A Multicenter, Open-Label Trial to Evaluate the Overall Performance of the Zalviso System (sufentanil sublingual tablet system) 15 mcg

Protocol No. IAP312

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IND #75,051

STUDY APPROVALS

A Multicenter, Open-Label Trial to Evaluate the Overall Performance of the Zalviso System (sufentanil sublingual tablet system) 15 mcg
IAP312

Sponsor Approval:

Signature: _____ **Date:** _____
Name: Pamela Palmer, M.D., Ph.D.
Title: Chief Medical Officer

Signature: _____ **Date:** _____
Name: Mark Evashenk
Title: VP Clinical Operations

Signature: _____ **Date:** _____
Name: Yu-Kun Chiang, Ph.D.
Title: AcelRx Pharmaceuticals Statistical Consultant

Signature: _____ **Date:** _____
Name: Kim Gaumer
Title: VP, Regulatory Affairs& Quality Assurance

Investigator Agreement:
I have read Protocol IAP312 Amendment #1 "A Multicenter, Open-Label Trial to Evaluate the Overall Performance of the Zalviso System (sufentanil sublingual tablet system) 15 mcg" dated 13 January 2016 and agree to conduct the study in accordance with it.

Signature: _____ **Date:** _____

Print Name: _____

SYNOPSIS

Title: A Multicenter, Open-Label Trial to Evaluate the Overall Performance of the Zalviso System (sufentanil sublingual tablet system) 15 mcg	
Sponsor: AcelRx Pharmaceuticals, Inc. **Investigational Product:** sufentanil sublingual tablet system, 15 mcg **Active Ingredient:** sufentanil citrate	
Investigators: Multicenter **Country:** USA	**Protocol No.:** IAP312 **Clinical Phase:** 3
Patients: Up to 330 adult postoperative in-patients who are expected to require opioid analgesia for at least 24 hours, and up to 72 hours, after surgery will be enrolled in order to ensure at least 315 patients will receive study drug and provide Zalviso (sufentanil sublingual tablet system) 15 mcg performance data for analysis.	
Study Objectives: The objectives of this study are: • Assess device dispense failure rate with the modified Zalviso System design • Assess impact of System error 302 mitigations on overall System usability • Assess the incidence of misplaced tablets and drug accountability while patients were using the Zalviso System • Evaluate patient and nurse usability of, and satisfaction with, the Zalviso System to treat moderate-to-severe postoperative pain • Evaluate the efficacy and safety of the Zalviso System to treat moderate-to-severe postoperative pain	
Trial Design: The study is a multicenter, open-label trial for 24 hours, and up to 72 hours, in patients 18 years and older who are undergoing surgery and are expected to require opioid analgesia for at least 24 hours. Patients who meet all inclusion and exclusion criteria at screening and following surgery will receive the Zalviso System. Non-opioid analgesics may be used at any time along with the Zalviso System in a multimodal approach to the treatment of the patient's postoperative pain. However, supplemental opioid medication (2 mg IV morphine) will only be allowed in the first 30 minutes after the first on-demand dose of study drug has been administered if necessary to keep a patient comfortable. Otherwise, supplemental opioid medication (2 mg IV morphine, no more frequently than hourly) is allowed only for pain due to ambulation or with the initiation of passive range of motion therapy throughout the remainder of the study. A pain intensity and pain relief score should be obtained prior to each administration of supplemental opioid medication. Overall device performance and usability of the Zalviso System will be assessed by: proportion of patients with system-generated (device) errors and other failures of the device to function properly, number of patients with misplaced tablets (tablets inadvertently dispensed or dosed outside of the mouth), as well as the number of misplaced tablets, as assessed by study staff checks every 2 hours, and the Patient Usability Questionnaire (PUQ). Usability will also be assessed using the Nurse Usability Questionnaire (NUQ) which will be completed by study staff after they have experience with 5 or more patients or at the end of the study at the site.	

Pain intensity will be self-recorded by the patient prior to first dose of study drug and then pain relief and pain intensity will be recorded by the patient at the following time points after the first on-demand dose of study drug: ¼ [15 min], ½ [30 min], ¾ [45 min], 1, 2, 4, 6, 8, 10, and 12 hours, then every 4 hours at 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 hours. **During the study period, all PI, PR, and the patient global assessment (PGA) scores will be self-recorded by the patient in a source document provided by investigator's staff per the study schema.** The study staff must not record the patient's PI, PR, or global scores for the patient.

Satisfaction with analgesia will be assessed by: patient global assessment (PGA) and healthcare professional global assessment (HPGA) of the method of pain control on a four point scale where 1 = poor, 2 = fair, 3 = good, and 4 = excellent, patient reports of pain intensity on an 11-point numerical rating scale (NRS), where 0 = no pain, and 10 = worst possible pain, a five-point pain relief scale (0 = no relief, 1 = a little relief, 2 = moderate relief, 3 = a lot of relief, 4 = complete relief), and percentage of patients dropping out of the study due to inadequate analgesia. Also, the total number of doses of study drug administered will be recorded and average hourly use will be calculated from the dosing information. Use of supplemental opioid medication will also be recorded.

Patients displaying any one of the following:

- oxygen saturation levels that cannot be maintained at 95% or greater with or without the use of supplemental oxygen
- respiratory rate less than 8 bpm
- excessive sedation

will not be allowed to have access to study drug or supplemental opioid medication until these vital signs have improved. **Sites must document improvement of these vital signs in the source and eCRF.**

If the oxygen saturation is below 95% with supplemental oxygen, even if no other vital sign is abnormal and the patient does not improve following 2 arousal and vital sign checks 3 minutes apart, then the patient should be removed from the study.

If the respiratory rate is low (below 8 bpm but oxygen saturation is greater than or equal to 95% and no excessive sedation is present) or if excessive sedation exists (respiration and oxygenation are above limits), and each adverse event does not improve within 20 minutes under supervision with every 3 minute arousal and vital sign checks after discontinuing access to study drug, the patient should be removed from the study. If these two adverse events (low respiratory rate and excessive sedation) should occur simultaneously, then the more conservative withdrawal criteria should be followed: the patient should be removed from the study if after two arousal and vital sign checks 3 minutes apart, these symptoms do not improve.

All vital signs measured to manage oxygen desaturation and decreased respiratory rate must be recorded in the source and eCRF.

Heart rate and blood pressure will be recorded prior to administration of the first dose of study drug, and then when pain intensity and pain relief assessments are recorded at the following time points after the first on-demand dose: ¼ [15 min], ½ [30 min], ¾ [45 min], 1, 2, 4, 6, 8, 10, and 12 hours, then every 4 hours at 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 hours. These assessments may be collected up to 5 minutes before scheduled time to allow for the PI and PR assessments to be made at the scheduled time.

During the first 24 hours after the first dose of study drug, respiratory rate and oxygen saturation will be recorded prior to the first dose of study drug, then 15, 30, 45, and 60 minutes after the first dose of study drug, and then every 30 minutes. After 24 hours, respiratory rate and oxygen saturation will be recorded every 2 hours. These assessments may be collected up to 5 minutes before scheduled time to allow for the PI and PR assessments to be made at the scheduled time.

Safety will be monitored via periodic measurement of vital signs, continuous monitoring of oxygen saturation, assessment of adverse events (AEs), and the use of concomitant medications.

Inclusion Criteria at Screening:

1. Male or female patients who are 18 years of age or older.
2. Patients who are scheduled to undergo surgery under general or spinal anesthesia that does not include intrathecal opioids during the operation.
3. Patients classified as American Society of Anesthesiologists (ASA) class I - III (Appendix I).
4. Female patients of childbearing potential must be using an effective method of birth control at the time of screening visit and for 30 days following the end of the study period. Acceptable methods of birth control include oral or transdermal contraceptives, condom, spermicidal foam, intrauterine device (IUD), progestin implant or injection, abstinence, vaginal ring, or sterilization of partner. The reason for non-child bearing potential, such as bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or postmenopausal for > 1 year, must be specified. Patients using hormonal forms of contraception must also be willing to use a barrier method of contraception from screening through 30 days following the study period.
5. Post-surgical patients who have been admitted to the PACU, and are expected to have acute pain requiring opioids for 24 – 72 hours after surgery.
6. Patients who have the manual dexterity to handle the Zalviso System and are able to follow directions for use.
7. Patients who are willing and capable of understanding and cooperating with the requirements of the study.
8. Patients able to understand and communicate in English.
9. Patients who have provided written informed consent and signed the IRB approved consent form.

Exclusion Criteria at Screening

1. Patients who have taken an opioid for more than 30 consecutive days, at a daily dose of 15 mg or more of morphine (or equivalent), within the past 3 months prior to surgery (e.g. more than 3 doses per day of Vicodin®, Norco®, Lortab® with 5 mg hydrocodone per tablet).
2. Patients with a positive drug of abuse urine screen unless the positive test result is consistent with a prescribed medication
3. Patients with a history of opioid dependence within two years before the start of the study, defined as meeting the DSM-IV-TR™ Criteria for Substance Dependence specified in Appendix II.
4. Patients who have used any illicit drugs of abuse within five years before the start of the study.
5. Patients who have abused any prescription medication or alcohol within one year before the start of the study.
6. Patients with an allergy or hypersensitivity to opioids.
7. Patients who are currently taking monoamine oxidase inhibitors (MAOIs) or have taken MAOIs within 14 days of the first dose of study drug.
8. Patients with current sleep apnea that has been documented by a sleep laboratory study or are on home continuous positive airway pressure (CPAP).
9. Female patients who are pregnant (positive pregnancy test at screening or after hospital admission), breastfeeding or planning to breastfeed within 30 days of the last dose of the study drug.
10. Patients with a medical condition that, in the Investigator's opinion, could adversely impact the patient's participation or safety, conduct of the study, or interfere with the pain assessments, including chronic pain or active infection.
11. Patients who have cancer and are receiving radiation/chemotherapy and are expecting to receive radiation/chemotherapy within 72 hours after surgery.
12. Patients who require an additional scheduled surgical procedure within 72 hours of the surgery.
13. Patients who are expected to have postoperative analgesia supplied by a long-acting or continuous regional technique (e.g., spinal opioids or continuous nerve block).
14. Patients who received surgical premedication with long-acting opioid analgesics.
15. Patients who are receiving oxygen therapy at the time of screening.
16. Patients who have participated in a clinical trial of an investigational drug or device within 30 days of screening visit or is scheduled to receive an investigational product while participating in this study.

Exclusion Criteria Post-Surgery:

1. Patients who are not awake, not breathing spontaneously or have a respiratory rate that is less than 8 breaths per minute or greater than 24 breaths per minute.
2. Patients with arterial oxygen saturation by pulse oximetry (SpO_2) that cannot be maintained at 95% or greater with or without supplemental oxygen.
3. Patients not able to answer questions and follow commands.
4. Patients who are vomiting and not responsive to standard treatment.

5. Patients who have any deviation from the surgical or anesthetic protocols as specified in Section 6.1.2.1 of the protocol

Efficacy Variables and Parameters are:

- Proportion of patients who experienced at least one system-generated error based on the Controller data while using the Zalviso System
- Proportion of patients, if any, with tablet dispensed but not requested
- Proportion of patients, if any, with tablet dispensed when the Zalviso System is in lockout
- Proportion of patients with misplaced tablet(s)
- Number of misplaced tablets (i.e., tablet found outside the patient's mouth)
- Proportion of patients who experienced either a system-generated error or a misplaced tablet (i.e. a dispense failure)
- Assessment of the number of Zalviso System notifications to the nurse to retrain patient to not pull down on Controller while dosing (i.e., mitigation of Error 302)
- Proportion of patients who rate the Patient Global Assessment (PGA) of method of pain control over 24, 48 and 72 hours as "good" or "excellent"
- Proportion of patients who responded in each category of the PGA
- Proportion of Healthcare Professionals who rate the Global Assessment (HPGA) of method of pain control over 24, 48 and 72 hours as "good" or "excellent"
- Proportion of Healthcare Professionals who responded in each category of the HPGA
- Proportion of patients who terminate from the study due to inadequate analgesia over the 24-hour, 48-hour and 72-hour study period
- Time-weighted summed pain intensity difference (SPID) over the 24-hour study period (SPID24), over the 48-hour study period (SPID48), and over the 72-hour study period (SPID72)
- Total pain relief (TOTPAR) over the 24-hour study period (TOTPAR24), over the 48-hour study period (TOTPAR48) and over the 72-hour study period (TOTPAR72)
- Pain intensity (PI) at each evaluation time point
- Pain intensity difference (PID) at each evaluation time point
- Pain relief (PR) at each evaluation time point
- Patient Usability Questionnaire (PUQ)
- Nurse Usability Questionnaire (NUQ)
- Total number of study drug doses used over 24, 48, and 72-hour study period, average hourly use, and average inter-dosing interval.
- Total amount of supplemental morphine utilized

Safety Variables: Safety assessments will include the assessment of adverse events, vital signs (blood pressure, heart rate, and respiratory rate), oxygen saturation, and the use of concomitant medications.

