**Protocol Title:** A phase 3, open-label study to evaluate the safety of oliceridine (TRV130) in patients with acute pain for which parenteral opioid therapy is warranted

**Protocol Number:** CP130-3003

**Protocol Version:** 5.0

**Protocol Date:** 14 September 2016

**NCT:** 02656875

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| **Protocol Title:** | A phase 3, open-label study to evaluate the safety of oliceridine (TRV130) in patients with acute pain for which parenteral opioid therapy is warranted |
| **Protocol Number:** | CP130-3003 |
| **Clinical Phase:** | Phase 3 |
| **Protocol Version and Date:** | Version 5.0<br>14 Sep 2016 |
| **US Investigational New Drug Number:** | 113,537 |
| **Sponsor:** | Trevena, Inc.<br>1018 West 8th Avenue, Suite A<br>King of Prussia, PA 19406 USA<br>Phone: 610-354-8840 |

-CONFIDENTIAL-

**SIGNATURE PAGE**

Protocol Title: A phase 3, open-label study to evaluate the safety of oliceridine (TRV130) in patients with acute pain for which parenteral opioid therapy is warranted.

The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol.

Any modifications of the clinical study protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Sponsor Approval:

Signature: DocuSigned by: David Soergel BBADC96C39AF46C... Date: 9/15/2016

Name (print): David Soergel

Title: Chief Medical Officer

Investigator Agreement:

I have read the clinical study protocol and agree to conduct the study as outlined herein.

Signature: _____ Date: _____

Name (print): _____

**SYNOPSIS**

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| PROTOCOL TITLE | A phase 3, open-label study to evaluate the safety of oliceridine (TRV130) in patients with acute pain for which parenteral opioid therapy is warranted |
| PROTOCOL NUMBER | CP130-3003. |
| INVESTIGATOR(S)/STUDY CENTER(S) | This study will be conducted at approximately 60-90 study centers located in the United States. |
| PHASE OF DEVELOPMENT | Phase 3. |
| OBJECTIVES | **Primary objective**<br>• To evaluate the safety and tolerability of oliceridine in patients with moderate to severe acute pain for which parenteral opioid therapy is warranted.<br><br>**Secondary objective**<br>• To evaluate the analgesic efficacy of oliceridine. |
| STUDY DESIGN AND PROCEDURES | This phase 3, open-label, safety study in surgical and medical patients will be conducted in inpatient hospitals, outpatient hospital departments, ambulatory surgical care centers, and emergency departments (EDs). Patients recruited in EDs may continue oliceridine treatment if hospitalized and parenteral opioid therapy is warranted.<br><br>Representative surgeries include orthopedic (eg, total hip replacement, total knee replacement, spine), abdominal (eg, upper or lower abdominal, perineal), gynecologic (eg, total abdominal hysterectomy), vascular, soft tissue, and surgical procedural pain.<br><br>Representative medical conditions include acute pancreatitis, acute exacerbation of existing noncancerous chronic pain, musculoskeletal pain, sickle-cell disease, inflammatory orofacial |

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| | muscle pain, and renal colic. Medical conditions that could confound the evaluation of oliceridine are excluded, such as acute pain without a specific etiology, undifferentiated acute abdominal pain, acute breakthrough pain in palliative "end of life" care, and pain associated with advanced cancer (somatic, visceral, or neuropathic) or with concurrent use of chemotherapeutic or biologic agents for the treatment of cancer.<br><br>Representative ED conditions include visceral pain (eg, renal colic, upper abdominal pain, abdominal pelvic pain); nonvisceral pain (eg, traumatic and atraumatic acute musculoskeletal pain, chest wall pain, burns, orofacial pain/headache, cutaneous and soft tissue pain); procedural analgesia (eg, reduction of orthopedic fractures and dislocations, abscess incision and drainage); acute painful episodes associated with a medical condition (eg, sickle cell painful vaso-occlusive episode). Oliceridine will not be used to intentionally suppress a patient's level of consciousness (procedural sedation and analgesia as defined by the American College of Emergency Physicians [ACEP]).<br><br>The study has four phases: a screening/baseline phase, a treatment phase (consisting of a predose period and a dosing period), an end-of-treatment phase, and a follow-up phase.<br><br>**Screening/baseline phase**<br><br>Written informed consent will be obtained before any protocol-related activities are conducted. All screening procedures will be completed within 14 days before the first oliceridine dose. Select standard of care assessments (eg, chemistry, hematology, urine or serum pregnancy test, urine or serum toxicology screen, electrocardiogram (ECG)) obtained before informed consent may be used as study data if protocol specifications and timeframes are met.<br><br>When screening and baseline procedures are anticipated to occur within 48 hours of each other, they may be executed as a single procedure, unless the clinical condition of the patient has significantly changed since screening.<br><br>Adverse events (AEs) occurring from time of informed consent to the follow-up phase will be recorded in source and will also be |

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| | recorded in eCRF if the patient receives oliceridine. Serious Adverse Events (SAEs) occurring from time of informed consent to the follow-up phase or 7 days after the last dose of oliceridine (whichever occurs later) will be recorded in source and eCRF; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to oliceridine, regardless of the time of onset after treatment, should be reported.<br><br>Prior medications taken or administered within the 14 days before the first dose of oliceridine will be recorded in source and will also be recorded in eCRF.<br><br>**Treatment phase**<br><br>The treatment phase begins with the predose period and ends when the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine.<br><br>The duration of treatment for each patient will be determined by the clinical need for parenteral opioid therapy. In current practice, parenteral opioids are used as-needed for up to several days. Although preclinical toxicology studies support intravenous (IV) administration of oliceridine for up to 14 days, it is unlikely that patients will receive oliceridine for that duration in the context of this study.<br><br>Predose period<br><br>Before dosing with oliceridine, vital signs (blood pressure, heart rate, respiratory rate), oxygen saturation, and somnolence/sedation will be measured. Somnolence/sedation will be measured using the Moline-Roberts Pharmacologic Sedation Scale (MRPSS). During the predose period, an additional, post-surgical ECG will be performed only in surgical patients. Prior medications and AEs/SAEs will be recorded.<br><br>Pain intensity will be measured using a 0-10 point numeric pain rating scale (NPRS).<br><br>Predose period procedures will occur within 30 minutes before the |

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| | first oliceridine dose. If the dosing period is delayed, predose period procedures (except the additional, post-surgical ECG performed only in surgical patients) will be repeated.<br><br>Dosing period<br><br>Oliceridine IV infusion may be administered either by clinician-administered bolus, patient-controlled analgesia device (PCA), or both bolus and PCA, according to the clinical situation.<br><br>During dosing with oliceridine, vital signs, oxygen saturation, and somnolence/sedation will be measured at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid. An ECG will be obtained 60 minutes after the first dose of oliceridine, and at every 24 hours of oliceridine treatment. Blood will be collected for oliceridine pharmacokinetics and future cytochrome P450 2D6 (CYP2D6) genotyping. Concomitant medications and AEs/SAEs will be recorded.<br><br>NPRS assessments will also be completed at 30 minutes +/-10 minutes after the first dose of oliceridine and at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid.<br><br>**End-of-treatment phase**<br><br>When the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine, the treatment phase is complete and the end-of-treatment phase begins. A physical examination will be performed at this time.<br><br>Within 1 hour after completion of the treatment phase, vital signs, oxygen saturation, and somnolence/sedation will be measured, and concomitant medications and AEs/SAEs will be recorded.<br><br>Within 3 hours after completion of the treatment phase, blood will be collected for clinical laboratory tests. Concomitant medications and AEs/SAEs will be recorded.<br><br>Patients will be observed for at least three hours after the last dose |

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| | of oliceridine; however, medically-required transfer of an ED patient to another facility takes precedence over study procedures.<br><br>The Subjective Opioid Withdrawal Scale (SOWS) will be administered to detect symptoms of opioid withdrawal. If the patient is discharged or transferred before the time when the SOWS is to be performed, it will be performed one day after completion of the treatment phase and returned to the site by mail or in person.<br><br>**Follow-up phase**<br><br>A follow-up contact will be made between 2 and 3 days after completion of the treatment phase. The contact may be conducted in person or by telephone. Concomitant medications and AEs/SAEs will be recorded.<br><br>The surgical procedure, medical diagnosis or ED diagnosis for which parenteral opioid therapy was warranted will be captured using the International Classification of Diseases, 10th Revision (ICD-10) terminology. |
| PLANNED SAMPLE SIZE | Approximately 1000 patients will be treated with oliceridine. |
| KEY PATIENT SELECTION CRITERIA | **Eligibility Criteria**<br><br>Inclusion criteria<br><br>Patients must meet all inclusion criteria:<br><br>1. Age >=18 years at screening.<br><br>2. Moderate to severe acute pain for which parenteral opioid therapy is warranted, defined as NPRS pain intensity of >=4 during the predose period.<br><br>3. Able to understand and comply with the procedures and study requirements, and to provide written informed consent before any study procedure.<br><br>4. If it is anticipated that the patient will be treated with oliceridine in the ED with subsequent discharge or transfer to |

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| | another facility, that the patient will remain under the care of the investigator for at least three hours after the last dose of oliceridine.<br><br>Exclusion criteria<br><br>Given that the primary objective of this study is to evaluate the safety and tolerability of oliceridine in patients with moderate to severe acute pain for which parenteral opioid therapy is warranted, inclusion of patients that would unduly increase patient risk or confound the evaluation of oliceridine's safety and tolerability is not acceptable. The stated exclusion criteria are not exhaustive and prudent clinical judgment must also be applied.<br><br>Patients must not meet any of the following exclusion criteria:<br><br>1. Participated in another oliceridine clinical study.<br><br>2. Clinically significant medical, surgical, postsurgical, psychiatric or substance abuse condition or history of such condition that would confound the interpretation of safety, tolerability, or efficacy data in the study.<br><br>3. Hemodynamic instability or respiratory insufficiency; or requires a tracheostomy or mechanically assisted ventilation.<br><br>4. If a surgical or medical patient, American Society of Anesthesiologists (ASA) Physical Status Classification System score of IV or worse; if an ED patient, Emergency Severity Index (ESI) triage score of 1.<br><br>5. If an ED patient, alcohol intoxication, acute substance impairment or positive urine or serum toxicology screen.<br><br>6. Advanced cancer in palliative or end-of-life care.<br><br>7. Concurrent use of chemotherapeutic or biologic agents for the treatment of cancer.<br><br>8. Another current painful condition (other than acute pain for which parenteral opioid therapy is warranted) that would confound the interpretation of safety, tolerability, or efficacy |

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| | data in the study.<br><br>9. Clinically significant, immune-mediated hypersensitivity reaction to opioids.<br><br>10. Pregnancy, breastfeeding, or positive urine or serum pregnancy test at screening.<br><br>11. Hepatic impairment (total bilirubin >2 × upper limit of normal [ULN], aspartate aminotransferase [AST] >=1.5 × ULN AND alanine aminotransferase [ALT] >=1.5 × ULN) or renal impairment (estimated Glomerular Filtration Rate [eGFR] <= 29 mL/min/1.73 $m^2$ based on the Modification of Diet in Renal Disease [MDRD] equation), known or obtained at screening.<br><br>12. History of human immunodeficiency virus, hepatitis B, or hepatitis C.<br><br>13. Clinically significant abnormal clinical laboratory values, known or obtained at screening.<br><br>14. Clinically significant abnormal ECG, including a QT interval corrected for heart rate (Fridericia; QTcF interval) of >450 msec in males and >470 msec in females, known or obtained at screening. |

