

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210730Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

## Second Cycle Review And Summary Basis for Approval

<b>Date</b>	8/07/2020
<b>From</b>	Elizabeth Kilgore (Primary Clinical Reviewer); James Travis (Primary Statistical Reviewer); Jinglin Zhong (Statistical Team Leader); Emily Deng (Cross-Discipline Team Leader Reviewer); Naomi Lowy (Acting Deputy Division Director); Eric Bastings (Acting Deputy Director, Office of Neuroscience)
<b>Subject</b>	Second Cycle Review And Summary Basis for Approval (Primary Clinical Review; Primary Statistical Review; Cross-Discipline Team Leader Review)
<b>NDA/BLA # and Supplement#</b>	210-730
<b>Applicant</b>	Trevena, Inc.
<b>Date of Re-Submission</b>	February 7, 2020
<b>PDUFA Goal Date</b>	August 7, 2020
<b>Proprietary Name</b>	Oliceridine injection
<b>Established or Proper Name</b>	Olinvyk
<b>Dosage Form(s)</b>	1 mg/mL in a glass vial for intravenous use  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
<b>Applicant Proposed Indication(s)/Population(s)</b>	Management of moderate to severe acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate, in adults
<b>Applicant Proposed Dosing Regimen(s)</b>	Initial dose should typically be 1 to 2 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 OLINVYK.  Maintenance analgesia is generally achieved with

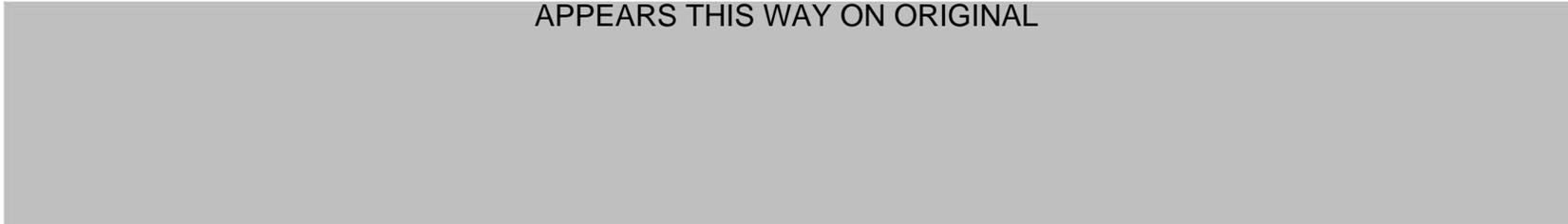
	OLINVYK administered at doses of 1 to 2 mg every 2 to 3 hours as needed, or as patient-controlled analgesia (PCA) demand doses of 0.1 to 0.35 mg as needed.
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s)</b> (if applicable)	Management of moderate to severe acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate, in adults
<b>Recommended Dosing Regimen(s)</b> (if applicable)	For patient-controlled analgesia (PCA), OLINVYK can be administered by a healthcare provider as a loading dose of 1.5 mg followed by access to patient demand doses with a 6-minute lock-out. The recommended demand dose is 0.35 mg. 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 OLINVYK can be administered by healthcare providers, beginning 1 hour after the initial dose, and hourly thereafter as needed.

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# 1 Benefit-Risk Assessment

## Benefit-Risk Assessment Framework

### Benefit-Risk Integrated Assessment

Trevena, Inc. (Trevena) submitted a 505 (b)(1) new drug application (NDA 210-730) on November 2, 2017, for oliceridine injection, a new molecular entity (NME) indicated for the management of moderate-to-severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Oliceridine is a full opioid agonist and is relatively selective for the mu-opioid receptor. The product is proposed to be administered by healthcare providers and/or delivered via patient-controlled analgesia (PCA) in monitored health care settings such as hospitals and emergency departments.

Acute pain is a serious medical condition. Adequate control of acute pain after surgery or painful procedures plays an important role in patient recovery. Prescription opioids are often a component of a multimodal analgesic approach, which is standard in many institutions. The treatment of acute pain with opioids must be balanced with public health considerations related to abuse, misuse, and accidental or intentional overdose.

The original application received a Complete Response (CR) action on November 2, 2018, because of clinical, nonclinical, and product quality deficiencies. This application was discussed at an Advisory Committee meeting during the first review cycle. Two of the concerns that the committee expressed were insufficient safety data and QT prolongation. There were two major clinical deficiencies identified in the CR letter: 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.

Trevena submitted a Complete Response on February 7, 2020. The resubmission included information to address the clinical, nonclinical, and product quality deficiencies listed in the CR letter. To address the clinical deficiencies, the applicant proposed a maximum daily dose of 27 mg, for which there is an adequate safety database, and submitted the results of a multiple-dose tQT study (CP130-1014) to support that repeat dosing up to a 27 mg total daily dose does not result in clinically significant QT prolongation.

Trevena conducted 18 clinical trials in support of this application, including 12 Phase 1 studies, three Phase 2 studies, and three Phase 3 studies.

Efficacy of oliceridine was evaluated in two randomized, double-blind, placebo- and morphine-controlled safety and efficacy studies (3001 and 3002). Study 3001 included a treatment duration of 48 hours in patients after bunionectomy, and Study 3002 included a 24-hour treatment duration in patients after abdominoplasty. Three doses of patient-controlled analgesia (PCA) were studied. Efficacy was established for the 0.35 mg and 0.5 mg PCA doses of oliceridine, compared to placebo, in both studies, based on a summed pain intensity difference (SPID) analysis. The 0.1 mg PCA dose was superior to placebo in one study only.

The safety profile of oliceridine in acute pain is consistent with that of a full opioid agonist. Dose-dependent adverse reactions for oliceridine include respiratory depression, hypoxia, nausea, vomiting, and constipation. All opioids, including oliceridine, carry serious risks including, but not limited to, abuse, misuse, and potential overdose, which may result in death. This product is to be administered only in clinical settings that are equipped to manage possible overdose. The review team agrees with the applicant that oliceridine should be classified as Schedule II.

Oliceridine has a benefit-risk profile similar to that of other opioids approved to treat acute pain; there is no evidence for a safety advantage of oliceridine over other opioids. Opioid-related safety risks of oliceridine can be managed through labeling. The oliceridine label will include a Limitations of Use statement that daily dosing should not exceed 27 mg. In addition, the label will include a Warnings and Precautions statement that cumulative total daily doses greater than 27 mg may increase the risk for QTc interval prolongation. The product label will also include class-wide opioid boxed warnings for opioids.

Based on the intended use of oliceridine for the treatment of moderate to severe acute pain in a highly controlled environment (i.e., parenteral administration under direct medical supervision), the prescribing information in the label will be sufficient to address the safe use of oliceridine injection in monitored healthcare settings, and a separate risk evaluation and mitigation strategy (REMS) is not required.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> <li>▪ Acute pain is a serious medical condition, which can affect function and quality of life.</li> <li>▪ Pain is a well-recognized medical condition in a variety of medical settings, especially post-operatively.</li> <li>▪ The goal of treatment is to control pain with minimal drug-related side effects.</li> </ul>	<p>Acute pain is a serious condition and is common in many medical and surgical conditions. Untreated acute pain can result in prolonged hospital stays, increased hospital readmission, and increased patient dissatisfaction.</p> <p>While there is heterogeneity in the types and causes of acute pain, adequate control of acute pain is important.</p>
Current Treatment Options	<ul style="list-style-type: none"> <li>▪ 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.</li> <li>• 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).</li> </ul>	<p>There are multiple current pharmacologic treatment options for patients with acute pain, including opioids. All opioids have potential risks that include respiratory depression, which may result in death as a result of overdose, and other known opioid-related adverse effects, such as constipation, nausea, and vomiting.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>▪ Parenteral opioids currently approved for acute pain in the United States include morphine, fentanyl, meperidine, and hydromorphone.</li> </ul>	
Benefit	<ul style="list-style-type: none"> <li>▪ Efficacy of oliceridine was evaluated in two randomized, double-blind, placebo- and morphine-controlled studies (3001 and 3002) in patients with postoperative pain (pain intensity of <math>\geq 4</math> on a 0-10 numeric rating scale). Study 3001 was a 48-hour treatment duration trial in patients after bunionectomy, and Study 3002 was a 24-hour treatment duration trial in patients after abdominoplasty.</li> <li>▪ In each study, patients were randomized to one of three oliceridine treatment regimens, a placebo-control regimen, or a morphine-control regimen. Each oliceridine regimen included a loading dose of 1.5 mg, followed by access to demand doses of 0.10 mg, 0.35 mg, or 0.5 mg, with a 6-minute lockout period between doses, and optional 0.75 mg supplemental doses, beginning 1 hour after the initial dose, and hourly thereafter, as needed. The morphine regimen included a loading dose of 4 mg, followed by access to a demand dose of 1 mg, with a 6-minute lockout period between doses, and 2 mg supplemental doses, beginning 1 hour after the initial dose, and hourly thereafter, as needed.</li> <li>▪ Protocol-specified rescue medication was etodolac. However, some patients across all treatment groups received alternative opioids as rescue medications, such as hydrocodone/APAP or oxycodone.</li> <li>▪ The primary efficacy endpoint was the time-weighted sum of pain intensity difference over 48 hours (SPID 48) for Study 3001, and over 24 hours for Study 3002 (SPID 24). Both the 0.35 mg and 0.5 mg PCA demand doses of oliceridine demonstrated a statistically greater reduction in pain intensity than placebo in both studies. Notably, morphine demonstrated a significantly greater reduction in pain intensity than all three regimens of oliceridine that were tested in the studies. The 0.1 mg demand dose of oliceridine was superior to placebo in Study 3001 but not in Study 3002.</li> <li>▪ The quality of both controlled efficacy studies was adequate, and the study population is an adequate representation of patients with acute moderate-to-severe pain in the United States.</li> </ul>	<p>There is a clear dose-response for the efficacy of oliceridine, with both the 0.35 mg and 0.5 mg PCA doses superior to placebo. The 0.5 mg PCA demand dose of oliceridine appears to provide additional analgesia compared to the 0.35 mg dose, and can be considered for some patients in which potential benefit outweighs risks.</p> <p>Oliceridine is an additional option to the already available intravenously-administered opioids for acute pain, and provides a new option for those who are unable to take currently approved opioid products due to allergies or other reasons.</p> <p>Most opioids are titrated to effect, without specific daily dose limit. For oliceridine, however, a cumulative total daily dose of 27 mg should not be exceeded because total daily doses greater than 27 mg may increase the risk for QTc interval prolongation. When patients reach the 27 mg cumulative total daily dose, an alternative analgesic regimen should be administered until oliceridine can be resumed the next day. Alternative analgesia may include multi-modal therapies.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	<ul style="list-style-type: none"> <li>▪ The safety of oliceridine was evaluated in a total of 1535 patients with moderate-to-severe acute postoperative pain. Of these, 1181 patients received a total daily dose <math>\leq 27</math> mg oliceridine, and 354 patients received a total daily dose <math>&gt; 27</math> mg oliceridine during the first 24-hour treatment period.</li> <li>▪ No death was reported in the oliceridine clinical development program. In Study 3001, no patient who received oliceridine experienced a serious adverse event (SAE). In Study 3002, five patients (2%) who received oliceridine experienced an SAE; the events include post-procedural hemorrhage, syncope, lethargy, deep vein thrombosis, and abdominal wall hematoma. Some of these events appear to be related to post-operative events, while others are likely opioid-related. No placebo-treated patient experienced an SAE in Study 3002. In open-label Study 3003, 26 patients (3%) who received oliceridine experienced a total of 32 treatment-emergent SAEs. Most SAEs did not appear drug-related.</li> <li>▪ There is clear dose-response for treatment-emergent adverse events (TEAE) with oliceridine treatment. The incidence of TEAEs was higher in patients randomized to 0.5 mg demand doses than in those randomized to 0.35 mg demand doses. The incidence of TEAE was also higher in patients who received a total daily dose <math>&gt; 27</math> mg than those who received a total daily dose <math>\leq 27</math> mg.</li> <li>▪ Common dose-dependent adverse reactions of oliceridine (<math>\geq 5\%</math> occurrence) were opioid-related, including nausea, vomiting, dizziness, headache, constipation, pruritis, hot flush, hypoxia, somnolence and oxygen saturation decreased.</li> <li>▪ In Study 3001, the incidence of TEAEs leading to oliceridine discontinuation was higher in patients randomized to 0.5 mg demand doses (6%) than in those randomized to 0.35 mg demand doses (1%). In Study 3002, the incidence of TEAE leading to oliceridine discontinuation was similar (5% in each group) between patients randomized to 0.5 mg demand doses and those randomized to 0.35 mg demand doses. The incidence of oliceridine discontinuation was higher in patients who received a total daily dose <math>&gt; 27</math> mg than those who received a total daily dose <math>\leq 27</math> mg. TEAEs leading to oliceridine discontinuation included hypotension, hypoxia, nausea, hypoventilation, oxygen saturation decreased, alanine aminotransferase increased, aspartate aminotransferase increased, electrocardiogram QT prolongation, and urticaria.</li> <li>▪ In order to meet safety database requirements and address the QT prolongation issue, the applicant, respectively, submitted the results of a new</li> </ul>	<p>The safety database is adequate to support the proposed maximum total daily dose of 27 mg. The safety profile of oliceridine is well characterized.</p> <p>Most opioids are titrated to effect, without specific daily dose limit. For oliceridine, however, a cumulative total daily dose of 27 mg should not be exceeded because total daily doses greater than 27 mg may increase the risk for QTc interval prolongation.</p> <p>When patients reach the 27 mg cumulative total daily dose, an alternative analgesic regimen should be administered until oliceridine can be resumed the next day. Alternative analgesia may include multi-modal therapies.</p> <p>The safety profile of oliceridine in acute pain is consistent with the safety profile of an opioid agonist. There is no evidence that oliceridine provides any safety advantage over other opioid drugs. Most dose-dependent adverse reactions for oliceridine were opioid-related and can be monitored in the acute pain setting.</p> <p>Oliceridine is to be administered intravenously only by healthcare providers and/or via patient-controlled analgesia in monitored healthcare settings.</p> <p>The current risks of oliceridine, as identified, can be addressed through labeling.</p> <p>The oliceridine label will include class-wide opioid risks, with boxed warnings for life-threatening respiratory depression, abuse, and misuse.</p> <p>The abuse potential study supports the recommendation that oliceridine be given Schedule II designation due to the potential for abuse.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>thorough QT study and proposed a maximum recommended cumulative daily dose of 27 mg.</p> <ul style="list-style-type: none"> <li>▪ Repeat dosing of oliceridine up to 27 mg per day resulted in a mean 10.7 msec QT prolongation, which is not considered clinically significant. However, the QT-effect of oliceridine with a daily dosage greater than 27 mg cannot be predicted from the multiple-dose thorough QT study.</li> <li>▪ Hepatic Safety: No Hy’s law case was identified in the oliceridine clinical development program. There was one case of elevated transaminases <math>\geq 3 \times \text{ULN}</math> leading to drug discontinuation in oliceridine treatment group. Incidence of elevated transaminases in patients treated with oliceridine was similar to or lower than in patients treated with morphine in pooled controlled studies.</li> </ul>	<p>The Limitations of Use and Warnings and Precautions section of the label will state that the cumulative total daily dosage of oliceridine should not exceed 27 mg, as total a daily dosage greater than 27 mg may increase the risk for QTc interval prolongation.</p>

## 2 Background

Trevena, Inc. (Trevena) submitted a 505 (b)(1) new drug application (NDA) 210-730 on November 2, 2017, for the new molecular entity (NME) oliceridine injection, 1 mg/mL. The proposed indication is for the management of moderate to severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom [REDACTED] (b) (4)

[REDACTED] The product is to be administered by a healthcare provider and/or via patient-controlled analgesia (PCA) in healthcare settings only.

Oliceridine is a full opioid agonist and is relatively selective for the mu-opioid receptor. The principal therapeutic action of oliceridine is analgesia. Oliceridine is described by the applicant as a G protein-biased ligand that binds to the  $\mu$ -opioid receptor and stimulates G protein-coupling with reduced  $\beta$ -arrestin 2 recruitment. According to the applicant, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug. Trevena recommends oliceridine be designated as Schedule II given that it has a similar nonclinical and clinical pharmacologic profile to existing Schedule II opioids.

Following an Advisory Committee meeting in October 2018, the original NDA submission was issued a Complete Response letter on November 2, 2018 (see Appendix A). Clinical, nonclinical, and product quality deficiencies identified in the Complete Response letter are briefly summarized below:

- Clinical deficiency #1: Inadequate data to support the safety of oliceridine due to concerns related to QT prolongation seen in a single-dose thorough QT study.
- Clinical deficiency #2: Inadequate safety database to support the proposed maximum daily dosage of 40 mg/day.
- Nonclinical deficiency: Inadequate data to confirm that the levels of a major human metabolite had been adequately characterized for potential embryo-fetal effects.
- Product quality deficiency: Validation reports for the analytical methods used for the leachables study were not provided to the Agency.

The Applicant submitted their Complete Response on February 7, 2020. The submission included information to address the clinical, nonclinical, and CMC deficiencies listed in the Complete Response letter.

This review will summarize how clinical, nonclinical, and product quality deficiencies have been addressed by the Applicant in each corresponding section, and will also summarize the safety and efficacy evidence that supports oliceridine approval for the proposed indication.

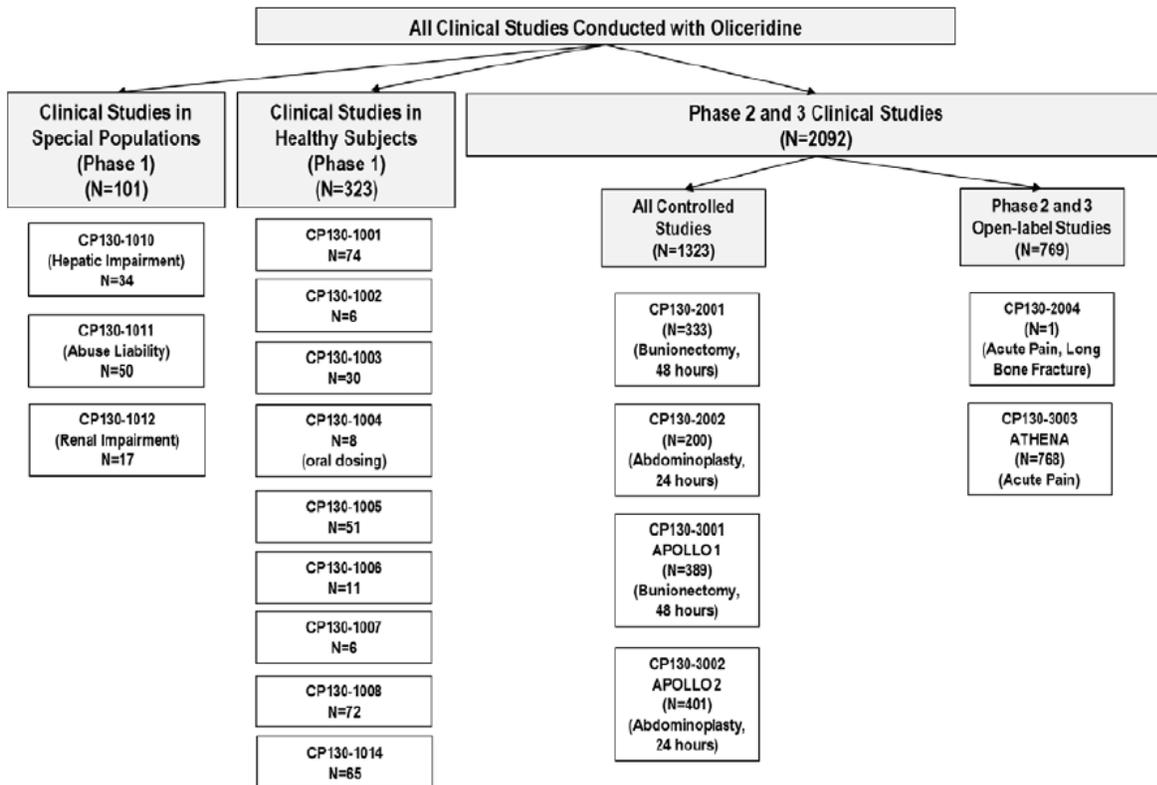
### 2.1 Overview of the Clinical Program

The clinical development of oliceridine was undertaken with advice from the Division. Trevena conducted 18 clinical trials in support of this application, including 17 clinical trials

for which results were presented in the original application, and one new clinical trial presented in this resubmission. The 18 clinical trials are categorized as follows:

- 12 Phase 1 studies
  - 9 studies in healthy subjects (single or multiple dose)
    - 8 studies via IV administration: Studies CP130-1001, -1002, -1003, -1005, -1006, -1007, -1008, -1014
    - 1 study via oral administration: Study CP130-1004
  - 2 studies in special populations:
    - Study CP130-1010 (Hepatic Impairment Study) and Study CP130-1012 (Renal Impairment Study)
  - 1 abuse liability study: 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)

Figure 1: Clinical Studies Conducted with Oliceridine



Applicant’s figure, Clinical Overview, p. 9, Resubmission. Abbreviations: N=number of subjects/patients treated with oliceridine or control; Source:

### Key Clinical Studies

A total of 1918 unique individuals were exposed to oliceridine (286 healthy subjects in Phase 1 studies, 97 special population subjects in Phase 1 studies, and 1535 patients in Phase 2 and Phase 3 studies). The safety of oliceridine was evaluated in 470 patients with acute post-operative pain in controlled Phase 3 studies 3001 and 3002, and in 768 patients in the uncontrolled Phase 3 study 3003.

*Phase 3 Controlled Studies:* 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). Both were double-blind, placebo- and active-controlled (morphine-comparator) studies in adults with moderate to severe pain. Patients in Study 3001 had undergone a bunionectomy, while patients in Study 3002 had undergone abdominoplasty. The treatment duration was 48 hours in Study 3001 and 24 hours in Study 3002. Patients using chronic opioid therapy (defined as >15 morphine equivalent units per day, for more than 3 out of 7 days per week, for more than 1 month, within 12 months before surgery) or who used any analgesic medication within five half-lives before surgery were excluded. These studies are described in more detail in Section 7 of this review.

The efficacy studies used a design that is typical for the proposed indication. The Agency also provided feedback to the applicant on study design during drug development.

The study design and treatment regimens are summarized in Table 1.

**Table 1: Study Design and Treatment Regimens in Controlled Phase 3 Studies 3001 and 3002**

Study ID	Study Objective(s)	Study Design	Treatment Regimen	Total Number of Subjects or Patients Randomized/ Treated/Completed
<b>Adequate and Well Controlled Studies Phase 3 Studies</b>				
CP130-3001 (APOLLO 1)	Efficacy, safety	MC, R, DB, PC, AC in patients undergoing bunionectomy	<p><u>IV oliceridine:</u> 1.5 mg loading dose and 0.1, 0.35, or 0.5 mg demand dose; 6 min lockout interval</p> <p><u>IV morphine:</u> 4 mg loading dose and 1 mg demand dose; 6 min lockout interval</p> <p><u>IV placebo:</u> volume and time matched treatments</p> <ul style="list-style-type: none"> <li>Supplemental doses permitted PRN 1 hr after loading dose and hourly thereafter</li> <li>Treatment period: 48 hours</li> </ul>	418/389/378
CP130-3002 (APOLLO 2)	Efficacy, safety	MC, R, DB, PC, AC in patients undergoing abdominoplasty	<p><u>IV oliceridine:</u> 1.5 mg loading dose and 0.1, 0.35, or 0.5 mg demand dose; 6 min lockout interval</p> <p><u>IV morphine:</u> 4 mg loading dose and 1 mg demand dose; 6 min lockout interval</p> <p><u>IV placebo:</u> volume and time matched treatments</p> <ul style="list-style-type: none"> <li>Supplemental doses permitted PRN 1 hr after loading dose and hourly thereafter</li> <li>Treatment period: 24 hours</li> </ul>	407/401/393

Applicant’s table 1, ISS 120-day safety update, p. 39; MC=multicenter; R=randomized; DB=double-blind; PC=placebo-controlled; AC=active control.

*Phase 3 Open-Label Study:* The primary objective of Phase 3 open-label study 3003 was to provide supportive safety in surgical and medical patients with moderate to severe acute pain for whom parenteral opioid therapy was warranted (i.e., NRS pain intensity  $\geq 4$ ), in hospital or outpatient center settings. A total of 768 patients were enrolled, and 698 completed the study. The study design and treatment regimens are shown in Table 2.

**Table 2: Study Design and Treatment Regimens in Open-Label Phase 3 Study 3003**

Study ID	Study Objective(s)	Study Design	Treatment Regimen	Total Number of Subjects or Patients Randomized/Treated/Completed
<b>Open-label Phase 3 Study</b>				
CP130-3003 (ATHENA)	Safety, effectiveness	MC, OL in surgical and medical patients	<p><b>IV oliceridine:</b> administered either by clinician-administered bolus, PCA, or both bolus and PCA, according to the clinical situation.</p> <p>Clinician-administered bolus dosing:</p> <ul style="list-style-type: none"> <li>Initial dose 1-2 mg;</li> <li>Supplemental dose 1 mg PRN, as early as 15 minutes after the initial dose;</li> <li>Subsequent doses 1-3 mg every 1-3 hours PRN.</li> </ul> <p>In settings where rapid analgesia is targeted (eg, ED or PACU):</p> <ul style="list-style-type: none"> <li>Initial dose 1-3 mg;</li> <li>Supplemental doses 1-3 mg every 5 minutes PRN;</li> <li>Subsequent doses 1-3 mg every 1-3 hours PRN.</li> </ul> <p>PCA Regimen:</p> <ul style="list-style-type: none"> <li>Loading dose: 1.5 mg;</li> <li>Demand dose: 0.5 mg;</li> <li>Lockout interval: 6 minutes.</li> </ul> <ul style="list-style-type: none"> <li>Supplemental 1 mg doses permitted PRN.</li> <li>Treatment period: The duration of treatment for each patient is determined by the clinical need for parenteral opioid therapy. In current practice, parenteral opioids are used PRN for up to several days.</li> </ul>	Nonrandomized/768/698

Applicant’s table 1, ISS 120-day safety update, p. 40; MC=multi-center; OL=open-label

*Second Review Cycle Clinical Studies:* The only new clinical study that the applicant submitted for the second review cycle was Study CP130-1014, a thorough QT study conducted in 65 healthy volunteers, intended to assess possible effects on cardiac repolarization of maximal daily dosing of intravenous (IV) oliceridine up to 27 mg over 24 hours. This study was conducted to address a deficiency described in the CR letter.

## 2.2 Therapeutic context: 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.”<sup>1</sup> 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 a few weeks, such as postoperative pain.

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

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 patient-controlled analgesia (PCA). Parenteral opioids currently approved for the treatment of 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 included as the active comparator in the oliceridine Phase 3 trials. Fentanyl and hydromorphone are more potent, have a more rapid onset of action, and a shorter half-life, compared with morphine. Oliceridine is intended to be used in adults who require intravenous acute pain management.

Although opioids are effective analgesics in the postsurgical setting, they have notable safety risks, including respiratory depression, nausea, vomiting, postoperative ileus, and allergic reactions. The applicant states that based on findings in animal studies, oliceridine has selective G-protein bias with less effect on  $\beta$  arrestin pathway, which is the pathway thought to cause many of the dose-dependent opioid-related adverse events, such as nausea, vomiting, and respiratory depression.

### 2.3 Regulatory background and marketing history

This product has not been previously approved or marketed. 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.

#### **February 19, 2016 Grant Breakthrough Therapy Designation**

- Trevena initially 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 again 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. (b) (4)

### **March 29, 2016 End-of-Phase 2 Meeting**

- FDA did not agree with the proposed dosing in the Phase 3 studies. The applicant proposed dosing up to 100 mg daily (including 0.75 mg doses administered as needed by the clinician, up to every hour), but had only studied maximum daily doses of 36.8 mg. Further, the applicant did not have adequate nonclinical support for the proposed doses.
- The applicant proposed as their primary endpoint a 30% improvement from baseline based on SPID. FDA did not agree, as it was unclear how this correlate to an improvement in pain intensity scores on the NRS in the proposed setting of acute postoperative pain, and whether that magnitude of improvement 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 that require further evaluation arose during development.
- 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.

### **June 22, 2017 Agreed iPSP**

- FDA agreed with Trevena's Initial Pediatric Study Plan (iPSP)

### **May 25, 2017 Pre-NDA Meeting**

- FDA explained the 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 applicant 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 applicant 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 was reached that a REMS did not need to be included in the NDA submission, on the basis that this drug is to be administered only in healthcare facilities under the direction of trained healthcare professionals.
- The applicant was informed that the NDA should address how data from the controlled Phase 3 studies, which excluded patients on chronic opioid therapy, would be generalized to the intended acute pain population. The sponsor stated that they would address this issue by including class labeling language related to opioid tolerance.

**November 2, 2018 Agency issued Complete Response Letter**

- Major clinical, nonclinical, and CMC deficiencies described in the CR letter. See Appendix A for list of deficiencies.

**December 19, 2018 End-of-Review Meeting**

- QT study: FDA provided advice to the applicant on the proposed multiple-dose thorough QT study.
- Safety database: Based on previously submitted safety database in the 1<sup>st</sup> review cycle, FDA informed the applicant that there appeared to be adequate exposure to support a maximum daily dose of 27 mg.

(b) (4)

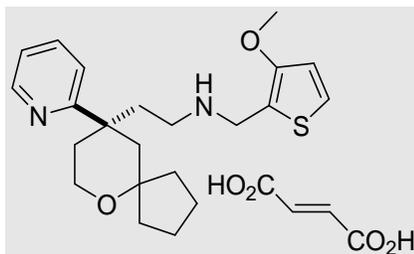
**February 7, 2020: Applicant submitted Complete Response to the NDA**

### 3 Product Quality

Drug Product quality review was conducted by Dr. Eric Bow and Dr. Julia Pinto; Drug Substance review was conducted by Dr. Sukhamaya Bain and Donna Christer; Manufacturing review was conducted by Dr. Cassandra Abellard and Dr. Frank Wackes; Microbiology review was conducted by Denise Miller and Bryan Riley.

The drug substance, drug product, process/facilities and microbiology review teams all recommend approval.

The active ingredient in OLINVYK is oliceridine. Oliceridine fumarate is a full opioid agonist. Oliceridine fumarate is a white to lightly-colored solid that is sparingly soluble in water. The chemical name for oliceridine fumarate is [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine fumarate, and the molecular formula is:  $C_{22}H_{30}N_2O_2S \cdot C_4H_4O_4$ . The theoretical average molecular mass is 502.62 (fumarate salt) and 386.55 (free base). The structural formula of oliceridine fumarate is:



OLINVYK (oliceridine injection) is a clear, colorless, sterile, preservative-free solution in a glass vial for intravenous use. It is proposed by the applicant to be supplied as follows:

- 1 mg/mL, equivalent to 1.3 mg/mL oliceridine fumarate salt, in single-dose, 2 mL, clear glass vials with gray plastic flip-off caps
- 2 mg/2 mL (1 mg/mL), equivalent to 2.6 mg/2 mL (1.3 mg/mL) oliceridine fumarate salt, in single-dose, 2 mL, clear glass vials with orange plastic flip-off caps
- 30 mg/30 mL (1 mg/mL), equivalent to 39 mg/30 mL (1.3 mg/mL) oliceridine fumarate salt, in single-patient-use, 30 mL, clear glass vials with purple plastic flip-off cap

The CR letter issued after the first review cycle included the following Product Quality deficiency:

The analytical methods used for controlling identified leachables must be validated. Validation reports for the analytical methods used for the leachables study have not been provided to the Agency.

Information Needed to Resolve the Deficiency:

Validate your newly developed analytical methods for leachables as per the ICH Q2 recommendation and provide the validation reports to the Agency. Further, also provide the data for the leachables found in the stability samples that are analyzed by your newly developed methods.

As noted in the CMC review, the applicant has provided adequate additional leachable data and method verification to resolve the deficiency. Based upon review of the stability data provided, the proposed shelf-life of 48 months is acceptable for all product presentations.

Drug substance and drug product facilities have been inspected. The (b) (4) included in the application, and recommended as inadequate by the Office of Facilities, has been withdrawn from the NDA by the applicant. The remaining manufacturing facilities for the drug substance and drug product are adequate.

## 4 Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Drs. Min Zhang, Jay Chang, and Daniel Mellon. The nonclinical review team recommends approval of this application, with recommended labeling changes and postmarketing requirements.

The CR letter issued after the first review cycle included the following nonclinical deficiency:

You have not provided adequate data to confirm that levels of TRV0109662, a major human metabolite, have been adequately characterized for potential embryo-fetal effects in either the rat or the rabbit embryo-fetal development study. You have not provided any data to document that the metabolite is formed in rabbits. Based on the data obtained to date, this metabolite does not appear to be formed at acceptable levels in the rat compared to the human, and the existing analytical assays for human and rat plasma levels of TRV0109662 do not appear to be consistently reproducible (i.e., failed rat incurred sample reanalysis for pivotal study).

Information Needed to Resolve the Deficiency:

Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated, reproducible pharmacokinetic data to support your 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 at the proposed maximum recommended human dose of 40 mg/day.

The nonclinical review team notes that the applicant has adequately addressed the nonclinical deficiency and now recommends approval. As noted in their review, the nonclinical team determined that the applicant submitted appropriate toxicology studies to support the safety of oliceridine in the original NDA submission. To address the nonclinical deficiency regarding the qualification of TRV0109662, the applicant developed a new analytical method to measure TRV0109662 in the plasma of rats and rabbits, respectively. Incurred Sample Reproducibility (ISR) was then assessed in a time-mated rat PK and rabbit PK study and was shown to be successful in these studies. With the newly validated analytical methods, the applicant measured the exposure of the metabolite in the rat and rabbit samples from the embryofetal studies. These exposure data were compared with the projected human exposure data at the MRHD of 27 mg/day to confirm that exposures (AUC) in at least one nonclinical toxicology species were greater than one-half of the human exposure, as recommended in the ICH M3(R2) Guidance, Questions and Answers (FDA 2012). As summarized in the nonclinical review, the TRV0109662 mean total daily exposure in pregnant rats and rabbits from the embryofetal studies was greater than the projected maximum human exposure, confirming adequate exposures in species used for assessing embryo-fetal development toxicity; thus, the toxicity of TRV0109662 has been adequately characterized in the rat and rabbit embryofetal studies in accordance with ICH M3(R2).

## 5 Clinical Pharmacology

The clinical pharmacology review was conducted by Dr. Sirkanth Nallani and Dr. Yun Xu. The clinical pharmacology team recommends approval of this application.

The CR letter issued after the first review cycle included the following clinical pharmacology deficiency:

You have not submitted adequate data to support the safety of oliceridine for the management of moderate-to-severe acute pain in adult patients for whom an intravenous (IV) opioid is warranted due to concerns related to QT prolongation.

Your thorough QT (tQT) study, CP130-1008, showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset (3 mg: 6.6 ms [upper 90% confidence interval (CI) 8.9 ms]; 6 mg: 11.6 ms [13.7 ms]). The delayed onset of QTcF prolongation suggests that the QTcF prolongation may not be mediated via direct inhibition of the hERG potassium channel by oliceridine. The proposed mechanism for the delayed onset of the QTcF prolongation observed with oliceridine remains unclear.

In your Phase 3 studies, only limited ECG monitoring was obtained in patients after baseline (i.e., at 1, 24, and 48-hours post-loading dose for Study 3001, 1 and 24 hours for Study 3002, and 1 hour and every 24 hours of oliceridine treatment in Study 3003). Further, you have proposed a wide range of doses up to a maximum daily dose of 40 mg, and oliceridine would be used in clinical situations in which patients may receive other drugs that can prolong the QTc.

Interpretation of the ECG data from your clinical studies has limitations. Specifically, none of the studies were designed to characterize the QT prolonging effects of oliceridine. In Study 3003, there was a lack of ECG replicates at each nominal time point and lack of a control arm. Despite these limitations, there were cases of QTc prolongation in Study 3003.

You have not provided adequate data to support that the QT prolonging effects of oliceridine can be mitigated by labeling or monitoring.

### Information Needed to Resolve the Deficiency:

To address the safety concern of QT prolongation at the maximum proposed daily dose, provide data from a randomized active-controlled study that will include 24-hour Holter monitoring and replicate QT measurements extracted every hour from the Holter monitors and compared to the control group. The study should be of adequate duration and sample size to allow reliable evaluation of oliceridine's QT prolongation effects.

To address the deficiency, the applicant submitted the results of a QT-IRT study (CP13-1014), entitled “A Phase 1, single center, multiple dose, randomized, single-blind, placebo- and positive-controlled crossover safety study to evaluate the effect of oliceridine (TRV130) on cardiac repolarization over 24 hours in healthy subjects.” In that study, healthy subjects were dosed with oliceridine 2-3 mg every two hours, up to a maximum 27 mg dosage within 24-hour period.

The thorough QT-IRT study was reviewed by the CDER QT-IRT team. The QT-IRT team noted that repeat dosing up to 27 mg resulted in a mean 10.7 ms QTc prolongation, which is transient, and is not hERG-mediated. Below is an excerpt from the QT-IRT consult review:

QTc prolongation was observed in this TQT study, which decreased with repeat dosing of oliceridine up to 27 mg. The underlying mechanism behind the observed QTc prolongation remains unknown, but is unlikely to be mediated via direct inhibition of ion channels, given that it is not observed with repeat dosing. The clinical relevance of the observed QTc prolongation is unknown, but is unlikely to be important given that it is transient and not hERG-mediated.

The clinical QTc prolongation observed with oliceridine diminished despite continued dosing in the second thorough QT study, suggesting that further QTc prolongation with dosing beyond what was studied is unlikely. However, 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.

The multiple dose QT-study supports the safety of total daily dosages up to 27 mg per day. However, QT effects beyond a 27 mg total daily dose are unknown, and total daily doses greater than 27 mg may increase the risk for QTc interval prolongation. The potential for QT prolongation with daily doses exceeding 27 mg will be described in the Warnings and Precautions section in oliceridine label.

Table 3 summarizes the general pharmacology and pharmacokinetic characteristics of oliceridine, as described in the first cycle NDA review:

**Table 3: General Pharmacology and Pharmacokinetic Characteristics for oliceridine**

<b>Mechanism of Action</b>	(b) (4)
<b>Active Moieties</b>	Oliceridine.
<b>QT Prolongation</b>	Oliceridine prolongs the QTcF interval in a dose-dependent manner with a delayed onset (3 mg: 6.8 ms [upper 90% CI: 8.9 ms]; 6 mg: 11.6 ms [13.7 ms]. See additional discussion below in section 3.2.1.
<b>General Information</b>	

<b>Bioanalysis</b>	Quantitation of the individual plasma samples of oliceridine, and primary amine metabolite TRV109662 was performed using HPLC with MS/MS detection. Pooled plasma samples were analyzed for non-acyl glucuronide conjugate of hydroxylated oliceridine (TRV0306954; M22) using HPLC with MS/MS detection. See Appendix for details.
<b>Healthy Volunteers vs. Patients</b>	Pharmacokinetic characteristics of oliceridine were similar in healthy volunteers and acute pain patients.
<b>Drug exposure at steady state following the therapeutic dosing regimen</b>	When oliceridine was administered four to six times daily, after 5 doses (1.5 – 4.5 mg) accumulation was less than 50% for AUC and up to 128% accumulation of C <sub>max</sub> .
<b>Dose Proportionality</b>	Oliceridine PK was dose-proportional between the doses of 0.1 – 3 mg intravenous infusion.
<b>Variability</b>	50% on clearance
<b>Absorption</b>	
<b>Bioavailability [oral]</b>	Oral bioavailability appears to be low due to extensive first pass metabolism. Cross-study comparison suggests <5% oral bioavailability.
<b>Distribution</b>	
<b>Volume of Distribution</b>	Volume of distribution was high, and ranged from 90 – 120 L in different Phase 1 and Phase 2 studies.
<b>Plasma Protein Binding</b>	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 protein binding, with the unbound fraction being essentially 100% in human plasma. (Study 797914 and TRE-R6804)
<b>Blood to Plasma Ratio</b>	The blood to plasma distribution ratio of oliceridine was not determined.
<b>Substrate transporter systems [in vitro]</b>	Oliceridine is a moderate substrate of MDR-1 (P-gp).
<b>Elimination</b>	

<b>Mean Terminal Elimination half-life</b>	In extensive metabolizers of CYP2D6, elimination half-life of oliceridine was 1.5 – 3 hours. In poor metabolizers of CYP2D6, elimination half-life of oliceridine was 3 – 4.5 hours.
<b>Metabolism</b>	
<b>Primary metabolic pathway(s) [in vitro]</b>	Cytochrome P450 2D6 predominantly mediates N-dealkylation (TRV109662) and oxidation (M23) of oliceridine. CYP3A4 plays a minor role in N-dealkylation (TRV109662) and oxidation (M23) of oliceridine.
	Oliceridine is metabolized by oxidation into Oxy-oliceridine (M23) followed by glucuronidation to TRV0306954 (M22).
<b>Inhibitor/Inducer</b>	Oliceridine and its metabolites M22 and TRV109662 may not inhibit or induce major CYP enzymes. Oliceridine and its metabolites may not significantly inhibit major transporters.
<b>Excretion</b>	
<b>Primary excretion pathways (% dose) ±SD</b>	A mean of 70% of the administered dose was recovered in urine and 18.4% was recovered in feces.

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 can be individualized to balance pain relief and tolerability aspects. Dedicated PK studies in patients with end-stage renal disease or different grades of hepatic impairment did not show significant change in exposure that would require dosage adjustment. However, a reduction in initial loading dose should be considered in patients with severe hepatic impairment. A population pharmacokinetic analysis suggests that age and race do not explain the variability in pharmacokinetic parameters. 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.

Clinically significant drug interactions with oliceridine are described in Table 4.

**Table 4: Clinically Significant Drug Interactions with OLINVYK**

<b>Moderate to Strong Inhibitors of CYP2D6</b>	
<i>Clinical Impact:</i>	Concomitant administration of a moderate to strong CYP2D6 inhibitor can increase the plasma concentration of oliceridine, resulting in increased or prolonged opioid effects.
<i>Intervention:</i>	If concomitant use is necessary, patients taking a moderate to strong CYP2D6 inhibitor may require less frequent dosing of OLINVYK. Monitor closely for respiratory depression and

	<p>sedation at frequent intervals and base subsequent doses on the patient's severity of pain and response to treatment.</p> <p>If a CYP2D6 inhibitor is discontinued, increase of the OLINVYK dosage may be considered until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</p>
<i>Examples:</i>	Paroxetine, fluoxetine, quinidine, bupropion
<b>Moderate to Strong Inhibitors of CYP3A4</b>	
<i>Clinical Impact:</i>	<p>The concomitant administration of moderate to strong CYP3A4 inhibitors can increase the plasma concentration of oliceridine, resulting in increased or prolonged opioid adverse reactions.</p> <p>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oliceridine concentration may decrease, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oliceridine.</p>
<i>Intervention:</i>	<p>Caution should be used when administering OLINVYK to patients taking inhibitors of the CYP3A4 enzyme. If concomitant use is necessary, patients taking a CYP3A4 inhibitor may require less frequent dosing. Monitor patients for respiratory depression and sedation at frequent intervals.</p> <p>If a CYP3A4 inhibitor is discontinued, increase of the OLINVYK dosage may be considered until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</p>
<i>Examples:</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir).
<b>Strong and Moderate CYP3A4 Inhibitors and CYP2D6 Inhibitors</b>	
<i>Clinical Impact:</i>	<p>OLINVYK is primarily metabolized by both CYP3A4 and CYP2D6. Compared to inhibition of either metabolic pathway, inhibition of both pathways can result in a greater increase of the plasma concentrations of oliceridine and prolong opioid adverse reactions [See <i>Clinical Pharmacology (12.3)</i>].</p>
<i>Intervention:</i>	<p>Patients who are CYP2D6 normal metabolizers taking a CYP2D6 inhibitor, and a strong CYP3A4 inhibitor (or discontinuation of CYP3A4 inducers) may require less frequent dosing.</p> <p>Patients who are known CYP2D6 poor metabolizers and taking a CYP3A4 inhibitor (or discontinuation of CYP3A4 inducers) may require less frequent dosing.</p> <p>These patients should be closely monitored for respiratory depression and sedation at frequent intervals, and subsequent doses should be based on the patient's severity of pain and response to treatment.</p>

<i>Examples:</i>	Inhibitors of CYP3A4: Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole, itraconazole), anti-retroviral agents, selective serotonin re-uptake inhibitors (SSRIs), protease inhibitors (e.g., ritonavir), NS3/4A inhibitors Inhibitors of CYP2D6: Paroxetine, fluoxetine, quinidine, bupropion
<b>Inducers of CYP3A4</b>	
<i>Clinical Impact:</i>	The concomitant use of OLINVYK and CYP3A4 inducers can decrease the plasma concentration of oliceridine, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oliceridine. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oliceridine plasma concentration may increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
<i>Intervention:</i>	If concomitant use with CYP3A4 inducer is necessary, increase of the OLINVYK dosage may be considered until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider OLINVYK dosage reduction and monitor for signs of respiratory depression.
<b>Examples:</b>	Rifampin, carbamazepine, phenytoin.
<b>Benzodiazepines and Other Central Nervous System (CNS) Depressants</b>	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of hypotension, respiratory depression, profound sedation, coma, and death [see <i>Warnings and Precautions (5.4)</i> ].
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see <i>Warnings and Precautions (5.4)</i> ].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol
<b>Serotonergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OLINVYK if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs,) serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT <sub>3</sub> receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
<b>Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics</b>	
<i>Clinical Impact:</i>	May reduce the analgesic effect of OLINVYK and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine,
<b>Muscle Relaxants</b>	
<i>Clinical Impact:</i>	OLINVYK may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OLINVYK and/or the muscle relaxant as necessary.
<b>Diuretics</b>	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
<b>Anticholinergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when OLINVYK is used concomitantly with anticholinergic drugs.

## 6 Clinical Microbiology

The microbiology and biopharmaceutics review teams recommended approval in the first review cycle. Below is an excerpt from their NDA original review:

The drug substance, oliceridine fumarate, as a new molecular entity, and is manufactured

(b) (4)

The drug substance manufacturing process, characterization,

release specification, container closure system, and stability are satisfactory. The granted retest period for the drug substance is [REDACTED]<sup>(b) (4)</sup>, when stored [REDACTED]<sup>(b) (4)</sup>

## 7 Clinical/Statistical- Efficacy

To support the proposed indication, Trevena completed two Phase 3 studies in patients with nociceptive pain: one in nonvisceral pain (hard tissue model of bunionectomy; Study 3001; N=389) and one in visceral pain (soft tissue model of abdominoplasty; Study 3002; N=401). Both were double-blind, placebo- and active-controlled studies in adults with moderate-to-severe pain. Morphine is a commonly used opioid in the post-operative setting and was included as the active comparator in both Phase 3 trials. According to the applicant, the purpose of the controlled Phase 3 studies was to evaluate whether oliceridine provides an increased therapeutic window compared with morphine (i.e., an increased level of efficacy with similar tolerability to morphine; or improved safety and tolerability at equianalgesic doses to morphine; or, optimally, both benefits achieved with titration of therapy).

Patients in Study 3001 had undergone a bunionectomy, while patients in Study 3002 had undergone abdominoplasty. The treatment duration was 48 hours in Study 3001, and 24 hours in Study 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 who used any analgesic medication within five half-lives of the date of surgery were excluded from the studies.

In each study, pain intensity was measured using a patient-reported numeric rating scale (11-point numerical scale ranging from 0-10, where zero corresponds to no pain and 10 corresponds to worst pain imaginable).

In each study, patients were randomized 1:1:1:1 to one of three oliceridine treatment regimens, a placebo-control regimen, or a morphine-control regimen (see Table 5). Each blinded treatment regimen consisted of a loading dose, incremental doses delivered as needed via patient-controlled analgesia (PCA) device beginning 10 minutes after the loading dose, and supplemental doses, beginning 1 hour after the initial dose, and hourly thereafter, as needed. A lockout interval of 6 minutes was used for all PCA regimens. Supplemental doses were administered, taking into account the patient's utilization of PCA demand doses, severity of pain, and response to study medication. The loading dose for all oliceridine treatment regimens was 1.5 mg; demand doses were 0.1, 0.35 or 0.5 mg, according to the assigned treatment group; supplemental doses were 0.75 mg. The loading dose for the morphine treatment regimen was 4 mg; the demand dose was 1 mg; supplemental doses were 2 mg. The placebo-control regimen was volume-matched.

**Table 5: Dosing Regimen in Phase 3 Controlled Studies**

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

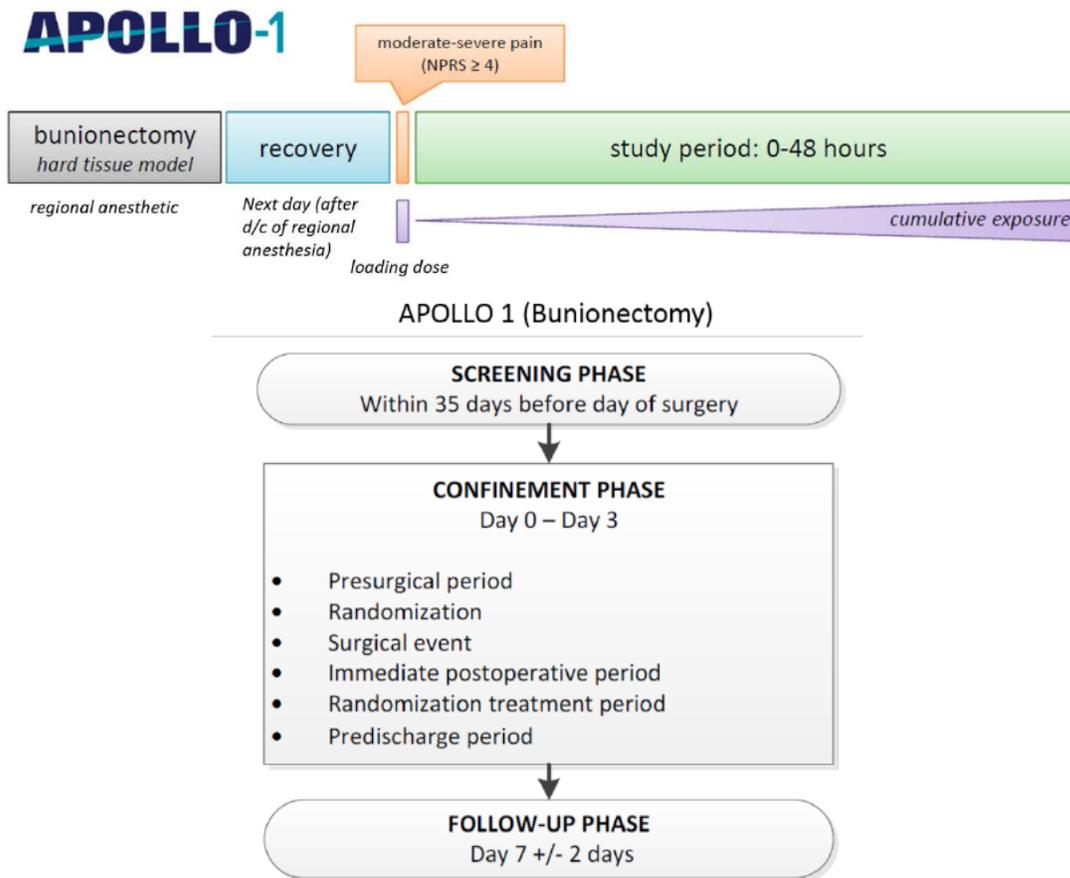
Source: Modified from Clinical Study Report CP130-3001, Table 2, page 25, submitted 11/2/17

In both studies, patients may have received rescue pain medication (pre-defined in the protocols as etodolac 200 mg every 6 hours, as needed) if the patient requested rescue pain medication and reported a Numeric Rating Scale score  $\geq 4$ .

- Study CP-130-3001 (Apollo 1 or Study 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. The study enrolled adult patients ( $\geq 18$  and  $\leq 75$  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 q 4 h 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)  $\geq 4$  within 9 hours after discontinuation of regional anesthesia were eligible to begin study treatment.

The study design and phases are displayed in Figure 2.

**Figure 2: Design and Key Phases of Study 3001**



Source: Integrated Summary of Effectiveness, 1<sup>st</sup> review cycle, page 21.

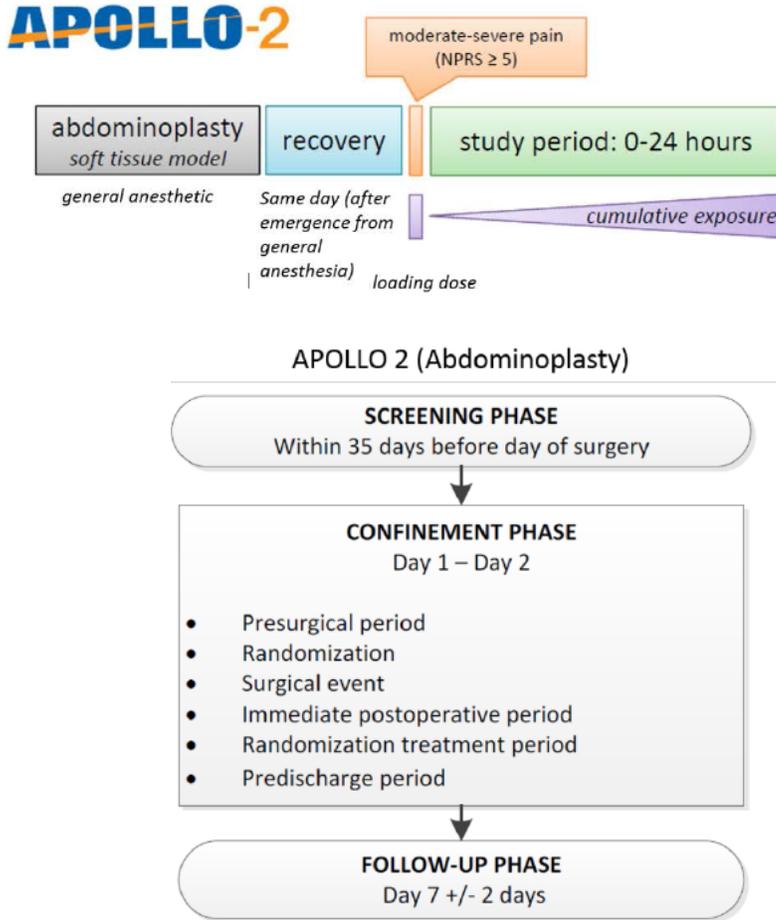
- **Study CP-130-3002 (Apollo 2 or Study 3002):** This was a multicenter, randomized, double-blind, placebo- and active-controlled study of the efficacy and safety of oliceridine in patients with moderate to severe acute pain after abdominoplasty. The study included a 24-hour placebo- and active-controlled period.

Key inclusion and exclusion criteria were generally similar to those of Study 3001. There were minor differences in when the qualifying pain assessments occurred in the two studies. In Study 3001, 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)  $\geq 4$  within 9 hours after discontinuation of regional anesthesia were eligible to begin study treatment. In Study 3002, 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  $\geq 5$  within 4 hours after end of surgery 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 study design schematic and key phases are shown in Figure 3.

**Figure 3: Design and Key Phases of Study 3002**



Source: Integrated Summary of Effectiveness, 1<sup>st</sup> review cycle, page 21.

The medication regimen in Study 3002 was the same as Study 3001 (see Table 5). As in Study 3001, clinician-administered blinded supplemental doses were permitted.

**Rescue Pain Medication:** For both studies 3001 and 3002, if study medication was utilized (PCA demand doses plus supplemental doses) and analgesia was still inadequate, patients were allowed to receive rescue pain medication (etodolac 200 mg q 6 h PRN), if the patient requested rescue pain medication and reported an NRS  $\geq 4$ . 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. 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 (i.e., non-oliceidine analgesics according to standard clinical practice).

*Applicant's Proposed Primary Efficacy Endpoint:* The Applicant's pre-specified primary efficacy endpoint for both Studies 3001 and 3002 was the proportion of patients who responded to study medication vs. placebo at the 48-hour (Study 3001) or 24-hour (Study 3002) NRS assessment. A patient was considered a responder if all of the following criteria were met:

- Patient's final time-weighted sum of pain intensity differences (SPID) from baseline at 24/48 hours (SPID-24/48) corresponded to or was greater than a 30% improvement
- Patient did not receive rescue pain medication during the randomized treatment period
- Early discontinuation of study medication for any reason did not occur
- Patient 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 applicant's proposed responder endpoint is not scientifically justified and has never been the basis for approval for any drugs in this class<sup>2</sup>. This was conveyed to the applicant multiple times during clinical development. Rather, FDA efficacy conclusions for oliceridine are based on a SPID analysis (SPID over 48 hours for Study 3001 and SPID over 24 hours for Study 3002), which is the typical primary analysis method for acute pain studies.

The efficacy conclusions for the first cycle review are presented below:

*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 statistically significantly greater reduction in pain intensity relief than two of the doses of oliceridine (0.1 mg and 0.35 mg). The reduction in pain intensity by morphine was greater but not statistically significant compared to the highest oliceridine dose (0.5 mg). Currently, Trevena is only seeking approval of the 0.1 mg and 0.35 mg doses.

The conclusions noted above were based on an FDA re-analysis of the applicant's submitted data, shown in Table 6 and Table 7, for Study 3001 and Study 3002, respectively. The purpose of this analysis was to address several issues. First, responder endpoints based on a reduction in SPID with a threshold (in this case 30%) have not been previously used in acute pain studies; and second, the applicant's classification of any use of rescue medication as non-

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<sup>2</sup> Please refer to original CDTL clinical /stats combined review for details.

response harshly penalizes rescue medication usage, which was mostly early and relatively light (see Table 8 and Figure 4 for Study 3001 and Table 9 and Figure 5 for Study 3002).

**Table 6: 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=79	Oliceridine 0.5 mg N=79	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)
Estimated mean SPID (SE)	85.0 (9.50)	131.6 (9.68)	138.1 (9.50)	163.7 (9.53)	192.6 (9.72)
Estimated mean 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	
Estimated mean 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: Previous FDA CDTL Review

**Table 7: SPID24 Pre-Rescue Scores Carried Forward 6 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)	70.4 (37.9)	74.4 (45.4)	88.0 (44.5)	93.3 (41.9)	100.6 (48.6)
Estimated mean SPID (SE)	74.8 (4.56)	76.8 (4.66)	89.72 (4.6)	94.0 (4.61)	103.0 (4.52)
Estimated mean 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	
Estimated mean 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	

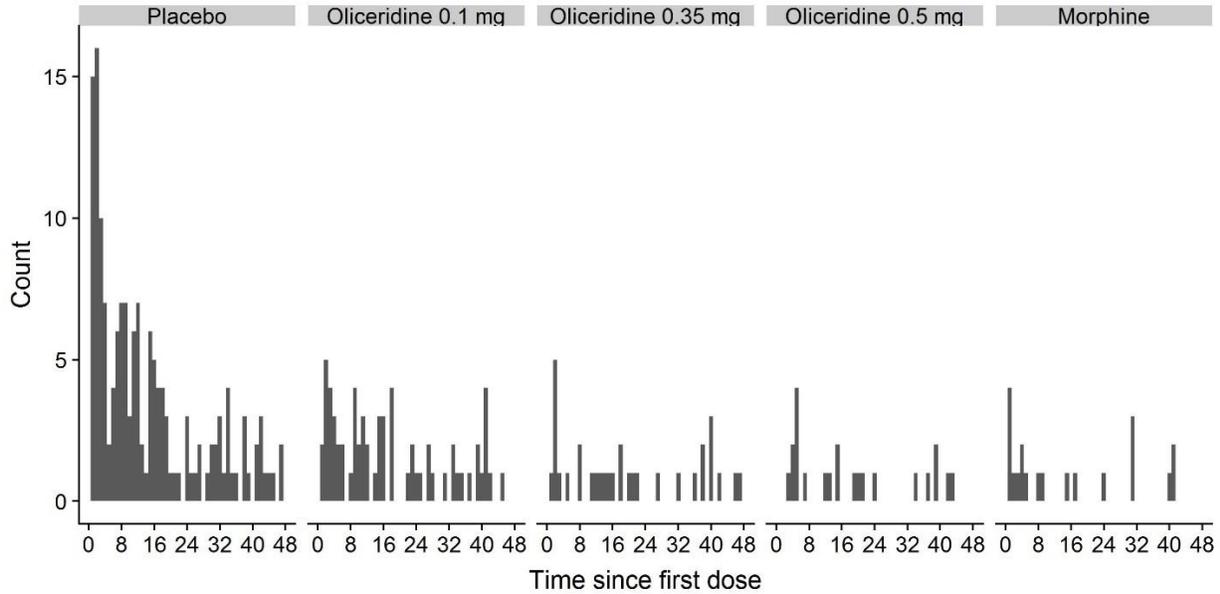
Abbreviations: Diff=difference; LSM=least-squares mean; SD=standard deviation; SE=standard error  
Source: Previous FDA CDTL Review

**Table 8: 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: Previous FDA CDTL Review

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



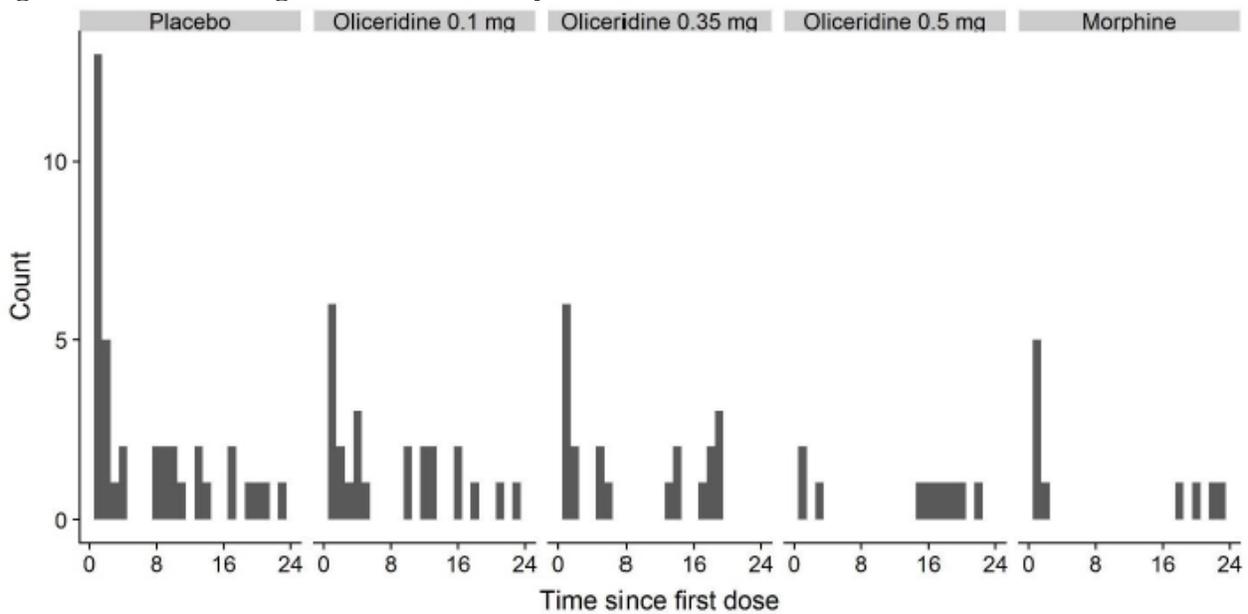
Source: Previous FDA CDTL Review

**Table 9: 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: Previous FDA CDTL Review

**Figure 5: Rescue Usage over Time (Study 3002)**



Source: Previous FDA CDTL Review

The types of rescue medication received are summarized in Table 10 and Table 11. In both studies, the majority of rescue medication was etodolac, which was the protocol-specified allowable rescue. There were however several patients who received another opioid rescue medication, across treatment arms.

**Table 10: 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

Abbreviations: APAP=acetaminophen  
Source: Previous FDA CDTL Review

**Table 11: Rescue Medication Breakdown (Study 3002)**

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: Previous FDA CDTL Review

To address one of the clinical deficiencies in the first-cycle CR letter, the applicant proposed a maximum total daily dosage of 27 mg, for which safety is supported by an adequate database (see below).

First, we will discuss the overall dosing patterns in Studies 3001 and 3002. We will then discuss the implications of the total daily dosage limit of 27 mg on the efficacy assessments.

In both studies, there was a substantial number of patients who exceeded the proposed maximum dose of 27 mg. In Study 3001 (Table 12Table 1), approximately 60% of patients randomized to the 0.35 mg or 0.5mg oliceridine regimen exceeded a 27 mg total daily dose on the first day. As would be expected, the cumulative daily dose decreased on the second day. For Study 3002, cumulative daily doses received were lower than those in Study 3001, and there were fewer, but still a substantial number of patients, who exceeded the maximum dose (30% for 0.35 mg and 43% for 0.5 mg, see Table 14). Additional summary statistics of the dosing are available in Table 12 and 13 for Study 3001, Table 14 and 15 for Study 3002, and histograms of the daily doses are shown in Figure 6 and Figure 7.

**Table 12: Number (Percentage) of Patients Requiring Doses Above 27 mg, Study 3001**

Treatment Arm	Day 1	Day 2	Either Day
Oliceridine 0.1 mg	1/76 (1.3%)	0/76 (0.0%)	1/76 (1.3%)
Oliceridine 0.35 mg	47/79 (59.5%)	21/79 (26.6%)	47/79 (59.5%)
Oliceridine 0.5 mg	50/79 (63.3%)	27/79 (34.2%)	51/79 (64.6%)

Note: Day 1 was defined as hours 0-24 after the start of study treatment and Day 2 was defined as hours 24-48.  
Source: Reviewer

**Table 13: Dose Summary Statistics, Study 3001**

Day	Statistic	Oliceridine 0.1 mg	Oliceridine 0.35 mg	Oliceridine 0.5 mg
	N	76	79	79
Day 1	Mean (SD)	13 (5.77)	30 (14.37)	35 (18.19)
	Median	12.85	30.4	34.75
	(Min, Max)	(2.5, 27.3)	(2.5, 65.8)	(3.8, 88.2)
Day 2	Mean (SD)	6 (6.21)	19 (15.01)	22 (19.06)
	Median	4.1	18.2	21.5
	(Min, Max)	(0.0, 22.1)	(0.0, 65.0)	(0.0, 82.5)
Both Days Combined	Mean (SD)	19 (11.20)	49 (27.16)	57 (34.66)
	Median	16.8	46.3	58
	(Min, Max)	(2.7, 47.8)	(2.5, 119.6)	(3.8, 159.8)

Note: Day 1 was defined as hours 0-24 after the start of study treatment and Day 2 was defined as hours 24-48.

Source: Reviewer

**Table 14: Number (Percentage) of Patients Requiring Doses Above 27 mg, Study 3002**

Treatment Arm	Day 1
Oliceridine 0.1 mg	0/77 (0.0%)
Oliceridine 0.35 mg	22/79 (27.8%)
Oliceridine 0.5 mg	34/80 (42.5%)

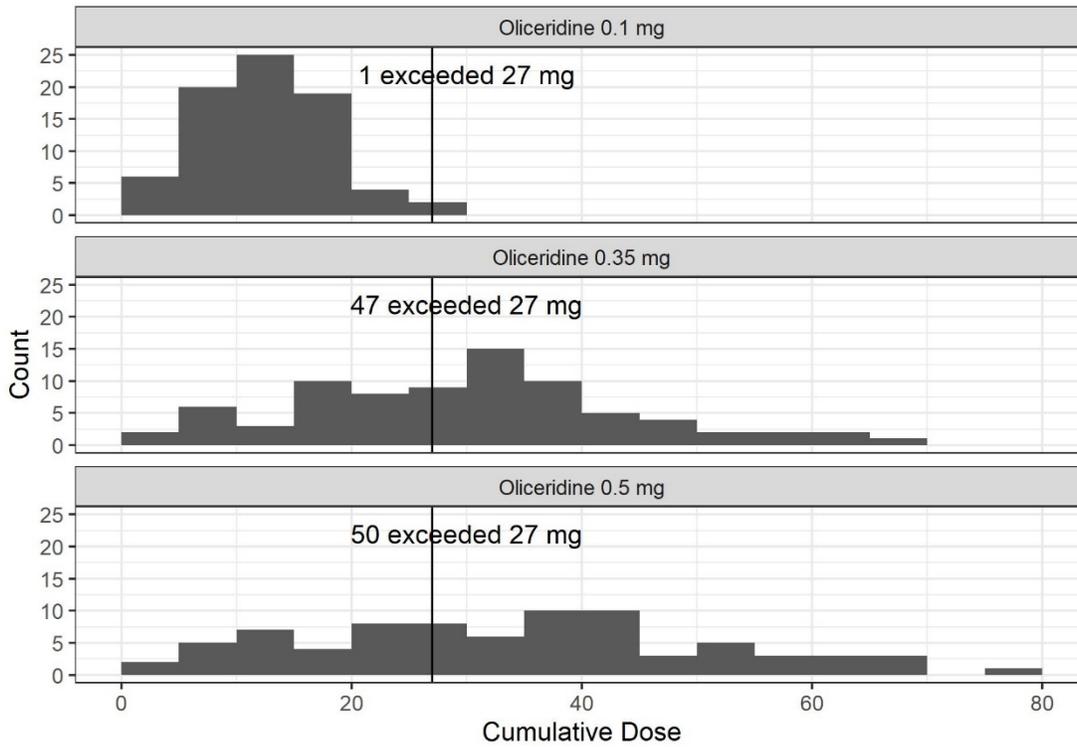
Source: Reviewer

**Table 15: Dose Summary Statistics, Study 3002**

Statistic	Oliceridine 0.1 mg	Oliceridine 0.35 mg	Oliceridine 0.5 mg
N	77	79	80
Mean (SD)	10 (5.14)	21 (12.92)	26 (18.22)
Median	8.95	19.7	23
(Min, Max)	(1.7, 21.6)	(2.2, 64.8)	(1.5, 77.2)

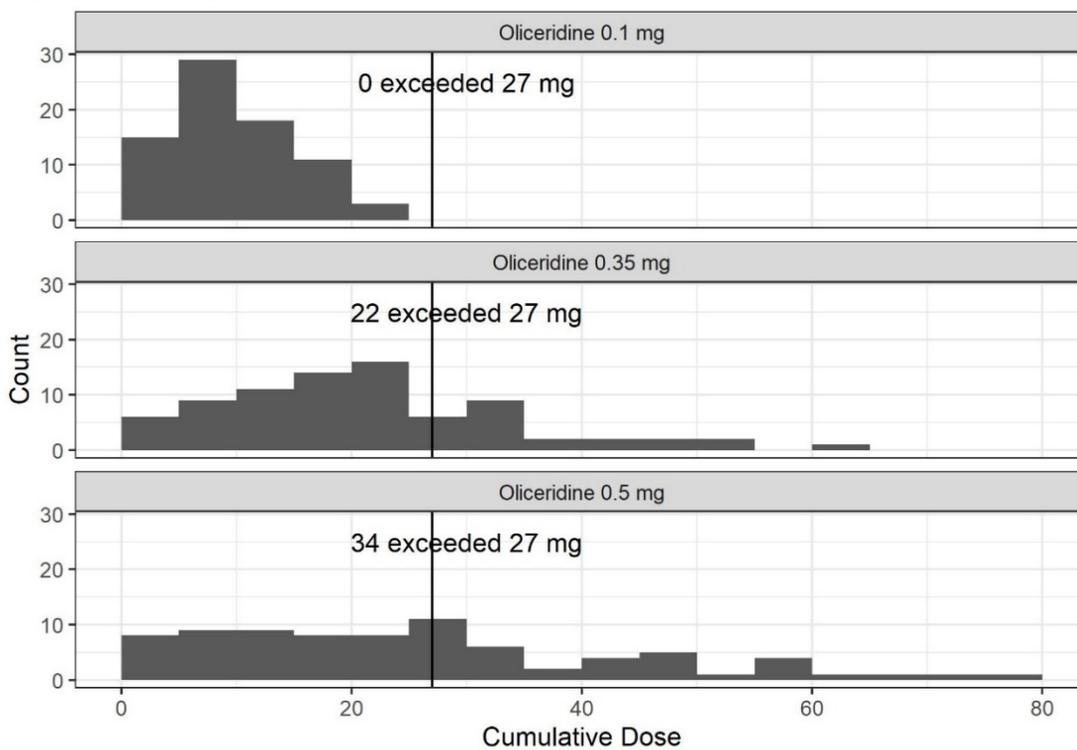
Source: Reviewer

**Figure 6: Histogram of Doses Received within the First 24 Hours (Study 3001)**



Source: Reviewer

**Figure 7: Histogram of Doses Received within the First 24 Hours (Study 3002)**



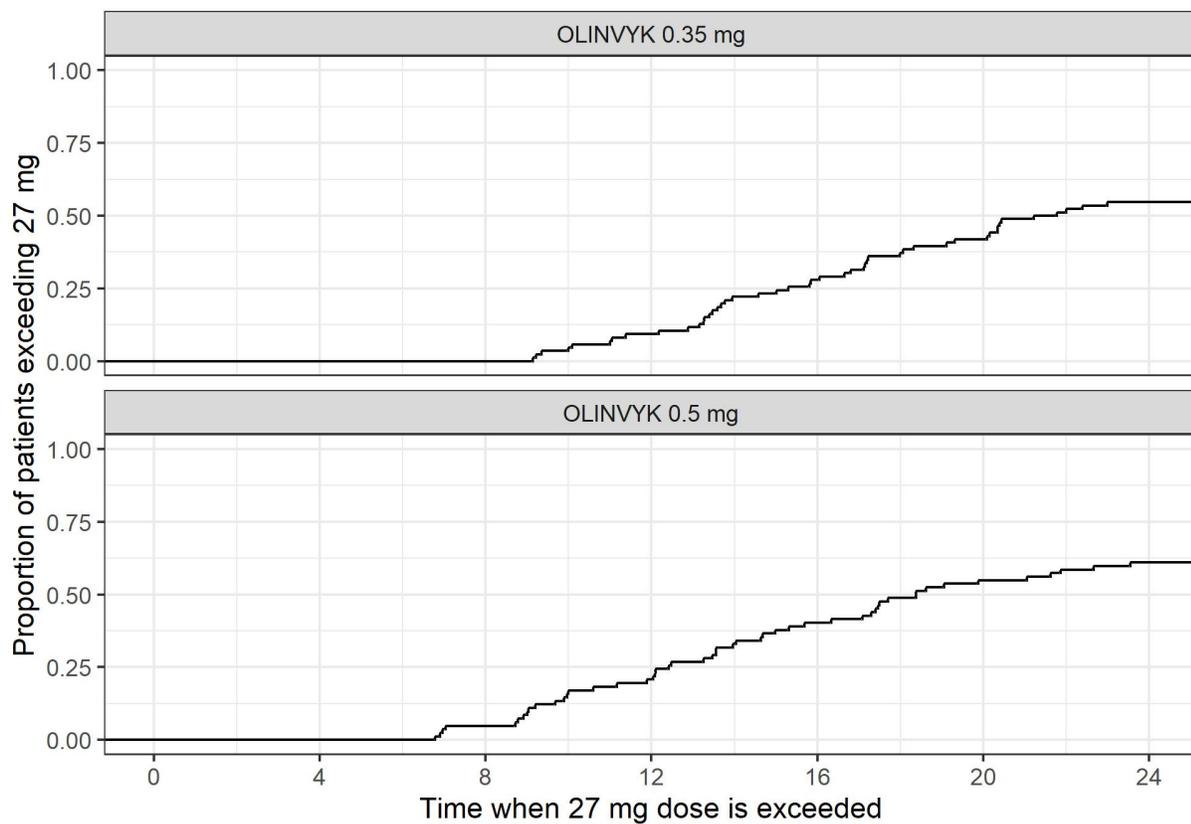
Source: Reviewer

The review team analyzed how quickly patients reached the proposed maximum daily dosage of 27 mg. These data are summarized in Figure 8: and Table 16 for Study 3001 and in Figure 9 and Table 1 17 for Study 3002.

In Study 3001, patients randomized to the 0.35 mg or 0.5 mg oliceridine regimen reached a total daily dosage of 27 mg by a median of 15.8 and 13.6 hours, respectively.

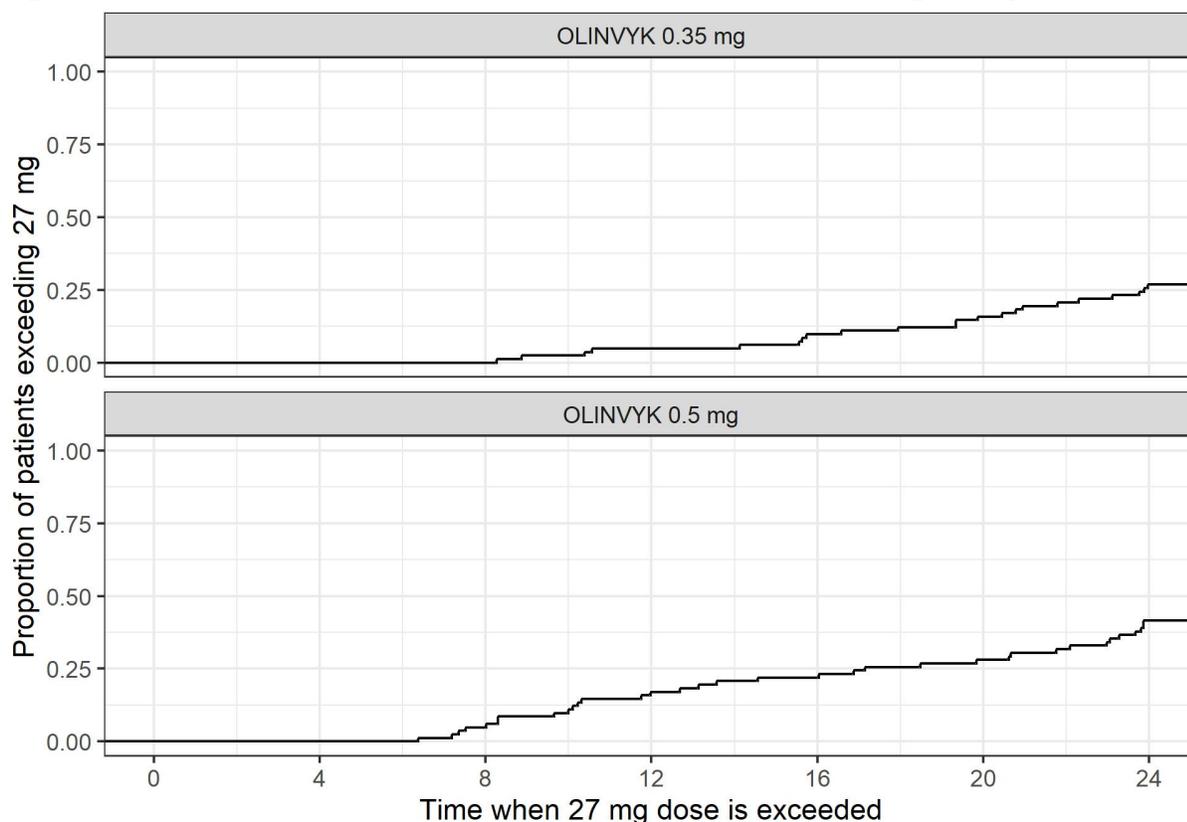
In Study 3002, patients randomized to the 0.35 mg or 0.5 mg oliceridine regimen reached a total daily dosage of 27 mg by a median of 19.4 and 14.1 hours, respectively. Therefore, there will likely be patients who reach the maximum recommended daily dosage of 27 mg and require additional analgesia with another drug.

**Figure 8: Cumulative Distribution Function of Time to Reach 27 mg (Study 3001)**



Source: Reviewer

**Figure 9: Cumulative Distribution Function of Time to Reach 27 mg (Study 3002)**



Source: Reviewer

**Table 16: Summary Statistics of the Time to Reach a Total Dose of 27 mg in the First 24 hours (Study 3001)**

Summary Statistic	Oliceridine 0.1 mg N=1	Oliceridine 0.35 mg N=47	Oliceridine 0.5 mg N=50
Mean (SD)	23.4 (NA)	15.9 (3.9)	14.0 (4.5)
Median	23.4	15.8	13.6
(Min, Max)	(23.4, 23.4)	(9.1, 23.0)	(6.8, 23.6)

**Table 17: Summary Statistics of the Time to Reach a Total Dose of 27 mg in the First 24 hours (Study 3002)**

Summary Statistic	Oliceridine 0.35 mg N=22	Oliceridine 0.5 mg N=34
Mean (SD)	17.9 (5.0)	15.3 (6.2)
Median	19.4	14.1
(Min, Max)	(8.3, 24.0)	(6.4, 23.9)

In both studies, oliceridine doses after the loading dose could be administered in one of two ways: through the self-administered patient-controlled analgesia (PCA) pump, or through physician-administered injection. The total number of doses of both are summarized in Table 18 for Study 3001 and Table 19 for Study 3002. Overall, in both studies, the majority of drug was administered via the PCA pump.

**Table 18: Number of PCA and Physician-administered Supplemental Doses, Study 3001**

Treatment Arm	Dose Type	Mean (SD)	Median	(Min, Max)
Placebo	PCA Dosing	105.5 (86.31)	78.5	(4, 295)
Oliceridine 0.1 mg		149.2 (88.62)	140	(12, 314)
Oliceridine 0.35 mg		132.6 (73.45)	126	(3, 317)
Oliceridine 0.5 mg		110.2 (67.81)	113	(3, 305)
Morphine		62.9 (50.94)	50	(1, 246)
Placebo	Physician administered injection	2.7 (1.83)	2	(1, 9)
Oliceridine 0.1 mg		5.1 (4.50)	4	(1, 20)
Oliceridine 0.35 mg		3.7 (3.67)	2	(1, 17)
Oliceridine 0.5 mg		3.8 (3.65)	3	(1, 13)
Morphine		1.6 (1.64)	1	(1, 9)

Source: Reviewer

**Table 19: Number of PCA and Physician-administered Supplemental Doses, Study 3002**

Treatment Arm	Dose Type	Mean (SD)	Median	(Min, Max)
Placebo	PCA Dosing	58.7 (45.73)	54	(1, 164)
Oliceridine 0.1 mg		71.6 (44.76)	67	(2, 163)
Oliceridine 0.35 mg		54.8 (35.20)	50.5	(2, 168)
Oliceridine 0.5 mg		50.9 (35.07)	44.5	(2, 150)
Morphine		36.7 (27.95)	26	(2, 124)
Placebo	Physician administered injection	2.3 (1.71)	2	(1, 8)
Oliceridine 0.1 mg		3.1 (1.84)	3	(1, 6)
Oliceridine 0.35 mg		2.0 (1.46)	1	(1, 6)
Oliceridine 0.5 mg		2.1 (1.95)	1	(1, 8)
Morphine		1.16 (0.47)	1	(1, 3)

Source: Reviewer

The applicant's proposed maximum daily dosage of 27 mg necessitated additional analyses to understand whether oliceridine provides benefit in the context of this total daily dosage. To address this issue, the review team conducted analyses in which drug doses beyond the total cumulative 27 mg daily dosage are treated the same as rescue medication. The results of these analyses are shown in Table 20 and Table 21 for Studies 3001 and 3002, respectively. For Study 3001, all three oliceridine dosing regimens continue to exhibit statistically significantly greater pain relief than placebo. However, for Study 3002, only the 0.5 mg dosing regimen reaches statistical significance. In addition, Figure 10 and Figure 11 show the average pain scores over the entire duration of the study.

**Table 20: SPID Analysis, Doses over 27 mg Treated as Rescue, Study 3001**

<b>Statistic</b>	<b>Placebo N=83</b>	<b>Oliceridine 0.1 mg N=78</b>	<b>Oliceridine 0.35 mg N=79</b>	<b>Oliceridine 0.5 mg N=78</b>	<b>Morphine N=83</b>
Estimated Mean SPID (SE)	76.2 (10.03)	126.2 (10.14)	123.7 (9.96)	156.1 (9.99)	180.9 (10.19)
Estimated mean diff. vs placebo (SE)		50.1 (14.21)	47.5 (14.11)	80.0 (14.15)	104.8 (14.24)
p-value vs placebo		0.0005	0.0008	<0.0001	
Superiority vs placebo		Yes	Yes	Yes	

Source: Reviewer

**Table 21: SPID Analysis, Doses over 27 mg Treated as Rescue, Study 3002**

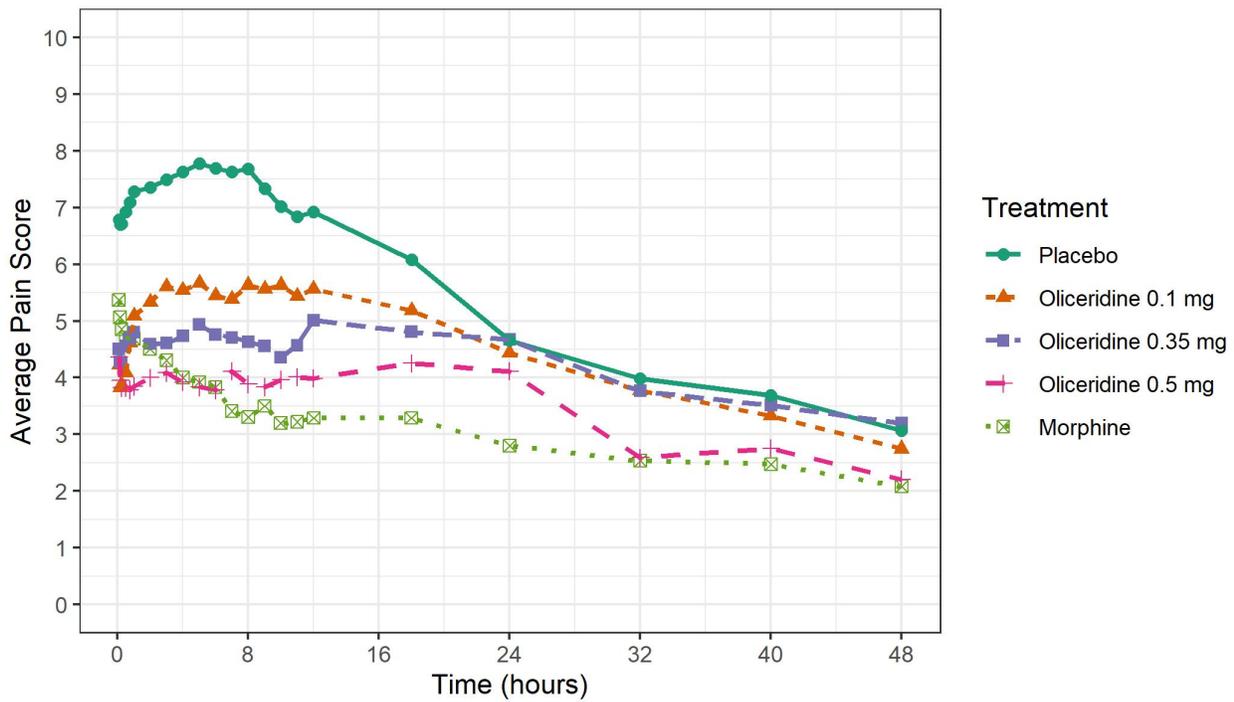
<b>Statistic</b>	<b>Placebo N=81</b>	<b>Oliceridine 0.1 mg N=77</b>	<b>Oliceridine 0.35 mg N=80</b>	<b>Oliceridine 0.5 mg N=80</b>	<b>Morphine N=83</b>
Estimated Mean SPID (SE)	72.8 (4.64)	76.1 (4.73)	86.4 (4.63)	90.4 (4.74)	102.5 (4.64)
Estimated mean diff. vs placebo (SE)		3.3 (6.33)	13.6 (6.27)	17.6 (6.34)	29.7 (6.25)
p-value vs placebo		0.6077	0.0309 <sup>†</sup>	0.0058 <sup>†</sup>	
Superiority vs placebo		No	No	Yes	

Source: Reviewer

<sup>†</sup> The applicant used a Hochberg<sup>3</sup> adjustment to control the familywise type-1 error rate. Since the p-value for the 0.1 mg dose exceeds 0.05, the p-value for the 0.35 mg dose is tested against a threshold of 0.025. The p-value for the 0.5 mg dose is then compared against a threshold of 0.0167.

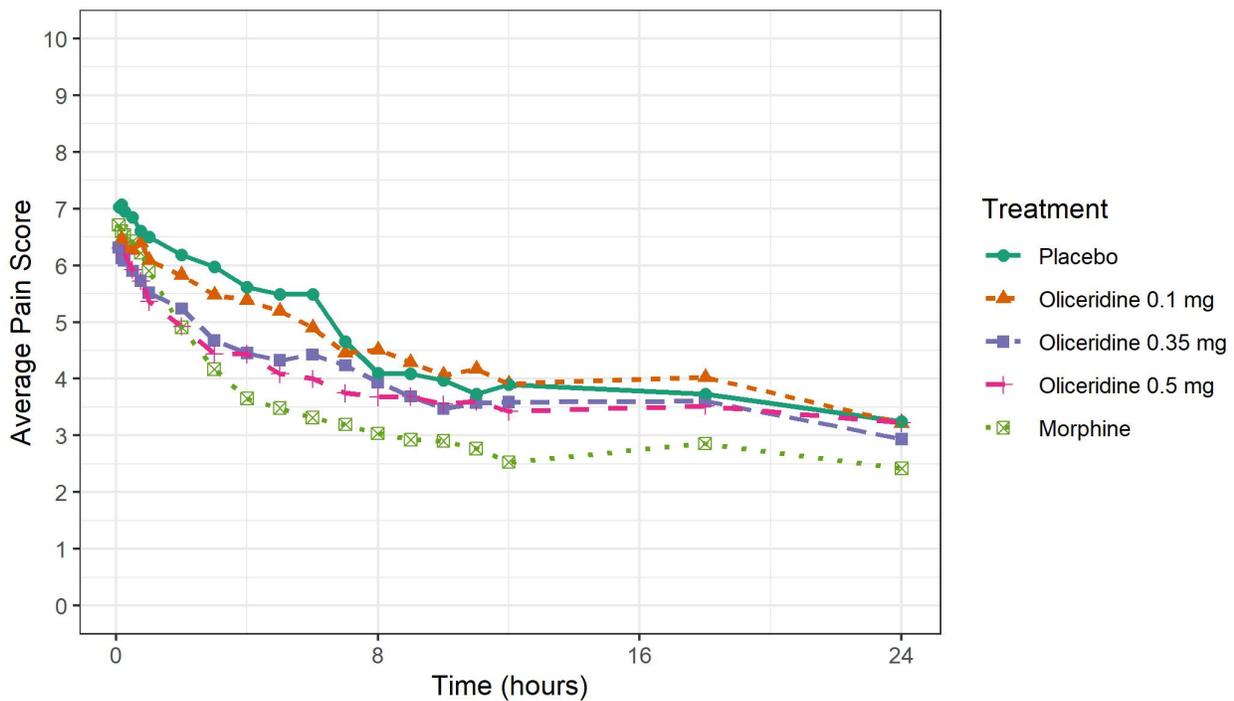
<sup>3</sup> Hochberg Y. A Sharper Bonferroni Procedure for Multiple Tests of Significance. *Biometrika* 1998; 75(4): 800-2

**Figure 10: Average Pain Score Over Time with Doses Over 27 mg Classified as Rescue (Study 3001)**



Source: Reviewer

**Figure 11: Average Pain Score Over Time with Doses Over 27 mg Classified as Rescue (Study 3002)**



Source: Reviewer

For Study 3002, two additional sensitivity analyses that explore the efficacy results are included below. For the comparisons between the oliceridine arms and the placebo arm, the analysis does not need to include data from the morphine treatment arm.

In the first analysis (Table 22), we repeated the analysis done to generate the results in Table 21, but excluded the information from the morphine treatment arm. In this analysis, the p-value for the 0.35 mg dosing regimen falls below the threshold for statistical significance (0.025). As noted, the previous analysis (Table 21) was designed to match as closely as possible the original analysis, which included the information from the morphine treatment arm, and would therefore typically be our preferred analysis from a statistical perspective.

Both analysis models are acceptable and valid to assess the treatment difference between the oliceridine arms and the placebo arm. There are more assumptions for the model that includes the morphine arm than for the model that excludes the morphine arm. The assumptions are that the variance and profile of the morphine arm are the same as those of the oliceridine arms. If all of these assumptions are true, including the morphine arm increases the precision of the estimates and reduces the p-value. If one of these assumptions is not true, including the morphine arm in the analysis may increase the variability or bring bias into the estimates and increase the p-value. Examining the time plots in Figure 11, the morphine arm shows a pattern different from the three oliceridine arms. We compared the estimated treatment difference between the oliceridine arms and placebo from the two models to determine whether there is any consistent shift suggesting that a bias was introduced by the inclusion of the morphine arm. The model that includes the morphine arm yielded consistently lower treatment differences from placebo for all three oliceridine arms than the model that excludes the morphine arm.

We conclude that not all the additional assumptions for the model with morphine arms are true. Therefore, although the model excluding the morphine arm is not the closest match to the pre-specified original model, we consider the results from this model more reliable. There are many similar minor adjustments that could be made to the analysis, and each of these adjustments could have an impact on the results.

**Table 22: SPID Analysis, Doses over 27 mg Treated as Rescue with Morphine Excluded, Study 3002**

<b>Statistic</b>	<b>Placebo N=81</b>	<b>Oliceridine 0.1 mg N=77</b>	<b>Oliceridine 0.35 mg N=80</b>	<b>Oliceridine 0.5 mg N=80</b>
Mean (SD)	68.8 (39.1)	74.1 (45.6)	85.5 (46.2)	90.0 (40.8)
Estimated Mean SPID (SE)	73.1 (4.64)	76.6 (4.73)	87.2 (4.62)	91.2 (4.74)
Estimated mean diff. vs placebo (SE)		3.5 (6.26)	14.1 (6.21)	18.1 (6.27)
p-value vs placebo		0.572	0.024†	0.004†
Superiority vs placebo		No	Yes	Yes

Source: Reviewer

† The applicant used a Hochberg<sup>4</sup> adjustment to control the familywise type-1 error rate. Since the p-value for the 0.1 mg dose exceeds 0.05, the p-value for the 0.35 mg dose and 0.5 mg doses are compared to a threshold of 0.025.

In the second sensitivity analysis (Table 23), patients in the oliceridine 0.35 and 0.5 mg arms were stratified according to the received cumulative dosage ( $\leq 27$  mg vs  $> 27$  mg). In this analysis, patients in both oliceridine arms had statistically significantly greater pain reductions than patients treated with placebo. These results should be interpreted with caution, as this analysis does not preserve the integrity of the randomization. That is, patients were not randomized between the dose groups used in the analysis.

**Table 23: SPID Analysis, Patients in Oliceridine 0.35 mg and 0.5 mg Treatment Groups Stratified by Dose Received, Study 3002**

<b>Statistic</b>	<b>Placebo N=81</b>	<b>Oliceridine <math>\leq 27</math> mg N=102</b>	<b>Oliceridine <math>&gt; 27</math> mg N=55</b>	<b>Morphine N=83</b>
Estimated Mean SPID (SE)	72.7 (4.32)	88.2 (3.85)	93.1 (5.27)	100.6 (4.26)
Estimated mean diff. vs placebo (SE)		15.6 (5.78)	20.4 (6.83)	28.0 (6.07)
p-value vs placebo		0.0074	0.0031	<0.0001

Source: Reviewer

Finally, we examined the data to determine whether there were any associations between any demographic group and the likelihood of exceeding the 27 mg cumulative daily dosage. Results of these analyses are shown in Table 24 and Table 25 for Studies 3001 and 3002, respectively. Except for baseline pain score, where there is an apparent correlation between higher baseline pain scores and higher oliceridine usage, there do not appear to be any

<sup>4</sup> Hochberg Y. A Sharper Bonferroni Procedure for Multiple Tests of Significance. *Biometrika* 1998; 75(4): 800-2

demographic factors that correspond with higher oliceridine doses in either study. Study 3002 only included 3 men, so breakdown by sex was omitted.

**Table 24: Dose/Demographic Group Interaction (Study 3001)**

Demographic group		Oliceridine 0.35 mg		Oliceridine 0.5 mg	
		≤27 mg (n=32)	>27mg (n=47)	≤27 mg (n=29)	>27mg (n=50)
Sex	Female	27/32 (84.4%)	38/47 (80.9%)	27/29 (93.1%)	39/50 (78.0%)
	Male	5/32 (15.6%)	9/47 (19.1%)	2/29 (6.9%)	11/50 (22.0%)
Race	White	27/32 (84.4%)	29/47 (61.7%)	22/29 (75.9%)	39/50 (78.0%)
	Black	4/32 (12.5%)	13/47 (27.7%)	5/29 (17.2%)	8/50 (16.0%)
	Other	1/32 (3.1%)	5/47 (10.6%)	2/29 (6.9%)	3/50 (6.0%)
Age Group	18-65	28/32 (87.5%)	45/47 (95.7%)	28/29 (96.6%)	47/50 (94.0%)
	65+	4/32 (12.5%)	2/47 (4.3%)	1/29 (3.4%)	3/50 (6.0%)
Metabolizer Status	Extensive Metabolizer	25/32 (78.1%)	44/47 (93.6%)	25/29 (86.2%)	46/50 (92.0%)
	Poor Metabolizer	6/32 (18.8%)	2/47 (4.3%)	2/29 (6.9%)	3/50 (6.0%)
	Not Reported	1/32 (3.1%)	1/47 (2.1%)	2/29 (6.9%)	1/50 (2.0%)
Baseline	Pain	6.0	7.0	6.1	6.7

Source: Reviewer

**Table 25: Dose/Demographic group interaction (Study 3002)**

Demographic group		Oliceridine 0.35 mg		Oliceridine 0.5 mg	
		≤27 mg (n=58)	>27mg (n=22)	≤27 mg (n=45)	>27mg (n=34)
Race	White	38 (65.5%)	17 (77.3%)	28 (62.2%)	21 (61.8%)
	Black	18 (31.0%)	4 (18.2%)	16 (35.6%)	12 (35.3%)
	Other	2 (3.4%)	1 (4.5%)	1 (2.2%)	1 (2.9%)
Age Group	18-65	56 (96.6%)	22 (100%)	44 (97.8%)	34 (100.0%)
	65+	2 (3.4%)	0	1 (2.2%)	0
Metabolizer Status	Extensive Metabolizer	44 (75.9%)	19 (86.4%)	38 (84.4%)	29 (85.3%)
	Poor Metabolizer	9 (15.5%)	3 (13.6%)	4 (8.9%)	5 (14.7%)
	Not Reported	5 (8.6%)	0	3 (6.7%)	0
Baseline	Pain	7.3	7.7	7.3*	7.7†

Source: Reviewer

\*2 patients had missing baseline pain scores

†1 patient had missing baseline pain scores

**Efficacy Conclusions**

The applicant has provided independent substantiation of the efficacy of oliceridine for the treatment of acute pain. Both the 0.35 mg and 0.5 mg PCA demand doses of oliceridine were significantly better than placebo in both studies. It must also be noted that morphine demonstrated a greater reduction in pain intensity than all three dosing regimens of oliceridine that were tested in the studies. The 0.1 mg PCA demand dose of oliceridine was superior to placebo in Study 3001, but not in Study 3002.

## 8 Safety

Safety data from all clinical trials submitted in the original NDA were reviewed by the clinical team in the first review cycle and considered in the safety assessment of this product. See the Combined CDTL first-cycle review for details<sup>5</sup>. This section of the review focuses on the safety data to address the clinical CR deficiencies related to the inadequate safety database and QT prolongation, and provides a summary of key safety findings from the first and second review cycles.

The major safety analysis of oliceridine discussed in this section of the review is based on 470 patients with acute post-operative pain in the controlled Phase 3 studies 3001 and 3002, and 768 patients in the uncontrolled Phase 3 study 3003.

During drug development, oliceridine was referred to as TRV130. In the discussion below, oliceridine may be referred to as TRV130, oliceridine, or OLINVYK.

This product is an NME. According to the 2005 Guidance for Industry Premarketing Risk Assessment,<sup>6</sup> determining the appropriate size of a safety database depends on a number of factors specific to that product such as novelty, intended population and condition being treated, availability of alternative therapies, relative safety of those alternatives compared to the new product, and intended duration of use. The Guidance further states that, *“For products intended for short-term or acute use (e.g., treatments that continue for, or are cumulatively administered for, less than 6 months), FDA believes it is difficult to offer general guidance on the appropriate target size of clinical safety databases. This is because of the wide range of indications and diseases (e.g., acute strokes to mild headaches) that may be targeted by such therapies. Sponsors are therefore encouraged to discuss with the relevant review division the appropriate size of the safety database for such products.”*

The applicant discussed their planned safety database size with the division during the development program. At the End-of-Phase 2 meeting, the division agreed with the applicant’s plan to provide safety data in approximately 1,100 patients across the targeted dose range from the Phase 2 and Phase 3 studies, but also informed the applicant that those patient exposures should occur within the dose range intended for marketing, with at least 350 patients exposed to the highest intended doses for the longest expected duration of use.

### 8.1 Safety database summary

A significant consideration during the first review cycle was whether the size of the safety database was adequate.

During drug development, the division and the applicant discussed the factors to be considered when determining an expected duration of use for an acute pain medication with PRN dosing.

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<sup>5</sup> Please refer to first review cycle CDTL combined November 1, 2018 review for details.

<sup>6</sup> Guidance for Industry Premarketing Risk Assessment  
<http://www.fda.gov/cder/guidance/index.htm>

The division considered that acute pain patients generally require the highest dose for the first 24 hours after the treatment initiation, and that the dose is expected to decrease in the second day of the treatment. Therefore, the division and the applicant agreed that the longest expected duration for determining the safety database should be the first 24 hours after treatment initiation.

The division asked the applicant to identify the highest dose that had at least 350 patients exposed for the longest actual cumulative duration of use, and also to identify the highest dose with at least 350 patients exposed for the first 24 hours. The applicant provided data that showed that the highest dose with the longest actual cumulative duration that had at least 350 patients exposed was 37.2 mg, administered over a duration of at least 35.5 hours. The highest dose of oliceridine that had at least 350 patients exposed during the first 24 hours of dosing was 27 mg.

Since the applicant was initially proposing a total daily dosage of 40 mg, one major clinical deficiency from the first submission was inadequate safety data to support the proposed maximum daily dosage. The Complete Response letter stated:

The submitted exposure database is not of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. You have proposed a maximum daily dose of 40 mg without a limit on the duration of use. You were advised at the End-of-Phase 2 and pre-NDA meetings that the safety database needed to include at least 350 patients exposed to the highest doses for the longest duration of use. In your Phase 2 and Phase 3 studies, the highest dose that at least 350 patients were exposed to during the first 24 hours was 27 mg of oliceridine. The highest dose with the longest actual duration that had at least 350 patients exposed was 37.2 mg administered over an actual duration of at least 35.5 hours.

Information Needed to Resolve the Deficiency: Provide an exposure database that is of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. Specifically, the safety database must include at least 350 patients exposed to the highest dose proposed for the longest duration of use indicated in the labeling.

To respond to the clinical deficiency, the applicant proposed a maximum oliceridine daily dosage of 27 mg in the resubmission.

As shown in Table 27 below, of the 1,535 patients who received oliceridine in Phase 2 and Phase 3 studies, a total of 1,181 patients received  $\leq 27$  mg/day and 354 received  $>27$  mg/day.

**Table 27: Exposure of Oliceridine Treatment Stratified by Daily Dosage**

STUDY ID	Treatment arm	$\leq 27$ mg	$>27$ mg	n
CP130-2001	TRV130	197	21	218
CP130-2002	TRV130	75	3	78
CP130-2004	TRV130	1	0	1
CP130-3001	Oliceridine 0.1 mg	75	1	76

<b>STUDY ID</b>	<b>Treatment arm</b>	<b>≤27 mg</b>	<b>&gt;27 mg</b>	<b>n</b>
CP130-3001	Oliceridine 0.35 mg	32	47	79
CP130-3001	Oliceridine 0.5 mg	29	50	79
CP130-3002	Oliceridine 0.1 mg	77	0	77
CP130-3002	Oliceridine 0.35 mg	57	22	79
CP130-3002	Oliceridine 0.5 mg	46	34	80
CP130-3003 <sup>7</sup>	TRV130	592	176	768
Total		1181	354	1535

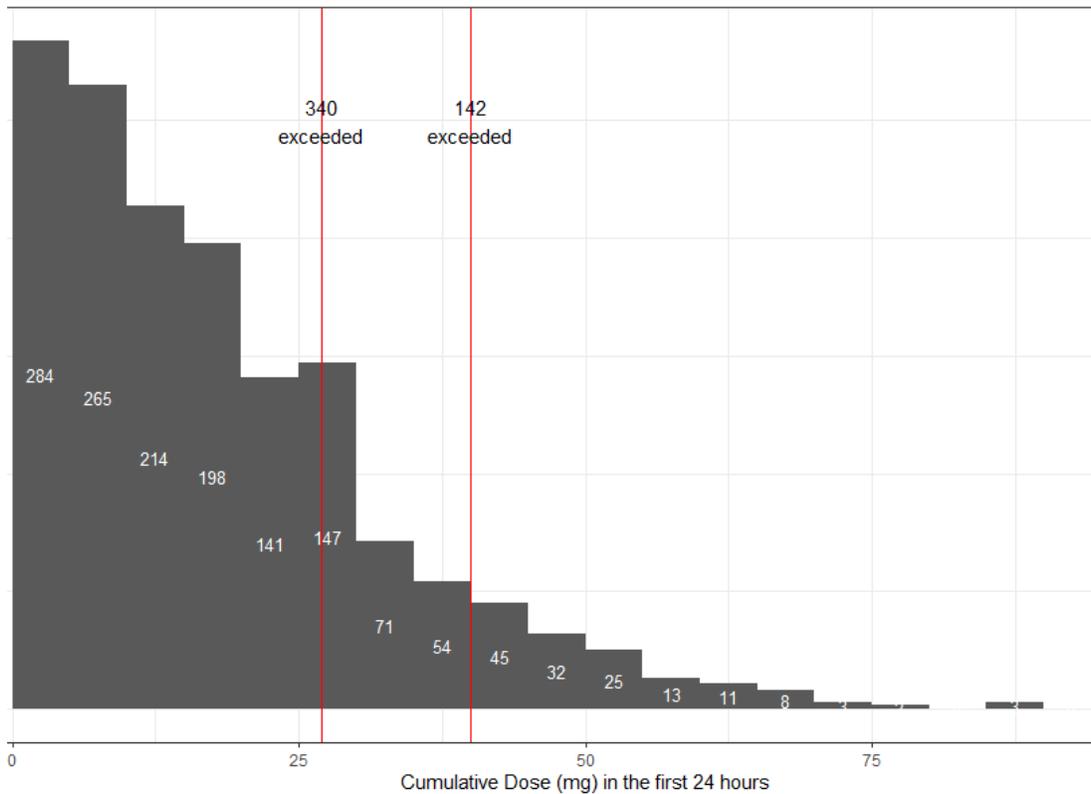
CDTL Reviewer; n=number

Figure 12 shows the distribution of cumulative dosages of oliceridine during the first 24 hours of treatment in Phase 2 and 3 studies. Among patients who received a daily dosage >27 mg, 198 patients received a daily dosage between 27 mg and 40 mg, and 142 patients received a daily dosage >40 mg. The maximum daily dosage was 88 mg.

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<sup>7</sup> There was a “3 patients” discrepancy between the applicant’s method for patient allocation and the FDA’s method for patient allocation for the Phase 3 open-label study 3003. All three of these subjects have a missing value for total dosing duration. Applicant accepted FDA’s method for patient allocation in their response to FDA’s clinical information request on 7/28/2020.

**Figure 12 Distribution of Cumulative Dosage (mg) of Oliceridine in the First 24 hours among Patients in Phase 2 and Phase 3 Studies<sup>8</sup>**



Agency’s statistical reviewer

Due to the PRN dosing regimen, patients received a wide range of exposure to oliceridine. Table 28 below displays the exposure by cumulative dosage and duration for all oliceridine-treated patients in Phase 2 and Phase 3 studies. The mean oliceridine cumulative duration of exposure was approximately 32 hours, with a maximum of approximately 143 hours. The mean cumulative dosage exposure across all Phase 2 and Phase 3 studies was approximately 29 mg, with a maximum of approximately 223 mg.

<sup>8</sup> Histogram was made by FDA statistical reviewer using the dataset provided by the applicant dated on 15 June 2020. In response to FDA’s clinical information request, on July 28, 2020, the applicant confirmed that a total of 354 patients received a daily dose of more than 27 mg; 198 patients received a daily dose between 27 mg and 40 mg, and 142 patients received a daily dose >40 mg. The remaining 14 patients were classified as receiving >27 mg total daily dose, based on the total oliceridine dose received for the study, but the details of their dosing is unknown, and therefore these records have a missing total daily dose and are not further classifiable within this stratum.

**Table 28: Oliceridine Exposure by Treatment Regimen in All Phase 2 and Phase 3 Studies**

Characteristic	Placebo N=252	OLI Total N=1535	Morphine N=305
<b>Exposure duration (hours)<sup>a</sup></b>			
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 <sup>b</sup>
<b>Cumulative exposure (mg)<sup>c</sup></b>			
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 <sup>(b)</sup> (6) 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: Reviewer, Modified from Integrated Summary of Safety 120-day safety update, Table 16, page 94, submitted 03/05/18

Table 29 summarizes the exposure for the pooled controlled Phase 3 studies. In Studies 3001 and 3002, the duration of dosing was limited per protocol to 48 hours and 24 hours, respectively. The median cumulative dosage for oliceridine-treated patients was 22.2 mg in the pooled controlled Phase 3 studies. The median cumulative dosage in the first 24 hours was 18.3 mg.

**Table 29: Cumulative Exposure by Treatment Regimen in Controlled Phase 3 Studies**

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
<b>Cumulative exposure (mg)<sup>a</sup></b>						
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
<b>Cumulative exposure quartile, n (%)</b>						
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)	--
<b>Cumulative exposure (mg) in the first 24 hours<sup>a</sup></b>						
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
<b>Total number of demand doses</b>						
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)
<b>Total number of supplemental doses</b>						
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)

Applicant's table; 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

For Study 3003 (see Table 30), the median cumulative duration of oliceridine exposure was 20.3 hours (range 0 to 142.7 hours) and the median cumulative dosage of oliceridine for the patient population was 19.25 mg (range 0.9 to 223.5 mg).

**Table 30: Cumulative Exposure Open-Label Phase 3 Study 3003**

	Oliceridine ≤4 mg N=156	Oliceridine >4 to 8 mg N=85	Oliceridine >8 to 16 mg N=121	Oliceridine >16 to 36 mg N=168	Oliceridine >36 mg N=238	All Treated Patients N=768
Method of administration, n (%)						
Bolus	148 (94.9)	66 (77.6)	71 (58.7)	70 (41.7)	65 (27.3)	420 (54.7)
PCA	8 (5.1)	19 (22.4)	50 (41.3)	98 (58.3)	173 (72.7)	348 (45.3)
Exposure to oliceridine (hours), n (%) <sup>a</sup>						
N	156	84	117	163	229	749
Mean (SD)	1.465 (3.6097)	10.462 (12.2738)	19.203 (16.8104)	35.877 (20.4942)	53.698 (22.9052)	28.704 (26.8853)
Median	0.200	4.500	16.400	36.300	52.300	20.300
Min. max	0.00, 26.80	0.30, 51.70	0.20, 73.90	0.60, 93.10	5.80, 142.70	0.00, 142.70
Missing <sup>b</sup>	0	1	4	5	9	19
Cumulative oliceridine dose (mg)						
N	156	85	121	168	238	768
Mean (SD)	2.51 (0.987)	6.20 (1.157)	12.26 (2.326)	25.70 (5.461)	67.48 (28.600)	29.66 (31.089)
Median	3.00	6.00	12.00	25.50	59.00	19.25
Min. max	0.9, 4.0	4.5, 8.0	8.5, 16.0	17.0, 36.0	36.5, 223.5	0.9, 223.5

max=maximum; min=minimum; PCA=patient-controlled analgesia; SD=standard deviation

Note: Percentages were based on the total number of nonmissing values in each cumulative dose group.

<sup>a</sup> Duration was defined as the difference in total hours from the first dose to the last dose of study medication.

<sup>b</sup> Missing cumulative exposure duration occurred because of a technical issue with PCA pumps. In these occurrences, the cumulative dose was computed using the volume of remaining drug in the PCA syringe and not using dose-by-dose records.

Applicant's Table 15, ISS Update

## Conclusion regarding Adequacy of the Safety Database

The applicant satisfactorily addressed the CR deficiency related to the safety database by lowering the maximum recommend total daily dosage from 40 mg to 27 mg. The number of patients exposed for total daily dosages up to 27 mg meets the division's expectations that were discussed during the development program, i.e., at least 350 patients treated for the highest dosage proposed for labeling.

## 8.2 Deaths

No deaths were reported in the Phase 1, Phase 2, or Phase 3 clinical studies.

## 8.3 Serious Adverse Events (SAEs)

An SAE was defined in the Phase 3 protocols as any untoward medical occurrence that, at any dose:

- Resulted in death.
- Was life-threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It did not refer to an event that hypothetically might have caused death if it were more severe.
- Required hospitalization or prolongation of existing hospitalization.
  - In general, hospitalization signified that the patient had been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occurred during hospitalization were AEs. If a complication prolonged the hospitalization or fulfilled any other seriousness criteria, the event was considered serious. When

in doubt as to whether “hospitalization” occurred or was necessary, the AE was considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline was not considered an SAE, nor was prolongation of hospitalization for non-medically driven circumstances (e.g., transportation issues).
- Resulted in persistent or significant disability or incapacity. The term disability meant a substantial disruption of a person’s ability to conduct normal life functions. This definition was not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which might have interfered or
- Was a congenital anomaly/birth defect.
- Was an important medical event. Medical or scientific judgment was exercised in deciding whether reporting was appropriate in other situations, such as important medical events that might not have been immediately life-threatening or resulted in death or hospitalization but might have jeopardized the patient or might have required medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that did not result in hospitalization, or development of drug dependency or drug abuse.

No patient experienced a serious adverse event in Study 3001. A total of five patients (2%) experienced an SAE in Study 3002, with 4 SAEs in the oliceridine 0.5 mg treatment arm, and 1 SAE in the oliceridine 0.35 mg treatment arm (see Table 31). The five treatment-emergent SAEs were post-procedural hemorrhage, syncope, lethargy, deep vein thrombosis, and abdominal wall hematoma. Some of these events appear to be related to post-operative events, while some are likely opioid-related.

**Table 31: Serious Adverse Events Controlled Phase 3 Studies 3001 and 3002**

<b>Study 3001</b>					
	<b>Placebo N=79 n (%)</b>	<b>OLI 0.1 mg N=76 n (%)</b>	<b>OLI 0.35 mg N=79 n (%)</b>	<b>OLI 0.5 mg N=79 n (%)</b>	<b>Morphine N=76 n (%)</b>
Patients with any Serious TEAE	0	0	0	0	0
<b>Study 3002</b>					
	<b>Placebo N=83 N (%)</b>	<b>OLI 0.1 mg N=77 N (%)</b>	<b>OLI 0.35 mg N=79 N (%)</b>	<b>OLI 0.5 mg N=80 N (%)</b>	<b>Morphine N=82 N (%)</b>
Patients with any Serious TEAE	0	0	1 (1)	4 (5)	1 (1)

Clinical Reviewer; Abbreviations: OLI=oliceridine; TEAE=treatment-emergent adverse event. Source: Clinical Study Report CP130-3001, Table 29, Clinical Study Report CP130-3002, Table 29 and ISS Safety Update Table 33; Based on applicant’s tables modified by reviewer.

In open-label Study 3003, 26 patients (3%) experienced a total of 32 treatment-emergent SAEs. The primary clinical reviewer categorized the types of SAEs into three general types: a) postoperative adverse events, b) opioid-related adverse events, and c) other events. These

categories were based on whether, after review of the narratives, the reviewer determined that the SAEs were likely related to postoperative events, opioid-related adverse events, or other factors. The postoperative SAEs included bleeding and infection, anemia, flatulence, post procedural hematoma/hemorrhage, intra-abdominal hemorrhage, breast hematoma, graft infection, abdominal abscess, and sepsis. The opioid-associated SAEs included respiratory depression, nausea, and hypoxia. Some SAEs could have been related to postoperative, opioid-related, or a combination of factors, which included AE terms of small intestinal obstruction, syncope, mental status change, 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. There was no clear dose-response when assessing SAEs by total cumulative dose, although most occurred with a total cumulative dose >16 mg (Appendix C Table 46).

Based on the reviewer-designated categories above, the most common category of SAEs in open-label Study 3003 were post-operative (52%). Clearly defined opioid-related SAEs occurred with the lowest incidence (15%). The overall pattern of types and frequency of SAEs appears related primarily to post-operative adverse events, as might be expected in a post-operative and general medical/surgical population that would require IV analgesics. When SAEs are stratified by daily dosage > 27 mg or ≤ 27 mg in open-label Study 3003, there is no clear dose-response for SAEs, as most SAEs occurred in patients who received a daily dosage ≤ 27 mg. However, the comparison is limited because there are far more patients who received a daily dosage of oliceridine ≤ 27 mg (N=592) than a daily dosage > 27 mg (N=176) (Appendix C Table 47).

#### 8.4 Severe Adverse Events

As stated in the protocols for Studies 3001 and 3002, the intensity of an AE was scored according to the following scale:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity
- Severe: incapacitating with inability to work or perform usual activity

The majority of TEAEs in oliceridine-treated patients in the controlled Phase 3 studies were mild or moderate in intensity. No severe TEAEs were experienced by ≥5% of patients in any treatment group. The System Organ Class (SOC) GI disorders had the highest incidence of severe TEAEs, experienced by 2%, 3%, and 5% in the placebo, oliceridine, and morphine treatment groups, respectively, in the controlled trials.

In the controlled studies, when analyzing severe TEAEs stratified by daily dosage (> 27 mg or ≤ 27 mg), there were no clear dose-response for severe TEAEs. Higher daily dosages were not associated with a higher rate of severe TEAE. Severe TEAEs occurred in 7% of subjects who received a total daily oliceridine dosage of ≤27 mg, and 5% of subjects who received a total oliceridine daily dosage >27 mg. Severe AEs were reported in 9% of patients in the morphine-treatment group, and 3% in the placebo group (Table 32). Severe TEAEs possibly related to oliceridine treatment include nausea, drug withdrawal, alanine aminotransferase increased, aspartate aminotransferase increased, dizziness, somnolence, syncope, and headache.

**Table 32: Severe TEAEs Stratified by Total Daily Dosage (> 27 mg or ≤ 27 mg) in Studies 3001 and 3002**

MedDRA Preferred Term	Morphine N = 158		Oliceridine ≤ 27mg N = 316		Oliceridine > 27mg N = 154		Placebo N = 162	
	N	%	N	%	N	%	N	%
Subject with any severe TEAE	14	9	23	7	7	5	5	3
Dyspepsia	0	0	1	0	0	0	0	0
Flatulence	0	0	0	0	0	0	1	0
Nausea	6	0	9	0	2	0	2	0
Vomiting	3	0	1	0	0	0	0	0
Drug withdrawal syndrome	0	0	0	0	1	0	0	0
Non-cardiac chest pain	1	0	0	0	0	0	0	0
Alanine aminotransferase increased	0	0	1	0	0	0	0	0
Aspartate aminotransferase increased	0	0	1	0	0	0	0	0
Transaminases increased	1	0	1	0	0	0	0	0
Myalgia	0	0	0	0	1	0	0	0
Dizziness	0	0	4	0	0	0	0	0
Headache	1	0	2	0	1	0	0	0
Presyncope	1	0	1	0	0	0	0	0
Sleep paralysis	0	0	0	0	1	0	0	0
Somnolence	0	0	1	0	0	0	0	0
Syncope	0	0	1	0	0	0	0	0
Anxiety	0	0	0	0	1	0	0	0
Depression	0	0	0	0	1	0	0	0
Euphoric mood	0	0	1	0	0	0	0	0
Vaginal discharge	0	0	1	0	0	0	0	0
Vulvovaginal pruritus	0	0	1	0	0	0	0	0
Cough	0	0	0	0	1	0	0	0
Hyperventilation	0	0	0	0	0	0	1	0
Rhinorrhoea	1	0	0	0	0	0	0	0
Hot flush	1	0	0	0	0	0	0	0

CDTL reviewer using JMP clinical 7.1

In open-label Study 3003, severe TEAEs occurred in 2% of subjects who received a total daily oliceridine dosage of ≤27 mg, and 1% of subjects who received a total oliceridine daily dosage >27 mg. Severe TEAEs possibly related to oliceridine treatment were nausea, vomiting, and syncope (Appendix C Table 4able 48).

## 8.5 Adverse Events leading to drug discontinuation

In Study 3001, a higher percentage of patients in the morphine treatment arm discontinued treatment because of an adverse event, compared to the other treatment arms (see Table 33). In the oliceridine treatment arms, the percentage of subjects with TEAEs leading to drug discontinuation was higher in the 0.5 mg arm compared to the 0.35 mg arm. There was no adverse dropout in the oliceridine 0.1 mg arm. Approximately 5% of patients in the oliceridine 0.5 mg arm discontinued treatment due to decreased oxygen saturation or hypoxia, compared to 7% in the morphine treatment arm.

