# FDA Briefing Document

# Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

# October 11, 2018

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# Division Director Memorandum/Division Memorandum

**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**
**DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

**M E M O R A N D U M**

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| Date: | September 17, 2018 |
| From: | Sharon Hertz, M.D., Director<br>Division of Anesthesia, Analgesia, and Addiction Products<br>Office of Drug Evaluation II<br>Office of New Drugs |
| To: | Chair, Members, and Invited Guests<br>Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) |
| Subject: | Overview of the October 11, 2018 AADPAC Meeting to Discuss NDA 210730 |

During the October 11, 2018, AADPAC meeting, the committee will discuss the new drug application (NDA) 210730 for oliceridine 1mg/mL injection, submitted by Trevena, Inc. (Trevena), for the management of moderate-to-severe pain in adult patients for whom an intravenous opioid is warranted. The committee will discuss the efficacy and safety data and benefit-risk considerations.

Adequate control of acute pain after surgery or a painful procedure is important for helping patients recover. Prescription opioids are often a component of a multimodal analgesic

approach, which is standard in many institutions. However, the treatment of acute pain must be balanced with public health considerations related to abuse, misuse, and accidental exposure.

The proposed drug is oliceridine, a G protein-biased ligand that binds to the μ-opioid receptor and stimulates G protein-coupling with reduced β-arrestin2 recruitment compared to conventional opioids. Trevena hypothesizes that the mechanism of action will result in less respiratory depression, less slowing of gastrointestinal (GI) motility, and less sedation compared with morphine. Trevena recommends oliceridine be Schedule II given that it has a similar nonclinical and clinical pharmacologic profile to existing Schedule II opioids.

The clinical development program included three Phase 3 studies: CP130-3001 (3001), CP130-3002 (3002), and CP130-3003 (3003). Studies 3001 and 3002 were randomized, double-blind, placebo- and morphine-controlled key efficacy studies. Study 3001 was 48 hours in duration in patients after bunionectomy and Study 3002 was 24 hours in patients after abdominoplasty. Study 3003 was an open-label safety study in surgical and medical patients.

*Efficacy:* In FDA's analysis of efficacy for Study 3001, all three doses of oliceridine (0.1 mg, 0.35 mg, and 0.5 mg) demonstrated a statistically greater reduction in pain intensity than placebo. However, morphine demonstrated a greater reduction in pain intensity than all three doses of oliceridine that was also statistically significant. In FDA's analysis for Study 3002, two of the three doses of oliceridine (0.35 mg and 0.5 mg) demonstrated a statistically greater reduction in pain intensity than placebo, but the 0.1 mg dose did not. In Study 3002, morphine demonstrated a greater reduction in pain intensity relief than two of the doses of oliceridine (0.1 mg and 0.35 mg) that was statistically significant. The reduction in pain intensity by morphine was not greater than that of the highest oliceridine dose (0.5 mg). Currently, Trevena is only seeking approval of the 0.1 mg and 0.35 mg doses.

A secondary objective of the studies was to demonstrate the superiority of oliceridine to morphine in terms of respiratory safety burden. FDA did not agree with Trevena's proposed endpoint due to concerns with its clinical meaningfulness. Further, when evaluating this endpoint in both studies, none of the oliceridine treatment arms demonstrated a significant reduction in the expected cumulative duration of respiratory safety events compared to morphine. Further, any numeric trends in terms of respiratory safety must be considered in the context of the observed efficacy. A conclusion of benefit in a dose-related safety outcome cannot be made without a demonstration of similar efficacy.

*Safety:* Opioids are typically administered as needed (PRN) for acute pain. In the Phase 3 studies, the oliceridine dosing regimen included a clinician-administered loading dose, patient-delivered PRN dosing via patient-controlled analgesia (PCA) pump, clinician-administered PRN supplemental dosing, or some combination of these. This complex PRN dosing resulted in a wide range of patient exposures and added complexity to the safety analyses. Given the variability in doses administered, the Applicant and Agency analyzed safety in a variety of ways, including by randomized treatment regimen and by cumulative oliceridine exposure.

The agency analysis of the safety of oliceridine in the Phase 3, double-blind studies focused on comparisons of the randomized oliceridine treatment arms by study, so that the safety results

could be considered in the context of the efficacy of the evaluated doses. Many adverse events in the clinical program were consistent with opioid-related adverse events, including respiratory depression and hypoxia, and nausea and vomiting. When evaluating the controlled Phase 3 data by randomized treatment group, many of the adverse events were dose-related, including respiratory effects. While there were trends showing a decreased percentage of respiratory events as defined by the applicant with oliceridine than morphine for some parameters, this was not consistent across all parameters. Notable safety issues in the clinical program included hepatic adverse events and QT prolongation. An additional consideration is whether the safety database is adequate to support the proposed dosing.

The focus of this meeting will be the efficacy and safety of oliceridine for acute pain in adult patients for whom an opioid analgesic is warranted. A point of discussion for this Advisory Committee Meeting is whether the overall benefit-risk profile is favorable.

**Draft Points to Consider:**

1. Discuss the efficacy of oliceridine for the proposed indication of the management of moderate-to-severe acute pain in adults for whom an intravenous opioid is warranted.

2. Overall, do the data provide substantial evidence of the efficacy of oliceridine for the proposed indication of the management of moderate-to-severe acute pain in adults for whom an intravenous opioid is warranted.
    a. If not, what data are needed?

3. Discuss the safety findings in the oliceridine clinical program. Provide comment on the following issues:
    a. Hepatic safety
    b. Safety database
    c. QT prolongation
    d. Respiratory safety

4. Is the safety profile of oliceridine adequate to support approval of oliceridine for the proposed indication of the management of moderate-to-severe acute pain in adults for whom an intravenous opioid is warranted?
    a. If not, what data are needed?

5. Considering the abuse potential of oliceridine and its proposed use for acute pain in adults for whom an intravenous opioid is warranted, please discuss any concerns you have regarding the impact of this product, if approved, on public health.

6. Do you recommend approval of oliceridine at the proposed dose for the proposed indication of the management of moderate-to-severe acute pain in adults for whom an intravenous opioid is warranted?
    a. If not, what data are needed?

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| **NDA #** | NDA 210730 |
| **Applicant** | Trevena, Inc. |
| **Date of Submission** | November 2, 2017 |
| **PDUFA Goal Date** | November 2, 2018 |
| **Proprietary Name** | Oliceridine injection |
| **Proposed Established or Proper Name** | Olinvyk |
| **Dosage Form(s)** | 1 mg/mL in a glass vial for intravenous use<br><br>Supplied as: 1 mg/ml single-dose 2 mL glass vial, 2 mg/2 mL single-dose 2 mL glass vial, and 30 mg/30 mL single-dose 30 mL glass vial |
| **Applicant Proposed Indication(s)/Population(s)** | Management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted |
| **Applicant's Initially Proposed Dosing Regimen(s)** | Initial dose should typically be 1 to 3 mg. Subsequent doses may be given approximately 10 minutes following the initial dose and should be based on individual patient need and previous response to OLINVO.<br><br>Maintenance analgesia is generally achieved with OLINVO administered at doses of 1 to 3 mg every 1 to 3 hours as needed, or as patient-controlled analgesia (PCA) demand doses of 0.1 to 0.5 mg as needed |

# 1 Background

Trevena, Inc. (Trevena) submitted new drug application (NDA) 210730 on November 2, 2017, for the new molecular entity (NME) oliceridine injection, 1 mg/mL, for the management of moderate-to-severe acute pain in adult patients for whom an intravenous opioid is warranted. The product is for intravenous use by a health care provider or patient-controlled analgesia (PCA) in 1 mg/mL glass vials.

Oliceridine is a G protein-biased ligand that binds to the μ-opioid receptor and stimulates G protein-coupling with reduced β-arrestin2 recruitment compared to conventional opioids. Based on animal models, Trevena states that the mechanism of action will result in less respiratory depression, less slowing of gastrointestinal (GI) motility, and less sedation compared with morphine. Trevena recommends oliceridine be Schedule II given that it has a similar nonclinical and clinical pharmacologic profile to existing Schedule II opioids.

In the initially submitted label, the dosage and administration instructions were divided into initial dosing and a maintenance dosing. The initial doses of oliceridine were 1 to 3 mg, with subsequent doses given within approximately 10 minutes following the initial dose. It was noted that the initial dose should be based on individual patient need and multiple doses may be needed during titration. Maintenance dosing was 1 to 3 mg every 1 to 3 hours as needed, or PCA demand doses of 0.1 to 0.5 mg as needed. The initial maximum daily dose was 100 mg.

A significant consideration during the review cycle was whether the available clinical and non-clinical data were adequate to support the Applicant's proposed dosing regimen. Trevena modified the proposed dosing regimen several times during the review cycle. The most recently proposed dosing is included below:

> Titration Phase
> The initial dose of oliceridine should be 1 to 2 mg. Onset of analgesic effect is expected within 5 minutes of the initial dose. As multiple doses may be needed during titration, subsequent doses of 1 to 2 mg may be given as soon as 10 minutes after the previous dose based on individual patient need and previous response to oliceridine.
>
> Maintenance Phase
> Maintenance of analgesia is generally achieved with oliceridine administered as bolus doses of 1 to 2 mg every 1 to 3 hours as needed. Doses of 3 mg may be used in patients with more severe pain.
>
> For patient-controlled analgesia (PCA) demand doses of 0.1 to 0.35 mg, with a 6-minute lockout, may be given as needed based upon patient response to initial bolus doses. Patients receiving multimodal therapy may be adequately treated with a lower demand dose. Supplemental bolus doses of 1 mg (as often as hourly, as needed) can also be used in conjunction with demand doses.
>
> Individual single doses greater than 3 mg and total daily dosages greater than 40 mg have not been adequately studied. If dosing above these levels is anticipated, patients should be monitored closely for signs of opioid-related adverse reactions.

In the NDA, Trevena requested a priority review based on the justification that oliceridine provides comparable levels of analgesic effectiveness to morphine, with faster onset of action, and higher predictability of effect. Trevena did not mention safety considerations in their request for a priority review. The NDA was not granted priority review because Trevena did not provide adequate evidence to support that, if approved, oliceridine would provide a significant improvement in safety or effectiveness.

***Background on acute pain and intravenous opioids***

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or

described in terms of such damage."[1] Pain can be categorized in a variety of ways. For drug development, pain has frequently been categorized as acute or chronic. Acute pain can be defined as pain that is self-limited and generally requires treatment for no more than up to a few weeks, such as postoperative pain.

While there is heterogeneity in the types and causes of acute pain, adequate control of acute pain is important. Inadequately controlled acute pain can extend hospital stays, increase hospital readmission, and drive patient dissatisfaction.

Prescription medications are often a component of a multimodal analgesic approach, which is standard in many institutions. Pharmacologic options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical agents (e.g., local anesthetics), and opioids.

Opioids are commonly used to control postoperative pain. They can be administered via oral, transdermal, parenteral, neuraxial, and rectal routes. In the postoperative setting, opioids are frequently administered intravenously (IV), either through clinician administered boluses or via PCA. Parenteral opioids currently approved for acute pain in the United States include morphine, fentanyl, meperidine, and hydromorphone. Morphine is a commonly used opioid in the post-operative setting, and was the active comparator in the oliceridine Phase 3 trials. Fentanyl and hydromorphone are more potent, have a more rapid onset of action, and shorter half-lives compared with morphine.

Although opioids are effective analgesics in the postsurgical setting, they have notable safety risks, including respiratory depression, nausea, vomiting, postoperative ileus, and allergic reactions.

## 1.1 Key Regulatory Interactions

Key regulatory interactions are listed below by date. Points of discussion or Agency recommendations are provided as a bulleted list for each meeting or interaction. The development program for oliceridine (TRV130) occurred under IND 113537. The IND was submitted on December 22, 2011, and was allowed to proceed.

**October 3, 2014 – Type C (written responses only)**

- FDA provided recommendations regarding the assessment of patients who are poor metabolizers at the CYP2D6 receptor and the proposed dosing paradigm for the Phase 2 study, CP130-2002.

**December 2, 2015 – Fast Track Designation**

- Fast track designation of oliceridine for the management of moderate-to-severe acute pain where use of IV opioid analgesics is appropriate was granted on December 2, 2015. Fast track was granted based on the potential ability to provide benefits similar to those of alternatives with a more favorable adverse event profile.

[1] Merskey H. Logic, truth, and language in concepts of pain. Qual Life Res. 1994;3(Suppl 1):S69-76.

**February 21, 2016 – Initial PSP**
Non-agreement with the initial Pediatric Study Plan (iPSP) due to multiple issues, including the study design (which needed to be changed to an add-on design) and dose selection.

**March 3, 2016 – Advice regarding ECGs – Written Advice**
FDA issued written advice to the Applicant because QTcF prolongation exceeded the 10-ms regulatory threshold at clinically relevant exposures. The Applicant was instructed to submit amendments to modify all protocols for ongoing clinical trials to include the following safety assessments, and incorporate them into any future clinical trials:

1. Conduct safety ECG monitoring at baseline, following the first dose, and periodically thereafter. The timing of ECGs will need to reflect the delayed response relative to time of peak concentrations that was observed in the thorough QT study. Include additional ECG monitoring until ECGs return to baseline in patients discontinued from the trial or requiring dose reduction due to QTc interval prolongation.
2. Periodic monitoring of electrolytes (subjects already participating in the study with serum potassium, magnesium, or calcium levels outside of the central laboratory's reference range should be carefully monitored and brought to normal values).
3. Propose dose-modification and discontinuation criteria in subjects with posttreatment QTc > 500 ms or post-baseline increases > 60 ms.

**March 29, 2016 (meeting minutes April 28, 2016) –End-of-Phase 2 Meeting**

- FDA did not agree with the proposed dosing in the Phase 3 studies. The Sponsor proposed dosing up to 100 mg daily (including a 0.75 mg every 1 hour as needed clinician administered dose), but had only studied maximum daily doses of 36.8 mg. Further, the Sponsor did not have adequate non-clinical support for the proposed doses.
- FDA did not agree with the proposed primary endpoint, as it was unclear how a 30% improvement from baseline based on SPID correlates to an improvement in pain intensity scores on the NRS in the proposed setting of acute postoperative pain and if that change is clinically relevant.
- FDA did not agree with the proposed non-inferiority (NI) margin for comparing morphine to oliceridine.
- FDA noted that the safety database must include at least 350 patients exposed to the highest intended dose for the longest expected duration of use. It was noted that the safety database requirements might change if safety signals arise during development that require further evaluation.
- Any comparative safety claims must be replicated, adequately justified for clinical relevance, and established in the setting of comparable efficacy between comparators to be considered for inclusion in labeling
- The Applicant provided details of a proposed approach to missing data. This approach included replacing pain scores in the window determined dosing interval described in the label of the rescue medication following rescue with the pain score recorded immediately prior to rescue.

**April 25, 2016 – Proprietary Name Request Conditionally Accepted**

- The proposed proprietary name, Olinvo, was concluded to be conditionally acceptable.

**May 6, 2016 – The Applicant submitted a Justification for their Responder Definition**

- Trevena provided their justification for a 30% improvement in pain from baseline. In an analysis of Study QS130-3002, the Applicant found an average percent improvement from baseline of 18% for placebo and 44% for morphine. Trevena justified the 30% improvement by stating that it was approximately the midpoint between the placebo and morphine. See the efficacy section below for additional discussion regarding efficacy and analysis considerations.

**November 8, 2016 (meeting minutes December 19, 2016) – Type C teleconference**

- FDA did not agree with Trevena's proposal to evaluate the respiratory safety of oliceridine as compared to morphine because the definition of Respiratory Safety Events (RSEs) was not clearly defined and the determination of the presence of an RSE relied largely on clinical acumen. Even though the parameters proposed in the evaluation of an RSE (respiratory rate, oxygen saturation, and MRPSS somnolence/sedation scores) are well accepted criteria used for the assessment of patients at risk for experiencing an RSE, it is unclear that a small change in these parameters is of clinical significance. Trevena was told to specify a clinically meaningful definition of an RSE, such as patients who require a clinical intervention after meeting a specific criterion (e.g., naloxone administration and/or oxygen administration with a reduction in oxygen saturation). Further, FDA did not agree with inclusion of sedation and somnolence in the RSE definition.
- FDA stated that the statistical model proposed to evaluate the respiratory safety of oliceridine incorporates both the population prevalence of RSEs and the population conditional mean cumulative duration of RSEs to describe respiratory safety burden (RSB). Based on this model, a small change in event duration could result in a statistically significant result without clinical significance. In addition, the RSB endpoint is difficult to interpret and apply directly to clinical practice. Trevena was asked to analyze and report event duration separately from the event prevalence.

**April 11, 2017 (meeting minutes April 19, 2017) – Pre-NDA CMC-Only Meeting**

- Discussion of drug substance, drug product, and presentations

**May 5, 2017 – Advice on Integrated Statistical Analysis Plan (ISAP) for the Integrated Summary of Safety**

- Agency agreed with the proposed pooling for the ISAP, the planned subgroups for analysis of intrinsic and extrinsic factors, and planned summarization of adverse events.
- FDA reiterated the concerns noted at the November 8, 2016, teleconference regarding the assessment of respiratory safety. It was noted that the RSE as described in the ISS statistical plan would be considered exploratory and would not be acceptable for a proposed labeling claim.

**June 22, 2017 – Agreed iPSP**

- FDA agreed with Trevena's Agreed iPSP

**May 25, 2017 – Pre-NDA Meeting**

- Need for an adequate nonclinical assessment of potential extractables/leachables and qualification data for metabolites, impurities, and degradation products
- FDA stated that the safety database must include at least 350 patients exposed to the highest intended dose for the longest expected duration of use. FDA stated that the NDA must be complete, including a complete safety database, at the time of NDA submission.
- The Sponsor was informed that positive results from the primary endpoints for the two key efficacy studies, along with support from the secondary endpoints will likely be adequate to demonstrate efficacy of the proposed product, but the final determination would be made following review of the entire NDA submission.
- FDA requested and the sponsor agreed to conduct analyses of the components of the responder definition and sensitivity analyses using the SPID endpoints.
- There was discussion on the what methods of handling missing data in the key efficacy studies would be appropriate.
- Agreement reached that a REMS did not need to be included in the NDA submission

**Breakthrough Therapy Designation**

- Initially, Trevena requested breakthrough therapy designation on January 28, 2014, and the request was denied on March 25, 2014. The preliminary efficacy results were not adequate as they were based on studies conducted in healthy volunteers and the primary efficacy endpoint was cold pain testing, which is not an acceptable primary endpoint for acute pain trials.
- Subsequently, Trevena requested breakthrough designation on April 3, 2015, and the request was denied on May 27, 2015. This breakthrough designation request was for "the anticipatory treatment of pain associated with therapeutic burn care procedures where IV therapy is appropriate." The available efficacy and safety data were not adequate to support breakthrough designation for the proposed indication at that time.
- Trevena requested breakthrough designation on December 23, 2015, and the request was granted on February 19, 2016, for the management of moderate-to-severe acute pain in patients 18 years of age or older for whom a parenteral opioid is warranted. The primary evidence to support that oliceridine provides substantial improvement over existing therapy was from Study 2001 in which oliceridine provided improved efficacy during the first three hours after dosing compared to morphine, and the results trended toward having a lower incidence of some opioid-related adverse events, in particular vomiting, at the doses that provided similar efficacy to morphine. Study 2002 suggested that oliceridine may have an improved safety profile compared to morphine in clinically important safety parameters of hypoventilation, nausea, and respiratory depression. (b) (4)

(b) (4)

# 2 Nonclinical Pharmacology/Toxicology

The Applicant completed a standard pharmacology toxicology development program for oliceridine and this section provides a summary of key non-clinical findings relevant to this advisory committee meeting. There are several outstanding issues currently under review by the Division. Oliceridine was shown to yield two major human metabolites which do not show significant pharmacological activity in *in vitro* studies except a weak partial agonism at mu-opioid receptor. Both of these two major metabolites have been adequately characterized for general and genetic toxicity. However, as per the ICH guidance (Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions and Answers[2]), an insufficient plasma level of metabolite M22, which represents greater than 60% of the total human drug-related exposure, was achieved in the rabbit embryofetal development study to adequately inform the risk to patients at the currently proposed maximum recommended human dose (MRHD) of 40 mg/day, although the data appears to support a MRHD of 27 mg/day. For the other major human metabolite TRV0109662 accounting for 17.4% of the total drug-related exposure, the measured plasma exposure to this metabolite in the rat embryofetal study samples is questionable because the majority of the data cannot be reproduced.

The potential effects of oliceridine on the cardiovascular system were evaluated in a GLP *in vitro* hERG assay, *in vitro* QPatch studies assessing effects of oliceridine on non hERG cardiac channels, an *ex vivo* rabbit left ventricular wedge preparation and a GLP *in vivo* monkey cardiovascular safety study. See Section 7 for discussion of nonclinical and clinical considerations related to QT/QTc interval prolongation.

General toxicology studies in rats and monkeys identified effects related to the opioid class of drugs such as decreased food consumption and body weights, decreased activity, and stereotypic behavioral changes, including repetitive biting, skin picking, or scratching, which led to skin lesions. Opioid-withdrawal-stress-related histopathological changes included minimal to marked stomach lesions, decreased lymphocytes in the spleen, thymus, mesenteric and mandibular lymph nodes. Gastric lesions have been observed as a drug withdrawal-induced stress in rats after 14 days of treatment at plasma exposure ≥1.3 times the estimated human exposure at the MRHD of 40 mg/day on an AUC basis. Stress- or dehydration-related changes in clinical chemistry, hematology (such as reduced white blood cells and lymphocytes), and histopathology (such as increased hypertrophy of adrenal cortex corresponding to increased adrenal weight as well as minimal thymus atrophy) were observed across nonclinical studies. A higher mortality rate was observed in rats after prolonged infusion of oliceridine in the 28-day repeat dose study. Lung thrombosis and injection site inflammation are considered to be oliceridine-related adverse findings in animal studies. An increased incidence of lung thrombosis was observed in oliceridine-treated rats in two out of

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf

the four rat studies and only occurred in oliceridine-treated rats when lung thrombosis was also observed in vehicle-treated animals, suggesting the occurrence may be attributable to the IV procedure with oliceridine exacerbating the effect. The clinical relevance of this finding remains unknown given that rats tend to have much stronger foreign body reactions compared to other species and no such finding was observed in the monkey study. A full battery of developmental and reproductive toxicology studies was conducted in rats and rabbits. In a female rat fertility study, oliceridine caused reproductive and early embryonic toxicity including prolonged estrous cycle lengths, increased pre-implantation loss and correspondingly reduced number of implantation sites and viable fetuses, resulting in a no observed adverse effect level (NOAEL) that corresponds to approximately 1 times the estimated total daily exposure at the MRHD of 40 mg/day. No teratogenic effects were observed in rats or rabbits at doses producing total daily plasma exposures approximately 5 times the MRHD exposure. In a pre- and post-natal development study in rats, maternal dosing of oliceridine between Gestation Day 6 (GD 6) and Lactation Day 21 (LD 21) resulted in a reduced live litter size relative to total number born at birth (Postnatal Day 0; PND 0), lower pup survival between birth and postnatal day (PND) 4, resulting in a NOAEL that corresponds to total daily plasma exposure 0.4 times the MRHD exposure. However, opioids have been reported to inhibit the synthesis and excretion of oxytocin, the hormone responsible for milk let-down, and inhibit maternal behavior which may provide a possible explanation for the early postnatal pup deaths. Similar effects have been reported with other opioid agonists. Oliceridine has been tested in a full battery of genetic toxicity studies. Results from these studies indicate that the risk of mutagenicity and clastogenicity in humans, if any, is minimal.

# 3 Clinical Pharmacology

Executive Summary:
Oliceridine is a synthetic molecule G protein biased ligand at the μ-opioid receptor with analgesic properties and an adverse event profile like other opioids. The Applicant's initially proposed dosing regimen was to administer oliceridine intravenously as a 1 to 3 mg loading dose followed by maintenance analgesia with doses of 1 to 3 mg every 1 to 3 hours as needed or patient-controlled analgesia (PCA) demand doses of 0.1 to 0.5 mg as needed. The proposed dosing was modified several times during the review cycle. Oliceridine is metabolized extensively, primarily by CYP2D6 with some role of CYP3A4, into metabolites that do not have analgesic activity. Oliceridine exhibited a half-life of approximately 1.5 to 3 hours when administered IV over 1 minute to 1 hour. A change in dosing regimen is not required for subpopulations based on intrinsic factors such as age, gender, race, body weight and hepatic/renal function status, since oliceridine doses will be individualized for each patient considering the patient's severity of pain, patient response, prior analgesic treatment experience, and tolerability.

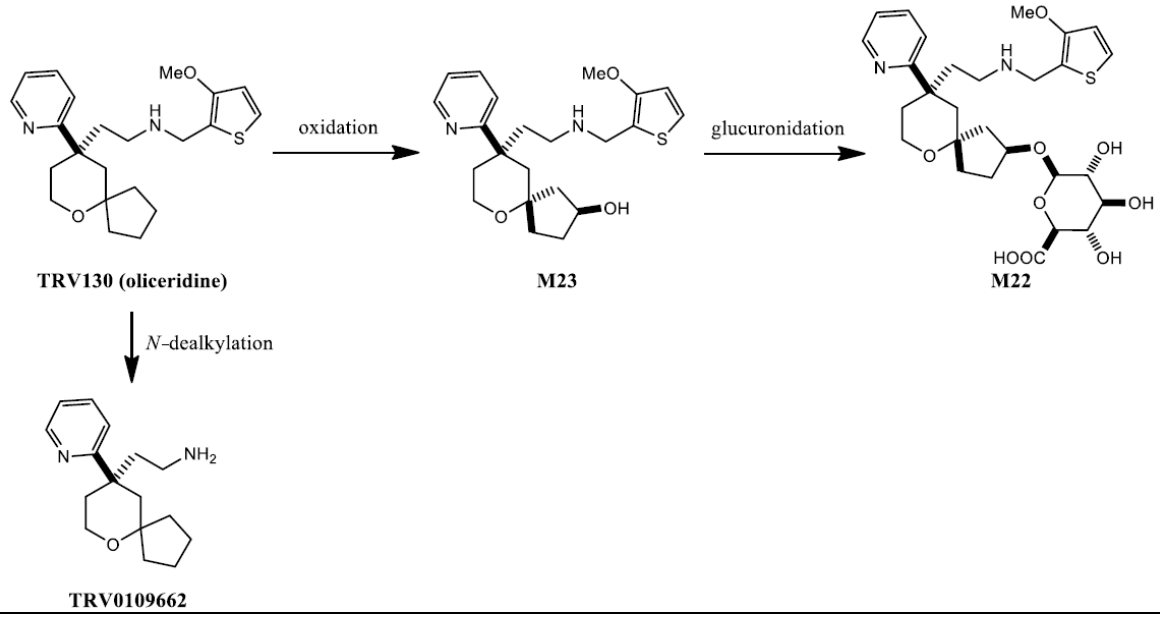
Summary of Oliceridine Clinical Pharmacology:
The bioavailability of oliceridine administered as an oral dose (100 μg) was very low in one oral study CP130-1004. Based on previously studied IV data as reference, oral bioavailability

was estimated to be 5.77%. Oliceridine exhibited a half-life of approximately 1.5 to 3 hours when administered IV over 1 minute to 1 hour.

Oliceridine is metabolized by oxidation into Oxy-oliceridine (M23) followed by glucuronidation to TRV0306954 (M22). N-dealkylation and oxidation of oliceridine produced circulating metabolite TRV0109662. After a single IV dose of $^{14}$C-oliceridine, TRV0306954 (M22) is the main circulating radioactive component, accounting for a mean of 61.9% of total [$^{14}$C]-drug related plasma exposure (AUC). TRV0109662 accounts for 17.4% of plasma AUC. Oxy-oliceridine (M23) accounts for 5.2% of plasma AUC, while oliceridine accounts for approximately 3.4% of total plasma exposure. M23 could not be consistently detected in human plasma perhaps due to rapid conversion to the glucuronide metabolite M22. Additionally, another glucuronide metabolite M16 (3% of plasma AUC) was detected but could not be characterized by NMR analysis due to insufficient sample in human plasma. In the thorough QT (tQT) study CP130-1008, plasma samples were pooled from ten individuals and analyzed for M22 levels. M22 concentrations ranged from 10 ng/mL (lower limit of quantitation) to 31.0 ng/mL following a 3 mg dose of oliceridine and from 10 ng/mL to 65.0 ng/mL following a 6 mg dose. Based on limited pooled sample data peak plasma concentrations of M22 appear to occur at 2 hours after oliceridine administration and plasma half-life appears to be four hours.

CYP2D6 is responsible for up to 76% of the in vitro metabolism of oliceridine, with up to 47% of oxidative metabolism contributed by CYP3A4 (Study No. XT144039). The sponsor indicates that many regioisomeric oxidation products were detected but were not unambiguously characterized. The UDP glucuronosyl transferase isozyme responsible for the conjugation of M23 (oxidized oliceridine) was not determined.

**Figure 1: Schematic diagram of oliceridine metabolic pathway.**




Source: Mass balance study CP130-1007.

Human plasma protein binding of oliceridine is 77% (23% free or unbound), as assessed by equilibrium dialysis. TRV0306954 (M22) was minimally bound to proteins in human plasma with the unbound (free) fraction being 83-85%. TRV0109662 is a primary amine metabolite with no measurable binding, with the unbound fraction being essentially 100% in human plasma, as determined by equilibrium dialysis.

Oliceridine and its major metabolites M22, and TRV1090662 are not direct, time- or metabolism-dependent inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5 enzymes in human liver microsomes. Oliceridine and TRV109662 did not significantly induce CYP1A2, CYP2B6 and CYP3A4 enzymes at clinically relevant concentrations. It is noteworthy that oliceridine is indicated for acute pain management which is anticipated to be limited over a few days so the treatment duration may not be long enough to induce CYP enzyme activity. Oliceridine was not a substrate of the human uptake transporters MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2. Oliceridine is a modest substrate for MDR1 (P-gp)-mediated efflux. Oliceridine did not significantly inhibit MATE1, MATE2-K, OAT1, OAT3, OATP1B1, or OATP1B3 in vitro, but inhibited OCT1 and OCT2 in a dose-dependent manner, with IC50 values of 3.2 and 6.9 μM, respectively. Oliceridine inhibition of MDR1 was not potent, with an IC50 of 46.3 μM, likely reflecting the poor affinity for the transporter. This mechanism for this impotent inhibition was further characterized, with calculated Ki values of 14.1 and 7.95 μM for mixed or competitive inhibition models, respectively. The plasma Cmax of oliceridine with 6 mg, supratherapeutic dose in TQT study, is 0.62 μM, much lower than the Ki values. Therefore, the potential inhibition of transporters by clinically relevant free and total concentrations of the major human metabolites TRV0109662 and TRV0306954 is also limited. Overall, oliceridine and its metabolites may not cause uptake or efflux transporter inhibition related drug interactions.
As described above, oliceridine is susceptible to CYP3A4 and CYP2D6 mediated metabolism. The impact of CYP2D6 polymorphism on the pharmacokinetics of oliceridine was evaluated in several Phase 1 clinical studies. In all subjects, clinically relevant doses (1.5 – 4.5 mg) of oliceridine administered as a 2-minute IV infusion resulted in dose-proportional increase of Cmax and AUC. However, clearance of oliceridine was reduced by 50% in CYP2D6 poor metabolizers (PM) consistently across the Phase 1 clinical studies. While Cmax was only slightly higher, AUC of oliceridine was about 2-fold higher in poor metabolizers of CYP2D6.

**Table 1: Descriptive Statistics of oliceridine pharmacokinetics in CYP2D6 Extensive Metabolizers (EM) and Poor Metabolizers (PM).**

**Cross-study Summary of the Single Dose PK of Oliceridine in EM and PM Subjects**

| Study Number | Dose (mg) | Infusion Time (min) | CYP2D6 Status | N | CL (L/hr) | $AUC_{0-\infty}$ (µg*hr/L) | $C_{max}$ (µg/L) | $t_{max}$ [a] (hr) | $t_{½}$ (hr) |
|---|---|---|---|---|---|---|---|---|---|
| CP130-1001 | 0.25 | 60 | EM | 5 | 47.2 (12.21) | 5.29 (12.30) | 2.29 (22.66) | 0.98 (0.98 - 0.98) | 1.56 (12.42) |
| | | | PM | 4 | 22.4 (16.24) | 11.14 (16.03) | 3.09 (14.44) | 1.03 (0.98 - 1.08) | 2.82 (24.6) |
| CP130-1003 | 1.5 | 2 | EM | 24 | 38.4 (27.5) | 39.1 (27.5) | 45.2 (71.3) | 0.17 (0.03 - 0.23) | 1.7 (15.8) |
| | | | PM | 5 | 19.8 (35.1) | 75.6 (35.1) | 54.7 (56.8) | 0.17 (0.03 - 0.17) | 3.49 (20.6) |
| CP130-1003 | 3 | 2 | EM | 25 | 40.7 (31.2) | 73.8 (31.2) | 81.3 (75.9) | 0.17 (0.03 - 0.20) | 1.68 (16.9) |
| | | | PM | 5 | 22.0 (28.1) | 136.6 (28.2) | 54.0 (12.2) | 0.17 (0.17 - 0.17) | 3.60 (15.8) |
| CP130-1008 | 3 | 5 | EM | 40 | 36.0 (21.4) | 83.3 (21.4) | 131.8 (72.5) | 0.09 (0.07 - 0.34) | 2.57 (37.1) |
| | | | PM | 5 | 24.4 (26.5) | 123.2 (26.5) | 143.4 (36.7) | 0.09 (0.06 - 0.09) | 3.79 (21.8) |
| CP130-1003 | 4.5 | 2 | EM | 25 | 41.6 (24.6) | 108.2 (24.6) | 117.3 (67.1) | 0.18 (0.03 - 0.50) | 1.70 (19.0) |
| | | | PM | 5 | 19.6 (31.0) | 229.3 (31.0) | 127.8 (66.6) | 0.18 (0.17 - 0.50) | 3.64 (7.7) |
| CP130-1008 | 6 | 5 | EM | 44 | 35.0 (26.3) | 171.6 (26.3) | 239.7 (77.8) | 0.09 (0.06 - 0.60) | 3.64 (42.1) |
| | | | PM | 5 | 24.7 (22.2) | 243.0 (22.2) | 183.8 (120.4) | 0.09 (0.09 - 0.60) | 4.07 (13.6) |

$AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 extrapolated to infinity; CL=clearance; $C_{max}$=maximum observed plasma concentration; CYP2D6=cytochrome P450 2D6 enzyme; EM=extensive metabolizers; GeoCV=coefficient of variation for the geometric mean; PK=pharmacokinetics; PM=poor metabolizer; $t_{½}$=apparent elimination half-life; $t_{max}$=time at which $C_{max}$ was observed

Numbers in the table are geometric mean (GeoCV) except where noted.

[a] Median (minimum - maximum).

Data sources: CP130-1001, CSR Table 14.2.1.4; CP130-1003, CSR Table 14.2.1.14; CP130-1008 PK Report, Report Table 11.1

The impact of strong CYP3A4 inhibitors on oliceridine pharmacokinetics was evaluated in two different studies. Study CP130-1005 evaluated the effect of 200 mg itraconazole for 5 days on 0.25 mg oliceridine administered as a 10-minute infusion in four CYP2D6 poor metabolizers (PM) and non-PM's. The 0.25 mg oliceridine dose was within the maintenance dose of 0.1 to 0.5 mg oliceridine used in the Phase 2 and 3 clinical trials. Compared to oliceridine only infusion, oliceridine Cmax increased 8% with itraconazole, $AUC_{0\text{-}inf}$ increased approximately 80% with itraconazole. In study CP130-1006, the effect of 200 mg ketoconazole administered 1 hour before oliceridine and another dose 11 hours later was investigated in CYP2D6 non-PM's. Overall data showed that IV oliceridine PK was not significantly altered. This observation may be due to a) limited role of CYP3A4 in metabolizing oliceridine in the presence of CYP2D6; and/or b) inadequate CYP3A4 inhibition with the use of a single dose of 200 mg ketoconazole. Usually, ketoconazole 200 to 400 mg is used over several days to completely inhibit CYP3A4 in clinical drug interaction studies. Physiologically-based pharmacokinetic (PBPK) modeling and simulation was proposed to support the drug-drug interaction (DDI) liability of oliceridine. This analysis was determined to be unnecessary. The available DDI clinical data and Phase 1 PK data in CYP2D6 PM population were considered sufficient to address oliceridine DDI potential with CYP3A4 and CYP2D6 inhibitors. See below for discussion regarding dose selection.

Study CP130-1010 evaluated the PK of a 2-minute IV infusion of oliceridine in healthy adult male and female subjects receiving 1 mg and subjects with mild, moderate, or severe hepatic

impairment receiving 0.5 mg. Dose-normalized Cmax and AUC of oliceridine did not show an increase in exposure with hepatic impairment. However, an increase in oliceridine elimination half-life was noted from about 2 hours in healthy volunteers and mildly impaired subjects, to about 4 hours in moderately impaired subjects, and about 6 hours in severely impaired subjects.

Study CP130-1012 evaluated the PK of a 2-minute IV infusion of 1 mg of oliceridine in healthy adult male and female subjects and 0.5 mg of oliceridine stage renal disease (ESRD) subjects. Dose-normalized Cmax and AUC were comparable between healthy subjects and ESRD subjects.

Oliceridine produces opioid-like pharmacodynamic effects. Oliceridine has an in vitro EC50 (binding affinity) of 8 nM at the human μ-opioid receptor. In comparison, morphine binds with the human μ-opioid receptor with affinity or EC50 of 50 nM. In the oliceridine clinical program, pupil constriction was consistently noted across several Phase 1, Phase 2 and Phase 3 studies. Dose-related increase in pupil constriction and duration of pupil constriction were also noted. While pupil constriction is clearly indicative of a typical opioid effect due to distribution into the central nervous system, its specific link to pain or abuse remains unestablished. Oliceridine improved the latency to painful stimulus (cold-pain) in a dose-dependent manner in Phase 1 studies within minutes following the 2-minute IV infusion. Although this observation is a measure of opioid analgesic effects, it is not pertinent to post-surgical pain relief. The onset of perceptible analgesia was noted within 5 minutes of initiating loading dose of IV oliceridine in the two Phase 3 studies. Meaningful pain relief was noted within 10 minutes of starting IV loading dose. In a nonclinical model, the analgesic activity due to the mu-opioid receptor agonist activity of oliceridine could be antagonized by a selective mu-opioid antagonist (naloxone).

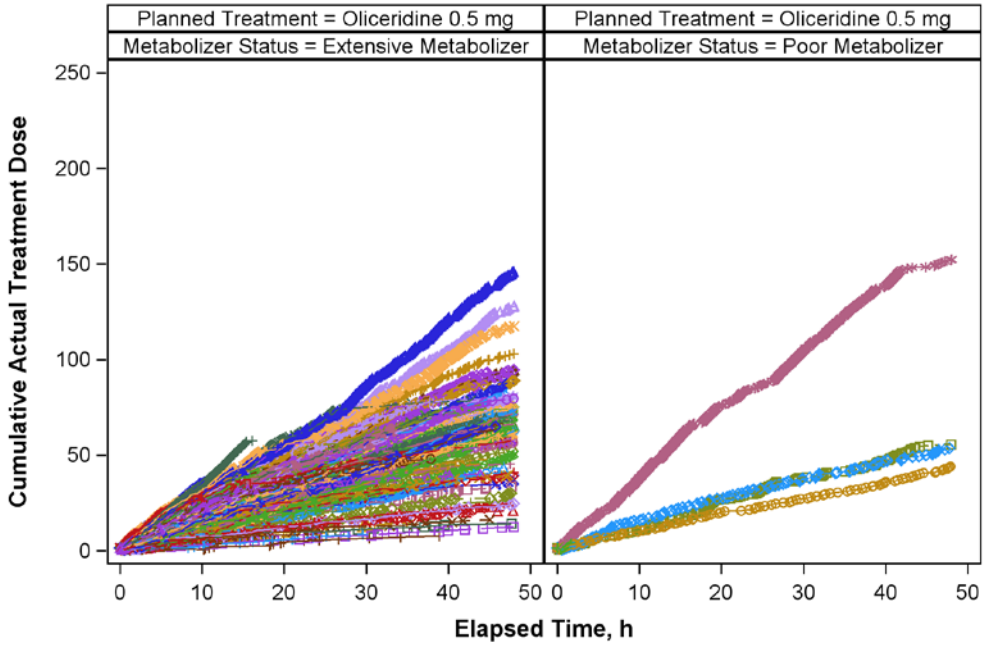
The proposed dosing regimen of oliceridine was selected on the basis of clinical pharmacology principles such as onset and duration of effect from dose finding studies such as CP130-2001 (A Phase 2, Multicenter, Randomized, Double-blind, Multiple-dose, Adaptive, Placebo- and Active-controlled Study of TRV130 for the Treatment of Acute Postoperative Pain after Bunionectomy) and Study CP130-2002 (A Phase 2, randomized, double-blind, placebo- and active-controlled study to evaluate the efficacy and tolerability of IV patient-controlled analgesia (PCA) administration of oliceridine in 200 patients with acute postoperative pain following abdominoplasty). Exposure-response analyses were conducted using the data from the Phase 2 studies to select doses for the Phase III studies (Phase 3 Bunionectomy trial CP130-3001 and Phase 3 abdominoplasty trial CP130-3002). In the two Phase 3 clinical trials, time to perceptible pain relief and time to meaningful pain relief were assessed using the two-stopwatch method. The majority of patients report perceptible pain relief in less than 5 minutes and meaningful pain relief in about 10 minutes in all treatment groups with greater proportion in oliceridine and morphine groups compared to placebo. See Section 6.2 for additional discussion regarding dose selection.