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| STUDY DRUG | Oliceridine will be administered as-needed (PRN) via the IV route. Depending on the clinical considerations for which parenteral opioid therapy is warranted (eg, anticipated duration of therapy, clinical site/setting), a patient could receive oliceridine using clinician-administered bolus dosing or PCA dosing. A patient may receive both methods of administration.<br><br>As in current practice, patient need, analgesic efficacy, and adverse responses will guide oliceridine use. Consistent with current opioid prescribing practices for acute pain, oliceridine should not be administered on a fixed, around-the-clock dosing schedule.<br><br>The oliceridine dosing regimen should be initiated for each patient individually, taking into account the patient's severity of pain, patient response and prior analgesic treatment experience. Individually titrate oliceridine to a dose that provides adequate analgesia and minimizes AEs. Continually reevaluate patients receiving oliceridine to assess the maintenance of pain control and the relative incidence of AEs.<br><br><u>Clinician-administered bolus dosing</u><br><br>For clinician-administered bolus dosing, the oliceridine initial dose is 1 mg to 2 mg. If clinically indicated, a 1 mg supplemental dose may be administered as early as 15 minutes after the initial dose. Subsequent doses are 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to oliceridine.<br><br>In settings where rapid analgesia is targeted (e.g., ED or post-anesthesia care unit (PACU)), the oliceridine initial dose is 1 mg to 3 mg. If clinically indicated, 1 mg to 3 mg supplemental doses may be administered every 5 minutes PRN. Subsequent doses are 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to oliceridine.<br><br><u>PCA Regimen</u><br><br>For PCA dosing, the oliceridine regimen will consist of a loading dose, a demand dose, and a lockout interval without a continuous baseline infusion. |

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| | Oliceridine PCA regimen:<br>• Loading dose: 1.5 mg.<br>• Demand dose: 0.5 mg.<br>• Lockout interval: 6 minutes.<br>If clinically indicated, throughout the treatment phase, a 1 mg supplemental dose may be administered PRN, taking into account the patient's utilization of PCA demand doses, individual patient need and previous response to oliceridine. |
| DURATION OF TREATMENT | The duration of treatment for each patient will be determined by the clinical need for parenteral opioid therapy. In current practice, parenteral opioids are used as-needed for up to several days. Although preclinical toxicology studies support IV administration of oliceridine for up to 14 days, it is unlikely that patients will receive oliceridine for that duration in the context of this study. |
| PERMITTED AND PROHIBITED PRIOR AND CONCOMITANT MEDICATIONS | Concomitant non-opioid analgesics are permitted. If a concomitant parenteral or oral opioid analgesic is used during the treatment phase, oliceridine treatment will cease, and the patient will be discontinued early and will undergo the end-of-treatment phase and follow-up phase procedures as scheduled.<br>Unless specifically prohibited, other medications are permitted, including common treatments of opioid-related adverse effects (eg, antiemetics, antacids, stool laxatives) and medications used to treat underlying medical conditions.<br>As with conventional opioids, prior and concomitant use of anxiolytics, sedative-hypnotics, or other potential CNS depressants |

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| | requires elevated vigilance, consistent with the Joint Commission Sentinel Event Alert for the safe use of opioids in hospitals (The Joint Commission, 2012). Similarly, the perioperative use of epidural or intrathecal opioids prior to oliceridine requires cautious administration and increased monitoring, consistent with the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration (American Society of Anesthesiologists 2016).<br><br>Patients receiving medications known to inhibit the CYP2D6 enzyme or potent cytochrome P450 3A4 (CYP3A4) inhibitors may require less frequent dosing of oliceridine. Given that oliceridine is administered PRN, differential dosing instructions are not required for these patients. |
| MAIN PARAMETERS OF SAFETY AND TOLERABILITY | The safety and tolerability of oliceridine will be measured as the incidence of self-reported or observed AEs, including those related to vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical examination findings, and clinical laboratory assessments. |
| MAIN PARAMETERS OF EFFICACY | Analgesic efficacy will be measured using NPRS at the following time points:<br>• During the predose period.<br>• 30 minutes +/-10 minutes after the first dose of oliceridine.<br>• At any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid. |
| STATISTICAL ANALYSES | **Sample size**<br>No formal sample size calculations were made. Approximately 1000 patients will be treated with oliceridine. |

**Study populations**

All enrolled patients receiving at least 1 dose of oliceridine constitute the safety and tolerability analysis data set.

**Safety and tolerability analyses**

The number and incidence of AEs/SAEs will be summarized overall and by severity and causality. The Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0) will be used to classify all events with respect to system organ class and preferred term. The World Health Organization Drug Dictionary (WHODD, March 2016) will be used to categorize prior and concomitant medications. Summaries will include only treatment-emergent AEs and will be summarized for the safety and tolerability analysis data set. Clinically significant changes in vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical examination findings, and clinical laboratory assessments will be summarized via descriptive summary statistics.

Summary statistics for observed values and change from baseline values for vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical examination findings, and clinical laboratory assessments will be summarized. Baseline values are defined as the last measurements taken before the first dose of oliceridine. SOWS total scores will be summarized.

Prior and concomitant medications will be summarized.

**Exposure analyses**

The total number of patients treated and the percentage of the overall sample treated by method of administration (bolus, PCA, both bolus and PCA) will be presented. Exposure data including date, time, and dose for each administration of oliceridine will be listed for each patient and will include the total amount of oliceridine administered using any method of administration within 0-1 hours, 1-2 hours, 2-3 hours, and every subsequent 3-hour period to 24 hours; 24-48 hours, 48-72 hours, and every subsequent 24-hour period of the treatment phase. Subsequently, the amount of oliceridine administered to all patients over these periods and the total amount administered during the treatment phase will be summarized (mean, standard deviation, median, minimum, and

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| | maximum) by the method of administration (bolus, PCA, both bolus and PCA) for the safety and tolerability population. All doses of oliceridine, whether administered by IV bolus or PCA, will be listed.<br><br>Additionally, data will be presented by subgroups for descriptive purposes.<br><br>**Efficacy analyses**<br><br>The NPRS scores at baseline and 30 minutes after the first dose of oliceridine, as well as the change from baseline to 30 minutes, will be summarized using descriptive summary statistics. All NPRS assessments will be listed at each time point where an assessment has occurred. |

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**TABLES**



**FIGURES**

## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACEP | American College of Emergency Physicians |
| AE | adverse event |
| ALT (SGPT) | alanine aminotransferase (serum glutamic pyruvic transaminase) |
| ASA | American Society of Anesthesiologists |
| AST (SGOT) | aspartate aminotransferase (serum glutamic oxaloacetic transaminase) |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| CFR | Code of Federal Regulations |
| CRA | clinical research associate |
| CYP2D6 | cytochrome p450 2d6 |
| CYP3A4 | cytochrome p450 3a4 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| ED | emergency department |
| EDC | electronic data capture |
| FDA | Food and Drug Administration |
| GCP | good clinical practice |
| HCV | hepatitis C virus |
| HR | heart rate |
| ICD-10 | International Classification of Diseases, 10$^{th}$ Revision |
| IEC | independent ethics committee |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IgM | immunoglobulin M |
| IND | investigational new drug |
| IB | investigator's brochure |
| IP | investigational product |
| IRB | institutional review board |
| IV | intravenous |
| LDH | lactate dehydrogenase |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MDRD | modification of diet in renal disease |

| Abbreviation | Definition |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram |
| mL | milliliter |
| MRPSS | Moline-Roberts Pharmacologic Sedation Scale |
| NPRS | numeric pain rating scale |
| PACU | post-anesthesia care unit |
| PCA | patient-controlled analgesia device |
| PK | pharmacokinetic |
| PRN | as-needed |
| Q6min | every 6 minutes |
| RBC | red blood cells |
| RR | respiratory rate |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOWS | Subjective Opiate Withdrawal Scale |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| WBC | white blood cells |
| WHODD | World Health Organization Drug Dictionary |

**ADMINISTRATIVE STRUCTURE**

| | |
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| Sponsor Responsible Physician/Back-up Medical Monitor: | Franck Skobieranda, MD<br>VP, Clinical Development<br>Trevena, Inc.<br>1018 West 8th Avenue, Suite A<br>King of Prussia, PA 19406 USA<br>Phone: (610) 354-8840<br>Email: fskobieranda@trevenainc.com |
| Medical Monitor: | Joseph "Josh" Krotec, MD, FACOG<br>Medical Director<br>Chiltern<br>1016 West 9th Avenue<br>King of Prussia, PA 19406 USA<br>Phone: (484) 832-8770<br>Email: Joseph.Krotec@Chiltern.com |

# 1 INTRODUCTION

## 1.1 Background

Inadequately treated pain has significant short- and long-term consequences, including prolonged emergency department stays, psychological disturbances, and dissatisfaction with medical care. Opioid analgesics like morphine, fentanyl, and hydromorphone are mainstays of acute pain management; however, their use is hampered by well-known adverse events (AEs), such as respiratory depression, nausea, vomiting, and sedation (Lubawski, 2008) (Philip, 2002). Ultimately, the unmet medical need in acute pain therapy is an increased level of efficacy with acceptable tolerability.

Beta-arrestin knock-out animals treated with morphine were shown to experience improved analgesic efficacy, less respiratory depression and less constipation, compared with wild-type animals (Bohn, 1999) (Raehal, 2005). This led to the hypothesis that analgesia and AEs are mediated by two distinct signaling pathways distal to the μ-opioid receptor and that a selective μ-opioid receptor ligand that stimulates G protein signaling without stimulating β-arrestin recruitment could be a better analgesic.

Oliceridine selectively binds to the μ-opioid receptor with high affinity; however, oliceridine is a G protein biased ligand at the μ-opioid receptor in that it stimulates G protein signaling without stimulating β-arrestin recruitment. In preclinical species, this biased signaling profile has led to potent analgesic efficacy, with less respiratory depression, slowing of gastrointestinal motility, and sedation, compared with morphine.

To date, oliceridine has been evaluated in phase 1 and 2 clinical studies. A total of 185 healthy subjects have received single intravenous (IV) infusions of oliceridine (0.15 mg to 7 mg), and 40 healthy subjects have received multiple IV infusions (<=4.5 mg every 6 hours; 4 mg every 4 hours) in phase 1 studies. At those doses, oliceridine was generally well tolerated. The most commonly reported AEs included dizziness, nausea, somnolence, and feeling hot.

A total of 296 patients have received IV infusions of oliceridine (0.5 mg to 4 mg) in two phase 2 studies. At those doses, oliceridine was generally well-tolerated. The most commonly reported AEs were nausea, dizziness, vomiting, and headache.

Oliceridine was evaluated for the treatment of moderate to severe acute pain following bunionectomy in a multicenter, double-blind, randomized, placebo- and active-controlled, 2-stage, adaptive-design, phase 2 study (Viscusi, 2016). A total of 339 subjects received oliceridine (0.5 mg to 4 mg every 3 or 4 hours), morphine (4 mg every 4 hours), or placebo. The oliceridine dosing frequency of every 4 hours was found to be suboptimal in the first stage of the study; thus, the frequency was shifted to every 3 hours in the second stage. Oliceridine 2 mg

(-1.4, *P*=0.0024) and oliceridine 3 mg (-2.4, *P*<0.0001) administered every 3 hours and morphine 4 mg (-1.3, *P*=0.0023) administered every 4 hours produced analgesic efficacy, as measured by time-weighted average change from baseline in numeric rating scale (NRS) pain intensity scores over 48 hours, compared with placebo. In a pre-specified secondary analysis, oliceridine 3 mg resulted in significant improvement (*P*=0.014) in NRS scores over 48 hours compared with morphine. Furthermore, oliceridine 2 mg and 3 mg resulted in significant categorical pain relief following the first dose, compared with placebo (*P*<0.0001) and morphine (*P*=0.0005 and *P*<0.001, respectively). The majority of subjects receiving oliceridine >=1 mg reported stopwatch-method meaningful pain relief. The most frequently reported AEs following treatment with oliceridine were nausea, dizziness, headache, and vomiting. AEs and their severity were generally dose related.

