CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210730Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210730
PDUFA Goal Date	August 7, 2020
OSE RCM #	2017-2277
Reviewer Name	Victoria Sammarco, Pharm.D., MBA
Team Leader	Carolyn Tieu, Pharm.D., MPH
Acting Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	August 7, 2020
Subject	Evaluation of Need for a REMS
Established Name	oliceridine
Trade Name	Olinvyk
Name of Applicant	Trevena Inc.
Therapeutic Class	opioid analgesic
Formulation(s)	1 mg/mL injection for intravenous use
Dosing Regimen	Initiate treatment with a 1.5 mg dose. For patient-controlled analgesia, recommended demand dose is 0.35 mg with a 6-minute lock out. A demand dose of 0.5 mg may be considered. Supplemental doses of 0.75 mg can be administered, beginning 1 hour after the initial dose, and hourly thereafter, as needed, not to exceed a daily dose of 27 mg

Table of Contents

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Olinvyk (oliceridine) is necessary to ensure the benefits outweigh its risks. Trevena Inc. submitted New Drug Application (NDA) 210730 for oliceridine with the proposed indication in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. The risks associated with oliceridine are consistent with other opioids which include addiction, abuse, misuse, life threatening respiratory depression, neonatal opioid withdrawal symptom, and concomitant use with benzodiazepines or other central nervous system depressants. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of oliceridine outweigh its risks. These risks will be mitigated through class-specific labeling including Boxed Warnings, Contraindications and Warnings and Precautions. This product will only be used in supervised healthcare settings able to appropriately monitor and manage intravenous opioid administration.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Olinvyk (oliceridine) is necessary to ensure the benefits outweigh its risks.[a] Trevena Inc. submitted New Drug Application (NDA) 210730 for oliceridine with the proposed indication in adults for the management of acute pain severe[b] enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.[1] This application is under review in the Division of Anesthesiology, Addiction, and Pain Medicine (DAAP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Oliceridine, a new molecular entity, is a full opioid agonist and relatively selective for the mu-opioid receptor. The mechanism of action is unknown but is thought to be related to coupling G protein with reduced β-arrestin 2 recruitment.[2] Oliceridine is a solution for intravenous injection supplied as 1mg/ml and 2mg/2ml single-dose vials, and 30mg/30ml single-patient use for patient-controlled analgesia (PCA) only. The recommended dosage includes initiating treatment with a 1.5 mg dose. For PCA, the recommend demand dose is 0.35 mg with a 6-minute lock-out.[1] A demand dose of 0.5 mg may be considered for some patients if the potential benefit outweighs the risks. Supplemental doses of 0.75 mg can be administered, beginning 1 hour after the initial dose, and hourly thereafter, as needed, not to

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

exceed a daily dose of 27 mg. The intended setting of use will only be in clinical settings that is equipped to appropriately monitor and manage potential overdose and life-threatening respiratory depression. Oliceridine is not currently marketed in any jurisdiction.

2.2 REGULATORY HISTORY

- 02/19/2016: FDA granted Trevena's breakthrough designation for the management of moderate-to-severe acute pain in patients 18 years of age or older for whom a parenteral opioid is warranted.
- 05/25/2017: Pre-NDA meeting where an agreement between Trevena and Agency was reached that a REMS did not need to be included in the NDA submission.
- 11/02/2017: Trevena submitted NDA 210730.
- 09/14/2018: FDA notified Trevena of the intent to rescind breakthrough designation because of emerging data no longer show substantial improvement over available therapies. Specifically, the data from the two Phase 3, double-blind, placebo- and morphine-controlled studies were not sufficient to support a conclusion that oliceridine has a safety advantage, relative to morphine.
- 10/11/2018: Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting was convened to discuss the safety and efficacy of oliceridine. Seven committee members voted in favor of approving and eight voted against. Some committee members expressed concern over a perception of decreased respiratory symptoms or improved safety over approved opioids that may not be accurate. They also commented on oliceridine not having a favorable benefit risk profile as compared to morphine. Some committee members did not express great concern over the hepatic or QT prolongation findings as these risks are commonly seen in many classes of medications and are commonly addressed with labeling; however, others expressed concerns over these potential adverse events and also concerns that the proposed dosing may not have adequate efficacy for moderate to severe pain.
- 11/02/2018 – Complete Response letter was sent to the applicant. The main clinical concerns were an inadequate safety database to support the proposed maximum daily dosing of 40 mg and identification of a QT prolongation effect with insufficient data to manage this safety concern through labeling.
- 02/07/2020 – Complete, class 2 Response resubmission received