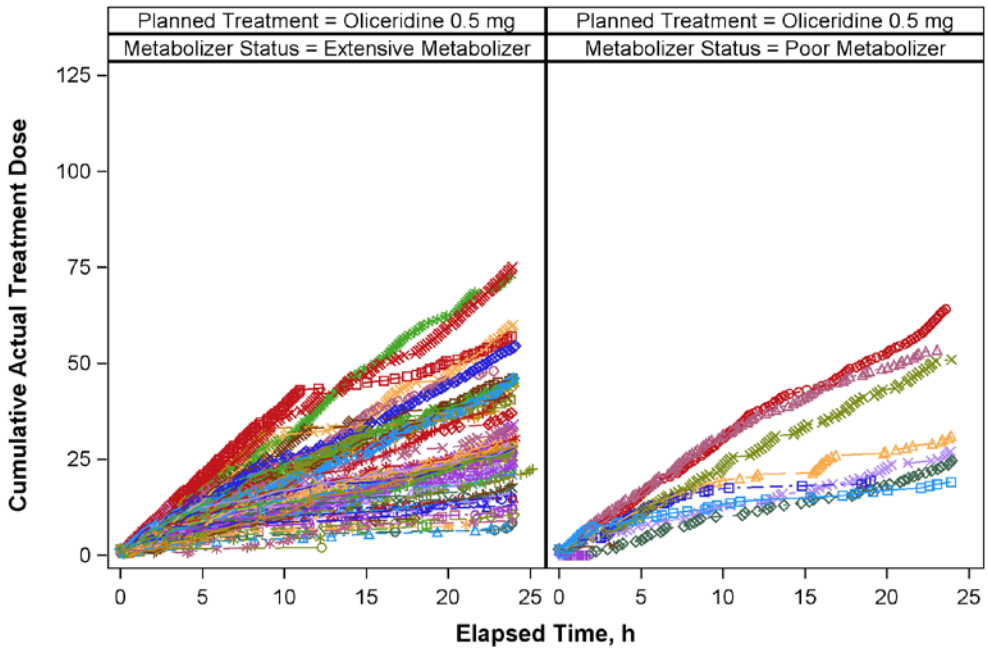
Population pharmacokinetic analysis showed that age and race did not explain the variability in pharmacokinetic parameters such as clearance and volume of distribution. The percent of unchanged oliceridine excreted in the urine is low (0.97-6.75% of dose) suggesting that age

related changes in renal function would not influence the pharmacokinetics of oliceridine. An alternate dosing regimen is not required for subpopulations based on intrinsic factors such as age, gender, race, body weight, and hepatic/renal function status since oliceridine doses will be individualized for each patient taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and tolerability.

The need for dose adjustment in patients who are phenotypic poor metabolizers of CYP2D6 was evaluated because the mean clearance of oliceridine is reduced by 50% in this group. Figure 2 shows the cumulative dose on a patient-controlled analgesia (PCA) basis in patients who are CYP2D6 ultra/extensive metabolizers (grouped as extensive metabolizers) and intermediate/poor metabolizers (grouped as poor metabolizers). It is expected that patients who are CYP2D6 poor metabolizers would have higher blood levels of oliceridine due to slower clearance and thereby would need fewer doses of oliceridine. However, Figure 2 shows that some patients who are CYP2D6 poor metabolizers needed higher doses of oliceridine for pain relief. Therefore, an alternate dosing regimen is not required in CYP2D6 poor and extensive metabolizers.

**Figure 2: Cumulative oliceridine dose in extensive and poor metabolizers with time in study CP 130-3001 (Top) and CP130-3002 (Bottom). Data from 0.5 mg PCA dose group is shown.**






Source: Reviewer's Analysis

# 4 Clinical Microbiology

Not applicable

# 5 Clinical/Statistical - Efficacy

*Clinical Primary Reviewer: Elizabeth Kilgore, MD; Clinical Team Leader Janet Maynard, MD, MHS*
*Statistical Reviewer: James Travis, PhD; Statistical Team Leader: David Petullo, PhD*

## 5.1 Overview of the Clinical Program

Trevena conducted 17 clinical trials in support of this application. At the time of the NDA submission, 16 trials were completed and one Phase 3, open-label (OL) Study CP130-3003 (3003) was ongoing. Interim findings from ongoing Study 3003 were included in the initial NDA and Trevena subsequently submitted the results of the completed study in the 120-day safety update.

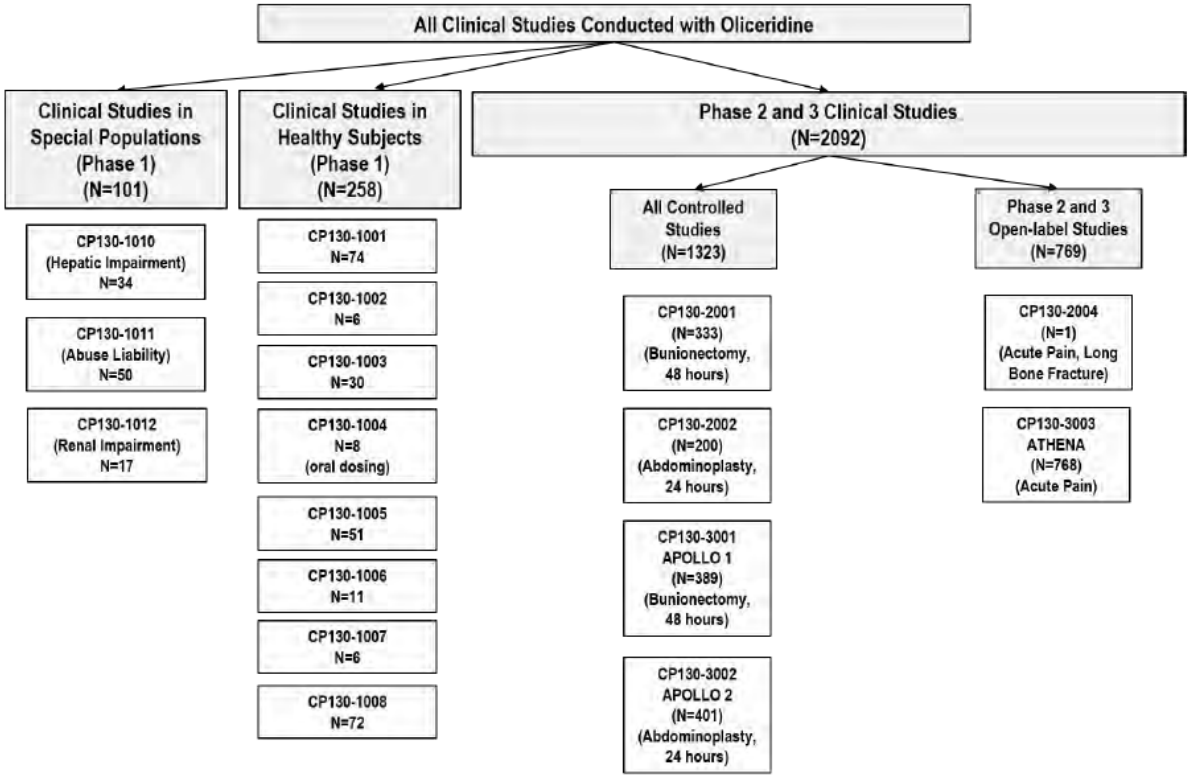
The 17 clinical trials are categorized as follows:

- Eleven Phase 1 studies
  - 8 studies in healthy subjects (single or multiple dose):
    - 7 studies via IV administration: Studies CP130-1001, -1002, -1003, -1005, -1006, -1007, -1008
    - 1 study via oral administration: Study CP130-1004

  - 2 studies in special populations: CP130-1010 (Hepatic Impairment Study) and CP130-1012 (Renal Impairment Study)
  - 1 abuse liability study: CP130-1011
- 3 Phase 2 studies
  - Study CP130-2001 (post-bunionectomy)
  - Study CP130-2002 (post-abdominoplasty)
  - Study CP130-2004 (long bone fracture)
- 3 Phase 3 studies
  - 2 double-blind, placebo-controlled, active-comparator studies:
    - Study CP130-3001 (post-bunionectomy)
    - Study CP130-3002 (post-abdominoplasty)
  - 1 open-label study:
    - Study CP130-3003 (surgical and medical patients)

An overview of the clinical development program is in Figure 3.

**Figure 3: Overview of Oliceridine Clinical Studies**




Note: N=number of subjects/patients treated with any study medication (oliceridine or control).

Source: Integrated Summary of Safety 120 day safety update, Figure 1, page 36, submitted 03/05/18

Results from two Phase 2 studies (CP130-2001 and CP130-220, referred to as 2001 and 2002, respectively) were submitted to support the doses selection in Phase 3 (Table 2). A third Phase 2 study, CP130-2004, was an open-label study in the treatment of moderate to severe acute pain associated with long bone fracture. The study only enrolled one patient who received two doses of oliceridine before the study was terminated by Trevena due to lack of enrollment.

Results from two phase 3 studies CP130-3001 and CP130-3002, referred to as 3001 and 3002, respectively, were submitted as the primary evidence of efficacy of oliceridine (Table 3).

**Table 2: Summary of Phase 2 Studies in the NDA**

| Trial #<br>NCT #<br>*Dates*<br>(# sites) | Patient population (rescue medication) | Design (duration in hours) | Treatment arms | Total N (treated) | 1° Endpoint |
|---|---|---|---|---|---|
| **Phase 2** | | | | | |
| **CP130-2001 (2001)**<br><br>NCT02100748<br><br>*April 2014-Sept. 2014*<br><br>(4 US sites) | Moderate to severe pain ≥4 on 11-point NRS within 9 hours after discontinuation of the anesthetic block after first metatarsal bunionectomy with osteotomy and internal fixation<br><br>(1st line: acetaminophen 650 mg q4h; 2nd line: ketorolac) | MC, R, DB, PC, AC, 2 part, adaptive, dose-finding study<br><br>(48) | **Stage A: IV fixed dosing (1:1:1:1:1:1)**<br>Oliceridine 1 mg q4h<br>Oliceridine 2 mg q4h<br>Oliceridine 3 mg q4h<br>Oliceridine 4 mg q4h<br>Morphine 4 mg q4h<br>Placebo<br><br>**Stage B: IV fixed dosing**<br>Oliceridine 0.5 mg q3h<br>Oliceridine 1 mg q3h<br>Oliceridine 2 mg q3h<br>Oliceridine 3 mg q3h<br>Morphine 4 mg q4h<br>Placebo | Stage A: 141<br><br>Stage B: 195 | TWA change from baseline in 0-10 NRS pain intensity across 0 to 48 hours |
| **CP130-2002 (2002)**<br><br>NCT02335294<br><br>*Dec 2014-Jul 2015*<br><br>(1 US site) | Moderate to severe pain after abdominoplasty ≥5 on NRS within 4 hours after end of surgery<br><br>(1st line: ibuprofen 400 mg po q6h PRN; 2nd line: oxycodone 5 mg po q2h PRN) | DB, PC, AC<br><br>(24) | PCA dosing (dosing modified from Protocol V1-4 to V5)<br>Placebo<br>Morphine<br>•Loading Dose: 4 mg (2 mg at T0 and T10)<br>•Demand Dose: 1 mg (Protocol V1-4 allowed up-titration to 1.5 mg)<br>•Lockout Interval: 6 minutes<br>Oliceridine<br>0.1mg nominal dose regimen<br>•Loading Dose: 1.5 mg (0.75mg at T0 and T10)<br>•Demand Dose: 0.1-0.15 mg (Protocol V1-4); 0.35 mg (Protocol V5)<br>•Lockout Interval: 6 minutes | Protocol V1-4: 100<br><br>V5: 100 | TWA change from baseline in 0-10 NPRS pain intensity ratings across 0 to 24 hours |

Source: Reviewer generated
Route of drug administration: IV
Study CP130-2004 was an open-label, Phase 2 study in patients with moderate to severe acute pain associated with long bone fracture. The study was terminated by Trevena due to lack of enrollment. One patient received 2 doses of oliceridine in the study.
Abbreviations: AC=active-controlled; DB=double-blind; h=hours; IV=intravenous; MC=multicenter; NPRS=numeric pain rating scale; NRS=numeric rating scale; PC=placebo controlled; PO=oral; PCA=patient controlled analgesia; PRN=as needed; q=every; R=randomized; T=time; TWA=time-weighted average; US=United States; V=version

**Table 3: Summary of Phase 3 Studies in the NDA**

| **Trial #<br>NCT #<br>Identifier in label<br>*Dates*<br>(# sites)** | **Patient population (rescue medication)** | **Design (duration in hours) [Total N*]** | **Treatment arms** | **1º Endpoint** |
|---|---|---|---|---|
| **CP130-3001 (3001)**<br><br>NCT02815709<br><br>APOLLO 1<br><br>*May 2016-October 2016*<br><br>(7 US sites) | Moderate to severe pain (NRS ≥4 within 9 hours after discontinuation of regional anesthesia) after unilateral, first metatarsal bunionectomy with osteotomy and internal fixation<br><br>(etodolac 200 mg q6h PRN if the patient requested rescue pain medication and reported an NRS ≥4) | MC, R, DB, PC, AC<br><br>(48)<br><br>[389] | Placebo<br>Morphine<br>•Loading Dose: 4 mg<br>•Demand Dose: 1 mg<br>•Lockout Interval: 6 minutes<br>•Supplemental dose: 2 mg q1h PRN<br>Oliceridine<br>0.1 mg nominal dose regimen<br>•Loading Dose: 1.5 mg<br>•Demand Dose: 0.1 mg<br>•Lockout Interval: 6 minutes<br>•Supplemental dose: 0.75 mg q1h PRN<br>0.35 mg nominal dose regimen<br>•Loading Dose: 1.5 mg<br>•Demand Dose: 0.35 mg<br>•Lockout Interval: 6 minutes<br>•Supplemental dose: 0.75 mg q1h PRN<br>0.5 mg nominal dose regimen<br>•Loading Dose: 1.5 mg<br>•Demand Dose: 0.5 mg<br>•Lockout Interval: 6 minutes<br>•Supplemental dose: 0.75 mg q1h PRN | Proportion of patients who responded to study medication vs placebo at the 48-hour NRS assessment. A patient was a responder if:<br>•Their final time-weighted SPID from Baseline at 48 hours (SPID-48) corresponded to or was greater than a 30% improvement<br>•Without rescue pain medication during the Randomized Treatment Period<br>•Without early discontinuation of study medication for any reason<br>•Without reaching the study medication dosing limit of three PCA syringes within the first 12 hours or six clinician-administered supplemental doses within the first 12 hours |
| **CP130-3002 (3002)**<br><br>NCT02820324<br><br>APOLLO 2<br><br>*May 2016-Dec 2016*<br><br>(5 US sites) | Moderate to severe acute pain (NRS ≥5 within 4 hours after surgery), after abdominoplasty<br><br>(Etodolac 200 mg q6h PRN if the patient requested rescue pain medication and reported an NRS ≥4) | MC, R, DB, PC, AC<br><br>(24)<br><br>[401] | Placebo<br>Morphine<br>•Loading Dose: 4 mg<br>•Demand Dose: 1 mg<br>•Lockout Interval: 6 minutes<br>•Supplemental dose: 2 mg q1h PRN<br>Oliceridine<br>0.1 mg nominal dose regimen<br>•Loading Dose: 1.5 mg<br>•Demand Dose: 0.1 mg<br>•Lockout Interval: 6 minutes<br>•Supplemental dose: 0.75 mg q1h PRN<br>0.35 mg nominal dose regimen<br>•Loading Dose: 1.5 mg<br>•Demand Dose: 0.35 mg<br>•Lockout Interval: 6 minutes | Same as study 3001, except assessed at 24 hours, rather than 48 hours |

| | | | | |
|---|---|---|---|---|
| | | | •Supplemental dose: 0.75 mg q1h PRN<br><u>0.5 mg nominal dose regimen</u><br>•Loading Dose: 1.5 mg<br>•Demand Dose: 0.5 mg<br>•Lockout Interval: 6 minutes<br>•Supplemental dose: 0.75 mg q1h PRN | |
| **CP130-3003 (3003)**<br><br>NCT02656875<br><br>APOLLO 3<br><br>*Dec 2015-May 2017*<br><br>(41 US sites) | Surgical and medical patients in hospitals or outpatient centers with moderate to severe acute pain for which parenteral opioid therapy was warranted (NRS pain intensity ≥4 | OL, MC<br><br>(up to 14 days)<br><br>[768] | Doses were clinician administered and/or PCA<br><br><u>For clinician-administered:</u><br>•Initial dose: 1-2 mg<br>•Supplemental doses 1 mg may be administered within 15 minutes after the initial dose. Subsequent doses are 1-3 mg q1 to 3h PRN<br><br>In settings where rapid analgesia is targeted (e.g. ED or PACU):<br>•Initial dose: 1-3 mg<br>•Supplemental doses 1-3 mg q5 min PRN. Subsequent doses are 1-3 mg q1 to 3h PRN<br><br><u>For PCA dosing:</u><br>•Loading dose: 1.5 mg<br>•Demand dose: 0.5 mg<br>•Lockout interval: 6 minutes<br>•Supplemental 1 mg doses permitted PRN | Safety and tolerability |

Source: Reviewer generated
Route of administration: IV
In studies 3002 and 3003, the initial loading dose was clinician-administered and then demand doses were delivered by PCA PRN beginning 10 minutes after the loading dose. Demand doses had a 6-minute lockout interval. Clinician-administered, blinded supplemental doses were permitted beginning 1 hour after loading dose and hourly thereafter PRN.
*Total N treated
Abbreviations: AC=active-controlled; DB=double-blind; ED=emergency department; h=hour; MC=multicenter; NRS=numeric rating scale; PACU=post-anesthesia care unit; PC=placebo-controlled; PCA=patient controlled analgesia; PRN=as needed; q=every; R=randomized; SPID=summed pain intensity difference; US=United States

## 5.2 Dose Selection

Study 2001 was conducted as an initial proof-of-efficacy study, and evaluated dose strengths and dose intervals. Unlike future studies, it employed a fixed dosing paradigm, rather than an as needed (PRN) paradigm. This Phase 2 study, enrolled patients with acute postoperative pain (≥4 on an 11-point NRS during the 9-hour period after discontinuation of the anesthetic block) after bunionectomy. The primary endpoint in Study 2001 was the time-weighted

average (TWA) change from Baseline in the 0-10 NRS pain intensity ratings across hours 0 to 48 (NRS $TWA_{0-48}$) in Stages A and B.

In Stage A, 144 patients were randomized (141 treated) to placebo, oliceridine 1 mg q4h, 2 mg q4h, 3 mg q4h, 4 mg q4h, or morphine 4 mg q4h. The TWA pain scores were similar across oliceridine treatment groups and were not statistically different than placebo. In contrast, the morphine treatment group had the largest $TWA_{0-48}$ change from baseline of pain intensity scores. To further investigate why the oliceridine doses in Stage A did not meet the primary endpoint (NRS $TWA_{0-48}$), Trevena evaluated secondary endpoints. One secondary endpoint was the NRS change from baseline in the first three hours, which showed a dose-dependent decrease in pain for the oliceridine treatment groups (Table 4). Trevena concluded that the every 4 hour dosing regimen for oliceridine was suboptimal and utilized an every 3 hour dosing regimen in Stage B.

**Table 4: Analysis of $TWA_{0-48}$ Change from Baseline of Pain Intensity Score (NRS) and TWA Change from Baseline of Pain Intensity Hours 0-3 (FAS – Stage A of Study 2001)**

| Statistic | PBO N=23 | OLI 1mg q4h N=25 | OLI 2mg q4h N=24 | OLI 3mg q4h N=22 | OLI 4mg q4h N=22 | Mor 4 mg q4h N=25 |
|---|---|---|---|---|---|---|
| **$TWA_{0-48}$ Change from Baseline of Pain Intensity** | | | | | | |
| LS means (SE) | -2.8 (0.4) | -2.3 (0.39) | -2.7 (0.42) | -2.2 (0.40) | -3.1 (0.42) | -3.5 (0.41) |
| LS mean difference from placebo | -- | 0.5 | 0 | 0.6 | -0.3 | -0.7 |
| 1-sided p-value | -- | 0.8479 | 0.5345 | 0.9028 | 0.2680 | 0.0520 |
| **TWA Change from Baseline of Pain Intensity Hours 0-3** | | | | | | |
| LS mean difference from placebo | -- | -1.0 | -1.3 | -1.4 | -2.7 | -1.3 |
| 1-sided p-value | -- | 0.0300 | 0.0068 | 0.0047 | <0.0001 | 0.0056 |

Abbreviations: FAS=full analysis set; LS=least squares; Mor=morphine; NRS=numeric rating scale; OLI=oliceridine; PBO=placebo; q4h=every 4 hours; SE=standard error; TWA=time-weighted average
Source: CP130-2001 Study Report, Table 14 (page 92) and Table 15 (page 94), submitted 11/02/17

In Stage B, 195 patients were randomized (192 treated) to oliceridine 0.5 mg q3h, 1 mg q3h, 2 mg q3h, or 3 mg q3h, placebo, or morphine 4 mg q4h. The two lower doses of oliceridine (0.5 mg q3h and 1 mg q3h) did not have statistically significant differences for the primary endpoint compared to placebo, while the two higher doses (2 mg q3h and 3 mg q3h) did and the highest oliceridine dose had a significantly lower NRS $TWA_{0-48}$ compared to morphine (Table 5). When comparing oliceridine doses, there was a dose-response relationship for efficacy between the two lower doses (oliceridine 0.5 mg q3h and 1 mg q3h) compared to oliceridine 2 mg q3h and oliceridine 3 mg q3h.

**Table 5: Analysis of $TWA_{0-48}$ Change from Baseline of Pain Intensity Score (NRS) (FAS – Stage B of Study 2001)**

| Statistic | PBO N=28 | OLI 0.5mg q3h N=20 | OLI 1mg q3h N=38 | OLI 2mg q3h N=36 | OLI 3mg q3h N=31 | Mor 4 mg q4h N=39 |
|---|---|---|---|---|---|---|
| **$TWA_{0-48}$ Change from Baseline of Pain Intensity** | | | | | | |
| LS means (SE) | -2.5 (0.40) | -2.9 (0.45) | -2.8 (0.35) | -3.8 (0.36) | -4.8 (0.38) | -3.8 (0.32) |
| LS mean difference from placebo | -- | -0.5 | -0.3 | -1.4 | -2.4 | -1.3 |
| 1-sided p-value | -- | 0.1832 | 0.2311 | 0.0024 | <0.0001 | 0.0023 |
| LS mean difference from morphine | 1.3 | 0.9 | 1.0 | 0 | -1.0 | -- |
| 1-sided p-value | 0.9977 | 0.9527 | 0.9898 | 0.4845 | 0.0144 | -- |

Abbreviations: FAS=full analysis set; LS=least squares; Mor=morphine; PBO=placebo; NRS=numeric rating scale; OLI=oliceridine; q=every; SE=standard error; TWA=time-weighted average
Source: CP130-2001 Study Report, Table 26, page 126, submitted 11/02/17

In Stage B, there was a dose-response relationship between increasing oliceridine dose and occurrence of adverse events. The percentage of patients with adverse events was higher for the highest oliceridine dose (3 mg q3h) compared to morphine (Table 6). There were no deaths or serious adverse events (SAEs) in the study. Five patients discontinued from the study due to treatment-emergent adverse events (TEAEs) during Stage B, all in the oliceridine treatment groups.

A total of one patient on oliceridine 2 mg q3h (2.8%) and two patients on morphine 4 mg q4h (5.1%) had an adverse event in the system organ class of respiratory, thoracic, and mediastinal disorders. Given the limited number of events, definitive conclusions are not possible.

**Table 6: Incidence of the Most Common TEAEs (≥10% of Patients in any Treatment Group) (TOL Population – Stage B, Study 2001)**

| PT | Placebo N=28 n (%) | Oliceridine 0.5 mg q3h N=20 n (%) | Oliceridine 1 mg q3h N=38 n (%) | Oliceridine 2 mg q3h N=36 n (%) | Oliceridine 3 mg q3h N=31 n (%) | Morphine 4 mg q4h N=39 n (%) |
|---|---|---|---|---|---|---|
| Number of patients with at least 1 TEAE | 20 (71.4) | 16 (80.0) | 31 (81.6) | 31 (86.1) | 28 (90.3) | 31 (79.5) |
| Nausea | 7 (25.0) | 7 (35.0) | 13 (34.2) | 20 (55.6) | 23 (74.2) | 22 (56.4) |
| Dizziness | 4 (14.3) | 4 (20.0) | 22 (57.9) | 17 (47.2) | 18 (58.1) | 17 (43.6) |
| Headache | 5 (17.9) | 5 (25.0) | 10 (26.3) | 7 (19.4) | 7 (22.6) | 9 (23.1) |
| Vomiting | 0 | 0 | 4 (10.5) | 10 (27.8) | 17 (54.8) | 12 (30.8) |
| Somnolence | 3 (10.7) | 4 (20.0) | 5 (13.2) | 4 (11.1) | 4 (12.9) | 7 (17.9) |
| Constipation | 1 (3.6) | 2 (10.0) | 6 (15.8) | 3 (8.3) | 5 (16.1) | 2 (5.1) |
| Flushing | 0 | 0 | 3 (7.9) | 6 (16.7) | 3 (9.7) | 4 (10.3) |
| Hot flush | 0 | 0 | 2 (5.3) | 5 (13.9) | 4 (12.9) | 4 (10.3) |
| Pruritus | 2 (7.1) | 0 | 1 (2.6) | 4 (11.1) | 3 (9.7) | 2 (5.1) |
| Dry mouth | 2 (7.1) | 0 | 2 (5.3) | 4 (11.1) | 1 (3.2) | 1 (2.6) |
| Hyperhidrosis | 0 | 0 | 0 | 3 (8.3) | 5 (16.1) | 1 (2.6) |
| Feeling hot | 0 | 0 | 0 | 2 (5.6) | 4 (12.9) | 1 (2.6) |
| Pruritus generalised | 0 | 0 | 0 | 1 (2.8) | 2 (6.5) | 4 (10.3) |

PT=preferred term; q3h=every 3 hours; q4h=every 4 hours; SOC=System Organ Class; TEAE=treatment-emergent adverse event; TOL=tolerability

Note: If a patient reported >1 event in a given SOC, that patient was counted only once for the SOC. If a patient reported >1 event with a given PT, that patient was counted only once for that PT.

Data sources: Table 14.3.1.1.B and Table 14.3.1.2.3.B

Source: Clinical Study Report CP130-2001, Table 33, page 143, submitted 11/2/17

Trevena performed simulations with an exposure-response model constructed from Study 2001, but notes that dose selection for Phase 3 was based in part on the results of Study 2002. Study 2002 was a Phase 2, randomized, double-blind, placebo- and active-controlled study to evaluate the efficacy and tolerability of IV PCA administration of oliceridine in patients with acute postoperative pain (≥5 on NPRS within 4 hours after end of surgery) after abdominoplasty. The treatment regimens consisted of a loading dose and a demand dose (with a 6-minute lockout interval). In protocol Versions 1-4 (V1-4), patients received placebo, oliceridine (loading dose 1.5 mg, demand dose 0.1 mg with up-titration to 0.15 mg), or morphine (loading dose 4 mg, demand dose 1 mg with up-titration to 1.5 mg). In protocol Version 5 (V5), the oliceridine demand dose was increased to 0.35 mg and the up-titration was eliminated from all treatment groups.

Data are shown for protocol V1-4 and V5 separately. In protocol V1-4, 107 patients were randomized, of which 100 were treated and 92 completed the study. In Protocol V5, 103 patients were randomized, of which 100 were treated and 94 completed the study. Both doses of oliceridine provided significant reductions in $TWA_{0-24}$ NPRS compared to placebo. Trevena states that the study showed similar efficacy for the studied doses of oliceridine (nominal dose regimens 0.1 mg and 0.35 mg) in comparison to morphine (4 mg loading dose, then 1 mg every 6 minutes PRN), but with less nausea, vomiting, and hypoventilation than morphine. While the LS mean time-weighted average NPRS change from baseline over 0-24 hours ($TWA_{0-24}$) was numerically similar for oliceridine and morphine in protocol V1-4 and V5, this study was not designed to definitively evaluate the comparative efficacy of oliceridine and morphine. Similarly, while there were fewer patients with adverse events in the system organ class (SOC) for gastrointestinal disorders and respiratory, thoracic, and mediastinal disorders for patients treated with the two doses of oliceridine compared to morphine (Table 8 and Table 9), there are limitations to drawing conclusions from this small Phase 2 study in terms of any potential safety differences between morphine and oliceridine.

**Table 7: Time-Weighted Average Numeric Pain Rating Scale (TWA NPRS) Change from Baseline over 0-24 Hours (FAS) (Study 2002)**

| | N | Mean (SD) | Median | Min, Max | LS Mean |
|---|---|---|---|---|---|
| **Protocol V1-4** | | | | | |
| Placebo | 19 | -1.7 (2.26) | -1.0 | -6.3, 1.0 | -1.67 |
| TRV130 | 39 | -3.8 (2.53) | -4.3 | -8.4, 1.0 | -3.73 |
| Morphine | 42 | -3.4 (2.74) | -3.9 | -9.1, 2.0 | -3.36 |
| **Protocol V5** | | | | | |
| Placebo | 20 | -1.2 (2.93) | -1.2 | -8.1, 2.9 | -1.20 |
| TRV130 | 39 | -3.5 (2.32) | -3.9 | -7.6, 2.0 | -3.49 |
| Morphine | 41 | -3.6 (2.61) | -3.7 | -8.0, 2.0 | -3.60 |

Imputation of NPRS score: Last observation carried forward (LOCF) if discontinued the study early due to lack of efficacy; LOCF from the first use of rescue medication until the end of the treatment period; no imputation was made for discontinuation due to an AE, dosing interruption, subject withdrawal or "other".
For all analyses, the TWA NPRS value is normalized to the time interval over which data are available. Subjects who provide less than the full complement of data during the time interval were still included.
[1]: LSMs from ANCOVA model, modeling TWA as a function of treatment and baseline score.
Source: Table 14.2.1.1, Listing 16.2.6.1, and Listing 16.2.6.1V.

Source: Clinical Study Report CP130-2002, Table 9, page 71, submitted 11/2/17

**Table 8: Treatment-Emergent Adverse Events by SOC in Study 2002 (Protocol V1-4)**

| Number of subjects | PBO N=19 n (%) | OLI 0.1 mg N=39 n (%) | Morphine 4 mg N=42 n (%) |
|---|---|---|---|
| Cardiac disorders | 1 (5.3) | 3 (7.7) | 3 (7.1) |
| Gastrointestinal disorders | 2 (15.8) | 17 (43.6) | 35 (83.3) |
| General disorders and administration site conditions | 1 (5.3) | 1 (2.6) | 1 (2.4) |
| Infections and Infestations | 1 (5.3) | 1 (2.6) | 0 |
| Musculoskeletal and connective tissue disorders | 1 (5.3) | 1 (2.6) | 1 (2.4) |
| Nervous system disorders | 2 (10.5) | 9 (23.1) | 18 (42.9) |
| Respiratory, thoracic, and mediastinal disorders | 0 | 6 (15.4) | 21 (50) |
| Skin and subcutaneous tissue disorders | 1 (5.3) | 1 (2.6) | 8 (19) |
| Vascular disorders | 1 (5.3) | 6 (15.4) | 4 (9.5) |

In protocol Versions 1-4, patients received placebo, oliceridine (loading dose 1.5 mg, demand dose 0.1 mg with up-titration to 0.15mg), or morphine (loading dose 4 mg, demand dose 1 mg with up-titration to 1.5 mg)
Abbreviations: OLI=oliceridine; PBO=placebo; SOC=system organ class
Source: Clinical Study Report CP130-2002, Table 15, pages 92-3, submitted 11/2/17

**Table 9: Treatment-Emergent Adverse Events by SOC in Study 2002 (Protocol V5)**

| Number of Subjects | PBO N=20 n (%) | OLI 0.35 mg N=39 n (%) | Morphine N=41 n (%) |
|---|---|---|---|
| Cardiac disorders | 1 (5) | 1 (2.6) | 2 (4.9) |
| Gastrointestinal disorders | 4 (20) | 20 (51.3) | 30 (73.2) |
| General disorders and administration site conditions | 4 (20) | 4 (10.3) | 4 (9.8) |
| Injury, Poisoning, and Procedural Complications | 1 (5) | 0 | 0 |
| Investigations | 1 (5) | 1 (2.6) | 2 (4.9) |
| Musculoskeletal and connective tissue disorders | 3 (15) | 2 (5.1) | 4 (9.8) |
| Nervous system disorders | 7 (35) | 12 (30.8) | 12 (29.3) |
| Psychiatric disorders | 1 (5) | 0 | 0 |
| Respiratory, thoracic, and mediastinal disorders | 5 (25) | 12 (30.8) | 23 (56.1) |
| Vascular disorders | 4 (20) | 4 (10.3) | 4 (9.8) |

In protocol Version 5, the oliceridine demand dose was increased to 0.35 mg.
Abbreviations: OLI=oliceridine; SOC=system organ class
Source: Clinical Study Report CP130-2002, Table 16, page 94, submitted 11/2/17

## 5.3 Phase 3 trial designs

The results from the two Phase 3 trials, 3001 and 3002, were submitted to support efficacy. Both were double-blind, placebo- and active-controlled studies in adults with moderate to severe pain. Patients in 3001 had undergone a bunionectomy, while patients in 3002 had undergone abdominoplasty. The treatment duration was 48 hours in 3001 compared to 24 hours in 3002. Patients using chronic opioid therapy (defined as >15 morphine equivalent units per day, for >3 out of 7 days per week, for >1 month, within 12 months before surgery) or use of any analgesic medication within five half-lives before surgery were excluded.

To support the proposed general acute pain indication, Trevena completed two Phase 3 studies in patients with nociceptive pain: one in nonvisceral pain (hard tissue model of bunionectomy; 3001; N=389) and one in visceral pain (soft tissue model of abdominoplasty; 3002; N=401).

## 5.3.1 Study Design

**3001**

This was a multicenter, randomized, double-blind, placebo- and active-controlled study of the efficacy and safety of oliceridine in patients with moderate to severe acute pain after bunionectomy. The study included a 48-hour placebo- and active-controlled period. Patients were randomly assigned to receive either placebo, morphine, oliceridine 0.1 mg, oliceridine 0.35 mg, or oliceridine 0.5 mg (1:1:1:1:1).

The study enrolled adult patients (≥18 and ≤75 years of age) who had undergone primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under popliteal sciatic nerve block (PSB) and midazolam and/or propofol sedation. During the immediate postoperative period, regional anesthesia was maintained until approximately 3 AM on postoperative Day 1. During this continuous infusion, patients may have had optimization of their regional anesthesia and then could receive oxycodone 5 mg q4h PRN. The patients who had moderate to severe pain on a four-point categorical pain rating scale (with categories of none, mild, moderate, or severe) and NRS ≥4 within 9 hours after discontinuation of regional anesthesia were eligible to begin study treatment. Patients using chronic opioid therapy (defined as >15 morphine equivalent units per day, for >3 out of 7 days per week, for >1 month, within 12 months before surgery) or use of any analgesic medication within five half-lives before surgery were excluded. In addition, patients on chronic NSAID therapy (defined as daily use for >2 weeks within 6 months before surgery) were excluded.

Study medication regimens consisted of an initial clinician-administered loading dose of study medication, demand doses delivered by PCA PRN beginning 10 minutes after the loading dose, and a 6-minute lockout interval. Clinician-administered, blinded supplemental doses were permitted beginning 1 hour after the loading dose and hourly thereafter PRN. Clinician administered, blinded supplemental doses were administered, taking into account the patient's utilization of PCA demand doses, severity of pain, and response to study medication. Study medication regimens are summarized in Table 10.

**Table 10: Randomized Treatment Regimens (Study 3001)**

| Nominal dose | Loading dose | Demand dose | Lockout interval | Supplemental dose |
|---|---|---|---|---|
| Placebo | Volume-matched placebo solution | Volume-matched placebo solution | 6 minutes | Volume-matched placebo solution |
| Morphine | 4 mg | 1 mg | 6 minutes | 2 mg q1h PRN |
| Oliceridine 0.1 mg | 1.5 mg | 0.1 mg | 6 minutes | 0.75 mg q1h PRN |
| Oliceridine 0.35 mg | 1.5 mg | 0.35 mg | 6 minutes | 0.75 mg q1h PRN |
| Oliceridine 0.5 mg | 1.5 mg | 0.5 mg | 6 minutes | 0.75 mg q1h PRN |

Source: Modified from Clinical Study Report CP130-3001, Table 2, page 25, submitted 11/2/17

**Rescue Pain Medication**

If study medication was utilized (PCA demand doses plus supplemental doses) and inadequate, patients may have received rescue pain medication (etodolac 200 mg q6h PRN) if the patient requested rescue pain medication and reported an NRS ≥4. Patients were encouraged to wait

at least 60 minutes before receiving the first dose of rescue pain medication. Unscheduled NRS assessments were performed before, and 5 minutes after, any clinician-administered, blinded supplemental dose, before any rescue pain medication, and before early discontinuation of study medication. Some patients used non-protocol specified rescue medications. Patients who received rescue pain medication continued to be treated with study medication PRN. If study medication and rescue pain medication were inadequate, the patient was discontinued from study medication and was managed conventionally.

**Rescue Antiemetic Medication**
Patients may have received rescue antiemetic medication if the patient was actively vomiting, or at the patient's request if the patient reported nausea graded as moderate or severe on a 4-category scale (none, mild, moderate, severe). Prophylactic antiemetic medication was not permitted.

**3002**
This was a multicenter, randomized, double-blind, placebo- and active-controlled study of the efficacy and safety of oliceridine in patients with moderate to severe acute pain after abdominoplasty. The study included a 24-hour placebo- and active-controlled period. Patients were randomly assigned to receive either placebo, morphine, oliceridine 0.1 mg, oliceridine 0.35 mg, or oliceridine 0.5 mg (1:1:1:1:1).

The inclusion and exclusion criteria were the same as those for 3001, except patients in Study 3002 underwent abdominoplasty rather than bunionectomy. There were also minor differences in terms of when the qualifying pain assessments occurred in the two surgeries. In Study 3002, patients had moderate to severe pain on a four-point categorical pain rating scale (with categories of none, mild, moderate, or severe) and NRS ≥5 within 4 hours after end of surgery (rather than 9 hours after discontinuation of regional anesthesia in 3001) were eligible to begin study treatment.

Patients received standardized anesthetic regimens with fentanyl and propofol, with or without volatile anesthetics or muscle relaxants. During surgery, patients were prohibited from receiving any opioid other than fentanyl.

The medication regimen in Study 3002 was the same as 3001 (Table 10) and consisted of an initial clinician-administered loading dose of study medication, demand doses delivered by PCA PRN beginning 10 minutes after the loading dose, and a 6-minute lockout interval. As in Study 3001, clinician-administered, blinded supplemental doses were permitted and patients received rescue analgesics (etodolac 200 mg every 6 hours as needed) or rescue antiemetics as needed.

## 5.3.2 Endpoints

The primary and secondary endpoints for the studies were the same, but the time of assessment was 48 hours for Study 3001 compared to 24 hours for Study 3002.

The primary efficacy endpoint was the proportion of patients who responded to study medication vs. placebo at the 48-hour (3001) or 24-hour (3002) NRS assessment. A patient was a responder if:

- his/her final time-weighted sum of pain intensity differences (SPID) from baseline at 48 hours (SPID-48) corresponded to or was greater than a 30% improvement
- did not receive rescue pain medication during the randomized treatment period
- early discontinuation of study medication for any reason did not occur
- did not reach the study medication dosing limit of three PCA syringes within the first 12 hours or six clinician-administered supplemental doses within the first 12 hours.

This endpoint is novel and has never been the basis for approval for any drugs in this class. Consequently, sensitivity analyses were also performed directly on the SPID scores which are typically used as the primary efficacy endpoint in this setting.

**The key secondary safety endpoint** was the respiratory safety burden, as measured by the occurrence and duration of respiratory safety events (RSEs) within patients. The Applicant also recorded information on the cumulative duration of supplemental oxygen administration and the cumulative duration of recovery from RSE.

A respiratory safety event (RSE) was defined as a clinically relevant worsening of respiratory status. The respiratory safety burden safety/tolerability endpoint incorporated both the prevalence of RSEs and the expected duration of time that a patient would experience an RSE if one occurred, into a single composite measure. The expected cumulative duration of an RSE was defined as the model-based product of the population prevalence (probability of having an RSE) and the population conditional mean cumulative duration (mean sum of durations given one or more RSEs occur). This endpoint was intended to correspond to the total amount of time a patient from the population should have expected to experience an RSE and represents the respiratory safety burden for a given treatment regimen. However, there is no precedent for use of this endpoint in a clinical study and the FDA did not agree that this was a clinically interpretable endpoint for the evaluation of a potential respiratory claim. During development, FDA informed the Applicant that their definition of RSE was not clearly defined and relied largely on clinical acumen. In addition to an RSE analysis, the Applicant also assessed the cumulative duration of supplemental oxygen administration. The results from an analysis of this endpoint were consistent with the findings from the RSE endpoint.