Oliceridine was evaluated for the treatment of moderate to severe acute pain following abdominoplasty in a double-blind, randomized, placebo- and active-controlled, phase 2 study. Study treatments were delivered by a patient-controlled analgesia (PCA) regimen, consisting of a loading dose, demand dose, and a lockout-interval. For the first half of the study, the oliceridine regimen was a 1.5 mg loading dose (as two 0.75 mg doses separated by 10 minutes), 0.1 mg demand doses, and a 6-minute lockout interval. The morphine regimen was a 4 mg loading dose (as two 2 mg doses separated by 10 minutes), 1 mg demand doses and a 6-minute lockout interval. As oliceridine was not previously administered in a PCA regimen, a prespecified interim analysis was planned to adjust the oliceridine PCA regimen after review of existing efficacy, safety and tolerability, and utilization data. For the second half of the study, the oliceridine demand dose was 0.35 mg with a 6-minute lockout interval. Oliceridine demonstrated statistically significant pain reduction compared to placebo and similar efficacy to morphine (oliceridine 0.1 mg regimen reduced average pain scores [LS mean change in time-weighted average over 24 hours] by 2.3 points [P<0.0001 vs. placebo]; oliceridine 0.35 mg by 2.1 points [P=0.0003 vs. placebo]; morphine, by 2.1 points [P=0.0001 vs. placebo]). The mean oliceridine utilization over the 24-hour treatment period for the 0.1 mg group was 7.6 mg, and for the 0.35 group, 14.8 mg. Rescue pain medication use was similar for both oliceridine (31% with oliceridine 0.1 mg, 21% with oliceridine 0.35 mg) and morphine (25%), and less than half the rate for placebo (64%; post hoc P<0.0005 for all three active groups vs. placebo). For the purpose of this study, hypoventilation events were defined as apparent and persistently decreased respiratory rate, respiratory effort or oxygen saturation. Oliceridine had a significantly lower prevalence of hypoventilation events, nausea, and vomiting than the morphine group (post hoc P<0.05 for both oliceridine regimens vs. morphine):

| | Placebo | Oliceridine 0.1 mg | Oliceridine 0.35 mg | Morphine |
|---|---|---|---|---|
| Hypoventilation | 10% | 15% | 31% | 53% |
| Vomiting | 8% | 15% | 15% | 42% |
| Nausea | 18% | 41% | 46% | 72% |

Oliceridine preclinical and clinical data are summarized in the current investigator's brochure (IB).

## 1.2 Rationale

Consistent with the Food and Drug Administration (FDA) requirements for premarketing safety databases, the proposed population in this clinical study is sufficiently diverse to adequately represent the target population (patients with moderate to severe acute pain for which parenteral opioid therapy is warranted) (Food and Drug Administration, 2005).

Consistent with the known pharmacological properties of oliceridine and clinical observations obtained from completed studies with oliceridine, essentially, only patients with contraindications to opioid therapy or other clinical considerations confounding an interpretation of safety, tolerability, or efficacy data have been excluded. Eligibility criteria therefore support evaluation of oliceridine in patients with a range of conditions warranting parenteral opioid therapy, treated across a clinical trial environment characterized by diverse site topologies (institutions, investigators) within the United States, for variable durations of treatment.

Oliceridine will be administered as-needed (PRN) via the IV route. Depending on the clinical considerations for which parenteral opioid therapy is warranted (eg, anticipated duration of therapy, clinical setting), a patient could receive oliceridine using clinician-administered bolus dosing, PCA, or both bolus and PCA.

## 1.3 Study Endpoints

### 1.3.1 Safety and Tolerability Endpoints

The safety and tolerability of oliceridine will be measured as the incidence of self-reported or observed AEs, including those related to vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical examination findings, and clinical laboratory assessments. Somnolence/sedation will be measured using the Moline-Roberts Pharmacologic Sedation Scale (MRPSS; see Section 9.1) (Moline, 2012). The MRPSS is designed to provide a consistent method of assessing pharmacologic sedation and assist in the decision-making process regarding the administration of opioids, sedatives, and other agents which produce sedation. For patients receiving a parenteral opioid in current practice, intensive monitoring is the standard of care. This monitoring will be used in the current study to evaluate

oliceridine. Protocol-specified patient monitoring is compatible with the Joint Commission Sentinel Event Alert for the safe use of opioids in hospitals (The Joint Commission, 2012).

### 1.3.2 Efficacy Endpoints

The analgesic efficacy of oliceridine will be measured using a 0-10 point numeric pain rating scale (NPRS, see Section 9.2). NPRS was selected given its frequent use in clinical practice and clinical research (McCaffery, 1989). The NPRS may be explained or shown to the patient, who responds by indicating a number (Hjermstad, 2011).

## 1.4 Risks and Benefits for Patients

The potential benefit of study participation is that patients may experience a reduction in pain as a result of treatment with oliceridine. Patients will also contribute to the clinical data set for oliceridine, an investigational product (IP). No other benefits of participation are anticipated.

The potential risks of study participation include lack of analgesic efficacy, known or unknown serious or non-serious AEs, and unknown risks inherent in the evaluation of an IP. Additional risks are those associated with medical evaluation, such as those associated with venipuncture.

Oliceridine preclinical and clinical data are summarized in the current IB. Investigators must become familiar with all sections of the IB before the start of the study.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective is to evaluate the safety and tolerability of oliceridine in patients with moderate to severe acute pain for which parenteral opioid therapy is warranted.

## 2.2 Secondary Objective

The secondary objective is to evaluate the analgesic efficacy of oliceridine.

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall Study Design and Plan

This phase 3, open-label, safety study will be conducted in inpatient hospitals, outpatient hospital departments, ambulatory surgical care centers, and emergency departments (EDs). Patients recruited in EDs may continue oliceridine treatment if hospitalized and parenteral opioid therapy is warranted.

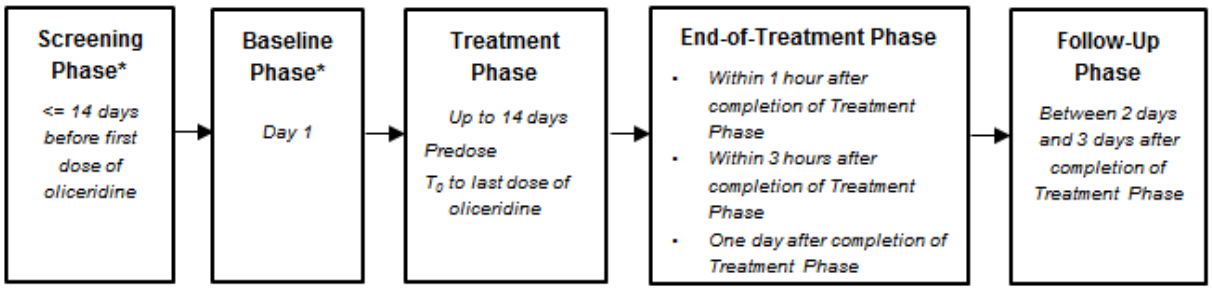
Representative surgeries include orthopedic (eg, total hip replacement, total knee replacement, spine), abdominal (eg, upper or lower abdominal, perineal), gynecologic (eg, total abdominal hysterectomy), vascular, soft tissue, and surgical procedural pain.

Representative medical conditions include acute pancreatitis, acute exacerbation of existing noncancerous chronic pain, musculoskeletal pain, sickle-cell disease, inflammatory orofacial muscle pain, and renal colic. Medical conditions that could confound the evaluation of oliceridine are excluded, such as acute pain without a specific etiology, undifferentiated acute abdominal pain, acute breakthrough pain in palliative “end of life” care, and pain associated with advanced cancer (somatic, visceral, or neuropathic) or with concurrent use of chemotherapeutic or biologic agents for the treatment of cancer.

Representative ED conditions include visceral pain (eg, renal colic, upper abdominal pain, abdominal pelvic pain); nonvisceral pain (eg, traumatic and atraumatic acute musculoskeletal pain, chest wall pain, burns, orofacial pain/headache, cutaneous and soft tissue pain); procedural analgesia (eg, reduction of orthopedic fractures and dislocations, abscess incision and drainage); acute painful episodes associated with a medical condition (eg, sickle cell painful vaso-occlusive episode). Oliceridine will not be used to intentionally suppress a patient’s level of consciousness (procedural sedation and analgesia as defined by the American College of Emergency Physicians [ACEP]).

The study has four phases: a screening/baseline phase, a treatment phase (consisting of a predose period and a dosing period), an end-of-treatment phase, and a follow-up phase.

**Figure 1: Study Schematic**




Abbreviations: T0 = time of first dose of oliceridine; h = hours
* Combined if occurring within 48 hours of each other, unless the clinical condition of the patient has significantly changed since screening

### 3.1.1 Screening/baseline phase

Written informed consent will be obtained before any protocol-related activities are conducted. All screening procedures will be completed within 14 days before the first oliceridine dose. Select standard of care assessments (eg, chemistry, hematology, urine or serum pregnancy test, urine or serum toxicology screen, electrocardiogram (ECG)) obtained before informed consent may be used as study data if protocol specifications and timeframes are met (see Section 3.6.1).

When screening and baseline procedures are anticipated to occur within 48 hours of each other, they may be executed as a single procedure, unless the clinical condition of the patient has significantly changed since screening.

Adverse events (AEs) occurring from time of informed consent to the follow up phase will be recorded in source and will also be recorded in eCRF if the patient receives oliceridine. Serious Adverse Events (SAEs) occurring from time of informed consent to the follow-up phase or 7 days after the last dose of oliceridine (whichever occurs later) will be recorded in source and eCRF; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to oliceridine, regardless of the time of onset after treatment, should be reported.

Prior medications taken or administered within the 14 days before the first dose of oliceridine will be recorded in source and will also be recorded in eCRF.

### 3.1.2 Treatment phase

The treatment phase begins with the predose period and ends when the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine.

The duration of treatment for each patient will be determined by the clinical need for parenteral opioid therapy. In current practice, parenteral opioids are used as-needed for up to several days.

Although preclinical toxicology studies support intravenous (IV) administration of oliceridine for up to 14 days, it is unlikely that patients will receive oliceridine for that duration in the context of this study.

### 3.1.3 Predose period

Before dosing with oliceridine, vital signs (blood pressure, heart rate, respiratory rate), oxygen saturation, and somnolence/sedation will be measured. Somnolence/sedation will be measured using the MRPSS. During the predose period, an additional, post-surgical ECG will be performed only in surgical patients. Prior medications and AEs/SAEs will be recorded.

Pain intensity will be measured using a 0-10 point numeric pain rating scale (NPRS).

Predose period procedures will occur within 30 minutes before the first oliceridine dose. If the dosing period is delayed, predose period procedures (except the additional, post-surgical ECG performed only in surgical patients) will be repeated.

### 3.1.4 Dosing period

Oliceridine IV infusion may be administered either by clinician-administered bolus, PCA, or both bolus and PCA, according to the clinical situation.

