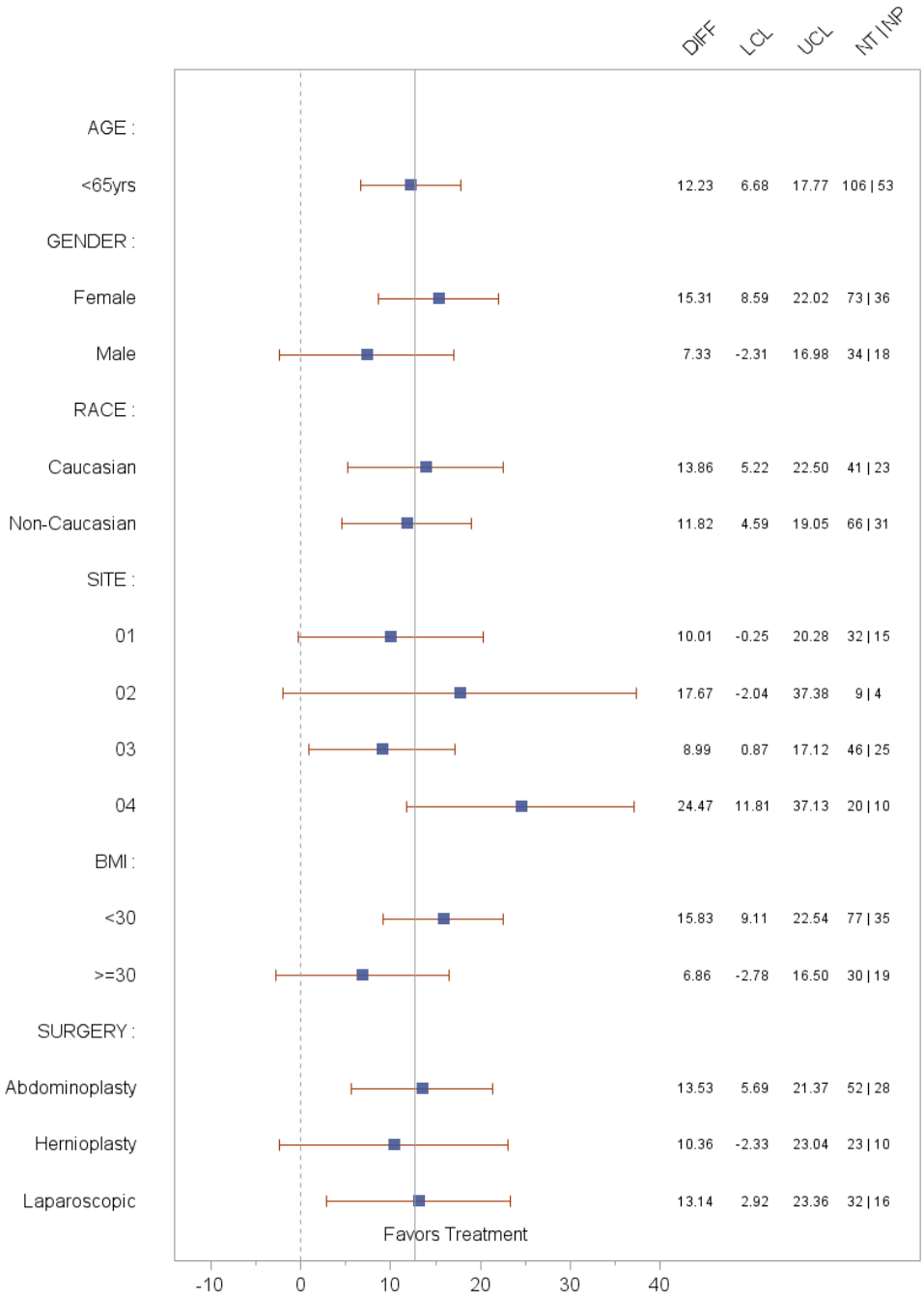
Number of Doses Used over 12 Hours	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)	P-value
Mean (SD)	4.4 (2.0)	4.7 (2.3)	
Median	4	4	
Range	(1, 9)	(1, 11)	
LS mean difference	-0.3 (-1.0, 0.4)		0.360
Number (%) by category			
<4	40 (37.4)	16 (29.6)	
4-8	65 (60.8)	34 (63.0)	0.180
>8	2 (1.9)	4 (7.4)	

Source: Reviewer
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.

The primary efficacy analysis was also performed by subgroup of interest, including age (<65 years), gender (male and female), race (Caucasian and non-Caucasian), BMI (<30 kg/m^2 and ≥30 kg/m^2), investigational site (Sites 1-4), and type of surgery (abdominoplasty, hernioplasty, and laparoscopic abdominal surgery).

For each subgroup, the 95% CI for the mean difference in SPID12 comparing sufentanil sublingual tablet 30 mcg with placebo is presented in Figure 5. Since there were only two patients older than 65 years of age, this subgroup analysis was not performed. For all subgroups, while not significant, numerically the sufentanil group had more pain relief than placebo based on SPID12. Subgroups such as Sites 2 and 4 and hernioplasty surgery had limited number of patients, and therefore resulted in large variability and unreliable results.

Figure 5. Subgroup Analyses for Primary Efficacy Endpoint SPID12



Source: Reviewer
The least squares mean difference of sufentanil over placebo with respect to SPID12 was analyzed using ANCOVA with treatment, baseline pain intensity, and interaction between treatment and the subgroup of interest.
DIFF: least squares mean difference
LCL: lower 95% confidence limit
UCL: upper 95% confidence limit
NT: number of subjects in the SST 30 mcg group
NP: number of subjects in the placebo group
Solid vertical line represents mean overall estimated effect size.
Dashed vertical line represents no effect.

In summary, the primary and secondary analyses support the efficacy of sufentanil sublingual tablets 30 mcg for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Since sufentanil sublingual tablet 30 mcg was only compared to placebo in the single completed Phase 3 study, there are no data available on the efficacy of sufentanil sublingual tablet 30 mcg compared to other therapies.

8. Safety

8.1 Summary of safety review from 1st review cycle

Studies contributing to integrated safety analyses

A summary of the studies contributing to the safety analyses in the first review cycle is shown in Table 3. The safety database in the original NDA included data from the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg programs. From the sufentanil sublingual tablet 30 mcg program, there were three Phase 3 studies (SAP301 [Phase 3 efficacy trial] and SAP302 and SAP303 [open-label safety studies]). SAP301 was a randomized, double-blind, placebo-controlled trial in adults with moderate-to-severe pain following outpatient abdominal surgery. Patients could receive sufentanil sublingual tablet 30 mcg every hour as needed for up to 48 hours. SAP302 was an 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 numeric rating scale (NRS).

There were two additional clinical studies in the sufentanil sublingual tablet 30 mcg program (SAP101 and SAP202) that were not included in the pooled safety analyses. SAP101 was a Phase 1 study conducted in healthy subjects who received naltrexone to block the opioid agonist effects of sufentanil. SAP202 was a Phase 2 study in a bunionectomy population using a different formulation and the in vitro data were not sufficient to bridge the formulation used to the final to-be-marketed formulation.

Sufentanil sublingual tablet 15 mcg (proposed tradename Zalviso) is another sufentanil sublingual tablet drug-device combination product that, in contrast to sufentanil sublingual tablet 30 mcg, contains 15 mcg of sufentanil and is administered by a patient with a different device that has a 20-minute lockout between doses. The sufentanil sublingual tablet 15 mcg application received a complete response, primarily due to issues surrounding the device and inadvertent loss of dispensed tablets. In the sufentanil sublingual tablet 30 mcg NDA, the Applicant provided safety data from the sufentanil sublingual tablet 15 mcg program. From the sufentanil sublingual tablet 15 mcg program, the Applicant provided safety data from selected patients who received the first dose of sufentanil tablet 15 mcg followed by a second dose of sufentanil sublingual tablet 15 mcg within 20 to 25 minutes. This included data from six sufentanil sublingual tablet

15 mcg studies in patients with postoperative pain after open abdominal surgery, total knee arthroplasty, or total hip arthroplasty. While there were differences in the sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg clinical programs, including different devices, study designs, and patient populations, it was determined that it was reasonable to use data from the sufentanil sublingual tablet 15 mcg program to support the safety of sufentanil sublingual tablet 30 mcg given that both programs administered sufentanil. In addition, in the original NDA review, the Applicant established a pharmacokinetic bridge between two sufentanil sublingual tablet 15 mcg doses of sufentanil 15 mcg tablets administered within 20 to 25 minutes and a single sufentanil sublingual 30 mcg tablet.

Table 3: Summary of Studies Contributing to Sufentanil Safety Analyses

Study	Overview	Patient Population	Treatment/ Duration	Number of subjects (treated/completed/in pool)	Rescue
Sufentanil sublingual tablet (SST) 30 mcg clinical program					
SAP301 (pivotal efficacy study)	MC, R, DB, PC	Post-surgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery	SST: 30 mcg Placebo Up to 48 hours	SST 30 mcg: 107/102 Placebo: 54/41	Morphine IV
SAP302	MC, OL	Emergency room setting – adult patients 18 years of age and older with pain due to trauma or injury	SST 30 mcg Up to 4 doses Up to 5 hours	76/65 (2-hour period)	Morphine IV or oral oxycodone
SAP303	MC, OL	Post-surgical patients 40 years or older following any type of surgery	SST 30 mcg Up to 12 hours	140/132	Morphine IV
Selected patients* in the following studies from sufentanil sublingual tablet (SST) 15 mcg clinical program					
IAP310 Phase 3	MC, R, DB, PC	Open abdominal surgery, with postoperative pain of at least 4 on an 11-point NRS	SST 15 mcg Placebo Up to 72 hours	SST: 114/78/51 Placebo: 58/27/27	Morphine IV
IAP311 Phase 3	MC, R, DB, PC	Total knee or hip replacement	SST 15 mcg Placebo Up to 72 hours	SST: 315/215/142 Placebo: 104/43/54	Morphine IV
IAP309 Phase 3	MC, R, OL, AC	Open abdominal surgery or knee or hip replacement	SST 15 mcg Morphine 1 mg SL Up to 72 hours	SST: 177/146/94 Morphine: 180/136	Morphine IV
ARX-COO1 Phase 2	MC, R, DB, PC	Total knee replacement	SST 5 mcg, 10 mcg, and 15 mcg Placebo Up to 12 hours	SST 15 mcg: 20/13/12 Placebo: 24/7/15	No rescue
ARX-COO5 Phase 2	MC, R, DB, PC	Open abdominal surgery	SST 10 and 15 mcg Placebo Up to 12 hours	SST 15mcg: 29/25/6 Placebo: 30/9/8	No rescue
ARX-COO4 Phase 2	MC, OL; no control	Knee replacement	SST 15 mcg Up to 12 hours	SST 15mcg: 30/26/18	No rescue

* The selected sufentanil sublingual tablet 15 mcg population includes patients who self-administered sufentanil sublingual tablet 15 mcg (SST 15 mcg) or placebo with the second dose administered within 20 to 25 minutes after the first dose.
Abbreviations: AC=active controlled; DB=double blind; MC=multicenter; PC=placebo-controlled; R=randomized
Source: Adapted from Integrated Summary of Safety Table 1 and Table 3, pages 17-19, submitted 5/3/2018 and Clinical Summary of Safety, Table 2.7.4:3, pages 9-10, submitted 12/12/16

Adequacy of the drug exposure experience

During clinical development, the Division agreed that an overall safety database of at least 500 patients would be required with at least 350 subjects exposed to at least one dose of sufentanil sublingual tablets 30 mcg and 100 of these subjects exposed to multiple doses of sufentanil sublingual tablets 30 mcg over the anticipated duration of use.

As shown in Table 4, between 0-12 hours, a total of 646 patients were treated with sufentanil sublingual tablets (sufentanil sublingual tablet 30 mcg: 323 and sufentanil sublingual tablet 15 mcg: 323).[1] Of the 323 patients exposed to sufentanil sublingual tablet 30 mcg, 86% used fewer than six doses in the first 12 hours of the study, and the remaining 14% used between 6 to 12 doses. Between 0-24 hours, 107 patients received sufentanil sublingual tablet 30 mcg and they were all from study SAP301 as the other sufentanil sublingual tablet 30 mcg studies (SAP302 and SAP303) were less than 24 hours. Between 0-24 hours, only 9 patients received more than 12 doses of sufentanil sublingual tablet 30 mcg. The mean number of sufentanil sublingual tablet 30 mcg doses was 3.2 during the first 12 hours and 7 during the first 24 hours. In comparison, the mean number of sufentanil sublingual tablet 15 mcg doses was 13 during the first 12 hours and 25.1 during the first 24 hours. Thus, data from the sufentanil sublingual tablet 15 mcg program provided information on longer duration of exposure (to 48 hours and longer) and with higher mean number of doses. In the sufentanil sublingual tablet 30 mcg program, the more limited exposure to sufentanil was due to the short duration of the studies and the nature of the patient populations evaluated.

During the initial review, it was determined that an adequate number of patients had been exposed to sufentanil sublingual tablet 30 mcg given that 323 were exposed, which was close to the previously discussed requirement of 350 patients. However, the experience with repeated dosing of sufentanil sublingual tablet 30 mcg was not adequate since the maximum cumulative daily dose proposed in the label was 720 mcg or 24 tablets (24 hours x 30 mcg/dose). In addition, there was inadequate safety data at steady-state exposure to sufentanil from sufentanil sublingual tablet 30 mcg. It takes seven doses of sufentanil sublingual tablet 30 mcg, 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 sufentanil sublingual tablet 30 mcg clinical trials represents the adverse event profile of a less than steady-state exposure to sufentanil from sufentanil sublingual tablet 30 mcg. Thus, the adverse effects of the exposure of sufentanil following multiple dosing was not adequately evaluated.

[1] The Applicant notes that over half of the patients who received two doses of sufentanil sublingual tablet 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 sufentanil sublingual tablet 30 mcg.

