FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

AcelRx Pharmaceuticals, Inc.

DSUVIA™
(sufentanil) sublingual tablet, 30 mcg

MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE

MEETING DATE: October 12, 2018

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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ABBREVIATIONS AND DEFINITION OF TERMS

AAPCC	American Association of Poison Control Centers' National Poison Data System
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ASA	American Society of Anesthesiologists
AUC	Area under the concentration-time curve
AUC_{0-60}	Area under the concentration curve through 60 hours
AUC_{0-inf}	Area under the concentration curve extrapolated to infinity
BMI	Body mass index
CT	Computed tomography
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRL	Complete response letter
CYP	Cytochrome P450
DEA	Drug Enforcement Agency
EOP2	End-of-Phase 2
ER	Emergency room

EU	European Union
FDA	Food and Drug Administration
GRAS	Generally recognized as safe
H3G	Hydromorphone-3-glucuronide
H6G	Hydromorphone-6-glucuronide
HCP	Healthcare professional
IR	Immediate release
ISMP	Institute of Safe Medical Practices
ITT	Intent-to-treat
IV	Intravenous
LS	Least squares
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
NDA	New Drug Application
NPO	Nil per os; Nothing by mouth
NRS	Numerical rating scale
PBO	Placebo
PID	Pain intensity difference from baseline
PK	Pharmacokinetics

PRID	Pain relief intensity difference from baseline
prn	As needed
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SPID	Summed pain intensity difference from baseline
SPRID	Summed pain relief intensity difference from baseline
T_{max}	Time to maximum plasma concentration
TOTPAR	Total pain relief
US	United States

1 EXECUTIVE SUMMARY

AcelRx Pharmaceuticals, Inc. (AcelRx) is seeking approval of DSUVIA™ (sufentanil) sublingual tablet, 30 mcg, a novel, noninvasive sublingual form of sufentanil that is administered only by a healthcare professional in a medically supervised setting. Sufentanil citrate injection has been administered for over 30 years, primarily as an intravenous (IV) anesthetic agent at high doses (up to 30 mcg/kg), as an IV analgesic component of general anesthesia (up to 8 mcg/kg), and as an epidural analgesic for labor and delivery (up to 3 hourly doses of 15 mcg); Sufenta® (sufentanil citrate injection) serves as the reference product for the DSUVIA 505(b)(2) application. DSUVIA was recently approved as DZUVEO in June 2018 in the European Union (EU) for the management of acute moderate-to-severe pain in adults in medically monitored settings.

DSUVIA 30 mcg sufentanil tablet is housed in a disposable, single-dose applicator to aid in sublingual placement (Figure 1). Each single-dose applicator is individually packaged in a tamper-evident pouch with illustrated Directions for Use attached to each pouch. The single-dose applicator and unit packaging were designed to mitigate the possibility of dosing errors, misuse, and diversion in the medically supervised setting. Additional safety features include a mechanical lock, transparent housing to allow viewing of tablet, and non-retractable plunger. DSUVIA is to be dosed on an "as needed" basis, with a minimum of one hour between doses and a maximum cumulative daily dose of 360 mcg or 12 tablets per 24-hour period.

Figure 1: Single-Dose Applicator and Unit Packaging

The proposed indication for DSUVIA 30 mcg is for the management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. The indication for DSUVIA is similar to that for other approved opioids, while further adding the restriction of use in a medically supervised setting. A medically supervised setting is defined as a facility that meets the following criteria:

- Has a licensed pharmacy or healthcare provider with Drug Enforcement Agency (DEA) registration for Schedule II (CII) drugs who will manage DSUVIA ordering and administration;

- Has access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists.

Because DSUVIA is a single-strength, single-dose product designed to be administered to the patient only by a healthcare professional, the possibility of dosing errors in medically supervised settings is mitigated. Furthermore, limiting DSUVIA to medically supervised settings will mitigate the risk of misuse, abuse, and diversion, as DSUVIA will not be prescribed to patients for outpatient use.

This document provides detailed information on the development of DSUVIA, and the clinical and human factors studies performed to demonstrate the safety, efficacy, and risk-benefit of the product, taking into account the proposed Risk Evaluation and Mitigation Strategy (REMS).

Background and Unmet Need

Although novel classes of analgesics have been discovered recently, opioids remain the standard of care for treating moderate-to-severe acute pain (Blondell 2013; Miaskowski 2009; Patanwala 2010; Rasor 2005). In 2016, a multidisciplinary group of anesthesia and pain physicians issued clinical practice guidelines on the management of postoperative pain, which recognized opioids as an essential component of multi-modal analgesic treatment (Chou 2016). While many analgesics provide relief in limited settings (eg, anti-inflammatory agents used for mild-to-moderate inflammation and anticonvulsants used to manage nerve injury pain), opioids are effective for a wide variety of moderate-to-severe pain conditions.

Nonetheless, even in medically supervised settings, currently available opioid treatments have limitations regarding their use, safety, and effectiveness. These include logistical delays of IV administration, such as in emergency room (ER) settings; dosing errors associated with the large array of liquid opioid concentrations, volumes, and compounding variability (Bernstein 2009; ISMP 2018; ISMP 2011; Parshuram 2008); safety concerns due to accumulation of active metabolites (Smith 2011); and undesirable pharmacokinetic properties, such as delayed time to plasma:central nervous system (CNS) equilibration (2.8 hours for morphine; Lötsch 2001), resulting in a slow brain penetration and slow onset of analgesia. In addition, there is difficulty in accessing veins in obese, elderly, burn, and needle-phobic patients (Witting 2017).

While recent guidelines recommend oral opioids over IV opioids for acute postoperative care (Chou 2016), some patients have difficulty swallowing pills for a variety of reasons, and some perioperative patients are restricted from oral intake. Also, some patients need more rapid-acting analgesia, such as in the ER setting, to treat severe pain.

Thus, there is still a clinical need for a noninvasive, rapidly acting, opioid analgesic without active metabolites and which does not require swallowing pills. DSUVIA was developed to address these needs and was developed as a single-strength, single-dose product to avoid dosing errors. Furthermore, DSUVIA will have restricted distribution only to REMS-certified healthcare facilities to ensure safe use.

Overview of Product and Development Program

A sublingually administered form of sufentanil was developed by AcelRx in collaboration with the Department of Defense. The goal was to provide a noninvasive route of administration to treat moderate-to-severe acute pain in non-opioid tolerant patients, as the current rapidly-acting transmucosal opioid analgesic products are approved for opioid-tolerant cancer patients only. Sublingual delivery is a well-known and well-tolerated route that can also be used in patients who are NPO (nil per os; nothing by mouth). Sufentanil, a highly lipophilic opioid without active metabolites, was selected because it has the appropriate physicochemical properties for effective sublingual drug delivery and rapid mucosal absorption.

The development of the DSUVIA tablet was based on another AcelRx sublingual product, Zalviso® (sufentanil) sublingual tablet 15 mcg, a patient-controlled multi-dose combination drug/device 72-hour system that allows up to three 15 mcg sufentanil tablets to be administered per hour as needed, with a 20-minute lockout between doses (for up to a total of 45 mcg sufentanil/hour). Zalviso was designed for patients requiring multiple-day treatment of moderate-to-severe pain, whereas DSUVIA is intended for more short-term use not requiring patient-controlled administration.

Zalviso is commercially available in the EU for treatment of moderate-to-severe postoperative pain and has been marketed since April 2016 by AcelRx's commercial partner, Grunenthal GmbH. Zalviso has now been used in more than 26,000 postoperative patients in Europe.

The DSUVIA tablet formulation is identical to that of the Zalviso tablet, with the exception of a higher dosage strength (30 mcg vs 15 mcg) and different tablet color. The other major difference is the simple, disposable single-dose applicator that serves as the container closure and delivery device for DSUVIA, whereas the Zalviso system is a more complex drug delivery electromechanical device that contains 40 sufentanil 15 mcg tablets housed in a cartridge.

Clinical Pharmacology

Since IV access is not always available, and oral (swallowed) opioids can have slow and often erratic onset of action, the rationale for sublingual delivery of sufentanil was to take advantage of the highly lipophilic nature of sufentanil and its rapid plasma:CNS equilibration (6.2 minutes; Scott 1991) to develop a noninvasive route of administration in order to promptly treat acute pain. IV sufentanil has a very rapid onset of action and is mainly used in large doses (up to 30 mcg/kg) during anesthesia (Akorn, Inc. 2016). The duration of effect of small analgesic bolus doses of IV sufentanil in awake patients, however, is extremely short, given the plasma sufentanil distribution half-life of 1.4 minutes and rapid equilibration between plasma and brain concentrations. Therefore, the use of sufentanil for analgesia via the IV route is limited.

A series of pharmacokinetic (PK) studies was undertaken to establish the profile of DSUVIA. Sublingual administration of DSUVIA and Zalviso tablets results in 50 to 60% bioavailability. With this bioavailability, the DSUVIA 30 mcg sublingual tablet is approximately equianalgesic to IV morphine 5 mg (or oral oxycodone immediate release [IR] 10 mg), as corroborated by an earlier comparative study of sublingual sufentanil versus IV morphine dosing (Melson 2014).

DSUVIA has an approximately 15-fold reduction in maximum plasma concentration (C_{max}) compared to IV administration of sufentanil 30 mcg.

The mean C_{max} of a single 30 mcg dose of DSUVIA is 61 pg/mL, and at maximal dosing of 30 mcg per hour for 12 hours, the mean C_{max} is 151 pg/mL. The published median minimally effective plasma concentration of sufentanil used as an analgesic in postoperative patients has previously been reported as 24 pg/mL, with patients titrating to a mean plasma concentration of 86 pg/mL (Lehmann 1991), which falls between the C_{max} of a single dose of DSUVIA and the C_{max} following maximal hourly dosing with DSUVIA. Following a single dose of DSUVIA, the plasma concentrations of sufentanil reaches the 24 pg/mL analgesic threshold in approximately 15 minutes and remains above this threshold for approximately 3 hours. These PK time points correlate well with the onset of analgesia and average redosing interval with DSUVIA during the clinical trials (15- to 30-minute onset and approximately 3-hour interdosing interval).

The profile of a single sublingual dose of DSUVIA also has a more consistent plasma concentration over time compared to the rapid peak and trough associated with IV sufentanil bolus delivery. This is demonstrated by the time from C_{max} to 50% of C_{max}, which is a median of 2.3 hours for DSUVIA compared to a median of 6 minutes with a single bolus IV administration. Therefore, sublingual sufentanil does not have the limitation of an ultra-short duration of action that complicates the IV administration of sufentanil.

Efficacy

Evidence of the efficacy of DSUVIA for the treatment of moderate-to-severe acute pain comes from two pivotal, double-blind, randomized, placebo-controlled, multi-center clinical trials of DSUVIA conducted in the United States (US), Study 202 and Study 301. These studies included a total of 261 patients in postoperative settings (bunionectomy and outpatient abdominal surgery, respectively). Additionally, supportive evidence of efficacy comes from two open-label, uncontrolled studies, Study 302 and Study 303, which included a total of 216 patients. Study 302 evaluated patients in an ER/trauma setting, while Study 303 evaluated postoperative patients 40 years of age or older.

All studies were designed with input from the Food and Drug Administration (FDA) and all recommendations provided by the Agency were incorporated, including specific recommendations on the statistical imputation methodology.

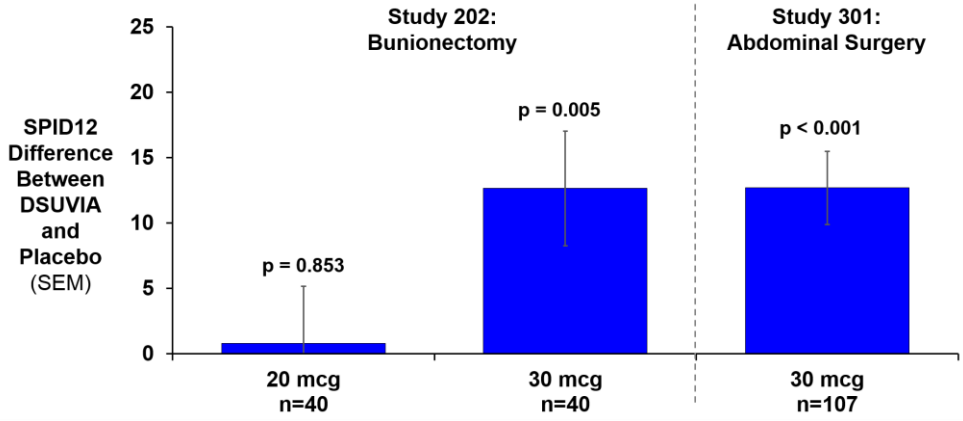
All studies evaluated the 30 mcg dose of DSUVIA; Study 202 (bunionectomy) also assessed a 20 mcg dose of DSUVIA. Treatment duration ranged from 5 to 48 hours and reflected the likely treatment settings for DSUVIA, including inpatient and outpatient postsurgical settings and the ER. Dosing was per patient request, but no more frequently than once per hour. Rescue opioid medications were available in all four studies to minimize early withdrawal due to inadequate analgesia.

Baseline demographic and disease characteristics were well balanced between randomized arms in the pivotal studies.

The primary endpoint in both pivotal studies (Study 202 [bunionectomy] and Study 301 [abdominal surgery]) was time-weighted summed pain intensity difference from baseline (SPID) between the placebo group and the DSUVIA group measured over 12 hours following the first dose (SPID12); in the 5-hour open-label study in the ER setting (Study 302), the primary efficacy endpoint was the time-weighted SPID over the first hour following the first dose (SPID1), while the primary efficacy endpoint for Study 303 (older postoperative patients) was time-weighted SPID12. SPID summarizes pain intensity changes from baseline as measured on an 11-point numerical rating scale. SPID is a commonly used endpoint for comparing analgesic responses between treatment groups. Analysis was based on the intent-to-treat (ITT) population. Multiple secondary endpoints were analyzed and considered supportive in nature.

In both pivotal studies, DSUVIA demonstrated efficacy by reducing patients' moderate-to-severe acute pain compared to placebo based on the primary efficacy endpoint of time-weighted SPID12 (Figure 2; Section 4.9). Efficacy did not vary by demographic or disease characteristics; analyses across different population subgroups, including those defined by age, sex, race, body mass index (BMI), as well as surgery type, showed consistent efficacy benefits from DSUVIA.

Figure 2: Primary Efficacy Endpoints in Pivotal Trials – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)



SEM = Standard error of the mean; SPID12 = Summed pain intensity difference from baseline over 12 hours
Least squares mean difference (DSUVIA minus Placebo)

In Study 202 (bunionectomy), a lower dosage strength, DSUVIA 20 mcg, was also evaluated; this dose did not demonstrate a statistical difference from placebo on the primary efficacy endpoint, confirming that DSUVIA 30 mcg is the minimum effective dose.

The primary efficacy endpoint findings were supported by pre-specified secondary pain measurements in both placebo-controlled studies. Specifically, DSUVIA was superior to placebo for key secondary endpoints, including SPID1, the percentage of patients using rescue opioid medication and the time to first use of rescue opioid medication, and the Patient Global Assessment (all $p \leq 0.006$; Section 4.12). In contrast to SPID12, which evaluates efficacy following multiple doses, SPID1 evaluates single-dose efficacy; the results for SPID1 corroborated the clinical efficacy demonstrated with the primary endpoint. Additionally,

DSUVIA patients used fewer doses of rescue opioid medication than those in the placebo group in both Study 202 (bunionectomy) and Study 301 (abdominal surgery; Table 12).

In both pivotal studies, onset of analgesia was determined by assessing the time to pain intensity/pain relief differences from baseline, the time to pain intensity/pain relief differences versus placebo, and the time to perceptible and meaningful pain relief using the double-stopwatch technique. In the two pivotal studies, all of these assessments indicated that the onset of analgesia occurred within 15 to 30 minutes (Section 4.12). Although dosing of study drug was available hourly as needed, the average DSUVIA redosing time for patients in the two pivotal studies was approximately three hours, consistent with the results from the PK studies previously mentioned.

In the two open-label studies, Study 302 (ER) and Study 303 (older postoperative), the onset of analgesia was measured by differences in pain intensity and pain relief compared to baseline since there was no comparison group. DSUVIA showed significant differences from baseline within 15 to 30 minutes for both pain intensity and pain relief. Specifically, in the ER setting (Study 302), the mean baseline pain intensity score was severe (8.1), and within 60 minutes after a single dose of DSUVIA, a mean pain intensity reduction of 2.9 was observed. A pain intensity reduction of 1.3 in an ER setting has been shown to be clinically meaningful (Bijur 2003).

Safety

The safety of DSUVIA is supported by over 30 years of commercial experience with sufentanil in its use both as an anesthetic and analgesic agent during surgery via the IV route and as an analgesic when given epidurally. Published data in postoperative patients with either IV or epidural sufentanil administration demonstrate that many patients tolerate plasma concentrations of sufentanil over 200 pg/mL (Sinatra 1996), higher than the average maximum concentrations produced with maximal dosing (hourly dosing for 12 consecutive hours) of DSUVIA in healthy Phase 1 subjects (151 pg/mL; Table 4) and higher than the mean peak concentrations observed from sparse sampling in the DSUVIA (44–51 pg/mL) and the Zalviso (71–101 pg/mL) Phase 2 and Phase 3 clinical trials.

The safety database for DSUVIA 30 mcg consists of 646 patients, including 323 patients treated with DSUVIA 30 mcg and 323 patients treated with Zalviso 15 mcg. As agreed during discussions with the FDA, safety data in 323 patients collected and submitted as part of the Zalviso program are used to support the DSUVIA safety assessment. As previously mentioned, Zalviso and DSUVIA share the same tablet composition (other than dosage strength and colorant). Importantly, bioequivalence in a Phase 1 study and PK modeling has been established between two Zalviso 15 mcg doses administered 20-25 minutes apart and a single DSUVIA 30 mcg tablet (Section 3.2). Of the 323 Zalviso patients who were exposed to the first two doses within 20-25 minutes, 243 patients took three doses in the first hour and were exposed to 45 mcg of sufentanil, a higher dose than that recommended for DSUVIA, which is not to exceed one 30 mcg sufentanil tablet per hour. Therefore, inclusion of these Zalviso patients into the DSUVIA safety database allows for a conservative assessment of safety.

The 323 patients exposed to DSUVIA 30 mcg came from one placebo-controlled study (Study 301 [abdominal surgery]) and two open-label studies (Study 302 [ER] and Study 303 [older postoperative]). Based on a request from the FDA, Study 202 (bunionectomy), the other placebo-controlled study of DSUVIA, was excluded from the DSUVIA safety analyses. This study did not use the commercial formulation of DSUVIA, and as such, the FDA felt it was possible that patients received a slightly lower systemic sufentanil exposure. The 323 patients treated with Zalviso were enrolled in four placebo-controlled studies and two non-placebo-controlled studies, all investigating the safety and efficacy of Zalviso 15 mcg (Table 14).

The overall safety population supporting the DSUVIA safety database included postoperative patients following major and laparoscopic abdominal surgery, major and minor orthopedic surgery (total hip, total knee, bunionectomy, and other surgeries), and acute injury or trauma patients presenting to the ER.

Overall Safety Population

Adverse events (AEs) observed throughout the duration of the studies (up to 72 hours) in the overall sublingual sufentanil safety population (n=646; Table 16) were generally consistent with those associated with opioids and the postsurgical or ER setting. The most common AEs overall for DSUVIA and Zalviso were nausea, headache, and vomiting.

There were no deaths in studies of DSUVIA. Among all patients treated with Zalviso 15 mcg, there was one death due to acute renal failure, which occurred 30 days after discontinuation of study drug and was considered unrelated to treatment by the study investigator.

In the overall safety population, there were a total of nine serious adverse events (SAEs) reported in seven patients. SAEs occurred in one patient treated with DSUVIA, four patients treated with Zalviso, and two patients on placebo. Specific SAEs included angina pectoris in the DSUVIA-treated patient; single events of oxygen saturation decreased, atrial fibrillation, and postoperative ileus in three patients receiving Zalviso, and pulmonary embolism followed by confusional state and hypoxia in another patient receiving Zalviso; and syncope and hemiparesis each in patients receiving placebo. All events were resolved, with study drug withdrawn from the Zalviso patient with oxygen saturation decreased and from the two placebo-treated patients. The SAEs experienced with active drug (angina pectoris, oxygen saturation decreased, atrial fibrillation, postoperative ileus, confusional state, hypoxia, and pulmonary embolism) are consistent with AEs of opioid treatment and/or the treatment setting, and none occurred in more than one patient.

Five patients in the overall safety population required treatment with naloxone. This included three Zalviso-treated patients who had AEs of oxygen saturation decreased, sedation, and narcotic reversal, and two placebo-treated patients for AEs of shaking and anxiety. No DSUVIA-treated patient required naloxone throughout the studies.

Placebo-Controlled Safety Population

To provide a relevant comparison of DSUVIA's safety versus patients exposed to placebo, additional safety analyses were conducted using patients from the DSUVIA and Zalviso placebo-

controlled studies. The placebo-controlled safety population included a total of 318 sufentanil and 158 placebo patients drawn from one DSUVIA study (Study 301 [abdominal surgery]; Study 202 [bunionectomy] was excluded for the reason discussed above) and four Zalviso placebo-controlled studies. While the overall safety population analysis evaluated AEs occurring over a period of up to 72 hours, the placebo-controlled safety analysis evaluated AEs over the first 24 hours, as less than 2% of the AEs occurred beyond 24 hours in the DSUVIA placebo-controlled study, which was in a setting of short-term use (ie, same-day surgeries).

Similar to the overall safety database, the most common AEs occurring in the placebo-controlled safety population for the active sufentanil-treatment group were nausea, headache, and vomiting (Table 18), with only nausea and vomiting occurring more frequently in the sufentanil group compared to the placebo group. The safety profile for sublingual sufentanil in general was consistent with that of other opioids given in a postsurgical or other medically supervised setting.

In the placebo-controlled studies, AEs leading to discontinuation were experienced by 11 patients (4%) among the 318 patients receiving sufentanil and 6 patients (4%) among the 158 patients receiving placebo.

DSUVIA, as with other opioids, may be associated with respiratory events. In the overall safety database, DSUVIA respiratory events were rare with the most common being decreased oxygen saturation (1.9%; Table 16). In the placebo-controlled trials of DSUVIA and Zalviso, most of the respiratory events seen with sufentanil treatment occurred in Zalviso-treated patients and were mild to moderate and self-limited, with only one event considered to be severe (Section 5.3.3). No DSUVIA-treated patient required naloxone for respiratory issues, and one Zalviso patient (who experienced a severe AE of decreased oxygen saturation) received naloxone.

High/Low Dosing Safety Population

To support the proposed labeled maximal daily dose of DSUVIA (12 tablets or 360 mcg in 24 hours), data from the DSUVIA and Zalviso studies with treatment periods of at least 24 hours were analyzed; this included one DSUVIA study (Study 301 [abdominal surgery]) and three Zalviso studies. Patient data were then analyzed by subgroups based on the sufentanil dosing received (≥ 300 mcg or < 300 mcg) during the first 24-hour study period. Allowing the safety analysis to encompass ≥ 300 mcg per day (equivalent to 10 or more DSUVIA 30 mcg tablets), instead of only ≥ 360 mcg per day (equivalent to 12 or more DSUVIA tablets), provides more DSUVIA-treated patients to be assessed near the proposed daily dosing limit. Given that the Zalviso patient exposures were as high as 825 mcg/24 hours (equivalent to 27.5 DSUVIA tablets), the upper end of the sufentanil exposure is more than double the maximal dosing proposed for DSUVIA (360 mcg/24 hours). Adverse events were collected up to 72 hours following the first study dose, as the majority of the higher-dosing patients were in Zalviso studies that were of longer duration (up to 72 hours) than the DSUVIA studies.

Overall, the rates of typical opioid-related gastrointestinal AEs were generally higher among patients in the higher dose groups (Table 23). However, the occurrence of opioid-related respiratory AEs, severe AEs, SAEs, AEs leading to discontinuation, and lowest oxygen saturation values, were comparable between the higher- and lower-dose subgroups.

A second set of analyses were performed in which patients were subdivided by maximal sufentanil plasma concentrations (> 150 pg/mL or ≤ 150 pg/mL) observed during the first 24 hours of the studies. This cutoff value of 150 pg/mL was selected as it was the mean C_{max} observed during hourly dosing for 12 hours in a Phase 1 study (SAP101; Section 3.2). Similar to the results by dose, higher concentrations of plasma sufentanil were associated with increased rates of common opioid-related gastrointestinal AEs but had no clinically significant impact on opioid-related respiratory events.

Abuse Potential and REMS

DSUVIA contains sufentanil, a DEA Schedule II opioid, and as such, it has abuse potential and the risk of respiratory depression, especially if not used appropriately. While opioids prescribed in the outpatient setting for home use have been abused with increasing frequency over the past few decades (hydrocodone, oxycodone, morphine, methadone, fentanyl, etc.), opioids restricted to administration by a healthcare provider and not contained in any outpatient products (sufentanil, alfentanil, and remifentanil) have shown extremely low rates of abuse over this same time period. DSUVIA is not intended for home use and will not be distributed through retail pharmacies. AcelRx has developed a DSUVIA REMS program, the goal of which is to mitigate the risk of respiratory depression resulting from inappropriate administration by ensuring that DSUVIA is dispensed only within certified healthcare facilities or services, and informing healthcare providers about the safe use of DSUVIA, including proper administration and monitoring. The REMS program consists of the following key components:

1. Distribution of DSUVIA only to healthcare facilities that are certified by AcelRx. Each healthcare facility must have an Authorized Representative who will attest to having the REMS-specified safeguards and healthcare professionals experienced in administering parenteral opioids, and who will oversee training on the DSUVIA REMS educational material.

   The proposed REMS mitigates the risk for misuse and diversion through a restricted distribution plan to limit product availability exclusively to certified healthcare facilities (ie, no retail pharmacy distribution). As part of the restricted distribution plan, REMS-certified healthcare facilities must have the required DEA CII registration (DEA license number and address are electronically verified by AcelRx) and an Authorized Representative to attest that the facility routinely handles IV opioids (cross-referenced by AcelRx against drug-acquisition databases [eg, Symphony Health pharmacy fulfillment database]), that the facility has healthcare professionals experienced in opioid administration, and that training on the DSUVIA REMS Program, including administration information (Directions for Use), will be made available to all staff involved in dispensing or administering DSUVIA. The attestation further includes a statement that the facility conducts/undertakes appropriate training of healthcare professionals to detect airway problems and that the facility has access to supplemental oxygen and opioid reversal agents, if needed. The REMS attestation further includes agreement by the Authorized Representative that the healthcare facility has processes and procedures in place to ensure DSUVIA is not dispensed for use outside of the certified healthcare facility.

2. Availability of REMS materials and tools to ensure that DSUVIA is used appropriately in these medically supervised settings.

   The REMS contains educational materials and tools such as the DSUVIA REMS Safety Brochure: Guide for Healthcare Providers and Pharmacists, which will be available for practitioners to educate themselves and their staff on the appropriate use and administration of the tablet for management of moderate-to-severe acute pain in adult patients. The Safety Brochure provides important safety information, such as the importance of a minimum one-hour redosing interval, the 12-tablet daily maximum dose, and the need to visually confirm tablet placement after dose administration.

3. Monitoring of the supply chain and certified healthcare facilities to ensure ongoing compliance.

   AcelRx will be responsible for monitoring and auditing the entire DSUVIA supply chain from point of packaging through use by the certified healthcare facilities/services to ensure that all processes and procedures are in place and functioning to support the requirements of the DSUVIA REMS Program. If non-compliance or DSUVIA use outside of a medically supervised setting is identified, corrective action, including immediate de-certification, will be instituted by AcelRx.

4. Participation in Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System to assess incidences of use of DSUVIA outside of the intended medically supervised setting.