Assessment of respiratory safety primarily relied on assessment of respiratory rate, oxygen saturation (using fingertip pulse oximetry), the Moline-Roberts Pharmacology Sedation Scale (MRPSS), and end-tidal CO2 (using noninvasive capnometry). A certified registered nurse anesthetist (CRNA) or anesthesiologist monitored for RSEs based on multifactorial considerations, rather than a specific objective cutpoint.

**The key secondary efficacy endpoint** was the proportion of patients who responded to study medication at the 48-hour NRS assessment vs morphine. This would be assessed first using a non-inferiority assessment followed by a superiority assessment.

**Other Secondary Efficacy Endpoints:** There were numerous other secondary efficacy endpoints.

The primary efficacy endpoint, the key secondary efficacy, and safety endpoints and analyses of the rescue medication usage are described in this review.

## 5.3.3 Statistical Analysis

The statistical analyses for studies 3001 and 3002 will be summarized in this section. The Applicant's statistical analyses was similar for both studies. The Applicant's primary efficacy endpoint was based on a novel responder definition, i.e. 30% improvement in SPIDs, and FDA considered an analysis of SPIDs to be more relevant. FDA also disagreed with how the Applicant handled use of rescue medication in their analysis of SPIDs. The Applicant's pre-specified analysis plan is described first, followed by the Agency's analyses.

***Applicant's Analysis***

**Primary efficacy analysis:** The proportion of responders was analyzed using a logistic regression model with assigned treatment, baseline NRS score, and site group as independent variables.

**Sensitivity Analyses:** The Applicant performed the following sensitivity analyses for the primary efficacy endpoint:

- Analysis of the SPID data using an analysis of covariance (ANCOVA) model with assigned treatment, baseline NRS score, and site group as independent variables using the following imputation scheme:
    - NRS scores following rescue are replaced by the final pre-rescue score.
    - NRS scores following treatment discontinuation due to lack of efficacy are replaced by the final pre-discontinuation score.
    - NRS scores following treatment discontinuation due to adverse events are replaced by the baseline observation.
- A modified responder definition where pre-rescue scores are imputed for 2, 4, 6, or 8 hours following use of rescue. The responder definition for these analyses is at least a ≥30% improvement in pain based on SPID score without either of the following disqualifying criteria:
    - Early discontinuation of study medication for any reason, or
    - Reaching study medication dosing limit of three PCA syringes within the first 12 hours or six clinician-administered supplemental doses within the first 12 hours.
- The responder analysis will be repeated on patients having 1 or fewer, 2 or fewer, and 3 or fewer allowable doses of rescue medication separately, with pre-rescue scores carried forward for 6 hours following rescue.

- Responder analyses where either the baseline or worst observations are used following rescue.
- Tipping point analysis.

**Analysis of key secondary efficacy and safety endpoints**:

1. Respiratory safety burden: This endpoint was using two different methodologies which are as follows:
    - Percentage of patients with RSE: Analyzed using the Firth penalized likelihood method[3]. Results are presented as odds ratios vs morphine.
    - Cumulative duration of RSE: Analyzed using a zero-inflated gamma mixture model. The percentage of patients with events was modelled using the Firth penalized likelihood method. The cumulative duration of events among patients who had events was analyzed using a gamma regression model. Both models included treatment, baseline pain score, baseline BMI, and site group. The model estimated proportion of patients with events was multiplied by the model estimated cumulation duration among patients who have events to produce an overall estimate.
2. Non-inferiority assessment of oliceridine to morphine: The Applicant used the same responder definition and logistic regression methodology for this analysis. In the briefing package for the End-of-Phase 2 meeting the Applicant proposed a margin of 50% of the effect of morphine vs placebo seen in each study. As discussed in Section 1.1, the Agency did not agree with this definition. The Applicant did not propose any alternatives.
3. Superiority assessment of oliceridine to morphine: The Applicant used the same responder definition and logistic regression methodology for this endpoint.

***Agency's Analysis***

Since the Applicant's primary efficacy analyses was based on a novel responder definition, i.e. 30% improvement in SPIDs, FDA conducted an analysis using SPIDs rather than the proposed responder definition. FDA disagreed with how information regarding use of rescue medication was used in the Applicant's derivation of SPIDs. Carrying forward the final pre-rescue score from the first use of rescue until the end of the observation period ignores the fact that the effect of the rescue medication will expire, and the fact that patient's pain scores would continue to improve throughout the study even in the placebo arm. The consequence is that it harshly penalizes patients who used rescue medication. FDA used an alternative analysis which carries forward the pre-rescue scores for the dosing interval of the rescue medication, which is commonly used in studies of analgesics in the post-surgical setting, and considered the most clinically relevant.

**Primary Efficacy Analysis:** Analysis of the SPID data using an ANCOVA model with treatment as the main effect of interest with site group and baseline NRS score as covariates. The following imputation scheme will be used for intercurrent events:

- NRS scores for 6 hours following rescue use are replaced by the final pre-rescue score.

[3] Firth, David. Bias Reduction of Maximum Likelihood Estimates. Biometrika. 1993; 80:27-38.

- NRS scores following study discontinuation due to lack of efficacy are replaced by the final pre-discontinuation score.
- NRS scores following study discontinuation due to adverse events are replaced by the baseline observation.
- Intermittently missing NRS scores are imputed using linear interpolation.
- NRS scores following treatment, but not study discontinuation will be used and not imputed where available.

This approach was proposed by the Applicant in the End-of-Phase 2 meeting described in Section 1.1.

**Sensitivity Analyses**:

- Analysis using the FDA primary analysis methodology with pre-rescue scores carried forward for 2, 4, and 8 hours after rescue use instead of 6 hours.
- Analysis of the SPID data with no imputation following use of rescue.

**Key Safety Analysis**: Additional analyses were conducted of the proportion of patients who were recorded to have any respiratory safety event or used any supplemental oxygen. These were analyzed using a logistic regression approach. The cumulative duration of supplemental oxygen administration which were analyzed using the same methodology as the respiratory safety event analysis is also provided.

**Secondary Efficacy Analysis**:

- Non-inferiority assessment of oliceridine to morphine: While this is critical in light of the application's objective of demonstrating a reduction in the respiratory safety burden for oliceridine compared to morphine, there was no agreement on the Applicant's definition of the non-inferiority criteria.
- Superiority assessment of oliceridine to morphine: Oliceridine was compared to morphine using the approach used for the primary analysis, specifically, the SPID data was analyzed using an ANCOVA model with treatment as the main effect with site group and baseline NRS score as covariates. The same approach to missing and post-rescue pain scores will be used.

**Multiple Comparisons and Multiplicity:**

A combination of a sequential gatekeeping method and the (Hochberg 1988)[4] method was used to control the overall type I error for the primary and key secondary endpoints. For any given endpoint, Hochberg adjustments were applied for each p-value for the three dose levels. Specifically, the smallest, median, and largest p-values from the primary endpoint family were compared with 0.0167, 0.025, and 0.05, respectively. The endpoints were tested in the following order:

1. The primary superiority assessment vs placebo for all oliceridine treatment groups.
2. The respiratory safety burden safety/tolerability endpoint.

[4] Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-2.

3. The noninferiority assessment of oliceridine to morphine with respect to the responder efficacy endpoint. The Agency did not agree with the Applicant's selected non-inferiority margin.
4. The superiority assessment of oliceridine to morphine with respect to the responder efficacy endpoint.

For this methodology, each endpoint could be tested only if all dose comparisons were statistically significant for each of the previous endpoints.

**Adjustment for Covariates**

For parameters analyzed with analysis of covariance (ANCOVA) or logistic regression, the treatment group was the main effect of interest, and Baseline NRS scores and pooled study site were the covariates. Baseline NRS score was included in each model as a continuous covariate, and pooled study site was included in each model as a class variable. Cumulative duration endpoints included BMI as a continuous covariate.

## 5.4 Patient disposition, demographic, and baseline characteristics

### 5.4.1 Study 3001

In Study 3001, of the 418 patients randomized (placebo [84 patients], morphine [84 patients], and oliceridine 0.1 [82 patients], 0.35 [86 patients], 0.5 mg [82 patients]), 389 patients were treated with study medication and 326 (78.0%) patients completed study medication (Table 11). Trevena defines the Full Analysis Set as all randomized patients who received at least one dose of study medication. A total of 63 (15.1%) patients discontinued study medication early. The most common reason for early discontinuation of study medication was lack of efficacy (44 patients [69.8% of patients who discontinued study medication early]) and this was the most common reason in the placebo group.

**Table 11: Patient Enrollment and Disposition (Study 3001)**

| | Placebo n (%) | Oli 0.1mg n (%) | Oli 0.35mg n (%) | Oli 0.5mg n (%) | Oli Total n (%) | Morphine n (%) |
|---|---|---|---|---|---|---|
| Randomized | 84 | 82 | 86 | 82 | 250 | 84 |
| Treated with study medication (Full analysis set)[a] | 79 (94.0) | 76 (92.7) | 79 (91.9) | 79 (96.3) | 234 (93.6) | 76 (90.5) |
| Completed study medication[a] | 50 (59.5) | 68 (82.9) | 75 (87.2) | 212 (84.8) | 212 (84.8) | 64 (76.2) |
| Completed study[a] | 76 (90.5) | 75 (91.5) | 78 (90.7) | 75 (91.5) | 228 (91.2) | 74 (88.1) |
| Reason for early discontinuation of study medication[b] | | | | | | |
| Adverse event | 0 | 0 | 1 (25.0) | 4 (40) | 5 (22.7) | 6 (50.0) |
| Protocol deviation | 0 | 0 | 0 | 0 | 0 | 0 |
| Withdrawal by subject | 1 (3.4) | 0 | 0 | 1 (10.0) | 1 (4.5) | 2 (16.7) |
| Lack of efficacy | 27 (93.1) | 7 (87.5) | 3 (75.0) | 4 (40.0) | 14 (63.6) | 3 (25.0) |
| Other | 1 (3.4) | 1 (12.5) | 0 | 1 (10.0) | 2 (9.1) | 1 (8.3) |
| Reason for early discontinuation from study[c] | | | | | | |
| Adverse event | 0 | 0 | 0 | 0 | 0 | 0 |
| Lost to Follow Up | 0 | 1 (50.0) | 0 | 3 (75.0) | 4 (57.1) | 0 |
| Withdrawal by Subject | 0 | 1 (50.0) | 0 | 0 | 1 (14.3) | 1 (50.0) |
| Lack of Efficacy | 2 (66.7) | 0 | 1 (100.0) | 1 (25.0) | 2 (28.6) | 0 |
| Other | 1 (33.3) | 0 | 0 | 0 | 0 | 1 (50.0) |

N=randomized to study medication
a=Percentage based on number of patients randomized
b=Percentages based on number of patients who discontinued the study medication early
c=Percentages based on number of patients who discontinued the study early
Abbreviations: Oli=oliceridine
Source: Modified from Clinical Study Report CP130-3001, Table 6, page 80-1, submitted 11/2/17

Baseline demographics and disease characteristics were well-balanced among the treatment groups and are shown in Table 12. Most patients were female (84.8%) and white (69.4%), with a mean age of 45 years (range 19 to 74 years) and a mean weight of 72 kg. Most patients were CYP2D6 extensive metabolizers (82%), which is consistent with the general population. The mean baseline pain intensity was 6.7.

**Table 12: Demographic Characteristics (Study 3001)**

| | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=79 | Oliceridine 0.5 mg N=79 | Morphine N=76 | Overall N=389 |
|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | |
| Female | 70 (88.6) | 64 (84.2) | 65 (82.3) | 66 (83.5) | 65 (85.5) | 330 (84.8) |
| Male | 9 (11.4) | 12 (15.8) | 14 (17.7) | 13 (16.5) | 11 (14.5) | 59 (15.2) |
| Race, n (%) | | | | | | |
| White | 56 (70.9) | 47 (61.8) | 56 (70.9) | 61 (77.2) | 50 (65.8) | 270 (69.4) |
| Black or African American | 21 (26.6) | 22 (28.9) | 17 (21.5) | 13 (16.5) | 21 (27.6) | 94 (24.2) |
| Asian | 1 (1.3) | 4 (5.3) | 4 (5.1) | 1 (1.3) | 4 (5.3) | 14 (3.6) |
| American Indian Or Alaska Native | 0 | 1 (1.3) | 0 | 2 (2.5) | 1 (1.3) | 4 (1.0) |
| Native Hawaiian Or Other Pacific Islander | 0 | 1 (1.3) | 1 (1.3) | 2 (2.5) | 0 | 4 (1.0) |
| Other | 1 (1.3) | 1 (1.3) | 1 (1.3) | 0 | 0 | 3 (0.8) |
| Age (Years) | | | | | | |
| Mean (SD) | 44.1 (12.58) | 47.5 (12.65) | 43.6 (13.91) | 46.9 (13.81) | 43.3 (14.13) | 45.1 (13.48) |
| Median | 46 | 48 | 42 | 51 | 45.5 | 47 |
| Min, Max | 19, 67 | 19, 74 | 19, 74 | 19, 71 | 20, 69 | 19, 74 |
| Ethnicity, n (%) | | | | | | |
| Hispanic Or Latino | 17 (21.5) | 17 (22.4) | 25 (31.6) | 19 (24.1) | 18 (23.7) | 96 (24.7) |
| Not Hispanic Or Latino | 62 (78.5) | 59 (77.6) | 54 (68.4) | 60 (75.9) | 58 (76.3) | 293 (75.3) |
| Height (cm) | | | | | | |
| Mean (SD) | 165.8 (8.12) | 166 (9.04) | 164.6 (8.59) | 165 (7.58) | 165.2 (8.2) | 165.3 (8.29) |
| Min, Max | 150, 189 | 152, 203 | 149, 185 | 145, 183 | 150, 195 | 149, 203 |
| Weight (kg) | | | | | | |
| Mean (SD) | 72.5 (14.57) | 73.2 (15.55) | 70.9 (13.89) | 73.9 (13.66) | 72.7 (15.77) | 72.7 (14.66) |
| Min, Max | 47.7, 120.8 | 47.6, 121.1 | 43.5, 108 | 49.3, 108.8 | 44.7, 112 | 43.5, 121.1 |
| CYP2D6 Metabolizer, n (%) | | | | | | |
| Extensive | 58 (73.4) | 65 (85.5) | 69 (87.3) | 71 (89.9) | 56 (73.7) | 319 (82.0) |
| Poor | 13 (16.5) | 9 (11.8) | 8 (10.1) | 5 (6.3) | 12 (15.8) | 47 (12.1) |
| Missing | 8 (10.1) | 2 (2.6) | 2 (2.5) | 3 (3.8) | 8 (10.5) | 23 (5.9) |
| Baseline Pain | | | | | | |
| Mean (SD) | 7 (1.51) | 6.8 (1.76) | 6.6 (1.88) | 6.5 (1.66) | 6.7 (1.64) | 6.7 (1.69) |
| Median | 7 | 7 | 6 | 6 | 7 | 7 |
| Min, Max | 4, 10 | 4, 10 | 4, 10 | 4, 10 | 4, 10 | 4, 10 |

Source: Reviewer generated

## 5.4.2 Study 3002

In Study 3002, of the 407 patients randomized (placebo [82 patients], morphine [83 patients], and oliceridine 0.1 [78 patients], 0.35 [82 patients], 0.5 mg [82 patients]), 401 patients were treated with study medication and 348 (85.5%) patients completed study medication (Table 13). A total of 53 (13.0%) patients discontinued study medication early. The most common reason for early discontinuation of study medication was lack of efficacy (39 patients [13.0% of patients who discontinued study medication early]) and this was the most common reason in the placebo group.

**Table 13: Patient Enrollment and Disposition (Study 3002)**

| | Placebo n (%) | Oli 0.1mg n (%) | Oli 0.35mg n (%) | Oli 0.5 mg n (%) | Oli Total n (%) | Morphine n (%) |
|---|---|---|---|---|---|---|
| Randomized | 82 | 78 | 82 | 82 | 242 | 83 |
| Treated with study medication (Full analysis set)[a] | 81 (98.8) | 77 (98.7) | 80 (97.6) | 80 (97.6) | 237 (97.9) | 83 (100) |
| Completed study medication[a] | 61 (74.4) | 67 (85.9) | 74 (90.2) | 71 (86.6) | 212 (87.6) | 75 (90.4) |
| Completed study | 79 (97.5) | 76 (98.7) | 78 (97.5) | 79 (98.8) | 233 (98.3) | 80 (96.4) |
| Reason for early discontinuation of study medication[b] | | | | | | |
| Adverse event | 0 | 0 | 4 (66.7) | 4 (44.4) | 8 (32.0) | 2 (25.0) |
| Protocol deviation | 0 | 0 | 0 | 0 | 0 | 0 |
| Withdrawal by subject | 1 (5.0) | 1 (10.0) | 0 | 1 (11.1) | 2 (8.0) | 0 |
| Lack of efficacy | 18 (90.0) | 9 (90.0) | 2 (33.3) | 4 (44.4) | 15 (60.0) | 6 (75.5) |
| Other | 1 (5.0) | 0 | 0 | 0 | 0 | 0 |
| Reason for early discontinuation from study[c] | | | | | | |
| Adverse event | 0 | 0 | 0 | 1 (100.0) | 1 (25.0) | 1 (33.3) |
| Lost to Follow Up | 1 (50.0) | 1 (100.0) | 0 | 0 | 1 (25.0) | 0 |
| Withdrawal by Subject | 0 | 0 | 2 (100.0) | 0 | 2 (50.0) | 0 |
| Lack of Efficacy | 1 (50.0) | 0 | 0 | 0 | 0 | 2 (66.7) |
| Other | 0 | 0 | 0 | 0 | 0 | |

N=randomized to study medication
a=Percentage based on number of patients randomized
b=Percentages based on number of patients who discontinued the study medication early
c=Percentages based on number of patients who discontinued the study early
Abbreviations: Oli=oliceridine
Source: Modified from Clinical Study Report CP130-3002, Table 6, page 79-80, submitted 11/2/17

Baseline demographics and disease characteristics were well-balanced among the treatment groups and are shown in Table 14. Most patients were female (99.3%) and white (64.1%), with a mean age of 41.4 years (range 20 to 71 years) and a mean weight of 71.9 kg. Most patients were CYP2D6 extensive metabolizers (80.3%), which is consistent with what would be anticipated in the general population. The mean baseline pain intensity was 7.4.

**Table 14: Demographic Characteristics (Study 3002)**

| | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 | Overall N=389 |
|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | |
| Female | 81 (100) | 76 (98.7) | 80 (100) | 80 (100) | 81 (97.6) | 398 (99.3) |
| Male | 0 | 1 (1.3) | 0 | 0 | 2 (2.4) | 3 (0.7) |
| Race, n (%) | | | | | | |
| White | 52 (64.2) | 45 (58.4) | 55 (68.8) | 50 (62.5) | 55 (66.3) | 257 (64.1) |
| Black or African American | 27 (33.3) | 24 (31.2) | 22 (27.5) | 28 (35.0) | 24 (28.9) | 125 (31.2) |
| Asian | 1 (1.2) | 3 (3.9) | 2 (2.5) | 1 (1.2) | 2 (2.4) | 9 (2.2) |
| American Indian Or Alaska Native | 0 | 1 (1.3) | 0 | 0 | 0 | 1 (0.2) |
| Native Hawaiian Or Other Pacific Islander | 0 | 2 (2.6) | 0 | 0 | 1 (1.2) | 3 (0.7) |
| Other | 1 (1.2) | 2 (2.6) | 1 (1.2) | 1 (1.2) | 1 (1.2) | 6 (1.5) |
| Age (Years) | | | | | | |
| Mean (SD) | 42.2 (10.25) | 41.8 (10.64) | 42 (9.97) | 40.4 (10.03) | 40.4 (10.35) | 41.4 (10.23) |
| Median | 42 | 41 | 40.5 | 41 | 41 | 41 |
| Min, Max | 24, 67 | 21, 69 | 23, 67 | 23, 71 | 20, 69 | 20, 71 |
| Ethnicity, n (%) | | | | | | |
| Hispanic Or Latino | 27 (33.3) | 28 (36.4) | 24 (30.0) | 24 (30.0) | 29 (34.9) | 132 (32.9) |
| Not Hispanic Or Latino | 54 (66.7) | 49 (63.6) | 56 (70.0) | 56 (70.0) | 54 (65.1) | 269 (67.1) |
| Height (cm) | | | | | | |
| Mean (SD) | 162.2 (5.69) | 161.8 (7.11) | 161 (6.41) | 162.3 (5.25) | 163.3 (7.44) | 162.1 (6.44) |
| Min, Max | 149.8, 180 | 138, 185.4 | 147, 177.8 | 147, 172.7 | 148.5, 197 | 138, 197 |
| Weight (kg) | | | | | | |
| Mean (SD) | 71.2 (10.44) | 73.7 (11.74) | 71.8 (9.79) | 71.3 (10.08) | 71.5 (10.97) | 71.9 (10.61) |
| Min, Max | 51, 96.6 | 44.9, 109.3 | 46.9, 96.6 | 49.2, 100 | 41.2, 112 | 41.2, 112 |
| CYP2D6 Metabolizer, n (%) | | | | | | |
| Extensive | 68 (84) | 58 (75.3) | 63 (78.8) | 67 (83.8) | 66 (79.5) | 322 (80.3) |
| Poor | 9 (11.1) | 14 (18.2) | 12 (15) | 10 (12.5) | 14 (16.9) | 59 (14.7) |
| Missing | 4 (4.9) | 5 (6.5) | 5 (6.2) | 3 (3.8) | 3 (3.6) | 20 (5) |
| Baseline Pain | | | | | | |
| Mean (SD) | 7.2 (1.38) | 7.4 (1.38) | 7.4 (1.57) | 7.5 (1.57) | 7.4 (1.51) | 7.4 (1.48) |
| Median | 7 | 7 | 7 | 7 | 7 | 7 |
| Min, Max | 4, 10 | 5, 10 | 4, 10 | 5, 10 | 5, 10 | 4, 10 |

Source: Reviewer generated

## 5.5 Efficacy Findings

### 5.5.1 Analgesic Efficacy

#### 5.5.1.1 Study 3001

The results of the Applicant's primary efficacy analysis are shown in Table 15. As shown in the table below, there were higher responder rates (those patients achieving at least a 30% improvement without any rescue pain medication, without early discontinuation, and without reaching the dosing limit) in the oliceridine treatment regimens compared with placebo: 48.7%, 59.4%, and 60.8% in the oliceridine 0.1, 0.35, and 0.5 mg regimens compared with 15.2% for the placebo regimen. The odds of achieving responder status were statistically significantly higher for all the oliceridine treatment regimens compared with the placebo treatment regimen ($p=<0.01$, $p<0.01$, and $p=<0.01$ for oliceridine 0.1, 0.35, and 0.5 mg regimens, respectively), demonstrating superiority over placebo. Similar results were obtained when data were adjusted by the Hochberg multiplicity adjustment. In addition, the odds of achieving responder status were statistically significantly higher for the morphine treatment regimen compared with the placebo treatment regimen ($p<0.01$).

**Table 15: Primary Efficacy Endpoint: 48-Hour Responder Analysis vs Placebo (FAS) (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Responder, n (%) | 12 (15.2%) | 37 (48.7%) | 46.9 (59.4%) | 48 (60.8%) | 48 (63.2%) |
| Odds Ratio vs placebo | | 5.4 | 8.4 | 8.8 | 9.8 |
| 95% CI | | (2.5, 11.7) | (3.9, 18.3) | (4.0, 19.1) | (4.5, 21.6) |
| p-value vs placebo | | <0.01 | <0.01 | <0.01 | <0.01 |
| Superiority vs placebo | | Yes | Yes | Yes | |

Abbreviations: CI=confidence interval
Source: FDA Reviewer

In addition to comparing the oliceridine to placebo, the efficacy results of oliceridine compared to morphine are provided in Table 16. The odds of response were lower for all three doses of oliceridine than morphine, though the differences were not statistically significant ($p=0.08$, $p=0.64$, $p=0.74$ for oliceridine 0.1, 0.35, 0.5 mg regimens, respectively). Similar comparisons in all of the subsequent analyses will be presented.

**Table 16: Efficacy in Comparison to Morphine: 48-Hour Responder Analysis vs Morphine (FAS) (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Responder, n (%) | 12 (15.2%) | 37 (48.7%) | 46.9 (59.4%) | 48 (60.8%) | 48 (63.2%) |
| Odds Ratio vs morphine | 0.10 | 0.55 | 0.86 | 0.89 | |
| 95% CI | (0.05, 0.22) | (0.28, 1.07) | (0.44, 1.66) | (0.46, 1.73) | |
| p-value vs morphine | <0.01 | 0.08 | 0.64 | 0.74 | |
| Morphine superior | Yes | No | No | No | |

Source: FDA Reviewer

As discussed in Section 5.3.3, this endpoint was novel and so it was especially important to conduct additional analyses to examine the contribution of the individual components of the Applicant's responder definition. Analyses will focus primarily on the summed pain intensity difference over time and use of rescue medication.

First are the results of the Applicant's analysis of the SPID48 scores where the last pre-rescue observation is used for all subsequent pain scores, the last observation is carried forward for patients who discontinued due to lack of efficacy, and where the baseline observation is carried forward for patients who discontinued for any reason other than lack of efficacy. There were greater reductions in pain intensity for the oliceridine 0.1, 0.35, and 0.5 mg regimens compared with placebo ($p<0.01$ for all three dose regimens). Morphine also demonstrated greater reductions in pain intensity than placebo ($p<0.01$). The comparison between all three dose regimens of oliceridine and morphine is also shown. Morphine provided statistically significantly greater pain relief than the oliceridine 0.1 mg dose regimen ($p=<0.01$) in this analysis.

**Table 17: SPID48 Pre-Rescue Carried Forward (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | -39.1 (111.18) | 83.4 (140.70) | 104.3 (126.58) | 129.1 (125.97) | 138.9 (124.98) |
| Least-Squares Mean (SE) | -43.79 (13.38) | 83.15 (13.62) | 108.18 (13.37) | 135.33 (13.41) | 141.01 (13.68) |
| LSM Diff. vs placebo (SE) | | 126.94 (19.02) | 151.97 (18.88) | 179.12 (18.94) | 184.80 (19.06) |
| P-value vs placebo | | <0.01 | <0.01 | <0.01 | <0.01 |
| Superiority vs placebo | | Yes | Yes | Yes | |
| LSM Diff. vs morphine (SE) | -184.80 (19.06) | -57.86 (19.20) | -32.83 (19.02) | -5.68 (19.04) | |
| P-value vs morphine | <0.01 | <0.01 | 0.08 | 0.77 | |
| Morphine superior | Yes | Yes | No | No | |

Abbreviations: Diff=difference; LSM=least-squares mean; SD=standard deviation; SE=standard error
Source: Applicant's table 1-1, July 31 IR Response

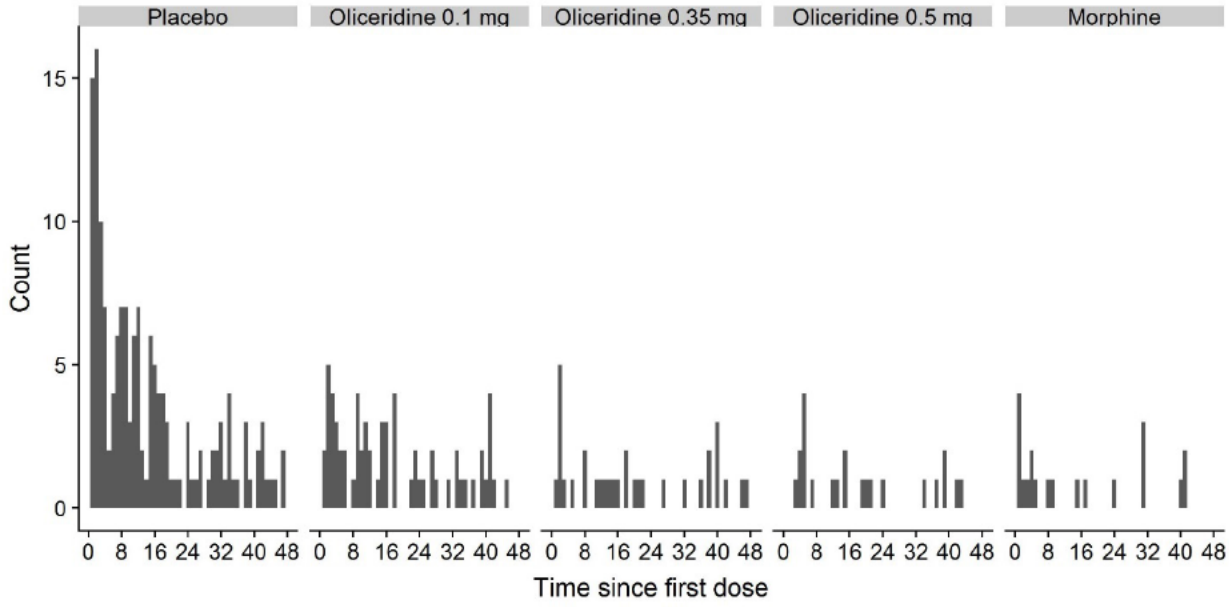
The results in Table 15 and Table 16 depend heavily on the relative patterns of rescue medication use between the different treatment arms. Table 18 shows the number and percentage of patients in each arm who required rescue medications, the mean number of protocol specified (etodolac) doses used and the mean number of other non-protocol specified rescue medication used. The pattern of rescue medication use over time is shown in Figure 4. The percent of patients with rescue medication use was highest in the placebo group and lowest in the morphine group. When comparing the oliceridine treatment arms, there was a dose-response relationship between increasing oliceridine dose and decreasing rescue medication use. The majority of the rescue medication use was in the first 24 hours with a clear decline over time, particularly for placebo.

**Table 18: Rescue Medication Usage (Study 3001)**

| Treatment Arm | Number (%) of patients with any rescue usage | Mean (SD) Number of Etodolac Doses | Mean Number of Non-Protocol Specified Rescue Doses |
|---|---|---|---|
| Placebo | 62/79 (78.5%) | 1.44 (1.47) | 0.54 (2.00) |
| Oliceridine 0.1 mg | 31/76 (40.8%) | 0.78 (1.30) | 0.09 (0.59) |
| Oliceridine 0.35 mg | 18/79 (22.8%) | 0.37 (0.89) | 0.05 (0.27) |
| Oliceridine 0.5 mg | 15/79 (19%) | 0.24 (0.63) | 0.04 (0.19) |
| Morphine | 11/79 (14.5%) | 0.21 (0.66) | 0.05 (0.32) |

Source: FDA Reviewer

**Figure 4: Rescue Usage over Time (Study 3001)**




Source: FDA Reviewer

The types of rescue medication used in this study are shown in Table 19. Etodolac, the protocol specified rescue medication was the most commonly used, but approximately 16% of the rescue medication used was not protocol specified.

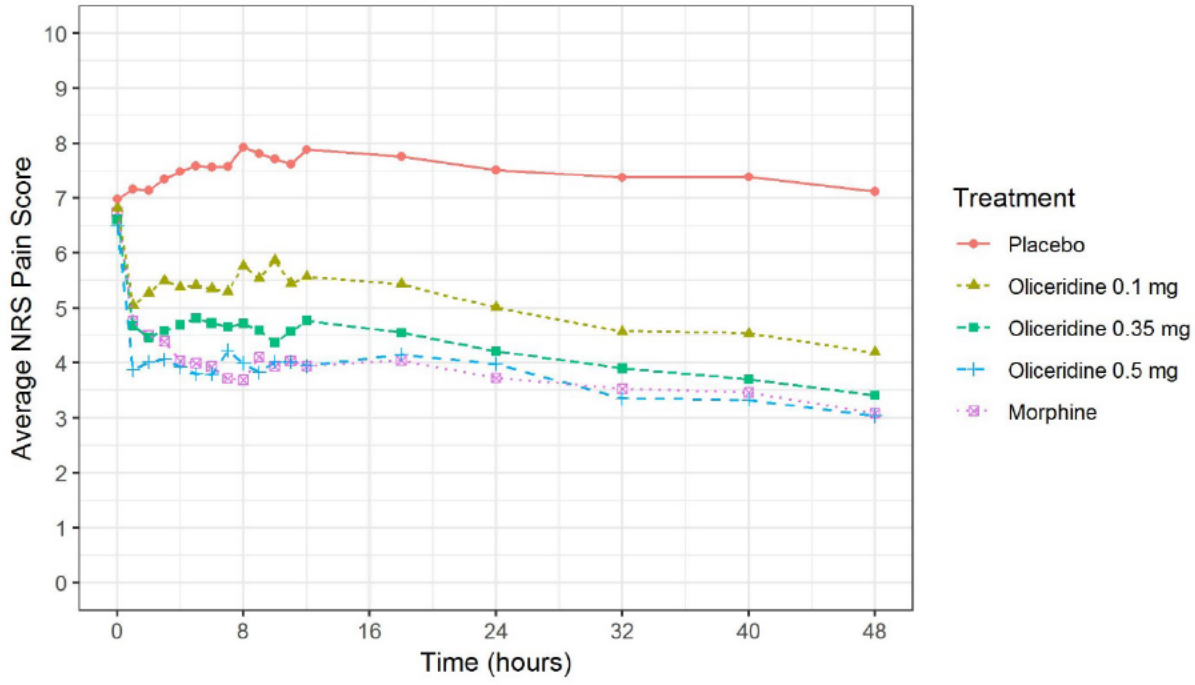
**Table 19: Rescue Medication Breakdown (Study 3001)**

| Rescue Medication | Number of Doses |
|---|---|
| Etodolac (Protocol Specified) | 236 |
| Ibuprofen | 14 |
| Oxycodone | 9 |
| Hydrocodone/APAP 5/325 mg | 9 |
| Hydrocodone/APAP | 6 |
| Hydrocodone/APAP 7.5/325 mg | 3 |
| APAP | 1 |
| Ketorolac | 1 |
| Hydrocodone/APAP 5/300 mg | 1 |

Abbreviation: APAP=acetaminophen
Source: FDA Reviewer

In analyzing the analgesic efficacy, it is important to understand how pain changes over time. Figure 5 shows the average NRS pain score over time where the pre-rescue score is used for all post-rescue pain scores as in the Applicant's SPID48 analysis in Table 15. There is a clear difference between the pain scores reported by the placebo patients compared to all other treatment regimens. There is also a clear dose-response for oliceridine, with greater pain reductions for the patients in the higher dose regimens.

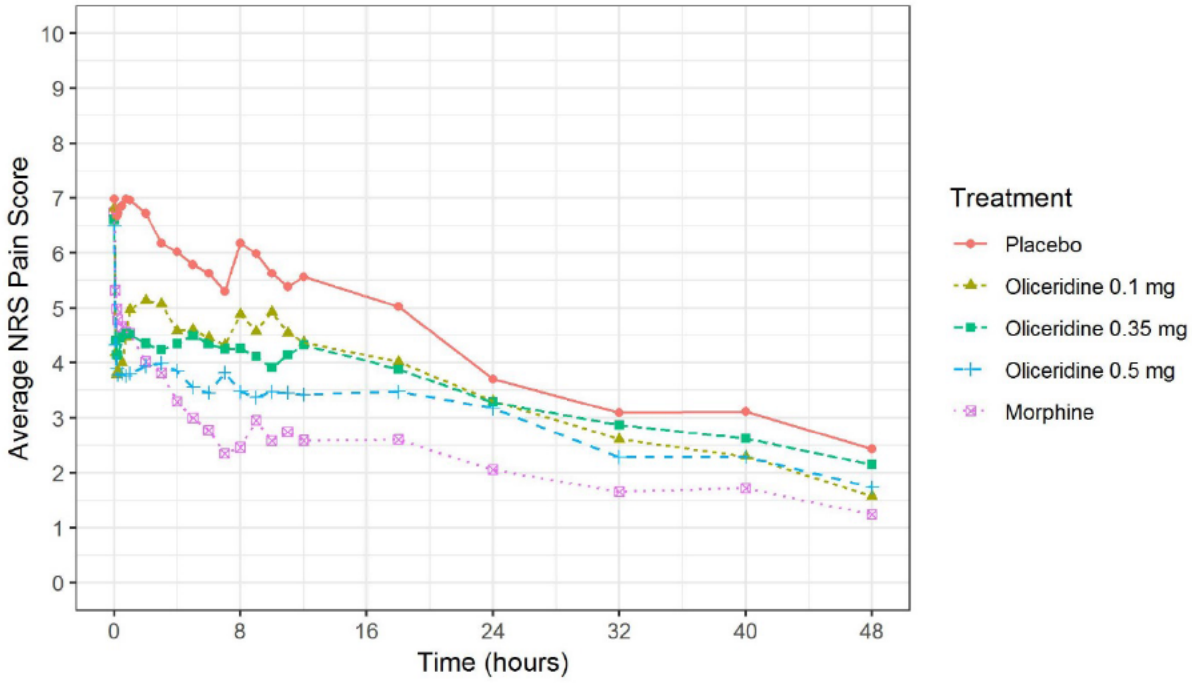
**Figure 5: Average NRS Pain Score Over Time with Post-Rescue Imputation (Study 3001)**




Source: FDA Reviewer

The average observed NRS pain score over time without any imputation is shown in Figure 6. Most of the difference in treatments occurs in the first 24 hours with a relatively small separation between treatment arms after this time.

**Figure 6: Average NRS Pain Score Over Time without Post-Rescue Imputation (Study 3001)**




Source: FDA Reviewer

Table 20 shows an analysis of the SPID48 scores of the data illustrated in Figure 6. In this analysis, there was no imputation following use of rescue. The objective of this analysis is compare the treatment outcomes without regard for rescue use. All three dose regimens of oliceridine provided greater pain relief than placebo ($p=0.02$, $p=0.01$, $p<0.01$ for oliceridine 0.1, 0.35, 0.5 mg, respectively). In this analysis morphine is superior to placebo ($p<0.01$) and all three doses of oliceridine ($p<0.01$, $p<0.01$, $p=0.03$ for oliceridine 0.1, 0.35, 0.5 mg, respectively).

**Table 20: SPID48 No Imputation Following Rescue (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | 115.8 (91.96) | 142.1 (96.19) | 139.3 (89.23) | 159.5 (96.38) | 193.2 (89.23) |
| Least-Squares Mean (SE) | 110.3 (9.02) | 141.2 (9.19) | 143.4 (9.02) | 167.2 (9.05) | 195.3 (9.23) |
| LSM Diff. vs placebo (SE) | | 30.9 (12.85) | 33.1 (12.73) | 56.9 (12.76) | 85.0 (12.85) |
| P-value vs placebo | | 0.02 | <0.01 | <0.01 | <0.01 |
| Superiority vs placebo | | Yes | Yes | Yes | |
| LSM Diff. vs morphine (SE) | -85.0 (12.85) | -54.1 (12.95) | -51.9 (12.84) | -28.1 (12.85) | |
| P-value vs morphine | <0.01 | <0.01 | <0.01 | 0.03 | |
| Morphine superior | Yes | Yes | Yes | Yes | |

Abbreviations: Diff=difference; LSM=least-squares mean; SD=standard deviation; SE=standard error
Source: FDA Reviewer

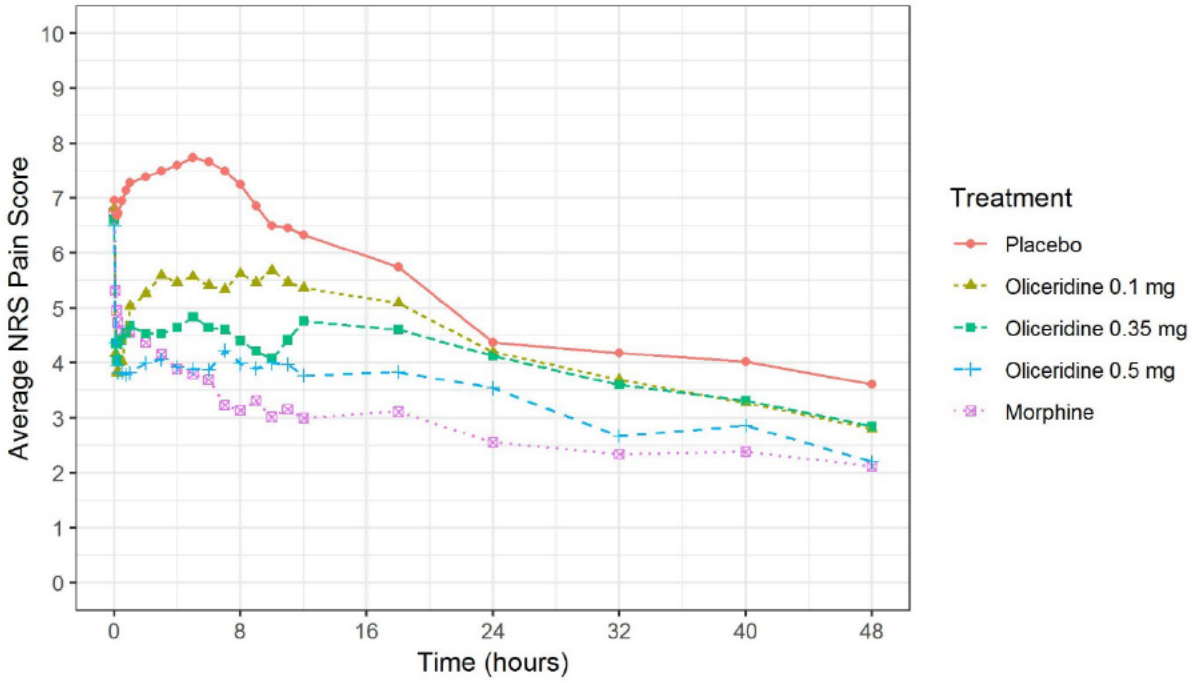
The final efficacy analysis that for Study 3001is considered the most clinically relevant and the results are shown in Table 21. In this analysis, the pre-rescue scores are carried forward for 6 hours following the use of rescue. This analysis is intended to evaluate what the pain scores would have been had rescue medication not been available. This type of analysis is commonly used in trials of analgesics in post-surgical settings and was proposed by the Applicant at the End-of-Phase 2 meeting (See Section 1.1). Consistent with the previous analyses, oliceridine and morphine demonstrated significantly greater pain relief than placebo ($p<0.01$, for all three dose regimens of oliceridine and morphine, respectively). In this analysis, morphine demonstrated superior pain relief to all three doses of oliceridine ($p<0.01$, $p<0.01$, $p=0.03$, respectively). Sensitivity analyses with varying window lengths are shown in the Appendix in Table 54 -Table 56. Average NRS pain scores over time with pre-rescue scores carried forward 6 hours are shown in Figure 7.