Determination of Sample Size: This is a multicenter, open-label, single treatment clinical study designed to evaluate the overall functionality of the Zalviso System (sufentanil sublingual tablet system) 15 mcg for the treatment of acute moderate-to-

severe postoperative pain. A sample size of approximately 330 patients is planned for this study in order to have at least 315 patients receive study drug and have available efficacy data for data analysis.

A sample size of 315 patients will have 90% power to demonstrate that the device dispense failure rate is non-inferior to a target of 2%. This failure rate is the proportion of patients who experienced at least one of following events: (1) a system-generated error, (2) a tablet dispensed but not requested, or (3) a tablet dispensed when the Zalviso System is in lockout. All events listed above will be obtained from the Controller patient usage data.

This is based on the criteria that the upper limit of a 90% confidence interval (CI) of the device dispense failure rate is not worse than 5%. This calculation is based on the exact binomial test of one-sample proportion for a one-sided case against a 2% target proportion with a delta of 3%, and a one-sided significance level of α=0.05. This sample size was generated from the SAS procedure PROC POWER for one-sample proportion. Exact power computations are based on the binomial distribution and computing formulas provided by Johnson and Kotz (1970). Assuming a 5% non-evaluable rate, a sample size of 330 patients is planned for this study.

Statistical Analysis: The main analysis of the efficacy variables will include the intent-to-treat (ITT) population. The ITT population includes enrolled patients who received study drug. Demographics and baseline characteristics will be summarized by sex group for all enrolled patients and ITT population. Data will be pooled for all study centers for the descriptive summary of baseline data. No formal hypothesis testing will be performed for baseline data.

The data from all study centers will be pooled for the analysis of efficacy data. Both continuous and categorical efficacy variables will be summarized descriptively. A point estimate of the device dispense failure rate and its 90% confidence interval based on the exact binomial test will be constructed. For the analysis of the dichotomous outcome data, a point estimate and its 90% confidence interval based on the exact binomial test will be constructed.

All patients who received at least one dose of study drug will be included in the summaries of safety data. An AE thesaurus, the Medical Dictionary for Regulatory Activities (MedDRA) will be used to map each AE verbatim term to lowest level term, preferred term, and System Organ Class for summary purposes. Adverse events occurring while patients are on study drug until 12 hours after the last dose will be summarized. Other safety data, such as premature terminations, vital signs (blood pressure, heart rate, and respiratory rate), oxygen saturation, and the use of concomitant medications will be tabulated.

Vital signs taken at baseline and follow-up time points will be summarized. Patients who had baseline data and at least one follow-up data will be included in the summary of vital signs by sex group. The descriptive summary statistics will be presented. A

paired t-test will be used for the test of mean change from baseline to follow-up time points within each group.

Study Schema – Screening

Procedures	Screening (within 30 days of surgery)
Patient Informed Consent	✓
Inclusion and Exclusion Criteria	✓
Medical History	✓
Vital Signs	✓
Physical Exam	✓
Urine Drug Abuse Screen	✓
Urine Pregnancy Test	✓

Study Schema– Randomization and Study Treatment

Procedures	Hospital Admission	Post-Surgery	0 - 24 hr Treatment Period	24 - 48 hr Treatment Period	48 – 72 hr Treatment Period	Study Completion or Early Termination
Urine pregnancy test	✓					
Confirm Patient Continue to Meet Entrance Criteria		✓				
Baseline Pain Intensity (just prior to 1st dose)			✓			
Dosing (record date/time 1st and last dose)			✓			✓
Continued Zalviso Dosing			✓	✓	✓	
Blood Pressure and Heart Rate			✓[A]	✓[B]	✓[B]	
Respiratory Rate and Oxygen Saturation			✓[C]	✓[D]	✓[D]	
Pain Intensity and Pain Relief Assessments			✓[A]	✓[B]	✓[B]	✓
Record Number of Doses from Controller			✓[A]	✓[B]	✓[B]	
Check for Misplaced Tablets			✓[E]	✓[E]	✓[E]	
Patient and Healthcare Professional Global Assessments			✓[F]	✓[F]	✓[F]	✓
Patient and Nurse Usability Questionnaire						✓[G]
System-Generated Errors			✓	✓	✓	
Study Drug Accountability						✓
Record Concomitant Meds	✓	✓	✓	✓	✓	✓
Record AEs			✓	✓	✓	✓

[A] Record prior to first dose and at ¼ [15 min], ½ [30 min], ¾ [45 min], 1, 2, 4, 6, 8, 10, and 12 hours after 1st on-demand dose, then every 4 hours at 16, 20, and 24 hours after 1st on-demand dose.
[B] Record every 4 hours at 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 hours after the 1st on-demand dose.
[C] Record prior to first dose and at 15, 30, 45, 60 minutes after 1st on-demand dose and then every 30 minutes after 1st on-demand dose through 24 hours.
[D] Record every 2 hours at 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, and 72 hours after the 1st on-demand dose.
[E] Check for and record any misplaced tablets every 2 hours after 1st on-demand dose.
[F] The PGA and HPGA will be completed at 24 hours, 48 hours and 72 hours. If the patient withdraws prior to 24 hours, the global assessments should be administered at the time of early termination.
[G] Each patient will complete an Usability Questionnaire at the end of his/her participation in the study and prior to completing the PGA; the study staff at each site will complete the Usability Questionnaire after he/she has completed 5 patients on the study or at the time the study is completed at the site.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
$AUC_{0\text{-}inf}$	area under the analyte concentration-time curve extrapolated to infinity
BMI	body mass index (BMI=weight (kg)/[height(m)]^2
BOCF	baseline observation carried forward
BPM	breaths per minute
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CRC	clinical research center
CPAP	continuous positive airway pressure
CRF	case report form
CV	coefficient of variation
ED_{50}	effective dose in 50% of population
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GRAS	generally recognized as safe
HCP	healthcare professional
HPGA	Healthcare Professional Global Assessment
HP-IFU	Healthcare Professional – Instructions for Use
HIPAA	Health Insurance Portability and Accountability Act
hr	hour
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IR	immediate release
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive Web Response System
kg	kilogram
LD_{50}	lethal dose in 50% of population
LOCF	last observation carried forward
LS	least squares

Abbreviation	Definition
MAOI	monoamine oxidase inhibitor
mcg	microgram
mcL	microliter
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NRS	numerical rating scale
PACU	post-anesthesia care unit
PCA	patient-controlled analgesia
pg	pictogram
PGA	Patient Global Assessment
PI	pain intensity
PID	pain intensity difference
PK	pharmacokinetics
PR	pain relief
PRM	passive range-of-motion
RASS	Richmond Agitation Sedation Scale
RCT	randomized controlled trial
RFID	radio-frequency identification
SAE	serious adverse event
SAS®	Statistical Analysis System
SPID	summed pain intensity difference
SpO_2	arterial oxygen saturation by pulse oximetry
$t_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
TOTPAR	total pain relief
WOCF	worst observation carried forward

1 INTRODUCTION

1.1 Background

AcelRx Pharmaceuticals, Inc. (hereafter AcelRx) is developing Zalviso (sufentanil sublingual tablet system) for the indication of management of moderate-to-severe acute pain in adult patients during hospitalization. In spite of the wide use and advantages of intravenous patient-controlled analgesia (IV PCA), its inherent complexity associated with ordering, dispensing, set-up, programming, and administration have resulted in many analgesia related postoperative medication errors (Grass, 2005; Hankin et al., 2007; Hicks et al., 2008a; 2008b; and Meissner et al., 2009). Errors utilizing IV PCA have been reported across all phases of the medication-use process, but human factors, such as programming or administering the wrong dose, are among the most common and serious type of errors. Among the human factors, the operator errors (81% involving pump programming errors) are the most concerning since they account for the majority of errors that cause harm to patients. Approximately 5% of operator errors reported in the MAUDE database (FDA mandatory device-error-reporting database) resulted in patient deaths (Hankin et al, 2007).

Although it is difficult to conclusively determine the incidence rate for IV PCA-related events due to significant under-reporting, recent analysis of MEDMARX (USP voluntary medication errors reporting database) and MAUDE databases has estimated the annual IV PCA error rates as 424 IV PCA-related errors per 10,000 people within the United States (Meissner et al., 2009). Assuming that approximately 13 million patients are requiring IV PCA therapy annually, it can be estimated that more than 500,000 patients are exposed to IV PCA errors every year and about 50,000 patients are harmed because of these errors (Meissner et al., 2009).

The non-invasive (sublingual), pre-programmed, single-dose strength Zalviso System addresses many of the limitations of the current IV PCA systems by reducing programming errors, IV catheter complications and inappropriate use of basal infusions. The Zalviso System is comprised of a disposable bar-coded Cartridge filled with a stack of 40 sufentanil tablets 15 mcg (approximately 2 day supply based on usage), a disposable Dispenser and a reusable, rechargeable Controller. The Zalviso System is designed so that with each actuation by the patient, a single sufentanil tablet will be dispensed sublingually with a manufacturer pre-programmed 20-minute lock-out to avoid overdosing. Furthermore, the Zalviso System has additional safety features of 1) a secure access system comprised of an adhesive patient identification Thumb Tag which uses radio-frequency identification (RFID), 2) an Authorized Access Card with RFID for the healthcare professional (HCP) and 3) a security tether.

Advantages of Sufentanil

Sufentanil, a synthetic opioid analgesic, is characterized by a high selectivity and affinity for mu opiate receptors. Sufentanil is an optimal opioid to use in the treatment of acute in-hospital pain, such as postoperative pain. Published studies demonstrate that sufentanil produces 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} = 25,000) 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).

Sufentanil, as opposed to morphine and meperidine, has no active metabolites, therefore reduced renal clearance in the elderly or in patients with active renal disease will not affect dosing in these populations to any significant extent. Pharmacokinetic studies of intravenous sufentanil have demonstrated no clinically significant 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 (PK) measurements of time and extent exposure to drug were unchanged in this population (Schwartz et al., 1991).

Sufentanil Sublingual Tablets

AcelRx has developed the sufentanil tablet using GRAS (generally recognized as safe) excipients. The sufentanil 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 sufentanil 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.

1.2 Previous Human Experience with Sufentanil Sublingual Tablets (ARX-F01)

To date, AcelRx has conducted seven Phase 1 studies, three Phase 2 studies, and three Phase 3 studies to support the clinical development of Zalviso. Two of the Phase 1 studies (ARX-C-002 and MPS101) were primarily performed for a separate clinical development program. Studies ARX-C-002 and MPS101 included a single-dose treatment of a sufentanil tablet in unblocked subjects (subjects not pretreated with the opioid antagonist naltrexone). A Phase 1 study to support registration of a higher dose strength SST (30 mcg) was conducted and included administration of SST 15 mcg.

Phase 1 Study Results

In the Phase 1 studies, a range of doses (2.5 to 80 mcg) were studied and each treatment arm resulted in either a single tablet administered or up to 40 tablets (one every 20 minutes) administered. The definitive PK studies evaluated only a 15 mcg dose.

- Administration of a single sublingual sufentanil tablet 15 mcg demonstrated high bioavailability, blunted C_{max}, and 15-fold longer plasma context-sensitive half-time (time from C_{max} to 50% of C_{max}; $CST_{½}$) compared to dose equivalent IV administration. The $CST_{½}$ was 0.14 hrs for IV sufentanil and 2.5 hrs for sublingual sufentanil.
- Relative to IV administration, bioavailability of the sufentanil tablet 15 mcg sublingually was 59%. Bioavailability of buccal placement of the sufentanil tablet was higher at 78%, and oral (swallowed) was much lower at 9%.
- The buccal route of administration resulted in a similar PK profile compared with sublingual administration.
- The C_{max} from a single-dose of the sufentanil tablet 15 mcg was 33 pg/mL (%CV = 35%), the overall C_{max} from 40 doses administered every 20 minutes over 13.3 hours was 265 pg/mL (%CV = 28%), and the C_{max} following the 40^{th} dose was240 pg/mL (%CV = 29%).
- Ketoconazole, a potent CYP3A4 inhibitor, can increase the systemic exposure to the sufentanil tablet, showing a higher $AUC_{0\text{-}inf}$ value. However, the peak plasma concentration, C_{max}, and $CST_{½}$ of the sufentanil tablet were not impacted to any clinically meaningful degree. The variable redosing interval of the sufentanil tablet should compensate for any increased AUC caused by concomitant administration of CYP3A4 inhibitors.
- Clearance of sufentanil was reduced in older subjects (61 to 80 years) compared to younger subjects (18 to 60 years). The differences were not clinically meaningful.