Conclusion

DSUVIA offers a PK profile that provides a relatively fast onset of action and an approximately 3-hour duration of analgesia, both desirable for the acute pain setting. The clinical program established DSUVIA as an effective analgesic with an AE profile consistent with the opioid class. No new safety issues were identified in any of these studies. The efficacy and safety of DSUVIA is further supported by more than 30 years of sufentanil use.

The single-dose applicator, tamper-evident packaging, and Directions for Use are designed to enable appropriate use and mitigate the possibility of dosing errors and misuse. The restricted distribution plan, which is the cornerstone of the proposed REMS, is expected to limit the potential for misuse, abuse, and diversion, since the product will not be available via retail prescription. With these guards in place, DSUVIA has the potential to benefit patients with moderate-to-severe acute pain in a medically supervised setting in need of a noninvasive, rapidly-acting opioid analgesic that does not have active metabolites, avoids the need to swallow pills, and has an appropriate and predictable duration of action and safety profile.

2 PRODUCT OVERVIEW

Summary

- DSUVIA is a single 30 mcg sufentanil sublingual tablet contained in a disposable, single-dose applicator, which is used by a healthcare professional to dispense the tablet. Because the product is unit packaged and administered only in a medically supervised setting with no retail availability, the risks of diversion and abuse, which are the hallmarks of the current opioid epidemic, are mitigated.
- DSUVIA was developed to overcome the limitations of existing treatment options and to provide an easy-to-administer dosage form for rapid relief of moderate-to-severe acute pain in a medically supervised setting. DSUVIA 30 mcg is to be dosed on an "as needed" basis, with a minimum of one hour between doses and a maximum cumulative daily dose of 360 mcg or 12 tablets per 24-hour period.
- While many non-opioid analgesics provide relief in limited settings, opioids are effective for a variety of moderate-to-severe acute pain conditions.
- Limitations of currently available opioid treatment options for moderate-to-severe acute pain include the sometimes difficult and time-consuming invasive nature of IV administration, slow onset times (with oral opioids and non-lipophilic IV opioids), an erratic and unpredictable duration of action, and safety concerns due to active metabolites.
- Given the challenges and limitations with current opioids in a medically supervised setting, many adult patients would benefit from a noninvasive, rapidly acting, opioid analgesic that does not have active metabolites, and, importantly, does not add to the opioid abuse problem in the US.
- DSUVIA was recently approved as DZUVEO in the EU for the management of acute moderate-to-severe pain in adults in medically monitored settings.
- The DSUVIA clinical program consists of multiple studies of safety and efficacy and builds upon the established safety and efficacy of the reference product, sufentanil citrate injection, which has been in commercial use for over three decades.

2.1 Currently Available Opioid Analgesia Options

Opioid analgesics are available via oral, transmucosal, and IV administration for acute pain treatment. Each route of administration and specific opioid agent has limitations, which may include challenges with practical delivery, suboptimal pharmacokinetic profiles, dosing errors, safety concerns due to active metabolites, and limited approval for select patient populations. In addition, opioids are highly addictive and abuse of opioids, mainly in the outpatient setting, has reached epidemic levels in the US. It is important to note that only 0.7% of abused pain relievers are stolen from a doctor's office, clinic, hospital, or pharmacy (Ahrnsbrak 2017). DSUVIA will only be available in these medically supervised settings.

Oral Opioids

Oral opioids containing hydrocodone or oxycodone can be used for management of acute pain but are fairly slow in onset of action (30 to 60 minutes; Smith 2012). Onset of analgesia can be erratic, since, with the stress of injury or trauma or following surgery, gastric stasis can further delay oral drug absorption. Oral opioids are often combined with acetaminophen, which has the potential to result in liver toxicity when doses are increased, especially when patients are using additional analgesics containing acetaminophen. Furthermore, patients who are dysphagic or who are NPO may not be able to utilize the oral route of administration.

Transmucosal Opioids

Transmucosal fentanyl products (eg, Teva Pharmaceuticals USA, Inc. 2016a; Teva Pharmaceuticals USA, Inc. 2016b) have been developed for breakthrough cancer pain episodes in opioid-tolerant patients. Because of their high dosage strength, and because they have only been adequately studied in opioid-tolerant patients, they are not suitable for, and have not been approved for use in, non-opioid-tolerant patients. Transmucosal buprenorphine products (eg, Indivior Inc. 2018) have been developed for opioid dependence and for chronic pain (BioDelivery Sciences International, Inc. 2016). Although transmucosal drug delivery has many advantages with respect to ease of care and onset of action, there are currently no transmucosal opioid products approved for management of moderate-to-severe acute pain.

IV Opioids

The use of IV opioids is limited due to logistical delays of IV set-up and insertion, such as in ER settings, as well as the added difficulty in accessing veins in obese, elderly, burn, and needle-phobic patients (Witting 2017). Patients can have an infiltrated (dislodged) IV which can go undiagnosed for hours until pain, swelling, or lack of IV drug effect brings the condition to the attention of the patient or healthcare provider. Recent pain management guidelines recommend oral opioids over IV opioids for acute postoperative care (Chou 2016).

In addition to these patient and hospital factors, there are also opioid-specific shortcomings. IV administration of morphine has a number of disadvantages including a delayed plasma:CNS equilibration half-life of 2.8 hours (Lötsch 2001). Thus, while IV administration is typically associated with an immediate onset of action, IV morphine has been shown to have a slower onset of analgesia compared to sufentanil sublingual tablets in postoperative patients (Melson 2014). Additionally, effects of the active metabolite morphine-6-glucuronide (M6G), which has a plasma:CNS equilibration half-life of 6.4 hours, are observed even later (Lötsch 2001). Therefore, the time to analgesia for IV morphine may require initiating an IV and then further waiting for brain concentrations to reach analgesic thresholds. In addition, morphine has a unique side effect, the release of histamine from mast cells, and can often produce hypotension and other histamine-related side effects when delivered as a bolus administration (Hermens 1985).

Hydromorphone is more lipophilic than morphine and IV administration results in a slightly faster plasma:CNS equilibration half-life (46 minutes; Shafer 2007). It is also approximately 5 to 7-fold more potent than morphine and medication errors between these two similar-sounding,

clear liquid opioids have been some of the most prevalent opioid errors in hospitals, with the Institute of Safe Medical Practices (ISMP) repeatedly reporting on mechanisms to avoid dosing errors due to confusion between these two opioids (ISMP 2011).

IV fentanyl, while resulting in a quick onset of action due to its lipophilic nature (plasma:CNS equilibration half-life of 6.6 minutes; Scott 1991), has demonstrated, similar to sufentanil, a limited duration of analgesia, resulting in frequent redosing and pain scores returning to baseline after only 30 minutes (Claxton 1997). This prompt offset of analgesia is most likely due to the rapid plasma fentanyl distribution half-life (0.8 to 2 minutes) following IV administration, coupled with the rapid plasma:CNS equilibration (Shafer 1991). As the patient's plasma fentanyl concentration rapidly falls, so does the fentanyl concentration in the brain. Sufentanil, and other lipophilic opioids, such as alfentanil and remifentanil, can have an even more abrupt offset of analgesia due to steep initial distribution phases and/or rapid metabolism following IV bolus administration, and are therefore rarely used as acute IV bolus analgesics.

Aside from the dosing confusion between morphine and hydromorphone mentioned above, dosing errors in general are an ongoing concern for IV opioids, as well as oral opioids, due to the extensive variety of concentrations, vial volumes, and dosage strengths available. The ISMP has recommended limiting the availability of opioid concentrations and strengths in automated dispensing cabinets (Barrett 2016). Additional errors due to the variability associated with hospital pharmacies compounding their own solutions is yet another issue with IV opioids (Parshuram 2008). The recent shortage in hospital IV opioids is also exacerbating the issue with IV opioid errors (ISMP 2018).

Active Metabolites

While sufentanil does not have active metabolites, many commonly used opioids do have active metabolites which may cause adverse effects, especially in vulnerable populations. This risk may be exacerbated in ER settings, where patients may arrive with no blood work and there is limited knowledge of renal or hepatic impairment.

Accumulation of the active glucuronide metabolites of morphine (morphine-3-glucuronide [M3G] and M6G) and hydromorphone (hydromorphone-6-glucuronide [H6G] and hydromorphone-3-glucuronide [H3G]) pose a potential risk for delayed or extensive side effects, especially after repeated use and in patients with impaired renal function (Ratka 2004; Sear 1989a; Sear 1989b; Smith 2011). Morphine metabolites can accumulate within 24 hours of initiating dosing to levels that are higher than the parent compound, especially in patients with renal impairment (Melson 2014). These metabolites are associated with a frequent rate of AEs, including nausea, vomiting, pruritus, urinary retention, sedation, and respiratory depression (Hutchison 2006).

In the past, meperidine was commonly used to treat acute pain episodes; however, its metabolite, normeperidine, produces seizures and therefore, the repetitive use of meperidine in the acute setting is now severely limited (McHugh 1999).

Both codeine and tramadol are metabolized by the cytochrome P450 (CYP) 2D6 enzyme, which is known to have extensive genetic polymorphism, leading to inter-individual variations in metabolism (Smith 2011). For these specific opioids, the active metabolites are more potent than the parent compound, potentially creating an overdose situation for ultra-rapid metabolizer patients. An increase in pediatric deaths with codeine was reported in this ultra-rapid metabolizer population, leading to recent FDA warnings regarding these opioids (FDA 2017).

2.2 Unmet Need/Target Population

While there are a variety of choices for managing moderate-to-severe acute pain, there is still a clinical need for a noninvasive, rapidly acting, opioid analgesic that does not have active metabolites, has an appropriate and predictable duration of action, avoids the need to swallow pills, and has been developed for and tested in opioid-naïve patients. These patients make up the majority of those suffering from moderate-to-severe acute pain in medically supervised settings (Gulur 2014).

DSUVIA was developed to provide a sublingual opioid for when IV or oral opioid options are impractical or difficult to administer. A noninvasive route of administration of sufentanil potentially offers several advantages over IV opioids. It would free both the patient and healthcare provider from the requirement and burden of establishing IV access, which may be especially relevant when IV access may be limited, such as in ER settings, or in obese, elderly, burn, and needle-phobic patients. Noninvasive delivery may also be useful in patients with dysphagia who are unable to take oral pain medications, and in ambulatory surgery centers after the patient has been stabilized postoperatively, particularly if analgesia is needed after IV access has been discontinued.

Sufentanil, a synthetic opioid analgesic, was chosen as a product candidate for management of moderate-to-severe acute pain based on known characteristics of the drug. It is characterized by a high selectivity and affinity for mu-opioid receptors and is 5-10 times more potent than fentanyl and more lipophilic, resulting in rapid onset of analgesia when administered via the transmucosal route (Gardner-Nix 2001). Sufentanil achieves rapid equilibration across the blood-brain barrier compared with other more hydrophilic and less potent opioids, such as hydromorphone, meperidine, and morphine (plasma:CNS equilibration half-life for IV sufentanil = 6.2 minutes compared to 2.8 hours for morphine; Lötsch 2001; Meuldermans 1982; Scott 1991; van den Hoogen 1987). Additionally, studies of comparative context-sensitive half-times (time from C_{max} at end of infusion to 50% of C_{max}) among opioids demonstrate that the exponential rise in context-sensitive half-time observed with prolonged IV fentanyl infusion does not occur with IV sufentanil infusion (Hughes 1992), suggesting a predictable and consistent offset of effect regardless of the duration of sufentanil exposure.

Sublingual delivery of sufentanil results in a slight delay in and prolongation of drug absorption compared to IV administration, thereby providing a more consistent plasma concentration over time than IV delivery and mitigating the short duration of analgesia plaguing the IV lipophilic opioids. Analgesia duration afforded by sublingual delivery more appropriately fits the needs of the target patient population and frees up the healthcare professional from having to frequently redose.

2.3 DSUVIA - Indications for Use and Dosing

AcelRx Pharmaceuticals, Inc. (AcelRx) is seeking approval for DSUVIA™ (sufentanil) sublingual tablet, 30 mcg for the proposed indication of 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. DSUVIA is not intended for home use or for use in children.

This indication is similar to the indication for other approved immediate-release opioids, and further includes the restriction of a medically supervised setting to mitigate the possibility of dosing errors, misuse, and diversion.

DSUVIA is to be administered sublingually to the patient only by a healthcare professional in a medically supervised setting on an as needed basis, per patient request, with a minimum of one hour between doses. The maximum cumulative daily dose proposed is 360 mcg or 12 tablets per 24-hour period, based on clinical utilization in the DSUVIA clinical trials.

2.4 Medically Supervised Setting

Distribution of DSUVIA will be limited to only REMS-certified medical institutions/healthcare facilities.

A medically supervised setting is defined in the proposed REMS as having components to control DSUVIA access, administration, and patient management. Specifically, the following are required:

- The healthcare facility or service offers management of moderate-to-severe acute pain in adult patients.
- The healthcare facility has a licensed pharmacy or healthcare provider with DEA registration for CII drugs who will manage DSUVIA acquisition and administration.
- The healthcare facility has access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone.
- The healthcare facility has recent experience administering IV opioids with documented ordering of IV opioids in the past 12 months.
- In order to become REMS-certified and be able to receive DSUVIA, an Authorized Representative from each healthcare facility will attest to understanding the risks of DSUVIA as identified in the DSUVIA REMS Safety Brochure and the DSUVIA Prescribing Information, including the Directions for Use; that training on the DSUVIA REMS, including the Directions for Use, will be made available, according to their institutional practices, to all staff involved in dispensing or administering DSUVIA; and that the healthcare facility or service has processes and procedures in place to ensure DSUVIA is not dispensed for use outside of the certified healthcare facility.

Settings which would potentially qualify to become REMS-certified include hospitals, same-day surgery centers, and procedural clinics treating acute moderate-to-severe pain. Importantly, these sites will only qualify for REMS certification if they are currently using IV opioid analgesics.

2.5 DSUVIA Product Overview

DSUVIA consists of a single 30 mcg sufentanil tablet housed in a single-dose applicator, which is used by the healthcare professional to dispense the tablet sublingually to the patient (Figure 1). Each tablet and single-dose applicator is individually packaged in a tamper-evident pouch with attached Directions for Use.

DSUVIA Sufentanil Sublingual Tablet

DSUVIA provides sufentanil, an established opioid, in a tablet formulated for sublingual delivery at a dose that is approximately equivalent to 5 mg IV morphine (or 10 mg oral oxycodone). This new dosage form of sufentanil has attributes suited for acute pain management, including:

- high lipophilicity, potency and transmucosal bioavailability (53-59%; Section 3.2, SAP101 and IAP102);
- tablet formulated with bioadhesive to minimize displacement once tablet is delivered to the sublingual space;
- small 3-mm diameter tablet size to limit dosing discomfort with repeated administration, while still being detectable;
- small tablet size to allow the tablet to dissolve under the tongue within 10 minutes and to avoid triggering the production of saliva, which would lead to inadvertent oral intake of solubilized sufentanil;
- minimal oral (swallowed) bioavailability (< 10%; Section 3.2, IAP102) that reduces delayed gastric absorption and the resultant erratic PK;
- rapid effect site occupancy due to a 6-minute plasma:CNS equilibration half-life allowing sufentanil to have a rapid effect once absorbed (Lötsch 2001; Meuldermans 1982; Scott 1991; van den Hoogen 1987);
- sufficient duration of action after sublingual transmucosal absorption, allowing less frequent redosing than may be needed following IV delivery;
- no active metabolites (Mather 1983), reducing risk of delayed side effects, particularly in elderly patients or those with hepatic or renal impairment; and
- a high therapeutic index in animal models and good cardiac stability.

As a single-strength, single-dose product, DSUVIA avoids medication errors and the need to document drug residual wastage, which is common with injectable opioids. The risks of misuse, abuse, and diversion are mitigated by the single tablet availability in each DSUVIA package, a restricted distribution only to REMS-certified healthcare facilities, and no retail pharmacy distribution.

Situations where DSUVIA may be particularly useful include:

- Medical situations when availability of IV access may be limited, such as patients presenting with trauma or injury to an ER.
- Patients with difficult to access veins, such as in obese, elderly, burn, and needle-phobic patients.
- Patients with dysphagia who are unable to take oral pain medication.
- Ambulatory surgery centers where the PK profile of DSUVIA may provide efficiencies in care of patients with moderate-to-severe pain following surgery.

Single-Dose Applicator and Packaging

The single-dose applicator and unit packaging (Figure 1) were designed to mitigate the possibility of dosing errors, misuse, and diversion in the medically supervised setting. Each single-dose applicator is prefilled with a single DSUVIA tablet and is sealed in a tamper-evident pouch. Additional safety features include a mechanical lock, transparent housing to allow viewing of tablet, and non-retractable plunger. Illustrated Directions for Use (Appendix 9.1) are attached to each unit package for ease of reference during dosing. Images of the DSUVIA pouch, single-dose applicator, and tablet are shown to scale in Appendix 9.2.

To administer the tablet, the healthcare professional first removes the white, mechanical lock from the single-dose applicator, which prevents accidental tablet dispensing during shipping and handling before dosing. Then, the healthcare professional places the tip of the applicator under the patient's tongue and gently presses the plunger to dispense the tablet out of the distal end of the single-dose applicator into the sublingual space. The empty single-dose applicator can then be discarded into waste.

2.6 Development and Regulatory History

Sufentanil citrate injection has been safely used for over 30 years, primarily as an IV anesthetic agent at high doses (up to 30 mcg/kg), as an IV analgesic component of general anesthesia (up to 8 mcg/kg), and as an epidural analgesic for labor and delivery (up to 3 doses of 15 mcg hourly).

A sublingual form of sufentanil was developed by AcelRx as a drug candidate with the intent to achieve rapid analgesia while avoiding invasive routes of administration and to minimize opioid dosing errors. Sublingual delivery is a well-known and well-tolerated route that can also be used in patients who are NPO. As few opioid agonists have the appropriate physicochemical properties for effective sublingual drug delivery, sufentanil was an ideal candidate, owing to its high lipophilicity which allows for rapid mucosal absorption.

The development of DSUVIA grew out of collaborations with the Department of Defense and the development of another sufentanil product, Zalviso (sufentanil sublingual tablet system) 15 mcg. Throughout the course of product development, AcelRx consulted with the FDA regarding the clinical pharmacology, efficacy, and safety requirements for approval of DSUVIA 30 mcg. The Agency agreed to the inclusion of 323 patients from the Zalviso clinical studies in

the DSUVIA clinical safety dataset. Consultations with the FDA Division of Anesthesia, Analgesia, and Addiction Products have included an End-of-Phase 2 (EOP2) meeting (18 December 2013), a Pre-New Drug Application (NDA) meeting (09 December 2015), and a Type A meeting following receipt of the complete response letter (CRL; 26 January 2018). At the post-CRL Type A meeting, AcelRx discussed reducing the daily maximum dosing of DSUVIA to 12 tablets from 24 tablets and revisions to the Directions for Use as recommended by the FDA. The FDA subsequently reviewed the human factors validation protocol. This study was designed to evaluate healthcare professional overall usability of DSUVIA, including the ability to confirm proper tablet placement and to evaluate the revised Directions for Use.

DSUVIA, known as DZUVEO in the EU, was recently approved by the European Commission for the management of acute moderate-to-severe pain in adults in medically monitored settings.

Zalviso Development

Zalviso, AcelRx's first sublingual sufentanil product, was approved in the EU in September 2015 and has been commercially distributed since April 2016 by AcelRx's commercial partner, Grunenthal GmbH. It is a combination drug-device sublingual tablet system created to allow patients to control their analgesia in a hospital setting (Figure 3). The Zalviso 15 mcg tablet is identical to the DSUVIA tablet except for dosage strength and color. The electronic dispensing device allows up to three 15 mcg sufentanil tablets to be administered by the patient per hour from a 40-count drug cartridge, using a factory pre-programmed 20-minute lockout between doses. The drug cartridge is locked into the device and can only be accessed by a healthcare professional with an access card. This system can be used for up to three days to manage moderate-to-severe postoperative pain.

The Zalviso NDA (NDA 205265) was submitted to the FDA in September 2013. The Agency issued a complete response letter, requesting a comprehensive use-related risk analysis and human factors validation testing as well as additional clinical evaluation. These studies have been completed and the resubmission of the Zalviso NDA is planned for the end of 2018. Zalviso has been used in approximately 1000 patients in US clinical trials and in more than 26,000 patients commercially in the EU.

Figure 3: DSUVIA versus Zalviso

- DSUVIA 30 mcg
  - Single-dose
  - Healthcare professional-administered as needed, no more than hourly
  - Maximum of 12 doses in 24 hours
  - Medically supervised setting

- Zalviso 15 mcg
  - 2 - 3 day supply
  - Patient-administered as needed
  - 20-minute lockout
  - Hospital setting

DSUVIA NDA Submission and Complete Response Letter

AcelRx submitted an NDA in December 2016 to seek approval for DSUVIA 30 mcg under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, whereby the approval of a drug with a new dosage form, route of administration, indication, etc. relies on literature or on an Agency finding of safety and/or effectiveness for an approved drug product, known as the "reference" product. Sufenta® (sufentanil citrate injection), which was approved in the US in 1984 (NDA 019050) for intravenous analgesia and anesthesia, is the reference product for DSUVIA.

A complete response letter was issued in 2017 citing two primary issues:

- The lack of sufficient safety data to support the initially proposed maximum available dose of 24 tablets (720 mcg) in a 24-hour period.
- Inadequate mitigation of the risk of dropped tablets.

In May 2018, AcelRx submitted an NDA resubmission to address the issues in the DSUVIA complete response letter; the NDA resubmission contained the following:

- The proposed maximum daily dose was reduced to 12 tablets (360 mcg) in a 24-hour period in order to be consistent with maximum dosing observed in DSUVIA clinical studies. A new analysis of safety data from a total of 206 DSUVIA and Zalviso patients who were dosed 300 mcg/day or greater, up to 825 mcg/day, was provided to support this proposed daily dosing limit. The safety by high/low dosing analysis was based on all DSUVIA and Zalviso patients who were exposed to sublingual sufentanil for at least 24 hours; these patients were a subset of the patients included in the original DSUVIA NDA. Additionally, a safety analysis was submitted based on high/low sufentanil peak plasma concentrations obtained from sparse PK sampling in the clinical studies.
- The DSUVIA labels and user instructions (Directions for Use) were updated to include changes that were proposed by the Agency in the complete response letter and to include additional instructional changes to mitigate the risk of dropped tablets. The changes include increasing the emphasis in the Direction for Use on visually confirming tablet placement after administration and physically attaching the Direction for Use to each DSUVIA unit package (pouch). The results of a human factors study, which validated the effectiveness of these changes, were also provided. Importantly, there were no dropped or misdosed DSUVIA tablets during this human factors study.

2.7 Clinical Program Overview

The DSUVIA 30 mcg clinical development program consists of the following studies:

- One Phase 1 single-dose and multiple-dose PK study that established the bioequivalence of DSUVIA 30 mcg to two doses of Zalviso 15 mcg administered 20 minutes apart and that compared the PK of DSUVIA 30 mcg to IV Sufenta® (sufentanil citrate injection) 30 mg (SAP101);

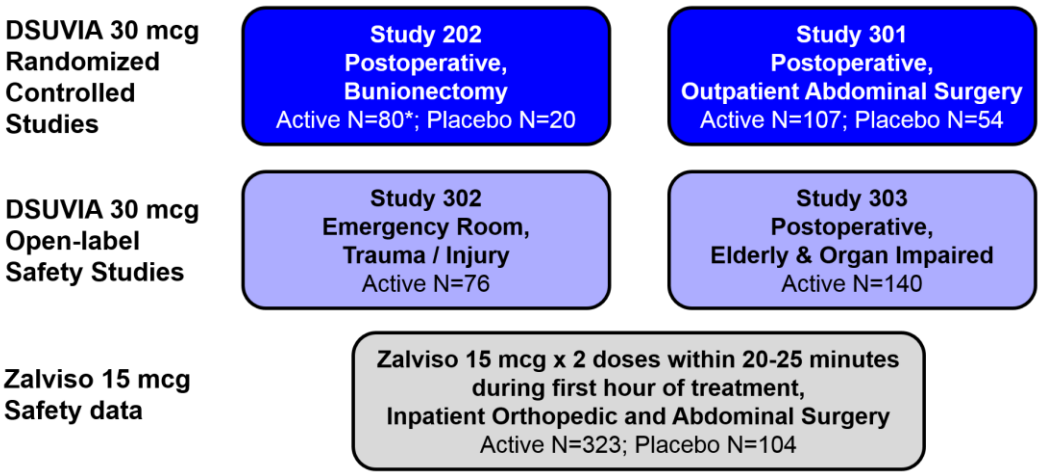
- One Phase 2 placebo-controlled, dose-ranging study of DSUVIA 20 mcg and 30 mcg (Study 202);
- Three Phase 3 studies of DSUVIA 30 mcg, including:
  - One placebo-controlled study (Study 301), and
  - Two open-label studies (Study 302 and Study 303).

The Phase 2 and Phase 3 placebo-controlled studies, as well as two open-label studies, provide the primary evidence of safety and efficacy of DSUVIA 30 mcg for the proposed indication (Figure 4; Table 24). These studies are complimentary to the nonclinical safety and PK studies used to bridge to the established safety and efficacy profile of Sufenta®, the reference product for DSUVIA. The two Phase 3 open-label DSUVIA studies provide supportive evidence of efficacy and safety for DSUVIA 30 mcg.

During pre-NDA discussions between AcelRx and the FDA, the Agency agreed that a cohort of patients from the Zalviso clinical development program could be included in the DSUVIA safety database based on the demonstrated bioequivalence of two doses of Zalviso 15 mcg tablets given 20-25 minutes apart to a single DSUVIA 30 mcg tablet. Importantly, these Zalviso patients were exposed to active drug treatment for up to 72 hours and often received higher doses of sublingual sufentanil per hour (45 mcg/hr) than proposed labelling will allow for DSUVIA (30 mcg/hr).

Thus, safety data from three Phase 2 studies (001, 004 and 005) and three Phase 3 studies (309, 310 and 311) conducted with Zalviso 15 mcg (Table 25), as well as EU post-marketing safety experience obtained from Zalviso 15 mcg, provide additional evidence of safety for DSUVIA 30 mcg.

Figure 4: Summary of Clinical Studies Supporting the Efficacy and Safety of DSUVIA



*Study 202 includes 40 patients exposed to DSVUIA 20 mcg and 40 patients exposed to DSVUIA 30 mcg
See Table 24 and Table 25 for a summary of key study design parameters.

In addition to the PK study conducted with DSUVIA, Zalviso, and Sufenta® (SAP101), supportive clinical pharmacology data are provided by two Phase 1 PK studies conducted with Zalviso 15 mcg (IAP102 and IAP104).

3 NONCLINICAL AND CLINICAL PHARMACOLOGY

Summary

- As a 505(b)(2) NDA supporting DSUVIA as a lower dosage strength sufentanil product with a new route of administration, most of the nonclinical safety support in the DSUVIA NDA relies on nonclinical safety studies conducted in support of Sufenta® IV injection. AcelRx conducted a 28-day local toxicity study which demonstrated no significant adverse effects at the sublingual administration site of the DSUVIA tablet.
- The DSUVIA tablet is composed of common oral excipients that are on the FDA's list of ingredients Generally Recognized as Safe (GRAS).
- Compared to a single bolus dose of IV sufentanil, DSUVIA had a lower C_{max} (15-fold) and a longer duration of time from C_{max} to 50% of C_{max}, providing a more consistent plasma concentration without the peaks and troughs of IV delivery.
- Sublingual administration of sufentanil resulted in a bioavailability of 53-59%, whereas oral (swallowed) bioavailability was less than 10%.
- Bioequivalence between a single dose of DSUVIA and two 15 mcg Zalviso tablets dosed within 20 minutes of each other was established justifying inclusion of select Zalviso patients in the DSUVIA safety database.
- Population PK analysis demonstrated a slight increase in sufentanil plasma clearance with increasing weight, a slight decrease in clearance with increasing age, and no effect on clearance due to hepatic or renal impairment.