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Acute pain is a serious condition and is common in many medical and surgical conditions. 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.[3] Inadequate treatment of postoperative pain can lead to worse outcomes, such as poor quality of life, function, and functional recovery, risk of post-surgical complications, and persistent postoperative pain.[c,4]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Pharmacologic options for acute pain management include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical agents (e.g., local anesthetics), and opioids. Parenteral opioids currently approved for acute pain in the United States include morphine, fentanyl, remifentanil, sufentanil, alfentanil, meperidine, and hydromorphone and were utilized in nearly 50 million hospitalized patients in 2017.[d,5] In the postoperative setting, opioids are frequently administered via the intravenous route, either through clinician directed boluses or through PCA devices.

4 Benefit Assessment

The data supporting this indication comes from two Phase 3 studies: CP130-3001 (3001) and CP130-3002 (3002). Both studies were randomized, double-blind, placebo- and morphine-controlled studies in adults with moderate to severe pain. Study 3001 was conducted in patients post-bunionectomy with a treatment duration of 48 hours. Study 3002 was conducted in post-abdominoplasty patients with a treatment duration of 24 hours. In both studies, oliceridine doses of 0.1 mg, 0.35 mg, and 0.5 mg were studied. Details of each study were previously summarized in a DRM review.[6]

In the previous submission, efficacy for general acute pain indication was established for the 0.35 mg and 0.5 mg PCA doses of oliceridine compared to placebo in both studies based on summed pain intensity difference (SPID) analysis.[e,2] Oliceridine 0.1 mg, however, was effective in one study (3001) but not the other (3002). In this resubmission, the applicant is using the same studies but proposing a maximum daily dose of 27 mg. To determine whether oliceridine would still be efficacious with the 27 mg dose limit, the Agency re-analyzed the applicant's original studies using SPID analyses. Oliceridine doses were categorized into <27mg and doses that exceed 27mg/day. Doses over the 27 mg daily dose limit were reclassified as rescue medication. In FDA's re-analysis of Study 3001, all three treatment arms (0.1 mg, 0.35mg, and 0.5 mg) still exhibit statistically significantly greater pain relief for oliceridine in comparison to placebo.[7] In FDA's re-analysis of Study 3002, two of the three doses of oliceridine (0.35

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

mg and 0.5 mg) demonstrated a statistically greater reduction in pain intensity than placebo but the 0.1 mg did not.[7]

The clinical reviewer concluded that the applicant provided substantial evidence of effectiveness based on the supplemental analyses, which demonstrated substantial, replicated evidence from both studies that the oliceridine 0.35 mg and 0.5 mg dose regimen was efficacious with the addition of a 27 mg per day dosing limit.[7]

5 Risk Assessment & Safe-Use Conditions

The major safety analysis of oliceridine is based on data from two phase 3 trials (3001 and 3002) and an open-label, uncontrolled safety study (3003). No deaths were reported in the clinical development program. Very few serious adverse events (SAE) were noted. Of those, most SAEs were not drug related and appeared to be related to post-operative events. Other common adverse events (AE) in the clinical program were dose-dependent and consistent with opioid-related adverse events, including respiratory events, such as respiratory depression and hypoxia, and gastrointestinal events, such as nausea and vomiting.[f] The safety profile of oliceridine for acute pain was consistent with the safety profile of a full opioid agonist and was well characterized in the previous clinical and DRM reviews.[6,7] With this resubmission, the Agency focuses on the safety data to address clinical and non-clinical deficiencies noted in the Complete Response letter.[8]

5.1 Inadequate Safety Database

One of the clinical concerns cited in the Complete Response letter was due to an inadequate safety database to support the proposed dosing of a maximum 40 mg/day. With this resubmission, the Applicant proposed a maximum daily dose of 27 mg. On review of the data, the Agency determined that a total of 354 patients received a daily dose of oliceridine greater than 27 mg in phase 2 and 3 studies. This met the Agency's prior advice to the applicant for NME safety database for an acute pain indication. Re-analysis of the safety data from the Phase 3 studies based on the daily dosing limit with stratification of AE into those patients receiving ≤27 mg vs >27 mg/day did not show any unexpected AEs. There were no major safety concerns identified in this subset of patients when applying a 27 mg/day dosing stratification.[7]