In contrast to Study 3001, in Study 3002, there was a higher percentage of patients in the oliceridine 0.35 mg and 0.5 mg treatment arms who discontinued treatment due to an adverse event, compared to the other treatment arms. The percentage of patients in the oliceridine 0.35 mg and 0.5 mg treatment arms who discontinued due to hypoxia (4% and 1%, respectively) was higher than the percentage of patients in the morphine treatment arm who discontinued due to hypoxia (0%).

Overall, there is no evidence for improved respiratory safety with oliceridine, compared to morphine, based on adverse events leading to discontinuation.

**Table 33: TEAEs leading to Study Medication Discontinuation by SOC and PT in Studies 3001 and 3002**

Study 3001					
System Organ Class Preferred Term	Placebo N=79 %	OLI 0.1 mg N=76 %	OLI 0.35 mg N=79 %	OLI 0.5 mg N=79 %	Morphine N=76 %
Any TEAE leading to early study medication discontinuation (%)	0	0	1	6	8
Gastrointestinal disorders	0	0	0	1	1
Nausea	0	0	0	1	0
Vomiting	0	0	0	0	1
Investigation	0	0	1	2	7
Oxygen saturation decreased	0	0	1	2	7
Nervous system disorders	0	0	0	2	0
Dizziness	0	0	0	1	0
Sedation	0	0	0	1	0
Respiratory, thoracic, and mediastinal disorders	0	0	0	2	0
Hypoxia	0	0	0	2	0
Oxygen saturation decreased + hypoxia combined	0	0	1	4	7
Study 3002					
	Placebo N=83 %	OLI 0.1 mg N=77 %	OLI 0.35 mg N=79 %	OLI 0.5 mg N=80 %	Morphine N=82 %
Any AE leading to early study medication discontinuation (%)	0	0	5	5	2
Gastrointestinal disorders	0	0	0	1	0
Nausea	0	0	0	1	0

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General disorders and administration site conditions	0	0	0	0	1
Non-cardiac chest pain	0	0	0	0	1
Injury, poisoning, and procedural complications	0	0	0	1	0
Post procedural hemorrhage	0	0	0	1	0
Nervous system disorders	0	0	0	1	1
Presyncope	0	0	0	0	1
Syncope	0	0	0	1	0
Respiratory, thoracic, and mediastinal disorders	0	0	4	1	0
Hypoxia	0	0	4	1	0
Vascular disorders	0	0	1	0	0
Hypotension	0	0	1	0	0

Clinical Reviewer; Abbreviations: OLI=oliceridine; TEAE=treatment-emergent adverse event

Source: Modified from Applicant's 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 open-label Study 3003, a total of 17 oliceridine-treated patients (2%) experienced 29 TEAEs leading to early drug discontinuation. Most TEAEs leading to early discontinuation occurred in one patient each. Many of the TEAEs leading to discontinuation appear to be opioid-related, including respiratory depression, hypotension, nausea, vomiting, and pruritus. Overall, the types of adverse events leading to discontinuation were across a broad spectrum, but mostly GI-related (Appendix Table 50).

The team also analyzed discontinuations due to AEs by daily dosage ( $\leq 27$  mg vs  $>27$  mg). In controlled Studies 3001 and 3002, discontinuation of oliceridine due to adverse events occurred in 4% of patients who received a total daily dosage  $\leq 27$  mg, and less than 1% of patients who received a total daily dosage  $>27$  mg (Table 34). In these same studies, discontinuation due to adverse events occurred in 5% of morphine-treated patients, and in no placebo-treated patient.

In the open-label safety Study 3003, discontinuation of oliceridine due to adverse events occurred in 3% of patients who received a total daily dosage  $\leq 27$  mg, and 1% of patients who received a total daily dosage  $>27$  mg (see Appendix C Table 49). TEAEs leading to discontinuation of oliceridine in patients who received a total daily dosage  $\leq 27$  mg were hypotension, hypoxia, nausea, hypoventilation, oxygen saturation decreased, alanine aminotransferase increased, aspartate aminotransferase increased, electrocardiogram QT prolongation, and urticaria. Hypoxia leading to oliceridine discontinuation occurred in 2 % of patients who received a total daily dosage  $\leq 27$  mg, vs. no discontinuation in the morphine treatment arm, which suggests that oliceridine with a maximum daily dosage of 27 mg does not provide safety any advantage on respiratory depression compared to morphine (Table 34).

**Table 34: TEAEs leading to Drug Discontinuation Stratified by Daily Dose ( $> 27$  mg or  $\leq 27$  mg) in Controlled Studies 3001 and 3002**

MedDRA Preferred Term	Morphine N = 158		Oliceridine $\leq 27$ mg N = 316		Oliceridine $>27$ mg N=154	
	N	%	N	%	N	%
Subject with any TEAE leading to drug discontinuation	8	5	13	4	1	0
Nausea	0	0	2	0	0	0
Vomiting	1	0	0	0	0	0
Non-cardiac chest pain	1	0	0	0	0	0
Post procedural haemorrhage	0	0	1	0	0	0
Oxygen saturation decreased	5	3	2	0	1	0
Dizziness	0	0	1	0	0	0
Presyncope	1	0	0	0	0	0
Sedation	0	0	1	0	0	0
Syncope	0	0	1	0	0	0
Hypoxia	0	0	6	2	0	0
Hypotension	0	0	1	0	0	0

CDTL reviewer using JMP clinical 7.1

## 8.6 Significant Adverse Events

### 8.6.1 Respiratory Depression/Hypoxia

Respiratory depression is a known opioid-related effect. The applicant attempted to design the controlled Phase 3 studies to examine their hypothesis that oliceridine has a better safety profile for the opioid-related adverse event of respiratory depression compared to morphine.

FDA determined, during the first review cycle, that the data do not suggest a safety advantage for oliceridine for respiratory depression, compared to morphine. The applicant submitted no new clinical data in the second review cycle related to respiratory depression.

In the first review cycle, in the controlled Phase 3 study protocols, the applicant assessed respiratory safety by measuring what they described as clinically relevant respiratory events (i.e., Respiratory Safety Event [RSE]) using a secondary safety/tolerability endpoint termed a Respiratory Safety Burden. The Respiratory Safety Burden was defined in the protocols as a clinically relevant worsening of respiratory status that met pre-defined clinical parameters.

During development, FDA informed the applicant that their definition of a Respiratory Safety Burden was not clinically interpretable and could not be used to support respiratory-related labeling claims. FDA, instead, analyzed oliceridine's respiratory safety based on relevant MedDRA preferred terms, and determined that the types of respiratory events in the Phase 3 controlled studies appear consistent with known opioid respiratory effects. The overall incidence of respiratory-related events in oliceridine's highest dosage groups was similar to the active comparator, morphine, when considering all respiratory-related parameters, as seen in Table 35.

**Table 35: Respiratory-related TEAEs in Controlled Studies 3001 and 3002**

<b>Study 3001</b>					
	<b>Placebo N=79 n (%)</b>	<b>OLI 0.1 mg N=76 n (%)</b>	<b>OLI 0.35 mg N=79 n (%)</b>	<b>OLI 0.5 mg N=79 n (%)</b>	<b>Morphine N=76 n (%)</b>
Oxygen saturation <90%	1 (1.3)	3 (3.9)	8 (10.1)	11 (13.9)	15 (19.7)
TEAEs in Respiratory, thoracic, and mediastinal disorders SOC	2 (2.5)	3 (3.9)	9 (11.4)	12 (15.2)	10 (13.2)
Patients with any O <sub>2</sub> administration	0	1 (1.3)	7 (8.9)	10 (12.7)	13 (17.1)
<b>Study 3002</b>					
	<b>Placebo N=83 n (%)</b>	<b>OLI 0.1 mg N=77 n (%)</b>	<b>OLI 0.35 mg N=79 n (%)</b>	<b>OLI 0.5 mg N=80 n (%)</b>	<b>Morphine N=82 n (%)</b>
Oxygen saturation <90%	7 (8.4)	6 (7.8)	15 (19.0)	16 (20.0)	20 (24.4)
TEAEs in Respiratory, thoracic, and mediastinal disorders SOC	9 (10.8)	9 (11.7)	23 (29.1)	25 (31.3)	25 (30.5)
Patients with any O <sub>2</sub> administration	5 (6.0)	6 (7.8)	16 (20.3)	18 (22.5)	23 (28.0)

Clinical Reviewer; Abbreviations: OLI=oliceridine, TEAE=Treatment Emergent Adverse Event; SOC=System Organ Class

### 8.6.2 Hepatic Safety

Oliceridine is an NME. Therefore, FDA conducted a detailed hepatic analysis in the first review cycle. Hepatic findings were fully discussed in the first review cycle, with key findings

briefly summarized below. No new hepatic-related data were submitted in the second review cycle.

In the first review cycle, the Agency determined that the overall incidence of elevated transaminases in the controlled Phase 3 studies was similar between the oliceridine and morphine treatment groups. In open-label Study 3003, there was one subject with a serious adverse event of hepatic/renal failure (Patient ID (b) (6)) and two subjects (Patient ID (b) (6)) who met laboratory criteria of possible Hy’s Law case (defined as ALT or AST transaminases  $\geq 3x$  upper limit of normal [ULN] with total bilirubin  $> 2x$  ULN)<sup>9</sup>. The Division consulted the Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE), to provide an assessment of whether oliceridine has a potential to cause drug-induced liver injury. The OSE hepatology consultants analyzed the applicant’s hepatic safety data submitted via the eDISH (Evaluation of Drug Induced Serious Hepatotoxicity) analytical tool. OSE determined that these hepatic cases were confounded, and the abnormal liver findings were possibly due to anesthesia and/or multiple concomitant perioperative medications. OSE concluded that no case met Hy’s Law criteria since other etiologies were possible contributors and/or causative. These hepatic findings were also discussed at the Advisory Committee (AC) meeting. The Committee members generally agreed that oliceridine did not appear to have a hepatic safety signal. FDA concluded that it could not be determined that transient elevations of hepatic transaminases were due to oliceridine alone.

In the second review cycle, hepatic findings for the Phase 3 controlled studies were analyzed stratified by total daily dosage ( $> 27$  mg or  $\leq 27$  mg). The incidence of elevated transaminases was similar in patients who received a total daily dosage  $> 27$  mg and those who received a total daily dosage  $\leq 27$  mg, and was similar to the incidence observed in the morphine treatment group (Table 36 and Table 37). In open-label Study 3003, the incidence of elevated transaminases was also similar in patients who received a total oliceridine daily dosage  $> 27$  mg and those who received a total daily dosage  $\leq 27$  mg.

**Table 36: Abnormal Hepatic-Related Laboratory Results by Total Daily dosage in Study 3001**

Hepatic Transaminases	Placebo N=79	Oliceridine $\leq 27$ mg N=136	Oliceridine $> 27$ mg N=98	Morphine N=76
<b>ALT Elevations (%)</b>				
Between 2x and 5x ULN	2.5	2	3.1	3.9
Between 5x and 10x ULN	0	0	1	0
Between 10x and 20x ULN	0	0	0	1.3
<b>AST Elevations (%)</b>				
Between 2x and 5x ULN	1.3	3.7	1	2.6

<sup>9</sup> Drug-Induced Liver Injury Guidance <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation>

Hepatic Transaminases	Placebo N=79	Oliceridine ≤ 27mg N=136	Oliceridine > 27mg N=98	Morphine N=76
Between 5x and 10x ULN	0	0	1	0
Between 10x and 20x ULN	0	0	0	1.3

CDTL reviewer using JMP clinical 7.1; Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase

**Table 47: Abnormal Hepatic-Related Laboratory Results by Total Daily Dosage in Study 3002**

Hepatic Transaminases	Placebo N=83	Oliceridine ≤27mg N=180	Oliceridine > 27mg N=56	Morphine N=82
<b>ALT Elevations (%)</b>				
Between 2x and 5x ULN	2.4	4.4	8.9	4.9
Between 5x and 10x ULN	0	0.6	0	1.2
Between 10x and 20x ULN	0	1.1	0	0
20x ULN or Greater	0	0.6	0	0
<b>AST Elevations (%)</b>				
Between 2x and 5x ULN	2.4	1.7	0	3.7
Between 5x and 10x ULN	1.2	0.6	0	1.2
Between 10x and 20x ULN	0	1.7	0	0

CDTL reviewer using JMP clinical 7.1; Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase

### 8.6.3 QT Prolongation

In this review cycle, the applicant submitted the results of a multiple-dose QT-study to address the clinical deficiency related to QT prolongation described in the CR letter. The multiple-dose QT study supports the safety of a total cumulative daily dosage of oliceridine up to 27 mg per day. However, QT effects beyond a total daily dosage of 27 mg were not studied, and there is evidence suggesting that QT prolongation may occur with doses greater than 27 mg. This information will be included in the Warnings and Precautions section of the oliceridine label. Labeling will also describe that the total cumulative daily dosage of oliceridine should not exceed 27 mg, as daily dosages greater than 27 mg may increase risk for QTc interval prolongation. Applying a maximum recommended dose of 27 mg addresses the clinical deficiency related to QT prolongation.

During the first review cycle, the applicant submitted a single dose QT-study to support the application. The thorough QT study showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset. The QT study did not evaluate the maximum proposed dosing regimen, but showed a delayed increase in QTc following a single dose. The mechanism of the delayed increase in QTc is unknown. Nonclinical data show that the QTc prolongation may not be mediated via direct inhibition of the hERG potassium channels. The exposure for the maximum proposed dosing regimen is projected to be 2 to 3-fold higher for the two major metabolites compared to highest dose in the thorough QT (tQT)

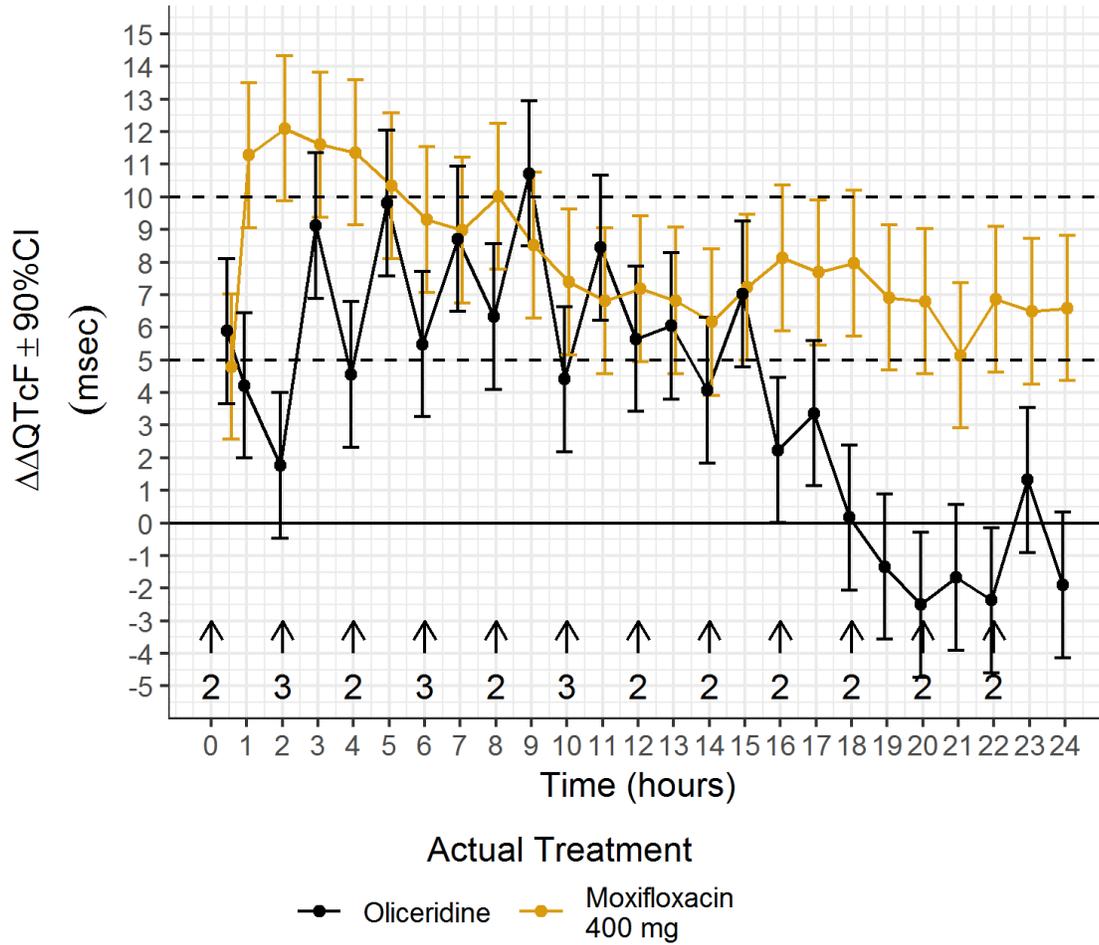
study. FDA determined that the submitted data were not adequate to evaluate the QT effects of oliceridine.

For both the controlled and open-label Phase 3 studies, the IRT team concluded that the incidence of QT prolongation based on ECG findings could not be adequately determined because of the infrequent ECG assessments.

To address the clinical deficiency regarding QT safety concerns stated in the CR letter, the applicant submitted the findings from a multiple-dose tQT Study (CP130-1014). The division consulted the QT-Interdisciplinary Review Team (IRT), which concluded that the new QT study supports the safety of repeat dosing up to 27 mg daily, a dosage that does not result in clinically significant QT prolongation.

As noted in Dr. Lars Johannsen's QT- IRT consult review dated 4/16/2020, the tQT study showed that repeat dosing of 2-3 mg oliceridine every 2 hours resulted in the maximum QTc prolongation at 9 hours post-dosing, which decreased with repeat dosing of oliceridine up to 27 mg thereafter. As indicated in Figure 13, the largest estimated mean for  $\Delta\Delta\text{QTcF}$  is 10.7 msec (8.5, 12.9) at 9 hours post-dose, using a mixed-effects model with compound symmetry covariance. The underlying mechanism for the QTc prolongation remains unknown, but is unlikely to be mediated via direct inhibition of ion channels, given that it is not observed with repeat dosing beyond 9 hours post-dosing. The clinical relevance of the observed QTc prolongation is unknown, but is unlikely to be important, given that it is transient and not hERG-mediated. The clinical QTc prolongation observed with oliceridine decreased despite continued dosing beyond 9 hours in the second thorough QT study, suggesting that further QTc prolongation with dosing beyond what was studied is unlikely. However, given that the mechanism behind the observed QTc prolongation is unknown, it is not possible to predict the QTc effects outside the observed dosing schedule.

**Figure 13** Mean and 90% CI of  $\Delta\Delta\text{QTcF}$  Timecourse (unadjusted CIs).



Source: QT-IRT reviewer

In Phase 3 studies, only limited ECG monitoring was obtained in patients after baseline, as follows: a) 1, 24, and 48 hours post-loading dose for Study 3001; b) at 1 hour and 24 hours post-loading dose for Study 3002; and c) at 1 hour and every 24 hours of oliceridine treatment in Study 3003. None of the Phase 3 studies were adequately designed to characterize the QT prolonging effects of oliceridine. Based on ECG data, Dr. Johannesen found that the percentage of patients in the placebo, oliceridine, and morphine treatment arms with a QT interval >450 msec was similar (13.0%, 9.6%, and 8.9%, respectively). No patients in any treatment arm had a QTcF >500 msec in the controlled Phase 3 studies (Table 38).

**Table 5 QT-related Potentially Clinically Significant ECG results by Treatment Regimen (Controlled Phase 3 Safety Analysis Dataset)**

PCSA Criterion	Placebo N=162 n (%)	Oliceridine 0.1 mg N=153 n (%)	Oliceridine 0.35 mg N=158 n (%)	Oliceridine 0.5 mg N=159 n (%)	Oliceridine Total N=470 n (%)	Morphine N=158 n (%)
QT Interval change from Baseline >30 msec	22 (13.8)	25 (16.3)	10 (6.3)	18 (11.4)	53 (11.3)	21 (13.4)
QTcF change from Baseline >30 msec	12 (7.5)	15 (9.8)	11 (7.0)	13 (8.2)	39 (8.3)	13 (8.3)
QTcF change from Baseline >60 msec	0	1 (0.7)	0	0	1 (0.2)	0
QTcF change from Baseline >60 msec	0	1 (0.7)	0	0	1 (0.2)	0
QT Interval >450 msec	21 (13.0)	19 (12.4)	9 (5.7)	17 (10.7)	45 (9.6)	14 (8.9)
QTcF >500 msec	0	0	0	0	0	0

ECG = electrocardiogram; PCSA = potentially clinically significant abnormality

Note: Patients summarized by actual treatment. Percentages were based on the number of patients in each treatment group within the ECG result of interest.

Data source: ISS Table 14.6.1.1

Source: QT-IRT 6/6/2018 consult review

As described in Dr. Johannesen's IRT consult review, there were 6 patients in Study 3003 with  $\Delta$ QTcF >60 ms, 11 patients with QTcF >500 ms, and 5 patients that met both criteria (Table 39). Per the applicant, 11 patients had at least one identified potential confounding factor that may have contributed to QTc prolongation. However, Dr. Johannesen determined that a drug effect could not be excluded in 8 of the 11 cases. In the MedDRA SMQ Torsade de Pointes/QT Prolongation, he found 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 39: Adverse Events Associated with MedDRA SMQ Torsade de Pointes/QT Prolongation**

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

<sup>1</sup>Largest QTcF interval (440 ms) occurred at baseline. <sup>2</sup>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

The QT-IRT reviewer considered it possible that several of the cases of QTc prolongation observed in Study 3003 are related to oliceridine, particularly since QTc prolongation was also observed in the thorough QT study. However, the IRT consultant found that interpretation of

the open-label ECG data was complicated by lack of ECG replicates at each nominal timepoint and the fact that the study did not include a control arm to understand the background rates of QTc prolongation due to concomitant medications and comorbid conditions in the patient population.

When stratified by daily dosage ( $\leq 27$  mg or  $>27$  mg), the incidence of adverse events associated with MedDRA SMQ Torsade de Pointes/QT Prolongation in the controlled studies and open-label study was similar in patients who received a total daily oliceridine dosage  $> 27$  mg and those who received a total daily dosage  $\leq 27$  mg (Table 40, Table 41), and similar to the morphine treatment group.

**Table 40: Adverse Events Associated with MedDRA SMQ Torsade de Pointes/QT Prolongation by Daily Dose of 27 mg in Study 3001 and Study 3002**

MedDRA Preferred Term	Placebo N = 162		Oliceridine $\leq 27$ mg N = 316		Oliceridine $> 27$ mg N = 154		Morphine N = 158	
	N	%	N	%	N	%	N	%
Diastolic dysfunction	0	0	0	0	0	0	1	0.6
Nodal rhythm	0	0	1	0.3	0	0	0	0
Palpitations	1	0.6	3	0.9	0	0	0	0
Tachycardia	2	1.2	2	0.6	3	1.9	4	2.5
Ventricular extrasystoles	1	0.6	0	0	0	0	0	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	1	0.6
Electrocardiogram ST segment abnormal	0	0	1	0.3	0	0	0	0
syncope	1	0.6	3	0.9	0	0	1	0.6

CDTL reviewer using JMP clinical 7.1

**Table 41: Adverse Events Associated with MedDRA SMQ Torsade de Pointes/QT Prolongation by Daily Dose in Study 3003**

MedDRA Preferred Term	Oliceridine $\leq 27$ mg N = 592		Oliceridine $> 27$ mg N = 176	
	N	%	N	%
Atrial fibrillation	1	0.2	0	0
Bradycardia	5	0.8	0	0
Sinus tachycardia	2	0.3	0	0
Tachycardia	10	1.7	4	2.3
Ventricular extrasystoles	1	0.2	1	0.6
Ventricular tachycardia	1	0.2	0	0
Electrocardiogram QT prolonged	2	0.3	1	0.6

	<b>Oliceridine ≤ 27mg N = 592</b>		<b>Oliceridine &gt; 27mg N = 176</b>	
Syncope	1	0.2	0	0

CDTL reviewer using JMP clinical 7.1

#### 8.6.4 Gastrointestinal Safety

The applicant’s hypothesis was that oliceridine had a better safety profile and a safety advantage over morphine for opioid-related adverse events of nausea and vomiting. During drug development, the applicant proposed to establish a potential gastrointestinal (GI) safety benefit of oliceridine over morphine by analyzing the proportion of patients with nausea or vomiting AEs by treatment arm. At the End-of-Phase 2 meeting, FDA informed the applicant that “Evaluating the proportion of patients with AEs to demonstrate a GI safety advantage is not acceptable, as the clinical meaningfulness of any difference between groups is unclear. Any improvement between treatments should be based on a “Complete Response” endpoint, defined on a per-subject basis as the absence of vomiting or rescue medication usage in a prespecified time period. 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.”

Despite the FDA’s advice, the applicant chose to design the controlled Phase 3 protocols based on the proportion of patients who experienced nausea and/or vomiting and those who had rescue antiemetic use as protocol-specified secondary safety and tolerability endpoints, instead of using a Complete Response with the parameters described above.

The applicant analyzed GI safety/tolerability using a Customized MedRA Query (CMQ) for the GI tolerability terms listed in Table 42. As shown in the table below, 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. A higher percentage of patients with GI tolerability TEAEs was seen with higher oliceridine doses (Table 42).

FDA determined during the first review cycle that the protocol-specified GI-related secondary endpoints were not adequately defined in the protocols to provide clinically meaningful interpretation and would not be able to serve as a basis of support for any GI-related labeling claims, consistent with prior End-of-Phase 2 meeting advice.

**Table 42: Incidence of Gastrointestinal (GI) Tolerability by Treatment Regimen by Study (3001 and 3002)**

Study 3001					
	Placebo 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					
	Placebo 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

Primary Clinical reviewer; Abbreviations: OLI=oliceridine

### 8.6.5 Drug abuse

See Dr. Katherine Bonson's Controlled Substance Staff (CSS) review dated October 4, 2018 for a full discussion of the Agency's assessment of oliceridine's abuse potential during the first review cycle.

Although no new data related to abuse potential were submitted in the second review cycle, the Division again consulted CSS to evaluate the resubmission from a CSS perspective. As taken from Dr. Bonson's review dated July 17, 2020:

- a. No new abuse potential-related data were submitted or reviewed in the present NDA resubmission for oliceridine.
- b. CSS affirms our conclusion in our consult from the first review cycle (October 4, 2018), that oliceridine is a mu opioid agonist with abuse potential.
- c. CSS provides recommendations for product labeling in this new review cycle in *Recommendations* (below).

*CSS Recommendations:* Based on the CSS evaluation of the nonclinical and clinical abuse-related data, CSS concludes that if the NDA for oliceridine is approved:

- a. Oliceridine should be recommended for placement in Schedule II of the Controlled Substances Act (CSA). The applicant also proposes that oliceridine should be recommended for Schedule II placement.
- b. The text for Section 5.1 (Addiction, Abuse, and Misuse) and Section 9 (Drug Abuse and Dependence) of the drug label should reflect that oliceridine produced significant abuse signals.

## 8.7 Common Adverse Events

In both Phase 3 controlled studies, there was a higher percentage of patients with TEAEs in the oliceridine treatment arms than in patients who received placebo. There was also a higher percentage of patients with TEAEs in the morphine arm. An important limitation in the comparison of rates of events between the oliceridine treatment groups and the morphine treatment group is that the oliceridine and morphine dosing regimens studied are not equipotent.

In general, the most common adverse events in the oliceridine-treated subjects 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 (see Table 43).

**Table 43: Common Adverse Events (≥5% occurrence) in Studies 3001 and 3002**

Study 3001					
MedDRA Preferred Term	Placebo N=79	OLI 0.1 mg N=76	OLI 0.35 mg N=79	OLI 0.5 mg N=79	Morphine N=76
Patients with any TEAE (%)	68	74	86	91	96
Nausea	24	35	56	64	64
Vomiting	6	17	39	40	50
Dizziness	10	28	32	35	34
Headache	30	25	25	33	30
Somnolence	6	5	19	13	13
Constipation	11	10	11	14	17
Pruritus	8	3	15	4	20
Hot flush	1	3	4	8	8
Hypoxia	0	0	5	9	9
Dry mouth	1	1	5	5	16
Hyperhidrosis	2	4	5	2	4
Sedation	1	3	5	4	3
Anxiety	1	1	5	4	4
Oxygen saturation ↓	0	1	4	5	9
Muscle twitching	5	1	1	5	0
Pruritus generalized	0	0	4	2	12
Infusion site extravasation	8	3	0	4	3

Study 3001					
MedDRA Preferred Term	Placebo N=79	OLI 0.1 mg N=76	OLI 0.35 mg N=79	OLI 0.5 mg N=79	Morphine N=76
Chest discomfort	1	0	1	0	5
Study 3002					
MedDRA Preferred Term	Placebo N=83	OLI 0.1 mg N=77	OLI 0.35 mg N=79	OLI 0.5 mg N=80	Morphine N=82
Patients with any TEAE (%)	78	90	94	95	98
Nausea	46	44	62	75	74
Vomiting	13	23	21	42	54
Headache	29	16	29	26	29
Hypoxia	5	8	20	17	23
Constipation	7	16	16	11	11
Pruritus	5	13	16	11	18
Dizziness	11	14	9	9	16
Sedation	8	6	14	9	23
Back pain	6	4	13	11	8
Hot flush	7	3	7	6	7
Anxiety	2	1	5	7	4
Rash	2	4	1	7	0
Restlessness	4	1	6	4	5
Hyperhidrosis	2	3	5	2	2
Pruritus generalized	1	1	1	7	8
Myalgia	1	3	5	1	0
Abdominal pain upper	4	6	1	0	2
Flatulence	5	5	1	1	2
Presyncope	0	5	1	1	2
Somnolence	1	3	0	5	7

Clinical Reviewer; ↓=decreased

The team analyzed adverse events reported in  $\geq 5\%$  of patients in open-label Study 3003 based on the total cumulative dosage patients received, and found a clear dose-response for overall TEAEs and opioid- related adverse events, such as nausea, vomiting constipation (Appendix Table 51).

The incidence of TEAEs in the Phase 3 studies was analyzed by total daily dosage ( $>27$  mg or  $\leq 27$  mg). The incidence of TEAE was higher in patients who received a cumulative daily dosage of oliceridine  $>27$  mg than in patients with a  $\leq 27$  mg cumulative daily dosage. The most common adverse drug reactions (occurrence  $>10\%$  and greater than placebo) for oliceridine were nausea, vomiting, headache, dizziness, vomiting, constipation, hypoxia and pruritus (see Table 44). Incidence of hypoxia in patients with a  $\leq 27$  mg cumulative oliceridine daily dosage was higher than in patients who received a cumulative daily dosage of oliceridine  $>27$  mg, but lower than in the morphine treatment arm (Table 44). Oliceridine-treated patients had a lower incidence of TEAEs compared to morphine in both controlled studies.

**Table 44: Adverse Events ( $\geq 5\%$  occurrence) Stratified by Total Daily dosage in Study 3001 and 3002**

	Placebo N = 162	Oliceridine $\leq 27$ mg N = 316	Oliceridine > 27 mg N = 154	Morphine N = 158
Patients with any TEAE (%)	73	86	92	96
Nausea	35	52	66	70
Vomiting	10	26	42	52
Headache	30	26	26	30
Dizziness	11	18	27	25
Constipation	9	14	12	14
Hypoxia	3	12	6	17
Pruritus	6	9	14	19
Sedation	5	7	7	13
Somnolence	4	6	10	10
Back pain	4	6	4	6
Hot flush	4	4	7	8
Dry mouth	1	2	4	9
Oxygen saturation decreased	0	2	3	6
Pruritus generalized	1	2	5	10

CDTL reviewer using JMP clinical 7.1

Adverse drug reactions reported in  $\geq 5\%$  of patients who received oliceridine in Study 3003 stratified by daily dosage  $\geq 27$  mg or  $< 27$  mg are presented in Table 45. The most common adverse drug reactions ( $\geq 10\%$ ) were nausea, constipation and vomiting, with a slightly higher percentage in patients who received a cumulative daily dosage of oliceridine  $> 27$  mg than in patients with a cumulative daily dosage  $< 27$  mg. Overall, however, the incidence of adverse drug reactions with an incidence  $\geq 5\%$  was higher in patients who received a cumulative daily dosage of oliceridine  $> 27$  mg.

**Table 45: TEAEs Reported in  $\geq 5\%$  patients by daily dose of 27 mg in 3003**

	Oliceridine $\leq 27$ mg N = 592	Oliceridine > 27mg N = 176
<b>Patient with any TEAE (%)</b>	62	69
Nausea	29	38
Constipation	10	13
Vomiting	9	15
Headache	4	5
Hypokalaemia	4	7
Pruritus	4	8
Pyrexia	3	5

CDTL reviewer using JMP clinical 7.1

## 8.8 Safety Analyses by Demographic Subgroups

The applicant conducted analyses of safety data by age, sex, race, body mass index (BMI), and CYP2D6 metabolizer status (i.e., extensive or poor metabolizer) for all Phase 2 and 3 studies. Key safety findings related to demographic subgroups were reviewed during the first review cycle, and are briefly summarized below.

*Sex:* In the Phase 3 controlled studies, the overall incidence of TEAEs was higher in females (90%) than in males (67%) in oliceridine-treated patients. However, females comprised approximately 91% of the enrolled oliceridine-treated population. The high enrollment of females is likely driven by the much higher proportion of women who obtain abdominoplasty, compared to men.<sup>10</sup> Because of this imbalance of enrollment in treatment arms, interpretation of results is challenging. The most common AE in females was nausea (59%), compared to 32% in males. The most common AEs in males were nausea (32%) and dizziness (32%). Women had a much higher incidence of vomiting (32%) compared to males (15%). The exact reason for the AE incidence difference is unknown.

*Age:* There was considerable variability in the incidence of AEs by age. In general, there were no meaningful age differences in the percentages of the most common TEAEs. However, there were too few patients in the  $\geq 65$  and  $\geq 70$  years to draw conclusions regarding this age subgroup.

*Race:* In the controlled Phase 3 studies, most patients were white (approximately 68%, 66%, and 66% for placebo, total oliceridine, and morphine, respectively). The proportion of Black or African American patients was approximately 30%, 27%, and 28% in patients who received placebo, any dosing regimen of oliceridine, or morphine, respectively. The remainder of patients were categorized as other. Overall, the percentage of patients who received oliceridine and reported at least one TEAE was similar between white and African American patients (approximately 89% and 86%, respectively).

The only new clinical study included in the second cycle submission was thorough QT study CP130-1014, which was conducted in 65 healthy volunteers. Approximately 52% of subjects were male and most (52%) were white. The mean age was 32.5 years. Findings from this study in a healthy population do not change the overall demographic safety findings in the patient population from the first review cycle.

## 8.9 Other Safety concerns

In order to inform safety related to the use of non-oliceridine opioids after patients reached the maximum recommended cumulative daily dosage of 27 mg in a given day, the applicant submitted data in response to information requests sent by the Division.

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<sup>10</sup> Plastic Surgery Statistics Report American Society of Plastic Surgeons, 2018, <https://www.plasticsurgery.org/documents/News/Statistics/2018/plastic-surgery-statistics-full-report-2018.pdf>

In open-label Phase 3 Study 3003, approximately 73% of patients received alternative opioids either before or after oliceridine discontinuation, with approximately 75% of these receiving opioids after oliceridine was discontinued. In controlled Study 3001, approximately 60% of patients received opioids either before or after oliceridine was discontinued, with approximately 91% of these receiving opioids after oliceridine was discontinued. In Study 3002, approximately 83% of patients received opioids either before or after oliceridine was discontinued, with approximately 91% of these receiving the opioid after oliceridine was discontinued. The dosing interval from the time oliceridine was discontinued to the time of use of another opioid varied widely, from as short as a few minutes to many hours. When stratified by daily dosage  $\leq 27$  mg or  $> 27$  mg, there were no major safety concerns identified in the subset of patients who received non-oliceridine opioids after discontinuing oliceridine. Overall, these data support that transition from parenterally administered oliceridine to other non-oliceridine opioid analgesic treatment can occur in a clinically appropriate manner when determined to be clinically warranted.

#### 8.10 Conclusion on comparative safety claims

In the resubmission, the applicant included three new analyses to try to re-assess the potential comparative safety claim of oliceridine relative to morphine. In one analysis, the applicant tried to reassess the utility function analysis conducted in Phase 2 with the additional data collected in their Phase 3 program. In two additional analyses, the applicant examined the relative safety of oliceridine compared to the morphine comparator arm using logistic regression models of the probability of various composite safety events. The logistic models included treatment (oliceridine vs morphine), baseline pain score, SPID score and a baseline pain score-SPID interaction term. The two composites the applicant used were as follows:

- Complete GI response (defined as no vomiting or use of anti-emetic);
- Composite safety endpoint (any event in the following list: nausea, vomiting, hypoxia, sedation, pruritus, dizziness).

As these analyses were post hoc and exploratory, the findings will not be discussed in this review.

## 9 Advisory Committee Meeting

During the first review cycle, the application was discussed at an Anesthetic and Analgesic Drug Products Advisory Committee meeting on October 11, 2018. The majority of committee members did not recommend approval (8 against approval; 7 for approval) citing concerns related to the available safety database and QT prolongation.<sup>11</sup> See Appendix B for the meeting minutes' summary of discussion points and voting.

This NDA was not taken to Advisory Committee in the second review cycle, as FDA determined that the applicant had addressed the deficiencies from the first review cycle and no

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<sup>11</sup> <https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-public-participation-information-october-11-2018-meeting-anesthetic-and-analgesic-drug>

new issues that would warrant voting and decisions from committee members were identified by the review team.

## 10. Pediatrics

The applicant is requesting deferral for the pediatric assessment for ages birth to <17 years until oliceridine is determined to be safe and effective in the adult population for the indication of management of moderate-to-severe acute pain. The applicant plans to fulfill the Pediatric Research Equity Act (PREA) requirement through the following studies in pediatric patients with acute pain as proposed in an agreed June 22, 2017, Initial Pediatric Study Plan (iPSP).

The Division discussed this NDA application deferral extension request at a Pediatric Review Committee (PeRC) meeting on June 30, 2020. The timelines below represent revised agreed to timelines based on input from PeRC.

### **TIMELINE OF PEDIATRIC DEVELOPMENT PLAN**

1. Formulation Development: N/A

2. Nonclinical Studies:

- Toxicity Study in Juvenile Rats to Support Dosing in Patients 3 years to <17 years (GLP)
  - Draft protocol submission date: 30 Sep 2020
  - Final protocol submission date: 30 Dec 2020
  - Study completion date: 30 Sep 2021
  - Final Report date: 30 Jan 2022
- Toxicity Study in Neonatal/Juvenile Rats to Support Dosing in Patients <3 years
  - Draft protocol submission date: 30 Sep 2020
  - Final protocol submission date: 30 Dec 2020
  - Study completion date: 30 Sep 2021
  - Final Report date: 30 Jan 2022

3. Clinical Studies:

- A Phase 3, Randomized, Double-Blind, Placebo-Controlled (Added to Standard-of-Care Analgesia and Rescue), Dose (Exposure)-Response Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of Oliceridine in Patients 6 to <17 Years of Age for Whom Parenteral Opioid Therapy is Warranted
  - Estimated final protocol submission date: 30 Dec 2020
  - Estimated study completion date: 30 Dec 2022
  - Estimated Final Report date: 30 Jun 2023
- A Phase 3, Randomized, Double-Blind, Placebo-Controlled (Added to Standard-of-Care Analgesia and Rescue), Dose (Exposure)-Response Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of Oliceridine in Patients 3 to <6 Years of Age for Whom Parenteral Opioid Therapy is Warranted
  - Estimated final protocol submission date: 30 Dec 2020
  - Estimated study completion date: 30 Dec 2022
  - Estimated Final Report date: 30 Jun 2023

- A Phase 1b, Randomized, Double-blind, Placebo-Controlled (Added to Standard-of-Care Analgesia and Rescue), Ascending Dose Study of the Pharmacokinetics, Pharmacodynamics, Safety, Tolerability, and Efficacy of Oliceridine in Patients from Birth to <3 Years of Age for Whom Parenteral Opioid Therapy is Warranted
  - Estimated final protocol submission date: 31 Jan 2023
  - Estimated study completion date: 31 Jan 2025
  - Estimated Final Report date: 31 Jul 2025

(b) (4)

## 11. Other Relevant Regulatory Issues

- *Application Integrity Policy (AIP)*: Not applicable.
- *Exclusivity or patent issues of concern*: No exclusivity or patent issues have been identified.
- *Financial disclosures*: The submissions included the necessary financial disclosures. Financial disclosures are required for all covered clinical studies. A covered clinical study, as defined in 21 CFR 54.2, is that used to establish effectiveness, to show equivalence to an effective product, or any study in which a single investigator makes a significant contribution to the demonstration of safety. In the first review cycle, the NDA submission included completed Form 3454 “Certification: Financial Interests and Arrangements of Clinical Investigators” in compliance with 21 CFR part 54. This certified that the applicant had not entered into any financial arrangements with the listed clinical investigators as defined in 21 CFR 54.2(a), that no clinical investigator was required to disclose any financial interests as defined in 21 CFR 54.2 (b), and that no listed investigator was the recipient of significant payments from the Applicant as defined in 21 CFR 54.2(f). The applicant stated that no investigators were full- or part-time employees of Trevena, Inc. Financial disclosures for covered clinical studies are included in the first cycle review.

In the second review cycle, there were no clinical studies that met the regulatory definition of a covered clinical study. The applicant did disclose financial interests/arrangements with clinical investigators on Form 3454, as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators* for the thorough QT Study CP130-1014, in which the investigator certified no financial arrangements had been entered.

- *Other Good Clinical Practice (GCP) issues*: No issues were identified. The applicant states the following in each of the Phase 3 study protocols:

This study was conducted in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) requirements (including archiving of essential study documents), the ethical principles originating from the Declaration of Helsinki, and the applicable US Food and Drug Administration (FDA) regulations.

- *Office of Scientific Investigations (OSI) audits:* In the first review cycle, according to Dr. Damon Green's July 30, 2018, Office of Scientific Investigations (OSI) Clinical Inspection Summary review, inspections were conducted for select sites based on Agency-determined criteria. All inspections were completed, and the final classification of the inspections was No Action Indicated (NAI). Inspection findings supported the acceptability of the clinical data submitted. No inspections were requested to be performed for the one Phase 1 study submitted in the second review cycle.
- *Any other outstanding regulatory issues:* There will be Postmarketing Requirements for pediatric studies (see Sections 10 and 13).

## 12. Labeling

The proprietary name, OLINVYK, was reviewed by the Division of Medication Prevention and Analysis (DMEPA) and found to be conditionally accepted. See DMEPA review dated August 6, 2018.

The Division of Pediatric and Maternal Health (DPMH) reviewed the label and provided input and comments related to pediatric and maternal health. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the label and provided input to identify deficiencies that may lead to medication errors.

Agreement has been reached on labeling with the applicant.

## 13. Postmarketing Recommendations

### Risk Evaluation and Management Strategies (REMS)

Based on the intended use of oliceridine for the treatment of moderate to severe acute pain in a highly controlled environment (i.e., parenteral administration under direct medical supervision), the prescribing information in the label will address safe use of oliceridine injection in monitored healthcare settings and a separate risk evaluation and mitigation strategy (REMS) is not required at this time.

### Postmarketing Requirements (PMRs) and Commitments (PMCs)

The Pediatric Research Equity Act (PREA) applies to this NDA. Under PREA, the Applicant is required to conduct studies to assess safety, efficacy, and appropriate dosing.

The Agreed Pediatric Study Plan (PSP) describe efficacy, safety, and PK/PD studies (see above). The PMR timelines, updated by the Applicant in response to an Information Request from the Division after meeting with the Pediatric Review Committee, are described under Section 10 of this review.

#### 14. Recommended Comments to the Applicant

None.

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## Appendix A: November 2, 2018, Complete Response Letter

### CLINICAL

1. You have not submitted adequate data to support the safety of oliceridine for the management of moderate-to-severe acute pain in adult patients for whom an intravenous (IV) opioid is warranted due to concerns related to QT prolongation.

Your thorough QT (tQT) study, CP130-1008, showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset (3 mg: 6.6 ms [upper 90% confidence interval (CI) 8.9 ms]; 6 mg: 11.6 ms [13.7 ms]). The delayed onset of QTcF prolongation suggests that the QTcF prolongation may not be mediated via direct inhibition of the hERG potassium channel by oliceridine. The proposed mechanism for the delayed onset of the QTcF prolongation observed with oliceridine remains unclear.

In your Phase 3 studies, only limited ECG monitoring was obtained in patients after baseline (i.e., at 1, 24, and 48-hours post-loading dose for Study 3001, 1 and 24 hours for Study 3002, and 1 hour and every 24 hours of oliceridine treatment in Study 3003). Further, you have proposed a wide range of doses up to a maximum daily dose of 40 mg, and oliceridine would be used in clinical situations in which patients may receive other drugs that can prolong the QTc.

Interpretation of the ECG data from your clinical studies has limitations. Specifically, none of the studies were designed to characterize the QT prolonging effects of oliceridine. In Study 3003, there was a lack of ECG replicates at each nominal time point and lack of a control arm. Despite these limitations, there were cases of QTc prolongation in Study 3003.

You have not provided adequate data to support that the QT prolonging effects of oliceridine can be mitigated by labeling or monitoring.

#### Information Needed to Resolve the Deficiency

To address the safety concern of QT prolongation at the maximum proposed daily dose, provide data from a randomized active-controlled study that will include 24-hour Holter monitoring and replicate QT measurements extracted every hour from the Holter monitors and compared to the control group. The study should be of adequate duration and sample size to allow reliable evaluation of oliceridine's QT prolongation effects.

2. The submitted exposure database is not of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. You have proposed a maximum daily dose of 40 mg [REDACTED] (b) (4). You were advised at the End-of-Phase 2 and pre-NDA meetings that the safety database needed to include at least 350

patients exposed to the highest doses for the longest duration of use. In your Phase 2 and Phase 3 studies, the highest dose that at least 350 patients were exposed to during the first 24 hours was 27 mg of oliceridine. The highest dose with the longest actual duration that had at least 350 patients exposed was 37.2 mg administered over an actual duration of at least 35.5 hours.

Information Needed to Resolve the Deficiency

Provide an exposure database that is of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. Specifically, the safety database must include at least 350 patients exposed to the highest dose proposed for the longest duration of use indicated in the labeling.

**NONCLINICAL**

3. You have not provided adequate data to confirm that levels of TRV0109662, a major human metabolite, have been adequately characterized for potential embryo-fetal effects in either the rat or the rabbit embryo-fetal development study. You have not provided any data to document that the metabolite is formed in rabbits. Based on the data obtained to date, this metabolite does not appear to be formed at acceptable levels in the rat compared to the human, and the existing analytical assays for human and rat plasma levels of TRV0109662 do not appear to be consistently reproducible (i.e., failed rat incurred sample reanalysis for pivotal study).

Information Needed to Resolve the Deficiency

Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated, reproducible pharmacokinetic data to support your 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 at the proposed maximum recommended human dose of 40 mg/day.

**PRODUCT QUALITY**

4. The analytical methods used for controlling identified leachables must be validated. Validation reports for the analytical methods used for the leachables study have not been provided to the Agency.

Information Needed to Resolve the Deficiency

Validate your newly developed analytical methods for leachables as per the ICH Q2 recommendation and provide the validation reports to the Agency. Further, also provide the data for the leachables found in the stability samples that are analyzed by your newly developed methods.

## Appendix B: First Review Cycle October 11, 2018 Advisory Committee Meeting Minute

This NDA was discussed at an Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) meeting on October 11, 2018. The following is a brief summary of the questions to the committee and surrounding discussions. See the full transcript of the meeting for complete details.

The majority of committee members did not recommend approval (8 against approval; 7 for approval) citing concerns related to the available safety data and QT prolongation. Several AC members that voted to approve the drug still recommended Phase 4 studies to establish safety of oliceridine in a representative patient population employing higher doses as may be used in realistic settings.

**DISCUSSION:** Discuss the efficacy of oliceridine and whether the data provide substantial evidence for efficacy of oliceridine for the proposed indication of the management of acute moderate-to-severe pain in adults for whom an intravenous opioid is warranted.

*Committee Discussion:* Overall, the committee was in agreement that oliceridine showed efficacy compared to placebo in relatively healthy individuals. However, these committee members also agreed that the controlled Phase 3 post-operative study populations were not indicative of complex populations that may have multiple drug interactions and comorbidities, and therefore agreed that the efficacy of oliceridine is not clear compared to an active comparator. Several committee members expressed concern that the dosing recommendations are unclear and there was agreement that there would be challenges treating patients with different conditions and with dose titration in real-world situations. Some committee members stated that there was not substantial evidence of the efficacy of the 0.1 mg dose based on the data presented. Other committee members noted their appreciation of the rapid onset of efficacy. Please see the transcript for details of the committee discussion.

**DISCUSSION:** Discuss the safety profile of oliceridine and whether the safety profile of oliceridine is 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. Provide comment on the following issues:

- a. Safety database
- b. Hepatic safety
- c. Respiratory safety
- d. QT prolongation

*Committee Discussion:* The committee's general consensus was that oliceridine is relatively safe overall. Some committee members noted that the agonist-bias that was displayed appeared to have potential benefits, as providers are looking for new ways to find a tailored approach to treatment of acute pain. Several members of the committee

*expressed concerns of possible safety signals that could arise with higher doses, comorbid conditions, multimodal therapy, and use of concomitant medications, including other opioids, in real-world situations. One committee member noted that the decreased incidence of vomiting compared to morphine was notable. In regards to hepatic safety, overall, the committee was in agreement that there wasn't much concern for a hepatic safety signal. In terms of respiratory safety, some committee members made note that the hypercapnic testing that was performed in young healthy volunteers does not indicate a lower risk of respiratory depression compared to morphine. One member noted the decreased  $\beta$ -arrestin activation shown in animal models is suggestive of decreased respiratory depression, but other members noted limitations in the available clinical data. Some committee members noted there was insufficient data on QT prolongation and agreed more ECG data were needed. Other committee members agreed that real world implications were unclear, as there was a disconnect between pharmacokinetic and QT effects. One committee member added that although there were modest effects on QT prolongation used in the thorough QT study, the effects of the 40 mg per day in the proposed labeling is unknown. Several committee members expressed concerns regarding the available safety database that doesn't appear to represent what will be used in terms of doses in practice or the types of patients who are anticipated to receive the drug. Please see the transcript for details of the committee discussion.*

**DISCUSSION:** 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.

**Committee Discussion:** *Overall, the committee found no superiority for abuse deterrence and considered Schedule II appropriate for oliceridine. Some committee members agreed that people may presume that oliceridine is a safer medication, which may increase its abuse potential. One committee member added that healthcare professionals managing patients with opioid use disorders may improperly perceive oliceridine as safer, which could limit vigilance and amplify public health concern. Another committee member added that abuse of oliceridine may lead to unforeseen adverse effects with respiratory depression, hepatic pathology, and QT prolongation. Please see the transcript for details of the committee discussion.*

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

**Vote Result:** Yes: 7 No: 8 Abstain: 0

**Committee Discussion:** *The committee did not reach a general consensus on the approval of the proposed dose of oliceridine for the proposed indication of the management of moderate- to-severe acute pain in adults for whom an intravenous opioid is warranted. Committee members who voted "Yes" recommended inclusion of "not safer than traditional opioids" on the label and that further studies be required. Considerations in favor of recommending approval included a potentially favorable PK*

*data, no active metabolites, decreased  $\beta$ -arrestin activation, and positive GI profile with decreased nausea and vomiting. Committee members who voted "No" stated that the benefit/risk profile was not favorable enough, with a need for more data regarding demographic variability, including patients with comorbidities, drug interactions, and real-world dosing. Some members voiced concerns that the perception of oliceridine being safer may lead to increased abuse and downstream problems. Several committee members discussed the need for additional data. One member suggested a study showing decrease in length of hospital stay (time to discharge) as possible compelling data for approval. Please see the transcript for details of the committee discussion.*

## Appendix C Additional Adverse Events Tables

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**Table 46: Patients with Treatment-Emergent SAEs in Study 3003**

#	Patient ID	Age (yrs)/Sex	Cumulative dose group	Cum exp SAE start	Preferred Term	General Category <sup>a</sup>	
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/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	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		

## Second Cycle Review And Summary Basis for Approval

Primary Clinical Reviewer; 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 This one patient experienced two separate SAEs

Source: Modified from ISS: 120-day Safety Update; Table 52, page 186-190, submitted 3/5/18

**Table 47: Treatment-Emergent SAEs stratified by Daily Dosage in Study 3003**

MedDRA Preferred Term	Oliceridine ≤27 mg N=592		Oliceridine > 27 mg N=176	
	N	%	N	%
<b>Subjects with any SAE</b>	23	4	3	2
Atrial fibrillation	1	0	0	0
Nausea	2	0	0	0
Flatulence	1	0	0	0
Intra-abdominal haemorrhage	1	0	0	0
Small intestinal obstruction	1	0	0	0
Hepatic failure	1	0	0	0
Abdominal abscess	1	0	0	0
Clostridium difficile colitis	1	0	0	0
Graft infection	1	0	0	0
Pelvic abscess	0	0	1	1
Postoperative wound infection	1	0	0	0
Sepsis	1	0	0	0
Post procedural haematoma	2	0	0	0
Anaemia postoperative	1	0	0	0
Post procedural haemorrhage	1	0	0	0
Postoperative ileus	1	0	0	0
Wound dehiscence	0	0	1	1
Blood creatinine increased	0	0	1	1
Hyponatraemia	0	0	1	1
Endometrial cancer	1	0	0	0
Syncope	1	0	0	0
Mental status changes	1	0	0	0
Acute kidney injury	1	0	0	0
Renal failure	1	0	0	0
Breast haematoma	1	0	0	0
Chronic obstructive pulmonary disease	1	0	0	0
Hypoxia	0	0	1	1
Pleural effusion	1	0	0	0
Pulmonary edema	1	0	0	0
Respiratory depression	1	0	0	0

CDTL Reviewer using JMP clinical 7.1

**Table 48: Severe TEAEs stratified by Daily Dosage in Open-label Study 3003**

MedDRA Preferred Term	Oliceridine ≤ 27mg		Oliceridine > 27mg	
	N = 592		N = 176	
	N	%	N	%
Subjects with any severe TEAE	13	2	2	1
Leukocytosis	0	0	1	0
Neutrophilia	0	0	1	0
Flatulence	1	0	0	0
Intra-abdominal haematoma	1	0	0	0
Intra-abdominal haemorrhage	1	0	2	0
Nausea	0	0	1	0
Small intestinal obstruction	1	0	0	0
Vomiting	1	0	0	0
Hepatic failure	1	0	0	0
Abdominal abscess	1	0	0	0
Graft infection	1	0	0	0
Sepsis	1	0	0	0
Postoperative ileus	1	0	0	0
Procedural pain	1	0	0	0
Endometrial cancer	1	0	0	0
Syncope	1	0	0	0
Anxiety	2	0	0	0
Insomnia	1	0	0	0
Acute kidney injury	1	0	0	0
Renal failure	1	0	0	0
Urinary retention	1	0	0	0

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**Table 49: TEAEs Leading to Early Study Medication Discontinuation in Study 3003**

#	Patient ID	Age (yrs)/Sex	Cumulative dose group	Cum exp SAE start	Preferred Term	General Category <sup>a</sup>	
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		

Primary Clinical Reviewer; Abbreviations: AE=adverse event; Cum=cumulative; Exp=exposure; F=female; M=male;

TEAE=treatment-emergent adverse event; yrs=years. <sup>a</sup> Categories were reviewer generated

Source: 120-day Safety Update; Table 53, page 193-196, submitted 3/5/18;modified by clinical reviewer

**Table 50: TEAEs Leading to Drug Discontinuation by Daily Dosage in Open-label Study 3003**

MedDRA Preferred Term	Oliceridine ≤ 27mg N = 592		Oliceridine > 27mg N = 176	
	N	%	N	%
Subject with any TEAE leading to drug discontinuation	16	3	1	1
Bradycardia	1	0	0	0
Tachycardia	1	0	0	0
Diplopia	1	0	0	0
Miosis	1	0	0	0
Lip pruritus	1	0	0	0
Lip swelling	1	0	0	0
Nausea	3	0	1	0
Vomiting	2	0	0	0
Abdominal abscess	1	0	0	0
Procedural pain	1	0	0	0
Procedural vomiting	1	0	0	0
Alanine aminotransferase increased	0	0	1	0
Aspartate aminotransferase increased	0	0	1	0
Electrocardiogram QT prolonged	1	0	0	0
Dizziness	1	0	0	0
Breast haematoma	1	0	0	0
Respiratory depression	1	0	0	0
Pruritus	1	0	0	0
Pruritus generalised	2	0	0	0
Urticaria	2	0	0	0
Hypotension	2	0	0	0

CDTL reviewer using JMP clinical 7.1

**Table 51: Adverse Events Reported in  $\geq 5\%$  of Patients in Open-Label Study 3003**

<b>SOC/MedDRA Preferred Term</b>	Oliceridine $\leq 4$ mg N=156	Oliceridine $>4$ to 8 mg N=85	Oliceridine $>8$ to 16 mg N=121	Oliceridine $>16$ to 36 mg N=168	Oliceridine $> 36$ mg N=238
Subjects with any TEAE (%)	38	61	65	74	73
Blood and lymphatic system disorders	2	0	4	1	3
Anaemia	2	0	4	1	3
Cardiac disorders	0	4	4	4	5
Tachycardia	0	4	4	4	5
Gastrointestinal disorders	16	34	46	52	52
Constipation	2	7	16	16	14
Flatulence	1	2	8	4	0
Nausea	14	28	38	42	45
Vomiting	3	6	11	11	19
General disorders and administration site conditions	1	0	5	5	4
Pyrexia	1	0	5	5	4
Injury, poisoning and procedural complications	7	18	12	11	3
Procedural hypotension	1	8	8	10	1
Procedural nausea	6	9	3	1	2
Investigations	4	0	6	5	5
Blood pressure increased	0	0	3	2	4
Oxygen saturation decreased	4	0	3	3	1
Metabolism and nutrition disorders	3	6	5	9	17
Hypocalcaemia	1	2	2	3	7
Hypokalaemia	2	4	3	5	11
Hypomagnesaemia	3	1	3	3	4
Hypophosphataemia	0	2	1	4	6
Nervous system disorders	4	9	12	10	9
Dizziness	2	6	7	5	4
Headache	2	4	6	5	6
Psychiatric disorders	2	2	7	11	6
Anxiety	1		3	4	2
Insomnia	1	2	4	7	4
Respiratory, thoracic and mediastinal disorders	0	4	3	6	2
Hypoxia	0	4	3	6	2
Skin and subcutaneous tissue disorders	1	5	8	5	8

Second Cycle Review And Summary Basis for Approval

<b>SOC/MedDRA Preferred Term</b>	Oliceridine <= 4 mg N=156	Oliceridine >4 to 8 mg N=85	Oliceridine >8 to 16 mg N=121	Oliceridine >16 to 36 mg N=168	Oliceridine > 36 mg N=238
Pruritus	1	5	8	5	8
Vascular disorders	6	7	12	10	6
Hypertension	3	2	6	3	1
Hypotension	4	5	7	7	5

CDTL review using JMP Clinical 7.1

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NAOMI N LOWY  
08/07/2020 06:13:49 PM

ERIC P BASTINGS  
08/07/2020 06:19:47 PM

# Office of Clinical Pharmacology Review

<b>NDA or BLA Number</b>	210730 SDN46, Class 2 Resubmission
<b>Link to EDR</b>	<a href="\\CDSESUB1\evsprod\NDA210730\0047">\\CDSESUB1\evsprod\NDA210730\0047</a>
<b>Submission Date</b>	02/07/2020
<b>Submission Type</b>	<i>Standard review</i>
<b>Brand Name</b>	OLINVYK
<b>Generic Name</b>	Oliceridine
<b>Dosage Form and Strength</b>	1 mg/mL IV Injection
<b>Route of Administration</b>	IV bolus or Patient-controlled Analgesia
<b>Proposed Indication</b>	Management of moderate to severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.
<b>Applicant</b>	Trevena Inc.
<b>Associated IND</b>	<i>IND113537</i>
<b>OCP Division:</b>	Division of Neuropsychiatric Products
<b>OND Division:</b>	Division of Anesthesiology, Addiction, and Pain Medicine
<b>Clinical Pharmacology Reviewer</b>	<i>Srikanth C. Nallani, Ph.D.</i>
<b>Clinical Pharmacology Team Leader</b>	<i>Yun Xu, Ph.D.</i>

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## 1. EXECUTIVE SUMMARY

This NDA was submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FDCA) on November 2, 2017. Reference is made to the pending New Drug Application, NDA 210730, for Oliceridine Injection, 1 mg/mL for the proposed indication for the management of moderate to severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. A Complete Response Letter (CRL) was issued by the Agency on November 2, 2018. The purpose of this submission is to provide a complete response to the Agency issued Complete Response Letter (CRL). Trevena considers this amendment to be a complete response to all the deficiencies outlined in the CRL.

This memo documents the labeling recommendations for the product with regard to clinical pharmacology related information. Clinical Pharmacology review of the original NDA (dated 10/23/2018) and comments from Drs. Srikanth C. Nallani, Yun Xu, Oluseyi Adeniyi, Manuela Grimstein, Atul V. Bhattaram, Christian Grimstein are reflected in these recommendations.

## 2. Labeling

General Comments: CYP2D6 is responsible for up to 76% of the in vitro metabolism of oliceridine, with up to 47% of oxidative metabolism contributed by CYP3A4 in vitro (Study No. XT144039 reviewed in original NDA). The prevalence of the CYP2D6 poor metabolizer (PM) phenotype differs according to race and is reported to be 5 to 10% in white populations and 1 to 2% in Asians [Meyer UA, Zanger UM 61997) Molecular mechanism of genetic polymorphism of drug metabolism. Annu Rev Pharmacol Toxicol 37:269-296]. Across different Phase 1 studies systemic exposure (AUC<sub>0-inf</sub>) of oliceridine was 100% higher in CYP2D6 poor metabolizers (PM) compared to extensive metabolizers, consistent with the observations from in vitro studies. CYP2D6 inhibitor drug interactions with oliceridine should be labeled based on observations from the Phase 1 studies showing higher exposure (AUC<sub>0-inf</sub>) in CYP2D6 poor metabolizers. However, peak plasma concentrations (C<sub>max</sub>) were only 10-30% higher in CYP2D6 PMs compared to nonpoor metabolizers in Phase 1 studies (See Table 5 of original NDA clinical pharmacology review dated 10/23/2018). Safety of Olinvyk was evaluated in CYP2D6 PM's recruited in the pivotal clinical trials CP130-3001 and CP130-3002 (See Figure 5 of Original NDA clinical pharmacology review and Medical officer review).

A drug interaction study with CYP3A4 inhibitor in CYP2D6 extensive metabolizer (nonpoor metabolizer) population was not conducted. However, in study CP130-1005 treatment of CYP2D6 poor metabolizers with itraconazole increased exposure of oliceridine by 78% in terms of AUC<sub>0-inf</sub>, without any clinically relevant impact on C<sub>max</sub>. Because inhibition of CYP2D6 and CYP3A4 with strong inhibitors is expected to increase AUC more than C<sub>max</sub>, the concern is of persistent plasma of oliceridine and not of peak plasma levels. Patients that are normal metabolizers receiving oliceridine may experience significantly increased plasma levels (AUC<sub>0-</sub>

inf) of oliceridine when concomitantly treated with strong inhibitors of CYP2D6 and CYP3A4. As summarized above, compared to nonpoor metabolizers, poor metabolizers of CYP2D6 have 100% higher AUC<sub>0-inf</sub> of oliceridine and treatment of CYP2D6 poor metabolizers with itraconazole increased exposure of oliceridine by 78% in terms of AUC<sub>0-inf</sub>, without clinically relevant impact on C<sub>max</sub>. In other words, around 4-fold increase in AUC<sub>0-inf</sub> and 70% reduction of clearance could be expected in CYP2D6 nonpoor metabolizers in the worst-case scenario of receiving concomitant medications that strongly inhibit CYP3A4 and CYP2D6 metabolism. Because inhibition of CYP2D6 and CYP3A4 with strong inhibitors is expected to increase AUC<sub>0-inf</sub> more than C<sub>max</sub>, the concern is of persistent plasma of oliceridine and not of peak plasma levels.

A drug interaction study with CYP3A4 inhibitors or CYP3A4 inducers was not conducted. CYP3A4 drug interaction studies were not conducted in CYP2D6 nonpoor metabolizers; however, in vitro data clearly indicates role for CYP3A4 in oliceridine metabolism.

The sponsor submitted Physiologically Based Pharmacokinetic (PBPK) modeling and simulation to address drug interactions of oliceridine with CYP3A4 inhibitors in the predominant extensive metabolizer population. However, the PBPK modeling and simulation was not acceptable due to the reasons specified in the original NDA clinical pharmacology review.

Labeling recommendations: The following revisions should be made in the product label as it relates to clinical pharmacology information.

## **5 Warnings and Precautions**

...

### **5.6 Risk of Use in Patients with Decreased Cytochrome P450 2D6 Function or Concomitant Use or Discontinuation with Cytochrome P450 3A4 Inhibitors and Inducers**

#### Risk of Increased Oliceridine Plasma Concentrations

Increased plasma concentrations of oliceridine, which may result in prolonged opioid adverse reactions and exacerbated respiratory depression, may occur when OLINVYK is used under the following conditions:

- In patients with decreased Cytochrome P450 (CYP) 2D6 function (poor metabolizers of CYP2D6 or normal metabolizers taking moderate or strong CYP2D6 inhibitors) [*See Drug Interaction (7) and Use in Specific Populations (8.8)*]
- In patients taking a moderate or strong CYP3A4 Inhibitor
- In patients with decreased CYP2D6 function who are also receiving a moderate or strong CYP3A4 inhibitor
- Discontinuation of a CYP3A4 inducer

These patients may require less frequent dosing of OLINVYK. Closely monitor these patients for respiratory depression and sedation at frequent intervals and base subsequent doses of OLINVYK on the patient’s severity of pain and response to treatment. [see *Drug Interactions (7)*, *Use in Specific Populations (8.8)* *Clinical Pharmacology (12.3, 12.5)*]

**Risk of Lower than Expected Oliceridine Plasma Concentrations**

Lower than expected concentrations of oliceridine, which may lead to decreased efficacy, may occur under the following conditions:

- Concomitant use of OLINVYK with CYP3A4 inducers
- Discontinuation of a moderate or strong CYP3A4 or CYP2D6 inhibitor

Closely monitor these patients at frequent intervals and consider supplemental doses of OLINVYK [see *Dosage and Administration (2.2)* and *Drug Interactions (7)*].

**7 Drug Interactions**

Table 6 includes clinically significant drug interactions with OLINVYK.

**Table 6: Clinically Significant Drug Interactions with OLINVYK**

<b>Moderate to Strong Inhibitors of CYP2D6</b>	
<i>Clinical Impact:</i>	Concomitant administration of a moderate to strong CYP2D6 inhibitor can increase the plasma concentration of oliceridine, resulting in increased or prolonged opioid effects.
<i>Intervention:</i>	If concomitant use is necessary, patients taking a moderate to strong CYP2D6 inhibitor may require less frequent dosing of OLINVYK. Monitor closely for respiratory depression and sedation at frequent intervals and base subsequent doses on the patient’s severity of pain and response to treatment.  If a CYP2D6 inhibitor is discontinued, increase of the OLINVYK dosage may be considered until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
<i>Examples:</i>	Paroxetine, fluoxetine, quinidine, bupropion
<b>Moderate to Strong Inhibitors of CYP3A4</b>	
<i>Clinical Impact:</i>	The concomitant administration of moderate to strong CYP3A4 inhibitors can increase the plasma concentration of oliceridine, resulting in increased or prolonged opioid adverse reactions.  After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oliceridine concentration may decrease, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oliceridine.

<i>Intervention:</i>	<p>Caution should be used when administering OLINVYK to patients taking inhibitors of the CYP3A4 enzyme. If concomitant use is necessary, patients taking a CYP3A4 inhibitor may require less frequent dosing. Monitor patients for respiratory depression and sedation at frequent intervals.</p> <p>If a CYP3A4 inhibitor is discontinued, increase of the OLINVYK dosage may be considered until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</p>
<i>Examples:</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir).
<b>Strong and Moderate CYP3A4 inhibitors and CYP2D6 inhibitors</b>	
<i>Clinical Impact:</i>	OLINVYK is primarily metabolized by both CYP3A4 and CYP2D6. Compared to inhibition of either metabolic pathway, inhibition of both pathways can result in a greater increase of the plasma concentrations of oliceridine and prolong opioid adverse reactions [See Clinical Pharmacology 12.3].
<i>Intervention:</i>	<p>Patients who are CYP2D6 normal metabolizers taking a CYP2D6 inhibitor, and a strong CYP3A4 inhibitor (or discontinuation of CYP3A4 inducers) may require less frequent dosing.</p> <p>Patients who are known CYP2D6 poor metabolizers and taking a CYP3A4 inhibitor (or discontinuation of CYP3A4 inducers) may require less frequent dosing.</p> <p>These patients should be closely monitored for respiratory depression and sedation at frequent intervals, and subsequent doses should be based on the patient's severity of pain and response to treatment.</p>
<i>Examples:</i>	<p>Inhibitors of CYP3A4: Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole, itraconazole), anti-retroviral agents, selective serotonin re-uptake inhibitors (SSRIs), protease inhibitors (e.g., ritonavir), NS3/4A inhibitors</p> <p>Inhibitors of CYP2D6: Paroxetine, fluoxetine, quinidine, bupropion</p>
<b>Inducers of CYP3A4</b>	
<i>Clinical Impact:</i>	<p>The concomitant use of OLINVYK and CYP3A4 inducers can decrease the plasma concentration of oliceridine, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oliceridine.</p> <p>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oliceridine plasma concentration may increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.</p>

<i>Intervention:</i>	<p>If concomitant use with CYP3A4 inducer is necessary, increase of the OLINVYK dosage may be considered until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</p> <p>If a CYP3A4 inducer is discontinued, consider OLINVYK dosage reduction and monitor for signs of respiratory depression.</p>
<b>Examples:</b>	Rifampin , carbamazepine, phenytoin.

## 8.8 Poor Metabolizers of CYP2D6 Substrates

In patients who are known or suspected to be poor CYP2D6 metabolizers, based on genotype or previous history/experience with other CYP2D6 substrates, less frequent dosing of OLINVYK may be required. These patients should be closely monitored, and subsequent doses should be based on the patient's severity of pain and response to treatment. [see *Warnings and Precautions* (5.6), *Clinical Pharmacology* (12.5)].

## 12.3 Pharmacokinetics

### Distribution

The steady-state volume of distribution ranged between 90-120 L indicating extensive tissue distribution. The plasma protein binding of oliceridine is 77%. *In vitro* data indicate that oliceridine is not an inhibitor of any of the major transporters, including breast cancer resistance protein (BCRP) and MDR1, at clinically relevant concentrations.

### Elimination

#### *Metabolism*

*In vitro* studies suggest that oliceridine is metabolized primarily by CYP3A4 and CYP2D6 P450 hepatic enzymes, with minor contributions from CYP2C9 and CYP2C19 into inactive metabolites.

The mean clearance of oliceridine decreases slightly with increasing dose, resulting in greater-than-proportional exposure, particularly at doses greater than 2 mg. The percent of unchanged oliceridine excreted in the urine is low (0.97-6.75% of dose), reflecting its low renal clearance. The pharmacokinetics of oliceridine were not changed substantially (except for peak concentrations) when administered over different infusion times.

#### *Excretion*

Metabolic clearance is the major route of elimination of oliceridine, primarily by oxidation with subsequent glucuronidation. Additional biotransformation pathways included *N*-dealkylation, glucuronidation, and dehydrogenation. The majority of the metabolites (approximately 70%) are eliminated in the urine, with the remainder eliminated in the feces. Only a small amount of unchanged drug (0.97-6.75% of a dose) is found in the urine. The half-life of these metabolites (~44 hours) is much longer than that of unchanged oliceridine (1.3-3 hours). *In vitro* binding studies have demonstrated that none of these metabolites has any appreciable activity at the mu-opioid receptor.

## Specific Populations

### *Renal Impairment*

In a study comparing subjects with end stage renal disease (N=8) to healthy age and sex-matched healthy subjects (N=8), no significant difference in oliceridine clearance was observed. OLINVYK doses do not need to be adjusted in patients with renal impairment.

### *Hepatic Impairment*

In a study of mild (N=8), moderate (N=8) or severe hepatic impairment (N=6), both clearance and total exposure were similar to age and sex-matched healthy controls (N=8). The mean half-life of oliceridine was increased in subjects with moderate (4.3 hours) or severe (5.8 hours) hepatic impairment, as compared with healthy subjects (2.1 hours), or patients with mild hepatic impairment (2.6 hours). The estimated volume of distribution of oliceridine was significantly higher in subjects with moderate or severe hepatic impairment (212 and 348 L, respectively), as compared to healthy subjects (126 L) or patients with mild hepatic impairment (167 L).

Based on these data, the initial dose of OLINVYK does not need to be reduced in patients with mild or moderate hepatic impairment, but these patients may require less frequent dosing. Use caution when dosing OLINVYK in patients with severe hepatic impairment. Consider reducing the initial dose, and administer subsequent doses only after a careful review of the patient's severity of pain and overall clinical status.

## Drug Interaction Studies

*In vitro* studies suggest that oliceridine is metabolized primarily by the CYP3A4 and CYP2D6 P450 hepatic enzymes, with minor contributions from CYP2C9 and CYP2C19. Inhibition studies using selective inhibitors of all the major CYP enzymes show that only the inhibition of CYP3A4 and CYP2D6 significantly affects the metabolism of oliceridine in these assays, suggesting that the contribution of CYP2C9 and CYP2C19 to the metabolism of oliceridine is minor.

The effect of concomitant administration of a CYP2D6 inhibitor on the pharmacokinetics of OLINVYK, although not studied, may be similar to that noted in subjects who are CYP2D6 poor metabolizers. The plasma clearance of oliceridine in CYP2D6 poor metabolizers is approximately 50% of plasma clearance in subjects who are nonpoor CYP2D6 metabolizers [See *Pharmacogenomics (12.5)*].

In healthy subjects CYP2D6 poor metabolizers (n=4) given a single 0.25-mg dose of OLINVYK after 5 days of itraconazole 200 mg QD (a strong CYP3A4 inhibitor), the total exposure (AUC) of OLINVYK was increased by approximately 80%; however, the peak concentration was not significantly affected [See *Pharmacogenomics 12.5*]. The mean clearance of oliceridine was reduced to approximately 30% of that observed in nonpoor metabolizers of CYP2D6 [see *Drug Interactions*

(b) (4)

(b) (4)

## 12.5 Pharmacogenomics

Oliceridine is metabolized by polymorphic enzyme CYP2D6. CYP2D6 poor metabolizers have little to no enzyme activity. Approximately 3 to 10% of Whites, 2 to 7% of African Americans and <2% of Asians, generally lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers.

In healthy subjects who are CYP2D6 poor metabolizers, the  $AUC_{0-inf}$  of oliceridine was approximately 2-fold higher than in subjects who are not poor CYP2D6 metabolizers. [see *Warnings and Precautions* (5.6), *Use in Specific Populations* (8.8)].

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

NDA #: 210-730 – Resubmission

**Related IND #** IND 113,537

Drug Name: Olinvyk (Oliceridine)

Indication(s): Management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted.

Applicant: Trevena Inc.

Date(s): Submission Date: February 7, 2020  
PDUFA Date: August 7, 2020

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: James Travis, Ph.D.

Concurring Reviewers: Jinglin Zhong, Ph.D., HM James Hung, Ph.D.

Medical Division: Division of Anesthesia, Analgesia, and Addictions Products (DAAAP)

Clinical Team: Medical Officer: Elizabeth Kilgore, MD  
Medical Team Leader: Emily Deng, MD

Project Manager: Eva Yuan

The statistical review is complete and has been added to the Cross-Discipline Team Leader Review, which will be uploaded to DARRTS when it is finalized. Refer to the Cross-Discipline Team Leader Review for additional details.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## **SECONDARY/TERTIARY REVIEW (Second Cycle) PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

Application number: NDA 210730  
Supporting documents: 46, 56  
CDER stamp dates: 2/7/2020, 6/15/2020  
Product: OLINVYK (oliceridine) injection for intravenous use  
Indication: Management of moderate to severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate  
Applicant: Trevena, Inc.  
Clinical Review Division: Division of Anesthesiology, Addiction Medicine, and Pain Medicine  
Reviewer: Min Zhang, PhD  
Team Leader: Jay H. Chang, PhD  
Supervisor: R. Daniel Mellon, PhD  
Clinical Division Director: Rigoberto Roca, MD  
Project Manager: Eva Yuan, PharmD

# 1 Executive Summary

## 1.1 Introduction

NDA 210730 was initially submitted by Trevena, Inc. on November 2, 2017 to support marketing authorization of intravenous oliceridine fumarate, a new molecular entity, for the management of moderate-to-severe acute pain in adult patients for whom an intravenous (IV) opioid is warranted. Dr. Min Zhang completed the primary review, Dr. Jay Chang was the team leader on the project, and Dr. Dan Mellon was the supervisor. A tertiary review was completed by Dr. Timothy McGovern. The application was not approved in the first cycle and a complete response letter was issued on November 2, 2018. The complete response letter included the following nonclinical deficiency:

You have not provided adequate data to confirm that levels of TRV0109662, a major human metabolite, have been adequately characterized for potential embryo-fetal effects in either the rat or the rabbit embryo-fetal development study. You have not provided any data to document that the metabolite is formed in rabbits. Based on the data obtained to date, this metabolite does not appear to be formed at acceptable levels in the rat compared to the human, and the existing analytical assays for human and rat plasma levels of TRV0109662 do not appear to be consistently reproducible i.e., failed rat incurred sample reanalysis for pivotal study).

### Information Needed to Resolve the Deficiency

Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated, reproducible pharmacokinetic data to support your 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 at the proposed maximum recommended human dose of 40 mg/day.

In addition, the complete response letter included the following product quality deficiency:

The analytical methods used for controlling identified leachables must be validated. Validation reports for the analytical methods used for the leachables study have not been provided to the Agency.

### Information Needed to Resolve the Deficiency

Validate your newly developed analytical methods for leachables as per the ICH Q2 recommendation and provide the validation reports to the Agency. Further, also provide the data for the leachables found in the stability samples that are analyzed by your newly developed methods.

Relevant to this discussion, the complete response letter also stated that adequate clinical data were not submitted to support the proposed maximum daily dose of 40 mg (b) (4). The deficiency letter noted that the data submitted in the initial submission supported a maximum daily dose of 27 mg of oliceridine (see deficiency letter for exact language). The Applicant submitted a complete response to the deficiency letter on February 7, 2020.

## 1.2 Brief Discussion of Nonclinical Findings

To address the lack of adequate data to support the safety of the major human metabolite, 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 (EFD) studies. As noted in Dr. Zhang's review, these data confirmed that the original EFD studies adequately characterized the safety of this major human metabolite for the revised maximum daily dose of 27 mg/day. The nonclinical deficiency has been adequately addressed.

Because the analytical methods employed to evaluate leachables were not validated in the first cycle, and additional leachable data for later timepoints were submitted in the second cycle, the nonclinical review team also reevaluated the revised leachable data submitted to support the safety of the container closure system. As noted in Dr. Zhang's review, there are no nonclinical concerns with the levels of reported leachables from the container closure system.

As discussed in the nonclinical reviews from the first review cycle, the Applicant

 (b) (4)  
there are no data to support clinical significance of these data. As such, we continue to recommend that the established pharmacological class for oliceridine be "opioid agonist" and that descriptions suggesting potentially unique pharmacological properties without evidence of clinical significance be removed from the proposed labeling.

As noted in the first review, the Applicant provided adequate data to support the proposed drug substance and drug product specifications, drug product formulation, and, with the new data submitted, the adequacy of the proposed container closure system. The completed pharmacology and general toxicology development program is consistent with ICH M3(R2) recommendations. The general toxicology profile is consistent with that of an opioid agonist, including the potential for opioid withdrawal effects. The effects noted in the standard reproductive and developmental battery of studies are also consistent with a typical opioid agonist. The exposure margins in these studies suggest the potential for adverse effects on reproduction and development at clinically relevant doses compared to the currently proposed maximum human daily dose of 27 mg.

## 1.3 Recommendations

### 1.3.1 Approvability

I concur with Drs. Min Zhang and Jay Chang. From a nonclinical pharmacology toxicology perspective, NDA 210730 may be approved. I also concur with the proposed labeling and post-marketing requirements (PMRs).

### **1.3.2 Additional Nonclinical Recommendations**

The following post-marketing requirements are recommended to support pediatric drug development as noted in the agreed pediatric study plan (PSP):

Conduct a juvenile animal study in the rat model to support pediatric dosing in patients 3 years of age to < 17 years of age.

Conduct a juvenile animal study in the rat model to support pediatric dosing in patients < 3 years of age.

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**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.**  
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/s/  
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RICHARD D MELLON  
07/16/2020 05:18:22 PM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 210730  
Supporting document/s: SDN 46, 56  
CDER stamp date: 2/7/2020, 6/15/2020  
Product: OLINVYK (oliceridine) injection for intravenous use  
Indication: Management of moderate to severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate  
Applicant: Trevena, Inc.  
Review Division: Division of Anesthesiology, Addiction Medicine, and Pain Medicine  
Reviewer: Min Zhang, PhD  
Team Leader: Jay H. Chang, PhD  
Supervisor: R. Daniel Mellon, PhD  
Division Director: Rigoberto Roca, MD  
Project Manager: Eva Yuan, PharmD

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 210730 are owned by Trevena Inc. or are data for which Trevena Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 210730 that Trevena Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 210730.

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# 1 Executive Summary

## 1.1 Introduction and Regulatory History

The Applicant, Trevena Inc, is developing oliceridine (TRV130) for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted. The proposed dosing regimen is patient-controlled analgesia (PCA). In this resubmission, the proposed maximum recommended human dose (MRHD) has been lowered to 27 mg/day from the originally proposed 40 mg/day. Oliceridine is described as a G protein-biased ligand at the mu-opioid receptor (MOR) in that it stimulates G protein coupling with reduced  $\beta$  arrestin-2 recruitment compared to conventional opioids like morphine, hydromorphone, and fentanyl. The overall hypothesis of the potential therapeutic benefits of a G protein-biased mu-receptor agonist is that it would provide an opioid analgesic with an increased therapeutic window compared with conventional opioids.

NDA 210730 was originally submitted on 11/2/2017 and reviewed by this Reviewer in 2018. The nonclinical team recommended a complete response (CR) given that it was not clear that a major metabolite, TRV0109662, had been adequately qualified for safety, because the exposure data for this metabolite from rat intravenous toxicity studies could not be reproduced. As such, it was not clear that effects of TRV0109662 on embryofetal development had been adequately characterized by the submitted studies. In the CR letter, the nonclinical review team provided the following advice:

Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated reproducible pharmacokinetic data to support your 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 at the proposed maximum recommended human dose of 40 mg/day.

The Applicant submitted a complete response submission to the NDA on 2/7/2020. To address the nonclinical deficiency, the Applicant has conducted the following investigation:

- Developed a new bioanalytical method (BTM-2918-R0 and BTM-2803-R0) for measuring TRV0109662 in rat and rabbit plasma, respectively.
- Measured TRV0109662 concentrations in rat plasma from the embryo-fetal development study (Study (b) (4) -141503; TRV130-27) and from a time-mated rat PK study (Study 037551).
- Measured TRV0109662 concentrations in plasma samples from the rabbit embryo-fetal development study (Study No. (b) (4) -141504; TRV130-28) and from a time-mated rabbit PK study (Study 037270).

## 1.2 Brief Discussion of Nonclinical Findings

The Applicant submitted appropriate toxicology studies to support the safety of oliceridine in the original NDA submission. During the first review cycle, this Reviewer performed the nonclinical safety assessment of oliceridine based on two possible MRHD doses as there were concerns regarding the adequacy of the clinical data to support the proposed MRHD of 40 mg/day. The two MRHDs under consideration included 40 mg/day with a projected total daily AUC exposure level of 786 ng\*h/mL and 27 mg/day with a projected daily AUC exposure level of 531 ng\*h/mL (See Dr. Zhang's previous NDA review dated 10/4/2018 in DARRTS; for safety margins, refer to Table 25-28 in the previous NDA review). These studies have adequately characterized the pharmacology and toxicology of oliceridine. This review is in response to the Applicant's new data in the resubmission attempting to address the nonclinical deficiency regarding the safety characterization of the major human metabolite, TRV0109662.

Radiochemical and mass spectrometric profiling of plasma collected from a human metabolism and excretion study (Study CP130-1007) with IV administration of [<sup>14</sup>C]-TRV130 identified two human metabolites with mean plasma AUC values greater than 10% of total drug-related material—M22 (61.9%) and TRV0109662 (17.4%).

In the last review cycle, M22 was considered qualified for safety at the proposed MRHD of 40 mg/day. Refer to Dr. Zhang's previous NDA review for detailed safety assessment of M22. However, the rat TK samples from a general toxicology study (Study 8336088) used to extrapolate the TRV0109662 exposure in the rat embryo-fetal study failed significantly in Incurred Sample Reproducibility (ISR). Thus, we were unable to conclude that TRV0109662 had been adequately qualified with respect to an impact on embryo-fetal development.

To address the nonclinical deficiency regarding the qualification of TRV0109662, the Applicant developed a new analytical method to measure TRV0109662 in the plasma of rats and rabbits, respectively. ISR was then assessed in a time-mated rat PK and rabbit PK study and was shown to be successful in these studies. With the newly validated analytical methods, the Applicant measured the exposure of the metabolite in the rat and rabbit samples from the embryofetal studies. These exposure data were compared with the projected human exposure data at the MRHD of 27 mg/day to confirm that exposures (AUC) in at least one nonclinical toxicology species were greater than one-half of the human exposure as recommended in the ICH M3(R2) Guidance, Questions and Answers (FDA 2012). As summarized in the table below, the TRV0109662 mean total daily exposure in pregnant rats and rabbits from the embryofetal studies was greater than the projected maximum human exposure, confirming adequate exposures in species used for assessing embryo-fetal development toxicity; thus, the toxicity of TRV0109662 has been adequately characterized in the rat and rabbit embryofetal studies in accordance with ICH M3(R2).

**Table 1: In Vivo Exposure to TRV0109662 in Human and Nonclinical Embryofetal Studies**

	Mean AUC <sub>0-24h</sub> (ng*h/mL)	PK Source	Bioanalytical Method	Exposure Multiples (AUC animal/AUC human at MRHD of 27 mg/day)

Rat, EFD Study (Study <sup>(b) (4)</sup> -141503)	27.3	TRV130-27	BTM-2918-R0	1.05X
Rabbit, EFD Study (Study <sup>(b) (4)</sup> -141504)	36.5	TRV130-28	BTM-2803-R0	1.41X
Human: MRHD of 27 mg/day	25.9	QS130-3001	TRV1HPP	

### 1.3 Recommendations

#### 1.3.1 *Approvability*

The Applicant has adequately addressed the nonclinical deficiency identified in the last review cycle; thus, the nonclinical review team recommends approval from a nonclinical pharmacology and toxicology perspective with the recommended labeling changes and post marketing requirements.

#### 1.3.2 *Additional Nonclinical Recommendations*

If the drug product is approved in this review cycle, the following additional studies are recommended as post-marketing requirements as outlined in the agreed initial Pediatric Study Plan:

- Toxicity Study in Juvenile Rats to Support Dosing in Patients 3 years to <17 years (GLP)
- Toxicity Study in Neonatal/Juvenile Rats to Support Dosing in Patients <3 years (GLP)

#### 1.3.3 *Labeling*

The table below contains the draft labeling proposed by the Applicant, changes suggested by this reviewer, and the rationale for this reviewer’s changes. For final labeling, the reader is referred to final labeling in the approval action letter.

Applicant’s proposed labeling	Reviewer’s proposed changes	Rationale for changes
<b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b>  <b>INDICATIONS AND USAGE</b> OLINVYK is <sup>(b) (4)</sup> indicated for the management <sup>(b) (4)</sup> acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative	<b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b>  <b>INDICATIONS AND USAGE</b> OLINVYK is an opioid agonist indicated for the management of <sup>(b) (4)</sup> acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.	This section must include an appropriate established pharmacologic class (EPC) for the drug substance(s) if available per 21 CFR 201.57. According to the guidance for industry and review staff: <i>Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing</i>

<p>treatments are inadequate.</p>		<p><i>Information</i>, the pharmacologic class of a drug can be defined on the basis of (1) the mechanism of action (MOA), (2) physiologic effect (PE), (3) chemical structure (CS). For (b) (4)</p> <p>The guidance notes that the EPC should be represented by a phrase that is scientifically <b>and</b> clinically meaningful.</p> <p>(b) (4)</p>
<p><b>2.3 Discontinuation</b> When a patient who has been taking opioids regularly and may be physically dependent no longer requires therapy with OLINVYK, taper the dose gradually while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more (b) (4). Do not abruptly discontinue OLINVYK in a physically-dependent patient [see <i>Warnings and Precautions (Error! Reference source not found.)</i>, <i>Drug Abuse and Dependence (Error! Reference source not found.)</i>].</p>	<p><b>2.4 Safe Reduction or Discontinuation of OLINVYK</b> When a patient who has been taking opioids regularly and may be physically dependent no longer requires therapy with OLINVYK, taper the dose gradually while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more (b) (4). Do not abruptly discontinue OLINVYK in a physically-dependent patient [see <i>Warnings and Precautions (Error! Reference source not found.)</i>, <i>Drug Abuse and Dependence (Error! Reference source not found.)</i> and <i>Nonclinical Toxicology (13.2)</i>].</p>	<p>We recommend adding a reference to the nonclinical data recommended for inclusion in 13.2 that describe the results of a 14-day intravenous rat toxicology study demonstrating gastric lesions following abrupt discontinuation of oliceridine (see below).</p>
<p><b>8 USE IN SPECIFIC POPULATIONS</b></p> <p><b>8.1 Pregnancy</b></p> <p><u>Risk Summary</u></p> <p>In animal reproductive studies Oliceridine had no effect on embryo-fetal development in rats and rabbits when administered (b) (4)</p>	<p><b>8 USE IN SPECIFIC POPULATIONS</b></p> <p><b>8.1 Pregnancy</b></p> <p><u>Risk Summary</u></p> <p>In animal reproductive studies, oliceridine reduced live litter size at birth and increased postnatal pup mortality between birth and Postnatal Day 4 when</p>	<p>Adverse animal findings are described before negative findings.</p> <p>(b) (4)</p>

<p>doses producing plasma exposures 7 <sup>(b) (4)</sup> to 8 times <sup>(b) (4)</sup> at the maximum recommended human dose (MRHD) on an area under the time-curve (AUC) basis (see Data).</p> <p><sup>(b) (4)</sup></p>	<p>administered intravenously to rats from organogenesis through weaning at <sup>(b) (4)</sup>. Oliceridine had no effect on embryo-fetal development in rats and rabbits when administered intravenously during organogenesis at 7- and 8-times the MRHD, respectively (see Data).</p>	<p><sup>(b) (4)</sup></p>
<p><u>Data</u></p> <p><i>Animal Data</i></p> <p><sup>(b) (4)</sup></p>	<p><u>Data</u></p> <p><i>Animal Data</i></p> <p>Oliceridine administered via continuous intravenous infusion during the period of embryofetal organogenesis at doses of 6, 12, or 24 mg/kg/day to pregnant rats from Gestation Day (GD) 6 to 20 and 1.5, 3, or 6 mg/kg/day to pregnant rabbits from GD 7 to 29 had no effect on embryonic development at exposures 7- (rats) to 8-times (rabbits) the estimated plasma exposure at the MRHD of 27 mg/day on an AUC basis. Maternal toxicity (reduced body weight gain) was observed at ≥12 mg/kg in rats and at 6 mg/kg in rabbits.</p>	
<p>In a pre- and post-natal development study in rats, continuous intravenous infusion <sup>(b) (4)</sup> at doses of 0.6, <sup>(b) (4)</sup> 2.4, and 6.0 mg/kg/day <sup>(b) (4)</sup></p> <p><sup>(b) (4)</sup></p>	<p>In a pre- and post-natal development study in rats, oliceridine administered via continuous intravenous infusion at doses of 0.6, 2.4, and 6.0 mg/kg/day from Gestation Day 6 through Lactation Day 21 resulted in reduced live litter size at birth at 1.5-times the estimated plasma exposure at the MRHD on an AUC basis and lower pup survival between birth and Postnatal Day 4 at 0.6-times the estimated plasma exposure at the MRHD on</p>	<p>The numbers of F<sub>1</sub> pups (litters) found dead or euthanized in extremis from PND 0 to PND 4 were 7(7), 9(7), 27(14), and 69(18) in the control, 0.6 (LD), 2.4 (MD), and 6.0 mg/kg/day (HD) groups, respectively. There was an increase of dead pups and litters with dead pups observed in the MD group producing approximately 0.6-times the estimated plasma exposure at the MRHD. The increase appears test article-</p>

<p>(b) (4)</p> <p>plasma exposure at the MRHD on an AUC basis.</p>	<p>an AUC basis.</p>	<p>related, although the magnitude is less than that observed in the HD group.</p>
<p><b>8.3 Females and Males of Reproductive Potential</b></p> <p><u>Infertility</u></p> <p>(b) (4)</p>	<p><b>8.3 Females and Males of Reproductive Potential</b></p> <p><u>Infertility</u></p> <p><b>Human Data</b>                  Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.</p> <p><b>Animal data</b>                  Oliceridine administered intravenously for 14 days prior to cohabitation and administered through GD15 caused prolonged estrous cycle lengths and decreased the number of implantations and viable embryos in female rats at doses producing plasma exposures <math>\geq 3</math> times the MRHD on an AUC basis [see <i>Nonclinical Toxicology (13.1)</i>].</p>	<p>The proposed language is class labeling for opioids.</p> <p>We recommend omitting the statement describing (b) (4)</p>
<p><b>9.3 Dependence</b></p>	<p><b>9.3 Dependence</b></p> <p>OLINVYK should not be abruptly discontinued in a physically-dependent patient [see Dosage and Administration (2.3)]. If OLINVYK is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and</p>	<p>This language was added by the review team as it is consistent with other opioid drug products and is considered class labeling. We recommend a cross reference to 13.2, which describes adverse GI effects observed in a rat study indicative of acute withdrawal.</p>

	<p>mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate [see <i>Nonclinical Toxicology</i> (13.2)].</p>	
<p><b>12 CLINICAL PHARMACOLOGY</b></p> <p><b>12.1 Mechanism of Action</b></p> <p>(b) (4)</p>	<p><b>12 CLINICAL PHARMACOLOGY</b></p> <p><b>12.1 Mechanism of Action</b></p> <p>Oliceridine is a full opioid agonist and is relatively selective for the mu-opioid receptor. The principal therapeutic action of oliceridine is analgesia.</p> <p>The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.</p>	<p>(b) (4)</p> <p>Opioid class labeling added.</p>
<p><b>12.2 Pharmacodynamics</b></p> <p>(b) (4)</p>	<p><b>12.2 Pharmacodynamics</b></p> <p>(b) (4)</p> <p>In nonclinical models, the antinociceptive effect of oliceridine can be antagonized by the opioid antagonist naloxone.</p> <p>(b) (4)</p>	<p>(b) (4)</p>

<p>(b) (4)</p>		
<p><b>13 NONCLINICAL TOXICOLOGY</b>  <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p>	<p><b>13 NONCLINICAL TOXICOLOGY</b>  <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p>	
<p>(b) (4)</p>	<p><u>Carcinogenesis:</u>          Long-term animal studies have not been completed to evaluate the carcinogenic potential of oliceridine.</p> <p><u>Mutagenesis:</u>          Oliceridine was negative in an in vitro Ames bacterial reverse mutation assay, the in vitro chromosomal aberration assay using human peripheral blood lymphocytes, and the in vivo rat micronucleus assay.</p> <p><u>Impairment of Fertility</u>          In a fertility and early embryonic development study, oliceridine administered to female rats via continuous intravenous infusion at 6, 12, or 24 mg/kg/day for 14 days prior to cohabitation and through GD 15 for a total of 29-42 days resulted in prolonged estrous cycle lengths and decreased number of implantations and viable embryos at doses <math>\geq 12</math> mg/kg/day (<math>\geq 3</math>-times the estimated plasma exposure at the MRHD of 27 mg/day on an AUC basis).</p> <p>Oliceridine did not alter male fertility at any dose tested. Males</p>	

	were dosed at 6, 12, or 24 mg/kg/day, producing plasma exposures up to 8-times the estimated plasma exposure at the MRHD, for 28 days prior to cohabitation, throughout the mating period and up to the time of scheduled necropsy for a total of 64-65 days of dosing.	
<b>13.2 Animal Toxicology and/or Pharmacology</b>	<b>13.2 Animal Toxicology and/or Pharmacology</b>	
(b) (4)	Continuous intravenous infusion of oliceridine for 14 days followed by one-day withdrawal from the treatment resulted in opioid withdrawal stress-related gastric lesions including erosions/ulcers in the glandular stomach, mucosal congestion/hemorrhage and degeneration/necrosis in the nonglandular stomach at all doses tested including the low dose producing plasma exposure 2-times the estimated human expose at the MRHD on an AUC basis. The effect is believed to be due to acute withdrawal stress, as similar findings were not noted in (b) (4) sacrificed immediately after the last dose of oliceridine.	The proposed language is inappropriate for the label since it summarizes negative findings. The nonclinical and clinical review teams recommend adding this language to describe the opioid withdrawal-induced stomach lesions noted in the 14-day study to reinforce the recommendations regarding discontinuation of the drug as noted above in the labeling.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 1467617-09-9

Generic Name: Oliceridine fumarate

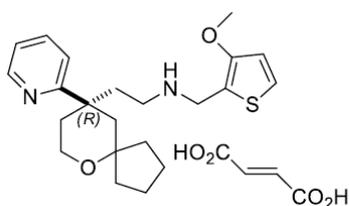
Code Name: TRV130 fumarate; FP-221; (TRV130A = HCl salt form)

Chemical Name: [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine, fumarate

Molecular Formula: C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S•C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

Molecular Weight: 502.62 g/mol (fumarate salt) and 386.55 g/mol (free base)

Structure:



Pharmacologic Class: Opioid agonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND	Drug/Compound	Applicant/Applicant	Indication	Division/Office	Status
IND 113537	Oliceridine	Trevena	Acute pain	DAAP	Active

DMF	Subject of DMF	Holder	Status	Application Status Date
(b) (4)	(b) (4)	(b) (4)	Active	4/30/2007
			Active	12/14/2015
			Active	9/11/1995
			Active	10/08/1997
			Active	09/25/2007

## 2.3 Drug Formulation

Refer to the NDA 210730 Pharmacology Toxicology review dated 10/4/2018 for details regarding the safety assessment of the clinical formulation of the product based upon the MRHD of 40 mg/day proposed in the first review cycle. With the lower proposed MRHD of 27 mg/day in the NDA resubmission, the conclusion of the safety assessment remains the same. No new issues have been identified with this NDA resubmission.

## 2.4 Comments on Novel Excipients

Refer to the NDA 210730 Pharmacology Toxicology review dated 10/4/2018 for details regarding the safety assessment of the excipients based upon the MRHD of 40 mg/day proposed in the last cycle. With the lower proposed MRHD of 27 mg/day in the NDA resubmission, the conclusion of the safety assessment remains the same. No new issues have been identified with this NDA resubmission.

## 2.5 Comments on Impurities/Degradants of Concern

Refer to NDA 210730 Pharmacology Toxicology review dated 10/4/2018 for details regarding the safety assessment of the impurities/degradants of the product based upon the MRHD of 40

mg/day proposed in the last cycle. With the lower proposed MRHD of 27 mg/day in the NDA resubmission, the conclusion of the safety assessment remains the same. No new issues have been identified with this NDA resubmission.

## 2.6 Extractables and Leachables

Oliceridine injection, 1 mg/mL is manufactured in three product presentations, a 1 mL fill volume in a 2 mL vial, a 2 mL fill volume in a 2 mL vial, and a 30 mL fill volume in a 30 mL vial. The primary container closure system is comprised of Type (b) (4) glass vials with (b) (4) stoppers.

The Applicant has conducted a one-time controlled extraction study on the drug product primary container system. Additionally, a preliminary assessment of potential leachable compounds was performed on an (b) (4) sample of oliceridine drug product. The results from these preliminary extraction and preliminary leachable studies were used to implement leachables analysis as part of the primary drug product stability program. These studies have been reviewed in the last review cycle and the CMC review team noted that the methods used in the extraction study were acceptable and that potential leachables would be detected in drug product samples on stability testing.

In the NDA resubmission, the Applicant reported new data on the later sampling time points. This Reviewer has revised the safety assessment of leachables conducted in the last review cycle given that new data have been reported and MRHD has been lowered from 40 mg/day to 27 mg/day.

### ***Leachable Testing on Primary Stability Batches:***

#### **Batches and Test time-points:**

Five representative primary stability batches of oliceridine injection, 1 mg/mL drug product batches have been placed on a long-term leachable study. The batches tested at the stability time points indicated in Table 1 below.

<b>Table 1: Oliceridine Injection Leachable Stability Study</b>									
Description	Batch Number (Manufacturer)	Orientation	Conditions	Test Points (Months)					
				3	6	12	24	36	48
Oliceridine Injection, 1 mg/mL, 1 mL vial	B160288	Inverted	25°C/60%RH	x	x	x	x	x	x
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	NT
Oliceridine Injection, 1mg/mL, 30 mL vial	B160285	Inverted	25°C/60%RH	x	x	x	x	x	x
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	NT
Oliceridine Injection, 1mg/mL, 2 mL vial <sup>a</sup>	B170190	Inverted	25°C/60%RH	x	x	x	x	x	x
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	NT
Oliceridine Injection, 1 mg/mL, 1 mL vial	CL7-018	Inverted	25°C/60%RH	x	x	x	x	x	x
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	NT
Oliceridine Injection, 1mg/mL, 30 mL vial	CL7-015	Inverted	25°C/60%RH	x	x	x	x	x	x
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	NT

a For batch B170190, results for the 1 month time point are also reported.  
x = Non-volatile leachables by LC-MS, volatile leachables by headspace GC-MS, semi-volatile leachables by GC-MS, elementals by ICP-MS  
NT = Not Tested

### Analytical Evaluation Threshold (AET):

The Applicant has applied AET of (b) (4) mcg/mL, (b) (4) mcg/mL to monitor the leachables in the early sampling timepoints and then lowered to (b) (4) mcg/mL during the primary stability studies based upon the Agency's advice on acceptable AET for the originally proposed MRHD of 100 mg delivered in 100 mL. The MRHD currently proposed in the resubmission is 27 mg/day, which would be administered in 27 mL. For an acute indication, to detect at least (b) (4) mcg in 27 mL, the assay must be able to detect at least (b) (4) mcg/mL in the final drug product format. Thus, the AET of (b) (4) mcg/mL is considered adequate. The earliest sampling time point with (b) (4) mcg/mL AET applied is the 10<sup>th</sup> month in the primary stability studies as shown in the tables below. Additional volatile and semi-volatile leachables were detected in the later sampling points with AET of (b) (4) mcg/mL. Given that these leachables may have higher concentration in the earlier sampling points but may not be detected with the higher reporting limit of (b) (4) mcg/mL, (b) (4) mcg/mL is considered by this Reviewer as the maximum potentially detected level for these leachables in the early sampling points.

The following is the Applicant's description of the history of AET changes in 3.2.P.2.4.2.7.

4.2.7. Analytical Evaluation Threshold (AET)

(b) (4)



**Results:**

**Non-volatile, volatile and semi-volatile leachables:**

Cumulative non-volatile, volatile, and semi-volatile leachable results are shown in the tables below for the five primary stability batches. The Applicant conducted toxicology risk assessment on the leachables detected.

Table 2: Oliceridine Injection, 1 mg/mL, 1 mL Vials, Batch B160288 (b) (4) Leachables Study						
Time Point/ Condition	Non-volatile Leachables by LC-MS		Volatile Leachables by headspace GC-MS		Semi-volatile Leachables by GC-MS	
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL(ppm)	compound
<b>25°C/60%RH</b>						
Initial	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
12 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
~22 Months <sup>a</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
24 months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Unknown (b) (4)
36 months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
<b>40°C/75%RH</b>						
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
a Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL. b Samples analyzed with updated methods utilizing the threshold limit of (b) (4) µg/mL.						

**Table 3: Oliceridine Injection, 1 mg/mL, 30 mL Vials, Batch B160285 (b) (4) Leachables Study**

Time Point/ Condition	Non-volatile leachables by LC-MS		Volatile leachables by headspace GC-MS		Semi-volatile leachables by GC-MS	
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound
<b>25°C/60%RH</b>						
Initial	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
12 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
~23 months <sup>a</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
24 months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
36 months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
<b>40°C/75%RH</b>						
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
<sup>a</sup> Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL. <sup>b</sup> Samples analyzed with updated methods utilizing the threshold limit of (b) (4) µg/mL.						

NT = Not Tested  
<sup>a</sup> Initial timepoint testing not performed, see 1 month time point for baseline.  
<sup>b</sup> Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL.  
<sup>c</sup> Samples analyzed with updated methods utilizing the threshold limit of (b) (4) µg/mL.

**Table 4: Oliceridine Injection, 1 mg/mL, 2 mL Vials, Batch B170190 (b) (4) Leachables Study**

Time Point/ Condition	Non-volatile leachables by LC-MS		Volatile leachables by headspace GC-MS		Semi-volatile leachables by GC-MS	
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound
<b>25°C/60%RH</b>						
Initial <sup>a</sup>	NT	(b) (4)	NT	NT	NT	(b) (4)
1 month	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
~12 Months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
12 months <sup>c</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
18 months <sup>c</sup>	(b) (4) Unknown	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
24 months <sup>c</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
<b>40°C/75%RH</b>						
1 month	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)

Table 5: Oliceridine Injection, 1 mg/mL, 1 mL Vials, Batch CL7-018 (b) (4) Leachables Study						
Time Point/ Condition	Non-volatile leachables by LC-MS		Volatile leachables by headspace GC-MS		Semi-volatile leachables by GC-MS	
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound
<b>25°C/60%RH</b>						
Initial	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
~10 months <sup>a</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
12 months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	Unknown (b) (4)
24 months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
<b>40°C/75%RH</b>						
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
a Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL. b Samples analyzed with updated methods utilizing the threshold limit of (b) (4) µg/mL.						

Table 6: Oliceridine Injection, 1 mg/mL, 30 mL Vials, Batch CL7-015 (b) (4) Leachable Study						
Time Point/ Condition	Non-volatile leachables by LC-MS		Volatile leachables by headspace GC-MS		Semi-volatile leachables by GC-MS	
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound
<b>25°C/60%RH</b>						
Initial	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
~11 months <sup>a</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
12 months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
24 months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
<b>40°C/75%RH</b>						
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
a Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL. b Samples analyzed with updated methods utilizing the threshold limit of (b) (4) µg/mL.						

- Non-volatile leachables: Non-volatile leachable analyses for the five batches showed no identified leachables above the reporting threshold for the time points studied except that at the 18-month timepoint for Batch B160285 (Table 4), three low-level non-volatile leachables were reported by retention time but remain unidentified. These leachables were not reported at any timepoint in any of the other batches in the long-term leachable studies. The Applicant stated that these batches will be closely monitored for the presence of these

unknown leachables throughout the remainder of the studies. An Information Request dated May 22, 2020 was sent to the Applicant regarding the unidentified leachable with a retention time of (b) (4). Based upon the maximum recommended daily dose volume of 27 mL, it would lead to a daily exposure of up to (b) (4)/day to this leachable, which exceeds the qualification threshold of (b) (4) mcg/day from a general toxicity perspective; thus, this leachable needs to be identified and a toxicological risk assessment is needed to justify the safety of the compound at the level detected. The Applicant responded that the leachable resulted from an instrument settings error that yielded an insufficient detector signal. As such, the reporting of this non-volatile leachable was not valid and should not have been reported. The Applicant submitted a Technical Document containing details of justification for invalidating this result. The CMC reviewer, Dr. Eric Bow, concurs with the Applicant's justification. Therefore, these unknown compounds are not considered a safety concern and no additional information is considered needed by the Reviewer.

- Volatile leachables: The volatile leachable analysis data is summarized in the table below.

**Table 2: Summary of Volatile Leachable Analysis**

Compound (CAS#)	Maximum Detected Level (mcg/mL)  Applicant's Value	Maximum Potentially Detected Level (mcg/mL)  Reviewer's Value	Maximum Potential Daily Exposure Level (mcg/day)*  Reviewer's Value	Acceptable?***
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(b) (4)

(b) (4)



- Semi-volatile leachables:**  
 Semi-volatile leachable analyses for the five batches showed reportable leachables in only one of the ad hoc samples (Batch B160288) tested against the threshold limit of (b) (4) mcg/mL. The semi-volatile leachables reported include (b) (4). The semi-volatile leachable analysis data are summarized in the table below. Similar to the volatile leachables, the highest reporting limit, (b) (4) mcg/mL, is considered by this Reviewer as the maximum potential detected level for these semi-volatile compounds and is used for calculating maximum potential daily exposure level when assessing toxicology risk.

**Table 3: Analysis of Semi-Volatile Leachables**

Compound (CAS#)	Maximum Level (mcg/mL)	Maximum Potential Level (mcg/mL)	Maximum Potential Daily Exposure Level (mcg/day)*	Acceptable?***
	Applicant's Value	Reviewer's Value	Reviewer's Value*	

(b) (4)



**Elemental Leachables:**

The results from testing the subset of primary (registration) batches of drug product which are being monitored on stability for leachable elemental impurities are provided in the resubmission. All results for each elemental impurity for each batch tested are below the limit of quantitation for the respective elemental impurity, which indicates that the drug product is not leaching elemental impurities from the container closure system.

**2.7 Proposed Clinical Population and Dosing Regimen**

The proposed indication for oliceridine is for the management of (b) (4) acute pain in adult patients (b) (4).

Dosing regimen has been revised several times during the NDA review course. The current proposed dosing regimen is stated as followed by the Applicant:

(b) (4)

**2.8 Regulatory Background****IND 113537**

- New IND: December 23, 2013
- Fast Track designation: December 2, 2015
- EOP2: March 29, 2016
- preNDA: May 25, 2017

**NDA 210730**

- New NDA: November 2, 2017
  - Complete response dated November 2, 2018

- NDA resubmission: February 7, 2020

### 3 Studies Submitted

#### 3.1 Pivotal Studies Reviewed

- TRV130 (Oliceridine): Continuous Intravenous Infusion Pharmacokinetic Study in Time-Mated Sprague-Dawley Rats (GLP; Study 037551)
- TRV130 (Oliceridine): Continuous Intravenous Infusion Pharmacokinetic Study in Time-Mated New Zealand White Rabbits (GLP; Study 037270)
- Quantification of TRV0109662 Concentrations in Rat Plasma from Embryo-Fetal Development Study Number (b) (4)-141503 (GLP; Study TRV130-27)
- Quantification of TRV0109662 Concentrations in Rabbit Plasma from Embryo-Fetal Development Study Number (b) (4)-141504 (GLP; Study TRV130-28)

#### 3.2 Pivotal Studies Not Reviewed

The Applicant conducted two additional nonclinical studies listed below to clarify the mechanism contributing to the delayed onset of the peak QTc prolongation observed in the single-dose through QT/QTc study (Study CP130-1008). These two studies have been reviewed by the QT-IRT team.

- Time course of effect of oliceridine on QT, Tp-e, and QRS duration in rabbit ventricular wedge preparations and its association with intracellular accumulation of the drug (Study TRV130-26)
- Oliceridine Effect on Late Cardiac Sodium Channel Current (Late INa) (Study TRV130-29)

#### 3.3 Previous Reviews Referenced

NDA 210730 (Dated 10/4/2018) reviewed by Dr. Min Zhang

### 4 Pharmacology of Oliceridine

Refer to NDA 210730 Pharmacology Toxicology review dated 10/4/2018 for details regarding the review on pharmacology of oliceridine. No new issues have been identified with this NDA resubmission.

## 5 Pharmacokinetics/ADME/Toxicokinetics

New PK data have been submitted on the major metabolite of TRV0109662. Refer to Section 9 for detailed assessment.

## 6 General Toxicology of Oliceridine

No new general toxicology studies were submitted with this NDA resubmission.

## 7 Genetic Toxicology of Oliceridine

No new genetic toxicology studies were submitted with this NDA resubmission.

## 8 Reproductive and Developmental Toxicology of Oliceridine

No new reproductive and developmental toxicology studies were submitted with this NDA resubmission.

## 9 Other Nonclinical Studies: Safety Evaluation of Major Human Metabolites

Radiochemical and mass spectrometric profiling of plasma collected from a human metabolism and excretion study (Study CP130-1007) with IV administration of [<sup>14</sup>C]-TRV130 identified two human metabolites with mean plasma AUC values greater than 10% of total drug-related material—M22 (61.9%) and TRV0109662 (17.4%).

In the last review cycle, M22 was considered qualified for safety at the proposed MRHD of 40 mg/day. Refer to Dr. Zhang's previous NDA review for detailed safety assessment on M22. However, the rat samples from a general toxicology study (Study 8336088) used to extrapolate for the exposure in the rat embryo-fetal study failed significantly in Incurred Sample Reproducibility (ISR). Thus, we were unable to conclude that TRV0109662 had been adequately characterized with respect to an impact on embryo-fetal development. In response to the Agency's request for reproducible PK data that demonstrate adequate exposure in at least one species used for embryo-fetal development studies to address this deficiency, the Applicant has conducted the following investigation:

- Developed a new bioanalytical method (BTM-2918-R0) for measuring TRV0109662 in rat and rabbit plasma.
- Measured TRV0109662 concentrations in rat plasma from the embryo-fetal development study (Study (b) (4)-141503; TRV130-27) and from a time-mated rat PK study (Study 037551).
- Measured TRV0109662 concentrations in plasma samples from the rabbit embryo-fetal development study (Study No. (b) (4)-141504; TRV130-28) and from a time-mated rabbit PK study (Study 037270).

ISR was performed in one nonclinical study for each species and was considered acceptable if at least two-thirds (rounded up) of the repeat results and original results were within 20.0% of the mean of the two values. A summary of ISR data for TRV0109662 is presented in the table below.

**Table 4: Summary of TRV0109662 ISR Data**

Study Sample	Study Number	Analytical Method Number	Number of Samples Tested	% of Sample Passed	Comments
14-day Rat Study	(b) (4)	TRV1RPP	24	83%	Passed; reviewed in the last review cycle
28-day Rat Study	8336088	TRV1RPP	24	17%	Failed; identified as a deficiency in the last review cycle
Time-mated Rat PK Study	037551	BTM-2918-R0	6	100%	Passed; new data submitted in this review cycle
Time-mated Rabbit PK Study	037270	BTM-2803-R0	6	100%	Passed; new data submitted in this review cycle

- In the last review cycle, Method TRV1RPP was used to quantitate the metabolite TRV0109662 in plasma samples from a 14-day toxicology bridging study (Study (b) (4)) in which rats were continuously infused with oliceridine drug product fortified with two impurities and two degradation products, including TRV0109662 at approximately 9%. As shown in the table above, ISR was successful from this study.
- In the last review cycle, Method TRV1RPP was used to quantitate TRV0109662 in plasma samples from a 28-day rat study (Study 8336088) and the PK data were used to extrapolate for the exposure in the rat embryofetal development study. As shown in the table above, ISR failed from this study.
- New analytical methods (BTM-2918-R0 and BTM-2803-R0) were subsequently developed to satisfy the Agency's request to provide PK data using a validated assay that demonstrates adequate exposure of the metabolite in an embryo-fetal development study. The Applicant conducted a time-mated rat PK study and rabbit PK study. ISR was successful in both studies.
  - Time-mated rat PK study (GLP; Study 037551): Four time-mated female Crl:CD(SD) rats were administered a 24-hour continuous intravenous (IV) infusion of oliceridine at 24 mg/kg/day (the high dose used in the rat embryofetal study) on Gestational Day (GD) 11.
  - Time-mated rabbit PK study (GLP; Study 037270): Four time-mated female New Zealand White rabbits were administered a 24-hour continuous intravenous (IV) infusion of oliceridine at 6 mg/kg/day (the high dose used in the rabbit embryofetal study) on Gestational Day (GD) 8.

The human plasma concentrations and PK parameters were used to project (by superpositioning) the relative daily exposure ( $C_{max}$  and  $AUC_{0-24}$ ) to TRV0109662 in patients administered the maximum recommended human dose (MRHD) of oliceridine (27 mg/day). The Clinical Pharmacology Reviewer agreed with the Applicant's projection on the human exposure. These exposure data were compared with data from the rat and rabbit toxicology studies to confirm that exposures (AUC) in at least one nonclinical toxicology species were greater than one-half of human exposure as recommended in the 2012 ICH M3(R2) Guidance, Questions and Answers (FDA 2012). As summarized in the table below, TRV0109662 mean total daily exposure in pregnant rats and rabbits was >50% of the projected maximum human exposure, confirming adequate exposure in species used for assessing embryo-fetal development toxicity. TRV0109662 mean total daily exposure in a 14-day rat bridging study was >50% of the projected maximum human exposure, confirming adequate exposure in a species used for assessing general toxicology. Data from these studies demonstrate adequate toxicological characterization of the TRV0109662 metabolite.

**Table 5: In Vivo Exposure to TRV0109662 in Human and GLP Toxicology Studies**

	Mean $AUC_{0-24h}$ (ng*h/mL)	PK Source	Bioanalytical Method	Exposure Multiples (AUC animal/AUC human at MRHD of 27 mg/day)
Rat, EFD Study (Study (b) (4) -141503)	27.3	TRV130-27	BTM-2918-R0	105%
Rat, Time-mated PK Study (Study 037551)	14.9	037551	BTM-2918-R0	58%
Rabbit, EFD Study (Study (b) (4) -141504)	36.5	TRV130-28	BTM-2803-R0	141%
Rabbit, Time-mated PK Study (Study 037270)	17.2	037270	BTM-2803-R0	66%
Human: MRHD of 27 mg/day	25.9	QS130-3001	TRV1HPP	

## 10 Special Toxicology Studies

No new special toxicology studies were submitted with this NDA resubmission.

## 11 Integrated Summary and Safety Evaluation

The Applicant has conducted adequate nonclinical studies to characterize the pharmacology and toxicology of oliceridine. Regarding the nonclinical deficiency identified in the last review cycle on the major human metabolite, TRV0109662, the Applicant has provided new data obtained with valid analytical methods to demonstrate that TRV0109662 is adequately formed in the rat and rabbit embryofetal studies; thus, the toxicity of TRV0109662 has been adequately characterized.

Refer to Dr. Zhang's previous NDA review for detailed Integrated Summary and Safety Evaluation on the drug substance and drug product formulation.

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/s/  
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MIN ZHANG  
07/16/2020 12:12:49 PM

JAY H CHANG  
07/16/2020 12:26:29 PM

RICHARD D MELLON  
07/16/2020 12:29:31 PM

I concur with Drs. Min Zhang and Jay Chang. From a nonclinical pharmacology toxicology perspective, NDA 210730 may be approved. I also concur with the proposed labeling and post-marketing requirements (PMRs).

# Office of Clinical Pharmacology Review

<b>NDA or BLA Number</b>	210730 SDN46, Class 2 Resubmission
<b>Link to EDR</b>	<a href="\\CDSESUB1\evsprod\NDA210730\0047">\\CDSESUB1\evsprod\NDA210730\0047</a>
<b>Submission Date</b>	02/07/2020
<b>Submission Type</b>	<i>Standard review</i>
<b>Brand Name</b>	OLINVYK
<b>Generic Name</b>	Oliceridine
<b>Dosage Form and Strength</b>	1 mg/mL IV Injection
<b>Route of Administration</b>	IV bolus or Patient-controlled Analgesia
<b>Proposed Indication</b>	Management of moderate to severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.
<b>Applicant</b>	Trevena Inc.
<b>Associated IND</b>	<i>IND113537</i>
<b>OCP Division:</b>	Division of Neuropsychiatric Products
<b>OND Division:</b>	Division of Anesthesiology, Addiction, and Pain Medicine
<b>Clinical Pharmacology Reviewer</b>	<i>Srikanth C. Nallani, Ph.D.</i>
<b>Clinical Pharmacology Team Leader</b>	<i>Yun Xu, Ph.D.</i>

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## **1. EXECUTIVE SUMMARY**

This NDA was submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FDCA) on November 2, 2017. Reference is made to the pending New Drug Application, NDA 210730, for Oliceridine Injection, 1 mg/mL for the proposed indication for the management of moderate to severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. A Complete Response Letter (CRL) was issued by the Agency on November 2, 2018. The purpose of this submission is to provide a complete response to the Agency issued Complete Response Letter (CRL). Trevena considers this amendment to be a complete response to all the deficiencies outlined in the CRL.

The submission consists of a study report titled CP13-1014 “A phase 1, single center, multiple dose, randomized, single-blind, placebo- and positive-controlled crossover safety study to evaluate the effect of oliceridine (TRV130) on cardiac repolarization over 24 hours in healthy subjects”, which was submitted to address the comment regarding QT prolongation listed in the CRL letter.

This memo documents the pharmacokinetics of oliceridine administered as a dosing regimen of IV bolus every two hours for 24-hours to a total of 27 mg per day in this study. From clinical pharmacology perspective, this submission is acceptable.