Across the Phase 1 studies, the incidence of AEs considered treatment-emergent ranged up to 91.7%. The highest incidence of AEs occurred in Study ARX-F01-01, a legacy study in naltrexone-blocked subjects with sufentanil doses ranging up to 80 mcg. In the other studies, the rate of AEs ranged up to approximately 50%. In Study ARX-F01-01 and other studies in naltrexone-blocked subjects (Studies IAP101, IAP102, and IAP104), it was not possible to fully distinguish whether the naltrexone or the sufentanil formulation being tested was likely to have caused a particular AE. In Study IAP101, which was a multiple-dose study unlike the other studies in naltrexone-blocked subjects, 40 consecutive sufentanil tablet 15 mcg doses were administered at 20-minute intervals, and AEs were experienced by 18 of 39 (46.2%) subjects.

In studies in non-naltrexone-blocked subjects (Studies MPS101, ARX-C-002, and ARX-C-006), the rates of AEs in subjects receiving sublingual tablet formulations containing sufentanil 15 mcg ranged from 0 of 12 subjects to 4 of 12 subjects (33.3%) experiencing AEs. In some patients the sublingual tablet treatments included triazolam. Across all Phase 1 studies, there were no SAEs or deaths and only 1 AE (mild nausea) leading to discontinuation.

Dose-Ranging Phase 2 Studies

AcelRx conducted 3 Phase 2 studies which provide supporting efficacy and safety data. These include 2 placebo-controlled, double-blind 12-hour studies and 1 uncontrolled, open-label 12-hour study conducted in patients who had undergone open abdominal

surgery or knee replacement. Study ARX-C-004 used a prototype version of the delivery device.

Phase 3 Study Results

In the Phase 3 studies (IAP309, IAP310 and IAP311), Zalviso was evaluated for efficacy and safety. The tablet was self-administered by the patient as needed for pain relief. The device had a pre-programmed 20-minute lockout between doses. In these studies, a placebo tablet was also administered using the Zalviso System. The active-comparator treatment evaluated in study IAP309 was IV PCA morphine, 1 mg as needed, with a 6-minute lockout.

In each of the 2 placebo-controlled Phase 3 studies (IAP310 and IAP311), the Zalviso System demonstrated superiority over placebo for the primary endpoint, time-weighted SPID48. Supporting the SPID48 results, key secondary endpoint results (total pain relief, drop out due to inadequate analgesia, proportion of patients using rescue medication, and patient global assessment (PGA) and healthcare professional global assessment (HPGA)) were also superior to placebo. The Zalviso System demonstrated efficacy that was rapid in onset and durable over time. The result of the open-label, active-comparator trial showed that Zalviso was superior to IV PCA morphine for the measure of "success" (patient rating of good or excellent for method of pain control over the 48-study period). Patients had the option to remain in the study past the 48-hour treatment period, up to 72 hours.

The most common AEs were generally consistent across studies and were consistent with opioid treatment and the postsurgical setting in Phase 2 and 3 studies. In the Phase 3, placebo-controlled studies, the most common AEs (experienced by > 5% of patients) with Zalviso treatment were nausea (46.9%), pyrexia (17.7%), vomiting (11.7%), headache (8.6%), oxygen saturation decreased (7.7%), pruritus (6.8%), hypotension (5.6%), dizziness (5.4%), and anemia, constipation, and anemia postoperative (each 5.1%). Of these, 3 common AEs occurred significantly more frequently with Zalviso compared with placebo: nausea (46.9% vs. 36.4%, $p = 0.026$), vomiting (11.7% vs. 6.2%, $p = 0.049$), and pruritus (6.8% vs. 0%, $p < 0.001$). The following 3 AEs showed nearly significant differences between Zalviso and placebo: pyrexia (17.7% vs. 11.1%, $p = 0.058$), oxygen saturation decreased (7.7% vs. 3.1%, $p = 0.058$), and dizziness (5.4% vs. 1.9%, $p = 0.073$). These AEs showing significant or nearly significant differences from placebo are consistent with expected AEs of opioid treatment. No other common AEs showed significant differences from the placebo System.

Across all 3 Phase 3 studies, including the open-label Study IAP309 which incorporated an IV PCA MS treatment group, the rates of common AEs with Zalviso were generally similar to or lower than the rates of AEs in the IV PCA morphine group. Comparing AEs experienced by > 5% of patients with the Zalviso to AEs in the IV PCA morphine, rates of pyrexia, oxygen saturation decreased, anemia, constipation, pruritus, hypotension, anemia postoperative, and hypoalbuminemia were at least somewhat greater with the IV PCA morphine. Rates of nausea and vomiting were similar, and rates of headache and dizziness were somewhat greater (by approximately 2%) with Zalviso.

2 STUDY OBJECTIVES

The study objectives are:

- Assess device dispense failure rate with the modified Zalviso System design
- Assess impact of System error 302 mitigations on overall System usability
- Assess the incidence of misplaced tablets and drug accountability while patients were using the Zalviso System
- Evaluate patient and nurse usability of, and satisfaction with, the Zalviso System to treat moderate-to-severe postoperative pain
- Evaluate the efficacy and safety of the Zalviso System to treat moderate-to-severe postoperative pain

3 STUDY DESIGN

3.1 Study Overview

The study is a multicenter, open-label trial for at least 24 hours and up to 72 hours in patients 18 years and older who are undergoing surgery and are expected to require systemic opioid analgesia for at least 24 hours after surgery to treat moderate-to-severe pain.

Patients who meet all inclusion and exclusion criteria at screening and following surgery, and transfer to the post-anesthesia care unit (PACU), will be treated with Zalviso System with a 20-minute re-dosing interval (lock-out).

Analgesic efficacy will be assessed by patient global assessment of method of pain control on a four-point scale where 1 = poor, 2 = fair, 3 = good, and 4= excellent, patient reports of pain intensity on an 11-point numerical rating scale (NRS), where 0 = no pain, and 10 = worst possible pain, a five-point pain relief scale (0= no relief, 1 = a little relief, 2 = moderate relief, 3 = a lot of relief, 4 = complete relief), percentage of patients dropping out of the study due to inadequate analgesia, and patient usability questionnaire.

Safety will be monitored via periodic measurement of vital signs and continuous monitoring of oxygen saturation, as well as assessment of AEs and the use of concomitant medications.

3.2 Dose and Administration

Patients will receive treatment with the Zalviso System for the duration of the study period.

Patients may have ice chips or swish with water if his/her mouth feels very dry prior to receipt of any dose of study drug. Patients will be instructed that the tablets must be allowed to dissolve under the tongue and may not be crushed, chewed, or swallowed. Expected time for erosion after administration is 6 to 8 minutes. Patients should not eat or drink, and should minimize talking for ten minutes after a tablet has been self-administered.

Administration of the first dose of study drug will start the study period. Additional doses may be self-administered by the patient but at least 20 minutes must lapse between doses as controlled by the Zalviso System's manufacturer pre-programmed 20-minute lock-out.

3.3 Blinding and Randomization

This is an open-label single treatment study. There is no randomization in this study. All patients will receive treatment using the Zalviso System.

3.4 Discussion of Study Design, Including the Choice of Control Groups

This is an open-label, non-controlled study. Validated instruments will be used to assess pain intensity, pain relief, and global assessment during the study.

3.5 Duration of Study

After screening, patients may have up to 30 days to begin receiving treatment with study drug. The duration of study treatment administration is at least 24 hours but may extend to 72 hours. The entire study is expected to last approximately nine months from the first patient screened through the last patient's study procedure.

4 SELECTION OF PATIENTS

4.1 Inclusion Criteria at Screening

1. Male or female patients who are 18 years of age or older.
2. Patients who are scheduled to undergo surgery under general or spinal anesthesia that does not include intrathecal opioids during the operation.
3. Patients classified as American Society of Anesthesiologists (ASA) class I - III (Appendix I).
4. Female patients of childbearing potential must be using an effective method of birth control at the time of screening visit and for 30 days following the end of the study period. Acceptable methods of birth control include oral or transdermal contraceptives, condom, spermicidal foam, intrauterine device (IUD), progestin implant or injection, abstinence, vaginal ring, or sterilization of partner. The reason for non-child bearing potential, such as bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or postmenopausal for > 1 year, must be specified. Patients using hormonal forms of contraception must also be willing to use a barrier method of contraception from screening through 30 days following the study period.
5. Post-surgical patients who have been admitted to the PACU, and are expected to have acute pain requiring opioids for 24 – 72 hours after surgery.
6. Patients who have the manual dexterity to handle the Zalviso System and are able to follow directions for use.
7. Patients who are willing and capable of understanding and cooperating with the requirements of the study.
8. Patients able to understand and communicate in English.

9. Patients who have provided written informed consent and signed the IRB approved consent form.

4.2 Exclusion Criteria at Screening

1. Patients who have taken an opioid for more than 30 consecutive days, at a daily dose of 15 mg or more of morphine (or equivalent), within the past 3 months prior to surgery (e.g. more than 3 doses per day of Vicodin®, Norco®, Lortab® with 5 mg hydrocodone per tablet).
2. Patients with a positive drug of abuse urine screen unless the positive test result is consistent with a prescribed medication.
3. Patients with a history of opioid dependence within two years before the start of the study, defined as meeting the DSM-IV-TR™ Criteria for Substance Dependence specified in Appendix II.
4. Patients who have used any illicit drugs of abuse within five years before the start of the study.
5. Patients who have abused any prescription medication or alcohol within one year before the start of the study.
6. Patients with an allergy or hypersensitivity to opioids.
7. Patients who are currently taking monoamine oxidase inhibitors (MAOIs) or have taken MAOIs within 14 days of the first dose of study drug.
8. Patients with current sleep apnea that has been documented by a sleep laboratory study or are on home continuous positive airway pressure (CPAP).
9. Female patients who are pregnant (positive pregnancy test at screening or after hospital admission), breastfeeding or planning to breastfeed within 30 days of the last dose of the study drug.
10. Patients with a medical condition that, in the Investigator's opinion, could adversely impact the patient's participation or safety, conduct of the study, or interfere with the pain assessments, including chronic pain or active infection.
11. Patients who have cancer and are receiving radiation/chemotherapy and are expecting to receive radiation/chemotherapy within 72 hours after surgery.
12. Patients who require an additional scheduled surgical procedure within 72 hours of the surgery.
13. Patients who are expected to have postoperative analgesia supplied by a long-acting or continuous regional technique (e.g., spinal opioids or continuous nerve block).
14. Patients who received surgical premedication with long-acting opioid analgesics.
15. Patients who are receiving oxygen therapy at the time of screening.
16. Patients who have participated in a clinical trial of an investigational drug or device within 30 days of screening visit or is scheduled to receive an investigational product while participating in this study.

4.3 Exclusion Criteria Post-Surgery

1. Patients who are not awake, not breathing spontaneously or have a respiratory rate that is less than 8 breaths per minute or greater than 24 breaths per minute.

2. Patients with arterial oxygen saturation by pulse oximetry (SpO_2) that cannot be maintained at 95% or greater with or without supplemental oxygen.
3. Patients not able to answer questions and follow commands.
4. Patients who are vomiting and not responsive to standard treatment.
5. Patients who have any deviation from the surgical or anesthetic protocols as specified in section 6.1.2.1 of the protocol.

4.4 Withdrawal Criteria

Patients will be informed that they are free to withdraw from the study at any time. The Investigator, the Investigator in consultation with the Medical Monitor, or the Medical Monitor may exercise his or her medical judgment to terminate a patient's participation in the study if it is in the best interest of the patient.

Patients displaying any one of the following:

- oxygen saturation levels that cannot be maintained at 95% or greater with or without the use of supplemental oxygen
- respiratory rate less than 8 bpm
- excessive sedation

will not be allowed to have access to study drug or supplemental opioids until these vital signs have improved. **Sites must document improvement of these vital signs in the eCRF.**

If the oxygen saturation is below 95%, even if no other vital sign is abnormal and the patient does not improve following supplemental oxygen and two arousal and vital sign checks 3 minutes apart, then the patient should be removed from the study.

If the respiratory rate is low (below 8 bpm but oxygen saturation is greater than or equal to 95% and no excessive sedation is present) or if excessive sedation exists (respiration and oxygenation are above limits), and each adverse event does not improve within 20 minutes under supervision with every 3 minute arousal and vital sign checks after discontinuing access to study drug, the patient should be removed from the study. If these two adverse events (low respiratory rate and excessive sedation) should occur simultaneously, then the more conservative withdrawal criteria should be followed: the patient should be removed from the study if after two arousal and vital sign checks 3 minutes apart, these symptoms do not improve.
All vital signs measured to manage oxygen desaturation and decreased respiratory rate must be recorded in the source and eCRF.