Table 4: Total Number of SST Doses Used in SST 30 mcg Studies and selected SST 15 mcg Studies (Pool 1N)

	Treatment group				Total
	SST 15 mcg (n=323)	SST 15 mcg placebo (n=104)	SST 30 mcg (n=323)	SST 30 mcg placebo (n=54)	(n=804)
Number of doses used (0-12 hours) - n (%)	323 (100%)	104 (100%)	323 (100%)	54 (100%)	804 (100%)
< 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	183 (22.8%)
>24	26 (8.0%)	11 (10.6%)	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)
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%)
< 6			42 (39.3%)		
6-12	16 (5.6%)	20 (24.7%)	56 (52.3%)	25 (46.3%)	103 (19.5%)
13-24	40 (13.9%)	10 (12.3%)	9 (8.4%)	25 (46.3%)	131 (24.8%)
>24	84 (29.3%)	14 (17.3%)	0	4 (7.4%)	111 (21.0%)
Mean (SD)	147 (51.2%)	37 (45.7%)	7.0 (3.6)	0	184 (34.8%)
Median	25.1 (12.9)	22.1 (15.8)	7.0	6.4 (3.8)	19.0 (14.1)
(Min, Max)	25.0	19.0	(1, 15)	6.0	15.0
	(2, 55)	(3, 55)		(1, 18)	(1, 55)

Abbreviation: SST = sufentanil sublingual tablet; SD: standard deviation; Max=maximum; Min=minimum
Source: Adapted from Applicant's Response to Information Request (5/18/17), Table 3, page 8, submitted 6/8/17

Safety review from available drug exposure data

In the first cycle, it was concluded that sufentanil sublingual tablet 30 mcg has a safety profile consistent with an opioid agonist. See the CDTL/Division Director review from the first cycle for additional details of the analyses and safety findings. While data from both the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg programs was analyzed to support the safety of sufentanil, this review will provide a summary of the safety data from SAP301, which was the only placebo-controlled study with sufentanil sublingual tablet 30 mcg.

Deaths
There were no deaths in Study SAP301.

Serious Adverse Events
Two patients experienced a nonfatal serious adverse event (SAE)—one case of syncope and one case of hemiparesis. Both cases occurred in the placebo group and there were no SAEs in the sufentanil sublingual tablet 30 mcg-treatment group.

Discontinuations due to Adverse Events
As shown in Table 5, in Study SAP301, a higher proportion of patients in the placebo group (3.7%) discontinued due to adverse events compared to the sufentanil sublingual tablet 30 mcg group (0.9%). The adverse event leading to discontinuation in the sufentanil sublingual tablet 30 mcg group was oxygen saturation decreased, which is an anticipated adverse event for an opioid.

Table 5: Adverse Events Causing the Discontinuation of Study Drug (Study SAP301)

Preferred term	Treatment group		Total n=161
	Sufentanil n=107	Placebo n=54	
Number (%) of Patients With At least One Adverse Event Causing Discontinuation of Study Drug	1 (0.9%)	2 (3.7%)	3 (1.9%)
Oxygen saturation decreased	1 (0.9%)	0	1 (0.6%)
Dizziness	0	1 (1.9%)	1 (0.6%)
Hemiparesis	0	1 (1.9%)	1 (0.6%)
Somnolence	0	1 (1.9%)	1 (0.6%)
Syncope	0	1 (1.9%)	1 (0.6%)

Source: Adapted from SAP301 Clinical Study Report, Table 30, page 106, submitted 12/12/16

Common Adverse Events

The most frequently reported AEs were nausea (sufentanil, 35 [32.7%]; placebo, 16 [29.6%]) and headache (sufentanil, 21 [19.6%]; placebo, 10 [18.5%]). The adverse events in the sufentanil sublingual tablet 30 mcg treatment group were consistent with an opioid's safety profile, such as dizziness and vomiting.

Table 6: Most Frequent Adverse Events in SAP301

	Treatment group		Total n=163
	Sufentanil n=107	Placebo n=54	
Number (%) of Patients With At least One Adverse Event	62 (57.9%)	34 (63.0%)	96 (59.6%)
Nausea	35 (32.7%)	16 (29.6%)	51 (31.7%)
Headache	21 (19.6%)	10 (18.5%)	31 (19.3%)
Vomiting	8 (7.5%)	1 (1.9%)	9 (5.6%)
Dizziness	6 (5.6%)	2 (3.7%)	8 (5.0%)
Hypotension	5 (4.7%)	2 (3.7%)	7 (4.3%)
Flatulence	4 (3.7%)	4 (7.4%)	8 (5.0%)
Tachycardia	3 (2.8%)	0	3 (1.9%)
Procedural nausea	3 (2.8%)	3 (5.6%)	6 (3.7%)
Somnolence	3 (2.8%)	2 (3.7%)	5 (3.1%)
Pruritus	2 (1.9%)	2 (3.7%)	4 (2.5%)
Procedural vomiting	2 (1.9%)	0	2 (1.2%)
Presyncope	1 (0.9%)	1 (1.9%)	2 (1.2%)
Pruritus generalized	1 (0.9%)	1 (1.9%)	2 (1.2%)
Hypertension	1 (0.9%)	1 (1.9%)	2 (1.2%)

Source: Reviewer and adapted from SAP301 Clinical Study Report, Table 26, page 100, submitted 12/12/16

Respiratory

In study SAP301, the proportions of patients who had oxygen saturation levels < 93% or < 95% during the study were higher in the sufentanil sublingual tablet 30 mcg group than in the placebo group (< 93%: 7.5% vs. 0%; < 95%: 23.4% vs. 7.4%). Two sufentanil sublingual tablet 30 mcg-treated patients had oxygen saturations less than 92% during the study.

8.1.a Safety concern associated with dropped tablets – 1st cycle review

A significant safety concern in the review of the NDA was the risk of dropped sufentanil sublingual tablet 30 mcg tablets, which could lead to accidental exposure, improper dosing, or misuse.

In the sufentanil sublingual tablet 30 mcg Phase 3 program, there were three dropped 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 details of these cases were reviewed in the first cycle:

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 health care provider (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.

Although no specific adverse events were associated with these instances of dropped tablets, these are serious errors with potentially serious consequences. These safety concerns precluded approval in the first review cycle.

Human factors validation study:

In the original NDA, the Applicant conducted a human factors validation study in 45 untrained participants that included 15 Post-Anesthesia Care Unit (PACU)/floor nurses, 15 emergency room (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.

Failures were identified related to both essential and critical tasks. The most concerning were 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 a 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, the Division of Medication Error Prevention and Analysis (DMEPA) recommended changes to the DFU so that visual confirmation of the tablet placement is a distinct separate task[2].

DMEPA recommended the applicant conduct another human factor validation study to evaluate the effectiveness of the changes to the DFU 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.

Summary of safety review in 1st review cycle:

Overall, although sufentanil sublingual tablet 30 mcg appears to have a typical safety profile of an opioid agonist, there were two areas of safety concern with this product that required further evaluation: the safety of sufentanil sublingual tablet 30 mcg in patients requiring the maximum dosing proposed for labeling and the risk of misplaced tablets.

A complete response letter was issued on October 11, 2017, outlining these deficiencies and the information needed to address the deficiencies.

8.2. Summary of safety review from 2nd review cycle

Overview of safety review from 2nd cycle
To address the safety database deficiency in terms of an inadequate number of patients dosed with sufentanil sublingual tablet 30 mcg at the maximum dosing proposed, the Applicant provided the following information in the resubmission:

[2] DMEPA recommended a revision to step 6 of the DFU so that visual confirmation of the tablet placement is a distinct separate task as follows: "Step 6: Depress the green Pusher to deliver the tablet to the patient's sublingual space. Step 7: Visually confirm tablet placement in the patient's sublingual space."

1. A reduced maximum daily dose from 24 sufentanil sublingual 30 mcg tablets (720 mcg sufentanil) to no more than 12 sufentanil sublingual 30 mcg tablets (360 mcg sufentanil) per day.

2. Pooled safety data from all studies of the sufentanil sublingual tablet (SST) with treatment periods of at least 24 hours (Pool 8). Pool 8 was analyzed and presented based on sufentanil dose received (<300 mcg or ≥300 mcg) and maximum measured sufentanil plasma concentration achieved (≤150 pg/mL or >150 pg/mL) from sparse sampling during the first 24-hour study period.

In terms of the reduced total daily dose in the proposed labeling, the Applicant noted that it is likely sufentanil sublingual tablet 30 mcg will be used in short-term settings, such as surgical centers or emergency rooms. Further, in the sufentanil sublingual tablet 30 mcg trials of short-duration, most patients required less than 6 sufentanil sublingual 30 mcg tablets and no patients required more than 10 tablets. In the one sufentanil sublingual tablet 30 mcg trial that extended to 48 hours (SAP301), the maximum number of tablets administered in a 24-hour period was 15. The patients treated with sufentanil sublingual tablet 15 mcg who provided supporting safety data were generally treated for longer durations (48-72 hours) and had increased sufentanil exposure compared to patients treated with sufentanil sublingual tablet 30 mcg because sufentanil sublingual tablet 15 mcg drug-device combination allowed 45 mcg/hr of sufentanil on a patient-controlled basis.

In terms of the safety analyses, the Applicant selected a dose cutoff of 300 mcg (equivalent to 10 sufentanil sublingual 30 mcg tablets), rather than 12 because this provides more patients exposed at higher doses and given that the sufentanil sublingual tablet 15 mcg patient exposures are as high as 825 mcg/24 hours (equivalent to 27.5 sufentanil sublingual 30 mcg tablets). The Applicant selected a plasma concentration cutoff of 150 pg/mL sufentanil concentration as it is the mean plasma sufentanil maximum concentration (Cmax) observed at steady-state with repeated hourly dosing of 12 sufentanil sublingual 30 mcg tablets in Study SAP101.

These analyses by dose and concentration were performed on safety data from Pool 8, which included all sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg studies that were at least 24 hours in duration.

Table 7 summarizes the studies included in Pool 8. The one study included from the sufentanil sublingual tablet 30 mcg program (SAP301) had a duration of treatment of up to 48 hours, while the three studies from the sufentanil sublingual tablet 15 mcg program (IAP310, IAP311, and IAP309) had durations of up to 72 hours. There were differences in the sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg clinical programs. The programs had different devices, sufentanil doses, and deliverers (patient for sufentanil sublingual tablet 15 mcg vs. health care professional for sufentanil sublingual 30 mcg tablet). In addition, the sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg clinical programs had different study designs and patient populations (Table 7). Generally, patients in the sufentanil sublingual tablet 15 mcg studies were older, had higher body mass index (BMI), and had undergone major surgeries compared to the patients in the sufentanil sublingual tablet 30 mcg studies. Further, patients in sufentanil sublingual tablet 15 mcg studies were generally treated for longer durations

and had more extensive sufentanil exposure. Despite these differences, it is reasonable to utilize data from the sufentanil sublingual tablet 15 mcg program to support the safety of the sufentanil sublingual tablet 30 mcg given that both programs administered sufentanil, the Applicant linked the PK of sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg, and the sufentanil sublingual tablet 15 mcg program included patients who were exposed to higher doses and longer durations of sufentanil in the setting of additional comorbidities.

Table 7: Overview of Studies Included in the Pooled Analysis Supporting Maximal Dosing (Pool 8)

Study	Study Design	Dosing Regimen; SL	Number of Subjects		Patient population	Duration / Rescue Analgesia
			All Subjects	Subjects in Pooled Analyses*		
Sufentanil sublingual tablet 30 mcg program (SST 30 mcg)						
SAP301	MC, R, DB, PC	SST 30 mcg Placebo	SST 30 mcg: treated 107; completed 102 Placebo: treated 54; completed 41	SST 30 mcg: treated 107; completed 102 Placebo: treated 54; completed 41	Post-surgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery	Up to 48 hours/ Morphine IV
Sufentanil sublingual tablet 15 mcg program (SST 15 mcg)						
IAP310	MC, R, DB, PC	SST 15 mcg Placebo	SST 15 mcg: treated 114; completed 78 Placebo: treated 58 completed 27	SST 15 mcg: 51 Placebo: 27	Open abdominal surgery	Up to 72 hours/ Morphine IV
IAP311	MC, R, DB, PC	SST 15 mcg Placebo	SST 15 mcg: treated 315; completed 215 Placebo: treated 104; completed 43	SST 15 mcg: 142 Placebo: 54	Total knee or hip replacement	Up to 72 hours/ Morphine IV
IAP309	MC, R, OL, AC	SST 15 mcg Morphine 1 mg over 6 minutes IV	SST 15 mcg: treated 177; completed 146 Morphine: treated 180; completed 136	SST 15 mcg: 94 Morphine: None	Open abdominal surgery or knee or hip replacement	Up to 72 hours/ N/A

All drugs administered SL and PRN, except morphine which was administered IV and PRN
Abbreviations: AC=active control; DB=double-blind; IV = intravenous; MC=multicenter; OL=open-label; PD = pharmacodynamics; PK = pharmacokinetics; PRN = as needed; R=randomized; SST = sufentanil sublingual tablet.

* For studies of the SST 15 mcg, pooled analyses included patients who received their first 2 SST 15 mcg tablets dosed within 20-25 minutes of each other in the first hour of dosing. Inclusion of these patients in pooled analyses with SST 30 mcg (ARX-04) is based on the establishment of bioequivalence of 1 SST 30 mcg tablet with 2 SST 15 mcg tablets dosed within 20 to 25 minutes of each other and PK modeling.
Source: Adapted from ISS Amendment 3, Table 1, page 9, submitted 5/3/2018.

Data from Pool 8 were analyzed and presented based on sufentanil dose received during the first 24 hours and maximum measured sufentanil plasma concentration achieved with sparse sampling during the first 24 hours. The number of patients treated in each study stratified by sufentanil dose (<300 mcg or ≥300 mcg) and included in Pool 8 is presented in Table 8. The one study from the sufentanil sublingual tablet 30 mcg program (SAP301) included 26 patients with sufentanil doses of at least 300 mcg. In contrast, there were three studies included in Pool 8 from the sufentanil sublingual tablet 15 mcg program, with 180 patients with sufentanil doses of at least 300 mcg. Thus, from the sufentanil sublingual tablet 30 mcg and sufentanil sublingual

tablet 15 mcg programs, there were a total of 206 patients with sufentanil doses of at least 300 mcg during the first 24 hours of study treatment.

Across the studies in the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg programs, 50 patients had sufentanil concentrations >150 pg/mL during the first 24 hours based on sparse PK sampling, including 3 patients from the sufentanil sublingual tablet 30 mcg study and 47 patients from the sufentanil sublingual tablet 15 mcg studies.