**Table 21: SPID48 Pre-Rescue Scores Carried Forward 6 hours (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | 90.1 (94.5) | 132.0 (102.3) | 133.9 (104.6) | 156.0 (100.1) | 190.3 (90.6) |
| Least-Squares Mean (SE) | 85.0 (9.50) | 131.6 (9.68) | 138.1 (9.50) | 163.7 (9.53) | 192.6 (9.72) |
| LSM Diff. vs Placebo (SE) | | 46.4 (13.51) | 53.1 (13.41) | 78.7 (13.44) | 107.6 (13.54) |
| P-value vs placebo | | <0.01 | <0.01 | <0.01 | <0.01 |
| Superiority vs placebo | | Yes | Yes | Yes | |
| LSM Diff. vs Morphine (SE) | -107.6 (13.54) | -61.1 (13.65) | -54.5 (13.52) | -28.9 (13.53) | |
| P-value vs Morphine | <0.01 | <0.01 | <0.01 | 0.03 | |
| Morphine Superior | Yes | Yes | Yes | Yes | |

Abbreviations: Diff=difference; LSM=least-squares mean; SD=standard deviation; SE=standard error
Source: FDA Reviewer

**Figure 7: Average NRS Pain Score Over Time with Pre-Rescue Scores Carried Forward 6 hours (Study 3001)**




Source: FDA Reviewer

Analyses of this endpoint for the demographic subgroups (age, sex, and race) are shown in the Appendix in Table 64 and Figure 22-Figure 24.

### 5.5.1.2 Study 3002

As Study 3002 utilized a similar design to Study 3001, the Applicant analyzed Study 3002 using the same analysis methodology as Study 3001.

Table 22 contains the results of the Applicant's primary analysis for Study 3002. There were a significantly greater number of responders for all three doses of oliceridine and morphine than placebo ($p=0.03$, $p<0.01$, $p<0.01$, $p<0.01$ for oliceridine 0.1, 0.35, 0.5 mg and morphine, respectively).

**Table 22: Primary Efficacy Endpoint: 24-Hour Responder Analysis vs Placebo (FAS) (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| Responder, n (%) | 33.1 (40.9%) | 44.3 (57.5%) | 55.8 (69.8%) | 53.7 (67.1%) | 61.7 (74.4%) |
| Odds Ratio vs placebo | | 2.2 | 4.2 | 3.7 | 5.3 |
| 95% CI | | (1.1, 4.4) | (2.1, 8.6) | (1.8, 7.6) | (2.6, 11.0) |
| P-value vs placebo | | 0.03 | <0.01 | <0.01 | <0.01 |
| Superiority vs placebo | | Yes | Yes | Yes | Yes |

Source: FDA Reviewer

In addition to comparing oliceridine to placebo, the efficacy results of oliceridine compared to morphine are provided in Table 23. The odds of response were significantly lower for the 0.1 mg oliceridine dose regimen (p=0.02) and numerically, but not significantly lower for the 0.35 and 0.5 mg oliceridine dose regimens (p=0.54 and p=0.36 for 0.35 and 0.5 mg, respectively).

**Table 23: Efficacy in Comparison to Morphine: 48-Hour Responder Analysis vs Morphine (FAS) (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| Responder, n (%) | 33.1 (40.9%) | 44.3 (57.5%) | 55.8 (69.8%) | 53.7 (67.1%) | 61.7 (74.4%) |
| Odds Ratio vs morphine | 0.19 | 0.42 | 0.79 | 0.71 | |
| 95% CI | (0.09, 0.39) | (0.20, 0.87) | (0.38, 1.67) | (0.34, 1.48) | |
| P-value vs morphine | <0.01 | 0.02 | 0.54 | 0.36 | |
| Morphine superior | Yes | Yes | No | No | |

Source: FDA Reviewer

With the exception of the length of the double-blind portion of the study (24 hours instead of 48 hours), this study used the same responder definition as Study 3001 and has the same issues previously discussed. Consequently, the same additional analyses used in Section 5.5.1.1 were explored for Study 3001. These analyses focus on the components of the Applicant's responder definition, particularly the summed pain intensity over time and use of rescue medication.

The Applicant's analysis of the SPID24 endpoint carries forward pre-rescue scores for all post-rescue pain scores. In this analysis, all three doses of oliceridine and morphine demonstrated significantly greater pain relief than placebo (p=0.01, p<0.01, p<0.01, p<0.01 for oliceridine 0.1, 0.35, 0.5 mg and morphine, respectively). Morphine also demonstrated significantly greater pain relief than oliceridine 0.1 mg (p<0.01).

**Table 24: SPID24 Pre-Rescue Carried Forward (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| Mean (SD) | 36.2 (56.54) | 58.6 (58.96) | 78.2 (54.05) | 79.9 (52.96) | 88.0 (59.60) |
| Least-Squares Mean (SE) | 42.90 (6.13) | 64.09 (6.26) | 83.11 (6.12) | 84.92 (6.15) | 94.04 (6.08) |
| LSM Diff. vs placebo (SE) | | 21.19 (8.38) | 40.21 (8.30) | 42.02 (8.31) | 51.14 (8.22) |
| P-value vs placebo | | 0.01 | <0.01 | <0.01 | <0.01 |
| Superiority vs placebo | | Yes | Yes | Yes | |
| LSM Diff. vs morphine (SE) | -51.14 (8.22) | -29.94 (8.33) | -10.93 (8.25) | -9.11 (8.26) | |
| P-value vs morphine | <0.01 | <0.01 | 0.19 | 0.27 | |
| Morphine superior | Yes | Yes | No | No | |

Abbreviations: Diff=difference; LSM=least-squares mean; SD=standard deviation; SE=standard error
Source: FDA Reviewer

The percentage of patients using rescue and the mean (SD) number of protocol specified (etodolac) and non-protocol specified rescue medication is summarized in Table 25. There were fewer patients using rescue medication in this study than in Study 3001. Similar to Study 3001, the percent of patients with rescue medication usage was highest for placebo (44.4%) and lowest for morphine (14.5%). When comparing the oliceridine treatment arms, there was a dose-response relationship between increased oliceridine dose and decreased percentage of patients with any rescue medication use.

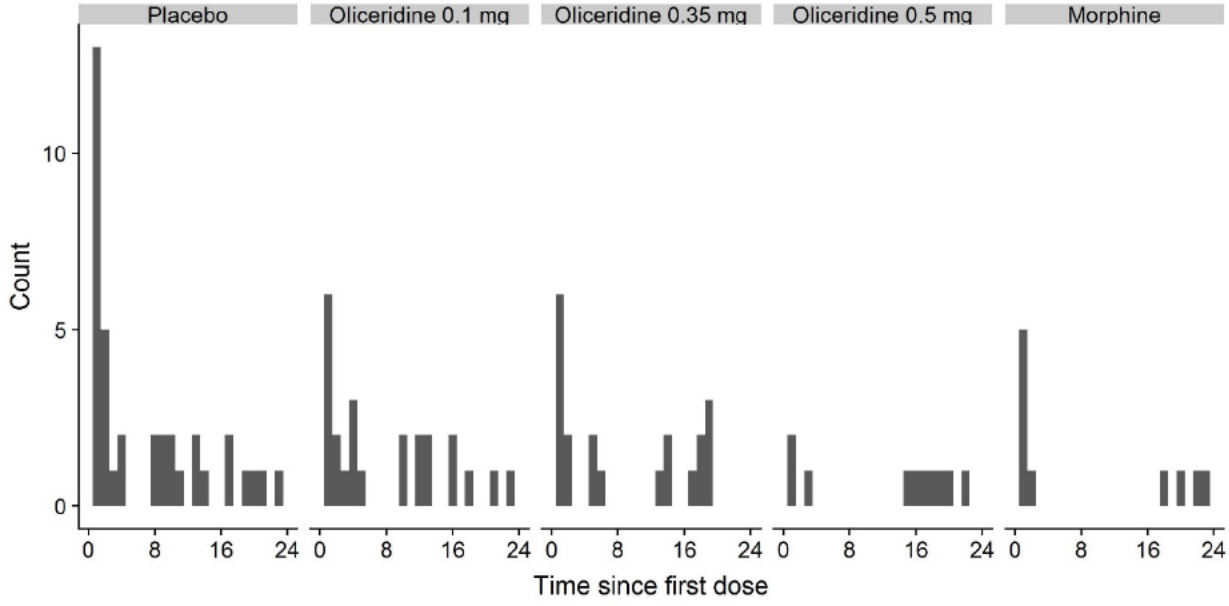
**Table 25: Rescue Medication Usage (Study 3002)**

| Treatment Arm | Number (%) of patients with any rescue usage | Mean (SD) Number of Etodolac Doses | Mean (SD) Number of Non-Protocol Specified Rescue Doses |
|---|---|---|---|
| Placebo | 36/81 (44.4%) | 0.58 (0.82) | 0.01 (0.11) |
| Oliceridine 0.1 mg | 22/77 (28.6%) | 0.33 (0.64) | 0.03 (0.16) |
| Oliceridine 0.35 mg | 16/80 (20%) | 0.18 (0.47) | 0.08 (0.31) |
| Oliceridine 0.5 mg | 13/80 (16.2%) | 0.12 (0.33) | 0.05 (0.27) |
| Morphine | 12/83 (14.5%) | 0.11 (0.31) | 0.04 (0.19) |

Source: FDA Reviewer

Figure 8 shows the rescue medication usage over time. Rescue use was highest in the first 2 hours then decreased rapidly. Again, placebo used more rescue medication than any other treatment arm.

**Figure 8: Rescue Usage over Time (Study 3002)**




Source: FDA Reviewer

The types of rescue medication used are shown in Table 26. The majority of rescue medication used in the study was etodolac. Approximately 15% of the rescue medication was

non-protocol specified.

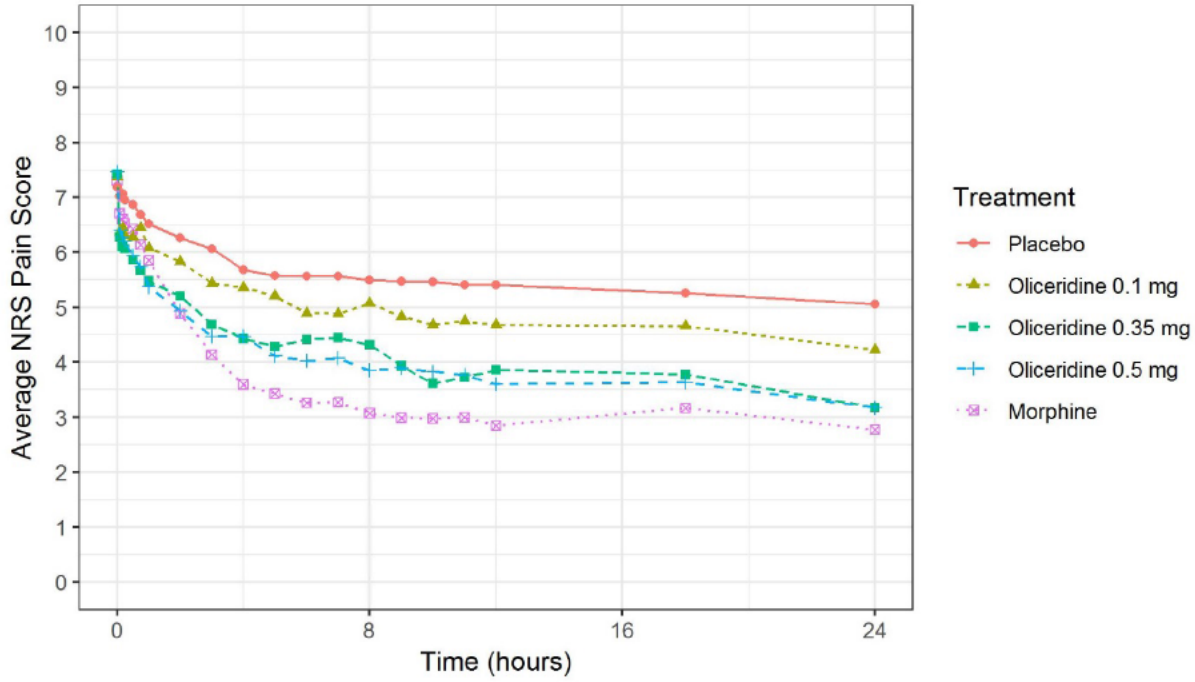
**Table 26: Rescue Medication Breakdown (Study 3001)**

| Rescue Medication | Number of Doses |
|---|---|
| Etodolac (protocol specified) | 105 |
| Hydrocodone/APAP 5/325mg | 7 |
| APAP | 5 |
| Hydrocodone/APAP | 3 |
| Oxycodone | 3 |
| Hydrocodone/APAP 5/300 mg | 1 |

Abbreviations: APAP=acetaminophen
Source: FDA Reviewer

The average NRS pain score over time with the post-rescue imputation is shown in Figure 9. There is a clear difference between placebo and the other treatment arms. There is also a clear difference between the oliceridine 0.1 mg dose regimen compared with the other two oliceridine doses and morphine.

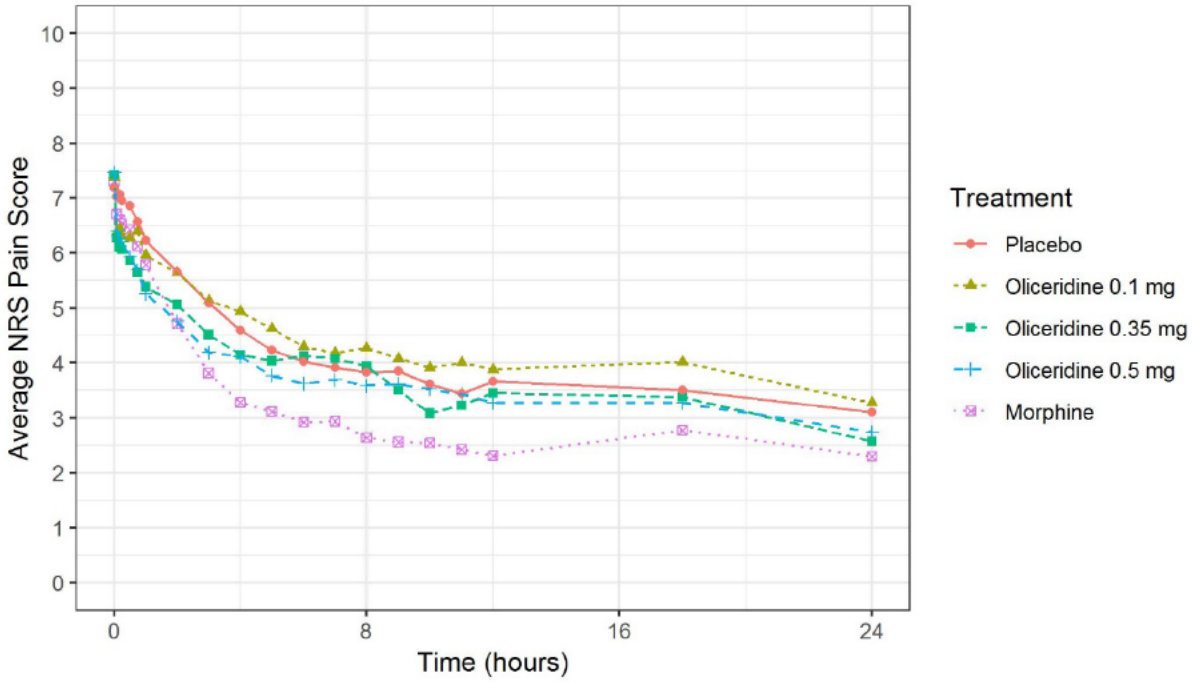
**Figure 9: Average NRS Pain Score Over Time with Post-Rescue Imputation (Study 3002)**




Source: FDA Reviewer

The observed pain scores over time without imputation following rescue are shown in Figure 10. In this figure the benefit of all the oliceridine dose regimens over placebo is no longer apparent, with placebo patients reporting on average lower pain scores than the oliceridine 0.1 mg dose for the majority of the study duration.

**Figure 10: Average NRS Pain Score Over Time without Post-Rescue Imputation (Study 3002)**




Source: FDA Reviewer

The SPID analysis corresponding to Figure 10 is shown in Table 27. In this analysis, observed pain score are used where available. Intermittent missing data was imputed using linear interpolation and post-discontinuation data was imputed using the same methodology as the Applicant's SPID analysis. After adjusting for multiple comparisons none of the oliceridine doses provided significantly greater pain relief than placebo (p=0.64, p=0.12, p=0.05 for oliceridine 0.1, 0.35, 0.5 mg. Significance threshold: 0.0167). In contrast, morphine provided statistically significantly greater pain relief compared to placebo.

**Table 27: SPID24 No Imputation Following Rescue (Study 3002)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | | | | | |
| Least-Squares Mean (SE) | 82.4 (4.36) | 79.6 (4.45) | 91.6 (4.39) | 94.3 (4.41) | 103.9 (4.32) |
| LSM Diff. vs placebo (SE) | | -2.8 (5.92) | 9.2 (5.91) | 11.9 (5.93) | 21.5 (5.83) |
| P-value vs placebo* | | 0.64 | 0.12 | 0.05* | <0.01 |
| Superiority vs placebo | | No | No | No | |
| LSM Diff. vs morphine (SE) | -21.5 (5.83) | -24.3 (5.88) | -12.33 (5.87) | -9.6 (5.89) | |
| P-value vs morphine | <0.01 | <0.01 | 0.04 | 0.10 | |
| Morphine superior | Yes | Yes | Yes | No | |

Abbreviations: Diff=difference; LSM=least-squares mean; SD=standard deviation; SE=standard error
*Using the Hochberg method gives a threshold of 0.0167 for significance
Source: FDA Reviewer

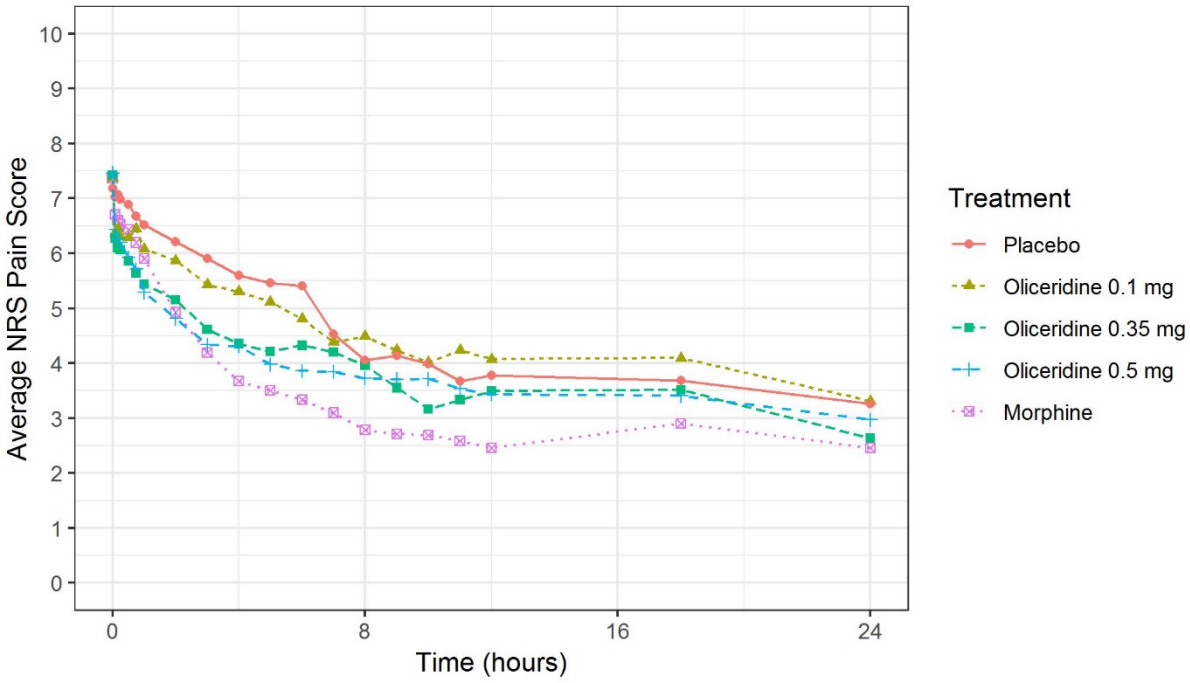
The results of final analysis, considered the most clinically relevant, are shown in Table 28. In this analysis, the pre-rescue pain scores are carried forward for six hours following rescue. In this analysis oliceridine 0.35 and 0.5 mg both provided statistically significantly greater pain relief than placebo ($p=0.017$, $p<0.01$ for oliceridine 0.35 and 0.5 mg, respectively. Significance threshold: 0.025) while oliceridine 0.1 mg did not ($p=0.7514$). Morphine provided significantly greater pain relief than placebo ($p<0.01$). Morphine also provided significantly greater pain relief than oliceridine 0.1 and 0.35 mg in this analysis ($p<0.01$, $p=0.03$ for oliceridine 0.1 and 0.35 mg, respectively). Sensitivity analyses with varying window lengths are shown in the Appendix in Table 57-Table 59. The average NRS pain score over time with pre-rescue scores carried forward 6 hours is shown in Figure 11.

**Table 28: SPID24 Pre-Rescue Scores Carried Forward 6 hours (Study 3002)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | 70.4 (37.9) | 74.4 (45.4) | 88.0 (44.5) | 93.3 (41.9) | 100.6 (48.6) |
| Least-Squares Mean (SE) | 74.8 (4.56) | 76.8 (4.66) | 89.72 (4.6) | 94.0 (4.61) | 103.0 (4.52) |
| LSM Diff. vs placebo (SE) | | 2.0 (6.20) | 14.9 (6.18) | 19.2 (6.21) | 28.1 (6.11) |
| P-value vs placebo* | | 0.75 | 0.017 | <0.01 | <0.01 |
| Superiority vs placebo | | No | Yes | Yes | |
| LSM Diff. vs morphine (SE) | -28.1 (6.11) | -26.2 (6.16) | -13.24 (6.14) | -8.9 (6.17) | |
| P-value vs morphine | <0.01 | <0.01 | 0.03 | 0.15 | |
| Morphine superior? | Yes | Yes | Yes | No | |

Abbreviations: Diff=difference; LSM=least-squares mean; SD=standard deviation; SE=standard error
*Using the Hochberg method gives a threshold of 0.025 for significance
Source: FDA Reviewer

**Figure 11: Average NRS Pain Score Over Time with Pre-Rescue Scores Carried Forward 6 hours (Study 3002)**




Source: FDA Reviewer

Analyses of this endpoint for the demographic subgroups (age, sex, and race) are shown in the Appendix in Table 65 and Figure 25-Figure 27.

## 5.5.2 Respiratory Safety Burden

As background, opioids can cause serious, life-threatening, and potentially fatal respiratory depression. Thus, assessment of respiratory safety is an important consideration during development.

Based on oliceridine's mechanism of action, the Applicant hypothesizes that it may be associated with less respiratory depression than other opioids. The Applicant pre-specified a safety endpoint referred to as respiratory safety burden to assess the respiratory safety of oliceridine compared to morphine and placebo. However, FDA did not agree with the Applicant's proposal to evaluate respiratory safety based on respiratory safety events (RSEs) or respiratory safety burden as discussed in Section 1.1. A significant Agency concern was whether the Applicant's definition of an RSE or a small change in RSE was clinically meaningful.

For each study the Applicant's results for this pre-specified analysis are provided with the limitations in this endpoint noted. Additional secondary analyses were performed with additional endpoints, such as proportion of patients with any use of supplemental $O_2$ or cumulative duration of supplemental $O_2$ administration. These analyses also have limitations

in terms of the assessment of respiratory safety, but were consistent with the other analyses. In addition to these statistical analyses, respiratory safety was considered in the safety review of adverse events (See Section 6). Of note, the Applicant performed study 1003, which assessed ventilatory response to hypercapnia and cold pain testing in healthy volunteers. The Agency considers this study to be a proof-of-concept study that is not adequate to provide regulatory support for a respiratory safety claim.

### 5.5.2.1 Study 3001

The results of the analysis of the expected cumulative duration of RSEs are shown in Table 29. After the multiplicity adjustment, none of the oliceridine treatment arms demonstrated significant reduction in the expected cumulative duration of respiratory safety events compared to morphine.

**Table 29: Expected Cumulative Duration of Respiratory Safety Events (hours) (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | 0 (0) | 0.04 (0.33) | 0.28 (1.11) | 0.80 (3.33) | 1.10 (3.03) |
| Maximum | 0 | 2.88 | 6.43 | 24.4 | 16.6 |
| Model-based estimate (95% CI) | - | 0.02 (-0.03, 0.06) | 0.15 (-0.02, 0.32) | 0.25 (0.01, 0.48) | 0.55 (0.08, 1.02) |
| Diff vs morphine (95% CI) | - | -0.53 (-0.99, -0.07) | -0.40 (-0.84, 0.04)) | -0.30 (-0.75, 0.14) | |
| P-value vs morphine* | - | 0.0241 | 0.0733 | 0.1786 | |

Source: FDA Reviewer
*Using the Hochberg method gives a threshold of 0.0167 for significance

In addition to the analysis of the cumulative duration of events, the results of the analysis of the proportion of patients with any RSEs for Study 3001are provided in Table 30. A smaller proportion of patients in the oliceridine 0.1 mg had respiratory safety events (RSEs) than patients receiving morphine ($p<0.01$), however these safety results are not felt to be clinically relevant given that patients in the 0.1 mg dose regimen reported statistically significantly less pain reduction than patients receiving morphine. Neither of the other two oliceridine dose regimens (0.35 and 0.5 mg) demonstrated a significant reduction in the proportion of patients with RSEs compared to morphine.

**Table 30: Proportion with any Respiratory Safety Events (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| n (%) | 0 | 1 (1.3) | 7 (8.9) | 11 (13.9) | 14 (18.4) |
| Model-based estimate (95% CI) | 0.00 (-0.00, 0.01) | 0.01 (-0.01, 0.02) | 0.04 (0.00, 0.08) | 0.07 (0.01, 0.13) | 0.11 (0.03, 0.19) |
| Odds Ratio vs morphine (95% CI) | 0.02 (0.00, 0.34) | 0.07 (0.01, 0.39) | 0.38 (0.14, 1.00) | 0.66 (0.28, 1.61) | |
| P-value vs morphine* | <0.01 | <0.01 | 0.05 | 0.36 | |

Source: FDA Reviewer

*Using the Hochberg method gives a threshold of 0.0167 for significance

Similar analyses of the supplemental oxygen usage are shown in the Appendix in Table 60 and Table 61.

### 5.5.2.2 Study 3002

Similar analyses were performed for Study 3002. Table 31 shows the analyses of the cumulative duration of RSEs and Table 32 shows the results of the analysis of the proportion of patients who experienced any RSEs. After the multiplicity adjustment, none of the oliceridine treatment arms demonstrated significant reduction in the expected cumulative duration of respiratory safety events compared to morphine. The results for the proportion of patients with any respiratory safety events were similar to Study 3001 and need to be considered in the context of the efficacy of these doses compared to morphine.

**Table 31: Expected Cumulative Duration of Respiratory Safety Events (hours) (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| Mean (SD) | 0.60 (2.83) | 0.43 (1.56) | 1.48 (3.83) | 1.59 (4.26) | 1.72 (3.86) |
| Maximum | 21.1 | 7.1 | 16.2 | 19.8 | 18.0 |
| Model-based estimate (95% CI) | 0.13 (-0.03, 0.29) | 0.08 (-0.02, 0.19) | 0.33 (0.05, 0.61) | 0.43 (0.05, 0.82) | 0.51 (0.09, 0.93) |
| Diff vs morphine (95% CI) | -0.38 (-0.76, -0.00) | -0.43 (-0.81, -0.04) | -0.18 (-0.54, 0.18) | -0.08 (-0.46, 0.31) | |
| P-value vs morphine* | 0.05 | 0.03 | 0.33 | 0.70 | |

Source: FDA Reviewer
*Using the Hochberg method gives a threshold of 0.0167 for significance

**Table 32: Proportion with any Respiratory Safety Events (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| n (%) | 5 (6.0) | 6 (7.8) | 17 (21.5) | 18 (22.5) | 22 (26.8) |
| Model-based estimate (95% CI) | 0.03 (0.00, 0.06) | 0.04 (0.00, 0.07) | 0.11 (0.04, 0.19) | 0.13 (0.04, 0.21) | 0.16 (0.06, 0.25) |
| Odds Ratio vs morphine (95% CI) | 0.17 (0.06, 0.47) | 0.20 (0.08, 0.54) | 0.67 (0.31, 1.44) | 0.77 (0.36, 1.65) | |
| P-value vs morphine* | <0.01 | <0.01 | 0.30 | 0.50 | |

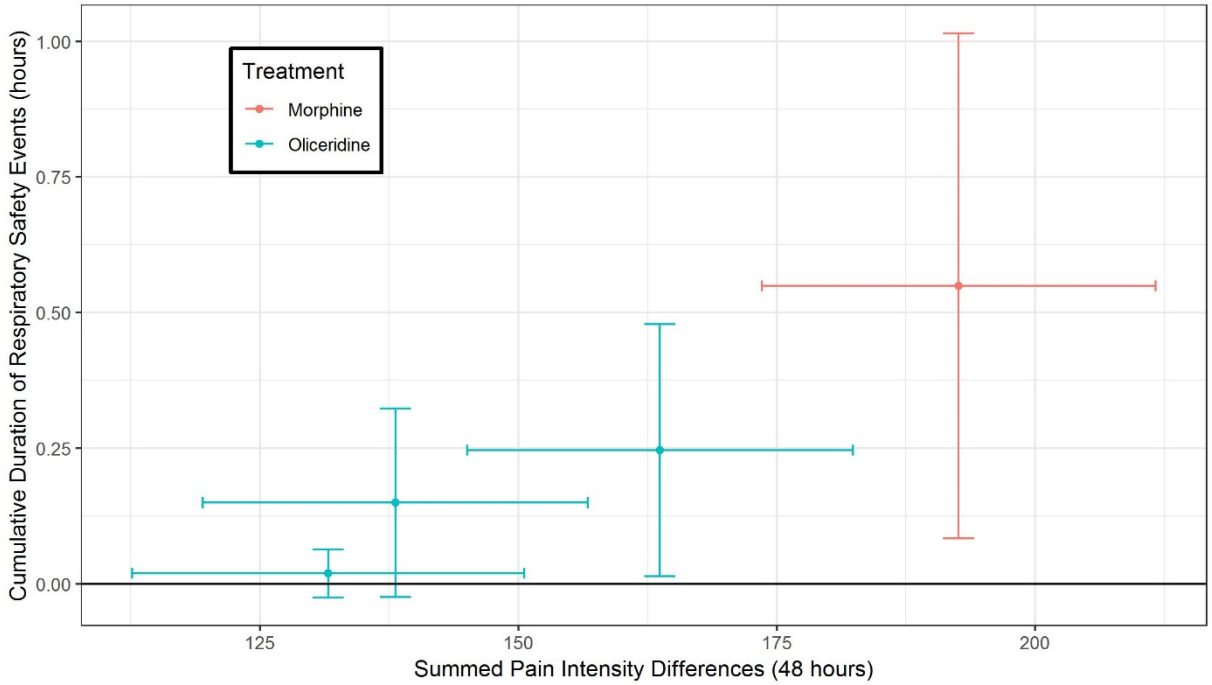
Source: FDA Reviewer
*Using the Hochberg method gives a threshold of 0.0167 for significance

Similar analyses of the supplemental oxygen usage is shown in the Appendix in Table 62 and Table 63.

## 5.5.3 Quantitative Efficacy/Safety Considerations

A key consideration when comparing the safety of two drugs is whether there is a similar level of efficacy. To explore this, a comparison between the respiratory safety and efficacy was conducted. Figure 12 displays this information for Study 3001. The objective for this plot is to examine the relative dose-response between efficacy and respiratory safety. Since there were no events for placebo the Applicant's analysis method did not produce valid estimates of the cumulative duration of RSEs and so only oliceridine and morphine will be presented. The x-axis of this figure shows the least squares mean estimate of the SPID48 for each treatment group from the analysis (Table 21), with the horizontal bars representing the span of the confidence intervals. The location is determined by the estimated cumulative duration presented in Table 29 with the vertical bars indicating the span of the corresponding confidence intervals. There is a clear correlation between the magnitude of the change in SPID48 score and the cumulative duration of respiratory safety events. Also, while there may be a numerical reduction in the duration of RSEs, there is also a corresponding decrease in the analgesic efficacy with oliceridine.

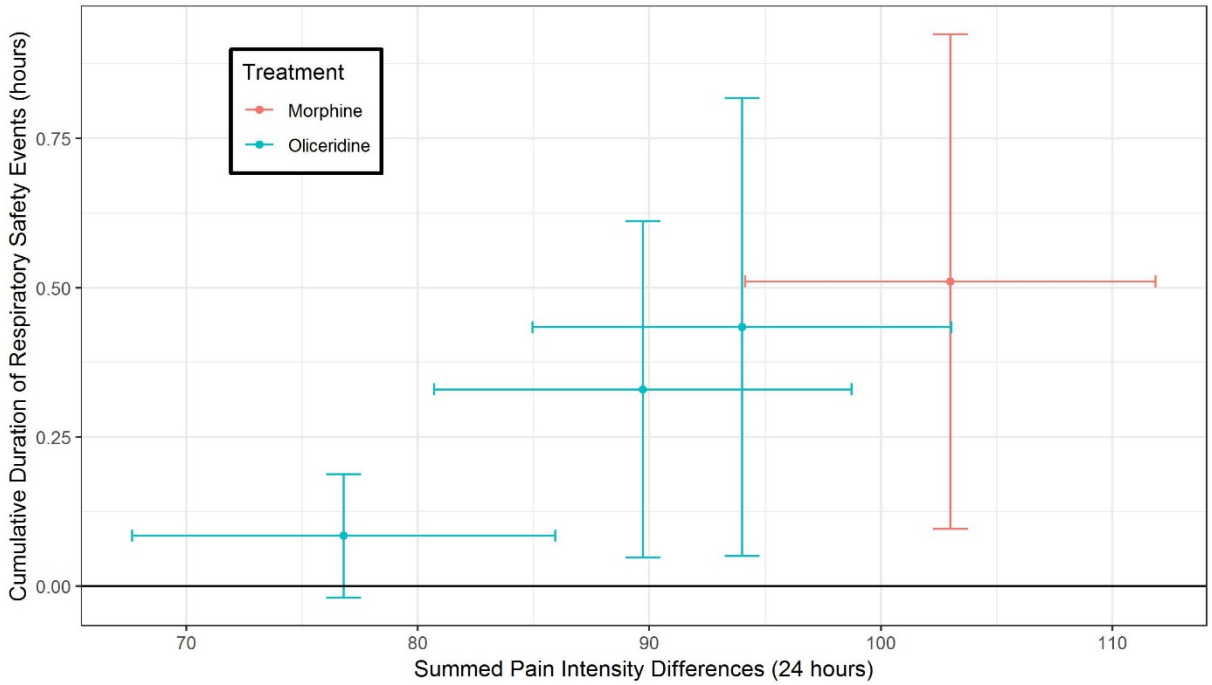
**Figure 12: Respiratory Safety vs Efficacy (Study 3001)**




Source: FDA Reviewer

Figure 13 shows the same presentation of respiratory safety vs analgesic efficacy measured by the SPID24 score from Study 3002. This figure uses the efficacy information from Table 28 for the x-axis and information regarding the cumulative duration of RSEs from Table 31 for the y-axis. There is a clear relationship in the magnitude of change in the SPID score and the cumulative duration of respiratory safety events. The cumulative duration of respiratory safety events for the most efficacious dose regimen of oliceridine (0.5 mg) is relatively close while the reduction in pain is comparatively less than morphine.

**Figure 13: Respiratory Safety vs Efficacy (Study 3002)**




Source: FDA Reviewer

# 6 Safety

## 6.1 Studies contributing to integrated safety analyses and the Applicant's pooling and attribution strategies

A summary of the studies contributing to the safety analyses may be found in Table 2 and Table 3. The primary source of safety data is from the two Phase 3 trials (3001 and 3002) and an open-label, uncontrolled safety study (3003). Additional data are available from two Phase 2 studies (2001 and 2002) and one pilot Phase 2 study (2004). Studies 2001 and 3001 were conducted in patients after bunionectomy, while study 2002 and 3002 were conducted in patients after abdominoplasty. Study 2004 collected data from a single patient with long bone fracture and was subsequently terminated by the sponsor due to lack of enrollment. Study 3003 was an open-label evaluation of oliceridine in medical and surgical patients. In addition, 11 Phase 1 studies evaluated oliceridine in healthy subjects and special populations, but these data are not pooled given important differences in patient populations and dosing.

As noted in Table 2 and Table 3, placebo-controlled periods were limited to 48 hours in studies 2001 and 3001 and 24 hours in studies 2002 and 3002. There was no control arm in Study 3003. At the time of NDA submission, an interim analysis was provided for Study 3003 that included all data through June 12, 2017, reported for all patients entered in the study

electronic data cut-off (EDC) database as of February 13, 2017. The final clinical study report was submitted with the 4-month safety update during review of the NDA.

The analysis of the safety data was complicated by the dosing utilized in the clinical studies. Study 2001 was the only Phase 2 or 3 study that utilized fixed doses. In contrast, the other Phase 2 and Phase 3 studies allowed dose titration, administered as needed (PRN). Study 2002 utilized demand dosing via a PCA and studies 3001, 3002, and 3003 utilized loading doses and demand doses via a PCA and supplemental doses administered by a clinician. Studies 3001 and 3002 utilized the same loading, demand, and supplemental doses, but Studies 2001, 2002, and 3003 utilized different nominal doses and these doses were changed during studies 2001 and 2002. The oliceridine treatment regimens used in Studies 3001 and 3002 consisted of a 1.5 mg loading dose, demand doses of 0.1, 0.35, and 0.5 mg depending on assigned regimen, and a 6-minute lockout interval. In addition, patients could receive supplemental (clinician-administered bolus) doses of 0.75 mg every 1 hour. The morphine treatment regimen in Studies 3001 and 3002 consisted of a 4-mg loading dose, a demand dose of 1 mg, and a 6-minute lockout interval. Patients could receive supplemental morphine doses of 2 mg every 1 hour as needed. In Study 3003, oliceridine could have been administered using clinician-administered bolus dosing, PCA dosing, or both. For clinician-administered bolus dosing, the oliceridine initial loading dose was 1 to 2 mg. If clinically indicated, a 1 mg supplemental dose could have been administered as early as 15 minutes after the initial dose. Subsequent supplemental doses were 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 was targeted (e.g., the emergency department [ED] or post-anesthesia care unit [PACU]), the oliceridine initial dose was 1 to 3 mg. If clinically indicated, 1 to 3 mg supplemental doses could have been administered every 5 minutes PRN. Subsequent doses were 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to oliceridine. For PCA dosing, patients received a 1.5 mg loading dose, 0.5 mg demand dose, and a 6-minute lockout interval. Patients could receive a 1 mg clinician-administered supplemental dose as needed.

The Applicant performed analyses for the individual studies and a variety of pooled populations (Table 33). For the individual controlled Phase 3 studies, the data were analyzed by treatment regimen and by oliceridine cumulative exposure quartile. For pooled analyses, the safety data were analyzed by treatment regimen and/or by oliceridine cumulative exposure quartile, as seen in Table 33. The cumulative dose of study medication was obtained from the loading dose, plus any PCA demand doses, plus any clinician-administered, blinded supplemental doses. The Applicant used cumulative exposure quartiles to account for the fact that treatment assignment to a given oliceridine treatment regimen could have resulted in different exposures.

For open-label study 3003, data were analyzed by the Applicant's pre-defined oliceridine cumulative exposure dose groups of ≤4 mg, >4 to 8 mg, >8 to 16 mg, >16 to 36 mg, and >36 mg. In contrast to the quartile analyses for studies 3001 and 3002, the patients were not evenly distributed into these groups.