## **2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT**

Background: The thorough QT (tQT) study, CP130-1008, submitted in the original NDA showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset (3 mg: 6.6 ms [upper 90% confidence interval (CI) 8.9 ms]; 6 mg: 11.6 ms [13.7 ms]). The delayed onset of QTcF prolongation suggests that the QTcF prolongation may not be mediated via direct inhibition of the hERG potassium channel by oliceridine. The proposed mechanism for the delayed onset of the QTcF prolongation observed with oliceridine remains unclear. The sponsor did not provide adequate data to support that the QT prolonging effects of oliceridine can be mitigated by labeling or monitoring.

Accordingly, Agency informed the sponsor in the CRL that the following information is needed to resolve the deficiency:

“To address the safety concern of QT prolongation at the maximum proposed daily dose, provide data from a randomized active-controlled study that will include 24-hour Holter monitoring and replicate QT measurements extracted every hour from the Holter monitors and compared to the control group. The study should be of adequate duration and sample size to allow reliable evaluation of oliceridine’s QT prolongation effects.”

To address Agency's comment, in this submission, the Sponsor submitted a study report CP13-1014 titled "A phase 1, single center, multiple dose, randomized, single-blind, placebo- and positive-controlled crossover safety study to evaluate the effect of oliceridine (TRV130) on cardiac repolarization over 24 hours in healthy subjects".

Please refer to IRT-QT review of this submitted study CP13-1014 in DARRTS dated 4/16/2020 for labeling recommendation. The reviewer concluded that "*QTc prolongation was observed in this TQT study, which decreased with repeat dosing of oliceridine up to 27 mg (Figure 1). The underlying mechanism behind the observed QTc prolongation remains unknown but is unlikely to be mediated via direct inhibition of ion channels given that it is not observed with repeat dosing. The clinical relevance of the observed QTc prolongation is unknown but is unlikely to be important given that it is transient and not hERG-mediated.*" The reviewer performed "by-time analysis" and did not perform "exposure/concentration-response" analysis of QT-prolongation effects of oliceridine. "*IRT-QT Reviewer's comment: A direct C-QT model for oliceridine is not appropriate because the QT effect is not correlated with time-matched oliceridine QTc concentration as we noted in our previous review (IND 113537, DARRTS 02/05/2016). Moreover, in the current study the observed delayed QTc effect decreased with repeat dosing. The reviewer did therefore not conduct C-QT analysis for this study.*" Therefore, pharmacokinetics of oliceridine were not evaluated by IRT-QT.

This memo documents the pharmacokinetics of oliceridine following 27 mg/day, the maximum recommended dose of Olinvyk, administered as IV bolus every two hours for 24 hours in study CP13-1014.

**Title of Study CP130-1014:** A Phase 1, single-center, multiple-dose, randomized, single-blind, placebo- and positive-controlled crossover safety study to evaluate the effect of oliceridine (TRV130) on cardiac repolarization over 24 hours in healthy subjects.

**Objectives:** The primary objective of the study was to assess possible effects on cardiac repolarization of maximal daily dosing of IV oliceridine (up to 27 mg over 24 hours). Additionally, pharmacokinetics and safety of oliceridine were also evaluated.

**Demographics:** A total of 65 healthy subjects were planned to be enrolled in this study. A total of 68 subjects were randomized to receive treatment. To be eligible to participate in the study, subjects must have been  $\geq 18$  and  $\leq 45$  years of age and had a low risk for future opioid abuse (defined as a score of  $\leq 3$  on the Opioid Risk Tool). Cytochrome P450 2D6 (CYP2D6) poor metabolizer or indeterminate results for CYP2D6 genotype were excluded at Screening.

Overall, approximately half of the subjects were male (52.3%), most were white (52.3%) or black/African-American (41.5%), and of non-Hispanic or Latino ethnicity (58.5%). The mean age was 32.5 years (ranging from 18 to 44 years). Mean weight, height, and BMI were 73.77 kg, 168.36 cm, and 25.97 kg/m<sup>2</sup>, respectively. Per protocol, rescue antiemetic medication of palonosetron 0.075 mg IV single dose was administered 1 hour before treatment. First rescue dose may have been administered any time after T0. A second dose may have been administered

at least 15 minutes after the previous dose. Other common concomitant medications included stool softeners (docusate, 10 [15.4%] subjects), laxatives (sennoside A+B, 9 [13.8%] subjects and bisacodyl, 2 [3.1%] subjects), and paracetamol (4 [6.2%] subjects).

**Treatments Administered:** There were three Dosing Periods on Days 1 to 2, 8 to 9, and 15 to 16. Subjects were randomized to a three-period crossover sequence in which they received oliceridine, volume-matched placebo, and moxifloxacin 400 mg:

Oliceridine Dosing (A): Oliceridine was administered by IV bolus every 2 hours (Q2hr) from T0 to T22hr (the start of dosing in each dosing period was designated as T0). At T0, T4hr, T8hr, T12hr, T14hr, T16hr, T18hr, T20hr, and T22hr the subject received 2 mg oliceridine; at T2hr, T6hr, and T10hr the subject received 3 mg oliceridine for a total cumulative dose of 27 mg.

Placebo Dosing (B): Volume-matched placebo was administered by IV infusion by clinician-administered bolus Q2hr from T0 to T22hr.

Moxifloxacin Dosing (C): Moxifloxacin 400 mg oral tablet was administered as a single dose with approximately 240 mL of water at T0.

**Evaluations:** In addition to the 12-lead Holter data, safety and tolerability was assessed at multiple time points. Pharmacokinetic (PK) samples were collected for analysis of oliceridine according to the following schedule during the oliceridine and placebo treatment periods: Pre-dose, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 25, 26, and 27 hours post dose. All PK samples collected following the initiation of oliceridine dosing were collected prior to the scheduled oliceridine dosing, and therefore represent trough plasma concentrations rather than peak plasma concentrations. It should be noted that the sampling scheme was not designed to determine peak concentrations over the 27-hour study period. The concentrations below are therefore considered as maximum trough concentrations.

**Pharmacokinetic Results:** The time course of oliceridine plasma concentrations is shown in Figure 1 below. Mean C<sub>max</sub> values of oliceridine was observed at 8 hours post-dose. Maximum pre-dose (trough) plasma concentrations were reached at 8 hours (T<sub>max</sub>). In this study, oliceridine exhibited a mean t<sub>1/2</sub> of approximately 1.6 hours, which is in line with previous studies in healthy volunteers who are CYP2D6 extensive metabolizers. Mean (SD) clearance of oliceridine was 72.8 (23.3) L/hr.

Figure 1: Mean (SD) Oliceridine Plasma Concentrations over Time following intermittent bolus dosing of IV oliceridine injection over 24 hours.

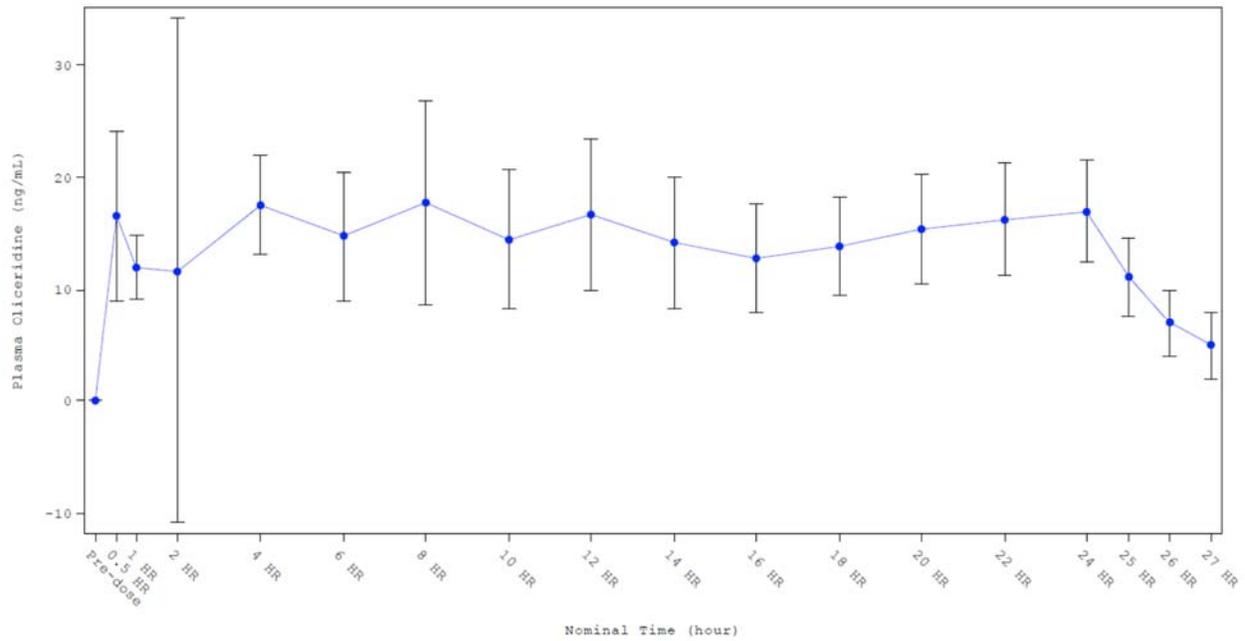


Table 1: Plasma Oliceridine PK Parameters following intermittent IV bolus of 27 mg/day oliceridine over 24 hours.

Parameter	n	GeoMean (CV [%])
AUC <sub>(0-t)</sub> (ng*hr/mL)	65	365.044 (106.1)
AUC <sub>(0-inf)</sub> (ng*hr/mL)	62	374.180 (106.3)
Max Trough Concentration (ng/mL) <sup>a</sup>	65	23.01 (110.8)
t <sub>max</sub> (hr) <sup>b</sup>	65	8.00 (0.5, 24.0)
t <sub>1/2</sub> (hr)	62	1.56704 (103.0)

AUC<sub>(0-inf)</sub>=area under the concentration-time curve from time 0 to infinity; AUC<sub>(0-t)</sub>=area under the concentration-time curve from time 0 to time t; C<sub>max</sub>=maximum plasma concentration.

CV=coefficient of variation; GeoMean=geometric mean; max=maximum; min=minimum; PK=pharmacokinetic; t<sub>1/2</sub>=half-life; t<sub>max</sub>=time to maximum concentration

<sup>a</sup> Due to the sampling scheme, the parameter of C<sub>max</sub> should be interpreted as the maximum trough concentration.

<sup>b</sup> Median (min, max) t<sub>max</sub> presented.

Data source: Table 14.2.1.4

### 3. APPENDICES

#### 3.1 Summary of Bioanalytical Method Validation and Performance

(b) (4) conducted the bioanalysis of blood samples collected in study CP130-1014 ( (b) (4) Number 8407216). Calibration standard data, QC sample data, incurred sample reproducibility data, and chromatograms indicate that the method performed acceptably during the sample analysis. There were 128 samples reanalyzed to test the reproducibility of the method for quantifying TRV130. It was observed that 94.5% of the ISR results had a relative % difference within  $\pm$  (b) (4) %; this is within the acceptance criteria. All samples were analyzed within 75 days of collection following storage at -60 to -80°C. Stability of plasma QC samples after storage in a freezer set to maintain -60 to -80°C for 366 days was established and reported in the method validation, (b) (4) 8334538. The bioanalytical study report is acceptable.

Analyte	TRV130
Species	Human
Analytical matrix	K <sub>2</sub> EDTA Plasma
Internal standard (ISTD)	TRV0110813A:2
Validated method	TRV1HPP
Validated range	0.0500 (LLOQ) to 50.0 (ULOQ) ng/mL
Quality Control (QC) levels	0.150 ng/mL, 2.50 ng/mL, 40.0 ng/mL
Analytical technique / method of detection	Supported-liquid extraction / LC-MS/MS
Sample volume	50.0 µL
Calibration model	Quadratic regression
Weighting factor	1/x <sup>2</sup>
Total number of samples analyzed	1480
Total number of samples reassayed	9 (0.6% of total number of samples analyzed)
Sample storage conditions	-60 to -80°C
Incurred sample reanalysis	Required / Pass
Samples analyzed within known stability	Yes

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SRIKANTH C NALLANI  
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YUN XU  
07/09/2020 04:45:06 PM

<b>NDA #</b>	NDA 210730
<b>Applicant</b>	Trevena, Inc.
<b>From</b>	Elizabeth Kilgore (clinical reviewer), James Travis (statistical reviewer), Janet Maynard (cross-discipline team leader), David Petullo (statistical team leader), Mark Rothmann (Acting Director Division of Biometrics II), Sharon Hertz (Division Director), Mary Thanh Hai (Office Director)
<b>Subject</b>	Cross-Discipline Team Leader Review; Division/Office Director Review; Primary Clinical Review; Primary Statistical Review
<b>Date of Submission</b>	November 2, 2017
<b>PDUFA Goal Date</b>	November 2, 2018
<b>Proprietary Name</b>	Oliceridine injection
<b>Proposed Established or Proper Name</b>	Olinvyk
<b>Dosage Form(s)</b>	1 mg/mL in a glass vial for intravenous use  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
<b>Applicant Proposed Indication(s)/Population(s)</b>	Management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted
<b>Applicant's Initially Proposed Dosing Regimen(s)</b>	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 (b) (4) .  Maintenance (b) (4) 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
<b>Recommendation on Regulatory Action</b>	Complete Response
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Not applicable

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## 1. Benefit-Risk Assessment

### Benefit-Risk Summary and Assessment

Acute pain is a serious medical condition. 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  $\mu$ -opioid receptor and stimulates G protein-coupling with reduced  $\beta$ -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 statistically significantly greater reduction in pain intensity relief than two of the doses of oliceridine (0.1 mg and 0.35 mg). The reduction in pain intensity by morphine was greater but not statistically significant compared to 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. Regardless, even if we did agree with the endpoint, 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.

*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.

Many adverse events in the clinical program were consistent with opioid-related adverse events, including respiratory depression, hypoxia, nausea, and vomiting. When evaluating the controlled Phase 3 data by randomized treatment group, many of the adverse events for oliceridine were dose-related, including respiratory effects. While there were trends showing a decreased percentage of respiratory events as defined by Trevena 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. Additionally, the safety database was not adequate to support the proposed dosing.

The application was discussed at an Anesthetic and Analgesic Drug Products Advisory Committee meeting on October 11, 2018, and the majority of committee members did not recommend approval (8 against approval; 7 for approval) citing concerns related to the available safety data and QT prolongation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#"><u>Analysis of Condition</u></a>	<ul style="list-style-type: none"> <li>Acute pain is a serious medical condition which can affect function and quality of life.</li> <li>Pain is a well-recognized medical condition in a variety of medical settings, especially post-operatively.</li> <li>The goal of treatment is to control pain with minimal side effects from pain medication. Due to the narrow therapeutic window of current opioid analgesics (i.e., the difference between doses that produce analgesic and those that produce adverse effects), additional options for acute pain management would be helpful.</li> </ul>	<p>Acute pain is a serious condition and is common in many medical and surgical conditions. Untreated acute pain can result in prolonged hospital stays, increased hospital readmission, and increased patient dissatisfaction.</p> <p>While there is heterogeneity in the types and causes of acute pain, adequate control of acute pain is important.</p>
<a href="#"><u>Current Treatment Options</u></a>	<ul style="list-style-type: none"> <li>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.</li> <li>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).</li> </ul>	<p>There are multiple current pharmacologic treatment options for patients with acute pain, including opioids. All opioids have potential risks that include respiratory depression and death as a result of overdose, and other known opioid-related adverse effects such as, constipation, nausea, and vomiting.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>Parenteral opioids currently approved for acute pain in the United States include morphine, fentanyl, meperidine, and hydromorphone.</li> </ul>	
<u>Benefit</u>	<ul style="list-style-type: none"> <li>Studies 3001 (bunionectomy) and 3002 (abdominoplasty) were randomized, double-blind, placebo- and morphine-controlled key efficacy studies.</li> <li>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).</li> <li>Using Trevena’s pre-specified respiratory safety burden endpoint (that FDA did not agree with) none of the oliceridine treatment arms demonstrated a significant reduction in the expected cumulative duration of respiratory safety events compared to morphine.</li> </ul>	<p>Two placebo- and active-comparator (morphine) adequate and well-controlled Phase 3 clinical trials were conducted. Compared to placebo, there is replicate evidence of efficacy of oliceridine 0.35 mg and 0.5 mg. Oliceridine 0.1 mg was effective in reducing post-operative pain compared to placebo in one study.</p> <p>Compared to morphine, oliceridine generally appeared less effective. There was no statistical difference between oliceridine and morphine in terms of respiratory safety.</p>
<u>Risk</u>	<ul style="list-style-type: none"> <li>A total of 1,853 unique individuals were exposed to oliceridine (221 healthy subjects in Phase 1 studies, 97 special populations subjects in Phase 1 studies, and 1535 patients in Phase 2 and Phase 3 studies). The safety of oliceridine was evaluated in 470 patients with acute post-operative pain in controlled Phase 3 studies 3001 and 3002 and 768 patients in uncontrolled Phase 3 study 3003. Due to the PRN dosing regimen, patients received a wide range of exposure to oliceridine. The drug exposure data are not adequate to support the Applicant’s proposed dosing in the label.</li> <li>Major safety concerns:</li> </ul>	<p>Hepatic Safety: There were cases of elevated transaminases <math>\geq 3 \times \text{ULN}</math> and total bilirubin <math>\geq 2 \times \text{ULN}</math> and a serious adverse event of hepatic failure in the oliceridine program. While these cases were confounded, all occurred in open-label study 3003, considered to represent “real-world” situations in which patients might receive oliceridine.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>•Hepatic Safety: There were two cases of elevated transaminases <math>\geq 3</math> x upper limit (ULN) with concurrent total bilirubin <math>\geq 2</math>x 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 Agency’s hepatology consultants determined that these cases were confounded, possibly due to anesthesia and multiple concomitant peri-operative medications.</li> <li>•Respiratory Safety: In general, there was a dose-response between increasing oliceridine dose and the percentage of patients experiencing respiratory safety events. Additionally, there was a higher percentage (3.8% and 1.3% in oliceridine 0.35 mg and 0.5 mg, respectively) of patients who discontinued due to hypoxia in the oliceridine arms compared to the morphine arm (0) in Study 3002. There were also discontinuations due to oxygen saturation decreased and hypoxia in both the oliceridine- and morphine-arms in Study 3001. Thus, there was not a consistent trend toward improved respiratory safety for oliceridine compared to morphine.</li> <li>•QT-Prolongation: The thorough QT study showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset. The QT study did not evaluate the maximum proposed dosing regimen, but showed a delayed increase in QTc following a single dose. The mechanism of the delayed increase in QTc is unknown. Nonclinical data show that the QTc prolongation may not be mediated via direct inhibition of the hERG potassium channels. The exposure for the maximum proposed dosing regimen is projected to be 2 to 3-fold higher for the two major metabolites compared to highest dose in the thorough QT study. The Agency has determined that the submitted data are not adequate to evaluate the QT effects of oliceridine.</li> <li>•Safety database: Currently, the Applicant proposes a maximum daily dose of 40 mg and PCA demand doses of 0.1 and 0.35 mg with a 6-minute lock-out. In prior</li> </ul>	<p>Respiratory Safety: There was not a consistent trend toward improved respiratory safety for oliceridine compared to morphine, especially when considering oliceridine doses that had similar efficacy to morphine.</p> <p>QT Prolongation: The submitted data are not adequate to evaluate the QT effects of oliceridine, these risks cannot be adequately mitigated by labeling or monitoring, and the risks associated with QT-prolongation require additional pre-marketing data.</p> <p>Safety Database: The Applicant’s exposure database is smaller than the Agency’s recommended database to evaluate and support the safety of oliceridine for the proposed label, that includes a maximum daily dose of oliceridine 40 mg (b) (4)</p> <p>Abuse potential: The Applicant and the Agency agree that oliceridine has a high potential for abuse.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>advice, the Applicant was advised of a required exposure for at least 350 patients at the highest planned dose. The highest dose that at least 350 patients were exposed to during the first 24 hours was 27 mg of oliceridine.</p> <ul style="list-style-type: none"> <li>• Abuse potential: Trevena proposes that oliceridine be Schedule II given the high potential for abuse.</li> </ul>	
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> <li>• Approved opioids have boxed warnings for numerous safety concerns, including respiratory depression and abuse and misuse.</li> <li>• It is anticipated that oliceridine would be used in clinical situations where other drugs that prolong QT are commonly used. While patients will be inpatients in monitored settings, oliceridine will be titrated to effect which needs to be considered when assessing the risks associated with QT prolongation.</li> </ul>	<p>Given the potential risks associated with oliceridine, additional data are needed pre-approval to support the overall benefit/risk profile of oliceridine. The size of the safety database for oliceridine is not adequate for this NME opioid at the proposed labeled dosing and the submitted data are not adequate to evaluate the QT effects of oliceridine. These risks cannot be adequately addressed through post-approval data, labeling, or monitoring.</p>

See the Appendix for the Patient Experience Data Table.

## 2 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  $\mu$ -opioid receptor and stimulates G protein-coupling with reduced  $\beta$ -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.”<sup>1</sup> 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.

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

- **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.

**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 Initial Pediatric Study Plan (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
- The Sponsor was informed that the NDA should address how data from the controlled Phase 3 studies, which excluded patients on chronic opioid therapy, would be generalized to the intended acute pain population. The Sponsor stated that they would address this issue by including class labeling language related to opioid tolerance.

**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)

### **March 9, 2018 Proprietary Name Request Denied**

- The proposed proprietary name, Olinvo, was determined to be unacceptable.

### **August 9, 2018 Proprietary Name Request Conditionally Accepted**

- The proposed proprietary name, Olinvyk, was determined by the Office of Surveillance and Epidemiology to be conditionally acceptable.

## **3. Product Quality**

Oliceridine injection is a clear, colorless, sterile, preservative-free solution stored in a glass vial for intravenous use. Oliceridine is manufactured in a single strength of 1 mg/mL, containing 1.0 mg of oliceridine free base (1.3 mg of oliceridine fumarate salt), as well as L-histidine and mannitol, in water for injection. Oliceridine injection solution is provided with three presentations, 1 mL in a 2-mL vial, 2 mL in a 2-mL vial and 30 mL in a 30-mL vial.

The drug product is filled in a clear USP Type <sup>(b)</sup><sub>(4)</sub> glass vial plugged with a <sup>(b)</sup><sub>(4)</sub> <sup>(b)</sup><sub>(4)</sub> rubber stopper and sealed by an aluminum seal with a flip-off cap. The 13-mm gray cap is used for 1-mL fill, the 13-mm orange cap is for 2-mL fill and the 20-mm purple cap is for 30-mL fill. Sufficient stability data is provided to support the proposed and granted expiry of 24 months for the product stored in vials 25 °C/60% RH.

The following information is from the product quality review:

“The analytical methods used for release and stability testing are well described and validated for the intended uses. Method verification is being carried out by the (b) (4) labs. The HPLC method used to detect leachables in the drug product has not been adequately validated. Therefore a leachable assessment of the container closure system could be not be determined.

Microbiology and Biopharmaceutics review of the drug product also recommend approval.

The drug substance, Oliceridine fumarate, as a new molecular entity, and is manufactured (b) (4)

(D) (4)

Drug substance and drug product facilities have been inspected. The (b) (4) Facility included in the NDA filing, and recommended as inadequate by the Office of Facilities, has been withdrawn from the NDA by the Sponsor. The remaining manufacturing facilities for the drug substance and drug product are adequate.”

The overall recommendation on approvability from CMC is summarized below:

“Adequate data is provided to ensure the identity, quality and purity of the drug substance and drug product manufactured as described in this NDA. Drug substance, process, facilities, microbiology and biopharmaceutic teams recommend approval. However, the HPLC method validation for detection of leachables in the drug product is a deficiency not currently resolved. Therefore the overall CMC recommendation is a Complete Response.”

#### **4. Nonclinical Pharmacology/Toxicology**

The following summary of the nonclinical pharmacology/toxicology issues is from the nonclinical review by Dr. Min Zhang:

“Pharmacology studies were submitted and demonstrated that oliceridine is a potent agonist at the MOR and is approximately 6-fold more potent than morphine (oliceridine  $EC_{50}=7.9$  nM, morphine  $EC_{50}=50$  nM). In vitro data demonstrated that oliceridine elicits less receptor phosphorylation and receptor internalization than morphine, consistent with its reduced  $\beta$  arrestin-2 recruitment. Oliceridine is selective for the MOR based on selectivity screening results examining greater than 100 receptors, channels, transporters and 33 different enzymes. In vitro data show that oliceridine exhibits 220-fold selectivity for MOR over the kappa opioid receptor (KOR) and 375-fold for MOR over the delta opioid receptor (DOR). In mice and rats, oliceridine elicits antinociception in multiple models of spinal reflexive and supraspinal affective nociceptive pain (potency reported to be 3 to 10 times that of morphine) with less respiratory depression and constipation in rodents compared to “equianalgesic” doses of morphine.

Potential systemic safety/toxicity of the drug product was evaluated in safety pharmacology, repeat-dose toxicity studies in rats and monkeys, reproductive toxicity studies in rats and rabbits. All the in vivo toxicology studies, including the in vivo genotoxicity studies, were conducted by

continuous IV infusion. Intravenous bolus administration is the intended clinical route of administration; however, continuous infusion was selected to maximize daily exposure in the toxicology studies. Although the nonclinical studies were not designed to mimic the clinical setting exactly (periodic bolus dosing) the concentrations obtained in the animal studies exceeded the  $C_{max}$  obtained clinically.

The cardiovascular safety pharmacology studies suggest that oliceridine is a weak hERG inhibitor with an  $IC_{50}$  of 2.2  $\mu$ M which is 367 times its binding affinity of 6 nM at the MOR and 43 times the estimated  $C_{max}$  of the unbound drug at the proposed maximum recommended human dose (MRHD) of 40 mg/day. No consistent effects on QTc interval have been observed in nonclinical studies. Hemodynamic data demonstrated that oliceridine caused a dose-dependent decrease in mean systolic, diastolic, and mean arterial pressures, mean arterial pulse pressure, and mean body temperature during infusion. The changes were followed by compensatory increases in these hemodynamic parameters from the end of infusion through the end of the telemetry collection period. A 6-hour infusion of oliceridine in rats did not cause any changes in respiratory parameters up to extrapolated plasma exposure approximately 2 times the projected median human  $C_{max}$  at the proposed daily MRHD of 40 mg.

General toxicology studies in rats and monkeys identified typical changes 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 were observed in rats treated with oliceridine for 14 days via constant infusion when the animals were sacrificed 24 hours post-dosing. These histopathological changes included minimal to marked stomach lesions such as erosions/ulcers in the glandular stomach, mucosal congestion/hemorrhage and degeneration/necrosis in the nonglandular stomach, minimal to slight adrenal cortical hypertrophy and atrophy of the seminal vesicles and prostate, and decreased lymphocytes in the spleen, thymus, mesenteric and mandibular lymph nodes. The gastric lesions were not observed after continuous IV infusion of oliceridine for 14 or 28 days in rats or in monkeys as long as the animals were sacrificed within 45 minutes after the termination of infusion. Furthermore, the occurrence of stomach lesions appears to correlate with the clinical observations reflecting withdrawal symptoms. Therefore, the gastric lesions identified in animals after withdrawal from the drug treatment appear to be a risk associated with drug withdrawal rather than a risk resulting directly from the drug effect. Stomach necrosis findings resolved by 7 days after termination of drug infusion in rats. 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 even when animals were sacrificed immediately after the termination of drug infusion. A greater incidence and severity of minimal to slight apoptosis in the pancreas observed in male rats after 28 days of drug infusion is likely attributed to reduction of food intake and was not associated with any evidence of inflammatory infiltrates in that tissue. A higher mortality rate (both found dead and moribund sacrifice) was observed in rats after prolonged infusion of oliceridine in the 28-day repeat-dose study, although the mortality was considered secondary to infusion-site inflammation and infection due to the presence of bacteria at the injection site.

In addition, lung thrombosis and injection-site inflammation were considered to be catheter related, although a possible oliceridine-related augmentation of the catheter response cannot be eliminated. Specifically, dose-dependent increases in inflammation were observed at infusion sites in the 28-day rat general toxicity study with a no observed adverse effect level (NOAEL) of 0.5 mg/kg/h at a concentration of 0.5 mg/mL, which is lower than the clinical concentration of 1 mg/mL. However, no increases in inflammation at infusion sites were observed at up to 1 mg/kg/h oliceridine (up to 1 mg/mL) in a 14-day study in rats. These studies suggest a low risk for local infusion site inflammation when the IV infusion is given for a short period for treating acute pain. An increased incidence of lung thrombosis was observed in oliceridine-treated rats in 2 out of the 4 rat toxicology studies and only occurred in oliceridine-treated rats when lung thrombosis was also observed in vehicle-treated animals, suggesting the occurrence may be related to IV procedure but oliceridine may increase the incidence. The clinical relevance of this finding is likely limited, because rats do tend to have much stronger foreign body reactions compared to other species and no such finding was observed in the monkey study. Further, *in vitro* hemolysis and flocculation assays showed that oliceridine is compatible with human blood, as well as plasma and serum proteins. Collectively, the product does not appear to have significant risk for short-term acute use and likely results in similar risk as other long-term indwelling catheters used for prolonged drug administration.

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 at doses equivalent to  $\geq 2$  times the MRHD of 40 mg/day. The NOAEL for female fertility and early embryonic findings corresponded to approximately 1 times the estimated total daily exposure at the MRHD. In the GLP studies evaluating the effects of oliceridine on embryo-fetal development in rats and rabbits that received continuous IV infusion of oliceridine from the time of implantation until 1 day prior to parturition, 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 an overall increase in pups found dead or sacrificed moribund from birth to weaning. More specifically, there was reduced live litter size relative to total number born at birth (Postnatal Day 0; PND 0), and lower pup survival between birth and PND 4, resulting in a NOAEL that corresponds to total daily plasma exposure equivalent to 0.1 times the estimated MRHD exposure. Chronic administration of opioids has been shown to inhibit the synthesis and excretion of oxytocin, the hormone responsible for milk let-down, and adversely impacts maternal care of pups, providing possible explanations for early postnatal pup deaths. There was decreased milk in the stomachs of pups found dead or who were sacrificed moribund, which supports this conclusion. However, a direct effect on the pups cannot be eliminated without cross-fostering studies. Oliceridine administration to F<sub>0</sub> dams produced no F<sub>0</sub> or F<sub>1</sub> maternal toxicity, had no effect on F<sub>1</sub> developmental landmarks or memory and learning, and had no effect on F<sub>1</sub> reproductive endpoints and produced no F<sub>2</sub> neonatal/early postnatal toxicity. The NOAEL corresponds to total daily plasma exposure approximately 1 times the estimated MRHD exposure.

Oliceridine has been tested for genotoxicity in a bacterial reverse mutation assay, an in vitro chromosome aberration assay, and in vivo rat micronucleus and comet assays. While incubation with oliceridine in HCL salt form at concentrations >1.6 mM in the presence of a metabolic activation system resulted in a positive result in the in vitro chromosome aberration assay, this finding was not corroborated by the results of a follow-up study testing the current limit concentration of oliceridine fumarate for this assay, or in an in vivo micronucleus or comet assays. Results from these studies indicate, by weight of evidence, that the risk of mutagenicity and clastogenicity in humans, if any, is minimal.

Radiochemical and mass spectrometric profiling of plasma collected from a human metabolism and excretion study with IV administration of [<sup>14</sup>C]-TRV130 identified two disproportionate human metabolites with mean plasma AUC values greater than 10% of total drug-related material—M22 (61.9%) and TRV0109662 (17.4%). Neither the major human metabolites show significant pharmacological activity in in vitro studies except a weak partial agonism at mu-opioid receptor. M22 has been adequately characterized for safety at the proposed MRHD of 40 mg/day. Although M22 was not present at adequate levels in the embryofetal development studies, this compound is an ether glucuronide of oliceridine, which is not believed to present any safety risks in accordance with the FDA guidance to industry on metabolites. As such, no further studies are required. For the other major human disproportionate metabolite TRV0109662, the plasma exposure to this metabolite in the rat 28-day repeat-dose study samples used to estimate the exposures in the rat embryo-fetal study suggests adequate coverage in this species. However, the Applicant is not able to reliably reproduce these exposure data assessments suggesting assay insensitivity. As such, the conclusion that the disproportionate metabolite is adequately characterized is uncertain due to lack of reproducibility. Thus, we cannot conclude that this disproportionate major metabolite has been adequately characterized with respect to an impact on embryo-fetal development. Because the drug will be labeled to reflect decreased postnatal pup survival at exposure less than the maximum recommended dose of 40 mg, the lack of complete characterization of this metabolite may not be absolutely essential to adequately inform labeling. Should this compound be deemed to provide a meaningful benefit over existing therapies, definitive embryo-fetal studies of the metabolite or validated reproducible analytical data could be considered as a post-marketing requirement at the discretion of the approving official based on a risk: benefit analysis. However, in the absence of a convincing risk: benefit analysis, adequate data should be provided to support an approval recommendation.

Regarding product quality (i.e., Drug Substance, Drug Product, Impurities, Excipients, and Extractables/Leachables), there are no nonclinical issues that preclude approval.”

The nonclinical team has concluded that “from a nonclinical pharmacology toxicology perspective, there are inadequate nonclinical data to support an approval recommendation at this time and we therefore, recommend a complete response. Specifically, it is not clear that the disproportionate major human metabolite, TRV0109662, has been adequately qualified for safety, because the exposure data for this metabolite from rat intravenous toxicity studies could not be reproduced. As such, it is not clear that effects of TRV0109662 on embryofetal development have been adequately characterized by the existing studies.

The following nonclinical deficiency exists:

1. You have not provided adequate data to confirm that levels of TRV0109662, a major human metabolite, have been adequately characterized for potential embryo-fetal effects in either the rat or the rabbit embryo-fetal development study. Based on the data obtained to date, this metabolite does not appear to be formed at acceptable levels in the rat compared to the human, you have not provided any data to document that the metabolite is formed in rabbit, and the existing analytical assays for human and rat plasma levels of TRV0109662 do not appear to be consistently reproducible (failed rat incurred sample reanalysis for pivotal study).

Information needed to resolve this deficiency:

Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated reproducible pharmacokinetic data to support your 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 at the proposed maximum recommended human dose of 40 mg/day.”

## 5. Clinical Pharmacology

The following assessment is from the clinical pharmacology review:

### “Pharmacology and Clinical Pharmacokinetics

Oliceridine is a new molecular entity that is a G protein biased ligand at the  $\mu$ -opioid receptor with analgesic properties. Oliceridine is being developed for the management of moderate to severe acute pain in patients 18 years of age or older for whom an intravenous (IV) opioid is warranted. Oliceridine produces pharmacodynamic effects like opioids. Oliceridine has an in vitro EC<sub>50</sub> (binding affinity) of 8 nM at the human  $\mu$ -opioid receptor. In comparison, morphine binds with the human  $\mu$ -opioid receptor with affinity or EC<sub>50</sub> of 50 nM. 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 was also noted. While pupil constriction is clearly indicative of typical opioid effect due to distribution into central nervous system, its specific link to pain or abuse remains unestablished. Oliceridine improved 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 can be antagonized by a selective  $\mu$ -opioid antagonist (naloxone).

**Absorption:** Oliceridine administration is by an IV route, on an as-needed basis. Bioavailability of oliceridine administered as an oral dose (100 µg) was very low in one oral study CP130-1004. Intravenous dose of oliceridine was not administered in that study. Based on a cross study comparison, oral bioavailability was estimated to be 5.77%.

**Distribution:** As noted above, based on pharmacodynamic effects, oliceridine distributes into central nervous system. 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 (Study 797914 and TRE-R6804).

**Metabolism:** Oliceridine is metabolized by oxidation into Oxy-oliceridine (M23) followed by glucuronidation to TRV0306954 (M22). N-dealkylation and oxidation of oliceridine produced circulating metabolites TRV0109662. After a single IV dose of <sup>14</sup>C-oliceridine, TRV0306954 (M22) is the main circulating radioactive component, accounting for a mean of 61.9% of total [<sup>14</sup>C]-drug related plasma exposure (AUC). TRV0109662 accounts for 17.4% of plasma AUC. Oxy-oliceridine (M23) accounts for 5.20% 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 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.

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.

**Elimination:** Oliceridine exhibited a half-life of approximately 1.5 to 3 hours when administered IV over 1 minute to 1 hour. The impact of CYP2D6 polymorphism on pharmacokinetics of oliceridine was evaluated in different 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 C<sub>max</sub> and AUC. Clearance of oliceridine was reduced by 50% in CYP2D6 poor metabolizers consistently across the Phase 1 clinical studies. While C<sub>max</sub> was only slightly higher, AUC of oliceridine was about 2-fold higher and plasma half-life was 3 to 4.5 hours in poor metabolizers of CYP2D6.

## Dosing and Therapeutic Individualization

### General dosing

The proposed dosing is based on the findings from registration trials (Study CP130-3001 in patients with medium to severe acute pain after bunionectomy and Study CP130-3002 in patients with medium to severe acute pain after abdominoplasty). The dose selection for registration

trials was based on the findings from dose-response studies (Studies CP130-2001 and CP130-2002).

The general dosing guidelines from the Phase 2 and Phase 3 studies are as follows:  
The initial dose of OLINVO 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.

Maintenance of analgesia is generally achieved with OLINVO administered as 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.”

The clinical pharmacology review noted the following outstanding issue: “The sponsor should conduct thorough QT-prolongation study before approval of this drug in a representative population that may receive wider range of oliceridine doses.”

A significant consideration during the review cycle was the QT effects of oliceridine. The clinical pharmacology review noted the following:

“The tQT-study CP130-1008 showed QT-prolongation with IV doses of 6 mg oliceridine, which appears not to be clinically relevant based on the magnitude of prolongation in this specific study. However, adequate ECG data was not collected in Phase 3 clinical trials following the positive signal in the tQT study. IRT-QT group indicated in review dated 9/28/2018 that “Due to the uncertainty about the mechanism causing the observed QTc prolongation it is not possible to predict the QTc prolongation with the currently proposed dosing paradigm, which results in exposures of the major metabolites that exceeds the exposures following the highest dose in the thorough QT study (~2.4-fold for M22 and ~2.8-fold for TRV9198662)”. Additionally, IRT-QT indicated “Because of the limitations with the available clinical data, a clinical study is necessary to characterize the effects of oliceridine on the QTc interval at the therapeutically relevant exposures to all major moieties. We propose that the clinical QT study is a multiple dose study with the maximum proposed dosing regimen in healthy volunteers, if feasible. If it is not feasible to administer the maximum proposed dosing regimen in healthy volunteers, a clinical QT study in patients who can tolerate the maximum proposed dosing regimen.”

On 10/2/2018 Clinical Pharmacology Briefing focused on the need for an additional tQT study. As indicated in the OCP briefing minutes page 4 “A PMR for another TQT study may be considered with labeling given that an adequate clinical monitoring plan for ECG may be implemented in the real clinical use setting. Of note, regulatory approval of a drug with QT-prolongation requires the following language in section 5 and 12.2: “ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.”

On 10/11/2018, the majority of the fifteen advisory committee panel members voted to not approve oliceridine (No=8, Yes=7). Several AC members that voted to approve the drug still

recommended Phase 4 studies to establish safety of oliceridine in a representative patient population employing higher doses as may be used in realistic settings.

Based on discussion at the Advisory Committee and internal discussions after the meeting, the review team decided that there is not enough support for the benefit-risk profile to approve the drug at this stage. The potential risk of QT prolongation is a major safety concern for this product. Therefore, the sponsor should conduct thorough QT-prolongation study before approval of this drug in a representative population that may receive wider range of oliceridine doses.”

## 6. Clinical Microbiology

Not applicable

## 7. 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, MS*

### • 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 1 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.

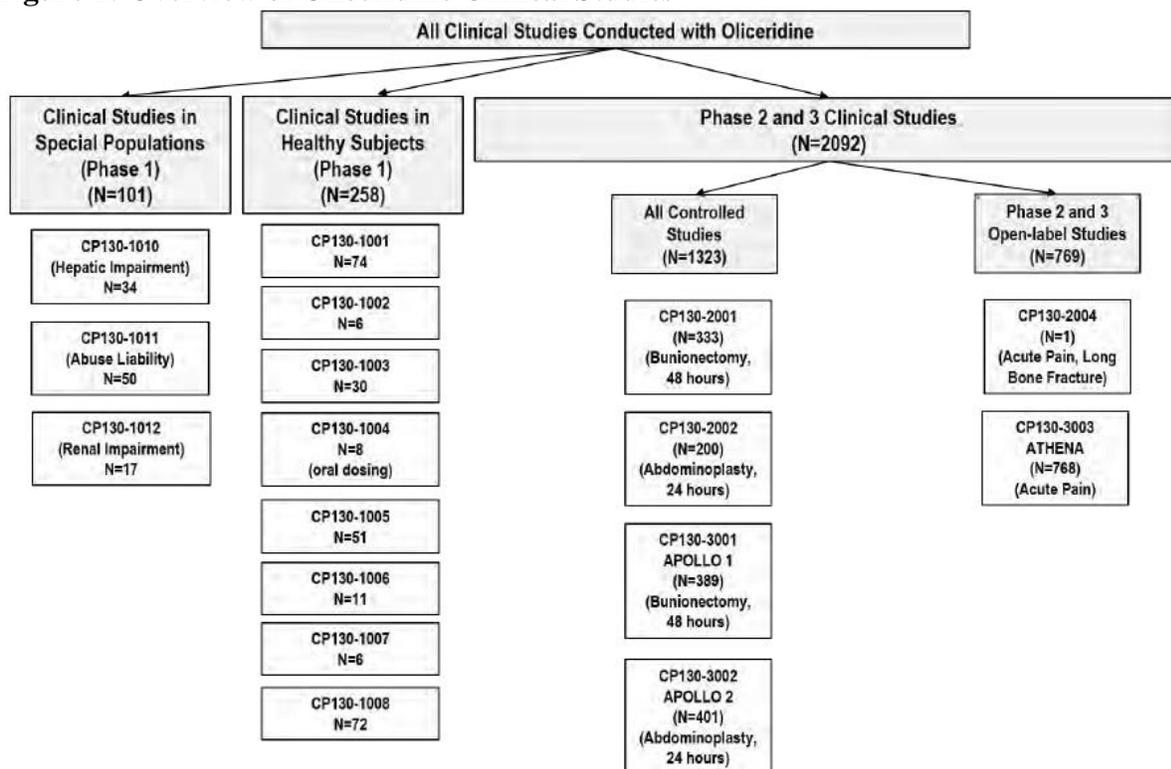
The 17 clinical trials are categorized as follows:

- 11 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 1.

**Figure 1: 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 2 Phase 2 studies (CP130-2001 and CP130-220, referred to as 2001 and 2002, respectively) were submitted to support the dose selection in Phase 3 (Table 1). 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 2 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 2).

**Table 1: Summary of Phase 2 Studies in the NDA**

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

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

			<ul style="list-style-type: none"> <li>•Supplemental dose: 0.75 mg q1h PRN</li> <li><u>0.5 mg nominal dose regimen</u></li> <li>•Loading Dose: 1.5 mg</li> <li>•Demand Dose: 0.5 mg</li> <li>•Lockout Interval: 6 minutes</li> <li>•Supplemental dose: 0.75 mg q1h PRN</li> </ul>	
<p><b>CP130-3003</b></p> <p>NCT02656875</p> <p>APOLLO 3</p> <p><i>Dec 2015-May 2017</i></p> <p>(41 US sites)</p>	<p>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 <math>\geq 4</math>)</p>	<p>OL, MC</p> <p>(up to 14 days)</p> <p>[768]</p>	<p>Doses were clinician administered and/or PCA</p> <p><u>For clinician-administered:</u></p> <ul style="list-style-type: none"> <li>•Initial dose: 1-2 mg</li> <li>•Supplemental doses 1 mg may be administered within 15 minutes after the initial dose. Subsequent doses are 1-3 mg q1 to 3h PRN</li> </ul> <p>In settings where rapid analgesia is targeted (e.g. ED or PACU):</p> <ul style="list-style-type: none"> <li>•Initial dose: 1-3 mg</li> <li>•Supplemental doses 1-3 mg q5 min PRN. Subsequent doses are 1-3 mg q1 to 3h PRN</li> </ul> <p><u>For PCA dosing:</u></p> <ul style="list-style-type: none"> <li>•Loading dose: 1.5 mg</li> <li>•Demand dose: 0.5 mg</li> <li>•Lockout interval: 6 minutes</li> <li>•Supplemental 1 mg doses permitted PRN</li> </ul>	<p>Safety and tolerability</p>

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

## • 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 ( $\geq 4$  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<sub>0-48</sub>) 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<sub>0-48</sub> 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<sub>0-48</sub>), 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 3). 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 3: Analysis of TWA<sub>0-48</sub> 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
<b>TWA<sub>0-48</sub> Change from Baseline of Pain Intensity</b>						
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
<b>TWA Change from Baseline of Pain Intensity Hours 0-3</b>						
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<sub>0-48</sub> compared to morphine (Table 4). 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 4: Analysis of TWA<sub>0-48</sub> 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
<b>TWA<sub>0-48</sub> Change from Baseline of Pain Intensity</b>						
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 5). 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 5: 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<sub>0-24</sub> 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<sub>0-24</sub>) 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 7 and Table 8), there are limitations to drawing conclusions from this small Phase 2 study in terms of any potential safety differences between morphine and oliceridine.

**Table 6: 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
<b>Protocol V1-4</b>					
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
<b>Protocol V5</b>					
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 7: 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 8: 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

## • Phase 3 Trial Designs

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). 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.

## i. Study Design

### Study 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 randomized equally to receive either placebo, morphine, oliceridine 0.1 mg, oliceridine 0.35 mg, or oliceridine 0.5 mg.

The study enrolled adult patients ( $\geq 18$  and  $\leq 75$  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  $\geq 4$  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 9.

**Table 9: 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  $\geq 4$ . 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.

### **Study 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 Study 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  $\geq 5$  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 Study 3001 (Table 9) 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.

## **ii. 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 24/48 hours (SPID-24/48) 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, has never been the basis for approval for any drugs in this class, and there are several issues with how a responder was defined.

First, we do not agree with the 30% cutoff for SPIDs. In a post-hoc analysis of CP130-2002 (see discussion of the May 6, 2016 submission in Section 2) the applicant found the SPID scores for patients who received morphine represented a 44% reduction from baseline compared to 18% for placebo. Thirty percent (30%) was selected as it roughly corresponds to the midpoint between the two averages. A 30% reduction has been used in studies of chronic pain, though it does not have the same meaning in this context as it represents a 30% reduction the theoretical outcome had the baseline pain score being carried forward for the entire duration of the study (either 24 or 48 hours). In summary, the scientific basis for a 30% cutoff remains unclear.

Second, use of a single cutpoint is also problematic as it truncates the improvement in SPID score to either less than or greater than a particular value, in this case 30%, and turns a continuous measure into a pass/fail. Patients who experience larger reductions are treated the same as patients who barely exceed the threshold. This has the effect of understating differences between the most effective treatment arms and those that provide pain relief closer to the threshold.

Finally, the responder definition classifies patients who use any quantity of rescue medication as non-responders which will underestimate the placebo or treatment effect in patients that used more rescue. The applicant planned and performed several sensitivity analyses to explore the effect of allowing small quantities of rescue medication or imputed the pre-rescue score for a limited duration, but these analyses used the 30% cutoff which we did not agree with for the reasons noted above.

To address these points, we performed our own analyses for each study which are described in Section 7.iii.

**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 CO<sub>2</sub> (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.

### iii. 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  $\geq 30\%$  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<sup>2</sup>. 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

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<sup>2</sup> Firth, David. Bias Reduction of Maximum Likelihood Estimates. *Biometrika*. 1993; 80:27-38.

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 1360797248.□, 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.
- 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 at the End-of-Phase 2 meeting described in Section 2. The model estimated values in this analysis were obtained by multiplying model estimated parameters by the overall average value of the covariates included in the model (site group and baseline NRS score). While single imputation methods are known to underestimate the uncertainty due to missingness, we don't believe that the conclusion would be changed in this case as the standard error of the differences would need to increase by at least 23% to change the conclusion of any of the comparisons of oliceridine to placebo.

### **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 using the ANCOVA model listed above, with no imputation following use of rescue.

**Estimands:** We believe that there are two methods for handling use of rescue medication that are discussed in ICH E9 (R1) document. We will give a short summary of these methods and a discussion of why they are relevant in this case:

- **Use an imputation scheme to replace observation following rescue medication usage (Hypothetical estimand):** The objective here is to estimate the effect of treatment compared to placebo had rescue medication not been available to patients. Since it not ethical to withhold treatment from patients, this method cannot be assessed directly and can only be targeted by statistical methods that impute the expected outcome had rescue not been available. The main advantage of this method is that it is more likely to demonstrate a difference in the effect between placebo and active, but it relies on subjective imputation methods. This method has commonly been used and accepted in studies of post-surgical analgesia.
- **Analyze the data without considering rescue medication usage (Treatment policy estimand):** If there was a significant difference in an analysis where rescue medication is not taken into account, with similar or lower levels of rescue medication usage for the active treatment, then it would be clear that the active treatment has an effect above and beyond the effect of rescue medication. The advantage of targeting this estimand is that you do not need to use a subjective imputation method following rescue medication, as you would for methods that we will discuss. The main disadvantage is that if sufficiently liberal use of effective rescue medication is permitted then there may be little difference in the primary outcome with very different patterns of rescue usage.

We used the Hypothetical estimand for the Agency's Primary Analysis and used the treatment policy estimand in a sensitivity analysis.

**Key Safety Analysis:** Since we did not agree with the applicant's definition of respiratory safety, 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 were analyzed using an ANCOVA model with treatment as the main effect with site group and baseline NRS score as covariates. This analysis used the same approach to missing and post-rescue pain scores as the primary analysis.

**Multiple Comparisons and Multiplicity:**

A combination of a sequential gatekeeping method and the (Hochberg 1988)<sup>3</sup> 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.
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.

## • **Patient Disposition, Demographic, and Baseline Characteristics**

### **i. 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 10). 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.

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<sup>3</sup> Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75(4):800-2.

**Table 10: 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) <sup>a</sup>	79 (94.0)	76 (92.7)	79 (91.9)	79 (96.3)	234 (93.6)	76 (90.5)
Completed study medication <sup>a</sup>	50 (59.5)	68 (82.9)	75 (87.2)	212 (84.8)	212 (84.8)	64 (76.2)
Completed study <sup>a</sup>	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 <sup>b</sup>						
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 <sup>c</sup>						
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 11. 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 11: 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

## ii. 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 12). 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 12: 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) <sup>a</sup>	81 (98.8)	77 (98.7)	80 (97.6)	80 (97.6)	237 (97.9)	83 (100)
Completed study medication <sup>a</sup>	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 <sup>b</sup>						
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 <sup>c</sup>						
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	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 13. 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 13: 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=401
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

- **Efficacy Findings**

**i. Analgesic Efficacy**

**1. Study 3001**

The results of the Applicant’s primary efficacy analysis are shown in Table 14. 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 14: Primary Efficacy Endpoint: 48-Hour Responder Analysis vs Placebo (FAS) (Study 3001)**

<b>Statistic</b>	<b>Placebo N=79</b>	<b>Oliceridine 0.1 mg N=76</b>	<b>Oliceridine 0.35 mg N=79</b>	<b>Oliceridine 0.5 mg N=79</b>	<b>Morphine N=76</b>
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 15. 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 15: 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=79	Oliceridine 0.5 mg N=79	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 the Statistical Analysis section, 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 16: SPID48 Pre-Rescue Carried Forward (Study 3001)**

Statistic	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	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)
Estimated mean SPID (SE)	-43.79 (13.38)	83.15 (13.62)	108.18 (13.37)	135.33 (13.41)	141.01 (13.68)
Estimated mean 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	
Estimated mean 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; SD=standard deviation; SE=standard error  
Source: Applicant's table 1-1, July 31 IR Response

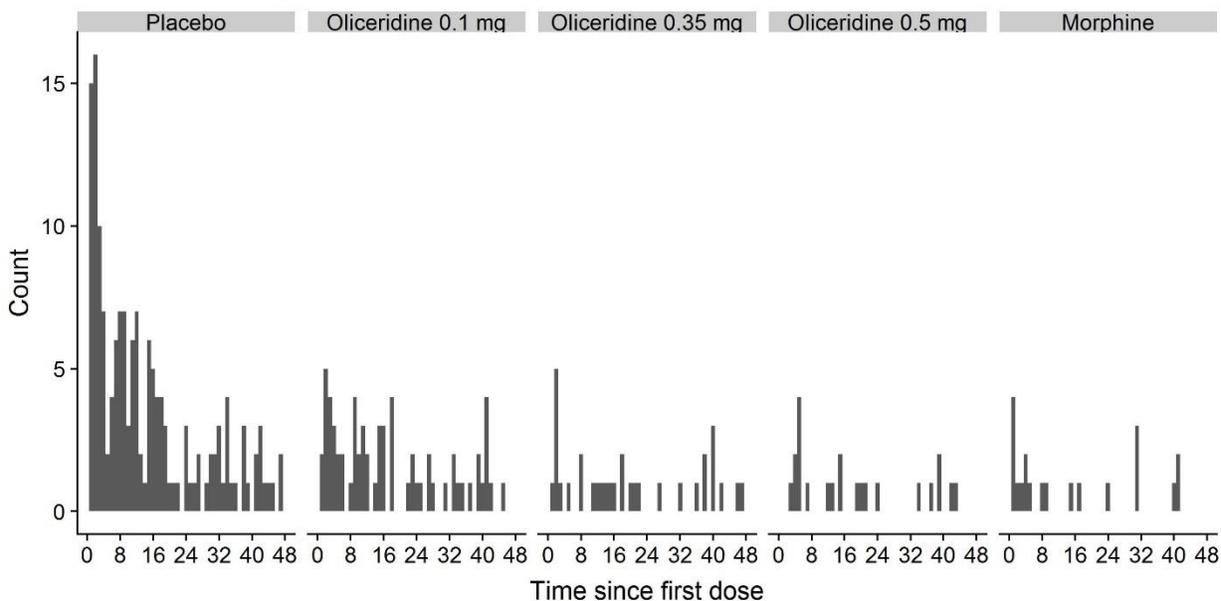
The results in Table 14 and Table 15 depend heavily on the relative patterns of rescue medication use between the different treatment arms. Table 17 shows the number and percentage of patients in each arm who required rescue medications, the mean number of protocol specified (etodolac) doses used and the mean number of other non-protocol specified rescue medication used. The pattern of rescue medication use over time is shown in Figure 2. 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 17: 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 2: Rescue Usage over Time (Study 3001)**



Source: FDA Reviewer

The types of rescue medication used in this study are shown in Table 18. Etodolac, the protocol specified rescue medication was the most commonly used, but approximately 16% of the rescue medication used was not protocol specified.

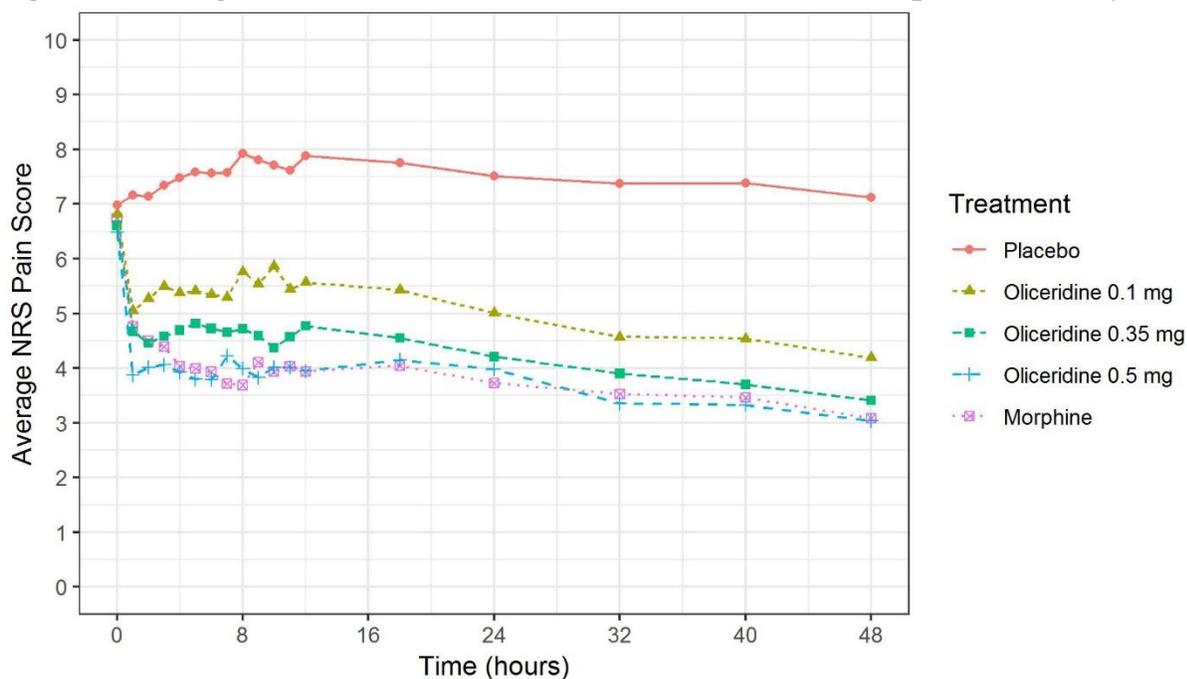
**Table 18: Rescue Medication Breakdown (Study 3001)**

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 3 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 14. 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.

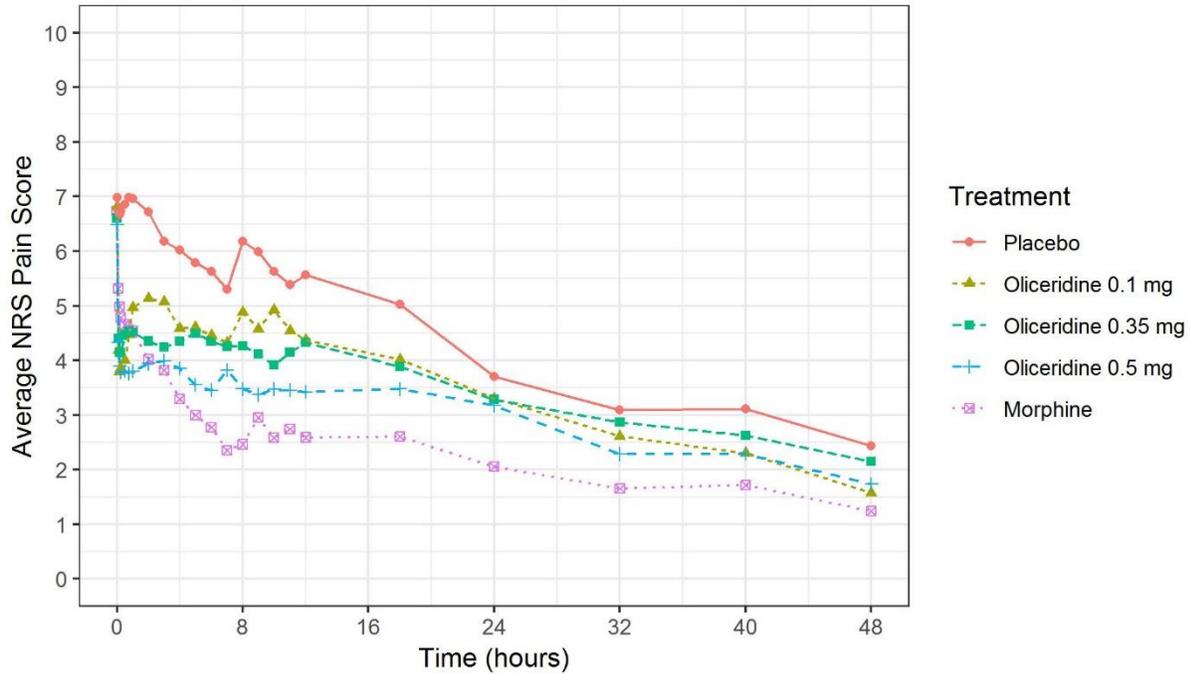
**Figure 3: Average NRS Pain Score Over Time with Post-Rescue Imputation (Study 3001)**



Source: FDA Reviewer

The average observed NRS pain score over time without any imputation is shown in Figure 4. Most of the difference in treatments occurs in the first 24 hours with a relatively small separation between treatment arms after this time.

**Figure 4: Average NRS Pain Score Over Time without Post-Rescue Imputation (Study 3001)**



Source: FDA Reviewer

Table 19 shows an analysis of the SPID48 scores of the data illustrated in Figure 4. In this analysis, there was no imputation following use of rescue and was designed to target the treatment policy estimand discussed in the Statistical Analysis section. 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 was also superior to placebo ( $p<0.01$ ) and to each dose of oliceridine ( $p<0.01$ ,  $p<0.01$ ,  $p=0.03$  for oliceridine 0.1, 0.35, 0.5 mg, respectively).

**Table 19: SPID48 No Imputation Following Rescue (Study 3001)**

Statistic	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	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)
Estimated mean SPID (SE)	110.3 (9.02)	141.2 (9.19)	143.4 (9.02)	167.2 (9.05)	195.3 (9.23)
Estimated mean 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	
Estimated mean 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

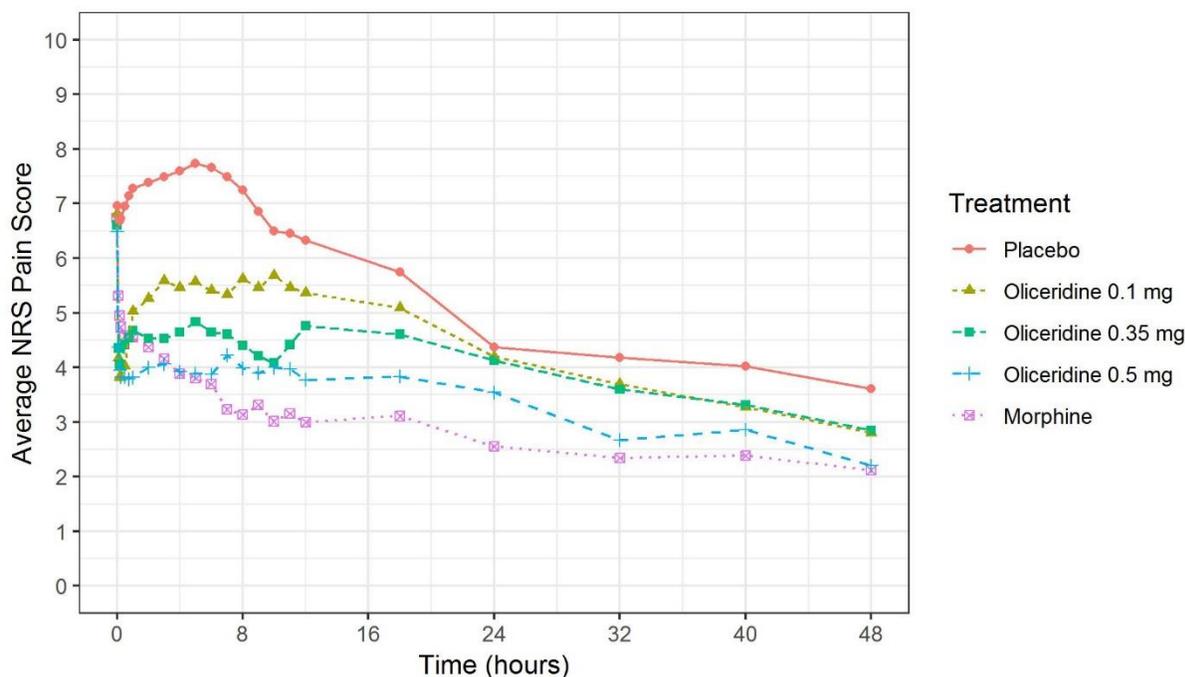
Finally, the results for the FDA primary efficacy analysis are shown in Table 20. In this analysis, the pre-rescue scores are carried forward for 6 hours following the use of rescue. This analysis is intended to evaluate what the pain scores would have been had rescue medication not been available. This analysis is common in acute pain trials and was proposed by the Applicant at the End-of-Phase 2 meeting (See Section 2). 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). However, morphine demonstrated superior pain relief to all three doses of oliceridine ( $p < 0.01$ ,  $p < 0.01$ ,  $p = 0.03$ , respectively). Sensitivity analyses using different imputation windows for rescue use are shown in the Appendix in Table 63 -Table 65. Average NRS pain scores over time with pre-rescue scores carried forward 6 hours are shown in Figure 5.

**Table 20: 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=79	Oliceridine 0.5 mg N=79	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)
Estimated mean SPID (SE)	85.0 (9.50)	131.6 (9.68)	138.1 (9.50)	163.7 (9.53)	192.6 (9.72)
Estimated mean 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	
Estimated mean 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; SD=standard deviation; SE=standard error  
Source: FDA Reviewer

**Figure 5: Average NRS Pain Score Over Time with Pre-Rescue Scores Carried Forward 6 hours (Study 3001)**



Source: FDA Reviewer

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**9. Analyses of this endpoint for the demographic subgroups of interest (age, sex, race, BMI category [ $<25$  vs  $\geq 25$ ], and CYP2D6 metabolizer status [extensive, poor, and unknown]) are shown in the**

This NDA was discussed at an Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) meeting on October 11, 2018. The following is a brief summary of the questions to the committee and surrounding discussions. See the full transcript of the meeting for complete details.

1. **DISCUSSION:** Discuss the efficacy of oliceridine and whether the data provide substantial evidence for efficacy of oliceridine for the proposed indication of the management of acute moderate-to-severe pain in adults for whom an intravenous opioid is warranted.

*Committee Discussion:* Overall, the committee was in agreement that oliceridine showed efficacy compared to placebo in relatively healthy individuals. However, these committee members also agreed that the controlled Phase 3 post-operative study populations were not indicative of complex populations that may have multiple drug interactions and comorbidities, and therefore agreed that the efficacy of oliceridine is not clear compared to an active comparator. Several committee members expressed concern that the dosing recommendations are unclear and there was agreement that there would be challenges treating patients with different conditions and with dose titration in real-world situations. Some committee members stated that there was not substantial evidence of the efficacy of

*the 0.1 mg dose based on the data presented. Other committee members noted their appreciation of the rapid onset of efficacy. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Discuss the safety profile of oliceridine and whether the safety profile of oliceridine is 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. Provide comment on the following issues:
  - a. Safety database
  - b. Hepatic safety
  - c. Respiratory safety
  - d. QT prolongation

***Committee Discussion:** The committee's general consensus was that oliceridine is relatively safe overall. Some committee members noted that the agonist-bias that was displayed appeared to have potential benefits, as providers are looking for new ways to find a tailored approach to treatment of acute pain. Several members of the committee expressed concerns of possible safety signals that could arise with higher doses, comorbid conditions, multimodal therapy, and use of concomitant medications, including other opioids, in real-world situations. One committee member noted that the decreased incidence of vomiting compared to morphine was notable. In regards to hepatic safety, overall, the committee was in agreement that there wasn't much concern for a hepatic safety signal. In terms of respiratory safety, some committee members made note that the hypercapnic testing that was performed in young healthy volunteers does not indicate a lower risk of respiratory depression compared to morphine. One member noted the decreased  $\beta$ -arrestin activation shown in animal models is suggestive of decreased respiratory depression, but other members noted limitations in the available clinical data. Some committee members noted there was insufficient data on QT prolongation and agreed more ECG data were needed. Other committee members agreed that real world implications were unclear, as there was a disconnect between pharmacokinetic and QT effects. One committee member added that although there were modest effects on QT prolongation used in the thorough QT study, the effects of the 40 mg per day in the proposed labeling is unknown. Several committee members expressed concerns regarding the available safety database that doesn't appear to represent what will be used in terms of doses in practice or the types of patients who are anticipated to receive the drug. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** 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.

***Committee Discussion:** Overall, the committee found no superiority for abuse deterrence and considered Schedule II appropriate for oliceridine. Some committee members agreed that people may presume that oliceridine is a safer medication, which may increase its abuse potential. One committee member added that healthcare*

*professionals managing patients with opioid use disorders may improperly perceive oliceridine as safer, which could limit vigilance and amplify public health concern. Another committee member added that abuse of oliceridine may lead to unforeseen adverse effects with respiratory depression, hepatic pathology, and QT prolongation. Please see the transcript for details of the committee discussion.*

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

**Vote Result:**            Yes: 7            No: 8            Abstain: 0

**Committee Discussion:** *The committee did not reach a general consensus on the approval of the proposed dose of oliceridine for the proposed indication of the management of moderate- to-severe acute pain in adults for whom an intravenous opioid is warranted. Committee members who voted “Yes” recommended inclusion of “not safer than traditional opioids” on the label and that further studies be required. Considerations in favor of recommending approval included a potentially favorable PK data, no active metabolites, decreased  $\beta$ -arrestin activation, and positive GI profile with decreased nausea and vomiting. Committee members who voted “No” stated that the benefit/risk profile was not favorable enough, with a need for more data regarding demographic variability, including patients with comorbidities, drug interactions, and real-world dosing. Some members voiced concerns that the perception of oliceridine being safer may lead to increased abuse and downstream problems. Several committee members discussed the need for additional data. One member suggested a study showing decrease in length of hospital stay (time to discharge) as possible compelling data for approval. Please see the transcript for details of the committee discussion.*

## 10. Pediatrics

The Applicant is requesting deferral for the pediatric assessment for ages birth to <17 years until oliceridine is determined to be safe and effective in the adult population for the indication of management of moderate-to-severe acute pain. The Applicant plans to fulfill the Pediatric Research Equity Act (PREA) requirement through the following studies in pediatric patients with acute pain as proposed in an agreed June 22, 2017 Initial Pediatric Study Plan (iPSP):



(b) (4)

The oliceridine pediatric plan was discussed at the Pediatric Review Committee (PeRC) meeting. While there were no significant concerns regarding the pediatric plan, given that the application will receive a complete response, additional modifications to the plan may occur in the future.

## 11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**

The NDA submission included completed Form 3454 “Certification: Financial Interests and Arrangements of Clinical Investigators” in compliance with 21 CFR part 54. This certified that the Applicant had not entered into any financial arrangements with the listed clinical investigators as defined in 21 CFR 54.2(a), that no clinical investigator was required to disclose any financial interests as defined in 21 CFR 54.2(b), and that no listed investigator was the recipient of significant payments from the Applicant as defined in 21 CFR 54.2(f). The Applicant stated that no investigators were full- or part-time employees of Trevena, Inc.

- **Other Good Clinical Practice (GCP) issues**

The clinical studies were conducted in accordance with Good Clinical Practices and a statement of compliance with Good Clinical Practices is located in each clinical study report.

- **Office of Scientific Investigations (OSI) audits**

According to Dr. Damon Green’s July 30, 2018, Office of Scientific Investigations (OSI) Clinical Inspection Summary review, inspections were conducted at the clinical sites of Dr. Joseph S. Gimbel (Site 10030 for Protocol CP130-3001 and 3002) and Dr. Artin Nazarian (Site 10001 for Protocol 3002). These sites were selected because of a large patient enrollment in the combined sites. All inspections have been completed and the final classification of the inspections was No Action Indicated (NAI). Inspection findings supported the acceptability of the clinical data submitted.

- **Any other outstanding regulatory issues**—Not applicable

## 12. Labeling

- **Proprietary name**

Initially, the proposed proprietary name was Olinvo, but this was found to be unacceptable. Currently, the proposed proprietary name for oliceridine is Olinvyk. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Medication Error Prevention and Risk Management (OMEPRM) and was found to be acceptable. As noted in the August 9, 2018 Grant Proprietary Name letter, if any of the proposed product characteristics as stated in the June 26, 2018 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

- **Physician labeling**

Not applicable as the recommended action is complete response.

### **13. Postmarketing Recommendations**

As the recommended regulatory action is complete response, there are no recommendations postmarketing requirements or REMS.

### **14. Recommended Comments to the Applicant**

#### **Clinical Deficiencies**

##### **1. Deficiency**

The submitted data are not adequate to support the safety of oliceridine for the management of moderate-to-severe acute pain in adult patients for whom an IV opioid is warranted due to concerns related to QT prolongation.

Your thorough QT (tQT) study, CP130-1008, showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset (3 mg: 6.6 ms [upper 90% CI 8.9 ms]; 6 mg: 11.6 ms [13.7 ms]). The delayed onset of QTcF prolongation suggests that the QTcF prolongation may not be mediated via direct inhibition of the hERG potassium channel by oliceridine. The proposed mechanism for the delayed onset of the QTcF prolongation observed with oliceridine remains unclear.

In your Phase 3 studies, only limited ECG monitoring was obtained in patients after baseline (1, 24, and 48-hours post-loading dose for Study 3001; and 1 and 24 hours for Studies 3002; and 1 hour and every 24 hours of oliceridine treatment in Study 3003). Further, you have proposed a wide range of doses up to a maximum daily dose of 40 mg and oliceridine would be used in clinical situations in which patients may receive other drugs that can prolong the QTc.

Interpretation of the ECG data from your clinical studies has limitations. Specifically, none of the studies were designed to characterize the QT prolonging effects of oliceridine. In Study 3003, there was a lack of ECG replicates at each nominal timepoint and lack of a control arm. Despite these limitations, there were cases of QTc prolongation in Study 3003.

You have not provided adequate data to support that the QT prolonging effects of oliceridine can be mitigated by labeling or monitoring.

#### **Information Needed to Resolve the Deficiency**

To support the safety of oliceridine for the management of moderate-to-severe acute pain in adult patients for whom an IV opioid is warranted, provide data from a randomized active-controlled study to address the safety concern of QT prolongation at the maximum proposed daily dose. The study should include 24-hour Holter monitors. Replicate QT measurements could be extracted every hour from the Holter monitors and compared to the control group. The study

should be of adequate duration and sample size to allow reliable evaluation of oliceridine's QT prolongation effects.

## 2. Deficiency

The submitted exposure database is not of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. You have proposed a maximum daily dose of 40 mg [REDACTED] (b) (4) You were advised at the End-of-Phase 2 and pre-NDA meetings that the safety database needed to include at least 350 patients exposed to the highest doses for the longest duration of use. In your Phase 2 and Phase 3 studies, the highest dose that at least 350 patients were exposed to during the first 24 hours was 27 mg of oliceridine. The highest dose with the longest actual duration that had at least 350 patients exposed was 37.2 mg administered over an actual duration of at least 35.5 hours.

### Information Needed to Resolve the Deficiency

Provide an exposure database that is of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. Specifically, the safety database must include at least 350 patients exposed to the highest dose proposed for the longest duration of use indicated in the labeling.

## Nonclinical Deficiencies

### 3. Deficiency

You have not provided adequate data to confirm that levels of TRV0109662, a major human metabolite, have been adequately characterized for potential embryo-fetal effects in either the rat or the rabbit embryo-fetal development study. Based on the data obtained to date, this metabolite does not appear to be formed at acceptable levels in the rat compared to the human, you have not provided any data to document that the metabolite is formed in rabbit, and the existing analytical assays for human and rat plasma levels of TRV0109662 do not appear to be consistently reproducible (failed rat incurred sample reanalysis for pivotal study).

### Information needed to resolve this deficiency:

Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated reproducible pharmacokinetic data to support your 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 at the proposed maximum recommended human dose of 40 mg/day.”

## Product Quality

### 4. Deficiency

The analytical methods used for controlling identified leachables are required to be validated. Validation reports for the analytical methods used for the leachables study have not been provided to the Agency.

### Information Needed to Resolve the Deficiency:

Validate your newly developed analytical methods for leachables as per the ICH Q2 recommendation, and provide the validation reports to the Agency. Further, also provide

the data for the leachables found in the stability samples that are analyzed by your newly developed methods.

Appendix in Table 73 and Table 74 and in Figure 22-Figure 27. The estimates for each demographic category were obtained by repeatedly fitting the ANCOVA model used in the primary analysis with the particular demographic factor included. The estimates and confidence intervals were obtained by multiplying the resulting parameter estimates for each model by the overall average covariate value (site group and baseline pain score). In general, there were no concerns noted in these analyses.

## 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 21 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 21: 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 22. 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 22: 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 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 23: 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)
Estimated mean SPID (SE)	42.90 (6.13)	64.09 (6.26)	83.11 (6.12)	84.92 (6.15)	94.04 (6.08)
Estimated mean 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	
Estimated mean 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 24. 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.

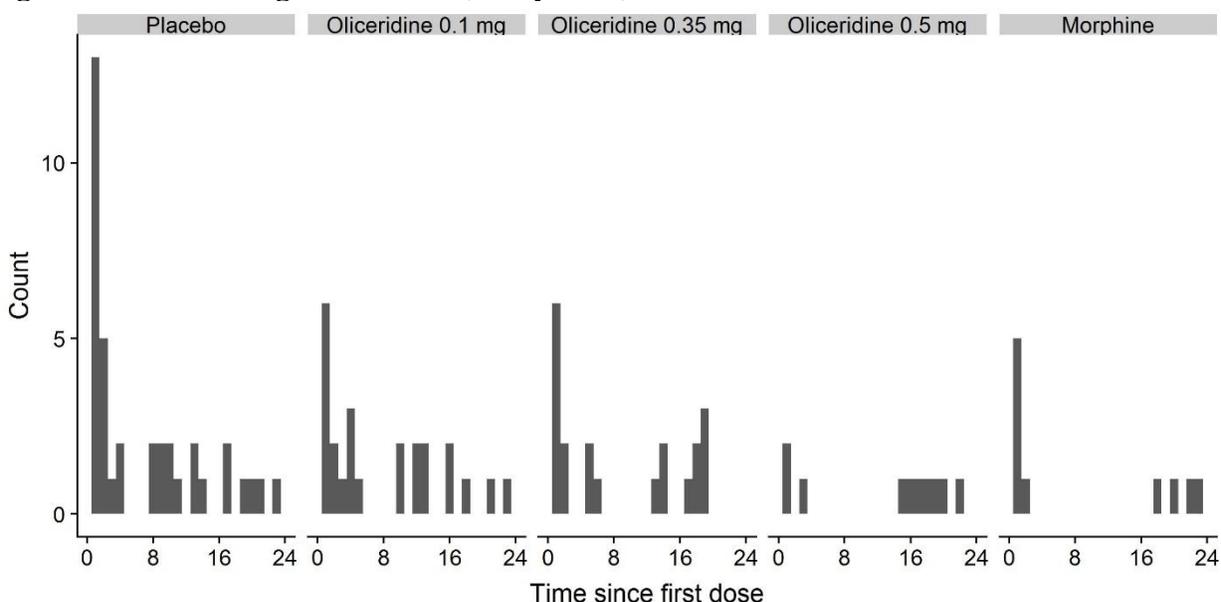
**Table 24: Rescue Medication Usage (Study 3002)**

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 6 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 6: Rescue Usage over Time (Study 3002)**



Source: FDA Reviewer

The types of rescue medication used are shown in Table 25. The majority of rescue medication used in the study was etodolac. Approximately 15% of the rescue medication was non-protocol specified.

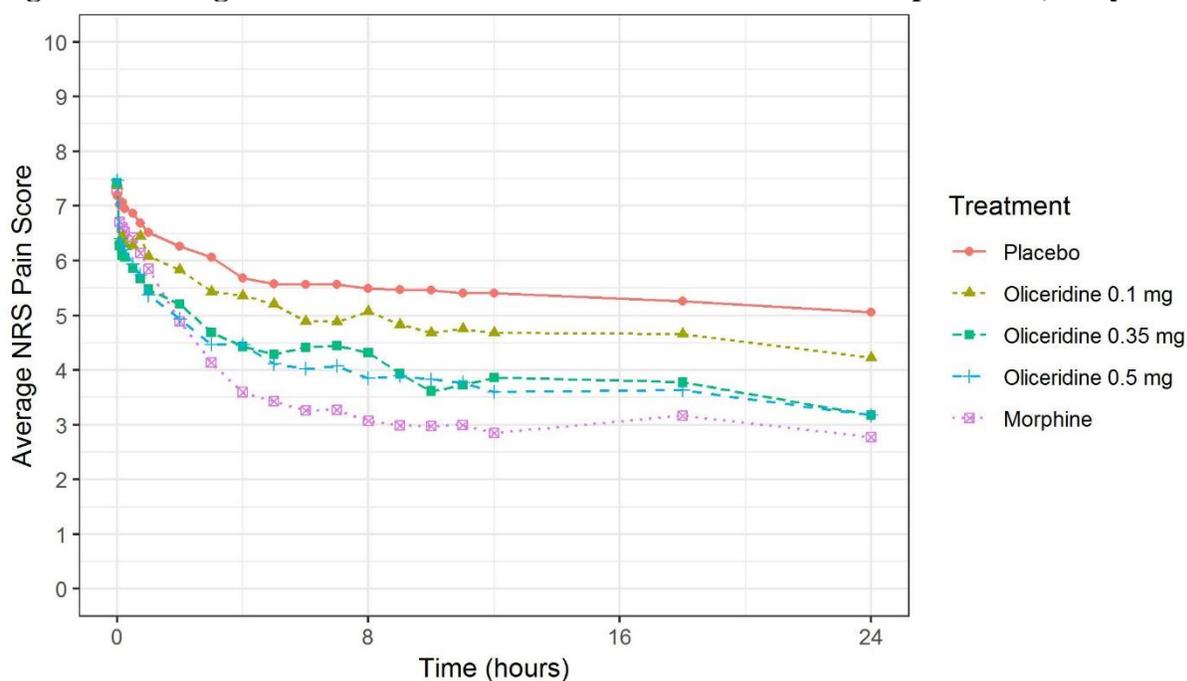
**Table 25: Rescue Medication Breakdown (Study 3001)**

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 7. 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.

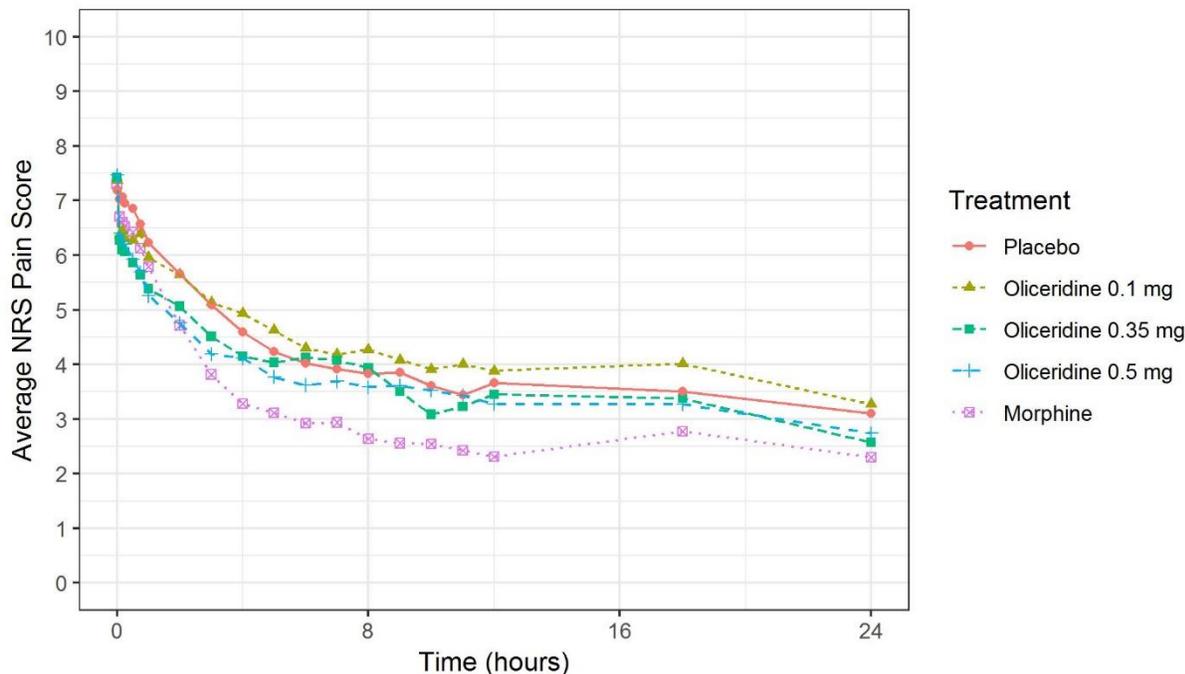
**Figure 7: Average NRS Pain Score Over Time with Post-Rescue Imputation (Study 3002)**



Source: FDA Reviewer

The observed pain scores over time without imputation following rescue are shown in Figure 8. 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 8: Average NRS Pain Score Over Time without Post-Rescue Imputation (Study 3002)**



Source: FDA Reviewer

The SPID analysis corresponding to Figure 8 is shown in Table 26. In this analysis, observed pain score are used where available. Intermittent missing data were imputed using linear interpolation and post-discontinuation data were 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 26: SPID24 No Imputation Following Rescue (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)					
Estimated mean SPID (SE)	82.4 (4.36)	79.6 (4.45)	91.6 (4.39)	94.3 (4.41)	103.9 (4.32)
Estimated mean 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	
Estimated mean 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 27. 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 66-Table 68. The average NRS pain score over time with pre-rescue scores carried forward 6 hours is shown in Figure 9.

**Table 27: SPID24 Pre-Rescue Scores Carried Forward 6 hours (Study 3002)**

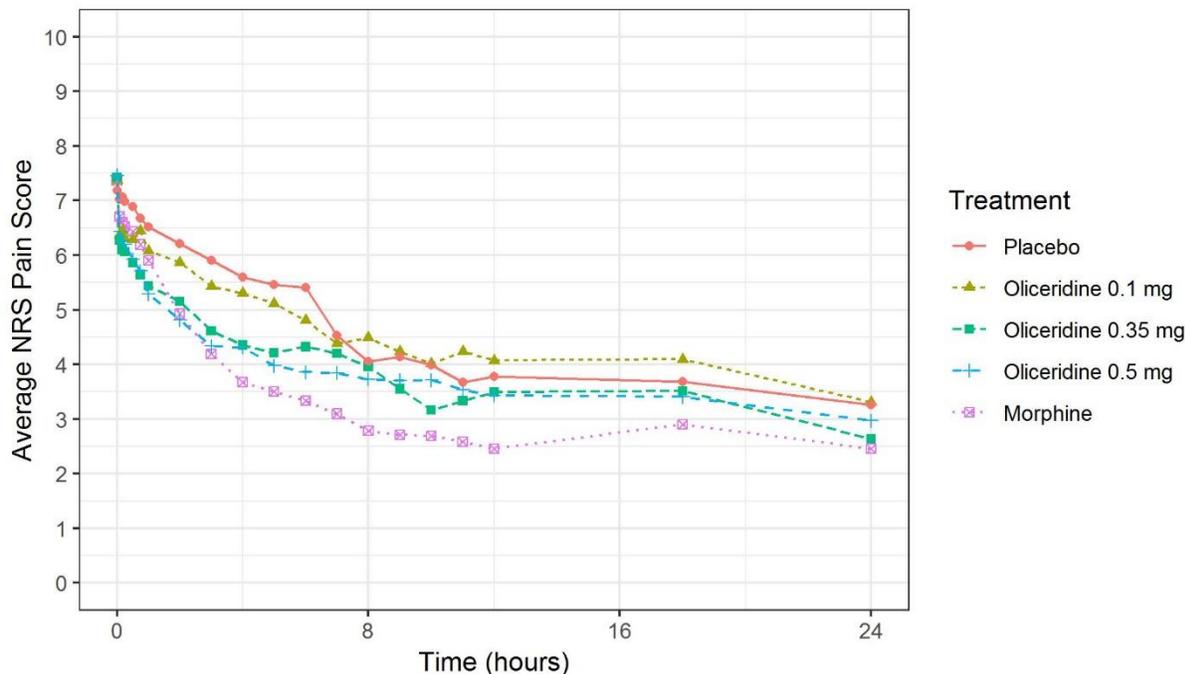
Statistic	Placebo N=81	Oliceridine 0.1 mg N=77	Oliceridine 0.35 mg N=80	Oliceridine 0.5 mg N=80	Morphine N=83
Mean (SD)	70.4 (37.9)	74.4 (45.4)	88.0 (44.5)	93.3 (41.9)	100.6 (48.6)
Estimated mean SPID (SE)	74.8 (4.56)	76.8 (4.66)	89.72 (4.6)	94.0 (4.61)	103.0 (4.52)
Estimated mean diff. vs placebo (SE)		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	
Estimated mean 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 9: 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 of interest (age category [ $\geq 18$  to  $< 65$  vs.  $\geq 65$ ], sex, race, BMI category [ $< 25$  vs.  $\geq 25$ ], and CYP2D6 metabolizer status [extensive, poor, and unknown]) are shown in the Appendix in Table 75 and Table 76 and in Figure 28-Figure 33. The estimates for each demographic category were obtained by repeatedly fitting the ANCOVA model used in the primary analysis with the particular demographic factor included. The estimates and confidence intervals were obtained by multiplying the resulting parameter estimates for each model by the overall average covariate value (site group and baseline pain score). As with Study 3001, there were no concerns noted in these analyses.

## ii. 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 subjectively defined respiratory safety events (RSEs) as discussed in Section 1.1. This subjectivity made it impossible to determine whether the Applicant's definition of an RSE or a small change in RSE duration was clinically meaningful.

Regardless of this disagreement, the results of the analyses for oliceridine were not statistically different from morphine with respect to this endpoint.

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<sub>2</sub> or cumulative duration of supplemental O<sub>2</sub> 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 8). In addition to these analyses in the efficacy studies, the Applicant also 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.

### 1. Study 3001

The results of the analysis of the expected cumulative duration of RSEs are shown in Table 28. 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 28: 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=79	Oliceridine 0.5 mg N=79	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 3001 are provided in Table 29. 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 29: 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 69 and Table 70.

## 2. Study 3002

Similar analyses were performed for Study 3002. Table 30 shows the analyses of the cumulative duration of RSEs and Table 31 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 30: 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 31: 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

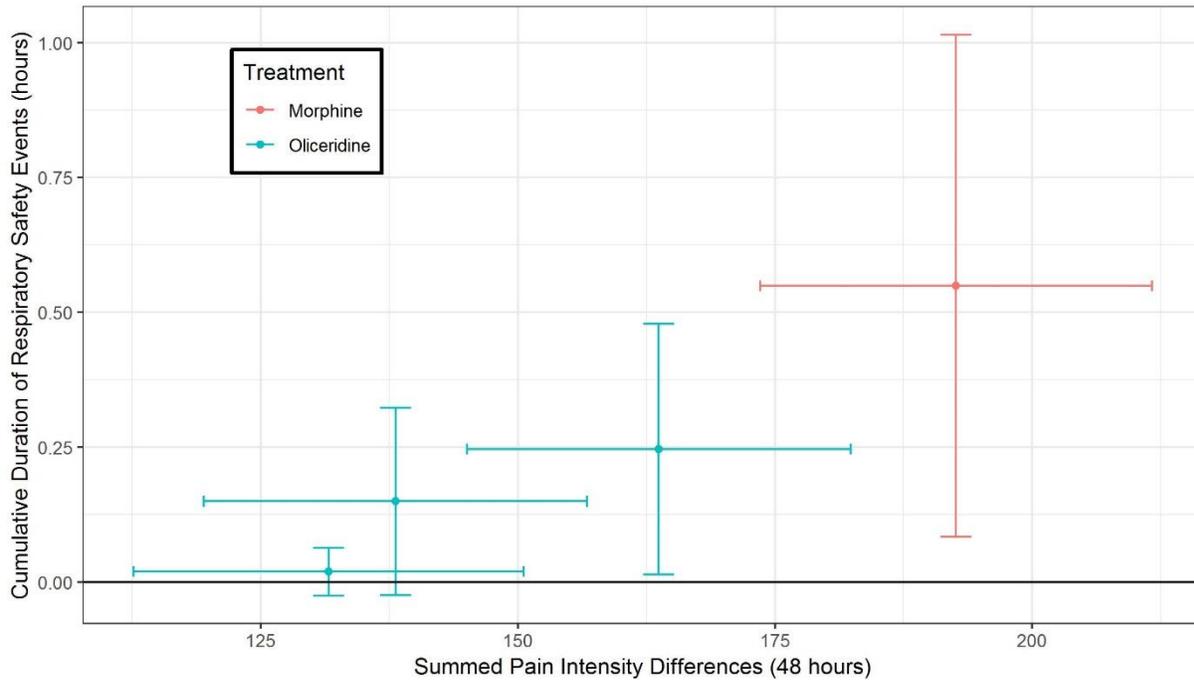
\*Using the Hochberg method gives a threshold of 0.0167 for significance

Similar analyses of the supplemental oxygen usage is shown in the Appendix in Table 71 and Table 72.

### iii. Quantitative Efficacy/Safety Considerations

A key consideration for comparative safety claims versus an active drug is whether there is a similar level of efficacy. Even though we did not agree with the Applicant's definition of respiratory safety, a comparison between the respiratory safety and efficacy was conducted. Figure 10 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 20), with the horizontal bars representing the span of the confidence intervals. The location is determined by the estimated cumulative duration presented in Table 28 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.

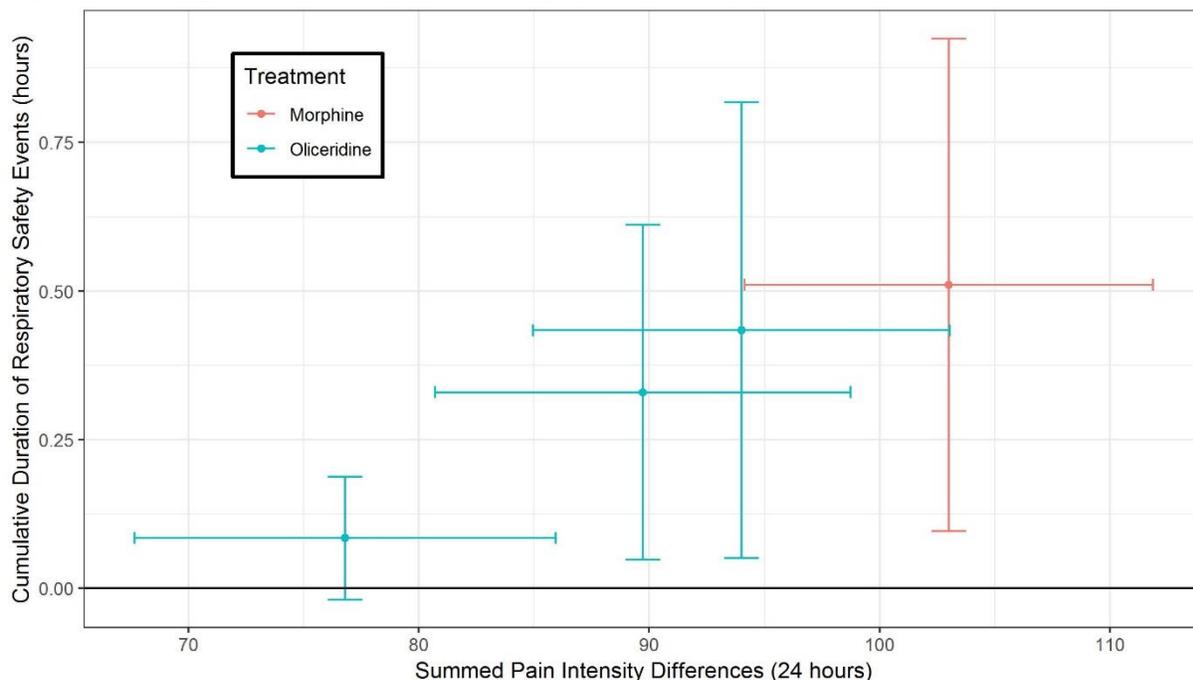
**Figure 10: Respiratory Safety vs Efficacy (Study 3001)**



Source: FDA Reviewer

Figure 11 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 27 for the x-axis and information regarding the cumulative duration of RSEs from Table 30 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 11: Respiratory Safety vs Efficacy (Study 3002)**



Source: FDA Reviewer

## 8. Safety

- **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 1 and Table 2. 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 1 and Table 2, 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 32). 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 32. 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  $\leq 4$  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 32: 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	<ul style="list-style-type: none"> <li>•By treatment regimen (oliceridine 0.1, 0.35, and 0.5 mg)</li> <li>•By oliceridine cumulative exposure quartiles</li> </ul>
All Phase 3	3001, 3002, and 3003	Phase 3 controlled and open-label studies	<ul style="list-style-type: none"> <li>•By treatment regimen: placebo, oliceridine, morphine</li> </ul>
All Phase 2 and Phase 3	2001, 2002, 2004, 3001, 3002, and 3003	Controlled and open-label studies	<ul style="list-style-type: none"> <li>•By treatment regimen: placebo, oliceridine, morphine</li> <li>•By oliceridine cumulative exposure quartiles</li> </ul>
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

- **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 33. 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 33: 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
<b>Exposure duration (hours)<sup>a</sup></b>			
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 <sup>b</sup>
<b>Cumulative exposure (mg)<sup>c</sup></b>			
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 (b) (6) 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 34, 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 34).

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 34: 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
<b>Cumulative exposure (mg)<sup>a</sup></b>						
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
<b>Cumulative exposure quartile, n (%)</b>						
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)	--
<b>Cumulative exposure (mg) in the first 24 hours<sup>a</sup></b>						
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
<b>Total number of demand doses</b>						
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)
<b>Total number of supplemental doses</b>						
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)

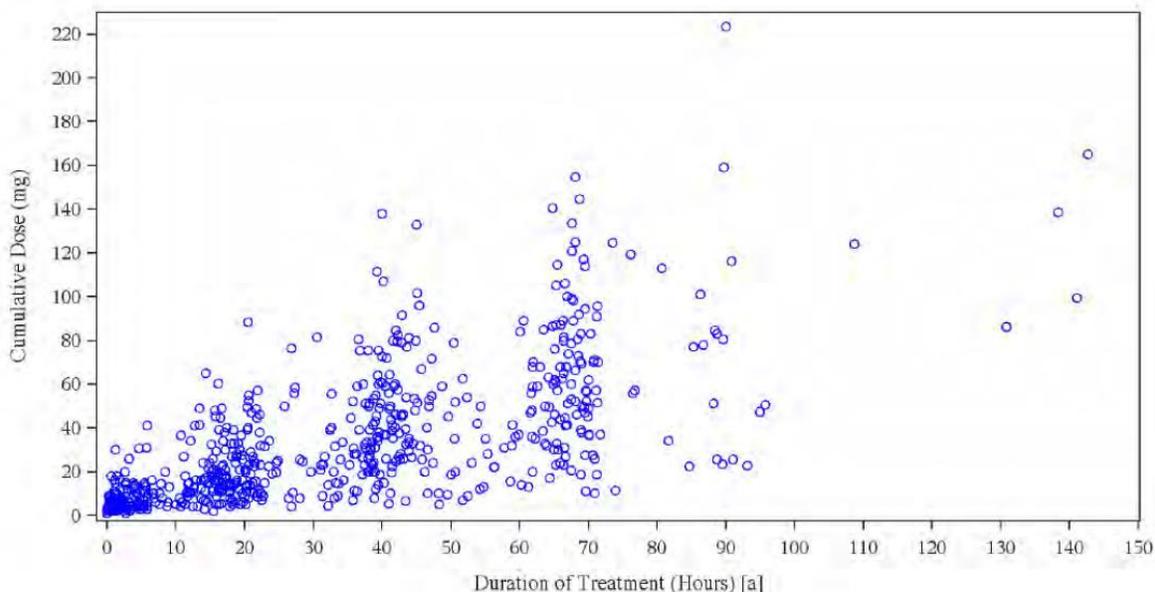
Abbreviations: max=maximum; min=minimum; OLI=oliceridine; Q=quartile; SD=standard deviation;

<sup>a</sup> 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 12.

**Figure 12: Cumulative Dose by Duration of Treatment (Study 3003 Safety Analysis Population)**



Note: Each dot in the graph represents a patient.

<sup>a</sup> 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

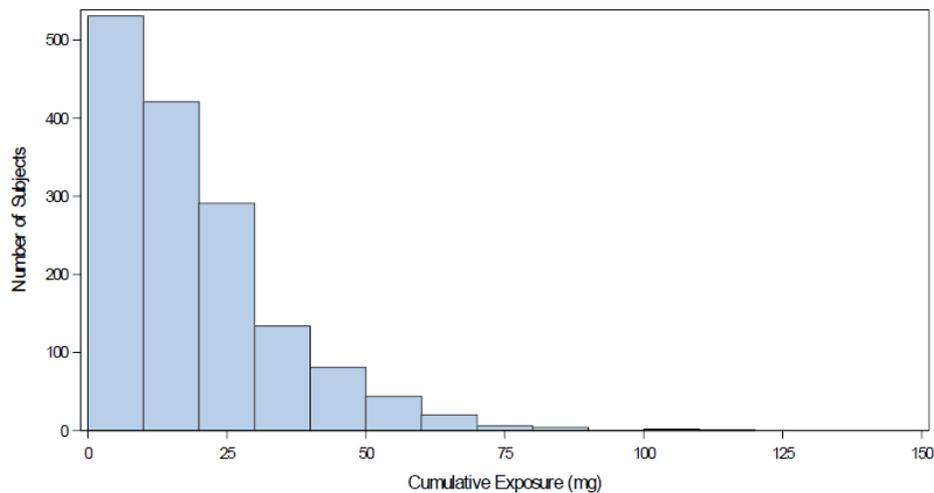
A significant consideration during the review cycle was whether the size of the safety database was adequate. Prior to submission of the NDA, the Applicant was told at the End-of-Phase 2 meeting and the pre-NDA meeting that they would need at least 350 patients exposed to the highest intended doses for the longest expected duration of use.<sup>4</sup> Figure 13 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.

<sup>4</sup> <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 13: 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

The complexity of the Applicant's proposed dosing is shown below:

## 2.2 Titration and Maintenance of Therapy

Individually titrate [BRANDNAME] to a dose that provides adequate analgesia and minimizes adverse reactions. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage.

### Titration Phase

The initial dose of [BRANDNAME] 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 [BRANDNAME].

### Maintenance Phase

Maintenance of analgesia is generally achieved with [BRANDNAME] 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 [see *Adverse Reactions (6.1) and Clinical Studies (14)*].

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.

Source: Applicant's Proposed Draft Labeling, NDA submission, submitted 7/6/18

During the review, it was determined by the review team that the available clinical data were not adequate to support this proposed dosing. The primary concern was the limited data available for patients dosed at the highest proposed daily dose. Additional safety data are needed to adequately assess the safety of oliceridine in the proposed patient populations at the proposed maximum doses.

- **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 35, 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 35: 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 ( $\leq 4$  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 36. 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 36: Patients with Treatment-Emergent SAEs in Study 3003**

#	Patient ID	Age (yrs)/Sex	Cumulative dose group	Cum exp SAE start	Preferred Term	General Category <sup>a</sup>
1	(b) (6)	49/F	$\leq 4$ mg	2 mg	Respiratory Depression	Opioid-related

2	(b) (6)	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	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 37).

**Table 37: Serious Adverse Events by Oliceridine Cumulative Exposure Quartile (All Phase 2 and Phase 3 Population Safety Analysis Set)**

	<b>OLI Q1</b> N=383 n (%)	<b>OLI Q2</b> N=390 n (%)	<b>OLI Q3</b> N=381 n (%)	<b>OLI Q4</b> 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 38, 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 38: TEAEs leading to Discontinuation by SOC and PT for Studies 3001 and 3002 (FAS)**

Study 3001					
System Organ Class Preferred Term	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 leading to early study medication discontinuation <sup>a</sup>	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 Preferred Term	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 leading to early study medication discontinuation <sup>a</sup>	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.

<sup>a</sup> 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 ( $\leq 4$  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 39.

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). The TEAEs leading to discontinuation that appeared allergic are notable. During the Advisory Committee meeting, there was some discussion about whether oliceridine would provide an option for patients who have allergies to other IV opioids. While it is not clear if patients with allergies to other opioids would also have allergies to oliceridine, the safety data indicates that there are patients who have allergic adverse events when exposed to oliceridine. There were also TEAEs related to QT prolongation and increased aminotransferases, discussed later in this safety section.

**Table 39: Patients with TEAEs Leading to Early Study Medication Discontinuation in Study 3003**

#	Patient ID	Age (yrs)/Sex	Cumulative dose group <sup>b</sup>	Cum exp SAE start	Preferred Term	General Category <sup>a</sup>
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 activities; TEAE=treatment-emergent adverse event; Tx=treatment; yrs=years

<sup>a</sup> Categories were reviewer generated

<sup>b</sup> 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 40, 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 40: Discontinuations due to Adverse Events by Oliceridine Cumulative Exposure Quartile (All Phase 2 and Phase 3 Population Safety Analysis Set)**

	<b>OLI Q1</b> N=383 n (%)	<b>OLI Q2</b> N=390 n (%)	<b>OLI Q3</b> N=381 n (%)	<b>OLI Q4</b> 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 41 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 41: 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 42, 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 42: Adverse Events by Oliceridine Cumulative Exposure Quartile (All Phase 2 and Phase 3 Population Safety Analysis Set)**

	<b>OLI Q1</b> N=383 n (%)	<b>OLI Q2</b> N=390 n (%)	<b>OLI Q3</b> N=381 n (%)	<b>OLI Q4</b> 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  $\geq 20xULN$  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 43 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.

**Table 43: 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 $\geq$ 3xULN	0	0	2 (2.5)	1 (1.3)	1 (1.3)
ALT $\geq$ 3xULN	1 (1.3)	0	1 (1.3)	1 (1.3)	1 (1.3)
AST or ALT $\geq$ 3xULN	1 (1.3)	0	2 (2.5)	1 (1.3)	1 (1.3)
AST $\geq$ 5xULN	0	0	1 (1.3)	0	1 (1.3)
ALT $\geq$ 5xULN	0	0	1 (1.3)	0	1 (1.3)
AST or ALT $\geq$ 5xULN	0	0	2 (2.5)	0	1 (1.3)
Bilirubin $\geq$ 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 $\geq$ 3xULN	0	2 (2.6)	2 (2.5)	0	3 (3.7)
ALT $\geq$ 3xULN	0	3 (3.9)	3 (3.8)	1 (1.3)	2 (2.4)
AST or ALT $\geq$ 3xULN	0	3 (3.9)	3 (3.8)	1 (1.3)	3 (3.7)
AST $\geq$ 5xULN	0	2 (2.6)	2 (2.5)	0	1 (1.2)
ALT $\geq$ 5xULN	0	2 (2.6)	2 (2.5)	0	1 (1.2)
AST or ALT $\geq$ 5xULN	0	2 (2.6)	2 (2.5)	0	2 (2.4)
AST $\geq$ 10xULN	0	2 (2.6)	1 (1.3)	0	0
ALT $\geq$ 10xULN	0	2 (2.6)	1 (1.3)	0	0
AST or ALT $\geq$ 10xULN	0	2 (2.6)	1 (1.3)	0	0
AST $\geq$ 20xULN	0	0	0	0	0
ALT $\geq$ 20xULN	0	1 (1.3)	0	0	0
AST or ALT $\geq$ 20xULN	0	1 (1.3)	0	0	0
Bilirubin $\geq$ 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 44), it was noted that there was a higher percentage of patients with AST or ALT  $\geq$ 10xULN, AST or ALT  $\geq$ 20xULN, and bilirubin  $\geq$ 10xULN in the total oliceridine group (0.5%, 0.3%, and 0.7%) respectively, compared to placebo (0) or morphine (0).

**Table 44: 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 $\geq$ 3xULN	2 (0.8)	23 (1.5)	5 (1.6)
ALT $\geq$ 3xULN	4 (1.6)	24 (1.6)	5 (1.6)
AST or ALT $\geq$ 3xULN	4 (1.6)	32 (2.1)	6 (2.0)
AST $\geq$ 5xULN	1 (0.4)	12 (0.8)	3 (1.0)
ALT $\geq$ 5xULN	1 (0.4)	14 (0.9)	2 (0.7)
AST or ALT $\geq$ 5xULN	1 (0.4)	17 (1.1)	4 (1.3)
AST $\geq$ 10xULN	1 (0.4)	7 (0.5)	1 (0.3)
ALT $\geq$ 10xULN	0	7 (0.5)	1 (0.3)
AST or ALT $\geq$ 10xULN	1 (0.4)	8 (0.5)	1 (0.3)
AST $\geq$ 20xULN	0	3 (0.2)	0
ALT $\geq$ 20xULN	0	4 (0.3)	0
AST or ALT $\geq$ 20xULN	0	4 (0.3)	0
Bilirubin $\geq$ 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<sup>5</sup> 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.

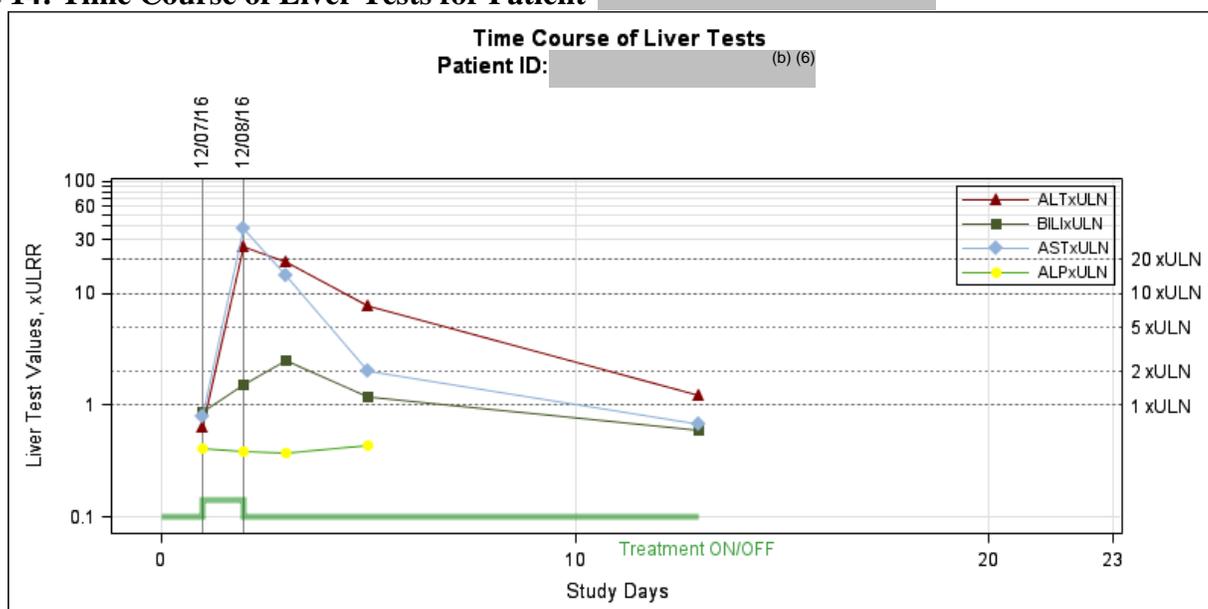
In the clinical, program, there were two patients with an elevated aminotransferase  $\geq$ 3xULN and concurrent bilirubin  $\geq$ 2xULN. Both patients were in Study 3003 and received oliceridine. These narratives were reviewed by the Agency hepatology consultant, who did not think there was definite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

<sup>5</sup> <https://www.fda.gov/downloads/guidances/UCM174090.pdf>

The first patient ( (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 14. 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  $\geq 2$ xULN (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 14: Time Course of Liver Tests for Patient (b) (6)

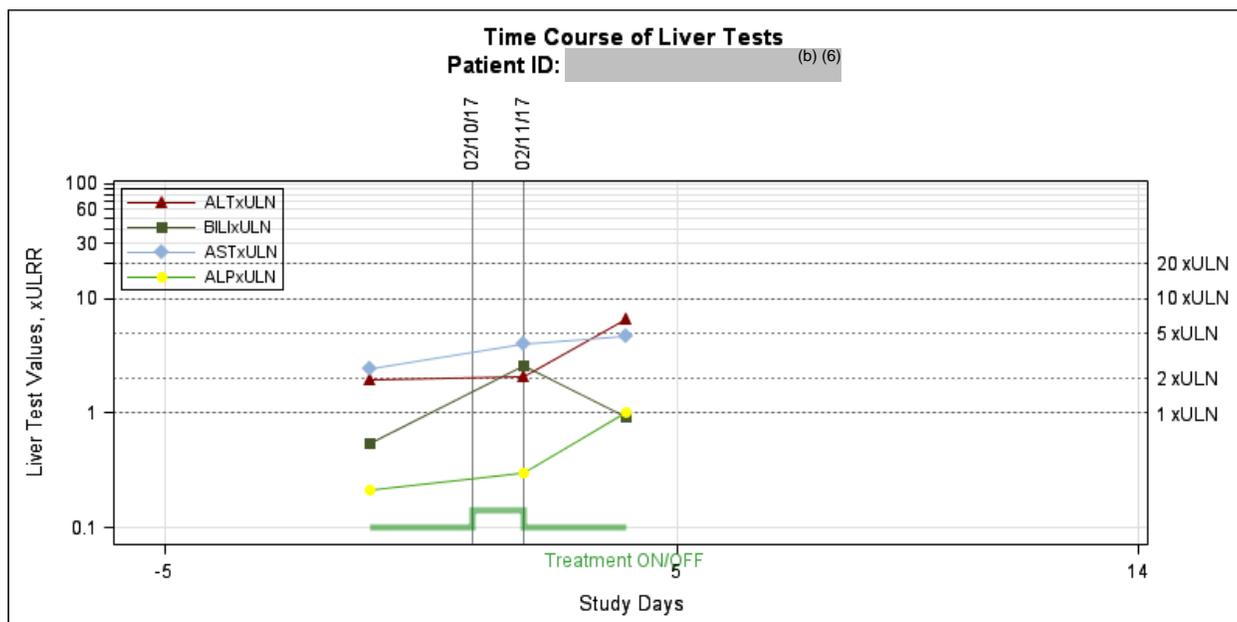


Source: OSE Hepatology Consult

The second patient, ( [REDACTED] <sup>(b) (6)</sup> ), 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 15.

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  $\geq 2$ xULN on Day 2, further rising to  $\geq 6$ xULN on Day 4. AST and ALP were also elevated on Day 4. The bilirubin level was  $\geq 2$ xULN 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 15: 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.

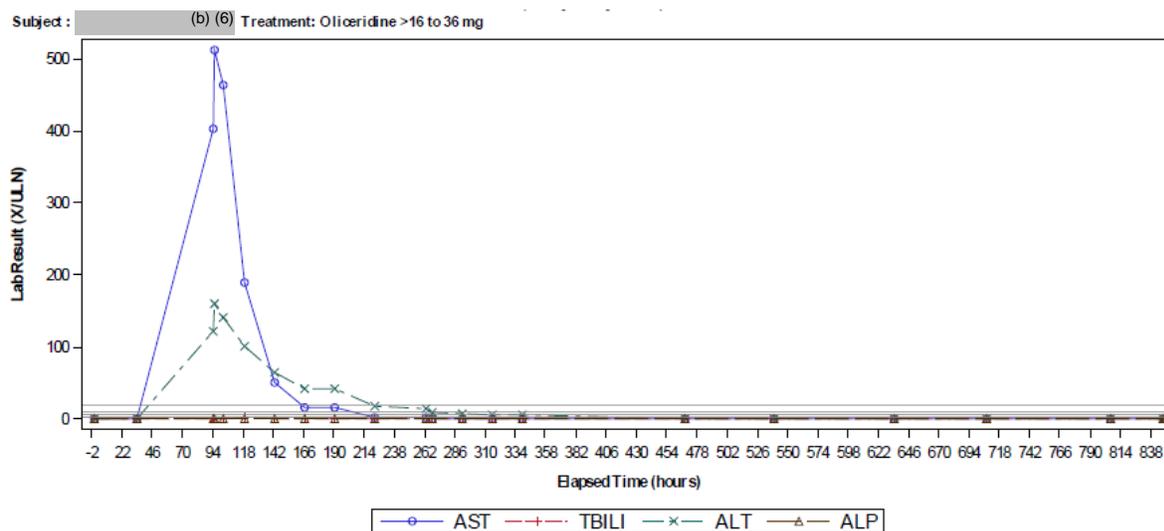
Peri-operative medications included APAP (acetaminophen), celecoxib, fentanyl, propofol, cefazolin, vancomycin, and warfarin.

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 hepatitis 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 centrilobular 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 16: 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  $\geq 10xULN$  may suggest more potential for hepatic injury. Therefore, the Agency placed particular emphasis on evaluating data for those patients with transaminases  $\geq 10xULN$ .

In the pooled Phase 2 and Phase 3 studies, four patients ( [REDACTED] (b) (6) ) experienced transaminases  $\geq 20xULN$ . 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  $\geq 10xULN$  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  $\geq 3xULN$  with total bilirubin  $\geq 2xULN$  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 development 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<sub>50</sub> for oliceridine in the hERG assay (Study No.110520.USF) was 2.2 μM, approximately 367 times the K<sub>i</sub> at the mu opioid receptor, 27 times the free C<sub>max</sub> after 3 mg IV infusion (CP130-1008), and 43 times the estimated free C<sub>max</sub> of the currently proposed maximum recommended human dose (MRHD) of 40 mg/day. Weak inhibition of hCav 1.2 (IC<sub>50</sub> of 39.6 μM) and of hNav1.5 (IC<sub>50</sub> of 19.5 μM for tonic and IC<sub>50</sub> 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<sub>max</sub> 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<sub>max</sub> 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. (b) (4)

### 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 45.

**Table 45: 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)**

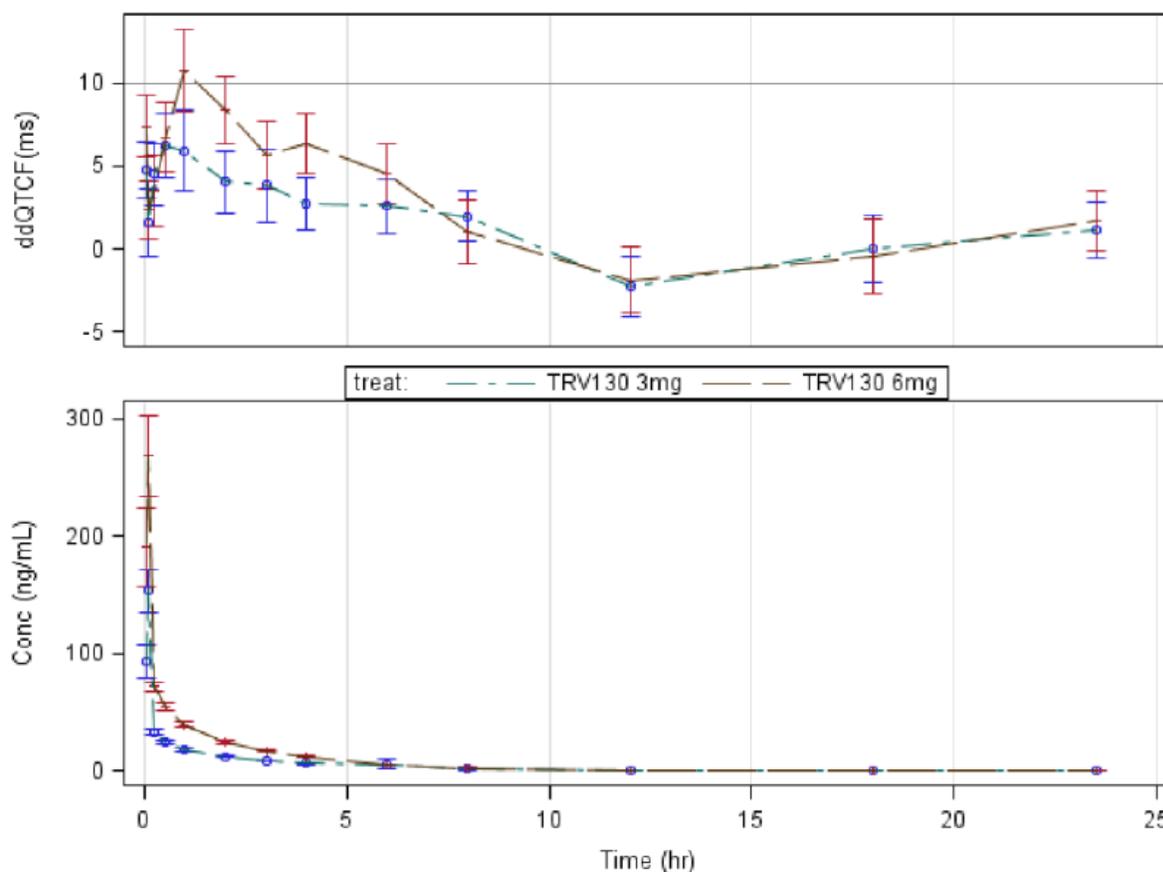
Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
TRV130 3 mg	0.5	6.8	(4.7, 8.9)
TRV130 6 mg	1	11.6	(9.5, 13.7)
Moxifloxacin 400 mg*	2	11.5	(8.6, 14.4)

\* 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 17).

**Figure 17:  $\Delta\Delta\text{QTcF}$  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 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 C<sub>max</sub> (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<sub>1/2</sub> of 4 hours is based on data collected up to 12 hours (only three T<sub>1/2</sub>'s). The table below compares simulated C<sub>max</sub> 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 46: 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  $\Delta$ QTcF >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 47).

**Table 47: Adverse Events Associated with MedDRA SMQ Torsade de Pointes/QT Prolongation**

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

<sup>1</sup>Largest QTcF interval (440 ms) occurred at baseline. <sup>2</sup>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 cases of QTc prolongation in ATHENA are notable and concerning. While patients in ATHENA were receiving other medications, it is anticipated that similar patients would use oliceridine if it were approved.