During dosing with oliceridine, vital signs, oxygen saturation, and somnolence/sedation will be measured at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid. An ECG will be obtained 60 minutes after the first dose of oliceridine, and at every 24 hours of oliceridine treatment. Blood will be collected for oliceridine pharmacokinetics and future cytochrome P450 2D6 (CYP2D6) genotyping. Concomitant medications and AEs/SAEs will be recorded.

NPRS assessments will also be completed at 30 minutes +/ 10 minutes after the first dose of oliceridine and at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid.

### 3.1.5 End of treatment phase

When the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine, the treatment phase is complete and the end of treatment phase begins. A physical examination will be performed at this time.

Within 1 hour after completion of the treatment phase, vital signs, oxygen saturation, and somnolence/sedation will be measured, and concomitant medications and AEs/SAEs will be recorded.

Within 3 hours after completion of the treatment phase, blood will be collected for clinical laboratory tests. Concomitant medications and AEs/SAEs will be recorded.

Patients will be observed for at least three hours after the last dose of oliceridine; however, medically-required transfer of an ED patient to another facility takes precedence over study procedures.

The Subjective Opioid Withdrawal Scale (SOWS) will be administered to detect symptoms of opioid withdrawal. If the patient is discharged or transferred before the time when the SOWS is to be performed, it will be performed one day after completion of the treatment phase and returned to the site by mail or in person.

### 3.1.6 Follow up phase

A follow up contact will be made between 2 and 3 days after completion of the treatment phase. The contact may be conducted in person or by telephone. Concomitant medications and AEs/SAEs will be recorded.

The surgical procedure, medical diagnosis or ED diagnosis for which parenteral opioid therapy was warranted will be captured using the International Classification of Diseases, 10th Revision (ICD-10) terminology.

## 3.2 Study Duration

The duration of treatment for each patient will be determined by the clinical need for parenteral opioid therapy. In current practice, parenteral opioids are used as-needed for up to several days. Although preclinical toxicology studies support IV administration of oliceridine for up to 14 days, it is unlikely that patients will receive oliceridine for that duration in the context of this study.

## 3.3 Study Population

The study population consists of patients with moderate to severe acute pain for which parenteral opioid therapy is warranted.

### 3.3.1 Inclusion Criteria

Patients must meet all the inclusion criteria:

1. Age >=18 years at screening.
2. Moderate to severe acute pain for which parenteral opioid therapy is warranted, defined as NPRS pain intensity of >=4 during the pre-dose period.
3. Able to understand and comply with the procedures and study requirements, and to provide written informed consent before any study procedure.

4. If it is anticipated that the patient will be treated with oliceridine in the ED with subsequent discharge or transfer to another facility, that the patient will remain under the care of the investigator for at least three hours after the last dose of oliceridine.

### 3.3.2 Exclusion Criteria

Given that the primary objective of this study is to evaluate the safety and tolerability of oliceridine in patients with moderate to severe acute pain for which parenteral opioid therapy is warranted, imprudent inclusion of unsuitable patients that would unduly increase patient risk or confound the evaluation of oliceridine is not acceptable. The stated exclusion criteria are not exhaustive and prudent clinical judgment must be applied.

Patients must not meet any of the following exclusion criteria:

1. Participated in another oliceridine clinical study.
2. Clinically significant medical, surgical, postsurgical, psychiatric or substance abuse condition or history of such condition that would confound the interpretation of safety, tolerability, or efficacy data in the study.
3. Hemodynamic instability or respiratory insufficiency; or requires a tracheostomy or mechanically assisted ventilation.
4. If a surgical or medical patient, American Society of Anesthesiologists (ASA) Physical Status Classification System score of IV or worse (see Section 9.3) (American Society of Anesthesiologists, 2014); if an ED patient, Emergency Severity Index (ESI) triage score of 1 (see Section 9.4) (Gilboy, 2011).
5. If an ED patient, alcohol intoxication, acute substance impairment or positive urine or serum toxicology screen.
6. Advanced cancer in palliative or end-of-life care.
7. Concurrent use of chemotherapeutic or biologic agents for the treatment of cancer.
8. Another current painful condition (other than acute pain for which parenteral opioid therapy is warranted) that would confound the interpretation of safety, tolerability, or efficacy data in the study.
9. Clinically significant, immune-mediated hypersensitivity reaction to opioids.
10. Pregnancy, breastfeeding, or positive urine or serum pregnancy test at screening.
11. Hepatic impairment (total bilirubin >2 × upper limit of normal [ULN], aspartate aminotransferase [AST] >=1.5 × ULN AND alanine aminotransferase [ALT] >=1.5 × ULN) or renal impairment (estimated Glomerular Filtration Rate [eGFR] <= 29 mL/min/1.73 $m^2$ based on the Modification of Diet in Renal Disease [MDRD] equation), known or obtained at screening (Levey, 2009).

12. History of human immunodeficiency virus, hepatitis B, or hepatitis C.
13. Clinically significant abnormal clinical laboratory values, known or obtained at screening.
14. Clinically significant abnormal electrocardiogram (ECG), including a QT interval corrected for heart rate (Fridericia; QTcF interval) of >450 msec in males and >470 msec in females, known or obtained at screening.

## 3.4 Early Discontinuation

All patients will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep patients in the study; however, patients must be withdrawn from the study if they withdraw consent to participate.

If a patient is discontinued early, the investigator will make every effort to complete end-of-treatment phase and follow-up phase procedures.

An electronic case report form (eCRF) should be completed for every patient who receives oliceridine, whether or not the patient completes the study. The reason for the early discontinuation should be indicated on this form. The following standard categories should be used to select a primary reason for early discontinuation:

- *Adverse event*: clinical or para-clinical 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 the IP.
- *Lack of efficacy*
- *Withdrawal of consent*: the patient desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the patient gave a reason for withdrawing, it should be recorded in the eCRF.
- *Investigator decision*
- *Protocol deviation:* the investigator or patient was noncompliant with study procedures or the patient did not satisfy the entry criteria for the study
- *Lost to follow-up*: the patient stopped coming for visits and study personnel were unable to contact the patient.
- *Other*: the patient was discontinued for a reason other than those listed above, such as “dosing limit”, pregnancy or termination of study by the sponsor. The reason(s) should be recorded in the eCRF.

## 3.5 Treatments

### 3.5.1 Details of Study Treatments

Information about oliceridine is provided in Table 1~~Table 1~~.

Format

**Table 1: Details of the Investigational Product**

| | Oliceridine |
|---|---|
| IP name | TRV130 fumarate for injection |
| Manufacturer | Trevena, Inc. |
| Vial size | 1, 2, 10 or 30 mL |
| Route | IV |
| Formulation | Injection |
| Strength(s) | 1 mg/mL as free base |

Oliceridine (TRV130 fumarate for injection) is formulated as a sterile aqueous solution (1 mg/mL, as free base) in a pH 7 solution containing L-histidine and mannitol.

Oliceridine is provided as a sterile, clear, colorless solution filled in 1, 2, 10, or 30 mL clear glass (type I) vials sealed with a coated rubber stopper, aluminum crimp, and flip-off plastic cap. The vial size(s) provided to the site will be determined by vial availability and the planned use at the site (e.g., 30 mL vials will only be provided to sites using the PCA regimen).

Refer to the Pharmacy and Oliceridine (TRV130) Medication Use Manual for the drug product stability, shipping, and storage conditions, and preparation instructions.

### 3.5.2 Oliceridine Dosing

#### 3.5.2.1 General considerations

Oliceridine will be administered PRN via the IV route. Depending on the clinical considerations for which parenteral opioid therapy is warranted (eg, anticipated duration of therapy, clinical site/setting), a patient could receive oliceridine using clinician-administered bolus dosing or PCA dosing. A patient may receive both methods of administration.

As in current practice, patient need, analgesic efficacy, and adverse responses will guide oliceridine use. Consistent with current opioid prescribing practices for acute pain, oliceridine should not be administered on a fixed, around-the-clock dosing schedule.

The oliceridine dosing regimen should be initiated for each patient individually, taking into account the patient's severity of pain, patient response and prior analgesic treatment experience. Individually titrate oliceridine to a dose that provides adequate analgesia and minimizes AEs.

Continually reevaluate patients receiving oliceridine to assess the maintenance of pain control and the relative incidence of AEs.

#### 3.5.2.2 Dosing schedule

##### 3.5.2.2.1 Clinician-administered bolus dosing

For clinician-administered bolus dosing, the oliceridine initial dose is 1 mg to 2 mg. If clinically indicated, a 1 mg supplemental dose may be administered as early as 15 minutes after the initial dose. Subsequent doses are 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to oliceridine.

In settings where rapid analgesia is targeted (e.g., ED or post-anesthesia care unit (PACU)), the oliceridine initial dose is 1 mg to 3 mg. If clinically indicated, 1 mg to 3 mg supplemental doses may be administered every 5 minutes PRN. Subsequent doses are 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to oliceridine.

##### 3.5.2.2.2 PCA Regimen

For PCA dosing, the oliceridine regimen will consist of a loading dose, a demand dose, and a lockout interval without a continuous baseline infusion.

Oliceridine PCA regimen:

- Loading dose: 1.5 mg.
- Demand dose: 0.5 mg.
- Lockout interval: 6 minutes.

If clinically indicated, throughout the treatment phase, a 1 mg supplemental dose may be administered PRN, taking into account the patient's utilization of PCA demand doses, individual patient need and previous response to oliceridine.

#### 3.5.2.3 Dosing Limit

For the current study, the dosing limit for oliceridine will be 60 mg in the first 12 hours. If a patient reaches this dosing limit within the first 12 hours, a PK sample will be obtained, the patient will early discontinue oliceridine and will be managed conventionally.

### 3.5.3 Drug Inventory and Accountability

The investigator must keep an accurate accounting of the number of IP units delivered to the site, dispensed to patients, returned to the investigator by site staff, returned to the sponsor, or any other disposition during and at completion of the study. The IP must be administered by an

appropriately qualified person. The IP is to be used in accordance with the protocol by patients who are enrolled in this clinical study. Investigators should maintain records that adequately document that patients were provided the doses specified by the protocol and reconcile all IP received at the site before final disposition. At the end of the study, or as directed, all study drugs, including unused, partially used, and empty containers will be accounted for.

### 3.5.4 Treatment Compliance

Treatment consists of parenteral opioid therapy administered by qualified medical personnel. There is no opportunity for self-administration outside of the confines of PCA, and the study drug is not dispensed to an enrolled patient outside of the confines of the investigative site.

### 3.5.5 Permitted and Prohibited Prior and Concomitant Medications

Prior medications are defined as those taken before the first dose of oliceridine. Concomitant medications are defined as those taken after the first dose of oliceridine.

Concomitant non-opioid analgesics are permitted. If a concomitant parenteral or oral opioid analgesic is used during the treatment phase, oliceridine treatment will cease, and the patient will be discontinued early and will undergo the end-of-treatment phase and follow-up phase procedures as scheduled.

Unless specifically prohibited, other medications are permitted, including common treatments of opioid-related adverse effects (eg, antiemetics, antacids, stool laxatives) and medications used to treat underlying medical conditions.

As with conventional opioids, prior and concomitant use of anxiolytics, sedative-hypnotics, or other potential CNS depressants requires elevated vigilance, consistent with the Joint Commission Sentinel Event Alert for the safe use of opioids in hospitals (The Joint Commission, 2012). Similarly, the perioperative use of epidural or intrathecal opioids prior to oliceridine requires cautious administration and increased monitoring, consistent with the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration (American Society of Anesthesiologists 2016).