For safety analyses, our primary analysis was on the individual studies, rather than the pooled studies, given important differences in the patient populations and study duration. This review

focused primarily on comparisons between oliceridine randomized dose groups, placebo, and morphine in the two controlled Phase 3 studies: 3001 and 3002. For Studies 3001 and 3002, the results are described based on randomized treatment arm (morphine, placebo, oliceridine 0.1 mg, oliceridine 0.35 mg, and oliceridine 0.5 mg). In general, the total oliceridine dose group was not displayed since it is important to consider the safety of the dose groups separately and to consider the safety results in the context of the efficacy results for a specific oliceridine dose. However, if a safety imbalance was noted when evaluating the total oliceridine group for an Agency-identified AE term of interest, such as for liver function test abnormalities, the results were based on placebo, total oliceridine, and morphine treatment arms.

The cumulative exposure quartile analyses from the Pooled Phase 2 and Phase 3 studies are shown for the cumulative exposure analyses. Cumulative exposure quartile analyses are shown only for the oliceridine treatment groups, since not all studies in these pooled analyses had a morphine or placebo group.

It is important to note that there are significant limitations to the safety analyses based on cumulative exposure. As is typical for an opioid, oliceridine was administered as needed, and while this was reasonable, it complicates the safety analyses. Specifically, safety analyses based on total cumulative dose received are difficult to interpret since the dose received is influenced by a variety of factors, such as the amount of pain experienced and the occurrence of adverse events. Given these issues, these safety analyses are exploratory.

**Table 33: Description of Applicant's Pooled Populations**

| Population | Studies Included | Description | Categories presented by Applicant |
|---|---|---|---|
| Controlled Phase 3 | 3001 and 3002 | Placebo- and active-controlled studies | •By treatment regimen (oliceridine 0.1, 0.35, and 0.5 mg)<br>•By oliceridine cumulative exposure quartiles |
| All Phase 3 | 3001, 3002, and 3003 | Phase 3 controlled and open-label studies | •By treatment regimen: placebo, oliceridine, morphine |
| All Phase 2 and Phase 3 | 2001, 2002, 2004, 3001, 3002, and 3003 | Controlled and open-label studies | •By treatment regimen: placebo, oliceridine, morphine<br>•By oliceridine cumulative exposure quartiles |
| Healthy Subjects | 1001, 1002, 1003, 1004, 1005, 1006, 1007, and 1008 | Healthy subjects | Data previously provided in EOP2 briefing package |

Abbreviations: EOP2=end-of-Phase 2
Source: Modified from Integrated Summary of Safety 120 day safety update, Table 3, page 59, submitted 03/05/18

## 6.2 Adequacy of the drug exposure experience (i.e., the safety database)

A total of 1,853 unique subjects have been exposed to oliceridine (221 healthy subjects in Phase 1 studies, 97 special population subjects in Phase 1 studies, and 1,535 patients in Phase 2 and Phase 3 studies). Exposure to study medication for all Phase 2 and Phase 3 studies is shown in Table 34. The mean cumulative exposure to oliceridine was 28.6 mg. The oliceridine cumulative exposure fourth quartile (Q4) from the Phase 2 and 3 studies includes 381 patients with a cumulative mean exposure of 67.3 mg and a cumulative mean duration of 50.1 hours

**Table 34: Exposure to Study Medication by Treatment Regimen (All Phase 2 and Phase 3 Population Safety Analysis)**

| Characteristic | Placebo N=252 | OLI Total N=1535 | Morphine N=305 |
|---|---|---|---|
| **Exposure duration (hours)[a]** | | | |
| Mean (SD) | 28.2 (16.7) | 31.7 (21.5) | 59.4 (501.0) |
| Median | 24.2 | 24.2 | 24.2 |
| Min, max | 0.2, 48.2 | 0, 142.7 | 0, 8777.3[b] |
| **Cumulative exposure (mg)[c]** | | | |
| Mean (SD) | 0 | 28.6 (27.5) | 44.7 (34.6) |
| Median | 0 | 20 | 41 |
| Min, max | 0, 0 | 0.5, 223.5 | 4, 268.0 |

Abbreviations: max=maximum; min=minimum; OLI=oliceridine; SD=standard deviation
a Duration was defined as the difference in total hours from the first dose to the last dose of study medication.
b Maximum duration from Study CP130-2002: Patient 342 of 8777.3 hours (i.e., 365.72 days), likely due to a transcription error.
c Cumulative exposure for oliceridine and morphine was calculated as the sum of the loading dose, the demand doses, and the supplemental doses in mg.
Source: Modified from Integrated Summary of Safety 120-day safety update, Table 16, page 94, submitted 03/05/18

As seen in Table 35, patients assigned to higher oliceridine treatment regimen doses (0.1 mg, 0.35 mg, and 0.5 mg) had higher mean cumulative exposures (14.4, 35.3, and 41.8 mg, respectively). Similarly, patients in the oliceridine 0.1 mg treatment regimen were more likely to be categorized in cumulative exposure Quartile 1 (Q1) or Quartile 2 (Q2) compared to the oliceridine 0.35 mg and 0.5 mg treatment regimens.

Patients in the oliceridine treatment regimen had a greater mean number of demand doses (94.0) compared with the placebo (80.9) and morphine (48.4) regimens. Similarly, patients in the oliceridine treatment regimen had a greater mean number of supplemental doses (1.6) compared with the morphine regimen (0.5), but less than placebo (1.8) (Table 35).

When considering the exposure in the individual, controlled Phase 3 studies, as expected based on treatment duration (48 hours in Study 3001 and 24 hours in Study 3002), the cumulative mean exposures were approximately two-fold higher overall in Study 3001 than Study 3002 for both the oliceridine and morphine regimens. Cumulative mean exposures for the oliceridine treatment regimen were 42.3 and 19.2 mg for Studies 3001 and 3002, respectively.

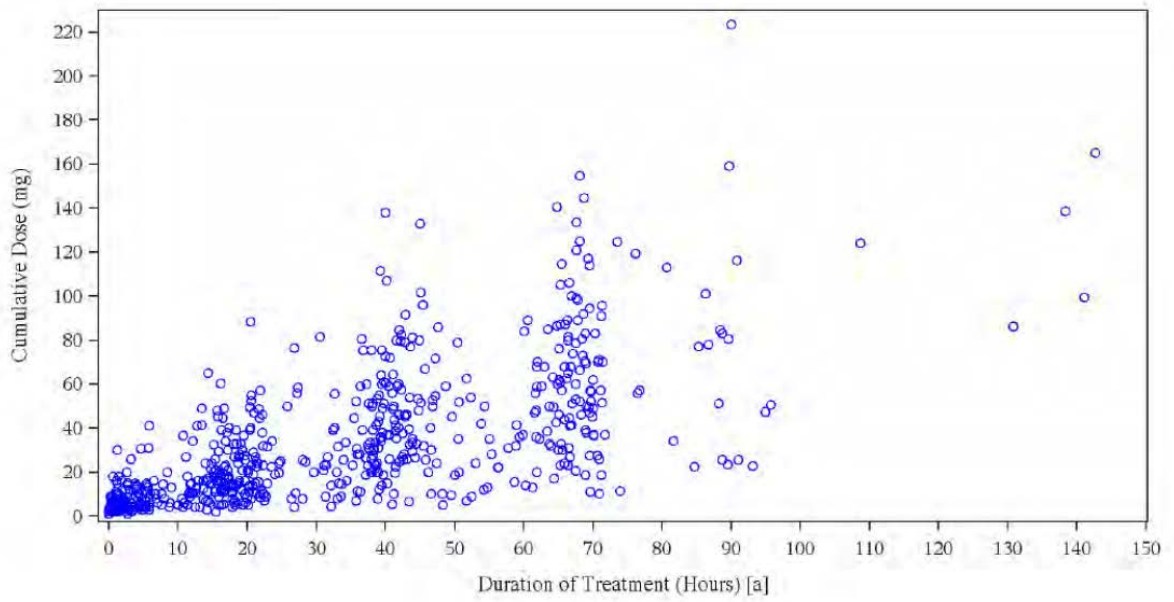
**Table 35: Overall Extent of Exposure by Treatment Regimen (Controlled Phase 3)**

| Characteristic | Placebo N=162 | OLI 0.1mg N=153 | OLI 0.35mg N=158 | OLI 0.5mg N=159 | OLI Total N=470 | Morphine N=158 |
|---|---|---|---|---|---|---|
| **Cumulative exposure (mg)[a]** | | | | | | |
| Mean (SD) | 0 | 14.4 (9.9) | 35.3 (25.5) | 41.8 (31.7) | 30.7 (26.9) | 53.4 (43.7) |
| Median | 0 | 11.3 | 27.4 | 33.4 | 22.2 | 40.0 |
| Min, max | 0, 0 | 1.7, 47.8 | 2.2, 119.7 | 1.5, 159.8 | 1.5, 159.8 | 4.0, 268.0 |
| **Cumulative exposure quartile, n (%)** | | | | | | |
| Q1: 1.5-10.55 | -- | 73 (47.7) | 21 (13.3) | 24 (15.1) | 118 (25.1) | -- |
| Q2: >10.55-22.15 | -- | 50 (32.7) | 40 (25.3) | 26 (16.4) | 116 (24.7) | -- |
| Q3: >22.15-42.625 | -- | 29 (19.0) | 47 (29.7) | 42 (26.4) | 118 (25.1) | -- |
| Q4: >42.625-159.750 | -- | 1 (0.7) | 50 (31.6) | 67 (42.1) | 118 (25.1) | -- |
| **Cumulative exposure (mg) in the first 24 hours[a]** | | | | | | |
| Mean (SD) | 0 | 11.2 (5.7) | 25.6 (14.3) | 30.6 (18.7) | 22.6 (16.2) | 42.1 (27.6) |
| Median | 0 | 10.6 | 24.7 | 28.0 | 18.3 | 34.0 |
| Min, max | 0, 0 | 1.7, 27.3 | 2.2, 65.9 | 1.5, 88.3 | 1.5, 88.3 | 4.0, 131.0 |
| **Total number of demand doses** | | | | | | |
| n | 162 | 153 | 158 | 159 | 470 | 158 |
| Mean (SD) | 80.9 (72.4) | 109.7 (80.1) | 93.8 (69.4) | 79.3 (62.1) | 94.0 (71.7) | 48.4 (42.8) |
| **Total number of supplemental doses** | | | | | | |
| n | 162 | 153 | 158 | 159 | 470 | 158 |
| Mean (SD) | 1.8 (1.9) | 2.6 (3.6) | 1.3 (2.5) | 0.8 (2.1) | 1.6 (2.9) | 0.5 (1.0) |

Abbreviations: max=maximum; min=minimum; OLI=oliceridine; Q=quartile; SD=standard deviation;
a Cumulative exposure for oliceridine and morphine was calculated as the sum of the loading dose, the demand doses, and the supplemental doses in mg.
Source: Modified from Integrated Summary of Safety 120 day safety update, Table 13, page 86-7, submitted 03/05/18

In Study 3003, the median cumulative duration of oliceridine exposure was 20.3 hours (range 0 to 142.7 hours). The median cumulative dose of oliceridine for the patient population was 19.25 mg (range 0.9 to 223.5 mg). The cumulative dose by duration of treatment in Study 3003 is shown in Figure 14.

**Figure 14: Cumulative Dose by Duration of Treatment (Study 3003 Safety Analysis Population)**




Note: Each dot in the graph represents a patient.
[a] Duration was defined as the difference in total hours from the start of the first dose of study medication to the end-time for the last dose of study medication administration.
Data source: ATHENA CSR Figure 2.1

Source: Integrated Summary of Safety 120 day safety update, Figure 4, page 91, submitted 03/05/18

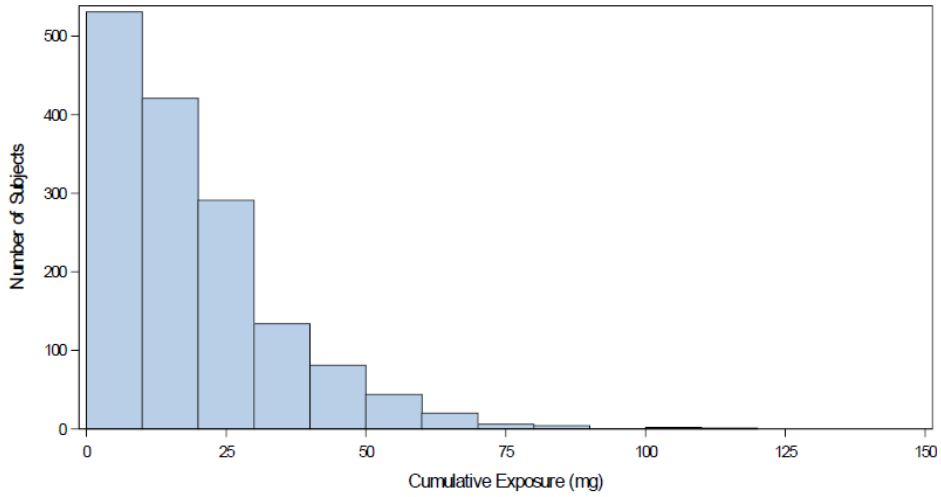
A significant consideration during the review cycle was whether the size of the safety database was adequate. Prior to submission of the NDA, the Applicant was told at the End-of-Phase 2 meeting and the pre-NDA meeting that they would need at least 350 patients exposed to the highest intended doses for the longest expected duration of use.[5] Figure 15 shows the frequency of cumulative exposure to oliceridine for the first 24 hours for the pooled Phase 2 and Phase 3 studies. The data are skewed, with most patients receiving doses less than 75 mg. The Applicant's initially proposed labeling included a maximum daily dose of 100 mg without a limit on the duration of use. The Applicant was asked to clarify the highest dose that has at least 350 patients exposed for 24 hours and the highest dose that has at least 350 patients exposed for the longest actual duration of use. The highest dose that has at least 350 patients exposed during the first 24 hours of dosing was 27 mg of oliceridine. The highest dose with the longest actual duration that has at least 350 patients exposed was 37.2 mg of oliceridine over an actual duration of at least 35.5 hours. During the review cycle, the Applicant reduced the proposed maximum daily dose from 100 mg daily to 40 mg daily to try to address the adequacy of the safety database and nonclinical concerns regarding the adequacy to qualify the major metabolites.

[5] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf

To assess the adequacy of the available clinical and nonclinical data to support the currently proposed dosing regimen, the maximum dose that a patient could receive was taken into consideration. According to the current label, a patient could receive 40 mg per day. Thus, a patient could receive a loading dose of 1.5 mg followed by 0.35 mg approximately every twelve minutes, resulting in a total daily dose of approximately 40 mg. In the current version of the label, the Applicant is not seeking approval of the 0.5 mg dosing regimen.

During the review cycle, Trevena modified the recommended maximum daily dose and dosing instructions in the proposed label several times.

**Figure 15: Frequency of Cumulative Exposure to Oliceridine in the First 24 Hours of the Study (All Phase 2 and Phase 3 Analysis Set)**




Source: IR Reponses, Figure 20180218 1.1.6, submitted 04/30/18

## 6.3 Key safety results, including deaths, serious adverse events (SAEs), discontinuations due to AEs, and other AEs

***Deaths***
There were no deaths in the Phase 1, Phase 2, or Phase 3 studies.

***Serious Adverse Events***
As shown in Table 36, there were no treatment-emergent serious adverse events (SAEs) in Study 3001, and there were five treatment-emergent SAEs in Study 3002. In Study 3002, there were no SAEs in the placebo or oliceridine 0.1 mg treatment arms. The percentage of patients with SAEs was higher in the oliceridine 0.35 mg (1.3%) and oliceridine 0.5 mg (3.8%) compared to morphine (1.2%). When comparing oliceridine doses, there was a dose-response for SAEs in Study 3002.

In the oliceridine treatment arms, the four treatment-emergent SAEs included: post-procedural hemorrhage, syncope, lethargy, and abdominal wall hematoma. The events of post-procedural hemorrhage and abdominal wall hematoma appeared to be post-operative, while the events of syncope and lethargy appeared to be opioid-related. In the morphine treatment arm, the one treatment-emergent SAE was pulmonary embolism and respiratory failure. Note that the Applicant stated that there is a discrepancy between the number of patients who experienced an SAE in study 3002 CSR compared to the ISS because in the CSR, treatment emergence was defined as ending at 7 days after the last dose of study medication whereas in the ISS, treatment emergence was defined as ending at 30 days after the last dose. As a result of the expanded definition in the ISS, one additional patient in the oliceridine 0.5 mg treatment arm was identified who experienced an SAE of deep vein thrombosis.

**Table 36: Serious Adverse Events by Treatment Regimen by Study (3001 and 3002) (FAS)**

| Study 3001 | | | | | |
|---|---|---|---|---|---|
| | **PBO N=79 n (%)** | **OLI 0.1 mg N=76 n (%)** | **OLI 0.35 mg N=79 n (%)** | **OLI 0.5 mg N=79 n (%)** | **Morphine N=76 n (%)** |
| Number of patients with at Least one Serious TEAE | 0 | 0 | 0 | 0 | 0 |
| **Study 3002** | | | | | |
| | **PBO N=83 n (%)** | **OLI 0.1 mg N=77 n (%)** | **OLI 0.35 mg N=79 n (%)** | **OLI 0.5 mg N=80 n (%)** | **Morphine N=82 n (%)** |
| Number of patients with at Least one Serious TEAE | 0 | 0 | 1 (1.3) | 3* (3.8) | 1 (1.2) |

Abbreviations: FAS=full analysis set; OLI=oliceridine; PBO=placebo; TEAE=treatment-emergent adverse event
TEAE were defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication.
*There was one additional SAE in study 3002 (deep vein thrombosis) that occurred more than 7 days after the last dose of study medication identified in the ISS but not included in the CSR due to a difference in the way the Applicant defined TEAEs in the CSR and ISS, making a total of 4 cases in the 0.5 mg treatment arm using the ISS definition of treatment emergence.
Source: Clinical Study Report CP130-3001, Table 29 (page 151-2) and Clinical Study Report CP130-3002, Table 29 (page 143-4), submitted 11/2/17

In Study 3003, 26 patients (3.4%) experienced a total of 32 treatment-emergent SAEs. The percentage of patients with SAEs tended to be similar across oliceridine cumulative dose groups, except for the lowest group, which had the lowest percentage of patients (≤4 mg: 0.6%; >4 to 8 mg: 4.7%; >8 to 16 mg: 4.1%; >16 to 36 mg: 4.2%, and >36 mg: 3.8%). The SAEs in Study 3003 are in Table 37. The Agency found that the SAEs generally fell into three major categories: postoperative adverse events, opioid-related adverse events, and other events, which could have been related to postoperative issues, opioid-related adverse events, other factors, or a combination of factors. The postoperative SAEs involved bleeding and infection, including anemia postoperative, flatulence, post procedural hematoma or hemorrhage (three events total), intra-abdominal hemorrhage, breast hematoma, graft infection, abdominal abscess, and sepsis (one event each). The opioid-associated SAEs included respiratory depression, nausea (two events), and hypoxia. Some SAEs could have been related to either postoperative or opioid-related adverse events or a combination of factors, such as small intestinal obstruction, syncope, mental status change, and postoperative ileus, acute kidney injury, endometrial cancer, hepatic failure/renal failure, pleural effusion,

chronic obstructive pulmonary disease, pulmonary edema, hyponatremia, blood creatinine increased, and atrial fibrillation.

**Table 37: Patients with Treatment-Emergent SAEs in Study 3003**

| # | Patient ID | Age (yrs)/Sex | Cumulative dose group | Cum exp SAE start | Preferred Term | General Category[a] |
|---|---|---|---|---|---|---|
| 1 | (b) (6) | 49/F | ≤4 mg | 2 mg | Respiratory Depression | Opioid-related |
| 2 | | 55/M | >8 to 16 mg | 2.5 mg | Anemia postoperative | Postoperative |
| 3 | | 49/M | >4 to 8 mg | 5 mg | Acute kidney injury | Other |
| 4 | | 57/M | >4 to 8 mg | 6 mg | Small intestinal obstruction | Other |
| 5 | | 34/F | >8 to 16 mg | 6 mg | Flatulence | Postoperative |
| 6 | | 67/F | >4 to 8 mg | 6.5 mg | Post procedural hematoma | Postoperative |
| 7 | | 67/M | >4 to 8 mg | 7 mg | Syncope | Other |
| 8 | | 44/M | >8 to 16 mg | 8 mg | Intra-abdominal hemorrhage | Postoperative |
| 9 | | 49/F | >8 to 16 mg | 12 mg | Endometrial cancer | Other |
| 10 | | 62/F | >8 to 16 mg | 12 mg | Graft infection | Post-operative |
| | | | | | Mental status change | Other |
| 11 | | 55/M | >8 to 16 mg | 14 mg | Postoperative ileus | Other |
| 12 | | 33/F | >36 mg | 16 mg at start of day of SAE; 32.5 mg at end of same day | Post procedural hematoma | Postoperative |
| 13 | | 47/F | >16 to 36 mg | 20.5 mg | Abdominal abscess | Postoperative |
| | | | | | Sepsis | Postoperative |
| 14 | | 51/F | >16 to 36 mg | 21 mg | Post procedural hemorrhage | Postoperative |
| 15 | | 55/M | >16 to 36 mg | 23 mg | Hepatic failure | Other |
| | | | | | Renal failure | Other |
| 16 | | 84/F | >16 to 36 mg | 24 mg | Pleural effusion | Other |
| 17 | | 61/F | >16 to 36 mg | 31 mg | Chronic obstructive pulmonary disease | Other |
| 18 | | 30/F | >16 to 36 mg | 32 mg | Breast hematoma | Postoperative |
| 19 | | 72/F | >16 to 36 mg | 32.8 mg | Pulmonary edema | Other |
| 20 | | 64/M | >36 mg | 34.5 mg | Nausea | Opioid-related |
| 21 | | 70/M | >36 mg | 35.5 mg | Hypoxia | Opioid-related |
| | | | | 41.5 mg | Hyponatremia | Other |
| | | | | 41.5 mg | Blood creatinine increased | Other |
| 22 | | 73/F | >36 mg | 38.8 mg | Postoperative wound infection | Postoperative |
| 23 | | 68/M | >36 mg | 48 mg | Wound dehiscence | Postoperative |
| 24 | | 68/F | >36 mg | 59 mg | Atrial fibrillation | Other |

| | | | | | | |
|---|---|---|---|---|---|---|
| 25 | (b) (6) | 54/M | >36 mg | 62.5 mg | Pelvic abscess | Postoperative |
| 26 | | 77/M | >36 mg | 84.5 mg | Clostridium difficile colitis | Postoperative |
| 27 | | 74/F | >36 mg | 138.6 mg | Nausea | Opioid-related |

Abbreviations: AE=adverse event; Cum=cumulative; Exp=exposure; F=female; ID=identification; ISS=integrated summary of safety; M=male; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Tx=treatment; yrs=years
a Categories were reviewer generated
b Patient experienced one SAE considered two separate SAEs
Source: Modified from ISS: 120-day Safety Update; Table 52, page 186-190, submitted 3/5/18

There was no clear relationship between oliceridine cumulative exposure and the percentage of patients with serious adverse events (Table 38).

**Table 38: Serious Adverse Events by Oliceridine Cumulative Exposure Quartile (All Phase 2 and Phase 3 Population Safety Analysis Set)**

| | OLI Q1 N=383 n (%) | OLI Q2 N=390 n (%) | OLI Q3 N=381 n (%) | OLI Q4 N=381 n (%) |
|---|---|---|---|---|
| Number of patients with at Least one Serious TEAE | 6 (1.6) | 8 (2.1) | 9 (2.4) | 8 (2.1) |

Abbreviations: OLI=oliceridine; Q=quartile; TEAE=treatment-emergent adverse event
TEAE were defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication.
Q1=0.5-8.187 mg; Q2=>8.187-20 mg; Q3=>20-41 mg; Q4=>41-223.5 mg
Source: Modified from ISS: 120-day Safety Update; Table 39, page 160, submitted 3/5/18

***Discontinuations due to Adverse Events***

As shown in Table 39, in Study 3001, there was a higher percentage of patients in the morphine treatment arm with discontinuations compared to the other treatment arms. In contrast, in Study 3002, there was a higher percentage of patients in the oliceridine 0.35 mg with discontinuations due to adverse events compared to the other treatment arms. When comparing the oliceridine treatment arms, the percentage of patients with discontinuations due to adverse events tended to be dose-dependent in both studies (Study 3001: oliceridine 0.1 mg: 0; oliceridine 0.35 mg: 1.3%; oliceridine 0.5 mg: 6.3%; Study 3002: oliceridine 0.1 mg: 0; oliceridine 0.35 mg: 5.1%; oliceridine 0.5 mg: 5.0%).

In Study 3001, the TEAEs leading to study medication discontinuation in the oliceridine treatment arms included nausea, oxygen saturation decreased, dizziness, sedation, and hypoxia. In the morphine treatment arm, the TEAE leading to study medication discontinuation were oxygen saturation decreased and vomiting. While a higher percentage of patients on morphine discontinued due to decreased oxygen saturation (6.6%) compared to oliceridine 0.5 mg (2.5%), the opposite was true for hypoxia where a higher percentage of patients on oliceridine 0.5 mg (2.5%) discontinued compared to morphine (0).

In Study 3002, the TEAEs leading to study medication discontinuation in the oliceridine treatment arms included nausea, post procedural hemorrhage, syncope, hypoxia, and hypotension. In the morphine treatment arm, the TEAEs leading to study medication discontinuation were non-cardiac chest pain and presyncope. The percentage of patients in the oliceridine 0.35 mg and 0.5 mg treatment arms who discontinued due to hypoxia (3.8% and

1.3%, respectively) was higher than the percentage of patients in the morphine treatment arm who discontinued due to hypoxia (0).

Thus, in studies 3001 and 3002 there was not a consistent trend towards improved respiratory safety for oliceridine compared to morphine based on adverse events leading to discontinuation.

**Table 39: TEAEs leading to Discontinuation by SOC and PT for Studies 3001 and 3002 (FAS)**

| Study 3001 | | | | | |
|---|---|---|---|---|---|
| **System Organ Class<br>Preferred Term** | **PBO<br>N=79<br>n (%)** | **OLI 0.1 mg<br>N=76<br>n (%)** | **OLI 0.35 mg<br>N=79<br>n (%)** | **OLI 0.5 mg<br>N=79<br>n (%)** | **Morphine<br>N=76<br>n (%)** |
| Patients with at least one TEAE leading to early study medication discontinuation[a] | 0 | 0 | 1 (1.3) | 5 (6.3) | 6 (7.9) |
| Gastrointestinal disorders | 0 | 0 | 0 | 1 (1.3) | 1 (1.3) |
| Nausea | 0 | 0 | 0 | 1 (1.3) | 0 |
| Vomiting | 0 | 0 | 0 | 0 | 1 (1.3) |
| Investigation | 0 | 0 | 1 (1.3) | 2 (2.5) | 5 (6.6) |
| Oxygen saturation decreased | 0 | 0 | 1 (1.3) | 2 (2.5) | 5 (6.6) |
| Nervous system disorders | 0 | 0 | 0 | 2 (2.5) | 0 |
| Dizziness | 0 | 0 | 0 | 1 (1.3) | 0 |
| Sedation | 0 | 0 | 0 | 1 (1.3) | 0 |
| Respiratory, thoracic, and mediastinal disorders | 0 | 0 | 0 | 2 (2.5) | 0 |
| Hypoxia | 0 | 0 | 0 | 2 (2.5) | 0 |
| **Study 3002** | | | | | |
| **System Organ Class<br>Preferred Term** | **PBO<br>N=83<br>n (%)** | **OLI 0.1 mg<br>N=77<br>n (%)** | **OLI 0.35 mg<br>N=79<br>n (%)** | **OLI 0.5 mg<br>N=80<br>n (%)** | **Morphine<br>N=82<br>n (%)** |
| Patients with at least one TEAE leading to early study medication discontinuation[a] | 0 | 0 | 4 (5.1) | 4 (5.0) | 2 (2.4) |
| Gastrointestinal disorders | 0 | 0 | 0 | 1 (1.3) | 0 |
| Nausea | 0 | 0 | 0 | 1 (1.3) | 0 |
| General disorders and administration site conditions | 0 | 0 | 0 | 0 | 1 (1.2) |
| Non-cardiac chest pain | 0 | 0 | 0 | 0 | 1 (1.2) |
| Injury, poisoning, and procedural complications | 0 | 0 | 0 | 1 (1.3) | 0 |
| Post procedural hemorrhage | 0 | 0 | 0 | 1 (1.3) | 0 |
| Nervous system disorders | 0 | 0 | 0 | 1 (1.3) | 1 (1.2) |
| Presyncope | 0 | 0 | 0 | 0 | 1 (1.2) |
| Syncope | 0 | 0 | 0 | 1 (1.3) | 0 |
| Respiratory, thoracic, and mediastinal disorders | 0 | 0 | 3 (3.8) | 1 (1.3) | 0 |
| Hypoxia | 0 | 0 | 3 (3.8) | 1 (1.3) | 0 |
| Vascular disorders | 0 | 0 | 1 (1.3) | 0 | 0 |
| Hypotension | 0 | 0 | 1 (1.3) | 0 | 0 |

Abbreviations: FAS=full analysis set; OLI=oliceridine; PBO=placebo; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
TEAE were defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication.

a TEAEs recorded as having an action taken of study medication discontinued.
Source: Clinical Study Report CP130-3001, Table 29 (page 151-2); Table 14.3.2.9 and Clinical Study Report CP130-3002, Table 29 (page 143-4); Table 14.3.2.9, submitted 11/2/17

In Study 3003, 17 patients (2.2%) experienced a total of 29 TEAEs leading to early discontinuation. Treatment-emergent AEs (TEAEs) leading to study discontinuation occurred in 5 patients (3.2%), 1 patient (1.2%), 3 patients (2.5%), 7 patients (4.2%), and 1 patient (0.4%) in the oliceridine ≤4 mg, >4 to 8 mg, >8 to 16 mg, >16 to 36 mg and >36 mg cumulative dose groups, respectively. Most TEAEs leading to early discontinuation occurred in 1 patient each. The TEAEs that occurred in more than one patient were nausea (4 patients) and vomiting, pruritus generalized, urticaria, and hypotension (2 patients each). The percentage of patients with TEAEs leading to early discontinuation did not appear related to the oliceridine cumulative dose groups (≤4 mg: 3.2%; >4 to 8 mg: 1.2%; >8 to 16 mg: 2.5%; >16 to 36 mg: 4.2%, and >36 mg: 0.4%). The TEAEs leading to study discontinuation in Study 3003 are in Table 40.

Many of the TEAEs leading to discontinuation appeared to be opioid-related, including respiratory depression, hypotension, nausea, vomiting, and pruritus. In addition, there were TEAEs leading to discontinuation that appeared to be allergic (such as urticaria) or post-operative (such as procedural pain and abdominal abscess). There were also TEAEs related to QT prolongation and increased aminotransferases, discussed later in this safety section.

**Table 40: Patients with TEAEs Leading to Early Study Medication Discontinuation in Study 3003**

| # | Patient ID | Age (yrs)/Sex | Cumulative dose group[b] | Cum exp SAE start | Preferred Term | General Category[a] |
|---|---|---|---|---|---|---|
| 1 | (b) (6) | 51/M | ≤4 mg | 2 mg | Procedural pain | Other |
| 2 | | 49/F | ≤4 mg | 2 mg | Diplopia | Other |
| | | | | 2 mg | Miosis | Other |
| | | | | 2 mg | Respiratory depression | Respiratory |
| 3 | | 74/F | ≤4 mg | 2 mg | Hypotension | Hypotension |
| 4 | | 55/M | ≤4 mg | 3 mg | Bradycardia | Cardiac arrhythmia |
| 5 | | 84/M | ≤4 mg | 4 mg | Hypotension | Hypotension |
| 6 | | 26/F | >4 to 8 mg | 5 mg | Nausea | GI |
| | | | | | Vomiting | GI |
| 7 | | 43/F | >16 to 36 mg | 8 mg | Urticaria | Allergic or pruritus |
| 8 | | 69/F | >8 to 16 mg | 8 mg | Nausea | GI |
| | | | | 8 mg | Dizziness | Other |
| | | | | 14.5 mg | Pruritus generalized | Allergic or pruritus |
| 9 | | 44/M | >8 to 16 mg | 13 mg | Tachycardia | Cardiac arrhythmia |
| 10 | | 25/F | >8 to 16 mg | 13 mg | Lip pruritus | Allergic or pruritus |
| | | | | 14 mg | Lip swelling | Allergic or pruritus |
| | | | | 13 mg | Pruritus | Allergic or pruritus |
| | | | | 13 mg | Urticaria | Allergic or pruritus |
| | | | | 13 mg | Urticaria | Allergic or pruritus |
| 11 | | 46/F | >16 to 36 mg | 17 mg | Procedural vomiting | GI |
| 12 | | 77/F | >16 to 36 mg | 17 mg | Nausea | GI |
| | | | | 17 mg | Vomiting | GI |
| 13 | | 24/F | >16 to 36 mg | 18.3 mg | Pruritus generalized | Allergic or pruritus |
| 14 | | 47/F | >16 to 36 mg | 21 mg | Abdominal abscess | Other |
| 15 | | 54/M | >16 to 36 mg | 23.5 mg | Electrocardiogram QT prolonged | Cardiac arrhythmia |
| 16 | | 81/F | >36 mg | 27 mg | Alanine aminotransferase increased | Drug-related hepatic disorders |
| | | | | | Aspartate aminotransferase increased | |
| | | | | 9 mg | Nausea | GI |
| 17 | | 30/F | >16 to 36 mg | 32 mg | Breast hematoma | Other |

Abbreviations: AE=adverse event; Cum=cumulative; Exp=exposure; F=female; ID=identification; ISS=integrated summary of safety; M=male; MedDRA=medical dictionary for regulatory activates; TEAE=treatment-emergent adverse event; Tx=treatment; yrs=years
a Categories were reviewer generated
b When patients discontinued due to multiple TEAEs, "Cumulative exposure at TEAE start" shows the cumulative dose at the start of each of the TEAEs that lead to discontinuation.
Note: All AE terms were coded using MedDRA Version 19.0
Source: Modified from ISS: 120-day Safety Update; Table 53, page 193-196, submitted 3/5/18

As seen in Table 41, when evaluating discontinuations due to adverse events by oliceridine cumulative exposure in all the Phase 2 and Phase 3 studies, the percentage of patients with discontinuations due to adverse events decreased with increasing oliceridine cumulative exposure quartile.

**Table 41: Discontinuations due to Adverse Events by Oliceridine Cumulative Exposure Quartile (All Phase 2 and Phase 3 Population Safety Analysis Set)**

| | OLI Q1 N=383 n (%) | OLI Q2 N=390 n (%) | OLI Q3 N=381 n (%) | OLI Q4 N=381 n (%) |
|---|---|---|---|---|
| Number of patients with at least one TEAE leading to early study medication discontinuation | 19 (5.0) | 12 (3.1) | 8 (2.1) | 2 (0.5) |

Abbreviations: OLI=oliceridine; Q=quartile; TEAE=treatment-emergent adverse event
TEAE were defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication.
Q1=0.5-8.187 mg; Q2=>8.187-20 mg; Q3=>20-41 mg; Q4=>41-223.5 mg
Source: Modified from ISS: 120-day Safety Update; Table 39, page 160, submitted 3/5/18

***Common Adverse Events***

Table 42 presents the common treatment-emergent adverse events (TEAEs) by preferred term (PT) in studies 3001 and 3002. In both studies, there was a higher percentage of patients with TEAEs in the oliceridine treatment arms compared to placebo (Study 3001: placebo: 68%; oliceridine 0.1 mg: 74%, oliceridine 0.35 mg: 86%; oliceridine 0.5 mg: 91%; Study 3002: placebo: 78%; oliceridine 0.1 mg: 90%; oliceridine 0.35 mg: 94%; oliceridine 0.5 mg: 95%). In both studies, the oliceridine 0.5 mg arm (Study 3001: 91%; Study 3002: 95) had a similar percentage of patients with TEAEs compared to morphine (Study 3001: 96%; Study 3002: 98%). For individual PTs, the percentage of patients in the oliceridine 0.5 mg arm tended to be similar the percentage of patients with these PTs in the morphine arm.

The ten most common preferred terms in the two studies were the same except Study 3001 included somnolence and dry mouth and Study 3002 included sedation and back pain. Nausea and vomiting were the most common TEAEs in both studies.

When comparing the three doses of oliceridine, in Study 3001, many of the adverse events were dose-dependent, including nausea, vomiting, dizziness, headache, constipation, hot flush, hypoxia, and oxygen saturation decreased. In Study 3002, the oliceridine 0.1 mg arm tended to have the lowest percentage of patients with a specific TEAE, but the percentage of patients with individual preferred terms tended to be similar for the 0.35 mg arm and the 0.5 mg arm.

**Table 42: Most Common TEAEs (≥5% of Patients in Any Treatment Regimen) by Treatment Regimen by Study (3001 and 3002) (FAS)**

| Study 3001 | | | | | |
|---|---|---|---|---|---|
| **PT** | **PBO N=79 n (%)** | **OLI 0.1 mg N=76 n (%)** | **OLI 0.35 mg N=79 n (%)** | **OLI 0.5 mg N=79 n (%)** | **Morphine N=76 n (%)** |
| Patients with at least one TEAE | 54 (68.4) | 56 (73.7) | 68 (86.1) | 72 (91.1) | 73 (96.1) |
| Nausea | 19 (24.1) | 27 (35.5) | 44 (55.7) | 50 (63.3) | 49 (64.5) |
| Vomiting | 5 (6.3) | 13 (17.1) | 31 (39.2) | 32 (40.5) | 38 (50.0) |
| Dizziness | 8 (10.1) | 21 (27.6) | 25 (31.6) | 28 (35.4) | 26 (34.2) |
| Headache | 24 (30.4) | 19 (25.0) | 20 (25.3) | 26 (32.9) | 23 (30.3) |
| Somnolence | 5 (6.3) | 4 (5.3) | 15 (19.0) | 10 (12.7) | 10 (13.2) |
| Constipation | 9 (11.4) | 8 (10.5) | 9 (11.4) | 11 (13.9) | 13 (17.1) |
| Pruritus | 6 (7.6) | 2 (2.6) | 12 (15.2) | 3 (3.8) | 15 (19.7) |
| Hot flush | 1 (1.3) | 2 (2.6) | 3 (3.8) | 6 (7.6) | 6 (7.9) |
| Hypoxia | 0 | 0 | 4 (5.1) | 7 (8.9) | 7 (9.2) |
| Dry mouth | 1 (1.3) | 1 (1.3) | 4 (5.1) | 4 (5.1) | 12 (15.8) |
| Hyperhidrosis | 2 (2.5) | 3 (3.9) | 4 (5.1) | 2 (2.5) | 3 (3.9) |
| Sedation | 1 (1.3) | 2 (2.6) | 4 (5.1) | 3 (3.8) | 2 (2.6) |
| Anxiety | 1 (1.3) | 1 (1.3) | 4 (5.1) | 3 (3.8) | 3 (3.9) |
| Oxygen saturation decreased | 0 | 1 (1.3) | 3 (3.8) | 4 (5.1) | 7 (9.2) |
| Muscle twitching | 4 (5.1) | 1 (1.3) | 1 (1.3) | 4 (5.1) | 0 |
| Pruritus generalized | 0 | 0 | 3 (3.8) | 2 (2.5) | 9 (11.8) |
| Infusion site extravasation | 6 (7.6) | 2 (2.6) | 0 | 3 (3.8) | 2 (2.6) |
| Chest discomfort | 1 (1.3) | 0 | 1 (1.3) | 0 | 4 (5.3) |
| **Study 3002** | | | | | |
| **PT** | **PBO N=83 n (%)** | **OLI 0.1 mg N=77 n (%)** | **OLI 0.35 mg N=79 n (%)** | **OLI 0.5 mg N=80 n (%)** | **Morphine N=82 n (%)** |
| Patients with at least one TEAE | 65 (78.3) | 69 (89.6) | 74 (93.7) | 76 (95.0) | 80 (97.6) |
| Nausea | 38 (45.8) | 34 (44.2) | 49 (62.0) | 60 (75.0) | 61 (74.4) |
| Vomiting | 11 (13.3) | 18 (23.4) | 17 (21.5) | 34 (42.5) | 44 (53.7) |
| Headache | 24 (28.9) | 12 (15.6) | 23 (29.1) | 21 (26.3) | 24 (29.3) |
| Hypoxia | 4 (4.8) | 6 (7.8) | 16 (20.3) | 14 (17.5) | 19 (23.2) |
| Constipation | 6 (7.2) | 12 (15.6) | 13 (16.5) | 9 (11.3) | 9 (11.0) |
| Pruritus | 4 (4.8) | 10 (13.0) | 13 (16.5) | 9 (11.3) | 15 (18.3) |
| Dizziness | 9 (10.8) | 11 (14.3) | 7 (8.9) | 7 (8.8) | 13 (15.9) |
| Sedation | 7 (8.4) | 5 (6.5) | 11 (13.9) | 7 (8.8) | 19 (23.2) |
| Back pain | 5 (6.0) | 3 (3.9) | 10 (12.7) | 9 (11.3) | 7 (8.5) |
| Hot flush | 6 (7.2) | 2 (2.6) | 6 (7.6) | 5 (6.3) | 6 (7.3) |
| Anxiety | 2 (2.4) | 1 (1.3) | 4 (5.1) | 6 (7.5) | 3 (3.7) |
| Rash | 2 (2.4) | 3 (3.9) | 1 (1.3) | 6 (7.5) | 0 |
| Restlessness | 3 (3.6) | 1 (1.3) | 5 (6.3) | 3 (3.8) | 4 (4.9) |
| Hyperhidrosis | 2 (2.4) | 2 (2.6) | 4 (5.1) | 2 (2.5) | 2 (2.4) |
| Pruritus generalized | 1 (1.2) | 1 (1.3) | 1 (1.3) | 6 (7.5) | 7 (8.5) |
| Myalgia | 1 (1.2) | 2 (2.6) | 4 (5.1) | 1 (1.3) | 0 |
| Abdominal pain upper | 3 (3.6) | 5 (6.5) | 1 (1.3) | 0 | 2 (2.4) |
| Flatulence | 4 (4.8) | 4 (5.2) | 1 (1.3) | 1 (1.3) | 2 (2.4) |
| Presyncope | 0 | 4 (5.2) | 1 (1.3) | 1 (1.3) | 2 (2.4) |
| Somnolence | 1 (1.2) | 2 (2.6) | 0 | 4 (5.0) | 6 (7.3) |

Abbreviations: FAS=full analysis set; MedDRA=Medical Dictionary for Regulatory Activities; OLI=oliceridine; PBO=placebo; PT=preferred term; TEAE=treatment-emergent adverse event

TEAE were defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication.
Note: All AE terms were coded using MedDRA dictionary Version 19.0.
Source: Clinical Study Report CP130-3001, Table 32 (page 159-160) and Clinical Study Report CP130-3002, Table 32 (page 152), submitted 11/2/17

As seen in Table 43, the percentage of patients with adverse events increased with increasing oliceridine cumulative exposure quartile in the all Phase 2 and Phase 3 analysis set. As previously noted, there are limitations to these analyses given that oliceridine was administered as needed.