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. (b) (4)

The QT-IRT team reviewed the additional reports submitted by the Applicant to support the assessment of proarrhythmic risk of oliceridine, which contained additional preclinical information (results of the assessment of oliceridine and major metabolites on hERG, Cav1.2 and Nav1.5) and clinical information (assessment of changes in QTcF, QTcI and J-T<sub>peakc</sub>). The QT-IRT team agrees with the Applicant that the additional preclinical data collected for the two major metabolites support that the metabolites do not inhibit hERG or Cav1.2. However, any potential effects of oliceridine on the late Nav1.5 current are unlikely to impact the QTc observations. This is because oliceridine is rapidly cleared. Moreover, the submitted results for the QTc and J-T<sub>peakc</sub> interval are not consistent with the drug being a mixed ion channel blocker as the changes in J-T<sub>peakc</sub> tracks with QTc changes. The information provided suggests that the mechanism behind the delayed and dose-proportional QTc prolongation is not explained by direct inhibition of the hERG potassium channel by oliceridine or any of its major metabolites.

Due to the uncertainty about the mechanism causing the observed QTc prolongation it is not possible to predict the QTc prolongation with the currently proposed dosing paradigm, which results in exposures of the major metabolites that exceeds the exposures following the highest dose in the thorough QT study (~2.4-fold for M22 and ~2.8-fold for TRV9198662).

The QT prolongation is a significant clinical concern given that oliceridine will be titrated to effect with dosing up to every 6 minutes over a wide range of clinical doses and will be administered in clinical settings where other drugs that prolong QT are frequently administered. In addition, the Applicant has not provided adequate data to support that labeling or patient monitoring will be adequate to mitigate the risks associated with oliceridine's QT-prolongation. Thus, additional pre-approval data are needed regarding the safety concerns related to QT-prolongation before approval of oliceridine.

### ***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 48 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 48: Selected Respiratory Parameters by Treatment Regimen by Study (3001 and 3002) (FAS)**

Study 3001					
	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]
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 <sub>2</sub> 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 <sub>2</sub> 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 anxiety (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 49: 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 50. 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 50: 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 51). 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 51: 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

### Safety Results by Demographic Subgroups

Subgroup analyses were presented by the Applicant for exposure and adverse events and were performed in the Controlled Phase 3 and the All Phase 2 and Phase 3 populations for the following measures:

- Exposure by treatment group
- Treatment-emergent AEs by treatment group
- Most common TEAEs by preferred term (PT)
- Treatment-emergent AEs by system organ class (SOC), PT, and treatment group
- Treatment-emergent AEs by maximum intensity and treatment group

### Key Subgroups

- Age:
  - Controlled Phase 3: Age:  $\geq 18$  to  $< 50$  years,  $\geq 50$  years to  $< 65$ ,  $\geq 65$  years to  $< 70$  years,  $\geq 70$  years
  - ATHENA study age groups:

- Age group 1: <65 years vs  $\geq 65$  years
- Age group 2:  $\geq 18$  to <study median years of ATHENA safety analysis population vs  $\geq$ study median years of ATHENA safety analysis population
- Gender: male/female
- Race: White, Black or African American, Other
- BMI (Body Mass Index): <25,  $\geq 25$  to <30,  $\geq 30$  kg/m<sup>2</sup>
- CYP2D6 Metabolizer Status: Extensive metabolizer (EM) or Poor metabolizer (PM)

Results for the Controlled Phase 3 and All Phase 2 and Phase 3 studies are discussed as follows:

#### *Age*

*Controlled Phase 3 Studies:* Age-related inclusion criterion for the controlled Phase 3 studies required an age of  $\geq 18$  years  $\leq 75$  years at screening. (Note that there was no upper age limit for inclusion criterion in the Phase 3 ATHENA study, but patients had to be  $\geq 18$  years at screening).

For the  $\geq 18$  to <50 years and  $\geq 50$  to <65 years categories, the mean cumulative exposure to study medication was similar. For the  $\geq 65$  to <70 years category, mean cumulative exposure to oliceridine and morphine treatment regimens was less than for the two younger categories of  $\geq 18$  to <65 years categories. For the  $\geq 70$  years category, exposure to oliceridine was similar to the two younger categories, although there were considerably fewer patients enrolled in this age group.

The table below shows the percentage of patients who experienced treatment emergent adverse events stratified by the Applicant's pre-defined age subgroups. The most common AEs across all treatment groups were generally opioid-related. Overall, there were no trends that oliceridine has a different TEAE profile in the  $\geq 18$  years to <65 years regarding the types of AEs. However, there were too few patients in the  $\geq 65$  years to make comparisons or draw conclusions regarding this age subgroup. In general, there were no meaningful differences in the percentages of the most common TEAEs for the total oliceridine treatment patients stratified by age for  $\geq 18$  years to <65 years.

**Table 52: Controlled Phase 3 Treatment-Emergent Adverse Events Stratified by Age Group**

	Subgroup			Subgroup			Subgroup			Subgroup		
	≥18-<50 years			≥50-<65 years			≥65-<70 years			≥70 years		
N treated (%) by Age Group	112 (69)	313 (67)	114 (72)	45 (28)	134 (28)	36 (23)	5 (3)	14 (3)	8 (5)	0	9 (2)	0
% with at least 1 TEAE	72	89	97	82	87	94	20	93	100	0	67	0
<b>Percent Experiencing Preferred Term AE≥10% or AE Terms of Interest</b>												
	≥18-<50 years			≥50-<65 years			≥65-<70 years			≥70 years		
<b>PT</b>	Pla	Oli	Mor	Pla	Oli	Mor	Pla	Oli	Mor	Pla	Oli	Mor
Nausea	38	57	76	31	55	56	0	57	37	0	33	0
Vomiting	10	32	53	11	29	44	0	36	62	0	22	0
Headache	26	23	25	42	31	39	0	43	50	0	11	0
Dizziness	13	20	23	4	23	31	0	21	25	0	33	0
Constipation	10	13	13	9	12	19	0	14	0	0	22	0
Pruritus	6	38	21	7	8	14	0	0	12	0	0	0
Hypoxia	0	9	15	9	13	17	0	14	37	0	0	0
Somnolence	5	7	11	0	7	6	0	14	12	0	0	0
Sedation	6	9	17	2	3	6	0	7	0	0	0	0
Ox sat ↓	0	2	5	0	3	8	0	7	12	0	0	0

The total number of patients enrolled in the treatment arms were: 162 (placebo); 470 (oliceridine); and 158 (morphine)  
Source: Reviewer; Pla=placebo, oli=oliceridine, mor=morphine; ↓=decreased; N=number; PT=preferred term

*All Phase 2 and Phase 3:* In the all Phase 2 and Phase 3 studies, for oliceridine-treated patients in general, the percentage of the most common TEAEs of nausea, vomiting, headache, and dizziness decreased with increasing age group. The most common TEAEs of constipation, somnolence, and pruritus were similar across age groups for oliceridine. A similar percentage (1.6 to 4.7%) of patients experienced hypoxia across all age groups.

**Gender:**

*Controlled Phase 3:* There were more females (n=728 [92.2%]) compared to males (n=62 [7.8%]) in the controlled Phase 3 studies across all treatment groups. In the Phase 3 studies a limited number of males (40) were exposed to oliceridine. In contrast, 430 females were exposed to oliceridine in the Phase 3 studies. Because of this imbalance, interpretation of results is challenging as far as extrapolating findings to males. As shown in the Table below, TEAEs were experienced by more females (90%) in the total oliceridine-treated group than males (67%). The Applicant opines that this may be due to the difference in effect of opioids between males and females. No definite conclusions regarding the AEs in females and males can be drawn because there were so few males for comparison.

**Table 53: Pooled Controlled Phase 3 Treatment-Emergent Adverse Events Stratified by Gender**

	Placebo N=162		Oliceridine N=470		Morphine N=158	
	Female	Male	Female	Male	Female	Male
N (%) Treated	153 (94)	9 (6)	430 (91)	40 (8)	145 (92)	13 (8)
% with at least 1 TEAE	115 (75)	4 (44)	388 (90)	27 (67)	141 (97)	12 (92)
	<b>Percent Experiencing Preferred Term AE<math>\geq</math>10% or AE Terms of Interest</b>					
<b>Preferred Term</b>	Female	Male	Female	Male	Female	Male
Nausea	37	11	59	32	72	46
Vomiting	10	0	32	15	53	38
Headache	31	11	26	17	30	31
Dizziness	10	11	20	32	25	15
Constipation	9	11	14	5	15	15
Pruritus	6	11	11	2	19	0
Hypoxia	3	0	10	5	18	0
Somnolence	3	11	7	7	10	15

Source: Reviewer based on Applicant's tables 14.3.2.1.4 and 14.3.2.2.4 ISS Update; percentages are rounded by reviewer

*All Phase 2 and Phase 3:* In the all Phase 2 and Phase 3 studies population, there were 94%, 78%, and 93% females in the placebo, total oliceridine, and morphine treatment groups, respectively compared to 6%, 22%, and 7% males in those groups, respectively. Overall, the most common TEAEs in the all Phase 2 and Phase 3 population were similar to those in the Controlled Phase 3 population. There was considerable variability in the incidences of TEAEs.

*Race:* In the controlled Phase 3 studies, most patients were white (approximately 68%, 66%, and 66% for placebo, total oliceridine, and morphine, respectively). Black or African American percentages were approximately 30, 27, and 28 for placebo, total oliceridine, and morphine, respectively. The remainder of patients were categorized as other. Overall, the percentage of patients reporting at least one TEAE was similar within the oliceridine treatment regimen between white and African American patients (approximately 89% and 86% respectively). Within the morphine treatment regimen, the percentage of patients experiencing at least one TEAE was also similar, being approximately 98% and 93% for patients reporting race as white and for patients reporting race as black or African American, respectively. The percentage of patients in any treatment regimen reporting as other was too small to draw meaningful conclusions regarding TEAEs.

There was no clear pattern in the percentage of the most common TEAEs for patients reporting race as white compared with patients reporting as black or African American in either the oliceridine or morphine treatment regimens; with the exception of nausea and vomiting, each of which occurred at a lower percentage in oliceridine-treated patients reporting race as black or African American (44.4% and 19.8%, respectively) compared with oliceridine-treated patients reporting as white (60.6% and 34.0%, respectively).

#### *Metabolizer Status*

*Controlled Phase 3 Studies:*

In Study 3001, the number of CYP2D6 Extensive Metabolizers (EM)s in the study was 65, 69, and 71 patients for the oliceridine 0.1, 0.35, and 0.5 mg, treatment regimens. The number of CYP2D6 Poor Metabolizers (PM)s in the study was small (9, 8, and 5 patients for the oliceridine 0.1, 0.35, and 0.5 mg treatment regimens). The overall incidence of patients experiencing at least one TEAE was greater in the CYP2D6 extensive metabolizers (EM)s compared with poor metabolizers (PM)s for oliceridine total (175 [85.4%] vs 15 [68.2%] patients, respectively). A greater number of CYP2D6 EMs in the oliceridine total regimen experienced at least one TEAE leading to early study medication discontinuation (6 [2.9%]) compared with PMs (0 patients).

In Study 3002, the number of CYP2D6 EMs in the study was 58, 62, and 68 patients for the oliceridine 0.1, 0.35, and 0.5 mg treatment regimens, respectively. The number of CYP2D6 PMs in the study was small (14, 12, and 9 patients for the oliceridine 0.1, 0.35, and 0.5 mg treatment regimens, respectively). The overall incidence of patients experiencing at least one TEAE was generally similar in the CYP2D6 EMs and PMs for oliceridine total (173 [92.0%] vs 34 [97.1%] patients, respectively). Twenty patients had metabolizer status not recorded (i.e., missing). There were 3 treatment-emergent SAEs, all occurring in EM patients. A greater number of CYP2D6 EMs in the oliceridine total regimen experienced at least one TEAE leading to early study medication discontinuation (7 [3.7%]) compared with PMs (0 patients).

The table below displays the overall percentage of patients who experienced at least one TEAE based on metabolizer status in Studies 3001 and 3002.

**Table 54: Incidence of TEAEs for Studies 3001 and 3002 (FAS) Extensive and Poor Metabolizers**

Study 3001					
Parameter of Interest	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 (%)
CYP2D6 Extensive Metabolizer	58 (81.7)	65 (87.8)	69 (89.6)	71 (93.4)	56 (82.4)
Patients with at least 1 TEAE	45 (77.6)	48 (73.8)	61 (88.4)	66 (93.0)	54 (96.4)
CYP2D6 Poor Metabolizer Status	13 (18.3)	9 (12.2)	8 (10.4)	5 (6.6)	12 (17.6)
Patients with at least 1 TEAE	6 (46.2)	7 (77.8)	5 (62.5)	3 (60.0)	11 (91.7)
Study 3002					
Parameter of Interest	PBO N=81 n (%)	OLI 0.1 mg N=77 n (%)	OLI 0.35 mg N=80 n (%)	OLI 0.5 mg N=80 n (%)	Morphine N=83 n (%)
CYP2D6 Extensive Metabolizer	69 (88.3)	58 (80.6)	62 (84.0)	68 (87.0)	65 (82.5)
Patients with at least 1 TEAE	54 (78.3)	51 (87.9)	58 (93.5)	64 (94.1)	63 (96.9)
CYP2D6 Poor Metabolizer	10 (11.7)	14 (19.4)	12 (16.0)	9 (13.0)	14 (17.5)
Patients with at least 1 TEAE	8 (80)	14 (100)	11 (91.7)	9 (100)	14 (100)

Table, reviewer based on Applicant's Table 14.3.2.1.3.CSRs 3001 and 3002; Note that numbers may not total 100% since the metabolizer status for some patients was missing; PBO=placebo; OLI=oliceridine

**BMI (Body Mass Index):**

*Controlled Phase 3 Studies:* Within each oliceridine treatment regimen, the mean cumulative exposure was similar across all BMI categories being 31.91, 31.15, and 28.03 mg for patients with a BMI of <25, ≥25-<30, and ≥30 kg/m<sup>2</sup>, respectively. Morphine-treated patients with a higher BMI had a greater mean cumulative exposure being 48.76, 52.82, and 63.23 mg for patients with BMI of <25, ≥25-<30, and ≥30 kg/m<sup>2</sup>, respectively.

There were 30.2%, 47.4%, and 22.3% of patients enrolled in the total oliceridine treatment groups in the BMI categories of <25, ≥25-<30, and ≥30 kg/m<sup>2</sup>, respectively. In the total oliceridine treatment group, 88.7%, 87.4%, and 89.5% of patients experienced at least one TEAE in the BMI categories of <25, ≥25-<30, and ≥30 kg/m<sup>2</sup>, respectively. The percentage of patients who experienced at least one TEAE by randomized treatment regimen is shown in the table

below. Across all treatment regimens, the most common AEs were nausea and vomiting, with a dose-response for nausea across all three BMI categories in the oliceridine-treated group. There was a dose-response for vomiting in the <25 and ≥25-<30 kg/m<sup>2</sup>, but a dose-response for vomiting was not seen in the ≥30 kg/m<sup>2</sup> BMI category. Overall, there was no definite pattern in the incidence of the most common TEAEs with response to BMI category.

**Table 55: Incidence of TEAEs for Pooled Phase 3 Controlled Studies 3001 and 3002 by BMI Subgroup**

Parameter of Interest	PBO N=162 n (%)	OLI 0.1 mg N=153 n (%)	OLI 0.35 mg N=158 n (%)	OLI 0.5 mg N=159 n (%)	Morphine N=158 n (%)
<25 kg/m <sup>2</sup> BMI					
Number enrolled (%)	59 (36.4)	51 (33.3)	45 (28.5)	46 (28.9)	55 (34.8)
Patients with at least 1 TEAE (%)	43 (72.9)	42 (82.4)	40 (88.9)	44 (95.7)	54 (98.2)
≥25-<30 kg/m <sup>2</sup> BMI					
Number enrolled (%)	67 (41.4)	58 (37.9)	87 (55.1)	78 (49.1)	73 (46.2)
Patients with at least 1 TEAE (%)	50 (74.6)	45 (77.6)	80 (92.0)	70 (89.7)	70 (95.9)
≥30 kg/m <sup>2</sup> BMI					
Number enrolled (%)	36 (22.2)	44 (28.8)	26 (16.5)	35 (22.0)	30 (19.0)
Patients with at least 1 TEAE (%)	26 (72.2)	38 (86.4)	22 (84.6)	34 (97.1)	29 (96.7)

Table, reviewer based on Applicant's Table 14.3.2.2.6, ISS Update; PBO=placebo; Oli=oliceridine

*All Phase 2 and Phase 3:* In the All Phase 2 and Phase 3 studies, cumulative mean exposure was similar for oliceridine-treated patients across the three BMI categories.

With regard to TEAEs, within the oliceridine treatment regimen, the percentage of patients with at least one TEAE decreased slightly with increasing BMI: 81.1%, 75.9%, and 69.7%, for the <25, ≥25 to <30, and ≥30 kg/m<sup>2</sup> groups, respectively. Within the morphine treatment regimen, the percentages were similar with increasing BMI.

Within the oliceridine treatment regimen, there was a decrease in the incidence of the most common TEAEs (nausea, vomiting, headache, and dizziness) from the lower to higher BMI categories; for the most common TEAEs of pruritus, constipation, and somnolence, the incidence was generally similar across BMI categories. No pattern was apparent within the morphine treatment.

### Laboratory and Vital Signs Safety Results

As would be expected with a population which included post-operative patients, there were a number of patients with abnormal laboratory and vital sign findings in the Phase 3 controlled and uncontrolled studies. However, overall, the laboratory findings were not determined to have patterns or trends which would suggest a safety signal or require additional language in the label. Interpretation of results is limited due to enrollment of a post-operative population.

### Abuse Potential

Please see the Controlled Substance Staff's (CSS's) review for a detailed discussion 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. Based on the CSS evaluation of the preclinical and clinical abuse-related data, CSS concluded that if the NDA for oliceridine is approved:

- a) "Oliceridine should be recommended for placement in Schedule II of the Controlled Substances Act (CSA). The Sponsor also proposed that oliceridine should be recommended for Schedule II placement.
- b) The text of the Section 9 (Drug Abuse and Dependence) of the drug label should reflect that the preclinical and clinical abuse-related studies with oliceridine produced significant abuse signals."

The clinical component of the abuse potential assessment included a Phase 1 study designed to evaluate the abuse potential of IV oliceridine compared to morphine and placebo in healthy, non-dependent, recreational, opioid users (CP130-1011), clinical pharmacodynamics (PD) and PK, and the assessment of existing

- Abuse Potential Study (CP130-1011): The Applicant evaluated the abuse potential of this product in one dedicated study titled, "A Randomized, Double-Blind, Crossover Study to Assess the Abuse Potential of Intravenous Oliceridine (TRV130) Compared to Morphine and Placebo in Healthy, Non-Dependent, Recreational, Opioid Users." In this study, 65 subjects were randomized, 60 treated, and 48 completed the study. Each study drug administration was separated by approximately 48 hours.
  - Treatment Periods:
    - Part A: 3-day Treatment Visit
    - Part B: Days 4, 6, 8, 10, 12, and 14
  - Part A For each subject, the treatment visit began on the day prior to first medication administration (Day -1) and ended on Day 2 (3 days, 2 nights). At least 12 hours prior to first study medication administration, a Naloxone Challenge Test was performed to confirm that subjects were not opioid dependent. Escalating oliceridine doses were evaluated in separate cohorts of 4 subjects each, randomized in a 3:1 fashion, such that 3 subjects received a single dose of oliceridine and 1 subject received a single dose of placebo within each cohort. Planned dose levels of oliceridine included 3, 5, and 7 mg.
  - Part B: Subjects were randomized to 1 of 6 treatment sequences. Subjects received each of the following 6 treatments (on Days 4, 6, 8, 10, 12, and 14), administered over 1 minute, in a randomized-sequence, double-blind, crossover manner following an overnight fast:
    - Oliceridine 3 mg (proposed maximum therapeutic dose)
    - Oliceridine low suprathreshold dose (as determined by Part A)
    - Oliceridine high suprathreshold dose (as determined by Part A)
    - Morphine low dose (dose-matched based on relative potency to low suprathreshold dose of oliceridine, as estimated by Part A pupillometry results)
    - Morphine high dose (dose-matched based on relative potency to high

- supra-therapeutic dose of oliceridine, as estimated by Part A pupillometry results)
- Placebo (saline infusion)
  - Pharmacodynamic Results:
    - Pharmacodynamics: The Applicant found that there was a statistically significant difference between both doses of morphine and placebo on the primary endpoint of Drug Liking VAS Emax. A positive dose-effect relationship was observed with morphine, as the morphine 20 mg dose had numerically higher scores than that of the 10 mg dose on the majority of measures, although morphine 20 mg was also associated with higher scores than placebo on the Bad Effects VAS, suggesting greater negative effects at the higher dose.
    - As with morphine, all 3 doses of oliceridine showed large increases in VAS scores, with peak effects occurring by 5 minutes post-dose. In contrast to morphine's effects which lasted approximately 4 hours, oliceridine had a shorter duration of effects, lasting for approximately 2 to 3 hours. Oliceridine also showed a positive dose-effect relationship, with scores for the oliceridine 2 mg dose numerically higher than those of the 1 mg dose, and for the 4 mg dose numerically higher than those of the 2 mg dose on the majority of measures.
    - In terms of absolute abuse potential, there were statistically significant differences between all 3 oliceridine doses and placebo on the primary endpoint of Drug Liking VAS Emax, as well as majority of secondary measures and endpoints.
    - With respect to relative abuse potential, oliceridine 1 mg was associated with weaker subjective effects compared to 2 mg and 4 mg doses; however, oliceridine 1 mg was still associated with greater subjective effects compared to placebo. On the majority of subjective measures, including the primary endpoint, Drug Liking VAS Emax, comparisons between similar dose-match levels of oliceridine and morphine (ie, 2 mg and 10 mg and 4 mg and 20 mg) were not significantly different.
    - Consistent with the prolonged duration of effect for morphine relative to oliceridine, both doses of morphine were associated with statistically greater TA\_AUE0-8 values on measures of positive and any effects.
    - Median scores on the Drug Similarity VAS for opioids were higher with morphine compared to similar dose levels of oliceridine. In addition, both doses of morphine were associated with statistically greater pupil constriction compared to similar dose levels of oliceridine, with pupil constriction lasting at least twice as long as that of oliceridine.
  - Safety Results: The most common TEAEs were typical of opioids, including euphoric mood, somnolence, pruritus generalized, dizziness, dry mouth, nausea, and pruritus. Vomiting was only observed following administration of morphine.

Overall, the results of the study demonstrate that IV oliceridine has similar abuse potential to that of IV morphine in healthy, non-dependent, recreational opioid users.

***Overdose:*** No overdoses were reported with oliceridine in the Phase 1, Phase 2, or controlled Phase 3 studies. One overdose (drug administration error) was reported in ATHENA patient (b) (6), a 68-year-old male who received a 10 mg dose of oliceridine on Day 1 rather than the intended 1 mg dose due to a dosing error by the bedside nurse. Before the End of Treatment Phase, the patient subsequently received 22 additional bolus doses of oliceridine (3 mg each, cumulative dose of 86 mg) on Days 2 through 7. Despite the dosing error, the patient did not exceed the dosing limit of 60 mg in the first 12 hours of treatment. The patient's vital signs, including pulse oximetry, respiratory rate (RR), and Moline-Roberts Pharmacologic Sedation Somnolence Scale (MRPSS) scores reportedly did not significantly worsen to a level that required treatment intervention after the drug administration error and he completed the study. He did not require an opioid reversal agent or assisted ventilation. No treatment emergent adverse events were reported.

The Applicant reports that some studies included higher dose strengths of oliceridine (single dose study CP130-001, thorough QT study CP130-1008, and Part A of Study CP130-1011). The AE profiles in those studies were consistent with an opioid. The limitation of using these studies to support safety at higher doses, however, is that the dosing regimens were not the same as those proposed and some of these supportive studies were only single-dose studies.

Although patient (b) (6) in ATHENA study received a single dose of oliceridine higher than intended due to a dosing error, since the dosing limit remained less than 60 mg in the first 12 hours of treatment, it is unclear if this constitutes an overdose. Therefore, we do not have clinical evidence of a case of overdose. As such, we cannot definitively state that naloxone would be effective to counteract signs and symptoms of oliceridine overdose, nor are signs and symptoms of oliceridine overdose clearly known. The supportive studies for higher dose strengths than proposed labeling are limited because some were single-dose studies and the dosing regimen in those studies was not the same as that for the proposed labeled indication.

Section 10.2 (Treatment of Overdose) of the Proposed Label includes class-wide language regarding treatment of overdose, as shown below:



The label should include a statement that no cases of overdose were experienced in the clinical development, so the definitive treatment for overdose has not been established.

### **Additional Adverse Events of Interest**

The following events were identified by the clinical Medical Officer reviewer as significant adverse events of interest:

- Seizure: One TEAE of seizure was reported in ATHENA study in patient (b) (6), a 48-year old female in the  $\leq 4$  mg oliceridine cumulative dose group. Her relevant medical history included epilepsy (generalized tonic-clonic seizure) since 2006, bipolar disorder, generalized anxiety disorder, type 2 diabetes mellitus. Relevant concomitant medications included topiramate 200 mg daily and klonopin 0.5 mg twice daily for seizure disorder and gabapentin and pregabalin for chronic back pain. The onset of the TEAE of generalized tonic-clonic seizure occurred one day after receiving 3 mg of oliceridine for treatment of exacerbation of cervical disc disorder. The seizure reportedly lasted approximately 5 minutes. She presented to the ED and reported that this was her tenth seizure since (b) (6), cited a propensity for seizures in the context of stress, and noted “severe sleep deprivation” for the previous 6 months. She had not seen a neurologist since (b) (6).

*Reviewer’s comment: The investigator rated this event as unlikely related to study medication. I find this event was possibly related to study drug. While causality of this event to oliceridine alone cannot be definitive, given this patient’s history of prior seizure disorder, it is possible that oliceridine was a contributor to the seizure (i.e., lowered seizure threshold). Opioids contain class-wide labeling in Section 5 (Warnings and Precautions) for Increased Risk of Seizures in Patients with Seizure Disorders. The proposed oliceridine language includes this class-wide labeling.*

- Schizophrenia: Patient (b) (6) was a 41-year-old male in the ATHENA  $>36$  mg oliceridine cumulative dose group. His relevant medical history included schizophrenia 2014 to ongoing. Relevant concomitant medications included aripiprazole (2014 to ongoing). The patient received 51 mg of oliceridine between (b) (6) for the treatment of pain s/p cholecystectomy. The patient was a CYP2D6 poor metabolizer. One day after the last dose of oliceridine, the patient experienced a TEAE of schizophrenia (verbatim term: schizophrenia symptoms increased). No time of onset was reported but reportedly the stop date of the event was five days later. No additional treatment was reported. The investigator assessed the event as not related to study medication.

*Reviewer’s comment: I agree with the Investigator’s assessment that this event was unlikely related to study drug. Further, there is insufficient information to determine if this was a documented schizophrenic event.*

- Drug hypersensitivity: Patient (b) (6) was a 47-year-old female in the ATHENA  $>4$  to 8 mg oliceridine cumulative dose group. Her relevant medical history included ongoing drug hypersensitivity (penicillin) and seasonal allergies. On Day 1, she received oliceridine 6 mg over approximately 11 hours for treatment of pain associated with laparoscopic sleeve gastrectomy. On Day 2, approximately 16 hours after her last dose of oliceridine, she experienced a non-serious TEAE of drug hypersensitivity (verbatim term: allergic reaction Tylenol 3; mild, not related, resolved in 2 hours). Concomitant medication administered prior to the TEAE included Vicodin (7.5/325 mg oral, twice) and paracetamol.

*Reviewer’s comment: It is unclear from the narrative whether this case of drug*

*hypersensitivity is due to an allergic reaction related to Tylenol 3, concomitant medications of Vicodin and paracetamol, or oliceridine. Given that the onset was 16 hours after the last dose of oliceridine and the half-life of oliceridine is 1-3 hours, it is unlikely that the allergic reaction was due to oliceridine. However, the half-life of metabolites of oliceridine are approximately 44 hours, so causality to oliceridine is possible. Due to multiple confounders and inadequate description of the allergic reaction, overall, there is insufficient information to draw any conclusions about this case. The proposed label includes a Contraindication for Immune-mediated hypersensitivity to oliceridine.*

- **Allergic Reaction TEAEs Leading to Study Discontinuation:** In addition to the above case categorized as drug hypersensitivity, there was also a disproportionately higher percentage of the terms “pruritus” and “urticaria” that led to study or study medication discontinuation in oliceridine-treated compared to morphine or placebo, where no cases with these terms were reported leading to discontinuation of study medication. Across all Phase 2 and Phase 3 studies, of the 43 oliceridine-treated patients who had early study medication or study discontinuation, 5 (12%) experienced the following terms:
  - Pruritus generalized:
    - (b) (6) (ATHENA): This 24- year-old female developed generalized pruritus on Day 2 after 33 PCA doses. The TEAE was treated with Benadryl and the event resolved on Day 3.
    - (b) (6) (ATHENA): This 69- year-old female developed dizziness and nausea on Day 1 and generalized pruritus on Day 2. Study medication was withdrawn on Day 2. The pruritus was treated with Benadryl and resolved on Day 3. The other TEAEs were treated accordingly.
  - Urticaria:
    - (b) (6) (Study 2001): This 61-year-old female discontinued due to generalized pruritus on Day 2 due to the AE. The patient was treated with diphenhydramine and the AE resolved on Day 3. Other AEs included dizziness, nausea, vomiting, headache, and hot flush.
    - (b) (6) (ATHENA): This 43-year-old female had a relevant medical history to include drug hypersensitivity (1998), drug eruption (2016), anaphylactic reaction (1998), and seasonal allergy. The patient experienced the onset of urticaria on Day 1. She was treated with Benadryl and DuoNeb nebulizer. No respiratory TEAEs were reported. The TEAE of urticaria resolved on Day 2 after study medication was withdrawn.
  - Lip pruritus/Lip swelling/Pruritus/Urticaria (leg)/Urticaria (lip): (b) (6) (ATHENA). Symptoms resolved without treatment after study medication was discontinued.

*Reviewer’s comments:* All of the TEAEs potentially related to allergic reaction events that led to study discontinuation were rated as mild or moderate and resolved. No trends were noted with regard to treatment dose. Four of the five cases occurred in the ATHENA study. Except for Case (b) (6), prior medical history or concomitant

medications were not co-suspect by this reviewer. While it is notable that these allergic reactions leading to study discontinuation all occurred in oliceridine-treated, none of the cases were severe, serious, or described as anaphylactic. The overall incidence of pruritus was less in oliceridine-treated compared to morphine in APOLLO 1 and APOLLO 2. The proposed label includes pruritus in the Adverse Drug Reactions, which appears reasonable.

- **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. The current data are not adequate to evaluate QT prolongation at the proposed doses and the risks of QT prolongation cannot be adequately mitigated by labeling or monitoring given the context of clinical use and the concomitant medications that patients taking oliceridine would be using. An additional concern is that the safety database is not adequate to support the proposed dosing.

## 8.1 Benefit-Risk Considerations

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

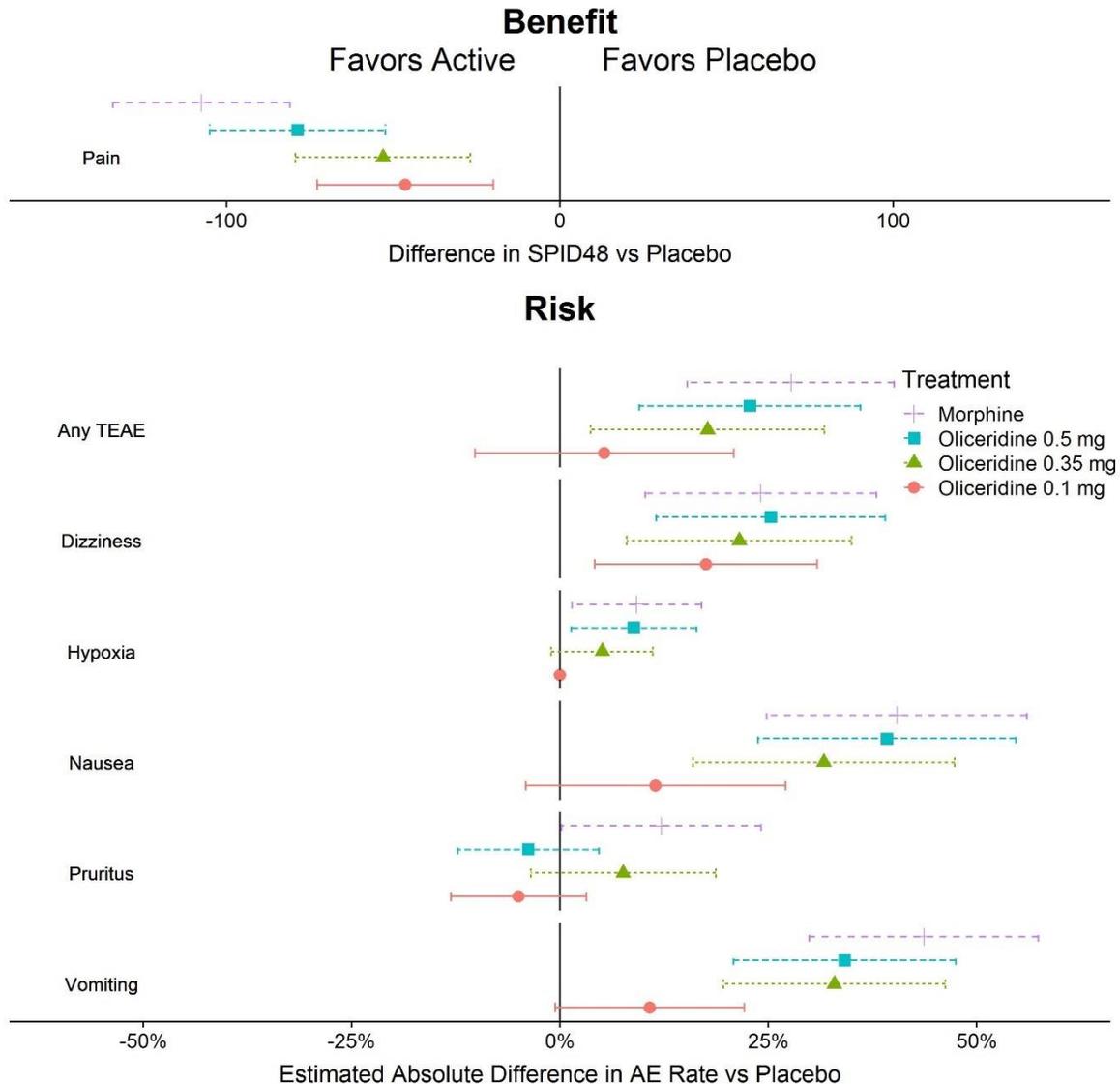
Figure 18 simultaneously presents the benefit and risk of all active treatments versus placebo from Study 3001. The displayed benefit is in terms of the difference in summed pain intensity differences from placebo (Table 20). The displayed risks are the adverse events where there was a significant difference ( $p < 0.05$ ) 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. Even though the oliceridine 0.5 mg dose regimen looks to be slightly less efficacious than morphine, there were 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, we could not explore a dose response relationship with respect to efficacy and safety.

**Figure 18: Risk vs Benefit for Active Treatments Compared to Placebo (Study 3001)**



Source: FDA Reviewer

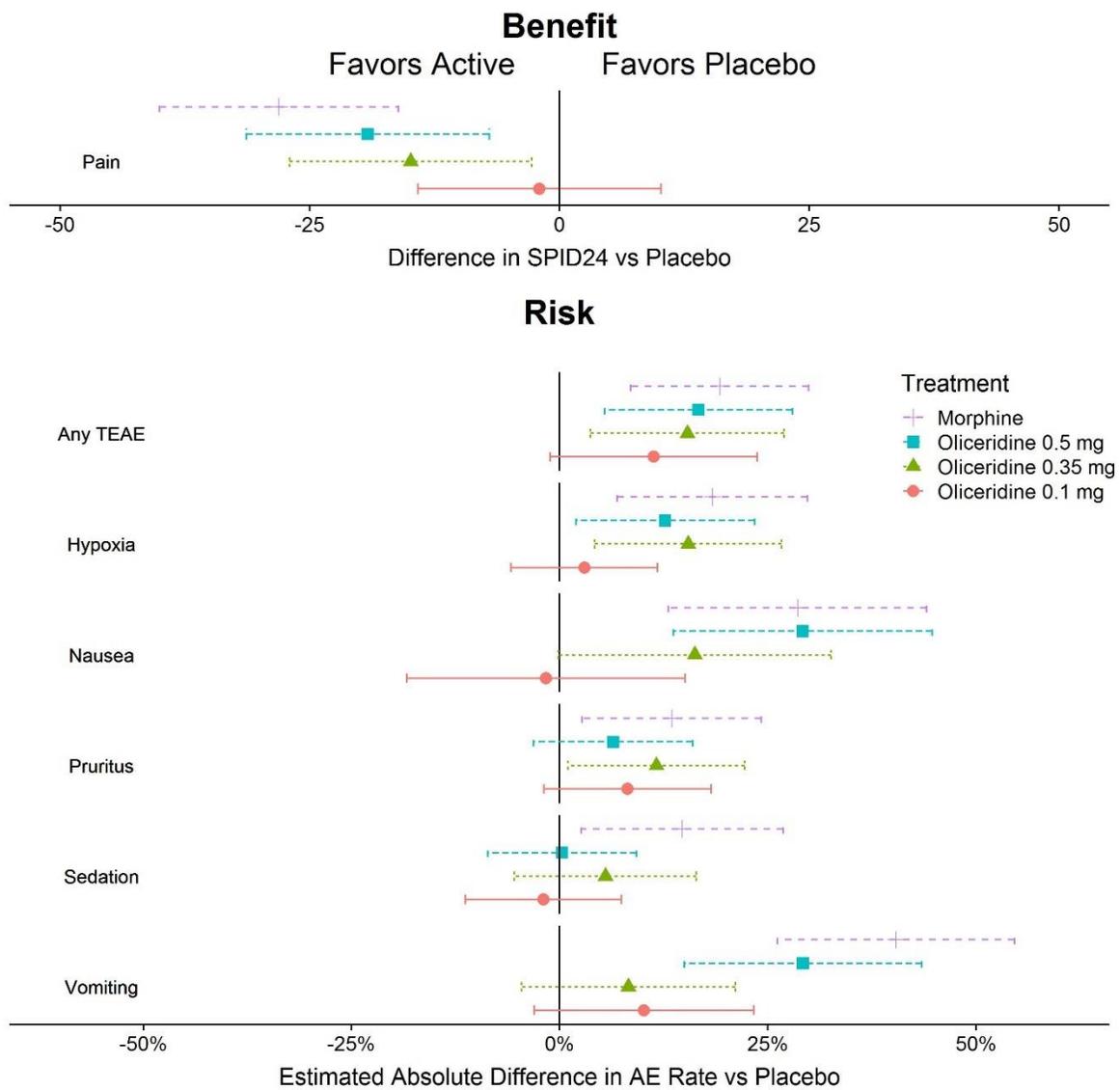
Figure 19 shows a similar plot of the efficacy and safety of oliceridine vs morphine for Study 3002. The displayed benefit is in terms of the difference in summed pain intensity differences from placebo from the analysis considered to be most clinically relevant (Table 27) and the displayed risks are 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 19: Risk vs Benefit for Active Treatments Compared to Placebo (Study 3002)**



Source: FDA Reviewer

## 11. Advisory Committee Meeting

This NDA was discussed at an Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) meeting on October 11, 2018. The following is a brief summary of the questions to the committee and surrounding discussions. See the full transcript of the meeting for complete details.

5. **DISCUSSION:** Discuss the efficacy of oliceridine and whether the data provide substantial evidence for efficacy of oliceridine for the proposed indication of the management of acute moderate-to-severe pain in adults for whom an intravenous opioid is warranted.

*Committee Discussion:* Overall, the committee was in agreement that oliceridine showed efficacy compared to placebo in relatively healthy individuals. However, these committee members also agreed that the controlled Phase 3 post-operative study populations were not indicative of complex populations that may have multiple drug interactions and comorbidities, and therefore agreed that the efficacy of oliceridine is not clear compared to an active comparator. Several committee members expressed concern that the dosing recommendations are unclear and there was agreement that there would be challenges treating patients with different conditions and with dose titration in real-world situations. Some committee members stated that there was not substantial evidence of the efficacy of the 0.1 mg dose based on the data presented. Other committee members noted their appreciation of the rapid onset of efficacy. Please see the transcript for details of the committee discussion.

6. **DISCUSSION:** Discuss the safety profile of oliceridine and whether the safety profile of oliceridine is 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. Provide comment on the following issues:
  - a. Safety database
  - b. Hepatic safety
  - c. Respiratory safety
  - d. QT prolongation

*Committee Discussion:* The committee's general consensus was that oliceridine is relatively safe overall. Some committee members noted that the agonist-bias that was displayed appeared to have potential benefits, as providers are looking for new ways to find a tailored approach to treatment of acute pain. Several members of the committee expressed concerns of possible safety signals that could arise with higher doses, comorbid conditions, multimodal therapy, and use of concomitant medications, including other opioids, in real-world situations. One committee member noted that the decreased incidence of vomiting compared to morphine was notable. In regards to hepatic safety, overall, the committee was in agreement that there wasn't much concern for a hepatic safety signal. In terms of respiratory safety, some committee members made note that the hypercapnic testing that was performed in young healthy volunteers does not indicate a

*lower risk of respiratory depression compared to morphine. One member noted the decreased  $\beta$ -arrestin activation shown in animal models is suggestive of decreased respiratory depression, but other members noted limitations in the available clinical data. Some committee members noted there was insufficient data on QT prolongation and agreed more ECG data were needed. Other committee members agreed that real world implications were unclear, as there was a disconnect between pharmacokinetic and QT effects. One committee member added that although there were modest effects on QT prolongation used in the thorough QT study, the effects of the 40 mg per day in the proposed labeling is unknown. Several committee members expressed concerns regarding the available safety database that doesn't appear to represent what will be used in terms of doses in practice or the types of patients who are anticipated to receive the drug. Please see the transcript for details of the committee discussion.*

7. **DISCUSSION:** 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.

***Committee Discussion:** Overall, the committee found no superiority for abuse deterrence and considered Schedule II appropriate for oliceridine. Some committee members agreed that people may presume that oliceridine is a safer medication, which may increase its abuse potential. One committee member added that healthcare professionals managing patients with opioid use disorders may improperly perceive oliceridine as safer, which could limit vigilance and amplify public health concern. Another committee member added that abuse of oliceridine may lead to unforeseen adverse effects with respiratory depression, hepatic pathology, and QT prolongation. Please see the transcript for details of the committee discussion.*

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

**Vote Result:**            Yes: 7            No: 8            Abstain: 0

***Committee Discussion:** The committee did not reach a general consensus on the approval of the proposed dose of oliceridine for the proposed indication of the management of moderate- to-severe acute pain in adults for whom an intravenous opioid is warranted. Committee members who voted "Yes" recommended inclusion of "not safer than traditional opioids" on the label and that further studies be required. Considerations in favor of recommending approval included a potentially favorable PK data, no active metabolites, decreased  $\beta$ -arrestin activation, and positive GI profile with decreased nausea and vomiting. Committee members who voted "No" stated that the benefit/risk profile was not favorable enough, with a need for more data regarding demographic variability, including patients with comorbidities, drug interactions, and real-world dosing. Some members voiced concerns that the perception of oliceridine being safer may lead to increased abuse and downstream problems. Several committee members discussed the need for additional data. One member suggested a study showing*

*decrease in length of hospital stay (time to discharge) as possible compelling data for approval. Please see the transcript for details of the committee discussion.*

## **12. Pediatrics**

The Applicant is requesting deferral for the pediatric assessment for ages birth to <17 years until oliceridine is determined to be safe and effective in the adult population for the indication of management of moderate-to-severe acute pain. The Applicant plans to fulfill the Pediatric Research Equity Act (PREA) requirement through the following studies in pediatric patients with acute pain as proposed in an agreed June 22, 2017 Initial Pediatric Study Plan (iPSP):

(b) (4)



The oliceridine pediatric plan was discussed at the Pediatric Review Committee (PeRC) meeting. While there were no significant concerns regarding the pediatric plan, given that the application will receive a complete response, additional modifications to the plan may occur in the future.

## 11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**

The NDA submission included completed Form 3454 “Certification: Financial Interests and Arrangements of Clinical Investigators” in compliance with 21 CFR part 54. This certified that the Applicant had not entered into any financial arrangements with the listed clinical investigators as defined in 21 CFR 54.2(a), that no clinical investigator was required to disclose any financial interests as defined in 21 CFR 54.2(b), and that no listed investigator was the recipient of significant payments from the Applicant as defined in 21 CFR 54.2(f). The Applicant stated that no investigators were full- or part-time employees of Trevena, Inc.

- **Other Good Clinical Practice (GCP) issues**

The clinical studies were conducted in accordance with Good Clinical Practices and a statement of compliance with Good Clinical Practices is located in each clinical study report.

- **Office of Scientific Investigations (OSI) audits**

According to Dr. Damon Green’s July 30, 2018, Office of Scientific Investigations (OSI) Clinical Inspection Summary review, inspections were conducted at the clinical sites of Dr. Joseph S. Gimbel (Site 10030 for Protocol CP130-3001 and 3002) and Dr. Artin Nazarian (Site 10001 for Protocol 3002). These sites were selected because of a large patient enrollment in the combined sites. All inspections have been completed and the final classification of the

inspections was No Action Indicated (NAI). Inspection findings supported the acceptability of the clinical data submitted.

- **Any other outstanding regulatory issues**—Not applicable

## 15. Labeling

- **Proprietary name**

Initially, the proposed proprietary name was Olinvo, but this was found to be unacceptable. Currently, the proposed proprietary name for oliceridine is Olinvyk. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Medication Error Prevention and Risk Management (OMEPRM) and was found to be acceptable. As noted in the August 9, 2018 Grant Proprietary Name letter, if any of the proposed product characteristics as stated in the June 26, 2018 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

- **Physician labeling**

Not applicable as the recommended action is complete response.

## 16. Postmarketing Recommendations

As the recommended regulatory action is complete response, there are no recommendations postmarketing requirements or REMS.

## 17. Recommended Comments to the Applicant

### Clinical Deficiencies

#### 5. Deficiency

The submitted data are not adequate to support the safety of oliceridine for the management of moderate-to-severe acute pain in adult patients for whom an IV opioid is warranted due to concerns related to QT prolongation.

Your thorough QT (tQT) study, CP130-1008, showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset (3 mg: 6.6 ms [upper 90% CI 8.9 ms]; 6 mg: 11.6 ms [13.7 ms]). The delayed onset of QTcF prolongation suggests that the QTcF prolongation may not be mediated via direct inhibition of the hERG potassium channel by oliceridine. The proposed mechanism for the delayed onset of the QTcF prolongation observed with oliceridine remains unclear.

In your Phase 3 studies, only limited ECG monitoring was obtained in patients after baseline (1, 24, and 48-hours post-loading dose for Study 3001; and 1 and 24 hours for Studies 3002; and 1 hour and every 24 hours of oliceridine treatment in Study 3003). Further, you have proposed a wide range of doses up to a maximum daily dose of 40 mg and oliceridine would be used in clinical situations in which patients may receive other drugs that can prolong the QTc.

Interpretation of the ECG data from your clinical studies has limitations. Specifically, none of the studies were designed to characterize the QT prolonging effects of oliceridine. In Study 3003, there was a lack of ECG replicates at each nominal timepoint and lack of a control arm. Despite these limitations, there were cases of QTc prolongation in Study 3003.

You have not provided adequate data to support that the QT prolonging effects of oliceridine can be mitigated by labeling or monitoring.

### **Information Needed to Resolve the Deficiency**

To support the safety of oliceridine for the management of moderate-to-severe acute pain in adult patients for whom an IV opioid is warranted, provide data from a randomized active-controlled study to address the safety concern of QT prolongation at the maximum proposed daily dose. The study should include 24-hour Holter monitors. Replicate QT measurements could be extracted every hour from the Holter monitors and compared to the control group. The study should be of adequate duration and sample size to allow reliable evaluation of oliceridine's QT prolongation effects.

### **6. Deficiency**

The submitted exposure database is not of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. You have proposed a maximum daily dose of 40 mg without a limit on the duration of use. You were advised at the End-of-Phase 2 and pre-NDA meetings that the safety database needed to include at least 350 patients exposed to the highest doses for the longest duration of use. In your Phase 2 and Phase 3 studies, the highest dose that at least 350 patients were exposed to during the first 24 hours was 27 mg of oliceridine. The highest dose with the longest actual duration that had at least 350 patients exposed was 37.2 mg administered over an actual duration of at least 35.5 hours.

### **Information Needed to Resolve the Deficiency**

Provide an exposure database that is of adequate size to evaluate and support the safety of oliceridine for the proposed labeling. Specifically, the safety database must include at least 350 patients exposed to the highest dose proposed for the longest duration of use indicated in the labeling.

### **Nonclinical Deficiencies**

#### **7. Deficiency**

You have not provided adequate data to confirm that levels of TRV0109662, a major human metabolite, have been adequately characterized for potential embryo-fetal effects in either the rat or the rabbit embryo-fetal development study. Based on the data obtained to date, this metabolite does not appear to be formed at acceptable levels in the rat compared to the human, you have not provided any data to document that the metabolite is formed in rabbit, and the

existing analytical assays for human and rat plasma levels of TRV0109662 do not appear to be consistently reproducible (failed rat incurred sample reanalysis for pivotal study).

**Information needed to resolve this deficiency:**

Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated reproducible pharmacokinetic data to support your 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 at the proposed maximum recommended human dose of 40 mg/day.”

**Product Quality**

**8. Deficiency**

The analytical methods used for controlling identified leachables are required to be validated. Validation reports for the analytical methods used for the leachables study have not been provided to the Agency.

**Information Needed to Resolve the Deficiency:**

Validate your newly developed analytical methods for leachables as per the ICH Q2 recommendation, and provide the validation reports to the Agency. Further, also provide the data for the leachables found in the stability samples that are analyzed by your newly developed methods.

## 18. Appendix

a.

### Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input checked="" type="checkbox"/>	Patient reported outcome (PRO)	Section 7
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input checked="" type="checkbox"/>	Clinician reported outcome (ClinRO)	Section 7
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

## b. Phase 3 Study Protocols

### i. Study CP130-3001 - Overview and Objectives

Study CP130-3001, also referred to as APOLLO 1 or Study 3001, was one of the key Phase 3 efficacy studies to support the proposed indication. The discussion below pertains to Protocol Version 3.0, the last protocol and the one under which all patients were enrolled.

**Title/Design:** A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study of Oliceridine (TRV130) for the Treatment of Moderated to Severe Acute Pain after Bunionectomy

**Primary Objective:** The primary objective of this study was to evaluate the analgesic efficacy of intravenous (IV) oliceridine administered as needed (PRN) compared with placebo in patients with moderate to severe acute pain after bunionectomy.

**Secondary Objectives:** 1) To evaluate the safety/tolerability of oliceridine compared with morphine, 2) To evaluate the analgesic efficacy of oliceridine compared with morphine, and 3) To evaluate the safety/tolerability of oliceridine compared with placebo

**Overview:** This study consisted of Screening, Confinement, and Follow-Up Phases as discussed below:

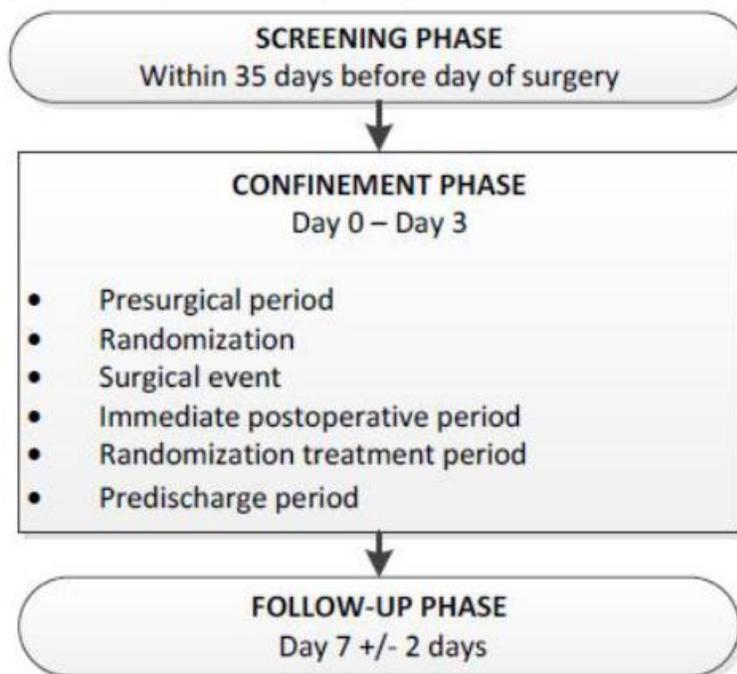
- Screening Phase: Screening procedures were to have been completed within 35 days before surgery
- Confinement Phase: The Confinement Phase was to have covered the period to include the day of surgery (Day 0) and was to end on postoperative Day 3 (4 days, 3 nights). The confinement Phase was to have included the following key procedures:
  - *Pre-surgical Period:* This period was to have been completed before surgery and included training on pain assessment, placebo response, and patient controlled analgesia (PCA) utilization
  - *Randomization Period:* Patients were to have been randomized in a 1:1:1:1 ratio to placebo, morphine or one of three oliceridine regimens (0.1 mg, 0.35 mg, 0.5 mg)
  - *Surgical Event:* Patients were to undergo primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under popliteal sciatic nerve block (PSB) and propofol sedation.
  - *Immediate Post-operative Period (IPP):* Regional anesthesia was to have been maintained during the IPP until approximately 3 AM on postoperative Day 1. After that, when a patient requested pain treatment, they were to rate their pain intensity using an 11-point numeric rating scale (NRS) and a four-point categorical plain rating scale.
    - *Entry Criteria:* Patients could enter the randomized treatment period if they met IPP entry criteria within 9 hours after discontinuation of regional

- anesthesia. If the patient did not qualify, they were considered to be screening failures and were to have been managed conventionally.
- *Randomized Treatment Period:* During this period, safety and efficacy were assessed at multiple prespecified time points (see discussion under Endpoints section of this review for further details regarding types and frequency of assessments). Blood was also collected for pharmacokinetics (PK).
  - *Pre-discharge Period:* Following the randomized treatment period, patients were to have been assessed for discharge and received outpatient diary to record adverse events, outpatient analgesic therapy and any other new medications, a Subjective Opiate Withdrawal Scale (SOWS), and a prescription for outpatient analgesic therapy (per the investigator's discretion).
  - *Follow-up:* The patient was to have returned to the study site on postoperative day 7±2 days and return the outpatient diary and SOWS.

The Figure below displays the study design schematic.

**Figure 20: Study Design Schematic**

**Figure . Study 3001 Study Design Schematic**



Source: Sponsor's Figure, Study 3001 Protocol Version 3.0, p. 28

**Choice of control group:** The APOLLO 1 study included a placebo control and an active morphine comparator, both supplied in a volume-matched, blinded manner.

**Pre-operative Entry Inclusion and Exclusion Criteria:**

*Inclusion Criteria:*

1. Age  $\geq 18$  and  $\leq 75$  years at screening.
2. Scheduled to undergo primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation.
3. Able to understand and comply with the study procedures and requirements, and able to provide written informed consent before any study procedure.

*Exclusion Criteria*

1. Participated in another oliceridine clinical study.
2. Received any investigational drug, device or therapy within 35 days before surgery.
3. Clinically significant medical, surgical, postsurgical, psychiatric or substance abuse condition or history of such condition that could confound the interpretation of efficacy, safety or tolerability data in the study.
4. American Society of Anesthesiologists (ASA) Physical Status Classification System classification III or worse.
5. Current malignancy, current systemic chemotherapy, or cancer diagnosis within 5 years before surgery (excluding squamous or basal cell carcinoma of the skin that has been clinically stable and fully excised in a curative procedure).
6. Current painful condition that could confound the interpretation of efficacy, safety or tolerability data in the study.
7. Body weight  $< 40$  kg or body mass index (BMI)  $> 35$  kg/m<sup>2</sup>.
8. Pregnancy, breastfeeding, or positive urine pregnancy test at screening or on the day of surgery.
9. History of clinically significant, immune-mediated hypersensitivity reaction to opioids.
10. History of clinically significant, immune-mediated hypersensitivity reaction, clinically significant intolerance, or contraindication to anesthetics, adjunctive analgesia, rescue pain medication, rescue antiemetics, or antibiotics used in the study.
11. Current diagnosis of sleep apnea or suspicion of sleep apnea on review of systems.
12. Used chronic opioid therapy, defined as  $> 15$  morphine equivalent units per day, for  $> 3$  out of 7 days per week, for  $> one$  month, within 12 months before surgery.
13. Used any analgesic medication within 5 half-lives (or, if half-life is unknown, within 48 hours) before surgery, or used chronic NSAID therapy, defined as daily use for  $> 2$  weeks within 6 months before surgery (aspirin  $\leq 325$  mg daily is permitted for cardiovascular prophylaxis if the patient has been on a stable regimen for  $\geq 30$  days before surgery).
14. Used agents that could affect the analgesic response (such as central alpha adrenergic agents [clonidine and tizanidine], antiepileptic drugs, neuroleptic agents, antidepressants and other antipsychotic agents) that have not been stably dosed for at least 30 days before surgery.
15. Used oral, inhaled or parenteral corticosteroids within 3 months before surgery (nasal corticosteroids and limited topical corticosteroids are permitted, per the investigator's discretion).
16. Positive urine drug screen or alcohol breathalyzer test at screening or on the day of surgery.
17. Hepatic impairment (total bilirubin  $> 2 \times$  upper limit of normal [ULN], aspartate aminotransferase [AST]  $\geq 1.5 \times$  ULN AND alanine aminotransferase [ALT]  $\geq 1.5 \times$  ULN) or renal impairment (estimated Glomerular Filtration Rate [eGFR]  $\leq 29$  mL/min/1.73 m<sup>2</sup> based on the Modification of Diet in Renal Disease [MDRD] equation) at screening or on

- the day of surgery.
18. Clinically significantly abnormal clinical laboratory value at screening or on the day of surgery.
  19. Positive human immunodeficiency virus antibody, hepatitis B virus surface antigen, or hepatitis C virus antibody status at screening.
  20. Clinically significantly abnormal electrocardiogram, including a QT interval corrected for heart rate (Fridericia; QTcF interval) of > 450 milliseconds in males and > 470 milliseconds in females, at screening.

**Immediate Postoperative Period Entry Inclusion and Exclusion Criteria:**

*Inclusion criteria*

1. Underwent primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation.
2. Moderate or severe pain on a four-point categorical pain rating scale (with categories of none, mild, moderate, or severe) within 9 hours after discontinuation of regional anesthesia.
3. NRS  $\geq$  4 within 9 hours after discontinuation of regional anesthesia.

*Exclusion criteria*

1. Duration of surgical event from incision to skin closure > 90 minutes.
2. Surgical, postsurgical or anesthetic complication that could confound the interpretation of efficacy, safety or tolerability data in the study.
3. Deviation from the surgical, postsurgical or anesthetic protocol that could confound the interpretation of efficacy, safety or tolerability data in the study.
4. Evidence of hemodynamic instability or respiratory insufficiency.

**Drugs in Study During Randomized Treatment Period:**

- *Study drug:* Oliceridine 0.1, 0.35, and 0.5 mg PCA demand randomized dosing groups with dosing prn via PCA or clinician-administered supplemental dosing
- *Active comparator:* Morphine 4 mg
- *Placebo:* Volume-match solution (i.e., the active formulation without the active pharmaceutical ingredient)
- *Rescue analgesics:* Etodolac 200 mg every 6 hours PRN if PCA demand doses plus supplemental dose are inadequate and NRS  $\geq$ 4
- *Rescue antiemetic:* If requested or if nausea grade as moderate or severe on a 4-category scale (none, mild, moderate, severe). Prophylactic antiemetic medication was not to have been permitted. No specific antiemetic was prespecified in the protocol.

**Study treatments:** Patients were to have been randomized 1:1:1:1:1 ratio to one of five study medication regimens: placebo, morphine, oliceridine 0.1 mg, oliceridine 0.35 mg, or oliceridine 0.5 mg.

**Table 56: Study 3001 Randomized Treatment Regimens**

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

PRN=as needed; q1h=every 1 hour  
Applicant's table, Study 3001 Protocol, Version 3.0, p. 31

**Key Procedures: Schedule of Activities:**

**Table 57: Schedule of Events Confinement Phase (Pre-surgical, Surgery, Immediate Post-Operative)**

	Screening Phase (Day -35 to Day -1)	Confinement Phase					Follow-up Phase (Day 7 +/- 2 days)	
		Presurgical Period (Day 0)	Surgery (Day 0)	Immediate Postoperative Period (Day 0 to Day 1)	Randomized Treatment Period (Day 1 to Day 3)	Predischarge Period (Day 3)		
Informed consent	X				Refer to Detailed SOE			
Entry criteria <sup>a</sup>	X	X		X				
Demographics	X							
Medical history	X							
Physical examination <sup>b</sup>	X						X	X
Podiatric examination & x-ray <sup>c</sup>	X							
ASA physical status classification	X	X						
Vital signs <sup>d</sup>	X	X		X			X	X
Height, weight & BMI <sup>e</sup>	X	X						
12-lead electrocardiogram (ECG)	X			X				
Clinical laboratories (hematology, chemistry)	X	X					X	X
Coagulation panel	X							
Viral serology	X							
Pregnancy test for female patients	X	X						
Urine drug screen	X	X						
Alcohol breathalyzer test	X	X						
Patient training <sup>f</sup>	X	X						
Establish PSB			X					
Bunionectomy			X					
Discontinue regional anesthesia				Day 1 ~3 AM				
Randomization		X						
NRS				X				
Four-point categorical pain rating scale				X				
Clinician satisfaction with study medication						X		

NDA 210730  
Oliceridine injection

Patient satisfaction with study medication					Refer to Detailed SOE	X	
Blood sample for CYP2D6 genotyping						X	
Prior/concomitant medications	← X →					← X →	
AEs/SAEs <sup>f</sup>	← X →					← X →	
Outpatient diary, Subjective Opiate Withdrawal Scale (SOWS) and prescription for outpatient analgesic therapy						X	
Collect, review outpatient diary & SOWS						X	

**Footnotes for Schedule of Events**

- Preoperative entry criteria will be evaluated at screening and during the presurgical period. Immediate postoperative period entry criteria will be evaluated during the IPP.
- A complete physical examination (excluding the breast and genitourinary examination) will be performed at screening. A physical examination assessing changes from the initial physical examination, including an examination of the patient’s surgical site, will be performed at the other times.
- Podiatric x-ray performed within 6 months before screening are acceptable.
- Vital signs are sitting or supine BP, HR, RR, and oral temperature. Oral temperature at the follow-up visit will be performed if clinically indicated.
- Height at screening only.
- Patient training on pain assessment, placebo response and PCA utilization will occur at screening and during the presurgical period; training may be repeated to ensure patient understanding.
- AEs occurring from the time of signed informed consent to the follow up phase will be recorded in source and will also be recorded in electronic data capture (EDC) if the patient is randomized. SAEs occurring from the time of signed informed consent to the follow-up phase or 7 days after the last dose of study medication (whichever occurs later) will be recorded in source and EDC; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to study medication, regardless of the time of onset after treatment, should be reported. (Study 3001 Protocol, Version 3.0, p. 34-35)

**Table 58: Detailed Schedule of Events Randomized Treatment Period**

Study min Study hour	Base line <sup>a</sup>	T0 <sup>b</sup>	5	10	15	30	45	1	2	3	4	5	6	7 <sup>c</sup>	8	9	10	11	12	18	24	32	40	48		
			0.08	0.17	.25	.5	.75																			
Loading dose		X																								
Demand doses <sup>d</sup>			→																							
Clinician-administered supplemental doses			→																							
Start stopwatches		X																								
NRS <sup>e</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Categorical pain relief scale <sup>e</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs <sup>f</sup>	X				X			X	X	X	X		X		X		X		X	X	X	X	X	X		
Pulse oximetry <sup>g</sup>			→																							
Moline-Roberts Pharmacologic Sedation Scale	X					X		X	X	X	X		X		X		X		X	X	X	X	X	X		
ECG <sup>h</sup>								X													X			X		
PK sampling <sup>i</sup>						1		2								3		4								
Concomitant medications			→																							
RSE evaluation <sup>j</sup>			→																							
AEs/SAEs <sup>k</sup>			→																							

**Footnotes for Detailed Schedule of Events – Randomized Treatment Period**

- Baseline measures will be completed within 10 minutes before T0.
- T0 is defined as the start of the loading dose.
- T7 hours and thereafter: if patient is asleep at any scheduled time point or points, indicated procedures will be performed within one hour after awakening.
- Demand dose availability will conclude at T48 hours with a +15 minute window.
- NRS and categorical pain relief scale will be assessed at the indicated time points. Additionally, an unscheduled NRS will be performed before, and 5 minutes after, any clinician-administered, blinded supplemental dose, before any rescue pain medication, and before early discontinuation of study medication. For time points where several procedures are scheduled, the following sequence will be followed: NRS, pain relief scale, vital signs, ECG and PK.

- f) Vital signs during the randomized treatment period are BP, HR and RR. For time points where several procedures are scheduled, the following sequence will be followed: NRS, pain relief scale, vital signs, ECG and PK.
- g) Pulse oximetry will be continuously monitored during the randomized treatment period; values will be recorded when vital signs are recorded.
- h) For time points where several procedures are scheduled, the following sequence will be followed: NRS, pain relief scale, vital signs, ECG and PK.
- i) Sample 1 at T30 minutes +/- 10 minutes; sample 2 at T1 hr +/- 10 minutes; sample 3 between T6 hr and T12 hr, and sample 4 between T12 hr and T18 hr. Samples 3 and 4 will be at least one hour apart from one another. In addition to the scheduled PK sampling, unscheduled PK samples will be obtained after a patient uses three PCA syringes within the first 12 hours or before a patient would receive a seventh clinician-administered, blinded supplemental dose within the first 12 hours; or if a patient experiences a serious AE or a severe AE during the Confinement Phase. As the determination of a serious AE or a severe AE is sometimes retrospective, unscheduled PK samples obtained when an event that is suspected to be serious or severe are also permitted.
- j) Please see methodology of RSE evaluation in Section 13.2.1. Given the multifactorial nature of RSE evaluation, a certified registered nurse anesthetist (CRNA) or anesthesiologist will monitor the patient for RSEs.
- k) AEs occurring from the time of signed informed consent to the follow up phase will be recorded in source and will also be recorded in EDC if the patient is randomized. SAEs occurring from the time of signed informed consent to the follow-up phase or 7 days after the last dose of study medication (whichever occurs later) will be recorded in source and EDC; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to study medication, regardless of the time of onset after treatment, should be reported.

(Study 3001 Protocol, Version 3.0, p. 37-38)

### **Concurrent Medications:** During the Randomized Treatment Period

Patients were to have received rescue analgesic (etodolac) and rescue antiemetic if needed. Ice packs were allowed after T12 hours. If used, ice packs were to have been removed at least 15 minutes before scheduled pain assessments (NRS and pain relief).

### **Outcome Measures Assessments**

- *Efficacy Assessments:* The pain parameters to be assessed in this study were to have been pain intensity and pain relief. Pain intensity was to be assessed using the NRS. Pain relief was to be assessed using the qualitative, categorical pain relief scale. Both were to have been assessed at the following time points:
  - NRS and Pain Relief Assessments:
    - Baseline: within 10 minutes before T0 (NRS only)
    - 5, 10, 15, 30, and 45 minutes (post T0)
    - 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 12, 18, 24, 32, 40, and 48 hours
    - Before, and 5 minutes after, any clinician-administered, blinded supplemental dose
    - Before any rescue pain medication
    - Before early discontinuation of study medication
  - NRS and pain relief scale assessments were to have been performed using the following time windows:
    - T5, T10, T15 minutes: +/- 2 minutes
    - T30 minutes - T6 hours, inclusive: +/- 5 minutes
    - T7 hours and thereafter: +/- 10 minutes, if patient awake; if patient asleep at any scheduled time point, within one hour after awakening
    - After a clinician-administered, blinded supplemental dose: +/- 2 minutes
  - Pain relief assessed:
    - using the qualitative, categorical pain relief scale
    - using the two stopwatch technique
- *Safety Assessments:*
  - Adverse Events

- Clinical laboratories and vital signs
- Physical examination
- Electrocardiogram (ECG)
- Respiratory Safety Events (defined as a clinically relevant worsening of respiratory status)
- Opioid Withdrawal Syndrome
- *Tolerability Assessments*
  - Nausea events
  - Vomiting events
  - Rescue antiemetic medication utilization
- *Scheduled PK Assessments:* PK samples were to be collected at four times during the randomized treatment period:
  - Sample 1 at T30 minutes +/- 10 minutes;
  - Sample 2 at T1 hr +/- 10 minutes;
  - Sample 3 between T6 hr and T12 hr;
  - Sample 4 between T12 hr and T18 hr.
- *Unscheduled PK Assessments:* In addition to the scheduled PK sampling, unscheduled PK samples will be obtained under the following circumstances:
  - After a patient uses three PCA syringes within the first 12 hours or before a patient would receive a seventh clinician-administered, blinded supplemental dose within the first 12 hours; or
  - If a patient experiences a serious AE or a severe AE during the Confinement Phase. As the determination of a serious AE or a severe AE is sometimes retrospective, unscheduled PK samples obtained when an event that is suspected to be serious or severe are also permitted.
- *Other Assessments*
  - Analgesic Therapeutic Success: To assess the proportion of patients who experience analgesic therapeutic success, defined as primary endpoint responders who, additional, had no dosing interruptions compared to morphine
  - Clinician Satisfaction with Study Medication: Using a 7-point Likert scale
  - Patient Satisfaction with Study Medication: Using a 7-point Likert scale

### **Study Endpoints:**

- *Primary Efficacy Endpoint:* The proportion of patients who respond to study medication at the 48-hour NRS assessment. The responder efficacy endpoint was also to have been used for key secondary non-inferiority and superiority efficacy assessments of oliceridine compared to morphine. A patient is a responder if:
  - Their final time-weighted Sum of Pain Intensity Differences from baseline (SPID-48) corresponds to, or is greater than, a 30% improvement,
  - Without rescue pain medication during the randomized treatment period,
  - Without early discontinuation of study medication for any reason,
  - Without reaching the study medication dosing limit.
- *Key Secondary Efficacy Endpoint:*
  - The respiratory safety burden safety/tolerability endpoint measured as the expected cumulative duration of a RSE

- The proportion of patients who responded to study medication at the 48-hour NRS assessment vs morphine (superiority and non-inferiority)
- *Other Secondary Efficacy Endpoints:*
  - Response variables (Responder Type)
    - The proportion of patients who respond to study medication over time (e.g., 3 hr, 6 hr, 12 hr, 24 hr and 48 hr)
    - The proportion of patients who both respond to study medication and have no dosing interruptions over time (e.g., 3 hr, 6 hr, 12 hr, 24 hr and 48hr)
    - The proportion of patients who respond to study medication across the full range of outcomes by computing the percent of subjects, y, that achieve a reduction of pain of x percent, for x ranging from 0 to 100. These proportions will require that the other conditions of primary endpoint response are met.
  - Pain intensity-related variables
    - Time weighted sum of pain intensity differences (SPID) from T0 to each scheduled time point after T0
    - Pain intensity difference (PID) at each scheduled time point after T0
    - Pain intensity score at each scheduled time point
    - Time-weighted average change from baseline over different time intervals
    - Categorical pain relief at scheduled time points
  - Time-to Onset-Related Variables
    - Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief)
    - Time to first perceptible pain relief
    - Time to first meaningful pain relief
  - Other
    - Proportion of patients using rescue pain medication
    - Time to first use of rescue pain medication
    - Total use of rescue pain medication over different time intervals
  - Clinician and Patient Satisfaction with Study Medication
- *Key Secondary Safety Endpoint:*
  - Respiratory Safety Event (RSE): The respiratory burden, as measured by the occurrence and duration of Respiratory Safety Events was to have been a key secondary safety endpoint. A respiratory safety event (RSE) is defined as a clinically relevant worsening of respiratory status and have the following parameters:
    - A RSE may be identified at any time during the randomized treatment period and may extend beyond the randomized treatment period. Identification of a RSE will lead to recurrent evaluations with the goals of determining the duration of the event and tracking any interventions provided in response to the RSE.
    - The expected cumulative duration of a RSE will be computed to measure the “respiratory safety burden” for each treatment group
    - The respiratory safety burden safety/tolerability endpoint incorporates both the prevalence of RSEs and the expected time that a patient would experience a RSE if one occurred in a single composite measure that is

interpretable and relevant to clinical practice.

- This endpoint corresponds to the total amount of time a patient from the population should expect to experience a RSE and represents the respiratory safety burden for a given treatment group. The respiratory safety burden will be a key secondary safety/tolerability endpoint for the superiority assessment of oliceridine to morphine.
- *Other Secondary Safety and Tolerability Endpoints*
  - Proportion of patients who experience a dosing interruption
  - Cumulative duration of dosing interruptions
  - Proportion of patients who experience nausea and/or vomiting
  - Differences in oxygen saturation measurements
  - Somnolence/sedation scores
  - Incidence of adverse events

### **Statistical Analysis Plan**

See Section 7 (Clinical/Statistical Efficacy) for full details and discussion regarding the Statistical Analysis Plan (SAP) and discussions of efficacy findings.

### **Protocol Amendments**

APPEARS THIS WAY ON ORIGINAL

Protocol CP130-3001 was amended three times as follows.

- Version 1: Dated January 20, 2016
- Version 2: Dated April 22, 2016
- Version 3: Dated May 19, 2016

The first patient was enrolled on May 13, 2016 and the last patient completed on October 19, 2016. No patients were enrolled under Protocol Versions 1 or 2. Most of the protocol changes were made in Version 2 after an End-of-Phase 2 meeting which was held on March 29, 2016. There were no major changes from Version 2 to Version 3 that would significantly impact efficacy or safety, therefore, Version 2 changes are discussed. The key changes from Protocol Version 1 to protocol Version 2 are as follows:

- Added new text to clarify the dosing limit of oliceridine. With regard to total exposure, the cumulative dose of study medication was obtained from the loading dose, plus any PCA demand doses, plus any clinician-administered, blinded supplemental doses. For the current study, the dosing limit for oliceridine was 60 mg in the first 12 hours. This high level of utilization was only achievable with the oliceridine 0.5 mg dose regimen, as it was the most concentrated oliceridine regimen, and established the dosing limit for all treatment groups. Therefore, as a conservative estimation, after a patient used three PCA syringes within the first 12 hours or before a patient received a seventh clinician-administered, blinded supplemental dose within the first 12 hours, a PK sample was obtained, the patient was to be discontinued early from study medication, and was to be managed conventionally.
- Clarified the instructions regarding clinical monitoring of RSEs (Respiratory Safety Events).
- Added instructions to clarify clinician-administered, blinded supplemental dosing.
- Added use of SOWS (Subjective Opioid Withdrawal Scale) to assess opioid withdrawal
- Added instructions to clarify PK sampling
- Updated the responder efficacy endpoint, as described for the primary endpoint, to be used for the key secondary noninferiority and superiority efficacy assessments of oliceridine vs morphine.
- Replaced the proportion of patients who experienced an RSE with the respiratory safety burden as a key secondary safety/tolerability endpoint.
- Updated the statistical methods to state the sample size of 375 patients (75 per treatment group) was estimated to provided 88% power to demonstrate that at least two oliceridine treatment groups were simultaneously superior to placebo for the responder efficacy endpoint, superior to morphine for the respiratory safety burden safety/tolerability endpoint, and noninferior to morphine for the responder efficacy endpoint. In addition, definitions of analysis sets and imputation of NRS scores were clarified.

## **ii. Study CP130-3002 - Overview and Objectives**

Study CP130-3002, also referred to as APOLLO 2 or Study 3002, was one of the key Phase 3 efficacy studies to support the proposed indication.

The discussion below pertains to Protocol Version 3.0, dated May 20, 2016 which was the last protocol and the one under which all patients were enrolled. Study 3002 has the same general study design as Protocol 3001 but differs in the following key areas:

- Patient population is s/p abdominoplasty (versus s/p bunionectomy in Study 3001)
- Confinement is for two days and one night (i.e., duration of treatment is 24 hours vs 48 hours in Study 3001)
- Primary efficacy endpoint is over a 24-hour assessment period (vs 48 hrs in Study 3001)
- Postoperative Pain Entry Criteria is  $NRS \geq 5$  on NRS (vs  $NRS \geq 4$  in Study 3001)
- General anesthesia is used (vs regional anesthesia in Study 3001)

**Title/Design:** A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study of Oliceridine (TRV130) for the Treatment of Moderate to Severe Acute Pain after Abdominoplasty

**Primary Objective:** To evaluate the analgesic efficacy of intravenous (IV) oliceridine administered as needed (PRN) compared with placebo in patients with moderate to severe acute pain after abdominoplasty.

**Secondary Objectives:** 1) To evaluate the safety/tolerability of oliceridine compared with morphine, 2) To evaluate the analgesic efficacy of oliceridine compared with morphine, and 3) To evaluate the safety/tolerability of oliceridine compared with placebo

**Overview:** This was to have been a Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled to be conducted in three phases:

- Screening Phase: Screening procedures were to have been completed within 35 days before surgery
- Confinement Phase: The Confinement Phase was to have covered the period to include the day of surgery (Day 1) and was to end on postoperative Day 2 (2days, 1 night). The confinement Phase included the following key periods:
  - *Pre-surgical Period:* This period was to have been completed before surgery and include training on pain assessment, placebo response, and patient controlled analgesia (PCA) utilization
  - *Randomization Period:* Patients were to have been randomized in a 1:1:1:1:1 ratio to placebo, morphine or one of three oliceridine regimens (0.1 mg, 0.35 mg, 0.5 mg)
  - *Surgical Event:* Patients were to undergo abdominoplasty procedure with no additional collateral procedures. Surgical anesthesia was to have been initiated on the day of surgery no later than approximately 5:00 pm.
  - *Immediate Postoperative Period (IPP):*
    - Following surgery, patients were to have been transferred to the post anesthesia care unit (PACU). If necessary, analgesia after surgery, but before investigational product administration, could be maintained with IV bolus doses of fentanyl until the patient met the Immediate Postop Period entry criteria (see below). At least 20 minutes was to elapse between the final dose of fentanyl (either intraoperative or postoperative) and initiation of study medication. After this, when a patient requested pain treatment, they were to rate their pain intensity using an 11-point NRS and a four-point categorical pain rating scale.
    - *IPP Entry Criteria:* Patients could enter the randomized treatment period if they met IPP entry criteria within 4 hours after the end of surgery (defined as time of last suture or staple placement). If the patient did not qualify, they were considered to be screening failures and were to have been managed conventionally.
  - *Randomized Treatment Period:* During this period, safety and efficacy were assessed at multiple prespecified time points (see discussion under Endpoints section of this review for further details regarding types and frequency of assessments). Blood was also collected for pharmacokinetics (PK).
  - *Pre-discharge Period:* Following the randomized treatment period, patients were to have been assessed for discharge and received an outpatient diary to

record adverse events, outpatient analgesic therapy, any new medications, a Subjective Opiate Withdrawal Scale (SOWS), and a prescription for outpatient analgesic therapy (per the investigator's discretion).

- Follow-up: The patient was to have returned to the study site on postoperative day 7±2 days and return the outpatient diary and Subjective Opioid Withdrawal Scale (SOWS)

**Pre-Operative Inclusion and Exclusion Criteria:** The inclusion and exclusion criteria are the same as those for Study 3001, except any specific references to bunionectomy in Study 3001 are abdominoplasty in Study 3002.

**Immediate Post-Operative Inclusion and Exclusion Criteria:**

*Inclusion criteria:*

1. Underwent abdominoplasty procedure with no additional collateral procedures and recovered from the intraoperative anesthetic and analgesic regimen to the point where they were lucid enough to accurately complete protocol-mandated questionnaires, in the opinion of the investigator.
2. Moderate or severe pain on a four-point categorical pain rating scale (with categories of none, mild, moderate, or severe) within 4 hours after EoSx (End of Surgery).
3. NRS  $\geq$  5 within 4 hours after EoSx.

*Exclusion Criteria:*

1. Duration of surgical event from incision to EoSx > 2.5 hours.
2. Surgical, postsurgical or anesthetic complication that could confound the interpretation of efficacy, safety or tolerability data in the study.
3. Deviation from the surgical, postsurgical or anesthetic protocol that could confound the interpretation of efficacy, safety or tolerability data in the study.
4. Evidence of hemodynamic instability or respiratory insufficiency.

**Key Procedures:** The schedule of events with key procedures is shown in the tables below.

**Table 59: Study 3002 Schedule of Events**

	Screening Phase (Day -35 to Day 0)	Confinement Phase					Follow-up Phase (Day 7 +/- 2 days)	
		Presurgical Period (Day 1)	Surgery (Day 1)	Immediate Postoperative Period (Day 1)	Randomized Treatment Period (Day 1 to Day 2)	Predischarge Period (Day 2)		
Informed consent	X				Refer to Detailed SOE			
Entry criteria <sup>a</sup>	X	X		X				
Demographics	X							
Medical history	X							
Physical examination <sup>b</sup>	X						X	X
ASA physical status classification	X	X						
Vital signs <sup>c</sup>	X	X		X			X	X
Height, weight & BMI <sup>d</sup>	X	X						
12-lead electrocardiogram (ECG)	X	X						
Clinical laboratories (hematology, chemistry)	X	X					X	X
Coagulation panel	X							
Viral serology	X							
Pregnancy test for female patients	X	X						
Urine drug screen	X	X						
Alcohol breathalyzer test	X	X						
Patient training <sup>e</sup>	X	X						
Initiate surgical anesthesia <sup>f</sup>			X					
Abdominoplasty			X					
Randomization		X						
NRS				X				
Four-point categorical pain rating scale				X				
Clinician satisfaction with study medication						X		
Patient satisfaction with study medication						X		
Blood sample for CYP2D6 genotyping						X		
Prior/concomitant medications		← X →			Refer to Detailed SOE	← X →		
AEs/SAEs <sup>g</sup>		← X →				← X →		
Outpatient diary, Subjective Opiate Withdrawal Scale (SOWS) and prescription for outpatient analgesic therapy						X		
Collect, review outpatient diary & SOWS							X	

**Footnotes for Schedule of Events**

- a) Preoperative entry criteria will be evaluated at screening and during the presurgical period. Immediate postoperative period entry criteria will be evaluated during the IPP.
- b) A complete physical examination (excluding the breast and genitourinary examination) will be performed at screening. A physical examination assessing changes from the initial physical examination, including an examination of the patient’s surgical site, will be performed at the other times.
- c) Vital signs are sitting or supine BP, HR, RR, and oral temperature. Oral temperature at the follow-up visit is performed if clinically indicated.
- d) Height at screening only.
- e) Patient training on pain assessment, placebo response and PCA utilization will occur at screening and during the presurgical period; training may be repeated to ensure patient understanding.
- f) Anesthesia to be initiated on the day of the surgery no later than approximately 5:00PM.
- g) AEs occurring from the time of signed informed consent to the follow up phase will be recorded in source and will also be recorded in electronic data capture (EDC) if the patient is randomized. SAEs occurring from the time of signed informed consent to the follow-up phase or 7 days after the last dose of study medication (whichever occurs later) will be recorded in source and EDC; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to study medication, regardless of the time of onset after treatment, should be reported.

Applicant’s table, Study 3002 protocol Version 3, p. 35-36

**Table 60: Detailed Schedule of Events – Randomized Treatment Period (Day 1 to Day 2)**

Study min Study hour	Base line <sup>a</sup>	T0 <sup>b</sup>	5	10	15	30	45	1	2	3	4	5	6	7 <sup>c</sup>	8	9	10	11	12	18	24
			0.08	0.17	.25	.5	.75														
Loading dose		X																			
Demand doses <sup>d</sup>																					
Clinician-administered supplemental doses																					
Start stopwatches		X																			
NRS <sup>e</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Categorical pain relief scale <sup>e</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs <sup>f</sup>	X					X		X	X	X	X		X		X		X		X	X	X
Pulse oximetry <sup>g</sup>																					
Moline-Roberts Pharmacologic Sedation Scale	X					X		X	X	X	X		X		X		X		X	X	X
ECG <sup>h</sup>								X													X
PK sampling <sup>i</sup>						1		2								3				4	
Concomitant medications																					
RSE evaluation <sup>j</sup>																					
AEs/SAEs <sup>k</sup>																					

**Footnotes for Detailed Schedule of Events – Randomized Treatment Period**

- a) Baseline measures will be completed within 10 minutes before T0.
- b) T0 is defined as the start of the loading dose.
- c) T7 hours and thereafter: if patient is asleep at any scheduled time point or points, indicated procedures will be performed within one hour after awakening.
- d) Demand dose availability will conclude at T48 hours with a +15 minute window.
- e) NRS and categorical pain relief scale will be assessed at the indicated time points. Additionally, an unscheduled NRS will be performed before, and 5 minutes after, any clinician-administered, blinded supplemental dose, before any rescue pain medication, and before early discontinuation of study medication. For time points where several procedures are scheduled, the following sequence will be followed: NRS, pain relief scale, vital signs, ECG and PK.
- f) Vital signs during the randomized treatment period are BP, HR, and RR. For time points where several procedures are scheduled, the following sequence will be followed: NRS, pain relief scale, vital signs, ECG and PK.
- g) Pulse oximetry will be continuously monitored during the randomized treatment period; values will be recorded when vital signs are recorded.
- h) For time points where several procedures are scheduled, the following sequence will be followed: NRS, pain relief scale, vital signs, ECG and PK.
- i) Sample 1 at T30 minutes +/- 10 minutes; sample 2 at T1 hr +/- 10 minutes; sample 3 between T6 hr and T12 hr, and sample 4 between T12 hr and T18 hr. Samples 3 and 4 will be at least one hour apart from one another. In addition to the scheduled PK sampling, unscheduled PK samples will be obtained after a patient uses three PCA syringes within the first 12 hours or before a patient would receive a seventh clinician-administered, blinded supplemental dose within the first 12 hours; or if a patient experiences a serious AE or a severe AE during the Confinement Phase. As the determination of a serious AE or a severe AE is sometimes retrospective, unscheduled PK samples obtained when an event that is suspected to be serious or severe are also permitted.
- j) Please see methodology of RSE evaluation in Section 13.2.1. Given the multifactorial nature of RSE evaluation, a certified registered nurse anesthetist (CRNA) or anesthesiologist will monitor the patient for RSEs.
- k) AEs occurring from the time of signed informed consent to the follow up phase will be recorded in source and will also be recorded in EDC if the patient is randomized. SAEs occurring from the time of signed informed consent to the follow-up phase or 7 days after the last dose of study medication (whichever occurs later) will be recorded in source and EDC; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to study medication, regardless of the time of onset after treatment, should be reported.

Applicant’s table, Study 3002 protocol Version 3, p. 37-38

**Pre-surgical and Surgical Event Concomitant Medications and Treatments:**

- Allowed Pre-surgical period and surgical event: The standardized anesthetic regimen is general anesthesia with fentanyl and propofol, with or without volatile anesthetics or muscle relaxants. Anesthetic doses are at the discretion of the anesthesia provider. The standardized anesthetic regimen is a guide that should be followed to minimize interpatient variability to the greatest extent possible.
- Prohibited surgical medications:
  - Any opioid other than fentanyl
  - Any intraoperative or postoperative steroids
  - Any NSAID (e.g., ketorolac, Celebrex, Caldolor, etc.)
  - Intravenous acetaminophen (Ofirmev™)
  - Epidural or intrathecal agents

- Regional or neuraxial anesthesia
- Long-acting local anesthetic agents (Exparel™)
- Prophylactic antiemetics including, but not limited to, 5HT receptor antagonists, scopolamine, dexamethasone

**Immediate postoperative period (IPP) Allowed Concomitant Medications:** During the IPP, analgesia, if necessary, may be maintained with IV bolus doses of approximately 25 ug of fentanyl until the patient meets the IPP entry criteria

**Randomized Treatment Period Allowed Concomitant Medications:**

- Rescue Pain Medication: See Study 3001
- Antiemetic Medication: See Study 3001

**Endpoints:**

- Primary Efficacy Endpoint: The efficacy and safety endpoints for Study 3002 are the same as those for Study 3001 but differ due to the time duration of 24 hours in Study 3002 versus 48 hours in Study 3001. The primary endpoint for this study was to have been the proportion of patients who respond to study medication at the 24-hour NRS assessment. See Study 3001 for Responder definition.
- Key Secondary Endpoints: See Study 3001.
- Other Secondary Endpoints: See Study 3001.

**Statistical Analysis**

The overall statistical analysis plan is the same as that for Study 3001, except for the differences in study duration which could affect timing of assessments used for analyses. See Study 3001 for details.

**Amendments:** Protocol CP130-3002 was amended three times as follows:

- Version 1: Dated January 20, 2016. No patients were enrolled.
- Version 2: Dated May 3, 2016. No patients were enrolled.
- Version 3: Dated May 20, 2016

The first patient was enrolled on May 27, 2016 and the study was completed (i.e., last patient visit) on December 15, 2016. Major protocol changes were made in Version 2 after an End-of-Phase 2 meeting which was held on March 29, 2016. There were no major changes from Version 2 to Version 3 that would significantly impact efficacy or safety. The key changes from Protocol Version 1 to protocol Version 2 are the same as those listed under Protocol 3001 discussion.

**iii. Study CP130-3003 – Overview and Objectives**

Study CP130-3003, also known as ATHENA or study 3003, was an open-label, Phase 3 study primarily designed for supportive safety and efficacy. There were five protocol amendments. The discussion below represents the last version, Version 5, under which most patients were enrolled.

**Protocol Number:** CP130-3003, Version 5.0; September 14, 2016

**Title/Design:** A Phase 3, Open-Label Study To Evaluate The Safety Of Oliceridine (TRV130) In Patients With Acute Pain For Which Parenteral Opioid Therapy Is Warranted

**Primary Objective:** To evaluate the safety and tolerability of oliceridine in patients with moderate to severe acute pain for which parenteral opioid therapy is warranted

**Secondary Objective:** To evaluate the analgesic efficacy of oliceridine

**Population:** Planned approximately 1000 surgical and medical patients in approximately 60-90 study centers in the U.S. The patient population types are listed below:

- Representative surgeries include orthopedic (e.g., total hip replacement, total knee replacement, spine), abdominal (e.g., upper or lower abdominal, perineal), gynecologic (e.g., total abdominal hysterectomy), vascular, soft tissue, and surgical procedural pain;
- Representative medical conditions include acute pancreatitis, acute exacerbation of existing non-cancerous chronic pain, musculoskeletal pain, sickle-cell disease, inflammatory orofacial muscle pain, and renal colic. Medical conditions that could confound the evaluation of oliceridine are excluded, such as acute pain without a specific etiology, undifferentiated acute abdominal pain, acute breakthrough pain in palliative “end of life” care, and pain associated with advanced cancer (somatic, visceral, or neuropathic) or with concurrent use of chemotherapeutic or biologic agents for the treatment of cancer;
- Representative emergency department (ED) conditions include visceral pain (e.g., renal colic, upper abdominal pain, abdominal pelvic pain); nonvisceral pain (e.g., traumatic and atraumatic acute musculoskeletal pain, chest wall pain, burns, orofacial pain/headache, cutaneous and soft tissue pain); procedural analgesia (e.g., reduction of orthopedic fractures and dislocations, abscess incision and drainage); acute painful episodes associated with a medical condition (e.g., sickle cell painful vaso-occlusive episode).

**Study Drug:** TRV130 1 mg/mL as free base via IV route delivered via clinician and patient.

**Dosing Limit:** The dosing limit for oliceridine was to be 60 mg in the first 12 hours. If a patient reaches this dosing limit within the first 12 hours, a PK sample will be obtained, the patient will early discontinue oliceridine and will be managed conventionally.

**Dosing:** Dosing during the study was to have been delivered via the clinician and/or patient as follows:

- Clinician administered
  - Initial dose: 1 mg to 2 mg
  - Supplemental dose: If clinically indicated, a 1 mg supplemental dose may be administered within 15 minutes after the initial dose

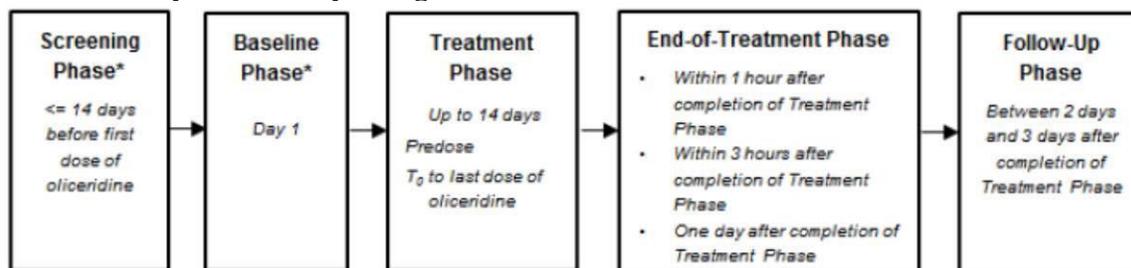
- Subsequent doses: 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to TRV130
- In settings where rapid analgesia is targeted (e.g., Emergency Department or post-anesthesia care unit (PACU)):
  - Initial dose: 1 to 3 mg.
  - If clinically indicated, 1 to 3 mg supplemental doses may be administered every 5 minutes PRN.
  - Subsequent doses: 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to oliceridine.
- PCA Regimen
  - Loading dose: 1.5 mg
  - Demand dose: 0.5 mg delivered via PCA (lock-out interval of 6 minutes via PCA device)
  - Supplemental dose: If clinically indicated, throughout the treatment phase, a 1 mg supplemental dose may be administered PRN, taking into account the patient's utilization of PCA demand doses, individual patient need, and previous response to oliceridine.

**Duration:** The duration of the treatment for each patient was to have been determined by the clinical need for parenteral opioid therapy. The Sponsor states that in current surgical and medical practice, depending on the clinical scenario, parenteral opioids are used as-needed for approximately 2-3 days and up to several days.

**Study Overview:** This phase 3, open-label, safety study was to be conducted in inpatient hospitals, outpatient hospital departments, ambulatory surgical care centers, and emergency departments (EDs). Patients recruited in EDs were to have been allowed to continue oliceridine treatment if hospitalized and parenteral opioid therapy is warranted.

The study was to have four phases: Screening/baseline; Treatment Phase (consisting of a Pre-dose period and a dosing period); End-of-Treatment Phase, and Follow-up Phase as shown below.

**Figure 21: Study 3003 Study Design Schematic**



Abbreviations: T0 = time of first dose of oliceridine; h = hours

\* Combined if occurring within 48 hours of each other, unless the clinical condition of the patient has significantly changed since screening

Applicant's Figure, Study 3003 Protocol (V. 5), p. 28

**Key Inclusion Criteria:**

1. Males and females  $\geq 18$  years at screening.
2. Moderate to severe acute pain for which parenteral opioid therapy is warranted, defined as Numeric Pain Rating Scale (NPRS) pain intensity  $\geq 4$  during the pre-dose period.
3. If it is anticipated that the patient will be treated with oliceridine in the emergency department (ED) with subsequent discharge or transfer to another facility, that the patient will remain under the care of the investigator for at least three hours after the last dose of oliceridine.

### Exclusion Criteria

1. Participated in another oliceridine clinical study.
2. Clinically significant medical, surgical, postsurgical, psychiatric or substance abuse condition or history of such condition that would confound the interpretation of safety, tolerability, or efficacy data in the study.
3. Hemodynamic instability or respiratory insufficiency; or requires a tracheostomy or mechanically assisted ventilation.
4. If a surgical or medical patient, American Society of Anesthesiologists (ASA) Physical Status Classification System score of IV or worse (American Society of Anesthesiologists, 2014); if an ED patient, Emergency Severity Index (ESI) triage score of 1.
5. If an ED patient, alcohol intoxication, acute substance impairment or positive urine or serum toxicology screen.
6. Advanced cancer in palliative or end-of-life care.
7. Concurrent use of chemotherapeutic or biologic agents for the treatment of cancer.
8. Another current painful condition (other than acute pain for which parenteral opioid therapy is warranted) that would confound the interpretation of safety, tolerability, or efficacy data in the study.
9. Clinically significant, immune-mediated hypersensitivity reaction to opioids.
10. Pregnancy, breastfeeding, or positive urine or serum pregnancy test at screening.
11. Hepatic impairment (total bilirubin  $> 2 \times$  upper limit of normal [ULN], aspartate aminotransferase [AST]  $\geq 1.5 \times$  ULN AND alanine aminotransferase [ALT]  $\geq 1.5 \times$  ULN) or renal impairment (estimated Glomerular Filtration Rate [eGFR]  $\leq 29$  mL/min/1.73 m<sup>2</sup> based on the Modification of Diet in Renal Disease [MDRD] equation), known or obtained at screening.
12. History of human immunodeficiency virus, hepatitis B, or hepatitis C.
13. Clinically significant abnormal clinical laboratory values, known or obtained at screening.
14. Clinically significant abnormal electrocardiogram (ECG), including a QT interval corrected for heart rate (Fridericia; QTcF interval) of  $> 450$  msec in males and  $> 470$  msec in females, known or obtained at screening.

### Key Phases and Procedures:

- *Screening/Baseline:* All screening procedures will be completed within 14 days before the first TRV130 dose. AEs were to be recorded from time of informed consent signing to follow-up; Key procedures include the following: Urine pregnancy, 12-lead ECG, PCA patient training; ASA physical status classification and physical examination; clinical laboratories; vital signs

- *Treatment Phase*: Begins with the pre-dose period and ends when the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine.
  - Pre-dose (Day 1): PI (pain intensity) will be measured on a 0-10 point Numeric Pain Rating Scale (NPRS) and the following assessments will be conducted:
    - Vital signs (BP, HR, RR, temperature)
    - Moline-Roberts Pharmacologic Sedation Scale (MRPSS); Oxygen saturation
    - Postsurgical ECG in surgical patients only
    - Prior and concomitant medications
    - AEs reporting
    - Predose procedures will occur within 30 minutes before the first oliceridine dose. If the dosing period is delayed, predose period procedures (except post-surgical ECG performed only in surgical patients) will be repeated.
  - Dosing Period (T0 [time of first dose of TRV130] to last dose):
    - Oliceridine IV infusion may be administered either by clinician-administered bolus, patient-controlled analgesia device (PCA), or both bolus and PCA, according to the clinical situation.
    - Safety Assessments:
      - Vital signs, oxygen saturation, and somnolence/sedation will be measured at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid
      - An ECG will be obtained 60 minutes after the first dose of oliceridine, and at every 24 hours of oliceridine treatment
      - Blood will be collected for clinical laboratory test, oliceridine PK and future cytochrome P450 2D6 (CYP2D6) genotyping
      - Concomitant medications and AEs/SAEs will be recorded
      - Oxygen saturation monitoring will be continuous but will be recorded at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid.
    - Efficacy Assessment: NPRS will be completed at 30 minutes  $\pm$  10 minutes after the first dose and at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid.
- *End-of-Treatment Phase*
  - Physical examination will be performed at the end of treatment
  - Within one hour after completion of Treatment Phase: Vital signs; MRPSS; Oxygen saturation; Prior and concomitant medications; AEs/SAEs will be recorded
  - Within 3 hours after completion of treatment, blood will be collected for clinical laboratory tests. Concomitant medications and AEs/SAEs will be recorded.

- Patients will be observed for at least three hours after the last dose of oliceridine. However, medically-required transfer of an ED patient to another facility takes precedence over study procedures.
- Subjective Opioid Withdrawal Scale (SOWS) will be administered to detect symptoms of opioid withdrawal. If the patient is discharged or transferred before the time when the SOWS is to be performed, it will be performed one day after completion of the treatment phase and returned to the site by mail or in person.
- *Follow-up Phase (Between 2 days and 3 days after completion of Treatment Phase): May be conducted in person (clinic) or by phone.*
  - Concomitant medications and AEs will be recorded
  - Surgical procedure or medical diagnosis will be captured using the International Classification of Diseases, 10th Revision (ICD-10) terminology.

### **Study Endpoints**

- Safety and Tolerability Endpoints
  - Adverse events (including those related to vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical examination findings, and clinical laboratory assessments).
  - Somnolence/sedation will be measured using the Moline-Roberts Pharmacologic Sedation Scale.
- Analgesic Efficacy: The Numeric Pain Rating Scale (NPRS), a 0-10 point scale, was to have been used. Analgesic efficacy was to have been measured using NPRS at the following time points:
  - During the predose period
  - 30 minutes  $\pm$  10 minutes after the first dose of oliceridine
  - At any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid

### **Statistical Analyses:**

- Safety: The number and incidence of AEs/SAEs will be summarized overall and by severity and causality. Summary statistics for observed values and change from baseline values for vital sign measurements, oxygen saturation measurements, somnolence/sedation scores, physical examination findings, and clinical laboratory assessments will be summarized. Baseline values are defined as the last measurements taken before the first dose of oliceridine. SOWS total scores will be summarized. Prior and concomitant medications will be summarized.
- Efficacy: The NPRS scores at baseline and 30 minutes after the first dose of TRV130, as well as change from baseline to 30 minutes, will be summarized using descriptive summary statistics. All NPRS assessments will be listed at each time point where an assessment has occurred.

**Protocol Amendments:** The protocol was amended five times with dates of the protocol versions and number enrolled under the protocols shown in the table below.

**Table 61: Study 3003 Protocol Amendments**

Version	Date	Number enrolled	Major Protocol Changes
1	November 16, 2015	0	No
2	December 9, 2015	58	No
3	May 6, 2016	0	Yes
4	June 2, 2016	147	No
5	September 14, 2016	326	Yes

Table, reviewer

The first patient was enrolled on December 23, 2015 and the study was completed (i.e., last patient visit) on May 12, 2017.

Major amendments occurred in Versions 3 and 5, summarized below:

- Protocol Version 3:
  - Merged the CP130-3004 ED (Emergency Department) open-label safety study with this study. (Reviewer’s Comment: Study CP130-3004 was a planned Open-Label study but was never initiated).
  - Added ED patient population and changed sample size estimate from 900 to 1000 patients
  - Edited exclusion criteria to include tracheostomy or manually-assisted ventilation, an Emergency Severity Index (ESI) triage score of 1, and alcohol intoxication, acute substance impairment, or positive urine/serum toxicology screen.
  - Added SOWS and PK sampling.
  - Changed oliceridine dosing limit from 36.8 mg in 24 hours to 60 mg in the first 12 hours.
  - Added ECG analyses and QT interval corrected for heart rate (Fridericia; QTcF) stopping procedures.
- Protocol Version 5: Allowed PCA regimen supplemental dose to be administered via PCA pump.
  - Demand dose: 0.5 mg delivered via PCA device PRN (lock-out interval of 6 minutes via PCA device)

### c. Additional Efficacy Tables

**Table 62: 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 63: 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=79	Oliceridine 0.5 mg N=79	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)
Estimated mean SPID (SE)	100.7 (9.17)	138.0 (9.34)	142.3 (9.17)	166.4 (9.20)	194.4 (9.38)
Estimated mean 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
Estimated mean 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 64: 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=79	Oliceridine 0.5 mg N=79	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)
Estimated mean SPID (SE)	92.7 (9.31)	134.4 (9.48)	139.7 (9.30)	165.0 (9.33)	193.6 (9.52)
Estimated mean 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
Estimated mean 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 65: 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=79	Oliceridine 0.5 mg N=79	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)
Estimated mean SPID (SE)	73.4 (9.85)	126.3 (10.03)	136.8 (9.85)	162.2 (9.88)	191.0 (10.07)
Estimated mean 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
Estimated mean 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 66: 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)
Estimated mean SPID (SE)	80.7 (4.39)	78.9 (4.48)	91.4 (4.42)	94.3 (4.44)	103.6 (4.35)
Estimated mean 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
Estimated mean 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 67: 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)
Estimated mean SPID (SE)	78.0 (4.45)	78.1 (4.41)	90.9 (4.48)	94.2 (4.50)	103.3 (4.41)
Estimated mean 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
Estimated mean 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 68: 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)
Estimated mean SPID (SE)	74.8 (4.56)	76.8 (4.66)	89.7 (4.60)	94.0 (4.61)	103.0 (4.52)
Estimated mean 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
Estimated mean 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 69: Expected Cumulative Duration of O<sub>2</sub> Administration (hours) (Study 3001)**

Statistic	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	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 70: Proportion with any O<sub>2</sub> Administration (Study 3001)**

Statistic	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	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 71: 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 72: 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	

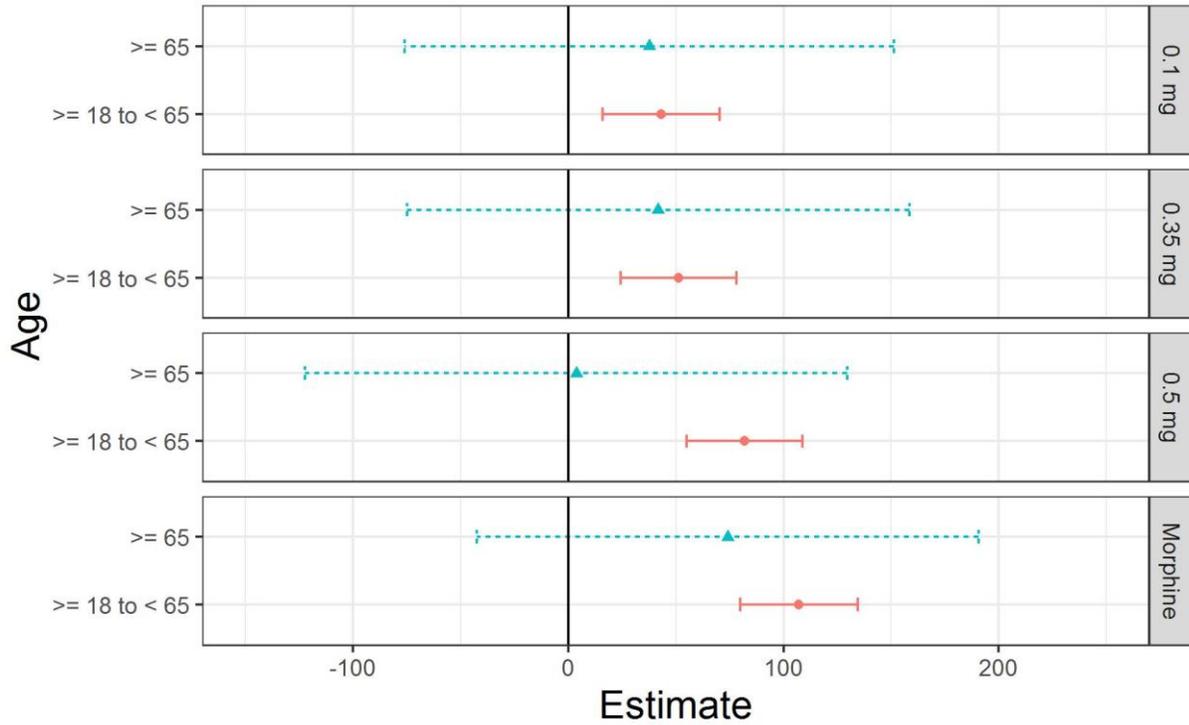
Source: FDA Reviewer

**Table 73: 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)
BMI	< 25	68.7 (28.6, 108.7)	65.4 (24.7, 106.1)	72.1 (30.1, 114.2)	124.1 (83.0, 165.1)
	≥ 25	28.1 (-7.8, 64.0)	41.7 (6.8, 76.6)	77.2 (42.6, 111.9)	93.5 (58.2, 128.9)

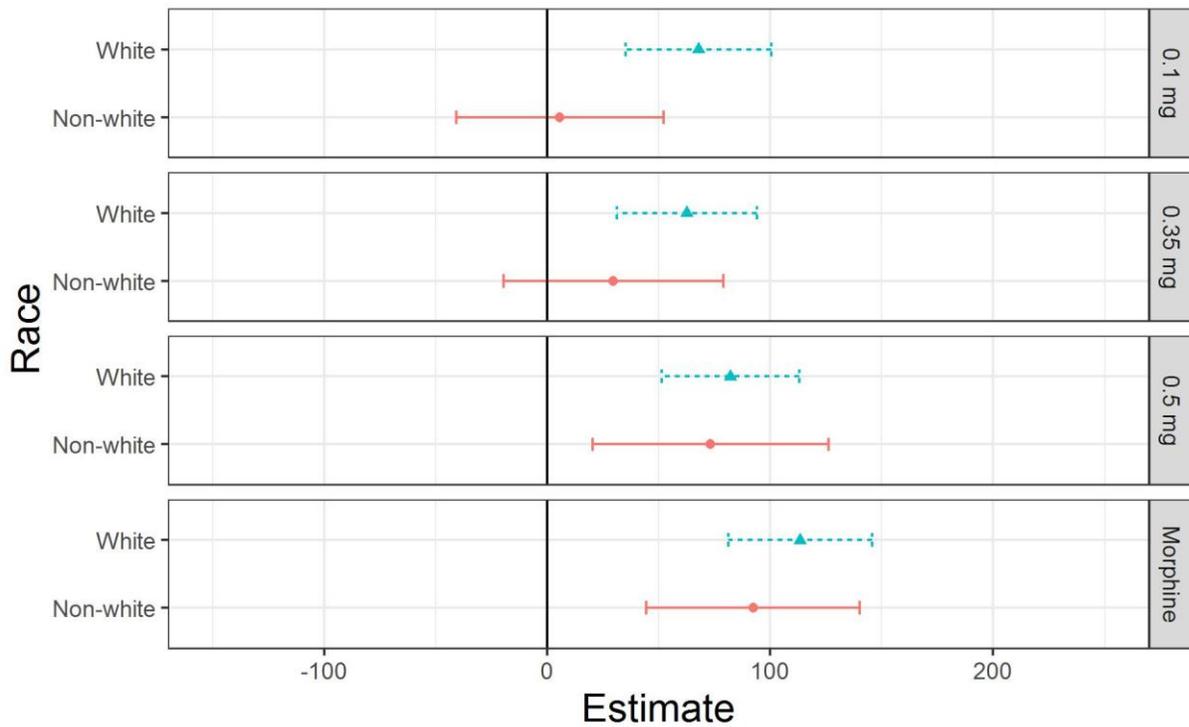
Source: FDA Reviewer

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



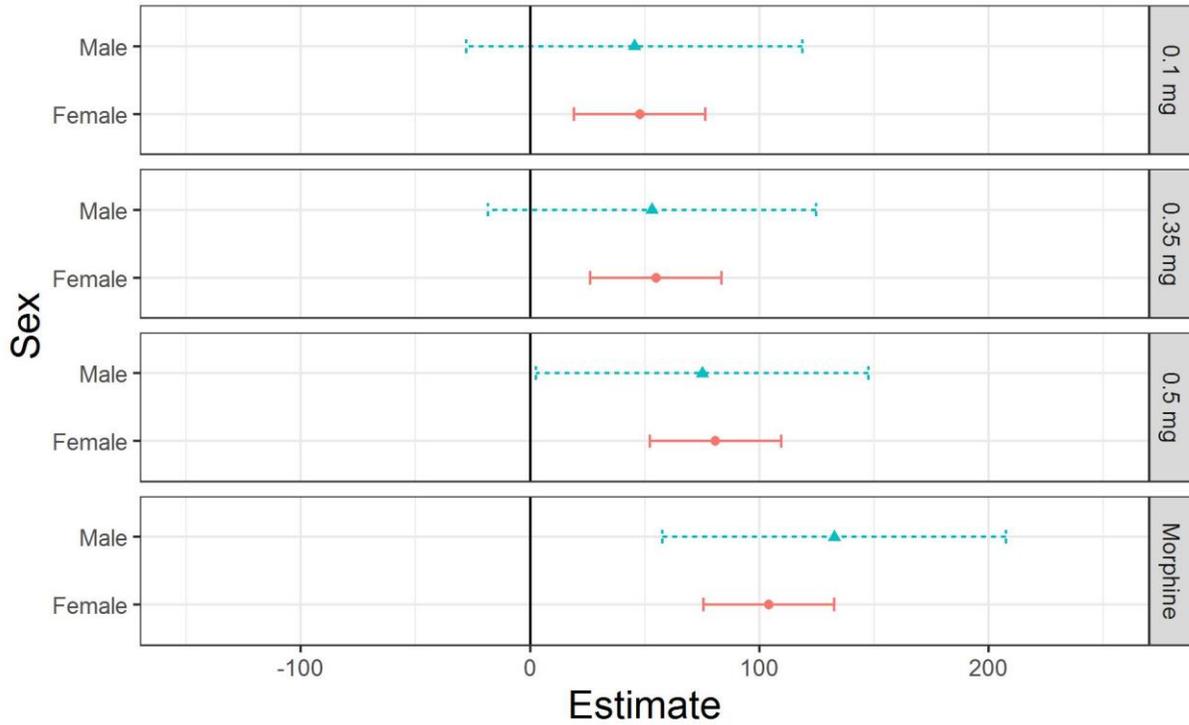
Source: FDA Reviewer

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



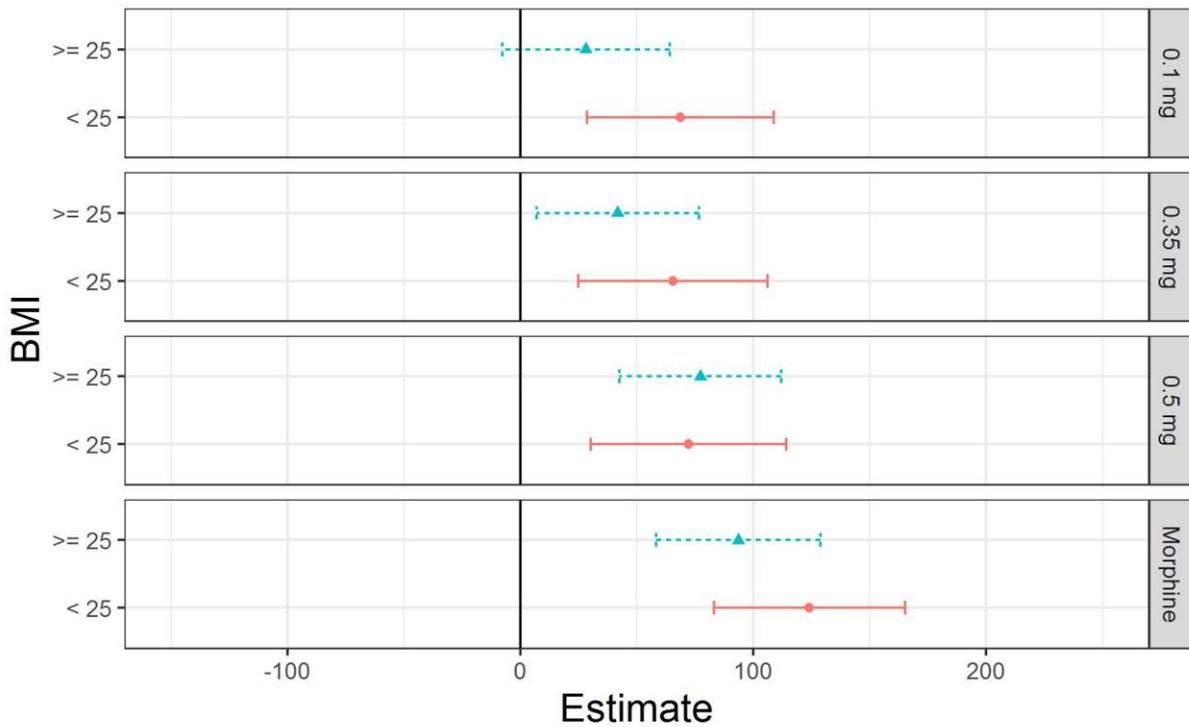
Source: FDA Reviewer

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



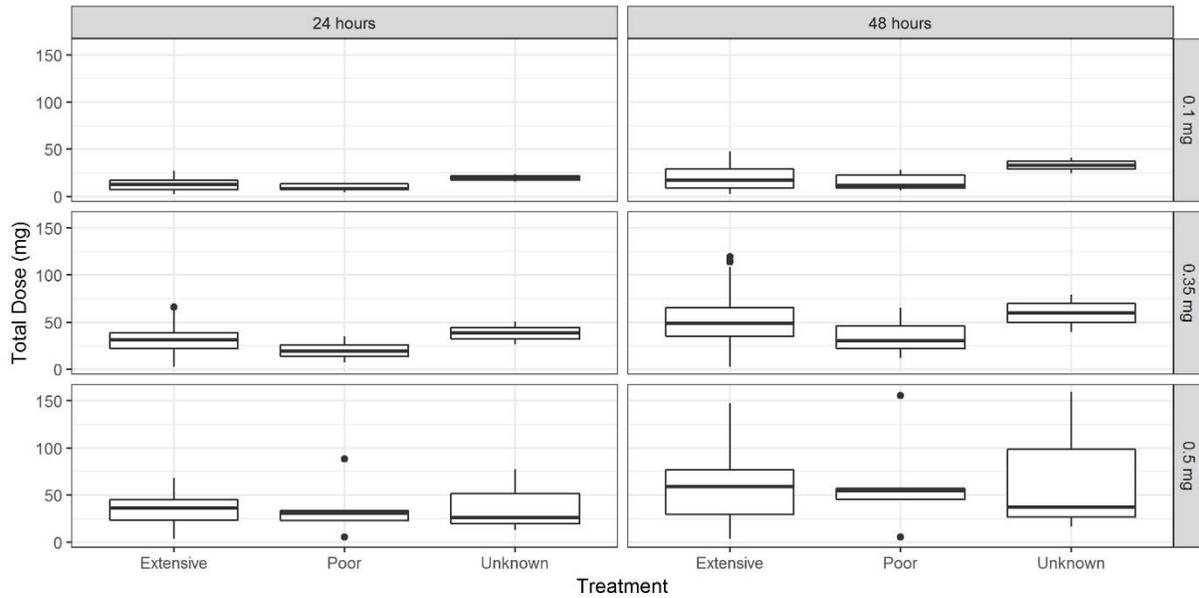
Source: FDA Reviewer

**Figure 25: Forest Plot of Treatment Effect vs Placebo by BMI Category (Study 3001)**



Source: FDA Reviewer

**Figure 26: Box Plots of Oliceridine Exposure by Dose Group and Metabolizer status at 24- and 48-hours (Study 3001)**



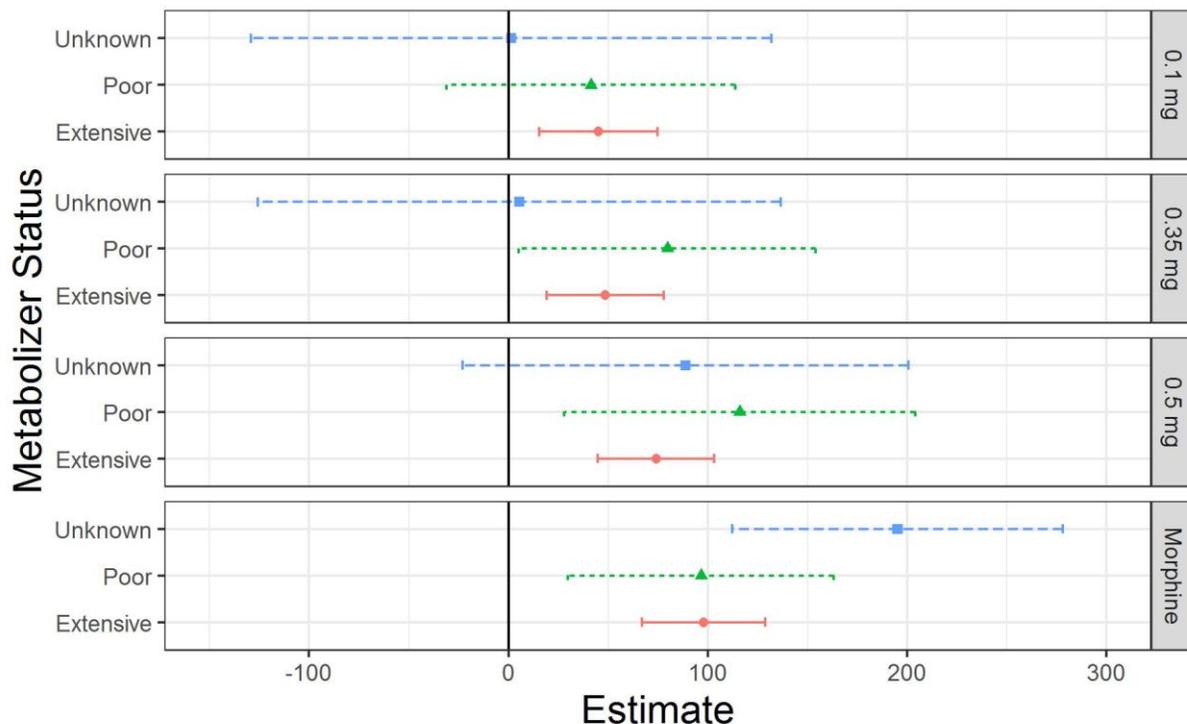
Source: FDA Reviewer

**Table 74: Estimated Treatment Effect vs Placebo by CYP2D6 Metabolizer Status (Study 3001)**

Metabolizer Status	Oliceridine 0.1 mg	Oliceridine 0.35 mg	Oliceridine 0.5 mg	Morphine
Extensive	45.1 (15.3, 74.9)	48.4 (19.1, 77.8)	74.0 (44.7, 103.3)	98.0 (67.1, 128.9)
Poor	41.4 (-31.2, 114.0)	79.7 (5.1, 154.2)	116.0 (27.8, 204.2)	96.5 (29.8, 163.3)
Unknown	1.4 (-129.2, 131.9)	5.5 (-125.6, 136.6)	88.8 (-22.9, 200.6)	195.2 (112.3, 278.1)