Table 8: Analysis Population Summary by Study, Treatment, and Dose Group: Sufentanil-treated Patients Enrolled in Sufentanil sublingual tablet 30 mcg study SAP301 and Sufentanil sublingual tablet 15 mcg Studies IAP309, IAP310, and IAP311

Study	Control	Treatment Group				Total (n = 394)
		SST 15 mcg		SST 30 mcg		
		< 300 mcg (0-24 hrs)	≥ 300 mcg (0-24 hrs)	< 300 mcg (0-24 hrs)	≥ 300 mcg (0-24 hrs)	
Sufentanil sublingual tablet 30 mcg program (SST 30 mcg)						
SAP301	PC	0	0	81	26	107
Sufentanil sublingual tablet 15 mcg program (SST 15 mcg)						
IAP309 IAP310 IAP311	AC, OL PC PC	34 23 50	60 28 92	0 0 0	0 0 0	94 51 142
Total for sufentanil sublingual tablet 15 mcg studies		107	180	-	-	287
Overall Total		107	180	81	26	394

Abbreviations: AC=active control; hrs=hours; OL=open label; PC=placebo-controlled; SST: sufentanil sublingual tablet
Source: Adapted from ISS Amendment 3, Table 4, page 18, submitted 5/3/2018.

It is important to note that there are significant limitations to the safety analyses based on dose received and sufentanil concentration. As is typical for an opioid, sufentanil sublingual tablets 30 mcg was administered as needed, and while this was reasonable, it complicates the safety analyses by dose and plasma concentration. Specifically, safety analyses based on dose received and plasma concentration are difficult to interpret since the dose received is influenced by a variety of factors, such as the amount of pain experienced and the occurrence of adverse events. Further, the analyses performed were based on total sufentanil dose and sufentanil concentration during the first 24-hour study period, but exposure, disposition, and safety data are presented for the entire study period. Recognizing these limitations, the analyses were felt to be reasonable in the context of supporting the maximum daily dose proposed.

This review will focus on the safety analyses presented by dose received, rather than sufentanil concentration. The dose groups will be referred to as the lower dose group (<300 mcg) and the higher dose group (≥300 mcg). The dose groups are shown stratified by clinical program (sufentanil sublingual tablet 15 mcg or 30 mcg) given differences in the study design and patient populations.

Demographics

Table 9 presents the demographics and baseline characteristics by sufentanil dose for Pool 8. Overall, the mean age was 58 years (SD 15.6) and most patients were female (66%) and white (82%).

For patients receiving sufentanil sublingual tablet 30 mcg, patients in the higher dose group compared to the lower dose group were slightly younger (mean age 38 versus 42 years) and more likely to be male (38.5% vs. 29.6%). For patients receiving sufentanil sublingual tablet 15 mcg, the lower and higher dose groups had similar demographics in terms of age and sex.

Across the sufentanil sublingual tablet 30 mcg and sufentanil sublingual tablet 15 mcg groups, all but one patient with a measured maximum sufentanil concentration >150 pg/mL during the first 24-hour study period received a total sufentanil dose >300 mcg during the first 24-hour study period. For patients in the higher dose sufentanil sublingual tablet 30 mcg group, 7.7% had a maximum sufentanil concentration >150 pg/mL during the first 24-hour study period. For patients in the higher dose sufentanil sublingual tablet 15 mcg group, 28.5% had a maximum sufentanil concentration >150 pg/mL during the first 24-hour study period. Therefore, patients with maximum sufentanil concentrations >150 pg/mL during the first 24-hour study period primarily represent a subset of the higher dose sufentanil sublingual tablet (SST) patients, while the patients with less than maximum sufentanil concentrations ≤150 pg/mL during the first 24-hour study period represent a combination of higher and lower dose SST patients. Since the patients had only sparse sampling, it is possible that additional patients at some point achieved sufentanil concentrations >150 pg/mL but were not included in the higher concentration group. Given these limitations and considerations, the focus of these safety analyses is based on sufentanil dose, rather than concentration.

Table 9: Demographics and Baseline Characteristics of Safety Population by Treatment and Dose Group: Sufentanil Sublingual Tablet 30 mcg Study and Sufentanil Sublingual Tablet 15 mcg Studies

	Treatment group				Total (n = 394)
	SST 15 mcg		SST 30 mcg		
	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	
	(n = 107)	(n = 180)	(n = 81)	(n = 26)	
Age (years) - n (%)					
≥ 75	27 (25.2%)	32 (17.8%)	0	0	59 (15.0%)
Mean (SD)	65.8 (12.0)	63.3 (12.1)	42.2 (10.9)	38.3 (9.2)	58.0 (15.6)
Median	66.0	64.0	41.0	37.5	60.0
(Min, Max)	(24.0, 86.0)	(19.0, 86.0)	(18.0, 69.0)	(22.0, 62.0)	(18.0, 86.0)
Sex					
Female	72 (67.3%)	115 (63.9%)	57 (70.4%)	16 (61.5%)	260 (66.0%)
Race - n (%)					
American Indian or Alaska Native	0	0	0	0	0
Asian	0	1 (0.6%)	2 (2.5%)	1 (3.8%)	4 (1.0%)
Black or African American	13 (12.1%)	24 (13.3%)	18 (22.2%)	3 (11.5%)	58 (14.7%)
Native Hawaiian or Another Pacific	1 (0.9%)	0	0	0	1 (0.3%)
White	93 (86.9%)	155 (86.1%)	58 (71.6%)	18 (69.2%)	324 (82.2%)
Other	0	0	3 (3.7%)	4 (15.4%)	7 (1.8%)
Surgery Type					
Orthopedic	77 (72.0%)	140 (77.8%)	0	0	217 (55.1%)
Abdominal	30 (28.0%)	38 (21.1%)	81 (100%)	26 (100%)	175 (44.4%)
Other Surgery	0	2 (1.1%)	0	0	2 (0.5%)
Body Mass Index					
Mean (SD) - kg/m^2	29.2 (6.5)	31.1 (7.3)	27.7 (4.9)	26.9 (4.6)	29.6 (6.6)
Maximum sufentanil concentration (pg/ml)					
≤ 150	92 (100%)	118 (71.5%)	79 (98.8%)	24 (92.3%)	313 (86.2%)
> 150	0	47 (28.5%)	1 (1.3%)	2 (7.7%)	50 (13.8%)
Mean (SD)	54.4 (32.9)	128.7 (55.7)	52.9 (26.0)	92.8 (33.3)	90.6 (56.6)

Abbreviations: Max=maximum; min=minimum; SD=standard deviation; SST: sufentanil sublingual tablet
Source: Adapted from ISS Amendment 3, Table 11, page 28, submitted on 5/3/2018.

Key safety results and the comparison of safety results in higher and lower sufentanil dose groups in Pool 8

The following section reviews the key safety findings from Pool 8, including deaths, serious adverse events, discontinuations due to adverse events, and common adverse events.

Deaths in Pool 8

No were no deaths reported in Pool 8.

Serious Adverse Events (SAEs) in Pool 8

Six SAEs were reported in a total of four patients in Pool 8 (Table 10). All the SAEs occurred in sufentanil sublingual tablet 15 mcg-treated patients and no SAEs were reported in sufentanil sublingual tablet 30 mcg-treated patients. The proportion of sufentanil sublingual tablet 15 mcg-treated patients with SAEs was higher in the lower dose group (2.8%) compared to the higher dose group (0.6%). Thus, there did not appear to be a relationship between increased dose and SAEs.

Table 10: Serious Adverse Events by Treatment and Dose Group in Pool 8

	Treatment Group				
	SST 15 mcg		SST 30 mcg		
	<300 mcg (0-24 hours) (n=107)	≥300 mcg (0-24 hours) (n=180)	<300 mcg (0-24 hours) (n=81)	≥300 mcg (0-24 hours) (n=26)	Total (n=394)
Number (%) of Patients With at Least 1 SAE	3 (2.8%)	1 (0.6%)	0	0	4 (1.0%)

Note: Adverse event mapping based on MedDRA Version 11.0.
Abbreviations: SST: sufentanil sublingual tablet; SAE: serious adverse event.
Source: Adapted from ISS amendment 3, Table 19, page 53, submitted on 5/3/2018

Table 11 displays additional details for the six SAEs (oxygen saturation decreased, confusional state, hypoxia, pulmonary embolism, atrial fibrillation, and postoperative ileus) that occurred in the four sufentanil sublingual tablet 15 mcg-treated patients.

Table 11: Treatment-emergent Serious Adverse Events in Selected Sufentanil sublingual tablet 15 mcg Studies IAP310, and IAP311

Patient ID/ Treatment	Adverse Event Preferred Term	Severity	Relationship to Treatment	Action Taken	Outcome
Study IAP311 (Placebo-controlled)					
(b) (6) Lower (< 300 mcg) sufentanil dose group	Oxygen saturation decreased	Severe	Probably Related	Drug withdrawn	Recovered/ resolved
(b) (6) Lower (< 300 mcg) sufentanil dose group	Confusional state	Moderate	Possibly Related	Dose not changed	Recovered/ resolved
	Hypoxia	Moderate	Not Related	Dose not changed	Recovered/ resolved
	Pulmonary embolism	Mild	Not Related	Dose not changed	Recovered/ resolved
(b) (6) Higher (≥ 300 mcg) sufentanil dose group	Atrial fibrillation	Moderate	Not Related	Dose not changed	Recovered/ resolved
Study IAP309 (Open-label)					
(b) (6) Lower (< 300 mcg) sufentanil dose group	Postoperative ileus	Severe	Not Related	Dose not changed	Recovered/ resolved

Source: Adapted from ISS Amendment 3, Table 20, page 54, submitted 5/3/2018.

There were two patients with SAEs related to hypoxia or oxygen saturation decreased in Pool 8. The first patient (b) (6) was a 65-year-old white female who underwent a total knee arthroplasty under spinal anesthesia on the day of the event. The patient received 14 doses of sufentanil sublingual 15 mcg tablets within seven hours of the event. In addition, she received a total of 11 mg of IV morphine in 4 separate doses within seven hours of the event, along with oxycodone/acetaminophen, fentanyl, meclizine, and propofol. The patient's oxygen saturation decreased to 40 to 50% and resolved with naloxone. She was withdrawn from the study and discharged two days later. The second SAE (patient (b) (6)) involved an 80-year-old female who developed aspiration pneumonia and a pulmonary embolism one day after undergoing total knee replacement. She also had hypoxia and encephalopathy with confusion/delirium (confusional state) and wide complex paroxysmal tachycardia/atrial fibrillation. The patient had taken five doses of sufentanil sublingual tablet 15 mcg in the postoperative period on the same day as the surgery. Serious respiratory depression is a known risk of opioids and is included as a Boxed Warning in opioid labeling.

The additional SAEs were atrial fibrillation and postoperative ileus. The event of atrial fibrillation occurred in a 78-year-old white male who underwent a total knee replacement the day before the event. He had received a total of 77 doses of sufentanil sublingual 15 mcg over approximately 47 hours. The SAE of new onset of atrial fibrillation occurred 1 day after the surgery and 28 hours after the first dose. The patient was treated with amiodarone and transferred

to the coronary care unit. The event was considered resolved three days after. There was a temporal relationship between the event and sufentanil, but there were other confounding factors, such as the surgical procedure. The SAE of a postoperative ileus occurred in a 68-year old white male patient with a history of diverticulitis who underwent a laparotomy for sigmoid resection and re-anastomosis.

Discontinuations due to AEs

As shown in Table 12 a total of 22 patients (5.6%) in Pool 8 discontinued due to AEs, and no AEs leading to discontinuation were reported by more than 2% of patients overall. In the sufentanil sublingual tablet 30 mcg study, only one patient discontinued the study due to a AE (decreased oxygen saturation), and this patient received the higher sufentanil dose. In the sufentanil sublingual tablet 15 mcg studies, a higher proportion of patients in the lower dose group (14%) discontinued due to an AE compared to the higher dose group (3.3%). The types of adverse events leading to discontinuation would be anticipated for an opioid (Table 13).

Table 12: Adverse Events Causing the Discontinuation of Study Drug by Sufentanil dose groups in Pool 8

	Treatment Group				**Total**
	SST 15 mcg		**SST 30 mcg**		
	< 300 mcg (0-24 Hours)	**≥ 300 mcg (0-24 Hours)**	**< 300 mcg (0-24 Hours)**	**≥ 300 mcg (0-24 Hours)**	
Number of Patients Enrolled in the Study	107	180	81	26	394
Number (%) of Patients With At least One Adverse Event Causing the Discontinuation of Study Drug	15 (14.0%)	6 (3.3%)	0	1 (3.8%)	22 (5.6%)

Abbreviation: SST: sufentanil sublingual tablet
Source: Adapted from ISS Amendment 3, Table 21, page 55-6, submitted 5/3/2018.

Table 13: Adverse Events Causing Discontinuation in Sufentanil Sublingual Tablet 30 mcg and Sufentanil Sublingual Tablet 15 mcg Studies

	Treatment Group				
	SST 15 mcg		SST 30 mcg		
	< 300 mcg (0-24 Hours)	≥300mcg (0-24 Hours)	< 300 mcg (0-24 Hours)	≥300mcg (0-24 Hours)	
Gastrointestinal disorders					
Nausea	2 (1.9%)	3 (1.7%)	0	0	5 (1.3%)
Investigations					
Oxygen saturation decreased	3 (2.8%)	0	0	1 (3.8%)	4 (1.0%)
Hepatic enzyme increased	1 (0.9%)	0	0	0	1 (0.3%)
Respiratory rate decreased	1 (0.9%)	0	0	0	1 (0.3%)
Musculoskeletal and connective tissue disorders					
Back pain	0	2 (1.1%)	0	0	2 (0.5%)
Nervous system disorders					
Sedation	4 (3.7%)	0	0	0	4 (1.0%)
Dizziness	1 (0.9%)	0	0	0	1 (0.3%)
Psychiatric disorders					
Agitation	1 (0.9%)	1 (0.6%)	0	0	2 (0.5%)
Confusional state	2 (1.9%)	0	0	0	2 (0.5%)
Respiratory, thoracic and mediastinal disorders					
Bradypnea	1 (0.9%)	0	0	0	1 (0.3%)
Hypoventilation	1 (0.9%)	0	0	0	1 (0.3%)
Hypoxia	1 (0.9%)	0	0	0	1 (0.3%)

Source: Adapted from ISS Amendment 3, Table 21, page 55-6, submitted 5/3/2018.

Common Adverse Events

As shown in Table 14, overall 74% of patients had an adverse event in Pool 8.

In the sufentanil sublingual tablet 30 mcg study, the proportion of patients with an adverse event (AE) was similar in the lower (58%) and higher (57.7%) dose groups. Some AEs, such as, nausea, pruritus, oxygen saturation decreased, tachycardia and dyspepsia, occurred more frequently in the higher dose group, while other AEs, such as, headache, vomiting, dizziness, hypotension, and hypertension, occurred more frequently in the lower dose group.