5.2 QT Prolongation

QT prolongation was an issue cited in the Complete Response letter as the applicant did not provide adequate data to support that the QT prolonging effects of oliceridine could be mitigated by labeling or monitoring. The applicant was asked to provide data from a randomized active-controlled study that included 24-hour Holter monitoring and replicate QT measurements extracted every hour from the

[f] Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Holter monitors. The applicant submitted tQT Study CP130-1014, a phase 1, single-center, multiple-dose, randomized, single-blind, placebo- and positive-controlled crossover study to evaluate the effect of oliceridine on cardiac repolarization over 24 hours in healthy subjects. Sixty-eight healthy volunteers were randomized with 64 completing the study. Subjects were given placebo by clinician-administered bolus every 2 hours over 24 hours, a single moxifloxacin 400 mg dose orally or oliceridine 3 mg or 2 mg by clinician-administered bolus every 2 hours over 24 hours.

The Agency's Interdisciplinary Review Team for Cardiac Safety Studies concluded that repeat dosing up to 27 mg resulted in mean 10.7ms QTc prolongation, which is considered not clinically significant.[9] The multiple dose QT-study supports the safety of repeating dose up to 27 mg per day.[7] Given that the mechanism behind the observed QTc prolongation is unknown, it's not possible to extrapolate the QTc effects outside the observed dosing schedule. Therefore, the label will include a Warning and Precaution section that QT effects beyond 27 mg daily dose is unknown. With the recommended labeling change, the applicant has adequately addressed the clinical deficiency related to QT-prolongation.

5.3 EMBRYO-FETAL TOXICITY

The initial Complete Response letter cited a lack of adequate data to confirm that levels of TRV0109662, a major human metabolite, had been adequately characterized for potential embryo-fetal effects. The applicant was advised to either conduct a dedicated embryo-fetal development study in either rat or rabbit with TRV0109662 or provide validated, reproducible pharmacokinetic data to support the conclusion that the existing rat or rabbit embryo-fetal development study resulted in exposures to TRV0109662 that were at least 50% of the levels present in humans. To address this deficiency, the applicant developed a new analytical method to evaluate TRV0109662 in rat and rabbit plasma and evaluated plasma samples from the original rat and rabbit embryo-fetal development studies. These data confirmed that the original embryo-fetal development studies adequately characterized the safety of this major human metabolite for the revised maximum daily dose of 27 mg/day.[10] The Agency's nonclinical team determined that the applicant submitted appropriate toxicology studies to support the safety of oliceridine in the original submission.

5.4 HEPATOXICITY

In the first review cycle, there were hepatic safety concerns as there were two cases of elevated transaminases ≥3 x upper limit (ULN) with concurrent total bilirubin ≥2x upper limit of normal and one serious adverse event of hepatic failure in the oliceridine-treated patients compared to none of these types of events in placebo or morphine. The Office of Surveillance and Epidemiology (OSE) was consulted to provide an assessment of whether oliceridine has potential to cause drug-induced liver injury. OSE concluded that these cases were confounded, and abnormal liver findings were possibly due to anesthesia and/or multiple concomitant perioperative medications and that no case met Hy's Law criteria.[7] Furthermore, incidence of elevated transaminases in oliceridine treatment group was similar to or less than morphine treatment group in pooled, controlled studies. The above hepatic findings were also discussed at an Advisory Committee (AC) meeting on October 11, 2018. The Committee members expressed a general consensus that oliceridine did not appear to have a hepatic safety signal. The

Agency concluded that it could not determine that transient elevations of hepatic transaminases were due to oliceridine alone.

When stratified by daily dose of 27 mg, the incidence of elevated transaminases was similar between ≤ 27 mg oliceridine group and >27 mg group, which is similar to the morphine treatment group in the phase 3 controlled studies.[7] The Agency concluded that hepatic safety is no longer a major safety issue that would require risk mitigation beyond labeling. If approved, labeling will acknowledge that patients with mild or moderate hepatic impairment may require less frequent dosing. For patients with severe hepatic impairment, the initial dose may be reduced, and subsequent doses may be administered only after a careful review of the patient's severity of pain and overall clinical status.