**Table 43: Adverse Events by Oliceridine Cumulative Exposure Quartile (All Phase 2 and Phase 3 Population Safety Analysis Set)**

| | OLI Q1 N=383 n (%) | OLI Q2 N=390 n (%) | OLI Q3 N=381 n (%) | OLI Q4 N=381 n (%) |
|---|---|---|---|---|
| Number of patients with at Least one TEAE | 230 (60.1) | 299 (76.7) | 309 (81.1) | 316 (82.9) |

Abbreviations: OLI=oliceridine; Q=quartile; TEAE=treatment-emergent adverse event
TEAE were defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication.
Q1=0.5-8.187 mg; Q2=>8.187-20 mg; Q3=>20-41 mg; Q4=>41-223.5 mg
Source: Modified from ISS: 120-day Safety Update; Table 39, page 160, submitted 3/5/18

***Hepatic safety considerations***

Hepatic safety was identified as a submission specific safety consideration because, during the review cycle, the Agency identified adverse events related to elevations in liver function tests (LFTs) that were of concern due to the severity or potential clinical significance (i.e., one case of severe, serious adverse event of hepatic/renal failure and two cases of transaminases >3x upper limit of normal [ULN] with total bilirubin >2xULN). In addition, there was a higher percentage of patients in the oliceridine-treatment group who experienced ≥20xULN transaminases compared to no cases in the placebo or morphine groups. These concerns were communicated to the Applicant in the Mid-Cycle Communication letter dated May 18, 2018, and at the subsequent Mid-Cycle teleconference on May 21, 2018.

Table 44 provides an overview of abnormal liver-related laboratory results of interest by treatment regimen by study (3001 and 3002). In both studies, the number of events of LFT abnormalities was small. In Study 3001, the percentage of patients with AST or ALT at least 5xULN was highest in the oliceridine 0.35 mg arm (2.5%) compared to the other treatment arms (placebo: 0; oliceridine 0.1 mg: 0; oliceridine 0.5 mg: 0, and morphine: 1.3%). No patients had a total bilirubin at least 2xULN.

In Study 3002, the percentage of patients with AST or ALT at least 5, 10, and 20xULN was highest in the oliceridine 0.1 mg treatment arm compared to the other treatment arms. No patients had total bilirubin levels at least 2xULN.

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**Table 44: Abnormal Liver-related Laboratory Results by Treatment Regimen by Study (3001 and 3002) (FAS)**

| Study 3001 | | | | | |
|---|---|---|---|---|---|
| **Patients with at Least One Abnormal Hepatic Laboratory Finding** | **PBO N=79 n (%)** | **OLI 0.1 mg N=76 n (%)** | **OLI 0.35 mg N=79 n (%)** | **OLI 0.5 mg N=79 n (%)** | **Morphine N=76 n (%)** |
| AST ≥3xULN | 0 | 0 | 2 (2.5) | 1 (1.3) | 1 (1.3) |
| ALT ≥3xULN | 1 (1.3) | 0 | 1 (1.3) | 1 (1.3) | 1 (1.3) |
| AST or ALT ≥3xULN | 1 (1.3) | 0 | 2 (2.5) | 1 (1.3) | 1 (1.3) |
| AST ≥5xULN | 0 | 0 | 1 (1.3) | 0 | 1 (1.3) |
| ALT ≥5xULN | 0 | 0 | 1 (1.3) | 0 | 1 (1.3) |
| AST or ALT ≥5xULN | 0 | 0 | 2 (2.5) | 0 | 1 (1.3) |
| Bilirubin ≥2xULN | 0 | 0 | 0 | 0 | 0 |
| **Study 3002** | | | | | |
| **Patients with at Least One Abnormal Hepatic Laboratory Finding** | **PBO N=83 n (%)** | **OLI 0.1 mg N=77 n (%)** | **OLI 0.35 mg N=79 n (%)** | **OLI 0.5 mg N=80 n (%)** | **Morphine N=82 n (%)** |
| AST ≥3xULN | 0 | 2 (2.6) | 2 (2.5) | 0 | 3 (3.7) |
| ALT ≥3xULN | 0 | 3 (3.9) | 3 (3.8) | 1 (1.3) | 2 (2.4) |
| AST or ALT ≥3xULN | 0 | 3 (3.9) | 3 (3.8) | 1 (1.3) | 3 (3.7) |
| AST ≥5xULN | 0 | 2 (2.6) | 2 (2.5) | 0 | 1 (1.2) |
| ALT ≥5xULN | 0 | 2 (2.6) | 2 (2.5) | 0 | 1 (1.2) |
| AST or ALT ≥5xULN | 0 | 2 (2.6) | 2 (2.5) | 0 | 2 (2.4) |
| AST ≥10xULN | 0 | 2 (2.6) | 1 (1.3) | 0 | 0 |
| ALT ≥10xULN | 0 | 2 (2.6) | 1 (1.3) | 0 | 0 |
| AST or ALT ≥10xULN | 0 | 2 (2.6) | 1 (1.3) | 0 | 0 |
| AST ≥20xULN | 0 | 0 | 0 | 0 | 0 |
| ALT ≥20xULN | 0 | 1 (1.3) | 0 | 0 | 0 |
| AST or ALT ≥20xULN | 0 | 1 (1.3) | 0 | 0 | 0 |
| Bilirubin ≥2xULN | 0 | 0 | 0 | 0 | 0 |

Abbreviations: ALT=alanine transferase; AST=aspartate aminotransferase; FAS=full analysis set; ULN=upper limit of normal
Source: Clinical Study Report CP130-3001, Table 42 (page 185) and Clinical Study Report CP130-3002, Table 42 (page 180), submitted 11/2/17

When looking at the liver safety data from all Phase 2 and Phase 3 studies (Table 45), it was noted that there was a higher percentage of patients with AST or ALT ≥10xULN, AST or ALT ≥20xULN, and bilirubin ≥10xULN in the total oliceridine group (0.5%, 0.3%, and 0.7%) respectively, compared to placebo (0) or morphine (0).

**Table 45: Select Hepatic Laboratory Findings on Treatment (All Phase 2 and Phase 3 Safety Analysis Set)**

| Patients with at Least One Hepatic Laboratory Finding | PBO N=252 n (%) | Total OLI N=1535 n (%) | Morphine N=305 n (%) |
|---|---|---|---|
| AST ≥3xULN | 2 (0.8) | 23 (1.5) | 5 (1.6) |
| ALT ≥3xULN | 4 (1.6) | 24 (1.6) | 5 (1.6) |
| AST or ALT ≥3xULN | 4 (1.6) | 32 (2.1) | 6 (2.0) |
| AST ≥5xULN | 1 (0.4) | 12 (0.8) | 3 (1.0) |
| ALT ≥5xULN | 1 (0.4) | 14 (0.9) | 2 (0.7) |
| AST or ALT ≥5xULN | 1 (0.4) | 17 (1.1) | 4 (1.3) |
| AST ≥10xULN | 1 (0.4) | 7 (0.5) | 1 (0.3) |
| ALT ≥10xULN | 0 | 7 (0.5) | 1 (0.3) |
| AST or ALT ≥10xULN | 1 (0.4) | 8 (0.5) | 1 (0.3) |
| AST ≥20xULN | 0 | 3 (0.2) | 0 |
| ALT ≥20xULN | 0 | 4 (0.3) | 0 |
| AST or ALT ≥20xULN | 0 | 4 (0.3) | 0 |
| Bilirubin ≥2xULN | 0 | 10 (0.7) | 0 |

Abbreviations: ALT=alanine transferase; AST=aspartate aminotransferase; ULN=upper limit of normal
Source: Modified from ISS: 120-day Safety Update; Table 88, page 260, submitted 3/5/18

FDA's Drug-Induced Liver Injury (DILI) Guidance[6] states the following:
"a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) …" Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo;
2. Among trial subjects showing such AT [aminotransferase] elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL [total bilirubin] to >2xULN, without initial findings of cholestasis (elevated serum ALP);
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

The Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE), was consulted to provide an assessment of whether oliceridine has potential to cause drug-induced liver injury.

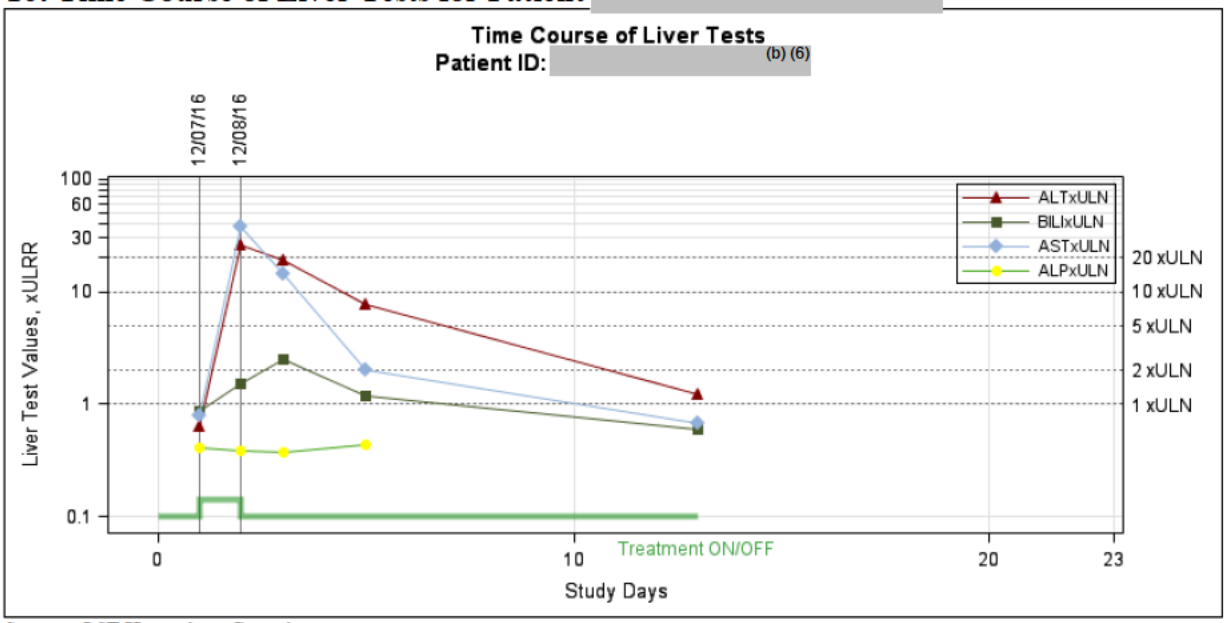
In the clinical, program, there were two patients with an elevated aminotransferase ≥3xULN and concurrent bilirubin ≥2xULN. Both patients were in Study 3003 and received oliceridine. These narratives were reviewed by the Agency hepatology consultant, who did not think there was definite evidence of oliceridine drug-induced liver injury. Narrative summaries of the cases are included below:

[6] https://www.fda.gov/downloads/guidances/UCM174090.pdf

The first patient ([redacted] (b) (6)) was a 70-year-old male in the oliceridine >4 to 8 mg cumulative dose group with normal ALT, AST, and bilirubin values at baseline. He had acute pain following hiatal hernia repair with general anesthesia. He received a loading dose of oliceridine (1 mg) on Relative Day 1, and subsequently received 5 bolus administrations of oliceridine (for a cumulative dose of 6 mg) over the 15-hour treatment period. An LFT time course plot for this patient is provided in Figure 16. The patient experienced an elevated ALT >26 xULN (1043 U/L [normal range: 10-40 U/L]) and AST >37xULN (1281 U/L [normal range: 5-34 U/L]) during the End of Treatment Period on Relative Day 2 with a slightly elevated bilirubin >1xULN (2.3 mg/dL [normal range 0-1.5 mg/dL]).

His medical history was pertinent for ischemic heart disease and use of a statin (pravastatin) for hypercholesterolemia. His anesthetic regimen included propofol and desflurane. The cumulative exposure of study medication was 6 mg over a 15-hour treatment period. Post-surgery on Day 2 he experienced marked elevations of ALT, AST and LDH and an increase in total bilirubin ≥2xULN (3.7 mg/dL) on Day 3. All LFT levels declined and were no longer clinically significant by Day 13. The differential diagnosis for a pattern of laboratory abnormalities such as these might include an ischemic etiology with the concomitant LDH rise, medication reaction to the anesthetic regimen, for which there are case reports of LFT abnormalities, or other medication with adverse hepatic effects (e.g. pravastatin, lisinopril). With a low level of exposure to the study medication (6 mg) and a variety of other potential etiologies an unlikely relationship to the study medication was determined by the investigator and agreed by the sponsor.

**Figure 16: Time Course of Liver Tests for Patient** [redacted] (b) (6)

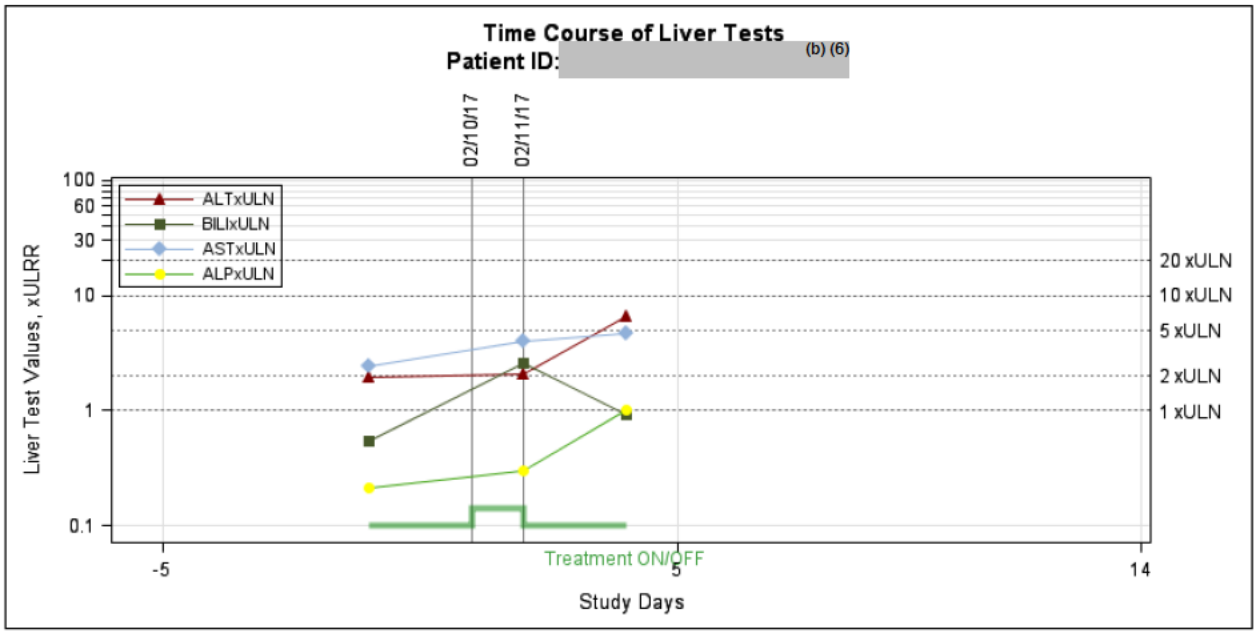



Source: OSE Hepatology Consult

The second patient, ( (b) (6) , was a 54-year-old male in the oliceridine >16 to 36 mg cumulative dose group. He was enrolled in Study 3003 to treat acute pain following aortic arch repair with general anesthesia. The patient received a loading dose of oliceridine (0.5 mg) on Relative Day 1 at 08:01 and subsequently self-administered 50 demand doses of oliceridine 0.5 mg (for a cumulative dose of 25.5 mg) over the 28-hour Treatment Period. An LFT time course plot for this patient is provided in Figure 17.

The sponsor assessed the relationship of the study medication to the elevation in ALT, AST, and bilirubin as unlikely related. This patient has significant cardiovascular disease and no reported history of underlying liver disease, though his baseline ALT and AST levels were above normal. He underwent a complicated surgical procedure where it appears he may have experienced transient ischemia judging from the references to hemorrhage, hypotension, and metabolic acidosis. The patient was given propofol and sevoflurane as anesthetic agents. Post-surgery he received a total of 25.5 mg of study medication over a 28-hour treatment period with discontinuation for QT prolongation. ALT increased from baseline to ≥2xULN on Day 2, further rising to ≥6xULN on Day 4. AST and ALP were also elevated on Day 4. The bilirubin level was ≥2xULN on Day 2 and then returned to normal by Day 4. Some of the complications noted as TEAEs during surgery, the extensive list of perioperative medications and anesthetics, some of which have known hepatic effects, and potential for unrecognized underlying hepatic disease at baseline, could be associated with this pattern of laboratory abnormalities. Also of note, the patient received acetaminophen 650 mg PO QID between Days 1 and 3. There are many confounding variables to be considered in causation, which led the investigator to conclude that the study medication was not related to the increase in transaminases and bilirubin.

**Figure 17: Time Course of Liver Tests for Patient** (b) (6)




Source: Hepatology OSE Consult

In addition to the above cases, the Agency also identified the following SAE of interest with the terms hepatic and renal failure that occurred in the Study 3003:

Patient (b) (6), a 55-year-old male who experienced treatment-emergent SAEs of hepatic failure and renal failure (both severe, resolved, but required hospitalization). On (b) (6), he underwent total knee arthroplasty. Post-operatively, on (b) (6), the patient received a bolus dose of oliceridine (1.5 mg). He subsequently received 43 PCA doses of oliceridine (0.5 mg each) until (b) (6) (approximately 30 hours) for a cumulative dose of 23 mg. Operative and post-operative periods were uneventful and no perioperative hypoperfusion event was reported.

His relevant medical history included alcohol use consisting of "3-6 beers and 1-3 whiskeys daily for > 30 years". The patient had no prior history of hepatic disease or renal disease. His ongoing medications since 2015 included lisinopril, simvastatin, metformin, and levothyroxine.

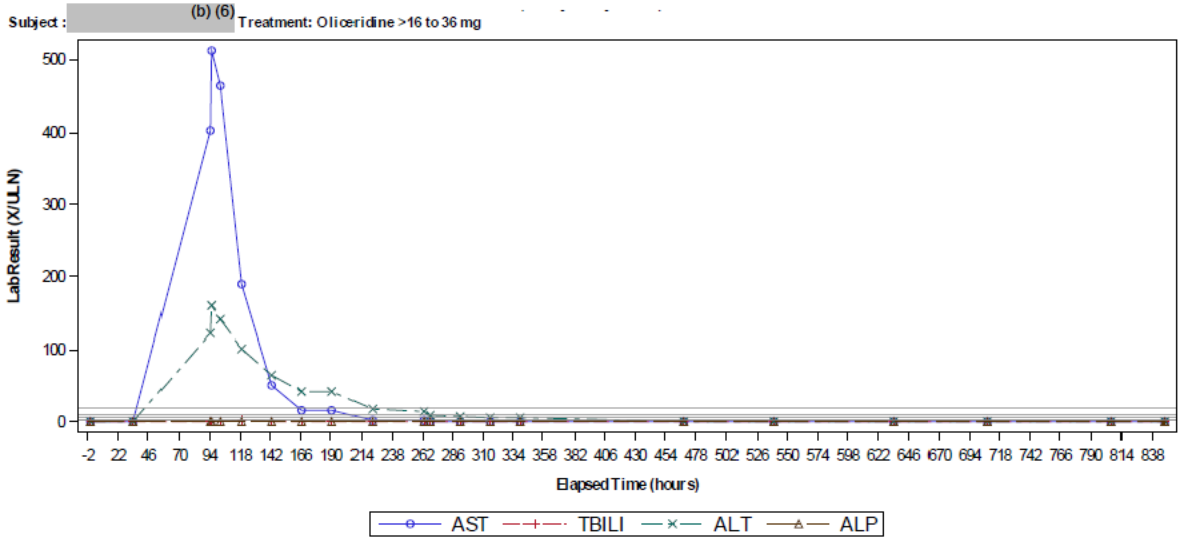
Peri-operative medications included APAP (acetaminophen), celecoxib, fentanyl, propofol, cefazolin, vancomycin, and warfarin.

His hepatic and relevant laboratory values were within normal limits at screening on (b) (6). On (b) (6) (1 day after oliceridine dosing was completed), the patient experienced nausea and was treated with ondansetron, but was subsequently discharged from the hospital. He also later began experiencing vomiting. On (b) (6) (2 days after oliceridine treatment ended) he presented to the Emergency

Department with nausea and vomiting. At that time, the AST was 16,509 (nl=41; >400xULN) and subsequently peaked at >21,000 that same day. The ALT was 6,845 (nl=56; 122xULN) and peaked at 8,989 that same day. Total bilirubin was not elevated at 1.3 mg/dL. The international normalized ratio (INR) was 4.7 and prothrombin time (PT) was 53.8. Hepatic ultrasound showed hepatic steatosis. Etoh level and hepatits screen were negative. This patient went on to be diagnosed with acute hepatic/renal failure. Other relevant labs on (b) (6) included hematocrit 20.0 and hemoglobin 6.7. A liver biopsy on (b) (6) showed "massive centriolobular necrosis with cholethiasis and increased iron deposition." By (b) (6), AST and ALT were trending down with values steadily normalizing over time. The time course for the abnormal LFTs are shown below. He was ultimately started on dialysis, which was subsequently stopped on (b) (6).

The investigators and Applicant determined that these SAEs may have been related to the patient's history of alcohol consumption (although hepatic values were normal at screening) and concomitant medications which resulted in a pattern suggestive of "ischemic hepatitis/hepatic shock" but considered the events as possibly related to study medication. There were confounding factors, including co-suspect medications, such as ketorolac tromethamine and simvastatin.

**Figure 18: Time Course of Liver Function Tests for Patient (b) (6)**




Source: Applicant's Figure 14.3.5.18, Study 3003, List of Figures, p. 36

Patient (b) (6) in Study 3003 was an 81-year-old female who discontinued early on Day 3 due to increased ALT and AST with nausea and vomiting on Day 2. The narrative for this patient revealed that there were no relevant, co-suspect concomitant medications listed. Transaminases were <3xULN and total bilirubin was within normal limits.

According to the DILI Guidance, peak aminotransferase elevations ≥10xULN may suggest

more potential for hepatic injury. Therefore, the Agency placed particular emphasis on evaluating data for those patients with transaminases ≥10xULN.

In the pooled Phase 2 and Phase 3 studies, four patients ([redacted] (b) (6) experienced transaminases ≥20xULN. Two of these patients ([redacted] (b) (6)) have already been discussed above. Narratives for the other two cases revealed that Patient [redacted] (b) (6) had a history of cholelithiasis and co-suspect medications of APAP and NSAID (ketorolac) and Patient [redacted] (b) (6) received co-suspect medications of APAP, propofol, and sevoflurane.

A total of eight patients experienced transaminases ≥10xULN in the oliceridine-treated group compared to one placebo and one morphine-treated. Four of these oliceridine-treated patients ([redacted] (b) (6) have already been discussed. Narratives for the other four cases revealed that all cases were confounded due to multiple concomitant and/or co-suspect medications such as propofol, APAP, Norco (APAP+oxycodone), Vicodin (APAP+hydrocodone), or Percocet (APAP+oxycodone).

It is worth noting that the two hepatic cases with transaminases ≥3xULN with total bilirubin ≥2xULN and the SAE of hepatic failure all occurred in the Study 3003, which was open-label, without a comparator group, limiting conclusions. Further, these cases appeared confounded. Study 3003 was designed to represent a "real world" population that may receive general anesthesia and multiple concomitant medications.

***QT/QTc Interval Prolongation***

An important consideration during drug develop is the potential effect of a drug on ventricular repolarization. A delay in cardiac repolarization can be measured as prolongation of the QT interval on the surface electrocardiogram (ECG). A delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias, most clearly torsade de pointes, but possibly other ventricular tachyarrhythmias as well.

In the oliceridine development program, the potential effect of the drug on ventricular repolarization was examined in both nonclinical and clinical studies, including a thorough QT study (tQT). A tQT study is intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation, at a dose that covers the high clinical exposure scenario, such as when a drug is given to patients with impaired elimination or given concomitantly with another drug that inhibits its clearance. The threshold level of regulatory concern is around 5 ms as evidenced by an upper bound of the 95% confidence interval (CI) around the mean effect on QTc of 10 ms. A finding of QT prolongation above the regulatory threshold of interest (a positive tQT study) might call for further electrocardiographic follow-up in late phase studies. As discussed below, the oliceridine tQT study showed QTcF prolongation that exceeded the 10 ms regulatory threshold and the doses included in the tQT study do not cover the projected exposure under therapeutic dosing regimens currently being considered. The potential effect of oliceridine on ventricular repolarization is a significant review issue that included review of nonclinical, clinical

pharmacology, and clinical data. FDA's QT Interdisciplinary Review Team (IRT) was consulted and provided review of the available data.

***Nonclinical cardiac safety***

The potential effects of oliceridine on the cardiovascular system were evaluated in a GLP *in vitro* hERG assay, *in vitro* QPatch studies assessing effects of oliceridine on non hERG cardiac channels, an *ex vivo* rabbit left ventricular wedge preparation, and a GLP *in vivo* monkey cardiovascular safety study. The $IC_{50}$ for oliceridine in the hERG assay (Study No.110520.USF) was 2.2 μM, approximately 367 times the $K_i$ at the mu opioid receptor, 27 times the free $C_{max}$ after 3 mg IV infusion (CP130-1008), and 43 times the estimated free $C_{max}$ of the currently proposed maximum recommended human dose (MRHD) of 40 mg/day. Weak inhibition of hCav 1.2 ($IC_{50}$ of 39.6 μM) and of hNav1.5 ($IC_{50}$ of 19.5 μM for tonic and $IC_{50}$ of 9 μM for phasic) were also identified (Study No. 101110.USF). In the rabbit wedge preparation (Study No. LIMRRWMU04), oliceridine did not cause any proarrhythmic events and had a composite torsadogenic risk score (TdP score) of zero or negative when tested up to 30 μM. The *in vivo* data collected from the monkey cardiovascular safety pharmacology study (Study 8242813) showed no effects on QTc intervals up to exposure of 3-5 times the $C_{max}$ levels observed in the clinical study (CP130-1008; 3 and 6 mg single IV infusion) where a QT prolongation signal was observed, and 7 times the projected human $C_{max}$ at the MRHD of 40 mg/day. The Applicant contends that oliceridine is a weak hERG blocker with some multi-channel effects that may abrogate inhibition of hERG current. The Applicant performed additional studies including a full ion channel evaluation of the two major human metabolites and these data are under review by the Agency.

***Clinical cardiac safety***

The Applicant conducted a thorough QT study (CP130-1008) and collected ECGs in the phase 3 trials (3001, 3002, and 3003).

*Thorough QT (tQT) study*

The tQT study (CP130-1008) showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with delayed onset (3 mg: 6 ms [upper 90% CI: 8.9 ms]: 6 mg: 11.6 ms [13.7 ms]). Overall, the largest upper bound of the 2-sided 90% CI for the mean difference between oliceridine 6 mg IV and placebo was 13.7 ms at 1 hour after dose.

The tQT study was performed in two parts: Part A and Part B. Part A was an open-label, fixed sequence, 2-period crossover design to assess the safety and tolerability of oliceridine 6 mg IV over 5 minutes in healthy male and female subjects. A total of 10 subjects participated in Part A to receive oliceridine 3 mg IV over 5 minutes on Day 1 and oliceridine 6 mg IV over 5 minutes on Day 2. Part B was a randomized, blinded, four-period crossover design. In Part B, a total of 62 healthy subjects received oliceridine 3 mg IV over 5 minutes, oliceridine 6 mg IV over 5 minutes, placebo IV over 5 minutes, and a single oral dose of moxifloxacin 400 mg. ECGs collected in Part A were evaluated by site investigator and were not included in this review. An overall summary of findings for Part B is presented in Table 46.

**Table 46: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Oliceridine (3 mg and 6 mg IV) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

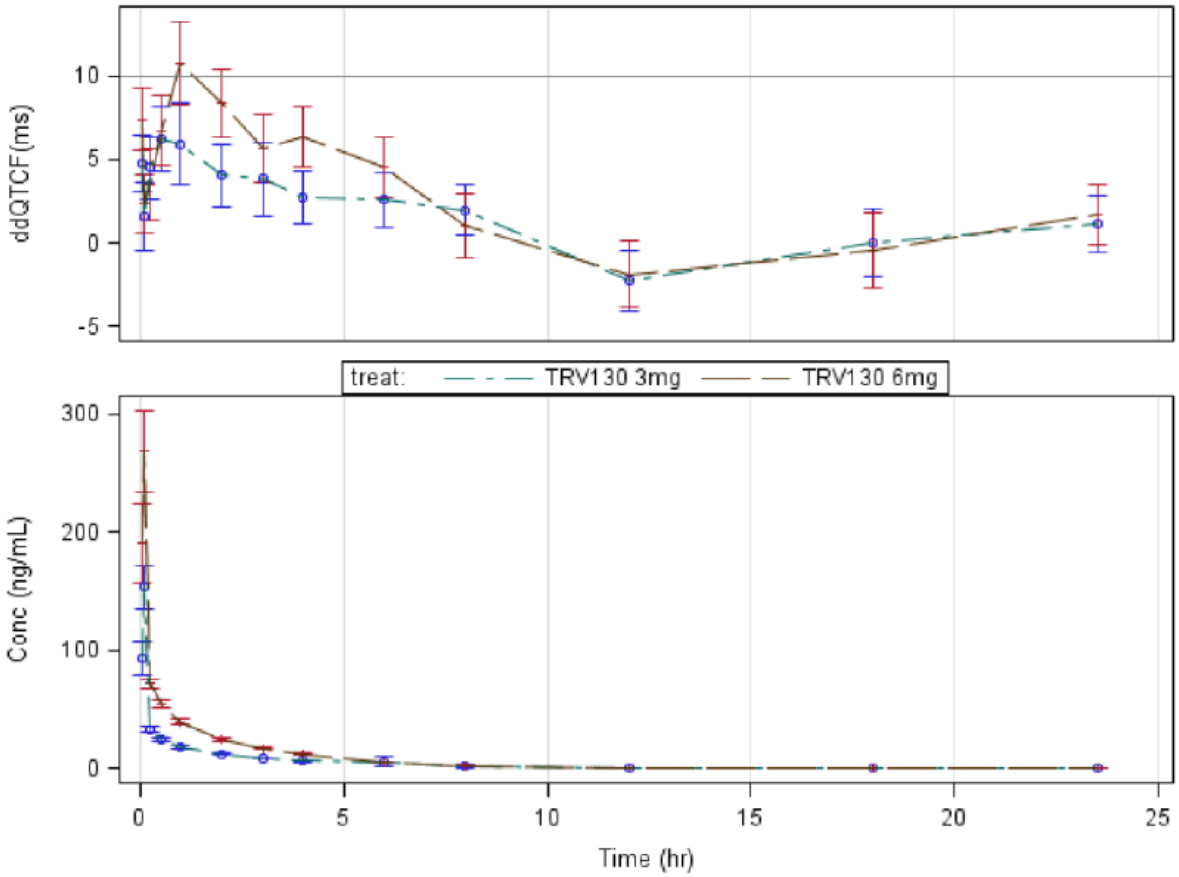
| Treatment | Time (hour) | ΔΔQTcF (ms) | 90% CI (ms) |
|---|---|---|---|
| TRV130 3 mg | 0.5 | 6.8 | (4.7, 8.9) |
| TRV130 6 mg | 1 | 11.6 | (9.5, 13.7) |
| Moxifloxacin 400 mg* | 2 | 11.5 | (8.6, 14.4) |

* Multiple endpoint adjustment of 4 time points was applied.

Source: Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review; Table 1, page 2, dated 2/8/16

The observed QTcF prolongation with oliceridine was dose-dependent and occurred after peak oliceridine plasma concentration (Figure 19).

**Figure 19: ΔΔQTcF time-course (top) and oliceridine PK time course (bottom)**




Source: Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review; Figure 6, page 22, dated 2/8/16

The delayed onset of QTcF prolongation suggests that the QTcF prolongation is not mediated via direct inhibition of the hERG potassium channel by oliceridine, consistent with the *in vitro* pharmacology safety studies. Alternative explanations for the delayed onsets include: (1) a hERG active metabolite of oliceridine or (2) a non-hERG mediated mechanism. Given that oliceridine undergoes extensive metabolism and that the time of maximum effect is like that of total radioactivity in blood, it is possible that the QTcF effect observed could be due to inhibition of hERG by a metabolite of oliceridine; however, based on the available data, no definitive conclusions can be drawn concerning the mechanism of the observed QTcF prolongation.

Because the QTcF prolongation exceeded the 10-ms regulatory threshold at clinically relevant exposures, FDA sent an advice letter/information request to the Applicant on March 3, 2016, indicating that the Applicant should incorporate safety ECG monitoring at baseline, following the first dose, and periodically thereafter. It was noted that the timing of the ECGs will need to reflect the delayed response relative to peak concentrations that was observed in the thorough QT study.

In the Applicant's Phase 3 studies, only limited ECG monitoring was obtained in patients (1, 24, and 48- hours post-loading dose for Study 3001 and 1 and 24 hours for Study 3002). Given that the QTcF prolongation associated with oliceridine is delayed and oliceridine is administered as needed with a wide range of doses up to a proposed maximum daily dose of initially 100 mg and then decreased by the Applicant to 40 mg, the data from a single dose tQT study (Table 2) and the limited ECG monitoring data obtained in Phase 3 do not appear to be adequate to evaluate the QT effects of oliceridine.

In tQT study CP130-1008, plasma samples were pooled from ten individuals and analyzed for M22 levels. M22 concentrations ranged from 10 ng/mL (lower limit of quantitation) to 31.0 ng/mL following a 3 mg dose of oliceridine and from 10 ng/mL to 65.0 ng/mL following a 6 mg dose. Plasma levels of M22 appear to peak at 2 hours after oliceridine administration and plasma half-life appears to be four hours. Limitations of available bioanalytical data on M22 include: a) Plasma M22 data are unavailable in the range of 0.1-1.5 mg oliceridine; b) PK parameters of M22 are based on limited pooled plasma samples; c) LLOQ (10 ng/mL) to Cmax (65 ng/mL) difference is narrow. The sponsor employed nonparametric superposition method to simulate steady-state M22 levels using the limited pooled sample data of M22 plasma levels in the dosing range of 1 – 3 mg/hr. A dosing regimen of 1.5 mg loading dose followed by 0.35 mg every 12 minutes for up to 24 hours were simulated by Agency reviewer. In addition to limitations of available data on M22, limitations of the simulation methodology include: a) Use of pooled sample data; b) Assuming M22 plasma levels will be dose-proportionally between 0.1 – 6 mg doses of oliceridine; c) Assumed plasma $T_{1/2}$ of 4 hours is based on data collected up to 12 hours (only three $T_{1/2}$'s). The table below compares simulated Cmax of M22 and TRV109662 at steady-state. Of note, the Agency's simulation results are different than the Applicant's simulation results, but the overall conclusion that M22 will accumulate after multiple doses of administration, is the same.

Table 47: Comparison of Cmax between thorough QT study and proposed dosing regimen (up to 40 mg/day)

| | M22 | TRV109662 |
|---|---|---|
| Thorough QT study (single 6 mg dose) | 65 ng/mL | 1.14 ng/mL |
| 1.5 mg followed by 0.35 mg every 12 min (up to 40 mg) | 154.7 ng/mL | 3.15 ng/mL |

During the review cycle, the Applicant was asked to provide the following information:

A) Provide a proposed mechanism for the delayed onset of the QTcF prolongation observed with oliceridine. In addition, provide data to support this hypothesized mechanism.
B) Taking into consideration the proposed clinical dose (including the range and frequency of dosing), provide additional data to adequately evaluate the QT effects of oliceridine, such as a multiple dose tQT study.

In follow-up to this request from the Agency, the Applicant stated that nonclinical studies with oliceridine failed to identify any non-hERG mediated effects on cardiac signaling. The QT-IRT team noted that the nonclinical hERG data suggests that oliceridine has a potential for inhibition of hERG as the safety margin is less than 30 compared to human free Cmax observed following IV administration of 3 or 6 mg (CP130-1008). It was further noted that while a monkey cardiovascular safety pharmacology study did not appear to suggest a potential for QT prolongation, that the highest evaluated exposure is ~7 times the maximum dose proposed in the label (40 mg/day).

In terms of clinical data, the Applicant stated that the observed changes in QTcF are rather modest increases for a supra-therapeutic dose, particularly for a drug which is to be used in the hospital, under close medical observation, and for short-term use. However, the Agency's concern is whether the increase could be greater, if its due to a metabolite that could accumulate with repeat dosing, or if patients are receiving other drugs, such as antiemetics with QT prolonging potential. While the Applicant states that there were no significant QTcF changes noted in the clinical studies, studies 3001, 3002, or 3003 were not designed to characterize the QT prolonging effect of oliceridine.

The Agency's QT Interdisciplinary Review Team (IRT) analyzed the clinical ECG findings in the oliceridine program. In study 3003 (ATHENA), ECGs were collected at baseline, at 1 hour after the first dose and every 24 hours of oliceridine treatment. In study 3003, there were 6 patients with ΔQTcF >60 ms, 11 patients with QTcF >500 ms, and 5 patients that met both criteria. Per the Applicant, 11 patients had at least one identified potential confounding factor that may have contributed to QTc prolongation; however, drug effect could not be excluded in some of these cases. The QT-IRT assessed that drug effect could not be excluded in 8 of the 11 cases. Further, it is worth noting that the ECG monitoring was sparse (baseline, 1 hour, and every 24 hours) and the absence of observed QTc prolongation is therefore not particularly reassuring. In the MedDRA SMQ Torsade de Pointes/QT Prolongation, there were 2 adverse

events (syncope and ventricular tachycardia) in subjects that did not have prolonged QTc intervals and 3 adverse events of electrocardiogram QT prolonged (Table 48).

**Table 48: Adverse Events Associated with MedDRA SMQ Torsade de Pointes/QT Prolongation**

| Subject ID | Adverse event | Severity | Serious | AE action | AE outcome |
|---|---|---|---|---|---|
| (b) (6) | Syncope[1] | Severe | Y | Not applicable | Recovered/resolved |
| | Electrocardiogram QT prolonged | Moderate | N | Drug withdrawn | Recovering/resolving |
| | Ventricular tachycardia[2] | Mild | N | Dose not changed | Recovered/resolved |
| | Electrocardiogram QT prolonged | Mild | N | Dose not changed | Unknown |
| | Electrocardiogram QT prolonged | Mild | N | Not applicable | Unknown |

*[1]Largest QTcF interval (440 ms) occurred at baseline. [2]Largest QTcF interval (436 ms) occurred 65 minutes after treatment. Source: Reviewer's MAED analysis using adae.xpt*

Source: QT IR Consult dated 6/6/18

Overall, the QT-IRT reviewer "considers it possible that several of the cases of QTc prolongation observed in ATHENA could be related to oliceridine and QTc prolongation was also observed in the thorough QT study. However, the interpretation of the ATHENA ECG data is complicated by lack of ECG replicates at each nominal timepoint and the study did not include a control arm to understand the background rates of QTc prolongation in the patient population due to concomitant medications and comorbid conditions."