3.1 Toxicology

All excipients in the DSUVIA tablet are Generally Recognized as Safe (GRAS) by the FDA. The maximum daily exposure to each of the excipients, based on 12 DSUVIA tablets, is within established safe limits based on oral or buccal use in the FDA's Inactive Ingredient Database. Nonclinical bridging toxicology studies of sufentanil sublingual tablets identified no new systemic or local tissue (oral mucosa) adverse effects associated with administration via the oral mucosa route, thus supporting the safety of sufentanil administered sublingually.

3.2 Clinical Pharmacology

The PK profile for DSUVIA was established in three Phase 1 studies. SAP101 was conducted with DSUVIA 30 mcg and Zalviso 15 mcg, while IAP102 and IAP104 were conducted with Zalviso 15 mcg (Table 1). Each study was a single-center, randomized, open-label, crossover study in naltrexone-blocked healthy male and female adult volunteers. PK studies examined single versus multiple doses, routes of administration, and PK drug interactions. Additionally, results established bioequivalence of a single DSUVIA 30 mcg tablet to two Zalviso 15 mcg tablets dosed within 20 minutes of each other (with additional PK modeling supporting

bioequivalence with up to 25 minutes between doses), enabling inclusion of safety data from Zalviso-treated patients per discussions with the Agency.

Table 1: Phase 1 Pharmacokinetic and Bioavailability Studies

Study	Objective(s)
SAP101	Single and multiple-dose PK of sublingual administration of DSUVIA 30 mcg and comparison to two Zalviso 15 mcg doses and Sufenta® (sufentanil citrate) 30 mcg, IV
IAP102	Single-dose Zalviso 15 mcg, PK of different routes of administration: sublingual, buccal, and oral compared to Sufenta® 15 mcg, IV
IAP104	PK of Zalviso 15 mcg when administered with ketoconazole 400 mg

IV = Intravenous; PK = Pharmacokinetics

Metabolism

Metabolism of sufentanil primarily occurs in the liver and small intestine via the CYP3A4 enzymatic pathway (Akorn, Inc. 2016).

SAP101

In SAP101, the PK of single- or multiple-dose DSUVIA 30 mcg was evaluated and compared to that of Sufenta® IV 30 mcg infused over one minute and two doses of Zalviso 15 mcg administered 20 minutes apart (DSUVIA and Zalviso were administered sublingually). This was a single-center, randomized, open-label, two-sequence, four-treatment, four-period, crossover study in healthy adults. Treatment periods were separated by a 48-hour washout period. Individuals received concomitant doses of 50 mg naltrexone orally to block the opioid effects of sufentanil at pre-specified times pre-dose and post-dose for each treatment. The total duration of the study for each participant (including the 28-day screening period) was approximately 38 days. Participants recruited were healthy, nonsmoking male and female adults, 18 to 45 years of age, with a BMI between 18 and 30 kg/m^2.

Results are summarized in Table 2 and Figure 5. Compared to a single IV bolus dose of sufentanil, DSUVIA had a lower C_{max}, a later time to maximum plasma concentration (T_{max}), and a more consistent plasma concentration without the peaks and troughs of IV delivery.

The median minimally effective plasma concentration of sufentanil used as an analgesic in postoperative patients has previously been reported as 24 pg/mL, with patients titrating to a mean plasma concentration of 86 pg/mL (Lehmann 1991). Following a single dose of DSUVIA, the plasma concentrations of sufentanil reached 24 pg/mL in approximately 15 minutes and remained above this analgesic threshold for approximately 3 hours.

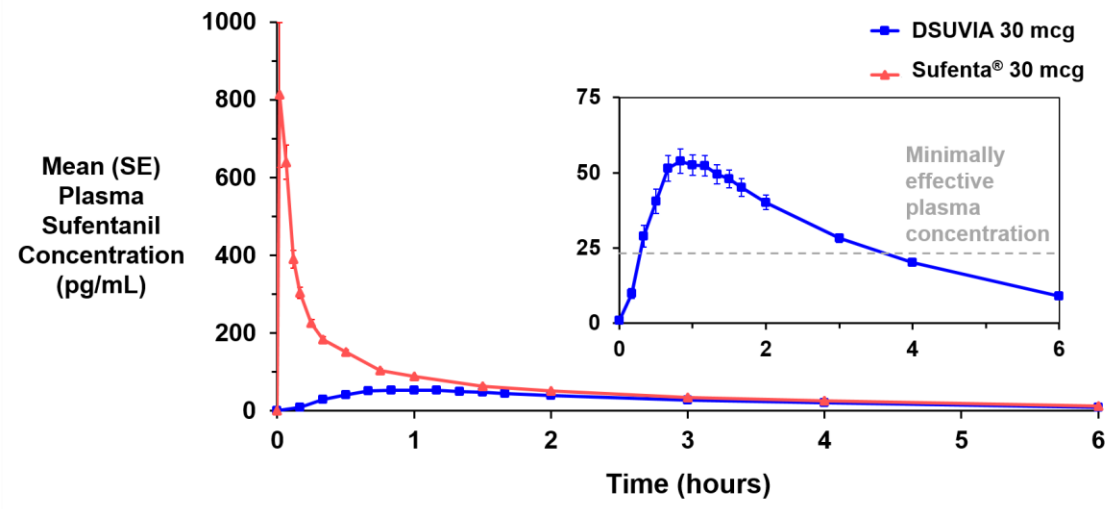
Table 2: Pharmacokinetic Results for DSUVIA 30 mcg and Sufenta® IV 30 mcg – SAP101

PK Parameter	DSUVIA 30 mcg N=35	Sufenta® IV 30 mcg N=35
Mean C_{max} (pg/mL) (standard deviation)	63.1 (23.5)	1073.9 (968.2)
Median T_{max} (hour) (min, max)	1.00 (0.50, 2.00)	0.07 (0.02, 0.17)
Median time from C_{max} to 50% of C_{max} (hour) (min, max)	2.3 (0.83, 4.83)	0.1 (0.03, 0.72)

C_{max} = Maximum plasma concentration; T_{max} = Time to maximum plasma concentration

One measure that represents the duration of analgesia is the time from C_{max} to 50% of C_{max}. Sublingual delivery of DSUVIA allows for drug uptake to occur over time, resulting in a median time from C_{max} to 50% of C_{max} of 2.3 hours, a more appropriate duration compared to IV administration, which had a median time of 6 minutes. Additionally, the sublingual administration of DSUVIA 30 mcg provides approximately a 15-fold decrease in C_{max} compared to the same dose of sufentanil administered IV.

Figure 5: Pharmacokinetic Comparison of DSUVIA 30 mcg and Sufenta® 30 mcg (sufentanil citrate injection)



SE = Standard error

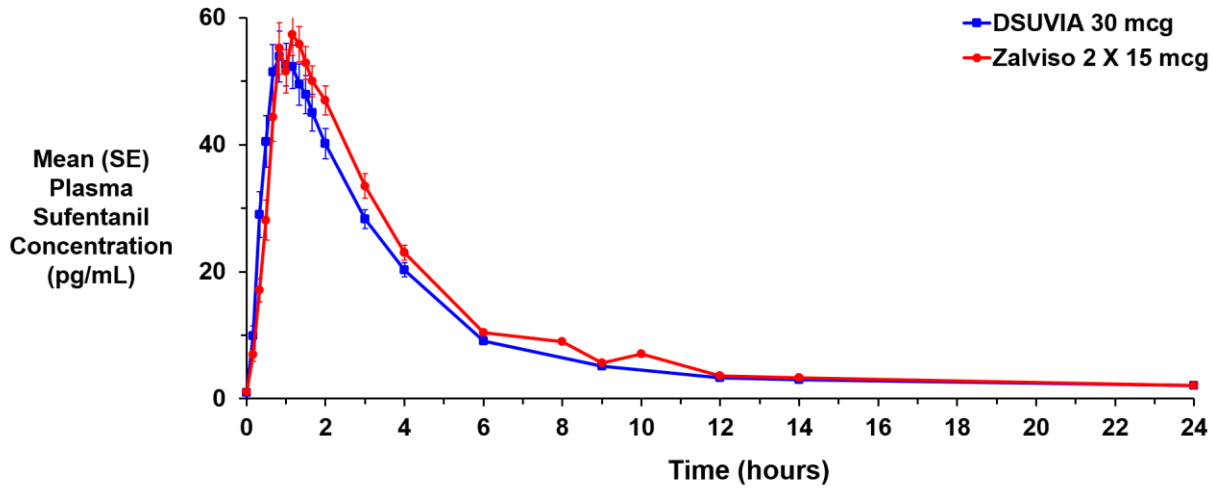
In support of the inclusion of select Zalviso patients in the safety database, DSUVIA 30 mcg and two doses of Zalviso 15 mcg met the criteria for bioequivalence for both C_{max} and $AUC_{0\text{-}inf}$ (the 90% confidence interval [CI] of the ratio of the log-transformed parameter falls within the range of 80% - 125%; Table 3 and Figure 6).

Table 3: Pharmacokinetic Results After Single-Dose DSUVIA 30 mcg and Zalviso 2x15 mcg Dosed 20 Minutes Apart – SAP101

PK Parameter	Statistic	DSUVIA vs Zalviso
C_{max}	**Ratio of LS Geometric Mean (90% CI)**	0.93 (0.84, 1.03)
$AUC_{0\text{-}inf}$	**Ratio of LS Geometric Mean (90% CI)**	0.89 (0.81, 0.97)

$AUC_{0\text{-}inf}$ = Area under the concentration curve extrapolated to infinity; CI = Confidence interval; C_{max} = Maximum plasma concentration; LS = Least Squares

Figure 6: PK Profile After Single-Dose of DSUVIA 30 mcg and Zalviso 2x15 mcg Dosed 20 Minutes Apart – SAP101



SE = Standard error

Systemic bioavailability was approximately the same after administration of single-dose DSUVIA 30 mcg or two doses of Zalviso 15 mcg. Mean bioavailability was approximately 53% after single-dose DSUVIA 30 mcg and 59% after two doses of Zalviso 15 mcg. Median T_{max} was 1.00 hours after administration of single-dose DSUVIA 30 mcg and 1.17 hours after administration of two doses of Zalviso 15 mcg ($p < 0.001$). Median elimination half-life was 14.22 hours after administration of single-dose DSUVIA 30 mcg and 13.66 hours after administration of two doses of Zalviso 15 mcg, and median time from C_{max} to 50% of C_{max} was 2.33 hours for both.

Sufentanil concentrations were measured following multiple dosing, where DSUVIA 30 mcg was administered hourly for 12 hours. This dosing regimen provides plasma concentration data to support the proposed maximum daily dose of DSUVIA within a 24-hour period. Compared to the first dose, after the last of 12 consecutive doses of DSUVIA 30 mcg, $AUC_{0\text{-}60}$ and C_{max} increased by 3.7-fold and 2.3-fold, respectively (Table 4). These increases were statistically

significant ($p < 0.001$). Importantly, the time from C_{max} to 50% of C_{max} was consistent following a single dose of DSUVIA and following the twelfth dose, demonstrating a predictable duration of action with repeat dosing. Upon multiple dosing of DSUVIA 30 mcg, steady-state was achieved after seven doses (or six hours) based on pre-dose plasma concentrations.

Table 4: Pharmacokinetic Results After Single vs Multiple Doses of DSUVIA 30 mcg – SAP101

PK Parameter	Single-Dose DSUVIA 30 mcg N=32	Multiple-Dose DSUVIA 30 mcg N=32	Last Dose[a] DSUVIA 30 mcg N=32
Mean C_{max} (pg/mL) (standard deviation)	60.6 (22.7)	150.8 (36.4)	134.1 (39.5)
Mean $AUC_{0\text{-}inf}$ (h*pg/mL) (standard deviation)	269.8 (79.5)	168.6 (44.4)[b]	-
Mean $AUC_{0\text{-}60}$ (h*pg/mL) (standard deviation)	33.7 (16.2)	-	118.3 (34.5)
Median time from C_{max} to 50% of C_{max} (hour) (min, max)	2.3 (0.8, 4.8)	-	2.3 (1.7, 5.7)

$AUC_{0\text{-}60}$ = Area under the concentration curve through 60 hours; $AUC_{0\text{-}inf}$ = Area under the concentration curve extrapolated to infinity; CI = Confidence interval; C_{max} = Maximum plasma concentration; LS = Least Squares PK = Pharmacokinetic
a. Following last of 12 consecutive doses administered hourly over 12 hours.
b. Normalized to a single dose of DSUVIA 30 mcg.

IAP102

IAP102 was a single-center, randomized, open-label, six-sequence, four-treatment, four-period, crossover study in naltrexone-blocked participants. In IAP102, single-dose administration of Zalviso 15 mcg via the sublingual, buccal, and oral (swallowed) routes was compared with IV sufentanil 15 mcg.

Sublingual, buccal, and swallowed routes of administration resulted in significantly lower C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ values, and later T_{max} compared with IV sufentanil. Additionally, median times from C_{max} to 50% C_{max} for sublingual, buccal, and swallowed sufentanil were 2.50, 2.28, and 2.00 hours, respectively, all of which were significantly longer than that observed for IV sufentanil (8 minutes).

Relative to IV administration, the bioavailability of sublingual, buccal, and swallowed sufentanil treatments was 59%, 78%, and 9%, respectively, demonstrating that systemic uptake of a swallowed tablet is minimal compared to absorption via the sublingual route.

IAP104

As sufentanil is metabolized by CYP3A4, Study IAP104 was conducted to examine the effects of ketoconazole, a potent CYP3A4 inhibitor, on the PK profile of Zalviso 15 mcg. This single-

center, open-label study in 19 naltrexone-blocked healthy, nonsmoking adults (18 to 45 years of age) assessed PK following administration of Zalviso 15 mcg alone (Day 1), oral ketoconazole 400 mg (Days 2 and 3), and Zalviso approximately one hour before ketoconazole on Day 4. Dosing of ketoconazole was based on recommendations by the FDA.

Co-administration of Zalviso 15 mcg and oral ketoconazole 400 mg resulted in higher C_{max} (19% increase; $p = 0.047$), $AUC_{0\text{-}last}$ (60% increase; $p < 0.001$), and $AUC_{0\text{-}inf}$ values (77% increase; $p < 0.001$) for plasma sufentanil compared with the corresponding values for Zalviso 15 mcg administered alone. Therefore, the effect on peak plasma concentrations were minimal, and while the differences in AUC were larger, they are unlikely to be clinically meaningful given the "as-needed" dosing schedule.

The median sufentanil elimination $t_{½}$ was statistically significantly longer when co-administered with ketoconazole (3.8 hours vs 13.6 hours), while median time from C_{max} to 50% C_{max} was similar when sufentanil was administered alone (2.2 hours) or with ketoconazole (2.5 hours).

In addition to the assessments in IAP104, AcelRx conducted a review of the published literature, Sufenta® labeling, and opioid IR class labeling (FDA 2016) to determine relevant potential drug-drug interactions. Warnings and precautions for drug-drug interactions with CYP3A4 inhibitors, CYP3A4 inducers, CNS depressants, and serotonergic drugs have been included in the proposed labeling for DSUVIA 30 mcg.

Pharmacokinetics in DSUVIA and Zalviso Phase 2/3 Studies

Sparse PK samples were collected in three DSUVIA safety and efficacy studies (Studies 202, 301, and 303) as well as three Zalviso safety and efficacy studies (Studies 309, 310, and 311). The mean peak sufentanil plasma concentrations were in the range of 44–51 pg/mL in the DSUVIA clinical studies and 71–101 pg/mL in the Zalviso studies. The higher exposure in the Zalviso trials is likely due to the higher dosing (45 mcg/hour) allowed with this product and the enrollment of patients undergoing only major surgeries, possibly resulting in a higher opioid requirement.

3.3 Pharmacokinetics in Subgroups

The population PK analysis was based on data from healthy volunteers and patients who were dosed with sublingual sufentanil (either DSUVIA or Zalviso; Fisher 2018). This included all 1,066 individuals who had at least one sufentanil plasma concentration measured from all Phase 1-3 studies of DSUVIA and Zalviso, specifically: SAP101, Study 202, Study 301, Study 303, IAP101, IAP102, IAP104, Study 001, Study 309, Study 310, and Study 311.

Based on the best-fit model from this analysis, the typical DSUVIA-dosed individual in the clinical trials, a 47-year old individual weighing 78.5 kg, would have a sufentanil clearance of 84.2 L/hour following a single dose of DSUVIA. As expected, clearance decreased with age (~1.6% per year, referenced to age 56 years) and increased with weight (~0.5% per kg, referenced to 80 kg). Since DSUVIA is to be administered on an “as needed” basis, these differences in apparent clearance would potentially affect dosing intervals in the clinical setting –

patients who weigh less or are older will possibly request doses less frequently compared to patients who weigh more or who are younger. Bioavailability was 18% lower and absorption rate was 30% slower in patients compared to healthy volunteers.

The analysis of sufentanil plasma concentrations within this population PK analysis from 158 hepatic-impaired individuals and 73 renal-impaired individuals in the clinical pharmacology program showed that mild to moderate hepatic or renal impairment had no effect on clearance. The labeling for Sufenta® notes that it should be administered with caution in patients with liver or kidney dysfunction due to the importance of these organs in the metabolism and excretion of sufentanil (Akorn, Inc. 2016). A similar caution has been proposed in DSUVIA labeling.

4 EFFICACY

Summary

- Evidence of DSUVIA efficacy is provided by two pivotal, randomized, placebo-controlled studies (Study 202 and Study 301) in postoperative patient populations with moderate-to-severe musculoskeletal pain (bunionectomy) and visceral pain (abdominal surgery).
- The primary efficacy endpoint measure in both pivotal trials was pain reduction based on time-weighted summed pain intensity difference from baseline over 12 hours (SPID12), a commonly used, cumulative measure of pain control in comparative clinical trials.
- In both pivotal studies, DSUVIA provided statistically significant reductions in patients' moderate-to-severe acute pain as demonstrated by the primary efficacy endpoint of time-weighted SPID12, with mean differences from placebo of 12.65 (Study 202 [bunionectomy]) and 12.70 (Study 301 [abdominal surgery]; both $p < 0.01$).
- Subgroup analyses (based on age, sex, race, BMI, and surgery type) showed consistent efficacy benefits from DSUVIA.
- Primary efficacy results were supported by pre-specified secondary pain measurements, with statistically and clinically significant differences favoring DSUVIA.
- DSUVIA demonstrated rapid pain control within 15 minutes (the first assessment time point) to 30 minutes and was superior to placebo.
- Time to first rescue opioid medication was markedly longer for patients in the DSUVIA group compared with placebo.
- DSUVIA patients used fewer doses of rescue opioid medication than those in the placebo group, with differences of 30% or greater between DSUVIA and placebo in the two pivotal studies (both $p < 0.01$).
- The average DSUVIA redosing time for patients in the two pivotal studies was 2.4 to 3 hours. On average, patients took 7 tablets over 24 hours (Study 301).
- Supportive evidence of efficacy on pain intensity and pain relief comes from two open-label, single-arm studies (Study 302 and Study 303); DSUVIA demonstrated a rapid, sustained, clinically and statistically significant improvement in pain intensity and pain relief from baseline in patients with trauma/injury as well as an older postoperative patient population.

4.1 Clinical Study Design

AcelRx conducted two placebo-controlled safety and efficacy studies in a total of 261 patients:

- Study 202 was a Phase 2 multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. In this study, patients who underwent bunionectomy with or without hammertoe repair received DSUVIA 30 mcg (n=40), DSUVIA 20 mcg (n=40), or placebo (n=20) over a 12-hour study period.
- Study 301 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled study. In this study, patients who underwent abdominal surgery received DSUVIA 30 mcg (n=107) or placebo (n=54) over a 48-hour study period.

Additionally, AcelRx conducted two open-label single-arm studies to provide safety and efficacy data on an additional 216 patients. Both were multicenter, open-label, single-arm studies. Study 303 included 140 abdominal and other postsurgical outpatients who were 40 years of age or older while Study 302 evaluated 76 acute trauma/injury patients in an ER setting.

Table 5 and Table 6 provide a summary of the design of the pivotal and open-label studies. All studies utilized a similar design, with only the specific patient population and dosing duration differing among the studies. The pivotal, randomized, placebo-controlled studies examined patients with acute musculoskeletal (Study 202 [bunionectomy]) and soft-tissue/visceral pain (Study 301 [abdominal surgery]) while the open-label studies included patients with moderate-to-severe acute pain due to injury or trauma in an ER setting (Study 302) or postsurgical patients 40 years of age or older (Study 303). Short-term studies, ranging from 5 to 48 hours, were conducted to reflect the likely settings of use for DSUVIA in a medically supervised setting.

Table 5: Pivotal Clinical Studies

Study	N	Design	Treatment Groups	Patient Population	Duration
202	100	Multicenter, randomized placebo-controlled	Placebo DSUVIA 20 mcg DSUVIA 30 mcg	Postoperative bunionectomy	Up to 12 hours
301	161	Multicenter, randomized placebo-controlled	Placebo DSUVIA 30 mcg	Postoperative outpatient abdominal surgery	Up to 48 hours

N = total patients in study (treatment and control)

Table 6: Open-Label Clinical Studies

Study	N	Design	Study Intervention	Patient Population	Duration
303	140	Multi-center, open-label	DSUVIA 30 mcg	Postoperative (abdominal/orthopedic/ other) Adults ≥ 40 years	Up to 12 hours
302	76	Multi-center, open-label	DSUVIA 30 mcg	Trauma/injury in ER	Up to 5 hours

ER = Emergency room

4.2 Study Drug, Concomitant Medication and Rescue Opioid Medication

In all four studies, repeat doses of study drug were administered as requested (prn) with a minimum inter-dosing interval of one hour.

All DSUVIA studies, with the exception of Study 303 (older postoperative), did not allow use of concomitant non-opioid analgesics. Use of concomitant non-opioid analgesics (eg, nonsteroidal anti-inflammatory drugs, acetaminophen, gabapentin) was permitted in Study 303.

For patients with inadequate analgesia, rescue opioid medication was permitted. Patients were encouraged to wait at least 60 minutes from first dose of study drug before use of rescue opioid medication across studies and to remain in the study even if rescue medication was used. If more than 60 minutes had elapsed since the last dose of study drug, another dose of study drug was administered rather than rescue opioid medication. The following rescue opioid medications were permitted:

- Study 301 (abdominal surgery): 1 mg IV morphine was permitted after at least ten minutes had elapsed since the last dose of study drug, and not more than once every 60 minutes.
- Study 202 (bunionectomy): Vicodin (5 mg hydrocodone/500 mg acetaminophen) was allowed after at least ten minutes had elapsed since the last dose of study drug, and not more than once every four hours.
- Study 302 (ER): 0.05 mg/kg IV morphine or 0.1 mg/kg oral oxycodone elixir was permitted after at least ten minutes had elapsed since the last dose of study drug.
- Study 303 (older postoperative): 1 mg IV morphine was permitted after at least ten minutes had elapsed since the last dose of study drug.

4.3 Inclusion/Exclusion Criteria

Key inclusion/exclusion criteria in the four studies included the following:

- ≥ 18 years of age (except for Study 303, where age was restricted to ≥ 40 years)
- ≤ 15 mg oral morphine per day

- Not dependent on supplemental oxygen as an outpatient
- No history of documented sleep apnea

Patients were required to have a baseline pain numerical rating score (NRS) ≥ 4 immediately prior to first dose of study drug.

4.4 Endpoint Selection – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

The primary efficacy endpoint in both placebo-controlled studies was the time-weighted summed pain intensity difference from baseline (SPID) over 12 hours (SPID12), a cumulative measurement of pain control over the course of 12 hours. This endpoint is a commonly used measure of pain control that facilitates comparisons between groups. Since DSUVIA was dosed as needed up to 12 times in a 12-hour interval, SPID12 evaluates multiple-dose efficacy.

Key secondary efficacy endpoints included pain intensity difference from baseline (PID), SPID at different time points (eg, 1, 12, 24, and 48 hours), pain relief as assessed by patients using the 5-point pain relief scale (0 = no relief, 1 = a little relief, 2 = moderate relief, 3 = a lot of relief, 4 = complete relief), time to perceptible and meaningful pain relief using the double-stopwatch method, use of rescue opioid medication due to inadequate analgesia, time to first use of rescue opioid medication, Patient Global Assessments, number of doses of study drug used, and duration of inter-dosing interval. The full list of secondary efficacy endpoints for Study 202 (bunionectomy) and Study 301 (abdominal surgery) are listed in Appendix 9.4. Secondary endpoints were not adjusted for multiple comparisons, so they are provided as supportive evidence of efficacy.

4.5 Statistical Considerations – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

4.5.1 Determination of Sample Size

For Study 202 (bunionectomy), a sample size of 100 evaluable patients (40 patients in each of the two DSUVIA treatment groups, and 20 patients in the placebo treatment group) was planned. The calculation of a sample size of 60 patients for treatment comparisons (ie, 40 patients in one DSUVIA treatment group and 20 patients in the placebo treatment group) was based on a two-sided two-sample t-test with a 2:1 sample size allocation ratio, an effect size of 0.8 for the primary efficacy endpoint, 80% power, and a significance level of $\alpha = 0.05$.

For Study 301 (abdominal surgery), a sample size of 159 evaluable patients (106 DSUVIA patients and 53 placebo patients) was planned. The calculation of this sample size was based on a two-sided two-sample t-test with a 2:1 sample size allocation ratio, an effect size of 0.55 for the primary efficacy endpoint, 90% power, and a significance level of $\alpha = 0.05$.

4.5.2 Randomization and Blinding of the Treatment Assignment

In Study 202 (bunionectomy), stratified randomization was applied with age (< 65 years and ≥ 65 years) as a stratification factor. Patients who met the eligibility requirements were randomly

assigned, in a 2:2:1 ratio, into one of three treatment groups (DSUVIA 20 mcg, DSUVIA 30 mcg, and placebo) within one of two age groups (< 65 years and ≥ 65 years) at each study center.

In Study 301 (abdominal surgery), stratified randomization was applied with sex as a stratification factor. Patients who met the eligibility requirements were randomly assigned, in a 2:1 ratio, into the DSUVIA 30 mcg treatment group or placebo treatment group within one of two groups (male or female) at each study center.

4.5.3 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint, time-weighted SPID12, was based on patient report of pain intensity as assessed using an 11-point NRS, where 0 was "no pain" and 10 was "worst possible pain." A higher SPID value signifies a larger reduction in pain intensity compared to a lower SPID value.

The patient's rating of pain intensity was measured at baseline (pre-dose) and at 0.25 (15 min), 0.5 (30 min), and 0.75 (45 min) hours, and every hour up to 12 hours following the first dose of study drug for both placebo-controlled studies. In addition, it was also measured every 2 hours until 24 hours and then every 4 hours until 48 hours following the first dose of study drug for the 48-hour study, Study 301 (abdominal surgery).

PID at each evaluation time point after the initiation of the first dose is the difference in pain intensity at the specific evaluation time point and baseline pain intensity [PID(evaluation time after the first dose) = Pain intensity(baseline) – Pain intensity(evaluation time after the first dose)]. The time-weighted SPID12 is the time-weighted summed PID over the 12-hour study period, calculated as:

$$\text{Time-weighted SPID12} = \sum [T(i) - T(i-1)] \times PID(i),$$

where: T(i) is the scheduled or unscheduled assessment time with T(0) = 0, and PID(i) is the PID score at time i, for i from 1 to n during the time period of 0 to 12 hours.