6 Expected Postmarket Use

Oliceridine is proposed as a parenteral analgesic therapy for patients for whom an intravenous opioid is warranted. It can be delivered as prescribed boluses or as part of a PCA regimen. As a result, this product will only be administered by healthcare providers in supervised healthcare settings able to sufficiently monitor for adverse effects. This medication will be most likely be used postoperatively.

7 Risk Management Activities Proposed by the Applicant

Trevena Inc. did not propose a REMS or risk management plan. Their rationale is that oliceridine is proposed to be used in healthcare settings under supervision of healthcare providers.

8 Discussion of Need for a REMS

The applicant has addressed all deficiencies noted in the Complete Response letter. Based on the pre-marketing efficacy and safety data submitted with this NDA, the Agency's clinical and statistical review team recommends approval of oliceridine PCA dosing regiments (0.35 mg and 0.5mg) with the limitation of use of 27 mg per day for acute pain management. The Agency agrees with Trevena's proposal that oliceridine should be given Schedule II designation if approved due to the potential for abuse.

Oliceridine is a full opioid agonist and will be administered intravenously only by healthcare providers via PCA in monitored healthcare settings. It has a similar benefit-risk profile to previously approved opioids for acute pain management. During clinical trials, it appears to have a similar safety profile, when used as labeled, to the active comparator, morphine. Like all opioids, oliceridine carries serious risks of abuse, misuse, and potential overdose which may result in death.

There are several REMS programs approved to mitigate the risks of abuse and misuse of various products in outpatient settings where there is less monitoring. Intravenous opioids have traditionally not required a REMS because they are primarily used in healthcare settings equipped to appropriately monitor patients. Likewise, oliceridine is to be administered in a healthcare setting compliant with DEA requirements for controlled substance usage and that can sufficiently monitor patients that require intravenous opioids. Furthermore, in these inpatient, post-surgical, or other settings in which acute pain

is managed, the duration of therapy is usually short, and oversight of therapy is robust. The risks of abuse and misuse of intravenous opioids in these settings are much less like than in outpatient settings.

If approved, the oliceridine label will include class-wide opioid risks with boxed warnings for numerous safety concerns, including life-threatening respiratory depression, abuse, and misuse. The oliceridine label will also include Limitations of Use that daily dosing should not exceed 27 mg and will include Warnings and Precautions that cumulative total daily doses greater than 27 mg may increase the risk for QTc interval prolongation. The benefit of an additional opioid to treat acute pain for patients in a supervised healthcare setting outweighs the known safety risks related to opioids. A REMS is not required for oliceridine as these risks will be mitigated through labeling.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with oliceridine are well documented. Like other opioids, oliceridine carries the risks of respiratory depression and sequelae of misuse and abuse in addition to other risks inherent to opioid medications. Oliceridine is an intravenous opioid and will only be used in supervised healthcare settings able to appropriately monitor and manage intravenous opioid administration. The oliceridine label will include class-wide opioid risks with Boxed Warnings, Contraindications and Warnings and Precautions.

Should DAAP have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

1. Treva. Proposed Prescribing Information for oliceridine. [August 7, 2020].

2. Kilgore E, Travis J, Maynard J, Petullo P, Rothman M, Hertz S, et al. Cross-Discipline Team Leader Review; Division/Office Director Review; Primary Clinical Review; Primary Statistical Review for oliceridine NDA 210730 injection, daarted November 1, 2018.

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

4. Chou R, Gordon DB, Leon-Casasola OAde, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *The Journal of Pain*. 2016:17(2):31-157

5. IMS charge detail master hospital cost database, FY 2017 data.

6. Dunn S. Evaluation of Need for a REMS for oliceridine NDA 210730, daarted November 1, 2018.

7. Deng E, Kilgore E, Travis J, Bastings E. Cross-Discipline Team Leader Review; Primary Clinical Review; Primary Statistical Review for oliceridine NDA 210730 injection, daarted August 7, 2020.