The concerns regarding QT prolongation were noted by the Agency at the Midcycle Communication with the Applicant on May 21, 2018. In follow-up, the Applicant proposed simulations of the QTcF under various dosing scenarios and re-analysis of the tQT study using different ECG biomarkers. The Agency responded that since mechanism of the delayed QTcF prolongation is unknown, it is not appropriate to extrapolate information from single 3 mg and 6 mg doses to the proposed multiple dose scenarios (up to 3 mg every 1 hour). Instead, the Agency recommended additional nonclinical experiments to elucidate the mechanism of the delayed QTcF prolongation. Trevena performed a full ion channel evaluation of oliceridine and its two major metabolites and submitted a draft report to the Agency on August 14, 2018. Review of this submission is ongoing at this time.

***Respiratory***

Respiratory safety was assessed in a variety of ways in the clinical program. See the Efficacy Section above for a discussion of the Applicant's pre-specified respiratory analyses.

Table 49 displays select respiratory parameters by treatment regimen and by study. In Studies 3001 and 3002, there were dose-response relationships between increasing oliceridine dose and the percentage of patients with oxygen saturation less than 90%, TEAEs in the respiratory, thoracic, and mediastinal disorders SOC, and patients with any oxygen administration. Similarly, the number of events of oxygen saturation less than 90% and the number of TEAEs in the respiratory, thoracic, and mediastinal disorders SOC increased with increasing oliceridine dose. For the parameters oxygen saturation less than 90% and patients with any oxygen administration, the percentage of patients with these respiratory events tended to be higher in the morphine group than the oliceridine 0.5 mg group. In contrast, the percentage of

patients with TEAEs in the respiratory, thoracic, and mediastinal disorders SOC was higher in the oliceridine 0.5 mg than the morphine group in both studies. Thus, while there were trends showing a decreased percentage of respiratory events with oliceridine than morphine for some parameters, this was not consistent across all parameters, which was similar to what was also noted for discontinuations secondary to respiratory adverse events. In addition, there was a dose-response relationship between oliceridine and these respiratory safety parameters.

**Table 49: Selected Respiratory Parameters by Treatment Regimen by Study (3001 and 3002) (FAS)**

| | PBO N=79 n (%) [E] | OLI 0.1 mg N=76 n (%) [E] | OLI 0.35 mg N=79 n (%) [E] | OLI 0.5 mg N=79 n (%) [E] | Morphine N=76 n (%) [E] |
|---|---|---|---|---|---|
| **Study 3001** | | | | | |
| Oxygen saturation <90% | 1 (1.3) [1] | 3 (3.9) [7] | 8 (10.1) [15] | 11 (13.9) [25] | 15 (19.7) [46] |
| TEAEs in Respiratory, thoracic, and mediastinal disorders SOC | 2 (2.5) [3] | 3 (3.9) [3] | 9 (11.4) [12] | 12 (15.2) [16] | 10 (13.2) [13] |
| Patients with any $O_2$ administration | 0 | 1 (1.3) | 7 (8.9) | 10 (12.7) | 13 (17.1) |
| **Study 3002** | | | | | |
| | **PBO N=83 n (%) [E]** | **OLI 0.1 mg N=77 n (%) [E]** | **OLI 0.35 mg N=79 n (%) [E]** | **OLI 0.5 mg N=80 n (%) [E]** | **Morphine N=82 n (%) [E]** |
| Oxygen saturation <90% | 7 (8.4) [14] | 6 (7.8) [11] | 15 (19.0) [42] | 16 (20.0) [50] | 20 (24.4) [45] |
| TEAEs in Respiratory, thoracic, and mediastinal disorders SOC | 9 (10.8) [10] | 9 (11.7) [11] | 23 (29.1) [27] | 25 (31.3) [30] | 25 (30.5) [43] |
| Patients with any $O_2$ administration | 5 (6.0) | 6 (7.8) | 16 (20.3) | 18 (22.5) | 23 (28.0) |

Abbreviations: E=Number of events; FAS=full analysis set; OLI=oliceridine; PBO=placebo; SOC=system organ class
TEAE were defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication.
Note: All AE terms were coded using MedDRA dictionary Version 19.0.
Source: Clinical Study Report CP130-3001, Tables 14.3.4.5.3, 14.3.2.2.1, and 37 (page 172) and Clinical Study Report CP130-3002, Tables 14.3.4.5.3, 14.3.2.2.1, and 37 (page 165), submitted 11/2/17

***Somnolence/Sedation***

Somnolence and sedation were assessed with the Moline-Roberts Pharmacologic Sedation Scale (MRPSS) (at scheduled and unscheduled timepoints) and TEAEs of somnolence and sedation.

Based on the MRPSS, most patients in all treatment regimens (placebo, oliceridine, and morphine) were rated as having none to minimal somnolence/sedation (level 1) at Baseline in studies 3001 and 3002. Within 30 minutes of treatment, there was an increase in the percentage of patients with anxiolysis (level 2) in both the oliceridine and morphine treatment arms, but over the treatment period, most patients remained at level 1 or level 2.

These results based on MRPSS scores were consistent with TEAEs of sedation and somnolence. In Study 3001, the percentage of patients with TEAEs of sedation or somnolence was highest in the oliceridine 0.35 mg treatment arm (5.1% and 19%, respectively) compared

to the other treatment arms. In contrast, in Study 3002, the percentage of patients with TEAEs of sedation or somnolence was highest in the morphine arm (23.2% and 7.3%, respectively) compared to the other treatment arms. In both Studies 3001 and 3002, when comparing the oliceridine dose groups, the percentage of patients with TEAEs of sedation was highest in the 0.35 mg group compared to the 0.1 mg and 0.5 mg groups. In both studies, there was not a clear dose-response for the oliceridine arms, but the oliceridine 0.5 mg arm had a higher percentage of patients with somnolence and sedation than the 0.1 mg arm.

**Table 50: TEAEs of Somnolence and Sedation by Treatment Regimen by Study (3001 and 3002) (FAS)**

| Study 3001 | | | | | |
|---|---|---|---|---|---|
| **TEAE PT** | **PBO N=79 n (%) [E]** | **OLI 0.1 mg N=76 n (%) [E]** | **OLI 0.35 mg N=79 n (%) [E]** | **OLI 0.5 mg N=79 n (%) [E]** | **Morphine N=76 n (%) [E]** |
| Sedation | 1 (1.3) [1] | 2 (2.6) [2] | 4 (5.1) [4] | 3 (3.8) [3] | 2 (2.6) [2] |
| Somnolence | 5 (6.3) [7] | 4 (5.3) [4] | 15 (19.0) [16] | 10 (12.7) [10] | 10 (13.2) [10] |
| **Study 3002** | | | | | |
| **TEAE PT** | **PBO N=83 n (%) [E]** | **OLI 0.1 mg N=77 n (%) [E]** | **OLI 0.35 mg N=79 n (%) [E]** | **OLI 0.5 mg N=80 n (%) [E]** | **Morphine N=82 n (%) [E]** |
| Sedation | 7 (8.4) [7] | 5 (5.6) [5] | 11 (13.9) [12] | 7 (8.8) [9] | 19 (23.2) [20] |
| Somnolence | 1 (1.2) [1] | 2 (2.6) [3] | 0 | 4 (5.0) [4] | 6 (7.3) [6] |

Abbreviations: E=Number of events; FAS=full analysis set; OLI=oliceridine; PBO=placebo; PT=preferred term; TEAE=treatment-emergent adverse event
TEAE were defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication.
Note: All AE terms were coded using MedDRA dictionary Version 19.0.
Source: Clinical Study Report CP130-3001, Table 14.3.2.2.1 and Clinical Study Report CP130-3002, Table 14.3.2.2.1, submitted 11/2/17

### *Subjective Opiate Withdrawal Scale*

The Subjective Opiate Withdrawal Scale (SOWS) was used to assess for opiate withdrawal. Patients were instructed to complete the SOWS during the day after their last dose of study medication. Patients scored each of 16 symptoms on an intensity scale ranging from zero ("not at all") to four ("extremely"). The value of each of the individual 16 symptoms were summed for a total SOWS score.

Total SOWS scores by treatment regimen and by study are shown in Table 51. The mean total SOWS scores were low for all treatment regimens. In Study 3001, the scores ranged from 2.6 (oliceridine 0.1 mg arm) to 4.7 (morphine arm). In Study 3002, the scores ranged from 2.3 (placebo arm) to 3.0 (oliceridine 0.35 mg arm). When comparing oliceridine arms, there was no clear relationship between oliceridine dose and SOWS score. In both studies, most patients had SOWS scores that were categorized as mild or moderate and the percentages of patients with mild SOWS scores was similar across treatment arms.

**Table 51: SOWS Total Score by Treatment Regimen by Study (3001 and 3002) (FAS)**

| Study 3001 | | | | | |
|---|---|---|---|---|---|
| | **PBO N=79** | **OLI 0.1 mg N=76** | **OLI 0.35 mg N=79** | **OLI 0.5 mg N=79** | **Morphine N=76** |
| n | 77 | 74 | 78 | 78 | 70 |
| Mean (SD) | 2.7 (4.31) | 2.6 (5.08) | 4.4 (6.90) | 3.7 (5.30) | 4.7 (7.16) |
| Median (range) | 1 (0, 26) | 0.5 (0, 32) | 2 (0, 36) | 1 (0, 24) | 2 (0, 41) |
| **SOWS Categorical Score, n (%)** | | | | | |
| Mild (<17) | 76 (96.2) | 72 (94.7) | 74 (93.7) | 75 (94.9) | 66 (86.8) |
| Moderate (≥17 to ≤32) | 1 (1.3) | 2 (2.6) | 2 (2.5) | 3 (3.8) | 3 (3.9) |
| Severe (>32) | 0 | 0 | 2 (2.5) | 0 | 1 (1.3) |
| **Study 3002** | | | | | |
| | **PBO N=83** | **OLI 0.1 mg N=77** | **OLI 0.35 mg N=79** | **OLI 0.5 mg N=80** | **Morphine N=82** |
| n | 81 | 75 | 78 | 79 | 80 |
| Mean (SD) | 2.3 (4.19) | 2.4 (3.44) | 3.0 (4.97) | 2.6 (3.69) | 2.6 (4.02) |
| Median (range) | 0 (0, 19) | 0 (0, 12) | 1 (0, 28) | 1 (0, 17) | 1 (0, 22) |
| **SOWS Categorical Score, n (%)** | | | | | |
| Mild (<17) | 79 (95.2) | 75 (97.4) | 76 (96.2) | 78 (97.5) | 79 (96.3) |
| Moderate (≥17 to ≤32) | 2 (2.4) | 0 | 2 (2.5) | 1 (1.3) | 1 (1.2) |
| Severe (>32) | 0 | 0 | 0 | 0 | 0 |

Abbreviations: FAS=full analysis set; OLI=oliceridine; PBO=placebo; SD=standard deviation; SOWS=Subjective Opiate Withdrawal Scale
Note: The SOWs total score was the sum of the values for each of the individual 16 systems on an intensity scale ranging from 0 to 4. If greater than eight items were missing, the score was set to missing.
Note: The Applicant considered a total score of <17 was considered no to mild symptoms, ≥17 to ≤32 was considered moderate symptoms, and >32 was considered severe symptoms
Source: Clinical Study Report CP130-3001, Table 45 (page 194) and Clinical Study Report CP130-3002, Table 45 (page 189), submitted 11/2/17

### *Gastrointestinal*

The Applicant assessed for gastrointestinal safety utilizing the CMQ for GI tolerability. In studies 3001 and 3002, the percentage of patients with GI tolerability TEAEs was similar in the morphine treatment arm and the oliceridine 0.5 mg treatment arm (Table 52). When comparing among the oliceridine treatment arms, there was a dose-response in both studies with increasing oliceridine dose associated with a higher percentage of patients with GI tolerability TEAEs. Similar trends were seen for nausea and vomiting.

**Table 52: Incidence of GI Tolerability by Treatment Regimen by Study (3001 and 3002) (FAS)**

| Study 3001 | | | | | |
|---|---|---|---|---|---|
| | PBO N=79 n (%) | OLI 0.1 mg N=76 n (%) | OLI 0.35 mg N=79 n (%) | OLI 0.5 mg N=79 n (%) | Morphine N=76 n (%) |
| Number of patients with at least one GI tolerability TEAE | 19 (24.1) | 31 (40.8) | 47 (59.5) | 56 (70.9) | 55 (72.4) |
| Nausea | 19 (24.1) | 27 (35.5) | 44 (55.7) | 50 (63.3) | 49 (64.5) |
| Vomiting | 5 (6.3) | 13 (17.1) | 31 (39.2) | 32 (40.5) | 38 (50.0) |
| Retching | 0 | 0 | 1 (1.3) | 0 | 0 |
| Procedural nausea | 0 | 0 | 0 | 0 | 0 |
| Procedural vomiting | 0 | 0 | 0 | 0 | 0 |
| Regurgitation | 0 | 0 | 0 | 0 | 0 |
| Vomiting projectile | 0 | 0 | 0 | 0 | 0 |
| **Study 3002** | | | | | |
| | PBO N=83 n (%) | OLI 0.1 mg N=77 n (%) | OLI 0.35 mg N=79 n (%) | OLI 0.5 mg N=80 n (%) | Morphine N=82 n (%) |
| Number of patients with at least one GI tolerability TEAE | 39 (47.0) | 38 (49.4) | 52 (65.8) | 63 (78.8) | 65 (79.3) |
| Nausea | 38 (45.8) | 34 (44.2) | 49 (62.0) | 60 (75.0) | 61 (74.4) |
| Vomiting | 11 (13.3) | 18 (23.4) | 17 (21.5) | 34 (42.5) | 44 (53.7) |
| Retching | 0 | 0 | 0 | 1 (1.3) | 0 |
| Procedural nausea | 0 | 1 (1.3) | 1 (1.3) | 0 | 0 |
| Procedural vomiting | 0 | 0 | 0 | 0 | 0 |
| Regurgitation | 0 | 0 | 0 | 0 | 0 |
| Vomiting projectile | 0 | 0 | 0 | 0 | 0 |

Abbreviations: FAS=full analysis set; OLI=oliceridine; PBO=placebo; TEAE=treatment-emergent adverse event
There were no events of procedural vomiting, regurgitation, or vomiting projectile in either study.
Source: Clinical Study Report CP130-3001, Table 39 (page 178) and Clinical Study Report CP130-3002, Table 39 (page 171), submitted 11/2/17

***Abuse Potential***

Please see the Controlled Substance Staff's (CSS's) memorandum in the Appendix for a review of the abuse potential of oliceridine. In summary, CSS was in agreement with the Applicant that nonclinical and clinical studies conducted with oliceridine show that the drug is a mu-opioid agonist with high abuse potential, based on abuse-related data.

## 6.4 Safety summary

The Agency's safety review focused on the two randomized, placebo- and active-controlled studies of oliceridine and the randomized oliceridine treatment arms within these studies, rather than the pooled oliceridine group, so that the safety results could be considered in the context of the efficacy of the evaluated doses and to assess for a dose-response for safety issues. Many adverse events in the clinical program were consistent with opioid-related adverse events, including respiratory events, such as respiratory depression and hypoxia, and gastrointestinal events, such as nausea and vomiting. When evaluating the controlled Phase 3 data by randomized treatment group, many of the adverse events were dose-related, including respiratory safety parameters. While there were trends showing a decreased percentage of

respiratory events with oliceridine than morphine for some parameters, this was not consistent across all parameters. Notable safety issues in the clinical program included hepatic adverse events and QT prolongation. An additional consideration is whether the safety database is adequate to support the proposed dosing.

The focus of this meeting will be the efficacy and safety of oliceridine for treatment of acute pain in adult patients for whom an opioid analgesic is warranted. A point of discussion for this Advisory Committee Meeting is whether the overall benefit-risk profile is favorable.

# 7 Benefit-Risk Considerations

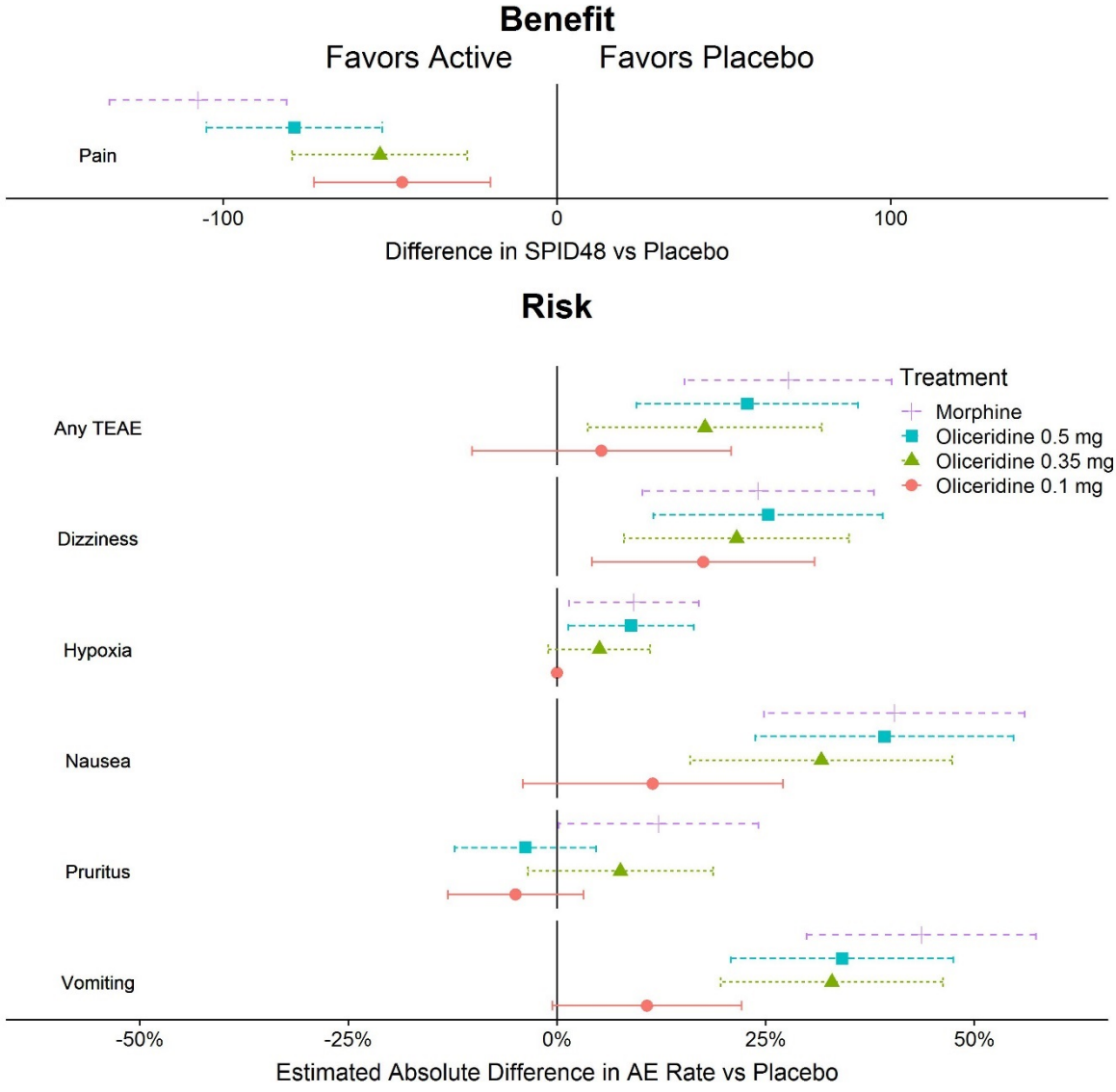
In this section, the benefits and risks of oliceridine are compared to placebo and morphine. The focus is on the data collected in the two controlled Phase 3 trials, Study 3001 (in patients undergoing a bunionectomy) and Study 3002 (in patients undergoing an abdominoplasty).

Figure 20 simultaneously presents the benefit and risk of all active treatments versus placebo from Study 3001. The displayed benefit is in terms of the difference in summed pain intensity differences from placebo (Table 21). The displayed risks are the adverse events where there was a significant difference ($p < 0.05$) between morphine and placebo.

In terms of benefit, morphine and all three oliceridine treatment regimens demonstrated a greater reduction in pain than placebo. There is a clear dose-response relationship for both benefit and risk for oliceridine, with the higher dose regimens showing a greater reduction in pain, and a greater rate of adverse events.

An additional consideration is the overall benefit-risk of oliceridine in comparison to morphine. The oliceridine 0.5 mg dose regimen looks to be slightly less efficacious than morphine, but with similar rates of dizziness, hypoxia, nausea, and vomiting. The oliceridine 0.1 and 0.35 mg dose regimens appear to be even less effective than morphine, with correspondingly lower rates of selected adverse events. Since only one dose of morphine was evaluated, there is have comparative efficacy and safety data for this one dose.

**Figure 20: Risk vs Benefit for Active Treatments Compared to Placebo (Study 3001)**



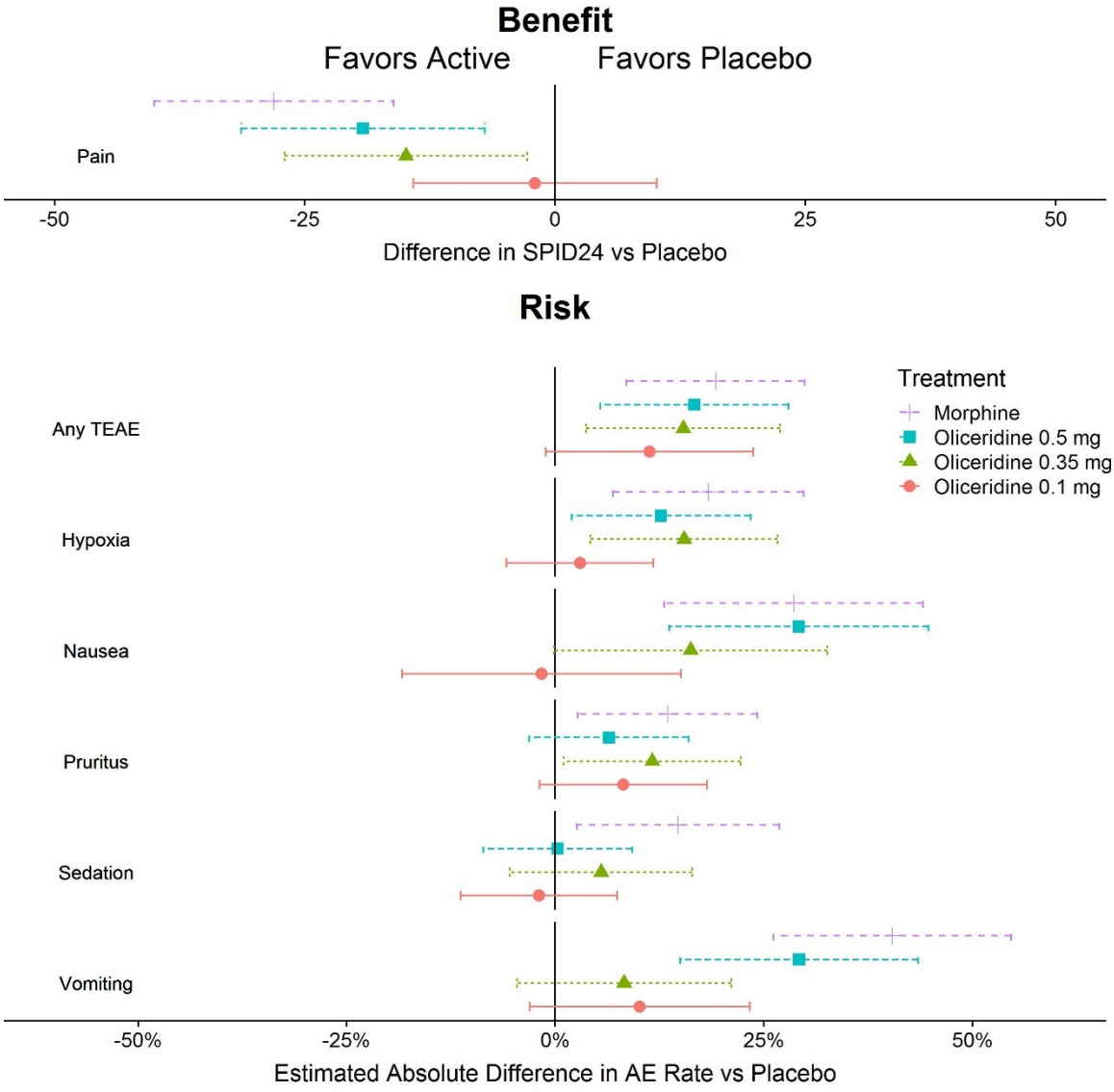

Source: FDA Reviewer

Figure 21 shows a similar plot of the efficacy and safety of oliceridine vs morphine for Study 3002. The displayed benefit is in terms of the difference in summed pain intensity differences from placebo from the analysis considered to be most clinically relevant (Table 28) and the displayed risks are the adverse events where there was a significant difference ($p < 0.05$) between morphine and placebo.

In this study morphine and the two higher oliceridine dose regimens (0.35 and 0.5 mg) demonstrated greater pain relief than placebo. There is again a clear dose-response relationship for oliceridine, with the higher dose regimens providing greater pain relief with a corresponding increase in adverse events. While the oliceridine 0.1 mg dose regimen did not demonstrate greater efficacy than placebo, it demonstrated similar rates of hypoxia, nausea, and sedation to placebo.

Compared to morphine, the oliceridine 0.5 mg dose regimen provided less pain relief, and similar rates of the selected adverse events. The lower dose regimens again provide lower levels of pain relief, but also lower rates of adverse events, particularly for nausea and vomiting. Again, since only one dose of morphine was evaluated, only comparative efficacy and safety data are available for this one dose.

**Figure 21: Risk vs Benefit for Active Treatments Compared to Placebo (Study 3002)**




Source: FDA Reviewer

# 8 Appendix

## 8.1 Additional Efficacy Tables

**Table 53: Percentage of Patients Requiring Oliceridine Doses Above 27 mg and 40 mg in the First 24 Hours (Studies 3001 and 3002)**

| Study | Dose Regimen | N (%) Above 27 mg | N (%) Above 40 mg | N in Arm |
|---|---|---|---|---|
| 3001 (Bunionectomy) | 0.1 mg | 1 (1%) | 0 (0%) | 76 |
| | 0.35 mg | 47 (59.5%) | 16 (20.3%) | 79 |
| | 0.5 mg | 50 (63.3%) | 29 (36.7%) | 79 |
| 3002 (Abdominoplasty) | 0.1 mg | 0 (0%) | 0 (0%) | 77 |
| | 0.35 mg | 22 (27.8%) | 7 (8.9%) | 79 |
| | 0.5 mg | 34 (42.5%) | 18 (22.5%) | 80 |
| 3003 (Safety Study) | | 97 (23.2%) | 43 (10.3%) | 418 |

Source: FDA Reviewer

**Table 54: SPID48 Pre-Rescue Scores Carried Forward 2 hours (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | 106.0 (92.1) | 138.7 (98.8) | 138.0 (102.2) | 158.7 (97.1) | 192.3 (89.9) |
| Least-Squares Mean (SE) | 100.7 (9.17) | 138.0 (9.34) | 142.3 (9.17) | 166.4 (9.20) | 194.4 (9.38) |
| LSM Diff. vs placebo (SE) | | 37.3 (13.04) | 41.6 (12.94) | 65.8 (12.98) | 93.8 (13.07) |
| P-value vs placebo | | 0.0044 | 0.0014 | <0.0001 | <0.0001 |
| LSM Diff. vs morphine (SE) | -93.8 (13.07) | -56.4 (13.17) | -52.2 (13.05) | -28.0 (13.06) | |
| P-value vs morphine | <0.0001 | <0.0001 | 0.0001 | 0.0327 | |
| Morphine Superior | Yes | Yes | Yes | Yes | |

Source: FDA Reviewer

**Table 55: SPID48 Pre-Rescue Scores Carried Forward 4 hours (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | 98.0 (92.1) | 135.0 (101.4) | 135.4 (103.5) | 157.2 (98.2) | 191.3 (90.2) |
| Least-Squares Mean (SE) | 92.7 (9.31) | 134.4 (9.48) | 139.7 (9.30) | 165.0 (9.33) | 193.6 (9.52) |
| LSM Diff. vs placebo (SE) | | 41.6 (13.23) | 46.9 (13.13) | 72.3 (13.17) | 100.8 (13.26) |
| P-value vs placebo | | 0.0018 | 0.0004 | <0.0001 | <0.0001 |
| LSM Diff. vs morphine (SE) | -100.8 (13.26) | -59.2 (13.36) | -53.9 (13.24) | -28.5 (13.25) | |
| P-value vs morphine | <0.0001 | <0.0001 | 0.0001 | 0.0320 | |
| Morphine Superior | Yes | Yes | Yes | Yes | |

Source: FDA Reviewer

**Table 56: SPID48 Pre-Rescue Scores Carried Forward 8 hours (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | 78.4 (99.0) | 126.8 (106.6) | 132.5 (105.5) | 154.5 (102.2) | 188.7 (91.7) |
| Least-Squares Mean (SE) | 73.4 (9.85) | 126.3 (10.03) | 136.8 (9.85) | 162.2 (9.88) | 191.0 (10.07) |
| LSM Diff. vs placebo (SE) | | 52.9 (14.00) | 63.5 (13.90) | 88.9 (13.93) | 117.7 (14.03) |
| P-value vs placebo | | 0.0002 | <0.0001 | <0.0001 | <0.0001 |
| LSM Diff. vs morphine (SE) | -117.7 (14.03) | -64.7 (14.14) | -54.2 (14.01) | -28.8 (14.02) | |
| P-value vs morphine | <0.0001 | <0.0001 | 0.0001 | 0.0406 | |
| Morphine Superior | Yes | Yes | Yes | Yes | |

Source: FDA Reviewer

**Table 57: SPID24 Pre-Rescue Scores Carried Forward 2 hours (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| Mean (SD) | 76.7 (37.4) | 77.0 (43.7) | 90.4 (42.6) | 94.1 (41.5) | 101.8 (48.2) |
| Least-Squares Mean (SE) | 80.7 (4.39) | 78.9 (4.48) | 91.4 (4.42) | 94.3 (4.44) | 103.6 (4.35) |
| LSM Diff. vs placebo (SE) | | -1.8 (5.97) | 10.74 (5.95) | 13.6 (5.98) | 22.9 (5.87) |
| P-value vs placebo | | 0.7581 | 0.0718 | 0.0239 | 0.0001 |
| LSM Diff. vs morphine (SE) | -22.9 (5.87) | -24.8 (5.93) | -12.2 (5.91) | -9.4 (5.93) | |
| P-value vs morphine | 0.0001 | <0.0001 | 0.0399 | 0.1148 | |
| Morphine Superior | Yes | Yes | Yes | No | |

Source: FDA Reviewer

**Table 58: SPID24 Pre-Rescue Scores Carried Forward 4 hours (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| Mean (SD) | 73.8 (37.3) | 76 (44.3) | 89.6 (43.1) | 93.8 (41.6) | 101.2 (48.4) |
| Least-Squares Mean (SE) | 78.0 (4.45) | 78.1 (4.41) | 90.9 (4.48) | 94.2 (4.50) | 103.3 (4.41) |
| LSM Diff. vs placebo (SE) | | 0.0 (6.05) | 12.9 (6.03) | 16.1 (6.06) | 25.3 (5.95) |
| P-value vs placebo | | 0.9944 | 0.0335 | 0.0081 | <0.0001 |
| LSM Diff. vs morphine (SE) | -25.3 (5.95) | -25.2 (6.01) | -12.4 (5.99) | -9.1 (6.01) | |
| P-value vs morphine | <0.0001 | <0.0001 | 0.0394 | 0.1299 | |
| Morphine Superior | Yes | Yes | Yes | No | |

Source: FDA Reviewer

**Table 59: SPID24 Pre-Rescue Scores Carried Forward 8 hours (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| Mean (SD) | 67.1 (38.8) | 72.9 (46.5) | 87.3 (45.1) | 92.8 (42.2) | 100 (48.9) |
| Least-Squares Mean (SE) | 74.8 (4.56) | 76.8 (4.66) | 89.7 (4.60) | 94.0 (4.61) | 103.0 (4.52) |
| LSM Diff. vs placebo (SE) | | 2.0 (6.20) | 14.9 (6.18) | 19.18 (6.21) | 28.1 (6.11) |
| P-value vs placebo | | 0.7514 | 0.0165 | 0.0022 | <0.0001 |
| LSM Diff. vs morphine (SE) | -28.1 (6.11) | -26.2 (6.16) | -13.2 (6.14) | -8.9 (6.17) | |
| P-value vs morphine | <0.0001 | <0.0001 | 0.0318 | 0.1475 | |
| Morphine Superior | Yes | Yes | Yes | No | |

Source: FDA Reviewer

**Table 60: Expected Cumulative Duration of $O_2$ Administration (hours) (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| Mean (SD) | 0 (0) | 0.04 (0.33) | 0.24 (0.90) | 0.78 (3.25) | 0.94 (2.71) |
| Maximum | 0 | 2.9 | 6.1 | 23.8 | 13.3 |
| Model-based estimate (95% CI) | | 0.02 (-0.03, 0.07) | 0.12 (-0.02, 0.27) | 0.23 (-0.01, 0.47) | 0.49 (0.02, 0.97) |
| Diff vs morphine (95% CI) | | -0.47 (-0.94, -0.01) | -0.37 (-0.80, 0.06) | -0.26 (-0.69, 0.17) | |
| P-value vs morphine | | 0.04 | 0.09 | 0.23 | |

Source: FDA Reviewer

**Table 61: Proportion with any $O_2$ Administration (Study 3001)**

| Statistic | Placebo N=79 | Oliceridine 0.1 mg N=76 | Oliceridine 0.35 mg N=76 | Oliceridine 0.5 mg N=76 | Morphine N=76 |
|---|---|---|---|---|---|
| n (%) | 0 | 1 (1.3%) | 7 (8.9%) | 10 (12.7%) | 13 (17.1%) |
| Model-based estimate (95% CI) | 0.00 (-0.00, 0.01) | 0.01 (-0.00, 0.02) | 0.04 (-0.00, 0.07) | 0.05 (0.00, 0.11) | 0.08 (0.01, 0.15) |
| Odds Ratio vs morphine (95% CI) | 0.02 (0.00, 0.37) | 0.08 (0.02, 0.43) | 0.42 (0.15, 1.16) | 0.66 (0.26, 1.70) | |
| P-value vs morphine | <0.01 | <0.01 | 0.09 | 0.38 | |

Source: FDA Reviewer

**Table 62: Expected Cumulative Duration of O2 Administration (hours) (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| Mean (SD) | 0.54 (2.63) | 0.40 (1.48) | 1.36 (3.68) | 1.54 (4.13) | 1.75 (3.86) |
| Maximum | 19.7 | 6.7 | 16.0 | 19.8 | 18.5 |
| Model-based estimate (95% CI) | 0.11 (-0.03, 0.24) | 0.08 (-0.02, 0.17) | 0.26 (0.03, 0.50) | 0.42 (0.04, 0.80) | 0.52 (0.09, 0.94) |
| Diff vs morphine (95% CI) | -0.41 (-0.80, -0.05) | -0.44 (-0.83, -0.05) | -0.26 (-0.67) | -0.10 (-0.48, 0.29) | |
| P-value vs morphine | 0.04 | 0.03 | 0.17 | 0.63 | |

Source: FDA Reviewer

**Table 63: Proportion with any O2 Administration (Study 3002)**

| Statistic | Placebo N=81 | Oliceridine 0.1 mg N=77 | Oliceridine 0.35 mg N=80 | Oliceridine 0.5 mg N=80 | Morphine N=83 |
|---|---|---|---|---|---|
| n (%) | 5 (6.0%) | 6 (7.8%) | 16 (20.3%) | 18 (22.5%) | 23 (28.0%) |
| Model-based estimate (95% CI) | 0.03 (0.00, 0.06) | 0.04 (0.00, 0.07) | 0.10 (0.03, 0.17) | 0.12 (0.04, 0.20) | 0.16 (0.06, 0.26) |
| Odds Ratio vs morphine (95% CI) | 0.16 (0.06, 0.43) | 0.19 (0.07, 0.51) | 0.58 (0.27, 1.25) | 0.71 (0.33, 1.53) | |
| P-value vs morphine | <0.01 | <0.01 | 0.16 | 0.39 | |

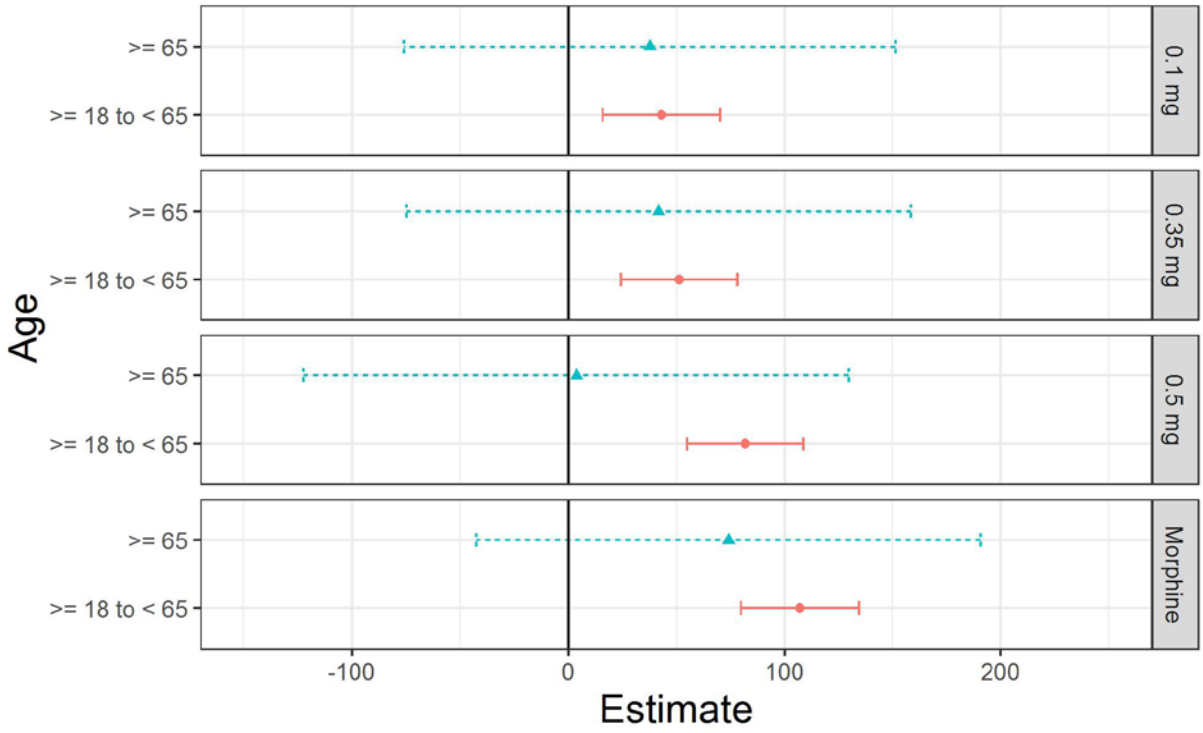
Source: FDA Reviewer

**Table 64: Estimated Treatment Effect vs Placebo by Demographic Subgroup (Study 3001)**

| Factor | Group | Oliceridine 0.1 mg | Oliceridine 0.35 mg | Oliceridine 0.5 mg | Morphine |
|---|---|---|---|---|---|
| Age Group | ≥ 18 to < 65 | 43.1 (15.8, 70.5) | 51.3 (24.3, 78.3) | 81.8 (55, 108.7) | 107.2 (79.9, 134.5) |
| | ≥ 65 | 37.6 (-76, 151.3) | 41.8 (-75, 158.5) | 3.7 (-122.3, 129.7) | 74.2 (-42.5, 190.8) |
| Race | Non-white | 5.6 (-40.8, 52.1) | 29.6 (-19.7, 78.9) | 73.2 (20.3, 126.2) | 92.3 (44.4, 140.1) |
| | White | 67.8 (35.1, 100.5) | 62.6 (31.2, 94) | 82.2 (51.3, 113) | 113.4 (81.1, 145.6) |
| Sex | Female | 47.8 (19.1, 76.5) | 54.9 (26.3, 83.4) | 80.9 (52.3, 109.5) | 104.1 (75.5, 132.7) |
| | Male | 45.4 (-27.8, 118.6) | 53.2 (-18.3, 124.6) | 75 (2.6, 147.4) | 132.5 (57.6, 207.4) |