Source: FDA Reviewer

**Figure 27: Forest Plot of Treatment Effect vs Placebo by CYP2D6 Metabolizer Status (Study 3001)**



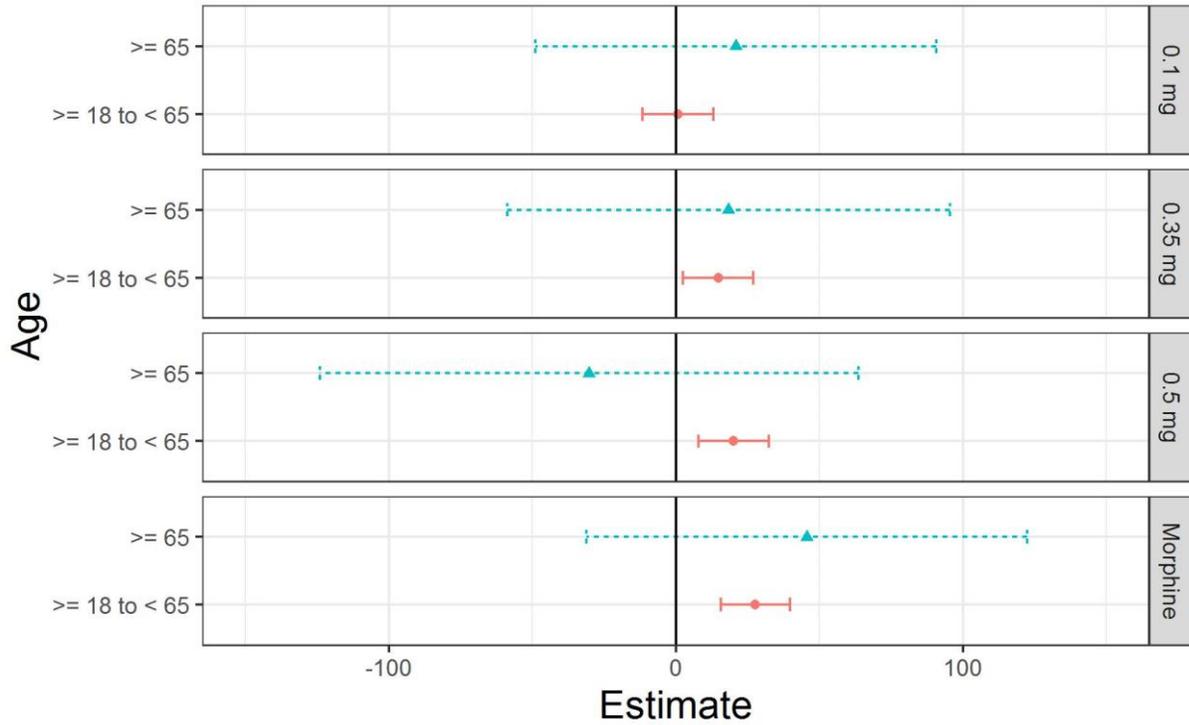
Source: FDA Reviewer

**Table 75: 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	-	-	-	-
BMI	< 25	-3.7 (-28.4, 20.9)	-0.3 (-26.4, 25.8)	11.2 (-13.1, 35.6)	13.9 (-8.4, 36.2)
	≥ 25	4.9 (-9.3, 19.0)	20.2 (6.3, 34.1)	22.6 (8.3, 36.9)	33.8 (19.5, 48.1)

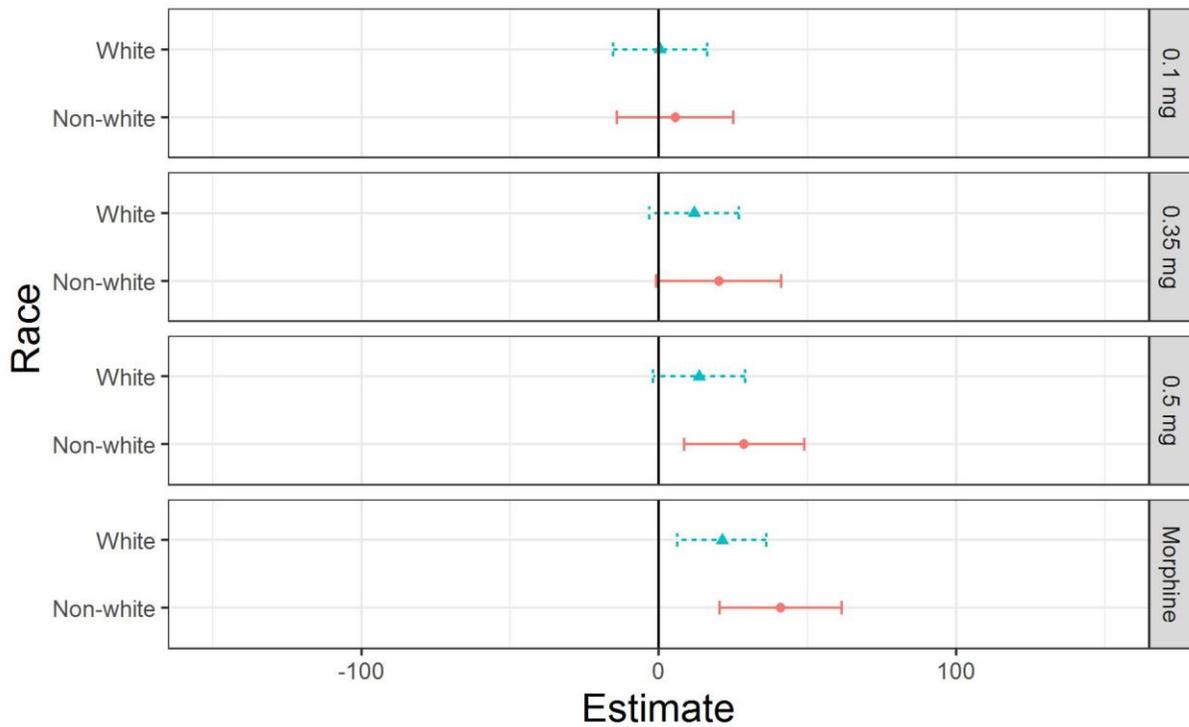
Source: FDA Reviewer

**Figure 28: Forest Plot of Treatment Effect vs Placebo by Age Group (Study 3002)**



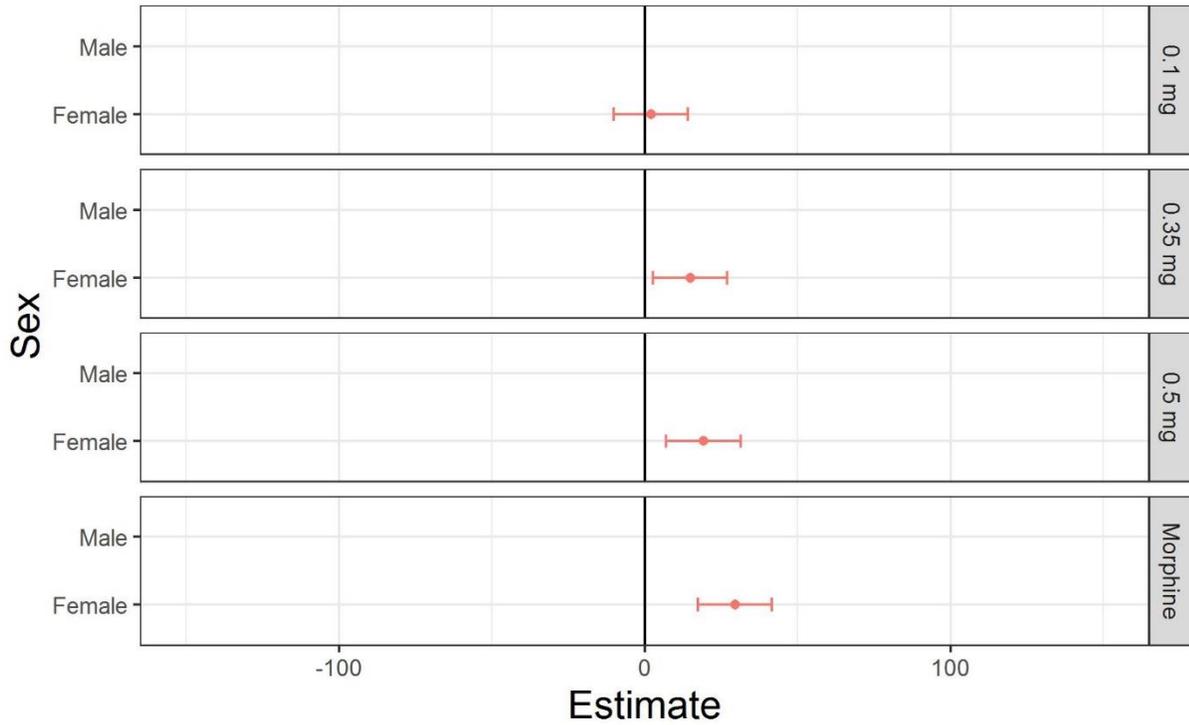
Source: FDA Reviewer

**Figure 29: Forest Plot of Treatment Effect vs Placebo by Race Group (Study 3002)**



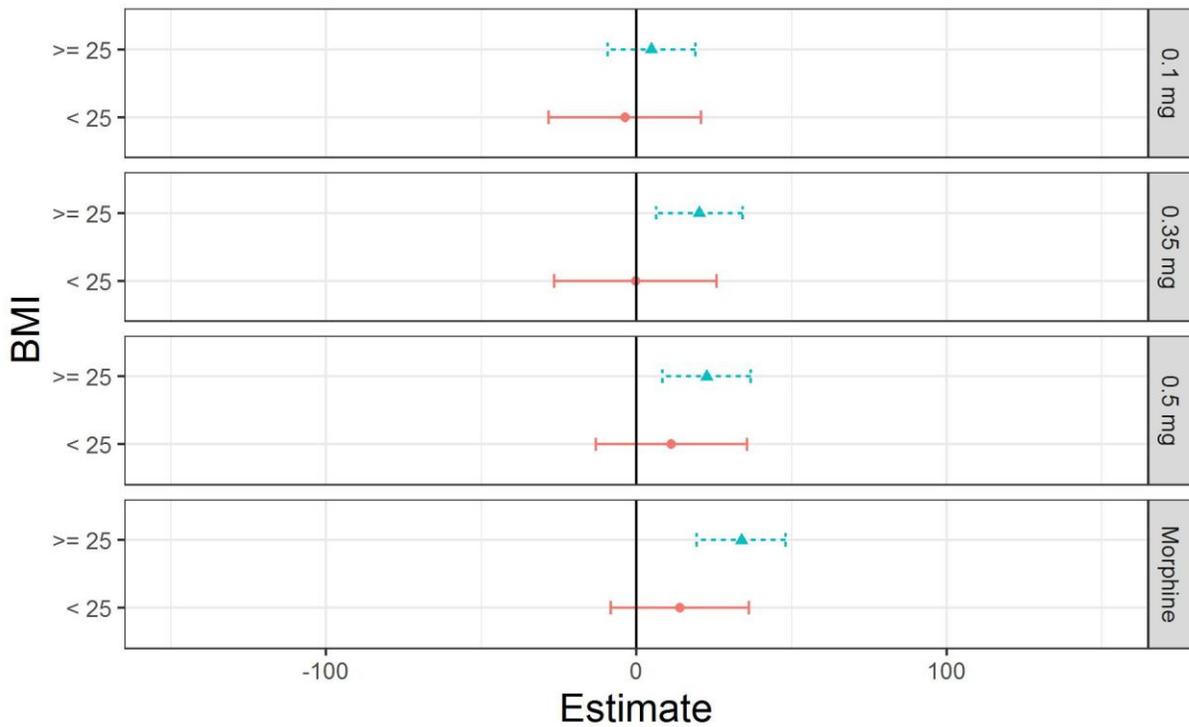
Source: FDA Reviewer

**Figure 30: Forest Plot of Treatment Effect vs Placebo by Sex (Study 3002)**



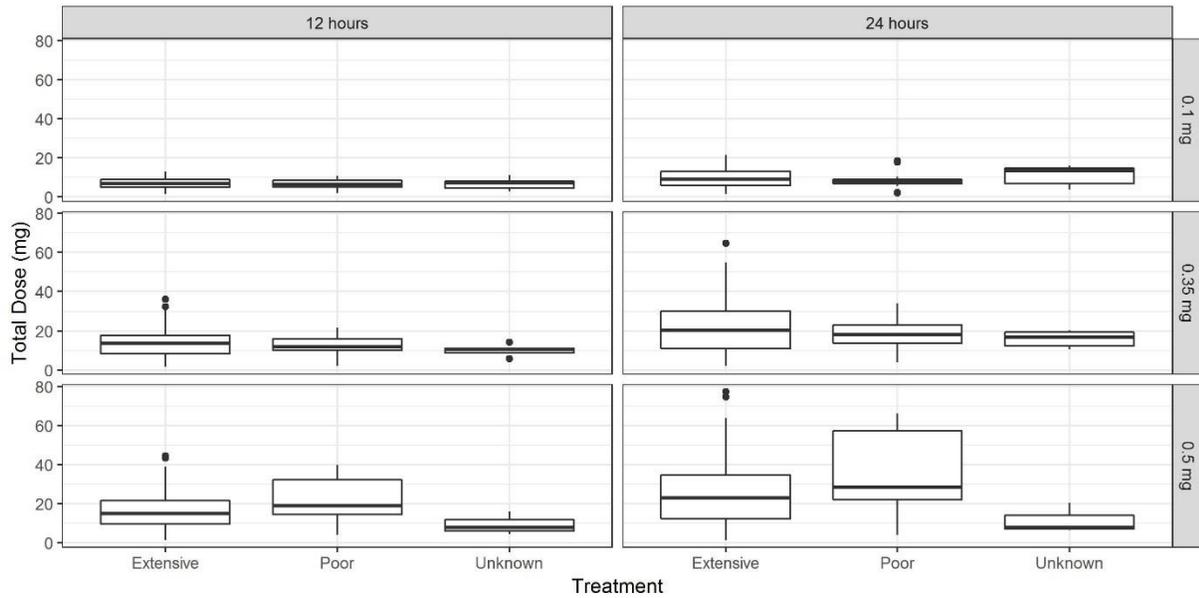
Source: FDA Reviewer

**Figure 31: Forest Plot of Treatment Effect vs Placebo by BMI Category (Study 3002)**



Source: FDA Reviewer

**Figure 32: Box Plots of Oliceridine Exposure by Dose Group and Metabolizer status at 24- and 48-hours (Study 3002)**



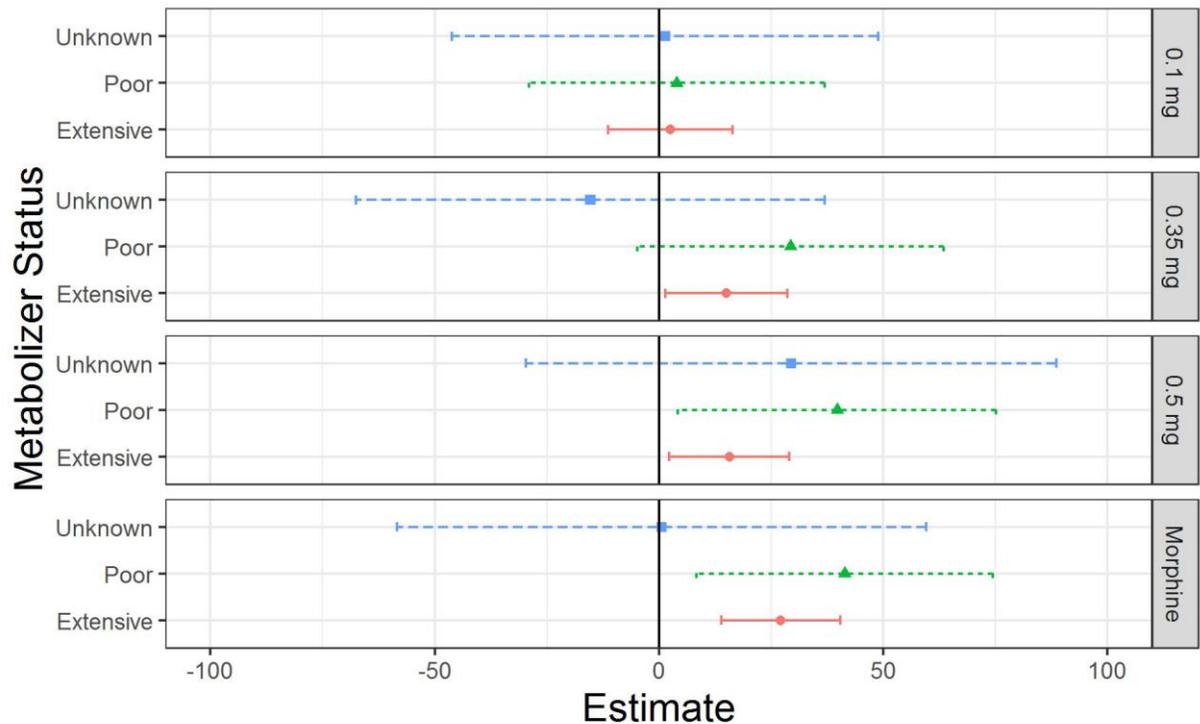
Source: FDA Reviewer

**Table 76: Estimated Treatment Effect vs Placebo by CYP2D6 Metabolizer Status (Study 3001)**

Metabolizer Status	Oliceridine 0.1 mg	Oliceridine 0.35 mg	Oliceridine 0.5 mg	Morphine
Extensive	2.5 (-11.4, 16.4)	15.0 (1.4, 28.6)	15.7 (2.3, 29.1)	27.2 (13.9, 40.5)
Poor	4.0 (-29.0, 36.9)	29.3 (-4.8, 63.5)	39.7 (4.2, 75.2)	41.4 (8.4, 74.4)
Unknown	1.3 (-46.2, 48.9)	-15.3 (-67.6, 37.0)	29.5 (-29.6, 88.6)	0.6 (-58.4, 59.6)

Source: FDA Reviewer

**Figure 33: Forest Plot of Treatment Effect vs Placebo by CYP2D6 Metabolizer Status (Study 3002)**



Source: FDA Reviewer

**d. Clinical Investigator Financial Disclosure**

**Definition in 21 CFR part 54 Covered Clinical Study:** Any study of a drug, biologic, or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the drug product is effective (including studies that show equivalence to an effective drug product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. In general, this does not include phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, or expanded access protocols.

**Appendix: Clinical Investigator Financial Disclosure**

**Covered Clinical Study: CP130-2001**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <u>Not Applicable</u></p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</p> <p>Significant payments of other sorts:</p> <p>Proprietary interest in the product tested held by investigator:</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study:</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation

reason:		from Applicant)
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**Covered Clinical Study: CP130-2002**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <u>Not Applicable</u></p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</p> <p>Significant payments of other sorts:</p> <p>Proprietary interest in the product tested held by investigator:</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study:</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study: CP130-3001**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 7		
Number of investigators who are Sponsor employees (including both full-time and part-time		

employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <u>Not Applicable</u>  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:  Significant payments of other sorts:  Proprietary interest in the product tested held by investigator:  Significant equity interest held by investigator in S  Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study: CP130-3002**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 7		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <u>Not Applicable</u>  Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

**Covered Clinical Study: CP130-3003**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 42		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <u>Not Applicable</u>  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)

NDA 210730  
Oliceridine injection

Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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/s/  
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ELIZABETH M KILGORE  
11/01/2018

JAMES E TRAVIS  
11/01/2018

DAVID M PETULLO  
11/01/2018  
I concur.

MARK D ROTHMANN  
11/01/2018  
I concur

JANET W MAYNARD  
11/01/2018

MARY T THANH HAI  
11/01/2018  
Concur with the recommendations

## Tertiary Pharmacology/Toxicology Review

**Date:** October 31, 2018  
**From:** Timothy J. McGovern, PhD, ODE Associate Director for  
Pharmacology and Toxicology, OND IO  
**NDA:** 210730  
**Agency receipt date:** November 2, 2017  
**Drug:** Oliceridine fumarate injection, 1 mg/mL  
**Sponsor:** Trevana Inc.

**Indication:** Management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted

**Reviewing Division:** Division of Anesthesia, Analgesia, and Addiction Products

The primary pharmacology/toxicology reviewer and team leader concluded that the nonclinical data for Oliceridine do not support approval and recommended a Complete Response due to concerns surrounding the safety qualification for a disproportionate human metabolite. The metabolite TRV0109662 represents ~ <sup>(b)</sup><sub>(4)</sub> % of the total drug related material observed in humans. While the metabolite was adequately qualified in a 14-day general toxicity study in rats, TK samples from a rat embryo-fetal development study failed Incurred Sample Reanalysis; therefore, it is questionable whether sufficient exposure to the metabolite was achieved to adequately characterize potential effects on development. The reviewer recommends that the sponsor either provide adequate TK data to demonstrate sufficient exposure was achieved in an embryo-fetal development (EFD) study or conduct a new EFD study of the metabolite in rats or rabbits. It was noted that if the overall risk:benefit of the product is supportive, the deficiency could be addressed as a Post Marketing Requirement.

Oliceridine is a 1 mg/mL sterile injection solution in product presentations including 1 mL, 2 mL, and 30 mL. The maximum proposed clinical dosing is 40 mg/day. The Established Pharmacologic Class (EPC) for Oliceridine is “opioid agonist”.

The nonclinical program supporting clinical development of Oliceridine included a pharmacology, ADME, general toxicology studies (28 days duration in rats and 14 days duration in monkeys), genetic toxicology, and reproductive toxicity studies. The primary findings impacting clinical safety included cardiovascular effects (weak hERG inhibition though no consistent effects on QTc were observed in in vivo studies), typical effects associated to the opioid class of drugs, findings related to opioid withdrawal/stress and findings associated with the placement of the indwelling catheter (lung thrombosis, injection site inflammation). Overall the findings are either monitorable in the clinical or do not represent a significant safety concern for the proposed short-term use of the product. Oliceridine was not associated with any findings of concern in genetic toxicity studies. A battery of reproductive toxicity studies identified effects on female fertility (longer estrous cycle, reduced number of implantation sites, increased preimplantation loss, and reduced viable embryos) and postnatal development (reduced live litter size, postnatal survival, and body weight). No effects on male fertility or EFD were observed.

Studies to address the human disproportionate metabolites were also conducted and did not result in findings of concern though, as noted above, questions remain as to whether sufficient exposure was achieved in a rat EFD study.

**Conclusion:** I agree with the Division pharmacology/toxicology conclusion that this NDA is deficient from the pharmacology/toxicology perspective based on the lack of adequate safety assessment for the disproportionate human metabolite TRV0109662. I agree with the Division recommendations regarding how this deficiency can be addressed. I have reviewed and agree with revisions to the nonclinical sections of the product label proposed by the Division.

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/s/  
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TIMOTHY J MCGOVERN  
10/31/2018

# Office of Clinical Pharmacology Review

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<b>NDA or BLA Number</b>	210730
<b>Link to EDR</b>	\\cdsesub1\evsprod\NDA210730
<b>Submission Date</b>	11/2/2017
<b>Submission Type</b>	<i>Standard Review</i>
<b>Brand Name</b>	Olinvo
<b>Generic Name</b>	Oliceridine Fumarate Injection
<b>Dosage Form and Strength</b>	IV Injection,
<b>Route of Administration</b>	Intravenous
<b>Proposed Indication</b>	Management of Acute Pain where an intravenous opioid is indicated.
<b>Applicant</b>	Trevena Inc.
<b>Associated IND</b>	113537
<b>OCP Review Team</b>	<i>Srikanth C. Nallani, Ph.D.</i>
<b>Pharmacometrics Reviewer</b>	<i>Venkatesh Atul Bhattaram, Ph.D.</i>
<b>PBPK Reviewer</b>	<i>Manuela Grimstein, PhD; Xinyuan Zhang, Ph.D.</i>
<b>PGx Reviewer</b>	<i>Oluseyi Adeniyi, Ph.D.</i>
<b>PM TL</b>	<i>Kevin Krudys, Ph.D.</i>
<b>PGx TL</b>	<i>Christian Grimstein, Ph.D.</i>
<b>OCP Final Signatory</b>	<i>Yun Xu, Ph.D.</i>

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## 1. EXECUTIVE SUMMARY

### 1.1 Recommendations

Review Issue	Recommendations and Comments
<b>Supportive evidence of effectiveness</b>	Primary evidence of effectiveness is derived from two Phase 3 clinical trials oliceridine for treatment of moderate to severe acute pain (bunionectomy trial CP130-3001 and abdominoplasty trial CP130-3002).
<b>General dosing instructions</b>	The initial dose of Olinvyk should be 1 to 2 mg. 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 initial previous dose based on individual patient need and previous response to Olinvyk. Maintenance of analgesia is generally achieved with Olinvyk administered as doses of 1 to 2 mg every 1 to 3 hours as needed, or as patient-controlled analgesia (PCA) demand doses of 0.1 to 0.35 mg as needed.
<b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b>	Patients taking both a strong CYP3A4 and a strong CYP2D6 inhibitors or patients who are CYP2D6 poor metabolizers may require less frequent dosing. Monitor closely and administer subsequent doses based on severity of pain and patient response.
<b>Labeling</b>	Generally acceptable. See specific recommendations below in section 2.4
<b>Bridge between the to-be-marketed and clinical trial formulations</b>	Oliceridine solutions were provided describing base amount (for example, 1 mg/mL of oliceridine) solution for IV injection in clinical studies. Oliceridine fumarate and HCl solution were studied following intravenous administration in pivotal clinical trials and supportive clinical pharmacology studies.

The tQT-study CP130-1008 showed QT-prolongation with IV doses of 6 mg oliceridine, which appears not to be clinically relevant based on the magnitude of prolongation in this specific study. However, adequate ECG data was not collected in Phase 3 clinical trials following the positive signal in the tQT study. IRT-QT group indicated in review dated 9/28/2018 that “Due to the uncertainty about the mechanism causing the observed QTc prolongation it is not possible to predict the QTc prolongation with the currently proposed dosing paradigm, which results in exposures of the major metabolites that exceeds the exposures following the highest dose in the thorough QT study (~2.4-fold for M22 and ~2.8-fold for TRV9198662)”. Additionally, IRT-QT indicated “Because of the limitations with the available clinical data, a clinical study is necessary to characterize the effects of oliceridine on the QTc interval at the therapeutically relevant exposures to all major moieties. We propose that the clinical QT study is a multiple dose study

with the maximum proposed dosing regimen in healthy volunteers, if feasible. If it is not feasible to administer the maximum proposed dosing regimen in healthy volunteers, a clinical QT study in patients who can tolerate the maximum proposed dosing regimen.”

On 10/2/2018 Clinical Pharmacology Briefing focused on the need for an additional tQT study. As indicated in the OCP briefing minutes page 4 “A PMR for another TQT study may be considered with labeling given that an adequate clinical monitoring plan for ECG may be implemented in the real clinical use setting. Of note, regulatory approval of a drug with QT-prolongation requires the following language in section 5 and 12.2: “ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.”

On 10/11/2018, the majority of the fifteen advisory committee panel members voted to not approve oliceridine (No=8, Yes=7). Several AC members that voted to approve the drug still recommended Phase 4 studies to establish safety of oliceridine in a representative patient population employing higher doses as may be used in realistic settings.

Based on discussion at the Advisory Committee and internal discussions after the meeting, the review team decided that there is not enough support for the benefit-risk profile to approve the drug at this stage. The potential risk of QT prolongation is a major safety concern for this product. Therefore, the sponsor should conduct thorough QT-prolongation study before approval of this drug in a representative population that may receive wider range of oliceridine doses.

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

### 2.1 Pharmacology and Clinical Pharmacokinetics

Oliceridine is a new molecular entity [REDACTED] <sup>(b) (4)</sup> opioid receptor with analgesic properties. Oliceridine is being developed for the management of moderate to severe acute pain in patients 18 years of age or older for whom an intravenous (IV) opioid is warranted. Oliceridine produces pharmacodynamic effects like opioids. Oliceridine has an in vitro EC50 (binding affinity) of 8 nM at the human  $\mu$ -opioid receptor. In comparison, morphine binds with the human  $\mu$ -opioid receptor with affinity or EC50 of 50 nM. 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 was also noted. While pupil constriction is clearly indicative of typical opioid effect due to distribution into central nervous system, its specific link to pain or abuse remains unestablished. Oliceridine improved 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 can be antagonized by a selective mu-opioid antagonist (naloxone).

**Absorption:** Oliceridine administration is by an IV route, on an as-needed basis. Bioavailability of oliceridine administered as an oral dose (100  $\mu$ g) was very low in one oral study CP130-1004. Intravenous dose of oliceridine was not administered in that study. Based on a cross study comparison, oral bioavailability was estimated to be 5.77%.

**Distribution:** As noted above, based on pharmacodynamic effects, oliceridine distributes into central nervous system. 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 (Study 797914 and TRE-R6804).

**Metabolism:** Oliceridine is metabolized by oxidation into Oxy-oliceridine (M23) followed by glucuronidation to TRV0306954 (M22). N-dealkylation and oxidation of oliceridine produced circulating metabolites TRV0109662. After a single IV dose of <sup>14</sup>C-oliceridine, TRV0306954 (M22) is the main circulating radioactive component, accounting for a mean of 61.9% of total [<sup>14</sup>C]-drug related plasma exposure (AUC). TRV0109662 accounts for 17.4% of plasma AUC. Oxy-oliceridine (M23) accounts for 5.20% 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 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.

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.

**Elimination:** Oliceridine exhibited a half-life of approximately 1.5 to 3 hours when administered IV over 1 minute to 1 hour. The impact of CYP2D6 polymorphism on pharmacokinetics of oliceridine was evaluated in different 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 C<sub>max</sub> and AUC. Clearance of oliceridine was reduced by 50% in CYP2D6 poor metabolizers consistently across the Phase 1 clinical studies. While C<sub>max</sub> was only slightly higher, AUC of oliceridine was about 2-fold higher and plasma half-life was 3 to 4.5 hours in poor metabolizers of CYP2D6.

## 2.2 Dosing and Therapeutic Individualization

### 2.2.1 General dosing

The proposed dosing is based on the findings from registration trials (Study CP130-3001 in patients with medium to severe acute pain after bunionectomy and Study CP130-3002 in patients with medium to severe acute pain after abdominoplasty). The dose selection for registration trials was based on the findings from dose-response studies (Studies CP130-2001 and CP130-2002).

The general dosing guidelines from the Phase 2 and Phase 3 studies are as follows:

The initial dose of OLINVO 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.

Maintenance of analgesia is generally achieved with OLINVO administered as 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.

### 2.2.2 Therapeutic individualization

Patient-controlled analgesia that would balance pain relief and tolerability issues such as nausea and vomiting is a form of therapeutic individualization. In the registration trials, patients were administered a loading dose of 1.5 mg followed by doses of 0.1, 0.35 or 0.5 mg as needed. The ability for the patients to take demand doses of 0.1 to 0.5 mg as needed would obviate the need for specific dose adjustment strategies for intrinsic factors such as body weight, poor/extensive metabolizer status and extrinsic factors such as concomitant medications. The current label would suggest a maximum daily dose of 40 mg.

## 2.3 Outstanding Issues

The sponsor should conduct thorough QT-prolongation study before approval of this drug in a representative population that may receive wider range of oliceridine doses.

## 2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts in the final package insert.

The labeling statements regarding (b) (4) adverse experience relationships, as described in Section 12.2, should not be included the label. They do not provide any additional information towards patient care. (b) (4)

(b) (4) relationships were not explored using the data from pivotal Studies CP130-3001 and CP130-3002.

## 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

### 3.1 Overview of the Product and Regulatory Background

Oliceridine is proposed for IV administration as a loading dose of 1 – 3 mg followed by a maintenance dose of 0.1 – 0.5 mg using patient-controlled analgesia.

### 3.2 General Pharmacology and Pharmacokinetic Characteristics

<b>Mechanism of Action</b>	(b) (4)
<b>Active Moieties</b>	Oliceridine.
<b>QT Prolongation</b>	Oliceridine prolongs the QTcF interval in a dose-dependent manner with a delayed onset (3 mg: 6.8 ms [upper 90% CI: 8.9 ms]; 6 mg: 11.6 ms [13.7 ms]. See additional discussion below in section 3.2.1.
<b>General Information</b>	
<b>Bioanalysis</b>	Quantitation of the individual plasma samples of oliceridine, and primary amine metabolite TRV109662 was performed using HPLC with MS/MS detection. Pooled plasma samples were analyzed for non-acyl glucuronide conjugate of hydroxylated oliceridine (TRV0306954; M22) using HPLC with MS/MS detection. See Appendix for details.
<b>Healthy Volunteers vs. Patients</b>	Pharmacokinetic characteristics of oliceridine were similar in healthy volunteers and acute pain patients.
<b>Drug exposure at steady state following the therapeutic dosing regimen</b>	When oliceridine was administered four to six times daily, after 5 doses (1.5 – 4.5 mg) accumulation was less than 50% for AUC and up to 128% accumulation of Cmax.

<b>Dose Proportionality</b>	Oliceridine PK was dose-proportional between the doses of 0.1 – 3 mg intravenous infusion.
<b>Variability</b>	50% on clearance
<b>Absorption</b>	
<b>Bioavailability [oral]</b>	Oral bioavailability appears to be low due to extensive first pass metabolism. Cross study comparison suggests <5% oral bioavailability.
<b>Distribution</b>	
<b>Volume of Distribution</b>	Volume of distribution was high and ranged from 90 – 120 L in different Phase 1 and Phase 2 studies.
<b>Plasma Protein Binding</b>	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 protein binding, with the unbound fraction being essentially 100% in human plasma. (Study 797914 and TRE-R6804)
<b>Blood to Plasma Ratio</b>	The blood to plasma distribution ratio of oliceridine was not determined.
<b>Substrate transporter systems [<i>in vitro</i>]</b>	Oliceridine is a moderate substrate of MDR-1 (P-gp).
<b>Elimination</b>	
<b>Mean Terminal Elimination half-life</b>	In extensive metabolizers of CYP2D6, elimination half-life of oliceridine was 1.5 – 3 hours. In poor metabolizers of CYP2D6, elimination half-life of oliceridine was 3 – 4.5 hours.
<b>Metabolism</b>	
<b>Primary metabolic pathway(s) [<i>in vitro</i>]</b>	Cytochrome P450 2D6 predominantly mediates N-dealkylation (TRV109662) and oxidation (M23) of oliceridine. CYP3A4 plays a minor role in N-dealkylation (TRV109662) and oxidation (M23) of oliceridine.
	Oliceridine is metabolized by oxidation into Oxy-oliceridine (M23) followed by glucuronidation to TRV0306954 (M22).

<b>Inhibitor/Inducer</b>	Oliceridine and its metabolites M22 and TRV109662 may not inhibit or induce major CYP enzymes. Oliceridine and its metabolites may not significantly inhibit major transporters.
<i>Excretion</i>	
<b>Primary excretion pathways (% dose) ±SD</b>	A mean of 70% of the administered dose was recovered in urine and 18.4% was recovered in feces.

### 3.2.1 Does the drug or metabolite prolong QT?

Source: Excerpt from Agency's AC background package.

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). 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 1 below.

**Table 1: 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)**

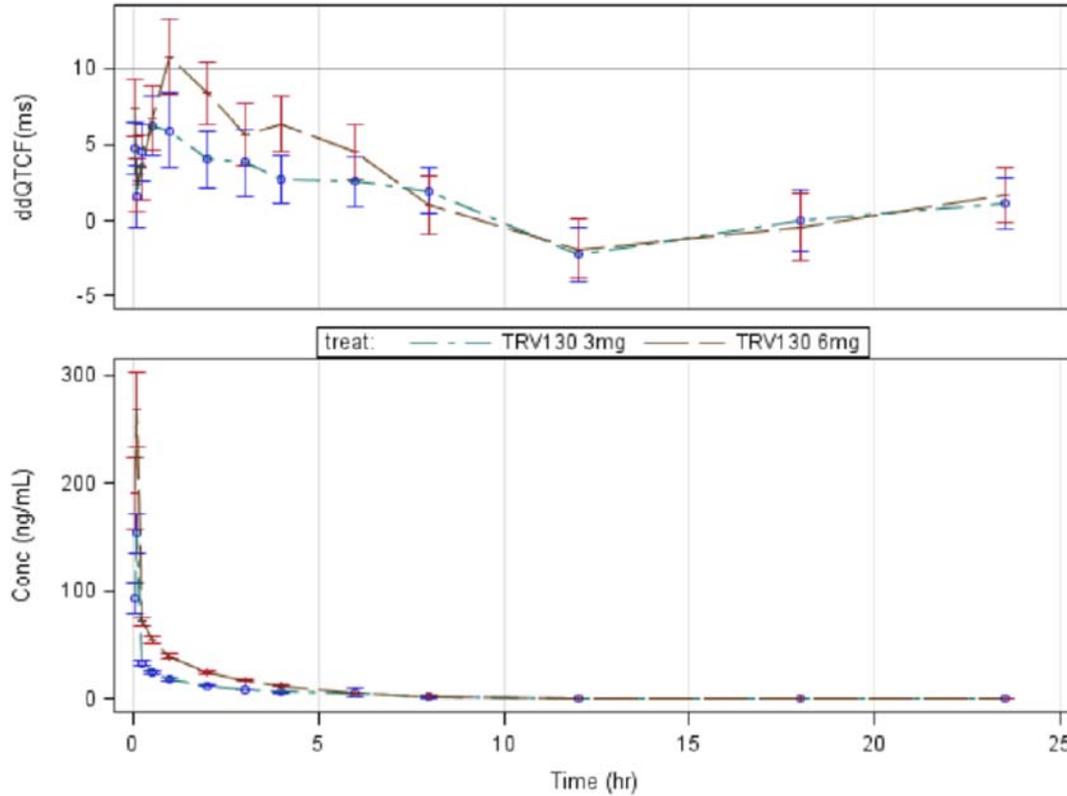
Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
TRV130 3 mg	0.5	6.8	(4.7, 8.9)
TRV130 6 mg	1	11.6	(9.5, 13.7)
Moxifloxacin 400 mg*	2	11.5	(8.6, 14.4)

\* 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 1**). 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.

**Figure 1:  $\Delta\Delta$ QTcF 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

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 bioanalytical data on M22, limitations of the simulation methodology include: a) Use of pooled sample data of a metabolite; 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). Table 2 below compares simulated Cmax of M22 and TRV109662 at steady-state (see attached simulations in bioanalytical method validation). The overall conclusion is that M22 will accumulate after multiple doses of administration.

**Table 2: 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

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. IRT-QT indicated in review dated 9/28/2018 “We have reviewed the study report, which documented the effects of OLINVO (oliceridine; TRV-130 fumarate) and its two major metabolites (M22 and TRV0109662) at room temperature on hERG, CaV1.2, and NaV1.5 current (peak and late components) obtained using automated patch clamp equipment QPatch. The two major metabolites (M22 and TRV0109662) appear to not inhibit hERG current at clinically relevant concentrations, suggesting that they are unlikely to contribute to QTc prolongation by blocking hERG channels. Oliceridine and its metabolites do not appear to block CaV1.2 channels at clinically relevant concentrations. However, oliceridine appears to suppress late NaV1.5 current. Suppression of late NaV1.5 current may mitigate the proarrhythmia risk associated with QTc prolongation...”

Perioperative medications are commonly used to manage nausea and vomiting. Medications such as, 5HT3 blockers (ondansetron (Zofran), granisetron, palonosetron) may have QT prolongation potential. Drugs that prolong QT interval may need to be avoided. At the OCP briefing on 10/2/2018 the issue of QT-prolongation and concomitant use of medications that may prolong QT was discussed. The SLT recommended that we hear input from advisory panel regarding benefit-risk profile of oliceridine, with attention to feedback on QT-prolongation issue. PMR for another TQT study may be considered with labeling, provided in the real clinical use setting, there will be an adequate clinical monitoring plan for ECG to mitigate the concern of QT prolongation. When a drug with QT-prolongation is labeled for marketing, section 5 and 12.2 would require “ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.”

### 3.3 Clinical Pharmacology Review Questions

#### 3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Oliceridine produces pharmacodynamic effects like opioids. Pupil constriction was consistently noted across several Phase 1, Phase 2 and Phase 3 studies. Oliceridine dose-related increase in pupil constriction and duration of pupil constriction was also noted. While pupil constriction is clearly indicative of typical opioid effect due to distribution into central nervous system, its specific link to pain or abuse remains unestablished.

Oliceridine improved latency to painful stimulus (cold water-induced pain) in a dose-dependent manner in Phase 1 studies (CP130-1003 and 1005, Table 3). This observation is a typical centrally-mediated analgesic effect of opioids. Use of cold pain test in early clinical development of oliceridine allowed for an assessment of the onset, magnitude, and duration of action of oliceridine in healthy subjects prior to moving into clinical studies of patients with acute pain. The cold pain latency model is considered exploratory in analgesic drug development.

**Table 3: Effect of Oliceridine on Latency of Hand Removal Time (sec) (Study CP130-1003).**

Dose (mg)	N	Time Point						
		Predose Mean (SD)	10 min Mean (SD)	30 min Mean (SD)	1 h Mean (SD)	2 h Mean (SD)	3 h Mean (SD)	4 h Mean (SD)
1.5	29	45.7 (16.29)	94.8 (53.58)	79.9 (47.79)	67.9 (44.19)	54.8 (30.44)	52.7 (30.53)	54.2 (32.04)
3.0	30	45.4 (17.86)	120.9 (55.52)	119.5 (60.45)	87.2 (55.24)	64.5 (45.14)	62.9 (40.60)	58.8 (36.66)
4.5	30	49.9 (24.83)	129.3 (51.29)	124.3 (54.32)	102.6 (59.83)	68.2 (44.71)	64.1 (46.23)	58.5 (32.88)
Morphine 10 mg	30	49.2 (23.85)	85.9 (56.37)	89.8 (55.87)	86.0 (52.37)	71.2 (47.09)	66.1 (39.71)	64.4 (38.16)

CPT=Cold Pain Test; N=number of subjects; SD=standard deviation  
Data sources: CP130-1003, CSR Table 14.2.2.1

In Study CP130-1005, healthy subjects were administered with multiple doses of oliceridine four to six times daily. After 5 doses (1.5 – 4.5 mg) accumulation was less than 50% for AUC and up to 128% accumulation of C<sub>max</sub>. Cold pain test was administered after first dose and last dose of oliceridine. With each oliceridine treatment group (Treatment Groups A-D), removal time increased from baseline with a peak at 10 minutes postdose followed by a return to baseline by 3 hours postdose of the first and last TRV130 doses. Removal time did not change over time with placebo. Removal time increased with increased doses of TRV130, with the longest removal time in Treatment Group C (TRV130 4.5 mg) and shortest removal time in Treatment Group A (TRV130 1.5 mg) (Table 4).

**Table 4: Effect of Oliceridine on Latency in Hand Removal Time (sec) (Study CP130-1005)**

	N	Predose Mean (SD)	Time Point		
			10 min Mean (SD)	1 h Mean (SD)	3 h Mean (SD)
1.5 mg Q6h	9	30.6 (14.94)	49.0 (34.72)	31.2 (20.10)	29.6 (22.18)
3.0 mg Q6h	9	39.0 (24.91)	103.8 (42.38)	44.7 (24.77)	29.8 (16.01)
4.5 mg Q6h	9	40.1 (12.65)	124.4 (51.39)	75.3 (45.57)	55.2 (36.07)
4 mg Q4h	9	31.3 (11.95)	66.5 (27.98)	44.2 (31.86)	32.5 (18.48)

Data Sources: CP130-1005, Table 14.2.2.5.

In this study, subjects were not administered the drug effects questionnaire to assess drug liking, high, etc. Subjects reported increased incidence of feeling of relaxation, nausea, vomiting, somnolence and dizziness with increased doses of oliceridine.

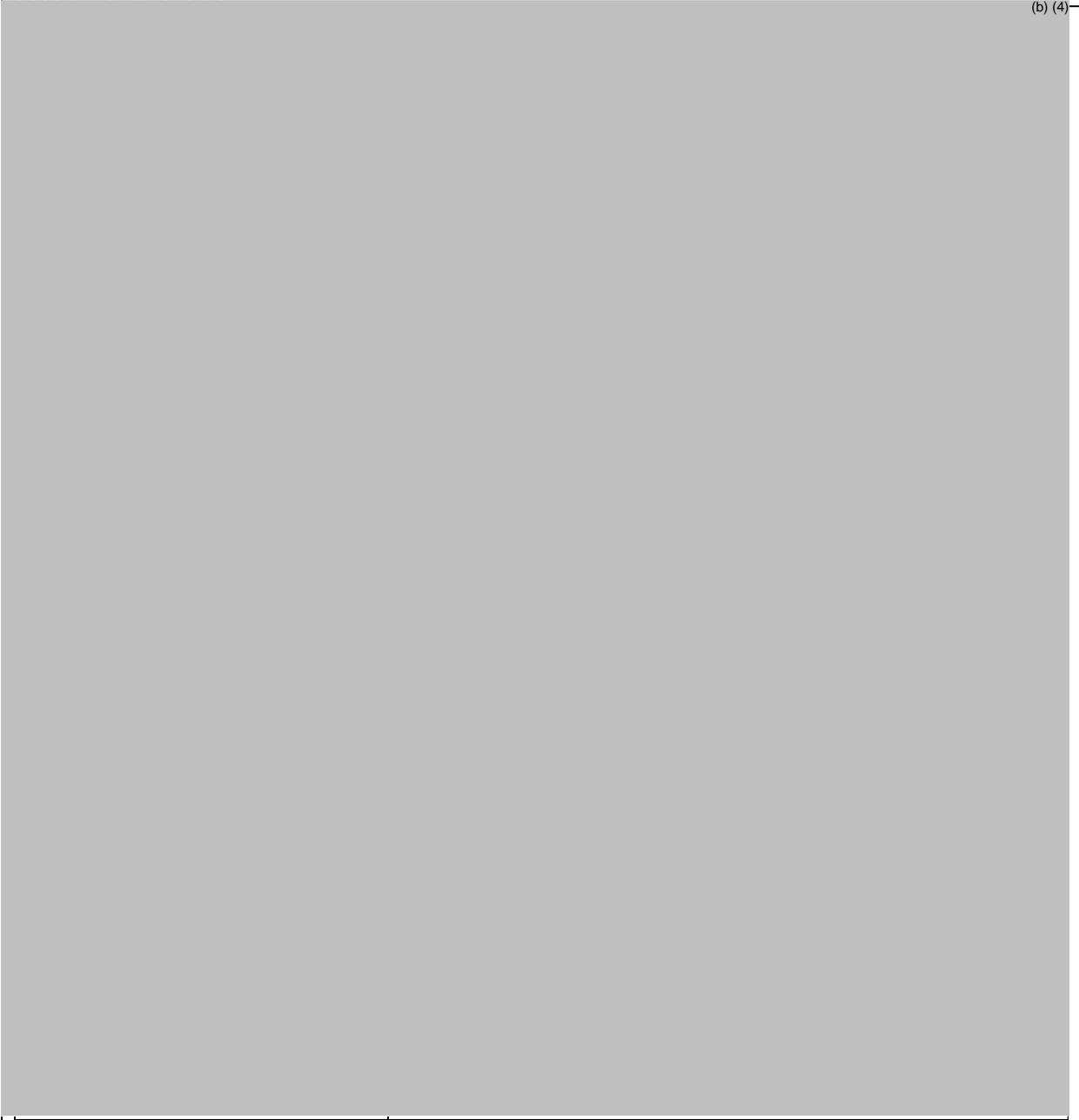
### ***3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?***

Yes, the proposed dosing regimen is appropriate for the general patient population if the safety aspects are acceptable (refer to the review by Dr. Elizabeth Kilgore, Medical Officer, DAAAP). The dosing regimen 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 CP130-2001 to select doses for the Phase III studies (CP130-3001 and CP130-3002).

The evidence contributing to the initial dose, re-dosing time following initial dose and maintenance dosing regimen (not patient controlled analgesia) from CP130-2001 are provided in **Figure 2**.

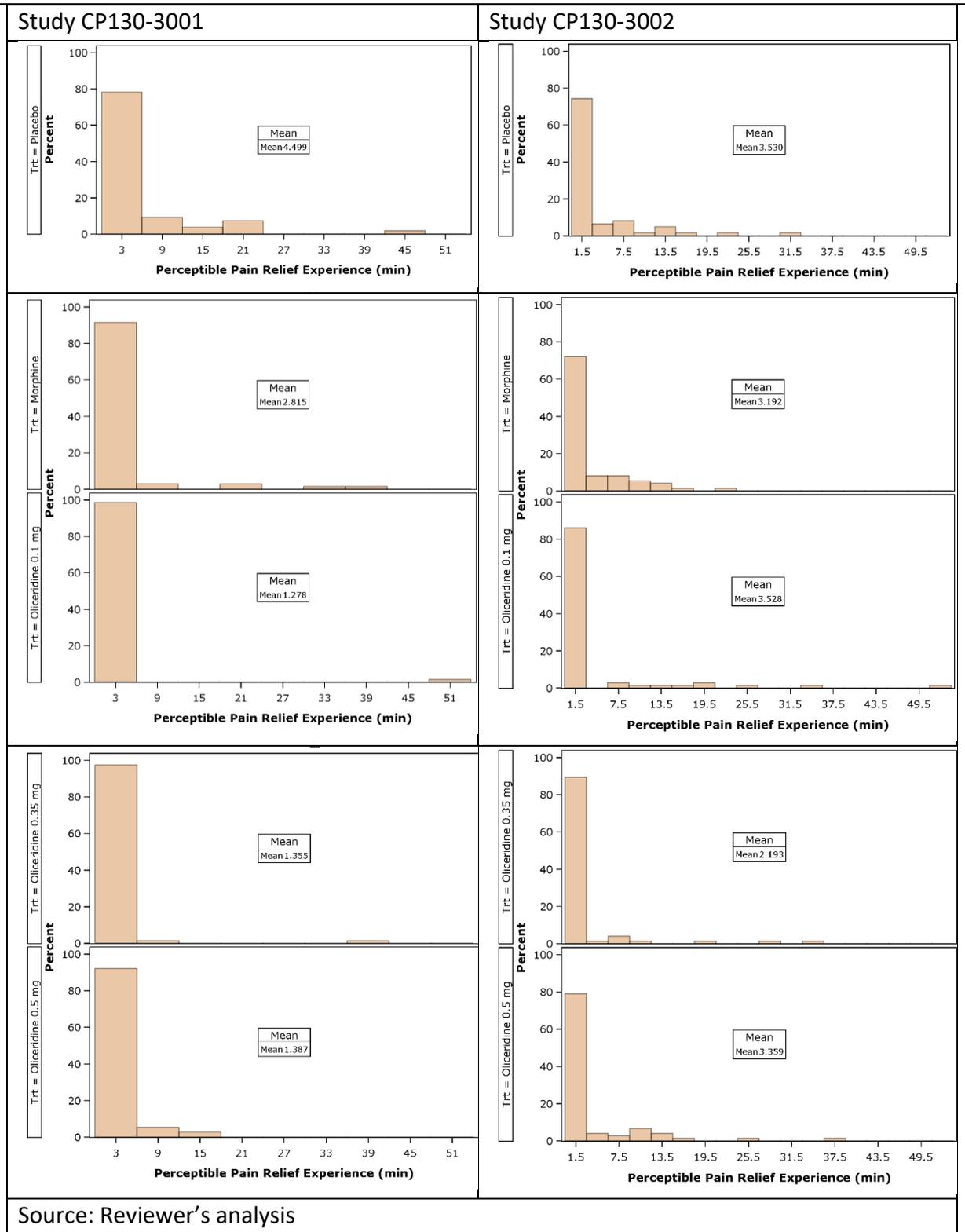
**Figure 2. (Left) Proposed language in DOSAGE AND ADMINISTRATION section of the label (Right) Evidence supporting the proposed language in DOSAGE AND ADMINISTRATION section of the label.**

(b) (4)



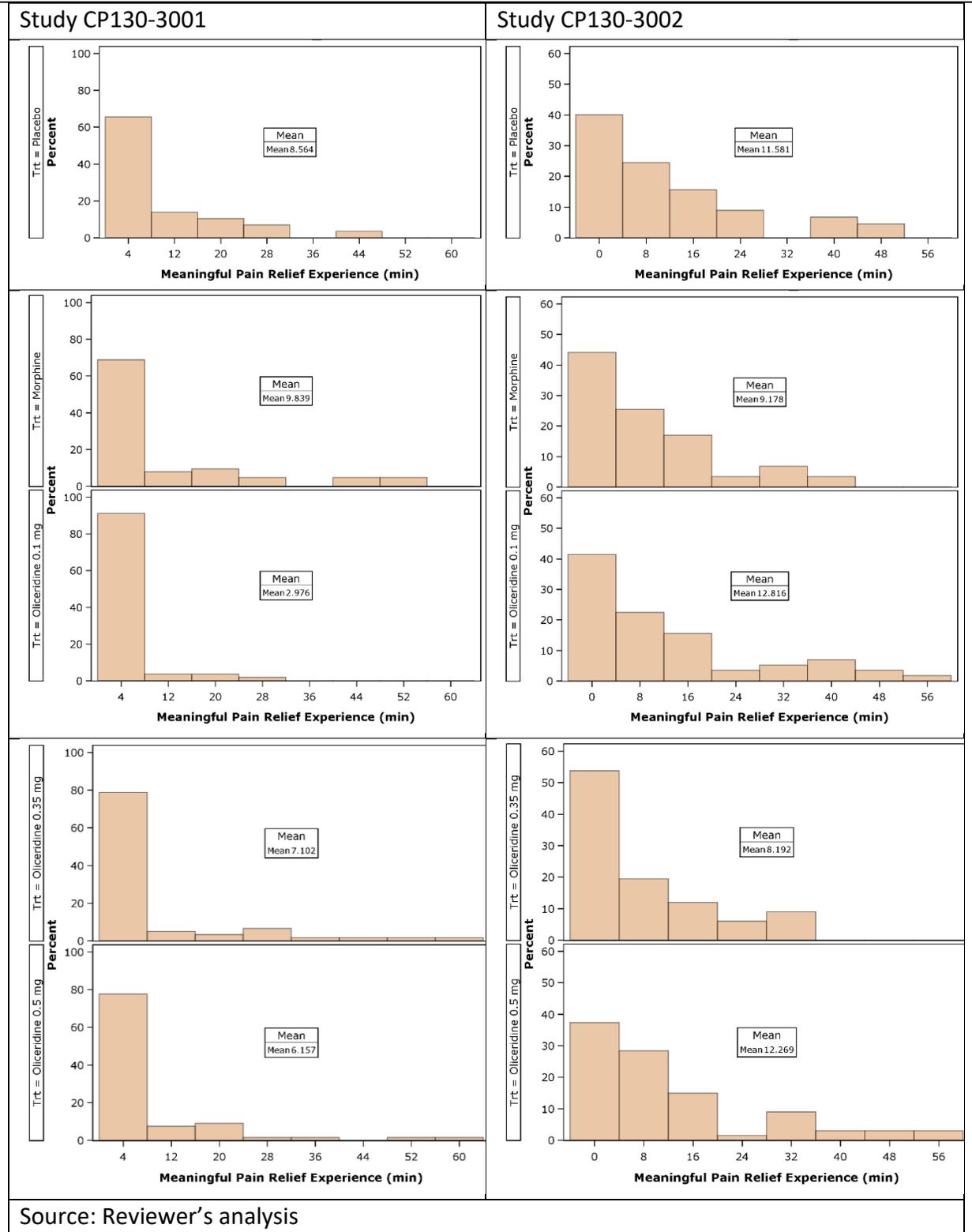
The review team looked at time to perceptible and meaningful pain relief in Study CP130-3001 and CP130-3002 (**Figure 3** and **Figure 4**). The data suggests that the majority of patients report perceptible pain relief in less than 5 minutes and meaningful pain relief in about 10 minutes in all treatment groups with greater proportion in oliceridine and morphine groups compared to placebo.

**Figure 3. Time to perceptible pain relief in Study CP130-3001 and CP130-3002**



Source: Reviewer's analysis

**Figure 4. Time to meaningful pain relief in Study CP130-3001 and CP130-3002**



### ***3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?***

No. 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 to balance pain relief and tolerability aspects. Dedicated PK studies in patients with end stage renal disease or different grades of hepatic impairment did not show significant change in exposure warranting dose-adjustment (See appended study reports). However, a reduction in initial loading dose may be considered in patients with severe hepatic impairment (see below). 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.

**Hepatic Impairment (Study CP130-1010):** Pharmacokinetics of two-minute IV oliceridine infusion was evaluated in patients with mild, moderate or severe hepatic impairment (0.5 mg) and healthy volunteers (1 mg). Patients with severe HI had prolonged half-life (6 hrs) compared to healthy (2 hrs), mild (2.6 hrs), or moderate HI subjects (4 hrs). Otherwise, no major changes in exposure were noted with the short infusion; hence, dose adjustment is not necessary in mild and moderate HI. A reduction in initial dose may not be necessary in mild or moderate HI patients based on the study results. However, in patients with severe hepatic impairment clinical status of patient (liver function tests, age, concomitant medications, severity of pain following surgery, etc.) may need to be considered in selecting the initial loading dose of oliceridine. A reduced initial dose (for example, 1 mg) may be an adequate loading dose in patients with severe hepatic impairment.

**Renal Impairment (Study CP130-1012):** Pharmacokinetics of two-minute IV oliceridine infusion was evaluated (CP130-1012) in patients with end-stage renal disease (0.5 mg) and healthy subjects (1 mg). There was no clinical significant difference in oliceridine clearance between the two groups. Since ESRD did not result in any difference in oliceridine clearance, mild, moderate and severe renal impairment is not expected to result in any changes. In Study 1012, the sponsor evaluated levels of TRV109662. Only 3 subjects in the ESRD cohort had sufficient plasma concentration data to conduct PK analysis and no subjects in the healthy cohort had sufficient plasma TRV109662 concentration. M22 levels were not evaluated in this study. Yoshida K et al., (2016) observed that “Analysis of these data suggested that CYP2D6-mediated clearance is generally decreased in parallel with the severity of CKD. There was no apparent relationship between the severity of CKD and CYP3A4/5-mediated clearance.” <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5024330/>. Nevertheless, a theoretical concern for accumulation of metabolites of oliceridine in case of severe renal impairment exists. Since the drug is used only for a short duration (up to 48 hours) in a monitored setting, additional dose adjustment may not be necessary, but monitoring may be warranted for potential adverse events.

**Pharmacogenomics:** The need for dose adjustment in patients who are phenotypic poor metabolizers of CYP2D6 was evaluated since the mean clearance of oliceridine is reduced by 50% in this subgroup (see Table below). Across different Phase 1 studies, systemic exposure

(AUC) of oliceridine was 100% higher in CYP2D6 poor metabolizers compared to extensive metabolizers (See Table below). However, C<sub>max</sub> was 10 – 30% higher in CYP2D6 poor metabolizers compared to extensive metabolizers (See **Table 5** below).

**Table 5: Descriptive Statistics of oliceridine pharmacokinetics in CYP2D6 Extensive Metabolizers (EM) and Poor Metabolizers (PM).**

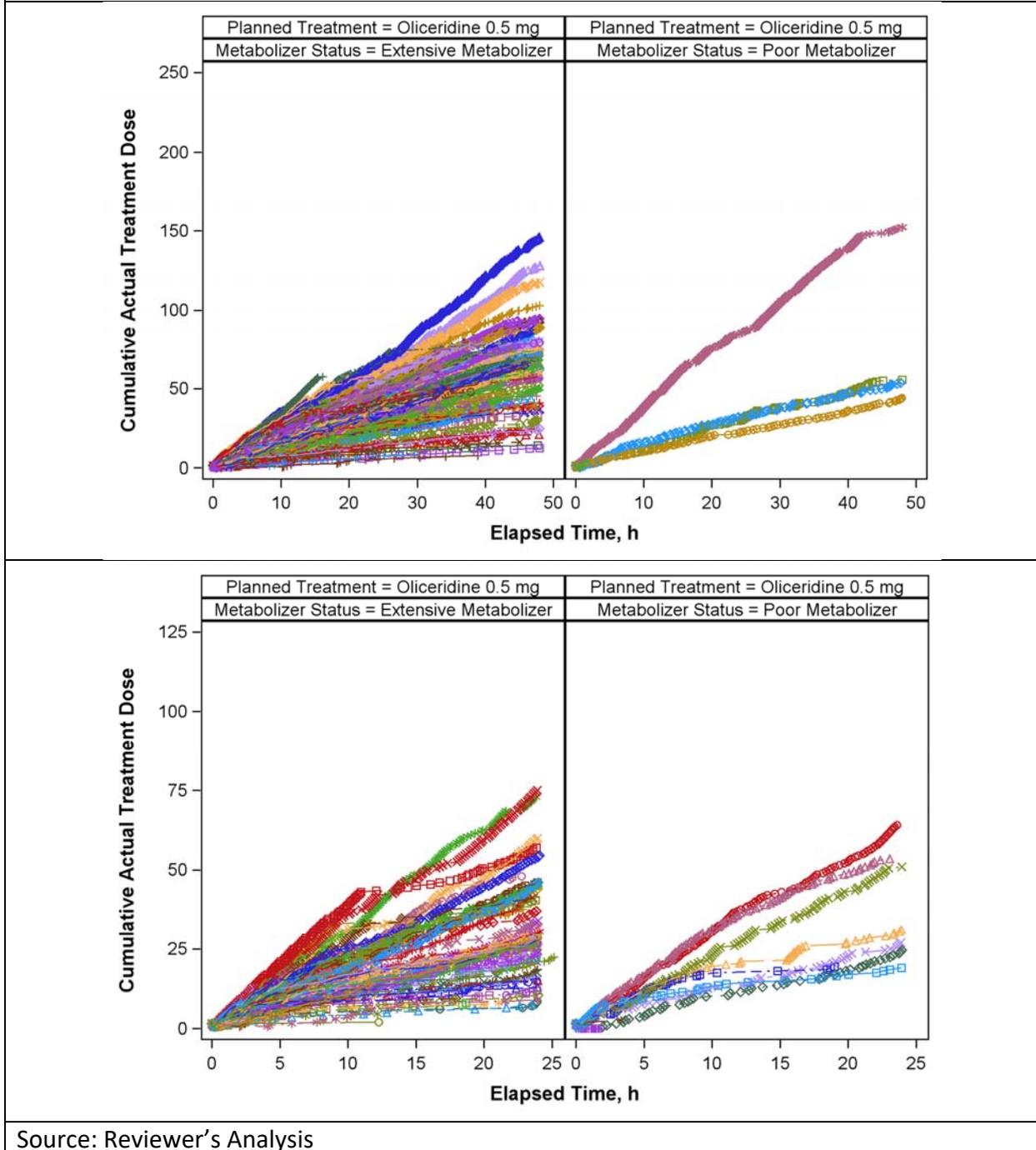
Study Number	Dose (mg)	Infusion Time (min)	CYP2D6 Status	N	CL (L/hr)	AUC <sub>0-∞</sub> (µg*hr/L)	C <sub>max</sub> (µg/L)	t <sub>max</sub> <sup>a</sup> (hr)	t <sub>1/2</sub> (hr)
CP130-1001	0.25	60	EM	5	47.2 (12.21)	5.29 (12.30)	2.29 (22.66)	0.98 (0.98 - 0.98)	1.56 (12.42)
			PM	4	22.4 (16.24)	11.14 (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<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; CL=clearance; C<sub>max</sub>=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<sub>1/2</sub>=apparent elimination half-life; t<sub>max</sub>=time at which C<sub>max</sub> was observed  
 Numbers in the table are geometric mean (GeoCV) except where noted.  
<sup>a</sup> 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

**Figure 5** shows the cumulative dose on PCA basis in patients who are CYP2D6 ultra/extensive (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 5** shows that some patients who are CYP2D6 poor metabolizers needed higher doses of oliceridine for pain relief. To allow for this individualized need for various levels of dose for managing pain, we are not recommending alternate dosing regimens that would aim to achieve similar blood levels of oliceridine in CYP2D6 poor and extensive metabolizers.

**Figure 5. 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.**



### 3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Oliceridine IV loading infusion or maintenance dosing does not require specific dose-adjustment regarding drug-drug interactions; however, these patients may require less frequent dosing which is possible with a patient-controlled analgesia pump. A reduced initial dose (1 mg) needs to be considered for patients receiving CYP3A4 inhibitors when also on CYP2D6 inhibitors or if they are CYP2D6 PM's.

The impact of strong CYP3A4 inhibitors on oliceridine pharmacokinetics were evaluated in two different studies. In drug-drug interaction study CP130-1005, the effect of itraconazole on oliceridine clearance in CYP2D6 poor metabolizers was investigated. 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 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 C<sub>max</sub> increased 8% with itraconazole, AUC<sub>0-inf</sub> increased approximately 80% with itraconazole (Table 6).

**Table 6. Effect of Itraconazole (ITZ) on Oliceridine PK (Study CP130-1005).**

PK Parameter	Geometric LS Mean		Ratio of Geometric LS Mean (Test/Reference)	90% CI
	Test	Reference		
ITZ (N=4)				
C <sub>max</sub>	5.18	4.81	107.68	67.39, 172.05
AUC <sub>0-∞</sub>	18.96	10.64	178.14	168.76, 188.04
AUC <sub>0-24</sub>	17.75	10.62	167.14	153.51, 181.99

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 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.

## **4. APPENDICES**

### **4.1 Summary of Bioanalytical Method Validation and Performance**

#### **Methods of Analysis of Oliceridine in Human Samples**

##### **Validation of a Method for the Determination of Oliceridine Concentrations in Human Plasma by HPLC with MS/MS Detection (Study 8242827):**

Study 8242827 was conducted to validate Method T30HPP for the quantitation of oliceridine in human plasma containing K2EDTA using high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection. Oliceridine and the internal standard, [REDACTED]<sup>(b) (4)</sup>, were extracted from human plasma by a supported liquid extraction method. Results were calculated using peak area ratios of analyte to internal standard, and calibration curves were generated using a weighted (1/x<sup>2</sup>) quadratic regression. The maximum batch size investigated was a total of [REDACTED]<sup>(b) (4)</sup> injections.

Assay validation performance results and sample stability results are presented in Table 7 and Table 8, respectively. A method for the determination of oliceridine in human plasma was validated over the concentration range of 0.05 to 50 ng/mL. The lower limit of quantification (LLOQ) for oliceridine in human plasma was established to be 0.05 ng/mL. Linearity was demonstrated up to 50 ng/mL (upper limit of quantitation), using a sample volume of 0.100 mL. The coefficient of determination was in the range of 0.9919 to 0.9995. The accuracy (%Bias) and % relative standard deviation (RSD) for intra- and inter-assay evaluations were ≤13.8% and ≤8.0%. The overall recovery for oliceridine was within a 30% range and was determined to be adequate. All other assay validation parameters met the acceptance criteria (Table 7).

**Table 7. Oliceridine in Human Plasma – Assay Validation Performance (Study 8242827)****Oliceridine in Human Plasma – Assay Validation Performance  
(Study 8242827)**

Test	Performance	Acceptance Criteria
Lower limit of quantification	0.05 ng/mL	NA
Linearity range	0.05 to 50 ng/mL R <sup>2</sup> : 0.9919 to 0.9995	NA
Recovery	Oliceridine: 66.2% to 73.2% Internal Standard: 73.7% to 75.7%	% Recovery: Within 30% across concentration range
QC Accuracy (%Bias)	Intra-run: -9.3% to 5.3% Inter-run: -5.8% to 1.3%	Mean % Bias: ±15%
QC Accuracy (%Bias) at LLOQ	Intra-run: 1.2% to 13.8% Inter-run: 9.4%	Mean %Bias at LLOQ: ±20%
QC Precision (RSD)	Intra-run: 1.9% to 6.5% Inter-run: 5.5% to 7.4%	RSD: ≤15.0%
QC Precision (RSD) at LLOQ	Intra-run: 5.8% to 7.3% Inter-run: 8.0%	RSD at LLOQ: ≤20.0%
Hemolysis Assessment	Mean %Bias: -11.3% RSD: 4.3%	Mean % Bias: ±15% RSD: ≤15.0%

LLOQ=lower limit of quantification; NA=not applicable; QC=quality control; R<sup>2</sup>=coefficient of determination;  
RSD=relative standard deviation

Data sources: Study 8242827, Table 4, Table 5, Table 8, Table 11, and Table 18

The stability of oliceridine in human whole blood was confirmed for 2 hours at room temperature or under wet ice conditions. Oliceridine stability in human plasma was confirmed for 26 hours when stored at room temperature and for 645 days when frozen at -10°C to -30°C or -60°C to -80°C. The validation confirmed stability for five freeze/thaw cycles at -10°C to -30°C or -60°C to -80°C (Table 8).

**Table 8: Stability of Oliceridine in Human Plasma (Study 8242827)**

Test	Conditions	Established Stability
Sample collection stability	Room temperature or wet ice	2 h
Short-term in matrix	Freeze-thaw (-10°C to -30°C and -60°C to -80°C)	5 cycles
Short-term in matrix	Room temperature	26 h
Frozen in matrix	-10°C to -30°C and -60°C to -80°C	645 d

Data sources: Study 8242827, Table 13, Table 14; and Addendum 4, Table 7.5

The assay validation report was amended six times. A list of these amendments, their purpose, and the results are shown in Table 9.

**Table 9: Oliceridine in Human Plasma – Assay Validation Report (Study 8242827) Amendments.**

Amendment	Date	Purpose	Results
1	10 Jan 2012	Extend frozen matrix stability	93 d at -10°C to -30°C 112 d at -60°C to -80°C
2	10 Jul 2012	Site transfer	Intra- and inter-assay precision <15% Intra- and inter-assay accuracy ±15%
3	05 Jun 2013	Extend frozen matrix stability	232 d at -60°C to -80°C
4	04 Mar 2014	Extend frozen matrix stability	645 d at -10°C to -30°C or -60°C to -80°C
5	28 Apr 2015	Processed sample stability, hyperlipidemic samples, and extended analytical run size	Stability of processed extracts 124 h at 2°C to 8°C Acceptable precision and accuracy of hyperlipidemic samples Run size of (b) (4) samples met validation criteria
6	22 Dec 2015	Processed sample viability	Processed sample viability confirmed for 26 h at room temperature

Data sources: Study 8242827, Addendum 1, Table 5; Addendum 2, Table 6.4; Addendum 3, Table 6.3; Addendum 4, Table 7.5; Addendum 5, Table 6.5, Table 6.9; and Addendum 6, Table 5.5

**Results from the amended assay validation methods demonstrated increased stability of oliceridine in frozen matrix (from 112 days to 645 days when frozen at -10°C to -30°C or -60°C to -80°C), increased stability of oliceridine in extracts (up to 124 hours at 2°C to 8°C), and increased run size (from (b) (4) samples to (b) (4) samples) (**

Table 9 ).

**Validation of an LC-MS/MS Method for the Measurement of Oliceridine in Human Plasma**

**(Study QBR115169QB02):** Study QBR115169QB02 was conducted to validate Method MWI2726 V1.0 for the quantitation of oliceridine in human plasma containing K2EDTA using liquid chromatography-MS/MS detection to support a microdose study. Oliceridine and the internal standard, (b) (4) were extracted from human plasma by a supported liquid extraction method. Results were calculated using peak area ratios of analyte to internal standard, and calibration curves were generated using a weighted (1/x<sup>2</sup>) linear regression analysis. Assay validation performance results and sample stability results are presented in Table 5 and Table 6. A method for the determination of oliceridine concentrations in human plasma was validated over the concentration range of 4 to 4000 pg/mL to support a human microdose study. The LLOQ for oliceridine in human plasma was established to be 4 pg/mL. Linearity was demonstrated up to 4000 pg/mL (upper limit of

quantitation). The coefficient of determination was in the range of 0.9950 to 0.9982. The precision (% coefficient of variation [CV]) and accuracy (% relative error [RE]) for the quality control (QC) samples at the three concentration levels were  $\leq 7.9\%$  and were within  $-10.2\%$  to  $3.2\%$ , respectively. All assay validation parameters met the acceptance criteria (Table 10).

**Table 10: Concentration of Oliceridine in Human Plasma – Assay Validation Performance (Study QBR115169QB02)**

Test	Performance	Acceptance Criteria
Lower limit of quantification	4 pg/mL	NA
Linearity range	4 to 4000 pg/mL R2: 0.9950 to 0.9982	NA
QC Accuracy (%RE)	Intra-run: $-10.2\%$ to $3.2\%$ Inter-run: $-7.4\%$ to $-0.4\%$	Mean %RE: $\pm 15\%$
QC Accuracy (%RE) at LLOQ	Intra-run: $-9.5\%$ to $2.0\%$ Inter-run: $-2.8\%$	Mean %RE at LLOQ: $\pm 20\%$
QC Precision (%CV)	Intra-run: $0.8\%$ to $3.5\%$ Inter-run: $3.0\%$ to $4.4\%$	%CV: $\leq 15\%$
QC Precision (%CV) at LLOQ	Intra-run: $5.5\%$ to $7.9\%$ Inter-run: $8.1\%$	%CV at LLOQ: $\leq 20\%$
Hemolysis Assessment	Mean %RE: $-3.1\%$ to $0.0\%$ %CV: $1.6\%$ to $4.2\%$	Mean %RE: $\pm 15\%$ %CV: $\leq 15\%$

CV=coefficient of variation; LLOQ=lower limit of quantification; QC=quality control; R<sup>2</sup>=coefficient of determination; RE=relative error

Data sources: Study QBR115169QB02, Table 3, Table 4 and Table 9

The stability of oliceridine in human whole blood was confirmed for 2 hours at room temperature. Oliceridine stability in human plasma was confirmed for 24 hours when stored at room temperature and for 30 days when frozen at  $-80^{\circ}\text{C}$ . The validation confirmed stability for four freeze/thaw cycles at  $-80^{\circ}\text{C}$  (Table 11).

**Table 11: Stability of Oliceridine in Human Plasma (Study QBR115169QB02).**

Test	Conditions	Established Stability
Sample collection stability	Room temperature	2 h
Short-term in matrix	Freeze-thaw ( $-80^{\circ}\text{C}$ )	4 cycles
Short-term in matrix	Room temperature	24 h
Frozen in matrix	$-80^{\circ}\text{C}$	30 d

Data sources: Study QBR115169QB02, Table 11 and Table 12

The incurred sample reanalysis (ISR) data for oliceridine passed the acceptance criterion for all clinical studies with  $\geq 96\%$  of the re-assay values falling within 20% of the mean of the original and ISR results.

<b>Validation of Method BTM-2387-R0: Determination of TRV0306954 (M22) in K2EDTA Human Plasma by LC-MS/MS Detection (Study TRE-R7572):</b>			
Report location	Central Data Room at (b) (4)		
Method description	Method BTM-2387-R0 is an LC-MS/MS method for the determination of TRV0306954 (M22) in K <sub>2</sub> EDTA human plasma using (b) (4) as the internal standard (IS). TRV0306954 (M22) and the internal standard were extracted by protein precipitation from human plasma using acetonitrile. Reversed-phase HPLC separation was achieved with an ACE C8 column (50 x 2.1 mm, 5 micron). MS/MS detection was set at mass transitions of $m/z$ 579.1 $\rightarrow$ 127.1 for TRV0306954 (M22) and $m/z$ 391.2 $\rightarrow$ 130.9 for (b) (4) (IS) in TIS positive mode.		
Sample volume	30 $\mu$ L		
Regression	Linear regression		
Weighting factor	$1/x^2$		
Dynamic range	10.0 – 2000 ng/mL		
QC concentrations	10.0 ng/mL (LLOQ), 30.0 ng/mL, 250 ng/mL, 1500 ng/mL, and 15000 ng/mL (Dilution QC)		
Analyte	TRV0306954 (M22)		
Internal standard	(b) (4)		
Linearity	$R^2 \geq 0.9940$		
Lower limit of quantitation (LLOQ)	10.0 ng/mL		
Average recovery of the Analyte (%)	85.9		
Average recovery of the IS (%)	97.8		
QC level		LLOQ	Low, Mid, and High
QC Intra-run precision range (%CV)	Run 1	5.1	3.3 to 7.8
	Run 2	14.4	4.2 to 6.2
	Run 5	6.6	2.7 to 8.5
QC Intra-run accuracy range (%Bias)	Run 1	3.0	-7.3 to 4.0
	Run 2	2.0	-9.3 to -1.3
	Run 5	-6.4	-10.0 to -2.7
QC Inter-run precision range (%CV)		10.2	5.4 to 6.7
QC Inter-run accuracy range (%Bias)		-0.1	-8.7 to -0.8
QC sample bench-top stability	17 hours at room temperature		
Stock solution stability	To be determined (Refer to Section 11)		
Processed sample stability	99 hours at room temperature		
Reinjection reproducibility	90 hours at room temperature		
QC sample freeze/thaw stability	5 freeze(-20 °C)/thaw cycles 5 freeze(-70 °C)/thaw cycles		
QC sample long-term storage stability	To be determined (Refer to Section 11)		
Dilution integrity	15000 ng/mL diluted 10-fold		
Matrix effect	IS-Normalized Matrix Factor = $1.07 \pm 0.07$ at 30.0 ng/mL with %CV = 6.5 IS-Normalized Matrix Factor = $0.98 \pm 0.02$ at 1500 ng/mL with %CV = 2.0		
2% Hemolyzed QC precision range (%CV)	3.4 to 6.8		
2% Hemolyzed QC accuracy range (%Bias)	1.3 to 1.7		

Blank selectivity	The blank selectivity samples were within the acceptance criteria (peak area at the retention time of the analyte was no more than 20% of the LLOQ standard and peak area at the retention time of the IS was $\leq$ 5% of the mean peak area of the IS of accepted calibration standards and QC samples in all 6 blank samples).
Batch size	127 samples
Carryover evaluation	No carryover was observed in the double blank samples that were evaluated for injection carryover.
Whole blood stability	120 minutes in an ice-water bath (0-4 °C) and at room temperature
Interference from Analyte on Internal Standard	There was no interference detected from the analyte on the internal standard.

TRV0306954 (M22) was stable in human whole blood for 2 hours at room temperature or on wet ice. TRV0306954 (M22) in plasma was stable for 15.5 hours at room temperature and processed samples were stable for 145.5 hours when stored at room temperature. The validation confirmed stability for five freeze/thaw cycles at -20°C or -70°C.

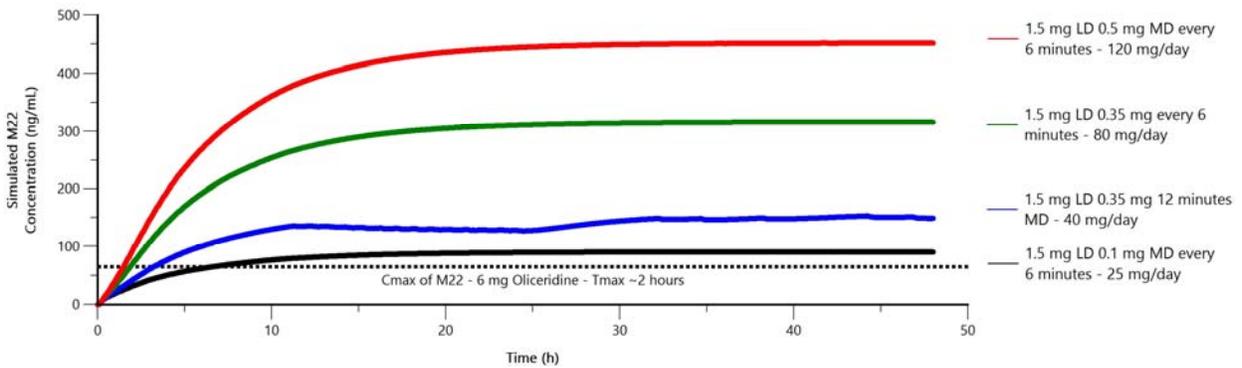
Bioanalytical Report TRE-R7642: LC-MS/MS Analysis for the Determination of TRV0306954 (M22) in K<sub>2</sub>EDTA human plasma samples from TQT study CP 130-1008. The individual plasma samples were analyzed for oliceridine and TRV109662; however, plasma samples were pooled from 9 individuals and analyzed for M22 levels. M22 (TRV0306954) was unambiguously identified by high resolution nuclear magnetic resonance (NMR) and chemical synthesis as an unreactive, non-acyl, ether glucuronide conjugate of hydroxylated oliceridine (Study 8325011) that does not present inherent toxicological concern. At the Agency's request (Pre-NDA Meeting, 25 May, 2017) a bioanalytical method was developed and validated to quantify M22 in human plasma (Study TRE-R7572). The bioanalytical method was used to quantify M22 concentrations in pooled plasma samples collected from human subjects dosed IV with a therapeutic (3 mg) or suprathapeutic (6 mg) dose of oliceridine in a thorough corrected QT interval (QTc) study (Study CP130-1008). 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 (Study R7642) (Table 12). The six samples used for ISR passed the acceptance criterion, with 100% of the re-assay values in Study CP130-1008 falling within 20% of the mean of the original and ISR results.

**Table 12. Concentrations of TRV0306954 (M22) in Pooled Human Plasma Samples from Study CP130-1008.**

Subject*	Treatment ID	Subject Group	Hour Nominal	Biological Matrix	Analyte	Concentration (ng/mL)	Run ID
(b) (6)	DS	1	0	Plasma	TRV0306954	BQL	1
	DS	1	0.03333	Plasma	TRV0306954	BQL	1
	DS	1	0.08333	Plasma	TRV0306954	BQL	1
	DS	1	0.25	Plasma	TRV0306954	26.3	1
	DS	1	0.5	Plasma	TRV0306954	42.8	1
	DS	1	1	Plasma	TRV0306954	55.2	1
	DS	1	2	Plasma	TRV0306954	65.0	1
	DS	1	3	Plasma	TRV0306954	64.7	1
	DS	1	4	Plasma	TRV0306954	55.8	1
	DS	1	6	Plasma	TRV0306954	38.3	1
	DS	1	8	Plasma	TRV0306954	27.3	1
	DS	1	12	Plasma	TRV0306954	13.7	1
	DT	1	0	Plasma	TRV0306954	BQL	1
	DT	1	0.03333	Plasma	TRV0306954	BQL	1
	DT	1	0.08333	Plasma	TRV0306954	BQL	1
	DT	1	0.25	Plasma	TRV0306954	18.4	1
	DT	1	0.5	Plasma	TRV0306954	23.4	1
	DT	1	1	Plasma	TRV0306954	27.8	1
	DT	1	2	Plasma	TRV0306954	31.0	1
	DT	1	3	Plasma	TRV0306954	28.3	1
	DT	1	4	Plasma	TRV0306954	27.7	1
	DT	1	6	Plasma	TRV0306954	19.9	1
	DT	1	8	Plasma	TRV0306954	16.3	1
	DT	1	12	Plasma	TRV0306954	BQL	1

\*Each pooled sample (PS) was obtained by mixing 10 individual samples except for (b) (6) DS, 0.03333 hours, which was pooled from 9 individual samples.  
 BQL: Below the lower quantitation limit

**Figure 6. Simulated Plasma M22 Levels based on nonparametric superposition of above data in Table 12 using dosing regimen described in Table 13 below figure.**



**Table 13.** Dosing regimen of oliceridine and Cmax and AUC of M22 simulated using loading dose and maintenance dose described below. Ratio of Cmax simulated/Cmax noted in TQT study with 6 mg dose is indicated in the last row.

	0.1 mg every 6 minutes MD	0.1 mg every 6 minutes MD	0.35 mg every ~12 minutes MD	0.35 mg every ~6 minutes MD	0.5 mg every 6 minutes MD
Loading Dose	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg
Daily Dose	25 mg	27.5 mg	40 mg	80 mg	120 mg
Cmax (ng/mL)	90.25	90.29	154.7	306.6	451.8
AUC <sub>0-24</sub> (ng*h/mL)	1696	1916	2717	5384	7976
Cmax/Cmax (TQT 6mg)	1.4	1.4	2.4	4.7	7.0

Validation of a Method for the Determination of Oliceridine and TRV0109662 in Human Plasma by HPLC with MS/MS Detection (Study 8334538)

Analytes	TRV130 (TRV110130) and TRV0109662 (CML-353)
Species	Human
Analytical matrix	K <sub>2</sub> EDTA plasma
Internal standard (ISTD)	TRV0110813A:2
Validated method	TRV1HPP
Validated range	0.0500 to 50.0 ng/mL
Quality Control (QC) levels	0.0500 ng/mL, 0.150 ng/mL, 2.50 ng/mL, 40.0 ng/mL, and 250 ng/mL
Analytical technique/method of detection	Supported-liquid extraction / LC-MS/MS
Sample Volume	50.0 µL
Calibration model	Quadratic regression
Weighting factor	1/x <sup>2</sup>
Precision and accuracy	Requirements fulfilled
Stability of primary standard solutions	TRV130: 5 hours at room temperature TRV0109662: 6 hours at room temperature TRV130: 71 days at -10 to -30°C* TRV0109662: 36 days at -10 to -30°C*
Stability of intermediate solutions	6 hours at room temperature 35 days at -10 to -30°C*
Processed-sample stability	127 hours at 2 to 8°C
Processed-sample viability	135 hours at 2 to 8°C
Sample collection stability	2 hours at room temperature 2 hours on wet ice
Freeze-thaw matrix stability	4 cycles at -10 to -30°C 4 cycles at -60 to -80°C
Wet ice matrix stability	24 hours on wet ice
Long-term frozen matrix stability	206 days at -10 to -30°C 206 days at -60 to -80°C
Hemolysis assessment	Passes acceptance criteria
Hyperlipidemic plasma assessment	Passes acceptance criteria
Maximum validated analytical run size	(b) (4) injections
* 83 days of stability at -10 to -30°C established under (b) (4) 8344539	

TRV0109662 concentrations were quantified in plasma samples collected from human subjects dosed with a) 3 mg or 6 mg oliceridine dose in TQT study CP130-1008 (n=15);

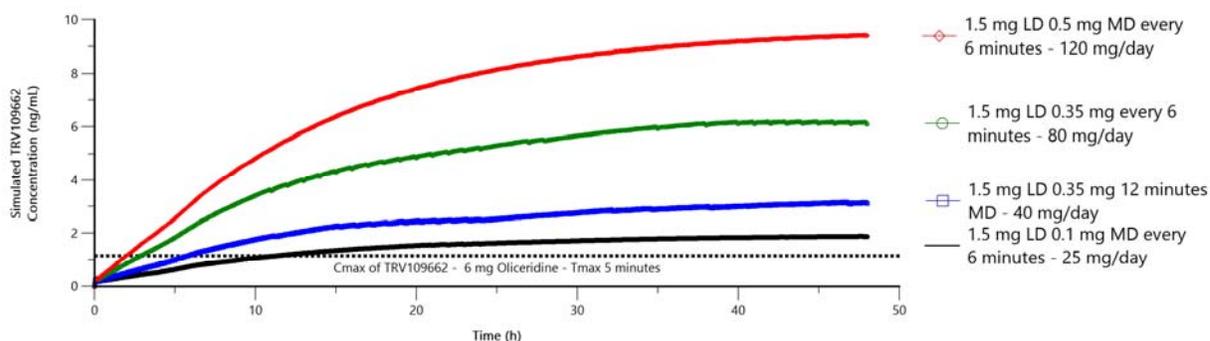
and b) 0.5 mg or 1 mg oliceridine in a renal impairment (CP130-1012) and a hepatic impairment study (CP130-1010). A full set of PK samples were collected in studies utilizing 0.5 mg and 1 mg dose, but TRV0109662 concentrations were below the limit of quantitation (0.05 ng/mL) in the majority of samples from these two studies. This bioanalytical method was also used to quantify TRV0109662 concentrations in plasma samples collected from 15 human subjects dosed IV with a therapeutic (3 mg) or supratherapeutic (6 mg) dose of oliceridine in a thorough corrected QT interval study (Study CP130-1008). Plasma C<sub>max</sub> values ranged from 0.284 to 1.47 ng/mL following a 3 mg dose of oliceridine and 0.582 to 3.30 ng/mL following a 6 mg dose (Study 8346251, Table 14).

**Table 14. Concentrations of TRV109662 in Human Plasma Samples from Study CP130-1008.**

Time (Hr)	Mean (ng/mL) ± SD	
	3 mg Dose	6 mg Dose
0	0.00 ± 0.00	0.00 ± 0.00
0.033	0.56 ± 0.33	0.86 ± 0.72
0.083	0.84 ± 0.36	1.14 ± 0.79
0.25	0.30 ± 0.13	0.55 ± 0.30
0.5	0.31 ± 0.17	0.62 ± 0.36
1	0.29 ± 0.21	0.59 ± 0.42
2	0.29 ± 0.23	0.59 ± 0.49
4	0.22 ± 0.18	0.53 ± 0.49
6	0.28 ± 0.28	0.66 ± 0.74
8	0.26 ± 0.29	0.51 ± 0.54
12	0.20 ± 0.24	0.39 ± 0.46
18	0.12 ± 0.15	0.24 ± 0.30
23.5	0.08 ± 0.12	0.16 ± 0.22

n=15 human subjects

**Figure 7.** Simulated Plasma M22 Levels based on nonparametric superposition of above data in **Table 17** using oliceridine dosing regimen described in Table 13 below figure.



**Table 15.** Dosing regimen of oliceridine and Cmax and AUC of TRV109662 simulated using loading dose and maintenance dose described below. Ratio of Cmax simulated/Cmax noted in TQT study with 6 mg dose is indicated in the last row.

	0.1 mg every 6 minutes MD	0.1 mg every 6 minutes MD	0.35 mg every ~12 minutes MD	0.35 mg every ~6 minutes MD	0.5 mg every 6 minutes MD
<b>Loading Dose</b>	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg
<b>Daily Dose</b>	25 mg	27.5 mg	40 mg	80 mg	120 mg
Cmax (ng/mL)	1.88	1.89	3.15	6.19	9.4
AUC <sub>0-24</sub> (ng*h/mL)	25.8	29.7	41.44	81.48	119
Cmax/Cmax (TQT 6mg)	1.7	1.7	2.9	5.6	8.5

## 4.2 Clinical PK and/or PD Assessments

### 4.2.1 CP130-1001 Synopsis

Study CP130-1001 was a multipart, randomized, single-blind, placebo-controlled, parallel-group, single ascending dose study in healthy adult males. In each session of Part A, a dose of oliceridine or placebo was infused over 1 hour to subjects who were phenotypic cytochrome P450 2D6 enzyme (CYP2D6) extensive metabolizers (EMs). Forty-eight subjects received a dose of oliceridine and 16 subjects received placebo in Part A. The doses studied in Part A were 0.15, 0.25, 0.4, 0.7, 1.2, 2.2, 4, and 7 mg, administered over 1 hour. In Part B, 4 CYP2D6 PMs received oliceridine 0.25 mg administered over 1 hour. In Part C, 6 subjects received a 1.5 mg dose of oliceridine as an IV infusion, the duration of which was progressively shortened. Infusion durations of 30, 15, 5, and 1 minute were studied.

In Part A, oliceridine peak and overall exposure increased across the dose range of 0.15 to 7 mg for a fixed infusion duration of 60 minutes (**Figure 8**). Over this dose range, the average C<sub>max</sub> increased from 1.04 to 102 ng/mL and the average area under the concentration curve for time zero (0) to infinity ( $\infty$ ) (AUC<sub>0- $\infty$</sub> ) increased from 2.52 to 205.97 ng\*hr/mL. Oliceridine clearance (CL) tended to be higher for the lower doses, with associated shorter apparent terminal half-life ( $t_{1/2}$ ). In Part B, overall oliceridine exposure was approximately 2-fold higher following a 60-minute infusion of 0.25 mg administered to subjects with PM phenotype compared with the corresponding dose in Part A, associated with a lower CL in the PM subjects in Part B. The C<sub>max</sub> was also 35% higher in the PM subjects, consistent with the protracted infusion duration.

In Part C, following a 1.5 mg dose, oliceridine C<sub>max</sub> increased as the duration of infusion decreased from 30 to 15 minutes, with little/no change when the infusion duration was further shortened to 5 or 1 minute (Figure 9). Both the overall exposure and CL were comparable for the different infusion durations. For the treatments with extremely short infusion durations (1.5 mg over 5 minutes or 1 minute) in Part C, the first sample was scheduled for 2 minutes after the end of infusion (EOI) and the concentrations at the EOI may have been higher than those observed. The overall assessment of dose proportionality suggested that increases in C<sub>max</sub>, area under the concentration curve for time zero (0) to the end of the last measurable plasma concentration (AUC<sub>0-t</sub>), and AUC<sub>0- $\infty$</sub>  were, on average, 17.1%, 13.7%, and 11.7% greater than dose proportional for the 1-hour infusion of oliceridine over the dose range of 0.15 to 7 mg. Overall exposure (area under the concentration curve [AUC]) in CYP2D6 PMs was approximately 2-fold higher than in EMs; however, the C<sub>max</sub> was within the upper range in PMs compared with EMs (**Table 16**). Clearance did not appear to be affected by the duration of infusion.

**Table 16. Summary of Oliceridine PK Parameters (Study CP130-1001)**

Part	Number of Subjects	Dose (mg)	Infusion Duration (min)	C <sub>max</sub> <sup>a</sup> (ng/mL)	t <sub>max</sub> <sup>b</sup> (hr)	AUC <sub>0-t</sub> <sup>a</sup> (ng•h/mL)	AUC <sub>0-∞</sub> <sup>a</sup> (ng•h/mL)	AUC <sub>extr</sub> <sup>a</sup> (%)	t <sub>1/2</sub> <sup>a</sup> (h)	CL <sup>a</sup> (L/h)
A	6	0.15	60	1.04 (28.32)	0.98 (0.98 - 1.22)	2.26 (27.33)	2.52 (28.55)	9.49 (37.51)	1.63 (27.79)	59.63 (28.68)
	5	0.25	60	2.29 (22.66)	0.98 (0.98 - 0.98)	5.12 (13.55)	5.29 (12.30)	2.98 (42.61)	1.56 (12.42)	47.24 (12.21)
	6	0.4	60	3.55 (21.07)	0.98 (0.98 - 1.17)	8.46 (12.98)	8.74 (11.56)	2.75 (60.26)	1.72 (23.56)	45.82 (11.48)
	6	0.7	60	6.43 (18.05)	0.98 (0.98 - 1.08)	13.64 (14.90)	13.97 (13.97)	2.00 (65.77)	1.77 (33.15)	50.11 (14.13)
	6	1.2	60	11.53 (27.01)	0.98 (0.98 - 1.08)	22.54 (19.54)	22.86 (19.20)	1.35 (39.42)	1.81 (21.38)	52.48 (19.21)
	6	2.2	60	28.28 (27.75)	0.99 (0.98 - 1.25)	52.63 (14.73)	53.04 (14.86)	0.54 (104.00)	1.96 (40.45)	41.5 (14.83)
	6	4	60	47.92 (19.12)	0.98 (0.98 - 1.00)	104.29 (22.82)	104.92 (23.01)	0.35 (33.31)	1.98 (47.49)	38.15 (22.97)
	6	7	60	102.36 (24.45)	0.98 (0.98 - 1.05)	204.41 (19.12)	205.97 (19.38)	0.28 (176.51)	2.66 (39.03)	34 (19.55)
B	4	0.25	60	3.09 (14.44)	1.03 (0.98 - 1.08)	10.49 (14.01)	11.15 (16.03)	5.09 (70.68)	2.82 (24.6)	22.43 (16.24)
C	6	1.5	30	23.99 (27.45)	0.51 (0.25 - 0.57)	35.19 (9.46)	35.51 (9.30)	0.89 (45.94)	1.83 (17.25)	42.18 (9.25)
	6	1.5	15	35.46 (30.92)	0.28 (0.20 - 0.28)	37.91 (13.18)	38.28 (13.10)	0.88 (37.86)	2.24 (38.58)	39.17 (13.12)
	6	1.5	5	32.28 (34.46)	0.13 (0.12 - 0.17)	32.54 (9.31)	32.94 (9.07)	1.16 (42.36)	1.85 (14.97)	45.54 (9.13)
	6	1.5	1	34.80 (32.77)	0.08 (0.05 - 0.10)	31.76 (14.26)	32.10 (14.28)	0.90 (61.39)	1.86 (11.50)	46.73 (14.32)

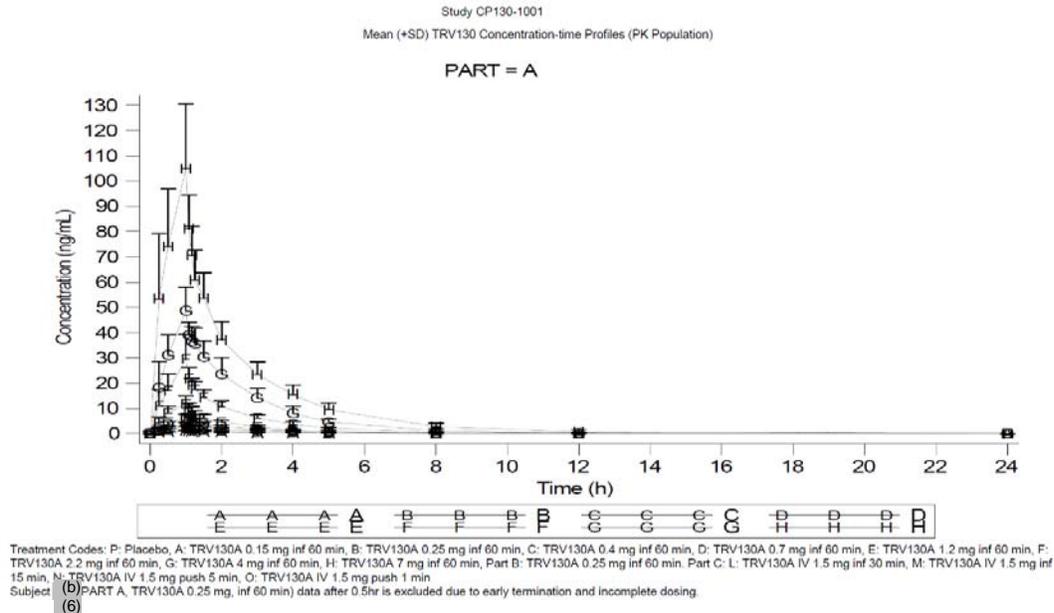
AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>0-t</sub>=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; AUC<sub>extr</sub>=percent of total area extrapolated to infinity; CL=clearance; C<sub>max</sub>=maximum observed plasma concentration; GeoCV=coefficient of variation for the geometric mean; PK=pharmacokinetics; t<sub>1/2</sub>=apparent terminal half-life; t<sub>max</sub>=time to peak concentration

<sup>a</sup> Geometric Mean (GeoCV%).

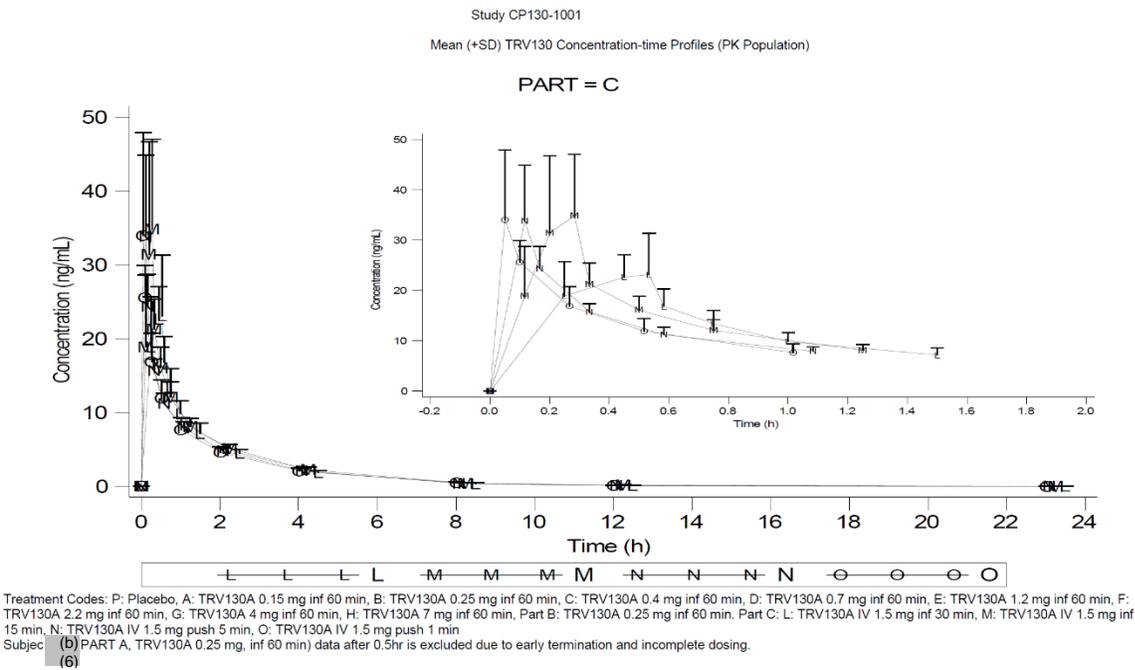
<sup>b</sup> Median (minimum - maximum).

Data source: CP130-1001, CSR Table 14.2.1.4

**Figure 8. Mean Oliceridine concentration profiles in Part A of study CP130-1001**



**Figure 9. Mean Oliceridine concentration profiles in Part C of Study CP130-1001**



Adverse events which are typical of opioids were reported in this single dose escalation study (See tables below).

Table 14.3.1.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Treatment and Study Part Safety Population (N=74)

MedDRA System Organ Class (SOC) Preferred Term (PT)	Number (%) of Subjects(1) and [Number of Events]					
	Study Part A (Treatment)					
	A (N=6)	B (N=6)	C (N=6)	D (N=6)	E (N=6)	F (N=6)
Subjects with any TEAE	2 ( 33.3%) [ 5]	3 ( 50.0%) [ 7]	0	4 ( 66.7%) [ 5]	0	2 ( 33.3%) [ 2]
Nervous system disorders	1 ( 16.7%) [ 2]	2 ( 33.3%) [ 3]	0	3 ( 50.0%) [ 3]	0	1 ( 16.7%) [ 1]
Dizziness	1 ( 16.7%) [ 1]	1 ( 16.7%) [ 1]	0	1 ( 16.7%) [ 1]	0	0
Dysarthria	0	0	0	0	0	0
Headache	1 ( 16.7%) [ 1]	0	0	0	0	0
Lethargy	0	1 ( 16.7%) [ 1]	0	0	0	0
Sedation	0	0	0	0	0	0
Somnolence	0	0	0	2 ( 33.3%) [ 2]	0	1 ( 16.7%) [ 1]
Syncope	0	1 ( 16.7%) [ 1]	0	0	0	0
Tremor	0	0	0	0	0	0
General disorders and administration site conditions	2 ( 33.3%) [ 2]	1 ( 16.7%) [ 1]	0	1 ( 16.7%) [ 1]	0	0
Fatigue	1 ( 16.7%) [ 1]	1 ( 16.7%) [ 1]	0	0	0	0
Feeling drunk	0	0	0	0	0	0
Feeling hot	0	0	0	0	0	0
Feeling of relaxation	0	0	0	1 ( 16.7%) [ 1]	0	0
Infusion site pain	0	0	0	0	0	0
Infusion site paraesthesia	1 ( 16.7%) [ 1]	0	0	0	0	0
Infusion site warmth	0	0	0	0	0	0
Thirst	0	0	0	0	0	0
Gastrointestinal disorders	1 ( 16.7%) [ 1]	1 ( 16.7%) [ 1]	0	0	0	0

Data Source: Appendix 16.2.8.2

Treatment Codes: P: Placebo, A: TRV130A 0.15 mg inf 60 min, B: TRV130A 0.25 mg inf 60 min, C: TRV130A 0.4 mg inf 60 min, D: TRV130A 0.7 mg inf 60 min, E: TRV130A 1.2 mg inf 60 min, F: TRV130A 2.2 mg inf 60 min, G: TRV130A 4 mg inf 60 min, H: TRV130A 7 mg inf 60 min, Part B: TRV130A 0.25 mg inf 60 min. Part C: L: TRV130A IV 1.5 mg inf 30 min, M: TRV130A IV 1.5 mg inf 15 min, N: TRV130A IV 1.5 mg push 5 min, O: TRV130A IV 1.5 mg push 1 min.

(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

Note: All events starting or worsening after commencement of treatment with investigational product.

Table 14.3.1.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Treatment and Study Part Safety Population (N=74)

MedDRA System Organ Class (SOC) Preferred Term (PT)	Number (%) of Subjects(1) and [Number of Events]				Study Part B (N=4)
	Study Part A (Treatment)				
	G (N=6)	H (N=6)	P (N=16)	Overall (N=64)	
Subjects with any TEAE	6 (100.0%) [ 9]	6 (100.0%) [ 24]	2 ( 12.5%) [ 3]	25 ( 39.1%) [ 55]	1 ( 25.0%) [ 1]
Nervous system disorders	0	6 (100.0%) [ 7]	2 ( 12.5%) [ 3]	15 ( 23.4%) [ 19]	1 ( 25.0%) [ 1]
Dizziness	0	2 ( 33.3%) [ 2]	0	5 ( 7.8%) [ 5]	0
Dysarthria	0	0	0	0	0
Headache	0	2 ( 33.3%) [ 2]	1 ( 6.3%) [ 1]	4 ( 6.3%) [ 4]	1 ( 25.0%) [ 1]
Lethargy	0	0	0	1 ( 1.6%) [ 1]	0
Sedation	0	1 ( 16.7%) [ 1]	0	1 ( 1.6%) [ 1]	0
Somnolence	0	1 ( 16.7%) [ 1]	2 ( 12.5%) [ 2]	6 ( 9.4%) [ 6]	0
Syncope	0	0	0	1 ( 1.6%) [ 1]	0
Tremor	0	1 ( 16.7%) [ 1]	0	1 ( 1.6%) [ 1]	0
General disorders and administration site conditions	6 (100.0%) [ 7]	2 ( 33.3%) [ 2]	0	12 ( 18.8%) [ 13]	0
Fatigue	1 ( 16.7%) [ 1]	0	0	3 ( 4.7%) [ 3]	0
Feeling drunk	0	1 ( 16.7%) [ 1]	0	1 ( 1.6%) [ 1]	0
Feeling hot	2 ( 33.3%) [ 2]	1 ( 16.7%) [ 1]	0	3 ( 4.7%) [ 3]	0
Feeling of relaxation	3 ( 50.0%) [ 3]	0	0	4 ( 6.3%) [ 4]	0
Infusion site pain	0	0	0	0	0
Infusion site paraesthesia	0	0	0	1 ( 1.6%) [ 1]	0
Infusion site warmth	0	0	0	0	0
Thirst	1 ( 16.7%) [ 1]	0	0	1 ( 1.6%) [ 1]	0
Gastrointestinal disorders	0	5 ( 83.3%) [ 9]	0	7 ( 10.9%) [ 11]	0

Data Source: Appendix 16.2.8.2

Treatment Codes: P: Placebo, A: TRV130A 0.15 mg inf 60 min, B: TRV130A 0.25 mg inf 60 min, C: TRV130A 0.4 mg inf 60 min, D: TRV130A 0.7 mg inf 60 min, E: TRV130A 1.2 mg inf 60 min, F: TRV130A 2.2 mg inf 60 min, G: TRV130A 4 mg inf 60 min, H: TRV130A 7 mg inf 60 min, Part B: TRV130A 0.25 mg inf 60 min. Part C: L: TRV130A IV 1.5 mg inf 30 min, M: TRV130A IV 1.5 mg inf 15 min, N: TRV130A IV 1.5 mg push 5 min, O: TRV130A IV 1.5 mg push 1 min.

(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

Note: All events starting or worsening after commencement of treatment with investigational product.

#### 4.2.2 CP130-1002 Synopsis

Study CP130-1002 was an open-label, non-randomized, 4-day single ascending dose crossover study conducted in healthy adult males and females. Six subjects received a single, daily 2-minute IV infusion dose of oliceridine on Days 1 to 4 in an ascending fashion (2, 2.5, 3, and 3.5 mg). All subjects received four single doses of oliceridine.

Oliceridine peak and overall exposure generally increased across the dose range of 2.0 to 3.5 mg after the 2-minute infusions. Over this dose range, the geometric mean of  $C_{max}$  increased from 31.94 to 75.06 ng/mL and the geometric mean of  $AUC_{0-\infty}$  increased from 44.69 to 88.34 ng\*hr/mL. Oliceridine CL and  $t_{1/2}$  were relatively constant over the dose range.

**Table 17. Summary of Oliceridine PK Parameters (Study CP130-1002)**

Dose (mg)	$C_{max}^a$ (ng/mL)	$t_{max}^b$ (h)	$AUC_{0-t}^a$ (ng*h/mL)	$AUC_{0-\infty}^a$ (ng*h/mL)	$t_{1/2}^a$ (h)	CL <sup>a</sup> (L/h)
2.0	31.94 (39.04)	0.08 (0.08 - 0.08)	44.07 (41.28)	44.69 (41.30)	2.21 (32.03)	44.75 (41.31)
2.5	59.77 (38.09)	0.08 (0.03 - 0.08)	58.42 (41.42)	59.03 (41.44)	2.92 (47.98)	42.35 (41.44)
3.0	55.56 (12.27)	0.08 (0.03 - 0.08)	72.75 (40.39)	73.40 (40.47)	3.14 (41.54)	40.88 (40.46)
3.5	75.06 (39.62)	0.08 (0.08 - 0.08)	87.64 (42.56)	88.34 (42.73)	2.62 (45.52)	39.62 (42.74)

$AUC_{0-\infty}$ =area under the plasma concentration-time curve from time 0 extrapolated to infinity;  $AUC_{0-t}$ =area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; CL=clearance;

$C_{max}$ =maximum observed plasma concentration; GeoCV=coefficient of variation for the geometric mean;

PK=pharmacokinetics;  $t_{1/2}$ =apparent terminal half-life;  $t_{max}$ =time to peak concentration

<sup>a</sup> Geometric Mean (GeoCV%).

<sup>b</sup> Median (minimum - maximum).

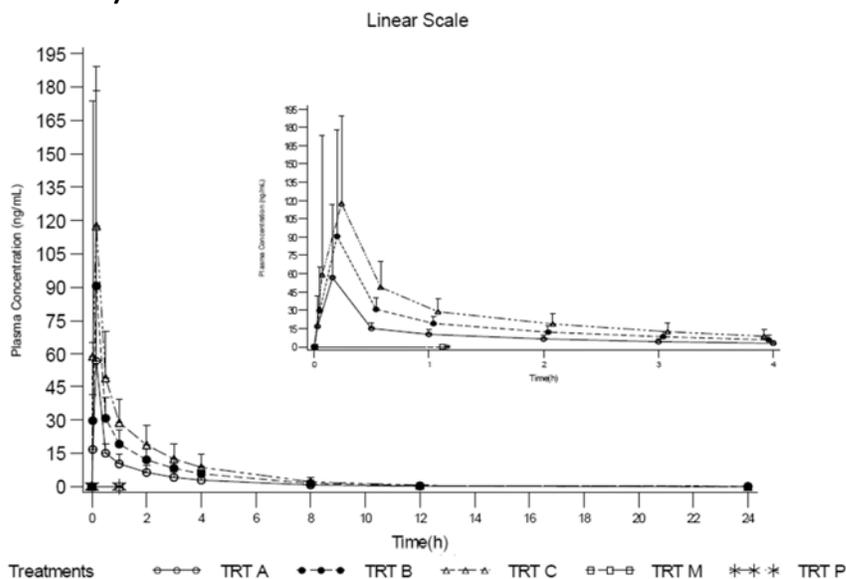
Data source: CP130-1002, CSR Table 14.2.1.3

Clearance was notably lower, and relatively constant, at all dose levels for Patient (b) (6), the only CYP2D6 PM in the study (Study CP130-1002, CSR Listing 16.2.4.7, Listing 16.2.6.2).

### 4.2.3 CP130-1003 Synopsis.

Study CP130-1003 was a randomized, double-blind, placebo-controlled, five-period crossover study in healthy adult males. A total of 30 subjects were enrolled and received at least one dose of oliceridine. In each period, each subject was administered one of five treatments: placebo, morphine 10 mg, or three different doses of oliceridine (1.5, 3, or 4.5 mg); 2-minute IV infusions were used. Following administration of oliceridine 1.5, 3, or 4.5 mg by IV infusion over 2 minutes, mean plasma concentrations of oliceridine increased with dose. The mean peak concentration was observed at the first PK sample after end of infusion (EOI) for all three doses. Elimination of oliceridine was multiphasic and similar for the three doses. Both clearance and half-life were relatively constant across the doses studied within each CYP2D6 metabolic status group. Clearance in PMs was roughly 50% of what was observed in the EM group. A commensurate increase in total exposure was also noted in the PM group, consistent with the decreased clearance observed. Overall, mean C<sub>max</sub> values in PM subjects were slightly higher than in EM subjects. For the majority of the subjects receiving 1.5 and 3 mg doses and for all subjects receiving 4.5 mg dose, plasma oliceridine was above the lower limit of quantification (LLOQ) by 12 hours after infusion. For each of the three doses, only 4 to 6 subjects had quantifiable plasma oliceridine concentrations by 24 hours after EOI. With one exception, all subjects with quantifiable oliceridine concentrations at 24 hours after infusion were CYP2D6 PMs. For all subjects, predose concentrations were below LLOQ during all treatment periods, indicating a complete washout at 48 hours after administration. Section 9.5.5 Drug Concentration Measurements of the study report describes that “Blood samples (approximately 4 mL) were to be collected at the sampling time points indicated in Table 9.3 and Table 9.4 to determine the plasma concentrations of TRV130 and for possible future metabolite analysis.”

**Figure 10. Mean (SD) Oliceridine Plasma Concentration-Time Profiles (PK Population) (Study CP130-1003)**



D5W=5% dextrose in water; IV=intravenous; PK=pharmacokinetic; SD=standard deviation; TRT=treatment

Note: Embedded plots are concentration-time profiles from 0 (predose) to 4 hours.

TRT A: Oliceridine 1.5 mg IV over 2 minutes; TRT B: Oliceridine 3 mg IV over 2 minutes; TRT C: Oliceridine

Data source: CP130-1003, Figure 14.2.1.1

**Table 18. Summary of Oliceridine PK Parameters by CYP2D6 Metabolic Status (Study CP130-1003).**

Parameter (unit)	Metabolizer Status	Number of Subjects	Treatment		
			A <sup>a</sup> Oliceridine 1.5 mg	B Oliceridine 3.0 mg	C Oliceridine 4.5 mg
C <sub>max</sub> <sup>b</sup> (ng/mL)	EM	25	45.20 (71.3)	81.28 (75.9)	117.29 (67.1)
	PM	5	54.70 (56.8)	54.00 (12.2)	127.77 (66.6)
t <sub>max</sub> <sup>c</sup> (h)	EM	25	0.17 (0.03 - 0.23)	0.17 (0.03 - 0.20)	0.18 (0.03 - 0.50)
	PM	5	0.17 (0.03 - 0.17)	0.17 (0.17 - 0.17)	0.18 (0.17 - 0.50)
AUC <sub>0-t</sub> <sup>b</sup> (ng*h/mL)	EM	25	38.68 (27.8)	73.31 (31.3)	107.61 (24.5)
	PM	5	74.68 (36.0)	135.61 (27.8)	227.98 (30.9)
AUC <sub>0-∞</sub> <sup>b</sup> (ng*h/mL)	EM	25	39.08 (27.5)	73.78 (31.2)	108.17 (24.6)
	PM	5	75.62 (35.1)	136.56 (28.2)	229.29 (31.0)
t <sub>1/2</sub> <sup>b</sup> (h)	EM	25	1.70 (15.8)	1.68 (16.9)	1.70 (19.0)
	PM	5	3.49 (20.6)	3.60 (15.8)	3.64 (7.7)
CL <sup>b</sup> (L/h)	EM	25	38.39 (27.5)	40.66 (31.2)	41.60 (24.6)
	PM	5	19.83 (35.1)	21.97 (28.1)	19.63 (31.0)

AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>0-t</sub>=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; CL=clearance; C<sub>max</sub>=maximum observed plasma concentration; EM=extensive metabolizer; GeoCV=coefficient of variation for the geometric, PK=pharmacokinetics; PM=poor metabolizer; t<sub>1/2</sub>=apparent terminal half-life; t<sub>max</sub>=time to peak concentration

<sup>a</sup> Number of subjects=24 for EMs.

<sup>b</sup> Geometric Mean (GeoCV%).

<sup>c</sup> Median (minimum – maximum).

Data source: CP130-1003, CSR Table 14.2.1.14

Cold pain test results were discussed in the question-based review.

#### 4.2.4 CP130-1004 Synopsis

Study CP130-1004 was a single-center, open-label, non-randomized study in which 8 healthy adult males received a single oral dose of oliceridine 100 µg.

Following oral administration, plasma concentrations of oliceridine were in general quantifiable starting at 0.5 hours in all subjects, with maximum concentrations occurring between 0.50 to 1.50 hours postdose. Subsequently, concentrations remained quantifiable for up to 12 hours postdose. A terminal phase rate constant could only be determined for 3 of the 8 subjects (one of which was a CYP2D6 PM; Patient (b) (6) showed oliceridine exposure consistent with his metabolic status).

**Table 19. Summary of Oliceridine PK Parameters after a Single Oral Dose (Study CP130-1004).**

Parameters (unit)	Oliceridine 100 µg N=8	Oliceridine 100 µg N=7 (Excluding Subject (b) (6))
AUC <sub>0-t</sub> <sup>a</sup> (pg*hr/mL)	67.4 (202.3)	47.0 (99.4)
AUC <sub>0-∞</sub> <sup>a</sup> (pg*hr/mL)	252 (151.4) [n=3]	134 (10.5) [n=2]
C <sub>max</sub> <sup>a</sup> (pg/mL)	25.8 (151.8)	19.5 (97.1)
t <sub>max</sub> <sup>b</sup> (h)	0.75 (0.50 - 1.50)	0.75 (0.5 - 1.5)
t <sub>1/2</sub> <sup>a</sup> (h)	1.9 (29.4) [n=3]	1.62 (13.0) [n=2]
CL/F <sup>a</sup> (L/h)	397 (151.4) [n=3]	744 (10.5) [n=2]

AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>0-t</sub>=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; CL/F=total body clearance; C<sub>max</sub>=maximum observed plasma concentration; GeoCV=coefficient of variation for the geometric mean; PK=pharmacokinetic; t<sub>1/2</sub>=apparent terminal half-life; t<sub>max</sub>=time to peak concentration

<sup>a</sup> Geometric mean (GeoCV%).

<sup>b</sup> Median (minimum - maximum).

Data source: CP130-1004, CSR Table 14.2.2.1, Table 14.2.2.2

Subject (b) (6) showed plasma levels much higher than those observed in the rest of the subjects. This subject's C<sub>max</sub> and AUC<sub>0-∞</sub> values were 183 pg/mL and 886 pg.h/mL which were 7.1-fold and 3.5-fold greater than the overall geometric means, respectively. The CL/F observed in this individual was approximately 30% of the overall geometric mean. Specific CYP2D6 phenotyping identified this subject as a CYP2D6 PM (with a DMDX ratio of approximately 3.0 compared with the DMDX ratios for the remaining subjects [approximately 0.002 to 0.023] who were non-PMs) which is consistent with the reduced clearance observed.

Using AUC of IV PK parameter from another study the sponsor estimated the absolute bioavailability of TRV130 to be 5.77%. It is not optimal to compare parameters across studies.

#### 4.2.5 CP130-1005 Synopsis

CP130-1005 was a two-part, randomized, double-blind, placebo-controlled study in healthy adult males. Part A assessed the safety, tolerability, PK, and PD of multiple ascending IV doses of oliceridine (1.5, 3, and 4.5 mg) in CYP2D6 EMs. In Part A, 42 subjects were randomized to oliceridine or placebo in a 3:1 ratio. Part B consisted of two phases in CYP2D6 PMs:

- A multiple-dose phase where safety, tolerability, PK, and PD was evaluated in 4 PMs, who were randomized to oliceridine (0.4 mg) or placebo in a 3:1 ratio and received study medication every 6 hours (q6h) for 6 doses on Days 1 through 3, and
- A DDI phase where 4 PMs received oliceridine (0.25 mg) on Day 5, followed by 5 doses of itraconazole (ITZ; a strong CYP3A4 inhibitor) (oral, 200 mg daily) on Days 6 to 10, with ITZ administered 1 hour prior to oliceridine administration on Day 10.

Following multiple-dose administration of oliceridine 1.5, 3, or 4.5 mg q6h by a 2-minute IV infusion, AUC of oliceridine was proportional with dose while C<sub>max</sub> showed substantial variability, likely due to the short time between the start of infusion and collection of sample for analysis. For all treatments and for both EMs and PMs, the PK profile of oliceridine was similar following a single dose or multiple dosing. Consistent with the short t<sub>1/2</sub> (approximately 2 to 3 hours), accumulation of systemic oliceridine was modest (~50%). For the EMs, oliceridine CL was relatively constant across the various dosing schemes, suggesting dose linearity. The t<sub>1/2</sub> and steady-state volume of distribution in EMs were similar across dose levels and following single or multiple doses. Data suggested that distribution and elimination of oliceridine were dose-independent within the relatively narrow dose range tested (1.5 to 4.5 mg), and did not change with time following 2 days of dosing. Consistent with previous data in PMs, the oliceridine CL in the PMs was about 50% lower, and the t<sub>1/2</sub> was extended (4.5 hours) in this population. Urine PK parameters after the first and final doses and oliceridine concentrations were evaluated. Renal clearance in both PMs and EMs was low, representing about 2.2% to 5.1% of total CL (CP130-1005 CSR Table 14.2.1.6).