8. Complete Response Letter for oliceridine NDA 210730, daarted November 2, 2018.

9. Johannsen L. QT-IRT Review for oliceridine NDA 210730 solution, daarted 4/16/2020.

10. Zhang M, Chang JH, Mellon DR. Pharmacology/Toxicology Review and Evaluation for oliceridine NDA 210730 solution, daarted July 16, 2020.

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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type/Number	NDA 210730
PDUFA Goal Date	November 2, 2018
OSE RCM #	2017-2277
Reviewer Name(s)	Somya Dunn, MD
Team Leader	Selena Ready, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	November 1, 2018
Subject	Evaluation of Need for a REMS
Established Name	Oliceridine
Name of Applicant	Trevena Incorporated
Therapeutic Class	Opioid
Formulation	1 mg/mL Injection for intravenous use
Dosing Regimen	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

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, oliceridine, is necessary to ensure the benefits outweigh its risks. Trevena Incorporated (Trevena) submitted a New Drug Application (NDA 210730) for oliceridine with the proposed indication for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted. Oliceridine is a G protein-biased ligand that binds to the μ-opioid receptor under review by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). Trevena did not submit a proposed REMS or risk management plan with this application.

The risks associated with oliceridine are similar to those known with other approved intravenous (IV) opioid analgesics and include physical dependence, withdrawal, Neonatal Opioid Withdrawal Syndrome (NOWS), risks from the concomitant use with benzodiazepines or other CNS depressants and life-threatening respiratory depression. In addition, during the clinical development, oliceridine raised concerns of QT prolongation, hepatic safety and respiratory safety.

DAAAP has determined that the submission currently under review will likely receive a complete response (CR) as the review of the submission raised concerns with QT prolongation, the size of safety database was not adequate and there was also Agency concerns that levels of TRV0109662, a major human metabolite, had not been adequately characterized for potential embryo-fetal effects. Therefore, DRISK defers comment on the evaluation of the need for a REMS for oliceridine. Evaluation of the need for a REMS for oliceridine, will be undertaken by DRISK after the Applicant resubmits the NDA for review.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) oliceridine is necessary to ensure the benefits outweigh its risks. Trevena Incorporated (Trevena) submitted a New Drug Application (NDA 210730) for oliceridine with the proposed indication for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted. The risks associated with IV opioid analgesics are attributable to oliceridine and include physical dependence, withdrawal, Neonatal Opioid Withdrawal Syndrome (NOWS), risks from concomitant use with benzodiazepines and other CNS depressants and respiratory depression. In addition, oliceridine raised concerns of QT prolongation, hepatic safety and respiratory safety. Trevena did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Oliceridine is a new molecular entity, 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 asserted that oliceridine would have faster, more complete pain relief with improved safety and better tolerability than conventional opioids due the difference in mechanism of action. 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. Trevena is seeking approval of the 0.1 mg and 0.35 mg doses. Opioids are typically administered as needed (PRN) for acute pain.

2.2 REGULATORY HISTORY

- 02/19/2016: FDA granted Trevena's breakthrough designation for the management of moderate-to-severe acute pain in patients 18 years of age or older for whom a parenteral opioid is warranted.
- 05/25/2017: Pre-NDA meeting where an agreement between Trevena and Agency was reached that a REMS did not need to be included in the NDA submission.
- 11/02/2017: Trevena submitted NDA 210730.
- 09/14/2018: FDA notified Trevena of the intent to rescind breakthrough designation because emerging data no longer show substantial improvement over available therapies. Specifically, the data from the two Phase 3, double-blind, placebo- and morphine-controlled studies were not sufficient to support a conclusion that oliceridine has a safety advantage, relative to morphine.
- 10/11/2018: Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting was convened to discuss the safety and efficacy of oliceridine. Seven committee members voted in favor of approving and eight voted against. Some committee members expressed concern over a perception of decreased respiratory symptoms or improved safety over approved opioids that may not be accurate. They also commented on oliceridine not having a favorable benefit risk profile as compared to morphine. Some committee members did not express great concern over the hepatic or QT prolongation findings as these risks are commonly seen in many classes of medications and are commonly addressed with labeling; however, others expressed concerns over these potential adverse events and also concerns that the proposed dosing may not have adequate efficacy for moderate to severe pain.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION AND TREATMENT OPTIONS

Pharmacologic options for pain management 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, sublingual, transdermal, parenteral, neuraxial, and rectal routes. In the postoperative setting, opioids are frequently administered intravenously (IV), either through clinician administered boluses or via patient-controlled analgesia

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

4 Benefit Assessment

The main efficacy results came from the two Phase 3 trials, 3001 and 3002. Both of these studies were double-blind, placebo- and active-controlled studies in adults with moderate to severe pain. Patients in 3001 had undergone a bunionectomy and patients in 3002 had undergone abdominoplasty.