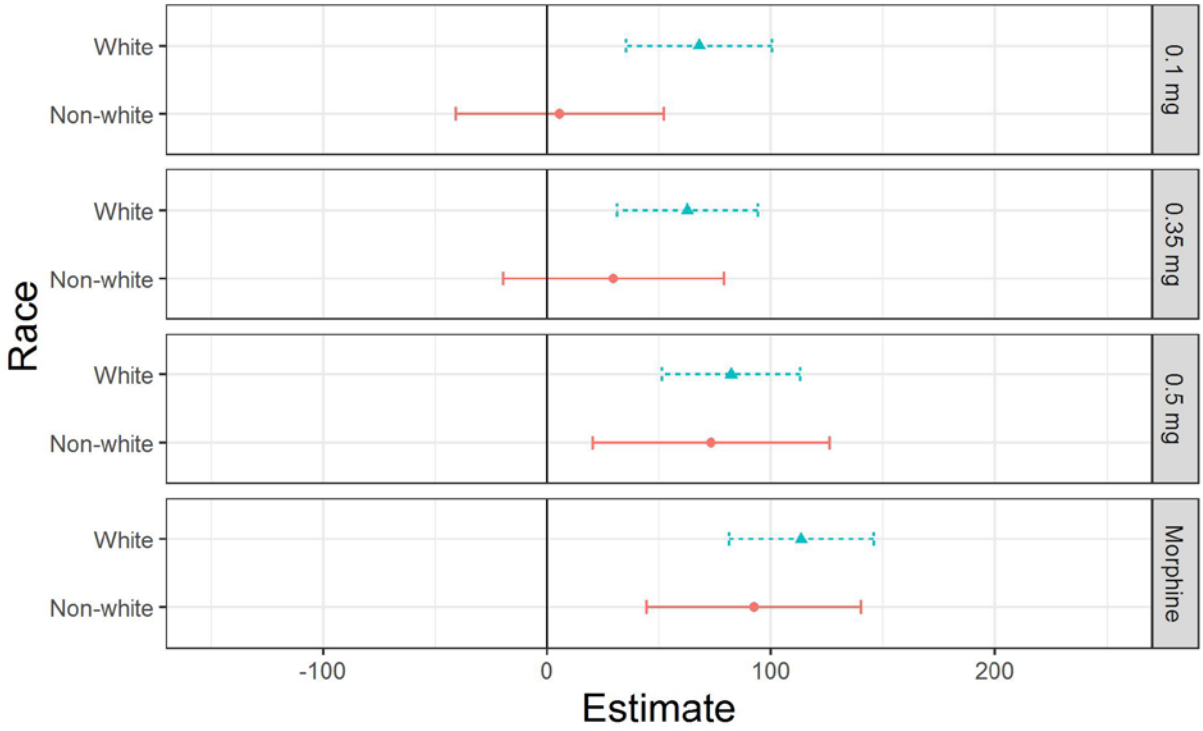
Source: FDA Reviewer

**Figure 22: Forest Plot of Treatment Effect vs Placebo by Age Group (Study 3001)**



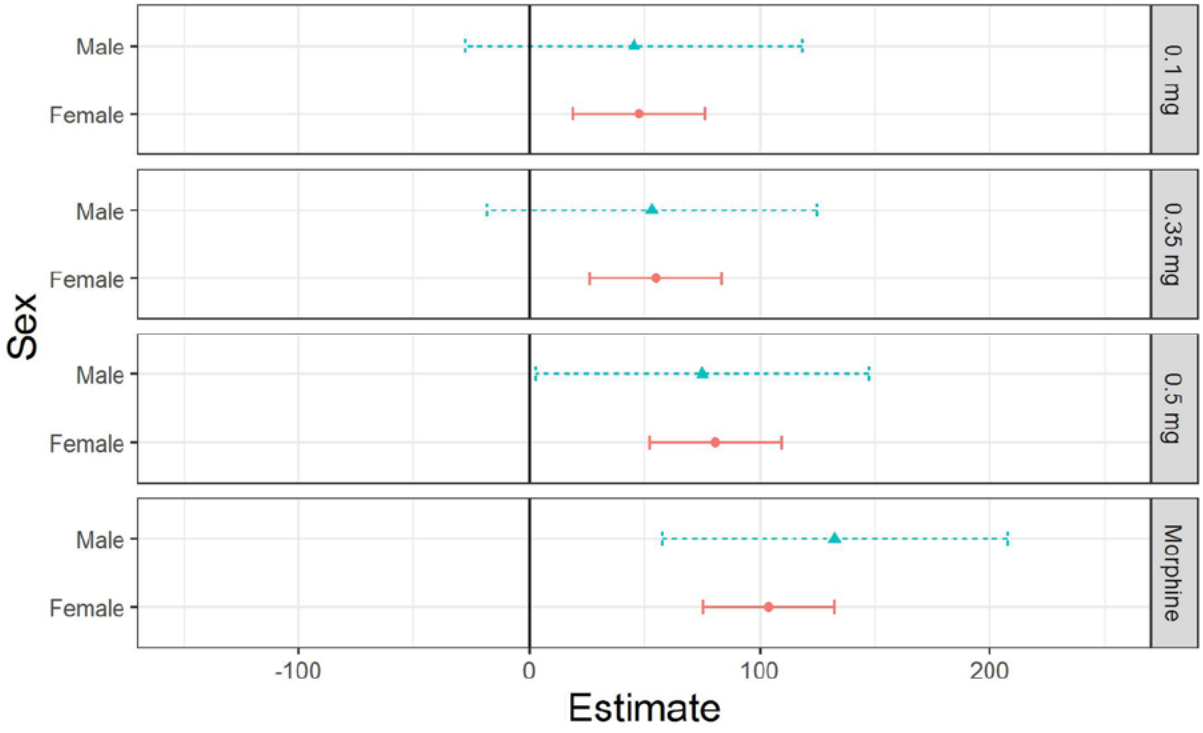

Source: FDA Reviewer

**Figure 23: Forest Plot of Treatment Effect vs Placebo by Race Group (Study 3001)**




Source: FDA Reviewer

**Figure 24: Forest Plot of Treatment Effect vs Placebo by Sex (Study 3001)**



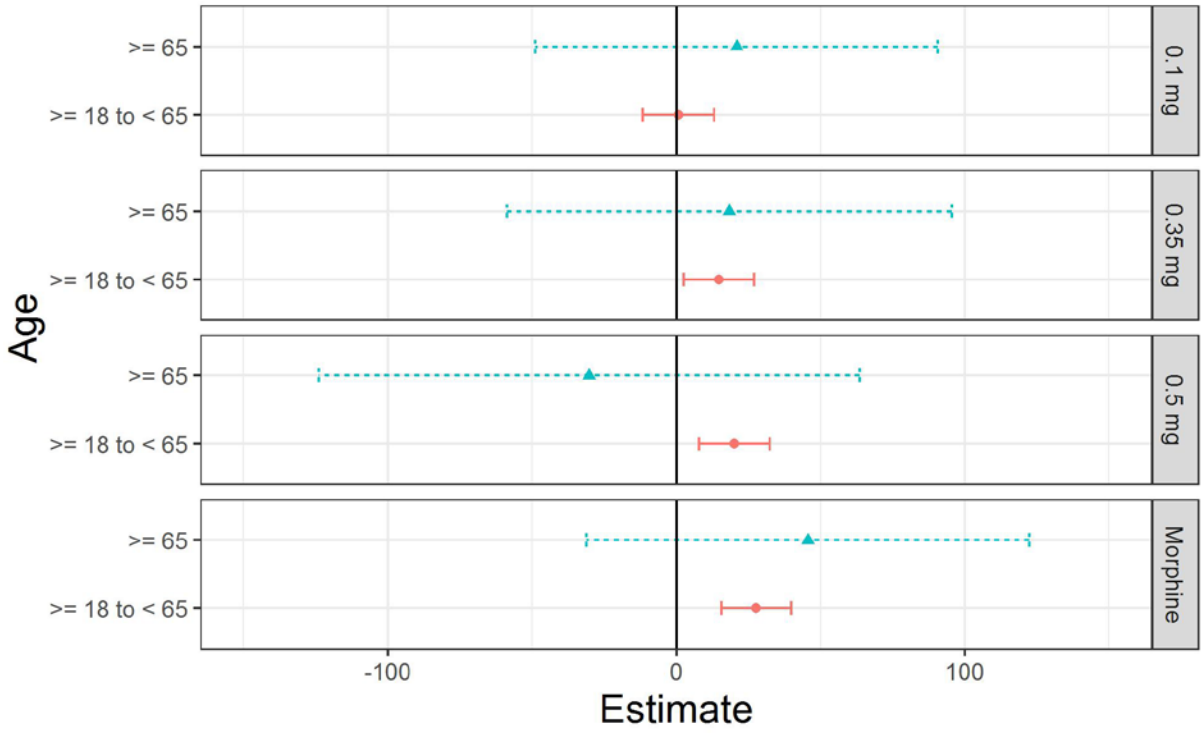

Source: FDA Reviewer

**Table 65: Estimated Treatment Effect vs Placebo by Demographic Subgroup (Study 3002)**

| Factor | Group | Oliceridine 0.1 mg | Oliceridine 0.35 mg | Oliceridine 0.5 mg | Morphine |
|---|---|---|---|---|---|
| Age Group | ≥ 18 to < 65 | 0.7 (-11.6,13.0) | 14.7 (2.5,26.9) | 20.1 (7.9,32.3) | 27.7 (15.6,39.8) |
| | ≥ 65 | 20.8 (-49.1,90.7) | 18.4 (-58.7,95.4) | -30.2 (-124.0,63.6) | 45.6 (-31.2,122.5) |
| Race | Non-white | 5.5 (-14.0,25.0) | 20.2 (-0.8,41.3) | 28.7 (8.6,48.9) | 41.1 (20.6,61.6) |
| | White | 0.5 (-15.3,16.3) | 11.9 (-3.1,26.9) | 13.6 (-1.9,29.1) | 21.2 (6.3,36.2) |
| Sex | Female | 2.0 (-10.2,14.2) | 14.9 (2.8,27.0) | 19.2 (7.0,31.4) | 29.5 (17.4,41.5) |
| | Male | - | - | - | - |

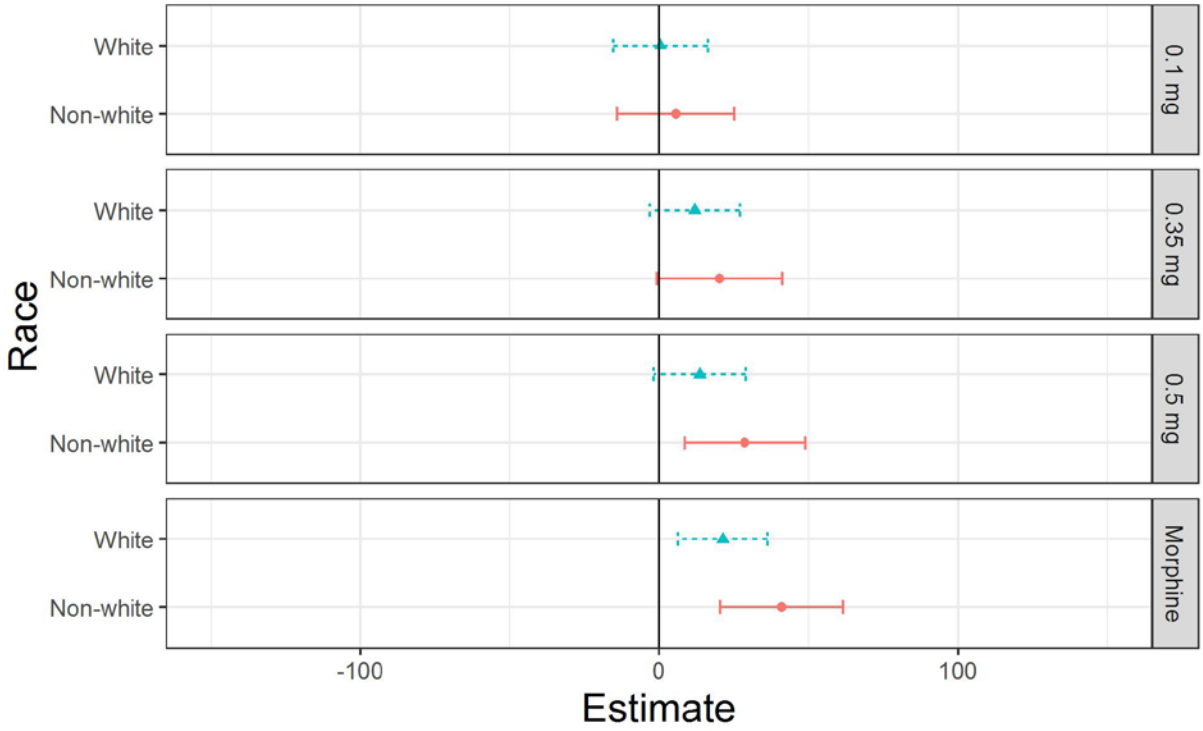
Source: FDA Reviewer

**Figure 25: Forest Plot of Treatment Effect vs Placebo by Age Group (Study 3002)**



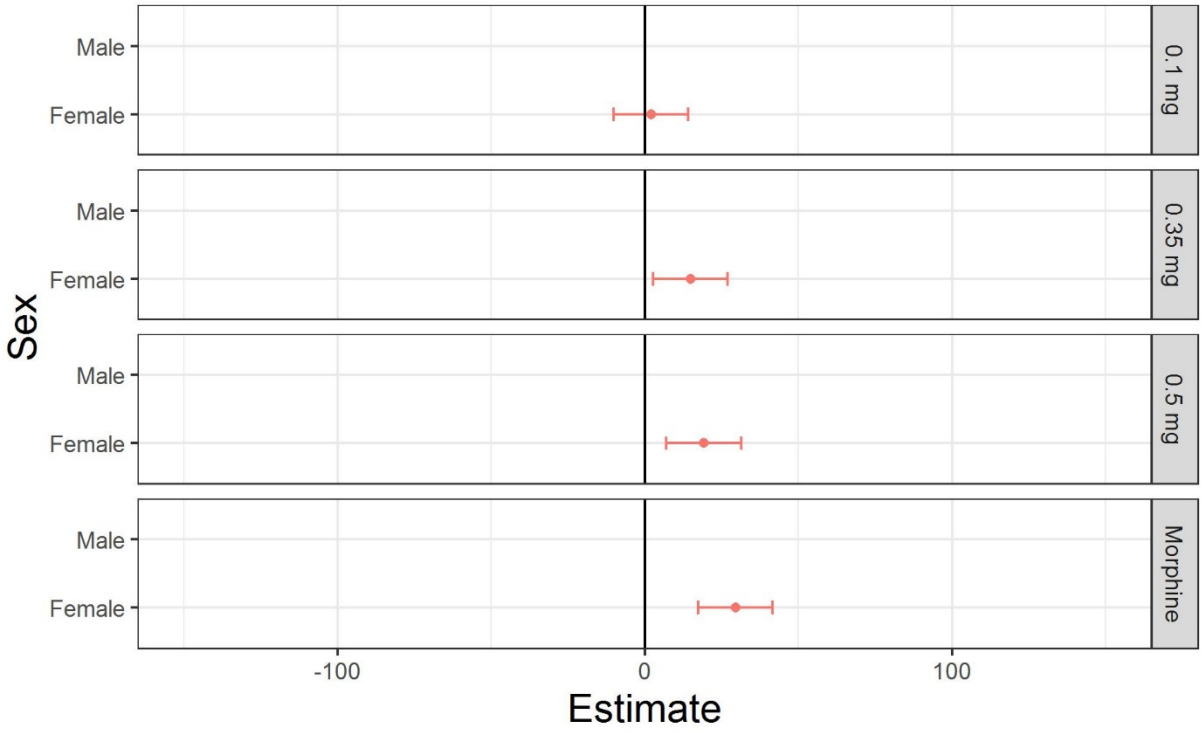

Source: FDA Reviewer

**Figure 26: Forest Plot of Treatment Effect vs Placebo by Race Group (Study 3002)**




Source: FDA Reviewer

**Figure 27: Forest Plot of Treatment Effect vs Placebo by Sex (Study 3002)**




Source: FDA Reviewer

## 8.2 Controlled Substance Staff Memorandum

**M E M O R A N D U M**
**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

| | |
|---|---|
| **Date:** | September 10, 2018 |
| **To:** | Sharon Hertz, M.D., Director<br>Division of Anesthesia, Analgesia and Addiction Products |
| **Through:** | Dominic Chiapperino, Ph.D., Director<br>Silvia Calderon, Ph.D., Senior Pharmacologist<br>Controlled Substance Staff |
| **From:** | Katherine Bonson, Ph.D., Pharmacologist<br>Controlled Substance Staff |
| **Subject:** | **BACKGROUND DOCUMENT ON**: Abuse Potential Assessment of Oliceridine (NDA 210730)<br><br>Document prepared for FDA Anesthetic and Analgesic Drug Products Advisory Committee on October 11, 2018 regarding oliceridine, proposed for treatment of moderate-to-moderately-severe pain<br>Sponsor: Trevena, Inc. |

### I. Background

Oliceridine in a sterile aqueous solution (1.0 mg oliceridine free base equivalents/ml) for intravenous injection under inpatient hospital or clinic settings. It is being developed under NDA 210730 by Trevena, Inc., the Sponsor, for the management of "moderate-to-severe pain in adult patients for whom an intravenous opioid is warranted".

The Sponsor states that, "The development rationale for oliceridine stemmed from the finding that β-arrestin-2 knock-out mice treated with morphine demonstrated enhanced analgesia while reducing respiratory and gastrointestinal dysfunction compared with wild-type animals. Oliceridine is a full agonist for G protein coupling at the mu-opioid receptor, but exhibits lower β-arrestin2 recruitment to the mu-opioid receptor than morphine or other conventional opioid full agonists. In nonclinical models, this biased signaling profile resulted in potent analgesic efficacy, with less respiratory depression, less slowing of GI motility, and less

sedation compared with morphine." A failure to recruit β-arrestin2 has also been predicted to reduce the ability of an opioid to produce the rewarding properties that underlie abuse potential (Crowley et al, 2016), or withdrawal signs indicative of physical dependence (Hales, 2011).

The search for an opioid that can produce analgesia without the risk of addiction, or overdose resulting in death from respiratory depression, has been a research and drug development goal for over a century. Numerous candidate compounds that act as mu opioid agonists, but have reduced recruitment of β-arrestin2 compared to G-protein, have been proposed to fulfill this role. In addition to oliceridine, these compounds include herkinorin (Groer et al, 2007), kurkinorin (Crowley et al, 2016), mitragynine and 7-hydroxymitragynine (Kruegel et al., 2016), and PZM21 (Hill et al., 2018).

However, oliceridine is the only drug that has been thoroughly evaluated in FDA-vetted clinical trials for its ability to produce analgesia, respiratory depression, abuse potential and physical dependence. The data from these large-scale human studies will help inform whether the lack of interaction with β-arrestin2 predicts an improved safety profile for a mu opioid agonist.

The following review evaluates the abuse potential of oliceridine based on the abuse-related data from preclinical studies (chemistry, receptor binding, functional, and animal behavioral studies) and the abuse-related data from Phase 1 and Phase 2/3 clinical studies (including a human abuse potential study, as well as analyses of abuse-related adverse events in all clinical studies) conducted with oliceridine.

## II. Conclusions

CSS is in agreement with the Sponsor that an evaluation of the preclinical and clinical studies conducted with oliceridine show that the drug is a mu opioid agonist with high abuse potential, based on abuse-related data showing that oliceridine:

- Has high affinity at mu opioid receptors in receptor binding studies, similar to other mu opioid agonists
- Acts as a mu opioid agonist that preferentially recruits G-protein rather than β-arrestin2
- Produces overt behaviors in animals similar to those produced by mu opioid agonists
- Produces full generalization to morphine in drug discrimination studies in animals, showing that it produces effects similar to mu opioid agonists
- Produces self-administration in animals, suggesting it has rewarding properties like mu opioid agonists
- Produces physical dependence in animals, similar to mu opioid agonists

- Produces positive subjective responses and euphoric effects in opioid abusers who participated in a human abuse potential study, similar to mu opioid agonists

- Produces euphoria and other abuse-related adverse events in Phase 1 clinical studies conducted with healthy subjects, similar to mu opioid agonists

These results from animal and human studies consistently show that oliceridine produces rewarding effects and withdrawal effects that would be expected from a mu opioid agonist.

Additionally, CSS has considered the effects of oliceridine on respiratory depression observed in Phase 1 and Phase 2/3 clinical studies as an indicator of overdose potential. As discussed in the clinical safety section of this AC Briefing Document, there was no clear advantage for oliceridine over morphine in relation to respiratory safety.

Thus, an overall assessment of the abuse-related data from preclinical and clinical studies leads to the finding that oliceridine is a mu opioid agonist with an abuse potential, overdose potential and ability to produce physical dependence that is similar to other mu opioid agonists.

Therefore, it does not appear that the biased agonism of oliceridine with regard to preferential recruitment of G-protein over β-arrestin2 translates into a human safety advantage for oliceridine compared to traditional mu opioid agonists.

## III. Abuse-Related Preclinical and Clinical Study Data

**Receptor Binding Studies** (Study # TRV130-01, TRV130-18, 797915)

In receptor binding studies with oliceridine, there was significant affinity of oliceridine for mu opioid receptors. There was also no significant affinity of oliceridine for other sites associated with abuse potential: opioids (kappa, or delta), GABA/ benzodiazepine, dopamine (D1 or D2), serotonin (1A, 1B, 2A, 3, 5A, 6, or 7), cannabinoid, NMDA/glutamate, channels (calcium, potassium, sodium, or chloride), transporters (dopamine or norepinephrine). Drugs such as sedatives, stimulants, cannabinoids, and hallucinogens (among many others) have high affinity for these sites. These data show that oliceridine has a mechanism of action similar to that of other mu opioid agonists.

**Functional Studies** (Study # TRV130-02 and TRV130-02)

Mu opioid receptor agonists have second messenger functioning that typically involves activation of both G-protein and β-arrestin2 pathways. However, oliceridine has been shown in published studies to preferentially recruit only G-protein. In this way, oliceridine is described as a biased agonist.

*In vitro* functional studies were conducted in human embryonic kidney (HEK-293) cells expressing recombinant human mu opioid receptors. Oliceridine produced inhibition of forskolin-stimulated cAMP accumulation (a measure of G-protein activation). This occurred with an efficacy slightly greater that of morphine. As shown in Table 1 (below), oliceridine has a potency that is slightly greater than that of fentanyl, 2 times that of hydromorphone and 6 times that of morphine ($EC_{50}$ of ~8 nM vs. ~6 nM, ~16 nM and ~50 nM, respectively).

HEK-293 cells were also stably transfected to overexpress β-arrestin2 fused to a β-galactosidase (PathHunter β-arrestin assay). In this assay, oliceridine did not produce a measurable recruitment of β-arrestin2. However, fentanyl, hydromorphone, and morphine all recruited β-arrestin2 with an $EC_{50}$ ranging from 126 to 501 nM.

**Table 1: Functional Activity in Human Cells of Oliceridine, Fentanyl, Hydromorphone, and Morphine (from Study #TRV130-02)**

| | **cAMP** | | **β-arrestin2** | |
|---|---|---|---|---|
| **Compound** | **EC50 (nM)** | **pEC50** | **EC50 (nM)** | **pEC50** |
| oliceridine | 7.9 | 8.1 | N.Q. | N.Q. |
| fentanyl | 6.3 | 8.2 | 251 | 6.6 |
| hydromorphone | 15.8 | 7.8 | 126 | 6.9 |
| morphine | 50.1 | 7.3 | 501 | 6.3 |

N.Q.: not quantifiable

These data suggest that oliceridine acts as a mu opioid agonist that preferentially recruits G-protein rather than β-arrestin2.

## Animal Behavioral Effects

***General Behavioral Studies*** (Study # 8242814 and TRV130-19)

Administration of drugs with known abuse potential produce standard and predictable changes in overt observable behavior. If a test drug produces these behaviors, it is likely that the drug produces effects similar to known drugs of abuse. In the studies below, the oliceridine doses used produce plasma levels of oliceridine that are equivalent to or greater than the plasma levels of oliceridine produced by therapeutic doses.

In an Irwin test of general behavior in rats, low doses of oliceridine (0.25, 0.5, 1.0 mg/kg/hour, i.v.) administered over a 6 hour period did not produce any changes in overt behavior, excretion of urine or fecal boli, or body temperature relative to vehicle. However, when a higher dose of oliceridine (1.5 mg/kg/hour, i.v.) was administered over a 24 hour period in a toxicity study, it produced behavioral impairment as well as reduced food consumption and reduced body weight. At the lower dose of 1.0 mg/kg/hour, oliceridine decreased forelimb grip strength over the 24-hour monitoring period.

In the rotorod test (which measures ability of a rat to hold onto a slowly rotating rod), oliceridine (0.3 mg/kg, s.c.) and morphine (3 mg/kg, s.c.) produced a similar impairment in motor ability.

These general behavioral tests demonstrate that oliceridine produces sedative and motor effects, as would be expected from a mu opioid agonist.

***Drug Discrimination Study (Similarity to Known Drugs of Abuse)*** *(Study# 8317098)*

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In a drug discrimination study, rats were trained to discriminate morphine (3.0 mg/kg, s.c.) from vehicle using a fixed ratio (FR) 10 schedule of reinforcement. When rats could stably discriminate morphine from vehicle, challenge sessions with oliceridine began at doses of 0.1, 0.3, and 1.0 mg/kg (s.c.). Morphine was also tested as a positive control at doses of 0.3, 1.0, 1.7, 3.0, and 10.0 mg/kg (s.c.).

As expected, morphine (3 and 10 mg/kg) produced full generalization (98%) to the morphine cue. Similarly, oliceridine (0.3-1.0 mg/kg) produced full generalization (75-99%) to the morphine cue. Lower doses of both drugs produced only partial generalization or no generalization to the morphine cue, showing that the responses were dose-dependent.

Overall, these data show that oliceridine produces interoceptive effects in rats similar to those produced by morphine.

***Self-Administration Studies (Rewarding Effects)*** *(Study #8317099)*

Self-administration is a method that assesses whether a drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug. Drugs that are self-administered by animals are likely to produce rewarding effects in humans, which is indicative that the drug has abuse potential.

A self-administration study was conducted in rats to evaluate whether oliceridine produces reward sufficient enough to be reinforcing. Animals were initially trained to press a lever to receive morphine (0.56 mg/kg/infusion, i.v.), using a fixed ratio (FR)5 final schedule of reinforcement. Once responding for morphine was stable, animals were allowed to lever press to receive a range of doses of oliceridine (0.00125, 0.0125, 0.04, 0.125 mg/kg/infusion, i.v.), morphine (the positive control; 0.01, 0.10, 0.30, 0.56, 1.0 mg/kg/infusion), or vehicle (i.v.) over a one-hour session.

As expected, morphine produced a high degree of self-administration (~12-27 infusions/ session at doses of 0.10-0.56 mg/kg/infusion), while vehicle produced a low degree of self-administration (<5 infusions/session). Oliceridine also produced a high degree of self-administration (~13-19 infusions/session at doses of 0.0125 and 0.04 mg/kg/infusion) compared to vehicle. The two rewarding doses of oliceridine produced cumulative oliceridine plasma levels that represent 3-8 times the human $EC_{50}$.

These self-administration data show that oliceridine produces sufficiently rewarding effects be reinforcing. These effects are similar to those produced by morphine. This indicates that oliceridine has abuse potential similar to that of morphine.

***Animal Physical Dependence Study*** *(Study #8317097)*

An animal physical dependence study was conducted in which rats received a continuous intravenous infusion of oliceridine (0.05, 0.15, 0.5 mg/kg/hr), morphine (the positive control; 4 mg/kg/hr), or vehicle for 14 days. Observations were taken daily during drug administration and during the 7-day drug discontinuation phase.

During the drug discontinuation phase, both oliceridine and morphine produced (respectively) decreases in food consumption (26-44% vs. 50%), body weight (10-17% vs. 22%), and classic opioid withdrawal signs including hunched posture, vocalizing, aggression, squinting, twitching, soft feces, decreased locomotion, decreased muscle tone and grasp strength.

These data show that chronic administration of oliceridine produces opioid withdrawal signs after drug discontinuation, similar to that produced by morphine. This shows that oliceridine produces physical dependence, as would be expected of a mu opioid agonist.

## Human Behavioral Effects

***Subjective Responses to Oliceridine in Healthy Individuals*** *(Study #CP130-1001 and CP130-1003)*

In a Phase 1 ascending dose study, the subjective effects of a 1 hour infusion of oliceridine (0.15, 0.25, 0.4, 0.7, 1.2, 2.2, 4, and 7 mg) or placebo was tested in 8 separate groups of healthy adult men. These doses of oliceridine are less than, equal to, and 2X, 4X and 7X greater than the proposed therapeutic dose. Prior to and throughout the drug infusion, subjects were asked to fill out questionnaires about their feelings of sedation, anxiety, and dysphoria

using the Bond-Lader mood rating scale. Oliceridine did not produce any changes on these subjective measures except at the 7 mg dose (7X therapeutic dose), where there were increases in sedation, anxiety, and dysphoria responses compared to baseline.

In a second Phase 1 study, oliceridine (1.5, 3.0, and 4.5 mg, equal to 1.5X, 3X and 4.5X the proposed therapeutic dose) was compared to morphine (10 mg) and placebo during a 2-minute intravenous infusion in healthy adult men using the Drug Effects Questionnaire (DEQ). Although the DEQ is validated for use with individuals who have a history of drug abuse, use of this questionnaire in healthy subjects can provide information about whether persons without a history of drug use will experience sensations that suggest the test drug has abuse potential. In this study, 10 mg morphine produced subjective responses on DEQ subscales (Drug Liking, High, Good Effects, Any Effects, Sleepy, Dizzy, Bad Effects, Nausea and Feel Sick) that were intermediate to those produced by 1.5 and 3 mg oliceridine. The 4.5 mg oliceridine dose produced the highest scores on all measures compared to morphine and placebo. The time course of the effects for oliceridine peaked for the positive subjective measures 30-120 min and returned to baseline 4 hours after drug administration.

These results in healthy individuals show that oliceridine can produce subjective responses that would be expected from a mu opioid agonist, such as morphine.

***Human Abuse Potential Study*** *(Study # CP130-1011)*

Human abuse potential (HAP) studies evaluate the ability of a test drug to produce positive subjective responses in subjects compared to a known drug of abuse and to placebo. Subjects in HAP studies are individuals with a history of recreational drug use but not drug dependent. When the test drug produces consistently high responses on scales such as “Drug Liking,” “Good Drug Effects,” and “High” significantly different from placebo, it is likely that the test drug has abuse potential.

A human abuse potential study was conducted to evaluate the abuse potential, safety, tolerability, and pharmacokinetics of 1 minute intravenous infusions of oliceridine (1, 2 and 4 mg) compared to morphine (10 and 20 mg), and placebo using a randomized, double-blind, 6-period, crossover design in healthy non-dependent recreational opioid abusers. The doses of oliceridine tested represent the proposed therapeutic doses (1 mg) and two supratherapeutic dose (2 and 4 times greater than the therapeutic doses). Since oliceridine has an analgesic potency that is ~3 to 10 times greater than morphine, the doses selected for the two drugs were expected to produce similar effects.

*Subjective Responses*

As shown below in Table 2, on the primary subjective measure of Drug Liking visual analog scale (VAS), morphine (the positive control; 10 and 20 mg), produced statistically significantly higher maximum ($E_{max}$) scores compared to placebo, which validates the study. Oliceridine at each of the doses tested (1, 2, and 4 mg) also produced statistically significantly higher $E_{max}$ scores compared to placebo.

**Table 2: Statistical Comparisons of Oliceridine, Morphine and Placebo on Subjective Measure Responses (from Study # CP130-1011)**

| **Subjective Measure (VAS)** (Emax) | **Morphine vs. Placebo** | | **Oliceridine vs. Placebo** | | | **Oliceridine vs. Morphine 10 mg** | | **Oliceridine vs. Morphine 20 mg** |
|---|---|---|---|---|---|---|---|---|
| | **10 mg** | **20 mg** | **1 mg** | **2 mg** | **4 mg** | **1 mg** | **2 mg** | **4 mg** |
| Drug Liking | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | NS | NS |
| Good Effects | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | NS | NS |
| High | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | NS | NS |
| Overall Drug Liking | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | NS | NS |
| Take Drug Again | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | NS | NS |
| Bad Effects | ↑ | ↑ | NS | ↑ | ↑ | ↓ | NS | NS |
| Drowsiness | ↑ | ↑ | ↑ | ↑ | ↑ | NS | NS | NS |
| Any Effects | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | NS | NS |

↑ = statistically significant increase, ↑ = statistically significant decrease,
NS = not statistically significant different

Morphine and oliceridine at each dose tested produced statistically significant increases compared to placebo on the other positive subjective measures of Good Drug Effects and High, as well as on measures taken at the end of the study, Overall Drug Liking and Take Drug Again. Each dose of oliceridine and morphine also produced statistically significant increases compared to placebo on Bad Effects (with the exception of 1 mg oliceridine), Drowsiness, and Any Drug Effects.

When oliceridine was compared to 10 mg morphine, the 1 mg oliceridine dose produced statistically significantly lower scores on all of the subjective measures (except for Drowsiness), while the 2 mg dose was statistically similar to morphine on all subjective measures. When the 4 mg dose of oliceridine was compared to 20 mg morphine, there were no statistically significant differences between the two drugs at these doses.

These data show that oliceridine produces positive and negative subjective responses at therapeutic and supratherapeutic doses that are similar to those produced by morphine.

***Drug Similarity Questionnaire***

On the Drug Similarity question, oliceridine and morphine were both identified as an "opioid" (72-84 points vs. 88-99 points, respectively) on the opioid VAS (evaluating similarity to morphine, hydrocodone, oxycodone, or hydromorphone). Oliceridine and morphine also were identified as "codeine" (53-57 points vs. 11-34 points, respectively) and "heroin" (37-40 points vs. 51-71 points, respectively).

***Pupillometry***

When pupil size was measured following administration of oliceridine and morphine, all doses of the two drugs produced miosis. The degree of miotic response was statistically significantly less for oliceridine at 1 and 2 mg compared to 10 mg morphine. Miosis was also statistically significantly less for 4 mg oliceridine compared to 20 mg morphine.

***Abuse-Related Adverse Events***

As shown in Table 3 (below), the most frequently-reported abuse-related adverse event resulting from administration of any dose of oliceridine or any dose of morphine was euphoric mood (38-58% vs. 50-69%, respectively). A high rate of somnolence was also reported in response to administration of oliceridine (8-20%) and morphine (15-33%). Paresthesia was also reported at a high rate for both oliceridine (3-8%) and morphine (8-19%). Placebo administration did not produce any of these abuse-related adverse events.

**Table 3: Abuse-Related Adverse Events (from Study # CP130-1011)**

| **Preferred Term** | **Oliceridine (N[%])** | | | **Morphine (N[%])** | | **Placebo (N[%]) N=40** |
|---|---|---|---|---|---|---|
| | **1 mg N=40** | **2 mg N=40** | **4 mg N=40** | **10 mg N=40** | **20 mg N=42** | |
| Euphoric mood | 15 (38%) | 20 (50%) | 23 (58%) | 20 (50%) | 29 (69%) | 0 |
| Somnolence | 3 (8%) | 8 (20%) | 7 (18%) | 6 (15%) | 14 (33%) | 0 |
| Paresthesia | 1 (3%) | 3 (8%) | 2 (5%) | 3 (8%) | 8 (19%) | 0 |

Each of these abuse-related adverse events reported in response to oliceridine show that this drug produces mu opioid agonists effects.

*Overall Conclusions*

Oliceridine at therapeutic and supratherapeutic doses produced subjective measures such as Drug Liking, High, Good Drug Effects and Take Drug Again. It also produced miosis as well as adverse events that included a high rate of euphoric effects. These drug responses parallel those produced by the positive control drug, morphine. Thus, oliceridine produces classic opioid responses in healthy individuals with a history of opioid abuse.

***Adverse Events in Clinical Safety and Efficacy Studies with Oliceridine***

*Phase 1 Clinical Safety Studies (Excluding HAP Study) (Study # CP130-1001, CP130-1002, CP130-1003, CP130-1005, CP130-1006, CP130-1007, and CP130-1008)*

In Phase 1 clinical studies conducted with 0.15 to 7.0 mg intravenous oliceridine in healthy subjects, there was a high rate of abuse-related adverse events (Table 4, below). These included ~12% euphoria, 13% relaxation, and 29% somnolence, with a ~2-5% rate of feeling abnormal, feeling drunk, fatigue, lethargy, hypoaesthesia, and paresthesia. Administration of 10 mg intravenous morphine produced many of the same abuse-related adverse events, but at an incidence that was lower than that reported for oliceridine.

**Table 4: Abuse-Related Adverse Events in Phase 1 Studies**

| **Preferred Term** | **Overall (N [%])** | | |
|---|---|---|---|
| | **Placebo (N=114)** | **Morphine 10 mg (N=30)** | **Oliceridine 0.15-7.0 mg (N=221)** |
| Euphoric mood | 1 (0.9%) | 1 (3.3%) | 26 (11.8%) |
| Somnolence | 3 (2.6%) | 8 (26.7%) | 65 (29.4%) |
| Feeling of relaxation | 0 | 0 | 29 (13.1%) |
| Fatigue | 0 | 2 (6.7%) | 12 (5.4%) |
| Lethargy | 1 (0.9%) | 1 (3.3%) | 9 (4.1%) |
| Hypoaesthesia | 0 | 0 | 8 (3.6%) |
| Paraesthesia | 0 | 1 (3.3%) | 7 (3.2%) |
| Feeling abnormal | 0 | 0 | 5 (2.3%) |
| Feeling drunk | 0 | 0 | 7 (3.2%) |

When the abuse-related adverse events produced by oliceridine are analyzed on the basis of dose (Table 5, below), there is a dose-dependent response for only certain adverse events such as euphoric mood, fatigue, lethargy, sluggishness, and hypoaesthesia. For some adverse events, such as somnolence, feeling abnormal and paresthesia, there was little difference dependent on dose. When relaxation was evaluated, there was a higher incidence at moderate doses compared to low or higher doses.

**Table 5: Abuse-Related Adverse Events in Phase 1 Studies by Dose Level**

| **Preferred Term** | **Oliceridine by Dose Level (N [%])** | | |
|---|---|---|---|
| | **<2.0 mg (N=42)** | **2.0-4.5 mg (N=148)** | **>4.5 mg (N=66)** |
| Euphoric mood | 6 (14.3%) | 22 (14.9%) | 17 (25.8%) |
| Somnolence | 15 (35.7%) | 57 (38.5%) | 26 (39.4%) |
| Fatigue | 0 | 8 (5.4%) | 8 (12.1%) |
| Lethargy | 0 | 8 (5.4%) | 7 (10.6%) |
| Hypoaesthesia | 1 (2.4%) | 7 (4.7%) | 7 (10.6%) |
| Feeling of relaxation | 2 (4.8%) | 21 (14.2%) | 5 (7.6%) |
| Feeling abnormal | 2 (4.8%) | 5 (3.4%) | 2 (3.0%) |
| Sluggishness | 0 | 2 (1.4%) | 2 (3.0%) |
| Paraesthesia | 1 (2.4%) | 7 (4.7%) | 2 (3.0%) |

Overall, the abuse-related adverse events reported in Phase 1 clinical studies show that oliceridine produces classic opioid-related effects such as euphoria and sedation, which often occurred on a dose-dependent basis.

*Phase 2/3 Clinical Efficacy Studies (Study # CP130-3001, CP130-3002, CP130-3003).*

In Phase 2/3 clinical efficacy studies conducted with 1-4 mg intravenous oliceridine for the treatment of pain, there was a moderate rate of abuse-related adverse events, as shown in Table 6 below. Somnolence was the most frequently reported adverse event (~7%), followed by sedation (~3%), anxiety (~2%), restlessness (~1%) and paraesthesia (~1%). Notably, euphoric effects were not reported, but this is common when abuse-related adverse events are assessed in a subject population being treated for pain conditions.

**Table 6: Abuse-Related Adverse Events in Phase 2/3 Studies**

| **Preferred Term** | **Placebo (N=252)** | **Morphine (N=305)** | **Oliceridine (N=1185)** |
|---|---|---|---|
| Somnolence | 10 (4.0%) | 41 (13.4%) | 79 (6.7%) |
| Sedation | 8 (3.2%) | 24 (7.9%) | 40 (3.4%) |

| | | | |
|---|---|---|---|
| Anxiety | 3 (1.2%) | 6 (2.0%) | 27 (2.3%) |
| Restlessness | 5 (2.0%) | 5 (1.6%) | 14 (1.2%) |
| Paraesthesia | 3 (1.2%) | 4 (1.3%) | 15 (1.3%) |

Overall, the abuse-related adverse events reported in Phase 2/3 clinical studies show that oliceridine produces some opioid-related effects similar to those produced by morphine.

## REFERENCES

Crowley RS, Riley AP, Sherwood AM, Groer CE, Shivaperumal N, Biscaia M, Paton K, Schneider S, Provasi D, Kivell BM, Filizola M, Prisinzano TE (2016) Synthetic Studies of Neoclerodane Diterpenes from Salvia divinorum: Identification of a Potent and Centrally Acting μ Opioid Analgesic with Reduced Abuse Liability. J Med Chem. 59(24):11027-11038.

Groer CE, Tidgewell K, Moyer RA, Harding WW, Rothman RB, Prisinzano TE, Bohn LM (2007) An Opioid Agonist that Does Not Induce μ-Opioid Receptor—Arrestin Interactions or Receptor Internalization. Molecular Pharmacology 71 (2) 549-557.

Hales TG (2011) Arresting the development of morphine tolerance and dependence. British Journal of Anaesthesia 107(5): 653–5.

Hill R, Disney A, Conibear A, Sutcliffe K, Dewey W, Husbands S, Bailey C, Kelly E, Henderson G (2018) The novel μ-opioid receptor agonist PZM21 depresses respiration and induces tolerance to antinociception. Br J Pharmacol. 175(13):2653-2661.

Kruegel AC, Gassaway MM, Kapoor A, Váradi A, Majumdar S, Filizola M, Javitch JA, Sames D (2016) Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. J Am Chem Soc. 138(21):6754-64.