At any time the investigator can remove a patient from the study for any adverse event, regardless of the above guidance, if deemed necessary for patient safety.

AcelRx also reserves the right to terminate the study at any time. All data normally collected at completion of the study must be collected either at the time of the patient's early termination, or before the scheduled study closeout visit.

A termination case report form (CRF) page should be completed for every patient who received study drug, whether or not the patient completed the study. The reason for any early discontinuation from the study should be indicated on this form. The primary reason for a premature withdrawal should be selected from the following standard categories of early termination:

Adverse Event: Clinical or laboratory events occurred that in the medical judgment of the investigator for the best interest of the patient are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to study drug.

Death: The patient died.

Withdrawal of Consent: The patient desired to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the investigator. If the patient gave a reason for this desire, this should be recorded on the CRF.

Protocol Violation: The patient's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits). The violation necessitated premature termination from the study.

Lack of efficacy: The patient was discontinued from the study due to lack of response.

Lost to Follow-Up: The patient stopped coming for visits and study personnel were unable to contact the patient.

Other: The patient was terminated for a reason other than those listed above. The Investigator must specify the reason.

Separate CRF entries will document whether each patient completed all doses of study drug, or if not, the reason a patient terminated study drug early.

5 TREATMENTS

5.1 Identification and Description

5.1.1 Sufentanil Tablets

The sufentanil tablet is an orange-colored tablet with a volume of approximately 7 mcL with dimensions of approximately 3 mm in diameter and 0.85 mm in thickness. Each sufentanil tablet contains 15 mcg of sufentanil base corresponding to 22.5 mcg of sufentanil citrate. All excipients are inactive and are generally recognized as safe (GRAS) status.

5.1.2 Zalviso System

The Zalviso System is a handheld, patient-controlled device designed for sublingual, self-administration of sufentanil tablets by patients requiring postoperative opioid analgesia in

the hospital setting. The Zalviso System also provides the following general functionality:

- Single-patient identification to ensure that only the intended patient may use the System
- Manufacturer pre-programmed lockout interval to ensure that patient cannot exceed prescribed dose
- Recorded dosing and use history, to assist HCPs in keeping accurate patient medical records
- Error monitoring and safety features to monitor and control tablet dispensing, to control access to the drug cartridge, and to mitigate diversion

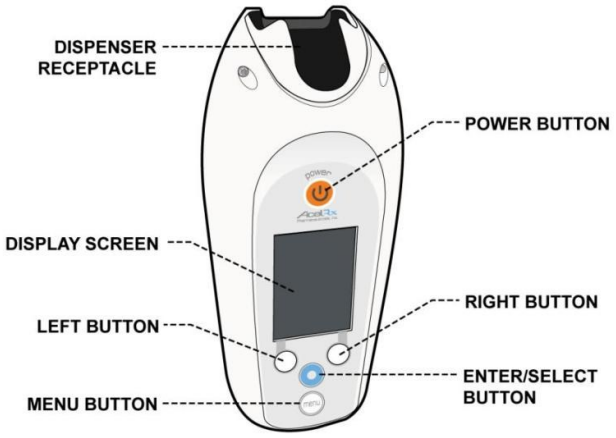
The Zalviso System houses an internal electro-mechanical system that singulates and delivers a tablet to the sublingual space. Furthermore, the System contains electronics that detect the successful singulation of a tablet, provide a means to track use data, provide a simple user interface that displays the System status and dosing information, and utilize a non-contact identification reader for identifying the proper patient (adhesive patient ID Thumb Tag with RFID).

Controlled access is required to limit use of the Zalviso System to the HCP when performing setup, take down, patient linking, or un-tethering. Authorized controlled access for patient identification and dosing is also required for medication delivery. Access is restricted in order to mitigate theft of the Zalviso System (tethering), identify the patient for dosing, mitigate drug diversion, and to identify the HCP.

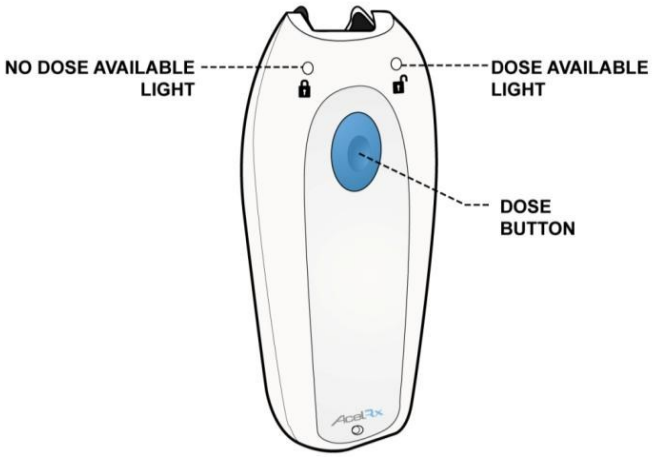
The Zalviso System is comprised of three main components as follows:

- A reusable *Controller* that houses the electro-mechanical elements of the PCA System and the power source (rechargeable battery)

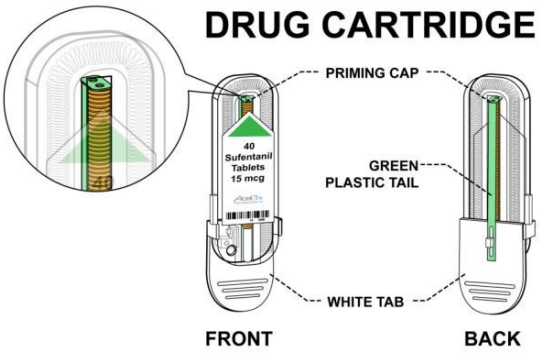
Front Side / Nurse Side



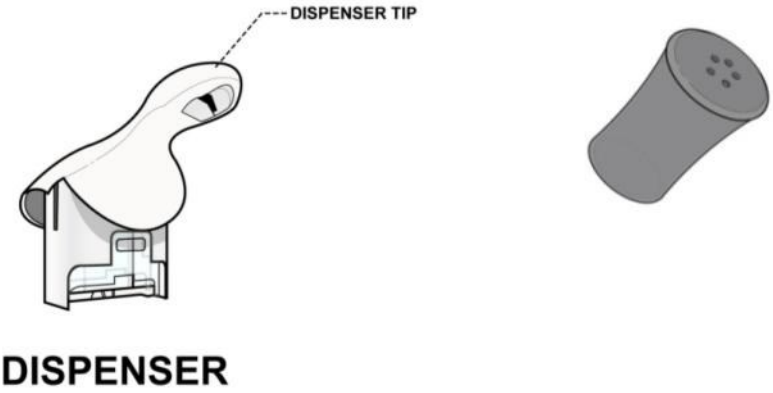
Back Side / Patient Side



- A pre-filled drug *Cartridge* containing 40 tablets and a green plastic priming cap



- A single-patient use *Dispenser* that contacts the sublingual space of the patient and directs placement of the tablets. Included with the *Dispenser* is a cap to cover the tip when not in use.



Ancillary Components:

- A *Tether* to lock the PCA System to the bedside, along with a holster for ease of bedside storage in between dosing

- *Secure access system* comprised of an adhesive patient ID Thumb Tag with RFID to limit dosing to only the patient, plus Authorized Access Card with RFID that will be used only by the HCP or study monitor to setup, takedown, and to interact with the System

All components are supplied non-sterile in separate packages.

5.2 Storage and Dispensing of Drug

The drug cartridges will be stored in the controlled access of the facility pharmacy to ensure adequate controls for a Drug Enforcement Agency (DEA) Schedule II narcotic

substance or to the required governing agency standard. Drug cartridges must be stored at room temperature (15°C - 30°C) until time of dispensing.

When a post-surgery patient is transferred to the PACU and meets all criteria for start of dosing, study staff will prepare a Zalviso System for the patient's use.

The pouched cartridge will be taken from inventory and labeled with the patient identification. The tear-off section of the two-part label affixed to the pouch will be removed and placed in the inventory records and the date and time of dispensing will be recorded. The pouch containing the cartridge labeled with the patient identification will be dispensed to the qualified study staff from the pharmacy. When additional pouched cartridges are needed by a patient, the study staff will follow the same process. If a patient uses three drug cartridges and needs an additional drug cartridge, the dispenser must be replaced prior to use of the fourth drug cartridge.

5.3 Treatment Administration

Study drug will be self-administered only when a patient needs treatment for his/her pain.

There is a manufacturer pre-programmed 20-minute lock-out to prevent overdosing.

The tablets must 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 a tablet has been self-administered, although ice chips may be used to avoid excessively dry mouths in patients during the study period.

5.4 Managing Suspected Zalviso System Errors and Failures

Refer to the Healthcare Professional-Instructions for Use (HP-IFU) for complete information on Zalviso System alarm, error and notification messages (HP-IFU to be sent under separate cover).

If during patient use an error message is displayed on the controller screen (e.g., Error 301, Error 302, etc), the error displayed will be recorded in the source record and on the suspected technical failure e-CRF. Per the Zalviso System design, if a system error occurs, the Zalviso System will no longer dispense tablets and must be discontinued. The patient will be discontinued from the study and alternate form of postoperative analgesia per standard practice at the site should be instituted.

If either the patient or the investigator's staff observes that the Zalviso System may not be operating properly during patient use, but there are no notification or error messages displayed on the Zalviso System Controller screen, the Zalviso System will be evaluated for the presence of a technical failure in accordance with the procedures detailed in the Zalviso System HP-IFU. If the Zalviso System is suspected of having a technical failure, the System must be discontinued, the patient discontinued from the study and an alternate form of postoperative analgesia per standard practice at the site should be instituted. In the event any Zalviso System is judged to have a suspected technical failure, the Zalviso System will be sent to AcelRx for evaluation and may not be used further until a review by AcelRx is complete and the System is approved for further use. Suspected technical

failures must be documented in the source and the eCRF.
If a misplaced tablet (i.e. any tablet inadvertently dispensed or found outside of the patient's mouth) is found by a patient or study staff, this must be documented in the source record and eCRF. The tablet must be stored securely until CII study drug accountability is conducted. The study staff should document who found the tablet, when and where the tablet was found, and query the patient to determine the likely cause of the misplaced tablet.

5.5 Drug Accountability

The Investigator, dispensing pharmacist, and nursing staff will be responsible for maintaining the medication accountability log, which will contain inventory records acknowledging receipt of study drug, and dispensing records tracking distribution of medication to patients. All used and unused cartridges will be kept at the site until study completion. At study closeout, the Investigator will be required to reconcile all received, dispensed, used, and unused drug cartridges, and return to AcelRx, or its designee for destruction as per instructions from AcelRx. Unused Zalviso System supplies will be handled according to directions from AcelRx.

When a patient is discontinued or a replacement Drug Cartridge is needed, the number of tablets remaining in the used Drug Cartridge as displayed on the Zalviso System display screen will be recorded in the source records. Appropriate source records will be sent to AcelRx or designee along with the used and unused Drug Cartridges for tablet accountability. AcelRx or designee will count the number of tablets remaining in each used Drug Cartridge using the HP-IFU manual method and compared to the site's source records. Any discrepancies will be investigated.

5.6 Emergency Anaphylactic or Overdose Procedures, Dose Modification

Emergency medical treatment for anaphylaxis including the use of epinephrine, antihistamine, and/or corticosteroid therapy should be immediately available during the administration of Zalviso. The most serious effect of overdose is respiratory depression. Intravenous administration of an opioid antagonist such as naloxone, titrated to effect, should be employed as a specific antidote to manage respiratory depression. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal, oral airway, or endotracheal tube may be indicated. Other supportive measures such as intravenous fluids and vasopressors for the treatment of hypotension may be employed.

There is no provision for dosage strength modification, although the frequency of dosing is determined by the patient (within the constraints of the manufacturer pre-programmed 20-minute lockout).

5.7 Prior and Concomitant Medications

5.7.1 Prior and Concomitant Medications

Patients may continue the scheduled use of their regular medications throughout the study. Patients are to be dosed only with the Zalviso System during the study period for opioid analgesia, with the exception of the supplemental opioid medication as described in Section 5.7.2. Non-opioid analgesics are allowed prior to and throughout the study period to be consistent with the current multimodal standard of care. Deep venous thrombosis prophylaxis, as per local best practice, is permitted postoperatively.

Patients may receive prophylactic anti-emetics based on assessment of risks for postoperative nausea and vomiting and investigator's judgment. Postoperative anti-emetics for symptomatic treatment are also allowed.

The use of any concomitant medications from 30 days prior to the first dose of study drug through the completion of the study, or changes in the dose or dosing frequency of medications used prior to the study start will be documented in the CRF. All appropriate information (e.g. trade name, formulation, dosage, dates and times (24-hour clock of beginning and end), reason for use) of concomitant medications, therapies, and medical procedures will be reported in the CRF. Any change to concomitant therapy will be noted in the CRF. This includes concomitant medications taken for the treatment of AEs.