In the sufentanil sublingual tablet 15 mcg studies, the proportion of patients with an AE was higher in the higher dose group (82.8%) compared to the lower dose group (76.6%). Similarly to the sufentanil sublingual tablet 30 mcg study, some AEs such as nausea, pyrexia, vomiting, anemia, pruritus, constipation, hypotension, insomnia, leukocytosis, sinus tachycardia, dyspepsia, body temperature increased, hypokalemia, hypertension, and hyponatremia, occurred more frequently in the higher dose group, while other AEs, such as headache, dizziness, decreased oxygen saturation, hypocalcemia, tachycardia, anemia postoperative, hypoalbuminemia, and confusional state, occurred more frequently in the lower dose group. There were no clear trends in terms of dose-response and similar terms (such as anemia/anemia postoperative and sinus tachycardia/tachycardia) did not follow a similar dose-response pattern.

Table 14: Adverse Events (≥ 2% in Total Across All Treatments) and Dose Group in Sufentanil sublingual tablet 30 mcg and Sufentanil sublingual tablet 15 mcg studies

	Treatment Group				Total
	SST 15 mcg		SST 30 mcg		
	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	< 300 mcg (0-24 Hours)	≥ 300 mcg (0-24 Hours)	
Number of Patients Enrolled in the Study	107	180	81	26	394
Number (%) of Patients Who	107 (100%)	180 (100%)	81 (100%)	26 (100%)	394 (100%)
Number (%) of Patients With At least One Adverse Event	82 (76.6%)	149 (82.8%)	47 (58.0%)	15 (57.7%)	293 (74.4%)
Nausea	43 (40.2%)	93 (51.7%)	24 (29.6%)	11 (42.3%)	171 (43.4%)
Pyrexia	17 (15.9%)	38 (21.1%)	0	0	55 (14.0%)
Headache	13 (12.1%)	21 (11.7%)	18 (22.2%)	3 (11.5%)	55 (14.0%)
Vomiting	10 (9.3%)	20 (11.1%)	7 (8.6%)	1 (3.8%)	38 (9.6%)
Anemia	5 (4.7%)	28 (15.6%)	0	0	33 (8.4%)
Pruritus	7 (6.5%)	15 (8.3%)	1 (1.2%)	1 (3.8%)	24 (6.1%)
Dizziness	8 (7.5%)	8 (4.4%)	5 (6.2%)	1 (3.8%)	22 (5.6%)
Oxygen saturation	9 (8.4%)	11 (6.1%)	0	1 (3.8%)	21 (5.3%)
Constipation	3 (2.8%)	17 (9.4%)	0	0	20 (5.1%)
Hypotension	4 (3.7%)	10 (5.6%)	4 (4.9%)	1 (3.8%)	19 (4.8%)
Hypocalcemia	7 (6.5%)	5 (2.8%)	0	0	12 (3.0%)
Insomnia	3 (2.8%)	9 (5.0%)	0	0	12 (3.0%)
Leukocytosis	4 (3.7%)	7 (3.9%)	0	0	11 (2.8%)
Sinus tachycardia	0	11 (6.1%)	0	0	11 (2.8%)
Tachycardia	4 (3.7%)	4 (2.2%)	2 (2.5%)	1 (3.8%)	11 (2.8%)
Dyspepsia	3 (2.8%)	6 (3.3%)	0	1 (3.8%)	10 (2.5%)
Anemia postoperative	6 (5.6%)	4 (2.2%)	0	0	10 (2.5%)
Body temperature	3 (2.8%)	7 (3.9%)	0	0	10 (2.5%)
Hypoalbuminemia	6 (5.6%)	4 (2.2%)	0	0	10 (2.5%)
Hypokalemia	3 (2.8%)	6 (3.3%)	0	0	9 2.3%)
Hypertension	1 (0.9%)	7 (3.9%)	1 (1.2%)	0	9 2.3%)
Hyponatremia	0	8 (4.4%)	0	0	8 2.0%)
Confusional state	8 (4.4%)	8 (4.4%)	0	0	8 2.0%)

Abbreviation: SST: sufentanil sublingual tablet
Source: Adapted from Applicant's response to clinical IR, Table 1, pages 3-4, submitted 8/13/2018

Respiratory

Respiratory safety is a key consideration for opioids and all patients in the sufentanil sublingual tablet 15 mcg and sufentanil sublingual tablet 30 mcg studies were monitored with continuous pulse oximetry. Table 15 provides a summary of lowest oxygen saturation by dose group in Pool 8. There was no clear relationship between higher sufentanil dose and decreased oxygen saturation in the sufentanil sublingual tablet 30 mcg or sufentanil sublingual tablet 15 mcg programs.

In the sufentanil sublingual tablet 30 mcg study, the lowest oxygen saturation value recorded was 86% and this occurred in the higher dose group. This was the only incidence of decreased oxygen saturation reported as an adverse event. In the sufentanil sublingual tablet 15 mcg studies, the lowest oxygen saturation value recorded was 40% and this occurred in the lower dose group. Additional details regarding this adverse event are included in the discussion of SAEs.

Table 15: Lowest Oxygen Saturation by Treatment and Dose Group (Pool 8)

	Treatment group				**Total (n=394)**
	SST 15 mcg		**SST 30 mcg**		
	< 300 mcg (0-24 hours) (n=107)	**≥ 300 mcg (0-24 hours) (n=180)**	**< 300 mcg (0-24 hours) (n=81)**	**≥ 300 mcg (0-24 hours) (n=26)**	
SPO_2 < 93% -n (%)	17 (15.9%)	15 (8.3%)	7 (8.6%)	1 (3.8%)	40 (10.2%)
SPO2 < 95% -n (%)	35 (32%)	41 (22.8%)	22 (27.2%)	3 (11.5%)	101 (25.6%)
SPO2 (%) -n (%)					
≥ 95%	72 (67.3%)	139 (77.2%)	59 (72.8%)	23 (88.5%)	293 (74.4%)
93-94	18 (16.8%)	26 (14.4%)	15 (18.5%)	2 (7.7%)	61 (15.5%)
90-92	10 (9.3%)	11 (6.1%)	7 (8.6%)	0	28 (7.1%)
< 90	7 (6.5%)	4 (2.2%)	0	1 (3.8%)	12 (3.0%)
Mean (SD)	93.5 (6.2)	94.5 (1.7)	95.2 (1.6)	95.4 (2.2)	94.5 (3.6)
Median	95.0	95.0	96.0	96.0	95.0
(Min, Max)	(40, 100)	(83, 99)	(91, 98)	(86, 98)	(40, 100)

Abbreviation: SST: sufentanil sublingual tablet
Source: ISS amendment 3, Table 23, page 59, submitted on 5/3/2018.

8.2.a Safety concern associated with dropped tablets – 2nd cycle review

As noted in Section 8.1.a, there are significant safety concerns associated with dropped tablets. The overall safety evaluation of sufentanil sublingual tablet 30 mcg must consider the combination of the sublingual tablet and device. The small tablet size (3 mm in diameter and 0.85 mm in thickness) increases the potential risk of tablet dropping and misplacement and increases the risk of accidental exposure, overdose, and death, particularly in children. Sufentanil is a high potency opioid agonist (5 to 10 times more potent than fentanyl).

As described previously in Section 8.1.a, the Applicant reported a total of three dropped tablets in the sufentanil sublingual tablet 30 mcg Phase 3 program and the human factors validation study submitted in the 1st review cycle identified failures related to both essential and critical tasks. The most concerning were the eight failures associated with a critical task to confirm tablet placement in the patient's sublingual space. The Agency recommended changes to the DFU so that visual confirmation of the tablet placement is a distinct separate task. The changes to the DFU were evaluated in a second human factors validation study. The Applicant's proposed DFU is included in the Appendix.

In this resubmission, the Applicant submitted the second human factors validation study. All the Agency's recommendations made for the DFU in the last review cycle were incorporated and the revised DFU was tested. The human factors validation study was conducted with 45 untrained participants (15 PACU/Floor nurses,15 ER nurses, and 15 Paramedics) that were representative of the intended user groups. Each participant was asked to administer the medication three times (3 separately observed use scenarios), and all steps were tested.

No failures or close calls occurred during the simulated use task portion of the second study. Additionally, there was no incidence of dropped tablets. However, there was a study protocol deviation that occurred in the knowledge assessment portion of the study. The Applicant provided acceptable response to address the deviations and no additional mitigation strategies were identified.

Based on the data from this study, DMEPA has determined the product-user interface supports the safe and effective use of the product by the intended users, for its intended uses, and intended use environments.

HF studies are generally designed to help us identify and minimize (to an acceptable level) anticipated errors but unanticipated errors may still occur after the product is marketed.

8.2.b Risk assessment following accidental exposure to sufentanil sublingual 30 mcg tablets

The Applicant conducted a risk analysis based on simulated pharmacokinetic (PK) data, clinical trial data, and the published literature to evaluate the potential severity levels of harm due to accidental exposure to sufentanil sublingual 30 mcg tablets. Table 16 shows the Applicant's definitions of the various severity rankings. The severity levels ranged from negligible/cosmetic to catastrophic.

Table 16: Severity of Risk Factors

Severity of Effect (S)		
Scale	**Term**	**Definition of Clinical Effects**
1	**Negligible / Cosmetic**	No / virtually no injury to the patient or user; no / virtually no negative effect on the environment. No impact on product performance or user confidence in the product/company; user may or may not even notice the failure.
2	**Minor**	Minor injury to the patient or user; minor negative effect on the environment. Slight decline of product performance or user confidence in the product/company (e.g., customer slightly annoyed and/or inconvenienced). For example, this includes prolonging or delaying a clinical procedure that does not pose a risk of greater injury to the patient or user.
3	**Moderate**	Moderate injury to the patient or user; moderate negative effect on the environment. Decline of product performance or user confidence in the product/company (e.g., customer is very annoyed and/or dissatisfied). For example, this includes actions taken to treat the patient or user within the scope and type of treatment already in progress.
4	**Critical**	Serious injury (reversible) to the patient or user; severe negative effect on the environment. For example, this includes the need for a more invasive procedure such as surgery or increases case complication to fully treat the injury. NOTE: Any labeling issues that could lead to a field action must be ranked at a minimum of 4.
5	**Catastrophic**	Serious injury (irreversible) or death of the patient or user; or very severe negative effect on the environment.

Source: The Applicant's submission Document RSK-7025 Severity Levels of Harm due to Accidental Exposure to SST 30 mcg. Page 2/10, submitted on 5/3/2018

In terms of PK considerations, the Applicant submitted the results of a population pharmacokinetic (popPK) modeling and simulation analysis to assess the risk of accidental exposure of dropped sufentanil tablets in a pediatric population. The adult population pharmacokinetic model developed for sufentanil sublingual tablets during the sufentanil sublingual tablet 15 mcg program (b) (4) was used for simulating sufentanil blood levels following accidental exposures to doses of one and two 30 mcg sufentanil sublingual tablets (i.e., two and four sufentanil sublingual 15 mcg tablets, respectively) in a child weighing 12 kg as this is the 50th percentile for weight for an 18-24-month child. The Applicant assumed this would be the minimum age of a toddler likely to be in a hospital setting and independently ambulating. Importantly, it is possible that a younger child could be accidentally exposed to sufentanil sublingual tablet in an inpatient setting. This use of the previous popPK model is acceptable based on the sufentanil sublingual tablet 30 mcg PK study SAP101, which demonstrated that two 15 mcg sufentanil sublingual tablets were bioequivalent to a single 30 mcg sufentanil sublingual tablet.

Briefly, the steps followed were as follows:

(1) The popPK model developed with sufentanil sublingual tablet 15 mcg data only included data from an adult population. Therefore, the model was supplemented with sufentanil PK data from 19 pediatric patients undergoing cardiovascular procedures (Greeley et al., 1987[3]). The systemic clearance values reported in the literature seem to be in good agreement with the relationship between systemic clearance and body weight derived from the adult popPK model. Therefore, it is acceptable to use the adult popPK model for pediatric simulations.

(2) The adult popPK model was used to simulate the sufentanil blood levels following accidental doses of 30 and 60 mcg in a 2-year-old 'typical' child weighing 12 kg. Additionally, the Applicant made the following assumptions:
   a) Sufentanil's absorption characteristics from the sublingual space in the 'typical' child, such as absorption rate (Ka) and lag time (Tlag) are similar to adults.
   b) Doses are administered simultaneously and retained in the sublingual space. The tablet is absorbed through the sublingual space, and not swallowed.
   c) The relationships between apparent clearance (CL/F) and distributional clearance (Q/F) and body weight in the 'typical' child are similar to that described in the adult popPK model.
   d) The PK parameters are independent of the number of tablets (dose-linearity shown in PK studies of sufentanil sublingual tablets).