Supplemental oxygen will be recorded as a prior and/or concomitant medication.

### 3.5.6 Drug-Drug Interactions

Both non-clinical and clinical data show that oliceridine is metabolized by both CYP3A4 and CYP2D6, with each enzyme contributing approximately 50% to the clearance of oliceridine.

The CYP2D6 enzyme is subject to significant genetic polymorphism which may affect the clearance of drugs metabolized by CYP2D6. For example, about 7%-10% of the Caucasian population may have low functional levels of CYP2D6 in the liver and are classified as "poor metabolizers". The clearance of oliceridine in subjects who are poor metabolizers of CYP2D6 substrates is reduced by approximately 50% relative to extensive metabolizers. Patients who are taking concomitant medications known to inhibit the CYP2D6 enzyme (eg, paroxetine, fluoxetine, quinidine, bupropion) will have a similar reduction in oliceridine clearance compared to poor metabolizers. Patients who are CYP2D6 poor metabolizers, or who are taking a concomitant drug known to inhibit the CYP2D6 enzyme, may require less frequent dosing of oliceridine. Given that oliceridine is administered PRN, differential dosing instructions are not required for these patients.

Patients receiving oliceridine concomitantly with a potent CYP3A4 inhibitor (eg, clarithromycin, indinavir, itraconazole, ritonavir, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole) will also show a reduction in clearance of oliceridine of about 50%. These patients may require less frequent dosing of oliceridine. Given that oliceridine is administered PRN, differential dosing instructions are not required for these patients.

## 3.6 Study Procedures

Study procedures are outlined in the Schedule of Events (Table 2~~Table 2~~); selected procedures are described thereafter.

Format

**Table 2: Schedule of Events**

| Procedures | **Screening phase**[1] (<= 14 days before first dose of oliceridine) | **Baseline phase**[1] (Day 1) | **Treatment phase** (up to 14 days) | | **End-of-treatment phase**[2] | | | | **Follow-up phase**[3] (Between 2 days and 3 days after completion of treatment phase) |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Predose** (Day 1) | **T0 to last dose of oliceridine**[4] | End-of-treatment documentation[2] | Within 1hour after completion of treatment phase[2] | Within 3 hours after completion of treatment phase[2] | One day after completion of treatment phase | |
| Informed consent[5] | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical history | X | X | | | | | | | |
| Eligibility criteria | X | X | | | | | | | |
| ASA physical status classification[6] | X | X | | | | | | | |
| ESI[7] | X | | | | | | | | |
| Physical examination[2] | X | X | | | X | | | | |
| Clinical laboratories[8] | X | X | | | | | X | | |
| Blood sample for future CYP2D6 genotyping | | | | X | | | | | |
| Urine or serum pregnancy test[9] | X | X | | | | | | | |
| Urine or serum toxicology screen[10] | X | | | | | | | | |
| Weight | X | X | | | | | | | |
| Height[11] | X | | | | | | | | |
| ECG | X | X | X[12] | X[13] | | | | | |
| PK sampling[14] | | | | X | | | | | |
| PCA patient training[15] | X | X | X | X | | | | | |
| Oliceridine dosing | | | | X | | | | | |
| NPRS[16] | | X | X | X | | X | | | |
| Vital signs[17] | X | X | X | X | | X | | | |
| MRPSS[18] | | | X | X | | X | | | |
| SOWS[19] | | | | | | | | X | |
| Oxygen saturation[20] | | | ←---------X---------→ | | | | | | |
| Prior, concomitant medications[21] | ←----------X----------→ | | ←----------X----------→ | | | | | | |
| AE/SAE reporting[22] | ←----------X----------→ | | | | | | | | |

Abbreviations: AE = adverse event; ASA = American Society of Anesthesiologists; CYP2D6 = cytochrome P450 2D6; ECG = electrocardiogram; ESI = Emergency Severity Index; MRPSS = Moline-Roberts Pharmacologic Sedation Scale; NPRS = Numeric Pain Rating Scale; PCA = patient-controlled analgesia device; PK = pharmacokinetic; SAE = serious adverse event; SOWS = Subjective Opiate Withdrawal Scale; T0 = time of first oliceridine dose.

1. When screening and baseline procedures are anticipated to occur within 48 hours of each other, they may be executed as a single procedure, unless the clinical condition of the patient has significantly changed since screening.
2. When the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine, the treatment phase is complete and the end-of-treatment phase begins. A physical examination will be performed at this time.
3. Follow-up contact may be conducted in person or by telephone.
4. Procedures will be performed at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid.
5. Written informed consent.
6. If a surgical or medical patient. Refer to Section 9.3 for the ASA scale.
7. If an ED patient. Refer to Section 9.4 for the ESI scale.
8. Blood chemistry and hematology will be obtained using local laboratories and local laboratory range values.
9. Female patients of childbearing potential only.
10. If an ED patient.
11. Height may be obtained by measurement or patient attestation.
12. During the predose period, an additional, post-surgical ECG will be performed only in surgical patients.
13. ECG will be obtained during the Treatment Phase at 60 minutes after the first dose of oliceridine, and at every 24 hours of oliceridine treatment.
14. PK samples will be collected at two times during the treatment phase: sample 1 at 30 minutes (+/- 10 minutes) after the first dose; sample 2 between 1 and 2 hours after the first dose. Unscheduled PK samples may be required. Refer to Sections 3.5.2.3 and 3.6.3.
15. PCA patient training is required before PCA use. If PCA is planned, training will occur during the screening and baseline phases; if PCA is started during the treatment phase, training will occur before PCA use. Training is repeated according to patient need.
16. NPRS will be measured during the predose period, at 30 minutes +/-10 minutes after the first dose of oliceridine, and at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid (see Section 9.2).
17. Blood pressure, heart rate, respiratory rate, and temperature. Temperature will be measured at screening and baseline only.
18. Refer to Section 9.1 for the MPRSS.
19. Refer to Section 9.5 for the SOWS. If the patient is discharged or transferred before the time when the SOWS is to be performed, it will be performed one day after completion of the treatment phase and returned to the site by mail or in person.
20. Oxygen saturation monitoring will be continuous but will be recorded at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid. The date and time of initiation and discontinuation of continuous oxygen saturation monitoring will be recorded in the source documents.
21. Prior medications are defined as those taken before the first dose of oliceridine. Concomitant medications are defined as those taken after the first dose of oliceridine. Prior medications taken or administered within the 14 days before the first dose of oliceridine will be recorded in source and will also be recorded in eCRF. Supplemental oxygen will be recorded as a prior and/or concomitant medication.
22. AEs occurring from time of informed consent to the follow-up phase will be recorded in source and will also be recorded in eCRF if the patient receives oliceridine. SAEs occurring from time of informed consent to the follow-up phase or 7 days after the last dose of oliceridine (whichever occurs later) will be recorded in source and eCRF; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to oliceridine, regardless of the time of onset after treatment, should be reported.

### 3.6.1 Screening and Baseline Procedures

- When screening and baseline procedures are anticipated to occur within 48 hours of each other, they may be executed as a single procedure, unless the clinical condition of the patient has significantly changed since screening.

- For this study, AE reporting begins from time of informed consent.

- Height without shoes will be measured or obtained by patient attestation and recorded in inches. Weight without shoes will be measured and recorded in pounds.

- Urine or serum pregnancy test will be performed on female patients of childbearing potential only. Tests obtained before informed consent may be used as study data if obtained within 24 hours before the first dose of oliceridine or obtained during the current ED visit.

- Standard, 12-lead ECG will be captured using local equipment. Tests obtained before informed consent may be used as study data if obtained within 14 days before the first dose of oliceridine or obtained during the current ED visit.

- PCA patient training is required before PCA use. If PCA is planned, training will occur during the screening and baseline phases; if PCA is started during the treatment phase, training will occur before PCA use. Training is repeated according to patient need.

- American Society of Anesthesiologists (ASA) Physical Status Classification System score (if a surgical or medical patient); if an ED patient, Emergency Severity Index (ESI) triage score (if an ED patient) (see Sections 9.3 and 9.4).

- If an ED patient, urine or serum toxicology screen. Test results obtained before informed consent may be used as study data if obtained during the current ED visit.

- Clinical laboratories include blood chemistry and hematology. These will be obtained using local laboratories and local laboratory range values. Tests obtained before informed consent may be used as study data if obtained within 14 days before the first dose of oliceridine or obtained during the current ED visit.

- Physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system.

### 3.6.2 Safety and Tolerability Procedures

The safety and tolerability of oliceridine will be assessed through self-reported or observed AEs, vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical

examination findings, clinical laboratory assessments, and the subjective opiate withdrawal scale (SOWS).

#### 3.6.2.1 Adverse Events

AEs occurring from time of informed consent to the follow-up phase will be recorded in source and will also be recorded in eCRF if the patient receives oliceridine. SAEs occurring from time of informed consent to the follow-up phase or 7 days after the last dose of oliceridine (whichever occurs later) will be recorded in source and eCRF; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to oliceridine, regardless of the time of onset after treatment, should be reported.

AE reporting information is provided in Section 4.

#### 3.6.2.2 Vital Signs, Height, Weight

Vital signs will include blood pressure (BP), heart rate (HR), respiratory rate (RR), and temperature. Temperature will be measured at screening and baseline only.

#### 3.6.2.3 Oxygen Saturation

Oxygen saturation monitoring will be continuous but will be recorded at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid. The date and time of initiation and discontinuation of continuous oxygen saturation monitoring will be recorded in the source documents.

#### 3.6.2.4 Somnolence/Sedation

The MRPSS will be used to measure somnolence/sedation (Moline, 2012). This scale was developed to measure pharmacologic sedation in non-ICU patients, rather than many sedation scales that measure goal-directed sedation. Six levels describe the range of sedation from “non to minimal” to “general anesthesia”. Additionally, normal sleep is integrated into these levels, as opposed to being positioned as a separate category, easing quantitative analysis (Moline, 2012) (Pasero, 1994).

#### 3.6.2.5 Physical Examination

The physical examination will include general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. Clinically significant changes from screening/baseline in the physical examination for a surgical or medical patient will not be recorded as AEs unless they are of greater severity and/or intensity than would be expected.

#### 3.6.2.6 Clinical Laboratories

Clinical laboratories include blood chemistry and hematology obtained using local laboratories and local laboratory range values.

Chemistry includes: Albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, and uric acid.

Hematology includes: hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count (or estimate), and white blood cell (WBC) count including differential.

Urine or serum toxicology includes any standard of care analytes at the institution where the study is being conducted.

#### 3.6.2.7 Subjective Opiate Withdrawal Scale

Patients will be monitored for symptoms and signs of opioid withdrawal. Acute opioid withdrawal reflects μ opioid receptor upregulation: pain, autonomic hyperactivity, bowel hypermotility, temperature instability, and psychological symptoms. Subjective symptoms may include physical symptoms (e.g., myalgias, nausea, diarrhea, chills) and psychological symptoms (e.g., cravings, insomnia, fatigue). Objective signs may include: tachycardia, hypertension, tearing, runny nose, yawning; vomiting; sweating, piloerection; agitation and restlessness.

The SOWS will be administered to detect symptoms of opioid withdrawal (Handelsman, 1987). Patients will score each of 16 symptoms on an intensity scale ranging from 0 (“not at all”) to 4 (“extremely”).

### 3.6.3 Pharmacokinetic Procedures

PK samples will be collected at two times during the treatment phase:

- Sample 1 at 30 minutes (+/- 10 minutes) after the first dose;
- Sample 2 between 1 and 2 hours after the first dose.