A parallel lines analysis of covariance (ANCOVA) model was used for the analysis of the primary efficacy endpoint. For Study 202 (bunionectomy), this ANCOVA model included treatment and center factors, and baseline pain intensity as a covariate. For Study 301 (abdominal surgery), this ANCOVA model included treatment, center, and sex factors, and baseline pain intensity as a covariate. The least squares mean and its 95% CI were presented for each treatment group and the difference between the DSUVIA and placebo treatment groups.

4.5.4 Analysis of Secondary Efficacy Endpoints

Time-weighted SPID at various time points was derived using similar formulae as described for the primary efficacy endpoint. In addition, patients' data from all study centers were pooled for the analysis of the categorical outcome data. For the analysis of ordinal categorical data, a Cochran-Mantel-Haenszel test of general association (stratified by sex factor for Study 301 [abdominal surgery] data) with modified ridit scores was used for the comparison between the

DSUVIA and placebo treatment groups. For the analysis of dichotomous outcome data, a 2-sample Z test for two proportions between the DSUVIA treatment group and placebo treatment group was performed. The difference between the two proportions (DSUVIA minus placebo) and its 95% CI are presented.

Survival analysis methods were used to analyze time to event data based on data pooled from all study centers. Kaplan-Meier product limit estimators of cumulative rates of patients reaching the event (ie, time to take first rescue opioid medication, time to perceptible pain relief, and time to meaningful pain relief) at follow-up time points were calculated. A log-rank test was used to compare the DSUVIA and placebo treatment groups.

4.5.5 Imputation and Handling of Dropouts

The main analysis of the primary and secondary efficacy endpoints was based on the ITT population. The ITT population included randomized patients who received study drug. For patients missing pain intensity data, the following methods were applied to impute the missing data at evaluation time points for the duration of the study period:

- For patients who missed a scheduled pain intensity assessment, the linear interpolation method was used to impute missing data between two observed pain scale values.
- For patients using rescue opioid medication, the last observed pain intensity score obtained prior to dosing of rescue medication was carried forward for four hours in Study 202 (bunionectomy) and one hour in Study 301 (abdominal surgery), in accordance with the type of rescue opioid allowed in these studies.
- For early dropouts, a modified version of Brown's method (Brown 1992), recommended by the FDA, was used to impute post-termination missing data. This method imputes the missing data by assigning an appropriate percentile value from the distribution of the placebo group for each time point, as follows:
    - The percentile is (100 + X)/2, where X is the percent of dropouts in the placebo group at the given time point.
    - The distribution of the placebo group at the given time point contains observed pain intensity values and the worst pain intensity values (maximum pain intensity value observed from baseline to termination) for patients who terminated prior to the time point.

The primary efficacy endpoint, time-weighted SPID12, was derived from the modified set of pain intensity data that contain imputed missing data.

4.5.6 Multiple Comparisons/Multiplicity

Study 202 (bunionectomy) included three treatment groups. To control for multiplicity from comparisons of multiple treatments, a hierarchical fixed sequence test procedure was used to perform treatment comparisons of the primary efficacy endpoint. The DSUVIA 30 mcg treatment group was first compared to the placebo group. If this comparison was statistically

significant at the 0.05 level, the comparison of DSUVIA 20 mcg versus placebo was performed, again at the 0.05 level of significance without the adjustment of the significant level for this test.

Study 301 (abdominal surgery) included only two treatment groups. There was one primary efficacy variable, time-weighted SPID12, for one between-treatment comparison for the ITT population in the study. Therefore, there were no multiple-comparison/multiplicity issues for the analysis of the primary efficacy variable.

No corrections of significant levels due to multiplicity were made for the analysis of any other endpoints in either study.

4.6 Planned Efficacy Analyses – Study 302 (ER) and Study 303 (Older Postoperative)

The primary efficacy endpoint for the open-label safety studies was the time-weighted summed pain intensity difference from baseline over the 1-hour study period (SPID1) for Study 302 (ER) and time-weighted SPID12 for Study 303 (older postoperative). In addition, pain relief over time was assessed by patients using the 5-point pain relief scale.

The efficacy data were summarized for all enrolled patients. Data collected from all study centers were pooled for the descriptive summary of efficacy data. For the analysis of the dichotomous outcome data, the proportion of each group and its 95% CI were presented.

4.7 Demographics and Characteristics – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

Demographic characteristics were well-balanced between the randomized groups in both pivotal studies (Table 7). There was a relatively similar percentage of females and males in Study 202 (bunionectomy) and more females than males in Study 301 (abdominal surgery); most patients in both studies were Caucasian and non-Hispanic/Latino.

Table 7: Patient Demographics and Characteristics – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

	Study 202 (Bunionectomy)			Study 301 (Abdominal Surgery)	
	DSUVIA 20 mcg N=40	DSUVIA 30 mcg N=40	Placebo N=20	DSUVIA 30 mcg N=107	Placebo N=54
Sex					
Female	48%	50%	50%	68%	67%
Age (years), mean (SD)	43 (13)	43 (13)	42 (14)	41 (11)	40 (12)
Race					
Caucasian	75%	65%	75%	71%	69%
African American	18%	30%	20%	20%	19%
Other	7%	5%	5%	9%	13%
Hispanic/Latino	20%	13%	20%	39%	35%
BMI (kg/m^2)					
< 30	63%	70%	65%	72%	65%
≥ 30	37%	30%	35%	28%	35%
ASA status					
ASA I	70%	70%	70%	62%	69%
ASA II	27%	30%	30%	36%	24%
ASA III	3%	0%	0%	2%	7%

ASA = American Society of Anesthesiologists; BMI = Body mass index; SD = Standard deviation

4.8 Patient Disposition – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

Of the 264 patients randomized in the two pivotal trials, 261 (98.9%) received study drug and were included in the analysis for efficacy (Table 8). The most common reason for termination was lack of efficacy, which occurred most frequently in the placebo group of Study 301 (abdominal surgery).

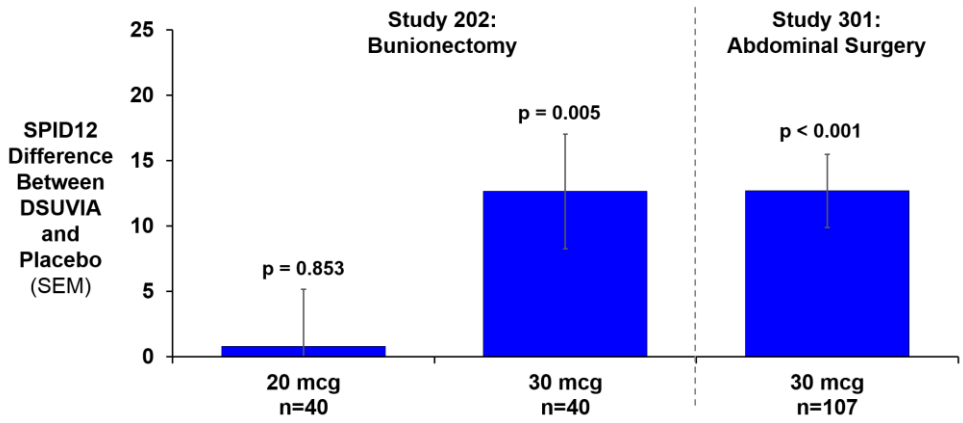
Table 8: Patient Disposition – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

	Study 202 (Bunionectomy)			Study 301 (Abdominal Surgery)	
	DSUVIA 20 mcg	DSUVIA 30 mcg	Placebo	DSUVIA 30 mcg	Placebo
Randomized	41	40	20	109	54
Received Study Drug	40	40	20	107	54
Terminated from Study Prematurely	2	3	1	4	10
Lack of efficacy	-	2	-	-	2
Adverse event	-	-	-	1	-
Patient withdrawal	-	-	-	-	1
Protocol violation	1	-	-	-	-
Other					
Analyzed for Efficacy	40	40	20	107	54

4.9 Primary Endpoint Results – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

There were clinically meaningful, statistically significant differences in the primary efficacy endpoint of SPID12 between the randomized DSUVIA 30 mcg and control groups in both Studies 202 (bunionectomy) and 301 (Abdominal Surgery; Figure 7), with a mean difference (95% CI) in SPID12 between DSUVIA and placebo of 12.65 (3.96, 21.33) and 12.70 (7.16, 18.23), respectively in Study 202 ($p = 0.005$) and Study 301 ($p < 0.001$). In contrast to the 30 mcg dose, the 20 mcg dose did not demonstrate a statistically significant difference in time-weighted SPID12 compared to placebo in the dose-ranging study, Study 202 (bunionectomy). These results indicate that DSUVIA 30 mcg is the minimum effective dose. The remainder of the results focus on the 30 mcg dose.

Figure 7: Primary Efficacy Endpoints in Pivotal Trials – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)



SEM = Standard error of the mean; SPID12 = Summed pain intensity difference from baseline over 12 hours
Least squares mean difference (DSUVIA minus Placebo)

In Study 202 (bunionectomy), the DSUVIA 30 mcg group mean baseline pain intensity was 6.48 and time-weighted SPID12 was 5.93, while the placebo group mean baseline pain intensity was 6.00 and time-weighted SPID12 was -6.72.

In Study 301 (abdominal surgery), the DSUVIA group mean baseline pain intensity was 5.61 and time-weighted SPID12 was 25.84, while the placebo group mean baseline pain intensity was 5.48 and time-weighted SPID12 was 13.14.

4.10 Sensitivity Analyses – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

In both placebo-controlled studies, a modified version of Brown's method, as described in Section 4.5.5, was used to impute the post-termination missing pain intensity data for dropouts prior to the 12-hour evaluation time point for the derivation of the primary efficacy endpoint. The amount of missing data which required imputation were as follows:

- Study 202 (bunionectomy): Among all 100 ITT patients, 92 (92%) patients completed the 12-hour study period and provided 100% data. On average, only 4.3% of post-termination missing pain intensity data were imputed for the derivation of time-weighted SPID12.
- Study 301 (abdominal surgery): Among all 161 ITT patients, 146 (90.7%) patients completed the 12-hour study period and provided 100% data. On average, only 5.4% of post-termination missing data, from four (3.7%) patients in the DSUVIA group and 11 (20.4%) patients in the placebo group, were imputed for the derivation of time-weighted SPID12.

In order to examine the impact of this pre-specified imputation method on the efficacy results of both studies, post-hoc sensitivity analyses were performed using the following alternative imputation methods:

1. Impute missing pain intensity values with the maximal observed pain intensity value for DSUVIA patients while using the modified Brown's method for placebo patients.
2. Impute missing pain intensity values with the maximal observed pain intensity value for DSUVIA patients and with the minimal observed pain intensity value to placebo patients.

The results obtained from the above listed sensitivity analyses of time-weighted SPID12 are presented in Table 9 and Table 10.

Table 9: Sensitivity Analysis – Study 202 (Bunionectomy)

Time-Weighted SPID12	DSUVIA 30 mcg N = 40	Placebo N = 20	Difference (DSUVIA 30 mcg – Placebo)	Treatment p-value
Primary Study Results:				
LS Mean	5.9	-6.7	12.6	0.005
Sensitivity Analysis (1):				
LS Mean	3.9	-6.6	10.5	0.027
Sensitivity Analysis (2):				
LS Mean	3.9	-5.3	9.2	0.051

LS = Least squares; SPID12 = Summed pain intensity difference from baseline over 12 hours
Sensitivity Analysis (1): Impute missing pain intensity: Maximal observed pain intensity for DSUVIA and modified Brown's method for placebo.
Sensitivity Analysis (2): Impute missing pain intensity: Maximal observed pain intensity for DSUVIA and minimal observed pain intensity for placebo.

Table 10: Sensitivity Analysis – Study 301 (Abdominal Surgery)

Time-Weighted SPID12	DSUVIA 30 mcg N = 107	Placebo N = 54	Difference (DSUVIA 30 mcg – Placebo)	Treatment p-value
Primary Study Results:				
LS Mean	25.8	13.1	12.7	< 0.001
Sensitivity Analysis (1):				
LS Mean	24.9	13.1	11.8	< 0.001
Sensitivity Analysis (2):				
LS Mean	24.4	19.1	5.3	0.088

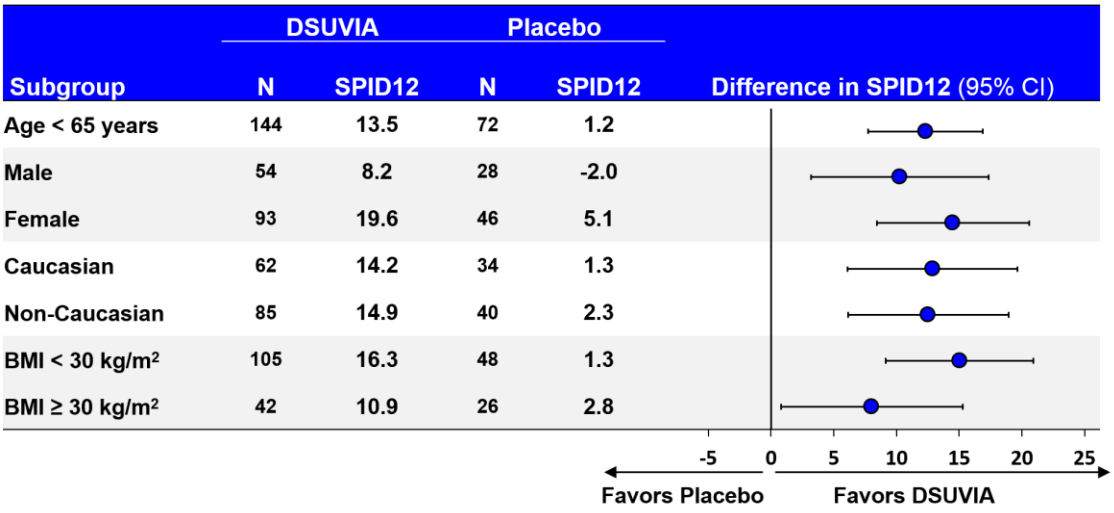
LS = Least squares; SPID12 = Summed pain intensity difference from baseline over 12 hours
Sensitivity Analysis (1): Impute missing pain intensity: Maximal observed pain intensity for DSUVIA and modified Brown's method for placebo.
Sensitivity Analysis (2): Impute missing pain intensity: Maximal observed pain intensity for DSUVIA and minimal observed pain intensity for placebo.

For Study 301 (abdominal surgery), 20% of patients dropped out prior to the 12-hour assessment time point in the placebo group and had on average 12% missing pain intensity data that required imputation. Therefore, there is a more positive impact on the efficacy of the placebo group in the second sensitivity analysis, which favored the placebo group by imputing the minimal observed pain intensity. The primary endpoint conclusions remained the same for both studies using the first sensitivity analysis.

4.11 Efficacy in Subgroups – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

Overall, DSUVIA 30 mcg is effective across age groups, races, both sexes, and following different procedures where patients would experience moderate-to-severe acute pain. Analyses across different population subgroups pooled across both pivotal studies showed consistent pain reduction benefits from DSUVIA (Figure 8).

Figure 8: Primary Efficacy for Subgroups Pooled Across Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)



BMI = Body mass index; CI = Confidence interval; SPID12 = Summed pain intensity difference from baseline over 12 hours

4.12 Secondary Endpoints – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

The findings for the primary efficacy endpoint were further supported by multiple secondary endpoints. Statistical comparison results from key secondary endpoints from the pivotal trials are displayed in Table 11, and each of these key measures are discussed in more detail below. These results indicate that DSUVIA led to a rapid onset of pain reduction from the first dose, lower and later use of rescue opioid medication, and marked improvements in Patient Global Assessment.

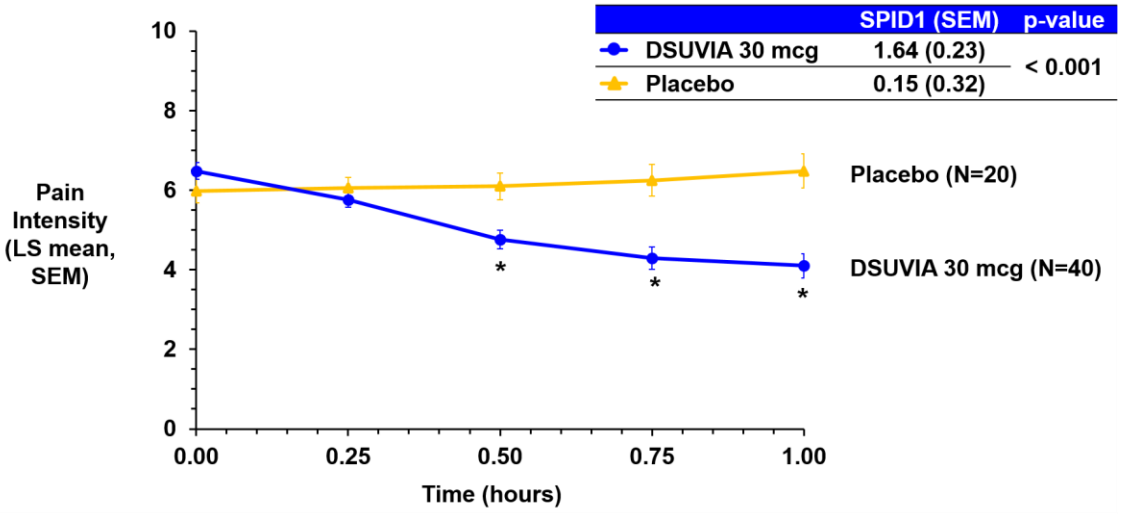
Table 11: Key Secondary Efficacy Endpoints in Pivotal Trials – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery); Data for these secondary endpoints are provided below the table

	P-value (DSUVIA vs Placebo)	
Secondary Endpoint	Study 202 (Bunionectomy) N=60	Study 301 (Abdominal Surgery) N=161
SPID 1 Difference over 1 hour	<0.001	<0.001
Patients (%) Using Rescue Opioid Medication	0.006	<0.001
Time to First Rescue Opioid Medication	<0.001	<0.001
Patient Global Assessment "Good" or "Excellent"	0.002	<0.001

SPID1 = Summed pain intensity difference from baseline over one hour

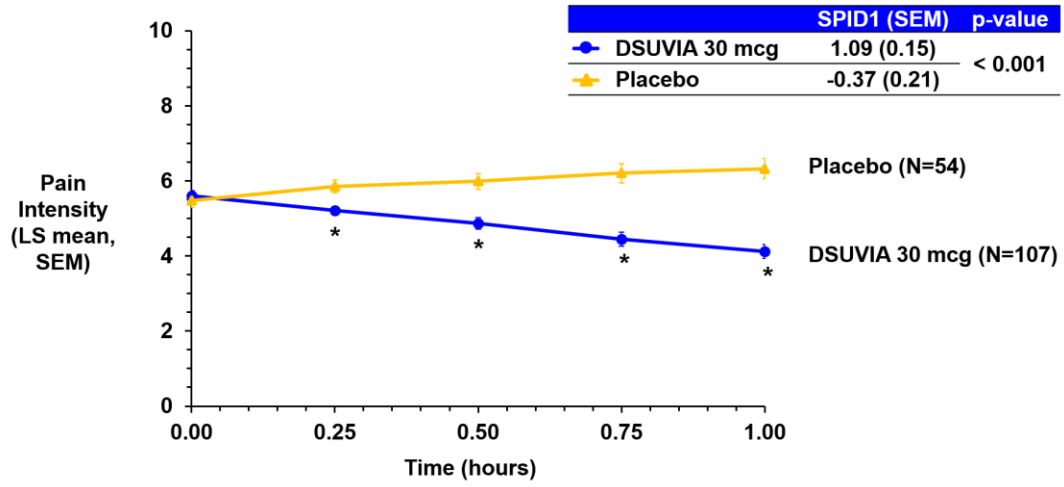
Pain intensity scores over the first hour following the first dose of DSUVIA are summarized in Figure 9 and Figure 10. A statistically significant improvement in pain intensity was detected within the first hour of dosing, as demonstrated by the difference in time-weighted SPID1 between the DSUVIA and placebo groups. These SPID1 results show that a single dose of DSUVIA provides significant pain reduction.

Figure 9: Pain Intensity Over Time Following a Single Dose (SPID1) – Study 202 (Bunionectomy)



LS= Least squares; SEM = Standard error of the mean
* p < 0.01 for pain intensity of DSUVIA 30 mcg vs Placebo

Figure 10: Pain Intensity Over Time Following a Single Dose (SPID1) – Study 301 (Abdominal Surgery)

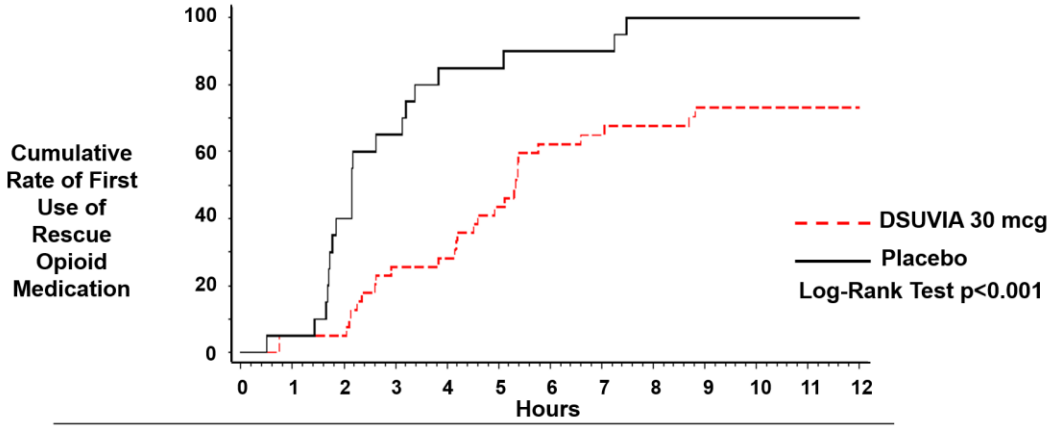


LS= Least squares; SEM = Standard error of the mean
* $p < 0.01$ for pain intensity of DSUVIA 30 mcg vs Placebo

In both studies, fewer patients treated with DSUVIA required rescue opioid medications, and did so at a later time compared to patients treated with placebo (Figure 11 and Figure 12; Table 12). In Study 202 (bunionectomy), 100% (20/20) of the placebo group compared to 70% (28/40) of the DSUVIA 30 mcg group required rescue opioid medication, with a median time to first use of 2.1 hours versus 5.3 hours, respectively. In Study 301 (abdominal surgery), 65% (35/54) of the placebo group compared to 27% (29/107) of the DSUVIA group required rescue opioid medication over the first 24 hours of the study; the median time to use of first rescue opioid medication was 2.5 hours for the placebo group and was not evaluable for the DSUVIA group (since ≥ 50% of patients did not use rescue). While rescue opioid medication was used more frequently in Study 202 (bunionectomy) than other DSUVIA studies, the rate in Study 202 is consistent with that reported for other postoperative pain studies following bunionectomy; in the literature, the proportion of patients in the investigational drug group who used rescue pain medication after bunionectomy ranged from 81% to 90% (Singla 2017). Finally, among patients who used rescue opioid medication, those in the DSUVIA group required fewer doses than those in the placebo group; DSUVIA-treated patients who used rescue medication received an average of 1.5 doses in Study 202 (bunionectomy) and 2.0 doses in Study 301 (abdominal surgery) compared to an average of 2.1 and 3.3 doses received by the corresponding placebo patients[1].

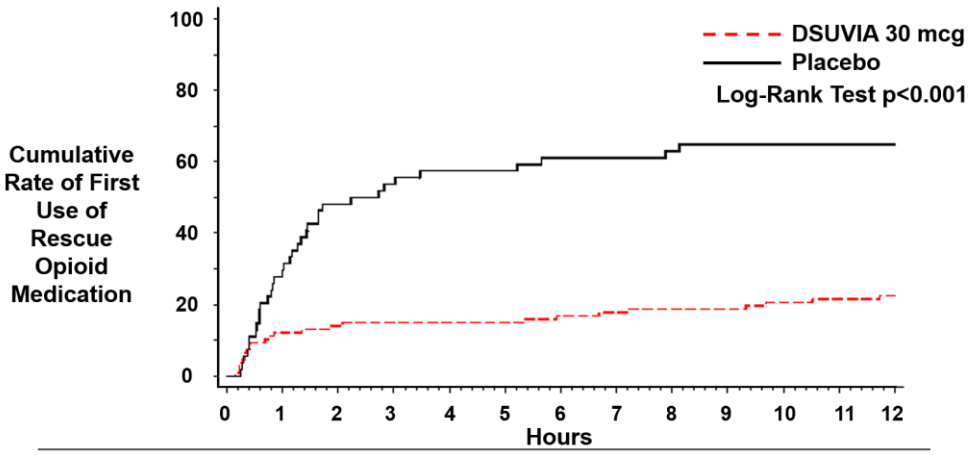
1 Doses calculated for the 12-hour treatment period of Study 202 and for Hours 0-24 of Study 301.

Figure 11: Kaplan-Meier Analysis of First Use of Rescue Opioid Medication – Study 202 (Bunionectomy)



DSUVIA 30 mcg	N=40	38	37	29	28	22	14	13	12	10	10	10	10
Placebo	N=20	19	12	7	3	3	2	2	0	0	0	0	0

Figure 12: Kaplan-Meier Analysis of First Use of Rescue Opioid Medication – Study 301 (Abdominal Surgery)



DSUVIA 30 mcg	N=107	94	92	91	91	91	89	88	87	87	85	84	83
Placebo	N=54	39	28	25	23	23	21	21	20	19	19	18	18

Table 12: Use of Rescue Opioid Medication – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

	Study 202 (Bunionectomy)		Study 301 (Abdominal Surgery)	
	DSUVIA N=40	**Placebo N=20**	**DSUVIA N=107**	**Placebo N=54**
Patients who used any rescue opioid medication, n (%)	28 (70%)	20 (100%)	29 (27%)	35 (65%)
p-value	0.006		<0.001	
Mean number of rescue doses (SD)[a]	1.5 (0.6)	2.1 (0.7)	2.0 (2.1)	3.3 (3.0)
Median	1	2	1	2
p-value	0.004		0.047	

SD = Standard deviation
a. Doses calculated for the 12-hour treatment period of Study 202 and for Hours 0-24 of Study 301.

Differences in the percentage of patients reporting "good" or "excellent" based on Patient Global Assessments of method of pain control were significant in each trial (both $p < 0.01$), with differences of 39% for Study 202 (43.6% for DSUVIA versus 5.0% for placebo) and 36% for Study 301 (87.9% for DSUVIA versus 51.9% for placebo).

Additional key secondary endpoints characterizing the analgesia onset are provided in Table 13. A 15- to 30-minute timeframe of analgesia onset was demonstrated based on a statistical difference in the pain intensity and pain relief scores of patients treated with DSUVIA compared to the baseline pain scores or compared to the placebo group ($p < 0.05$). The double-stopwatch method was used to assess perceived and meaningful analgesia in the pivotal studies. In Study 202 (bunionectomy), DSUVIA was superior compared to placebo ($p = 0.019$) for the time to perceptible analgesia; the median time to perceptible analgesia was 29 minutes and the placebo group never achieved this endpoint. Results were similar for Study 301 (abdominal surgery), with a shorter median time to perceptible analgesia in the DSUVIA group relative to the placebo group (24 vs 78 minutes, $p = 0.002$). Meaningful pain relief in the DSUVIA group was achieved at 78 minutes in Study 202 and was not achieved by the placebo group ($p = 0.016$). Meaningful pain relief in the DSUVIA group in Study 301 was achieved at 54 minutes and 85 minutes in the placebo group ($p = 0.156$).