Patients will receive full supportive care for the treatment of AEs. Treatment will be at the discretion of the Investigator, but initially will follow these guidelines:

- Oxygen saturation, respiratory rate or excessive sedation adverse events will be managed with discontinuation of the study drug and, if necessary, with resuscitative measures. (See Section 4.4 Withdrawal Criteria)
- Pruritus will be treated with appropriate therapy.
- Nausea and vomiting will be treated with appropriate anti-emetic therapy.
- Shivering may be treated with meperidine in the PACU.

5.7.2 Supplemental Medications

Patients may be treated with standard non-opioid analgesics as per the site's standard multimodal analgesia regimens (with the exception of continuous nerve blocks such as a continuous femoral block or a continuous epidural block). However, supplemental opioid medication (2 mg IV morphine) will only be allowed in the first 30 minutes after the first on-demand dose of study drug has been administered if necessary to keep a patient comfortable or for pain due to ambulation or with the initiation of passive range of motion (PRM) therapy throughout the remainder of the study. A pain intensity and pain relief score should be obtained prior to each administration of supplemental opioid medication.

Supplemental opioid medication should be delivered as a slow IV push by a HCP. **Patients cannot receive a dose of supplemental opioid medication more than once every 60 minutes**. If patients continue to have pain that is not controlled by the use of study drug, supplemental opioid medication, and other allowable non-opioid analgesics, then the patient should be discontinued from the study and an alternate form of postoperative analgesia per standard practice at the site should be instituted.

6 STUDY VISIT PROCEDURES

6.1 Measurements and Evaluations by Visit

6.1.1 Screening Visit

After obtaining written informed consent, patients will be instructed as to the nature of the study and the reason they are being asked to participate. Screening assessments will be performed after the informed consent form has been signed. The scheduled date of surgery will be verified to ensure that the first dose of study drug occurs within the 30-day window from screening.

Patients will provide a full medical and medication history and will have a physical examination including vital signs, height and weight, and an examination of the oral mucosa. A drug of abuse screen (urine) will be conducted. A positive result for any drug must be consistent with the patient's reported medical history and prescription drug use. Female patients of child bearing potential will have a pregnancy test. Patients will receive instruction and training on use of the Zalviso System and their ability to handle the Zalviso System will be assessed. Zalviso System demonstrators will be available for patient training and assessment of their ability to use the device. Patients will receive training on completion of the rating scales. Inclusion and exclusion criteria will be reviewed.

6.1.2 Inpatient Admission (Study Day 1)

Study staff will verify admission and surgery schedule the day before the scheduled procedure and notify the Pharmacy that a potential patient may be enrolled into the study. Female patients of child bearing potential will have a urine pregnancy test. Patients who continue to meet all eligibility requirements for study enrollment are eligible to be dosed as long as none of the Exclusion Criteria following surgery (Section 4.3) apply.

6.1.2.1 Anesthetic, Surgical and Postoperative Care Protocols

A) Anesthetic Care

The patient may be administered general anesthesia or spinal anesthesia that does not include spinal opioids during the operation. Intra-operative analgesia will be provided using intravenous fentanyl, morphine or hydromorphone as deemed appropriate by the anesthesiologist. Surgeons must document any deviation from the pre-operative surgical plan. Long-acting oral opioids are not allowed prior to surgery, during, after surgery, or during the study period.

Non-opioid analgesic drugs may be administered prior to surgery, during, after surgery, and during the study period.

B) Surgical Care

Any surgery expected to result in moderate-to-severe acute pain, requiring the treatment of systemic opioids for at least 24 hours after surgery, is permitted.

C) Postoperative Care

Following surgery, patients will be admitted to the PACU, where they will recover from anesthesia and vital signs will be stabilized if necessary. Patients must be awake and breathing spontaneously, with a respiratory rate of 8 to 24 breaths per minute, arterial oxygen saturation by pulse oximetry (SpO_2) of at least 95% with or without supplemental oxygen, able to answer questions and to follow commands before they can be treated with study drug. A patient must begin using study drug within 8 hours of completion of surgery. If the patient does not meet entrance criteria within this 8 hour time limit, the patient will be documented as a screen failure.

Patients will be titrated to comfort (a pain intensity score of <5) in the PACU utilizing intravenous fentanyl, morphine, or hydromorphone, if needed, per local best practice.

When the patient has been discharged from the PACU (or is ready for discharge from the PACU) the patient must report a pain score of >4 and request medication for pain in order for the study drug treatment to begin. These pain scores collected just prior to the first dose of study drug **will be self-recorded by the patient in a source document provided by investigator's staff per the study schema.** The study staff must not record the patient's PI, PR, or global scores for the patient.

6.1.3 Study Period

The study period consists of a minimum of 24 hours and may extend up to 72 hours. There could be a situation where the patient is reporting pain scores that would allow initiation of the study, but study drug is not yet available from the Pharmacy. In order to keep patients comfortable, opioids (fentanyl, morphine or hydromorphone) may be administered intravenously, as per standard practice, prior to the start of the study. If a patient receives IV pain medication in this manner, he/she must still report a pain score of above 4 just prior to administration of the first dose of study drug.

The investigator's staff will monitor patient safety and oversee collection of efficacy data points during the study. The patient will be given the Zalviso System and be re-instructed on how to use the Zalviso System. Patient re-education on use of the Zalviso System by the study staff will be based on use of the GUI training screens on the Zalviso System, the instructions in the HP-IFU document, and the Patient Reference Sheet. The Patient Reference Sheet will be given to the patient with the instruction for the patient to use it as needed.

The study period starts with the self-administration of the first dose of study drug. A member of the research study staff must observe the patient self-administer their first dose and document correct dosing in the source record and eCRF. If the study staff member observes any incorrect behavior, the patient will be re-educated and the study staff member will document this additional training.

If during the study treatment period, the study staff believes the patient does not possess the cognitive ability or manual dexterity to properly use the Zalviso System, alternate analgesic therapy should be considered.

The following must be communicated to the patient during training on use of the Zalviso System:

- Keep the Cap on the Dispenser and the Zalviso System in Holster when not in use
- Remove the Cap and keep the Zalviso System upright when ready to self-administer a dose
- Place the Dispenser Tip under the tongue but do not touch the Dose Button before the Tip is under the tongue
- During dosing, do not pull down on the Controller or apply any upward pressure on the Dispenser Tip with the mouth or teeth
- Keep the Dispenser Tip in the mouth until they hear the dose tone and feel/hear the motor stop
- If the patient cannot take a dose, the Zalviso System's blue and green lights are continuously flashing and the Zalviso System is beeping, call the study staff
- If the patient notices a misplaced tablet, call the study staff

The criteria for the study period to begin are:

- the patient has been discharged from the PACU (or is ready for discharge)
- the patient has reported a pain score of >4 just prior to the first dose of study drug (baseline pain intensity)
- the patient has requested medication for pain

Patients should not eat or drink and should minimize talking for 10 minutes after a tablet has been self-administered. Ice chips may be used to avoid excessively dry mouths in patients during the study period. Additional doses will be self-administered by the patient as needed to maintain analgesia.

During the study period all pain intensity, pain relief, and global assessment scores will be self-recorded by the patient in a source document provided by investigator's staff per the study schema. The patient and study staff will complete a PGA and HPGA, respectively, 24 hours, 48 hours and 72 hours after the first dose of study drug. If the patient discontinues before 24 hours, the PGA and HPGA assessments will be completed by the patient and study staff at the time of early termination.

During the study treatment period, the study staff will check for any misplaced tablets every 2 hours starting with the 1st on-demand dose. This would include checking the Zalviso System cap, within the patient's bed and linens, and on the hospital room floor. If a misplaced tablet is found, the study staff will document in the source and eCRF including the details of when and where found, and query the patient to determine the likely cause of the misplaced tablet. The patient will be retrained on proper dosing technique.

The study staff will record the date and time of the first and last doses of study drug taken during the study period from the Controller's detailed history log.

Should a patient use all 40 tablets and require additional analgesia within the study period, an additional drug cartridge will be provided.

If a patient is asleep at the time of a protocol-specified pain rating or vital signs assessment, the patient will be allowed to sleep, but the study staff will record the respiratory rate and oxygen saturation. A patient will not be allowed to sleep through 2 consecutive assessments.

Sleeping patients will be observed for signs of opioid overdose, such as bradypnea and airway obstruction. If a patient does not appear to have signs of opioid overdose the patient will be allowed to continue to sleep.

If a patient is unable to obtain satisfactory analgesia using the study drug, other allowable medications, and supplemental opioid medication allowed in the protocol-specified dosing regimen, he/she should be withdrawn from the study. Pain management, as deemed appropriate by the Investigator, will be provided.

Passive range-of-motion therapy is permitted starting 12 hours after the first dose of study drug.

Safety Assessments

The patient will be monitored continuously by a study staff member for the first hour following the first dose of study drug.

Heart rate and blood pressure will be recorded prior to administration of the first dose of study drug, and when pain intensity and pain relief assessments are made i.e. 15, 30, and 45 minutes, and 1, 2, 4, 6, 8, 10, and 12 hours after the first on-demand dose. Blood pressure and heart rate will then be measured every four hours during the 12 to 72 hour

study period. During the first 24 hours of treatment, respiratory rate and oxygen saturation will be recorded prior to the first dose of study drug, 15,30, 45, and 60 minutes after the first dose of study drug, and then every 30 minutes. During the 24 to 72 hour study period, the respiratory rate and oxygen saturation will be recorded every 2 hours.

When vital signs are to be measured at the same time as PI and PR scores, the vital sign measurements may be taken up to 5 minutes before the scheduled time, in order for PI and PR scores to be self-recorded by patient at the scheduled time.

The Investigator or the Medical Monitor may exercise his/her judgment to terminate a patient's participation in the study due to clinically significant changes in any clinical parameter.

Patients will be instructed to report any AEs they experience throughout the duration of the study. Reported AEs and any concomitant medications administered during the study period will be recorded in the CRF. SAEs that occur within 30 days of the last dose of study drug will be reported.

6.1.4 End of Study

Patients will be considered completers if they complete the study for a minimum of 24 hours. Patients who are withdrawn from the study for any reason prior to 24 hours will be considered early terminations.

At the time the patient discontinues from the study or a Drug Cartridge is changed, the number of tablets remaining in the Drug Cartridge as displayed on the Zalviso System display screen will be recorded in the source records.

The Patient Usability Questionnaire (Appendix IV) will be completed at the end of the study or at the time of early discontinuation. The Patient Usability Questionnaire will be completed before the patient completes the PGA (Appendix III).

Study staff will complete the Nurse Usability Questionnaire (Appendix V) when they have interacted with 5 patients, or when enrollment is completed at the study site. The study staff will download the controller data after its use by each patient using the data transfer cable and download utility software provided by AcelRx. The data files will then be transferred per AcelRx instructions.

6.2 Appropriateness of Measurements

Global evaluations are recognized as important indicators of efficacy based on a patient's perception of effect. Patient ratings of pain intensity on an 11-point numerical rating scale (0=no pain, 10=worst possible pain), and pain relief on a 5-point numerical rating scale (0=no relief, 1=a little relief, 2=moderate relief, 3=a lot of relief, and 4=complete relief) are commonly used and validated measures of the effect of a treatment for pain.

The following questions regarding pain intensity and pain relief will be asked of the patient at the protocol-specified time points:

"On a scale of 0 to 10, 0 being no pain and 10 being worst possible pain, how would you rate your current level of pain intensity?"

"How would you rate your current level of pain relief on a scale of 0 to 4 with 0 being no relief and 4 being complete relief?"

The Patient and Nurse Usability Questionnaires are not validated.