For all samples, the actual sampling time will be recorded. Drug plasma concentration data collected in this study and detailed dosing times for each patient will be incorporated into a previously developed PK model in order to predict each individual’s oliceridine exposure.

In addition to the scheduled PK sampling, an unscheduled PK sample will be obtained under the following circumstances:

- If a patient reaches the dosing limit of 60 mg in the first 12 hours (see Section 3.5.2.3)

- If a patient experiences a serious AE or a severe AE during the treatment phase. As the determination of a serious AE or a severe AE is sometimes retrospective, unscheduled PK samples obtained when an event that is suspected to be serious or severe are also permitted.

### 3.6.4 Efficacy Procedures

Analgesic efficacy will be measured using NPRS (see Section 9.2) at the following time points:

- During the predose period.
- 30 minutes +/-10 minutes after the first dose of oliceridine.
- At any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid.

### 3.6.5 Other Procedures

A blood sample will be collected for future 2D6 genotyping. The sample will be collected after the first dose of oliceridine and before the conclusion of the end of treatment phase. It is recommended that this sample be collected at the time of the first PK sample.

# 4 ADVERSE EVENT REPORTING

The investigator and study staff are responsible for detecting and recording AEs and SAEs, during scheduled safety and tolerability evaluations and whenever such information is brought to their attention. This section of the protocol provides definitions and detailed procedures to be followed.

During each visit, the investigator will question a patient about AEs using an open-ended question approach, making sure not to influence that patient's answers, eg, "Have you noticed any change in your health?" or "How do you feel?."

## 4.1 Definitions and Criteria

### 4.1.1 Adverse Events

An AE is any untoward medical occurrence in a study patient that is temporally associated with the use of a medicinal product, regardless of its potential relationship to the medicinal product. An AE, therefore, can be any unfavorable or unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of the IP, whether or not it is considered to be IP related. This includes any newly occurring event or previous condition that has increased in severity or frequency from time of informed consent.

Examples of an AE include:

- Exacerbation of a pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- A new condition detected or diagnosed.
- Signs or symptoms of a drug interaction.
- Signs or symptoms of a suspected overdose of either IP or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- A new laboratory abnormality that results in patient withdrawal from the study or medical treatment or further follow-up.

  NOTE: abnormal laboratory values obtained during screening that preclude a patient from entering the study are not considered AEs, but they will be recorded.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (ie, invasive procedures, modification of patient's previous therapeutic regimen).

Symptoms or signs anticipated for a surgical or medical patient will not be recorded as AEs unless they are of greater severity and/or intensity than would be expected. Investigators will use

their clinical judgment in determining whether the symptoms or signs are of greater severity and/or intensity than would be expected.

A medical intervention to address an AE is an “action taken” and not an AE in itself.

### 4.1.2 Serious Adverse Events

A SAE or reaction is any untoward medical occurrence that at any dose:

(a) Results in death.

(b) Is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

(c) Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE, nor is prolongation of hospitalization for non-medically driven circumstances (eg, transportation issues).

(d) Results in persistent or significant disability or incapacity.

NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

(e) Is a congenital anomaly/birth defect.

(f) Is an important medical event.

NOTE: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes

listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note that the terms "serious" and "severe" ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 4.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

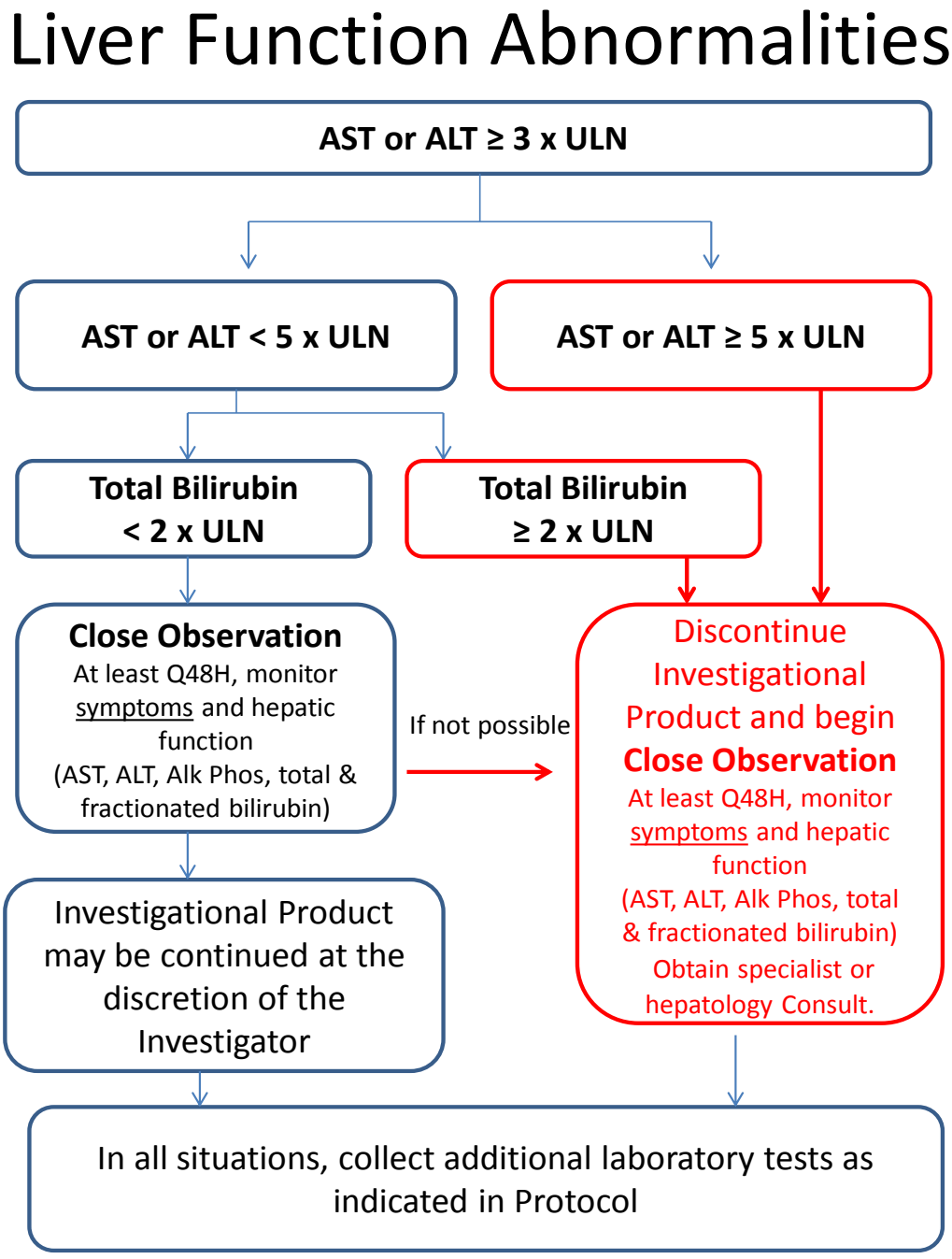
Abnormal laboratory findings (eg, clinical chemistry, hematology, and urinalysis) or other abnormal assessments (eg, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs, if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen from time of informed consent will be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Liver chemistry thresholds have been designed to assure patient safety. When patients meet the hepatic transaminase threshold criteria (AST or ALT >=3 × ULN), the patient should undergo close observation, including monitoring for symptoms (clinical symptoms of hepatitis or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash) and hepatic function (AST, ALT, alkaline phosphatase, and fractionated bilirubin) at least every 48 hours, until symptoms and/or hepatic function abnormalities resolve, stabilize, or return to baseline values. This event must be reported to Trevena within 24 hours of learning of its occurrence.

Figure 2~~Figure 2~~ represents the decision tree for whether or not IP will be discontinued. Specialist or hepatology consultation should be considered in cases of protocol-mandated IP discontinuation.

**Figure 2: Monitoring of Patients with Elevated Hepatic Transaminases**



In addition, every attempt must be made to obtain the following for any patient who meets the hepatic transaminase threshold criteria:

- Viral hepatitis serology including:
    - Hepatitis A immunoglobulin M (IgM) antibody.
    - Hepatitis B surface antigen and hepatitis B core antibody (IgM).
    - HCV RNA.
    - Cytomegalovirus IgM antibody.
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
    - Hepatitis E IgM antibody (if patient resides outside the USA or Canada, or has traveled outside USA or Canada in past 3 months).
- Serum creatine phosphokinase and LDH.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash, as relevant, on the AE report form.
- Record the use of concomitant medications, including acetaminophen, herbal remedies, other over the counter medications, putative hepatotoxins, or alcohol on the concomitant medications report form.
- The following are required for patients with AST or ALT >=3 × ULN and bilirubin >=2 × ULN but are optional for other abnormal liver chemistries:
    - Anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies.
    - Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

### 4.1.4 Evaluating Adverse Events and Serious Adverse Events

All AEs will be assessed on two descriptive parameters: intensity and relationship to the IP:

- Intensity refers to the severity of an event and references impact on a patient's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the IP.

#### 4.1.4.1 Severity Rating

Each AE will be classified according to the following criteria:

**Mild** Awareness of sign or symptom, but easily tolerated.

**Moderate** Discomfort enough to cause interference with usual activity.

**Severe** Incapacitating with inability to work or perform usual activity.

An AE that is assessed as severe should not be confused with a SAE. An event is defined as "serious" when it meets one of the predefined outcomes as described in Section 4.1.2.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

#### 4.1.4.2 Relationship to Investigational Product

For AEs and SAEs, the relationship to study treatment is to be assessed according to the following definitions:

**Not Related** There is no reasonable association between the study treatment and the suspected event.

**Unlikely Related** It is doubtful that there is an association between the study treatment and the suspected event. The event could have been produced by the patient's clinical state or other modes of therapy administered to the patient.

**Possibly Related** The suspected AE may or may not follow a reasonable temporal sequence from study treatment administration. The event could have been produced or mimicked by the patient's clinical state or by other modes of therapy concomitantly administered to the patient.

**Probably Related** The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the patient's clinical state.

When assessing the relationship to the IP, the following criteria will be considered:

- Positive rechallenge.

- Positive dechallenge (resolution upon stopping the suspect IP, in absence of other intervention or treatment).
- Known class effect.
- Biological plausibility.
- Lack of alternative explanation—concomitant drug or disease.

## 4.2 Reporting Procedures and Requirements

### 4.2.1 Adverse Events

AEs occurring from time of informed consent to the follow-up phase will be recorded in source and will also be recorded in eCRF if the patient receives oliceridine. All AEs must be recorded irrespective of whether they are considered medication-related. All AEs that are potentially related to IP will be followed until resolution or database lock, whichever occurs first. This includes any newly occurring event or previous condition that has increased in severity or frequency from time of informed consent.

Any AEs already documented at a previous assessment and designated as ongoing should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented. Changes in intensity or frequency of AEs should be recorded as separate events (ie, a new record started).

The investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (eg, “common cold” or “upper respiratory infection” rather than “runny nose, cough, mild fever”) and should be described with the attributes described in Section 4.1.

### 4.2.2 Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (see Section 4.1). If the AE is considered serious, the investigator should report this event to the sponsor. Additionally, a site using a local institutional review board (IRB) / Independent Ethics Committee (IEC) will report the event to that body according to its standard operating procedures. For sites using a central IRB/IEC, Trevena, or designee, will report to the central IRB/IEC.

SAEs occurring from time of informed consent to the follow-up phase or 7 days after the last dose of oliceridine (whichever occurs later) will be recorded in source and eCRF; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to oliceridine, regardless of the time of onset after treatment, should be reported.