Table 13: Onset of Analgesia Following the First Dose of DSUVIA – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

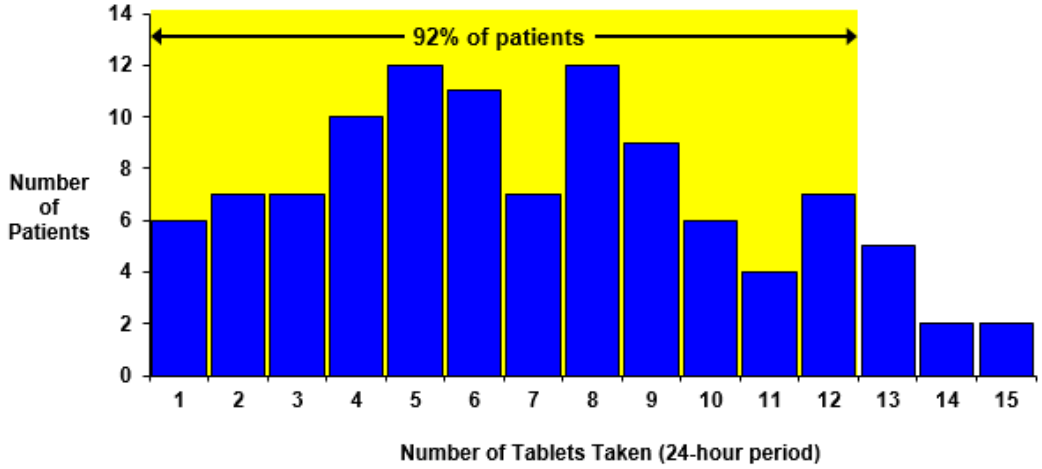
Secondary Endpoint	Study 202 (Bunionectomy) N=40	Study 301 (Abdominal Surgery) N=107
Time to a difference from baseline pain intensity/pain relief	15 min / 15 min	15 min / 15 min
Time to a difference from placebo pain intensity/pain relief	30 min / 30 min	15 min / 30 min
Double-stopwatch technique:		
Median time to perceptible pain relief	29 min	24 min
Median time to meaningful pain relief	78 min	54 min

4.13 Number of Doses and Inter-Dosing Interval – Study 202 (Bunionectomy) and Study 301 (Abdominal Surgery)

In Study 202 (bunionectomy), which had a 12-hour treatment period, patients received 1 to 10 tablets of DSUVIA 30 mcg, for an average of 5 tablets per 12 hours with approximately 2.4 hours in between doses.

Figure 13 shows the number of tablets taken by patients over the first 24 hours in Study 301 (abdominal surgery). On average, patients took 7 tablets over 24 hours with approximately 3 hours in between doses, which is consistent with the typical inter-dosing interval for opioid analgesics (eg, oral hydromorphone, IV morphine) in a medically supervised setting (Pain Assessment and Management Initiative 2017). Opioid requirements often vary considerably between patients and as such, the range of DSUVIA doses consumed within the 24-hour period was from 1 to 15 tablets. Importantly, 92% of patients used 12 tablets or less per day, which supports the clinical relevance of the proposed maximum daily dose of 12 tablets.

Figure 13: DSUVIA Doses Administered over the First 24 Hours – Study 301 (Abdominal Surgery)



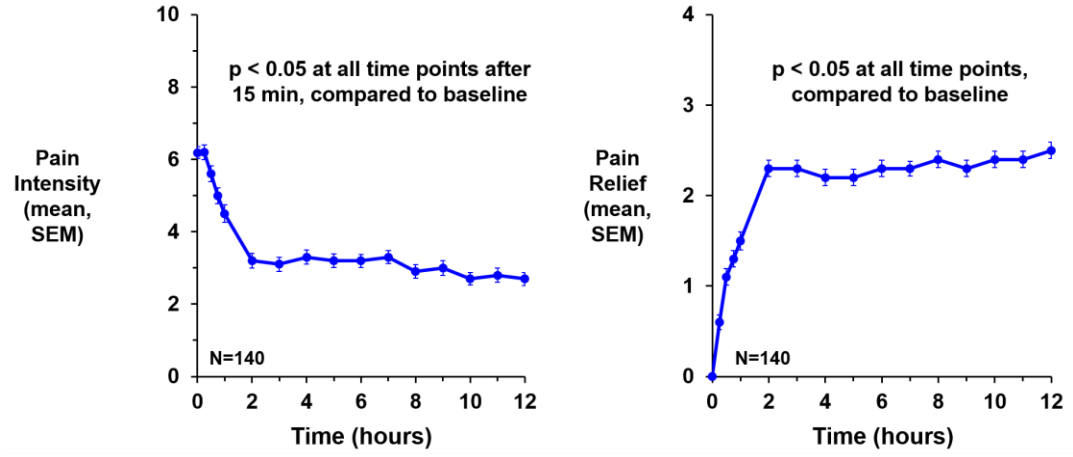
4.14 Pain Intensity and Pain Relief – Study 303 (Older Postoperative) and Study 302 (ER)

Similar to the placebo-controlled DSUVIA studies, both open-label studies showed a consistent improvement in pain intensity and pain relief over time (Hutchins 2017; Miner 2018). Statistically significant differences from baseline were noted within 15 to 30 minutes and were maintained for the duration of each study.

In Study 303 (older postoperative), mean pain intensity decreased approximately 50% by 2 hours and was sustained through 12 hours (Figure 14). Mean pain relief was on average greater than 2 "moderate" at 2 hours and this was also sustained through 12 hours (Hutchins 2017).

Literature on the clinical meaningfulness of changes in pain intensity using the 11-point (0-10) NRS for postsurgical patients on opioid treatment showed that an improvement of 1.3 points corresponds to a minimal improvement, an improvement of 2.4 points corresponds to "much" improvement, and an improvement of 3.5 points corresponds to "very much" improvement (Cepeda 2003), though the degree of relief varies as a function of baseline pain. In Study 303, patients experienced a 3.0-point improvement in pain intensity by two hours.

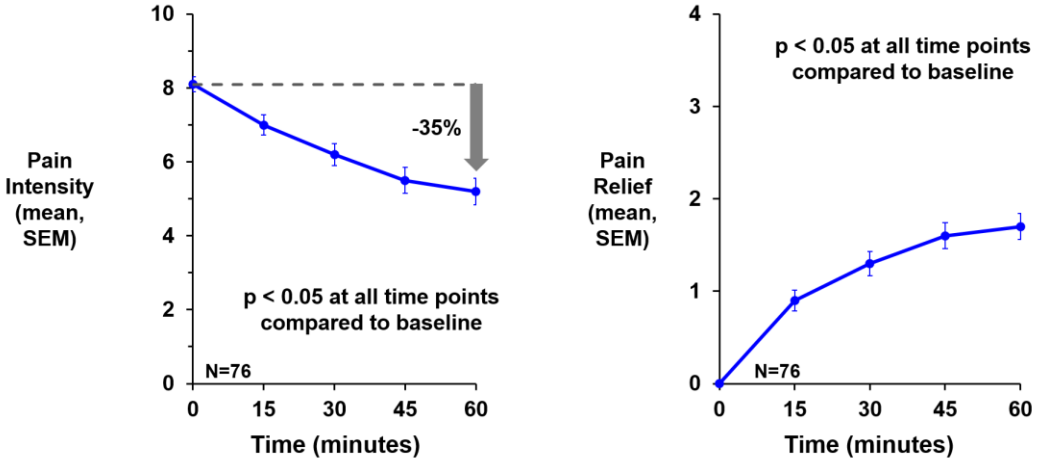
Figure 14: Pain Intensity and Pain Relief in Open-Label Study – Study 303 (Older Postoperative)



SEM = Standard error of the mean
No correction for multiplicity

Study 302 (ER) consisted of two cohorts, an initial single-dose group (n=40) followed by a multi-dose group (n=36). The second cohort was added to address the FDA's request to allow repeated dosing in this ER study if needed. Figure 15 shows the data for the first hour from both groups combined (n=76), during which time all patients were exposed to a single dose of DSUVIA. In Study 302, the mean baseline pain intensity score was 8.1, indicating that patients were in severe pain. In an ER patient population, a clinically meaningful reduction in pain intensity has been demonstrated to be 1.3 using the 11-point NRS (Bijur 2003). Following the first dose of DSUVIA in Study 302, mean pain intensity decreased significantly by 15 minutes and a mean reduction of 1.3 was observed by approximately 20 minutes (data interpolated). Pain scores continued to decline through 60 minutes, reaching a 35% reduction from baseline in pain intensity (difference of 2.9) (Miner 2018). Beyond the first hour, patients in the multi-dose group continued to maintain analgesia, with only 25% of patients requiring additional doses of DSUVIA during the 5-hour study duration. Correspondingly, mean pain relief was 0.85 at 15 minutes and increased to a mean of 1.7 at 60 minutes.

Figure 15: Single-Dose Pain Intensity and Pain Relief in Open-Label Study 302 (ER)



SEM = Standard error of the mean
No correction for multiplicity

4.15 Rescue Opioid Medication Usage – Study 303 (Older Postoperative) and Study 302 (ER)

In Study 303 (older postoperative), 20 (14.3%) of 140 treated patients took rescue opioid medication due to inadequate analgesia (Hutchins 2017).

In Study 302 (ER), 8.3% (3/36) of the patients in the multi-dose DSUVIA group received rescue opioid medication. In the single-dose DSUVIA group, 7.5% (3/40) of patients received rescue opioid medication in the first hour following a single dose of DSUVIA (post-hoc analysis).

5 SAFETY

Summary

- Overall, the safety profile of DSUVIA is consistent with that of other opioids used for the treatment of moderate-to-severe acute pain, including postoperative and acute trauma/injury pain.
- The safety profile of sufentanil is well-established based on more than 30 years of experience with Sufenta® (sufentanil citrate injection) used to induce or supplement general anesthesia (at high doses, IV, with ventilated patients) and for epidural analgesia.
- The overall safety dataset for DSUVIA consists of 646 patients who received active drug, which includes 323 patients exposed to DSUVIA 30 mcg and 323 patients from the Zalviso database. In relevant placebo-controlled studies, there were a total of 318 patients exposed to sufentanil and 158 exposed to placebo.
- In the overall safety dataset, throughout the duration of the studies:
  - There were a total of nine SAEs reported in seven patients. SAEs occurred in one patient treated with DSUVIA, four patients treated with Zalviso and two patients on placebo. The DSUVIA and Zalviso patients experienced SAEs of angina pectoris, oxygen saturation decreased, atrial fibrillation, postoperative ileus, and pulmonary embolism followed by confusional state and hypoxia; these events are consistent with AEs of opioid treatment and/or the treatment setting.
  - There were no deaths in studies of DSUVIA. There was one death due to acute renal failure in a Zalviso-treated patient which occurred 30 days after discontinuation of study drug and was considered by the investigator to be unrelated to the treatment.
  - No opioid reversal agents (eg, naloxone) were required for patients receiving DSUVIA. Three patients receiving Zalviso and two patients receiving placebo required naloxone treatment.
- In the placebo-controlled analysis, which included AEs over the first 24 hours:
  - The most commonly occurring AEs were nausea, headache, vomiting, pyrexia, dizziness, and pruritus.
  - AEs leading to discontinuation were experienced by 4% of patients in both the sufentanil and placebo groups.
  - Adverse events of special interest (AESIs) included respiratory events, neuropsychiatric events, and gastrointestinal events; the most common event observed with sufentanil was oxygen saturation decrease (2.2%) for respiratory events, dizziness (5.0%) for neuropsychiatric events, and nausea (41.5%) for

gastrointestinal events. Most AESIs were mild-to-moderate and self-limited, and none led to discontinuation in more than 1% of sufentanil or placebo patients.

- Higher doses (≥ 10 DSUVIA tablets over 24 hours) of sufentanil were not associated with an increased risk of SAEs, opioid-related respiratory AEs, or the proportion of patients with oxygen saturation values < 93% over a 72-hour assessment period.

5.1 Safety Exposures and Analyses

The safety dataset for DSUVIA is based on a total of 646 patients who were treated with at least 30 mcg of sublingual sufentanil in the first hour across the DSUVIA and Zalviso clinical studies. This includes 323 patients who were exposed to DSUVIA 30 mcg and 323 patients exposed to Zalviso. As agreed with the FDA, Zalviso patients were included in the safety database if they received the first two 15 mcg doses within 25 minutes. Zalviso clinical studies ranged from 12 to 72 hours in duration. As detailed further below, because all Zalviso patients had undergone major surgery, could access up to 45 mcg of sufentanil per hour, and tended to use the Zalviso device for multiple days, they provide important safety margin data for DSUVIA 30 mcg. Total safety exposures are summarized in Table 14.

One of the two DSUVIA placebo-controlled studies, Study 202 (bunionectomy), which included both 30 mcg and 20 mcg dosages, used a non-commercial formulation of DSUVIA, and it is possible that patients in the DSUVIA 30 mcg group received slightly lower sufentanil systemic exposures than they would have with the commercial formulation. Study 202 was therefore excluded from all safety analyses, as requested by the FDA. The synopsis of Study 202 is presented in Appendix 9.5. The safety profile from this study is consistent with that of other mu-agonist opioids.

Table 14: Overall Exposure to Sufentanil in DSUVIA Safety Dataset

	Sufentanil N=646	Placebo N=158	Population
DSUVIA (30 mcg) Studies	**323**	**54**	
Study 301	107	54	Abdominal surgery
Study 302	76	0	Trauma/injury in emergency room setting
Study 303	140	0	Postoperative, ≥ 40 years
Zalviso (2x15 mcg) Studies*	**323**	**104**	
Studies 001, 005, 310, 311	211	104	Abdominal, knee-, or hip-replacement surgery
Studies 004, 309	112	0	Abdominal, knee-, or hip-replacement surgery

* Zalviso studies include patients from six different clinical trials of Zalviso. Included patients are only those who received their second dose of study drug within 25 minutes of the first dose. Zalviso studies were up to 72 hours duration, with access of up to 45 mcg/hour as needed; therefore, these patients have higher overall sufentanil exposures than DSUVIA patients.

The Phase 3 DSUVIA studies were conducted in patients after surgery (primarily abdominal or orthopedic) or in an ER setting to examine the effect of study drug on pain caused by injury or trauma. The supporting Zalviso Phase 2 and 3 studies were conducted in patients who had undergone open abdominal, knee-replacement, or hip-replacement surgery. The DSUVIA studies, with study durations of 5-48 hours, were of shorter duration than Zalviso studies, which were designed to last for 12-72 hours.

In the DSUVIA studies, DSUVIA 30 mcg was dosed as needed with a 1-hour minimum redosing interval. In studies of Zalviso 15 mcg, the minimum dosing interval was 20 minutes, which allowed for a maximum dose of 45 mcg/hour. Among the 323 patients exposed to DSUVIA 30 mcg, the majority of patients (73.7%) received 1-5 doses (30-150 mcg), 22.0% received 6-12 doses (180-360 mcg), and 4.3% received 13-24 doses (390-720 mcg); among the 323 patients exposed to two doses of Zalviso 15 mcg dosed 20-25 minutes apart within the first hour, the majority of patients (63.2%) received more than 24 doses (> 360 mcg), 18.9% received 13-24 doses (195-360 mcg), and 18.0% received 2-12 doses (30-180 mcg).

Under prn dosing, DSUVIA 30 mcg was administered to 178 patients for ≥ 6 hours, 93 patients for ≥ 12 hours, 25 patients for ≥ 24 hours, and 1 patient for ≥ 48 hours. Zalviso 15 mcg was administered by 292 patients for ≥ 6 hours, 255 patients for ≥ 12 hours, 226 patients for ≥ 24 hours, 101 patients for ≥ 48 hours. Out of the 323 Zalviso-treated patients, 243 took 3 Zalviso doses, or 45 mcg, in the first hour.

Rationale for Use of Supporting Studies of Zalviso

As discussed with the FDA, safety data collected and submitted as part of the Zalviso (sufentanil sublingual tablet system) NDA are used to support the DSUVIA safety assessment. Safety data from patients in the Zalviso clinical program are relevant and applicable to the safety evaluation of DSUVIA as DSUVIA 30 mcg is bioequivalent to two doses of Zalviso 15 mcg administered within 20 to 25 minutes of each other, as demonstrated in the pharmacokinetic study, SAP101, and PK modeling (Section 3.2). This group of Zalviso patients provides a conservative safety assessment since they were exposed to a minimum of 30 mcg sufentanil/hour; 243 of these 323 patients took a third dose within the first hour and were exposed to 45 mcg sufentanil/hour, exceeding the maximum DSUVIA dose of 30 mcg/hour. Further, Zalviso patients were generally older and heavier compared to DSUVIA patients and had undergone major orthopedic or abdominal surgery.

Among Zalviso patients supporting the DSUVIA safety database, the median and maximum sufentanil dose over the first 24 hours was 375 mcg and 825 mcg, respectively, demonstrating that more than half of the patients in the Zalviso studies exceeded the proposed DSUVIA daily maximum dosing of 360 mcg. In addition, the Zalviso Phase 3 studies were up to 72 hours in duration. Therefore, the Zalviso studies provide important safety information that is relevant to the maximum cumulative daily dose proposed in DSUVIA labeling.

Different Safety Populations and Analyses

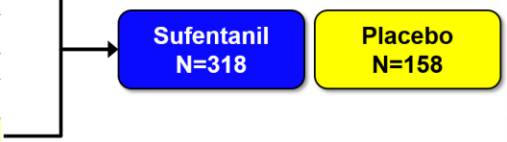
Safety analyses presented in this briefing document were derived from three safety populations, as specified in Table 15.

The overall safety population includes patients from the non-placebo-controlled studies and placebo-controlled studies of DSUVIA and Zalviso (total of 646 sufentanil patients and 158 placebo patients) and provide a comprehensive analysis of all events that occurred through the end of each study (up to 72 hours) including those that were serious, fatal, and required intervention with naloxone.

The placebo-controlled safety population allows for an isolated evaluation of events related to sufentanil. Patients from DUSVIA Study 301 (abdominal surgery) and Zalviso Studies 001, 005, 310, and 311 were pooled into either the sufentanil or placebo group, depending on the treatments they received (Figure 16). The placebo-controlled safety database consists of 318 sufentanil-treated patients and 158 placebo-treated patients. As less than 2% of the AEs occurred beyond 24 hours in the DSUVIA placebo-controlled study, AE comparisons between active and placebo groups in the first 24-hour period for each study was deemed the most relevant analysis for the safety of DSUVIA.

Figure 16: Pooled Placebo-Controlled Safety Population

	Sufentanil N=646	Placebo N=158
DSUVIA (30 mcg) Studies	323	54
Study 301	107	54
Study 302	76	0
Study 303	140	0
Zalviso (2x15 mcg) Studies*	323	104
Studies 001, 005, 310, 311	211	104
Studies 004, 309	112	0



* Zalviso studies include patients from six different clinical trials of Zalviso. Included patients are only those who received their second dose within 25 minutes of their first dose.

The high/low dosing safety population provides safety data to support the maximum daily dose of DSUVIA, which is not to exceed 12 tablets (360 mcg) per 24 hours. Data from the DSUVIA and Zalviso studies which had treatment periods of at least 24 hours were analyzed based on whether patients had a high or low dose of sufentanil (≥ 300 mcg or < 300 mcg) and again based on patients' plasma sufentanil concentrations (> 150 pg/mL or ≤ 150 pg/mL). The high/low dosing safety population was drawn from DSUVIA Study 301 (abdominal surgery) and Zalviso Studies 309, 310, and 311. A cut-off of 150 pg/mL was selected because in PK study SAP101, in which DSUVIA 30 mcg was administered hourly for 12 hours for a total sufentanil dose of 360 mcg, a mean plasma sufentanil C_{max} of 151 pg/mL was observed.

Table 15: DSUVIA Safety Populations

Population	N[a]	Studies[b]	Analysis
Overall safety population	DSUVIA 30 mcg: 323 PBO: 54; Zalviso 15 mcg: 323 PBO: 104	**All DSUVIA and Zalviso studies** - DSUVIA Studies 301, 302, 303 - Zalviso Studies 001, 004, 005, 309, 310, 311	AEs, deaths, SAEs, use of naloxone – up through 72 hours
Placebo-controlled safety population	Combined sufentanil: 318 Combined PBO: 158	**Placebo-controlled DSUVIA and Zalviso studies** - DSUVIA Study 301 - Zalviso Studies 001, 005, 310, 311	AEs, AEs leading to discontinuation, AESIs – over the first 24 hours
High/low dosing safety population	DSUVIA 30 mcg: 107 - High dose: 26 - Low dose: 81 Zalviso 15 mcg: 287 - High dose: 180 - Low dose: 107	**DSUVIA and Zalviso studies ≥ 24 hours in duration** - DSUVIA Study 301 - Zalviso Studies 309, 310, 311	AEs, SAEs, AEs leading to discontinuation – through up to 72 hours

AEs = Adverse events; AESIs = Adverse events of special interest; PBO = Placebo; SAEs = Serious adverse events
a. For Zalviso studies, includes only patients who received their second dose of study drug within 25 minutes of the first dose.
b. Phase 2/3 studies, excluding DSUVIA Study 202 (bunionectomy).

5.2 Overall Safety Population (AEs Through up to 72 Hours)

5.2.1 Adverse Events

Table 16 summarizes the AEs that occurred in 2% or more of patients in the studies of DSUVIA or Zalviso throughout the duration of the studies (up to 72 hours). Overall, 61.7% of patients experienced an AE, and the types of AEs were consistent with those associated with opioid treatment given in a postsurgical or other medically supervised setting. The most common events seen with DSUVIA or Zalviso included nausea, headache, vomiting, pyrexia, dizziness, and pruritus. Events were generally more frequent in Zalviso patients than DSUVIA patients, which was expected as 243 of the 323 Zalviso patients included as supportive in the DSUVIA safety database took higher (45 mcg) than DSUVIA 30 mcg equivalent doses of Zalviso in the first hour, and many patients received higher doses throughout the study. In addition, patients in the Zalviso studies were generally older and had more major surgeries compared with the DSUVIA population, as reflected in the higher incidence of AEs in the Zalviso placebo group.

Table 16: Adverse Events Occurring in ≥ 2% of DSUVIA 30 mcg or Zalviso Patients

	DSUVIA Studies		Zalviso Studies		Combined	
	DSUVIA 30 mcg N=323	Placebo N=54	Zalviso 15 mcg N=323	Placebo N=104	DSUVIA/ Zalviso N=646	Combined Placebo N=158
Patients with at least 1 AE	**130 (40.2%)**	**34 (63.0%)**	**261 (80.8%)**	**63 (60.6%)**	**391 (60.5%)**	**97 (61.4%)**
Nausea	80 (24.8%)	16 (29.6%)	155 (48.0%)	33 (31.7%)	235 (36.4%)	49 (31.0%)
Headache	29 (9.0%)	10 (18.5%)	34 (10.5%)	5 (4.8%)	63 (9.8%)	15 (9.5%)
Vomiting	12 (3.7%)	1 (1.9%)	41 (12.7%)	5 (4.8%)	53 (8.2%)	6 (3.8%)
Pyrexia	0	1 (1.9%)	56 (17.3%)	12 (11.5%)	56 (8.7%)	13 (8.2%)
Anaemia	0	0	33 (10.2%)	3 (2.9%)	33 (5.1%)	3 (1.9%)
Dizziness	13 (4.0%)	2 (3.7%)	18 (5.6%)	2 (1.9%)	31 (4.8%)	4 (2.5%)
Pruritus	7 (2.2%)	2 (3.7%)	24 (7.4%)	2 (1.9%)	31 (4.8%)	4 (2.5%)
Oxygen saturation decreased	6 (1.9%)	0	20 (6.2%)	1 (1.0%)	26 (4.0%)	1 (0.6%)
Hypotension	8 (2.5%)	2 (3.7%)	14 (4.3%)	4 (3.8%)	22 (3.4%)	6 (3.8%)
Constipation	1 (0.3%)	0	20 (6.2%)	1 (1.0%)	21 (3.3%)	1 (0.6%)
Hypertension	3 (0.9%)	1 (1.9%)	11 (3.4%)	4 (3.8%)	14 (2.2%)	5 (3.2%)
Tachycardia	4 (1.2%)	0	9 (2.8%)	2 (1.9%)	13 (2.0%)	2 (1.3%)
Hypocalcaemia	0	0	12 (3.7%)	2 (1.9%)	12 (1.9%)	2 (1.3%)
Insomnia	0	1 (1.9%)	12 (3.7%)	2 (1.9%)	12 (1.9%)	3 (1.9%)
Leukocytosis	0	0	11 (3.4%)	3 (2.9%)	11 (1.7%)	3 (1.9%)
Sinus tachycardia	0	1 (1.9%)	11 (3.4%)	1 (1.0%)	11 (1.7%)	2 (1.3%)
Somnolence	7 (2.2%)	2 (3.7%)	3 (0.9%)	1 (1.0%)	10 (1.5%)	3 (1.9%)
Dyspepsia	1 (0.3%)	0	9 (2.8%)	1 (1.0%)	10 (1.5%)	1 (0.6%)
Anaemia postoperative	0	0	10 (3.1%)	1 (1.0%)	10 (1.5%)	1 (0.6%)
Body temperature increased	0	0	10 (3.1%)	1 (1.0%)	10 (1.5%)	1 (0.6%)
Hypoalbuminaemia	0	0	10 (3.1%)	1 (1.0%)	10 (1.5%)	1 (0.6%)
Hypokalaemia	0	0	10 (3.1%)	1 (1.0%)	10 (1.5%)	1 (0.6%)
Confusional state	1 (0.3%)	0	8 (2.5%)	2 (1.9%)	9 (1.4%)	2 (1.3%)
Muscle spasms	1 (0.3%)	0	7 (2.2%)	3 (2.9%)	8 (1.2%)	3 (1.9%)
Anxiety	0	1 (1.9%)	8 (2.5%)	1 (1.0%)	8 (1.2%)	2 (1.3%)
Hyponatraemia	0	0	8 (2.5%)	1 (1.0%)	8 (1.2%)	1 (0.6%)
Urinary retention	0	0	8 (2.5%)	0	8 (1.2%)	0 (0.0%)

AE = Adverse event

5.2.2 Deaths

There were no deaths throughout all clinical studies of DSUVIA. Among all patients receiving Zalviso 15 mcg, there was one death which was considered unrelated to treatment by the study

investigator. This was a 69-year old white female who had elective unilateral total knee replacement. The patient died of acute renal failure 30 days after discontinuing Zalviso.

5.2.3 Serious Adverse Events

The observed SAEs are consistent with AEs associated with opioid treatment and the treatment setting. Overall, seven patients experienced nine SAEs. One SAE occurred in a DSUVIA-treated patient, six SAEs occurred in a total of four Zalviso patients, and two SAEs occurred in two placebo patients enrolled in a DSUVIA clinical trial. Table 17 displays the patients with SAEs. All events were resolved, with study drug withdrawn from the Zalviso patient with oxygen saturation decreased and from the two placebo-treated patients.

In Study 202 (bunionectomy), there were two SAEs reported in the DSUVIA 20 mcg group (severe osteomyelitis of the foot, and moderate cellulitis of the foot), neither of which was related to study drug (see Appendix 9.5). The onset of these events was more than one week after the last dose of study drug.

Table 17: Serious Adverse Events

Treatment	Adverse Event Preferred Term	Severity	Related to Treatment	Naloxone Used
DSUVIA	Angina pectoris	Moderate	Possibly	No
Zalviso	Oxygen saturation decreased	Severe	Probably	Yes
Zalviso	Confusional state	Moderate	Possibly	No
	Hypoxia	Moderate	Not related	No
	Pulmonary embolism	Mild	Not related	No
Zalviso	Atrial fibrillation	Moderate	Not related	No
Zalviso	Postoperative ileus	Severe	Not related	No
Placebo	Syncope	Moderate	n/a	No
Placebo	Hemiparesis	Severe	n/a	No

5.2.4 Use of Naloxone

Across the overall safety population, five patients required treatment with naloxone. No patients treated with DSUVIA required naloxone; three patients in the Zalviso group received naloxone following AEs of oxygen saturation decreased, sedation, and narcotic reversal, while two patients in the placebo group received naloxone for shaking and anxiety.