For Study 3001, the treatment duration was 48 hours. 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 numeric rating scale (NRS) ≥4 within 9 hours after discontinuation of regional anesthesia were eligible to begin study treatment. Patients using chronic opioid therapy, chronic NSAIDs, or use of any analgesic medication within five half-lives before surgery were excluded.

Study medication regimens consisted of an initial clinician-administered loading dose of study medication, demand doses delivered by patient-controlled analgesia (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. 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).

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.

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). 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).

The inclusion and exclusion criteria were the same in Study 3002 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 were eligible to begin study treatment. The medication regimen in Study 3002 was the same as 3001 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

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). 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).

5 Risk Assessment & Safe-Use Conditions

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 came from two Phase 2 studies (2001 and 2002). Studies 2001 and 3001 were conducted in patients after bunionectomy, while study 2002 and 3002 were conducted in patients after abdominoplasty. The analysis of the safety data was complicated by the differing dosing regimens utilized in the clinical studies. As a result, the Agency focused on the two controlled Phase 3 studies.

The Agency identified an imbalance in adverse events related to elevations in liver function tests (LFTs) that were of concern. There was 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. There was also an overall higher percentage of patients in the oliceridine-treatment group who experienced ≥20xULN transaminases compared to no cases in the placebo or morphine groups. During the course of the review, the Agency also identified and investigated concerns regarding QT prolongation.

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. 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%, treatment emergency adverse events (TEAEs) in the respiratory, thoracic, and mediastinal disorders, and patients with any oxygen administration. There were trends showing a decreased percentage of respiratory events with oliceridine than morphine for some parameters, this was not consistent across all parameters. In Study 3001, the percentage of patients with TEAEs of sedation or somnolence was highest in the oliceridine 0.35 mg treatment arm 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 arms compared to the other treatment arms, see Table 1.

Table 1: Sedation and Somnolence Rates in Studies 3001 and 3002[a]

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

The mechanism of action of oliceridine is similar to standard opioids. The Controlled Substance Staff's (CSS's) review of the abuse potential[b] of oliceridine was in agreement with Trevena that nonclinical and clinical studies show that the drug is a μ-opioid agonist with high abuse potential, based on abuse-related data.

Overall, 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. Concerns with QT prolongation, and also levels of TRV0109662, a major human metabolite that has potential embryo-fetal effects require additional studies. The safety database also needs to be expanded to better understand these risks.

6 Expected Postmarket Use

Oliceridine is proposed as a parenteral pain therapy for patients for whom an intravenous opioid is warranted. It can be delivered as part of a PCA. As a result, this product would be administered by healthcare providers in healthcare settings. Most likely this mediation would be used following surgical procedures as it was studied in the clinical development program.

7 Risk Management Activities Proposed by Trevena

[a] FDA Advisory Committee Background Document for Oliceridine, Table 50, 10/11/2018.

[b] Bonson, K. FDA CSS Consult Review for oliceridine 10/23/2018.

Trevena did not propose a EMS or risk management plan. Their rationale is that oliceridine is proposed to be used in healthcare settings under supervision of healthcare providers.

8 Conclusions

DAAAP has determined that the submission currently under review will likely receive a complete response (CR) as the review of the submission raised concerns with QT prolongation, the size of safety database was not adequate and there was also Agency concerns that levels of TRV0109662, a major human metabolite, had not been adequately characterized for potential embryo-fetal effects. Additional studies to address these concerns will be needed. Therefore, DRISK defers comment on the evaluation of the need for a REMS for oliceridine. Evaluation of the need for a REMS for oliceridine, will be undertaken by DRISK after the Applicant resubmits the NDA for review.

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

/s/

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