The predicted sufentanil blood levels following accidental doses of sufentanil sublingual tablet (30 or 60 mcg) in a typical 2-year-old child weighing 12 kg are shown in Figure 6 below. The predicted peak plasma concentrations were about 208 pg/ml and 416 ng/ml following accidental doses of 30 and 60 mcg sufentanil sublingual tablets respectively and occurred approximately 1-hour post-dose. These values can be viewed as conservative, as heavier children would have lower plasma concentrations. Also, the assumption that the tablet is absorbed through the sublingual space is conservative, since swallowing results in <10% bioavailability, compared to a bioavailability of approximately 60% following sublingual absorption. The applicant compared these levels to those reported in the literature:

   a) In a correspondence letter to the editor (Haynes et al. 1993)[4], it is reported that intranasal administration of 2 mcg/kg in 15 pediatric outpatients resulted in average peak plasma concentrations of 300 pg/mL and no respiratory depression was reported. It is important to note that the average time to peak sufentanil blood levels occurred at about 15 and 30 min in 8 and 7 subjects respectively, which seems shorter than that predicted following sublingual administration (1 hour).
   b) In another study conducted by Zedia et al[5], 2 mcg/kg sufentanil was administered intranasally before anesthetic induction in 60 pediatric outpatient surgery patients, aged 0.5 to 6 years old. It was reported that during a period of 15 to 20 minutes of observation

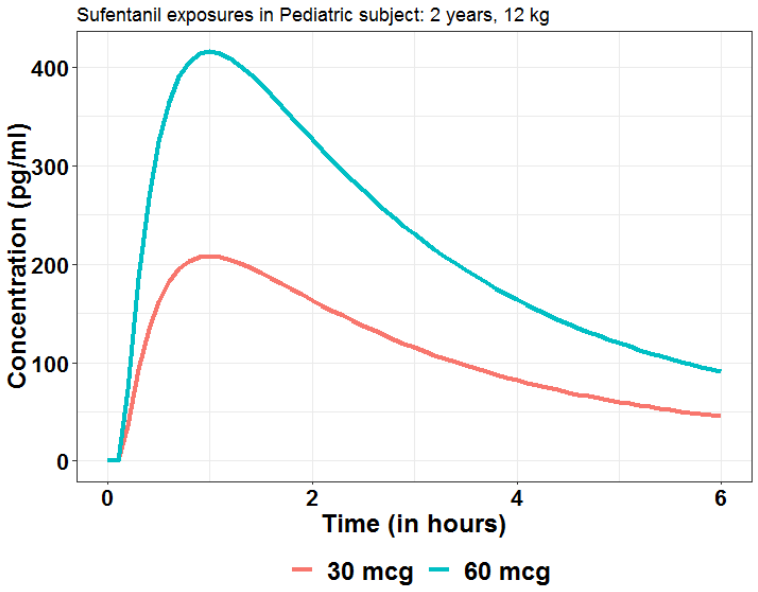
[3] Greeley WJ, de Bruijn NP, Davis DP. Sufentanil pharmacokinetics in pediatric cardiovascular patients. Anesthesia & Analgesia 1987; 66:1067-1072.
[4] Haynes G, Brahen NH, Hill HF. Plasma sufentanil concentration after intranasal administration to paediatric outpatients. Canadian Journal of Anaesthesia 1993; 40:286.
[5] Zedie N, Amory DW, Wagner BKJ, O'Hara DA. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. Clinical Pharmacology and Therapeutics 1996; 59:341-348.

before surgery, the vital signs and oxygen saturation did not change significantly before or after surgery.

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

Overall, the Office of Clinical Pharmacology (OCP) review team agrees with the Applicant's methodology described above to assess the risk associated with accidental dosing of sufentanil sublingual tablets in a 12-kg child.

Figure 6: Predicted sufentanil blood levels following accidental doses of 1 and 2 sufentanil sublingual tablets 30 mcg in a typical 2-year-old child weighing 12 kg



From a clinical perspective, there are significant limitations in using data from intranasal sufentanil in children as pre-anesthesia to predict the pharmacodynamic effects of an accidental exposure to sufentanil sublingual tablet 30 mcg. Specifically, the context of use of sufentanil in the cited published literature is very different than the context of accidental exposure relevant to sufentanil sublingual tablet 30 mcg's risk assessment. Patients in the cited studies were medically monitored prior to and during surgery and received concomitant medications, including anesthesia, while the context of the risk assessment is accidental exposure in a setting where children are not anticipated to be medically monitored. These differences limit the use of data from the published literature to inform risk in the proposed setting. However, they are useful in that they do show the potential for adverse events associated with administration of sufentanil.

For example, Henderson et al., 1988[6] showed that sufentanil 4.5 µg/kg nasally can result in detrimental effects in some patients, including "rigidity, postoperative vomiting, perhaps convulsive activity, and occasionally a need for antagonism of its respiratory depressant effect" (page 674). Similarly, in Zedie 1996[7], "two patients were judged to have a mild decrease in chest wall compliance during induction (i.e. rigidity), and another two patients experienced transient apneic episodes with SaO2 values between 92% to 93%. Because all patients were intubated immediately, these adverse effects did not become clinically significant" (page 346). These patients received 2 µg/kg. While there are significant differences in the clinical setting, limiting conclusions, the data indicate that opioid-related adverse events can occur with intranasal sufentanil at doses of 2 and 4.5 µg/kg.

Based on the literature, the Applicant defined the sufentanil plasma concentration of 300 pg/mL to be well-tolerated in young children (12 kg). One sufentanil sublingual tablet 30 mcg could reach peak plasma level of approximately 200 pg/ml and two 30 mcg sufentanil sublingual tablets could reach peak plasma levels of approximately 400 pg/ml. The Applicant graded a toddler (12 kg) with sublingual administration of 1 sufentanil sublingual tablet 30 mcg an "Overdosing" (scale 3 in Table 17) and ≥ 2 sufentanil sublingual 30 mcg tablets a "Serious Injury or Death" (scale 5 in Table 17). Based on predictions from the popPK model, the Applicant graded the severity of harm to toddler, child, and adult due to accidental exposure to sufentanil sublingual tablet 30 mcg, as seen in Table 17.

Table 17: The severity of hard to toddler, child and adult due to accidental exposure to sufentanil sublingual tablet 30 mcg SST

PHA Item#	Hazardous Situation [Circumstance in which people, property, or the environment are exposed to one of more hazard(s)]	Harm or Effect [*Physical injury or damage to the health of people*]	Severity
8	Patient receives dose more frequently than hourly	Minor Overdosing	2
11	Non-Patient adult (50kg) takes one dose	Minor Overdosing	2
12	Patient or Non-Patient adult (50kg) takes two doses	Overdosing	3
13	Patient or Non-Patient adult (50kg) takes ≥ 3 doses	Serious Injury or Death	5
14	Non-Patient toddler (12kg) or child (20kg) Takes One Dose	Overdosing	3
15	Non-Patient child (20kg) Takes Two Doses	Moderate to Severe Overdosing	4
15.5	Non-Patient toddler (12kg) Takes Two Doses	Serious Injury or Death	5
16	Non-Patient child (20kg) takes ≥ 3 doses	Serious Injury or Death	5

Source: Applicant's submission document RSK-7025 Severity Levels of Harm due to Accidental Exposure to DSUVIA 30 mcg SST, page 9/10, submitted on 5/3/2018.

[6] Henderson JM, Brodsky DA, Fisher DM, Brett CM, Herzka RE. Pre-induction of Anesthesia in Pediatric Patients with Nasally Administered Sufentanil. Anesthesiol. 1988;68:671-5.
[7] Zedie N, Amory DW, Wagner BKJ, O'Hara DA. Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. Clinical Pharmacology and Therapeutics 1996; 59:341-348.

Discussion and conclusion of risk analysis

There are limitations in the Applicant's risk analysis given different contexts of use of sufentanil in the cited published literature and in the context of accidental exposure.

Overall summary of safety review in 2nd review cycle

In this resubmission, the Applicant reduced the maximum daily dose from 24 sufentanil sublingual 30 mcg tablets (720 mcg sufentanil) to no more than 12 sufentanil sublingual 30 mcg tablets (360 mcg sufentanil) per day to address the safety concern of sufentanil sublingual tablet 30 mcg in patients requiring the maximum dosing proposed for labeling. In addition, the Applicant submitted pooled safety analyses comparing the safety of sufentanil sublingual tablets based on dose received (≥ 300 mcg and < 300 mcg) and plasma sufentanil concentration (>150 pg/mL and ≤150 mg/mL). While there are limitations in these analyses by dose and plasma sufentanil concentration, they appeared adequate in the context of the Applicant's proposal to support a maximum daily dose of 12 sufentanil sublingual 30 mcg tablets. Consistent with the first review cycle, overall sufentanil sublingual tablet 30 mcg appeared to have a typical safety profile of an opioid agonist.

Another safety concern considered in this review cycle was the risk of misplaced tablets. Given the potency of sufentanil and the small size of the tablet, there is concern that tablets could be misplaced. The Applicant modified the DFU so that visual confirmation of the tablet placement is a distinct separate task. The changes to the DFU were evaluated in a second human factors validation study that was reviewed by DMEPA. No failures or close calls occurred during the simulated use task portion of the second study.

Based on the data from this study, DMEPA has determined the product-user interface supports the safe and effective use of the product by the intended users, for its intended uses, and intended use environments. However, there remain concerns regarding the risk of misplaced tablets, which could lead to accidental exposure. To mitigate this risk, sufentanil sublingual tablets 30 mcg will have a REMS with ETASU. The REMS will help ensure that DSUVIA is dispensed only to patients in certified medically supervised healthcare settings to mitigate the risk of respiratory depression resulting from accidental exposure outside of these settings.

9. Advisory Committee Meeting

This NDA was discussed at an Anesthetic and Analgesic Advisory Committee meeting on October 12, 2018. The following is a brief summary of the questions to the committee and surrounding discussions. Please refer to the transcript of the meeting for full details.

1. **DISCUSION:** Discuss whether the data are adequate to support a finding of efficacy for sufentanil sublingual tablets 30 mcg for the proposed indication: the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting.

Committee discussion: Many committee members noted that sufentanil sublingual tablets 30 mcg appeared effective compared to placebo. Several committee members noted the lack of data compared to other drugs and noted that this was a limitation in the available information. A committee member noted concerns related to the onset of action in one hour given that the drug will be used for acute pain.

2. **DISCUSSION**: Based on the available safety data, discuss any concerns you may have about the safety profile of sufentanil sublingual tablets 30 mcg.

Committee discussion: Several committee members noted that the safety appeared similar to an opioid. Some committee members noted limitations in the available data, such in older patients.

3. DISCUSSION: Discuss whether data from the human factors studies and the clinical trials support the safe and effective use of the proposed product administered by healthcare professionals in certified settings such as hospitals, emergency departments, and surgical centers. In your discussion, consider whether the REMS proposed by FDA can be expected to mitigate the risks associated with dropped sufentanil tablets and including the risk of accidental exposure.

Committee discussion: There was discussion of whether the education would be sufficient. Members noted that the medication needs to be used in a certified healthcare setting, and additional clarity is needed on the types of healthcare settings. Several committee members thought the risk of accidental exposure is anticipated to be low.

4. DISCUSION: Discuss any concerns you may have regarding the abuse or misuse of sufentanil sublingual tablets and whether, based on the available data, the benefits to patients are expected to outweigh public health risks related to abuse, misuse, and accidental exposure.

Committee discussion: There was discussion of the risks associated with this Schedule II opioid.

5. VOTE: Overall, do the benefits of sufentanil sublingual tablets 30 mcg with the REMS proposed by FDA outweigh the risks for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting, supporting approval of sufentanil sublingual tablets 30 mcg?

Committee discussion: The overall vote was 10 Yes; 3 No; 0 Abstain. Committee members voting no noted the slow onset of action, potential dose stacking, and the broad patient population as concerns. Committee members voting yes stated that medically supervised needs to be clearly defined.

10. Pediatrics

This NDA triggers PREA as a new formulation with a new dosing regimen and route of administration.

The Applicant submitted an Agreed Pediatric Study Plan (PSP) on October 5, 2016, under IND 113059 and the Agency issued an initial agreement on November 2, 2016.

In the NDA resubmission, the Applicant proposed modifications to the Agreed PSP as outlined below:

- Partial waiver request:

  In the Agreed PSP, the Applicant requested a partial waiver from birth to <6 years of age based on the justification that children in this age group do not have the cognitive ability to comply with Dsuvia's sublingual dosing instructions. Specifically, a younger child might not be able to keep the tablet sublingually and this could lead to either swallowing the pill or spitting it out. If the tablet is spit out, there is the potential for accidental exposure to other vulnerable pediatric patients. If the tablet is swallowed or chewed, the systemic exposure will be lower, and this could result in decreased analgesic effects.

  During review of the NDA resubmission, the Applicant submitted a revised partial waiver request on August 27, 2018, for children (b) (4) based on the same rationale. The Division does not agree with the Applicant's revised proposal for a partial waiver for children (b) (4). This revised partial waiver request was reviewed by the Agency's Pediatric Review Committee (PeRC) on October 3, 2018. The majority of the PeRC members agreed with the Division's position. Thus, the partial waiver will be from birth to <6 years of age based on the rationale that there is evidence strongly suggesting that the product would be ineffective or unsafe in this age groups.

- Deferral request:

  The Applicant requested a deferral for patients aged (b) (4) years of age, but the Division recommends a deferral for patients aged 6 to <17 years of age as agreed in the original Agreed PSP. PeRC supported the Division's proposal. Specifically, pediatric studies in patients ages 6 to <17 years will be deferred until 2-years after approval. This will allow review of post marketing data from adult patients to be collected and reviewed prior to initiation of studies in children. Specifically, it is anticipated that data from the 6 and 12-month REMS assessments will be available and reviewed prior to initiation of studies in children. The Division will review post marketing data for cases of respiratory depression and dropped/misplaced tablet that lead to accidental exposure before the initiation of the pediatric study.

The Division recommends the following overall timeline for the pediatric study:

- Draft Protocol Submission: May 2020
- Final Protocol Submission: August 2020
- Study Completion: December 2022
- Study Submission: March 2023

There are ongoing discussions with the Applicant regarding to timeline for the pediatric study. The recommended deferred pediatric study is:

A safety and pharmacokinetic study of sufentanil sublingual tablet in pediatric patients ages 6 to (b) (4) years with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate (study SAP305).

11 Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues

There are no patent issues that prohibit the Applicant's manufacture, use, or sale of sufentanil sublingual 30 mcg tablet.

In accordance with 21 Code of Federal Regulations, Part 314.108(b)(4)(iv), and 314.50 (j), the Applicant claims three years marketing exclusivity for the sufentanil sublingual 30 mcg tablet.

- **Financial disclosures**

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

- **Other Good Clinical Practice (GCP) issues**

The clinical studies were conducted in accordance with Good Clinical Practices and a statement of compliance with Good Clinical Practices is located in each study report.

- **Office of Scientific Investigations (OSI) audits**

Navid Homayouni, MD, from the Office of Scientific Investigations (OSI) completed the Clinical Inspection Summary for this application during the original NDA review. See the CDTL/Division Director review from the original NDA submission for details regarding the clinical sites inspections.

- **Any other outstanding regulatory issues**—Not applicable

12 Labeling

Proprietary name

The proposed proprietary name for sufentanil sublingual tablet 30 mcg is Dsuvia. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and was found to be acceptable.

Physician labeling

The prescribing information required major revisions. The proposed prescribing information was inconsistent with other opioid class products. Additional revisions were recommended to reflect product specific risks for DSUVIA. Further revisions were made to Sections 6, 8, and 14, to remove data (b) (4). In Section 14, the Applicant included data (b) (4) (b) (4) and they were removed from Section 14. A summary of some changes is included below. Labeling discussions are ongoing at the time of this review.