5.3 Placebo-Controlled Safety Analyses (Adverse Events over the First 24 Hours)

5.3.1 Adverse Events

Table 18 summarizes AEs in the placebo-controlled studies for the 318 patients treated with sufentanil and the 158 placebo-treated patients. The most common events seen with sufentanil were nausea, headache, vomiting, pyrexia, dizziness, and pruritus. Events observed more

frequently in the sufentanil group compared to the placebo group were nausea and vomiting ($p < 0.05$).

Table 18: Adverse Events Occurring in ≥ 2% of Sufentanil Patients

	Pooled Sufentanil N=318	Pooled Placebo N=158
Patients with at least 1 AE	215 (67%)	91 (58%)
Nausea	132 (42%)	49 (31%)
Headache	31 (10%)	15 (10%)
Vomiting	31 (10%)	5 (3%)
Pyrexia	16 (5%)	8 (5%)
Dizziness	16 (5%)	4 (3%)
Pruritus	15 (5%)	4 (3%)
Anaemia	14 (4%)	2 (1%)
Hypotension	12 (4%)	4 (3%)
Tachycardia	10 (3%)	1 (1%)
Hypertension	8 (3%)	5 (3%)
Insomnia	8 (3%)	2 (1%)
Oxygen saturation decreased	7 (2%)	0

AE = Adverse event

Importantly, there were very few AEs that were rated by investigators as severe in nature, with approximately 2% of patients in both the sufentanil and the placebo groups experiencing a severe AE (Table 19). The most common severe AEs were nausea, procedural nausea, and procedural vomiting in the pooled sufentanil group, with only one patient having severe oxygen saturation decreased and one patient having severe headache.

Table 19: Severe Adverse Events

	Pooled Sufentanil N=318	Pooled Placebo N=158
Patients with at least 1 severe AE	7 (2.2%)	3 (1.9%)
Nausea	3 (0.9%)	0
Procedural nausea	2 (0.6%)	1 (0.6%)
Procedural vomiting	2 (0.6%)	0
Vomiting	1 (0.3%)	0
Headache	1 (0.3%)	0
Oxygen saturation decreased	1 (0.3%)	0
Abdominal pain	0	1 (0.6%)
Hemiparesis	0	1 (0.6%)

AE = Adverse event

5.3.2 Adverse Events Leading to Discontinuation

Overall, there were few AEs leading to discontinuation in the placebo-controlled studies, with a total of 17 patients (4%) experiencing such events (Table 20). In the sufentanil group, the only AEs leading to discontinuation experienced by more than one patient were nausea (n=3) and

sedation (n=2). These AEs are consistent with AEs associated with opioid treatment and the postsurgical setting.

Table 20: Adverse Events Leading to Discontinuation

	Pooled Sufentanil N=318	Pooled Placebo N=158
Patients with at least 1 AE leading to discontinuation	**11 (3.5%)**	**6 (3.8%)**
Nausea	3 (0.9%)	0
Sedation	2 (0.6%)	0
Respiratory rate decreased	1 (0.3%)	1 (0.6%)
Oxygen saturation decreased	1 (0.3%)	0
Back pain	1 (0.3%)	1 (0.6%)
Dizziness	1 (0.3%)	1 (0.6%)
Anxiety	1 (0.3%)	0
Confusional state	1 (0.3%)	0
Hypoventilation	1 (0.3%)	0
Hemiparesis	0	1 (0.6%)
Somnolence	0	1 (0.6%)
Syncope	0	1 (0.6%)
Tremor	0	1 (0.6%)
Abdominal pain	0	1 (0.6%)

AE = Adverse event

5.3.3 Adverse Events of Special Interest

Adverse events of special interest were evaluated in the pooled placebo-controlled studies. Events of special interest included respiratory, neuropsychiatric, and gastrointestinal events. As with any opioid, DSUVIA may be associated with respiratory or neuropsychiatric events, particularly in a postoperative setting where patients are recovering from anesthesia or have been administered concomitant CNS depressants, including other opioids during the surgery and during the initial stay in the recovery room. Most of the AESIs observed with sufentanil in the placebo-controlled studies were mild-to-moderate and self-limited.

Respiratory and Oxygen Saturation AESIs

Table 21 displays the respiratory events reported in the placebo-controlled studies. The most common respiratory AE in the sufentanil-treated group was decreased oxygen saturation (2.2% compared to 0% in placebo group). There were no DSUVIA patients who had a respiratory SAE or discontinued due to a respiratory AE (in Study 202 [bunionectomy], one patient discontinued due to decreased respiratory rate and sedation; see Appendix 9.5). There were two Zalviso patients with respiratory SAEs and three additional patients (two Zalviso and one placebo) who discontinued due to respiratory AEs; safety narratives for these patients are provided below.

Table 21: Respiratory and Oxygen Saturation AESIs

	Pooled Sufentanil N=318	Pooled Placebo N=158
Oxygen saturation decreased	7 (2.2%)	0
Hypoxia	4 (1.3%)	1 (0.6%)
Respiratory rate decreased	2 (0.6%)	1 (0.6%)
Bradypnea	1 (0.3%)	0
Hypoventilation	1 (0.3%)	0
Respiratory failure	1 (0.3%)	0

AESI = Adverse event of special interest

Two patients treated with Zalviso experienced respiratory-related SAEs within 24 hours of the first dose (one patient with oxygen saturation decreased, and one patient with pulmonary embolism, resulting in hypoxia and confusional state). All events were resolved, with study drug being withdrawn from the Zalviso patient with severe oxygen saturation decreased. Study drug had previously been withdrawn in the patient with the pulmonary embolism due to lack of efficacy.

A Zalviso-treated patient from Study 311 had an SAE of "oxygen saturation decreased" which was rated as severe and related to study drug. The patient was a 65-year-old white female (weight 102 kg) with significant medical history, including type I diabetes, gastroesophageal reflux, asthma, osteoarthritis, osteoporosis, and multiple surgeries. She underwent a total knee replacement. Within six minutes after dosing her initial Zalviso 15 mcg dose, she received morphine IV 5 mg. She then received additional IV morphine boluses of 2 mg over the next several hours. In total, she used 14 doses of Zalviso 15 mcg over six hours with a mean inter-dosing interval of 28.5 minutes, along with 11 mg IV morphine over that same period. After pulse oximetry readings in the 40s and 50s, and periods of apnea, excessive sedation, and diaphoresis, she was treated with IV naloxone 0.9 mg. She then became more alert and the event was deemed resolved the same day. Study drug was discontinued, and she recovered without sequelae. It is likely that the combined use of excessive IV morphine (recorded as a deviation at the site) with the use of Zalviso in this patient with significant comorbidities led to her respiratory events, requiring the use of naloxone.

A Zalviso-treated patient from Study 311 had an initial SAE of "pulmonary embolism" (mild and not related) followed by an SAE of "hypoxia" (moderate and not related) and an SAE of "confusional state" (moderate and possibly related). The patient was an 80-year-old white female (weight 61 kg) with a medical history significant for seasonal allergies, gastroesophageal reflux disease, hearing and vision loss, osteoporosis, rheumatoid arthritis, right hand fracture, anxiety, depression, and insomnia. She underwent a total knee replacement. She used 5 doses of Zalviso 15 mcg with a mean inter-dosing interval of 24.8 minutes and discontinued due to inadequate analgesia within four hours of the initial dose. Twelve hours after the initial dose, she suffered a pulmonary embolism with resultant hypoxia, encephalopathy with confusion/delirium, aspiration pneumonia, wide complex paroxysmal tachycardia/atrial fibrillation, and anemia. A chest computed tomography (CT) scan documented the pulmonary embolism on the same day. A CT of the head revealed no

intracranial hemorrhage. Her various AEs were treated, and the events resolved within 30 days.

In addition, two Zalviso-treated patients and one placebo-treated patient discontinued study drug due to a respiratory related AE:

A Zalviso patient in Study 310 discontinued due to an AE of "respiratory rate decreased." The AE was rated as moderate in severity and possibly related to study drug. This patient was a 54-year-old white female (weight 62 kg) with a medical history of high cholesterol, heart murmur, hypertension, gastric cancer and three prior caesarean sections. She underwent an open cholecystectomy. The respiratory rate decrease occurred prior to initial dose of study drug and worsened after dosing. The event resolved the same day. The patient received a total of three Zalviso 15 mcg doses. Study drug was discontinued, and the AE resolved spontaneously the same day without use of opioid reversal agents. The patient recovered without sequelae.

A Zalviso patient in Study 311 discontinued due to an AE of "hypoventilation." The event was rated moderate in severity and possibly related to study drug. This was a 68-year-old white male (weight 115 kg) with a medical history including diabetes, obesity, degenerative joint disease, and osteoarthritis. He underwent a total knee arthroplasty. After randomization, he received 10 doses of Zalviso 15 mcg with a mean inter-dosing interval of 36.6 minutes. An hour and 45 minutes after his last dose of Zalviso 15 mcg, he was reported to have an AE of hypoventilation. He was withdrawn from the study after onset of the AE. The AE resolved spontaneously without use of opioid reversal agents, and the patient recovered without sequelae.

A patient in the placebo group of Study 311 discontinued due to an AE of "respiratory rate decreased." The event was rated moderate in severity and possibly related to study drug. This patient was a 54-year-old black male (weight 81 kg) with a medical history significant for arthrosis right knee and flexion contractures. He underwent a total knee arthroplasty. After randomization, he used three doses of placebo with a mean inter-dosing interval of 24.5 minutes. He had a slowed respiratory rate that began between his 2nd and 3rd (last) dose of placebo. His lowest respiratory rate was five breaths per minute. He was withdrawn from the study. The AE resolved spontaneously without use of opioid reversal agents, and the patient recovered without sequelae. The only IV opioid this patient received prior to the event was fentanyl IV 350 mcg during surgery.

In addition, a slightly greater proportion of patients in the sufentanil group reached oxygen saturation levels below 93% (8.5% vs 4.4% for placebo). Further, the sufentanil and placebo groups had the following oxygen saturation levels: 1.3% vs 0% of patients had levels < 90%, 7.2% vs 4.2% had levels 90-92%, 13.2% vs 12.7% had levels 93-94%, and 78.3% vs 82.9% had levels of at least 95%, respectively.

Neuropsychiatric Adverse Events of Special Interest

Neuropsychiatric events among patients treated with sufentanil were dizziness (5.0%), somnolence (1.6%), confusional state (1.3%), sedation (0.9%), lethargy (0.3%), and hallucination (0.3%), while patients receiving placebo experienced dizziness (2.5%), somnolence (1.9%), confusional state (1.3%), and disorientation (0.6%). No patients receiving sufentanil experienced neuropsychiatric AESIs considered to be severe. Discontinuation due to neuropsychiatric events occurred at low rates; specific events leading to discontinuation for the sufentanil group included sedation (0.6%), dizziness (0.3%), and confusional state (0.3%). Discontinuation for neuropsychiatric events in the placebo group occurred due to dizziness (0.6%) and somnolence (0.6%).

Gastrointestinal Adverse Events of Special Interest

The most common gastrointestinal AESIs were nausea and vomiting for both sufentanil and placebo-treated patients (nausea: 41.5% and 31.0%, respectively; vomiting: 9.7% and 3.2%, respectively), with all other gastrointestinal events occurring in less than 1% of patients in the sufentanil or placebo arms. Patients receiving sufentanil treatment experienced severe events of nausea (0.9%) and vomiting (0.3%). In the placebo group, severe abdominal pain (0.6%) was reported. Discontinuation due to gastrointestinal events occurred with sufentanil treatment due to nausea (0.6%) and occurred with placebo treatment due to abdominal pain (0.6%).

5.4 High/Low Dosing Safety Analyses (Adverse Events Through up to 72 Hours)

The proposed maximum daily dose of DSUVIA is 12 tablets (360 mcg sufentanil) in 24 hours. This 12-tablet daily limit was based on the doses used in the DSUVIA clinical studies (Section 4.13) and not due to an observed safety signal. To provide safety data supporting maximal dosing of DSUVIA, data from the DSUVIA and Zalviso studies which had treatment periods of at least 24 hours were analyzed; this included DSUVIA Study 301 (abdominal surgery) and Zalviso Studies 309, 310, and 311. Patient data were then compared based on sufentanil dosing received during the first 24-hour study period and then again based on maximum measured sufentanil plasma concentration achieved during the first 24 hours of the studies. These analyses included all AEs reported throughout the duration of the studies up to 72 hours, providing safety data for a period following high or low dosing.

In the analysis by sufentanil dose, patients were divided into those who received sufentanil doses ≥ 300 mcg or < 300 mcg during the first 24 hours of the studies. Allowing the safety analysis to encompass ≥ 300 mcg per day (equivalent to 10 or more DSUVIA 30 mcg tablets), instead of only ≥ 360 mcg per day (equivalent to 12 or more DSUVIA tablets), provides more sufentanil patients to be assessed at these higher doses. Given that the Zalviso patient exposures were as high as 825 mcg/24 hours (equivalent to 27.5 DSUVIA tablets), the upper end of the sufentanil exposure is more than double the maximal dosing proposed for DSUVIA (360 mcg/24 hours). In total, 206 patients received ≥ 300 mcg sufentanil during the first 24 hours, and 188 patients received < 300 mcg.

Overall, the rate of AEs, severe AEs, SAEs and AEs leading to discontinuation were comparable between the higher- and lower-dose groups (Table 22).

Table 22: Overview of Adverse Events by Dose Group

	DSUVIA Study		Zalviso Studies	
	< 300 mcg (0-24 Hours) N=81	**≥ 300 mcg (0-24 Hours) N=26**	**< 300 mcg (0-24 Hours) N=107**	**≥ 300 mcg (0-24 Hours) N=180**
Patients with at least 1 AE	47 (58.0%)	15 (57.7%)	82 (76.6%)	149 (82.8%)
Patients with at least 1 severe AE	4 (4.9%)	1 (3.8%)	3 (2.8%)	1 (0.6%)
Patients with at least 1 SAE	0	0	3 (2.8%)	1 (0.6%)
Patients with at least 1 AE leading to discontinuation of study drug	0	1 (3.8%)	15 (14.0%)	6 (3.3%)

AE = Adverse event; SAE = Serious adverse event

Table 23 displays the typical opioid-induced AEs occurring throughout the duration of the studies among patients who received either higher (≥ 300 mcg) or lower (< 300 mcg) total doses of sufentanil during the first 24 hours in the DSUVIA and Zalviso studies. Nausea and pruritus occurred more frequently in the higher-dose group in both Zalviso and DSUVIA studies. Vomiting, constipation, and hypotension occurred more frequently in the higher-dose group in the Zalviso studies, but not in the DSUVIA study. The AEs of oxygen saturation decreased and somnolence occurred more frequently in the higher-dose group of the DSUVIA study (each occurring in only a single patient), but not in the Zalviso studies.

For DSUVIA-treated patients, the mean (standard deviation [SD]) lowest oxygen saturation in the lower- versus higher-dose group was 95.2% (1.6%) versus 95.4% (2.2%), respectively. For Zalviso-treated patients, the mean (SD) lowest oxygen saturation was 93.5% (6.2%) and 94.5% (1.7%) in the lower- and higher-dose groups, respectively. Furthermore, the proportion of patients with oxygen saturation values < 93% was higher in the lower-dose groups (8.6% in the DSUVIA lower-dose group compared with 3.8% in the higher-dose group; 15.9% in the Zalviso lower-dose group compared with 8.3% in the higher-dose group).

Table 23: Typical Opioid-Induced Adverse Events that Occurred in ≥ 1% of Patients by Dose Group

	DSUVIA Studies		Zalviso Studies	
	< 300 mcg (0-24 Hours) N=81	≥ 300 mcg (0-24 Hours) N=26	< 300 mcg (0-24 Hours) N=107	≥ 300 mcg (0-24 Hours) N=180
Patients with at least 1 AE	**47 (58.0%)**	**15 (57.7%)**	**82 (76.6%)**	**149 (82.8%)**
Nausea	24 (29.6)	11 (42.3)	43 (40.2)	93 (51.7)
Vomiting	7 (8.6)	1 (3.8)	10 (9.3)	20 (11.1)
Pruritus	1 (1.2)	1 (3.8)	7 (6.5)	15 (8.3)
Dizziness	5 (6.2)	1 (3.8)	8 (7.5)	8 (4.4)
Oxygen saturation decreased	0	1 (3.8)	9 (8.4)	11 (6.1)
Constipation	0	0	3 (2.8)	17 (9.4)
Hypotension	4 (4.9)	1 (3.8)	4 (3.7)	10 (5.6)
Confusional state	0	0	5 (4.7)	3 (1.7)
Hypoxia	1 (1.2)	0	3 (2.8)	3 (1.7)
Sedation	0	0	4 (3.7)	1 (0.6)
Somnolence	2 (2.5)	1 (3.8)	2 (1.9)	0
Respiratory rate decreased	0	0	2 (1.9)	0

AE = Adverse event

In addition to the analysis by dose, patients were analyzed based on maximum measured plasma sufentanil concentration during the first 24-hour study treatment period. In the PK study, SAP101, in which DSUVIA 30 mcg was administered hourly for 12 hours for a total sufentanil dose of 360 mcg, a mean plasma sufentanil C_{max} of 151 pg/mL was observed. Therefore, patients were divided into subgroups based on the maximum measured sufentanil concentrations obtained from sparse sampling (> 150 pg/mL or ≤ 150 pg/mL) during the first 24 hours of the studies. Across the four studies, 50 patients had sufentanil concentrations > 150 pg/mL during the first 24 hours, and 313 patients had concentrations ≤ 150 pg/mL. The analysis by sufentanil concentrations corroborated the results of the sufentanil dose analysis; a similar trend was observed between higher and lower sufentanil concentration groups as between higher- and lower-dose groups.

Overall, generally similar or slightly higher AE rates were observed in patients receiving higher total sufentanil doses or who had higher sufentanil plasma concentrations. Patients receiving higher doses with subsequently higher sufentanil plasma concentrations tended to be older and undergoing more major surgeries as they were enrolled in the Zalviso studies. While typical opioid-related gastrointestinal AEs occurred more frequently in the higher-dose group, no increased risk of SAEs, opioid-related respiratory AEs, or low oxygen saturation values was observed for these higher doses, thus supporting the safety of the proposed maximum daily dose of 12 DSUVIA tablets.

5.5 Safety by Subgroups

Safety analysis across different population subgroups in the overall safety population showed consistency with the known risks of opioids. Rates of AEs were higher in older patient groups, higher in women than in men, slightly higher in patients with a BMI < 30 kg/m^2 than in patients with a BMI ≥ 30 kg/m^2, and slightly higher in American Society of Anesthesiologists (ASA) status I patients compared to ASA status II and III patients. While occurring at a relatively low frequency, not unexpectedly, the rate of respiratory events increased in older patients up through the advanced elderly (≥ 75 years), increased in heavier patients, and increased with worsening ASA status. There was no difference between men and women with respect to respiratory events.

5.6 Non-US Safety Experience with Zalviso

DSUVIA 30 mcg has not been marketed in any country to date. In April 2016, Zalviso became available in Europe for patient-controlled management of moderate-to-severe postoperative pain in a hospital setting. As of June 30, 2018, over 26,000 patients have used Zalviso commercially. Adverse event reports are similar to the sublingual sufentanil clinical trial results and are consistent with the AE profile for opioids; there have been no expedited safety reports. Nine patients (0.03%) have required naloxone reversal for respiratory depression. This is in comparison to a rate of 0.3% from a published meta-analysis of patients exposed to postoperative opioid analgesia (Cashman 2004). It is possible that the lower rate of naloxone use for Zalviso may be related to the nature of post-marketing safety reporting, where reporting of AEs is typically an underestimate of the true AE rate. There have been five deaths reported to date, but none of them are suspected to be causally related to treatment with Zalviso.

5.7 Safety Summary

Clinical studies demonstrated an appropriate safety profile for the DSUVIA 30 mcg in support of the proposed indication for management of moderate-to-severe acute pain in adult patients in a medically supervised setting. Adverse events were consistent with those seen for other opioids in similar clinical settings consistent with the indication and similar safety profiles were observed with higher daily dosing as compared with lower dosing; no new safety signals were detected.

6 PUBLIC HEALTH CONSIDERATIONS

Summary

- Sufentanil is currently administered only by healthcare professionals, with no retail distribution, and has a very low rate of abuse.
- DSUVIA will also be restricted to healthcare professional administration in a medically supervised setting, which combined with the design of the single-dose applicator and product packaging, is expected to mitigate the potential for abuse, misuse, or diversion.
- AcelRx has planned a thorough REMS program for DSUVIA to mitigate the risk of respiratory depression and mitigate the risk for abuse, misuse, or diversion.
  - DSUVIA distribution will be restricted to only REMS-certified healthcare facilities that attest to having healthcare professionals with experience administering IV opioids, that are trained to detect and treat respiratory depression, and that have access to oxygen and opioid reversal agents.
  - REMS educational material will be provided to educate healthcare professionals on the appropriate use of DSUVIA and to ensure that DSUVIA will not be dispensed outside of a medically supervised setting.
  - AcelRx will conduct routine audits of the entire supply chain to evaluate compliance and implement corrective actions; it will also participate in the Researched Abuse, Diversion, and Addition-Related Surveillance (RADARS) monitoring programs to assess abuse, misuse, and diversion.
- The DSUVIA user interface, including the Directions for Use, further mitigates the risk of abuse, misuse, and diversion by facilitating the safe and effective delivery of tablets for the intended use, user, and setting, as demonstrated by human factors testing.
  - In the human factors study, all healthcare professionals successfully administered DSUVIA and visually confirmed tablet placement; there were no dropped tablets.
- The risk of accidental ingestion or diversion leading to serious harm as a result of a dropped tablet was assessed by a third party and was determined to be adequately mitigated.

6.1 Abuse Potential

DSUVIA contains sufentanil, a CII opioid, and consequently has the potential for abuse. For over three decades, sufentanil has been available as an injection for administration by healthcare professionals trained in the management of the respiratory depressive effects of opioids, similar to alfentanil and remifentanil. These opioids are not contained in any product prescribed for use at home.

The American Association of Poison Control Centers' National Poison Data System (AAPCC NPDS) is the data warehouse for the poison control centers in the US. For the past 32 years, the AAPCC has analyzed and published data from the previous year's reported cases. The reports for the past 18 years (1999 through 2016) are available online at http://www.aapcc.org/annual-reports/ (Bronstein 2012; Bronstein 2011; Bronstein 2010; Bronstein 2009; Bronstein 2008; Bronstein 2007; Gummin 2017; Lai 2006; Litovitz 2002; Litovitz 2001; Litovitz 2000; Mowry 2016; Mowry 2015; Mowry 2014; Mowry 2013; Watson 2005; Watson 2004; Watson 2003). These 18 reports include a total of nine cases where sufentanil was mentioned; there was one for each of the following years: 1999, 2011, 2013, and 2014, two in 2012, and three in 2016. The case in 1999 was a successful suicide where fentanyl was reported as the primary substance involved, and sufentanil and morphine were reported as contributing drugs; the 2011 case had a minor outcome; the 2014 case had a moderate outcome; and cases in 2012, 2013 and 2016 had outcomes that were not reported. Similarly low rates of abuse were reported for alfentanil and remifentanil.

Because the REMS program will restrict distribution only to certified healthcare facilities with no retail or outpatient prescription availability, the potential for abuse of DSUVIA in the lay public is low. DSUVIA does not offer specific abuse-deterrent properties and AcelRx is not seeking abuse-deterrent labeling; however, DSUVIA has some features which may thwart efforts to abuse, misuse, and divert the drug:

- Each DSUVIA 30 mcg tablet will be packaged as a single dose preloaded in a single-dose applicator. The single-dose applicator is disposable and is used by the healthcare professional to aid in placing the tablet in the patient’s sublingual space during dosing. Thus, unlike many oral tablet opioid formulations, multiple doses will not be available for dispensing from a single container. The foil pouch in which each tablet-applicator system is packaged provides evidence if the pouch has been torn open. Additionally, once the DSUVIA tablet has been dispensed, the plunger cannot be retracted, providing visual evidence of a used single-dose applicator and circumventing the possibility of the DSUVIA tablet being replaced with a dummy tablet.
- The solid dosage form of the sufentanil tablet avoids the in-hospital diversion issues related to clear liquid opioids, which may be diverted and substituted with saline or recovered from residual/partially used vials (Berge 2012; Burke 1999; Hellinger 2012).
- DSUVIA is available in only one dosage strength, which should limit dosing errors.

6.2 Risk Management

All FDA REMS programs help ensure that the benefits of a drug outweigh its risks. As with other opioid products, the safe use of DSUVIA includes minimizing the risk of respiratory depression resulting from inappropriate administration, as well as mitigating the serious risks associated with abuse, misuse, and diversion. Detailed information on the proposed DSUVIA REMS Program is provided in Appendix 9.6.

Administration of DSUVIA in a medically supervised setting by a qualified healthcare professional is intended to minimize the known risks of opioid abuse and overdose in the general

patient population. Distribution of DSUVIA will be restricted to only REMS-certified healthcare facilities that have the required DEA CII registration and that designate an Authorized Representative to attest to the facility having healthcare professionals who are experienced in IV opioid administration, are trained to detect airway problems, and have access to supplemental oxygen and opioid reversal agents. Further, the REMS educational materials will provide tools for practitioners to educate themselves and their staff on the appropriate use of DSUVIA for the management of moderate-to-severe acute pain in adult patients and to ensure that it will not be dispensed outside of a medically supervised setting. Materials that will be made available by AcelRx include, among others, the DSUVIA REMS Safety Brochure: Guide for Healthcare Providers and Pharmacists, which provides important safety information, such as the importance of a minimum one-hour redosing interval, the 12-tablet daily maximum dose, and the need to visually confirm tablet placement after dose administration; Dear Healthcare Provider letters; and an instructional video on the DSUVIA website which illustrates proper dosing and administration.

AcelRx will take reasonable steps to improve implementation of and compliance with the requirements in the DSUVIA REMS Program based on monitoring and evaluation of the Program. Evaluation strategies will include audits of wholesalers, audits of certified healthcare facilities/settings, reconciliation of shipping records across the entire supply chain and participation in the RADARS mosaic of programs for monitoring drug abuse and misuse. RADARS programs offering the greatest insight into potential diversion of DSUVIA outside of a medically supervised setting include Drug Diversion Program, Poison Center Program, Survey of Non-Medical Use of Prescription Drug Program, Street Rx Program and Web Monitoring Program, which collects qualitative drug abuse data as reported on the internet. AcelRx is currently working with the RADARS staff to identify the optimal combination of programs to meet the goal of the DSUVIA REMS. Corrective action will be instituted by AcelRx if noncompliance is identified; AcelRx has the ability and will be responsible for immediately de-certifying any facility that is unable to remain fully compliant with the DSUVIA REMS program.

AcelRx will submit REMS assessments to the FDA at six months and 12 months following initial REMS approval and then annually thereafter for a minimum of seven years. Assessments will include an evaluation of the effectiveness of the REMS and any areas for program improvements or modifications.

6.3 Safe DSUVIA Tablet Administration

A critical component of safe use within a medically supervised setting is the safe and effective delivery of DSUVIA tablets to patients by healthcare professionals. In the DSUVIA Phase 3 clinical studies, a total of 1782 tablets were dispensed to patients via single-dose applicators. There were three cases in which unsuccessful delivery resulted in the tablet being dropped. All three of the dropped tablets were located and secured for CII study drug accountability, and none of the events were associated with an AE or early study termination. The root cause of the user errors was identified in each case and was addressed via re-training or subsequent changes to the user interface.

To further address safe administration, AcelRx validated the usability of the DSUVIA user interface in human factors studies, as described in more detail below. The final human factors study (PRT-ARX04-R022) was conducted after making changes to the Directions for Use that increased emphasis for the healthcare professional to visually confirm tablet placement after administration. After these changes were made, no dropped tablets were observed in this study. An independent risk assessment was also performed to evaluate the potential risks associated with dropped tablets to unintended users, which concluded that the risk was very low.