7 ASSESSMENT OF EFFICACY

7.1 Efficacy Variables

Efficacy variables include:

- Proportion of patients who experienced at least one system-generated error based on the Controller data while using the Zalviso System
- Proportion of patients, if any, with tablet dispensed but not requested
- Proportion of patients, if any, with tablet dispensed when the Zalviso System is in lockout
- Proportion of patients with misplaced tablet(s)
- Number of misplaced tablets (i.e., tablet found outside the patient's mouth)
- Proportion of patients who experienced either a system-generated error or a misplaced tablet (i.e. a dispense failure)
- Assessment of the number of Zalviso System notifications to the nurse to retrain patient to not pull down on Controller while dosing (i.e., mitigation of Error 302)
- Proportion of patients who rate the Patient Global Assessment (PGA) of method of pain control over 24, 48 and 72 hours as "good" or "excellent"
- Proportion of patients who responded in each category of the PGA
- Proportion of Healthcare Professionals who rate the Global Assessment (HPGA) of method of pain control over 24, 48 and 72 hours as "good" or "excellent"
- Proportion of Healthcare Professionals who responded in each category of the HPGA
- Proportion of patients who terminate from the study due to inadequate analgesia over the 24-hour, 48-hour and 72-hour study period
- Time-weighted summed pain intensity difference (SPID) over the 24-hour study period (SPID24), over the 48-hour study period (SPID48), and over the 72-hour study period (SPID72)
- Total pain relief (TOTPAR) over the 24-hour study period (TOTPAR24), over the 48-hour study period (TOTPAR48) and over the 72-hour study period (TOTPAR72)
- Pain intensity (PI) at each evaluation time point
- Pain intensity difference (PID) at each evaluation time point
- Pain relief (PR) at each evaluation time point
- Patient Usability Questionnaire (PUQ)
- Nurse Usability Questionnaire (NUQ)
- Total number of study drug doses used over 24, 48, and 72-hour study period, average hourly use, and average inter-dosing interval.

- Total amount of supplemental morphine utilized

8 ASSESSMENT OF SAFETY

8.1 Safety Variables

Safety assessments will include the assessment of adverse events, vital signs (blood pressure, heart rate and respiratory rate), oxygen saturation, and the use of concomitant medications.

8.1.1 Physical Examination/Vital Signs

The physical examination will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, oral mucosa, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. Height and weight will be measured.

Vital signs will include respiratory rate, radial pulse rate, and systolic and diastolic blood pressures. The patient may be sitting, semi-recumbent or lying down. Recordings are to be made after the patient has been in the same position for 5 minutes or more and the position will be recorded. Heart rate will be measured over 30 seconds and respiratory rate will be measured over 1 minute.

Respiratory rate and other vital signs may be checked at additional times on an ad hoc basis per the judgment of the study staff. Oxygen saturation (SpO_2) will be measured continuously by pulse oximetry but will only be recorded at the time points when respiratory rates are measured and recorded.

8.1.2 Laboratory Parameters

A urine drug of abuse screen (barbiturates, benzodiazepines, cocaine, marijuana, phencyclidine, and opiates) will be performed at screening. A test for pregnancy will be done at screening and after admission to the hospital for women who are of childbearing potential.

8.1.3 Adverse Events

An adverse event is any illness, sign, laboratory value or symptom which appears or worsens during the clinical trial, regardless of causal relationship to the investigational drug. AEs that occur from the first dose of study drug and for 12 hours after the last dose of study drug will be documented on the AE CRF. The Investigator will assess the AE severity and relationship of the AE to study drug. The Investigator will treat the patient as medically required until the AE either resolves or becomes medically stable. Treatments and medications required to treat AEs will be recorded on the appropriate pages of the CRFs.

8.1.3.1 Adverse Event Severity is Defined as Follows:

Mild: The event may be noticeable to the patient, but does not influence the patient's daily activities. The event usually does not require special treatment.

Moderate: The event may result in slight discomfort for the patient and performance of the patient's daily activities may be influenced. The event may require intervention.

Severe: The event may result in severe discomfort for the patient and usually interferes with the patient's daily activities. The patient may not be able to continue in the study and treatment or other intervention is usually needed.

8.1.3.2 Adverse Event Relationship to Study Drug is Defined as Follows:

Probably related: Study drug administration and AE occurrence are reasonably related in time; AND, the AE is more likely explained by exposure to study drug than by other mechanisms.

Possibly related: Study drug administration and AE occurrence are reasonably related in time; AND, AE is explained equally well by causes other than study drug.

Not related: AE is obviously explained by another cause; OR, the time of occurrence of AE is not reasonably related to administration of the study drug.

8.1.3.3 Serious Adverse Events

Serious, life-threatening, and unexpected AEs will be identified and handled in accordance with the guidelines specified in the US Code of Federal Regulations (CFR).

A serious adverse event (SAE) is defined as any event that is fatal or life-threatening, permanently or substantially disabling or incapacitating (causing a substantial disruption of a person's ability to conduct normal life functions), prolongs hospitalization, a congenital anomaly, or an important medical event. Important medical events are defined as events that may not result in death, be life threatening, or prolongs hospitalization but, based on appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of an SAE.

A life-threatening AE is one that, in the view of the Investigator, places the patient at immediate risk of death from the reaction as it occurred.

An unexpected AE is any event, for which the specificity or severity is not consistent with the AE profile in the current package insert for Sufenta (Appendix VI) or the Zalviso System Investigator Brochure.

All SAEs, regardless of cause(s) or relationship to study drug, must be reported immediately to AcelRx or designee. Additional contact numbers and AE/SAE reporting instructions will be provided to each site in a separate document.

The name of the Medical Monitor and contact information will be provided to each study site.

The Investigator must report via phone or fax an SAE within 24 hours of learning of the event. The investigator must complete the Serious Adverse Event Report Form and

submit it along with other relevant pages of the CRF within 1 working day to AcelRx or its designee. The Investigator will also compile with urgent priority other relevant documentation (e.g., copies of test results, hospital discharge summary, autopsy report, etc.) and send this information to AcelRx or its designee. All SAEs will also be reported on the AE page of the CRF, and concomitant medications administered in association with the SAE will be documented on the Concomitant Medication page of the CRF.

Regulatory agencies and all participating Investigators will be notified in writing of any SAE that is both associated with the use of the study drug and unexpected within 15 calendar days from when the SAE was reported to AcelRx or safety designee. Safety reporting shall also include events described in the scientific literature. Regulatory agencies will be notified by telephone or fax within 7 calendar days of any unexpected fatal or life-threatening AE associated with the use of the study drug.

AEs and SAEs that occur during the study treatment period will be documented. Any SAEs reported during the 30 days after the last dose of study drug will be reported and captured in the CRF.

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Determination of Sample Size

This is a multicenter, open-label, single treatment clinical study designed to evaluate the overall functionality of the Zalviso System (sufentanil sublingual tablet system) 15 mcg for the treatment of acute moderate-to-severe postoperative pain. A sample size of approximately 330 patients is planned for this study in order to have at least 315 patients receive study drug and have available efficacy data for data analysis.

A sample size of 315 patients will have 90% power to demonstrate that the device dispense failure rate is non-inferior to a target of 2%. This failure rate is the proportion of patients who experienced at least one of following events: (1) a system-generated error, (2) a tablet dispensed but not requested, or (3) a tablet dispensed when the Zalviso System is in lockout. All events listed above will be obtained from the Controller patient usage data.

This is based on the criteria that the upper limit of a 90% confidence interval (CI) of the device dispense failure rate is not worse than 5%. This calculation is based on the exact binomial test of one-sample proportion for a one-sided case against a 2% target proportion with a delta of 3%, and a one-sided significance level of α=0.05. This sample size was generated from the SAS procedure PROC POWER for one-sample proportion. Exact power computations are based on the binomial distribution and computing formulas provided by Johnson and Kotz (1970). Assuming a 5% non-evaluable rate, a sample size of 330 patients is planned for this study.

9.2 Tests of Hypothesis and Significance Levels

Both continuous and categorical efficacy variables will be summarized descriptively. A point estimate of the device dispense failure rate and its 90% confidence interval based on the exact binomial test will be constructed.

9.3 Randomization and Blinding of the Treatment Assignment

This is an open-label single treatment study. There is no randomization of patients or blinding of treatment. Patients who meet the eligibility requirements will be enrolled into this study sequentially within each study center to receive study treatment.

9.4 Baseline Comparability

Demographics and baseline characteristics will be summarized by sex group for all enrolled patients and all patients received study drug. Data will be pooled for all study centers for the descriptive summary of baseline data. No formal hypothesis testing will be performed for baseline data.

9.5 Analysis of Efficacy Data

Sections related to the analysis of efficacy data are specified below by topic.

9.5.1 Efficacy Variables and Parameters

The efficacy variables and parameters are:

1. Proportion of patients who experienced at least one system-generated error based on the Controller data while using the Zalviso System
2. Proportion of patients, if any, with tablet dispensed but not requested
3. Proportion of patients, if any, with tablet dispensed when the Zalviso System is in lockout
4. Proportion of patients with misplaced tablet(s)
5. Number of misplaced tablets (i.e., tablet found outside the patient's mouth)
6. Proportion of patients who experienced either a system-generated error or a misplaced tablet (i.e. a dispense failure)
7. Assessment of the number of Zalviso System notifications to the nurse to retrain patient to not pull down on Controller while dosing (i.e., mitigation of Error 302)
8. Proportion of patients who rate the Patient Global Assessment (PGA) of method of pain control over 24, 48 and 72 hours as "good" or "excellent"
9. Proportion of patients who responded in each category of the PGA
10. Proportion of Healthcare Professionals who rate the Global Assessment (HPGA) of method of pain control over 24, 48 and 72 hours as "good" or "excellent"
11. Proportion of Healthcare Professionals who responded in each category of the HPGA
12. Proportion of patients who terminate from the study due to inadequate analgesia over the 24-hour, 48-hour and 72-hour study period
13. Time-weighted summed pain intensity difference (SPID) over the 24-hour study period (SPID24), over the 48-hour study period (SPID48), and over the 72-hour study period (SPID72)

14. Total pain relief (TOTPAR) over the 24-hour study period (TOTPAR24), over the 48-hour study period (TOTPAR48) and over the 72-hour study period (TOTPAR72)
15. Pain intensity (PI) at each evaluation time point
16. Pain intensity difference (PID) at each evaluation time point
17. Pain relief (PR) at each evaluation time point
18. Patient Usability Questionnaire (PUQ)
19. Nurse Usability Questionnaire (NUQ)
20. Total number of study drug doses used over 24, 48, and 72-hour study period, average hourly use, and average inter-dosing interval.
21. Total amount of supplemental morphine utilized

9.5.2 Analysis Population and Handling of Dropouts

The main analysis of the efficacy variables will include the intent-to-treat (ITT) population. The ITT population includes enrolled patients who received study drug.

For patients missing PI or PR data, the following methods will be applied to impute the missing data at evaluation time points for the duration of study period:

(1) Missing data will be first imputed on a patient-by-patient basis by linear interpolation method between two observed pain scale values.

(2) Data occurring after a patient terminated from study or did not provide any follow-up data after last available data prior to the end of study period, the pain scale values at follow-up time points post-termination up to the end of the study period will be imputed on a patient-by-patient basis as described below.

The last observation carried forward (LOCF) method will be used to impute any remaining missing data points after termination due to reasons other than adverse event up to the end of the study period. For patients who prematurely terminated from the study due to adverse event, the worst observation carried forward (WOCF) method will be used to impute the remaining missing data points up to the end of the study period. The worst PID is the smaller number between number zero and the last PID obtained prior to termination. The worst PR is number zero.

For patients who used any supplemental opioid during the study period, the last observed pain intensity prior to using each dose of supplemental opioid will be carried throughout a follow-up 1-hour time interval. Any pain intensity collected within 1 hour after the start of any supplemental opioid will be excluded from the calculation of the time-weighted SPID24. This same imputation method will also be used to calculate the efficacy endpoints derived from pain assessment data.

9.5.3 Definition of Baseline Measurements

Baseline measurements are those taken prior to the start of study drug administration.

9.5.4 Methods for the Analysis of Device Dispense Failure Rate

For the analysis of the device dispense failure rate, a point estimate of the device dispense failure rate and its 90% confidence interval based on the exact binomial test will be constructed. Patients from all study centers will be pooled for the descriptive summary of these efficacy data by sex group.

9.5.5 Pooling of Investigators

The data from all study centers will be pooled for the analysis of efficacy data.

9.5.6 Methods for the Analysis of Categorical Efficacy Variables

For the analysis of the dichotomous outcome data, a point estimate and its 90% confidence interval based on the exact binomial test will be constructed. Patients from all study centers will be pooled for the descriptive summary of the efficacy data by sex group.

9.5.7 Methods for the Analysis of Continuous Efficacy Variables

The method used to derive the efficacy endpoint time-weighted summed pain intensity difference (SPID) over the study period is described in this section. Pain intensity will be measured using an 11-point NRS with 0 (no pain) and 10 (worst possible pain).

Patients will provide the pain intensity (PI) and pain relief (PR) measures at baseline and at each evaluation time point after the initiation of the first on-demand dose of study drug: ¼ [15 min], ½ [30 min], ¾ [45 min], 1, 2, 4, 6, 8, 10, and 12 hours, then every 4 hours at 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 hours.

The 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 SPID24 is the time-weighted summed PID over the 24-hour study period.

$$\text{Time-weighted SPID24} = \sum [T(i) - T(i-1)] \times PID(i),$$

Where : T(0) = Time 0 (baseline), T(i) is the scheduled or unscheduled assessment time, and PID(i) is the PID score at time i for i=0 to 24 hours

Other time-weighted SPID, SPID48 and SPID72 will be derived similarly. TOTPAR over follow-up evaluation time periods (e.g., TOTPAR24, TOTPAR48, and TOTPAR72, etc.) will be derived from the PR data collected during the study using similar formula described above.