- INDICATIONS AND USAGE section:
  - Proposed indication: 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
  - The indication will be revised to specify the names of the medically supervised settings (hospitals, surgical centers, and emergency departments) and to be consistent with the DSUVIA REMS.
  - It is anticipated that the indication will for use in adults in certified medically supervised healthcare settings, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
  - In addition, there will be limitations of use, such as that the product is not for home use or for use in children, not for use for more than 72 hours, and only to be administered by a healthcare provider.
- DOSAGE AND ADMINISTRATION section:
  - A subsection of “Important Administration Instructions” was added under the proposed Dosage and Administration section to emphasize the product specific administration instructions including that DSUVIA is only to be administered by the healthcare provider, only to be used in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, and must be discontinued prior to the patient leaving the certified medically supervised setting.
  - We removed some of the figures/symbols under the subsection of administration of DSUVIA as those figures/symbols were potentially confusing. The remaining figures will be changed to black and white color.
- DOSAGE FORMS AND STRENGTHS section:

    - The dosage form and strength were modified to include a description of the DSUVIA tablets.
- CONTRAINDICATIONS section:
    - Contraindications of known or suspected gastrointestinal obstruction, including paralytic ileus will be added to be consistent with the labeling of other opioid products
- BOXED WARNING, WARNINGS AND PRECAUTIONS sections:
    - The order of the Boxed Warning and Warnings and Precautions were updated to reflect the relative safety risks associated with DSUVIA.
    - A Boxed Warning/Warning was added to reflect the goal of the REMS, i.e., risk of respiratory depression and death due to accidental exposure
    - A Boxed Warning of risks from concomitant use with benzodiazepines or other CNS depressants was added to be consistent with the labeling of other opioid products. Similarly, information in the Warnings section was modified to align with the labeling language of other opioid class products.
    - Neonatal Opioid Withdrawal Syndrome was moved (b) (4) to the Warning section.
    - The following additional Warnings and Precautions were added and updated to reflect opioid class product Warnings:
        - Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness.
        - Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
        - Risks of Use in Patients with Gastrointestinal Conditions
        - Increased Risk of Seizures in Patients with Seizure Disorders
        - Bradycardia
    - A Warning (b) (4) was removed (b) (4) (b) (4)
    - A Warning (b) (4) was removed since the information included in section 8.
- ADVERSE REATIONS section:
    - Clinical Trial Experience:
        - Patients from study SAP 202 were not included in the description of safety data
        - The cutoff for Frequently Reported Adverse Reactions was modified to (b) (4)
        - Other Reported Adverse Reactions were updated to be consistent with opioid class labeling.
    - Post-marketing Experience Section:
        - Information on anaphylaxis has been reported with ingredients contained in DSUVIA and was added.
- USE IN SPECIFIC POPULATIONS section:
    - PLLR information needs modification to be consistent with the language in opioid class labeling
    - Pediatric use:

        - The Applicant proposed that the safety and efficacy of the use of DSUVIA in pediatric patients has not been established.
    - Information was added to indicate that younger patients may not be able to follow the sublingual dosing instructions for DSUVIA and could be at risk of swallowing the tablet or spitting it out. If the tablet is swallowed, it is anticipated that the effectiveness would be reduced. If the tablet is spit out, this could increase the risk of accidental exposure to other patients.
    - Geriatric use:
        - Information will be added regarding cautious use in elderly patients given the known risk of respiratory depression
        - Information in population of Hepatic and Renal Impairment will be added to be consistent with other sufentanil products.
- CLINICAL STUDIES section:
    - The Applicant included data from (b) (4) two open-label studies SAP 302 and 303. (b) (4)

(b) (4)

14. Postmarketing Recommendations

Risk Evaluation and Mitigation Strategy (REMS)

The Applicant submitted a proposed REMS during the first review cycle. The complete response letter stipulated that a REMS will be necessary for sufentanil sublingual tablet 30 mcg, if it is approved, to ensure that the benefits of the drug outweigh the risk of respiratory depression resulting from accidental exposure.

Applicant's Risk Mitigation Proposal

The Applicant submitted a proposed REMS to mitigate the risk of respiratory depression resulting from inappropriate administration by dispensing only within certified healthcare facilities or services and informing healthcare providers about the safe use of sufentanil sublingual tablet 30 mcg, including proper administration and monitoring. The use setting proposed by the Applicant is healthcare facilities or services that meet the following criteria: a) licensed pharmacy or healthcare provider with DEA registration for CII drugs who will oversee ordering and administration of the medication and b) access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone.

The Applicant asserts that all healthcare facilities and services that order, prescribe or distribute sufentanil sublingual tablet 30 mcg, will be required to become certified in the sufentanil sublingual tablet 30 mcg REMS Program and comply with the program requirements. Healthcare facility certification includes enrollment in the REMS by completion of a *Healthcare Facility/Service Enrollment Form* by an Authorized Representative (AR). The AR will attest that the healthcare facility or service: is a licensed pharmacy or healthcare provider with DEA registration for CII drugs who will oversee ordering and administration of the medication; has access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone; and has documented processes and procedures in place to ensure sufentanil sublingual tablet 30 mcg is not dispensed for use outside of the certified setting.

The Applicant has proposed the following materials relevant to their proposed REMS:

- *Healthcare Facility/Service REMS Enrollment Form*;
- *Dear Healthcare Provider (DHCP) Letters*;
- *Sufentanil Sublingual Tablet 30 mcg (proposed tradename Dsuvia) REMS Safety Brochure: Guide for Healthcare Providers and Pharmacists*;
- *Directions for Use (DFU)* – A short guide detailing the appropriate administration of Sufentanil Sublingual Tablet 30 mcg (proposed tradename Dsuvia)
- REMS Website- Sufentanil Sublingual Tablet 30 mcg (proposed tradename Dsuvia) REMS Website.

Agency's Proposed REMS

Because of the small tablet size (3 mm in diameter and 0.85 mm in thickness) of sufentanil sublingual tablet 30 mcg there is a risk of dropping or misplacing the tablet during administration which increases the risk of accidental exposure, overdose, and death, particularly in children. Sufentanil sublingual tablet 30 mcg is an immediate-release (IR) opioid analgesic, and therefore, also carries the risks of abuse and misuse.

In general, the Agency agreed with the Applicant's risk mitigation proposal. However, we determined that respiratory depression resulting from inappropriate administration (included in the Applicant's proposed goal) will be mitigated since sufentanil sublingual tablet 30 mcg will be administered by a HCP, not the patient. DMEPA reviewed the second human factors validation study to demonstrate the safe and effective administration of sufentanil sublingual tablet 30 mcg by intended users (HCPs) and concluded that the product-user interface supports the safe and effective use of sufentanil sublingual tablet 30 mcg by the intended users, for its intended uses, and intended use environments.

The FDA proposes the following REMS goal:
The goal of the sufentanil sublingual tablet 30 mcg REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by:

- Ensuring that sufentanil sublingual tablet 30 mcg is dispensed only to patients in certified medically supervised settings.

Please see the DRISK reviews for the final components of the REMS, including the elements to ensure safe use. Final REMS negotiations are ongoing at the time of this review.

PMRs
See the Pediatric Section for a discussion of the PREA PMRs.

15 Recommended Comments to the Applicant

None

16 Appendix

16.1. Applicant's Proposed Directions for Use

(b) (4)

16.2. Exploded View Figure of Single-dose Applicator

(b) (4)

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

/s/

NING HU
11/01/2018

YI N REN
11/01/2018

DAVID M PETULLO
11/01/2018
I concur.

JANET W MAYNARD
11/01/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209-128
Drug Name:	Dsuvia (Sufentanil sublingual tablet) 30 mcg
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
Applicant:	AcelRx Pharmaceuticals, Inc.
Date(s):	Stamp Date: 12/12/2016 Primary Review Due Date: 9/7/2017 PDUFA Due Date: 10/12/2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Yi Ren, Ph.D.
Concurring Reviewers:	David Petullo, M.S.
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Steven Galati, M.D., Medical Reviewer Joshua Lloyd, M.D., Team Lead
Project Manager:	Allison Meyer

Keywords: NDA review, clinical trials, missing data, imputation

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1 EXECUTIVE SUMMARY

AcelRx Pharmaceuticals, Inc. submitted a new drug application for sufentanil sublingual tablet 30 mcg for the management of moderate-to-severe acute pain in adult patients in a medically supervised setting. The proposed indication is not for outpatient use. This review focuses on the results from a Phase 3, multicenter, randomized, double-blind, and placebo-controlled study (SAP301). Patients in this study reported moderate-to-severe pain after undergoing an outpatient abdominal surgery. Procedures included abdominoplasty, open tension-free inguinal hernioplasty, and laparoscopic abdominal surgery. Patients who had previously taken an opioid for more than 30 consecutive days, at a daily dose of more than 15 mg of oral morphine (or equivalent) within the 3 months prior to surgery were excluded from the study.

Study SAP301 randomized 161 patients to sufentanil 30 mcg or placebo at a 2:1 ratio within each gender and investigational site. The primary efficacy endpoint was the time-weighted sum of pain intensity difference from baseline over 12 hours after the first dose (SPID12). There was statistically significant evidence of benefit for sufentanil with respect to SPID12. The estimated mean difference of 12.70 (95% confidence interval: [7.17, 18.24]) in SPID12 between two treatment groups reflected a superior pain control with sufentanil. This evidence was supported by the results from two clinically relevant secondary endpoints, time to first use of rescue mediation and amount of rescue medication used over the first 12 hours.

Based on my review of the data from study SAP301, there is sufficient evidence to support the efficacy of sufentanil 30 mcg for the treatment of moderate to severe pain following an outpatient abdominal surgery. However, this application will receive a Complete Response (CR) letter due to higher than acceptable error rates when administering study drug. This included 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.

2 INTRODUCTION

2.1 Overview

AcelRx has submitted a 505(b)(2) new drug application (NDA) for sufentanil sublingual tablet 30 mcg for the management of moderate-to-severe acute pain in adult patients in a medically supervised setting and is not intended for outpatient use.

This application relies on data available in the published literature and findings of safety and efficacy for Sufenta® (sufentanil citrate injection; NDA 19050) approved in the U.S. in 1984. Also part of this application included data previously submitted with the Zalviso ((b) (4) which has been on the market in the European Union.

All relevant communications with the FDA are summarized below:

> During the End-of-Phase 2 (EOP2) meeting held on December 18, 2013, FDA provided comments on missing data with regard to the proposed last observation carried forward (LOCF)/worst observation carried forward (WOCF) method in the protocol SAP301. FDA recommended approaches that attribute a bad score to a patient discontinuing due to adverse event, such as Brown's method (1992).
>
> In the Advice Letter dated June 13, 2014, FDA accepted time-weighted summed pain intensity difference from baseline over 12 hours (SPID12) as the primary efficacy endpoint for SAP301, as long as patients were allowed to remain in the study and continue to be evaluated for up to 48 hours.
>
> On October 5, 2016, FDA agreed with the Agreed Initial Pediatric Study Plan (Agreed iPSP) requested on the pre-NDA meeting held on 9 December 2015. (b) (4)
>
> (b) (4)

Two randomized, placebo-controlled studies (SAP202, SAP301) were conducted in postoperative patients. However, study SAP202 cannot be used to support safety or efficacy as the formulation used in this study was different from the to-be-marketed formulation. There were also two phase 3 open-label studies (SAP302, SAP303) submitted. Since these were open-label uncontrolled studies they were not reviewed. This review focuses on the phase 3 placebo-controlled study (SAP301) to support efficacy.

2.2 Data Sources

All documentation including the study protocol, statistical analysis plan (SAP), clinical study report, and literature referenced, as well as the SDTM and ADaM datasets were submitted under the network path \\CDSESUB1\evsprod\NDA209128\0001. Datasets were submitted by the applicant to the CDER electronic data room in SAS transport format.

In response to the information request sent on March 22, 2017, the applicant resubmitted datasets, corrected define files, as well as the SAS programs used to generate the efficacy analysis datasets under the network path \\CDSESUB1\evsprod\NDA209128\0009.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets were of acceptable quality and were adequately documented. I was able to reproduce the results of all primary and secondary analyses. All results in this review concur with those from the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study SAP301 was an inpatient multicenter, randomized, double-blind, and placebo-controlled study. The study was designed to evaluate the efficacy and safety of Sufentanil 30 mcg for the management of moderate-to-severe acute pain in adult patients undergoing outpatient abdominal surgical procedures.

The study was conducted at four investigational sites across the United States. Randomization was stratified by gender and investigational site. Patients were randomly assigned to treatment with Sufentanil 30 mcg or placebo at a 2:1 ratio within each stratum. Study drug was administered by a health care professional using the single-dose applicator on an as needed basis with a minimum postoperative pain intensity (PI) score of 4 on a 0 to 10 numerical rating scale (NRS) just prior to the administration of first dose of study drug. This reported PI score was used as baseline pain score. The study period was up to 48 hours. The administration of the first dose of study drug marked the beginning of the study. PI score was recorded at baseline, and then PI and pain relief (PR) scores were recorded at 15, 30, and 45 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after the first dose of study drug, every two hours between 12 and 24 hours, then every four hours between 24 and 48 hours. Once a patient had stayed in the study for 24 hours, a minimum PI score of 4 was required for the patient to continue the study and receive the next dose of study drug. Likewise, once a patient had been in the study for 36 hours, a minimum PI score of 4 was required for the patient to continue the study and receive the next dose of study drug.

Study drug could not be more than once every 60 minutes. Additional doses could be given when the patient requested additional study drug with a minimum 60-minute dosing interval. If rescue medication was requested prior to the next dose of study drug, 1 mg IV morphine was allowed.

The primary efficacy endpoint was SPID12. Even though SPID48 or SPID24 are usually used for acute pain studies, the Division accepted SPID12 under the outpatient setting as long as the

applicant continued to collect patient information for 48 hours. Secondary efficacy endpoints (in Appendix) were derived from PI and PR scores, patient global assessment, health professional global assessment, and the use of rescue medications. There were no adjustments for multiplicity for any of the secondary endpoints. However, the medical reviewer, Dr. Steven Galati, considered several secondary endpoints as clinical relevant. These 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

These endpoints are considered supportive only and should not be included in the product label.

3.2.2 Statistical Methodologies

The primary and secondary efficacy endpoints were analyzed using the ITT population. The ITT population included all randomized patients who received study drug.

Due to limited number of male patients enrolled at Sites 1, 2, and 4, these sites were pooled as Center 1 in the analysis. Site 3 was considered as Center 2. The center was included as a factor in the analysis of the primary and secondary efficacy endpoints.

The primary efficacy analysis was an analysis of covariance (ANCOVA) model. The ANCOVA model included treatment, center and gender as factors. The baseline PI score was included as a covariate. The least squares (LS) mean and its 95% CI were calculated for each treatment group, as well as the difference between two treatment groups.