6.3.1 Human Factors Validation Studies

AcelRx conducted two human factors studies to validate the usability of DSUVIA. The first study (PRT-ARX04-R009, submitted with the original NDA) evaluated the DSUVIA user interface (ie, single-dose applicator, pouch, and Directions for Use) employed in the DSUVIA clinical studies while the second (PRT-ARX04-R022) evaluated an updated user interface, which included changes to the Directions for Use (eg, improved graphics) and pouch labeling designed to further mitigate the risk of dropped tablets. The updated user interface is the configuration proposed for the commercial product.

PRT-ARX04-R009 and Subsequent User Interface Changes

In PRT-ARX04-R009, 45 healthcare professional participants consisting of 15 ER nurses, 15 floor nurses, and 15 paramedics were tested on the essential and critical tasks associated with the use of the product. Each participant administered one tablet each to three mock patients after being instructed to read the Directions for Use. Of the total 135 tablets administered in the study, 133 (98.5%) were successfully delivered to the patients. The two tablets not correctly delivered were located and appropriately disposed of. Furthermore, 82% of participants (37 of 45) confirmed tablet placement in the patient's mouth after delivery of the first dose, and 100% confirmed tablet placement after delivery of the second and third doses.

During review of the DSUVIA NDA, the FDA cited that PRT-ARX04-R009 did not demonstrate that the user interface supported safe and effective use of the product and requested that AcelRx implement Directions for Use changes along with additional mitigation strategies to address the risk of dropped sufentanil tablets. To mitigate the risk of dropped tablets, the following changes were made to the DSUVIA pouch labeling and Directions for Use:

- The simplified graphics on the pouch back label have been replaced with the complete Directions for Use. The Directions for Use is now physically attached to each pouch as a foldout leaflet label (Figure 1), rather than being provided separately with the carton of pouches.
- Additional emphasis and instructions have been incorporated into the Directions for Use text and figures to prevent accidental ejection of the tablet, confirm tablet placement in the sublingual space after delivery, and retrieve and dispose of dropped tablets according to institutional CII opioid waste procedures (see Appendix 9.1 for copy of the DSUVIA Directions for Use).

- A reference to an educational video describing dosing and administration of DSUVIA has been added to the pouch label. The video will be available for viewing on the DSUVIA website.

These changes incorporated the FDA's recommendations in the complete response letter. No changes were made to the single-dose applicator or the DSUVIA tablet. The updated Directions for Use and pouch together with the same single-dose applicator and tablet system were validated in a second human factors study (PRT-ARX04-R022).

PRT-ARX04-R022 Human Factors Validation Study and Usability Conclusions

PRT-ARX04-R022 recruited and tested 45 healthcare professional participants consisting of 15 ER nurses, 15 floor nurses, and 15 paramedics. All participants were naïve to administration of DSUVIA and they were required to perform all essential and critical tasks associated with the use of the product including administering tablets to mock patients and answering knowledge questions regarding the Directions for Use. Importantly, participants did not receive any training regarding the single-dose applicator nor were they directed to read the Directions for Use prior to attempting study tasks. Each of the 45 participants administered one tablet each to three mock patients for a total of 135 tablet administrations in the study.

In this study, 43 of 45 healthcare professionals read the fold out Directions for Use attached to the DSUVIA pouch even though they were not directed to do so by the study moderator. All 45 healthcare professional participants successfully administered and visually confirmed the placement of the three tablets that they administered to mock patients (total of 135 tablets). In addition, 44 of 45 participants successfully answered all six knowledge questions regarding the Directions for Use. Lastly, no new use errors, hazards, hazardous situations or hazard-related use scenarios were discovered during the study.

These results demonstrate that the changes recommended by the FDA and implemented by AcelRx to the user interface significantly improved the usability of DSUVIA:

- There were no dropped tablets in PRT-ARX04-R022 compared to two dropped tablets in PRT-ARX04-R009.

- Additionally, 100% of the participants confirmed tablet placement of the first administered tablet in the patient's mouth in PRT-ARX04-R009 compared to 82% in PRT-ARX04-R022. The success rate in both studies for the second and third dose administrations was 100%.

The changes made to the Directions for Use and pouch labeling successfully mitigate the risk of dropped tablets and do not introduce any new risks to the use of DSUVIA. No device design changes were necessary to the single-dose applicator or DSUVIA tablet. The results of PRT-ARX04-R022 demonstrate that the DSUVIA user interface has been successfully validated for the intended use, users, and use environments.

6.3.2 Risk Assessment of Dropped Tablets

Dropped sufentanil tablets resulting from improper administration of DSUVIA pose a risk for accidental exposure, misuse, and diversion. The potential risks associated with dropped DSUVIA tablets were assessed by a third-party independent review and risk evaluation which considered the probability and severity of potential hazards resulting from dropped tablets. The evaluation estimated the probability that DSUVIA tablets, dropped in the medically supervised setting, would lead to a potential overdose hazard. These estimates were performed based on the clinical use data and took into account the sequence of independent events that would need to occur. For example, the sequence of events for accidental exposure due to a single dropped tablet would include:

1. Probability of dropped DSUVIA tablet
2. Probability of healthcare professional not noticing the dropped tablet
3. Probability of a patient not noticing the dropped tablet
4. Probability of non-patient adult/toddler/child in the room
5. Probability of adult/toddler/child detecting the dropped tablet (3 mm diameter)
6. Probability of adult/toddler/child picking up the dropped tablet
7. Probability of placing dropped tablet in mouth (without swallowing)

To examine the severity of accidental exposure, a simulated PK analysis based on scientific literature and the PK profile of DSUVIA was performed to determine the minimum number of tablets that could result in serious harm to toddlers, children, and adults. The analysis concluded that in a toddler (12 kg), sublingual administration of ≥ 2 DSUVIA 30 mcg tablets would lead to plasma sufentanil concentrations above the concentration known to be well-tolerated in young children (300 pg/mL; Haynes 1993). In children (20 kg) and adults (50 kg), sublingual administration of ≥ 3 DSUVIA 30 mcg tablets simultaneously could result in serious harm.

The risk of accidental exposures is mitigated by DSUVIA's single-dose design, unit dose packaging, improved Directions for Use, and the fact that DSUVIA distribution will be restricted to healthcare facilities, with no retail pharmacy distribution. The residual risk of overdose hazards from dropped tablets was analyzed and rated as extremely low (< 1/1,000,000) and acceptably mitigated.

7 BENEFIT/RISK CONCLUSION

Two randomized, double-blind, placebo-controlled studies and two additional open-label studies demonstrated the safety and efficacy of DSUVIA 30 mcg for the proposed indication of management of moderate-to-severe acute pain in adult patients in a medically supervised setting. Safety was further supported by studies of Zalviso 15 mcg. AcelRx considers the data from these studies and the clinical pharmacology studies, data from the literature, and the FDA's findings of safety for the reference drug, Sufenta®, to be sufficient to demonstrate the clinical properties of DSUVIA 30 mcg and show a favorable benefit-risk profile for approval.

The primary benefit of DSUVIA 30 mcg is its efficacy for management of moderate-to-severe acute pain as demonstrated for different types of pain (acute soft-tissue/visceral and musculoskeletal surgical pain and acute pain due to trauma) and supported by the characteristics of the sublingual sufentanil tablet, including:

- rapid transmucosal uptake and analgesic response
- moderate-to-high sublingual bioavailability and a sufficient duration of action
- no active metabolites, which might favor its use in debilitated patients or patients with renal or hepatic impairment
- negligible oral bioavailability, providing a safety margin in the event that a tablet is inadvertently swallowed
- a noninvasive route of administration that:
    - allows rapid and easy administration when availability or feasibility of IV access is limited
    - does not require tablets/fluids to be swallowed, which may be useful in patients with dysphagia or patients who are not allowed to have oral intake
    - uses a solid dosage form that cannot be substituted or partially diverted like a liquid opioid

Risks associated with DSUVIA are similar to those for other opioids in this patient population and are consistent with the risks of sufentanil. No new safety signals were identified throughout DSUVIA's clinical program.

Overall, DSUVIA is effective in reducing moderate-to-severe acute pain and represents a noninvasive opioid option with unique pharmacological characteristics that address many of the shortcomings of other opioids used today. Furthermore, DSUVIA's safety profile is similar to that of other opioids for the intended patient populations, but its use will be restricted to administration by healthcare professionals in a medically supervised settings under a comprehensive REMS to reduce the risks of abuse, misuse, and diversion.

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9 APPENDICES

9.1 DSUVIA Directions for Use

DSUVIA® (sufentanil) sublingual tablet 30 mcg

DIRECTIONS FOR USE

Single-Use Product / Do Not Reuse

Do Not Use If Pouch Seal Is Broken.

Do Not Use If the Single-Dose Applicator (SDA) Is Damaged.

PATIENT INFORMATION:

- Instruct the patient to not chew or swallow the tablet.
- Instruct the patient to not eat or drink and minimize talking for 10 minutes after receiving the tablet.

1. Only when ready to administer the medication, **TEAR OPEN** the notched pouch across the top.

The pouch contains one clear plastic SDA with a single blue-colored tablet housed in the tip, and an oxygen absorber packet. *See Figure 1.*

REMOVE SDA from pouch.

DISCARD the oxygen absorber packet.

Figure 1
DSUVIA Pouch Contents

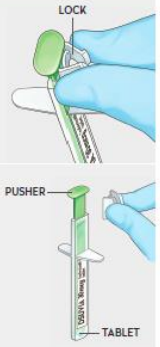
2. REMOVE the white Lock from the green Pusher by squeezing the sides together and detaching from Pusher. *See Figure 2.*

DISCARD the Lock.

NOTE: To prevent ejecting the tablet accidentally:

- Do not remove Lock until ready to administer
- Avoid touching the green Pusher before placing the SDA in the patient's mouth for administration

Figure 2
Lock Removal



3. TELL the patient to open their mouth and touch their tongue to the roof of their mouth if possible.

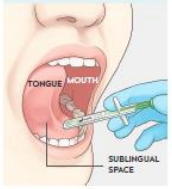
4. REST the SDA lightly on the patient's lower teeth or lips. *See Figure 3.*

5. PLACE the SDA tip under the tongue and aim at the floor of the patient's mouth or sublingual space. *See Figure 3.*

NOTE: Avoid direct mucosal contact with the SDA tip.

6. GENTLY DEPRESS the green Pusher to deliver the tablet to the patient's sublingual space. *See Figure 3.*

Figure 3
SDA Placement for Administration

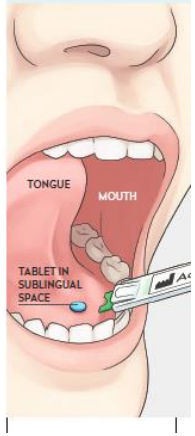


7. VISUALLY CONFIRM tablet placement in the sublingual space. *See Figure 4.*

NOTE: If tablet is NOT in the patient's mouth, it is important to retrieve and dispose of the tablet according to institutional CII waste procedures.

8. DISCARD the used SDA in biohazard waste after administration.

Figure 4
Tablet Placement in Sublingual Space



9.2 DSUVIA Pouch, Single-Dose Applicator, and Tablet (Actual Size)

9.3 DSUVIA and Zalviso Clinical Studies Relevant to the Efficacy and Safety Assessment of DSUVIA

Table 24: DSUVIA Clinical Studies

	Study 202	Study 301	Study 303	Study 302
Phase	2	3	3	3
Design	Multicenter, randomized placebo-controlled	Multicenter, randomized placebo-controlled	Multicenter, open-label	Multicenter, open-label
N	100	161	140	76
Treatment	Placebo (20) DSUVIA 20 mcg (40) DSUVIA 30 mcg (40)	Placebo (54) DSUVIA 30 mcg (107)	DSUVIA 30 mcg	DSUVIA 30 mcg
Purpose	Pivotal Efficacy; Dose-Finding	Pivotal Efficacy and Safety	Supportive Efficacy and Safety	Supportive Efficacy and Safety
Population	Postoperative bunionectomy	Postoperative outpatient abdominal surgery	Postoperative abdominal/ortho-pedic/other; Adults ≥ 40 years	Trauma/injury in emergency room
Duration	Up to 12 hours	Up to 48 hours	Up to 12 hours	Up to 5 hours
Primary endpoint	SPID12	SPID12	SPID12	SPID1

SPID = Summed pain intensity difference from baseline over 12 hours

Table 25: Zalviso Clinical Studies Contributing to DSUVIA Safety Dataset

	Study 001	Study 005	Study 310	Study 311	Study 004	Study 309
Phase	2	2	3	3	2	3
Design	Multicenter, randomized placebo-controlled	Multicenter, randomized placebo-controlled	Multicenter, randomized placebo-controlled	Multicenter, randomized placebo-controlled	Multicenter, open-label	Multicenter, randomized, open-label, comparative study against IV PCA morphine
N[a]	27	14	78	196	18	94
Treatment	Placebo (15) Zalviso 15 mcg (12)	Placebo (8) Zalviso 15 mcg (6)	Placebo (27) Zalviso 15 mcg (51)	Placebo (54) Zalviso 15 mcg (142)	Zalviso 15 mcg	Zalviso 15 mcg
Population	Total knee replacement	Open abdominal surgery	Open abdominal surgery	Total knee or hip replacement	Knee replacement	Open abdominal surgery or knee or hip replacement
Duration	Up to 12 hours	Up to 12 hours	Up to 72 hours	Up to 72 hours	Up to 12 hours	Up to 72 hours

IV = Intravenous; PCA = Patient controlled analgesia

a. Includes only patients who received their second dose of study drug within 20-25 minutes of the first dose; patients had access to up to 45 mcg/hour as needed.

9.4 Additional Details for Clinical Studies

Table 26: Summary of Secondary Endpoints

Study	Endpoint
Study 202 (bunionectomy)	• SPID by evaluation time point • Total pain relief by evaluation time point • Pain intensity by evaluation time point • PID by evaluation time point • Pain relief by evaluation time point • PRID by evaluation time point • Proportion of patients requiring analgesics due to inadequate analgesia over the 12-hour study period. • Proportion of patients who responded in each category of the Patient Global Assessment • Total number of doses used over the 12-hour study period • Time to first use of rescue opioid medication and total number of doses of rescue opioid medication used • Time to onset of perceived and meaningful analgesia
Study 301 (abdominal surgery)	• SPID1 • SPID24 and SPID48 • TOTPAR12, TOTPAR24, and TOTPAR48 • SPRID12, SPRID24, and SPRID48 • Proportion of patients who terminate from the study due to inadequate analgesia • Proportion of patients requiring rescue opioid medication due to inadequate analgesia • Proportion of patients and healthcare professionals who responded to the global assessments as “excellent” or “good” • Proportion of patients and healthcare professionals who responded in each category of the global assessments • Pain intensity by evaluation time point • PID by evaluation time point • Pain relief by evaluation time point • PRID by evaluation time point • Proportion of patients who complete 24 hours in the study and do not require study drug after the 24-hour study period • Time to first use of rescue opioid medication • Total number of doses of study drug and rescue opioid medication used over 48-hour study period • Mean duration of inter-dosing interval over the 48-hour study period

Study 302 (ER)	• TOTPAR1 • SPID up to each evaluation time point • TOTPAR up to each evaluation time point • Pain intensity at each evaluation time point • PID at each evaluation time point • Pain relief at each evaluation time point • PRID at each evaluation time point • Proportion of patients who terminate from the study due to inadequate analgesia • Proportion of patients requiring rescue opioid medication due to inadequate analgesia • Proportion of patients and healthcare professionals who responded to the global assessments as "excellent" or "good" • Proportion of patients and healthcare professionals who responded in each category of the global assessments • Total number of doses of study drug used • Mean duration of inter-dosing interval • Time to first use of rescue opioid medication • Total number of doses of rescue opioid medication used
Study 303 (older post-operative)	• SPID1 • TOTPAR1 • TOTPAR12 • SPID up to each evaluation time point • TOTPAR up to each evaluation time point • Pain intensity at each evaluation time point • PID at each evaluation time point • Pain relief at each evaluation time point • PRID at each evaluation time point • Proportion of patients who terminate from the study due to inadequate analgesia • Proportion of patients requiring rescue opioid medication due to inadequate analgesia • Proportion of patients and healthcare professionals who responded to the global assessments as "excellent" or "good" • Proportion of patients and healthcare professionals who responded in each category of the global assessments

PID = Pain intensity difference from baseline; PRID = Pain relief intensity difference from baseline; SPID = Summed pain intensity difference from baseline; SPRID = Summed pain relief intensity difference from baseline; TOTPAR = Total pain relief

9.5 Study 202 (Bunionectomy) – Synopsis of Safety

In Study 202, the 12-hour placebo-controlled, post-bunionectomy study, 95.0% of patients in the DSUVIA 30 mcg group received study drug for at least 4 hours, 40.0% received study drug for at least 10 hours, and 27.5% received study drug for at least 11 hours. In the DSUVIA 20 mcg group, 97.5% of patients received study drug for at least 4 hours, 40.0% received study drug for at least 10 hours, and 15.0% received study drug for at least 11 hours. In the placebo group, 95.0% of patients received study drug for at least 4 hours, 35.0% received study drug for at least 10 hours, and 15.0% received study drug for at least 11 hours.

There were two SAEs, both reported in the DSUVIA 20 mcg group (severe osteomyelitis of the foot and moderate cellulitis of the foot), neither of which was related to study drug. The onset of these events was more than one week after the last dose of study drug.

Two patients (both in 30 mcg group) each had two AEs that resulted in the discontinuation of study drug. The AEs causing discontinuation were chest discomfort and worsening anxiety in one patient, and respiratory rate decreased and sedation in the second patient. The patient who discontinued due to respiratory rate decreased and sedation was a 45-year old white male who had a relevant medical history of chills and asthma. Ongoing medical conditions included seasonal allergies and bunion on the left foot. Concomitant medications included subcutaneous lidocaine for block anesthesia; intravenous midazolam, fentanyl, and propofol for anesthesia; Ancef for prophylaxis infection; supplemental oxygen; and Zofran for nausea. He recovered after study medication was withdrawn. Naloxone reversal was not required as his oxygen saturation never decreased below 95%.

AEs were reported in 15.0%, 57.5%, and 80.0% of patients in the placebo group, DSVUVIA 20 mcg group, and DSVUIA 30 mcg group, respectively. All AEs were mild or moderate in severity, except for a severe event of respiratory rate decreased in one patient in the DSUVIA 30 mcg group and a severe event of osteomyelitis of the foot in a patient in the DSUVIA 20 mcg group. The most frequently reported AEs for all patients were nausea (39.0%), vomiting (17.0%), dizziness (14.0%), and somnolence (11.0%). There were significant dose-dependent differences among treatment groups for nausea ($p < 0.001$), vomiting ($p = 0.021$), and somnolence ($p = 0.011$).

9.6 REMS Supporting Document

Note: There has been one important modification made to the proposed DSUVIA REMS program appended here. Following consultation with pharmacists, emergency medicine physicians, and pain management experts, AcelRx has decided to mandate any healthcare facility wishing to become REMS-certified, that they have "recent experience administering IV opioids." This language has been added to the attestations required of the Authorized Representative during the REMS certification process and can be quickly and effectively verified against existing pharmacy fulfillment databases. AcelRx believes this additional requirement/distribution restriction will further protect patients by keeping DSUVIA out of healthcare facilities that lack experience with IV opioids and airway management.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) SUPPORTING DOCUMENT

NDA 209,128
DSUVIA™ (sufentanil sublingual tablet 30 mcg)

Class of Product: Opioid Agonist

AcelRx Pharmaceuticals, Inc.
351 Galveston Drive
Redwood City, CA 94063

Contact Information:
Pamela Palmer, MD, PhD
Chief Medical Officer
650-216-3504

March 2018

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1 BACKGROUND

The goal of this Risk Evaluation and Mitigation Strategy (REMS) is to mitigate the risk of respiratory depression resulting from inappropriate administration by ensuring that the sufentanil sublingual tablet 30 mcg ("DSUVIA") is dispensed only in certified healthcare facilities or services and that healthcare providers ("HCP") are informed about the safe use of DSUVIA, including proper administration and monitoring. Healthcare facilities and services for purposes of the DSUVIA REMS are defined as those meeting the following criteria:

a. A licensed pharmacy or HCP with DEA registration for CII drugs who will oversee ordering and administration of the medication;

b. Access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone.

DSUVIA is a non-invasive, hand-held, pre-loaded, single-dose applicator ("SDA") containing one 30 mcg tablet of sufentanil that is designed to provide HCP-controlled analgesia in medically supervised settings. Sufentanil tablets are a new immediate-release formulation of sufentanil, an opioid agonist which is subject to abuse and/or diversion and which has a CII class designation under the Controlled Substances Act (21U.S.C. 811[b], 811[c]). DSUVIA comes in a sealed, tamper-evident pouch and will only be opened by the HCP just prior to administration of a dose, once it is determined that the patient needs an opioid analgesic. The HCP places the SDA under the patient's tongue and deploys the tablet to the sublingual space. DSUVIA can be readministered as needed for pain control, with no less than one hour between doses, by opening a new pouch and beginning the process over again. The maximum cumulative daily dose available of sufentanil is 360 mcg or 12 tablets within 24 hours (12 hours x 30 mcg/dose). The proposed indication for DSUVIA 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 medically supervised settings. DSUVIA will not be available via retail pharmacies and is not intended for home use or for use in children.

1.1 Design Features and Proper Administration

The 30 mcg formulation is a blue-colored tablet with a volume of approximately 7 mcL with dimensions of approximately 3 mm in diameter and 0.85 mm in thickness. Each sublingual tablet contains 30 mcg of sufentanil base corresponding to 45 mcg of sufentanil citrate. All excipients are inactive and are generally recognized as safe (GRAS) status. The tablet has been designed in a disc-shaped form with a flattened face in order to provide increased surface area for adhesion and drug elution. By virtue of its very small size, the tablet can comfortably adhere to the sublingual mucosa within seconds after administration and provoke minimal taste or saliva response which minimizes amount of swallowed drug. One tablet is pre-filled in the single-dose applicator (SDA) and is to be administered only by an HCP in a certified, medically supervised setting.

The SDA is individually packaged and sealed in a foil pouch with an oxygen absorber. All SDA components are molded from Profax (polypropylene) and depending on the component, may contain colorant. All components are suitable for short-term (< 24 hour) contact with oral mucosa and meet ISO 13485 requirements for biocompatibility. Prior to dosing the patient, the HCP should remove the pouch from the controlled access storage unit appropriate for a Drug Enforcement Agency (DEA) Schedule II narcotic, tear open at the notch across the top and remove the single SDA. The two sides of the opaque lock should be squeezed together simultaneously to release it from the pusher. The patient should be asked to elevate his/her tongue, to the roof of his/her mouth if possible, and the HCP will place the tip of the SDA, near the patient's sublingual space, without touching the patient's tongue or mouth. It is recommended that the SDA rest lightly on the patient's lower teeth or lip. The HCP will depress the pusher which will allow the sufentanil tablet to be delivered in the sublingual space.

The sufentanil tablet should be allowed to dissolve under the tongue and should not be crushed, chewed, or swallowed. Patients should not eat or drink, and should minimize talking for 10 minutes after the drug has been administered. Ice chips may be used if the patients' mouth is excessively dry. After dosing, the empty SDA should be properly discarded by the HCP into a biohazard container.

1.2 Current Treatment Options and Advantages of Sufentanil and the Tablet Formulation

Although novel classes of analgesics have been discovered recently, opioids still remain the most powerful of pain relievers. While many analgesics provide relief in limited settings, for example, anti-inflammatory agents relieve the pain of mild-to-moderate inflammation and anti-convulsant therapy is often used to treat the pain of nerve injury, opioids are effective for a variety of painful conditions. Many patients suffer from acute pain in settings where the availability of intravenous (IV) access may be limited. Additionally, certain patient populations such as the elderly, obese, hypovolemic and needle-phobic have historically presented unique challenges with regard to vascular access in Emergency Medicine settings (Witting et al, 2017). Therefore, there is a need for rapid-acting opioid analgesics for patients with moderate-to-severe acute pain, and optimally, an opioid without an invasive route of delivery.

To date, the most common opioid used to treat moderate-to-severe pain is morphine. Morphine, while often an effective analgesic, can produce many undesirable side effects, such as sedation, which can lead to oxygen desaturation and respiratory depression. Accumulation of the active metabolites of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), also pose a risk, especially after repeated use and in patients with impaired renal function (Sear et al., 1989a; 1989b; Ratka et al., 2004). M3G can accumulate rapidly and may cause dysphoria and agitation. M6G is a more potent opioid analgesic than morphine, which builds up less rapidly than M3G, but can lead to delayed respiratory depression. Morphine is associated with a frequent rate of adverse events, including nausea, vomiting, pruritus, urinary retention, sedation, and respiratory depression (Hutchison et al., 2007). Morphine is known to release histamine from mast

cells and can often produce hypotension and other histamine-related side effects when delivered as a bolus administration (Hermens et al., 1985). Meperidine has also been commonly used to treat acute pain episodes, however, its metabolite, normeperidine, can produce seizures and therefore the repetitive use of meperidine in the acute setting has been essentially eliminated (McHugh, 1999).

Due to the side effects of morphine and meperidine and their metabolites, opioids such as hydromorphone, oxycodone and fentanyl are gaining popularity for use in the treatment of acute pain. Oral opioids are fairly slow in onset of action (30 - 60 minutes) and are often combined with acetaminophen, thereby limiting their usefulness in moderate-to-severe pain, since sudden and dramatic increases in the dosing of these medications can result in liver toxicity. Transmucosal fentanyl products (e.g., Actiq®, Fentora®) avoid the issue of acetaminophen-induced liver toxicity and slow onset of analgesia but suffer from long plasma half-lives (ranging from 6-20 hours depending on dose and the product). Also, due to the 35% bioavailability of the large fraction of swallowed fentanyl from these large dosage forms, the time to peak plasma concentration (T_{max}) is quite variable (20 – 240 minutes) depending on the percent of drug taken up transmucosally versus from the stomach. Both the prolonged half-life and erratic T_{max} can make titration difficult in the acute pain setting due to the dangerous phenomenon of "dose-stacking." This can occur when a repeat dose is administered before the peak effect of the previous dose and a summation of peak plasma concentrations can lead to significant side effects, such as respiratory depression. As a result, a clinical need remains for a rapidly acting, potent analgesic which does not contain acetaminophen and which has a less prolonged half-life and more consistent T_{max} than fentanyl to avoid dose-stacking.

Sufentanil, a synthetic opioid analgesic, is characterized by rapid CNS penetration and high selectivity and affinity for mu opiate receptors, suggesting it may be an appropriate therapy for treatment of acute pain in medically supervised settings. Due to the highly lipophilic nature of sufentanil, the brain-plasma equilibration half-life (referred to as $t_{1/2ke0}$) has been demonstrated to be approximately 6 minutes, where the $t_{1/2ke0}$ for morphine averages approximately 3 hours (Lötsch, 2005). Rapid equilibration with CNS opioid receptors helps avoid delayed dose-stacking with repeated dosing events. The lipophilicity of sufentanil also allows this drug to be rapidly absorbed from sublingual tissues, enabling a non-invasive route of administration. Published studies also demonstrate that sufentanil may produce significantly less respiratory depressive effects relative to its analgesic effects than other opioids (Clark et al., 1987; Ved et al., 1989; Bailey et al., 1990; Conti et al., 2004). This evidence fits well with preclinical data demonstrating that the therapeutic index of sufentanil (lethal dose in 50% of animals/effective dose in 50% of animals; LD_{50}/ED_{50} = 26,700) is significantly higher than most clinically used opioids, such as fentanyl (LD_{50}/ED_{50} = 300) and morphine (LD_{50}/ED_{50} = 70) (Mather, 1983, 1995).