For the analysis of the continuous efficacy data, a point estimate and its 90% confidence interval will be constructed. Patients from all study centers will be pooled for the descriptive summary of the efficacy data by sex group

9.6 Analysis of Safety Data

All patients who received at least one dose of study drug will be included in the summaries of safety data. An AE thesaurus, the Medical Dictionary for Regulatory Activities (MedDRA) will be used to map each AE verbatim term to lowest level term, preferred term, and System Organ Class for summary purposes. Adverse events occurring while patients are on study drug until 12 hours after the last dose will be summarized. Other safety data, such as premature terminations, vital signs (blood pressure, heart rate, and respiratory rate), oxygen saturation, and the use of concomitant medications will be tabulated.

Vital signs taken at baseline and follow-up time points will be summarized. Patients who had baseline data and at least one follow-up data will be included in the summary of vital signs by sex group. The descriptive summary statistics will be presented. A paired t-test will be used for the test of mean change from baseline to follow-up time points within each group.

10 STUDY MANAGEMENT

10.1 Regulatory and Ethical Considerations

10.1.1 Regulatory Guidelines

The Investigator agrees to conduct the study in accordance with the protocol, ICH guidelines on Good Clinical Practice (GCP), and national, state, and local laws of the pertinent regulatory authorities.

10.1.2 Institutional Review Board

The protocol, informed consent form (ICF), investigator's brochure, patient information, recruiting materials, subject compensation program (if any) must be approved in writing by an Institutional Review Board (IRB) before the study can be initiated at a site.

If the protocol is amended, AcelRx or the Investigator must obtain IRB for approval prior to implementation of the amendment. The Investigator must report promptly to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, including all SAEs that have resulted in an expedited safety reporting.

The Investigator is responsible for obtaining continued review of the clinical study as specified by the IRB but at least annually.

10.1.3 Informed Consent

Each patient must provide written informed consent before any study-related procedures are started. It is the responsibility of the Investigator or designated staff member(s) to give a copy of the ICF to each potential patient and to be available to answer any questions the patient may have about the nature of the study and his or her participation in it. The individual responsible for explaining the consent form to the patient must witness the patient's signature on the form. It is the responsibility of the Investigator to

provide a copy of the IRB-approved consent form to the Sponsor (or designee) prior to the start of the study. If a protocol amendment substantially alters a study design or increases the potential risk to the patient, the consent form must be revised and submitted to the IRB(s) for review and approval prior to implementation. The revised consent must be used to obtain consent from patients currently in the study if they are affected by the amendment and from new patients prior to their enrollment in the study.

All enrolling patients are required to sign an IRB-approved Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization document.

10.1.4 Study Documentation

The protocol and any amendments signed and dated by the investigator, the completed financial disclosure form, and signed and dated statement of the investigator (e.g. Form FDA 1572), if applicable, and all other essential documents specified by ICH GCP will be provided to AcelRx or designee prior to initiation of the study at the investigational center.

Adequate source documentation will be maintained by the investigator and may be recorded on paper or directly into an electronic system. At a minimum this documentation will verify subject identification, eligibility, proper informed consent, visit dates, adherence to study procedures, reporting of safety and efficacy parameters, study drug dispensing, and study completion.

Source data may be recorded on paper or directly into an electronic system. A list of data directly entered into an electronic data capture system will be maintained.

Data should be entered into the CRF within 3 days of a patient completing the study. Queries should be resolved within 5 days of being issued.

10.2 Withdrawals

Individual patients might voluntarily drop from the study without completing all assessments. In such cases, the Investigator will document the specific reason for the incomplete information (e.g., withdrawal of consent) on the appropriate page of the CRF.

10.3 Study Or Study Site Termination

AcelRx may suspend or stop the study at all centers or at specific study centers due to (but are not limited to) the discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study, a decision on the part of AcelRx to suspend or discontinue development of the product, failure of the Investigator to enroll patients into the study at an acceptable rate, failure of the Investigator to comply with regulatory authority or ICH Guidelines, or submission of knowingly false information.

10.4 Study Monitoring

AcelRx or designee will assign monitors who will perform on site monitoring as frequently as necessary and in accordance with ICH GCP.

Source documents and CRFs will be reviewed at monitoring visits and any findings will be discussed with the investigational staff. AcelRx expects that at monitoring visits study documents and staff will be available and a suitable space will be provided for review of the study documents. The monitor will meet with the investigator on a regular basis to provide feedback on the conduct of the study.

10.5 Data Quality Assurance

Study auditing, data entry, verification and validation, and subsequent analysis will be performed by AcelRx, or its designees, in accordance with GCPs and established Standard Operating Procedures.

10.6 Access to Records

The study may be subject to audit by AcelRx, its designee, or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required patient records. The Investigator should notify AcelRx promptly of regulatory authority audits that are scheduled, and must forward copies of any findings or audit reports to AcelRx promptly.

By signing this protocol, the Investigator grants permission to personnel from AcelRx, its representatives, and appropriate regulatory authorities for on-site monitoring and review of all appropriate study documentation, as well as on-site review of the procedures employed in data collection, where clinically appropriate.

10.7 Retention of Records

The Investigator must arrange for retention of study records at the site for 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with AcelRx. It is the responsibility of AcelRx to inform the Investigator/Institution as to when these documents no longer need to be retained. The Investigator should take measures to prevent any accidental or premature destruction of these documents.

11 Publications

All information related to this study is considered confidential information belonging to AcelRx. Data on the use of the study drug and results of all clinical and laboratory studies are considered private and confidential. None of the details, results, or other information for this study shall be published or made known to a third party without written consent from AcelRx, except for disclosure to regulatory agencies if required by law.

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APPENDIX I

American Society of Anesthesiologists Physical Status Classification System

I	Normal healthy patient
II	Patient with mild systemic disease; no functional limitation–eg, smoker with well-controlled hypertension
III	Patient with severe systemic disease; definite functional impairment–eg, diabetes and angina with relatively stable disease, but requiring therapy
IV	Patient with severe systemic disease that is a constant threat to life–eg, diabetes and angina and congestive heart failure; patientswith dyspnea on mild exertion and chest pain
V	Unstable moribund patient who is not expected to survive 24 hours with or without the operation
VI	Brain-dead patient whose organs are removed for donation to another
E	Emergency operation of any type, which is added to any of the above six categories, as in ASA II E

APPENDIX II

DSM-IV Criteria for Substance Dependence

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same twelve-month period:

1. tolerance, as defined by either of the following:
   a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b. markedly diminished effect with continued use of the same amount of the substance
2. withdrawal, as manifested by either of the following:
   a. the characteristic withdrawal syndrome for the substance (see specific withdrawal syndromes in the DSM-IV)
   b. the same substance (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. the substance is often taken in larger amounts or over a longer period than was intended
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use
5. a great deal of time is spent in activities necessary to get the substance, use the substance, or recover from its effects
6. important social, occupational, or recreational activities are given up or reduced because of substance use
7. the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

NOTE: In an individual who denies dependence, substance dependence is assumed if there is evidence of a mental or physical disorder or condition that is usually a complication of prolonged substance use, e.g., DTs, cirrhosis, alcoholic neuropathy, esophageal varices from alcohol use, needle marks or abscesses from substance use.

*Based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV Criteria for Substance Dependence)

APPENDIX II (continued)

DSM-IV Criteria for Substance Abuse

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring at any time in the same 12-month period:

(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance related absences, suspensions, or expulsions from school; neglect of children or household)
(2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance-related disorderly conduct)
(3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)
(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

NOTE: If a subject does not meet any of the above criteria, alcohol abuse will be assumed if the patient is consistently drinking more than 28 units of alcoholic beverages per week or female subjects who drink more than 21 units per week. 1 unit is defined as ½ pint of beer, 1 glass of wine or 1 measure of spirits.

* Based on Diagnostic and Statistical manual of Mental Disorders, Fourth Edition (DSM-IV Criteria for Substance Abuse)

APPENDIX III
Patient Global Assessment

The following question will be answered by the patient 24 hours after the first on-demand dose:
"Overall, how would you rate the method of pain control during the last 24 hours?"

The following question will be answered by the patient 48 hours after the first on-demand dose:
"Overall, how would you rate the method of pain control during the last 48 hours?"

The following question will be answered by the patient 72 hours after the first on-demand dose:
"Overall, how would you rate the method of pain control during the last 72 hours?"

- ☐ Poor (1)
- ☐ Fair (2)
- ☐ Good (3)
- ☐ Excellent (4)

Healthcare Professional Global Assessment

The following question will be answered by the HP 24 hours after the first on-demand dose:
"Overall, how would you rate the method of pain control during the last 24 hours?"

The following question will be answered by the HP 48 hours after the first on-demand dose:
"Overall, how would you rate the method of pain control during the last 48 hours?"

The following question will be answered by the HP 72 hours after the first on-demand dose:
"Overall, how would you rate the method of pain control during the last 72 hours?"

- ☐ Poor (1)
- ☐ Fair (2)
- ☐ Good (3)
- ☐ Excellent (4)

APPENDIX IV

Patient Usability Questionnaire

How would you rate your experience with Zalviso regarding:

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
I thought Zalviso was easy to use				
I had confidence in my ability to dose with Zalviso				
Zalviso consistently worked as I expected it to				
I did not understand how to use Zalviso				
I knew what to do if I dropped a tablet				
The use of Zalviso was not fully explained to me				
I would request to use Zalviso after my next surgery				

APPENDIX V
Nurse Usability Questionnaire

How would you rate your experience with Zalviso regarding:

	Disagree	Somewhat Disagree	Somewhat Agree	Agree
I thought Zalviso was easy to set-up				
I had confidence in my ability to set-up Zalviso				
I did not spend much time having to trouble-shoot Zalviso during patient use				
Dropped tablets were disposed and accounted for appropriately and did not become a risk to the patient or others				
I found Zalviso time-consuming to set-up				
The Zalviso set-up instructions were not clear to me				
I would recommend Zalviso for the treatment of moderate to severe pain after surgery				

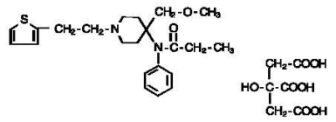
APPENDIX VI: Sufenta Package Insert

SUFENTA®
(SUFENTANIL CITRATE) INJECTION

R_x only

DESCRIPTION

SUFENTA® (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. The structural formula of SUFENTA is:



SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per mL of sufentanil base for intravenous and epidural injection. The solution has a pH range of 3.5-6.0.

CLINICAL PHARMACOLOGY

Pharmacology

SUFENTA is an opioid analgesic. When used in balanced general anesthesia, SUFENTA has been reported to be as much as 10 times as potent as fentanyl. When administered intravenously as a primary anesthetic agent with 100% oxygen, SUFENTA is approximately 5 to 7 times as potent as fentanyl.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

(See dosage chart for more complete information on the intravenous use of SUFENTA.)

Pharmacodynamics

Intravenous use

At intravenous doses of up to 8 µg/kg, SUFENTA is an analgesic component of general anesthesia; at intravenous doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

At intravenous dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. At dosages of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia. The vagolytic effects of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA-nitrous oxide/oxygen produced reductions in cerebral blood flow comparable to those of enflurane-nitrous oxide/oxygen. During cardiovascular surgery, SUFENTA-oxygen produced EEG patterns similar to fentanyl-oxygen; these EEG changes were judged to be compatible with adequate general anesthesia.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Skeletal muscle rigidity is related to the dose and speed of administration of SUFENTA. This muscular rigidity may occur unless preventative measures are taken (see WARNINGS).

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

Epidural use in Labor and Delivery

Onset of analgesic effect occurs within approximately 10 minutes of administration of epidural doses of SUFENTA and bupivacaine. Duration of analgesia following a single epidural injection of 10-15 µg SUFENTA and bupivacaine 0.125% averaged 1.7 hours.

During labor and vaginal delivery, the addition of 10-15 µg SUFENTA to 10 mL 0.125% bupivacaine provides an increase in the duration of analgesia compared to bupivacaine without an opioid. Analgesia from 15 µg SUFENTA plus 10 mL 0.125% bupivacaine is comparable to analgesia from 10 mL of 0.25% bupivacaine alone. Apgar scores of neonates following epidural administration of both drugs to women in labor were comparable to neonates whose mothers received bupivacaine without an opioid epidurally.

Pharmacokinetics

Intravenous use

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

Epidural use in Labor and Delivery

After epidural administration of incremental doses totaling 5-40 µg SUFENTA during labor and delivery, maternal and neonatal sufentanil plasma concentrations were at or near the 0.05-0.1 ng/mL limit of detection, and were slightly higher in mothers than in their infants.