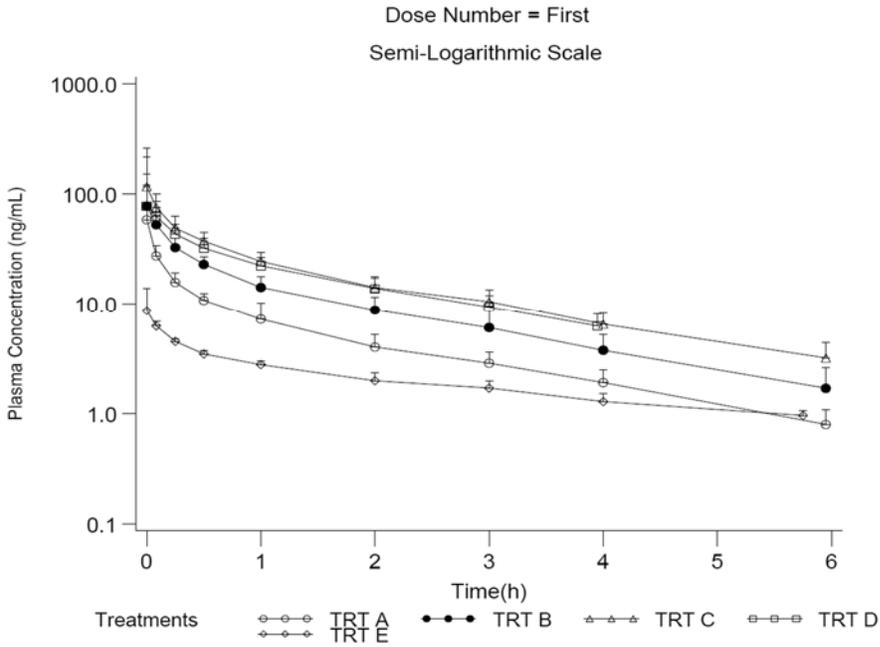
**Table 20. Summary of Oliceridine PK Parameters by CYP2D6 Status after the Last Infusion (Study CP130-1005)**

Dose	Infusion Time (min)	Number of Subjects	CYP2D6 Status	CL (L/hr)	CL <sub>renal</sub> (L/hr)	V <sub>ss</sub> (L)	AUC <sub>τ</sub> (ng*hr/L)	C <sub>max</sub> (ng/L)	t <sub>max</sub> <sup>a</sup> (hr)	t <sub>1/2</sub> (hr)
1.5 mg q6h x5 doses	2	8	EM	45.6 (22.4)	1.91 (23.4)	93.6 (29.7)	32.9 (22.5)	48.2 (99.8)	0.1 (0.03 - 0.1)	2.06 (20.3)
3 mg q6h x5 doses	2	9	EM	48.4 (17.1)	1.06 (60.0)	86.6 (33.2)	61.9 (17.1)	95.6 (88.8)	0.1 (0.03 - 0.18)	2.18 (40.5)
4.5 mg q6h x5 doses	2	7	EM	43.8 (13.1)	1.19 (62.3)	88.6 (34.1)	103 (13.1)	144 (107.7)	0.1 (0.03 - 0.12)	2.66 (35.6)
4 mg q4h x7 doses	2	6	EM	39.1 (22.8)	NA	87.9 (59.7)	102 (22.8)	166 (142.2)	0.1 (0.03 - 0.1)	3.07 (32.2)
0.4 mg q6h x6 doses	10	3	PM	25.2 (10.5)	1.29 (77.1)	116 (7.1)	15.9 (10.6)	8.98 (46.8)	0.17 (0.16 - 0.25)	4.50 (8.8)

AUC<sub>τ</sub>=area under the plasma concentration-time curve from time 0 to time tau (τ), where τ is the length of the dosing interval; CL=clearance; CL<sub>renal</sub>=renal clearance; C<sub>max</sub>=maximum observed plasma concentration; GeoCV=coefficient of variation for the geometric mean; EM=extensive metabolizers; PK=pharmacokinetic; PM=poor metabolizer; qxh=every x hours (eg; q3h is every 3 hours; q4h is every 4 hours); t<sub>1/2</sub>=apparent terminal half-life; t<sub>max</sub>=time to peak concentration; V<sub>ss</sub>=steady-state volume of distribution  
 Note: Numbers in the table are geometric mean (GeoCV%) except where noted.  
<sup>a</sup> Median (minimum - maximum).

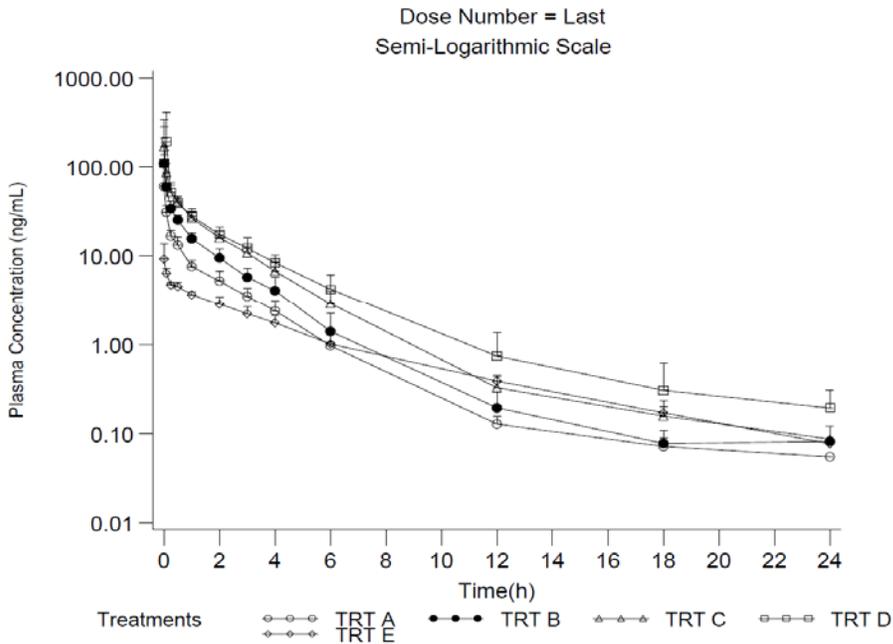
Data source: CP130-1005, CSR Table 14.2.1.6

Trevena, Inc.  
 Study CP130-1005 (b) (4)  
 Figure 14.2.1.1 Mean (+SD) TRV130 Plasma Concentration-Time Profiles by Treatment (Semi-log and Linear)  
 (Part A and Part B Multiple Dose Phase)  
 Pharmacokinetic Full Population



Data Source: Table 14.2.1.4  
 Treatment Codes: Part A: A: TRV130 1.5 mg IV Q6H x 5, B: TRV130 3 mg IV Q6H x 5, C: TRV130 4.5 mg IV Q6H x 5, D: TRV130 4 mg IV Q4H x 7, Part B: E: TRV130 0.4 mg IV Q6H x 6.  
 Non-poor Metabolizer: Treatments A, B, C, and D; Poor Metabolizer: Treatment E

Trevena, Inc.  
 Study CP130-1005 (b) (4)  
 Figure 14.2.1.1 Mean (+SD) TRV130 Plasma Concentration-Time Profiles by Treatment (Semi-log and Linear)  
 (Part A and Part B Multiple Dose Phase)  
 Pharmacokinetic Full Population



Data Source: Table 14.2.1.4  
 Treatment Codes: Part A: A: TRV130 1.5 mg IV Q6H x 5, B: TRV130 3 mg IV Q6H x 5, C: TRV130 4.5 mg IV Q6H x 5, D: TRV130 4 mg IV Q4H x 7, Part B: E: TRV130 0.4 mg IV Q6H x 6.  
 Non-poor Metabolizer: Treatments A, B, C, and D; Poor Metabolizer: Treatment E

**Table 21. Effect of Itraconazole on Oliceridine Pharmacokinetics: Part B Drug Drug Interaction Phase (Study CP130-1005)**

Parameter	Comparison	Geometric LS Mean (N=4)		Ratio of Geometric LS Mean	90% CI for Geometric LS Mean Ratio
		G (Oliceridine+ITZ)	F (Oliceridine)		
C <sub>max</sub>	G vs F	5.18	4.81	107.68	(67.39, 172.05)
AUC <sub>0-∞</sub>	G vs F	18.96	10.64	178.14	(168.76, 188.04)
AUC <sub>0-24</sub>	G vs F	17.75	10.62	167.14	(153.51, 181.99)

AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>0-24</sub>=area under the plasma concentration-time curve from time 0 to 24h; CI=confidence interval; C<sub>max</sub>=maximum observed plasma concentration; CYP2D6=cytochrome P450 2D6 enzyme; DDI=drug-drug interaction; ITZ=itraconazole; IV=intravenous; LS=least squares; PK=pharmacokinetic; PM=poor metabolizer; QD=once daily  
 Note: Estimates are from an analysis of variance model of the log-transformed PK parameters with treatment as a fixed and subject as repeated measure.

Treatment codes: F: Oliceridine 0.25 mg IV 10 minutes; G: Oliceridine 0.25 mg IV 10 minutes+ITZ 200 mg QD×5.  
 All subjects in Part B were CYP2D6 PMs.

Data source: CP130-1005, CSR Table 14.2.1.18

Cold pain test results are discussed in question-based review above.

**Table 22. Adverse events in the Part A and B of Study CP130-1005.**

MedDRA System Organ Class Preferred Term	Treatment A <sup>b</sup> (n = 9)	Treatment B <sup>b</sup> (n = 9)	Treatment C <sup>b</sup> (n = 10)	Treatment D <sup>b</sup> (n = 8)	Placebo (n = 11)
<b>Subjects with any TEAE</b>	9 (100.0%)	9 (100.0%)	10 (100.0%)	8 (100.0%)	3 (27.3%)
<b>Nervous system disorders</b>	7 (77.8%)	9 (100.0%)	8 (80.0%)	5 (62.5%)	1 (9.1%)
Dizziness	6 (66.7%)	8 (88.9%)	8 (80.0%)	4 (50.0%)	0
Somnolence	1 (11.1%)	4 (44.4%)	4 (40.0%)	2 (25.0%)	0
Headache	1 (11.1%)	0	1 (10.0%)	3 (37.5%)	1 (9.1%)
Paraesthesia	0	3 (33.3%)	0	1 (12.5%)	0
<b>Gastrointestinal disorders</b>	2 (22.2%)	4 (44.4%)	7 (70.0%)	6 (75.0%)	0
Nausea	2 (22.2%)	4 (44.4%)	6 (60.0%)	4 (50.0%)	0
Vomiting	0	1 (11.1%)	3 (30.0%)	4 (50.0%)	0
<b>General disorders and administration site conditions</b>	6 (66.7%)	9 (100.0%)	7 (70.0%)	5 (62.5%)	2 (18.2%)
Feeling hot	4 (44.4%)	4 (44.4%)	5 (50.0%)	1 (12.5%)	1 (9.1%)
Feeling of relaxation	0	6 (66.7%)	3 (30.0%)	5 (62.5%)	0
Feeling drunk	1 (11.1%)	0	1 (10.0%)	0	0
<b>Psychiatric disorders</b>	2 (22.2%)	1 (11.1%)	2 (20.0%)	0	0
Euphoric mood	2 (22.2%)	1 (11.1%)	1 (10.0%)	0	0

The observed adverse events are classic opioid effects.

#### 4.2.6 CP130-1006 Synopsis

Study CP130-1006 was a single-center, open-label, single-sequence, crossover study with 48 hours between oliceridine doses. Eleven healthy adult CYP2D6 EM males and females were enrolled to receive oliceridine (2 mg IV) alone, followed by oliceridine (2 mg IV) with concomitant oral ketoconazole (KTZ; a strong CYP3A4 inhibitor; 200 mg) administered 1 hour before and 11 hours after oliceridine.

The PK profile of oliceridine was similar with or without KTZ. The concomitant administration of KTZ did not have a statistically significant effect on the AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> of oliceridine and did not alter the t<sub>1/2</sub> and CL. The variability in C<sub>max</sub> was likely due to the short time between the start of the infusion and collection of PK samples. Due to the substantial variability in the observed peak concentration, this study did not allow for a definitive conclusion on the impact of KTZ on C<sub>max</sub> of oliceridine.

**Table 23. Summary of Oliceridine PK Parameters (Study CP130-1006)**

Parameter (unit)	Treatment	
	TRT A (N=10)	TRT B (N=10)
C <sub>max</sub> <sup>a</sup> (ng/mL)	43.44 (78.27)	52.47 (67.72)
t <sub>max</sub> <sup>b</sup> (h)	0.12 (0.03 - 0.28)	0.07 (0.03 - 0.12)
C0 <sup>a</sup> (ng/mL)	39.9 (26.5)	40.7 (28.6)
AUC <sub>0-t</sub> <sup>a</sup> (ng*h/mL)	43.85 (14.89)	44.63 (13.82)
AUC <sub>0-∞</sub> <sup>a</sup> (ng*h/mL)	44.16 (14.82)	44.83 (13.82)
t <sub>1/2</sub> <sup>a</sup> (h)	1.87 (19.36)	1.87 (20.75)
CL <sup>a</sup> (L/h)	45.29 (14.81)	44.61 (13.81)

AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>0-t</sub>=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; C0=predicted concentration at the end of the 2 minute infusion by back extrapolation; CL=clearance; C<sub>max</sub>=maximum observed plasma concentration; GeoCV=coefficient of variation for the geometric mean; IV=intravenous;

KTZ=ketoconazole; PK=pharmacokinetic; t<sub>1/2</sub>=apparent terminal half-life; t<sub>max</sub>=time to peak concentration

Note: TRT A: Oliceridine 2 mg IV infusion over 2 minutes. TRT B: Oliceridine 2 mg IV infusion over 2 minutes and 2 doses of 200 mg KTZ orally given 12 hours apart (first KTZ dose administered 1 hour prior to oliceridine infusion).

<sup>a</sup> Geometric Mean (GeoCV%).

<sup>b</sup> Median (minimum - maximum).

Data source: CP130-1006, CSR Table 14.2.1.3

**Table 24. Effect of KTZ (a Strong CYP3A4 Inhibitor) on Oliceridine PK (Study CP130-1006)**

Parameter (unit)	Geometric LS Mean		Ratio of Geometric LS Mean (Test/Reference)	90% CI
	TRT B (N=10) (Test)	TRT A (N=10) (Reference)		
C <sub>max</sub> (ng/mL)	52.47	43.44	1.208	0.762, 1.915
AUC <sub>0-t</sub> (ng*h/mL)	44.63	43.85	1.018	0.942, 1.100
AUC <sub>0-∞</sub> (ng*h/mL)	44.83	44.16	1.015	0.941, 1.095
C0 (ng/mL)	40.69	39.90	1.020	0.867, 1.200

AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>0-t</sub>=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; C0=predicted concentration at the end of infusion by back extrapolation; CI=confidence interval; C<sub>max</sub>=maximum observed plasma concentration; IV=intravenous; KTZ=ketoconazole; LS=least squares; PK=pharmacokinetic

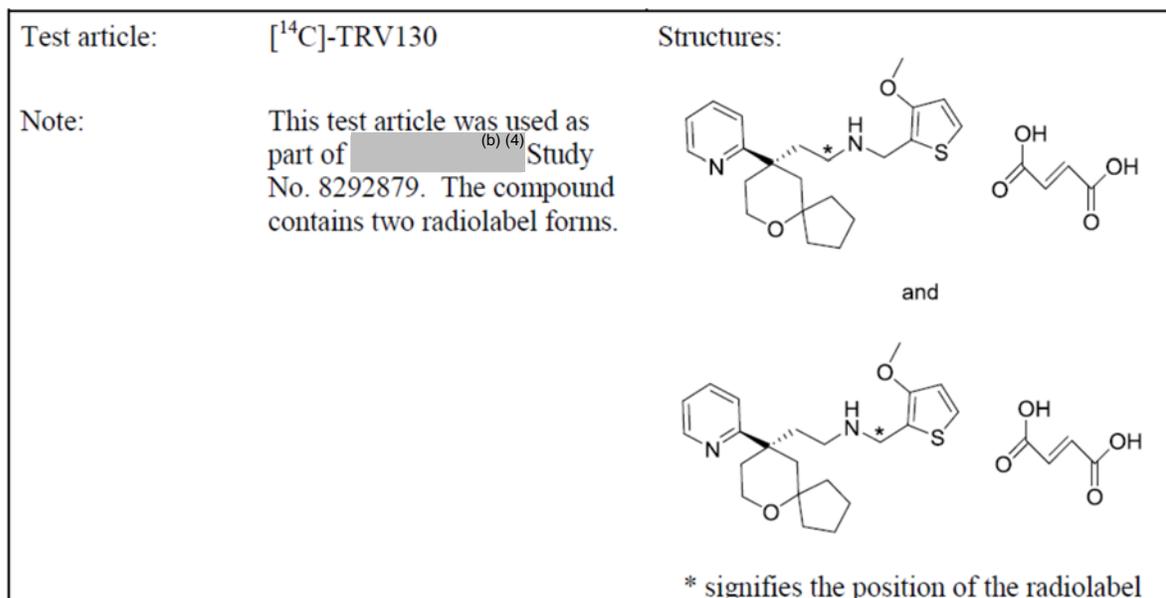
Note: TRT A (Reference): Oliceridine 2 mg IV infusion over 2 minutes. TRT B (Test): Oliceridine 2 mg IV infusion over 2 minutes and 2 doses of 200 mg KTZ orally given 12 hours apart (first KTZ dose administered 1 hour prior to oliceridine infusion).

Data source: CP130-1006, CSR Table 14.2.1.8

#### 4.2.7 CP130-1007 (mass balance study) Synopsis.

Study CP130-1007 was an open-label, nonrandomized, metabolism and excretion study of a single 2 mg/100  $\mu$ Ci dose of [ $^{14}$ C]-TRV130 administered as a 10 mL IV infusion over 2 minutes to 6 healthy male subjects. All subjects enrolled in Study CP130-1007 were non-poor metabolizers, as identified by urine dextromethorphan/dextrorphan testing.

**Figure 11. The radiolabeled test article was used as part of (b) (4) Study No. 8292879 (or Trevena Protocol CP130-1007).**



For plasma oliceridine, the concentration vs time profile was predictably characterized by rapid appearance after completion of the IV push, with a  $t_{max}$  of 7.2 minutes. Following attainment of  $C_{max}$ , plasma concentrations appeared to decline in a multiphasic manner. The mean  $t_{1/2}$  was 1.80 hours. The plasma total radioactivity (TRA) vs time profile after completion of the IV push showed a median  $t_{max}$  of 46.8 minutes. The apparent elimination of TRA following  $C_{max}$  appeared to be multiphasic. The mean  $t_{1/2}$  was approximately 44.6 hours and was approximately 25 times longer than for oliceridine. Consistent with delayed  $t_{max}$  and  $t_{1/2}$  values for radioactivity in plasma compared with oliceridine, which are indicative of one or more significant metabolites, there was a notable difference in exposure parameters. Respective mean values for  $C_{max}$  and  $AUC_{0-inf}$  were approximately 2.5-fold and 16-fold higher for TRA in plasma compared with oliceridine. Exposure to oliceridine, as assessed from  $C_{max}$  and  $AUC_{0-inf}$ , accounted for approximately 40% and 6% of TRA, respectively. The whole blood TRA vs time profile after completion of the IV push showed a median  $t_{max}$  of 1.03 hours. The apparent elimination of TRA following  $C_{max}$  appeared to be multiphasic. The mean  $t_{1/2}$  in whole blood was 15.6 hours; approximately nine times longer than for oliceridine in plasma and three times shorter than for TRA in plasma.

Low association of radioactivity with blood cells was indicated from the mean whole blood-to-plasma radioactivity concentration ratios (ranged from 0.47 to 0.85 through 72 hours postdose)

and the geometric mean (coefficient of variation for the geometric mean [GeoCV%]) ratio of whole blood AUC<sub>0-inf</sub> to plasma AUC<sub>0-inf</sub> (0.46 [17.0]).

**Table 25. Summary of PK Parameters for Oliceridine and TRA in Plasma and Whole Blood (Study CP130-1007)**

Parameter (unit)	Oliceridine in Plasma (N=6)	TRA in Whole Blood (N=6)	TRA in Plasma (N=6)
C <sub>max</sub> (ng/mL)	13.7 (20.0)	18.6 (13.7) <sup>a</sup>	34.3 (23.7) <sup>a</sup>
t <sub>max</sub> <sup>b</sup> (h)	0.12 (0.11, 0.28)	1.03 (0.02, 2.03)	0.78 (0.28, 2.03)
AUC <sub>0-t</sub> (ng*h/mL)	27.7 (11.8)	174 (16.1) <sup>c</sup>	387 (14.7) <sup>c</sup>
AUC <sub>0-∞</sub> (ng*h/mL)	28.1 (11.9)	199 (21.5) <sup>c</sup>	453 (16.4) <sup>c, d</sup>
t <sub>1/2</sub> (h)	1.80 (21.1)	15.6 (79.6)	44.6 (26.4) <sup>d</sup>
λ <sub>Z</sub> (1/h)	0.39 (21.1)	0.044 (79.6)	0.016 (26.4) <sup>d</sup>
CL (L/h)	71.2 (11.9)	10.1 (21.5)	4.41 (16.4) <sup>d</sup>
V <sub>ss</sub> (L)	181 (11.2)	171 (36.9)	166 (17.6) <sup>d</sup>
B:P Ratio	NA	0.46 (17.0) <sup>d</sup>	NA

AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>0-t</sub>=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; CL=clearance;

C<sub>max</sub>=maximum observed plasma concentration; GeoCV=coefficient of variation for the geometric mean; NA=not applicable; λ<sub>Z</sub>=apparent terminal rate constant; PK=pharmacokinetic; t<sub>1/2</sub>=apparent elimination half-life; t<sub>max</sub>=time to peak concentration; TRA=total radioactivity; V<sub>ss</sub>=steady-state volume of distribution

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

B:P Ratio=whole blood AUC<sub>0-∞</sub> of TRA/AUC<sub>0-∞</sub> of TRA in plasma.

<sup>a</sup> Units for TRA are ng equivalents/g and in plasma are ng equivalent/mL.

<sup>b</sup> Median (minimum – maximum).

<sup>c</sup> Units for TRA are ng equivalents\*hr/g for AUC values.

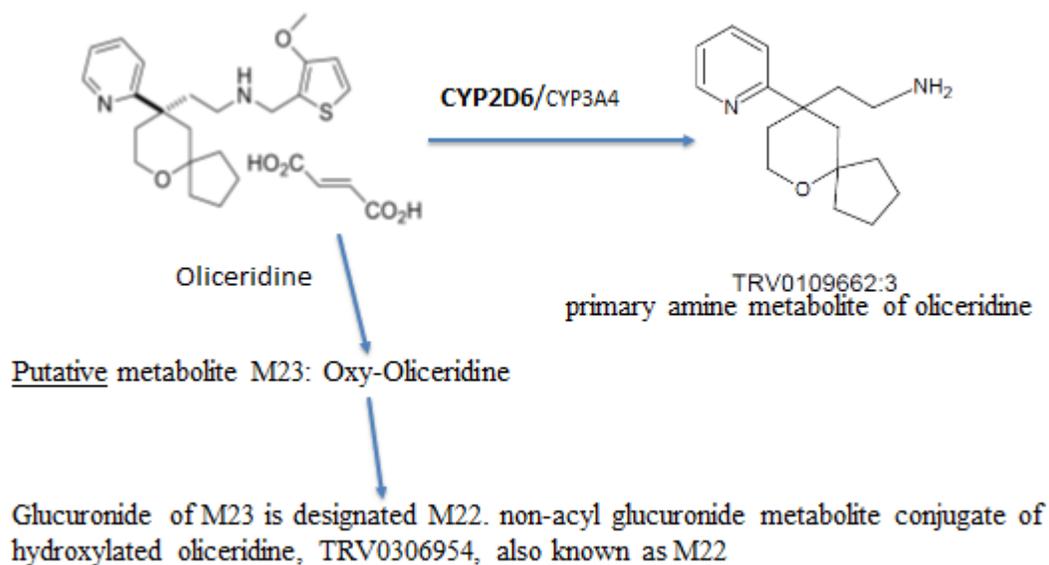
<sup>d</sup> N=5, as terminal elimination rate constant for Subject (b)(6) was not determined due to poor fit.

Data source: CP130-1007, CSR Table 14.2.2-1 to Table 14.2.2-3

A mean of 70.1% of the administered dose was recovered in urine and 18.4% was recovered in feces through the last collection interval. Most of the administered radioactivity was recovered in the first 72 hours postdose (83.9%). The mean overall total recovery of radioactivity in urine and fecal samples over the 144-hour postdose period was 88.5%, with recovery in individual subjects ranging from 72.4% to 94.2%.

Analysis of plasma extracts, urine, and fecal samples from 6 male human subjects after a single IV dose of <sup>14</sup>C-oliceridine (2 mg, 100 μCi) demonstrated extensive biotransformation of oliceridine to produce up to 36 metabolites, of which 10 were identified. As previously noted, the main metabolites of oliceridine are not active metabolites (Section 1.3.1). In plasma, oxy-oliceridine glucuronide (M22) was the main circulating radioactive component, accounting for a mean of 61.9% of plasma exposure (AUC). N-Dealkylation and oxidation of oliceridine produced circulating metabolites TRV0109662 (17.4 % of plasma AUC) and oxy-oliceridine (M23; 5.20% of plasma exposure). Oliceridine accounted for approximately 3.4% of total plasma exposure. Similar to plasma, the glucuronide conjugate, M22, was the most abundant radioactive component in urine and accounted for a mean of 23.6% of the dose, whereas its putative aglycone analog, M23, was the second most abundant metabolite in urine and accounted for 12.2% of the radioactive dose. In feces, M23 was the most abundant radioactive component that accounted for a mean of 3.34% of the dose across all subjects.

Figure 12. Metabolite Profile of Oliceridine.



#### **4.2.8 CP130-1008 Synopsis and QT/QTc Interval Prolongation**

Please see reviews in DARRTS for tQT study CP130-1008 dated 02/04/2016 under IND 113537 and CP130-3001 and 3002 in review dated 03/08/2018, CP130-3003 in review dated 06/06/2018, CiPA report review dated 09/27/2018 under NDA 210730. The following is a succinct summary of all the above memo's.

An important consideration during drug development 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<sub>50</sub> for oliceridine in the hERG assay (Study No.110520.USF) was 2.2 μM, approximately 367 times the K<sub>i</sub> at the mu opioid receptor, 27 times the free C<sub>max</sub> after 3 mg IV infusion (CP130-1008), and 43 times the estimated free C<sub>max</sub> of the currently proposed maximum recommended human dose (MRHD) of 40 mg/day. Weak inhibition of hCav 1.2 (IC<sub>50</sub> of 39.6 μM) and of hNav1.5 (IC<sub>50</sub> of 19.5 μM for tonic and IC<sub>50</sub> 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<sub>max</sub> 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 1.

**Table 26. 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)**

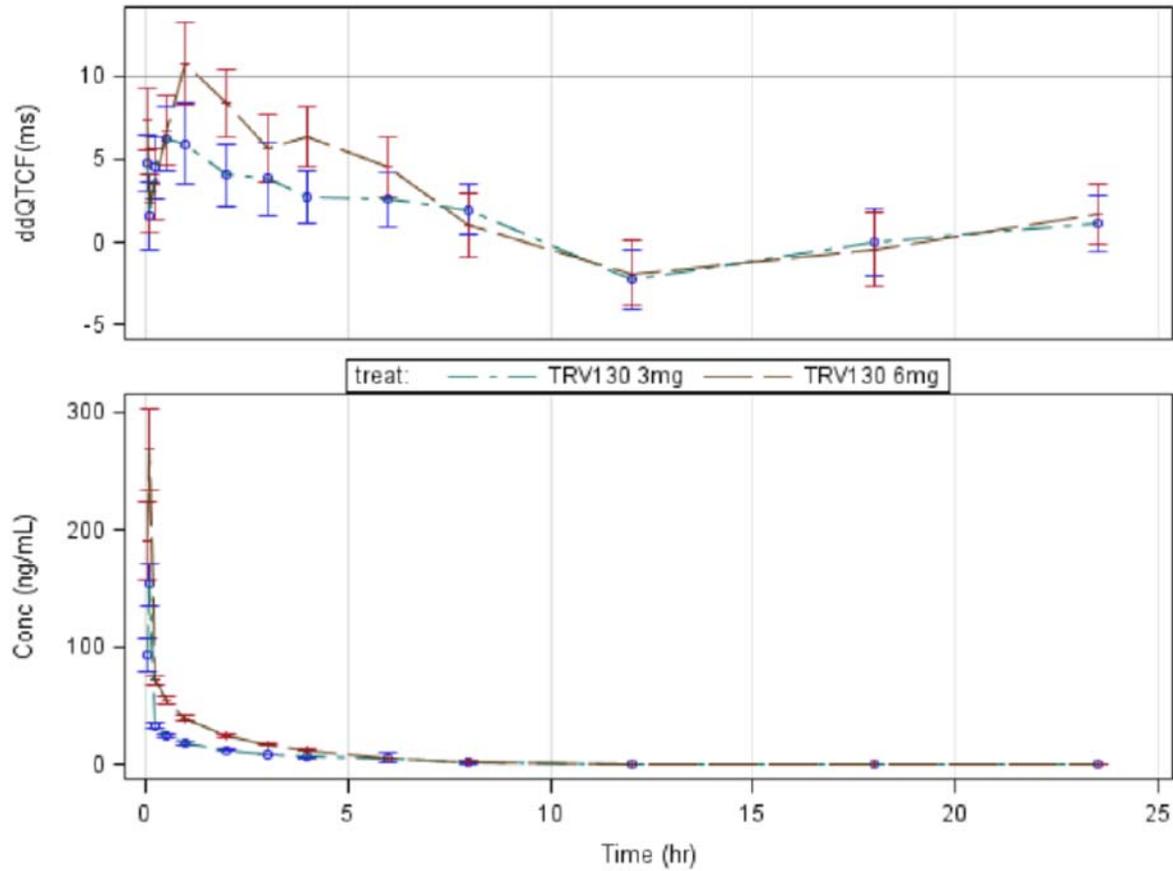
<b>Treatment</b>	<b>Time (hour)</b>	<b><math>\Delta\Delta QTcF</math> (ms)</b>	<b>90% CI (ms)</b>
TRV130 3 mg	0.5	6.8	(4.7, 8.9)
TRV130 6 mg	1	11.6	(9.5, 13.7)
Moxifloxacin 400 mg*	2	11.5	(8.6, 14.4)

\* 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 13).

Figure 13.  $\Delta\Delta$ QTcF 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

Table 27. Summary of Oliceridine Pharmacokinetics in Part B of Study CP130-1008.

Part B DT: Oliceridine 3 mg							
Statistic	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	AUC <sub>0-t</sub> (h*ng/mL) <sup>a</sup>	CL (L/h) <sup>a</sup>	V <sub>z</sub> (L) <sup>a</sup>	t <sub>1/2</sub> (h) <sup>a</sup>	AUC <sub>0-∞</sub> (h*ng/mL) <sup>a</sup>
n	55	55	55	45	45	45	45
GeoMean	132.9	NA	88.68	34.49	133.47	2.68	86.99
GeoCV(%)	69.45	NA	24.85	25.13	31.16	37.87	25.13
Minimum	21.7	0.06	54.42	15.90	67.81	1.43	54.68
Median	161.0	0.09	90.58	33.10	131.40	2.65	90.06
Maximum	343.0	0.34	185.86	54.86	266.9	4.98	188.69
Part B DS: Oliceridine 6 mg							
n	57	57	57	50	50	50	50
GeoMean	234.8	NA	180.20	33.60	179.61	3.71	178.61
GeoCV(%)	79.85	NA	26.86	27.89	40.40	39.85	27.88
Minimum	50.6	0.06	98.8	17.07	52.80	1.21	99.0
Median	302.0	0.09	190.86	31.71	187.50	4.15	189.22
Maximum	701.0	0.60	347.45	60.60	420.4	5.73	351.43

AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>0-t</sub>=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; CL=clearance;

C<sub>max</sub>=maximum observed plasma concentration; GeoCV=coefficient of variation for the geometric mean;

GeoMean=geometric mean; NA=not available; PK=pharmacokinetic; t<sub>1/2</sub>=apparent terminal half-life; t<sub>max</sub>=time to peak concentration; V<sub>z</sub>=volume of distribution

Note: Treatment codes: DS: Oliceridine 6 mg, DT: Oliceridine 3 mg.

Data source: CP130-1008, CSR Table 2623-0019.5a

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 upto 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 28. 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  $\Delta$ QTcF >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 (**Error! Reference source not found.**).

**Table 29. Adverse Events Associated with MedDRA SMQ Torsade de Pointes/QT Prolongation**

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

<sup>1</sup>Largest QTcF interval (440 ms) occurred at baseline. <sup>2</sup>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. (b) (4)

#### 4.2.9 CP130-1010 Synopsis

Study CP130-1010 was a multi-center, open-label, PK and safety study of a single 2-minute IV infusion of oliceridine in healthy adult male and female subjects and subjects with mild, moderate, or severe hepatic impairment. Healthy adults were administered a dose of 1 mg of oliceridine and subjects with hepatic impairment were administered a dose of 0.5 mg of oliceridine. Hepatic status was defined using the Child-Pugh classification at Screening, and data from subjects with mild and moderate impairment were reviewed prior to enrollment of subjects with severe hepatic impairment.

A total of 34 subjects were enrolled in the study (10 with mild hepatic impairment, 10 with moderate hepatic impairment, 6 with severe hepatic impairment, and 8 sex, age, and body mass index [BMI] matched normal subjects). None of the subjects were PMs. Two subjects in both the mild and moderate hepatic impairment groups were excluded from the PK analysis because plasma concentrations were below the limit of quantification. A subsequent investigation showed that this was due to a dosing error at the clinical site, and these subjects did not receive oliceridine.

**Table 30. Pharmacokinetics of Oliceridine in healthy volunteers and patients with hepatic impairment (CP130-1010)**

Parameter	Normal N=8	Mild N=8	Moderate N=8	Severe N=6
CL (L/h)	42.3 (27.2)	44.5 (48.9)	33.9 (32.1)	41.8 (36.5)
C <sub>max</sub> (ng/mL) <sup>a</sup>	34.8 (110.0)	41.4 (78.4)	41.9 (41.6)	8.4 (89.5)
AUC <sub>0-inf</sub> (h*ng/mL) <sup>a</sup>	23.7 (30.5)	22.5 (33.9)	29.5 (37.0)	23.9 (41.6)
t <sub>1/2</sub> (h)	2.07 (11.3)	2.61 (20.0)	4.33 (44.1)	5.77 (41.2)
AUC <sub>t</sub> (h*ng/mL) <sup>a</sup>	23.3 (30.8)	21.8 (33.8)	28.2 (37.9)	21.8 (44.0)
AUC <sub>0-24</sub> (h*ng/mL) <sup>a</sup>	23.6 (30.5)	22.5 (33.9)	28.5 (32.3)	22.1 (36.0)
λ <sub>z</sub> (1/h)	0.34 (11.0)	0.27 (18.9)	0.16 (36.8)	0.12 (52.5)
V <sub>z</sub> (L)	126.1 (21.6)	167.3 (44.8)	211.5 (18.2)	347.9 (35.2)

AUC<sub>0-24</sub>=area under the plasma concentration-time curve from time 0 to 24h postdose; AUC<sub>0-inf</sub>=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC<sub>t</sub>=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; CL=clearance; C<sub>max</sub>=maximum observed plasma concentration; CV=coefficient of variation; λ<sub>z</sub>=apparent terminal rate constant; PK=pharmacokinetics; t<sub>1/2</sub>=apparent terminal half-life, V<sub>z</sub>=volume of distribution

<sup>a</sup> C<sub>max</sub> and AUCs were dose normalized.

Note: All parameters are presented as Geometric Mean (%CV).

Data source: CP130-1010, CSR Table 14.2.2.1

The geometric means of the total plasma CL and of the dose-normalized AUC<sub>0-inf</sub>, AUC<sub>t</sub>, and AUC<sub>0-24</sub> were similar across groups with no discernable relationship with hepatic function. Dose-normalized C<sub>max</sub> values were similar for subjects with normal hepatic function and with mild and moderate hepatic impairment (range: 34.8 to 41.9 ng/mL) but were significantly lower in subjects with severe hepatic impairment (8.4 ng/mL). In addition, t<sub>1/2</sub> and V<sub>z</sub> values increased and apparent terminal rate constant (λ<sub>z</sub>) values decreased with increasing severity of hepatic impairment, suggesting a relationship to hepatic function. V<sub>z</sub> of oliceridine increased gradually with the degree of hepatic impairment, and its geometric mean was 167.3 L in mild,

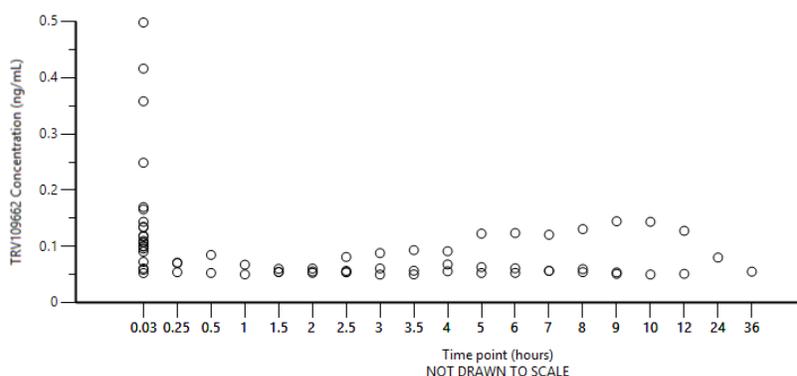
211.5 L in moderate, and 347.9 L in severe hepatic impairment, compared to 126.1 L in subjects with normal hepatic impairment. This could be attributed to the decreased metabolic capacity in hepatically impaired subjects, as evidenced by a decrease of  $V_z$  with the severity of the impairment. Additionally, the decreased albumin plasma concentration in hepatic impairment could have led to an increase in the free fraction of oliceridine which further contributed to an increase in the distribution of oliceridine into peripheral compartments. The presence of ascites in the more severely-impaired subjects may also play a role in the increased volume of distribution in these patients as compared to healthy subjects. As discussed at the 10/2/2018 OCP briefing, protein binding changes in severe HI may not play a major role because oliceridine protein binding is 77% with 23% unbound.

**Table 31. Dose-Normalized Cmax and AUC of Oliceridine in Patients with Hepatic Impairment.**

	Mild (N=10)	Moderate (N=10)	Severe (N=6)	Normal (N=8)
	8	8	6	8
	<b>Dose Normalized Cmax (ng/mL)</b>			
Mean (SD)	62.3 (48.8)	46.6 (19.4)	11.9 (10.6)	54.1 (59.5)
GeoMean (%CV)	41.4 (78.4)	41.9 (41.6)	8.4 (89.5)	34.8 (110.0)
Median (Min-Max)	66.0 (7.4–154.2)	47.9 (13.3–71.6)	8.8 (2.7–30.6)	33.1 (9.3–187.0)
	<b>Dose Normalized AUC(ng.h/mL)</b>			
Mean (SD)	24.1 (8.2)	31.2 (11.5)	25.5 (10.6)	24.5 (7.5)
GeoMean (%CV)	22.5 (33.9)	29.5 (37.0)	23.9 (41.6)	23.7 (30.5)
Median (Min-Max)	26.9 (10.9–32.4)	26.6 (21.0–51.0)	22.7 (13.9–45.4)	22.5 (15.1–40.6)

TRV0109662 Metabolite: The concentration of TRV0109662 was generally too low to assess PK parameters of relevance. The PK of the metabolite TRV0109662 could not be evaluated in this study because of the low plasma concentrations that could not be measured in most sampling time points. Accordingly, the results of the ANOVA and linear regression analysis were not relevant due to the insufficient data.

**Figure 14. Detected concentrations of TRV109662 in hepatic impairment study**



#### 4.2.10 CP130-1011 Synopsis

Study CP130-1011 was a single-dose, randomized, double-blind crossover study to assess the abuse potential of IV oliceridine compared with morphine and placebo in healthy, non-dependent, recreational, opioid users. The study consisted of two parts. **Part A** was a Dose Escalation Phase to evaluate the safety and tolerability of single IV doses of oliceridine up to 7 mg using a 1-minute infusion rate. Escalating oliceridine doses were evaluated in separate cohorts of 4 subjects each, randomized 3:1 to oliceridine or placebo, with oliceridine dose levels of 3 and 5 mg. Part B consisted of 3 visits: an outpatient screening visit (Day -28 to Day -1); an inpatient Qualification and Treatment Phase visit (Day -1 to Day 15), and a Follow-up visit (7 to 14 days after discharge). The Qualification Phase comprised a Naloxone Challenge Test to confirm subjects were not opioid-dependent, and a Drug Discrimination Test (subjects received IV morphine and matching placebo in a randomized-sequence, double-blind, crossover manner, separated by approximately 24 hours) to ensure subjects could discriminate and show positive subjective effects of morphine. Subjects who met the Drug Discrimination Test criteria entered the Treatment Phase. A minimum washout interval of approximately 48 hours was required between last study drug administration in the Qualification Phase (Day 2) and first study drug administration in the Treatment Phase (Day 4). Following confirmation of eligibility in the Qualification Phase, subjects were randomized to 1 of 6 treatment sequences including single doses of oliceridine 1, 2, and 4 mg; morphine 10 and 20 mg (doses were selected based on Part A results); and placebo according to a 6 × 6 Williams square in the Treatment Phase. Each treatment was separated by a 48-hour washout period. Subjects received 6 treatments (on Days 4, 6, 8, 10, 12, and 14) administered IV over 1 minute with a 48-hour washout interval between treatments. The six treatments, as determined based on results of Part A, were as follows:

- Oliceridine 1 mg
- Oliceridine 2 mg
- Oliceridine 4 mg
- Morphine 10 mg dose (dose-matched based on relative potency to oliceridine 2 mg)
- Morphine 20 mg dose (dose-matched based on relative potency to oliceridine 4 mg)
- Placebo

A total of 42 subjects were randomized to the Treatment Phase of Part B, with 7 subjects randomized to each treatment sequence. Two subjects discontinued prematurely due to AEs; 40 subjects completed the study.

Controlled Substance Staff reviewer Dr. Katherine Bonson's assessed abuse liability of oliceridine. However, pharmacodynamics of oliceridine in terms of bipolar drug liking visual analog scale recordings by subjects is reviewed.

Pharmacokinetics of oliceridine were not assessed in this study; hence, a concentration-response analysis could not be attempted.

**Table 32. Demographics of subjects in Study CP130-1011**

<b>Demographic Variable</b>	<b>Dose Escalation Phase Population (N=8)</b>	<b>Treatment Phase Safety Population (N=42)</b>
Age (years), mean (SD)	29.6 (6.44)	28.8 (8.66)
Sex, n (%)		
Male	6 (75.0)	30 (71.4)
Female	2 (25.0)	12 (28.6)
Race, n (%)		
White	7 (87.5)	34 (81.0)
Black or African American	0	6 (14.3)
Asian	1 (12.5)	0
Native Hawaiian or other Pacific Islander	0	1 (2.4)
Other	0	1 (2.4)
Ethnicity, n (%)		
Hispanic or Latino	2 (25.0)	4 (9.5)
Not Hispanic or Latino	6 (75.0)	38 (90.5)
BMI (kg/m <sup>2</sup> ), mean (SD)	24.83 (3.130)	24.55 (3.258)
CYP2D6 Metabolizer, n (%)		
Extensive metabolizer	6 (75.0)	36 (85.7)
Intermediate Metabolizer	0	4 (9.5)
Ultra-rapid metabolizer	0	1 (2.4)
Poor Metabolizer	0	1 (2.4)
Unable to Assign Status	2 (25.0)	0

BMI=body mass index; SD=standard deviation.  
Source Data: Table 14.1.5.1 and Table 14.5.1.3.

In healthy volunteers and in subjects that are nondependent, recreational opioid users, drug liking effects were observed immediately after 1-minute IV infusion of oliceridine (Study CP130-1011). Non-dependent subjects that qualified into treatment phase by their ability to discriminate morphine from placebo were administered with three different doses of oliceridine and compared with placebo and morphine 10 mg as positive control for drug liking effects at the moment on a bipolar visual analog scale. A baseline measure or a neutral point of 50 would indicate subjects neither like nor dislike drug effects. A threshold of 65 for significant drug liking effects was utilized to define time to onset, time to offset and duration of effects following initiation of IV infusions. The onset of drug liking effects “at the moment” was reported by most subjects immediately after receiving oliceridine and morphine. The offset of drug liking effects or decrease in drug liking “at the moment” to a value below 65 was observed sooner in oliceridine treatment groups compared to 10 mg IV morphine group. Accordingly, partial area under the effect curve (partial AUE) between onset and offset increase with dose of oliceridine and numerical values were lower for oliceridine compared to morphine doses. The clinical significance of this observed difference in partial AUE’s is unknown.

**Table 33. Descriptive statistics of drug liking “at the moment” measures.**

Variable	Treatment	N	NMiss	NObs	Mean	SD
Time (hours) to onset to threshold of 65 for “at the moment” drug liking on a bipolar visual analog scale	A: Oliceridine 1 mg	25	14	39	0.16	0.07
	B: Oliceridine 2 mg	31	7	38	0.13	0.02
	C: Oliceridine 4 mg	37	2	39	0.13	0.02
	D: Morphine 10 mg	34	4	38	0.17	0.15
	E: Morphine 20 mg	39	1	40	0.17	0.28
	F: Placebo	0	40	40	.	.
Emax or Peak “at the moment” drug liking on a bipolar visual analog scale	A: Oliceridine 1 mg	39	0	39	71.46	16.16
	B: Oliceridine 2 mg	38	0	38	81.87	14.93
	C: Oliceridine 4 mg	39	0	39	88.13	12.95
	D: Morphine 10 mg	38	0	38	80.13	14.55
	E: Morphine 20 mg	40	0	40	88.54	12.91
	F: Placebo	40	0	40	50.85	2.37
Time to Emax (hours)	A: Oliceridine 1 mg	39	0	39	0.44	0.98
	B: Oliceridine 2 mg	38	0	38	0.39	0.57
	C: Oliceridine 4 mg	39	0	39	0.21	0.10
	D: Morphine 10 mg	38	0	38	0.38	0.65
	E: Morphine 20 mg	41	0	41	0.39	0.55
	F: Placebo	40	0	40	0.46	0.81
Toffset (hours) from threshold of 65 on VAS Scale	A: Oliceridine 1 mg	25	14	39	1.10	1.43
	B: Oliceridine 2 mg	31	7	38	1.44	1.36
	C: Oliceridine 4 mg	37	2	39	1.62	1.45
	D: Morphine 10 mg	34	4	38	2.27	2.53
	E: Morphine 20 mg	39	2	41	3.00	2.68
	F: Placebo	0	40	40	.	.
Duration of Action (hours): Time to Toffset minus Tonset.	A: Oliceridine 1 mg	25	14	39	0.93	1.43
	B: Oliceridine 2 mg	31	7	38	1.31	1.37
	C: Oliceridine 4 mg	37	2	39	1.50	1.45
	D: Morphine 10 mg	34	4	38	2.10	2.56
	E: Morphine 20 mg	39	1	40	2.82	2.70
	F: Placebo	0	40	40	.	.

**Table 34. Partial AUE for drug liking for timepoints Tonset to Toffset.**

Treatment	N	NMiss	NObs	Mean	SD
A: Oliceridine 1 mg	25	0	25	75.17	128.38
B: Oliceridine 2 mg	31	0	31	104.32	110.18
C: Oliceridine 4 mg	37	0	37	119.63	116.42
D: Morphine 10 mg	34	0	34	167.35	207.05
E: Morphine 20 mg	39	0	39	234.79	244.07

#### 4.2.11 CP130-1012 Synopsis

Study CP130-1012 was a Phase 1, open-label, parallel-group, two-part study designed to evaluate the PK, safety, and tolerability of a single IV dose of oliceridine in subjects who regularly undergo hemodialysis as part of their treatment regimen for end-stage renal disease (ESRD) compared with healthy subjects (Part A), and in subjects with mild renal impairment compared with healthy subjects (Part B). Part B of the study was to be conducted if the ESRD group had a >50% increase in mean peak or total exposure to oliceridine compared with healthy subjects. Poor metabolizers were excluded from this study. A total of 17 subjects (9 subjects with ESRD and 8 healthy gender- and age-matched control subjects) were enrolled in Part A of the study and all subjects completed the study. Part B of the study was not conducted, as the ESRD group had a <50% increase in mean peak and total exposure to oliceridine compared with healthy subjects.

The geometric mean dose normalized C<sub>max</sub> was similar for the ESRD and healthy subjects with mean estimates of 9.87 ng/mL and 8.79 ng/mL, respectively. The geometric mean dose normalized AUC<sub>0-last</sub> and AUC<sub>0-∞</sub> estimates were also comparable with mean estimates of 19.1 hr\*ng/mL and 20.3 hr\*ng/mL for the ESRD subjects and 17.8 hr\*ng/mL and 18.1 hr\*ng/mL for healthy subjects, respectively. The geometric mean estimates for t<sub>1/2</sub>, CL, and V<sub>z</sub> were also similar among the groups.

**Table 35. Summary of Oliceridine PK Parameters in renal impairment study CP130-1012.**

Parameter	ESRD Subjects		Healthy Subjects	
	N	Geometric Mean (%CVb)	N	Geometric Mean (%CVb)
C <sub>max</sub> (ng/mL)	8	4.94 (14.8)	8	8.79 (22.4)
C <sub>max</sub> /Dose (ng/mL)/(mg)	8	9.87 (14.8)	8	8.79 (22.4)
T <sub>max</sub> (hr) <sup>a</sup>	8	0.25 (0.25 – 0.25)	8	0.25 (0.25 – 0.25)
AUC <sub>0-last</sub> (hr*ng/mL)	8	9.56 (27.3)	8	17.8 (17.8)
AUC <sub>0-last</sub> /Dose (hr*ng/mL)/(mg)	8	19.1 (27.3)	8	17.8 (17.8)
AUC <sub>0-∞</sub> (hr*ng/mL)	7	10.2 (28.3)	8	18.1 (17.8)
AUC <sub>0-∞</sub> /Dose (hr*ng/mL)/(mg)	7	20.3 (28.3)	8	18.1 (17.8)
t <sub>1/2</sub> (hr)	7	2.99 (31.9)	8	2.34 (31.9)
CL (L/hr)	7	49.2 (28.3)	8	55.3 (17.8)
V <sub>z</sub> (L/hr)	7	212 (27.8)	8	187 (34.5)

AUC<sub>0-∞</sub>=area under the plasma concentration versus time curve from time zero to infinity; AUC<sub>0-last</sub>=area under the plasma concentration versus time curve from time zero to time of last quantifiable concentration after dosing; CL=clearance; C<sub>max</sub>=maximum observed plasma concentration; ESRD=end-stage renal disease; max=maximum; min=minimum; N=number of subjects; PK=pharmacokinetics; %CVb=coefficient of variation; t<sub>1/2</sub>=apparent terminal half-life; T<sub>max</sub>=time to reach maximum plasma concentration, V<sub>z</sub>=volume of distribution

<sup>a</sup> T<sub>max</sub> = median (min-max)

Data source: CP130-1012, CSR Table 14.2.2.1 and Table 14.2.2.2

**Table 36. Results of ANCOVA of Oliceridine PK Parameters (Study CP130-1012)**

Parameter (Units)	Renal Function Group	Geometric Mean	Ratio of Geometric Mean	90% CI for Ratio
AUC <sub>0-last</sub> /Dose ((hr*ng/mL)/mg)	ESRD (Test)	17.0	108	90.07 - 130.08
	Healthy (Reference)	15.7		
AUC <sub>0-∞</sub> /Dose ((hr*ng/mL)/mg)	ESRD (Test)	18.9	123	102.09 - 148.39
	Healthy (Reference)	15.3		
C <sub>max</sub> /Dose (ng/mL/mg)	ESRD (Test)	9.89	113	95.36 - 133.16
	Healthy (Reference)	8.77		
CL (L/hr)	ESRD (Test)	53.0	81.2	67.39 - 97.96
	Healthy (Reference)	65.2		
t <sub>1/2</sub> (hr)	ESRD (Test)	2.99	128	95.94 - 169.81
	Healthy (Reference)	2.34		

ANCOVA=analysis of covariance; AUC<sub>0-∞</sub>= area under the plasma concentration versus time curve from time zero to infinity; AUC<sub>0-last</sub>= area under the plasma concentration versus time curve from time zero to time of last quantifiable concentration after dosing; BMI=body mass index; CL=clearance; C<sub>max</sub>=maximum observed plasma concentration; CI=confidence interval; ESRD=end-stage renal disease; PK=pharmacokinetics; t<sub>1/2</sub>=apparent terminal half-life

Note: Values for C<sub>max</sub>, AUC<sub>0-last</sub>, and AUC<sub>0-∞</sub> were dose normalized and log transformed. Values for CL and t<sub>1/2</sub> were log transformed.

Note: AUC<sub>0-∞</sub> and CL: The ANCOVA model included renal function group as factor, and sex, age, and BMI as covariates.

Note: AUC<sub>0-last</sub>: The ANCOVA model included renal function group as factor, and sex and BMI as covariates.

Note: C<sub>max</sub>: The ANCOVA model included renal function group as factor, and BMI as covariate.

Note: t<sub>1/2</sub>: The ANCOVA model included renal function group as factor.

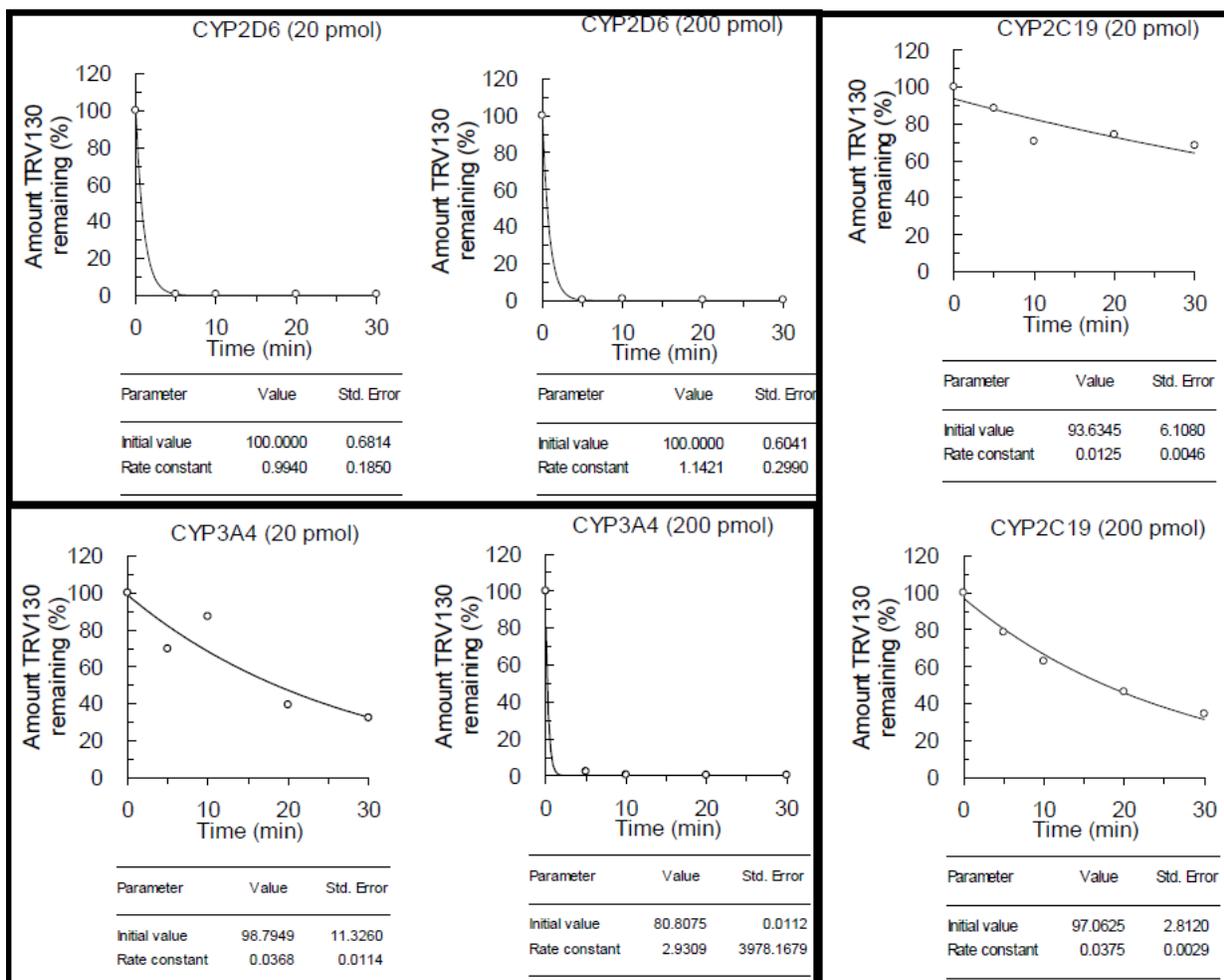
Data source: CP130-1012, CSR Table 14.2.3.1.

Mean oliceridine exposure in ESRD subjects was approximately 20% higher than that observed in subjects with normal renal function; however, the mean exposures observed in ESRD subjects were well within what has been previously reported for oliceridine in healthy subjects.

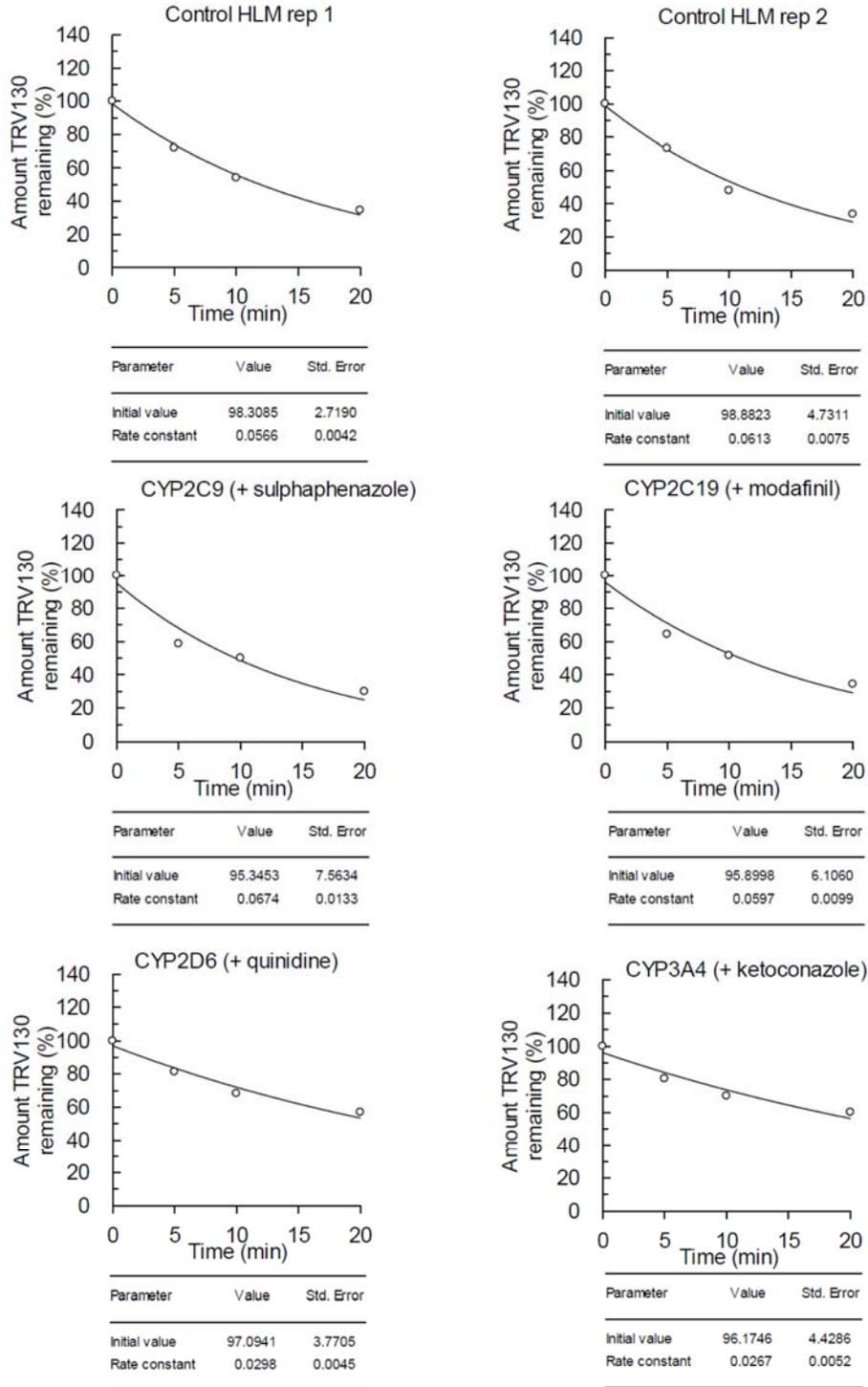
#### 4.2.12 In Vitro Metabolism, Drug-Drug Interaction studies

In vitro studies suggest that oliceridine is metabolized primarily by the CYP3A4 and CYP2D6 (In vitro Study QBRMU10130-TRV02 and Study 797914). TRV130 was incubated at a final concentration of 0.5  $\mu\text{M}$  with pooled human liver microsomes (HLM) at a protein concentration of 0.5 mg/mL. At pre-determined time intervals following the initiation of the reaction (0, 5, 10, 20, 30 and 60 minutes) enzymic reactions were terminated. TRV130 metabolism was observed to be linear for up to 20 minutes. Therefore, subsequent incubations were maintained over a 15 minutes time course. Only the incubations in the presence of quinidine (2D6) or ketoconazole (3A4) showed any major differences when compared to the rate of TRV130 metabolism in the control incubations. A reduction in the rate constant from approximately 0.0600 in the control incubations to 0.0298 for CYP2D6 and 0.0266 for 3A4 was observed (Figure 15). These results indicated that TRV130 metabolism was solely due to CYPs 2D6 and 3A4.

**Figure 15. Rate of TRV130 (0.5  $\mu\text{M}$ ) metabolism by recombinant CYP 450 enzymes: disappearance curves (QBRMU10130-TRV02).**

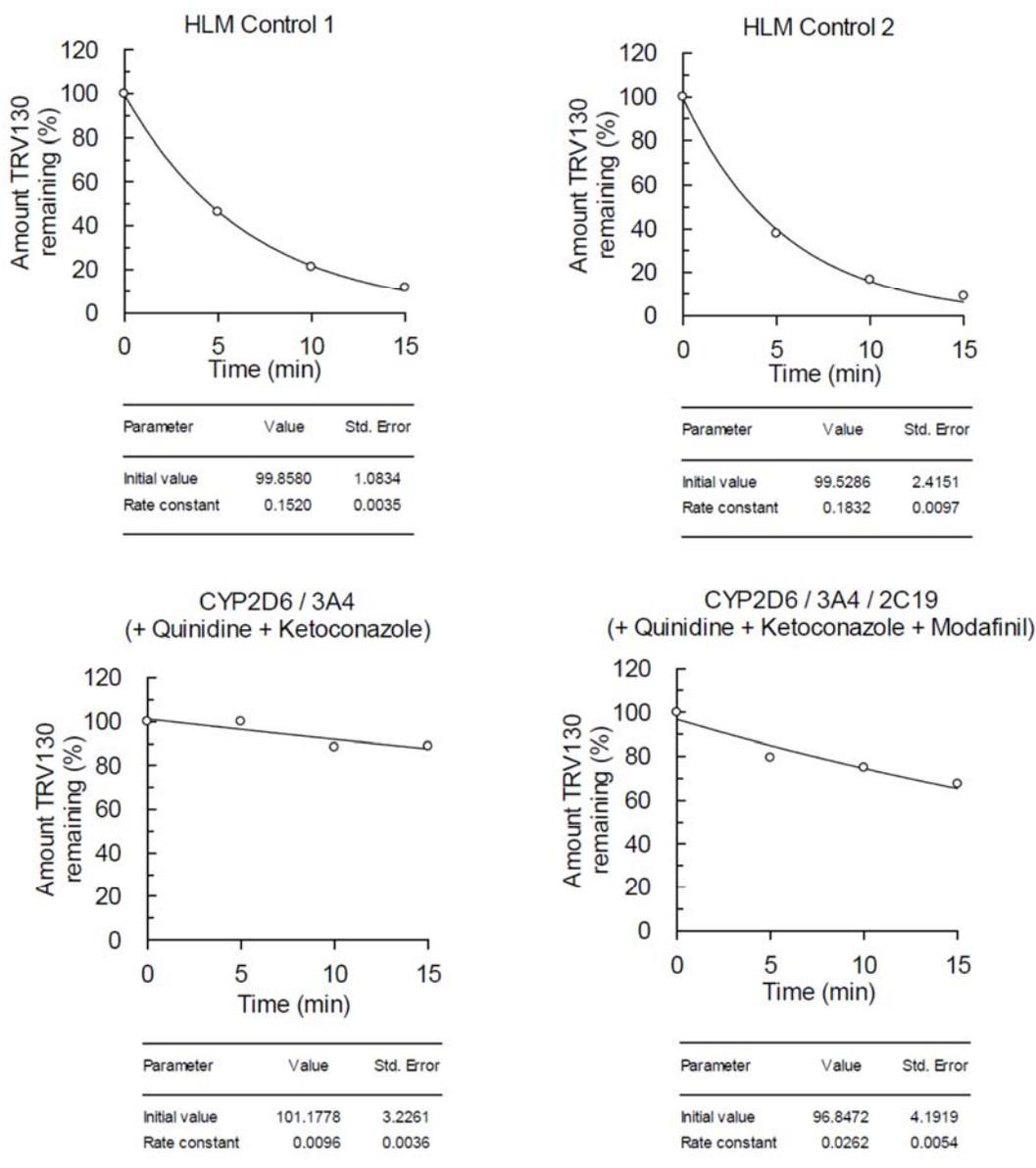


**Figure 16. Rate constants for the metabolism of TRV130 (0.5  $\mu$ M) by human liver microsomes (0.5 mg/mL) in the presence and absence of CYP450-selective chemical inhibitors (QBRMU10130-TRV02).**



To confirm the results from the previous experiment, TRV130 was incubated with HLM and a mix containing quinidine and ketoconazole (MIX 1) to assess both 2D6 and 3A4 activity and also a mix containing quinidine, ketoconazole and modafinil (MIX 2) to assess 2C19, 2D6 and 3A4 activity. The incubations in the presence of MIX 1 showed more inhibition when compared to the control incubations than MIX 2. A reduction in the rate constant from approximately 0.152 in the control incubations to 0.0096 for MIX 1 was observed, whereas MIX 2 showed a reduction in rate constants, from approximately 0.183 to 0.026

**Figure 17. Rate constants for the metabolism of TRV130 (0.5 µM) by human liver microsomes (0.5 mg/mL) in the presence and absence of multiple CYP450-selective chemical inhibitors. (Study QBRMU10130-TRV02).**



Collectively, these data strongly indicate that TRV130 metabolism in human liver microsomes is catalysed by CYPs 2D6 and 3A4 with only a minor role played by 2C19.

**Table 37. Metabolic stability of TRV130A (1 µM) in incubation with human liver microsomes in the presence and absence of quinidine (1 µM) (Study XT114104).**

0.25 mg protein/mL							1.5 mg protein/mL										
TRV130A (µM)	Quinidine (µM)	Incubation time (min)	NADPH (+/-)	TRV130A detected (µM)	Percent loss of substrate (%)	Percent remaining (%)	Half-life estimated from single exponential decay (min)	Estimated <i>in vitro</i> intrinsic clearance (µL/min/mg protein)	Percent CYP2D6 contribution (%)	Incubation time (min)	Quinidine (µM)	TRV130A detected (µM)	Percent loss of substrate (%)	Percent remaining (%)	Half-life estimated from single exponential decay (min)	Estimated <i>in vitro</i> intrinsic clearance (µL/min/mg protein)	Percent CYP2D6 contribution (%)
1	-	0	+	1.30	NA	100%	21.0	132	76.4	8.01	-	0	NA	100%	120	NA	NA
		2.5		1.29	0.8%	99.2%											
		5		1.22	6.2%	93.8%											
		10		0.964	25.8%	74.2%											
		20		0.654	49.7%	50.3%											
		40		0.357	72.9%	27.1%											
	+	0	+	1.26	NA	100%											
		2.5		1.36	No loss	100%											
		5		1.30	No loss	103%											
		10		1.25	0.8%	99.2%											
		20		1.16	7.5%	92.5%											
		40		0.586	21.7%	78.3%											
	-	0	-	1.24	NA	100%	NA	NA	NA								
		2.5		1.34	No loss	100%											
		5		1.33	No loss	106%											
		10		1.36	No loss	110%											
		20		1.35	No loss	109%											
		40		1.33	No loss	108%											

+ Present  
 - Absent  
 NA Not applicable  
 No loss indicates that the value was zero or negative.  
 Percentages < 100% are rounded to one decimal place. Percentages ≥ 100% are rounded to the nearest whole number.  
 Values are the mean of duplicate determinations and are rounded to three significant figures. Data are shown graphically in Figure 1.

Source: Table 1

Source: Table 2

**Table 38. (Study XT144039) Metabolic stability of TRV130 (1 µM) in incubations with human liver microsomes (low CYP2D6/ low CYP3A4)**

in the absence of CYP3A4 inhibitors.							in the presence of the CYP3A4 direct-acting inhibitor ketoconazole (1 µM).							
Individual HLM Lot	Incubation time (min)	TRV130 detected (pmol)	TRV130 loss (%)	TRV130 remaining (%)	Half-life estimated from single exponential decay (min)	Estimated <i>in vitro</i> intrinsic clearance (µL/min/mg protein)	Individual HLM lot	Incubation time (min)	TRV130 detected (pmol)	TRV130 loss (%)	TRV130 remaining (%)	Half-life estimated from single exponential decay (min)	Estimated <i>in vitro</i> intrinsic clearance (µL/min/mg protein)	Percent CYP3A4 contribution (%)
H499	0	204	NA	100	> 60.0	< 46.2	H499	0	206a	NA	100	> 60.0	< 46.2	ND
	2.5	212	No loss	104										
	5	208	No loss	102										
	10	205	No loss	100										
	20	178	12.5	87.5										
	40	164	19.4	80.6										
H534	0	206	NA	100	> 60.0	< 46.2	H534	0	208	NA	100	> 60.0	< 46.2	ND
	2.5	213	No loss	103										
	5	203	1.5	98.5										
	10	196	5.0	95.0										
	20	180	12.6	87.4										
	40	153	25.5	74.5										
H537	0	208	NA	100	> 60.0	< 46.2	H537	0	215	NA	100	> 60.0	< 46.2	ND
	2.5	223	No loss	107										
	5	220	No loss	106										
	10	213	No loss	102										
	20	219	No loss	105										
	40	200	3.9	96.1										

NA Not applicable  
 No loss indicates a negative or zero value.  
 Values are the average of duplicate determinations and are rounded to three significant figures.  
 Percentages < 100% are rounded to one decimal place, and those ≥ 100% are rounded to the nearest whole number.

Source: Table 1: Study XT144039

Source: Table 2 Study XT144039

**Metabolic stability of TRV130 (1 µM) in incubations with human liver microsomes (low CYP2D6/ low CYP3A4) in the presence of the CYP3A4 direct-acting inhibitor itraconazole (1 µM)**

Individual HLM lot	Incubation time (min)	TRV130 detected (pmol)	TRV130 loss (%)	TRV130 remaining (%)	Half-life estimated from single exponential decay (min)	Estimated <i>in vitro</i> intrinsic clearance ( $\mu\text{L}/\text{min}/\text{mg}$ protein)	Percent CYP3A4 contribution (%)
H499	0	200	NA	100	> 60	< 46.2	ND
	2.5	210	No loss	105			
	5	204	No loss	102			
	10	213	No loss	107			
	20	202	No loss	101			
	40	208	No loss	104			
H534	0	189	NA	100	> 60	< 46.2	ND
	2.5	183	3.1	96.9			
	5	176	6.8	93.2			
	10	174	8.2	91.8			
	20	159	16.3	83.7			
	40	152	19.5	80.5			
H537	0	206	NA	100	> 60	< 46.2	ND
	2.5	210	No loss	102			
	5	203	1.5	98.5			
	10	207	No loss	101			
	20	210	No loss	102			
	40	206	0.2	99.8			
	60	192	6.6	93.4			

NA Not applicable

ND Not determined. Substrate loss did not exceed 20% after 60 minutes incubation for the test system in the absence of inhibitor.

No loss indicates a negative or zero value.

Values are the average of duplicate determinations and are rounded to three significant figures.

Percentages < 100 % are rounded to one decimal place, and those  $\geq 100\%$  are rounded to the nearest whole number.

Source: Table 3 Study XT144039.

**Table 39. (Study XT144039) Metabolic stability of TRV130 (1  $\mu\text{M}$ ) in incubations with human liver microsomes (low CYP2D6/average CYP3A4, 0.25 mg protein/mL)**

**in the absence of CYP3A4 inhibitors.**

Individual HLM lot	Incubation time (min)	TRV130 detected (pmol)	TRV130 loss (%)	TRV130 remaining (%)	Half-life estimated from single exponential decay (min)	Estimated <i>in vitro</i> intrinsic clearance ( $\mu\text{L}/\text{min}/\text{mg}$ protein)
H523	0	212	NA	100	32.7	84.8
	2.5	218	No loss	103		
	5	195	7.8	92.2		
	10	176	16.9	83.1		
	20	142	33.2	66.8		
	40	90.5	57.3	42.7		
F008084	0	218	NA	100	12.2	228
	2.5	200	8.1	91.9		
	5	176	19.2	80.8		
	10	124	42.9	57.1		
	20	68.6	68.5	31.5		
	40	22.9	89.5	10.5		
M008084	0	231	NA	100	14.6	190
	2.5	220	4.8	95.2		
	5	191	17.5	82.5		
	10	149	35.4	64.6		
	20	87.4	62.2	37.8		
	40	36.4	84.2	15.8		
	60	BLQ	100	0.0		

BLQ Below limit of quantification (0.1  $\mu\text{M}$ , is equivalent to 20 pmol)

Source: Table 4: Study XT144039

**in the presence of the CYP3A4 direct-acting inhibitor ketoconazole (1  $\mu\text{M}$ ).**

Individual HLM lot	Incubation time (min)	TRV130 detected (pmol)	TRV130 loss (%)	TRV130 remaining (%)	Half-life estimated from single exponential decay (min)	Estimated <i>in vitro</i> intrinsic clearance ( $\mu\text{L}/\text{min}/\text{mg}$ protein)	Percent CYP3A4 contribution (%)
H523	0	210	NA	100	> 60	< 46.2	ND
	2.5	219	No loss	104			
	5	215	No loss	102			
	10	214	No loss	102			
	20	212	No loss	101			
	40	214	No loss	102			
F008084	0	200	NA	100	23.6	118	48.4
	2.5	190	5.0	95.0			
	5	173	13.6	86.4			
	10	151	24.7	75.3			
	20	108	46.2	53.8			
	40	65.6	67.3	32.7			
M008084	0	207	NA	100	34.3	80.8	57.6
	2.5	209	No loss	101			
	5	192	7.2	92.8			
	10	173	16.6	83.4			
	20	135	34.6	65.4			
	40	92.7	55.2	44.8			
	60	67.7	67.3	32.7			

Source: Table 5 Study XT144039

Metabolic stability of TRV130 (1  $\mu$ M) in incubations with human liver microsomes (low CYP2D6/average CYP3A4, 0.25 mg protein/mL) in the presence of the CYP3A4 direct-acting inhibitor itraconazole (1  $\mu$ M)

Individual HLM lot	Incubation time (min)	TRV130 detected (pmol)	TRV130 loss (%)	TRV130 remaining (%)	Half-life estimated from single exponential decay (min)	Estimated <i>in vitro</i> intrinsic clearance ( $\mu$ L/min/mg protein)	Percent CYP3A4 contribution (%)
H523	0	210	NA	100	> 60	< 46.2	ND
	2.5	214	No loss	102			
	5	215	No loss	102			
	10	211	No loss	100			
	20	210	No loss	100			
	40	196	6.6	93.4			
F008084	0	208	NA	100	18.3	151	33.7
	2.5	207	0.5	99.5			
	5	173	17.0	83.0			
	10	146	30.0	70.0			
	20	98.0	52.9	47.1			
	40	45.0	78.4	21.6			
M008084	0	206	NA	100	28.9	96.0	49.6
	2.5	205	0.4	99.6			
	5	200	3.2	96.8			
	10	169	18.1	81.9			
	20	130	36.8	63.2			
	40	80.6	60.9	39.1			
	60	51.6	75.0	25.0			

Source: Table 6 Study XT144039.

TRV130 is metabolized primarily by CYP2D6 and CYP3A4, and the relative contributions of each isozyme may vary with individual hepatic content. While patients with low enzymatic activity for both isozymes would metabolize TRV130 more slowly, patients with average CYP3A4 activity, even those with deficient CYP2D6 activity, could still metabolize TRV130. These data also suggest that patients deficient in CYP2D6 activity and in whom CYP3A4 is inhibited can metabolize TRV130, albeit at a slower rate.

**Note:** As demonstrated in study CP130-1005, itraconazole increased exposure of oliceridine by 78% in terms of AUC<sub>0-inf</sub>, without any impact on C<sub>max</sub>. In Study CP130-1006, suboptimal dose of ketoconazole produced no increase in AUC or C<sub>max</sub>. Across different Phase 1 studies systemic exposure (AUC) of oliceridine was 100% higher in CYP2D6 poor metabolizers compared to extensive metabolizers, consistent with the observations from *in vitro* studies.

- Oliceridine is metabolized into many moieties; however, oxy-oliceridine (M23) and its glucuronide M23, and TRV109662 have been detected in human plasma. Study report QBRMU10130\_TRV01 reports many metabolites following human hepatocyte incubation of oliceridine, of which only few are reported in human plasma as described in the question-based review above.
- Oliceridine or major human metabolites, TRV0109662 and TRV0306954 (M22), were not direct, time-, or metabolism-dependent inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4/5 in human liver microsomes (Study XT115085, Study XT155061, and Study XT165110).

**Table 40.** Selected Nonclinical Pharmacology studies of Oliceridine, TRV109662, and TRV0306954 (M22).

Study Number	Study Type	Study Title
CPB-P10-1311R01	Pharmacokinetics	Pharmacokinetics of TRV110130 Following Single Intravenous and Subcutaneous Administrations to Male Sprague Dawley Rats
QBRMU10130_TRV01	<i>In vitro</i> metabolism	TRV130: Comparative In Vitro Metabolism Studies with Freshly Isolated Rat, Dog, Mouse, Cynomolgus Monkey, and Human Hepatocytes
XT115085	CYP interaction	TRV130: In Vitro Evaluation as an Inhibitor of Cytochrome P450 Enzymes in Human Liver Microsomes
XT155061	CYP interaction	In Vitro Evaluation of TRV0109662 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
XT165110	CYP interaction	In Vitro Evaluation of TRV0306954 (M22) as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
XT153041	CYP interaction	In Vitro Evaluation of TRV130 and TRV0109662 as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes
MORIVSB-01	Transporters	In Vitro Interaction Studies of TRV130 with Human BCRP, BSEP and MDR1 Efflux (ABC) Transporters, and with Human MATE1, MATE2 K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters
Trevena-03-01Sep2016	Transporters	In Vitro Interaction Studies of TRV0109662 with the Human BSEP, BCRP and MDR1 Efflux (ABC) Transporters, and with the Human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters
Trevena-04-01Sep2016	Transporters	In vitro Interaction Studies of TRV0306954 (M22) with Human BSEP, BCRP, MDR1, MRP2, MRP3 and MRP4 Efflux (ABC) Transporters, and with Human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters

- Oliceridine inhibited CYP2D6 and CYP3A4 to a limited extent and there is no potential for clinical relevant drug interactions.
  - However, C<sub>max</sub> with 6 mg dose is 0.62 μM (TQT study suprathereapeutic dose)
  - IC<sub>50</sub> value of 4.3 μM for CYP2D6 inhibition (>10-fold compared to therapeutic concentrations of oliceridine)
  - IC<sub>50</sub> value of 30 μM for CYP3A4 inhibition (>10-fold compared to therapeutic concentrations of oliceridine)
- TRV130 was not a substrate of the human uptake transporters MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2, but was a modest substrate for MDR1 (Pgp)-mediated efflux (Study MORIVSB-01 or Trevena-01-06Sep2014). Specifically,
  - TRV130 did not significantly inhibit (<20% inhibition at 3 μM) human efflux transporters BCRP and BSEP, while inhibition of the human efflux transporter MDR1 was not potent, with an IC<sub>50</sub> of 46.3 μM.
  - TRV130 showed a concentration dependent inhibition of NMQ transport in the MDR1 vesicular transport assay. Curve fitting indicated that the type of inhibition is competitive in nature (alpha value: 29.9) with a calculated K<sub>i</sub> value of 7.95 μM. Fitting a mixed type inhibition model on the curves produced a K<sub>i</sub> value of 14.06 μM.
  - TRV130 did not significantly inhibit human uptake transporters MATE1, MATE2-K, OAT1, OAT3, OATP1B1 and OATP1B3 (<20% inhibition at 3 μM), but inhibited human uptake transporters OCT1 and OCT2 in a dose dependent manner (IC<sub>50</sub>:

- 3.2  $\mu\text{M}$  and 6.9  $\mu\text{M}$ , respectively). Cmax with 6 mg dose is 0.62  $\mu\text{M}$  (TQT study supratherapeutic dose).
- TRV130 was not a substrate of the human efflux transporter BCRP, while it was a substrate of human efflux transporter MDR1.
  - TRV130 was not a substrate of human efflux transporter BSEP.
  - TRV130 was not a substrate for human uptake transporters MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2.
- Oliceridine Inhibited OCT1 and OCT2 in a dose-dependent manner, with IC50 values of 3.2 and 6.9  $\mu\text{M}$ , respectively (>10-fold compared to therapeutic concentrations of oliceridine); MDR1 inhibition was not potent, with an IC50 of 46.3  $\mu\text{M}$  (>10-fold compared to therapeutic concentrations of oliceridine) (Study MORIVSB-01 or Trevena-01-06Sep2014).
    - did not significantly inhibit MATE1, MATE2-K, OAT1, OAT3, OATP1B1, or OATP1B3 in vitro.
  - Oliceridine did not induce major CYP enzymes. Treatment of cultured human hepatocytes with up to 10  $\mu\text{M}$  oliceridine had little or no effect (i.e., < 2.0-fold change and < 20% of the positive control) on CYP1A2, CYP2B6, and CYP3A4/5 activity or mRNA levels (Study XT153041). Treatment of cultured human hepatocytes with relevant concentrations (3  $\mu\text{M}$ ) of TRV0109662 had little or no effect on CYP1A2 activity and mRNA levels, CYP2B6 mRNA levels, and CYP3A4/5 activity and mRNA levels.
  - The potential inhibition of transporters by clinically relevant free and total concentrations of the major human metabolites TRV0109662 (Study Trevena-03-01Sep2016) and TRV0306954 (Study Trevena-04-01Sep2016) was also determined. TRV0109662 was not an inhibitor of any transporter at concentrations of up to 300 nM, the highest concentration tested and a concentration >10-fold above the projected mean clinical maximum observed plasma concentration (Cmax in **Table 13** and **Table 15**). Similarly, TRV0306954 did not inhibit any transporter (including MRP2, MRP3, and MRP4) at concentrations of up to 3  $\mu\text{M}$ , the highest concentration tested and a concentration at >10-fold above the projected mean clinical Cmax (Cmax in **Table 13** and **Table 15**). These data suggest that drug interactions mediated by uptake or efflux transporters is unlikely at clinically relevant plasma concentrations of oliceridine and metabolites.

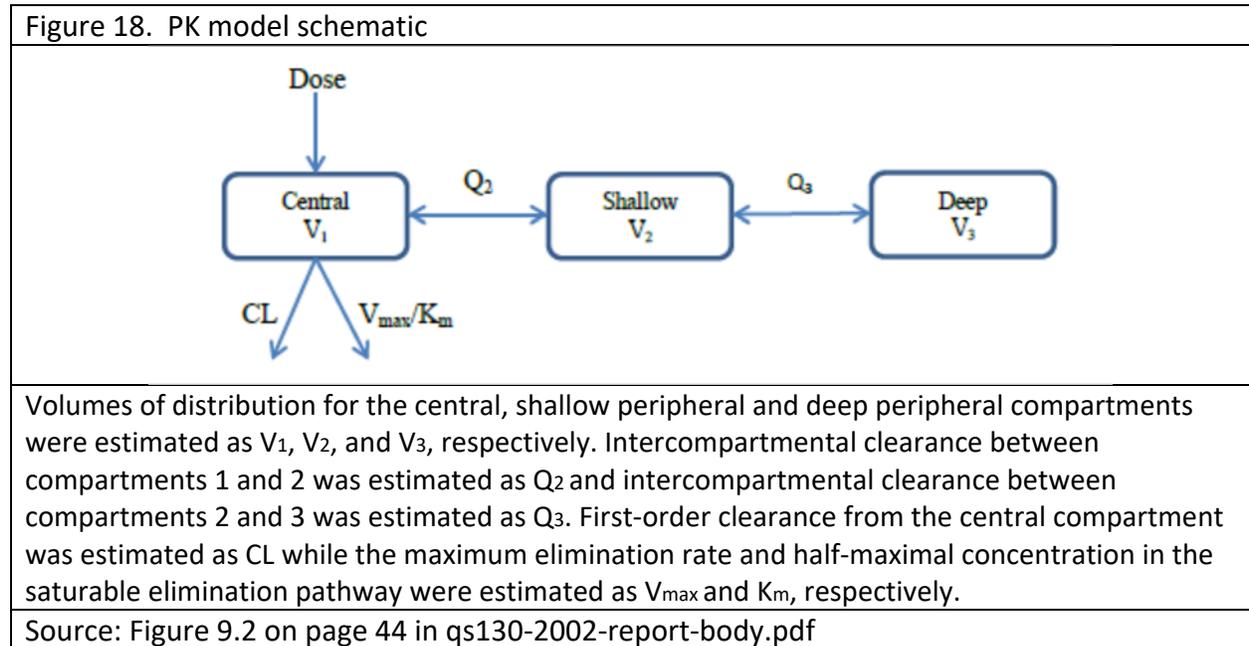
### 4.3 Population PK and/or PD Analyses

Applicant conducted population pharmacokinetic analysis using the data from Studies CP130-1001, CP130-1002, CP130-1003, CP130-1005, CP130-1006, and CP130-2001. Oliceridine plasma concentrations from 362 subjects were available evaluation in the population PK analysis. Brief details of the studies are provided in Table 41. NONMEM® software was used for parameter estimation.

Study	Population and No. Subjects	Formulation, Dose	Planned PK Data*	Planned Response Data Relevant to Present Analysis*
CP130-1001 (first-in-human, Phase 1, randomized, single-blind, placebo controlled, parallel group, SAD study)	<u>Population:</u> healthy adult males, CYP2D6 non-PM and PM  No. of subjects: 58	Part A (randomized, CYP2D6 non-PM): TRV130 60-min IV infusion 0.15, 0.25, 0.4, 0.7, 1.2, 2.2, 4, and 7 mg Part B (open label, CYP2D6 PM): TRV130 60-min IV infusion 0.25 mg Part C (open label, CYP2D6 PM): TRV130 4 x 1.5 mg single dose over 30, 15, 5 and 1 min each on Day 1 to 4.	<ul style="list-style-type: none"> <li>24-hour PK profile</li> </ul>	<ul style="list-style-type: none"> <li>O<sub>2</sub> saturation for 24 hr</li> </ul>
CP130-1002 (Phase 1, open-label, non-randomized, four session crossover, SAD study)	<u>Population:</u> healthy adults, CYP2D6 non-PM and PM  No. of subjects: 6	TRV130 2-min IV infusion 2.0, 2.5, 3.0 and 3.5 mg each day on Day 1 to 4	<ul style="list-style-type: none"> <li>24-hour PK profile</li> </ul>	<ul style="list-style-type: none"> <li>O<sub>2</sub> saturation for 8 hr</li> </ul>
CP130-1003 (Phase 1, randomized, double-blind, placebo-controlled, 5-period crossover PKPD study)	<u>Population:</u> healthy adults, CYP2D6 PM and non-PM  No. of subjects: 30	TRV130 1.5, 3, 4.5 mg over 2 min; morphine 10 mg, and placebo	<ul style="list-style-type: none"> <li>24-hour PK profile</li> </ul>	<ul style="list-style-type: none"> <li>O<sub>2</sub> saturation for 8 hr</li> <li>Ventilatory response to hypercapnia (VRH) at pre-dose, 0.5, 1, 2, 3, 4 hr</li> </ul>
CP130-1005 (Phase 1, multipart, MAD and DDI study)	<u>Population:</u> healthy adults, CYP2D6 non-PMs and PMs  No. of subjects: Approx. 36 CYP2D6 non-PMs and 5 PMs	Part A (randomized, double-blind, placebo-controlled, parallel group, adaptive, MAD study in CYP2D6 non-PMs): TRV130 IV over 2 min Q6H: 1.5 mg x 5, 3 mg x 5, 4.5 mg x 5, 4 mg x 7 (Q4H)	<ul style="list-style-type: none"> <li>PK profile on Days 1 to 3</li> </ul>	<ul style="list-style-type: none"> <li>O<sub>2</sub> saturation for 20.5 hr</li> </ul>
		Part B MAD (CYP2D6 PMs): TRV130 IV over 10 minutes: 0.4 mg Q6H over 30 hours (6 doses)	<ul style="list-style-type: none"> <li>PK profile on Days 1 to 3</li> </ul>	<ul style="list-style-type: none"> <li>O<sub>2</sub> saturation for 24.5 hr</li> </ul>
		Part B DDI (open-label, CYP2D6 PM): First dose of TRV130 0.25 mg over 10 minutes on Day 5 then, oral ITZ 200 mg daily for 5 days, then second dose of TRV130 0.25 mg on Day 10.	<ul style="list-style-type: none"> <li>24-hour PK profile on Days 5 and 10</li> </ul>	<ul style="list-style-type: none"> <li>O<sub>2</sub> saturation for 48 hr</li> </ul>
<b>Study</b>	<b>Population and No. Subjects</b>	<b>Formulation, Dose</b>	<b>Planned PK Data*</b>	<b>Planned Response Data Relevant to Present Analysis*</b>
CP130-1006 (Phase 1, open-label, single-sequence, crossover DDI study)	<u>Population:</u> healthy adults CYP2D6 non-PMs  No. of subjects: 11	Day 1: TRV130 2 mg over 2 min Day 3: 2 doses of KTZ 200 mg orally 12 hr apart, the first 1 hr before the TRV130 2 mg.	<ul style="list-style-type: none"> <li>PK profile up to 36 hr post dose</li> </ul>	<ul style="list-style-type: none"> <li>O<sub>2</sub> saturation for 8 hr</li> </ul>
CP130-2001 (Phase 2, double-blind, multiple-dose, adaptive placebo- and active-controlled study)	<u>Population:</u> bunionectomy patients  No. of patients: Approx. 400 (260 receiving TRV130)	Stage A: 1, 2, 3, 4 mg TRV130 IV over 2 minutes Q4H, morphine, placebo (1:1:1:1:1) approx. 150 patients Stage B: Two regimens (adaptive) of 1, 2, 3, 4 mg TRV130 IV over 2 minutes Q4H, morphine, placebo (8:8:5:4) - 10 successive cohorts of approx. 25 patients	<ul style="list-style-type: none"> <li>PK profile up to 28-30 hr post dose</li> </ul>	<ul style="list-style-type: none"> <li>VRH for 24 hr</li> <li>O<sub>2</sub> saturation for 24.5 hr</li> <li>Pain Score for 48 hr</li> </ul>
CP130-2002 (Phase 2, double-blind, placebo- and active-controlled study)	<u>Population:</u> abdominoplasty patients  No. of patients: Approx. 200 (80 receiving TRV130)	TRV130 loading dose 1.5 mg as 2 boluses 10 min apart. TRV130 on demand dose through a PCA device 0.1 mg (up-titration to 0.15 mg); morphine; placebo (2:2:1)	<ul style="list-style-type: none"> <li>Sparse PK sampling over 24 hr post first dose</li> </ul>	<ul style="list-style-type: none"> <li>O<sub>2</sub> saturation for 16 hr</li> <li>Pain Score for 24 hr</li> </ul>

Source: Table 7.1 on page 17 in qs130-2002-report-body.pdf

Figure 18 shows the pharmacokinetic model that best described the data.



CYP2D6 phenotype, body weight, gender, age, race, concomitant itraconazole (ITZ) and ketoconazole (KTZ) were evaluated as possible covariates.

The estimates of pharmacokinetic parameters are shown in Table 42.

Per applicant,

- The pharmacokinetics of TRV130 were well described by a 3-compartment, serial model with first-order and saturable clearance. Saturable clearance was turned off for CYP2D6 PM.
- Fixed allometric exponents were used to describe the effect of body weight on all clearance and volume terms.
- A full covariate model was implemented with the effect of gender on all clearance and volume terms, in addition to the WT-based allometric scaling. The variable FEM took on values of 0 for males and 1 for females. Covariate effects of age and race were not included in the full covariate model because there appeared to be no meaningful relationships between plots of IIV vs age or race.
- Itraconazole was estimated to reduce the first-order clearance of TRV130 by 44.8%.
- After correction for body weight, female subjects were estimated to have 13.3% lower first-order CL, 36.7% lower  $V_1$ , and 35.1% lower  $Q_2$  than males. This effect could be due to the gender imbalance between studies.

Table 42. PK parameter estimates for final PK model using data from Phase 1 and Phase 2 studies

Parameter	Units	Estimate	%RSE	Lower	Upper	IIV <sup>b</sup>
$\theta_{CL}$	L/h	22.6 <sup>a</sup>	5.13%	16.6 <sup>a</sup>	30.9 <sup>a</sup>	51.3%
$\theta_{V1}$	L	17.8 <sup>a</sup>	10.6%	9.78 <sup>a</sup>	32.5 <sup>a</sup>	142%
$\theta_{V2}$	L	36.6 <sup>a</sup>	1.56%	32.8 <sup>a</sup>	40.9 <sup>a</sup>	61.7%
$\theta_{Q2}$	L/h	61.6 <sup>a</sup>	4.54%	42.5 <sup>a</sup>	89.1 <sup>a</sup>	138%
$\theta_{V3}$	L	11.7 <sup>a</sup>	19.7%	4.53 <sup>a</sup>	30.3 <sup>a</sup>	85.4%
$\theta_{Q3}$	L/h	1.15 <sup>a</sup>	85.4%	0.912 <sup>a</sup>	1.44 <sup>a</sup>	248%
$\theta_{Vmax}$	mg/h	1.37 <sup>a</sup>	89.8%	0.787 <sup>a</sup>	2.39 <sup>a</sup>	66.9%
$\theta_{Km}$	ng/mL	105 <sup>a</sup>	4.67%	68.0 <sup>a</sup>	161 <sup>a</sup>	
$\theta_{ITZonCL}$	unitless	0.552	2.28%	0.527	0.577	
$\theta_{FEMonCL}$	unitless	0.867 <sup>a</sup>	72.0%	0.708 <sup>a</sup>	1.06 <sup>a</sup>	
$\theta_{FEMonV1}$	unitless	0.633 <sup>a</sup>	129%	0.198 <sup>a</sup>	2.02 <sup>a</sup>	
$\theta_{FEMonQ2}$	unitless	0.649 <sup>a</sup>	54.9%	0.408 <sup>a</sup>	1.03 <sup>a</sup>	
$\theta_{WTonCL}$	unitless	0.750	...			
$\theta_{WTonV1}$	unitless	1.000	...			
$\theta_{WTonV2}$	unitless	1.000	...			
$\theta_{WTonQ2}$	unitless	0.750	...			
$\theta_{WTonV3}$	unitless	1.000	...			
$\theta_{WTonQ3}$	unitless	0.750	...			
$\epsilon_1$	unitless	0.0336	16.3%	0.0229	0.0443	18.3% <sup>c</sup>
$\epsilon_2$	unitless	0.124	31.1%	0.0483	0.200	35.2% <sup>c</sup>

<sup>a</sup> Back-transformed from natural log scale.

<sup>b</sup> CV for IIV calculated as  $CV_{TV_p} = \sqrt{e^{\sigma^2} - 1}$ .

<sup>c</sup> Residual error expressed as CV.

Source: Table 9.10 on page 49 in qs130-2002-report-body.pdf

The applicant applied the model (Figure 18) to the data from Phase 3 studies (CP130-3001, CP130-3002, and CP130-3003). The estimates of pharmacokinetic parameters are shown in Table 43.

Table 43. PK parameter estimates for final PK model using data from Phase 3 studies

Parameter	Units	Estimate <sup>a</sup>	%RSE	Lower <sup>a</sup>	Upper <sup>a</sup>	IIV <sup>b</sup>	%Change from M038 <sup>c</sup>
$\theta_{CL}$	L/h	22.7	...			71.5%	0.0%
$\theta_{V1}$	L	17.9	...			240%	0.0%
$\theta_{V2}$	L	39.1	1.28%	35.7	42.9	73.5%	1.9%
$\theta_{Q2}$	L/h	61.5	...			1091%	0.0%
$\theta_{V3}$	L	12.00	14.1%	6.04	23.9	95.8%	1.2%
$\theta_{Q3}$	L/h	1.05	230%	0.842	1.31	4054%	-64.3%
$\theta_{V_{max}}$	mg/h	1.57	45.6%	1.05	2.34	79.7%	42.4%
$\theta_{K_m}$	ng/mL	134	4.12%	90.1	199		5.3%
$\theta_{ITZonCL}$	unitless	0.552	...				
$\theta_{FEMonCL}$	unitless	1.05	206%	0.868	1.26		132.4%
$\theta_{FEMonV1}$	unitless	0.92	435%	0.436	1.93		81.0%
$\theta_{FEMonQ2}$	unitless	0.783	98.0%	0.490	1.25		43.5%
$\theta_{W_{TonCL}}$	unitless	0.75	...				
$\theta_{W_{TonV1}}$	unitless	1	...				
$\theta_{W_{TonV2}}$	unitless	1	...				
$\theta_{W_{TonQ2}}$	unitless	0.75	...				
$\theta_{W_{TonV3}}$	unitless	1	...				
$\theta_{W_{TonQ3}}$	unitless	0.75	...				
$\sigma_1^2$	unitless	0.0730	27.6%	0.0336	0.112	27.0%	-41.0%
$\sigma_2^2$	unitless	0.115	21.1%	0.0674	0.162	33.9%	

<sup>a</sup> Back-transformed from natural log scale (except for  $\theta_{ITZonCL}$  and  $\sigma^2$ ).

<sup>b</sup> CV for all IIV calculated as  $CV_{IIV} = \sqrt{e^{\sigma^2} - 1}$ .

<sup>c</sup> %Change in  $\theta$  on natural log scale from prior PopPK model.

<sup>d</sup> Residual error expressed as CV.

Source: Table 10.5 on page 43 in qs130-3003-report-body.pdf

Per applicant,

- Although the final model slightly over-predicted the central tendency of the data, the model provided a good description of the individual data.
- The model was considered reliable for the purposes of obtaining individual exposure metrics.
- Oliceridine exposure in CYP2D6 PM subjects were within the range of values predicted for the CYP2D6 EM subjects.

Based on these findings, the applicant proposes the following statements in the label:

### *12.3 Pharmacokinetics*

#### *Distribution*

[REDACTED] (b) (4)

**Reviewer's Comments:** The reviewer was able to derive similar estimates as reported by the applicant. Based on internal discussions that took into account the relevance of information for the prescribers, the following labeling language is being proposed.

### *12.3 Pharmacokinetics*

#### *Distribution*

[REDACTED] (b) (4) volume of distribution ranges [REDACTED] (b) (4) 90-120 L, indicating extensive tissue distribution.

#### 4.4 Exposure-Response Analyses

Pain scores were reported on a scale of 0 to 10 in Study CP130-2001 and were temporally correlated with oliceridine concentrations in plasma ( $C_p$ ). Individual  $C_p$  over time were estimated using the individual PK parameters from the final PopPK model. Observed pain scores and predicted individual  $C_p$  served as the exposure and response metrics for E-R modeling. Pain score was considered to be a continuous variable for modeling purposes. Data from 51 subjects receiving placebo and 214 subjects receiving active drug were used for parameter estimation.  $C_p$  was assumed to be zero for subjects receiving placebo. Data from subjects receiving morphine sulfate were not included in E-R modeling as the primary objective was to characterize the response to oliceridine.

The indirect response model was selected over the effect compartment model since both the time-dependent and oliceridine-dependent effects enter the model in the same way. The change in pain score with time was fitted using an indirect response model as shown in Equation 1.

Equation 1. Indirect response model

$$\frac{d\text{Pain}}{dt} = k_{in} \cdot \left( \frac{PT_{max} \cdot t^{\gamma_{time}}}{PT_{50}^{\gamma_{time}} + t^{\gamma_{time}}} \right) \cdot \left( \frac{E_{max} \cdot C_p^{\gamma_{TRV}}}{EC_{50}^{\gamma_{TRV}} + C_p^{\gamma_{TRV}}} \right) - k_{out} \cdot \text{Pain}$$

where  $k_{in}$  and  $k_{out}$  were the rate constants describing, respectively, the increase and decrease in pain score without the modulating effects of either time ( $t$ ) or  $C_p$ ,  $PT_{max}$  was the maximum effect of time,  $PT_{50}$  was the time to half-maximal time effect,  $\gamma_{time}$  was the shape parameter for the time effect,  $E_{max}$  was the maximum effect of TRV130,  $EC_{50}$  was the  $C_p$  producing half-maximal oliceridine effect, and  $\gamma_{TRV}$  was the shape parameter for the oliceridine effect.

Source: On page 61 in qs130-2002-report-body.pdf

The estimates of the parameters from the exposure-response (E-R) analyses are shown in Table 44.

Table 44. E-R parameter estimates

Parameter	Units	Estimate	%RSE	Lower	Upper	IIV
$\text{Pain}_{\text{fit}}$	Pain Scale	6.89 <sup>a</sup>	0.907%	6.69 <sup>a</sup>	7.10 <sup>a</sup>	21.8%
$k_{out}$	h <sup>-1</sup>	31.5 <sup>a</sup>	2.42%	26.8 <sup>a</sup>	37.0 <sup>a</sup>	
$E_{max}$	unitless	0.828 <sup>b</sup>	14.6%	0.754 <sup>b</sup>	0.883 <sup>b</sup>	1507% <sup>c</sup>
$EC_{50}$	ng/mL	10.1 <sup>a</sup>	3.98%	8.41 <sup>a</sup>	12.1 <sup>a</sup>	148% <sup>c</sup>
$\gamma_{TRV}$	unitless	5.05 <sup>a</sup>	7.78%	3.94 <sup>a</sup>	6.49 <sup>a</sup>	157% <sup>c</sup>
$\epsilon_1$	Pain Scale	0.871	11.1%	0.682	1.06	0.933 <sup>d</sup>

<sup>a</sup> Back-transformed from natural log scale

<sup>b</sup> Back-transformed from the logit scale.

<sup>c</sup> CV for IIV calculated as  $CV_{IIV} = \sqrt{e^{\sigma^2} - 1}$ .

<sup>d</sup> SD for residual error

Source: Table 9.11 on page 62 in qs130-2002-report-body.pdf

Similar analyses were conducted using data from the Study CP130-2002. The change in pain score with time was fitted using an indirect response model as shown in Equation 2.

Equation 2. Indirect response model
$\frac{dPain}{dt} = k_{out} \cdot Pain_{BL} \cdot \left(1 - \frac{PT_{max} \cdot t^{\gamma_{time}}}{PT_{50}^{\gamma_{time}} + t^{\gamma_{time}}}\right) \cdot \left(1 - \frac{E_{max} \cdot C_p^{\gamma_{TRV}}}{EC_{50}^{\gamma_{TRV}} + C_p^{\gamma_{TRV}}}\right) - k_{out} \cdot Pain$
<p>k<sub>out</sub> was the first-order rate constant for the change in Pain, Pain<sub>BL</sub> was the baseline pain score, PT<sub>max</sub> was the maximum change for the time response, t was time, γ<sub>time</sub> was the slope factor for the time response, PT<sub>50</sub> was the time at which half of the maximum time response was predicted, E<sub>max</sub> was the maximum change for the oliceridine response, C<sub>p</sub> was the oliceridine concentration in plasma, γ<sub>TRV</sub> was the slope factor for the oliceridine response, and EC<sub>50</sub> was the oliceridine concentration at which half of the maximum oliceridine response was predicted.</p>
Source: On page 61 in qs130-2005-report-body.pdf

The estimates of the parameters from the exposure-response (E-R) analyses are shown in Table 44.

Table 45. E-R parameter estimates							
Parameter	Units	Estimate	%RSE	Lower	Upper	IIV	%Change in θ from Prior Model (Pain037b) <sup>f</sup>
Pain <sub>BL</sub>	Pain Scale	7.08 <sup>a</sup>	0.792%	6.87 <sup>a</sup>	7.30 <sup>a</sup>	20.8%	1.24%
k <sub>out</sub>	hr <sup>-1</sup>	29.0 <sup>a</sup>	3.63%	22.8 <sup>a</sup>	36.8 <sup>a</sup>		-2.52%
E <sub>max</sub>	unitless	0.732 <sup>b</sup>	24.3%	1.69 <sup>b</sup>	4.41 <sup>b</sup>	<sup>c</sup>	-36.0%
EC <sub>50</sub>	ng/mL	10.6 <sup>a</sup>	4.13%	8.77 <sup>a</sup>	12.9 <sup>a</sup>	435% <sup>d</sup>	2.22%
γ <sub>TRV</sub>	unitless	5.22 <sup>a</sup>	8.04%	4.02 <sup>a</sup>	6.77 <sup>a</sup>	215% <sup>d</sup>	2.11%
ε <sub>1</sub>	Pain Scale	0.798	11.7%	0.616	0.981	0.893 <sup>e</sup>	-8.32%
<sup>a</sup> Back-transformed from natural log scale <sup>b</sup> Back-transformed from the logit scale. <sup>c</sup> Value was not interpretable due to the logistic transformation. <sup>d</sup> CV for IIV calculated as $CV_{IIV} = \sqrt{e^{\sigma^2} - 1}$ . <sup>e</sup> SD for residual error <sup>f</sup> %Change in from prior Pain model on untransformed scale.							
Source: Table 9.12 on page 65 in qs130-2002-report-body.pdf							

Based on these analyses, the applicant is proposing the following labeling statements

## 12.2 Pharmacodynamics

### Concentration-Analgesia Relationships

(b) (4)

The minimum effective [redacted] (b) (4) analgesia varies (b) (4) widely among patients, especially among patients who have been previously treated with opioids.

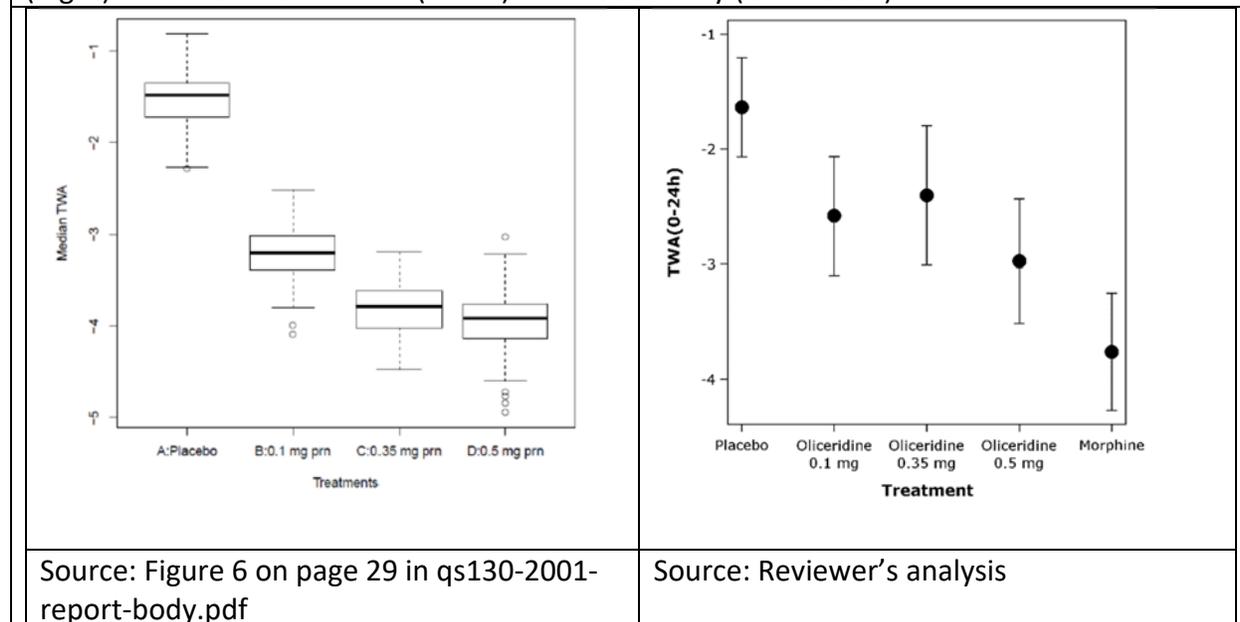
The applicant also proposed the following language regarding concentration-adverse relationship in Section 12.2 Pharmacodynamics based on opioid class labeling.

*Concentration-Adverse Experience Relationships*

There is a general relationship between increasing [redacted] (b) (4) and increasing frequency of adverse [redacted] (b) (4) such as nausea, vomiting, CNS effects, and respiratory depression.

**Reviewer’s Comments:** The reviewer did not conduct independent analyses to evaluate the structural E-R model. No specific issues with the dosing regimen, as proposed, were identified by the review team. However, modeling of the Phase 2 study data and subsequent simulations for the design of Phase 3 study played an important role. For example, simulations (left, Figure 19) showed that 0.1-0.5 mg PCA dose for the Phase 3 study would be reasonable. The TWA(0-24h) data (Right, Figure 19) from Phase 3 study support the projected trends in efficacy of these doses.

Figure 19. (Left) Simulated median TWA(0-24h) for Phase 3 study based on E-R analyses (Right) Observed median TWA(0-24h) in Phase 3 study (CP13-3001)



While recognizing the E-R analysis conducted by the applicant, the review team felt that the the proposed labeling language would not add additional value for the prescriber since the dose of oliceridine will be individualized. The review team recommends that this information be not included in the label.

## 4.5 Enrichment, Stratification, and/or Biomarker-based Assessment

### Submission Contents Related to Genomics

Oliceridine is metabolized via CYP2D6 and CYP3A4. The applicant assessed whether the variation resulting from CYP2D6 polymorphisms could impact the pharmacokinetics, efficacy, and safety of Oliceridine. In Studies CP130-1001, CP130-1002, CP130-1003, CP130-1004, CP130-1005, CP130-1006, CP130-1007, CP130-1008, CP130-2001, CP130-2002, the applicant performed CYP2D6 phenotyping, while in clinical Studies CP130-1010, CP130-1012, CP130-3001, CP130-3002, the applicant performed CYP2D6 genotyping.

#### Key Questions and Summary of Findings

##### Are the CYP2D6 phenotyping and genotyping appropriate?

###### *Published literature*

Dextromethorphan (DM) is widely reported in the literature as one of a few probe drugs used to determine the enzyme activity of CYP2D6 (PMID: 17273835). The rate of O-demethylation resulting in its main metabolite, dextrorphan (DX) can be expressed as the metabolic ratio of DM and DX. The metabolic ratio exhibits a bimodal distribution with the antimode separating the poor metabolizers from the non-poor metabolizers at the metabolic ratio of 0.3 (PMIDs: 4064464, 10579482). A 30-mg dose of Dextromethorphan is the dose primarily used in CYP2D6 phenotyping studies (PMID: 10579482), however, factors such as collection period, sample source (e.g., drug concentration measured in serum or plasma or urine or saliva) have been reported to influence the metabolic ratios derived in subjects.

While there can be a lack of consistency in what phenotypic categories such as extensive, normal, or ultra-rapid metabolizer, are called, efforts to standardize terms for allele functional status and phenotype have been published. Names of phenotypes standardized for drug metabolizing enzymes such as CYP2D6 are as follows: Ultrarapid metabolizer, i.e. two increased function alleles or more than 2 normal function alleles; rapid metabolizers, i.e. combinations of normal function and increased function alleles; normal metabolizer, i.e. combinations of normal function and decreased function alleles; intermediate metabolizer, i.e. combinations of normal function, decreased function and/or no function alleles; and poor metabolizer, i.e. combination of no function alleles and/or decreased function alleles (PMID: 27441996).

###### *Applicant's analysis*

The applicant reports giving a single oral dose of 30 mg DM to subjects. Each subject's urine was collected and pooled over a 4-hour period. A sample of each subject's urine was analyzed to measure concentrations of DM and DX. Subjects who had a DM/DX ratio <0.3 were classified as non-poor metabolizer (non-PMs) while subjects who had a DM/DX ratio >0.3 were classified as poor metabolizers (PMs).

In a response to an information request, the applicant reports performing the CYP2D6 genotyping for studies CP130-3001 and CP130-3002 using the AutoGenomics INFINITI® CYP2D6

Assay to detect 16 common CYP2D6 variants. Predicted phenotypes were assigned per the Table 46 and Table 47 below.

**Table 46. Designation of CYP2D6 variants**

AutoGenomics INFINITI® CYP450 2D6 Variants			
Allele (* Designation)	Variation	Effect	Enzyme Activity
*2	2850C>T <sup>a</sup>	R296C	Normal
*3	2549delA	Frameshift	Null
*4	1846G>A	Splicing defect	Null
*5	CYP2D6 deleted	No 2D6 Gene	Null
*6	1707delT	Frameshift	Null
*7	2935A>C	H324P	Null
*8	1758G>T	G169X	Null
*9	2615-2617delAAG	K281del	Decreased
*10	100 C>T <sup>b</sup>	P34S	Decreased
*12	124G>A	G42R	Null
*14	1758G>A	G169R	Null
*17	1023C>T	T107I	Decreased
*29	1659G>A	V136I	Decreased
*41	2988G>A	Splicing defect	Decreased
*2A	-1584C>G <sup>d</sup>	R296C; S486T	Normal
XN	Gene Duplication	↑ Copy number	Variable <sup>c</sup>

<sup>a</sup>2850C>T is found in a wide range of alleles including \*4, \*8, \*12, \*14, \*17, \*29 and \*41

<sup>b</sup>Also found in most \*4 subtypes

<sup>c</sup> Depends upon which allele is replicated and the copy number

<sup>d</sup>.1584C>G is also found in \*41

**Table 47. Predictive Phenotypes for various CYP2D6 genotypes**

**Table 2: Drug-Metabolizing Predictive Phenotypes for various CYP2D6 genotypes**

	*1	*2	*3	*4	*5	*6	*7	*8	*9	*10	*12	*14	*17	*29	*41	*1XN or *2XN
*1	EM	EM	EM	EM	EM	EM	UM									
*2		EM	EM	EM	EM	EM	EM	UM								
*3			PM	PM	PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	IM	NK <sup>1</sup>
*4				PM	PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	IM	NK <sup>1</sup>
*5					PM	PM	PM	PM	IM	IM	PM	PM	IM	IM	IM	NK <sup>1</sup>
*6						PM	PM	PM	IM	IM	PM	PM	IM	IM	IM	NK <sup>1</sup>
*7							PM	PM	IM	IM	PM	PM	IM	IM	IM	NK <sup>1</sup>
*8								PM	IM	IM	PM	PM	IM	IM	IM	NK <sup>1</sup>
*9									IM	IM	IM	IM	IM	IM	IM	NK <sup>1</sup>
*10										IM	IM	IM	IM	IM	IM	NK <sup>1</sup>
*12											PM	PM	IM	IM	IM	NK <sup>1</sup>
*14												PM	IM	IM	IM	NK <sup>1</sup>
*17													IM	IM	IM	NK <sup>1</sup>
*29														IM	IM	NK <sup>1</sup>
*41															IM	NK <sup>1</sup>

<sup>1</sup>In rare cases, duplicated alleles are reduced activity or null activity alleles, and individuals with this type of duplicated allele may have decrease in metabolism of some drugs.

EM= extensive metabolizer, IM= intermediate metabolizer, UM= ultra metabolizer, PM= poor metabolizer

The applicant reported that due to the rarity of the intermediate and ultra-metabolizer phenotypes, intermediate metabolizers were pooled with the poor metabolizers and the ultra-metabolizers were pooled with the extensive metabolizers. The pre-pooling assignments at the subject level is not presented in the study reports.

#### *Reviewer's Comments:*

*The phenotyping performed by the applicant and the assignment of metabolizer groups using a 30-mg dose of dextromethorphan, urine collection over 4 hours, and a DM/DX metabolic ratio of 0.3 as a cut off are consistent with CYP2D6 phenotyping procedures described in the literature.*

*Although the terms do not match the CPIC standardization suggestions, the phenotypes predicted from the genotype were assigned consistently with prevailing assignments in the literature where a PM phenotype is predicted if 2 copies of a non-functional allele is present, an IM phenotype is predicted when 2 copies of the reduced function alleles or 1 copy of a non-functional allele and 1 copy of the functional allele is present, or reduced function allele, an "EM" phenotype is predicted when 2 copies of a functional allele or 1 copy of a functional allele is present with 1 copy non-functional allele, and UM is predicted when functional alleles are present in duplicate.*

#### **4.6 Physiologically-based Pharmacokinetic Modeling**

The Applicant, Trevena, proposed to use physiologically based pharmacokinetic (PBPK) modeling and simulation to support the DDI liability of oliceridine. Specifically, PBPK was used to assess the impact of inhibitors of CYP3A4 or CYP2D6 on oliceridine exposure in CYP2D6 poor metabolizers (PM) and non-PM subjects. In addition, a static basic model was used to estimate the impact of combined inhibition of CYP3A4 and CYP2D6 metabolism by co-administration in PM and non-PM subjects.

An oliceridine PBPK model was built to characterize its disposition following administration via IV infusion to CYP2D6 PM and non-PM subjects. The Applicant proposed to validate the model by assessing its predictive performance via comparison of DDI liability observed in clinical studies (studies CP130-1005 part-B and CP130-1006). PBPK modeling and simulation was performed in the software GastroPlus (version 9.0.0007, Simulations Plus, Inc, Lancaster, CA, USA).

The PBPK team performed an initial review of the PBPK modeling and simulation report entitled "Physiologically -based PK modelling and simulation to quantify the impact of CYP3A4 and CYP2D6 inhibition on the pharmacokinetics of TRV130 in poor and non-poor metabolizers of CYP2D6 metabolism, and in renally impaired individuals (Version 1, 1st September 2015)", and PBPK model and simulation files submitted (SDN 2, 12/07/2017). This preliminary review showed that the Applicant has not developed and verified the PBPK model adequately. For example, (1) PK data from the clinical DDI studies CP130-1006 and CP130-1005 part B were used for model building as well for verification of CYP metabolic pathway; (2) other available clinical PK data (such as studies CP130-1002 and CP130-1003) were not used for model development; (3) the CYP2D6 clearance was assigned to the kidney compartment with no rationale provided; (4) sensitivity analysis of uncertain parameters (e.g. blood:plasma ratio) were not conducted; (5) modifications performed on the software's library perpetrator files were not clearly stated or justified.

In addition, discrepancies were found in the output files submitted. For example, in the DDI simulation files inconsistency was noted in the names of substrate files used and parameter values. Based on these reasons, the current PBPK modeling was not considered adequate to support DDI predictions.

Clinically, the effect of a strong CYP3A4 inhibitor, namely ketoconazole, on the PK of oliceridine in CYP2D6 non-PM subjects was evaluated in the study CP130-1006. Concomitant administration of single-dose ketoconazole did not have a significant effect on the PK parameters of oliceridine (C<sub>max</sub>, AUC, clearance and half-life). The effect of inhibitors of CYP2D6 on oliceridine PK was not evaluated; however, change in exposure resulting from lack of CYP2D6 metabolism, i.e., in CYP2D6 PM subjects, was characterized clinically in several phase 1 studies (e.g., CP130-1001 and CP130-1003). There was approximately 2-fold increase in AUC and 50% reduction of clearance in PMs compared to non-PMs. It is expected that the concomitant use of a strong CYP2D6 inhibitor would result in similar effect on CYP2D6 non-PMs, as result of complete inhibition of CYP2D6 pathway; and minimal effect on CYP2D6 PMs, given the absence of CYP2D6 expression/activity. The combined effect of inhibition of CYP3A4 and lack of CYP2D6 metabolism was clinically observed in the study CP130-1005 part-B evaluating the effect of itraconazole in CYP2D6 PM subjects. There was a 1.8-fold increase in AUC<sub>inf</sub> and 44% reduction of clearance following itraconazole administration in CYP2D6 PMs compared to oliceridine alone in PMs. Based on cross-study comparison of PK parameters, around 4-fold increase in AUC and 70% reduction of clearance could be expected in CYP2D6 non-PMs in the worst-case scenario of concomitant inhibition of CYP3A4 and CYP2D6 metabolism.