Sufentanil, as opposed to morphine and hydromorphone, has no active metabolites, therefore reduced renal clearance in the elderly or in patients with active renal disease will not significantly affect dosing in these populations. Pharmacokinetic studies of intravenous sufentanil have demonstrated no clinically meaningful differences based on age (Matteo et al., 1990), liver or kidney function (Fyman et al., 1988, Chauvin et al., 1989). Although

one study has demonstrated moderate increases in elimination half-life and volume of distribution in obese patients, plasma clearance and other pharmacokinetic measurements of time and extent exposure to drug were unchanged in this population (Schwartz et al., 1991).

In addition to the benefits of the active drug substance, sufentanil, the sufentanil tablet is a new formulation and route of sufentanil drug substance administration. The approved product is Sufenta for IV or epidural administration. The tablet formulation is an immediate-release drug formulation with high transmucosal bioavailability and low oral bioavailability (less than 10%; IAP101). AcelRx believes that the sufentanil sublingual tablet formulation presents no new or additional safety concerns and that the following additional attributes enhance the security of this opioid for use in medically supervised settings:

- The Cmax of DSUVIA is more than 17-fold lower than the Cmax of dose equivalent Sufenta (63.14 vs. 1073 pg/mL respectively, SAP101), and both the T_{max} and plasma context-sensitive half-time are prolonged in relation to IV sufentanil administration. This pharmacokinetic profile is usually considered less desirable for abusers. Sufentanil exposure after sublingual administration is similar to that reported in the literature for epidural administration (Hansdottir, 1995; Taverne, 1992).

- Unlike extended-release, long-acting opioid products, using another route of administration or tampering with the sufentanil tablet formulation would not expose the patient to a clinically meaningful higher amount of drug than the 30 mcg in each sufentanil tablet that is delivered through its intended route of administration.

- The tablet can be seen in the clear plastic SDA so visual verification is possible that the dose is present when removed from the foil pouch. Furthermore, when the tablet is dispensed from the SDA, the pusher portion of the SDA has been designed so it will not retract such that a counterfeit/dummy tablet could not be inserted and the SDA reassembled.

- The solid dosage form of the sufentanil tablet avoids the diversion issues related to clear liquid opioids in medically supervised settings, which has been documented as a significant in-hospital diversion issue and can result in patient nosocomial infections, such as hepatitis C, when infected HCPs divert and abuse clear liquid opioids and return materials into service (Berge 2012; Hellinger 2012; Burke 1999).

1.3 Summary of Efficacy and Safety from Phase 3 Clinical Trials

The primary endpoint for the two double-blind, placebo-controlled pivotal studies in bunionectomy (SAP202) and abdominal surgery (SAP301) patient populations was predefined as the summed pain intensity compared to baseline over the 12-hour study period (SPID12). In both studies, the SPID12 was statistically significantly higher for sufentanil sublingual tablet 30 mcg compared to placebo tablets, both administered via

HCP and with a minimum 60-minute dosing interval. Secondary endpoints, including SPID24, SPID48, total pain relief over various time points (TOTPAR12, TOTPAR24, and TOTPAR48), and patient and healthcare provider assessment of method of pain control, were all highly statistically superior for active drug compared to placebo. Safety assessments demonstrated that sufentanil tablets, were well tolerated, had an adverse event profile similar to that of placebo for the majority of adverse reactions, and were typical of post-operative patients receiving opioid analgesia. Drop-out rates due to adverse reactions were not significantly different from those of placebo. Adverse reactions suggestive of an abuse potential (euphoria, hallucinations, etc.) were minimal and also not significantly different from placebo.

The open-label studies in both emergency medicine and post-operative patients provided addional support for the efficacy and safety of the sufentanil subligual tablet 30 mcg in treating a wide variety of patients with moderate to severe acute pain. SAP302 enrolled trauma patients with fractures, joint dislocations, lacerations and burns while SAP303 included only patients over 40 years of age, and many with co-morbidities such as renal amd hepatic impairment. DSUVIA therapy provided prompt and effective pain relief across both studies and again, adverse reactions suggestive of an abuse potential (euphoria, hallucination, etc.) were minimal.

1.4 Risk Identification and Characterization

Sufentanil is a known addictive compound, and throughout the clinical studies, AcelRx has attempted to ascertain any signs or symptoms of abuse and determine whether diversion of the sufentanil tablets occurred. AcelRx collected and analyzed Phase 2 and Phase 3 data for abuse-related adverse reactions such as euphoria, altered mental states, dysphoria, hallucinations, etc. Site monitors and the clinical supply depot vendor performed 100% drug accountability assessments to ensure overall compliance and reconciliation of the study drug throughout the Phase 3 studies. There were no cases of abuse or diversion identified across the clinical development program, on behalf of either a patient, study staff or healthcare provider.

The sufentanil tablet will have a CII class designation under the Controlled Substances Act and will be subject to the restrictive CII regulations regarding manufacturing and production quotas, manufacturing and distribution site security requirements, dispensing and prescribing limitations, and import/export regulations. In addition, each facility and service will have its own standard operating procedures for handling and disposal of CII drugs. In-patient and out-patient hospitals as well as Emergency Medicine responders use CII drugs extensively, and the monitoring, documentation, and reconciliation of these medications is highly regulated.

1.5 Regulatory Advice Regarding REMS

At the End of Phase 2 Meeting for the Sufentanil Sublingual Tablet System (Zalviso®; NDA 205265), the Food and Drug Administration (FDA) informed AcelRx that a REMS program would be required for product registration and should be focused on keeping the

product's use confined to a hospital setting. AcelRx collaborated with the FDA over the next 2 years to develop an acceptable REMS program that would include Elements to Assure Safe Use (ETASU; parts B and C) as well as educational and communication tools. This Zalviso REMS program received a "pre-clearance" from the Agency in early 2015, and given the similarities between Zalviso and DSUVIA, an analgous REMS program is being proposed to ensure the benefits of the sufentanil sublingual tablet 30 mcg outweigh the risks. The *FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Draft Guidance for Industry: September 2016) and *Format and Content of a REMS Document* (Draft Guidance for Industry: October 2017) were also references in preparing this REMS proposal.

1.6 Proposed Risk Mitigation Approach

To mitigate the risk of respiratory depression resulting from inappropriate DSUVIA administration, AcelRx will implement a restricted distribution system such that DSUVIA will only be shipped to certified healthcare facilities and services. Healthcare facilities and services (medically supervised settings) for purposes of the DSUVIA REMS are defined as those meeting the following criteria:

a. A licensed pharmacy or healthcare provider with DEA registration for CII drugs who will oversee ordering and administration of the medication;

b. Access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone.

AcelRx will require that all healthcare facilities and services that order, prescribe or distribute DSUVIA, become certified by enrolling in the DSUVIA REMS Program and comply with the Program requirements. Enrollment in the REMS will be achieved through the execution of a *Healthcare Facility/Service Enrollment Form* and will include an attestation by an Authorized Representative (AR) of the healthcare facility or service. To further restrict use of the product to medically supervised settings only, healthcare facilities and services will be required to have provisions in place which prevent DSUVIA from being dispensed or prescribed for take home use. Product labeling will also include a boxed warning indicating that DSUVIA is not appropriate for take home use, that sufentanil, like other opioid agonists, carries the potential for abuse and that inappropriate administration and monitoring can lead to life-threatening respiratory depression. The REMS will ensure that the benefits of DSUVIA outweigh the risk of respiratory depression and will consist of Elements to Assure Safe Use (ETASU), an Implementation System and a timetable for submission of assessments. The ETASU (B & C; requiring healthcare facility/service certification and restriction to medically supervised settings only, respectively) portion of the REMS will focus exclusively on the safety messages related to the drug product, specifically the risk of respiratory depression, and will include the following materials:

- *Healthcare Facility/Service REMS Enrollment Form*;
- *Dear Healthcare Provider* (DHCP) Letters;
- *DSUVIA REMS Safety Brochure: Guide for Healthcare Providers and Pharmacists*;
- *Directions for Use* – A short guide detailing the appropriate administration of DSUVIA.
- DSUVIA REMS Website.

The following additional DSUVIA resources for the HCP will be available on the product website (www.DSUVIA.com):

- **Directions for Use** – A short guide detailing the appropriate administration of DSUVIA.
- **Dosing and Administration Video** – A brief video describing proper dosing and administration of DSUVIA

2 GOALS

The goal of the proposed REMS for the sufentanil sublingual tablet 30 mcg (DSUVIA) is to mitigate the risk of respiratory depression resulting from inappropriate administration by:

- Ensuring that DSUVIA is dispensed only within certified healthcare facilities or services; and
- Informing healthcare providers about the safe use of DSUVIA, including proper administration and monitoring.

3 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

3.1 Elements to Assure Safe Use

In accordance with FDCA 505-1(e)(3), AcelRx will implement ETASU B & C in order to support the goal of the REMS program, which is to mitigate the risk of respiratory depression resulting from inappropriate administration and monitoring. AcelRx will ensure that all healthcare facilities and services distributing DSUVIA are certified (B) and that the use of DSUVIA is limited to medically supervised settings only (C). FDA has worked with AcelRx to design the following materials in order to efficiently and effectively implement the REMS requirements and examples of each can be found in the appendices of the main REMS document:

3.1.1 Healthcare Facility/Service Enrollment Form

The Enrollment Form will be completed by an AR prior to receiving any drug product and includes an attestation that (1) the AR has been designated by the healthcare facility or service to complete the form, (2) the healthcare facility or service offers management of moderate to severe acute pain in adult patients, (3) the AR understands the risks of DSUVIA and has reviewed the *DSUVIA REMS Safety Brochure* and the DSUVIA Prescribing Information, including the *Directions for Use*; (4) the healthcare facility or service qualifies as a medically supervised setting by having: (a) a licensed pharmacy or HCP with DEA registration for CII drugs who will oversee ordering and administration of the medication;(b) access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone; (5) training on the DSUVIA REMS Program, including Administration Information (Directions for Use), will be made available to all staff involved in dispensing or administering DSUVIA per the institutions's standard operating procedures, (6) the healthcare facility or service has processes and procedures in place to ensure DSUVIA is not dispensed for use outside of this certified healthcare facility or service; (7) the DSUVIA REMS DHCP Letters may be distributed to staff and department heads, as appropriate, to inform them about the serious risks associated with DSUVIA, (8) the AR will comply with requests to be audited by AcelRx or designee to ensure that all processes and procedures are in place and are being followed for the DSUVIA REMS Program, and that appropriate documentation is available upon request, (9) the AR will renew this healthcare facility or service's enrollment in the DSUVIA REMS Program every 3 years after initial enrollment.

3.1.2 Dear Healthcare Provider (DHCP) Letters

AcelRx will make available a series of *Dear Healthcare Provider* Letters targeted only at providers in certified healthcare facilities and services. The purpose of the Letters will be to inform providers about the risk of respiratory depression resulting from inappropriate administration of the sufentanil sublingual tablet 30 mcg. The AR responsible for signing the attestation may distribute the Letters to the heads of the following departments, as appropriate, after the institution has enrolled in the DSUVIA REMS Program:

- Emergency Medicine
- Pharmacy
- Nursing
- Surgery
- Anesthesia

The *Dear Healthcare Provider* Letters will be distributed directly to the AR via electronic or hard copy mail. All DHCP Letters will also be available through a specific link on the

DSUVIA REMS website (www.DSUVIAREMS.com) as well as through the toll-free Medical Information Contact Center (1-855-925-8476).

3.1.3 DSUVIA REMS Safety Brochure: Guide for Healthcare Providers and Pharmacists

The *DSUVIA REMS Safety Brochure* will be provided along with the *Prescribing Information* to healthcare facilities or services that attempt to order DSUVIA and are not yet certified, inquire about how to become certified and upon REMS certification. The Guide will educate pharmacists and HCPs practicing in certified facilities or services on the following messages:

1. DSUVIA must be administered only by a healthcare professional, **within in a certified healthcare facility or service.**

2. The healthcare facility or service must have the following in order to qualify as a medically supervised setting:

    a. A licensed pharmacy or healthcare provider with DEA registration for CII drugs who will oversee ordering and administration of the medication;

    b. Access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone.

3. DSUVIA is to be administered no more frequently than once per hour, not to exceed 12 tablets in 24 hours. Patients should be monitored for signs and symptoms of respiratory depression.

4. With each dosing, the HCP should visually inspect that the DSUVIA tablet has been successfully delivered to the patient's sublingual space.

    - If the tablet is found outside of the mouth, the HCP should retrieve and discard in Scheduled drug waste container;

    - If the tablet cannot be located, the HCP should assume that the patient received the DSUVIA tablet and not dose again for one hour.

5. Patients on chronic opioid therapy or with a history of opioid use may require higher analgesic doses than are available with DSUVIA. **Therefore, these patients should be evaluated frequently** to ensure they are receiving adequate analgesia.

6. DSUVIA must never be dispensed for pain management at home or continued after the patient is discharged or released from the certified healthcare facility or service.

The REMS Safety Brochure will also be available through AcelRx representatives and will be sent to certified healthcare facilities and services with each shipment of DSUVIA.

3.1 REMS Website

Web-based information and REMS training materials for healthcare providers will be posted on a dedicated REMS website for DSUVIA (www.DSUVIAREMS.com) within 10 days of the REMS Program approval and will include the following materials:

- REMS Program Overview (to include goal of the DSUVIA REMS program and who should be informed about the DSUVIA REMS program)
- Healthcare Provider Resources
  - *REMS Safety Brochure: Guide for Pharmacists and Healthcare Practitioners*
  - DSUVIA Directions for Use
  - *Healthcare Facility/Service Enrollment Form*
  - Dear Director of Hospital Pharmacy Letter
  - Dear Chief of Emergency Medicine Letter
  - Dear Chief of Anesthesia Letter
  - Dear Chief of Nursing Letter
  - Dear Chief of Surgery Letter
- Indication
- Full Prescribing Information
- Important Safety Information
- Contact Information for Adverse Event Reporting
- Request for In-service Training and Medical Information (link to appropriate contact person)
- Links for Privacy, Terms of Use, Contact, etc. (bottom of page)

3.2 Implementation System

- AcelRx will ensure that DSUVIA is only distributed to certified healthcare facilities and services by:

- Ensuring that wholesalers/distributors who distribute DSUVIA to certified facilities or services comply with the program requirements for wholesalers/distributors. In order for a wholesaler/distributor to distribute DSUVIA, the wholesaler/distributor must:

  a. Put processes and procedures in place to verify, prior to distributing DSUVIA, that the healthcare facility or service is certified;

  b. Train all relevant staff on the DSUVIA REMS Program requirements;

  c. Agree to be audited to ensure that all processes and procedures for the DSUVIA REMS Program are in place and are being followed;

  d. Agree to maintain distribution records and provide distribution data to the DSUVIA REMS Program.

- Ensuring that wholesalers/distributors maintain distribution records of all shipments of DSUVIA to certified healthcare facilities or services and agree to provide the data to the DSUVIA REMS Program.

- Monitoring and auditing the wholesalers/distributors within 180 days of the date the wholesaler/distributor initiates its first DSUVIA shipment to ensure that all processes and procedures are in place and functioning to support the requirements of the DSUVIA REMS Program. Corrective action will be instituted by AcelRx if noncompliance is identified.

- AcelRx will maintain a validated, secure database of facilities and services that are certified to dispense DSUVIA under the DSUVIA REMS Program. AcelRx will ensure that the facility/service certification requirements are met and may de-certify any non-compliant facility or service if the requirements do not continue to be met.

- AcelRx will maintain a DSUVIA REMS Program Contact Center to support certified facilities and services interfacing with the DSUVIA REMS Program.

- AcelRx will ensure that all materials listed in or appended to the DSUVIA REMS document are available through the DSUVIA REMS Program Website [www.DSUVIAREMS.com] or can be accessed by calling the DSUVIA REMS Program Contact Center (1-855-925-8476).

- AcelRx will monitor and audit 100% of the first 10-15 certified healthcare facilities within 180 days of certification, to assess for compliance with DSUVIA REMS. The results of that assessment will infom a statistically verified sampling of certified healthcare facilities to be audited movinf forward to ensure that all processes and procedures are in place and functioning to support the requirements of the REMS Program. Corrective action will be instituted by AcelRx if noncompliance is identified.

- AcelRx will take reasonable steps to improve implementation of and compliance with the requirements in the DSUVIA REMS Program based on monitoring and evaluation of the Program.

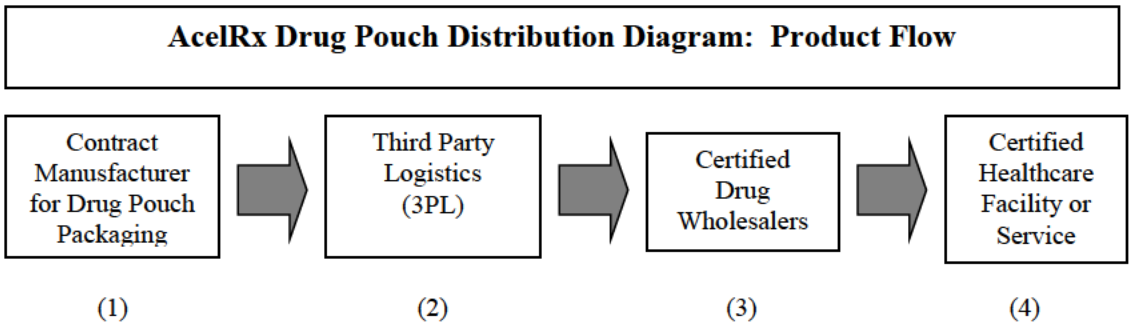
3.3 Supply Chain Integrity of the DSUVIA Drug Pouches

The SDA contains sufentanil which is designated as a CII product under the Controlled Substances Act. AcelRx will require a Drug Enforcement Administration (DEA) Form 222 or the equivalent electronic Controlled Substance Ordering System (CSOS) document for all Drug Pouch shipments.

AcelRx has an agreement in place with a contract manufacturer, Sharp Packaging Solutions, to package the final SDA product. AcelRx commits to a Drug Pouch distribution model from the contract manufacturer (Sharp) to a Third Party Logistics (3PL) supplier; from the 3PL supplier to a limited number of select certified wholesalers; and from the wholesalers to certified healthcare facilities and services to ensure that Drug Pouches are provided only to REMS certified institutions. The distribution model will define criteria for selection of only those drug wholesalers that can demonstrate successful implementation of class trade restrictions combined with DEA 222/CSOS order monitoring. By selecting and shipping only to wholesalers with these capabilities, limiting shipment from these wholesalers to specific class of trade customers and periodically auditing the class of trade shipped to by the wholesalers, AcelRx is assuring the integrity of the distribution of the Drug Pouch from Sharp to the healthcare facility/service. AcelRx anticipates having a narrow channel of distribution through less than six wholesalers that will serve as authorized distributors of record.

The distribution model will employ a strict linear supply chain designed to deter diversion of Drug Pouches into channels outside the healthcare facility/service market. Each component of the chain will have measures in place to maintain chain of custody control of the CII product to its final destination. A single 3PL supplier will be used and will be under contractual obligation to provide Drug Pouches only to authorized, pre-specified drug wholesalers that AcelRx has determined meet appropriate criteria for distribution only to certified facilities/services.

The linear chain of custody is displayed below:



Stage 1: AcelRx SDA Packaging Site. At the SDA packaging site (Sharp Packaging Solutions; number 1 in the diagram above), the following control measures are in place:

- Packaging and labeling of the Drug Pouches
    - Per DEA regulations covering CII drugs, strict inventory controls are in place at Sharp Packaging Solutions, the contract manufacturing facility responsible for packaging and labeling of the final SDA pouches. Yields are calculated with each batch, and after the tablet has been loaded on to the SDA, any discrepancies from expected final filled SDA count are investigated and documented in accordance with internal procedures.
- Recording of shipments to the 3PL supplier
    - Before shipment of any lot of filled Drug Pouches from Sharp to the 3PL supplier, AcelRx Quality Assurance must provide GMP review and approval of the batch. This will be done via review of batch records, deviation reports, and lot clearance test data. A check will be conducted to ensure that the number of SDAs packaged per lot (less those sampled for lot clearance, stability testing, and reserve samples per GMP regulations) is consistent with the lot quantity shipped to the 3PL supplier.

Stage 2: AcelRx 3PL Supplier. AcelRx plans to appoint a single company to handle third party logistics for the System (number 2 in the diagram above). Selection criteria for the appointment of a 3PL supplier warehouse to support distribution of the Drug Pouch include:

- Current experience successfully handling CII items, including, but not limited to:
    - Demonstration that the 3PL supplier maintains a DEA Controlled Substances License
    - Proof that the 3PL supplier maintains CII vault storage and handling processes at all potential distribution points
    - Demonstration that IT systems are in place to track and trace shipments to each customer in the chain of custody for which it is responsible
    - Demonstration that the 3PL supplier maintains shipping and handling relationships to licensed wholesalers only. It is anticipated that each selected wholesaler will meet AcelRx's strict definition for consideration as an authorized distributor of record.

- The 3PL supplier must be able to demonstrate that it has control processes that allow for:
    - Monitoring of shipments into the 3PL supplier from Sharp
    - Identifying current inventory on hand and shipments on order and in transit at any given time
    - Monitoring of shipments from the 3PL supplier to the certified wholesalers' distribution locations
- AcelRx will require the 3PL supplier to provide monthly inventory reports to AcelRx or designee to ensure strict monitoring of inventory control and shipment tracking into and out of the 3PL supplier.

Stage 3: Drug Wholesalers. Drug wholesalers (number 3 in the diagram above) will be the final conduit before the Drug Pouch is delivered to a certified healthcare facility or service and will play an important role in supporting the restriction of trade in supplying key data necessary to monitor and maintain restrictions within the channel. AcelRx plans to maintain a very select and limited number of wholesalers that can act as authorized distributors of record for DSUVIA. The selection criteria for these wholesalers will include:

- Demonstration of current licensure in all Distribution Centers to handle CII product distribution;
- Demonstration of existing account status with AcelRx's selected 3PL supplier;
- Demonstration of CII vault storage and handling processes that meet all DEA requirements for such storage;
- Demonstration that the wholesaler has IT systems in place to track and trace shipments to each customer in the chain of custody for which it is responsible;
- Demonstration that the wholesaler has existing shipping and handling relationships with healthcare facility/service accounts and that the wholesaler maintains complete records of each of those accounts in terms of their license to receive and dispense CII products.
- Demonstration that the wholesaler has the ability to limit sales to accounts if needed and to identify and flag accounts with suspicious ordering activity (i.e. facilities with frequent ordering or ordering substantially more than historical norm for their size/scope of practice);
- The ability to provide a weekly report of all Drug Pouches shipped to by location, date, and volume.

- Demonstration that the wholesaler can accept CSOS electronic ordering of the Drug Pouch and that it will be able to provide regular CSOS reports of orders for products shipped and not shipped where healthcare facilities/services have this ordering system in place. Items not shipped will include orders that were restricted due to filters put in place by the wholesaler;

- Willingness of the wholesaler to participate in the DSUVIA REMS Program and to comply with the Program requirements prior to shipment of drug product to any certified healthcare facility or service.

Supply Chain Integrity Monitoring by AcelRx. AcelRx will establish and maintain a supply chain integrity monitoring process covering movement of the Drug Pouch from Sharp to the 3PL supplier; from the 3PL supplier to the wholesalers (authorized distributors of record); and from the wholesalers to certified healthcare facilities/services, to identify any potential compromises in the supply chain that could result in diversion. AcelRx, or a third party contracted by AcelRx, will conduct periodic audits to verify compliance. Based on the results of the audits, AcelRx will take corrective actions, as necessary and appropriate.

Periodic audits may include:

- Quarterly audits and review of the contract manufacturer's (Sharp) inventory and handling of shipments to the 3PL supplier

- Quarterly audits of the 3PL supplier's inventory and storage, including shipments received from Sharp and shipments sent to the wholesalers

- Quarterly audits of wholesalers' shipments received and shipped, including inventory on hand, via Electronic Data Interchange (EDI) 852 Point of Sale data from the wholesalers, to which AcelRx will have direct access

- Quarterly audits of wholesalers' shipment names, addresses, and contacts of certified customers, via EDI 867 Product Transfer and Resale Reports, to which AcelRx will have direct access. AcelRx will immediately verify any account that appears not to be a certified healthcare facility/service customer.

Stage 4: Certified Healthcare Facilities & Services. Within 180 days of DSUVIA REMS certification, AcelRx will audit 100% of the first 10-15 active user facilities to assess variability with REMS compliance. Based on these findings, a statistically verified sampling of sites will be selected for audits moving forward. AcelRx will select facilities of varying size and scope to participate in this assessment from across diverse geographic areas in the US. These will include large and small community hospitals, academic institutions, inpatient hospitals and outpatient surgery centers. The information obtained from this assessment will enable AcelRx to determine whether the sufentanil tablet use can be accounted for within the healthcare facility/service boundaries and that HCPs are being trained properly on its use. It will also provide AcelRx with qualitative insight about what

is happening in a small sample of facilities to inform root cause analysis and potentially complement information on suspected diversion that may be received through the social conversation monitoring process (described below).

Audits are intended to determine the extent, if any, of diversion of Drug Pouches from the facility/service. This assessment will be in partnership with the facility/service and will assess missing Drug Pouches via DEA Form 106 submissions, thereby utilizing the facilities' or services' existing standard operating procedures for handling theft or loss of controlled substances. A recent report from the Minnesota Department of Health (MDH) and the Minnesota Hospital Association identified DEA Form 106 submissions as the most accurate means to follow healthcare facility drug diversion trends (MDH, 2012). Certified facilities/services will be requested to send reports to AcelRx quarterly and annually for at least the first two years after the assessment is initiated in the hospital.

AcelRx will additionally implement an online social conversation monitoring process to detect mentions and/or discussion surrounding DSUVIA that may indicate a potential diversion of product away from certified healthcare facilities/services. Targeting keywords related to the sufentanil sublingual tablet, millions of publically-accessible social and online media channels, including forums, blogs, Twitter, Facebook, Google+, etc., will be continuously monitored and then analyzed for mentions of these keywords, content insights, and information about the content publisher. In addition, AcelRx will participate in the RADARS® Program, which includes data from the Drug Diversion, Poison Center, Opioid Treatment, and Survey of Key Informants' Patients Programs. These findings will be compiled on an ongoing basis and will be consolidated for inclusion in the REMS Assessment Reports as needed.

AcelRx will notify the targeted healthcare providers and wholesalers, as applicable, if there are substantial changes to the DSUVIA REMS. Substantial changes include significant changes to the operation of the REMS Program or changes to the Full Prescribing Information that affect the risk-benefit profile of DSUVIA. Based on monitoring and evaluation of the DSUVIA REMS Elements to Assure Safe Use, AcelRx will take reasonable steps to improve implementation of these Elements and to maintain compliance with the DSUVIA REMS requirements to meet the goals of the REMS.

3.4 Timetable for Submission of Assessments

In order to assure that the REMS is meeting its goal; AcelRx will submit REMS Assessment Reports to the FDA at 6 months and 12 months from the initial date of approval of the REMS and yearly thereafter according to the following schedule:

Assessment Number	Reporting Interval (from time of original REMS approval)
1	6 months
2	12 months
3	24 months
4	36 months
5	48 months
6	60 months
7	72 months

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. AcelRx will submit each assessment so that it will be received by the FDA on or before the due date.

4 REMS ASSESSMENT PLAN

Assessments will include an evaluation of the effectiveness of the REMS and any areas for program improvements or modifications. Following approval of the DSUVIA REMS Program, FDA will communicate to AcelRx the exact data fields to be included in the REMS Assessment Reports.

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Format and Content of a REMS Document – Draft Guidance for Industry

Food and Drug Administration Center for Drug Evaluation and Research (CDER) & Center for Biologics Evaluation and Research (CBER). October 2017, Drug Safety, Revision 1

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