All information about SAEs will be collected and reported via the SAE form and sent by e-mail message (contact information will be contained in the investigator site file). The investigator should send the initial report within 24-hours of becoming aware of the SAE. At minimum, the initial report should include the following information:

- Event
- Serious criteria
- Study code
- Patient number, initials, and date of birth
- IP
- Reporter name and contact information.

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilization and, for reported deaths, the investigator should supply the sponsor and the IRB/IEC with all the additional information requested (eg, autopsy reports and terminal medical reports).

The original SAE form should be kept at the study site. The sponsor or its representative will be responsible for determining and, in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

Trevena, or designee, will be responsible for completing the safety report and for notifying the relevant authorities of any SAE as outlined in the International Conference on Harmonisation (ICH) guidelines and per local regulatory requirements. The investigator will also ensure that the appropriate IRB/IEC is notified of the SAE.

### 4.2.3 Prompt Reporting of Serious Adverse Events

Any SAE, occurring in a patient receiving treatment, or if the investigator becomes aware of any SAE post-treatment during the follow-up period, must be reported by the investigator to the sponsor **within 24 hours** even if the SAE does not appear to be medication related. This should be done by sending an e-mailed copy of the SAE form, plus any other related information to **SAETRV130@vigilareintl.com**. Additionally, it may be necessary for the medical monitor or sponsor to directly communicate with the investigator if additional information is required.

During both business and non-business hours, the telephone numbers listed should be used if discussion with the medical monitor is required:

**Primary Medical Monitor**
Joseph "Josh" Krotec, MD, FACOG
Medical Director
Chiltern
1016 West 9th Avenue
King of Prussia, PA 19406 USA
Phone: (484) 832-8770
Email: Jospeh.Krotec@Chiltern.com

**Back-up Medical Monitor**
Franck Skobieranda, MD
Phone: (610) 888-7269
Email: fskobieranda@trevenainc.com

All additional follow-up evaluations must be reported to the sponsor. Such data should be e-mailed to the address above within 10 calendar days. SAEs occurring from time of informed consent to the follow-up phase or 7 days after the last dose of oliceridine (whichever occurs later) will be recorded in source and eCRF; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to oliceridine, regardless of the time of onset after treatment, should be reported.

Trevena, or designee, will be responsible for completing the safety report for notifying the relevant authorities of any SAEs as outlined in the ICH guidelines, and per local regulatory requirements, and for notifying the central IRB/IEC. The investigator will also ensure that the appropriate local IRB/IEC is notified of the SAE.

## 4.3 Special Considerations

### 4.3.1 Pregnancy

All women of childbearing potential who participate in the study will be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of IP on female patients of childbearing potential. A woman who is found to be pregnant at screening or baseline will be excluded from the study and considered to be a screening failure.

If a female study patient becomes pregnant during the study, the investigator must report the pregnancy within 72 hours after learning of the pregnancy. The investigator should contact the

designated individual(s) who receive SAE notification and record information related to the pregnancy on the designated pregnancy form provided by Trevena or its designee.

Early discontinuation visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination if possible. These findings must be reported on the pregnancy form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

### 4.3.2 Individual Patient Stopping Criteria

Oliceridine is a μ-opioid receptor agonist; therefore, effects on BP and respiration should be anticipated.

As with conventional opioids, oliceridine will be administered PRN; for a patient, analgesia must be balanced with intolerability. In a situation of significant intolerability, temporary or permanent discontinuation may be warranted:

- Asymptomatic decreased BP, increased HR, or decreased or increased RR may require only temporary discontinuation without additional intervention.
- Symptomatic hypotension, tachycardia, advancing somnolence/sedation, or respiratory signs (bradypnea, tachypnea, decreased respiratory effort, and/or decreased oxygen saturation) require temporary discontinuation and may require additional intervention.
- Symptomatic hypotension, tachycardia, advancing somnolence/sedation, or respiratory signs (bradypnea, tachypnea, decreased respiratory effort, and/or decreased oxygen saturation) requiring urgent intervention also requires permanent discontinuation.
- Possibly or probably related increase in QTcF to >= 500 milliseconds, or increase in QTcF of > 60 milliseconds versus most recent pre-exposure QTcF requires: permanent discontinuation; urgent clinical laboratory assessment and correction of electrolyte abnormalities (eg, hypocalcemia, hypokalemia, hypomagnesemia); and hourly ECG until QTcF < 500 milliseconds.

Additionally, if a patient receives 60 mg of oliceridine within the first 12 hours, the patient will early discontinue oliceridine and will be managed conventionally. The assigned reason for early discontinuation will be “other” and with the comment “dosing limit” (see Section 3.5.2.3).

### 4.3.3 Site Requirements to Ensure Patient Safety

#### 4.3.3.1 Management of Overdose

Given that oliceridine will be administered by qualified medical personnel, and that there is no opportunity for self-administration outside of the confines of PCA, the risk of overdose is considered to be low.

No specific antidote of oliceridine is known; however, signs or symptoms of possible overdose should be treated supportively. While naloxone reversal of oliceridine's effects has not been established in humans, some pharmacological effects (analgesia) of oliceridine have been shown to be reversed by naloxone in animals. Should an AE occur that necessitates reversal of oliceridine's effects, naloxone may be administered at its prescribed dose. Since the duration of oliceridine's pharmacodynamic effects in patients has not yet been established, multiple administrations of naloxone may be necessary. Naloxone and supplemental oxygen should be readily available during dosing.

#### 4.3.3.2 Medication and Equipment Requirements

The following medication and equipment must be available on-site and readily accessible in the event of an emergency:

- Crash cart with appropriate devices (eg, cardiac monitor/defibrillator, suction devices, bag valve mask); advanced cardiac life support medications (eg, epinephrine, atropine); common crash cart medications (eg, dextrose, diazepam); oxygen; intubation medications (eg, succinylcholine), intubation equipment, and central and peripheral venous access equipment.
- Specific medication: naloxone.

# 5 DATA MANAGEMENT

eCRFs will be employed for this study. Case report forms are considered confidential documents and should be handled and stored accordingly. To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system.

The eCRFs may be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

Completed eCRFs for this study will be forwarded to the sponsor, or its representative, where editing and construction of a quality-assured database will occur. Data will be checked for quality and electronically verified after entry into the database. Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The statistical analysis of these data will be performed by the sponsor or its representative. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 19.0). Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHODD) (World Health Organization, March 2016). Data management details will be outlined in a separate data management plan.

# 6 STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) will be finalized and signed before locking the database or conducting study analyses. Any changes in the SAP from the analyses described below will be described in the SAP and the clinical study report.

## 6.1 Sample Size

No formal sample size calculations were made. Approximately 1000 patients will be treated with oliceridine.

## 6.2 Study Populations

All enrolled patients receiving at least 1 dose of oliceridine constitute the safety and tolerability analysis data set.

## 6.3 Safety and Tolerability Analyses

The number and incidence of AEs/SAEs will be summarized overall and by severity and causality. MedDRA Version 19.0 will be used to classify all events with respect to system organ class and preferred term. WHODD (March 2016) will be used to categorize prior and concomitant medications. Summaries will include only treatment-emergent AEs (TEAEs) and will be summarized for the safety and tolerability analysis data set. Clinically significant changes in vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical examination findings, and clinical laboratory assessments will be summarized via descriptive summary statistics.

Summary statistics for observed values and change from baseline values for vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical examination findings, and clinical laboratory assessments will be summarized. Baseline values are defined as the last measurements taken before the first dose of oliceridine. SOWS total scores will be summarized.

Prior and concomitant medications will be summarized.

## 6.4 Exposure Analyses

The total number of patients treated and the percentage of the overall sample treated by method of administration (bolus, PCA, both bolus and PCA) will be presented. Exposure data including date, time, and dose for each administration of oliceridine will be listed for each patient and will include the total amount of oliceridine administered using any method of administration within 0-1 hours, 1-2 hours, 2-3 hours, and every subsequent 3-hour period to 24 hours; 24-48 hours,

and 48-72 hours, and every subsequent 24-hour period of the treatment phase. Subsequently, the amount of oliceridine administered to all patients over these periods and the total amount administered during the treatment phase will be summarized (mean, standard deviation, median, minimum, and maximum) by the method of administration (bolus, PCA, both bolus and PCA) for the safety and tolerability population. All doses of oliceridine, whether administered by IV bolus or PCA, will be listed.

Additionally, data will be presented by subgroups for descriptive purposes.

## 6.5 Efficacy Analyses

The NPRS scores at baseline and 30 minutes after the first dose of oliceridine, as well as the change from baseline to 30 minutes, will be summarized using descriptive summary statistics. All NPRS assessments will be listed at each time point where an assessment has occurred.

## 6.6 Protocol Deviations

Protocol deviations will be listed by patient and summarized in a table.

# 7 STUDY MANAGEMENT

## 7.1 Ethics and Consent

### 7.1.1 Regulations and Guidelines

The study will be performed in accordance with this protocol, United States investigational new drug (IND) regulations (21 CFR 312), ICH guidelines for Good Clinical Practice (GCP), the regulations on electronic records and electronic signature (21 CFR 11), and the most recent guidelines of the Declaration of Helsinki. These guidelines are on file at Rho, Inc.

### 7.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB/IEC. Approval is required for the study protocol, protocol amendments, informed consent form (ICF) documents, patient information sheets, and advertising materials. No IP will be shipped to a site until written IRB authorization has been received by the sponsor or its representative.

### 7.1.3 Informed Consent

Written informed consent will be obtained before any protocol-related activities are conducted. Select standard of care assessments (eg, chemistry, hematology, urine or serum pregnancy test, urine or serum toxicology screen, ECG) obtained before informed consent may be used as study data if protocol specifications and timeframes are met. As part of this procedure, the investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the IP in such a manner that the patient and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or adverse effects that may occur. Patients should be informed that they may withdraw from the study at any time. They will receive all the information that is required by federal regulations and ICH guidelines. The principal investigator or a designated representative will provide the sponsor or its representative with a copy of the IRB-approved ICF before the start of the study.

## 7.2 Discontinuation of the Study by the Sponsor

The sponsor reserves the right to discontinue the study at any site or multiple sites for any reason at any time. Should the study be terminated and/or the site closed for whatever reason, all documentation and IP pertaining to the study must be returned to the sponsor or its representative.

## 7.3 Study Documentation

By signing a copy of the FDA 1572 form, the principal investigator acknowledges that he/she has read and understood the information in the IB and assures the sponsor that he/she will

comply with the protocol and the provisions stated in the FDA 1572 form. No changes in this protocol can be made without the sponsor's written approval.

By signing the Investigator's Agreement, the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all patients who provide written informed consent.

## 7.4 Study Monitoring and Auditing

Clinical research personnel will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Trevena personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site or through remote means, the CRA(s) will review the following:

- Regulatory documents
- Directly comparing entries in the EDC system with the source documents
- Consenting procedures
- AE procedures
- Storage and accountability of IP and study materials

Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. During the study, select eCRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files.

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in EDC guidelines. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement, the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation and to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Trevena or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

Medical advisors and CRAs or assistants may request to witness patient evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the sponsor to assure acceptable protocol execution. The study may be subject to audit by the sponsor or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required patient records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

## 7.5 Retention of Records

The investigator must arrange for retention of study records at the site for 2 years after the IP's new drug application is approved, or the IND is withdrawn, as required by FDA regulations. The investigator should take measures to prevent accidental or premature destruction of these documents.