For the secondary endpoints requested by the clinical review team, the following analyses were utilized. Time to first use of rescue medication and time to onset of meaningful pain relief were summarized using a Kaplan-Meier product-limit estimate. A Log-rank test was used to compare the two treatment groups. The analysis of the number of doses of study drug and total amount of rescue medication used over the first 12-hour study period was based on an ANCOVA model that included treatment, center, and gender as factors.

The hypothesis test for the primary and secondary efficacy endpoints was performed at $\alpha = 0.05$ significance level. All tests were two-sided. There was no multiplicity adjustment for the secondary endpoints as they were considered supportive and would not be included in the product label.

If rescue medication was given, the patient recorded a PI score prior to use. This pre-rescue PI score was carried forward for one hour following the dosing of rescue medication.

For missing data during the 48-hour study period, a linear interpolation method was used to impute the intermittent missing values between two observed pain scores. If patients prematurely withdrew from the study, the applicant used a modification of Brown's method to impute the

post-dropout missing values. The detailed imputation method for missing PI values is described as follows:

1. Define the worst PI for early dropouts in the placebo group as the maximum PI value of the baseline pain score and last observed pain score prior to withdrawal.
2. For any given time point, estimate the "imputing value k". This value k is the (100 + NR)/2 percentile of the distribution that includes dropouts, where NR is the non-responder (dropout) rate in the placebo group at the given time point. The distribution of PI values for the placebo group at that time point contains observed values from completers and the worst values from non-completers.
3. Replace the missing values at the given time point with the estimated "imputing value k".
4. Apply this method on missing values at all scheduled evaluation time points for all dropouts

To some extent, this modified Brown's method took into account the division's recommendation of not attributing a good pain score to a subject who discontinued early due to an adverse event or lack of efficacy. However, it was still a single imputation method which is not desirable. Therefore, as a sensitivity analysis, I utilized a multiple imputation method using the distribution of baseline PI scores to impute missing pain scores due to discontinuation. In the acute pain setting, the baseline pain score is usually the worst pain score. The normal distribution was assumed for the baseline PI distribution and 20 times of imputations was conducted.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Of 212 screened patients, 163 were randomly assigned to treatment with sufentanil 30 mcg or placebo at a 2:1 ratio within each stratum by gender and investigational site. The number of randomized patients varied from 13 to 72 at each site. The ITT population consisted of 161 patients. Two randomized patients in the sufentanil group did not receive study drug and were excluded.

A summary of patient disposition is presented in **Error! Reference source not found.**. There were 147 patients (104 patients in sufentanil, 53 patients in placebo) who completed the 12-hour study period. There were 14 patients (8.7%) who discontinued the study prematurely in the first 12 hours where 3 patients (2.8%) were from sufentanil group and 11 patients (20.4%) were from placebo group. Of these, three patients in the sufentanil group and eight patients in the placebo group discontinued due to lack of efficacy. There were 4 patients who discontinued the 24-hour study period after completing the first 12 hours.

After 24 and 36 hours, a minimum PI score of 4 was required for the patient to continue the study and receive the next dose of study drug. There were 90 patients who did not enter the 36-hour study period and 31 patients who completed the 36-hour study period. This information is presented in

Table 1.

Table 1. 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: Reviewer

Demographics for patients are presented in Table 2. There were only two patients in the ≥ 65 age group and there were approximately twice as many male patients than female patients. Almost half of the surgeries were abdominoplasty, 21% were hernioplasty, and 30% were laparoscopic abdominal surgeries. There were no statistically significant differences between treatment groups for any of the demographic and baseline variables.

Table 2. Demographics and Baseline Characteristics

	Sufentanil 30 mcg	**Placebo**	**Total**
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/m2) : 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 Table 14.1.10
SD: standard deviation

3.2.4 Results and Conclusions

I replicated the applicant's results for the primary efficacy analysis. As shown in Table 3, there was a statistically significant difference ($p < 0.001$) between treatment groups for time-weighted SPID12, with a higher mean SPID12 score in the sufentanil group (LS mean [SE]: 26.36 [1.83])

than in the placebo group (LS mean [SE]: 13.66 [2.44]). The LS mean (95% CI) difference between treatment groups was 12.70 (7.17, 18.24). There was not a significant difference in the baseline pain scores.

Table 3. 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	<0.0001
95% CI	(7.17, 18.24)		

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

The applicant did not conduct any sensitivity analyses. Therefore I conducted a sensitivity analysis to examine the impact of missing data on the primary efficacy analysis. Specifically, a multiple imputation method based on baseline distribution for all patients was used to replace the monotone missing PI values for early dropouts. Since almost all of the patients, 13 out of 14, discontinued due to lack of efficacy or because of an adverse event, I used the same method for imputing the data. One patient in the placebo group discontinued due to a protocol violation. To impute a bad score for these patients, I used the distribution of all baseline PI scores. The combined results of the sensitivity analysis were consistent with the primary results (

Table 4). There was a statistically significant difference between treatment groups in the first 12 hours.

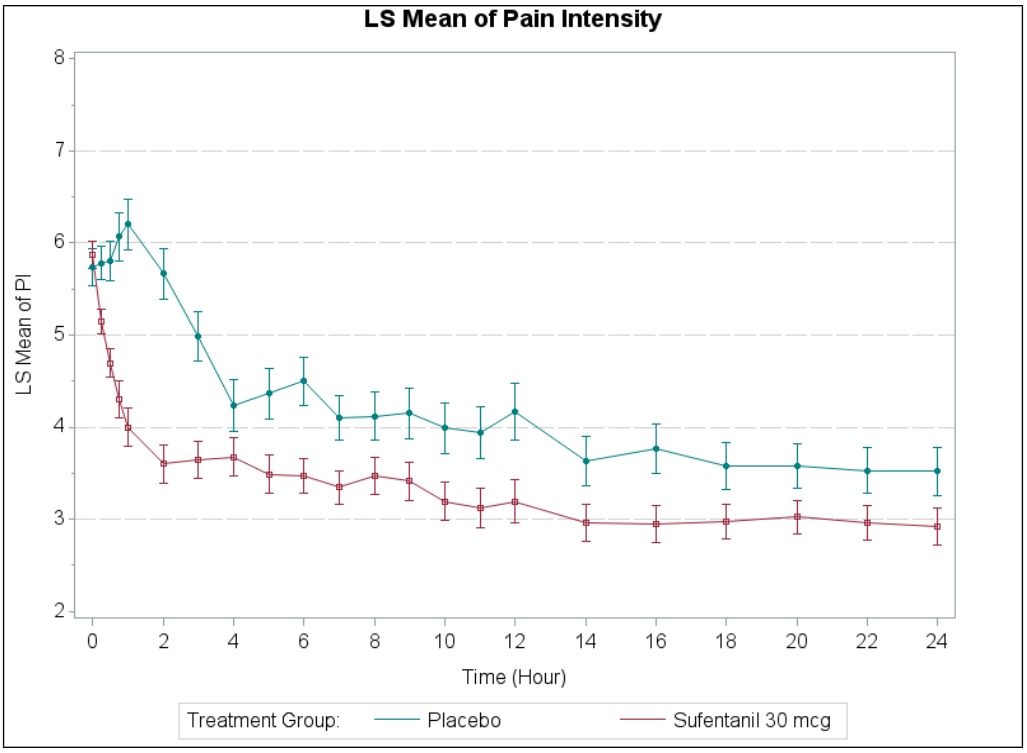
Table 4. Sensitivity Analysis Results for SPID12

	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: Reviewer

There was clinical interest in the pain curves out to 24 hours. The LS mean and its 95% CI at each time point for each treatment group were plotted in Figure 1. During this study period, the LS mean PI scores were significantly lower in the sufentanil 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).

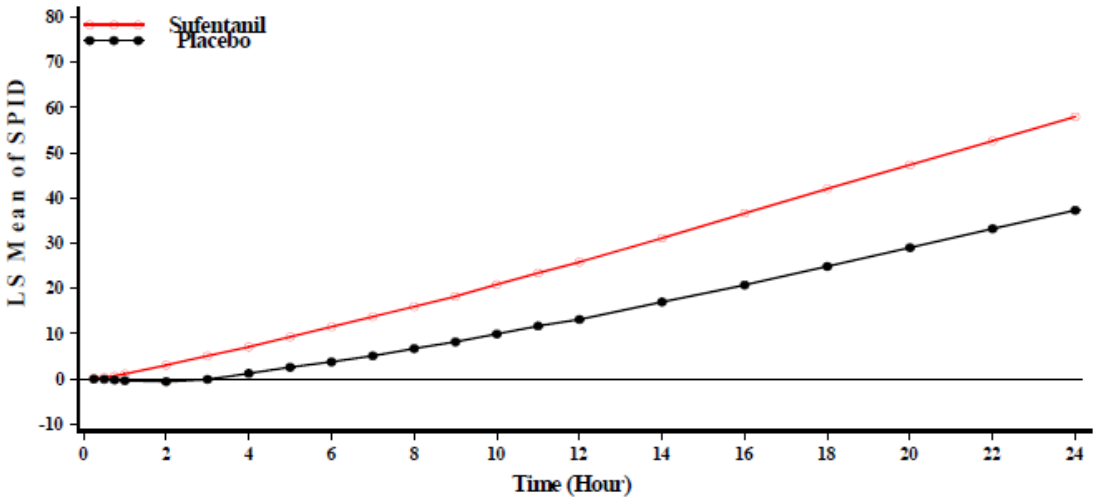
Figure 1. Least Squares Mean of Pain Intensity over the 24-Hour Study Period



Source: Reviewer

Similarly, the LS mean SPID12 and SPID24 were statistically higher in the sufentanil group than in the placebo group ($p < 0.001$) (Figure 2).

Figure 2. Least Squares Mean of SPID over the 24-Hour Study Period



Source: CSR Figure14.2.2

The results for the clinically relevant secondary efficacy endpoints are presented next. There was a statistically significant difference ($p < 0.001$) between Sufentanil and placebo with respect to

time to first use of rescue medication over the first 12-hour study period. Four hours after the administration of the first dose of study drug till the end of the 12-hour study period, there were approximately 40% difference in terms of cumulative probability of patients who took the first rescue medication due to inadequate analgesia (

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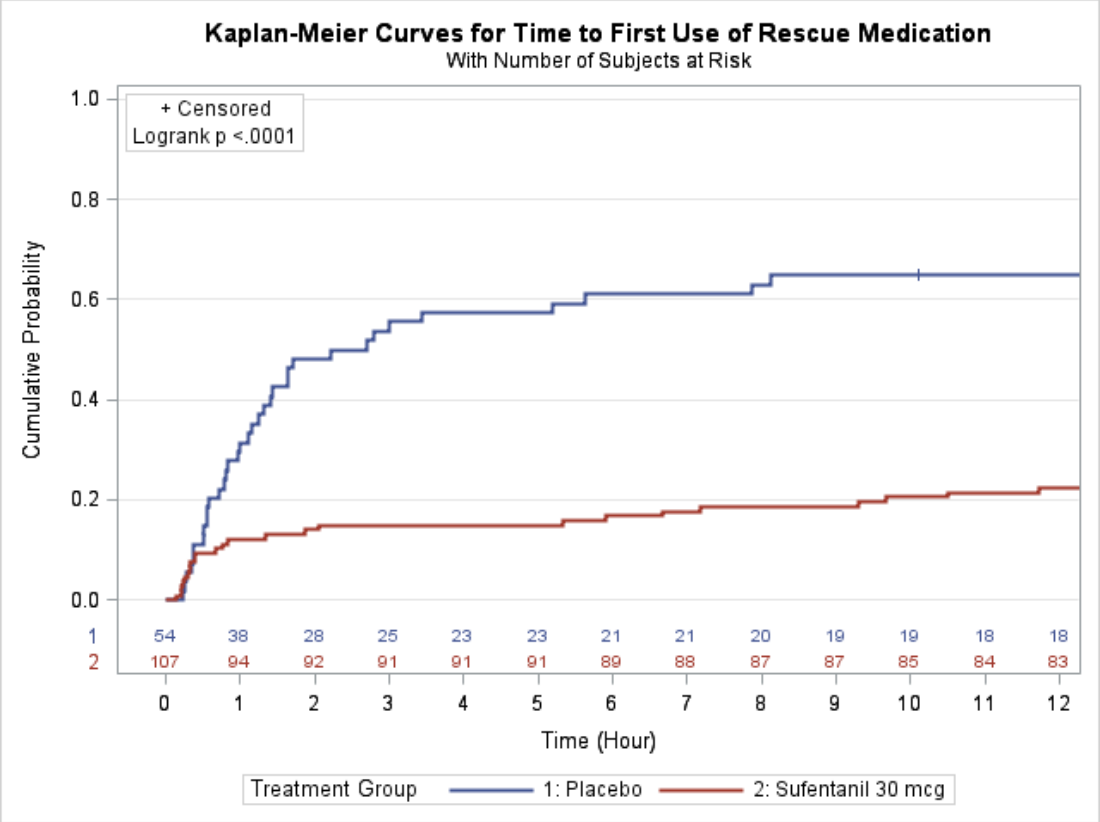
Figure 3).