## **Recommendations**

The current oliceridine PBPK model was not considered adequate to support DDI predictions for oliceridine. Based on discussion with the clinical pharmacology review team internally and at the OCP's midcycle meeting, the available clinical DDI data and phase 1 PK data in CYP2D6 PM population were considered sufficient to address oliceridine DDI potential with CYP3A4 and CYP2D6 inhibitors. In addition, the proposed dose is titrated to effect (based on patient's pain experience). Further review and improvement of oliceridine PBPK model was determined to be unnecessary.

The PBPK review team recommends deletion of any language based on PBPK prediction in the product labeling, specifically, simulations results presented in section 7, table 5.

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/s/  
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SRIKANTH C NALLANI  
10/22/2018

VENKATESH A BHATTARAM  
10/22/2018

XINYUAN ZHANG on behalf of MANUELA GRIMSTEIN  
10/23/2018

OLUSEYI A ADENIYI  
10/23/2018

KEVIN M KRUDYS  
10/23/2018

XINYUAN ZHANG  
10/23/2018

MICHAEL A PACANOWSKI on behalf of CHRISTIAN GRIMSTEIN  
10/23/2018

YUN XU  
10/23/2018

CHANDRAHAS G SAHAJWALLA  
10/23/2018

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 210730  
Supporting document/s: SDN 1, 7, 21, 28, 30, 33 and 38  
CDER stamp date: 11/2/2017  
Product: Oliceridine  
Indication: Acute Pain  
Applicant: Trevena, Inc.  
Review Division: Anesthesia, Analgesia, and Addiction Products  
Reviewer: Min Zhang, PhD  
Team Leader: Jay H. Chang, PhD  
Supervisor: R. Daniel Mellon, PhD  
Division Director: Sharon Hertz, MD  
Project Manager: Shelly Kapoor, PharmD  
Eva Yuan, PharmD

**Disclaimer**

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## 1 Executive Summary

### 1.1 Introduction

The Applicant, Trevena Inc, submitted a New Drug Application for oliceridine (TRV130), for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted. The proposed dosing regimen is patient-controlled analgesia (PCA). The Applicant initially proposed a maximum recommended human dose (MRHD) of 100 mg/day. However, the MRHD was subsequently lowered by the Applicant to 40 mg/day based on concerns conveyed by the Agency regarding the adequacy of both the clinical and nonclinical data to support the higher dose. Oliceridine is described as a G protein-biased ligand at the mu-opioid receptor (MOR) in that it stimulates G protein coupling with reduced  $\beta$  arrestin-2 recruitment compared to conventional opioids like morphine, hydromorphone, and fentanyl. The overall hypothesis of the potential therapeutic benefits of a G protein-biased mu-receptor agonist is that it would provide an opioid analgesic with an increased therapeutic window compared with conventional opioids.

### 1.2 Brief Discussion of Nonclinical Findings

Pharmacology studies were submitted and demonstrated that oliceridine is a potent agonist at the MOR and is approximately 6-fold more potent than morphine (oliceridine  $EC_{50}$ =7.9 nM, morphine  $EC_{50}$ =50 nM). In vitro data demonstrated that oliceridine elicits less receptor phosphorylation and receptor internalization than morphine, consistent with its reduced  $\beta$  arrestin-2 recruitment. Oliceridine is selective for the MOR based on selectivity screening results examining greater than 100 receptors, channels, transporters and 33 different enzymes. In vitro data show that oliceridine exhibits 220-fold selectivity for MOR over the kappa opioid receptor (KOR) and 375-fold for MOR over the delta opioid receptor (DOR). In mice and rats, oliceridine elicits antinociception in multiple models of spinal reflexive and supraspinal affective nociceptive pain (potency reported to be 3 to 10 times that of morphine) with less respiratory depression and constipation in rodents compared to “equianalgesic” doses of morphine.

Potential systemic safety/toxicity of the drug product was evaluated in safety pharmacology, repeat-dose toxicity studies in rats and monkeys, reproductive toxicity studies in rats and rabbits. All the in vivo toxicology studies, including the in vivo genotoxicity studies, were conducted by continuous IV infusion. Intravenous bolus administration is the intended clinical route of administration; however, continuous infusion was selected to maximize daily exposure in the toxicology studies. Although the nonclinical studies were not designed to mimic the clinical setting exactly (periodic bolus dosing) the concentrations obtained in the animal studies exceeded the  $C_{max}$  obtained clinically.

The cardiovascular safety pharmacology studies suggest that oliceridine is a weak hERG inhibitor with an  $IC_{50}$  of 2.2  $\mu$ M which is 367 times its binding affinity of 6 nM at the MOR and 43 times the estimated  $C_{max}$  of the unbound drug at the proposed maximum recommended human dose (MRHD) of 40 mg/day. No consistent effects on QTc interval have been observed in nonclinical studies. Hemodynamic data demonstrated that oliceridine caused a dose-dependent decrease in mean systolic, diastolic, and mean arterial pressures, mean

arterial pulse pressure, and mean body temperature during infusion. The changes were followed by compensatory increases in these hemodynamic parameters from the end of infusion through the end of the telemetry collection period. A 6-hour infusion of oliceridine in rats did not cause any changes in respiratory parameters up to extrapolated plasma exposure approximately 2 times the projected median human  $C_{max}$  at the proposed daily MRHD of 40 mg.

General toxicology studies in rats and monkeys identified typical changes 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 were observed in rats treated with oliceridine for 14 days via constant infusion when the animals were sacrificed 24 hours post-dosing. These histopathological changes included minimal to marked stomach lesions such as erosions/ulcers in the glandular stomach, mucosal congestion/hemorrhage and degeneration/necrosis in the nonglandular stomach, minimal to slight adrenal cortical hypertrophy and atrophy of the seminal vesicles and prostate, and decreased lymphocytes in the spleen, thymus, mesenteric and mandibular lymph nodes. The gastric lesions were not observed after continuous IV infusion of oliceridine for 14 or 28 days in rats or in monkeys as long as the animals were sacrificed within 45 minutes after the termination of infusion. Furthermore, the occurrence of stomach lesions appears to correlate with the clinical observations reflecting withdrawal symptoms. Therefore, the gastric lesions identified in animals after withdrawal from the drug treatment appear to be a risk associated with drug withdrawal rather than a risk resulting directly from the drug effect. Stomach necrosis findings resolved by 7 days after termination of drug infusion in rats. 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 even when animals were sacrificed immediately after the termination of drug infusion. A greater incidence and severity of minimal to slight apoptosis in the pancreas observed in male rats after 28 days of drug infusion is likely attributed to reduction of food intake and was not associated with any evidence of inflammatory infiltrates in that tissue. A higher mortality rate (both found dead and moribund sacrifice) was observed in rats after prolonged infusion of oliceridine in the 28-day repeat-dose study, although the mortality was considered secondary to infusion-site inflammation and infection due to the presence of bacteria at the injection site.

In addition, lung thrombosis and injection-site inflammation were considered to be catheter related, although a possible oliceridine-related augmentation of the catheter response cannot be eliminated. Specifically, dose-dependent increases in inflammation were observed at infusion sites in the 28-day rat general toxicity study with a no observed adverse effect level (NOAEL) of 0.5 mg/kg/h at a concentration of 0.5 mg/mL, which is lower than the clinical concentration of 1 mg/mL. However, no increases in inflammation at infusion sites were observed at up to 1 mg/kg/h oliceridine (up to 1 mg/mL) in a 14-day study in rats. These studies suggest a low risk for local infusion site inflammation when the IV infusion is given for a short period for treating acute pain. An increased incidence of lung thrombosis was observed in oliceridine-treated rats in 2 out of the 4 rat toxicology studies and only occurred in

oliceridine-treated rats when lung thrombosis was also observed in vehicle-treated animals, suggesting the occurrence may be related to IV procedure but oliceridine may increase the incidence. The clinical relevance of this finding is likely limited, because rats do tend to have much stronger foreign body reactions compared to other species and no such finding was observed in the monkey study. Further, in vitro hemolysis and flocculation assays showed that oliceridine is compatible with human blood, as well as plasma and serum proteins. Collectively, the product does not appear to have significant risk for short-term acute use and likely results in similar risk as other long-term indwelling catheters used for prolonged drug administration.

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 at doses equivalent to  $\geq 2$  times the MRHD of 40 mg/day. The NOAEL for female fertility and early embryonic findings corresponded to approximately 1 times the estimated total daily exposure at the MRHD. In the GLP studies evaluating the effects of oliceridine on embryo-fetal development in rats and rabbits that received continuous IV infusion of oliceridine from the time of implantation until 1 day prior to parturition, 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 an overall increase in pups found dead or sacrificed moribund from birth to weaning. More specifically, there was reduced live litter size relative to total number born at birth (Postnatal Day 0; PND 0), and lower pup survival between birth and PND 4, resulting in a NOAEL that corresponds to total daily plasma exposure equivalent to 0.1 times the estimated MRHD exposure. Chronic administration of opioids has been shown to inhibit the synthesis and excretion of oxytocin, the hormone responsible for milk let-down, and adversely impacts maternal care of pups, providing possible explanations for early postnatal pup deaths. There was decreased milk in the stomachs of pups found dead or who were sacrificed moribund, which supports this conclusion. However, a direct effect on the pups cannot be eliminated without cross-fostering studies. Oliceridine administration to  $F_0$  dams produced no  $F_0$  or  $F_1$  maternal toxicity, had no effect on  $F_1$  developmental landmarks or memory and learning, and had no effect on  $F_1$  reproductive endpoints and produced no  $F_2$  neonatal/early postnatal toxicity. The NOAEL corresponds to total daily plasma exposure approximately 1 times the estimated MRHD exposure.

Oliceridine has been tested for genotoxicity in a bacterial reverse mutation assay, an in vitro chromosome aberration assay, and in vivo rat micronucleus and comet assays. While incubation with oliceridine in HCL salt form at concentrations  $>1.6$  mM in the presence of a metabolic activation system resulted in a positive result in the in vitro chromosome aberration assay, this finding was not corroborated by the results of a follow-up study testing the current limit concentration of oliceridine fumarate for this assay, or in an in vivo micronucleus or comet assays. Results from these studies indicate, by weight of evidence, that the risk of mutagenicity and clastogenicity in humans, if any, is minimal.

Radiochemical and mass spectrometric profiling of plasma collected from a human metabolism and excretion study with IV administration of [<sup>14</sup>C]-TRV130 identified two disproportionate human metabolites with mean plasma AUC values greater than 10% of total drug-related material—M22 (61.9%) and TRV0109662 (17.4%). Neither the major human metabolites show significant pharmacological activity in in vitro studies except a weak partial agonism at mu-opioid receptor. M22 has been adequately characterized for safety at the proposed MRHD of 40 mg/day. Although M22 was not present at adequate levels in the embryofetal development studies, this compound is an ether glucuronide of oliceridine, which is not believed to present any safety risks in accordance with the FDA guidance to industry on metabolites. As such, no further studies are required. For the other major human disproportionate metabolite TRV0109662, the plasma exposure to this metabolite in the rat 28-day repeat-dose study samples used to estimate the exposures in the rat embryo-fetal study suggests adequate coverage in this species. However, the Applicant is not able to reliably reproduce these exposure data assessments suggesting assay insensitivity. As such, the conclusion that the disproportionate metabolite is adequately characterized is uncertain due to lack of reproducibility. Thus, we cannot conclude that this disproportionate major metabolite has been adequately characterized with respect to an impact on embryo-fetal development. Because the drug will be labeled to reflect decreased postnatal pup survival at exposure less than the maximum recommended dose of 40 mg, the lack of complete characterization of this metabolite may not be absolutely essential to adequately inform labeling. Should this compound be deemed to provide a meaningful benefit over existing therapies, definitive embryo-fetal studies of the metabolite or validated reproducible analytical data could be considered as a post-marketing requirement at the discretion of the approving official based on a risk: benefit analysis. However, in the absence of a convincing risk: benefit analysis, adequate data should be provided to support an approval recommendation.

Regarding product quality (i.e., Drug Substance, Drug Product, Impurities, Excipients, and Extractables/Leachables), there are no nonclinical issues that preclude approval.

## 1.3 Recommendations

### 1.3.1 *Approvability*

From a nonclinical pharmacology toxicology perspective, there are inadequate nonclinical data to support an approval recommendation at this time and we therefore, recommend a complete response. Specifically, it is not clear that the disproportionate major human metabolite, TRV0109662, has been adequately qualified for safety, because the exposure data for this metabolite from rat intravenous toxicity studies could not be reproduced. As such, it is not clear that effects of TRV0109662 on embryofetal development have been adequately characterized by the existing studies.

The following nonclinical deficiency exists:

1. You have not provided adequate data to confirm that levels of TRV0109662, a major human metabolite, have been adequately characterized for potential embryo-fetal effects in either the rat or the rabbit embryo-fetal development study. Based on the data obtained to

date, this metabolite does not appear to be formed at acceptable levels in the rat compared to the human, you have not provided any data to document that the metabolite is formed in rabbit, and the existing analytical assays for human and rat plasma levels of TRV0109662 do not appear to be consistently reproducible (failed rat incurred sample reanalysis for pivotal study).

Information needed to resolve this deficiency:

Either conduct a dedicated embryo-fetal development study in either the rat or rabbit with TRV0109662 or provide validated reproducible pharmacokinetic data to support your 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 at the proposed maximum recommended human dose of 40 mg/day.

### 1.3.2 Additional Nonclinical Recommendations

### 1.3.3 Labeling

The following labeling recommendations have not been discussed with the review team nor the Applicant. For final labeling, the reader is referred to final labeling in an approval action letter.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
<p><b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b></p> <p><b>INDICATIONS AND USAGE</b>                      [BRANDNAME] (oliceridine) is a G protein-biased ligand at the mu-opioid receptor indicated for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted (1).</p>	<p><b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b></p> <p><b>INDICATIONS AND USAGE</b>                      TRADENAME (b) (4) is an opioid agonist indicated for the management of (b) (4) acute pain in adult (b) (4) (1).</p>	<p>This section must include an appropriate established pharmacologic class (EPC) for the drug substance(s) if available per 21 CFR 201.57. According to the guidance for industry and review staff: <i>Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information</i>, the pharmacologic class of a drug can be defined on the basis of (1) the mechanism of action (MOA), (2) physiologic effect (PE), (3) chemical structure (CS). For (b) (4)</p> <p>The guidance notes that the EPC should be represented by a phrase that is scientifically</p>

		and clinically meaningful. (b) (4)
(b) (4)		
<p>[BRANDNAME] should not be abruptly discontinued in patients (b) (4)</p> <p>If [BRANDNAME] is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.</p>	<p>TRADENAME (b) (4) should not be abruptly discontinued in patient (b) (4)</p> <p>If TRADENAME (b) (4) is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.</p> <p>(b) (4)</p>	<p>Consistently observed in animals across studies as a response to drug withdrawal-induced stress, a safety concern if the treatment is disrupted abruptly. This will be discussed with the clinical team as clinical significance will be related to the ultimate labeled dose and duration of use.</p>
(b) (4)		(b) (4)

(b) (4)		
<b>8 USE IN SPECIFIC POPULATIONS</b>	<b>8 USE IN SPECIFIC POPULATIONS</b>	
<b>8.1 Pregnancy</b>	<b>8.1 Pregnancy</b>	
<u>Risk Summary</u>	<u>Risk Summary</u>	
(b) (4)	(b) (4)	This is class labeling.
Oliceridine had no effect on embryo-fetal development in rats and rabbits when administered (b) (4)	Oliceridine had no effect on embryo-fetal development in rats and rabbits when administered (b) (4)	The basis of the exposure comparison was removed from the risk summary as per standard PLLR practices.
(b) (4)	(b) (4)	
(b) (4)	The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background	This is standard PLLR labeling that is included in all drug products unless indication specific data exists.

	<p>risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.</p>	
<p><u>Data</u></p> <p><i>Animal Data</i></p> <p>Oliceridine (b) (4)                  continuous intravenous infusion during the period of embryofetal organogenesis. Doses of 6, 12, or 24 mg/kg/day (b) (4) rats and 1.5, 3, or 6 mg/kg/day in rabbits had no effect on embryonic development at exposures (b) (4) the plasma exposure at the MRHD on an AUC basis.</p> <p>In a pre- and post-natal development study in rats, continuous intravenous infusion (b) (4) at doses of 0.6, 2.4, and 6.0 mg/kg/day (b) (4)</p> <p>(b) (4)</p>	<p><u>Data</u></p> <p><i>Animal Data</i></p> <p>Oliceridine (b) (4)                  continuous intravenous infusion during the period of embryofetal organogenesis. Doses of 6, 12, or 24 mg/kg/day (b) (4) rats (b) (4) from Gestation Day (GD) 6 to 20 and 1.5, 3, or 6 mg/kg/day (b) (4) rabbits (b) (4) from GD 7 to 29 had no effects on embryonic development at exposures (b) (4) the estimated plasma exposure at the MRHD on an AUC basis.</p> <p>Maternal toxicity (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>	
<p><b>8.3 Females and Males of Reproductive Potential</b></p> <p><u>Infertility</u></p>	<p><b>8.3 Females and Males of Reproductive Potential</b></p> <p><u>Infertility</u></p>	

<p>(b) (4)</p>	<p><i>Human Data</i> Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.</p> <p><i>Animal Data</i> Oliceridine administered intravenously for 14 days prior to cohabitation caused prolonged estrous cycle lengths and decreased the number of implantations and viable embryos in female rats at doses (b) (4) times the MRHD on an AUC basis [see Nonclinical Toxicology (13.1)].</p>	<p>Opioid class labeling added; human data are listed first as per standard practice.</p> <p>(b) (4)</p>
<p><b>12 CLINICAL PHARMACOLOGY</b> <b>12.1 Mechanism of Action</b></p>	<p><b>12 CLINICAL PHARMACOLOGY</b> <b>12.1 Mechanism of Action</b></p>	<p>(b) (4)</p>
<p>(b) (4)</p>	<p>Oliceridine is a full opioid agonist and is relatively selective for the mu-opioid receptor. The principal therapeutic action of oliceridine is analgesia.</p> <p>The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.</p>	<p><i>Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information</i> notes that a new established pharmacologic class (EPC) term should be scientifically valid and clinically meaningful. Given the lack of clinical data to support a new EPC, both the proposed EPC and the descriptions of the information to support a novel mechanism of action in Section 12 of the labeling are not considered acceptable.</p>
<p><b>12.2 Pharmacodynamics</b></p>	<p><b>12.2 Pharmacodynamics</b></p>	<p>(b) (4)</p>
<p>(b) (4)</p>	<p>(b) (4)</p>	<p>(b) (4)</p>

(b) (4)



Effects on the Central Nervous System (CNS)

(b) (4)  
Opioids (b) (4)  
stem

respiratory centers. Respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. (b) (4)

(b) (4)  
Opioids, (b) (4), cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

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This statement is in all opioid labeling, it is class labeling. There is no reason to believe that oliceridine will function any differently than other opioid agonists.

Although true, we recommend removal as this drug is not indicated (b) (4).

<p><u>Effects on the Gastrointestinal Tract and on Other Smooth Muscle</u></p> <p>(b) (4)</p> <p>Opioid (b) (4) cause a reduction in (b) (4) motility (b) (4) associated with an increase in tone in the antrum of the stomach and duodenum. (b) (4)</p> <p>Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm (b) (4) result (b) (4) constipation. Opioid (b) (4) spasm of the sphincter of Oddi, and transient elevations in serum amylase. (b) (4)</p>	<p><u>Effects on the Gastrointestinal Tract and on Other Smooth Muscle</u></p> <p>(b) (4)</p> <p>Opioid (b) (4) cause a reduction in (b) (4) motility (b) (4) associated with an increase in tone in the antrum of the stomach and duodenum. (b) (4)</p> <p>Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm (b) (4) result (b) (4) constipation. Opioid (b) (4) spasm of the sphincter of Oddi, and transient elevations in serum amylase. (b) (4)</p>	<p>This statement is in all opioid labeling, it is class labeling. There is no reason to believe that oliceridine will function any differently than other opioid agonists.</p>
<p><u>Effects on the Endocrine System</u></p> <p>Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.</p>	<p><u>Effects on the Endocrine System</u></p> <p>Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see <i>Adverse Reactions</i>]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.</p>	<p>This statement is in all opioid labeling, it is class labeling. There is no reason to believe that oliceridine will function any differently than other opioid agonists.</p>
<p><u>Effects on the Immune System</u></p> <p>Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.</p>	<p><u>Effects on the Immune System</u></p> <p>Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.</p>	<p>Also class labeling for opioids.</p>
<p><b>13 NONCLINICAL TOXICOLOGY</b></p>	<p><b>13 NONCLINICAL TOXICOLOGY</b></p>	

<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>	<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>	
<p>(b) (4)</p>	<p><u>Carcinogenesis:</u> Long-term studies in animals have not been completed to evaluate the carcinogenic potential of oliceridine.</p> <p><u>Mutagenesis:</u> Oliceridine (b) (4) was negative in an in vitro Ames bacterial reverse mutation assay, the in vitro chromosomal aberration assay using human peripheral blood lymphocytes, and the in vivo rat micronucleus and comet assay.</p> <p><u>Impairment of Fertility</u></p> <p>(b) (4)</p>	<p>The proposed language is inappropriate for the label since it summarizes negative findings.</p>
<b>13.2 Animal Toxicology and/or Pharmacology</b>	<b>13.2 Animal Toxicology and/or Pharmacology</b>	
<p>Continuous intravenous infusion of oliceridine (b) (4)</p>	<p><del>Continuous intravenous infusion of oliceridine (b) (4)</del></p>	

(b) (4)	(b) (4)	
	<p>Continuous intravenous infusion of oliceridine for 14 days followed by one-day withdrawal from the treatment resulted in opioid withdrawal stress-related gastric lesions including erosions/ulcers in the glandular stomach, mucosal congestion/hemorrhage and degeneration/necrosis in the nonglandular stomach at exposures (b) (4) the estimated human expose at the MRHD on an AUC basis. The effect is believed to be due to acute withdrawal stress, as similar findings were not noted in animals sacrificed immediately after the last dose of oliceridine.</p>	<p>This reviewer proposed to add language regarding opioid withdrawal-induced stomach lesions to inform physicians that tapering may be needed if oliceridine is administered for at least 14 days. This may not be necessary pending review of adequate human data and/or if labeling restricts use to short-term treatment only.</p>

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 1467617-09-9

Generic Name: Oliceridine fumarate

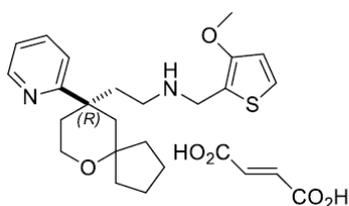
Code Name: TRV130 fumarate; FP-221; (TRV130A = HCl salt form)

Chemical Name: [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine, fumarate

Molecular Formula:  $C_{22}H_{30}N_2O_2S \cdot C_4H_4O_4$

Molecular Weight: 502.62 g/mol (fumarate salt) and 386.55 g/mol (free base)

Structure:



Pharmacologic Class: Opioid agonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND	Drug/Compound	Applicant/Applicant	Indication	Division/Office	Status
IND 113537	Oliceridine	Trevena	Acute pain	DAAAP	Active

DMF	Subject of DMF	Holder	Status	Application Status Date
		(b) (4)	Active	4/30/2007
			Active	12/14/2015
			Active	9/11/1995
			Active	10/08/1997
			Active	09/25/2007

## 2.3 Drug Formulation

Oliceridine injection, 1 mg/mL is a clear, colorless, sterile, preservative-free solution, supplied in a glass vial for intravenous administration in three product presentations, including 1 mL of solution in a 2 mL single-dose vial, 2 mL of solution in a 2 mL single-dose vial, and 30 mL of solution in a 30 mL single-dose vial. The composition of the dosage form is provided in the table below:

<b>Ingredient</b>	<b>Amount</b>	<b>Units</b>	<b>Primary Function</b>	<b>Reference to Standards</b>
Oliceridine fumarate salt ⇔ Oliceridine free base	1.3 (salt) ⇔ 1.0 (free base)	mg/mL	Active ingredient	Internal Monograph <sup>a</sup>
L-histidine				(b) (4) USP
Mannitol				USP
				(b) (4) NF
				NF
Water for Injection	q.s. to batch volume			(b) (4) USP
				(b) (4) NF
a Proposed commercial specifications for oliceridine fumarate drug substance are provided in <a href="#">Modules 3.2.S.4.1.</a>				

## 2.4 Comments on Novel Excipients

There are no novel excipients used in the drug product. The excipients in the product, their total daily intake based on the proposed MRHD of 40 mg/day in comparison to the maximum potency data from the FDA Inactive Ingredients database (IID), and the acceptability are presented in the table below:

Table 1. Acceptability of Excipients in the Drug Product

<b>Excipient</b>	<b>Concentration (mg/mL)</b>	<b>Max. Potency in Approved IV Products Listed in FDA IID</b>	<b>Max. Daily Consumption (mg)*</b>	<b>Max. Potency in Approved IV Products Listed in FDA IID (mg/day)</b>	<b>Acceptability and Rationale</b>
L-histidine					(b) (4) Yes; Covered via IID
Mannitol					Yes; Covered via IID

\* Calculated based upon proposed MRHD of 40 mg/day.

## 2.5 Comments on Impurities/Degradants of Concern

A list of drug substance (DS) and drug product (DP) impurity specifications, including comparisons to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and safety determination, are summarized in the table below.

Table 2: Specified Impurities in Oliceridine Fumarate and Oliceridine Injection (1 mg/mL)

Impurity	Origin	Proposed Specifications		Maximum Daily Exposure <sup>c</sup>		Comparison to ICH Identification and Qualification Thresholds		Acceptable?
		DS	DP	DS (mg/day)	DP (mg/day)	Q3A(R2) 0.15% or 1.0 mg/per day	Q3B(R2) 0.5% or 200 mcg/day, whichever is lower	
	(b) (4)				(b) (4)	Exceeds	Exceeds	Yes <sup>a</sup>
						Exceeds		Yes <sup>a</sup>
						Exceeds		Yes <sup>a</sup>
							Exceeds	Yes <sup>a</sup>
							Complies	Yes <sup>b</sup>
Unspecified Impurities	DS					Complies		Yes <sup>b</sup>
Unspecified Impurities	DP						Complies	Yes <sup>b</sup>

DS: Drug substance

DP: Drug product

a: Adequately qualified for safety in accordance with ICH Q3B(R2)

b: Within ICH Q3B(R2) thresholds

c: Calculated based upon proposed MRHD of 40 mg

**2.5.1 Specified Impurities:**

(b) (4)

Four impurities/degradation products exceed or are projected to exceed the appropriate ICH qualification threshold of NMT 0.15% or 1.0 mg/day, whichever is lower and 0.5% or 200 mcg/day, whichever, is lower as per ICH Q3A(R2) and Q3B(R2), respectively. In order to support specification levels above ICH qualification thresholds, the Applicant qualified the four

impurities/degradation products in accordance with ICH Q3A(R2) and ICH Q3B(R2) guidances by conducting a 14-day continuous IV infusion toxicology study in rats and in vitro genotoxicity assays (bacterial reverse mutation assay and in vitro micronucleus assay) up to the assay limit dose or up to the limit of cytotoxicity. These studies have been reviewed in Section 9.1.

In the 14-day continuous IV infusion toxicology study in rats, TRV130 fortified with (b) (4) did not produce any clear difference in toxicology assessment compared to animals administered TRV130 alone. The excess of the four impurities administered to rats in this study compared to the maximum exposure to these impurities in humans is presented in the table below. The calculated human exposure to impurities is based on the acceptance criterion proposed in finished API or DP specification and an oliceridine maximum daily dose of 40 mg. It appears that adequate safety margin for each impurity has been established in the 14-day IV repeat-dose toxicity.

Table 3. Impurity Dose Levels in Rats During a 14-Day Toxicology Study Compared to the Maximum Dose in Humans

Impurity	Concentration of Impurity in Fortified DP	Dose in the Animal Study (mg/kg/day) <sup>a</sup>	HED Based upon BSA (mg/day) <sup>(b) (4)</sup>	Proposed Specifications	Maximum Human Exposure (mg/day) <sup>b</sup>	Safety Margin (HED/Max Human Exposure) <sup>(b) (4)</sup>
(b) (4)						

a: The calculation is based upon the dose that did not produce human relevant adverse effects in the 14-day IV general toxicology study: 12 mg/kg/day

b: The calculation is based upon the MRHD: 40 mg/day

Tested up to the assay limit concentration of 5000 mcg/plate in a bacterial reverse mutation (AMES) assay, all four impurities/degradation products were negative for the ability to induce reverse mutations under the test conditions. In an in vitro mammalian cell micronucleus assay in human peripheral blood lymphocytes, all four drug substance impurities or drug product degradants were tested up to the assay limit concentration or up to the limit of cytotoxicity and were negative for the induction of micronuclei under the test conditions.

In summary, per ICH Q3A(R2) and ICH Q3B(R2), data from the 14-day rat general toxicology study and the in vitro genotoxicity studies adequately qualify the safety of these four impurities/degradation products to the proposed levels.

### **2.5.2 Unspecified Impurities:**

None of the unspecified impurities is observed in drug substance above (b) (4) % (area). Each of these impurities was assessed for mutagenic potential by two in-silico software tools (Derek Analysis and Vega-QSAR) and found to be negative and non-mutagenic as noted (see below for further assessment). No additional controls are necessary for these impurities from toxicology perspective.

### **2.5.3 Mutagenic Impurities:**

The Applicant conducted QSAR prediction studies with Derek (expert knowledge, rule-based tool) and VEGA-QSAR (statistical-based, quantitative structure-activity relationship tool derived from experimental data) assessment on all the specified impurities and unspecified impurities (except (b) (4), see safety assessment below) likely to arise during synthesis and storage of oliceridine fumarate drug substance and drug products for mutagenicity potentials. The assessments predicted that all of the impurities would be negative in the bacterial reverse mutation test. To confirm the Applicant's prediction, two impurities, (b) (4) were submitted for evaluation to CDER/Computational Toxicology Consultation Service for bacterial mutagenicity using (Q)SAR models (DEREK Nexus 5.0.2 (DX), Leadscope Model Applier 2.2.1-1 (LMA), and CASE Ultra 1.6.2.1 (CU)). Consistent with the Applicant's result, both impurities were predicted to be negative in the Ames test.

(b) (4)

### **2.5.5 Elemental Impurities:**

The Applicant has tested six batches of oliceridine injection drug product, four batches of oliceridine fumarate drug substance, three batches of mannitol (excipient), three batches of L-histidine (excipient) and no elemental impurities were detected above the control threshold, which is not more than 30% of the permitted daily exposure presented in ICH Q3D. The CMC review team has agreed with the Applicant's conclusion that routine testing of the drug product, drug substance, and excipients for elemental impurities is not required and does not need to be included in the specifications. Refer to the CMC review for a discussion of Applicant's approach and acceptability of the related to elemental impurities.

## **2.6 Extractables and Leachables**

### **2.6.1 Container Closure System**

Oliceridine injection, 1 mg/mL is manufactured in three product presentations, a 1 mL fill volume in a 2 mL vial, a 2 mL fill volume in a 2 mL vial, and a 30 mL fill volume in a 30 mL vial. The maximum daily dose currently proposed is 40 mg, (b) (4). This can be accomplished by use of any of the three formats listed above. This complicates the determination of an appropriate analytical evaluation threshold; however, for an acute indication, to detect at (b) (4), the assay must be able to detect at least (b) (4) mcg/mL in the final drug product format.

#### **Primary packaging:**

- A clear USP (b) (4) I glass vial (2 mL and 30 mL vials)
- A 13 mm or 20 mm (b) (4) rubber stopper (b) (4) for the 2 mL or 30 mL vial, respectively.
- An aluminum seal with plastic flip-off cap is also part of the finished drug product dosage form, but the seal/cap is non-product contact.

The Applicant noted that all components are commonly used for pharmaceutical packaging of aqueous injectable dosage forms, and their materials of construction comply with quality standards per the relevant compendia (USP).

#### **Secondary packaging:**

Labeled vials are placed in a (10 count) carton, which is the secondary packaging.

### 2.6.2 Extractables/Leachables Evaluation

In order to assess the safety of the selected container closure system, an extractables screening study was performed and based on the results of that screening study, leachable analysis was incorporated into the primary (registration) stability program. A preliminary assessment of potential leachable compounds was performed on an aged (12+ months) sample of oliceridine drug product (Lot P06814, DOM 09-Sep-2014) with ongoing leachable studies performed on five primary batches of drug product (Batch numbers B160288, B160285, B170190, CL7-018 and CL7-015).

The drug product solution is sterilized (b) (4)

The (b) (4) used to ensure the sterility of the drug product which are part of the manufacturing process were assessed for extractables. As per the Applicant, extractables from the manufacturing process were not assessed in the leachable studies as the potential for leachables is very low. The submission states:

(b) (4)

The CMC review team noted that the methods were acceptable and that potential leachables would be detected in drug product samples on stability testing. Refer to the CMC review for additional details.

(b) (4)

The commercial batch sizes for the different oliceridine presentations are shown in the table below.

<b>Table 1: Expected Commercial Batch Sizes for Oliceridine Injection, 1 mg/mL at</b> (b) (4)	
Oliceridine Injection, 1 mg/mL Product Presentation	Batch Size, Compounding
1 mL Fill Volume in 2 mL Vial	(b) (4)
2 mL Fill Volume in 2 mL Vial	
30 mL Fill Volume in 30 mL Vial	

(b) (4)

(b) (4) Therefore, this Reviewer does not consider the extractables from the to pose a safety risk.

**Extractable and Leachable Screening Study (DOCUMENT: RPT51440.00)**

A one-time controlled extraction study was performed on the drug product primary container closure system based on USP <1663> and USP <1664> guidance and PQRI-PODP Working Group recommendations.

The extraction study was only performed on the primary container closure components:

(b) (4)

The Applicant stated that each of these components has been commercially available, well characterized and used in the pharmaceutical industry for a considerable length of time.

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(b) (4)

**Results:**

The majority of the compounds that arise from the components and migrate into the formulation are expected to originate from the rubber stopper. No organic compounds are expected to originate from the glass vials.

**Non-volatile Extractables:**

- There were no non-volatile compounds present (b) (4) at concentrations above the reporting threshold. This extract is the most representative of contact solution of the actual drug product.
- As shown in the tables below, classes of compounds observed in aggressive extraction solvents, (b) (4). These classes of compounds are all common in pharmaceutical grade rubber components. A few unknown extractables were detected in these two extract conditions.

(b) (4)



**Volatile Extractables:**

The volatile extractable compounds observed

(b) (4)



(b) (4)

**Semi-volatile Extractables:**

- There were no compounds detected [REDACTED] (b) (4) the rubber stopper at concentrations observed above the reporting threshold of [REDACTED] (b) (4) mcg/stopper. This extract is the most representative of contact solution of the actual drug product.
- With aggressive solvents, [REDACTED] (b) (4) [REDACTED] (b) (4). These classes of compounds are all common in pharmaceutical grade rubber components.



(b) (4)

<sup>(b) (4)</sup> **Extractables:**

<sup>(b) (4)</sup> elements listed in the <sup>(b) (4)</sup> were monitored. The limits utilized are specifically for active pharmaceutical ingredients (API) and excipients. Elements listed as <sup>(b) (4)</sup> per <sup>(b) (4)</sup> were included in the standard solution at levels corresponding to the limits for materials used in parenteral dosage forms. All monitored elemental impurity results were observed to be lower than limits established in <sup>(b) (4)</sup> and/or <sup>(b) (4)</sup>

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(b) (4)

We defer to CMC on the adequacy of the extraction study.

***Preliminary Leachable Study in Aged Drug Product (12+ months; Lot P06814, DOM 09-Sep-2014):***

The controlled extraction study results show, that under aggressive extraction (solvent), extracted compounds that are common in rubber stoppers, are potential leachables, while the extraction (b) (4), which is the most clinically relevant solvent aside from the drug product vehicle, showed no extractables greater than the (b) (4) mcg/stopper reporting threshold. Using the observed potential extractables found in the extraction study, a preliminary leachable study was conducted on aged product with the same analytical techniques. Ten mL of the dug product was prepared for analysis for leachables compounds for each analytical technique.

**Reporting Threshold:** (b) (4)

**Results:**

**Nonvolatile Leachables:**

No leachables were observed above the reporting threshold.

**Volatile Leachables:**

The results indicate several compounds were observed that originate with the rubber stopper.

(b) (4)

**Semi-volatile Leachables:**

The results indicate that no compounds were observed above the reporting threshold of (b) (4) mcg/vial (b) (4) mcg/mL.

***Leachable Testing on Primary Stability Batches:*****Batches and Test time-points:**

Five representative primary stability batches of oliceridine injection, 1 mg/mL drug product batches have been placed on a long-term leachable study. The batches will be tested at the stability time points indicated in Table 1 below.

<b>Table 1: Oliceridine Injection Leachable Stability Study</b>									
Description	Batch Number (Manufacturer)	Orientation	Conditions	Test Points (Months)					
				3	6	12	24	36	
Oliceridine Injection, 1 mg/mL, 1 mL vial	B160288	Inverted	25°C/60%RH	x	x	x	x	x	
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	
Oliceridine Injection, 1mg/mL, 30 mL vial	B160285	Inverted	25°C/60%RH	x	x	x	x	x	
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	
Oliceridine Injection, 1mg/mL, 2 mL vial <sup>a</sup>	B170190	Inverted	25°C/60%RH	x	x	x	x	x	
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	
Oliceridine Injection, 1 mg/mL, 1 mL vial	CL7-018	Inverted	25°C/60%RH	x	x	x	x	x	
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	
Oliceridine Injection, 1mg/mL, 30 mL vial	CL7-015	Inverted	25°C/60%RH	x	x	x	x	x	
	(b) (4)	Inverted	40°C/75% RH	x	x	NT	NT	NT	

a For batch B170190, results for the 1 month time point are also reported.  
x = Non-volatile leachables by LC-MS, volatile leachables by headspace GC-MS, semi-volatile leachables by GC-MS, elementals by ICP-MS  
NT = Not Tested

### Analytical Evaluation Threshold (AET):

The Applicant originally employed a reporting threshold of (b) (4) mcg/mL to monitor leachables based upon existing data at the time of clinical development ( (b) (4) daily volume). Early leachable study data were reported with this threshold. For the commercial phase, a calculated AET was used, and this AET was originally applied going forward in all on-going leachable stability studies. The AET was calculated based on ICH (b) (4) guidance on acceptable intakes for an individual impurity. The calculated AET utilized the specified threshold of (b) (4) mcg/day for an acute indication ( $\leq 1$  month) and (b) (4) drug product/day (based on oliceridine solution concentration of 1 mg/mL and a worst case maximum daily dose for calculation purposes of (b) (4) mg/day) and a 50% uncertainty factor to arrive at (b) (4) mcg/mL (b) (4). The Agency communicated with the Applicant in the 74-day letter that "AET of (b) (4)

*mcg/mL may be acceptable from the genotoxicity perspective; however, from the general toxicity perspective, the AET must be set to detect any leachable that is present in the drug product at  $(b)_{(4)}$  mcg/day and higher. Given the maximum total daily dosing volume of  $(b)_{(4)}$  mL, the AET needs to be set at  $(b)_{(4)}$  mcg/mL ( $(b)_{(4)}$  mcg/day  $\div$   $(b)_{(4)}$  mL/day) to detect any leachables at  $(b)_{(4)}$  mcg/day or higher. Therefore, re-evaluate your leachables samples to detect appropriate compounds based on the extraction studies and set the AET at  $(b)_{(4)}$  mcg/mL.”* Per the Agency’s request, the applicant further developed the analytical methods for non-volatile, semi-volatile, and volatile leachables to achieve an AET of  $(b)_{(4)}$  mcg/mL (based upon the Applicant’s originally proposed MRHD of 100 mg/day). The updated analytical methods, each with a reporting limit of  $(b)_{(4)}$  mcg/mL, were used for the analysis of drug product samples from an unscheduled (ad hoc) stability pull from each of the five representative primary stability batches of oliceridine injection, 1mg/mL drug product batches currently on a long term leachable study. We defer to CMC on the validity of the analytical methods. The data from these ad hoc analyses are presented and discussed below. The updated analytical methods will be used for the remaining stability time points for each of the five representative primary stability batches being monitored for leachables.

*Reviewer’s note: Given that the Applicant lowered the reporting limit in order to achieve an AET of  $(b)_{(4)}$  mcg/mL after the issue had been communicated with them in the 74-day letter, the earliest sampling time point with  $(b)_{(4)}$  mcg/mL AET applied is the 10<sup>th</sup> month in the primary stability study as shown in the tables below. After the Applicant applied lowered reporting limit to achieve  $(b)_{(4)}$  mcg/mL, additional volatile and semi-volatile leachables were detected. Given that these leachables may have higher concentration in the earlier sampling points but may not be detected with the higher reporting limit, the highest reporting limit used by the Applicant during the course of the study,  $(b)_{(4)}$  mcg/mL, is considered by this Reviewer as the maximum potentially detected level for the leachables that have been detected with a level lower than  $(b)_{(4)}$  mcg/mL when reporting limit of  $(b)_{(4)}$  mcg/mL was applied.*

## **Results:**

### **Non-volatile, volatile and semi-volatile leachables:**

Cumulative non-volatile, volatile, and semi-volatile leachable results are shown in the tables below for the five primary stability batches. The Applicant has updated the tables to include the results from the analysis of ad hoc stability samples utilizing updated analytical methods (reporting limit of  $(b)_{(4)}$  mcg/mL) as discussed above. In addition, leachables stability data for sample pulls that occurred after the NDA submission and prior to the ad hoc sample pulls have been included. The Applicant conducted toxicology risk assessment on the leachables detected.

Table 2: Oliceridine Injection, 1 mg/mL, 1 mL Vials, Batch B160288 (b) (4) Leachables Study						
Time Point/ Condition	Non-volatile Leachables by LC-MS		Volatile Leachables by headspace GC-MS		Semi-volatile Leachables by GC-MS	
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound
<b>25°C/60%RH</b>						
Initial	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
12 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
~22 Months <sup>a</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
<b>40°C/75%RH</b>						
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
a Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL.						

Table 3: Oliceridine Injection, 1 mg/mL, 30 mL Vials, Batch B160285 (b) (4) Leachables Study						
Time Point/ Condition	Non-volatile leachables by LC-MS		Volatile leachables by headspace GC-MS		Semi-volatile leachables by GC-MS	
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound
<b>25°C/60%RH</b>						
Initial	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
12 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
~23 months <sup>a</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
<b>40°C/75%RH</b>						
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)

a Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL.

Table 4: Oliceridine Injection, 1 mg/mL, 2 mL Vials, Batch B170190 (b) (4) Leachables Study						
Time Point/ Condition	Non-volatile leachables by LC-MS		Volatile leachables by headspace GC-MS		Semi-volatile leachables by GC-MS	
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound
<b>25°C/60%RH</b>						
Initial <sup>a</sup>	NT	(b) (4)	NT	NT	NT	(b) (4)
1 month	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
~12 Months <sup>b</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
<b>40°C/75%RH</b>						
1 month	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)

NT = Not Tested  
a Initial timepoint testing not performed, see 1 month time point for baseline.  
b Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL.

Table 5: Oliceridine Injection, 1 mg/mL, 1 mL Vials, Batch CL7-018		(b) (4) Leachables Study					
Time Point/ Condition	Non-volatile leachables by LC-MS		Volatile leachables by headspace GC-MS		Semi-volatile leachables by GC-MS		
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound	
<b>25°C/60%RH</b>							
Initial	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
~10 Months <sup>a</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
<b>40°C/75%RH</b>							
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
a Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL.							

Table 6: Oliceridine Injection, 1 mg/mL, 30 mL Vials, Batch CL7-015		(b) (4) Leachable Study					
Time Point/ Condition	Non-volatile leachables by LC-MS		Volatile leachables by headspace GC-MS		Semi-volatile leachables by GC-MS		
	µg/mL (ppm)	compound	µg/mL (ppm)	compound	µg/mL (ppm)	compound	
<b>25°C/60%RH</b>							
Initial	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
~11 Months <sup>a</sup>	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
<b>40°C/75%RH</b>							
3 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
6 months	No leachables above (b) (4) µg/mL	(b) (4)	(b) (4)	(b) (4)	No leachables above (b) (4) µg/mL	(b) (4)	
a Ad hoc stability pull analyzed by updated analytical methods with an AET = (b) (4) µg/mL.							

- Non-volatile leachables: Non-volatile leachable analyses for the five batches, including the ad hoc samples tested against the threshold limit of (b) (4) mcg/mL, showed no leachables above the reporting threshold for the time points studied.
- Volatile leachables: The volatile leachable analysis data is summarized in the table below.

Table 6. Summary of Volatile Leachable Analysis

Compound (CAS#)	Maximum Detected Level	Maximum Potentially Detected	Maximum Potential Daily	Maximum Potential Daily	Acceptable?

	(mcg/mL)	Level (mcg/mL)	Exposure Level (mcg/day) <sup>a</sup>	Exposure Level (mcg/day) <sup>b</sup>	
	Applicant's Value	Reviewer's Value	Applicant's Value	Reviewer's Value	
(b) (4)					

<sup>a,b</sup>: Calculated based upon MRHD of 40 mg/day

After the Applicant applied lowered reporting limit to achieve (b) (4) mcg/mL, three additional leachables, (b) (4) were detected. Among these three leachables, (b) (4) have a detected level above (b) (4) mcg/mL but below (b) (4) mcg/mL, a reporting limit previous applied in the earlier sampling points. Given that the volatile leachables may have higher concentration in the earlier sampling points but cannot be detected with the higher reporting limits, the highest reporting limit, (b) (4) mcg/mL, is considered by this Reviewer as the maximum potentially detected level for (b) (4) and is used for calculating maximum potential daily exposure level as shown in the table above.

(b) (4)

(b) (4) The maximum potential daily exposure to this leachable from the product at MRHD of 40 mg/day is (b) (4) mcg, well below the calculated PDE of (b) (4) mcg; therefore, this leachable at the detected level presents low risk to human health.

- **Semi-volatile leachables:**  
Semi-volatile leachable analyses for the five batches showed reportable leachables in only one of the ad hoc samples (Batch B160288) tested against the threshold limit of (b) (4) mcg/mL. The semi-volatile leachables reported include (b) (4). The semi-volatile leachable analysis data is summarized in the table below. Similar to the volatile leachables, the highest reporting limit, (b) (4) mcg/mL, is considered by this Reviewer as the maximum potential detected level for these semi-volatile compounds and is used for calculating maximum potential daily exposure level when assessing toxicology risk.

Table 7. Analysis of Semi-Volatile Leachables

Compound (CAS#)	Maximum Level (mcg/mL)	Maximum Potential Level (mcg/mL)	Maximum Potential Daily Exposure Level (mcg/day)	Maximum Potential Daily Exposure Level (mcg/day)	Acceptable?
	Applicant's Value	Reviewer's Value	Applicant's Value <sup>a</sup>	Reviewer's Value <sup>b</sup>	
(b) (4)					

a,b: Calculated based upon MRHD of 40 mg/day

(b) (4)

**Elemental Leachables:**

In the initial NDA submission, it appears that the reporting thresholds employed were not low enough to detect the elemental compounds that exceed the permitted daily exposures indicated in (b) (4) for specific elementals. In the 74-day letter, the Applicant was requested to re-evaluate the leachable samples with appropriate thresholds that can detect elemental compounds exceeding their respective PED levels based upon the maximum daily dose of the product at 100 mL or provide a toxicological risk assessment to justify the safety of each elemental leachable if the maximum potential daily exposure calculated based upon the detecting thresholds exceed the PDEs.

The Applicant acknowledged the Agency's comments and has conducted a reevaluation, as requested. As part this reevaluation, an ICP-MS method has been developed further that is capable of analyzing oliceridine drug product for the (b) (4) elemental impurities addressed by (b) (4). The threshold limit for this updated method is at or below the PDE for each elemental impurity, based on the originally proposed MRHD of 100 mL (100 mg) of drug product, and a quantitation limit of (b) (4) % of the threshold limit was achieved and validated. The updated analytical method (TP75786) and validation report (RPT69411) are subject to review by CMC.

Ad hoc stability samples from each of the drug product registration batches being monitored on stability for leachables were analyzed using the updated ICP-MS method and the data are (b) (4) APPEARS THIS WAY ON ORIGINAL (b) (4) provided below. All results for each elemental impurity for each batch tested are below the limit of quantitation for the respective elemental impurity. These data are consistent with the elemental impurities extractables study conducted on the container closure system components (extracted with 5% nitric acid at 121°C for 2 hours) which showed no significant levels of any of the (b) (4) elemental impurities addressed by (b) (4) and support the conclusion that the drug product formulation and container closure system selected present minimal risk for patient exposure to elemental impurities.

With the commitment to use the updated ICP-MS method for continued monitoring of the ongoing leachable stability studies through their duration, this Reviewer believes the Applicant has satisfactorily addressed this observation.

3.2.P.2 Pharmaceutical Development [Oliceridine 1 mg/mL, Common, Injection]

<b>Table 12: Results of Leachables Elemental Impurities Testing using Updated ICP-MS Method</b>					
<b>Batch</b>	B160285	B160288	B170190	CL7-015	CL7-018
<b>Time Point<sup>a</sup></b>	21.5 months	21 months	9 months	10 Months	9 months
<b>Analyte</b>	ppm (µg/mL)				
(b) (4)					
[Redacted Content]					
<sup>a</sup> All samples stored inverted at 25°C/60%RH.					

**2.7 Proposed Clinical Population and Dosing Regimen**

The proposed indication for oliceridine is for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted.

Dosing regimen has been revised several times during the NDA review course. The current proposed dosing regimen is stated as followed:

Titration Phase

The initial dose of [BRANDNAME] 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 [BRANDNAME].

### Maintenance Phase

Maintenance of analgesia is generally achieved with [BRANDNAME] 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.

*Reviewer's note: In order to account for the wide range of potential clinical exposures, the Applicant originally proposed a maximum recommended human dose (MRHD) of 100 mg/day. The estimated total daily exposure at this MRHD is (b) (4) ng\*h/mL (assuming a mean CL of (b) (4) L/h) which was initially utilized to calculate the safety margins generated in nonclinical safety studies. In response to comments from the Agency at the mid-cycle review meeting, the MRHD of oliceridine was lowered to 40 mg/day and nonclinical safety margins were recalculated using a projected total daily exposure of (b) (4) ng\*h/mL. The Clinical Pharmacology team has concurred with the PK projection for MRHD.*

## **2.8 Regulatory Background**

### IND 113537

- New IND: December 23, 2013
- Fast Track designation: December 2, 2015
- EOP2: March 29, 2016
- preNDA: May 25, 2017

### NDA 210730

- New NDA: November 2, 2017

## **3 Studies Submitted**

### **3.1 Pivotal Studies Reviewed**

#### Safety Pharmacology

- TRV130: Effect on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells
- TRV130A: Intravenous Infusion Cardiovascular Safety Pharmacology Evaluation in Male Telemetry-Instrumented Conscious Nonhuman Primates
- TRV130: Intravenous Infusion Respiratory Safety Pharmacology Study in Male Rats
- TRV130: Intravenous Infusion Central Nervous System Safety Pharmacology Study in Male Rats

#### Repeat-dose toxicity

- Intravenous Infusion Range-Finding (Phase 1) and 7-Day Continuous Infusion Toxicity and

Toxicokinetics Study (Phase 2) with TRV110130 in Rats TRV130A: 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Study in Rats

- 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Study of TRV130 HCl and TRV130 Fumarate in Rats
- TRV130 (Oliceridine): 14-Day Continuous IV Infusion Toxicity and Toxicokinetic Study in Rats with a 28-Day Recovery Phase
- TRV130 (Oliceridine): 4-Week Continuous IV Infusion Toxicity and Toxicokinetic Study in Rats
- TRV130A: 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Study in Cynomolgus Monkeys
- Oliceridine (TRV130): 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Bridging Study in Rats

### Genotoxicity

- TRV130A: Reverse mutation study in four histidine-requiring strains of *Salmonella typhimurium* and one tryptophan-requiring strain of *Escherichia coli*
- TRV130 Fumarate: Bacterial Reverse Mutation Study
- TRV130A: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes
- TRV130 Fumarate and TRV130 HCl: Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes
- TRV130A: Intravenous 24-Hour Continuous Infusion Micronucleus Study Using Bone Marrow from Rats
- TRV 130A: Detection of DNA damage in the liver and blood of treated rats using the Comet assay
- TRV0109662 (b) (4): Bacterial Reverse Mutation Assay
- (b) (4): Bacterial Reverse Mutation Assay
- TRV130- (b) (4): Bacterial Reverse Mutation Assay
- TRV130 (b) (4) impurity: Bacterial Reverse Mutation Assay
- TRV0109662 (b) (4): In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)
- (b) (4): Bacterial Reverse Mutation Assay
- TRV130- (b) (4): In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)
- TRV130 (b) (4) impurity: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)
- TRV0306954 (M22): Bacterial Reverse Mutation Assay in 6-Well Plates
- TRV0306954 (M22): In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)

### Reproductive and developmental toxicity

- A Continuous Infusion Study of the Effects of TRV130 on Fertility in Male Sprague-Dawley Rats
- A Continuous Infusion Study of the Effects of TRV130 on Fertility and Early Embryonic Development in Female Sprague-Dawley Rats
- A Continuous Infusion Embryo/Fetal Development-Study of TRV130 in Sprague-Dawley Rats
- A Continuous Infusion Embryo/Fetal Development Study of TRV130 in New Zealand White Rabbits

- A Continuous Infusion Study of the Effects of TRV130 (Oliceridine) on Pre- and Postnatal Development, Including Maternal Function in Rats

#### Special toxicity

- TRV130: Evaluation of the Potential to Cause Hemolysis in Human Blood
- TRV130: Evaluation of the Potential to Cause Flocculation in Human Plasma and Serum

### **3.2 Pivotal Studies Not Reviewed**

Dose range-finding studies were not formally reviewed but were essential to dose selection in definitive studies. All the pivotal studies have been reviewed either in the previous reviews of IND 113537 or in the current NDA review.

### **3.3 Previous Reviews Referenced**

IND 113537 reviewed by Dr. Armaghan Emami

## **4 Pharmacology of Oliceridine**

### **4.1 Primary Pharmacology**

#### **4.1.1 *In vitro* Pharmacology**

In vitro, TRV130 is an agonist of G protein coupling with higher MOR (mu-opioid receptor) potency than morphine. In contrast to morphine, fentanyl, and hydromorphone, TRV130 is markedly less effective in stimulating recruitment of  $\beta$ -arrestin2 to the MOR. These findings define TRV130 as a G protein-biased ligand, a novel class of GPCR ligands that stimulate only a subset of the normal repertoire of receptor coupling mechanisms. The differentiated pharmacology of TRV130 is conserved across human, rat, and mouse orthologues of the MOR. TRV130 elicits less receptor phosphorylation and receptor internalization than morphine, consistent with its reduced engagement of  $\beta$ -arrestin2. The primary in vitro pharmacology is summarized as following:

- Potent mu-opioid agonism in a receptor functional assay measuring G protein coupling: The potency, efficacy, and bias of TRV130 were tested in human embryonic kidney (HEK-293) cells expressing recombinant human, mouse, or rat MOR. At the human receptor, TRV130 exhibits efficacy comparable to morphine and hydromorphone for inhibition of forskolin-stimulated cAMP accumulation, a measure of G protein coupling. TRV130 has G protein coupling efficacy similar to morphine and markedly higher than the partial agonist buprenorphine.

TRV130 has an  $EC_{50}$  of 8 nM at human MOR, which is approximately 6-fold more potent than morphine ( $EC_{50} = 50$  nM).

Table 8. Summary of Potency and Efficacy at the Human MOR

Compound	cAMP					β-arrestin2				
	EC <sub>50</sub> (nM)	pEC <sub>50</sub>	SD	Span <sup>1</sup>	N	EC <sub>50</sub> (nM)	pEC <sub>50</sub>	SD	Span <sup>1</sup>	N
TRV130	7.9	8.1	0.04	80	23		N.Q.			22
fentanyl	6.3	8.2	0.05	112	15	251	6.6	0.03	478	15
morphine	50.1	7.3	0.03	100	78	501	6.3	0.1	99	75
hydromorphone	15.8	7.8	0.03	100	46	126	6.9	0.11	89	49
buprenorphine	2.0	8.7	0.04	52	50		N.Q.			54

<sup>1</sup> span represents percent maximal activation compared to a full reference agonist.  
 N.Q.: not quantifiable

Figure 1 Inhibition of cAMP generation by human MOR in response to TRV130, morphine, or hydromorphone

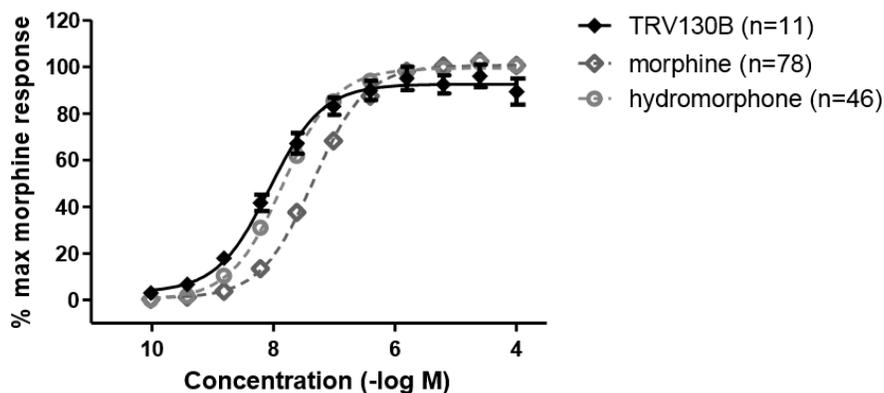
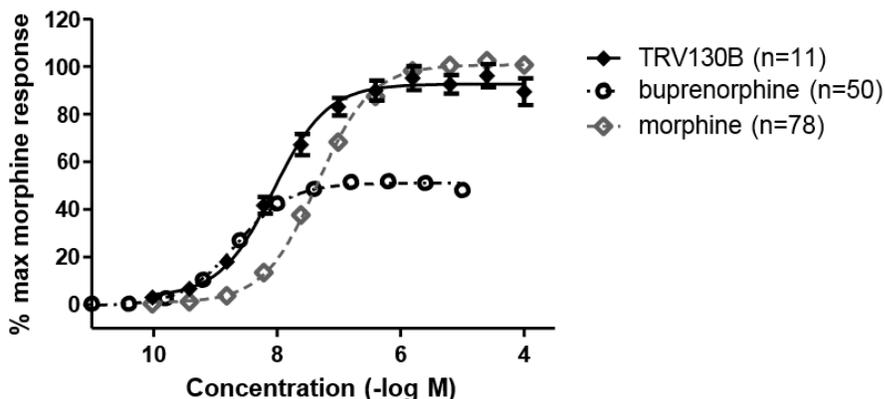


Figure 2: Inhibition of cAMP generation by human MOR in response to TRV130, morphine, or buprenorphine



- In vitro binding at mu and kappa opioid receptors:**

TRV130 radio-ligand binding studies reveal affinities consistent with the high potency of G protein coupling of TRV130, with  $K_i$  values of 1, 18, and 6 nM at the mouse, rat, and human MOR (see the table below). Kinetic binding studies revealed a rapid off-rate of TRV130 from the receptor with  $k_{off} = 0.37 \text{ min}^{-1}$ , similar to  $k_{off}$  values for morphine ( $0.54 \text{ min}^{-1}$ ) and fentanyl ( $0.22 \text{ min}^{-1}$ ). Consistent with this finding, TRV130 acts competitively with respect to naloxone, as measured by inhibition of forskolin-stimulated cAMP accumulation.

Table 9. Binding Affinities ( $K_{i \text{ high}}$  and  $K_{i \text{ low}}$ ) for TRV130 and Reference Compounds at Human, Mouse, and Rat MOR

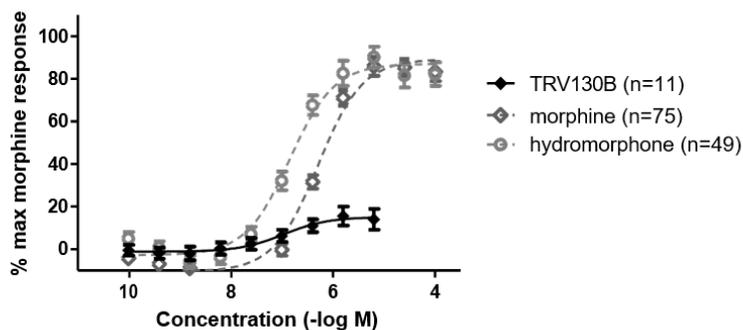
Compound	<b>human MOR (<math>K_i</math> nM)</b>					
	$K_{i \text{ high}}$	SEM	n	$K_{i \text{ low}}$	SEM	n
TRV130	6.0	1.7	4	551	263	4
morphine	6.3	1.8	3	885	254	3
fentanyl	5.7	2.1	3	1000	0.0	3
naloxone	7.6	1.4	3	-	-	-
Compound	<b>mouse MOR (<math>K_i</math> nM)</b>					
	$K_{i \text{ high}}$	SEM	n	$K_{i \text{ low}}$	SEM	n
TRV130	1.0	0.3	5	39	21	5
morphine	7.2	2.9	4	412	59	4
fentanyl	2.3	1.3	3	152	51	3
naloxone	16.7	2.6	5	-	-	-
Compound	<b>rat MOR (<math>K_i</math> nM)</b>					
	$K_{i \text{ high}}$	SEM	n	$K_{i \text{ low}}$	SEM	n
TRV130	18	3.7	3	203	26	3
morphine	20	0.0	2	897	102	2
fentanyl	1.3	-	1	631	-	1
naloxone	7.6	1.4	3	-	-	-

TRV130 has weak affinity for mouse and human kappa opioid receptor (KOR) with  $K_i$  values of 10 and 15.8  $\mu\text{M}$  respectively (see the table below). Results of this study demonstrate selective high affinity binding of the MOR biased agonist ligand TRV130.

Table 10: TRV130 Binding Affinities ( $K_{i\text{high}}$  and  $K_{i\text{low}}$ ) at the Human and Mouse  $\kappa$ -Opioid Receptor (KOR)

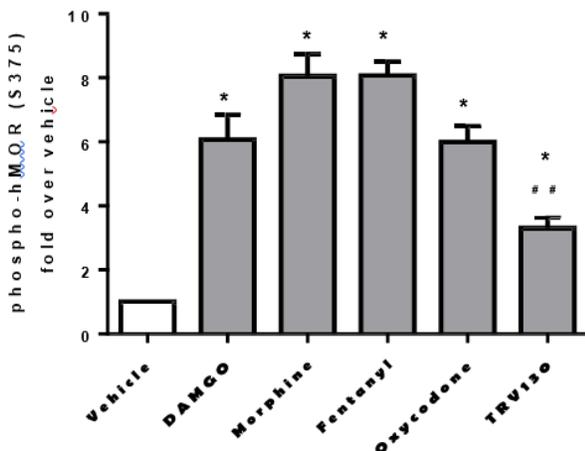
Compound	human KOR ( $K_i$ nM)					
	$K_{i\text{high}}$	SEM	n	$K_{i\text{low}}$	SEM	n
TRV130	15849	0.0	2	-	-	-
morphine	408	92	2	5145	1164	2
fentanyl	159	156	2	10000	0.0	2
naloxone	28	3.2	2	-	-	-
Compound	mouse KOR ( $K_i$ nM)					
	$K_{i\text{high}}$	SEM	n	$K_{i\text{low}}$	SEM	n
TRV130	10000	0.0	2	-	-	-
morphine	750	249	2	4100	924	2
fentanyl	871	713	2	6300	0.0	2
naloxone	25	0.0	2	-	-	-

- Reduced recruitment of  $\beta$ -arrestin2, a characterization as a biased agonist:  
The findings listed below are consistent with reduced recruitment of  $\beta$ -arrestin2 by TRV130 compared to morphine and fentanyl, and support the characterization of TRV130 as a biased ligand with selective effects on cellular responses subsequent to binding the MOR.
  - Despite its robust efficacy for G protein coupling, TRV130 stimulates significantly less recruitment of  $\beta$ -arrestin2 to the MOR than do morphine or hydromorphone.

Figure 3: Stimulation of  $\beta$ -arrestin2-recruitment to human MOR in response to TRV130, morphine, or hydromorphone

- TRV130 was tested for its ability to stimulate phosphorylation of the human MOR. This was evaluated using Western blotting with an antibody recognizing a specific phosphoserine residue in the MOR carboxy-terminal tail (Ser375). This phosphorylation site is specific for  $\beta$ -arrestin recruitment and reduced phosphorylation is consistent with lack of  $\beta$ -arrestin2 recruitment to the receptor. Compared to morphine and fentanyl, TRV130 elicited substantially less receptor phosphorylation at this site.

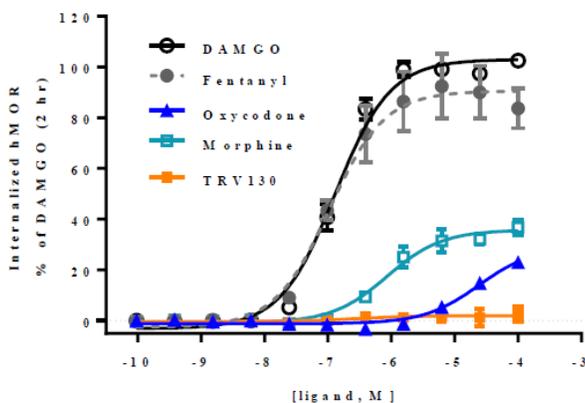
**Figure 6: MOR phosphorylation by TRV130 and reference compounds**



\*Significantly different from vehicle.  
## Significantly different from DAMGO, morphine, fentanyl and oxycodone.

- TRV130 was tested for its ability to stimulate internalization of the human MOR. This was evaluated by measuring colocalization of MOR and an endosomal protein, which only occurs when the receptor is internalized from the cell surface. Compared to morphine and fentanyl, which caused pronounced internalization, TRV130 was unable to stimulate any detectable receptor internalization.

**Figure 7: Representative receptor internalization curves for TRV130 and reference compounds at the human MOR**



### 4.1.2 In Vivo Pharmacology

The Applicant tested TRV130 in animal models for pain, constipation, respiratory depression and motoric dysfunction. In these *in vivo* animal assays, TRV130 showed potent analgesic effects with reduced constipation and respiratory depression when compared to morphine at equivalent analgesic dose. This Reviewer summarized the data in the following table:

Table 11: Summary of Analgesic, Constipating and Respiratory Depressing Effects of TRV130 in Comparison to Morphine

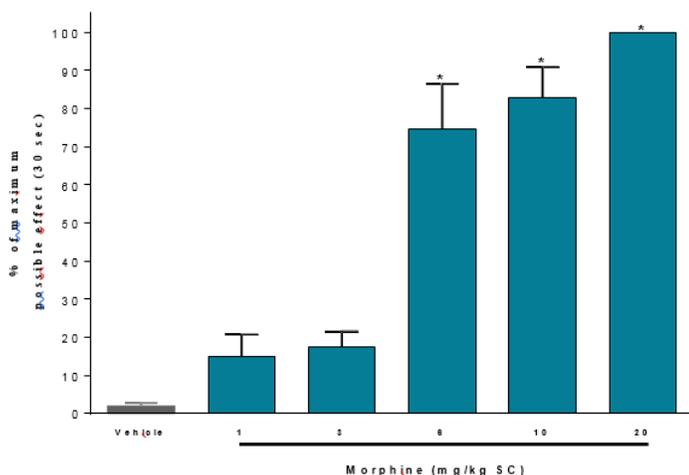
Test Article	Species	Analgesic Effect ED <sub>50</sub> (mg/kg) Hot plate assay	Constipating Effect			Constipating/Analgesic			Respiratory Depression/Analgesia	
			ED <sub>50</sub> (mg/kg) Glass bead assay	ED <sub>50</sub> (mg/kg) Fecal boli assay	ED <sub>50</sub> (mg/kg) Charcoal meal transit assay	ED <sub>50</sub> glass bead/ ED <sub>50</sub> hot plate	ED <sub>50</sub> fecal boli/ ED <sub>50</sub> hot plate	ED <sub>50</sub> charcoal meal/ ED <sub>50</sub> hot plate	NOAEL (mg/kg) Blood gas assay	NOAEL/ ED <sub>50</sub> hot plate
TRV130	Mouse	0.88	1.7	2.4	0.33	2	5	0.5		
	Rat	0.32							1.2	3.75
Morphine	Mouse	4.9	4.3	2.2	0.65	0.9	0.4	0.1		
	Rat	3.2							3	0.9

### 4.1.2.1 In Vivo Mouse Studies

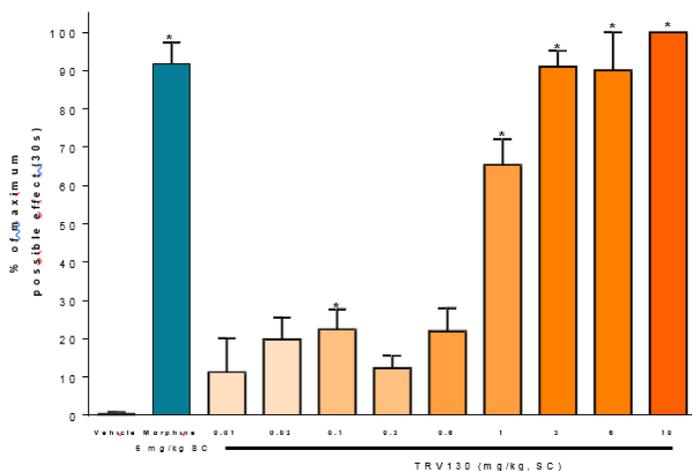
#### Analgesic Activity for TRV130 in the Mouse Hot Plate Assay (Study TRV130-09)

In a mouse hot plate assay, TRV130 was administered subcutaneously (SC) at various doses. A cutoff time of 30 seconds was used so that the paws of the animal displaying analgesia were not damaged by the heat stimulus. The cutoff time was considered to be a 100% response to the thermal insult. TRV130 exerts maximal efficacy in the 56°C hot-plate anti-nociceptive test, a model of supraspinal pain processing, with an ED<sub>50</sub> of 0.88 mg/kg. The ED<sub>50</sub> for morphine is 4.9 mg/kg, indicating increased potency for TRV130 relative to morphine in this model. In a study testing the time course of analgesia, TRV130 reaches maximal efficacy faster than morphine after SC injection, with a comparable duration of action to morphine.

Figure 11: Dose-dependent analgesic effect produced by morphine in the mouse hot plate assay

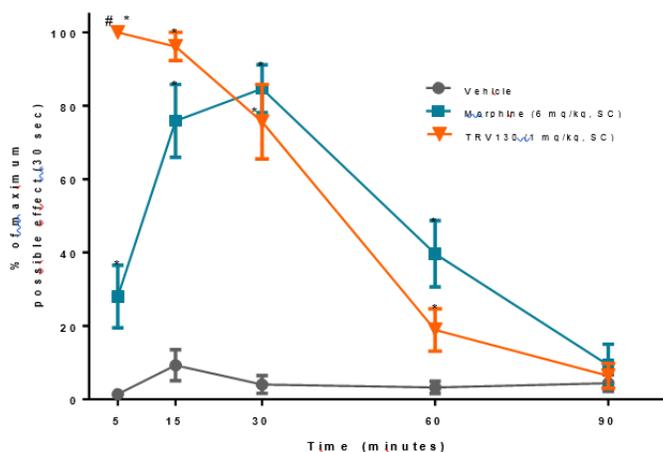


**Figure 12: Dose-dependent analgesic effect produced by TRV130 in the mouse hot plate assay**



Data shown are means with standard errors of 4-14 animals per group.  
\*p<0.05 compared to vehicle-treated mice.

**Figure 13: Time course of analgesia in the mouse hot plate assay after morphine and TRV130**

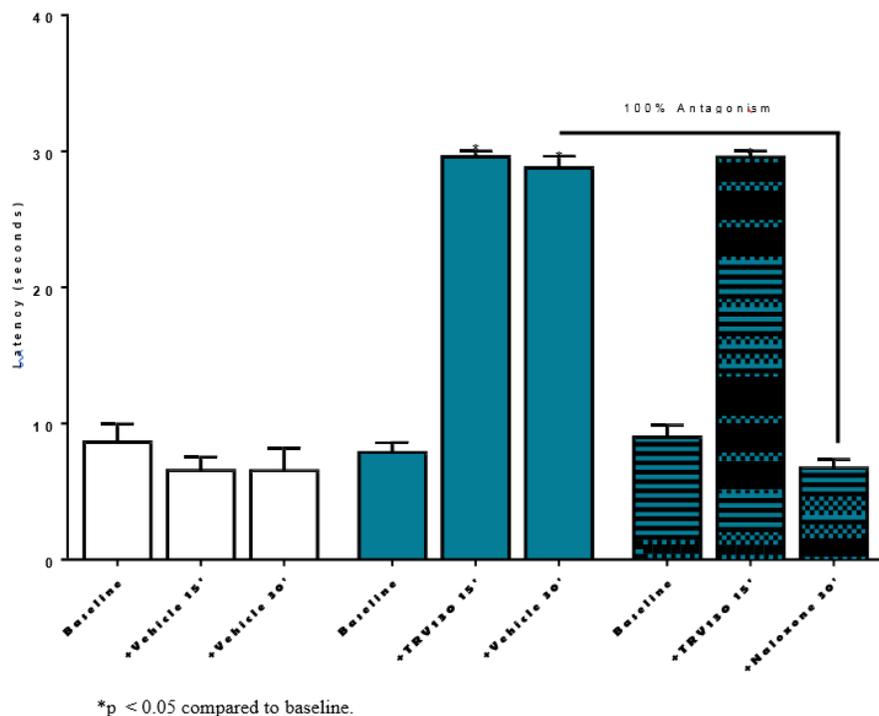


Data are mean +/- standard error for 8 animals per group.  
\*p < 0.05 compared to vehicle-treated mice and #p < 0.05 compared to morphine-treated mice.

### ***Analgesic Activity for TRV130 Is Reversed by Naloxone in the Mouse Hot Plate Assay (Study TRV130-16)***

The analgesic efficacy of SC administration of TRV130 is rapidly and completely reversed by SC naloxone administration, consistent with a rapid off-rate from the receptor (Studies TRV130-16 and TRV130-18) and competitive antagonism demonstrated from the in vitro study (Study TRV130-05). This indicates that like morphine, fentanyl, and other opioids, all pharmacological effects of TRV130 mediated by the MOR can be rapidly reversed by naloxone.

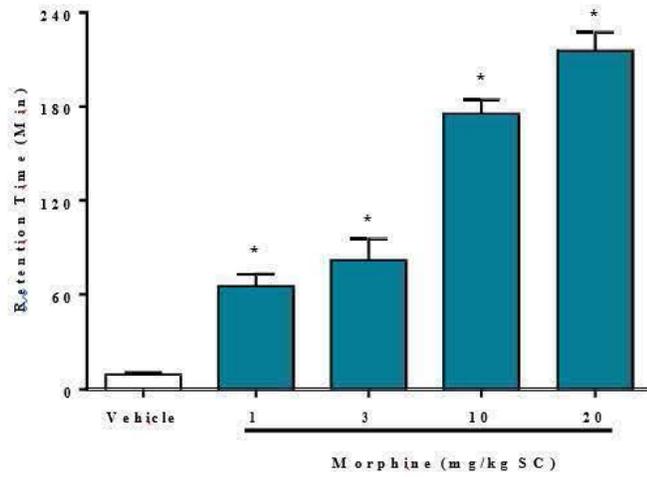
**Figure 14: Analgesic effect produced by TRV130 is antagonized by naloxone**



**Reduced Inhibition of Colonic Motility in the Mouse Glass Bead Assay at Equianalgesic Doses of Morphine (Study TRV130-13)**

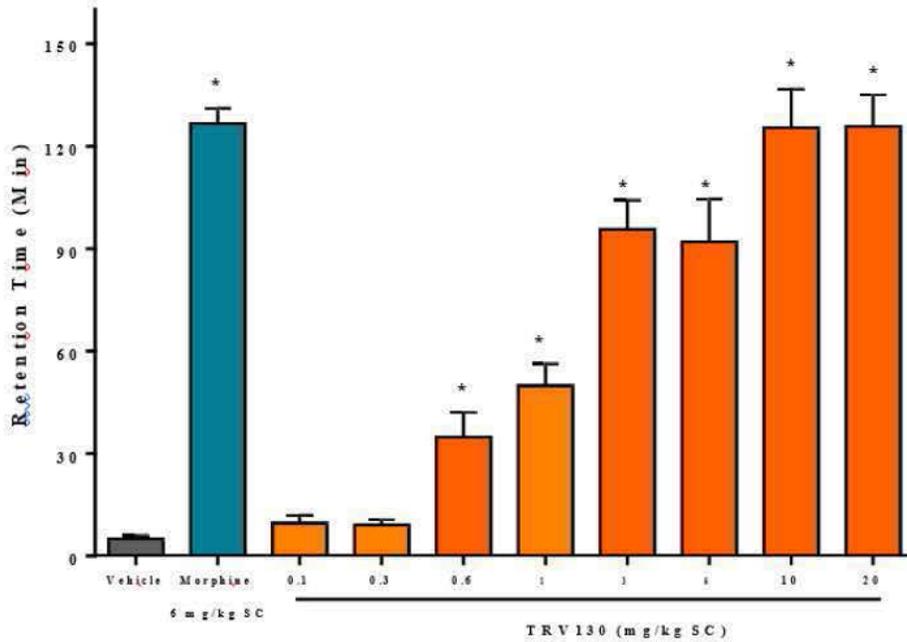
TRV130 was tested for its potential to cause constipation, a common and problematic effect of unbiased opioids. In the mouse glass bead colonic motility, TRV130, morphine, or vehicle was administered SC using a volume of 1 mL/100 grams of bodyweight at 20 minutes before the insertion of a single 2 mm glass bead 2 cm into the distal colon of each mouse. The assay assesses an effect on lower gastrointestinal motility. The latency in minutes for a mouse to expel the bead that was placed in the colon was determined. The ED<sub>50</sub> values were determined to be 1.7 mg/kg for TRV130 (95% confidence interval 0.78-3.56) and 4.3 mg/kg for morphine (95% confidence interval 1.2-12). The maximal effect on glass bead retention time produced by TRV130 was approximately 50% that of morphine. As described above, TRV130 is approximately 5.5-fold more potent than morphine in the mouse hot plate test of analgesia, with ED<sub>50</sub> values of 0.88 mg/kg SC vs. 4.9 mg/kg SC, respectively (Study TRV130-09). In contrast, TRV130 displays similar potency to morphine in the glass bead colonic motility assay with a lower magnitude of effect. The Applicant concluded these data suggest that TRV130 may exert less constipation at equianalgesic doses when compared to morphine and show that there is an improved therapeutic window of analgesia to gastrointestinal dysfunction for TRV130 vs morphine.

**Figure 15: Dose-dependent effect of morphine on glass bead retention time in the mouse**



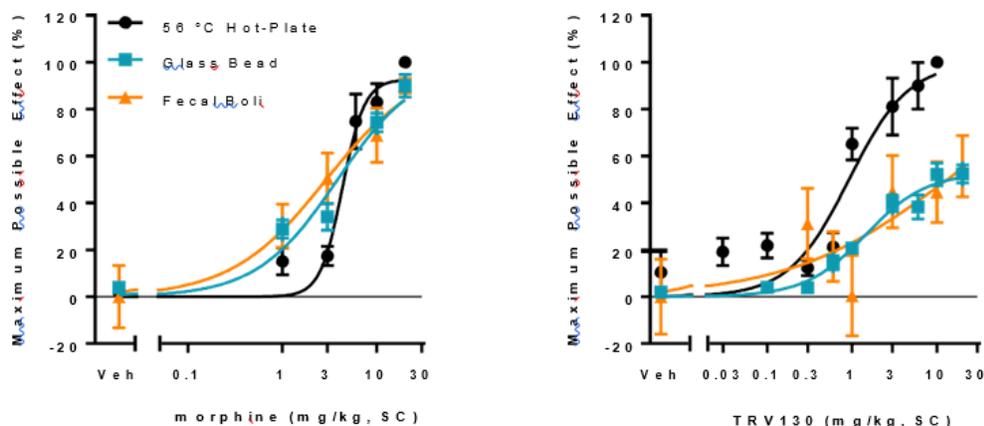
\*p < 0.05 compared to vehicle.

**Figure 16: Dose-dependent effect of TRV130 on glass bead retention in the mouse**



\*p < 0.05 compared to vehicle.

**Figure 10: TRV130 has an improved therapeutic window for analgesia with respect to gastrointestinal dysfunction in mice compared to morphine**

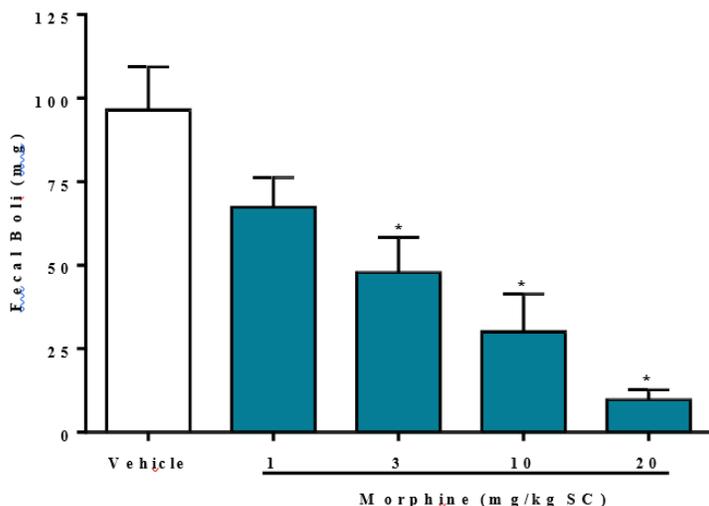


Maximum possible effect = 30 second latency in hot plate, 240 minute retention in glass bead assay, and zero fecal boli production, all compared to values in vehicle-treated animals (Study Nos. TRV130-09, TRV130-13, and TRV130-14).

### ***Reduced Constipation in the Mouse Fecal Boli Assay at Equianalgesic Doses of Morphine (Study TRV130-14)***

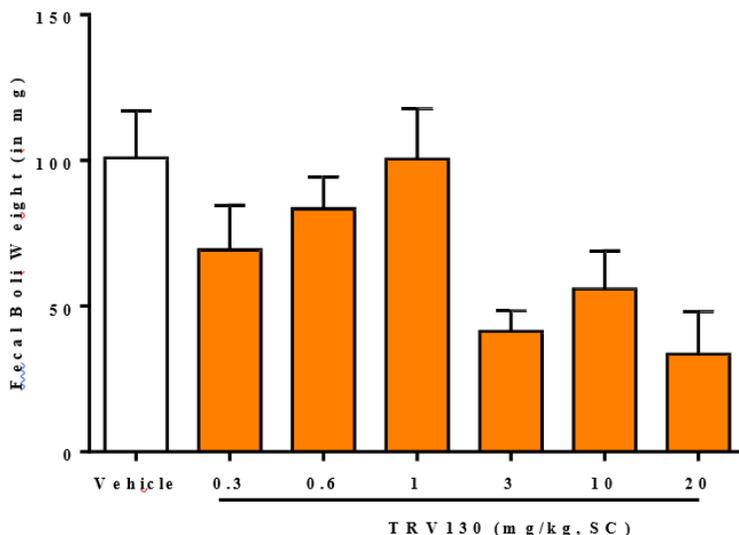
The purpose of this study was to determine the constipating effects of TRV130 using the mouse fecal boli assay. The weight of fecal boli produced over a 4-hour period was determined following administration of morphine or TRV130. This assay is used to determine the effect of compounds on whole gut transit. In the study ED<sub>50</sub> values were determined to be 2.4 mg/kg for TRV130 (95% confidence interval 0.6-10) and 2.2 mg/kg for morphine (95% confidence interval 0.8-5.9) as shown in the graphs below. As described above, TRV130 analgesic effect is approximately 5.5-fold more potent than morphine in the mouse hot plate assay (Study TRV130-09). Results of this study demonstrate that TRV130 has lower effects than morphine on gastrointestinal dysfunction in the mouse fecal boli assay at equivalent analgesic doses.

**Figure 17: Effect of morphine in the fecal boli assay**



All data were expressed as mean ± SEM. A one-way analysis of variance, followed by Tukey-Kramer post hoc test was used for analysis of data, and \*P < 0.05 was considered statistically significant compared to vehicle.

**Figure 18: Effect of TRV130 in the fecal boli assay**



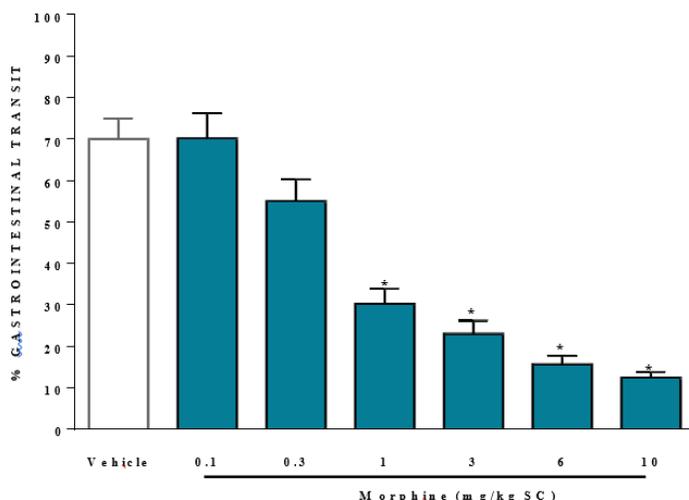
All data were expressed as mean ± SEM. A one-way analysis of variance, followed by Tukey-Kramer post hoc test was used for analysis of data.

***Inhibition of Colonic Motility for TRV130 in the Mouse Charcoal Meal Transit Assay (Study TRV130-15)***

TRV130 was also tested for its effects on upper gastrointestinal transit using the charcoal meal test. The length of the intestine and the distance travelled by the charcoal meal was measured in the study. In the study ED<sub>50</sub> values were determined to be 0.33 mg/kg for TRV130 (95%

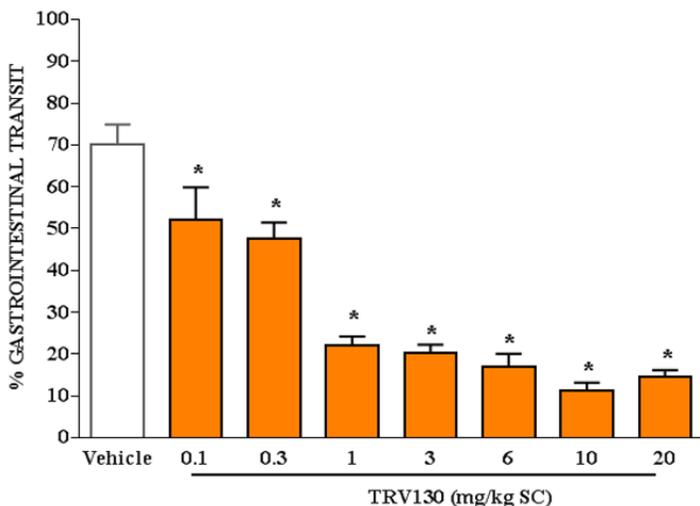
confidence interval 0.2-0.56) and 0.65 mg/kg for morphine (95% confidence interval 0.45-0.94). Thus, TRV130 was approximately 2-fold more potent than morphine in this assay. Given that TRV130 analgesic effect is approximately 5.5-fold more potent than morphine in the mouse hot plate assay and the lack of effect of TRV130 on gastrointestinal transit (GIT) at the sub-analgesic dose of 0.3 mg/kg SC, compared to the marked effect on GIT with a similar sub-analgesic dose of 1 mg/kg SC of morphine, the Applicant concluded this study indicate that TRV130 may induce less constipation than morphine at equianalgesic doses with an improved therapeutic window of analgesia to gastrointestinal dysfunction for TRV130 vs morphine.

**Figure 19: Morphine reduced gastrointestinal transit in a dose-dependent manner**



\*p < 0.05 compared to vehicle.

**Figure 20: TRV130 reduced gastrointestinal transit in a dose-dependent manner**



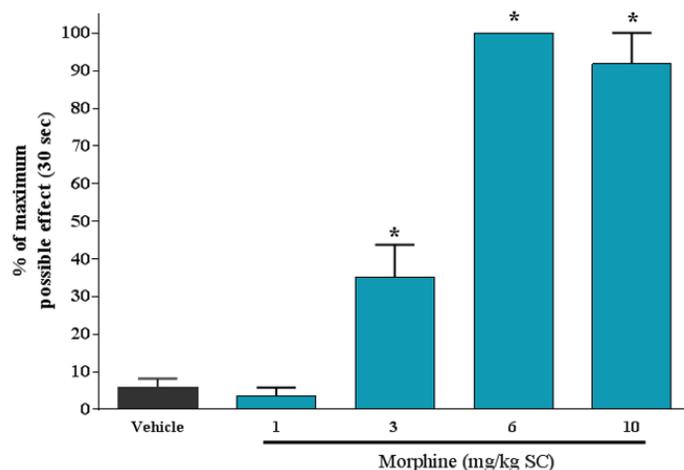
\*p < 0.05 compared to vehicle.

### 4.1.2.2 In Vivo Rat Studies

#### Antinociceptive Activity for TRV130 in the Rat Pain Models

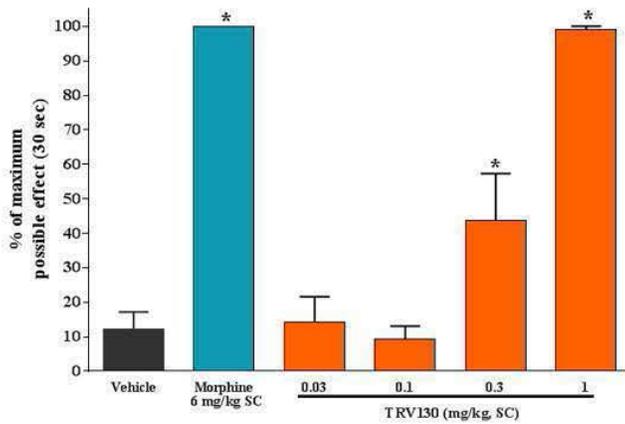
Consistent with findings in the mouse, TRV130 was fully analgesic and more potent than morphine in the 52°C hot-plate test 30 minutes after subcutaneous injection (Figure 22 and Figure 23), with ED<sub>50</sub> values of 0.32 and 3.2 mg/kg, respectively (Study TRV130-10). This increased potency was confirmed in the rat tail-flick test, a spinal pain reflex model (Figure 24 and Figure 25), with maximal efficacy and an ED<sub>50</sub> of 0.22 mg/kg 30 minutes after subcutaneous injection vs. ED<sub>50</sub> of 1.0 mg/kg for morphine (Study TRV130-11). TRV130 was also tested after intravenous administration to rats in the hindpaw incisional pain model, a model of both nociceptive and inflammatory pain. Twenty-four hours after surgery to mimic post-operative pain, TRV130 was administered IV (Study TRV130-12). Thirty minutes after injection, TRV130 was more potent than morphine and at least as efficacious as morphine in this model (Figure 26). The findings suggest that TRV130 has antinociceptive activity.

Figure 22: Analgesic effect produced by morphine in the rat hot plate assay



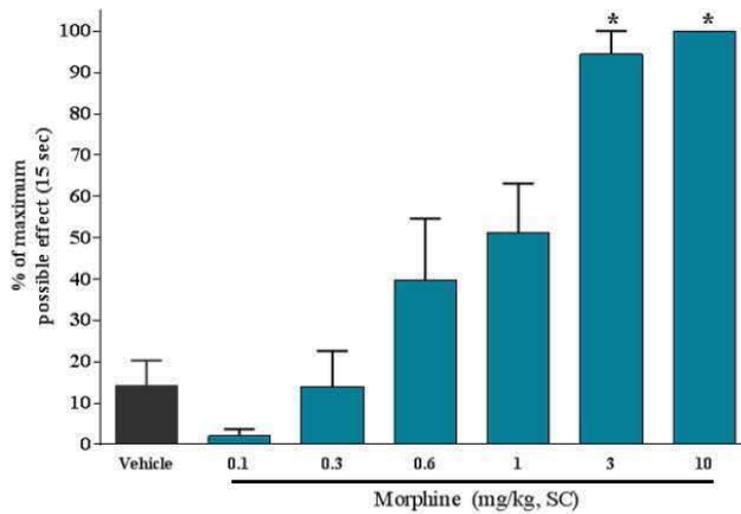
\*p < 0.05 compared to vehicle.

**Figure 23: Analgesic effect produced by morphine and TRV130 in the rat hot plate assay**



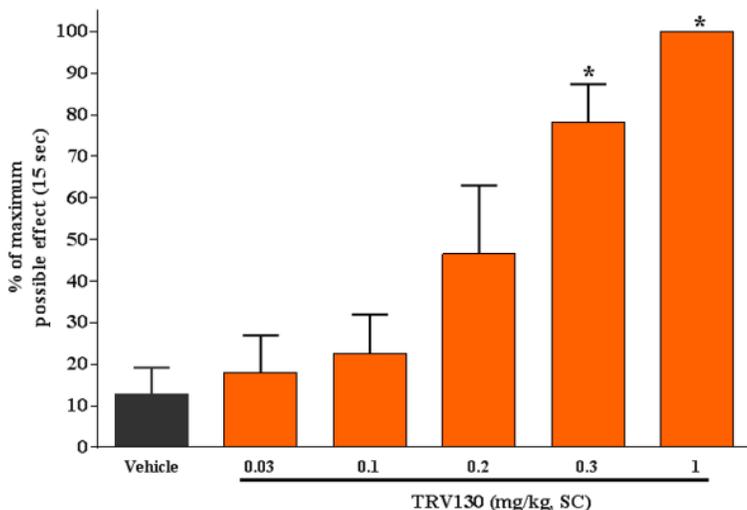
\*p < 0.05 compared to vehicle.

**Figure 24: Analgesic activity for morphine in the rat tail flick assay**



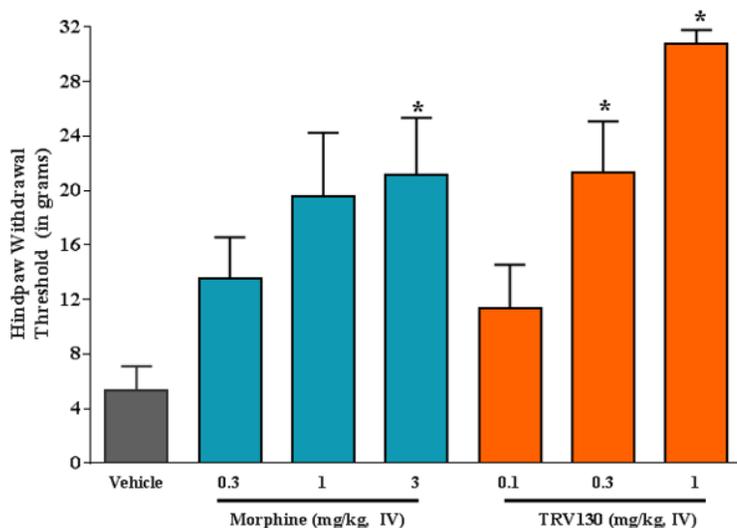
\*p < 0.05 compared to vehicle.

**Figure 25: Analgesic activity for TRV130 in the rat tail flick assay**



\*p < 0.05 compared to vehicle.

**Figure 26: Intravenous morphine and TRV130 produced dose-dependent anti-allodynic effect in hindpaw incised rats**



\*p < 0.05 compared to vehicle.

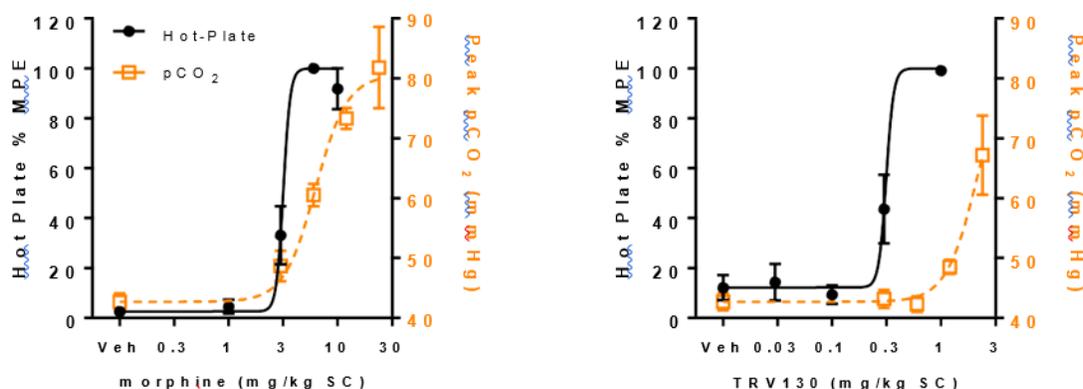
**Reduced Respiratory Depression for TRV130 in Blood Gas Analysis at Equianalgesic Doses of Morphine**

TRV130 was also tested for its ability to cause respiratory depression. TRV130 and morphine were administered to rats at doses matched to their respective potencies in the hot-plate anti-nociception test. The hot-plate model was chosen as the calibrating reference data because like respiratory depression and sedation, it involves supraspinal signal processing. TRV130 and morphine were administered subcutaneously, again to match the hot-plate anti-nociceptive

test, and pCO<sub>2</sub> (along with pO<sub>2</sub> and pH) was measured from arterial blood at 5, 30, 120, and 240 minutes after dosing (Studies 0406RT44.002 and 0406RT44.003). Morphine caused a substantial increase in pCO<sub>2</sub> (greater than 50 mmHg, compared to 35-40 mmHg at baseline and in vehicle-treated animals) at doses 4-fold and 8-fold over the hot-plate ED<sub>50</sub> (12 and 24 mg/kg, vs. 3.2 mg/kg ED<sub>50</sub> in the hot-plate test). In contrast, TRV130 did not cause this severe level of respiratory depression, even at 8-fold over its hot-plate ED<sub>50</sub> (2.4 mg/kg vs 0.32 mg/kg ED<sub>50</sub> in the hot-plate test). These findings indicate that in rats, TRV130 has an increased therapeutic window for analgesia vs. respiratory depression (Figure 21). These studies also revealed that morphine treatment induced marked decreased activity and slack body posture. These findings were minimal for TRV130. The Applicant concluded that the results of the studies suggest an improved therapeutic window for analgesia vs. sedation.

*Reviewer's note: Reduced activity could be a result of sedative effect. However, without EEG measurements, it is hard to draw a definitive conclusion that reduced activity is related to sedation.*

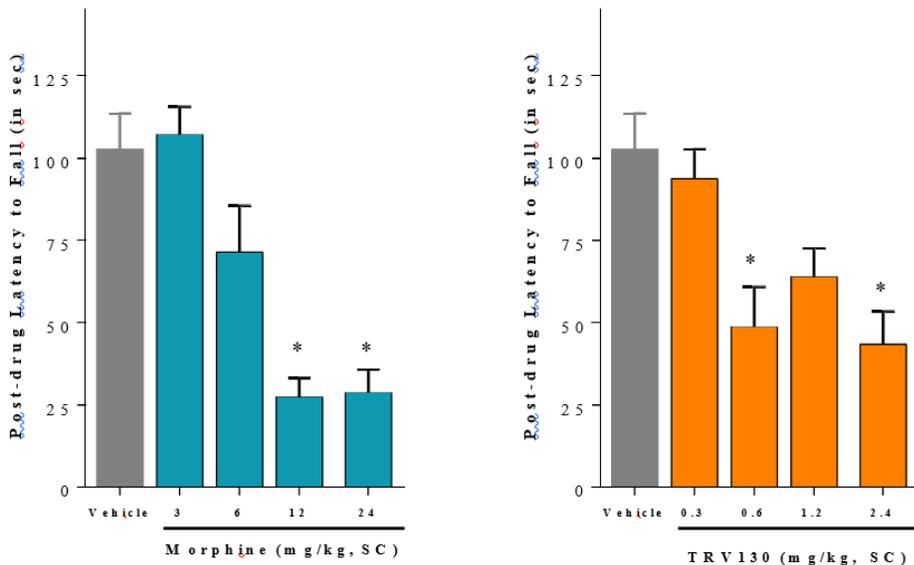
**Figure 21: TRV130 has an improved therapeutic window for analgesia with respect to respiratory depression in rats compared to morphine**



Maximum possible effect (MPE) for each dose (30 second latency in hot plate) is plotted against the left Y axis. In orange, the peak pCO<sub>2</sub> measurements for various doses from the experiment in (A) are plotted against the right Y axis to compare the analgesic and respiratory effects of these two compounds. Data are mean ± S.E. with n = 6 animals per group. (Study Nos. TRV130-10 and 0406RT44.003).

### Assessment of Neurobehavioral Effects of TRV130 in Rotarod Assay

The Applicant tested TRV130 in the rotarod assay, an assay traditionally used to detect the neurobehavioral effects of centrally acting MOR agonists. TRV130 and morphine had comparable effects on latency to fall at doses above 0.3 mg/kg and 3 mg/kg, respectively. Morphine resulted in minimum average latency of 27 seconds, whereas TRV130 resulted in minimum average latency of 43 seconds; although these differences are not statistically significant, they indicate TRV130 may have less severe effects. Results of this study demonstrate that TRV130 has neurobehavioral effects similar to, and potentially less severe, than morphine.

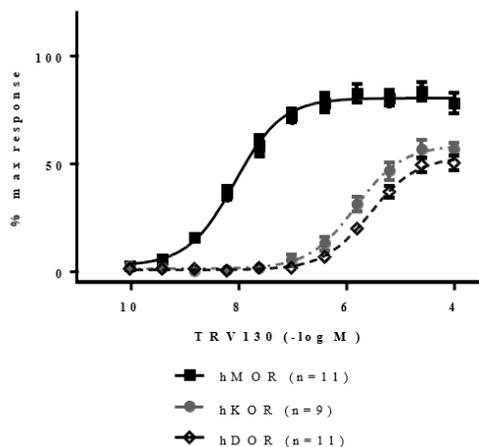


\*p < 0.05 compared to vehicle.

## 4.2 Secondary Pharmacology

TRV130 stimulates G protein activation as measured by inhibition of forskolin stimulated cAMP accumulation with an EC<sub>50</sub> at the human MOR of 8.0 nM (Study TRV130-02). TRV130 demonstrated agonist efficacy at KOR and DOR, with EC<sub>50</sub> values of 1.6 mcM and 3 mcM, respectively (Study TRV130-07). Morphine was more potent in the same assays (EC<sub>50</sub> values of 126 and 500 nM, respectively). In these assays morphine is 2.5- and 10-fold selective for MOR signaling over KOR and DOR signaling; in contrast TRV130 is more than 200-fold selective for MOR-signaling over KOR or DOR signaling.

Figure 28: Human MOR, human KOR and human DOR concentration-dependent responses to TRV130 in the cAMP G protein assay



In addition, the functional potency of TRV130 was measured in cell-based assays of G protein coupling for the adrenergic  $\alpha_2A$ , dopamine D2Long, and NOP receptors (Study TRV130-06). TRV130 had no measurable agonist or antagonist effect on cells expressing recombinant adrenergic  $\alpha_2A$  or dopamine D2Long receptors. TRV130 is a partial agonist (span = 58% compared to reference ligand) with an  $EC_{50}$  of 400 nM at human opioid receptor-like/nociception (NOP) receptors. This potency is 50-fold weaker than TRV130 potency at the human MOR. The Applicant stated that this degree of selectivity suggests that the off-target effects on NOP are unlikely to be pharmacologically relevant following clinical doses of TRV130. In addition, TRV130 shows negligible activity (not quantifiable) for  $\beta$ -arrestin2 recruitment at human NOP.

**Table 10: Summary of potency and efficacy at opioid receptor-like/nociception (NOP/ORL-1), human dopamine D<sub>2Long</sub>, and human adrenergic  $\alpha_{2a}$  receptors**

Receptor	cAMP Agonist Mode					cAMP Antagonist Mode				
	$EC_{50}$ ( $\mu$ M)	p $EC_{50}$	STDEV (p $EC_{50}$ )	% max response	N	$IC_{50}$ ( $\mu$ M)	p $IC_{50}$	STDEV (p $IC_{50}$ )	% max inhibition	N
ORL-1/NOP	0.4	6.4	0.1	58	6	8.0	5.1	1.1	57	2
D <sub>2Long</sub>	>100 <sup>†</sup>	<4 <sup>†</sup>	-	0	3	>100 <sup>†</sup>	<4 <sup>†</sup>	-	30	2
$\alpha_{2a}$	>100 <sup>†</sup>	<4 <sup>†</sup>	-	0	2	>100 <sup>†</sup>	<4 <sup>†</sup>	-	36	2

$EC_{50}$  and  $IC_{50}$  ( $\mu$ M) values represent the geometric mean.  
<sup>†</sup> Mean potencies of activity and inhibition listed as <4 log value or >100  $\mu$ M indicate that the compound was not active up to that concentration.

Further, the selectivity of TRV130 was tested by assessing the ability of 10 mcM TRV130 to displace radio-ligand binding at 101 receptors, channels, and transporters, and to inhibit activity of 29 different enzymes (Study 797915). This concentration of TRV130 is more than 1,000-fold greater than the  $K_i$  and  $EC_{50}$  of TRV130 at the human MOR. Inhibition of binding or activity by 40% or more was considered a significant effect. All significant effects were quantified for potency with competition radio-ligand binding curves and apparent affinity ( $K_i$ ) determination. The apparent binding affinity ( $K_i$ ) of TRV130 for the following receptors was determined: the alpha2C adrenergic receptor (3 mcM), the serotonin receptor 5-HT1a (1.2 mcM), the D2Short and D3 dopamine receptors (6.7 and 3.4 mcM respectively), and the sigma receptor (1.1 mcM). These apparent affinities are more than 200-fold lower than the 6 nM  $K_i$  for TRV130 binding to the human MOR (Study TRV130-01).

### 4.3 Safety Pharmacology

Safety pharmacology studies were conducted to evaluate the effects of TRV130 on the cardiovascular, respiratory, and central nervous systems. TRV130 was administered by continuous intravenous infusion in the in vivo rodent safety pharmacology studies for approximately 6 hours which fully covered the documented time (approximately 4 hours) to reach steady state concentrations ( $C_{ss}$ ) in rats (Study 8242808). The time to  $C_{ss}$  in monkeys was also approximately 4 hours (Study 8242809); however, animals were dosed for 10 hours in the monkey cardiovascular telemetry study in order to provide an equal number of light and dark animal room timepoints for data collection.

### 4.3.1 Cardiovascular Safety Pharmacology

#### **Effects of TRV130 on Ion Channels Expressed in Mammalian Cells (Study 101110.USF)**

The objective of this non-GLP study was to determine the concentration-dependent effect of TRV130 on currents recorded from cell lines stably expressing either the hERG, hCav1.2 or hNav1.5 cardiac ion channel utilizing the QPatch automated patch clamp platform. hERG channels were expressed in HEK293 (human embryonic kidney) cells whereas hCav1.2 channels (along with human beta2 and alpha2delta subunits) and hNav1.5 channels were expressed in CHO-K1 (Chinese Hamster Ovary) cells. The TRV130 IC<sub>50</sub> values for hERG, hCav1.2 and hNav1.5 (tonic and phasic) current inhibition were 6.2 mcM, 39.6 mcM, 19.5 mcM and 9 mcM, respectively (see the table below).

Table 12: Summary of TRV130 Cardiac Ion Channel Currents in an Automated Patch Clamp System

Compound	Channel	IC <sub>50</sub> (mcM)	
TRV130	hERG	6.2	
	hCav1.2	39.6	
	hNav1.5	Tonic	19.5
		Phasic	9.0

#### **Determination of TRV130 Binding to the Human Recombinant hERG Potassium Channel (Study TRV130-03)**

The objective of this non-GLP study was to examine the characteristics of TRV130 binding to the hERG channel. A fluorescence polarization (FP) competition binding assay was performed using the Predictor™ hERG FP binding kit reagents. TRV130 inhibited the binding of a specific hERG tracer ligand with an apparent IC<sub>50</sub> = 14.5 ± 4 mcM. The potency of the reference hERG blocker E-4031 was consistent with literature values IC<sub>50</sub> = 0.04 ± 0.013 mcM (see the table below)

Table 13: Summary of inhibition for TRV130 Binding to Recombinant Human hERG Potassium Channel

Compound	IC <sub>50</sub> mcM	SEM	N
TRV130	14.5	4	7
E-4031	0.04	0.013	21

**TRV130: Effect on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (Study 110520.USF)**

The objective of this GLP study was to examine the in vitro effects of TRV130 on ion currents in voltage-clamped human embryonic kidney cells (HEK293) that stably express hERG. TRV130 inhibited hERG current by  $15.8 \pm 1.9\%$  (mean  $\pm$  SEM) at 0.3 mcM,  $36.3 \pm 2.7\%$  at 1 mcM,  $55.8 \pm 1.7\%$  at 3 mcM and  $77.5 \pm 1.6\%$  at 10 mcM versus  $1.0 \pm 0.6\%$  in controls (see the table below). The IC<sub>50</sub> for the inhibitory effect of TRV130 on hERG potassium current was 2.2 mcM.

**Table 14: GLP hERG assay IC<sub>50</sub> results using voltage-clamped HEK cells**

TRV130 Concentration ( $\mu$ M)	hERG Current Percent Inhibition (mean $\pm$ SEM <sup>a</sup> )
0.3	$15.8 \pm 1.9$
1	$36.3 \pm 2.7$
3	$55.8 \pm 1.7$
10	$77.5 \pm 1.6$
IC <sub>50</sub>	2.2 $\mu$ M

SEM = standard error of the mean.

<sup>a</sup> Mean of 3 cells per concentration.

The Applicant's justification of the finding:

To properly utilize the GLP hERG electrophysiology data for assessment of potential QT prolongation and TdP induction risk, the concentrations of TRV130 required to inhibit hERG current by 50 percent was compared to target receptor affinity/ functional potency or expected therapeutic (free/unbound) plasma concentration (ETPC) (see the table below) by the Applicant. Two methods were used. The first simply compares the measured IC<sub>50</sub> of TRV130 at hERG to the binding affinity of TRV130 for the hMOR. This shows a 367-fold difference between the two, well above the 100-fold selectivity considered a benchmark predicting low risk of hERG QT prolongation. The second method compares the measured hERG IC<sub>50</sub> to the predicted therapeutic protein-free plasma concentration of TRV130. This value was estimated to be 5 ng/mL (13 nM), which is the plasma exposure of 20 ng/mL TRV130 30 minutes after SC injection of 0.5 mg/kg TRV130 (Study CPB-P10-1311R01), corrected for 77% binding to human plasma proteins (Study 797914). The measured hERG IC<sub>50</sub> is 169-fold of this estimate of 13 nM. These concentration comparisons suggest a low potential for TRV130 to induce QT prolongation or TdP at therapeutically-effective doses.

**Table 15: Interpretation of hERG results based on literature guidances**

Literature References	Desired Result	Calculations	Result
(Kongsamut 2002)	hERG IC <sub>50</sub> /MOR K <sub>i</sub> = at least 100 to predict little effect on QT prolongation in humans	2.2 μM/0.006 μM	367
(Redfern 2003) (Webster 2002)	hERG IC <sub>50</sub> /ETPC = at least 30 to predict that it is unlikely that the molecule will have the potential for significant QT prolongation or TdP in the clinic	2.2 μM/0.013 μM	169

Data Sources: hERG IC<sub>50</sub> = 2.2 μM (Study No. 110520.USF); MOR K<sub>i</sub> = 0.006 μM (Study No. TRV130-01); ETPC = 0.013 μM, approximately 5 ng/mL in rats (Study No. CPB-P10-1311R01, Study No. 797914, Study No. TRV130-10).

ETPC: effective therapeutic plasma concentration (protein free); IC<sub>50</sub>: 50% inhibitory concentration; MOR K<sub>i</sub>: mu-opioid receptor binding affinity; QT: time measurement of the Q to T wave interval from the surface electrocardiogram; TdP: Torsade de Pointes, a polymorphic ventricular tachycardia associated with prolongation of the QT interval.

### Reviewer's assessment:

The calculation in the Applicant's table above is based upon plasma exposure to the free TRV 130, 13 nM (about 5 ng/mL) after SC administration of 0.5 mg/kg TRV 130 (Study CPB-P10-1311R01). This is much lower than the plasma exposure to the free TRV 130 after 3 mg IV infusion or estimated free C<sub>max</sub> at MRHD of 40 mg (see Table 14 below). Therefore, the test article may have weak inhibition of hERG at clinical doses.

Table 14. Reviewer's Interpretation of hERG Assay Results

PD or PK Parameters	PD or PK Values	Calculations	Result (Safety Margin)
hERG IC <sub>50</sub> :	2.2 mcM		
K <sub>i</sub> at MOR	6 nM	2.2 mcM/6 nM	367
C <sub>max</sub> after 3 mg Infusion (CP130-1008):	132.9 ng/mL (Total) 30.6 ng/mL (Unbound)* =79 nM	2.2 mcM/79 nM	27
Projected C <sub>max</sub> at MRHD of 40 mg/day	86 ng/mL (Total) 19.8 ng/mL (Unbound)* =51 nM	2.2 mcM/51 nM	43

\*Corrected for 77% binding to human plasma proteins (Study 797914).

### **Ex Vivo Effects of TRV130 on QT, QRS, T(p-e) and Arrhythmogenesis in the Rabbit Left Ventricular Wedge Preparation (Study LIMRRWMU04)**

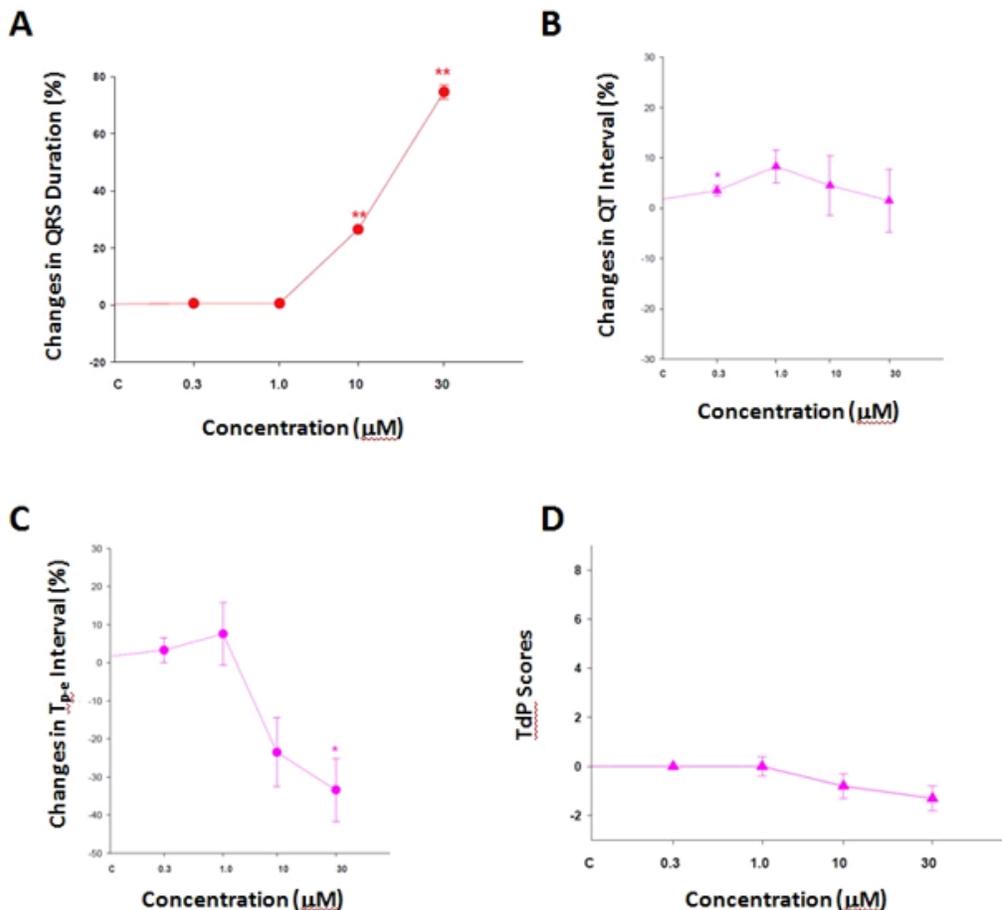
The objective of this non-GLP assay was to further evaluate the potential for TRV130 to cause QT prolongation or induce the lethal arrhythmia Torsade de Pointes (TdP) in vivo. Recent literature indicate that coincident inhibition of inward cardiac currents abrogates the effect of hERG inhibition and reduces torsadogenic potential of known hERG blockers (Fermini 2016; Kramer 2013). Therefore, additional in vitro or ex vivo assays that evaluate compound interactions at multiple channels/currents (such as NaV1.5 and CaV 1.2) provide a more rigorous, integrated risk assessment for QT prolongation and TdP than examination of effects on hERG alone.

The rabbit left ventricular wedge assay utilizes an ex vivo arterially-perfused, electrically-paced segment of the left ventricle that retains the structural, electrophysiological and ion channel expression found in vivo. The wedge assay has undergone blinded validation (using clinical drugs with known risk) to establish sensitivity, specificity and ability to accurately predict the relative risk of compounds by assessing their potential for QT prolongation and TdP (Chaudhary 2010; Liu 2006; Wu 2005; Yan 1996).

Following a one-hour period of stabilization, each of four wedge preparations was perfused with increasing concentrations (0.3 – 30 mcM) of TRV130 for a duration of 30 minutes. Continual recording of ventricular muscle contractility and a surface ECG was obtained over the entire time course of each experiment. If drug-induced prolongation of QT interval exceeded 30%, a floating microelectrode was placed on the endocardial surface to record transmembrane action potentials in order to determine the presence/absence of early afterdepolarizations (EADs).

TRV130 caused increased QRS duration at 10 mcM and 30 mcM (Figure 29a), indicating an inhibition of  $\text{Na}_{\text{V}1.5}$  conductance (in agreement with  $\text{IC}_{50}$  values for  $\text{hNa}_{\text{V}1.5}$  cited above). TRV130 at 0.3 mcM (2.3-fold of free unbound human  $\text{C}_{\text{max}}$  at MTDD) and 1.0 mcM caused a small (<10%) but statistically significant prolongation of QT interval, but there was no significant effect at higher concentrations (Figure 29b). TRV130 also caused a small (<7%) increase in the duration from the peak to the end of the T wave (Tp-e, a surrogate marker of transmural dispersion of repolarization) at 0.3 and 1 mcM, but decreased Tp-e interval at higher concentrations (Figure 29c). TRV130 did not cause any proarrhythmic events and had a composite torsadogenic risk score (TdP score) (Liu 2006) of zero or negative at all concentrations tested (Figure 29d). A TdP score above 2.5 in this model correlates with risk of Torsade de Pointes. The Applicant concluded that these results indicate that TRV130 is a weak hERG blocker with some multi-ion channel effects that could abrogate its inhibition of hERG current.

**Figure 29: Effect of TRV130 on cardiac electrophysiological measures and potential for proarrhythmias and Torsades de Pointes**



A: QRS interval, B: QT interval, C: Tp-e interval, D: TdP score, where scores above 2.5 correlates with risk of Torsades de Pointes. \*\*p < 0.01 and \*p < 0.05 vs. control.

**TRV130A: Intravenous Infusion Cardiovascular Safety Pharmacology Evaluation in Male Telemetry-Instrumented Conscious Nonhuman Primates (Study 8242813)**

In this GLP study, eight male cynomolgus monkeys (*Macaca fascicularis*) were dosed weekly using a Latin square crossover design. On each dosing day, animals were administered vehicle control article [0.2 mM sodium phosphate buffer in 5% (w/v) Dextrose Injection, USP] or 0.05, 0.2, or 1 mg/kg/h TRV130A (hydrochloride salt). Animals were dosed via intravenous infusion for approximately 10 hours at a volume of 1 mL/kg/h. The time to C<sub>ss</sub> in monkeys was previously shown to be approximately 4 hours (Study 8242809); however, infusion time for this study was approximately 10 hours in order to provide an equal number of light and dark time points for data collection.

**Table 17: Study design for the telemetered monkey cardiovascular study**

Dose Level <sup>a,b</sup> (mg/kg/hr)	Number of Male Animals	Dose Concentration (mg/mL)
0	8	0
0.05	8	0.05
0.2 (NOAEL)	8	0.2
1	8	1

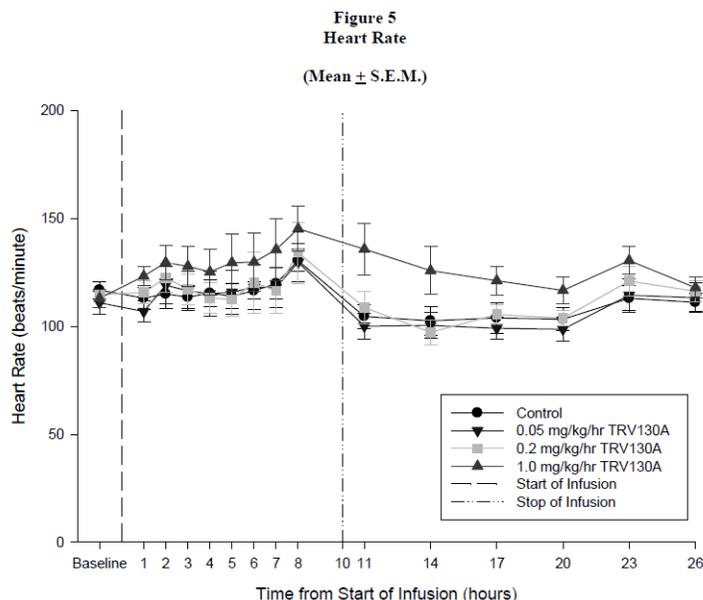
<sup>a</sup> Control animals received vehicle control article.