## 7.6 Use of Study Findings

By signing the study protocol, the investigator agrees to the use of the study results for the purpose of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. A clinical study report will be prepared by the sponsor or its representative.

## 7.7 Publications

As a multicenter trial, the sponsor intends to publish clinical data from all centers participating in the investigation. Additional publications may represent segments of the study; for example, publications based on site topology (inpatient hospital, outpatient hospital department, ambulatory surgical care center, ED), nature of pain (visceral or non-visceral), or method of administration (bolus, PCA, both bolus and PCA) may be developed.

In conformity with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors (Kassirer, 1991), investigators whose contribution consists solely in the collection of data will not be named individually as authors.

The information generated by this study is the property of Trevena. Publication or other public presentation of oliceridine data resulting from this study requires prior review and written approval of Trevena. Abstracts, manuscripts, and presentation materials should be provided to Trevena for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until the sponsor has reviewed and commented on such a presentation or manuscript for publication.

# 8 REFERENCES

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# 9 APPENDICES

## 9.1 Moline-Roberts Pharmacologic Sedation Scale[1]

**Moline - Roberts**
**Pharmacologic Sedation Scale©**
*9/08*

The purpose of this scale is to aid the decision-making process regarding administration of opioids and sedatives. At all times, the individual's physiologic status and unique response to opioids/sedatives must be included in the decision process.

Do not use this scale for any patient with neurological impairment which prevents normal response to a stimulus or ability to follow commands.

| Presentation | Auditory Stimulus | Tactile Stimulus | Response | Sedation |
|---|---|---|---|---|
| Awake, aware, alert<br>Airway and ventilation adequate | None | None | Spontaneous, sustained interaction | 1<br>None to Minimal |
| Restful, drowsy, dozing, lightly sleeping<br>Airway and ventilation adequate | Soft voice or ambient noise | None or light touch, rubbing or tapping | Sustains interaction | 2<br>Anxiolysis |
| Sleeping<br>Airway and ventilation adequate | Soft to normal voice | Light touch, rubbing or tapping | Limited or brief interaction | 3<br>Moderate Sedation |
| Sleeping<br>Airway and ventilation adequate | Normal to loud voice | Light touch, rubbing or tapping | Follows simple commands | 4<br>Moderate Sedation |
| **Sleeping<br>Airway and ventilation may be impaired** | **Loud voice** | **Intense to noxious** | **Purposeful response or non-purposeful movement** | **5<br>Deep Sedation** |
| **Sleeping<br>Airway and ventilation likely impaired** | **Loud voice** | **Noxious** | **No response, unarousable** | **6<br>General Anesthesia** |



[1] Moline, 2012

## 9.2 Numeric Pain Rating Scale[2]

**On a scale of 0-10, please rate your pain by marking an 'X" in the appropriate box that best describes your worst pain NOW.**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

*No pain* *Worst pain imaginable*

[2] McCaffery M, 1989

## 9.3 ASA Physical Status Classification System[3]

**ASA PHYSICAL STATUS CLASSIFICATION SYSTEM**

Last approved by the ASA House of Delegates on October 15, 2014

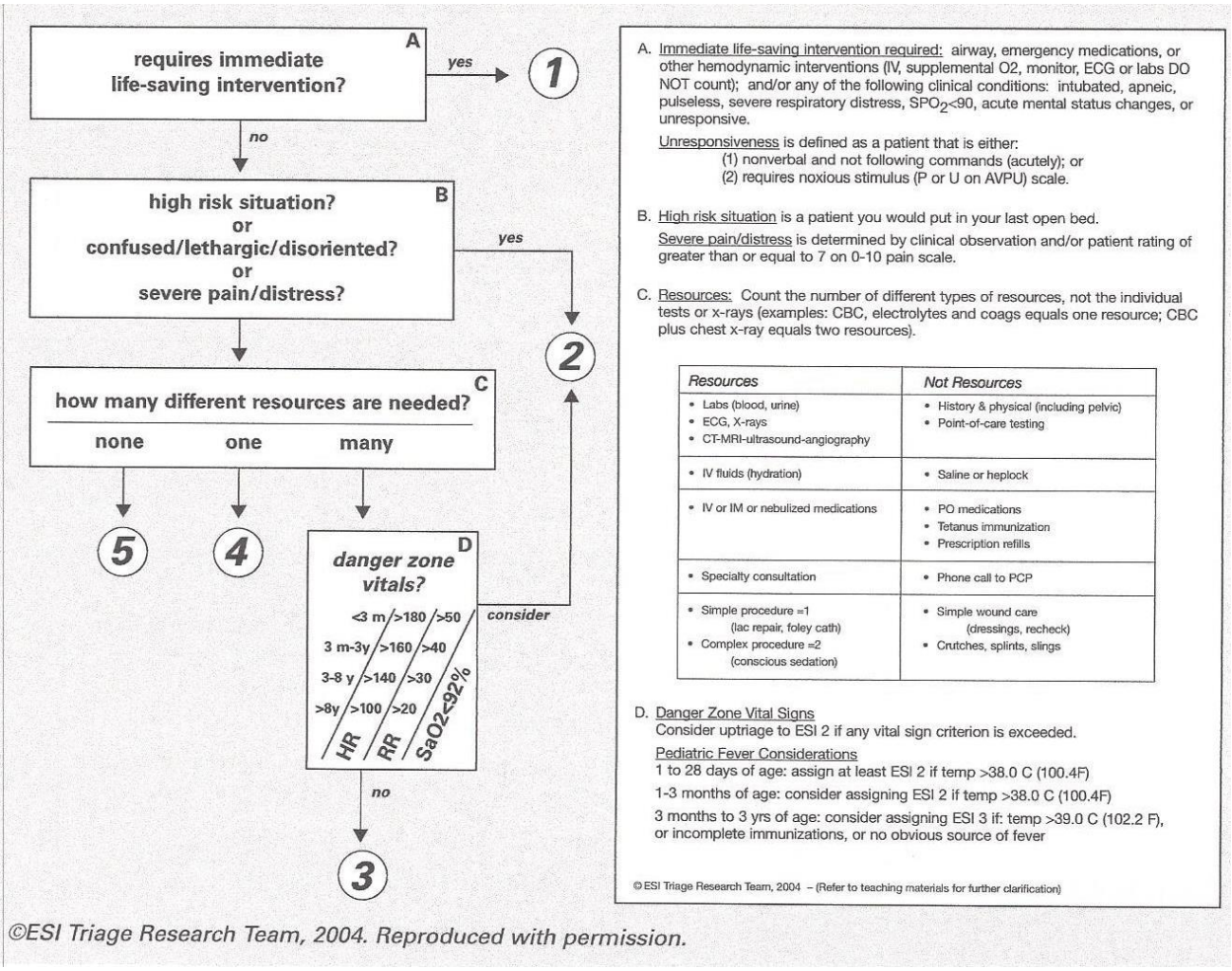
Current definitions (NO CHANGE) and Examples (NEW)

| ASA PS Classification | Definition | Examples, including, but not limited to: |
|---|---|---|
| **ASA I** | A normal healthy patient | Healthy, non-smoking, no or minimal alcohol use |
| **ASA II** | A patient with mild systemic disease | Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease |
| **ASA III** | A patient with severe systemic disease | Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA <60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents. |
| **ASA IV** | A patient with severe systemic disease that is a constant threat to life | Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis |
| **ASA V** | A moribund patient who is not expected to survive without the operation | Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction |
| **ASA VI** | A declared brain-dead patient whose organs are being removed for donor purposes | |

* The addition of “E” denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

[3] American Society of Anesthesiologists, 2014

## 9.4 Emergency Severity Index Triage Algorithm[4]




A. Immediate life-saving intervention required: airway, emergency medications, or other hemodynamic interventions (IV, supplemental O2, monitor, ECG or labs DO NOT count); and/or any of the following clinical conditions: intubated, apneic, pulseless, severe respiratory distress, $SPO_2$<90, acute mental status changes, or unresponsive.

Unresponsiveness is defined as a patient that is either:
(1) nonverbal and not following commands (acutely); or
(2) requires noxious stimulus (P or U on AVPU) scale.

B. High risk situation is a patient you would put in your last open bed.

Severe pain/distress is determined by clinical observation and/or patient rating of greater than or equal to 7 on 0-10 pain scale.

C. Resources: Count the number of different types of resources, not the individual tests or x-rays (examples: CBC, electrolytes and coags equals one resource; CBC plus chest x-ray equals two resources).

| *Resources* | *Not Resources* |
|---|---|
| • Labs (blood, urine)<br>• ECG, X-rays<br>• CT-MRI-ultrasound-angiography | • History & physical (including pelvic)<br>• Point-of-care testing |
| • IV fluids (hydration) | • Saline or heplock |
| • IV or IM or nebulized medications | • PO medications<br>• Tetanus immunization<br>• Prescription refills |
| • Specialty consultation | • Phone call to PCP |
| • Simple procedure =1 (lac repair, foley cath)<br>• Complex procedure =2 (conscious sedation) | • Simple wound care (dressings, recheck)<br>• Crutches, splints, slings |

D. Danger Zone Vital Signs
Consider uptriage to ESI 2 if any vital sign criterion is exceeded.

Pediatric Fever Considerations
1 to 28 days of age: assign at least ESI 2 if temp >38.0 C (100.4F)
1-3 months of age: consider assigning ESI 2 if temp >38.0 C (100.4F)
3 months to 3 yrs of age: consider assigning ESI 3 if: temp >39.0 C (102.2 F), or incomplete immunizations, or no obvious source of fever

© ESI Triage Research Team, 2004 – (Refer to teaching materials for further clarification)

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[4] Gilboy, 2011

## 9.5 Subjective Opiate Withdrawal Scale (SOWS)

### Assessment of Withdrawal from Opioids

**The Subjective Opiate Withdrawal Scale (SOWS)**

Date ..... Time .....

| | | PLEASE SCORE EACH OF THE 16 ITEMS BELOW ACCORDING TO HOW YOU FEEL NOW (CIRCLE ONE NUMBER) | | | | |
|---|---|---|---|---|---|---|
| | SYMPTOM | NOT AT ALL | A LITTLE | MODERATELY | QUITE A BIT | EXTREMELY |
| 1 | I feel anxious | 0 | 1 | 2 | 3 | 4 |
| 2 | I feel like yawning | 0 | 1 | 2 | 3 | 4 |
| 3 | I am perspiring | 0 | 1 | 2 | 3 | 4 |
| 4 | My eyes are teary | 0 | 1 | 2 | 3 | 4 |
| 5 | My nose is running | 0 | 1 | 2 | 3 | 4 |
| 6 | I have goosebumps | 0 | 1 | 2 | 3 | 4 |
| 7 | I am shaking | 0 | 1 | 2 | 3 | 4 |
| 8 | I have hot flushes | 0 | 1 | 2 | 3 | 4 |
| 9 | I have cold flushes | 0 | 1 | 2 | 3 | 4 |
| 10 | My bones and muscles ache | 0 | 1 | 2 | 3 | 4 |
| 11 | I feel restless | 0 | 1 | 2 | 3 | 4 |
| 12 | I feel nauseous | 0 | 1 | 2 | 3 | 4 |
| 13 | I feel like vomiting | 0 | 1 | 2 | 3 | 4 |
| 14 | My muscles twitch | 0 | 1 | 2 | 3 | 4 |
| 15 | I have stomach cramps | 0 | 1 | 2 | 3 | 4 |
| 16 | I feel like using now | 0 | 1 | 2 | 3 | 4 |

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)
Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.