CLINICAL STUDIES

Epidural use in Labor and Delivery

Epidural sufentanil was tested in 340 patients in two (one single-center and one multicenter) double-blind, parallel studies. Doses ranged from 10 to 15 µg sufentanil and were delivered in a 10 mL volume of 0.125% bupivacaine with and without epinephrine 1:200,000. In all cases sufentanil was administered following a dose of local anesthetic to test proper catheter placement. Since epidural opioids and local anesthetics potentiate each other, these results may not reflect the dose or efficacy of epidural sufentanil by itself.

Individual doses of 10-15 µg SUFENTA plus bupivacaine 0.125% with epinephrine provided analgesia during the first stage of labor with a duration of 1-2 hours. Onset was rapid (within 10 minutes). Subsequent doses (equal dose) tended to have shorter duration. Analgesia was profound (complete pain relief) in 80% to 100% of patients and a 25% incidence of pruritus was observed. The duration of initial doses of SUFENTA plus bupivacaine with epinephrine is approximately 95 minutes, and of subsequent doses, 70 minutes.

There are insufficient data to critically evaluate neonatal neuromuscular and adaptive capacity following recommended doses of maternally administered epidural sufentanil with bupivacaine. However, if larger than recommended doses are used for combined local and systemic analgesia, e.g. after administration of a single dose of 50 µg epidural sufentanil during delivery, then impaired neonatal adaption to sound and light can be detected for 1 to 4 hours and if a dose of 80 µg is used impaired neuromuscular coordination can be detected for more than 4 hours.

INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated for intravenous administration *in adults and pediatric patients:*

as an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures,in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

SUFENTA (sufentanil citrate) is indicated for epidural administration as an analgesic combined with low dose bupivacaine, usually 12.5 mg per administration, during labor and vaginal delivery.

SEE DOSAGE AND ADMINISTRATION SECTION FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug or known intolerance to other opioid agonists.

WARNINGS

SUFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND EPIDURAL ANESTHETICS AND MANAGEMENT OF THE RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

PRIOR TO CATHETER INSERTION, THE PHYSICIAN SHOULD BE FAMILIAR WITH PATIENT CONDITIONS (SUCH AS INFECTION AT THE INJECTION SITE, BLEEDING DIATHESIS, ANTICOAGULANT THERAPY, ETC.) WHICH CALL FOR SPECIAL EVALUATION OF THE BENEFIT VERSUS RISK POTENTIAL.

Intravenous use

Intravenous administration or unintentional intravascular injection during epidural administration of SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset of action than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. As with fentanyl, muscular rigidity has been reported to occur or recur infrequently in the extended postoperative period. The incidence of muscular rigidity associated with intravenous SUFENTA can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agents used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Respiratory depression may be enhanced when SUFENTA is administered in combination with volatile inhalational agents and/or other central nervous system depressants such as barbiturates, tranquilizers, and other opioids. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Respiration should be closely monitored following each administration of an epidural injection of SUFENTA.

Proper placement of the needle or catheter in the epidural space should be verified before SUFENTA is injected to assure that unintentional intravascular or intrathecal administration does not occur. Unintentional intravascular injection of SUFENTA could result in a potentially serious overdose, including acute truncal muscular rigidity and apnea. Unintentional intrathecal injection of the full sufentanil/bupivacaine epidural doses and volume could produce effects of high spinal anesthesia including prolonged paralysis and delayed recovery. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medications. SUFENTA should be administered epidurally by slow injection.

Neuromuscular Blocking Agents: The hemodynamic effects and degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia and hypotension have been reported with other muscle relaxants during SUFENTA-oxygen anesthesia; this effect may be more pronounced in the presence of calcium channel and/or beta-blockers. Muscle relaxants with no clinically significant effect on heart rate (at recommended doses) would not counteract the vagotonic effect of SUFENTA, therefore a lower heart rate would be expected. Rare reports of bradycardia associated with the concomitant use of succinylcholine and SUFENTA have been reported.

Interaction with Calcium Channel and Beta Blockers: The incidence and degree of bradycardia and hypotension during induction with SUFENTA may be greater in patients on chronic calcium channel and beta blocker therapy. (See Neuromuscular Blocking Agents.)

Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetic or other CNS depressants. In such cases of combined treatment, the dose of SUFENTA and/or these agents should be reduced.

The use of benzodiazepines with SUFENTA during induction may result in a decrease in mean arterial pressure and systemic vascular resistance.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility
No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human intravenous dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C
SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human intravenous dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

Labor and Delivery
The use of epidurally administered SUFENTA in combination with bupivacaine 0.125% with or without epinephrine is indicated for labor and delivery. (See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections.) SUFENTA is not recommended for intravenous use or for use of larger epidural doses during labor and delivery because of potential risks to the newborn infant after delivery. In clinical trials, one case of severe fetal bradycardia associated with maternal hypotension was reported within 8 minutes of maternal administration of sufentanil 15 µg plus bupivacaine 0.125% (10 mL total volume).

Nursing Mothers
It is not known whether sufentanil is excreted in human milk. Because fentanyl analogs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use
The safety and efficacy of intravenous SUFENTA in pediatric patients as young as 1 day old undergoing cardiovascular surgery have been documented in a limited number of cases. The clearance of SUFENTA in healthy neonates is approximately one-half that in adults and children. The clearance rate of SUFENTA can be further reduced by up to a third in neonates with cardiovascular disease, resulting in an increase in the elimination half-life of the drug.

Animal Toxicology
The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human intravenous dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results. Epidural and intrathecal injections of sufentanil in dogs and epidural injections in rats were not associated with neurotoxicity.

ADVERSE REACTIONS
The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity, particularly of the truncal muscles. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Urinary retention has been associated with the use of epidural opioids but was not reported in the clinical trials of epidurally administered sufentanil due to the use of indwelling catheters. The incidence of urinary retention in patients without urinary catheters receiving epidural sufentanil is unknown; return of normal bladder activity may be delayed.

The following adverse reaction information is derived from controlled clinical trials in 320 patients who received intravenous sufentanil during surgical anesthesia and in 340 patients who received epidural sufentanil plus bupivacaine 0.125% for analgesia during labor and is presented below. Based on the observed frequency, none of the reactions occurring with an incidence less than 1% were observed during clinical trials of epidural sufentanil used during labor and delivery (N=340).

In general cardiovascular and musculoskeletal adverse experiences were not observed in clinical trials of epidural sufentanil. Hypotension was observed 7 times more frequently in intravenous trials than in epidural trials. The incidence of central nervous system, dermatological and gastrointestinal adverse experiences was approximately 4 to 25 times higher in studies of epidural use in labor and delivery.

Probably Causally Related: Incidence Greater than 1% - Derived from clinical trials (See preceding paragraph)
Cardiovascular: bradycardia*, hypertension*, hypotension*.
Musculoskeletal: chest wall rigidity*.
Central Nervous System: somnolence*.
Dermatological: pruritus (25%).
Gastrointestinal: nausea*, vomiting*.
*Incidence 3% to 9%

Probably Causally Related: Incidence Less than 1% - Derived from clinical trials (Adverse events reported in post-marketing surveillance, not seen in clinical trials, are *italicized*.)
Body as a whole: anaphylaxis.
Cardiovascular: arrhythmia*, tachycardia*, *cardiac arrest.*
Central Nervous System: chills*.
Dermatological: erythema*.
Musculoskeletal: skeletal muscle rigidity of neck and extremities.
Respiratory: apnea*, bronchospasm*, postoperative respiratory depression*.
Miscellaneous: intraoperative muscle movement*.
*Incidence 0.3% to 1%

DRUG ABUSE AND DEPENDENCE
SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE
Overdosage is manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. The most serious and significant effect of overdose for both intravenous and epidural administration of SUFENTA is respiratory depression. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION
The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Because the clearance of SUFENTA is reduced in neonates, especially those with cardiovascular disease, the dose of SUFENTA should be reduced accordingly (see PRECAUTIONS).

Intravenous use
SUFENTA may be administered intravenously by slow injection or infusion 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia (see Dosage Range Chart). If benzodiazepines, barbiturates, inhalation agents, other opioids or other central nervous system depressants are used concomitantly, the dose of SUFENTA and/or these agents should be reduced (see PRECAUTIONS). In all cases dosage should be titrated to individual patient response.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART for Intravenous use

ANALGESIC COMPONENT TO GENERAL ANESTHESIA
•TOTAL DOSAGE REQUIREMENTS OF 1 µG/KG/HR OR LESS ARE RECOMMENDED

TOTAL DOSAGE	MAINTENANCE DOSAGE
ANALGESIC DOSAGES	
Incremental or Infusion: 1-2 µg/kg (expected duration of anesthesia 1-2 hours). Approximately 75% or more of total SUFENTA dosage may be administered prior to intubation by either slow injection or infusion titrated to individual patient response. Dosages in this range are generally administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**Incremental: 10-25 µg (0.2-0.5 mL)** may be administered in increments as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated. **Infusion:** SUFENTA may be administered as an intermittent or continuous infusion as needed in response to signs of lightening of analgesia. In absence of signs of lightening of analgesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation. Maintenance infusion rates should be adjusted based upon the induction dose of SUFENTA so that the total dose does not exceed 1 µg/kg/hr of expected surgical time. Dosage should be individualized and adjusted to remaining operative time anticipated.
ANALGESIC DOSAGES	
Incremental or Infusion: 2-8 µg/kg (expected duration of anesthesia 2-8 hours). Approximately 75% or less of the total calculated SUFENTA dosage may be administered by slow injection or infusion prior to intubation, titrated to individual patient response. Dosages in this range are generally administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures in which endotracheal intubation and mechanical ventilation are required. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**Incremental: 10-50 µg (0.2-1 mL)** may be administered in increments as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated. **Infusion:** SUFENTA may be administered as an intermittent or continuous infusion as needed in response to signs of lightening of analgesia. In the absence of signs of lightening of analgesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation. Maintenance infusion rates should be adjusted based upon the induction dose of SUFENTA so that the total dose does not exceed 1 µg/kg/hr of expected surgical time. Dosage should be individualized and adjusted to remaining operative time anticipated.
ANESTHETIC DOSAGES	
Incremental or Infusion: 8-30 µg/kg (anesthetic doses). At this anesthetic dosage range SUFENTA is generally administered as a slow injection, as an infusion, or as an injection followed by an infusion. SUFENTA with 100% oxygen and a muscle relaxant has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. The addition of N_2O to these dosages will reduce systolic blood pressure. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic response including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, in which endotracheal intubation and mechanical ventilation are required, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative observation is essential and postoperative mechanical ventilation may be required at the higher dosage range due to extended postoperative respiratory depression. Dosage should be titrated to individual patient response.	**Incremental:** Depending on the initial dose, maintenance doses of 0.5-10 µg/kg may be administered by slow injection in anticipation of surgical stress such as incision, sternotomy or cardiopulmonary bypass. **Infusion:** SUFENTA may be administered by continuous or intermittent infusion as needed in response to signs of lightening of anesthesia. In the absence of lightening of anesthesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation. The maintenance infusion rate for SUFENTA should be based upon the induction dose so that the total dose for the procedure does not exceed 30 µg/kg.

In patients administered high doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of SUFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

Epidural use in Labor and Delivery

Proper placement of the needle or catheter in the epidural space should be verified before SUFENTA is injected to assure that unintentional intravascular or intrathecal administration does not occur. Unintentional intravascular injection of SUFENTA could result in a potentially serious overdose, including acute truncal muscular rigidity and apnea. Unintentional intrathecal injection of the full sufentanil, bupivacaine epidural doses and volume could produce effects of high spinal anesthesia including prolonged paralysis and delayed recovery. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medications. SUFENTA should be administered by slow injection. Respiration should be closely monitored following each administration of an epidural injection of SUFENTA.

Dosage for Labor and Delivery: The recommended dosage is SUFENTA 10-15 µg administered with 10 mL bupivacaine 0.125% with or without epinephrine. SUFENTA and bupivacaine should be mixed together before administration. Doses can be repeated twice (for a total of three doses) at not less than one-hour intervals until delivery.

HOW SUPPLIED
SUFENTA (sufentanil citrate) Injection is supplied as a sterile aqueous preservative-free solution for intravenous and epidural use as:
NDC 11098-050-01 50 µg/mL sufentanil base, 1 mL ampoules in packages of 10
NDC 11098-050-02 50 µg/mL sufentanil base, 2 mL ampoules in packages of 10
NDC 11098-050-05 50 µg/mL sufentanil base, 5 mL ampoules in packages of 10
Protect from light. Store at controlled room temperature (59°-77°F/15°-25°C).

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