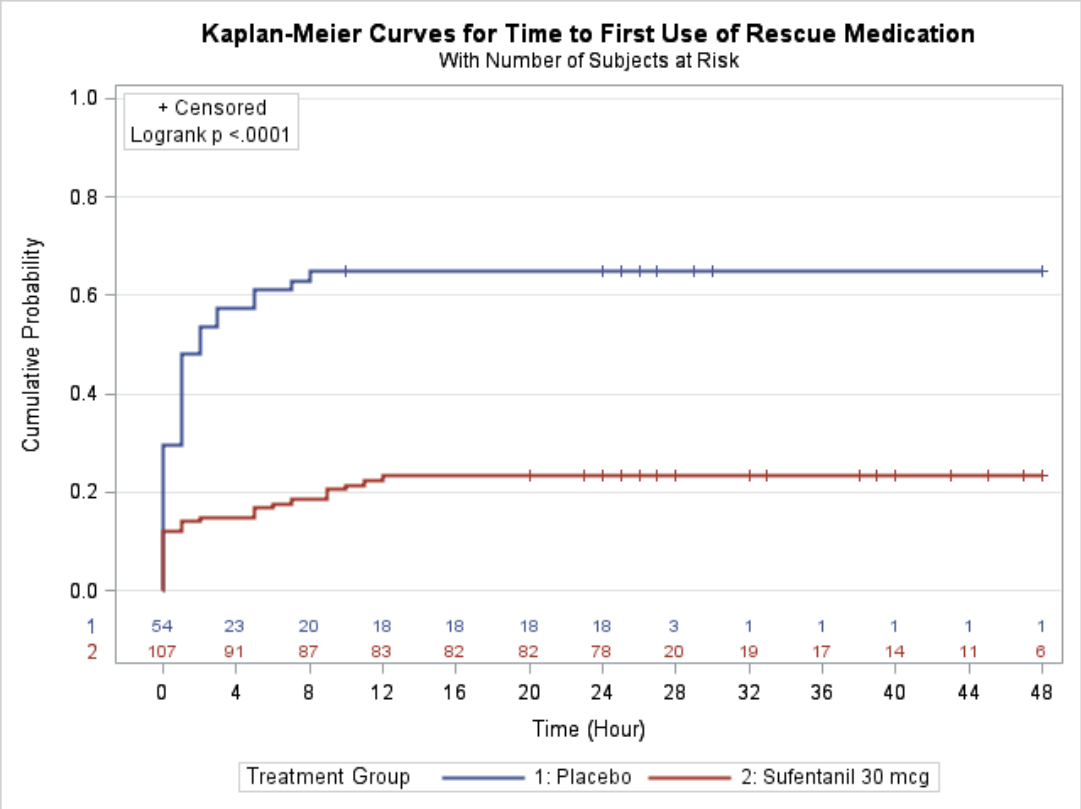
Figure 3. Kaplan-Meier Curves for Time to First Use of Rescue Medication over the 12-Hour Study Period



Source: Reviewer

I also checked the cumulative probability of patients who took the first rescue medication during the 48-hour study period. There was a statistically significant difference ($p < 0.001$) between sufentanil and placebo with respect to time to first use of rescue medication over the entire study period (Figure 4).

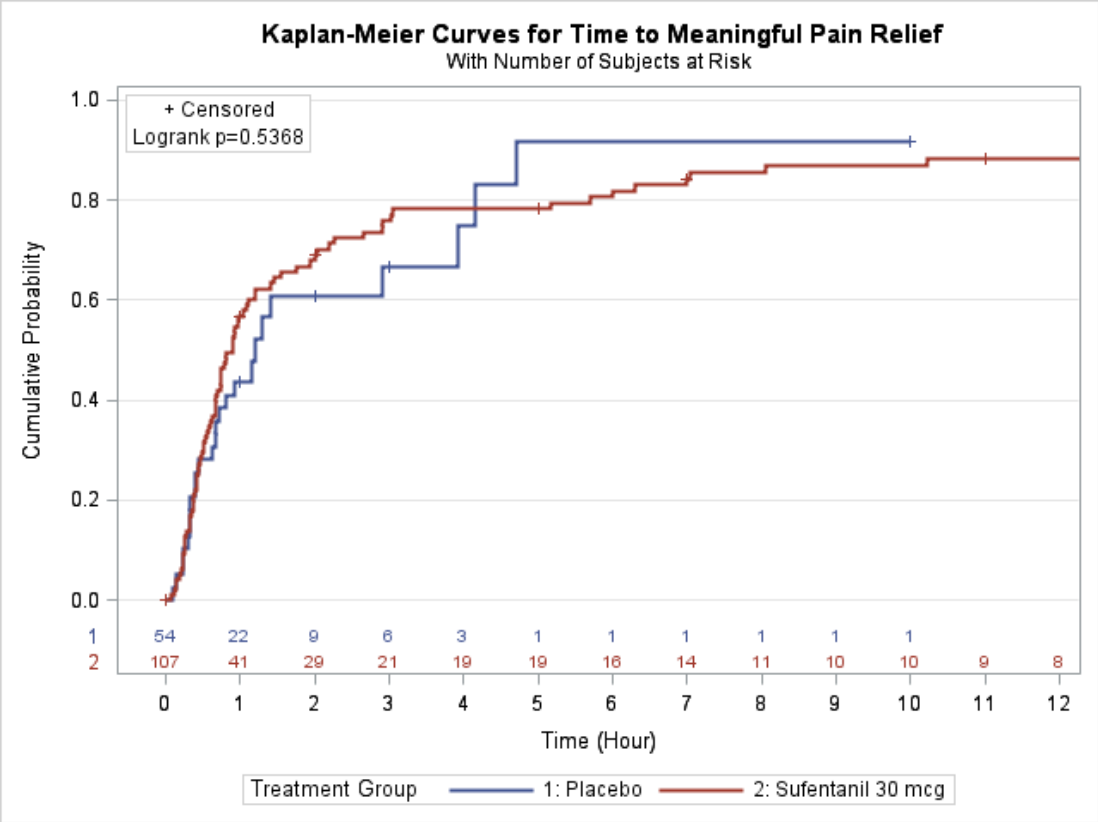
Figure 4. Kaplan-Meier Curves for Time to First Use of Rescue Medication over the 48-Hour Study Period



Source: Reviewer

Kaplan-Meier curves for time to meaningful pain relief over the 12-hour study period were presented in Figure 5. Although the median time to meaningful pain relief was numerically shorter in the sufentanil group than in the placebo group, there was no statistically significant difference between treatment groups for the time to meaningful pain relief ($p = 0.537$) during the first 12-hour study period.

Figure 5. Kaplan-Meier Curves for Time to Meaningful Pain Relief over the 12-Hour Study Period



Source: Reviewer

Due to clinical interest, I checked the total number of study drug and rescue medication doses used over the 12-hour study period instead of 48-hour period. There was no statistically significant difference between Sufentanil and placebo groups for the LS mean total number of study drug doses used ($p = 0.360$), and for the number of study drug doses used by category ($p = 0.180$) during this study period (Table 5. Number of Study Drug Doses Used over the 12-Hour Study PeriodTable 5).

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Table 5. Number of Study Drug Doses Used over the 12-Hour Study Period

Number of Doses Used over 12 Hours	Sufentanil 30 mcg (n = 107)	Placebo (n = 54)	P-value
Mean (SD)	4.4 (2.0)	4.7 (2.3)	
Median	4	4	
Range	(1, 9)	(1, 11)	
LS mean difference	-0.3 (-1.0, 0.4)		0.360
Number (%) by category			
<4	40 (37.4)	16 (29.6)	
4-8	65 (60.8)	34 (63.0)	0.180
>8	2 (1.9)	4 (7.4)	

Source: Reviewer
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.

There were statistically significant differences between sufentanil and placebo groups for the LS mean total number of rescue medication doses used during the 12-hour study period and for the number of rescue medication doses used by category (p-values < 0.001 for all), with higher proportion of doses used in the placebo group than in the sufentanil group (Table 6).

Table 6. Number of Rescue Medication Doses Used over the 12-Hour Study Period

Number of Doses Used over 12 Hours	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)	
1-2	21 (19.6)	23 (42.6)	<0.001
3-4	1 (0.9)	8 (14.8)	
>4	2 (1.9)	4 (7.4)	

Source: Reviewer
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.

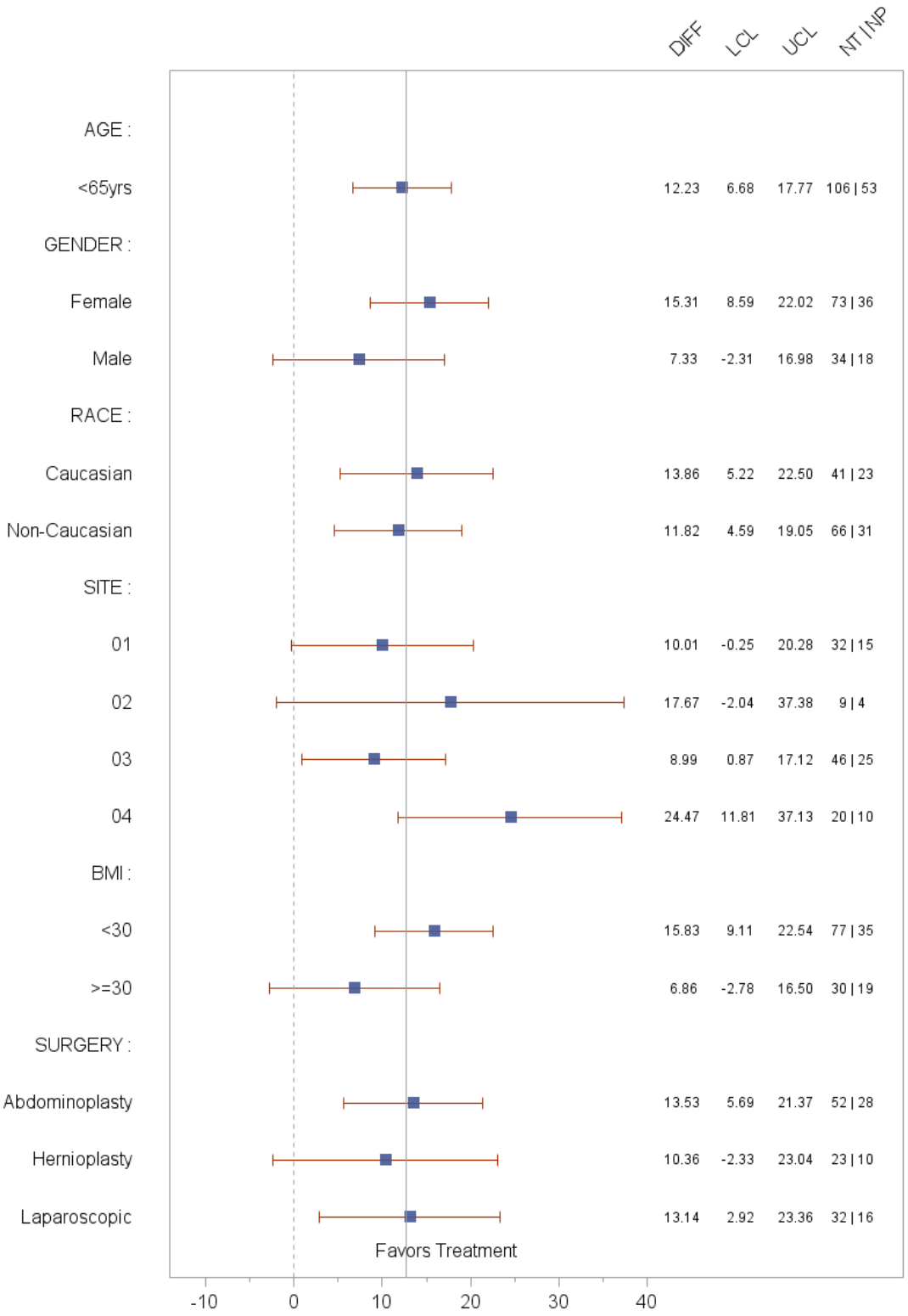
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

I conducted subgroup analyses for the primary efficacy endpoint SPID12 by age (<65 years), gender (male and female), race (Caucasian and non-Caucasian), BMI (<30 kg/m^2 and ≥30 kg/m^2), investigational site (Sites 1-4), and type of surgery (abdominoplasty, hernioplasty, and laparoscopic abdominal surgery).

For each subgroup I present the LS mean difference in SPID12 comparing sufentanil with placebo and its 95% CI. Results are shown in Figure 6. Since there were only two patients older than 65 years of age, this subgroup analysis was not performed. The mean differences were mostly consistent across all subgroups. Some subgroups such as Sites 2 and 4, and hernioplasty surgery had limited number of patients and resulted in large variability and unreliable results. However, there were no statistically significant interactions between treatment and the subgroup of interest. Numerically higher LS mean SPID12 scores for the sufentanil group were observed in all subgroups. This was also consistent in the direction of treatment effect although some were not statistically significant.

Figure 6. Subgroup Analyses for Primary Efficacy Endpoint SPID12



Source: Reviewer

The LS mean difference of sufentanil over placebo with respect to SPID12 was analyzed using ANCOVA with treatment, baseline pain intensity, and interaction of treatment and the subgroup of interest (including age group, gender, race, investigational site, BMI, and type of surgery).

DIFF: LS mean difference

LCL: lower confidence limit
UCL: upper confidence limit
NT: number of subjects in the active treatment group
NP: number of subjects in the placebo group
Solid vertical line represents mean overall estimated effect size.
Dashed vertical line represents no effect.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

I did have one concern regarding the imputation method utilized by the applicant in the primary analysis. The modification of Brown's method was considered a simple imputation method which underestimates the imputation variability. A method that can account for such variance, for example the multiple imputation method would be recommended as stated in Section 3.2.2, I used a multiple imputation method based on baseline distribution for early dropout. Results were consistent with the primary efficacy analysis using modified Brown's imputation method on missing data. This is not unexpected since only 14 patients (8.7%) prematurely discontinued the study within the first 12-hour study period.

5.2 Conclusions and Recommendations

Sufentanil sublingual tablet 30 mcg provided superior analgesia compared to placebo based on the primary efficacy endpoint of SPID12. The results of the primary efficacy analysis were supported by clinically relevant secondary efficacy endpoints, time to first use of rescue medication and total number of doses of rescue medication used over 12 hours.

However, this application will receive a Complete Response (CR) letter 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.

5.3 Labeling Recommendations

The label will not be reviewed during this review cycle.

Appendix

Secondary efficacy endpoints for Study SAP301:

1. SPID1
2. SPID24 and SPID48
3. TOTPAR12, TOTPAR24 and TOTPAR48
4. SPRID12, SPRID24, and SPRID48
5. Proportion of patients who terminate from the study due to inadequate analgesia
6. Proportion of patients requiring rescue medication due to inadequate analgesia
7. Proportion of patients and healthcare professionals who responded to the global assessments as “excellent” or “good”
8. Proportion of patients and healthcare professionals who responded in each category of the global assessments
9. PI at each evaluation time point
10. PID at each evaluation time point
11. PR at each evaluation time point
12. PRID at each evaluation time point; the PRID is the sum of PR and PID
13. Proportion of patients who complete 24 hours in the study and do not require study medication after the 24-hour study period
14. Time to first use of rescue medication
15. Total number of doses of study drug and rescue medication used over 48-hour study period
16. Mean duration of inter-dosing interval over the 48-hour study period
17. Time to onset of perceptible and meaningful pain relief

References

Morton B. Brown. A test for the difference between two treatments in a continuous measure of outcome when there are dropouts. *Controlled Clinical Trials*, 1992, 13: 213-225.

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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/

YI N REN
09/06/2017

DAVID M PETULLO
09/06/2017
I concur.