<sup>b</sup> Animals were dosed for approximately 10 hours via intravenous infusion at a volume of 1 mL/kg/hr.

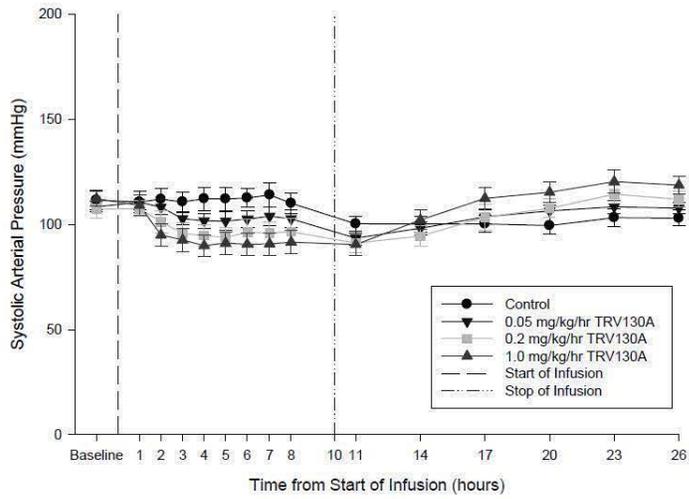
Telemetry data, including hemodynamic parameters (heart rate and arterial blood pressure), ECG parameters, and intraabdominal body temperature, were recorded for at least 90 minutes prior to the start of dose formulation infusion and continuously for at least 26 hours after the start of dose formulation infusion. Telemetry data were analyzed as baseline, Block 1 [nominal dosing time (start of infusion) through 8 hours post nominal dosing time], Block 2 (8 through 20 hours post nominal dosing time), and Block 3 (21 through 26 hours post nominal dosing time).

Administration of TRV130A caused low qualitative food consumption at 1.0 mg/kg/h. No relevant, test article-related changes in body weight or mortality were observed.

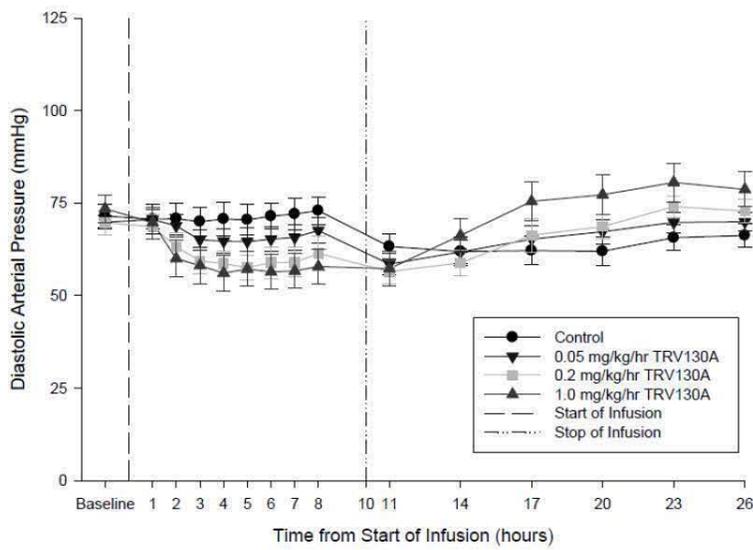
Hemodynamic data showed that TRV130 caused a dose-dependent decrease (less than 25%) in mean systolic, diastolic, and mean arterial pressures, mean arterial pulse pressure, and mean body temperature during infusion. These changes were considered of biologically relevant magnitude, but quickly reversed after the end of infusion. The changes were followed by compensatory increases (up to 20%) in these hemodynamic parameters from the end of infusion through the end of the telemetry collection period.



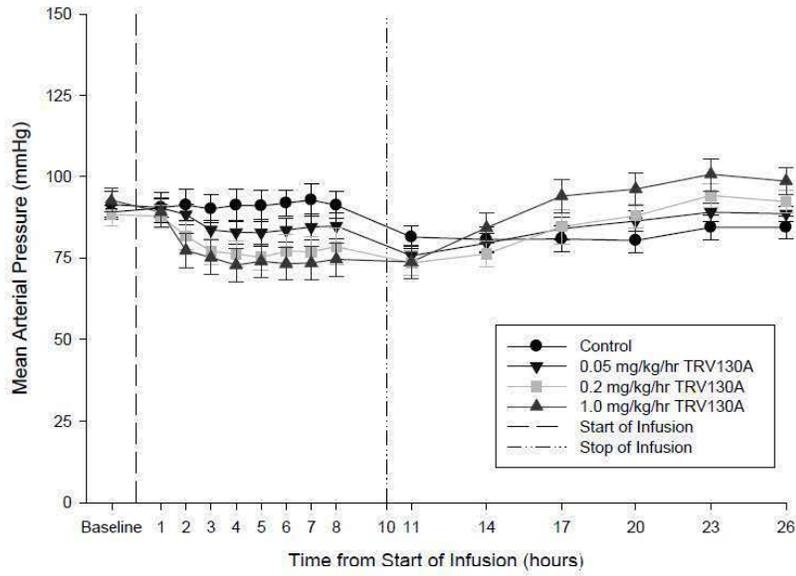
**Figure 6**  
Systolic Arterial Pressure  
(Mean ± S.E.M.)



**Figure 7**  
Diastolic Arterial Pressure  
(Mean ± S.E.M.)



**Figure 8**  
**MAP**  
(Mean ± S.E.M.)



**Figure 9**  
**Arterial Pulse Pressure**  
(Mean ± S.E.M.)

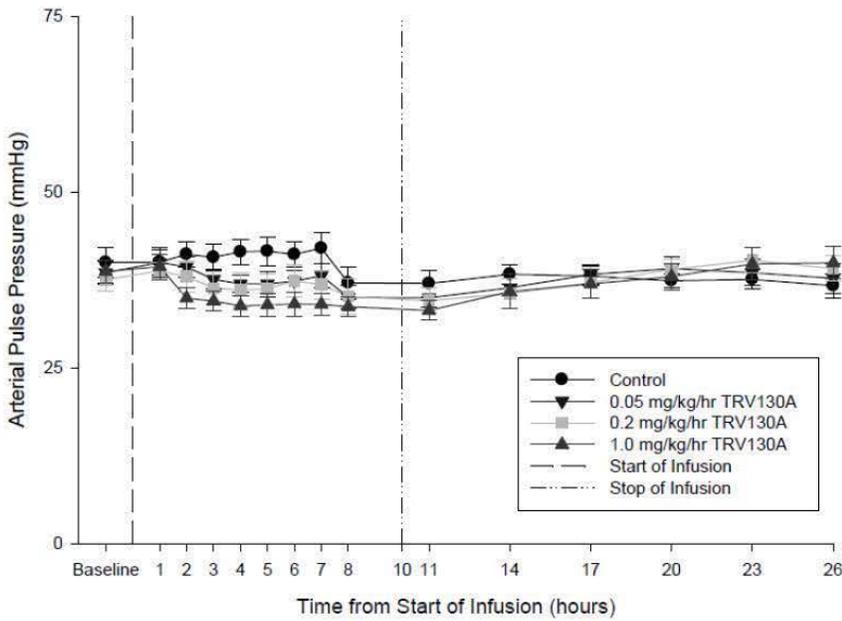
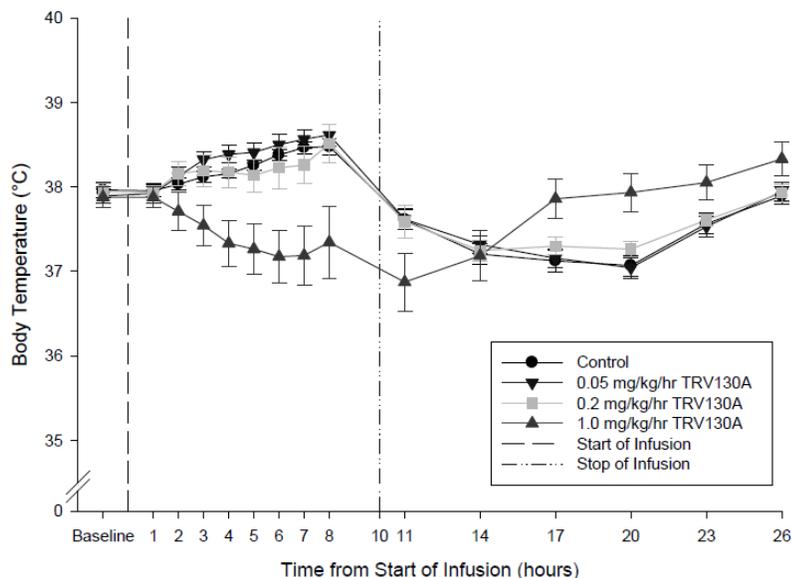


Figure 10  
Body Temperature  
(Mean  $\pm$  S.E.M.)



TRV130A did not have any biologically significant effect on QRS, PR, QT, or corrected QT (QTc) interval. In monkeys given 1.0 mg/kg/h, the QTc interval was shorter by 13 msec (3.8%) at 17 hours after the start of infusion. Based on the single occurrence and small magnitude, this change was considered incidental and not test article-related. No abnormal ECG waveforms or arrhythmias were attributable to the test article.

Based on these hemodynamic changes, the Applicant concluded that NOAEL in this study was 0.2 mg/kg/h, with extrapolated plasma concentrations (120 ng/mL) that were approximately 1.4 times the projected human  $C_{max}$  of 120 ng/mL at the maximum recommended human dose (MRHD) of 40 mg/day. Findings at this dose level include lower mean systolic, diastolic, mean arterial pressures, and mean arterial pulse pressure (up to 17%) during infusion, followed by higher mean systolic, diastolic, mean arterial pressures, and mean arterial pulse pressure (up to 12%) after the end of infusion. *Given the magnitude of changes of hemodynamic parameters at 0.2 mg/kg/h, this Reviewer considers 0.2 mg/kg/h (1.4 times human exposure at MRHD) to be the LOAEL and 0.05 mg/kg/h to be the NOAEL.*

#### 4.3.2 Respiratory Safety Pharmacology

##### **TRV130: Intravenous Infusion Respiratory Safety Pharmacology Study in Male Rats (Study 8242815)**

The purpose of this GLP study was to evaluate the potential effects of TRV130 on respiratory function (respiratory rate, tidal volume, and minute volume) in conscious male Sprague-Dawley rats when administered as a single intravenous infusion.

Thirty-two male rats were randomly assigned to four groups (eight rats/group). Each group was administered a single dose of vehicle control article [0.2 mM sodium phosphate buffer in 5% (w/v) Dextrose Injection, USP] or 0.25, 0.5, or 1 mg/kg/h TRV130. Dose formulations were administered via 6-hour intravenous infusion on Day 1 of the dosing phase at a dose volume of 1 mL/kg/h. The time to  $C_{ss}$  in rats was previously shown to be approximately 4 hours (Study 8242808).

All rats survived until the scheduled euthanasia following the final plethysmography data collection on Day 2 of the dosing phase. Administration of TRV130 had no effect on respiratory parameters (tidal volume, respiration rate, and minute volume) up to 24 hours post-dose. The TRV130 NOAEL for respiratory function is 1 mg/kg/h when administered as a 6-hour IV infusion, the highest dose tested.

*Reviewer's note: Based upon the TK reported in Study 8242808, the average  $C_{ss}$  of males and females was 176 ng/mL after 1 mg/kg/h treatment. The projected human  $C_{max}$  is 176 ng/mL at MRHD of 40 mg/day. Therefore, no respiratory suppression was observed in rats up to a plasma exposure 2 times the  $C_{max}$  at MRHD.*

### 4.3.3 Central Nervous System Safety Pharmacology

#### **TRV130: Intravenous Infusion Central Nervous System Safety Pharmacology Study in Male Rats (Study 8242814)**

The purpose of this study was to evaluate the potential neurological effects of TRV130 on the central nervous system when administered as a single dose via intravenous infusion to male Sprague-Dawley rats. Twenty-four male rats were randomly assigned to four groups (six rats/group). Each group was administered a single dose of vehicle control article [0.2 mM sodium phosphate buffer in 5% (w/v) Dextrose Injection, USP] or 0.25, 0.5, or 1 mg/kg/h TRV130. Dose formulations were administered via 6-hour intravenous infusion on Day 1 of the dosing phase at a dose volume of 1 mL/kg/h.

**Table 19: Study design for the central nervous system safety pharmacology study**

Dose Level <sup>a,b</sup> (mg/kg/hour)	Number of Male Animals	Dose Concentration (mg/mL)
0	6	0
0.25	6	0.25
0.5	6	0.5
1 (NOAEL)	6	1

<sup>a</sup> Control animals received vehicle control article.

<sup>b</sup> Animals were dosed for approximately 6 hours via intravenous infusion at a volume of 1 mL/kg/hr.

Evaluation of neurological effects was based on observations collected pre-dose and approximately 5 minutes and 1, 2, 4, 6, and 24 hours after the end of infusion for each rat using a modified Irwin battery of neurological assessments, including home cage, hand-held, open-field, and elicited response observations. In addition, general measures of toxicity consisting of mortality, clinical signs, and body temperature were evaluated.

No TRV130-related effects were observed in any of the home cage, hand-held, or open field components of the modified Irwin battery. No TRV130-related effects were observed in the number of urine pools or fecal boli, or on hindlimb grip strength or body temperature.

TRV130 at 1 mg/kg/h decreased forelimb grip strength across all time points. TRV130 blunted cranial reflexes, including pinna (at 5 minutes only), corneal, and pupillary responses, and caused miosis of one eye at 5 minutes post-dose for rats given 0.5 mg/kg/h (pinna and corneal responses only) and from 5 minutes to 2 hours post-dose for rats administered 1 mg/kg/h. The observed effects were consistent with expected pharmacological action of the compound and resolved rapidly after the end of infusion. Therefore, with respect to neurological function in rats, the LOAEL for TRV130 is 1 mg/kg/h when administered as a 6-hour IV infusion, the highest dose tested. As noted by this Reviewer above, 1 mg/kg/h led to plasma exposure to the test article that is approximately 2 times the estimated human exposure at MRHD of 40 mg/day.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

The applicant has characterized the metabolism, distribution, and pharmacokinetics of oliceridine and key metabolites in a comprehensive program of studies using human cells, subcellular fractions, and recombinantly expressed enzymes and transporters in vitro, and after single and multiple IV doses of oliceridine administered to male and female animals used in GLP-compliant toxicology studies. The in vitro studies were not compliant with GLP regulations but were conducted according to relevant FDA Guidance and EMA Guideline recommendations and in compliance with laboratory SOPs and current industry practice standards.

Oliceridine is a BCS Class 1, polar, weakly basic amine with excellent solubility and chemical stability. The studies showed there were no differences in PK after IV dosing of the HCl or fumarate salts in aqueous vehicles. A comparison of the PK and plasma exposure in animals and humans is presented in the table below:

Table 15: Mean Systemic Plasma Exposure and PK for Oliceridine after Single IV Doses to Animals and Humans

Species <sup>a</sup>	Dose (mg/kg)	C <sub>max</sub> (ng/mL)	AUC <sub>0-∞</sub> (ng*h/mL)	CLs (L/h/kg)	V <sub>ss</sub> (L/kg)	t <sub>1/2</sub> <sup>b</sup> (h)	References
C57 BL/6 Mice	0.3	93.2	36.3	8.3	4.5	0.4	CPB-P10-1373M01
Sprague Dawley Rat	0.5	74.8	73.3	7.0	6.9	0.7	CPB-P10-1311R01
Cynomolgus Monkey	0.3	206	167	1.8	2.9	1.1	CPB-P10-1348K01
Human	0.06 <sup>c</sup> (4.5 mg)	117	108	0.60 <sup>c</sup>	NR	1.7	CP130-1003

<sup>a</sup> nonclinical species, males only

<sup>b</sup>  $t_{1/2} = 0.001 \times \ln(2) \times V_{ss} \times AUC_{0-\infty} / \text{Dose}$

<sup>c</sup> expressed per 70 kg mass NR: not reported

## Absorption

Although not the focus of this application, oral bioavailability of oliceridine is poor, especially in monkeys, likely a result of extensive systemic metabolism by intestinal and hepatic CYP.

## Distribution

The half-life of oliceridine in animals was short, approximately 1 hour, reflecting the relatively high clearance and modest V<sub>ss</sub>. Although the blood: plasma ratio (B: P) for oliceridine was not determined, the average (n=2 animals) B:P ratio 5 minutes after the end of the infusion of <sup>14</sup>C-TRV130 to Long Evans or Sprague Dawley rats was 0.79, and this likely reflects distribution of mostly parent drug, with minimal contribution by later-appearing metabolites. Oliceridine was not extensively bound to plasma protein(s) in any species, including humans.

Plasma protein binding of oliceridine is species-dependent and low, with free (unbound) fractions ranging from 11% in dogs to 42% in monkeys, with 23% free in human plasma.

Table 16: Species-Dependent Plasma Protein Binding of TRV130

Species	Mean % Bound	Mean % Unbound	Mean % Recovery
CD-1 mouse	64.1	35.9	97.8
Sprague Dawley rat	72.3	27.7	96.4
Beagle dog	88.9	11.1	101.2
Cynomolgus monkey	58.0	42.0	101.4
Human	76.6	23.4	98.4

“This low plasma binding is somewhat unexpected for a small, lipophilic amine, but may reflect the contribution of the Spiro cycle ring system. This speculation is supported by the observation that the primary amine TRV0109662 is essentially free in plasma, with  $f_u > 90\%$  in rats and humans and  $> 85\%$  in monkeys. The negligible plasma binding of M22, the highly polar unreactive, non- acyl, ether glucuronide, is not unexpected.”

Table 17: Species-Dependent Plasma Protein Binding of TRV0109662

Species	Concentration (nM)	Mean % Bound	Mean % Unbound	Mean of % Recovery
Sprague Dawley rat	1	0.0	101	110.8
	10	5.0	95.0	124.7
Cynomolgus monkey	1	12.2	87.8	112.2
	10	15.3	84.7	105.2

Human	1	0.0	100	113.2
	10	4.5	95.5	99.4

Table 18: Human Plasma Binding of M22 (TRV0306954)

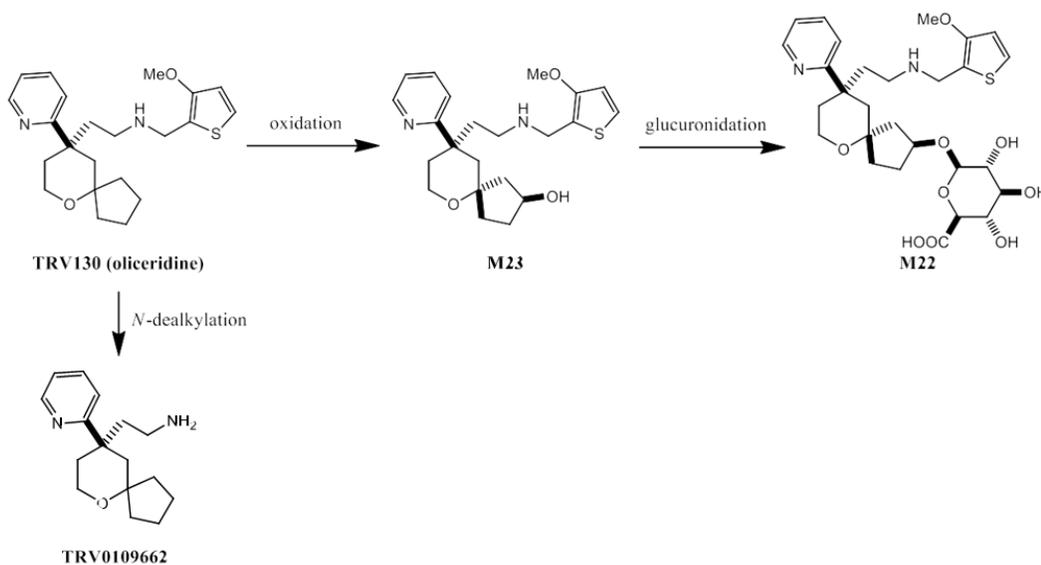
Species	Concentration (nM)	Mean % Bound	Mean % Unbound	% Recovery
Human	30	17	83	91
	100	15	85	95

### **Metabolism**

“Oliceridine is extensively metabolized by oxidation and subsequent glucuronidation. The relative contributions of CYP2D6 and 3A4 to the metabolism of oliceridine were examined using HLM incubations with selective chemical inhibitors, and hepatic microsomes and hepatocytes from donors phenotypically segregated into “high” and “low” enzyme activities. CYP2D6 is responsible for up to 76% of the in vitro metabolism of oliceridine, with up to 47% of the oxidative metabolism contributed by CYP3A4. Many regioisomeric oxidation products were detected but were not unambiguously characterized. Analysis by mass fragmentography of metabolites from Sprague Dawley rats, cynomolgus monkeys, and humans dosed IV with oliceridine identified similar metabolites; however, the abundance in plasma was low and detectable only by mass spectrometry (not UV-VIS detection). The UDP glucuronosyl transferase isozyme responsible for the conjugation of M23 (oxidized oliceridine) was not determined.”

“The metabolite profiles of [<sup>14</sup>C]-TRV130-derived radioactivity were determined in plasma collected from six male human subjects after a single IV dose of [<sup>14</sup>C]-TRV130 (Study CP130-1007). Sample analysis identified oxy-TRV130 glucuronide (M22; TRV0306954) as the main circulating radioactive component, accounting for a mean of 61.9% of total [<sup>14</sup>C]-drug related plasma exposure (AUC). *N*-dealkylation and oxidation of oliceridine produced circulating metabolites TRV0109662 (17.4% of plasma AUC) and oxy-TRV130 (M23; 5.20% of plasma AUC). Oliceridine accounted for approximately 3.4% of total plasma exposure (see the table below). Overall, these data indicate that [<sup>14</sup>C]-TRV130 undergoes extensive metabolism in human subjects, primarily by oxidation of the pyridine or oxaspirodecane moiety with subsequent glucuronidation (see the figure below). The potential pharmacological activity of these metabolites, as well as their potential to produce DDIs, have been characterized by the Applicant.”

Figure 1: Proposed Metabolic Pathway for Oliceridine

Table 19. Oliceridine Metabolite Exposure (Mean  $\pm$  SD) in Human Plasma (Study CP130-1007)

Metabolite/Parent	Percent of Sample Radioactivity (% of Total Exposure)
M16 (glucuronide)	3.41 $\pm$ 1.87
TRV0109662 ( <i>N</i> -dealkylated amine)	17.4 $\pm$ 5.70
M22 (TRV0306954; unreactive, non-acyl, ether glucuronide of M23)	61.9 $\pm$ 6.00
M23 (oxy-TRV130)	5.20 $\pm$ 3.13
<u>Oliceridine</u>	3.37 $\pm$ 2.96
Total %	91.3 $\pm$ 2.40

“In vitro studies with human liver microsomes support the conclusion that clearance of oliceridine is primarily via CYP2D6 and 3A4 oxidation. Clearance was not saturable across a wide range of IV doses administered to rats or monkeys, with  $C_{max}$  (generally the end of infusion),  $C_{ss}$ , and AUC increasing in proportion to the increased dosage. Systemic clearance of oliceridine (relative to hepatic blood flow) was very high in mice and rats (exceeding hepatic blood flow) and high in cynomolgus monkeys.”

“Substituted thiophenes are a structural alert for reactive intermediate formation, and the metabolic activation of the oliceridine thiophene moiety was tested in vitro using human liver microsomes fortified with GSH and incubated with oliceridine. While oxidation of the thiophene moiety of tienilic acid has been associated with irreversible CYP2C9 inactivation and both direct and idiosyncratic hepatotoxicity, other thiophene containing drugs like the thienopyridine P2Y12 antagonists clopidogrel and prasugrel are metabolically activated by CYP-mediated

metabolism of the thiophene (Hagihara 2009) and are widely and safely used clinically. Moreover, several factors influence the clinical risk of metabolism-dependent formation of reactive intermediates and potential toxicity (Leung 2012; Gramec 2014), including total clinical dosage, extent of metabolism, and the availability of alternative detoxification pathways like GSH conjugation. Hepatocyte incubates from several animal species, and plasma and urine from animals and humans dosed with oliceridine were profiled by mass spectrometry for the presence of metabolites including glutathione conjugates or subsequent metabolites of any glutathione conjugates. While isomeric GSH conjugates were formed after oxidation of oliceridine in microsomes, this occurred at high concentrations of substrate (50 mcM) and the conjugates were detectable only by MS (with minimal fragmentation support), not UV-VIS spectroscopy. Moreover, no conjugates were detected by MS after the incubation of lower concentrations of oliceridine (10 mcM) with hepatocytes from several species. No GSH conjugates were found after profiling rat or human plasma, urine and feces collected after a single IV dose of  $^{14}\text{C}$ -oliceridine with MS and radiochemical analysis. No metabolism dependent CYP inhibition was found after incubation of oliceridine with human liver microsomes. The Applicant concluded that metabolic activation of the thiophene with subsequent reactivity with tissue or soluble (GSH) nucleophiles is negligible. Other metabolic sites for CYP-mediated oxidation (e.g., *N*-dealkylation and spirocycle oxidation) appear to be more prevalent (see below for detailed discussion).” This Reviewer agrees with this assessment.

The primary amine metabolite TRV0109662 (Figure 8 above), a *N*-dealkylated human metabolite comprising approximately 17% of total  $^{14}\text{C}$ -related material in human plasma, has been characterized for pharmacological activity, potential to perpetrate CYP and transporter-mediated DDI, and exposure in nonclinical toxicology species. There are no structural alerts present in this primary amine. TRV0109662 is a weak ( $\text{EC}_{50} = 5$  mcM) partial agonist of the human mu-opioid receptor. The safety justification of this metabolite is discussed in Session 9.2.2.

Highly polar glucuronides are usually terminal elimination metabolites with minimal biological consequences. M22 was identified by high resolution nuclear magnetic resonance and chemical synthesis as a non-acyl ether glucuronide conjugate of hydroxylated TRV130. Radiochemical and mass spectrometric profiling of plasma collected from clinical Study CP130-1007 showed that M22 accounts for 61.9% total drug-related exposure. The safety justification for M22 is discussed in Session 9.2.1.

### **Excretion**

As per the Application, “The major routes of excretion for oliceridine and total radioactivity were determined with intact and bile duct-cannulated Sprague Dawley and Long Evans rats administered a single IV dose of unlabeled or [ $^{14}\text{C}$ ]-oliceridine. Oliceridine and metabolites were measured in excreta by either HPLC-MS/MS or directly by LSC. Recovery of the dose was high, with a mean ( $\pm\text{SD}$ ) of  $90.1 \pm 5.31\%$  within 168 hours postdose, most within 48 hours following the start of infusion (87%). The recovery of the administered dose in bile, feces, and urine was  $62.8\% \pm 5.61\%$ ,  $3.87\% \pm 1.02\%$ , and  $20.4\% \pm 4.27\%$ , respectively. Excretion of intact oliceridine in either bile or urine was negligible, and most of the drug-related material was metabolites.”

## 5.2 Toxicokinetics

(If not included in toxicity studies)

The TK for oliceridine were determined in GLP-compliant, repeat-dose studies with Sprague Dawley rats, NZW rabbits, and cynomolgus monkeys administered continuous IV infusions of oliceridine. Steady-state was achieved rapidly, generally within 4 hours of the start of the infusion, consistent with the half-life of approximately 1 hour. There were no sex differences (less than 2-fold differences) in TK. Exposure ( $C_{ss}$  or  $AUC_{0-24h}$ ) was generally proportional to increasing dose in rats, rabbits, and monkeys. There was no accumulation of oliceridine after continuous IV infusion of oliceridine for 14 to 28 days. The TK of oliceridine was similar in rats administered IV doses of oliceridine or oliceridine enriched with degradation products and impurities (including TRV0109662, the primary amine metabolite).

## 6 General Toxicology of Oliceridine

The Applicant conducted the studies presented in the following table for general toxicity characterization. In the End-of-Phase 2 (EoP2) meeting dated March 29, 2016, the Division agreed that 28-day monkey study will not be needed for this acute use product given that the toxicological potential appears to have been characterized in the previously conducted 14-day monkey study and, since stomach and pulmonary findings were not observed in this species. The studies of 8242806, 8242808, 8253529, 8242807 and 8242809 have been previously reviewed by Dr. Armaghan Emami. Refer to IND 113537 for her detailed review.

Oliceridine hydrochloride (HCl) salt was used in initial toxicology studies. But development studies have shown that the TRV130 fumarate salt yields an improved stability profile and has been used for clinical trial material beginning with active pharmaceutical ingredient (API) batch TRV130 fumarate, Lot FP-000016. In order to qualify oliceridine fumarate for use in clinical studies, a 14-day continuous IV infusion toxicity study in rats (Study 8292859), in addition to a bacterial reverse mutation assay and a chromosome aberration study in cultured human peripheral blood lymphocytes, was conducted to bridge data between the two salt forms.

### General Toxicity Studies Submitted by the Applicant:

Study Type and Duration	Route of Administration	Species	Test Article	Study Number	GLP Status
<b>Repeat Dose Toxicity</b>					
Dose range-finding	IV infusion	Rat	TRV130	8242806 <sup>a</sup>	No
14-day	IV infusion	Rat	TRV130	8242808 <sup>a</sup>	Yes
14-day with 7-day interim necropsy	IV infusion	Rat	TRV130	8253529 <sup>a</sup>	Yes
14-day	IV infusion	Rat	TRV130 fumarate and HCl	8292859 <sup>a</sup>	Yes
14-day	IV infusion	Rat	TRV130 with degradants and impurities	8354309 <sup>a</sup>	Yes
14-day with 28-day recovery	IV infusion	Rat	TRV130	8347111 <sup>a</sup>	Yes
28-day	IV infusion	Rat	TRV130	8336088 <sup>a</sup>	Yes
Dose range-finding	IV infusion	Monkey	TRV130	8242807 <sup>a</sup>	No
14-day	IV infusion	Monkey	TRV130	8242809 <sup>a</sup>	Yes

## 6.1 Single-Dose Toxicity

No dedicated single-dose studies were conducted to support this marketing application. It should be noted, however that the first phase of the dose range-finding studies in rats (Study 8242806) and monkeys (Study 8242807) were single intravenous infusions of approximately 24 hours duration.

## 6.2 Repeat-Dose Toxicity

### **Study title: TRV130A (HCL Salt): 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Study in Rats**

**Note: This study was reviewed by Dr. Armaghan Emami in IND 113537.**

<b>Study title: TRV130A: 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Study in Rats</b>	
Study no.:	8242808
Study report location:	eCTD 0003 (4) 4.2.3.2.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	06 July 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TRV130, lot # CMLW-423/11-TV3, purity: 99.1%

### **Key Study Findings**

- TRV130A, administered 24 hours/day via continuous intravenous infusion to rats for at least 14 days. Doses were administered as control, 0.25, 0.5, and 1 mg/kg/h.
- Clinical signs observed in rats given 1 mg/kg/h (HD) of TRV130A were swelling of the paws and excessive biting which resulted in the early sacrifice of one HD animal. These clinical signs were expected with this class of compound because the test article is a small molecule agonist at the mu-opioid receptor. These clinical signs were associated with changes in body weight and food consumption in HD animals.
- The Applicant stated that only the death of one animal (HD) was attributed to the test article because it was related to the excessive biting noted at this dose level. Two other HD animals were sacrificed either for septicemia or the blood collection procedure. The MD animal was found dead on Day 5 of the dosing phase; no clinical signs had been noted for this animal. According to the Applicant relationship of this death to the test article is uncertain, although in the absence of TRV130A-related clinical signs and death in toxicity animals, it is unlikely

administration of TRV130A was the cause of death in this animal. This reviewer believes that the death in MD is incidental since 1 out of 38 MD animals were found dead. Moreover, there is no mortality in this dose in the second repeat-dose study in rats.

- There was an approximate one-day interval between the end of intravenous infusion dosing and the scheduled necropsy. During this time, many of the rats displayed additional clinical signs consistent with opioid withdrawal (hunched posture, nonformed feces and cold to the touch) and had substantial elevations in serum corticosterone, findings consistent with stress.
- Several relatively minor to mild clinical pathology findings were observed that frequently involved all TRV130A-dosed groups. A dose-dependent response was generally not observed. These findings were consistent with dehydration and stress/inflammation.
- Other findings consistent with stress related to opioid withdrawal included erosions/ulcers in the glandular stomach and degeneration/necrosis in the nonglandular stomach, adrenal cortical hypertrophy, decreased lymphocytes in the spleen, thymus, mesenteric and mandibular lymph nodes. Animals also demonstrated atrophy of the seminal vesicles and prostate.
- With the data from the second 14-days study (No. 8253529) which confirmed the opioid withdrawal mediated stress in this study, the acceptable LOAEL is considered 0.5 mg/kg/h which is correspondent to the average C<sub>ss</sub> plasma concentrations of approximately 97 ng/mL.

*Reviewer’s note of Dr. Zhang: During the NDA review, it came to this Reviewer’s attention that there appears an increased incidence of pulmonary thrombosis in the HD group (lower doses were not examined except one in LD group) indicated in a summary table from the pathology report.*

(b) (4) 8242808  
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Table 15  
 Summary of Microscopic Observations  
 Dosing Phase - Final Phase Sacrifice

Controls from group(s): 1 Tissues With Diagnoses	Animal sex: Dosage group: No. in group:	-- Males --				Affected -- Females --			
		Animals				Animals			
		Ctls	2	3	4	Ctls	2	3	4
		10	10	10	10	10	10	10	9
Lung	Number examined:	10	0	0	10	10	1	0	9
	Unremarkable:	8	0	0	5	7	1	0	8
	Infiltrate, Eosinophils, Perivascular, Increased	2	0	0	2	1	0	0	0
	Thrombus	1	0	0	2	0	0	0	0
	Thrombus, Organized	0	0	0	3	0	0	0	1
	Inflammation, Chronic-Active	0	0	0	0	2	0	0	0
	Inflammation, Acute, Interstitial	0	0	0	0	0	0	0	0
	Inflammation, Vessel	0	0	0	0	0	0	0	0

Methods	
Doses:	0, 0.25, 0.5 or 1 mg/kg/hour
Frequency of dosing:	24 hours/day for 14 days
Route of administration:	Intravenous infusion
Dose volume:	at a dose rate of 1 mL/kg/hour
Formulation:	TRV130A (hydrochloride salt)
Vehicle:	0.2 mM sodium phosphate buffer in 5% dextrose
Species/Strain:	Hsd:Sprague Dawley®™SD®™ rats
Number/Sex/Group:	See below table
Age:	8 weeks old
Weight:	242 to 302 g for males and 174 to 224 g for females
Satellite groups:	TK group/ see below table
Unique study design:	N/A
Deviation from study protocol:	None of the deviations affected the results of the study

### Study design of 14-day Rat Study

Group <sup>b</sup>	No. of Animals		Dose Level (mg/kg/hour)	Dose Concentration <sup>a</sup> (mg/mL)
	Male	Female		
<b>Toxicity Animals</b>				
1 (Control)	10	10	0	0
2 (Low)	10	10	0.25	0.25
3 (Mid)	10	10	0.5	0.5
4 (High)	10	10	1	1
<b>Toxicokinetic Animals</b>				
5 (Control)	3	3	0	0
6 (Low)	9	9	0.25	0.25
7 (Mid)	9	9	0.5	0.5
8 (High)	9	9	1	1

a Concentrations were corrected for salt content using a correction factor of (b) (4)

b Group 1 received vehicle control article only.

### Observations and Results

**Mortality**

Three HD animals and one MD animal were sacrificed or died, see below table,

Main groups	Mortality	
	male	female
1 (control)		
2 (Low)		
3 (Mid)		
4 (High)		1/10 (B12954), this animal was sacrificed on Day 8 of the dosing phase due to general debilitation. Clinical signs included hunched posture, limited use of the right front leg, low carriage, thin appearance, red discharge from the nose and eyes, few feces, and rough haircoat. According to the Sponsor the moribundity was attributed to septicemia, likely related to a catheter-related infection that is not uncommon in this study model and not TRV130A-related. Septicemia resulted in acute inflammation of the lung (moderate), kidney (moderate), and heart (slight). Associated vascular inflammation (minimal) was evident in the lung, and bacterial colonies were present in the kidney and heart. A concomitant marked increase in extramedullary hematopoiesis was evident in the spleen
TK groups		
5 (control)		
6 (Low)		

7 (Mid)		1/10 (B12974), this animal was found dead on Day 5 of the dosing phase; no clinical signs had been noted for this animal. The Sponsor stated that the relationship of this death to the test article is uncertain, although in the absence of TRV130A-related clinical signs and death in toxicity animals, it is unlikely administration of TRV130A was the cause of death in this animal.
8 (High)	1/10 (B 12910) this animal was found dead after blood collection on Day 14 of the dosing phase. The Sponsor stated that this death was attributed to the blood collection procedure.	1/10 (B12978), this animal was sacrificed on Day 1 of the dosing phase after observations of red haircoat (perioral, front paws, right hind paw, and tail), missing left front digit(s), and sore/scab on the tail. According to the Sponsor this death was attributed to the test article because it was related to the excessive biting noted at this dose level.

## Clinical Signs

Selected clinical signs in main study

Main groups	Male (10 animals)				Female (10 animals)			
	1 (control)	2 (Low)	3 (Mid)	4 (High)	1 (control)	2 (Low)	3 (Mid)	4 (High)
Clinical sign								
Hunched	0	0	1	4	0	0	0	2
Excessive Biting	0	0	0	10	0	0	0	10
Feces, few	0	0	0	0	0	0	0	5
Feces, Nonformed	0	0	1	1	0	2	6	7
Red Discharge-Eyes	0	0	1	0	0	0	1	2
Red Discharge-right or left Eye	0	1	0	0	0	0	1	0
Squinted-Eyes	0	0	0	1	0	0	0	0
Squinted-Right Eye	0	1	0	0	0	0	0	0
Cold to touch, entire body	0	0	0	3	0	0	0	1
Red hair coat, perioral	0	0	1	8	0	0	0	1
Rough hair coat	0	0	1	3	0	0	0	1
Yellow haircoat, perineal area	0	1	5	8	0	0	1	1

TRV130A-related clinical signs observed during dosing occurred in HD animals and included swelling of the paws and excessive biting. Excessive biting occurred predominantly in the first few days of dosing and generally resolved after the first week. These clinical signs were associated with changes in body weight and food consumption.

Other TRV130A-related clinical signs observed after completion of dosing included hunched posture; nonformed feces ; cold to the touch; and red, brown, or yellow haircoat. The Sponsor stated that these clinical signs were associated with a stress response commonly observed following opiate withdrawal. These clinical signs were noted at >0.25 mg/kg/hour but were most common at 1 mg/kg/hour.

## Body Weights

Mean body weight in high dose (HD) males was reduced on Days 8 (-9.9%) and 15 (-11.1%) of the dosing phase relative to controls. Mean body weight change was also significantly reduced for the intervals of Days 1 to 8 (-47.6%) and Days 8 to 15 (-25.0%) and the duration of the dosing phase (-34.0%). Mean body weight change was significantly reduced in HD females but only for the interval of Days 1 to 8 of the dosing phase (-52.2%) and the duration of the dosing phase (-27.8%). This reviewer agrees with the Sponsor that the effects on body weight and body weight change are associated with clinical signs and correlated effects on food consumption therefore, they are considered adverse.

There are no test- article related body weight changes in MD and LD animals.

### Mean Body Weight Data

Test Article		Control	TRV130A		
Group		1	2	3	4
Level (mg/kg/hour)		0	0.25	0.5	1.0
-----					
Day		1M	Mean body weights (g) for Group:		Statistics
			2M	3M	
DSNG 1	Mean	282	269	262*	263*
	SD	11.0	15.5	9.0	10.8
	N	10	10	10	10
DSNG 8	Mean	303	298	292	273*
	SD	11.3	15.9	9.9	12.3
	N	10	10	10	10
DSNG 15	Mean	334	327	321	297*
	SD	10.1	17.2	12.3	14.2
	N	10	10	10	10

\* P < or = 0.05  
P = ANOVA (and Dunnett's, if applicable)

Mean Body Weight Data

Test Article	Control	TRV130A		
Group	1	2	3	4
Level (mg/kg/hour)	0	0.25	0.5	1.0

Day		Mean body weights (g) for Group:				Statistics
		1F	2F	3F	4F	
DSNG 1	Mean	192	195	189	192	P
	SD	11.3	13.4	9.1	9.2	
	N	10	10	10	10	
DSNG 8	Mean	215	210	209	203	P
	SD	11.7	11.9	10.6	15.4	
	N	10	10	10	10	
DSNG 15	Mean	228	219	219	218	P
	SD	13.4	8.2	11.7	9.2	
	N	10	10	10	9	

P = ANOVA (and Dunnett's, if applicable)

Mean Body Weight Change Data

Test Article	Control	TRV130A		
Group	1	2	3	4
Level (mg/kg/hour)	0	0.25	0.5	1.0

Day		Mean body weight gain (g) for Group:				Statistics
		1M	2M	3M	4M	
DSNG 1- DSNG 8	Mean	21	29	30*	11*	PK
	SD	6.0	12.0	5.9	3.4	
	N	10	10	10	10	
DSNG 8- DSNG 15	Mean	32	29	29	24*	P
	SD	2.6	4.2	4.5	4.5	
	N	10	10	10	10	
DSNG 1- DSNG 15	Mean	53	58	59	35*	PK
	SD	6.0	10.6	7.8	4.8	
	N	10	10	10	10	

\* P < or = 0.05

K = rank-transformed data

P = ANOVA (and Dunnett's, if applicable)

Mean Body Weight Change Data

Test Article	Control	TRV130A		
Group	1	2	3	4
Level (mg/kg/hour)	0	0.25	0.5	1.0

Day		Mean body weight gain (g) for Group:				Statistics
		1F	2F	3F	4F	
DSNG 1- DSNG 8	Mean	23	15	20	11*	P
	SD	7.6	6.6	8.2	11.3	
	N	10	10	10	10	
DSNG 8- DSNG 15	Mean	13	9	10	11	P
	SD	9.9	6.4	7.5	4.1	
	N	10	10	10	9	
DSNG 1- DSNG 15	Mean	36	24	30	26	P
	SD	12.4	9.0	10.1	5.4	
	N	10	10	10	9	

\* P < or = 0.05

P = ANOVA (and Dunnett's, if applicable)

Food Consumption

Mean food consumption was significantly reduced (-11.8 to -18.7%) compared to controls for the intervals of Days 1 to 7 and 8 to 14 of the dosing phase in HD males and females. Because reduced food consumption was present for Weeks 1 and 2 of the dosing phase and associated with clinical signs, it is considered adverse.

**Mean Food Consumption Data**

Test Article Group Level (mg/kg/hour)		Control	TRV130A		
		1	2	3	4
		0	0.25	0.5	1.0

Day	Mean food consumption (g/animal/period) for Group:				Statistics	
		1M	2M	3M		4M
DSNG 1- DSNG 7	Mean	192	190	182	161*	P
	SD	12.0	17.8	6.7	11.9	
	N	10	10	10	10	
DSNG 8- DSNG 14	Mean	195	187	181	161*	P
	SD	10.5	37.1	14.7	13.3	
	N	10	10	10	10	

\* P< or =0.05  
P = ANOVA (and Dunnett's, if applicable)

Mean Food Consumption Data

Test Article Group Level (mg/kg/hour)		Control	TRV130A		
		1	2	3	4
		0	0.25	0.5	1.0

Day	Mean food consumption (g/animal/period) for Group:				Statistics	
		1F	2F	3F		4F
DSNG 1- DSNG 7	Mean	155	141*	145	126*	P
	SD	12.4	7.5	7.9	12.8	
	N	10	10	10	10	
DSNG 8- DSNG 14	Mean	153	142	145	135*	P
	SD	15.3	7.2	18.7	9.3	
	N	10	10	10	9	

\* P< or =0.05  
P = ANOVA (and Dunnett's, if applicable)

There are no test- article related food consumption changes in MD and LD animals.

**Ophthalmoscopy**

No test article-related ophthalmic observations were noted.

**ECG**

NA

**Hematology**

Samples for clinical pathology (hematology and clinical chemistry) evaluation were collected on the day of scheduled sacrifice, one day following the completion of dose administration when clinical signs consistent with withdrawal were present.

Hematology findings:

- Minimally to mildly higher red cell mass (i.e., red blood cell count, hemoglobin, and hematocrit) in all TRV130A-dosed groups
- Minimally to mildly higher absolute reticulocyte count in all TRV130A-dosed groups
- Minimally to mildly higher absolute neutrophil count in HD and MD males and females and LD females.
- Mildly lower absolute lymphocyte count in HD and MD males and females
- Mildly higher absolute monocyte count in HD males and females and MD males.
- Mildly lower absolute eosinophil count in HD and MD females
- Coagulation parameters were unaffected.

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**Mean Hematology Data**

Occasion: D5NG 16

Test Article		Control		TRV130A					
Group	Level (mg/kg/hour)	1	2	3	4				
Group/ Sex	RBC E6/uL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETI E3/uL	PLT E3/uL	
1M	Mean SD N	8.69 0.227 10	16.5 0.43 10	51.2 1.54 10	58.9 1.06 10	18.9 0.51 10	32.2 0.53 10	275.8 34.65 10	1094 122.5 10
2M	Mean SD N	9.52* 0.211 10	18.1* 0.58 10	55.9* 1.79 10	58.7 1.69 10	19.0 0.76 10	32.5 0.69 10	321.0* 33.98 10	1110 87.2 10
3M	Mean SD N	9.67* 0.248 10	18.6* 0.49 10	57.6* 2.00 10	59.6 1.81 10	19.2 0.52 10	32.2 0.58 10	352.5* 29.10 10	1090 143.8 10
4M	Mean SD N	9.61* 0.528 10	18.3* 0.94 10	55.8* 2.61 10	58.1 2.92 10	19.1 0.64 10	32.8 0.86 10	455.3* 315.91 10	1100 264.9 10
Statistics	PK	PK	P	P	P	P	PK	P	

\* P < or = 0.05

K = rank-transformed data  
P = ANOVA (and Dunnett's, if applicable)

Test Article Group		Control				TRV130A			
Level (mg/kg/hour)		1	2	3	4	1	2	3	4
Group/ Sex		RBC E6/uL	HGB g/dL	HCT %	MCV fl	MCH pg	MCHC g/dL	RETI E3/uL	PLT E3/uL
1F	Mean	8.43	16.0	48.5	57.5	18.9	32.9	207.3	1078
	SD	0.401	0.68	2.17	1.15	0.43	0.61	33.51	187.6
	N	10	10	10	10	10	10	10	10
2F	Mean	8.71	16.6	50.2	57.6	19.1	33.1	261.5	1202
	SD	0.495	0.94	2.84	0.87	0.28	0.38	46.86	269.3
	N	10	10	10	10	10	10	10	10
3F	Mean	9.06*	17.1*	51.2*	56.5	18.9	33.4	249.3	1129
	SD	0.243	0.28	1.25	1.38	0.51	0.48	39.45	112.4
	N	10	10	10	10	10	10	10	10
4F	Mean	9.05*	17.3*	50.9*	56.4	19.2	34.0*	249.3	1047
	SD	0.546	0.79	1.94	2.33	0.79	0.47	74.75	137.3
	N	9	9	9	9	9	9	9	9
Statistics		P	P	P	P	P	P	PK	PK

\* P < or = 0.05

K = rank-transformed data  
P = ANOVA (and Dunnett's, if applicable)

Test Article Group		Control				TRV130A			
Level (mg/kg/hour)		1	2	3	4	1	2	3	4
Group/ Sex		WBC E3/uL	NEUT E3/uL	LYM E3/uL	MONO E3/uL	EOS E3/uL	BASO E3/uL	LUC E3/uL	PT seconds
1M	Mean	7.29	1.66	5.23	0.24	0.13	0.02	0.02	17.7
	SD	1.180	0.836	0.772	0.149	0.066	0.009	0.008	0.46
	N	10	10	10	10	10	10	10	10
2M	Mean	6.47	1.58	4.62	0.17	0.07*	0.01	0.02	18.3
	SD	0.852	0.354	0.870	0.080	0.020	0.005	0.007	0.47
	N	10	10	10	10	10	10	10	10
3M	Mean	6.44	2.21	3.70*	0.30	0.17	0.05	0.01	17.9
	SD	1.402	0.755	0.950	0.159	0.154	0.099	0.010	0.60
	N	10	10	10	10	10	10	10	9
4M	Mean	6.98	2.86*	3.50*	0.47*	0.12	0.02	0.01*	17.7
	SD	0.962	0.611	0.881	0.174	0.033	0.008	0.006	0.60
	N	10	10	10	10	10	10	10	10
Statistics		P	P	P	P	PK	PK	P	P

\* P < or = 0.05

K = rank-transformed data  
P = ANOVA (and Dunnett's, if applicable)

Test Article Group		Control				TRV130A			
Level (mg/kg/hour)		1	2	3	4	1	2	3	4
Group/ Sex		WBC E3/uL	NEUT E3/uL	LYM E3/uL	MONO E3/uL	EOS E3/uL	BASO E3/uL	LUC E3/uL	PT seconds
1F	Mean	5.39	0.76	4.28	0.15	0.19	0.01	0.01	19.0
	SD	0.977	0.203	0.871	0.065	0.116	0.003	0.008	0.81
	N	10	10	10	10	10	10	10	10
2F	Mean	6.83	2.07*	4.38	0.23	0.13	0.01	0.02	19.0
	SD	4.000	1.946	1.966	0.277	0.084	0.015	0.015	1.11
	N	10	10	10	10	10	10	9	10
3F	Mean	3.76*	1.38*	2.10*	0.19	0.08*	0.00	0.01	18.3
	SD	0.682	0.344	0.442	0.052	0.013	0.005	0.007	0.45
	N	10	10	10	10	10	10	10	10
4F	Mean	3.63*	1.40*	1.84*	0.32	0.07*	0.01	0.01	18.4
	SD	0.507	0.220	0.396	0.105	0.019	0.004	0.004	0.43
	N	9	9	9	9	9	9	9	9
Statistics		PK	PK	PK	P	PK	P	PK	P

\* P < or = 0.05

K = rank-transformed data  
P = ANOVA (and Dunnett's, if applicable)

**The Sponsor's justification for hematology changes: high red cell mass and reticulocyte count likely reflected dehydration. High neutrophil and monocyte counts and lower lymphocyte and eosinophil counts were consistent with stress and possible inflammation.**

**Clinical Chemistry**

- Mildly to moderately higher glucose in all TRV130A-dosed groups
- Minimally higher urea nitrogen in all TRV130A-dosed groups (except HD females)
- Minimally to mildly higher total serum protein and albumin in all TRV130A-dosed groups (except HD males)
- Minimally to mildly higher albumin-to-globulin ratio in all TRV130A-dosed females and males (except MD male)
- Minimally higher triglycerides in HD males and females and MD and LD females
- Mildly lower aspartate aminotransferase and alanine aminotransferase activities in all TRV130A-dosed groups
- Mildly higher alkaline phosphatase activity in all TRV130A-dosed males
- Mildly higher calcium in all TRV130A-dosed groups
- Minimally higher inorganic phosphorus in all TRV130A-dosed males
- Minimally lower sodium in all TRV130A-dosed females and chloride in all TRV130A-dosed males and females
- Mildly higher potassium in all TRV130A-dosed males
- Mildly to moderately higher corticosterone levels in all male TRV130-dosed group and in MD and HD females.

**Mean Clinical Chemistry Data**

Occasion: DSNG 16

Test Article Group		Control				TRV130A			
Level (mg/kg/hour)		1	2	3	4	1	2	3	4
		0	0.25	0.5	1.0	0	0.25	0.5	1.0
Group/ Sex		GLU mg/dL	UN mg/dL	CREA mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	AGR	CHOL mg/dL
1M	Mean	79	19	0.7	6.6	4.3	2.2	2.0	102
	SD	6.6	2.2	0.07	0.13	0.24	0.15	0.22	9.7
	N	10	10	10	10	10	10	10	10
2M	Mean	133*	25*	0.7	7.0*	4.9*	2.2	2.3*	94
	SD	9.8	2.6	0.08	0.40	0.28	0.16	0.13	22.6
	N	10	10	10	10	10	10	10	10
3M	Mean	153*	25*	0.7	6.9	4.7*	2.2	2.1	124*
	SD	14.7	3.0	0.08	0.42	0.29	0.14	0.07	18.5
	N	10	10	10	10	10	10	10	10
4M	Mean	171*	22*	0.6*	6.5	4.4	2.1*	2.2*	120
	SD	16.6	2.2	0.08	0.54	0.39	0.17	0.13	11.5
	N	10	10	10	10	10	10	10	10
Statistics		P	P	P	P	P	P	PK	P

\* P < or = 0.05

K = rank-transformed data  
 P = ANOVA (and Dunnett's, if applicable)

Test Article Group		Control				TRV130A			
Level (mg/kg/hour)		1	2	3	4	1	2	3	4
Group/Sex		GLU mg/dL	UN mg/dL	CREA mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	AGR	CHOL mg/dL
1F	Mean	91	22	0.8	6.5	4.5	2.1	2.2	101
	SD	5.9	2.1	0.04	0.32	0.30	0.21	0.28	13.1
	N	10	10	10	10	10	10	10	10
2F	Mean	129*	26*	0.7	7.6*	5.3*	2.3	2.4	101
	SD	14.9	1.7	0.05	0.39	0.86	0.51	0.64	17.0
	N	10	10	10	10	10	10	10	10
3F	Mean	163*	25*	0.7*	7.7*	5.6*	2.1	2.7	116
	SD	14.5	1.7	0.04	0.47	0.29	0.21	0.19	20.3
	N	10	10	10	10	10	10	10	10
4F	Mean	180*	22	0.6*	7.3*	5.2*	2.1	2.5	108
	SD	16.4	2.9	0.00	0.28	0.29	0.12	0.23	18.7
	N	9	9	9	9	9	9	9	9
Statistics		P	P	PK	P	P	P	P	P

\* P < or = 0.05  
 K = rank-transformed data  
 P = ANOVA (and Dunnett's, if applicable)

Test Article Group		Control				TRV130A			
Level (mg/kg/hour)		1	2	3	4	1	2	3	4
Group/Sex		TRIG mg/dL	TBIL mg/dL	AST U/L	ALT U/L	ALP U/L	GGT U/L	Ca mg/dL	PHOS mg/dL
1M	Mean	31	0.1	129	42	106	.	10.9	7.6
	SD	8.2	0.00	11.2	3.4	12.0	.	0.15	0.57
	N	10	10	10	10	10	0	10	10
2M	Mean	26	0.1	103*	38*	124*	3E	11.5*	8.7
	SD	4.1	0.00	9.0	3.3	15.9	0.0	0.46	0.68
	N	10	8	10	10	10	5	10	10
3M	Mean	38	0.1	99*	41	142*	3E	11.7*	9.9*
	SD	9.3	0.00	14.4	3.5	12.4	0.0	0.50	1.59
	N	10	9	10	10	10	4	10	10
4M	Mean	46*	0.1	93*	34*	123*	3E	11.8*	9.3*
	SD	14.2	0.00	10.2	3.7	14.4	.	0.66	1.25
	N	10	8	10	10	10	1	10	10
Statistics		P	X	P	P	P	X	P	P

\* P < or = 0.05  
 E = group excluded from analysis  
 P = ANOVA (and Dunnett's, if applicable)  
 X = not analyzed

Test Article Group		Control				TRV130A			
Level (mg/kg/hour)		1	2	3	4	1	2	3	4
Group/Sex		TRIG mg/dL	TBIL mg/dL	AST U/L	ALT U/L	ALP U/L	GGT U/L	Ca mg/dL	PHOS mg/dL
1F	Mean	31	0.1	126	42	72	.	11.0	7.2
	SD	4.3	0.00	12.3	3.8	15.0	.	0.20	0.33
	N	10	10	10	10	10	0	10	10
2F	Mean	50*	0.1	100*	35*	76	.	11.8*	7.6
	SD	12.1	0.00	21.3	3.9	29.3	.	0.37	0.43
	N	10	8	10	10	10	0	10	10
3F	Mean	47*	0.1	88*	35*	77	.	11.8*	7.1
	SD	9.3	0.00	14.0	4.4	7.5	.	0.41	0.37
	N	10	8	10	10	10	0	10	10
4F	Mean	44*	0.1	90*	32*	74	.	11.9*	7.1
	SD	8.5	0.00	9.8	6.7	12.4	.	0.30	0.74
	N	9	5	9	9	9	0	9	9
Statistics		P	X	P	P	P	X	P	P

\* P < or = 0.05  
 P = ANOVA (and Dunnett's, if applicable)  
 X = not analyzed

Occasion: DSNG 16

Test Article Group Level (mg/kg/hour)	Control 1 0	TRV130A 2 0.25	TRV130A 3 0.5	TRV130A 4 1.0
	Na mmol/L	K mmol/L	Cl mmol/L	
1M	Mean 147	5.6	104	
	SD 1.0	0.37	1.0	
	N 10	10	10	
2M	Mean 146	6.3*	101*	
	SD 2.0	0.90	1.6	
	N 10	10	10	
3M	Mean 148	6.7*	101*	
	SD 2.4	0.64	1.1	
	N 10	10	10	
4M	Mean 146	6.7*	101*	
	SD 2.7	0.76	1.3	
	N 10	10	10	
-----				
Statistics PK P P				
-----				
* P < or = 0.05				
K = rank-transformed data				
P = ANOVA (and Dunnett's, if applicable)				

Test Article Group Level (mg/kg/hour)	Control 1 0	TRV130A 2 0.25	TRV130A 3 0.5	TRV130A 4 1.0
	Na mmol/L	K mmol/L	Cl mmol/L	
1F	Mean 144	5.3	104	
	SD 0.6	0.32	0.7	
	N 10	10	10	
2F	Mean 143*	5.4	100*	
	SD 1.2	0.35	1.8	
	N 10	10	10	
3F	Mean 142*	5.6	99*	
	SD 1.2	0.31	1.2	
	N 10	10	10	
4F	Mean 141*	5.7*	99*	
	SD 1.9	0.20	2.0	
	N 9	9	9	
-----				
Statistics PK P PK				
-----				
* P < or = 0.05				
K = rank-transformed data				
P = ANOVA (and Dunnett's, if applicable)				

**Mean Corticosterone Data**

Dosing Phase - Final Phase Sacrifice

Males

Group	Dose Level (mg/kg/hour)		ng/mL
1	0	Mean	367
		SD	134.0
		N	10
2	0.25	Mean	682
		SD	162.2
		N	10
3	0.5	Mean	865
		SD	239.1
		N	10
4	1.0	Mean	725
		SD	149.9
		N	10

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 Mean Corticosterone Data  
 Dosing Phase - Final Phase Sacrifice  
 Females

Group	Dose Level (mg/kg/hour)		ng/mL
1	0	Mean	714
		SD	167.0
		N	10
2	0.25	Mean	573
		SD	309.0
		N	10
3	0.5	Mean	1392
		SD	264.9
		N	10
4	1.0	Mean	1196
		SD	208.1
		N	9

The Sponsor's justification for clinical chemistry changes: A dose-related response was usually not observed in these clinical chemistry parameters, except high glucose which appeared dose-related. High glucose was likely a stress response and possibly associated with nonspecific clinical signs of poor health that were observed in all TRV130A-dosed groups but were more prevalent at 1 mg/kg/hour. Mildly to moderately higher corticosterone levels in males given  $\geq 0.25$  mg/kg/hour and in females given  $\geq 0.5$  mg/kg/hour compared with the control also supported stress response in these TRV130A-dosed groups. Several histopathology changes consistent with stress were observed in the stomach, adrenal cortex, spleen, thymus, lymph nodes, prostate, and seminal vesicle. High urea nitrogen, serum protein, albumin, and inorganic phosphorus reflected dehydration, and high calcium was likely due to high albumin. A specific mechanism was undetermined for the remaining clinical chemistry findings. Low AST and ALT are usually not toxicologically important. A mechanism was also not known for high ALP. Increase in gamma glutamyltransferase activity and bilirubin was not observed and correlative histopathology changes were not observed in the liver to indicate cholestasis.

## Urinalysis

Test article-related urinalysis findings were moderately low urine volume and high urine specific gravity and mildly lower urine pH in all TRV130A-dosed groups. Low urine volume appeared dose-related, but a clear dose-dependent response was not observed in the remaining urinalysis findings. The Sponsor stated that these findings were likely associated with dehydration (reduced glomerular filtration rate). Remarkable histopathology changes were not observed in the kidney.

**Gross Pathology**

Discoloration of the stomach was a frequent macroscopic observation at the scheduled sacrifice. Discoloration was observed in the glandular stomach of all TRV130A-dosed groups with dose-related increasing incidence but was observed more often in males. Discoloration of the nonglandular stomach was also noted macroscopically in MD and HD females. Discoloration correlated with microscopic findings of erosion/ulcer in the glandular stomach and degeneration/necrosis in the nonglandular stomach.

	Group: Number in group:	Males				Females			
		1 10	2 10	3 10	4 10	1 10	2 10	3 10	4 9
Examined/No remarkable findings ...	9	3	1	0	8	6	4	0	
Stomach, G1 Discolored	0	7	9	10	0	1	5	9	
Total:	0	7	9	10	0	1	5	9	

**Organ Weights**

There are changes in the organ weigh of all TRV130A -dosed groups. See below the Sponsor's table.

Sex	Male				Female			
	0 (Control)	0.25 (Low)	0.5 (Mid)	1 (High)	0 (Control)	0.25 (Low)	0.5 (Mid)	1 (High)
Continuous Daily Dose (mg/kg/hour)	0 (Control)	0.25 (Low)	0.5 (Mid)	1 (High)	0 (Control)	0.25 (Low)	0.5 (Mid)	1 (High)
Number of Toxicity Animals at Study Start	10	10	10	10	10	10	10	10
Organ Weights								
Absolute weights (%) <sup>d</sup>								
Brain	1.8974 g	0.8	0.8	-0.8	1.7499 g	-2.0	-1.2	-3.5
Heart	1.4094 g	-5.0	-10.2*	-11.7*	0.9146 g	-4.7	-2.1	-4.7
Liver	9.3337 g	-10.9*	-10.6*	-16.9*	6.1267 g	5.7	7.0	0.9
Kidney	2.0602 g	-9.2*	-13.4*	-20.3*	1.3561 g	-4.0	-5.9	-11.8*
Adrenal	0.0606 g	26.7*	18.0*	13.2	0.0593 g	10.1	18.7*	13.3*
Spleen	0.8681 g	-25.8*	-39.8*	-38.3*	0.5929 g	-11.6	-35.1*	-34.9*
Seminal vesicle	1.0131 g	-26.6*	-41.3*	-45.2*	NA	NA	NA	NA
Prostate	0.7839 g	-14.2	-24.1*	-34.3*	NA	NA	NA	NA
Pituitary	0.0135 g	-10.4	-14.8	-18.5	0.0121 g	2.5	1.7	-14.9*
Lung	1.6782	-10.0	-10.9	-10.2	1.2552 g	-1.6	-5.6	-8.7
Ovary	NA	NA	NA	NA	0.1213 g	0.2	-12.4*	-16.3*
Testis	3.4832 g	1.6	-8.8	-0.6	NA	NA	NA	NA
Epididymis	1.0804 g	-5.2	-8.8	-5.9	NA	NA	NA	NA
Organ-to-body weights (%)								
Brain	0.6143	0.6756*	0.6876*	0.7249*	0.8481	0.9100*	0.9382*	0.9204*
Heart	0.4559	0.4729	0.4551	0.4787	0.4432	0.4619	0.4848	0.4752
Liver	3.0163	2.9336	3.0006	2.9867	2.9647	3.4283*	3.5431*	3.3646*
Kidney	0.6664	0.6596	0.6414	0.6317	0.6561	0.6894	0.6915	0.6507
Adrenal	0.0197	0.0271*	0.0257*	0.0264*	0.0287	0.0346*	0.0381*	0.0366*
Spleen	0.2814	0.2269*	0.1881*	0.2060*	0.2871	0.2763	0.2080*	0.2104*
Seminal vesicle	0.3279	0.2631*	0.2140*	0.2131*	NA	NA	NA	NA
Prostate	0.2536	0.2384	0.2142	0.1986*	NA	NA	NA	NA
Pituitary	0.0044	0.0043	0.0041	0.0042	0.0059	0.0066	0.0066	0.0056
Lung	0.5435	0.5322	0.5379	0.5802	0.6067	0.6538	0.6408	0.6236
Ovary	NA	NA	NA	NA	0.0587	0.0639	0.0576	0.0553
Testis	1.1276	1.2477*	1.1425	1.3340*	NA	NA	NA	NA
Epididymis	0.3500	0.3615	0.3541	0.3919*	NA	NA	NA	NA

The Sponsor's justification for organ weight changes:

- The statistically significant decrease in terminal body weights alone for animals given  $\geq 0.25$  mg/kg/hour accounted for the organ weight parameter changes in the brain, heart, liver, and kidney. Furthermore, no correlating microscopic findings were noted in these organs in animals given 1 mg/kg/hour.
  - Reviewer note: The statistically significant terminal body weight was seen in HD animal only, not all dose-group animals.
- Weight parameter changes in the adrenal, spleen, seminal vesicle, and prostate were attributed to the stress response. Each of these organs had correlating microscopic findings associated with stress, including adrenal cortical hypertrophy, splenic lymphocyte depletion, and seminal vesicle and prostate atrophy.

**Histopathology****Adequate Battery**

Stomach, adrenal cortex, spleen, thymus, mesenteric lymph node, mandibular lymph node, prostate, and seminal vesicles from all animals were processed and examined microscopically.

**Peer Review**

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### Histological Findings

#### Summary of Treatment-Related Microscopic Findings in Other Tissues

Sex	TRV130A							
	Male				Female			
Dose Level (mg/kg/hour)	0	0.25	0.5	1	0	0.25	0.5	1
Number Examined	10	10	10	10	10	10	10	10
<b>Adrenal Cortex - Hypertrophy</b>								
Unremarkable	10	-	-	-	10	10	10	7
Minimal	-	10	10	10	-	-	-	2
Slight	-	-	-	-	-	-	-	1
Incidence (Average Severity)	0(0.0)	10(1.0)	10(1.0)	10(1.0)	0(0.0)	0(0.0)	0(0.0)	3(0.4)
<b>Spleen - Decreased Lymphocytes</b>								
Unremarkable	10	10	10	-	10	10	10	1
Minimal	-	-	-	10	-	-	-	9
Incidence (Average Severity)	0(0.0)	0(0.0)	0(0.0)	10(1.0)	0(0.0)	0(0.0)	0(0.0)	9(0.9)
<b>Spleen - Extramedullary Hematopoiesis, Increased</b>								
Unremarkable	10	10	10	10	10	10	10	9
Marked	-	-	-	-	-	-	-	1
Incidence (Average Severity)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
<b>Thymus - Decreased Lymphocytes</b>								
Unremarkable	10	5	1	-	10	3	-	-
Minimal	-	5	5	5	-	5	2	-
Slight	-	-	4	5	-	2	6	8
Moderate	-	-	-	-	-	-	2	1
Marked	-	-	-	-	-	-	-	1
Incidence (Average Severity)	0(0.0)	5(0.5)	9(1.3)	10(1.5)	0(0.0)	7(0.9)	10(2.0)	10(2.3)
<b>Lymph Node, Mesenteric - Decreased Lymphocytes</b>								
Unremarkable	10	10	10	-	10	10	8	1
Minimal	-	-	-	10	-	-	2	6
Slight	-	-	-	-	-	-	-	3
Incidence (Average Severity)	0(0.0)	0(0.0)	0(0.0)	10(1.0)	0(0.0)	0(0.0)	2(0.2)	9(1.2)
<b>Lymph Node, Mandibular - Decreased Lymphocytes</b>								
Unremarkable	10	10	10	2	10	10	8	1
Minimal	-	-	-	8	-	-	2	8
Slight	-	-	-	-	-	-	-	1
Incidence (Average Severity)	0(0.0)	0(0.0)	0(0.0)	8(0.8)	0(0.0)	0(0.0)	2(0.2)	9(1.0)
<b>Seminal Vesicle - Atrophy</b>								
Unremarkable	10	4	3	1	NA	NA	NA	NA
Minimal	-	6	6	6	-	-	-	-
Slight	-	-	1	3	-	-	-	-
Incidence (Average Severity)	0(0.0)	6(0.6)	7(0.8)	9(1.2)	-	-	-	-

- = Not observed; NA = Not applicable.

The Sponsor included published articles to explain that the above microscopic changes are related to stress:

- Adrenal cortical hypertrophy can occur in rats as an adaptive, stress-related response (Greaves, 2007f).
- Loss of splenic lymphocytes can occur as a response to stress (Greaves, 2007b).
- Loss of thymic lymphocytes can occur in response to stress (Greaves, 2007c).

- Loss of lymphocytes in lymph nodes can occur in response to stress (Greaves, 2007a).
- Atrophy of the seminal vesicle can occur in response to stress (Gatenbeck et al., 1987).
- Atrophy and inflammation of the prostate can occur in response to stress (Greaves, 2007e).

While treatment-related microscopic findings occurred in the stomach, adrenal cortex, spleen, thymus, mesenteric lymph node, mandibular lymph node, prostate, and seminal vesicle (see below Sponsor's tables), the Sponsor stated that all of these changes were attributed to the stress response.

#### Summary of Treatment-Related Microscopic Findings in the Stomach

	Sex	TRV130A							
		Male				Female			
Dose Level (mg/kg/hour)		0	0.25	0.5	1	0	0.25	0.5	1
Number Examined		10	10	10	10	10	10	10	10
Stomach, Glandular - Erosion/Ulcer									
Unremarkable		9	6	1	1	10	10	7	3
Minimal		1	1	1	1	-	-	1	4
Slight		-	2	3	-	-	-	1	2
Moderate		-	1	3	5	-	-	1	1
Marked		-	-	2	3	-	-	-	-
Incidence (Average Severity)		1(0.1)	4(0.8)	9(2.4)	9(2.8)	0(0.0)	0(0.0)	3(0.6)	7(1.1)
Stomach, Nonglandular - Degeneration/Necrosis									
Unremarkable		10	5	1	1	10	9	6	5
Minimal		-	2	4	4	-	1	1	4
Slight		-	1	5	3	-	-	1	1
Moderate		-	2	-	2	-	-	1	-
Marked		-	-	-	-	-	-	1	-
Incidence (Average Severity)		0(0.0)	5(1.0)	9(1.4)	9(1.6)	0(0.0)	1(0.1)	4(1.0)	5(0.6)

- = Not observed.

Microscopic changes in the glandular stomach were generally dose-related in incidence and severity but occurred with greater frequency and severity in males. In the nonglandular stomach, microscopic changes were also generally dose-related in incidence but not in severity. Changes in the nonglandular stomach also occurred with greater frequency and severity in males.

The Sponsor described published articles that gastric erosion and ulceration can occur as a response to stress in laboratory animals (Greaves, 2007d). Moreover, severe gastric ulceration can occur in opiate agonist- (morphine) dependent rats stressed during spontaneous or naloxone-precipitated withdrawal (Glavin et al., 1986) since other forms of stress can produce stomach changes in rats in as little as 2 hours (File and Pearce, 1981).

## Special Evaluation

### Spermatogenesis Assessment:

According to the Sponsor no test article-related effects were noted in the testes and epididymis.

- Some findings noted, including tubule atrophy/degeneration and multinucleate cells in the testis of one control animal, tubule atrophy/degeneration in the testis of one animal given 0.5 mg/kg/hour, tubule degeneration/necrosis in the testis of two animals given 1 mg/kg/hour, hypospermia in the epididymis of one animal given 0.5 mg/kg/hour, spermatocele granuloma in the epididymis of one animal given 0.5 mg/kg/hour, and increased abnormal spermatocytes in the epididymis of two control animals and one animal given 1 mg/kg/hour were unilateral in all cases, and therefore, were considered spontaneous in origin and not test article-related.

## Toxicokinetics

Exposure to TRV130 free base increased with the increase in dose level from 0.25 to 1 mg of test article (mg/kg/hour). Steady state was achieved by 4 hours post the start of infusion on Day 1 of the dosing phase. Sex differences were less than 2-fold in TRV130 free base C<sub>ss</sub> values. Increases in C<sub>ss</sub> for males and females were roughly dose-proportional.

### Toxicokinetic Parameters for TRV130 Free Base in Rat Plasma

Group	Dose Level (mg/kg/hour)	Sex	C <sub>ss</sub> (ng/mL)	CL (mL/hr/kg)
6	0.25	Males	47.0	5323
		Females	36.8	6787
7	0.5	Males	117	4267
		Females	78.1	6403
8	1	Males	203	4934
		Females	149	6704

## Dosing Solution Analysis

A high-performance liquid chromatography method was used by (b) (4) to analyse the dosing solution. Two sets of duplicate samples (1.00 mL each) were taken from the vehicle control article and each test article formulation prepared for administration on Days 1 and 14 of the dosing phase. One set of duplicate samples was held at room temperature and analyzed on the day of test article formulation. Results were reported

to the study director prior to the start of dosing. The second set of samples served as a backup set and was stored in a refrigerator, set to maintain 2 to 8°C, until discarded after acceptable results were obtained.

**Study title: 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Study of TRV130 HCl and TRV130 Fumarate in Rats**

This study evaluated the toxicity and determined the toxicokinetics of the test articles, TRV130 HCl and TRV130 fumarate, when administered 24 hours/day via continuous intravenous infusion to rats for at least 14 days. Oliceridine hydrochloride (HCl) salt was used in initial toxicology studies. But development studies have shown that the TRV130 fumarate salt yields an improved stability profile and has been used for clinical trial material beginning with active pharmaceutical ingredient (API) batch TRV130 fumarate, Lot FP-000016. This study was conducted as a bringing study to qualify oliceridine fumarate for safety. Note the animals were sacrificed within 45 minutes after the termination of drug infusion.

Study no.: 8292859  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8292859\8292859-study-report.pdf>

Conducting laboratory and location:



Date of study initiation: 11/1/2013  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: TRV130 fumarate; 2417-14-1; 99.3%  
 TRV130 HCL; CMLW-423/11-TV3; 99.1%

**Key Study Findings**

There were no clear differences between TRV130 HCl and TRV130 fumarate effects apparent when administered 24 hours/day via continuous intravenous infusion to male and female SD rats for 14 days at 0.5 mg/kg/h. TRV130-related clinical observations, decreases in body weight gain and food consumption, and clinical pathology test results suggestive of mild dehydration were generally comparable between TRV130 HCl and TRV130 fumarate, mild in severity, not adverse, and not dose-limiting. In general, study findings were similar to those observed in previously conducted 14-day toxicology studies in rats (Study 8242808 and 8253529) except that a variable increase in the incidence of moderate or marked thrombus in pulmonary arteries was observed in animals administered TRV130 HCl or TRV130 fumarate in the current study. The cause and its relationship to the test article remain unknown. The applicant stated that pulmonary thrombosis is a common finding associated with IV infusion studies (Morton, 1997); therefore, the apparent increased incidence and severity of thrombus in the lung may have been the result of random variation in incidence.

*Reviewer's note: In this study, the animals were sacrificed within 45 minutes after termination of the drug infusion. Technically, this study did not assess the difference between the two salt*

forms on the withdrawal-induced stomach lesions that have been repeatedly found in rats. Dr. Armaghan has reviewed literature on FDA-approved products containing fumarate salt form. She noted that fumarate as a salt has been in approved products with different route of administration including IV for years and it appears it is unlikely fumarate in this formulation would carry an intrinsic risk.

## Methods

Doses: 0, 0.5 mg/kg/h (0, 12 mg/kg/day)  
 Frequency of dosing: Continuous IV infusion for at least 14 days  
 Route of administration: IV  
 Dose volume: 1 mL/kg/h  
 Formulation/Vehicle: 0.2 mM sodium phosphate buffer in 5% dextrose injection, USP.  
 Species/Strain: HSD: Sprague Dawley SD rats  
 Number/Sex/Group: 3.1.5 Study Design

Group	Subgroup	No. of Animals		Dose Level <sup>a,c</sup> (mg/kg/hour)	Dose Concentration <sup>a</sup> (mg/mL)
		Male	Female		
1 (Control) <sup>b</sup>	1 (Toxicity)	10	10	0	0
	2 (Toxicokinetic)	3	3	0	0
2 TRV130 (fumarate)	1 (Toxicity)	10	10	0.5	0.5
	2 (Toxicokinetic)	3	3	0.5	0.5
3 TRV130 (HCl)	1 (Toxicity)	10	10	0.5	0.5
	2 (Toxicokinetic)	3	3	0.5	0.5

a Dose levels were expressed as the free base. Concentrations were corrected for salt content using a correction factor of (b) (4) for TRV130 fumarate and (b) (4) for TRV130 HCl.

b Group 1 received vehicle control article only.

c Animals were dosed at a dose rate of 1 mL/kg/hour continuously (24 hours/day) for at least 14 days.

Age: 8-9 weeks old at initiation of dosing  
 Weight: 242 to 293 g for toxicity males; 185 to 234 g for toxicity females; 251 to 277 g for toxicokinetic males, and 181 to 205 g for toxicokinetic females.  
 Satellite groups: TK group; see the table above  
 Unique study design: No  
 Deviation from study protocol: No deviation from the study was identified to affect the data interpretation.

## Observations and Results

### Mortality

No test article-related deaths occurred.

### Clinical Signs

Common clinical observations included excessive biting (of the feet, cage, or enrichment), excessive licking (of the feet or cage), and hyperactivity in animals given TRV130 fumarate or TRV130 HCl.

- These observations were generally limited to Day 1 of the dosing phase, although several animals had these observations on Day 2 of the dosing phase.
- As a result of the excessive licking and biting, a few animals developed swollen feet, red discharge (from the digits, foot, or leg), alopecia of the front legs, red skin of the feet, or a scab on the foot; these observations were most prevalent in animals given TRV130 fumarate.

**Text Table 4.1: Noteworthy Clinical Observations**

	Males			Females		
	Control	TRV130 fumarate	TRV130 HCl	Control	TRV130 fumarate	TRV130 HCl
Excessive Biting	0 (0)	9 (12)	9 (11)	0 (0)	6 (6)	9 (9)
Excessive Licking	0 (0)	6 (7)	1 (1)	0 (0)	2 (2)	1 (1)
Hyperactivity	0 (0)	5 (5)	3 (3)	0 (0)	6 (6)	3 (3)

Note: Values represent the number of animals affected with the numeral listed in parentheses representing the total number of occurrences.

### Body Weights

- Mean body weight gain during Week 1 of the dosing phase was reduced in males given TRV130 fumarate or TRV130 HCl such that mean body weights were minimally lower than controls (-4.6% for both groups) on Day 8 of the dosing phase.
- Mean body weight gain was comparable in all groups during Week 2 of the dosing phase, although males given TRV130 HCl still had slightly lower mean body weights on Day 14 of the dosing phase (-5.2%).

### Food Consumption

Consistent with the transient reductions in mean body weight gain relative to controls, mean food consumption during Week 1 of the dosing phase was lower in males given TRV130 fumarate or TRV130 HCl (-8.3 and -4.2%, respectively), albeit only reaching statistical significance in males given TRV130 fumarate. Mean food consumption was 15.3 and 21.5% less than controls for Week 2 of the dosing phase in females given TRV130 fumarate or TRV130 HCl, respectively. However, this reduction did not correlate with clinical observations or effects on body weights, so the significance of this finding was uncertain.

### Ophthalmoscopy

Corneal dystrophy was noted in one male given TRV130 HCl and one control female and two females given TRV130 fumarate; due to the relatively low frequency, as findings were also noted in control animals, and because corneal dystrophy is not uncommon in surgicized rodents, these findings were not considered test article-related by the Applicant.

**ECG**

NA

**Hematology**

Administration of TRV130 HCl or TRV130 fumarate had several similar effects on clinical pathology test results when compared with administration of the vehicle control article. When compared with the vehicle control group, test article-related hematology effects included the following:

- Minimally lower red blood cell count for males and females given TRV130 fumarate and minimally lower hematocrit for females given TRV130 fumarate
- Mildly lower platelet count for males given either test article. No changes were observed in females.

Table  
Summary of Hematology

		Test Article		(dosage)		
				1	2	3
				mg/kg/hour	0.5	-
		TRV130 (HCl)		0	-	0.5

Group/ Subgroup/ Sex	Phase Day	RETIC E3/uL	PLT E3/uL	WBC E3/uL	NEUT E3/uL	LYM E3/uL	MONO E3/uL
		Dosing	Dosing	Dosing	Dosing	Dosing	Dosing
		15	15	15	15	15	15
1/1/M	Mean	267.8	1036	10.72	1.53	8.55	0.32
	SD	35.98	142.1	2.062	0.824	1.268	0.188
	N	10	10	10	10	10	10
	P(overall)	0.6797	0.0026	0.0020	0.0137	0.0010	0.2115
2/1/M	Mean	268.4	838	8.56	0.78	7.21	0.28
	SD	54.32	126.5	1.413	0.149	1.272	0.114
	N	10	10	10	10	10	10
	P(v1)	-	0.0014*	0.0046*	0.0037*	0.0129*	-
3/1/M	Mean	251.8	865	8.13	1.18	6.45	0.22
	SD	50.95	100.0	1.045	0.720	0.739	0.072
	N	10	10	10	10	10	10
	P(v1)	-	0.0047*	0.0010*	0.1503	0.0003*	-
	P(v2)	-	0.6318	0.5467	0.1013	0.1382	-
Statistics		AP	AP	AP	APT	AP	AP

\* P<=0.05  
 AP = ANOVA and protected t-tests  
 T = Rank-transformed data

- Minimally to mildly lower white blood cell and absolute lymphocyte counts for males given either test article and females given TRV130 HCl
- Minimally to mildly lower absolute neutrophil count for males and females given either test article
- Minimally lower absolute eosinophil count for females given either test article.
- No test-article related changes in coagulation parameters.

Applicant’s justification on the findings:

Some effects, including lower absolute lymphocyte and eosinophil counts, were consistent with a mild stress response. Lower platelet counts for males may have been associated with the microscopic observation of increased incidence of moderate or marked thrombus in pulmonary arteries. Most of the effects were of very small magnitude, and none were considered adverse. A clear difference between the two test articles with respect to clinical pathology was not apparent.

### **Clinical Chemistry**

When compared with the vehicle control group, test article-related clinical chemistry effects included the following:

- Minimally higher urea nitrogen concentration for females given either test article
- Mildly higher total protein concentration for females given either test article
- Minimally to mildly higher albumin concentration and albumin: globulin ratio for males and females given either test article
- Minimally lower globulin concentration for males given either test article
- Minimally to mildly higher cholesterol concentration for males given either test article
- Minimally lower aspartate aminotransferase activity for males and females given TRV130 fumarate
- Minimally to mildly lower alkaline phosphatase activity for males and females given either test article
- Minimally to mildly higher calcium concentration for females given either test article
- Minimally higher sodium and chloride concentrations for males and females given either test article

#### Applicant's justification for the findings:

Although none of the effects were indicative of direct target organ toxicity, higher urea nitrogen, total protein, albumin, sodium, and chloride concentrations were consistent with mild dehydration. Higher calcium concentration was considered secondary to higher albumin concentration because approximately half of circulating calcium is bound to albumin. Mechanisms for other minor effects were not apparent, but none of the effects were considered adverse because of their small magnitudes. Clear differences were not apparent between the two groups given test article.

### **Urinalysis**

Test article-related urinalysis effects were limited to mildly lower urine volume and mildly higher urine specific gravity for males and females given either test article. These differences were often not statistically significant because of a few outlier results for individuals given the test articles. Outliers for these parameters typically occur because of water contamination and sometimes result from animals manipulating their water valves. Lower urine volume and higher urine specific gravity were consistent with mild dehydration and appropriate renal conservation of water.

### Terminal Procedure

On Day 15 of the dosing phase, animals fasted overnight were anesthetized with sodium pentobarbital, exsanguinated within 45 minutes after the discontinuation of infusion, and necropsied. At scheduled sacrifice, macroscopic examinations were conducted. The following tissues (when present) from each animal were preserved in 10% neutral-buffered formalin unless otherwise indicated.

Organ/Tissue			Organ/Tissue		
adrenal (2)	W	P,E	mesenteric lymph nodes		P,E
animal identification			muscle (biceps femoris)		P,E
aorta		P,E	optic nerve (2) <sup>a</sup>		P,E
brain	W	P,E	ovary (2)	W	P,E
catheterization sites		P,E	pancreas		P,E
cecum		P,E	pituitary gland	W	P,E
cervix		P,E	prostate	W	P,E
colon		P,E	rectum		P,E
duodenum		P,E	salivary gland (mandibular [2])	W	P,E
epididymis (2)	W	P,E	sciatic nerve		P,E
esophagus		P,E	seminal vesicle	W	P,E
eye (2) <sup>a</sup>		P,E	skin and subcutaneous tissue		P,E
femur with bone marrow (articular surface of the distal end)		P,E	spinal cord (cervical, thoracic, and lumbar)		P,E
gross lesions		P,E	spleen	W	P,E
Harderian gland <sup>a</sup>		P,E	sternum with bone marrow		P,E
heart	W	P,E	stomach		P,E
ileum		P,E	testis (2) <sup>a</sup>	W	P,E
infusion sites		P,E	thymus	W	P,E
jejunum		P,E	thyroid (2 lobes) with parathyroid	W	P,E
kidney (2)	W	P,E	tongue		P,E
liver	W	P,E	trachea		P,E
lungs with large bronchi	W	P,E	urinary bladder		P,E
mammary gland (females)		P,E	uterus	W	P,E
mandibular lymph nodes		P,E	vagina		P,E

E = Examined microscopically; P = Processed; W = Weighed.

a Collected in modified Davidson's fixative and stored in 10% neutral-buffered formalin.

### Gross Pathology

No test article-related macroscopic findings occurred at the scheduled sacrifice.

### Organ Weights

No statistically significant or test article-related organ weight changes occurred.

### Histopathology

**Adequate Battery: Yes**

**Peer Review: No**

- Continuous intravenous infusion procedure-related microscopic changes in the skin were observed. Skin sections often included the catheter tract; minimal or slight inflammation was occasionally observed and associated with this tract. At the catheter site and infusion site, a variety of microscopic findings were observed, including minimal to moderate intimal hyperplasia, minimal to slight fibrosis, minimal to moderate inflammation in the skin/subcutis, and minimal to marked thrombus formation. These findings were comparable between animals given vehicle control article and animals given either test article.
- In animals given TRV130 HCl or TRV130 fumarate, increased incidence and/or severity of thrombus were observed in arteries in the lung. The effect was most notable in males given TRV130 HCl (Text Table 4.2).

**Text Table 4.2: Incidence and Severity of Test Article-Related Microscopic Findings**

	Sex	TRV130 fumarate or TRV130 HCl <sup>a</sup>					
		Males			Females		
Dose Group		1	2	3	1	2	3
Dose Level (mg/kg/hour)		0	0.5	0.5	0	0.5	0.5
Lung							
	Number Examined	10	10	10	10	10	10
Thrombus							
	Not Present	9	7	4	10	9	8
	Minimal	1	0	0	0	0	0
	Slight	0	0	3	0	0	0
	Moderate	0	3	2	0	1	1
	Marked	0	0	1	0	0	1

<sup>a</sup> Group 2, TRV130 fumarate; Group 3, TRV130 HCl.

#### Applicant's justification for the lung finding:

It was unlikely moderate or marked thrombus in the pulmonary arteries of the lung was due to a PR coagulation effect of either test article because the incidence and severity of thrombus at the catheter site and infusion site were comparable between animals given either test article and animals given vehicle control article. Therefore, the apparent increased incidence and severity of thrombus in the lung may have been the result of random variation in incidence and is of uncertain direct relationship to the test articles. Pulmonary thrombosis is a common finding associated with intravenous infusion studies (Morton et al., 1997).

Reviewer's note:

*See reviewer's discussion in Integrated Summary under the session of Toxicology Summary.*

## Special Evaluation

NA

## Toxicokinetics

Exposure to TRV130 freebase was similar when animals were administered TRV130 HCl or TRV130 fumarate at a free base dose level of 0.5 mg/kg/h. Steady state was achieved within 8 hours post the start of infusion. Sex differences were less

than 2-fold in TRV130 freebase mean  $C_{ss}$  and CL values.

Exposure to TRV130 freebase was similar when animals were given TRV130 HCl or TRV130 fumarate at a free base dose level of 0.5 mg/kg/h.

Table 10: Mean ( $\pm$ SD) Toxicokinetic Parameters for TRV130 in Sprague-Dawley Rats Administered a Continuous IV Infusion for 14 Day

Test Article	Dose Level (mg/kg/h)	Sex	C <sub>ss</sub> (ng/mL)	CL (mL/h/kg)
TRV130 (Fumarate)	0.5	Male	92.2 $\pm$ 15.8	5530 $\pm$ 989
		Female	68.2 $\pm$ 2.6	7340 $\pm$ 274
TRV130 (HCl)	0.5	Male	79.2 $\pm$ 8.1	6360 $\pm$ 695
		Female	73.7 $\pm$ 2.3	6790 $\pm$ 213

### Dosing Solution Analysis

All formulations were within +10% of the target concentrations (ranging from 97.4 to 99.7% of theoretical). Test article was not detected in the vehicle control formulations. Thus, all formulations met the acceptance criteria for study use.

### **Study title: TRV130 (Oliceridine): 14-Day Continuous IV Infusion Toxicity and Toxicokinetic Study in Rats with a 28-Day Recovery Phase**

The objective of this GLP study was to confirm that stomach erosions/ulcerations observed in a previous rat study (Study 8242808) resulted from withdrawal-induced stress, and that these findings resolve during a 28-day recovery phase.

*Reviewer's note: The TRV130 doses for this study were selected based on results from previously conducted 14-day continuous intravenous infusion studies in rats (Studies 8242808 and 8253529). The Applicant's NOAEL in these studies was 0.5 mg/kg/h, based on adverse clinical observations (swelling of the paws and excessive biting, both common findings in rats administered opioids) and decreased food consumption and body weights in rats at the next highest dose of 1 mg/kg/h. In Study 8242808, an approximate 24-hour period occurred between the end of intravenous infusion and scheduled necropsy, which led to clinical observations consistent with opioid withdrawal. Treatment-related microscopic findings consistent with withdraw-induced stress responses, including but not limited to, erosions/ulcerations in the nonglandular stomach, were observed in TRV130-treated rats. None of these findings were observed when the study was repeated (Study 8253529), with rats sacrificed 45 minutes following the end of intravenous infusion. In the current study, rats were sacrificed at four different time points (within 45 minutes, one day, 7 days, and 28 days) following the discontinuation of infusion to confirm that stomach erosions/ulcerations result from withdrawal-induced stress, and that these findings can resolve during a 28-day recovery*

*phase. Investigation of the recoverability of the stomach finding was suggested by the Division in EOP2 meeting.*

Study no.: 8347111  
Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8347111\8347111-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: 8/2016  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: TRV130 Fumarate, FP-000326, 99.6%

### **Key Study Findings**

As previously reported, administration of TRV130 as a 24-hour continuous infusion for 14 days in male rats at doses up to 1 mg/kg/h resulted in stomach epithelial erosion/ulcer, mixed cell inflammation, degeneration of the epithelial stratum corneum, and mucosal congestion/hemorrhage and degeneration/necrosis in animals administered  $\geq 0.5$  mg/kg/h 24 hours following the end of infusion. This effect resolved by 7 days after discontinuation of dosing. Clinical pathology correlates were suggestive of an underlying stress response and generally resolved, or had evidence of reversibility, by the end of the recovery phase. Thus, these observations were attributed to withdrawal-induced stress and were resolvable.

- Clinical observation: TRV130-related, dose-dependent clinical observations during the dosing phase included, but were not limited to, excessive grooming and biting or licking of the cage, digit gnawing and swelling, and discolored haircoat. After cessation of dosing, TRV130-related dose-dependent nonformed feces were noted, while animals administered 1 mg/kg/h were also noted with sensitivity to touch and vocalization. These observations resolved later in recovery phase.
- Body weight and food consumption: TRV130-related reductions in body weight were noted during the dosing phase at 0.5 or 1 mg/kg/h, persisting until Day 7 or 21 of the recovery phase, respectively. The effect on the body weight correlates with the effect on food consumption.
- Clinical pathology: A few TVR130-related minor changes in clinical pathology test results were observed. These effects were reversible by the end of the recovery phase and are not considered adverse.

- Hematological changes included changes in white blood cell parameters that were suggestive of an underlying stress response.
- Clinical chemistry changes included minimal to mild stress-induced increases in glucose and minimal increases in urea nitrogen, most likely due to dehydration.
- Organ weight:
  - No TRV130-related changes in organ weight parameters when animals were sacrificed within 45 minutes after the discontinuation of infusion.
  - When the sacrificed was delayed by 24 hours, a TRV130-related decrease in spleen, prostate, and seminal vesicle weights and an increase in adrenal gland weights was observed in animals from both treatment groups. The decreased prostate and seminal vesicle organ weight parameters may have been secondary to decreased food consumption and/or decreased body weight gain, while the increased adrenal gland organ weight parameters may have been secondary to stress.
  - All organ weight changes resolved by the final recovery necropsy, 28 days following the end of dosing.
- Macroscopic and microscopic findings (only stomach tissue was examined microscopically in this study):
  - No TRV130-related changes in macroscopic or microscopic observations occurred at the terminal sacrifice when animals were sacrificed within 45 minutes after the discontinuation of infusion.
  - TRV130-related discoloration (red or dark red) of the glandular stomach was observed macroscopically in animals euthanized 24 hours following the completion of dosing (Day 2 of Recovery Phase). Microscopic findings were noted in the nonglandular (epithelial erosion/ulcer, mixed cell inflammation, and degeneration of the epithelial stratum corneum) and glandular stomachs (mucosal congestion/hemorrhage, mucosal degeneration/necrosis, and mixed cell inflammation) of animals from both dose-levels of TRV130 on Day 2 of the Recovery Phase.
  - Microscopic findings in the stomach resolved by Day 8 and Day 29 of the Recovery Phase.

**Methods**

Doses: 0, 0.5, and 1 mg/kg/h (0, 12 and 24 mg/kg/day)  
 Frequency of dosing: Continuous infusion for 14 days  
 Route of administration: IV  
 Dose volume: 1mL/kg/h  
 Formulation/Vehicle: (b) (4) mg/mL L-histidine and (b) (4) mg/mL mannitol in Sterile Water for Injection, USP, pH (b) (4).  
 Species/Strain: Crl:CD(SD) rats

Number/Sex/Group:

**3.1.5 Study Design**

Group <sup>a</sup>	No. of Males <sup>b</sup>	Dose Level <sup>c</sup> (mg/kg/day)	Dose Concentration <sup>d</sup> (mg/mL)
1 (Control)	40	0	0
2 (Low)	40	12	0.5
3 (High)	40	24	1

- a Group 1 was administered the vehicle control article only ( (b) (4) mg/mL L-histidine and (b) (4) mg/mL mannitol in Sterile Water for Injection, USP, pH (b) (4) )
- b Ten animals/group/interval were sacrificed following completion of dosing (on Day 15, within 45 minutes following the end of infusion); approximately 24 hours following the end of infusion (Day 2 of the recovery phase), 7 days after dose completion (Day 8 of the recovery phase), and 28 days after dose completion (Day 29 of the recovery phase).
- c Dose levels were expressed as the free base. Concentrations were corrected for lot-specific potency using a correction factor of (b) (4)
- d Animals were dosed at a dose rate of 1 mL/kg/hour continuously (approximately 24 hours/day) for at least 14 days.

*Reviewer’s note: Only males were used in this study. In the previous 14-day rat studies, there were no gender differences observed.*

Age: 6-7 weeks old at catheterization  
 Weight: 258 g-337 g at initiation of dosing  
 Satellite groups: No  
 Unique study design: No  
 Deviation from study protocol: No deviation from study protocol was identified to affect the data interpretation.

**Observations and Results**

**Mortality**

All animals survived to their scheduled sacrifice.

**Clinical Signs**

- TRV130-related, dose-dependent clinical observations during the dosing phase included excessive grooming and biting or licking of the cage; digit gnawing, swelling, discoloration, and loss; swelling of the feet, penis, and leg; sores and scabs on the feet; and discolored haircoat.
  - These observations were predominantly noted in males administered 24 mg/kg/day and only sporadically in males administered 12 mg/kg/day.
  - Observations of excitability tended to be limited to the first week of dosing, while haircoat discolorations persisted throughout the dosing phase.
- After cessation of dosing, TRV130-related dose-dependent nonformed feces was noted for a majority of the animals administered 12 or 24 mg/kg/day, while animals administered 24 mg/kg/day were also noted with sensitivity to touch and vocalization.
  - These observations were no longer present by Day 4 of the recovery phase, and discolored haircoat, noted during the dosing phase, was no longer present by Day 8 of the recovery phase.

### Body Weights and Feed Consumption

- TRV130-related reductions in body weight were noted during the dosing phase for males administered 12 or 24 mg/kg/day, persisting until Day 7 or 21 of the recovery phase, respectively. Reduced mean body weights were generally reflective of reduced mean body weight gain, with the most pronounced effects occurring during the first week of the dosing phase.
- Consistent with effects on body weights, a TRV130-related reduction in food consumption was noted during the dosing phase for males administered 12 or 24 mg/kg/day; mean food consumption was comparable in all groups by the second week of the recovery phase.

### Ophthalmoscopy

NA

### ECG

NA

### Hematology

A few TVR130-related minor changes in hematology test results were observed in animals on Day 15 of the dosing phase and/or at one or more time points (Days 2 and/or 8) of the recovery phase. These changes occurred in animals administered 12 or 24 mg/kg/day, were variably dose-dependent, occasionally statistically significant, and recovered by the end of the recovery phase (Day 29). All changes in hematology parameters were considered not adverse given their small magnitude of change, evidence of reversibility, and absence of microscopic correlates. Hematology changes consisted of one or more of the following:

- Changes in red blood cell parameters suggestive of dehydration consisted of one or more of the following:
  - Mildly increased red blood cell count (RBC) on Day 2 of the recovery phase in animals administered 12 or 24 mg/kg/day.
  - Minimally to mildly increased hemoglobin (HGB) concentration and hematocrit (HCT) on Days 2 and 8 of the recovery phase in animals administered 12 or 24 mg/kg/day
- Overall, changes in white blood cell parameters, which occurred on Day 15 of the dosing phase and/or in one or more time points of the recovery phase (Days 2 and/or 8) in one or more animals administered 12 or 24 mg/kg/day, were suggestive of an underlying stress response.
- No TVR130-related changes in coagulation parameters were noted in animals administered 12 or 24 mg/kg/day.

**Table 5.1: Summary of Hematology**

Test Article		(dosage)			
TRV130		1M	2M	3M	
		mg/kg/day			
		0	12	24	
Group/ Sex	Phase	RBC E6/uL			
	Day	Dosing	Recovery		
		15	2	8	29
1/M	Mean	7.88	7.63	8.30	8.77
	SD	0.362	0.538	0.594	0.482
	N	9	9	9	10
	P(overall)	0.5363	<0.0001	0.2402	0.7273
2/M	Mean	7.96	8.82*	8.55	8.71
	SD	0.393	0.585	0.431	0.279
	N	10	10	10	10
	P(v1)	-	<0.0001	-	-
3/M	Mean	7.72	8.72*	8.67	8.62
	SD	0.654	0.354	0.403	0.461
	N	10	10	10	9
	P(v1)	-	0.0001	-	-
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table  
Summary of Hematology  
Test Article (dosage) 1M 2M 3M  
TRV130 mg/kg/day 0 12 24

Test Article		(dosage)			
TRV130		1M	2M	3M	
		mg/kg/day			
		0	12	24	
Group/ Sex	Phase	HGB g/dL			
	Day	Dosing	Recovery		
		15	2	8	29
1/M	Mean	15.2	15.2	15.9	16.0
	SD	0.64	0.70	0.70	0.46
	N	9	9	9	10
	P(overall)	0.4268	<0.0001	0.0046	0.2127
2/M	Mean	15.5	17.8*	16.7*	16.2
	SD	0.45	0.74	0.74	0.57
	N	10	10	10	10
	P(v1)	-	<0.0001	0.0223	-
3/M	Mean	15.1	17.5*	17.0*	15.8
	SD	1.06	0.50	0.56	0.46
	N	10	10	10	9
	P(v1)	-	<0.0001	0.0032	-
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table

Summary of Hematology

Test Article	(dosage)	1M	2M	3M
TRV130	mg/kg/day	0	12	24

Group/ Sex	Phase Day	RETIC E3/uL Recovery			
		Dosing 15	2	8	29
1/M	Mean	333.4	268.1	206.5	234.9
	SD	40.24	81.52	53.92	43.32
	N	9	9	9	10
	P(overall)	0.2568	0.0322	0.0923	0.9062
2/M	Mean	285.6	371.8*	170.1	227.4
	SD	55.16	74.56	35.24	23.95
	N	10	10	10	10
	P(v1)	-	0.0282	-	-
3/M	Mean	350.5	358.8	156.2	225.2
	SD	128.90	101.75	37.06	31.68
	N	10	10	10	9
	P(v1)	-	0.0573	-	-
Statistics		AT	A	AT	AT

\* P<=0.05  
A = ANOVA and Dunnett's  
T = Rank-transformed data

Table

Summary of Hematology

Test Article	(dosage)	1M	2M	3M
TRV130	mg/kg/day	0	12	24

Group/ Sex	Phase Day	Hct % Recovery			
		Dosing 15	2	8	29
1/M	Mean	48.4	45.6	49.0	48.4
	SD	2.09	2.68	3.13	1.99
	N	9	9	9	10
	P(overall)	0.5764	<0.0001	0.0418	0.5418
2/M	Mean	48.9	54.9*	51.4	48.2
	SD	1.76	3.63	2.94	2.35
	N	10	10	10	10
	P(v1)	-	<0.0001	0.1314	-
3/M	Mean	47.7	53.3*	52.4*	47.4
	SD	3.27	2.16	2.09	1.55
	N	10	10	10	9
	P(v1)	-	<0.0001	0.0265	-
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table

Summary of Hematology

Test Article	(dosage)	1M	2M	3M
TRV130	mg/kg/day	0	12	24

Group/ Sex	Phase Day	WBC E3/uL			
		Dosing 15	2	Recovery 8	29
1/M	Mean	7.78	9.61	10.01	9.97
	SD	1.282	2.292	1.860	2.667
	N	9	9	9	10
	P(overall)	0.2695	0.0261	0.1465	0.8445
2/M	Mean	6.26	7.70	9.39	10.49
	SD	2.056	2.408	2.450	2.642
	N	10	10	10	10
	P(v1)	-	0.0982	-	-
3/M	Mean	7.11	6.90*	8.15	9.95
	SD	2.423	1.428	1.747	1.429
	N	10	10	10	9
	P(v1)	-	0.0162	-	-
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table

Summary of Hematology

Test Article	(dosage)	1M	2M	3M
TRV130	mg/kg/day	0	12	24

Group/ Sex	Phase Day	LYM E3/uL			
		Dosing 15	2	Recovery 8	29
1/M	Mean	6.06	5.92	7.35	7.38
	SD	1.011	1.824	1.356	2.369
	N	9	9	9	10
	P(overall)	0.1015	0.0888	0.0740	0.8526
2/M	Mean	4.80	5.48	6.94	7.73
	SD	1.633	1.759	1.521	2.032
	N	10	10	10	10
	P(v1)	-	-	-	-
3/M	Mean	4.84	4.35	5.81	7.22
	SD	1.406	0.902	1.482	1.499
	N	10	10	10	9
	P(v1)	-	-	-	-
Statistics		A	A	A	A

A = ANOVA and Dunnett's

### Clinical Chemistry

Several TVR130-related minor changes in clinical chemistry test results were observed in animals on Day 15 of the dosing phase and/or at one or more time points (Days 2 and/or 8) of the recovery phase. These changes occurred in animals administered 12 or 24 mg/kg/day, were variably dose-dependent, occasionally statistically significant, and recovered by the end of the recovery phase. All changes in clinical pathology parameters were considered nonadverse given the small magnitude of change, evidence of reversibility, and absence of microscopic correlates. Clinical chemistry changes consisted of one or more of the following:

- Stress-induced increases in GLU occurred on Day 15 of the dosing phase in individuals administered 24 mg/kg/day and on Day 2 of the recovery phase in animals administered 12 or 24 mg/kg/day.
- Minimally increased UN (most likely due to subclinical dehydration) occurred on Day 15 of the dosing phase in animals administered 24 mg/kg/day and on Day 2 of the recovery phase in animals administered 12 or 24 mg/kg/day.
- Decreased total protein and/or albumin occurred on Day 15 of the dosing phase and increased total protein and/or albumin on Day 2 of the recovery phase in one or more animals administered 12 or 24 mg/kg/day.
- Increased CHOL concentration occurred on Day 15 of the dosing phase and on Days 2 and/or 8 (only in animals at the highest dose) of the recovery phase in one or more animals administered 12 or 24 mg/kg/day.
- Decreased triglycerides occurred on Day 15 of the dosing phase and inconsistently persisted during the recovery phase (Day 2, 8, or 29) in one or more animals administered 12 or 24 mg/kg/day.
- Minimally to mildly increased potassium concentration occurred on Day 15 of the dosing and on Day 2 of the recovery phase in animals administered 12 or 24 mg/kg/day. Minimal decreases in triglycerides.
- Corticosterone analysis: Minimally to mildly increased corticosterone concentration occurred on Day 15 of the dosing phase in individuals administered 12 (Animals B71566 and B71567) or 24 mg/kg/day (Animals B71599, B71604, B71606, and B71607). During the recovery phase, corticosterone concentration was highly variable when TRV130-treated animals were compared with respective control animals. Overall, these changes correlated with changes in blood cell parameters, which were suggestive of an underlying stress response.

Test Article	(dosage)	1M	2M	3M
TRV130	mg/kg/day	0	12	24

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Group/ Sex	Phase Day	GLU mg/dL			
		Dosing 15	2	Recovery 8	29
1/M	Mean	83	93	74	92
	SD	7.5	20.2	7.9	10.8
	N	10	10	10	10
	P(overall)	0.0315	<0.0001	0.8009	0.2622
2/M	Mean	86	128*	72	86
	SD	8.2	12.1	11.7	6.2
	N	10	10	10	10
	P(v1)	0.5864	<0.0001	-	-
3/M	Mean	94*	144*	75	89
	SD	11.1	13.9	9.1	7.6
	N	10	10	10	10
	P(v1)	0.0197	<0.0001	-	-
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1M 2M 3M  
TRV130 mg/kg/day 0 12 24

Group/ Sex	Phase Day	UN mg/dL			
		Dosing 15	2	Recovery 8	29
1/M	Mean	12	15	12	12
	SD	0.9	3.2	1.6	1.1
	N	10	10	10	10
	P(overall)	0.0001	0.0357	0.2042	0.6633
2/M	Mean	14	19*	11	11
	SD	2.0	2.6	1.6	1.9
	N	10	10	10	10
	P(v1)	0.1948	0.0215	-	-
3/M	Mean	17*	17	11	11
	SD	2.5	2.6	1.6	2.1
	N	10	10	10	10
	P(v1)	<0.0001	0.1586	-	-
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1M 2M 3M  
TRV130 mg/kg/day 0 12 24

Group/ Sex	Phase Day	TP g/dL			
		Dosing 15	2	Recovery 8	29
1/M	Mean	6.4	5.9	6.4	7.1
	SD	0.21	0.41	0.32	0.30
	N	10	10	10	10
	P(overall)	0.0196	0.0020	0.3167	0.0139
2/M	Mean	6.1*	6.6*	6.6	6.9
	SD	0.27	0.30	0.31	0.17
	N	10	10	10	10
	P(vl)	0.0267	0.0019	-	0.2135
3/M	Mean	6.1*	6.5*	6.5	6.7*
	SD	0.33	0.38	0.26	0.31
	N	10	10	10	10
	P(vl)	0.0267	0.0076	-	0.0071
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1M 2M 3M  
TRV130 mg/kg/day 0 12 24

Group/ Sex	Phase Day	ALB g/dL			
		Dosing 15	2	Recovery 8	29
1/M	Mean	4.2	3.6	4.0	4.3
	SD	0.18	0.43	0.40	0.25
	N	10	10	10	10
	P(overall)	0.0691	<0.0001	0.0451	0.0945
2/M	Mean	4.0	4.4*	4.2	4.4
	SD	0.21	0.26	0.31	0.14
	N	10	10	10	10
	P(vl)	-	<0.0001	0.2651	-
3/M	Mean	4.0	4.1*	4.4*	4.2
	SD	0.21	0.23	0.23	0.21
	N	10	10	10	10
	P(vl)	-	0.0077	0.0257	-
Statistics		A	AT	A	A

\* P<=0.05  
A = ANOVA and Dunnett's  
T = Rank-transformed data

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1M 2M 3M  
TRV130 mg/kg/day 0 12 24

Group/ Sex	Phase Day	CHOL mg/dL			
		Dosing 15	2	Recovery 8	29
1/M	Mean	74	68	67	74
	SD	15.4	17.5	19.4	19.6
	N	10	10	10	10
	P(overall)	0.0062	0.0418	0.0901	0.0846
2/M	Mean	100*	83	75	59
	SD	21.3	17.0	12.4	10.2
	N	10	10	10	10
	P(v1)	0.0030	0.1059	-	-
3/M	Mean	88	87*	85	64
	SD	12.0	17.0	20.8	12.6
	N	10	10	10	10
	P(v1)	0.1262	0.0308	-	-
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1M 2M 3M  
TRV130 mg/kg/day 0 12 24

Group/ Sex	Phase Day	ALP U/L			
		Dosing 15	2	Recovery 8	29
1/M	Mean	188	152	134	122
	SD	35.5	26.3	18.5	17.7
	N	10	10	10	10
	P(overall)	0.0533	0.0009	0.3068	0.6518
2/M	Mean	162	206*	130	130
	SD	29.0	31.6	19.8	26.3
	N	10	10	10	10
	P(v1)	-	0.0004	-	-
3/M	Mean	154	183*	121	121
	SD	29.0	26.6	19.8	21.0
	N	10	10	10	10
	P(v1)	-	0.0414	-	-
Statistics		A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1M 2M 3M  
TRV130 mg/kg/day 0 12 24

Group/ Sex	Phase Day	K mmol/L			
		Dosing 15	2	Recovery 8 29	
1/M	Mean	5.4	5.5	6.1	5.9
	SD	0.33	0.28	0.57	0.29
	N	10	10	10	10
	P(overall)	<0.0001	0.0011	0.8460	0.3202
2/M	Mean	6.3*	6.3*	6.1	5.6
	SD	0.36	0.67	0.57	0.40
	N	10	10	10	10
	P(v1)	0.0002	0.0039	-	-
3/M	Mean	6.4*	6.6*	6.3	5.9
	SD	0.62	0.92	0.57	0.49
	N	10	10	10	10
	P(v1)	<0.0001	0.0013	-	-
Statistics		A	AT	A	A

\* p<=0.05  
A = ANOVA and Dunnett's  
T = Rank-transformed data

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1M 2M 3M  
TRV130 mg/kg/day 0 12 24

Group/ Sex	Phase Day	CORST ng/mL			
		Dosing 15	2	Recovery 8 29	
1/M	Mean	<64.09	125.64	<31.40	<41.60
	SD	32.556	105.863	21.017	24.650
	N	10	10	10	10
	P(overall)	-	0.8453	-	-
2/M	Mean	91.30	142.71	<37.92	<35.82
	SD	46.826	67.575	28.021	17.354
	N	10	10	10	10
	Statistics	X5	A	X5	X5
3/M	Mean	102.25	124.19	<49.69	<38.12
	SD	49.581	55.153	43.397	19.365
	N	10	10	10	10
	Statistics	X5	A	X5	X5

X5 = Not analyzed (values above/below the limit of quantitation)  
A = ANOVA and Dunnett's

### Urinalysis

NA

*Reviewer's note: In the previous 14-day rat study (Study 8248208), test article-related urinalysis findings were moderately low urine volume and high urine specific gravity and mildly lower urine pH in all TRV130A-dosed groups. Low urine volume appeared dose-related, but a clear dose-dependent response was not observed in the remaining urinalysis findings. The Applicant stated that these findings were likely*

*associated with dehydration (reduced glomerular filtration rate).*

### **Terminal Procedure**

On Day 15 of the dosing phase, ten animals/group, having been fasted overnight, were anesthetized with sodium pentobarbital, exsanguinated, and necropsied. Animals were exsanguinated within 45 minutes after the discontinuation of infusion. On Day 2 (about 24 hours following the end of infusion), Day 8 and Day 29 of the recovery phase, 10 animals for each time point were anesthetized and necropsied.

Organ weights, as indicated in the following table, were recorded at each scheduled sacrifice. The following tissues (when present) from each animal were preserved in 10% neutral-buffered formalin, unless otherwise indicated.

<u>Organ/Tissue</u>		<u>Organ/Tissue</u>	
adrenal (2)	W	prostate	W
animal identification		seminal vesicle	W
lesions		spleen	W
lymph nodes (mandibular)		stomach	P,E
lymph nodes (mesenteric)		thymus (or thymic region)	

E = Examined microscopically; P = Processed; W = Weighed.

*Reviewer's note: A limited number of organs/tissue was examined in the current study based upon the findings from the previous 14-day rat study (Study 8248208) that examined a full battery of organs/tissue.*

### **Gross Pathology**

- No test article-related changes in macroscopic observations occurred at the terminal sacrifice when animals were exsanguinated within 45 minutes after the discontinuation of infusion.
- On Day 2 of the recovery phase, test article-related red or dark red discoloration of the glandular stomach was observed macroscopically in animals administered  $\geq 12$  mg/kg/day and was correlated with the microscopic finding of mucosal congestion/hemorrhage.
- On Day 8 and Day 29 of the recovery phase, no test article-related macroscopic findings were observed.

**Text Table 4.6: Incidence of Test Article-Related Macroscopic Findings - Recovery Sacrifice 1**

	Sex	TRV130		
		Males		
Dose Level (mg/kg/day)		0	12	24
Number Examined		10	10	10
Stomach, Glandular Discoloration, red/dark red		0	4	8

**Organ Weights**

- No test article-related changes in organ weight observations occurred at the terminal sacrifice when animals were exsanguinated within 45 minutes after the discontinuation of infusion.
- On Day 2 of the recovery phase, approximately 24 hours following the end of infusion, test article-related decreased organ weight parameters were observed for the spleen, prostate, and seminal vesicle of animals administered  $\geq 12$  mg/kg/day, and test article-related increased organ weight parameters were observed for the adrenal gland of animals administered  $\geq 12$  mg/kg/day.
- On Day 8 of the recovery phase, test article-related decreased organ weight parameters were observed for the spleen and prostate of animals administered  $\geq 12$  mg/kg/day.
- On Day 29 of the recovery phase, although not statistically significant, test article-related decreased organ weight parameters were observed for the spleen of animals administered 24 mg/kg/day.

**Text Table 4.2: Test Article-Related Changes in Organ Weight Parameters - Spleen**

	Sex	TRV130 Spleen		
		Males		
Dose Level (mg/kg/day)		0	12	24
Terminal Sacrifice				
Absolute Weight (g)		0.9433	88	101
Body Weight Ratio (%)		0.2646	96	114
Recovery Sacrifice 1				
Absolute Weight (g)		0.9310	70*	68*
Body Weight Ratio (%)		0.2578	79	80
Recovery Sacrifice 2				
Absolute Weight (g)		1.0699	80*	69*
Body Weight Ratio (%)		0.2897	88	80*
Recovery Sacrifice 3				
Absolute Weight (g)		0.9699	88	87
Body Weight Ratio (%)		0.2139	91	96

\* = Statistically significant difference (absolute or relative) compared with respective control mean value.  
 Note: Values for absolute weight and ratio of organ weights (relative to body) for TRV130-dosed groups expressed as percentage control mean value.

**Text Table 4.3: Test Article-Related Changes in Organ Weight Parameters - Prostate**

Sex	TRV130 Prostate		
	Males		
Dose Level (mg/kg/day)	0	12	24
Terminal Sacrifice			
Absolute Weight (g)	1.0815	92	86
Body Weight Ratio (%)	0.3034	100	97
Recovery Sacrifice 1			
Absolute Weight (g)	1.0284	74*	63*
Body Weight Ratio (%)	0.2874	83*	74*
Recovery Sacrifice 2			
Absolute Weight (g)	1.0907	74*	80*
Body Weight Ratio (%)	0.2929	81*	93
Recovery Sacrifice 3			
Absolute Weight (g)	1.1725	102	94
Body Weight Ratio (%)	0.2624	105	103

\* = Statistically significant difference (absolute or relative) compared with respective control mean value.

Note: Values for absolute weight and ratio of organ weights (relative to body) for TRV130-dosed groups expressed as percentage control mean value.

**Text Table 4.4: Test Article-Related Changes in Organ Weight Parameters - Seminal Vesicle**

Sex	TRV130 Seminal Vesicle		
	Males		
Dose Level (mg/kg/day)	0	12	24
Terminal Sacrifice			
Absolute Weight (g)	1.0429	91	79
Body Weight Ratio (%)	0.2929	99	89
Recovery Sacrifice 1			
Absolute Weight (g)	0.9791	67*	62*
Body Weight Ratio (%)	0.2730	75*	73*
Recovery Sacrifice 2			
Absolute Weight (g)	1.3434	92	90
Body Weight Ratio (%)	0.3621	101	105
Recovery Sacrifice 3			
Absolute Weight (g)	1.4960	98	96
Body Weight Ratio (%)	0.3395	99	103

\* = Statistically significant difference (absolute or relative) compared with respective control mean value.

Note: Values for absolute weight and ratio of organ weights (relative to body) for TRV130-dosed groups expressed as percentage control mean value.

**Text Table 4.5: Test Article-Related Changes in Organ Weight Parameters - Adrenal Gland**

Sex	TRV130 Adrenal		
	Males		
Dose Level (mg/kg/day)	0	12	24
Terminal Sacrifice			
Absolute Weight (g)	0.0712	103	95
Body Weight Ratio (%)	0.0200	113	108
Recovery Sacrifice 1			
Absolute Weight (g)	0.0735	111	103
Body Weight Ratio (%)	0.0204	125*	121*
Recovery Sacrifice 2			
Absolute Weight (g)	0.0698	100	98
Body Weight Ratio (%)	0.0189	110	115
Recovery Sacrifice 3			
Absolute Weight (g)	0.0595	94	98
Body Weight Ratio (%)	0.0133	96	108

\* = Statistically significant difference (absolute or relative) compared with respective control mean value.  
 Note: Values for absolute weight and ratio of organ weights (relative to body) for TRV130-dosed groups expressed as percentage control mean value.

#### The Applicant's justification of organ weight change:

The decreased prostate and seminal vesicle organ weight parameters may have been secondary to decreased food consumption and/or decreased body weight gain, while the increased adrenal gland organ weight parameters may have been secondary to stress.

*Reviewer's note: These findings were similar to those reported in the previous 14-day toxicity studies. In the previous study (Study 8248208), the Applicant conducted spermatogenesis assessment and reported that no test-article-related effects were observed.*

#### Histopathology

**Adequate Battery: Yes**

**Peer Review: No**

*Reviewer's note: **Only stomach tissue was examined microscopically in the current study.** This is considered adequate given that the purpose of the current study was to investigate whether the stomach lesions observed in the previous studies are resolvable. In the previous 14-day rat study (Study 8248208; Peer reviewed), the Applicant examined a full battery of organs/tissue and microscopic findings included erosions/ulcers in the glandular stomach and degeneration/necrosis in the nonglandular stomach, adrenal cortical hypertrophy, decreased lymphocytes in the spleen, thymus, mesenteric and mandibular lymph nodes and atrophy of the seminal vesicles and prostate.*

- No test article-related changes in microscopic observations occurred at the terminal sacrifice when animals were exsanguinated within 45 minutes after the discontinuation of infusion.
- On Day 2 of the recovery phase, test article-related microscopic findings were present in the nonglandular (epithelial erosion/ulcer, mixed cell inflammation, and degeneration of the epithelial stratum corneum) and glandular stomachs (mucosal congestion/hemorrhage, mucosal degeneration/necrosis, and mixed cell inflammation) of animals administered  $\geq 12$  mg/kg/day.

**Table 17: Incidence and Severity of TRV130-Related Microscopic Findings in the Stomach at Day 2 Recovery Phase in 14-Day Rat Study**

Dose Level (mg/kg/hour)	0	0.5	1
Number Examined	10	10	10
<i>Stomach, Nonglandular</i>			
<b>Erosion/ulcer, epithelium</b>			
Minimal	0	1	2
Slight	0	1	3
Moderate	0	0	1
<b>Inflammation, mixed cell</b>			
Minimal	0	2	3
Slight	0	0	3
<b>Degeneration, epithelium, stratum corneum</b>			
Minimal	1	4	9
Slight	0	1	0
<i>Stomach, Glandular</i>			
<b>Congestion/hemorrhage, mucosa</b>			
Minimal	0	6	7
Slight	0	1	1
Moderate	0	0	1
<b>Degeneration/necrosis, mucosa</b>			
Minimal	1	0	0
Slight	0	0	1
Marked	0	0	1
<b>Inflammation, mixed cell</b>			
Minimal	0	0	1
Slight	0	0	1

- On Day 8 and Day 29 of the recovery phase, no test article-related microscopic findings were observed.

**Table 5.11: Summary of Severity of Microscopic Observations - Recovery Sacrifice 2 (Recovery Phase)**

Test Article	(dosage)	1M	2M	3M
TRV130	mg/kg/day	0	12	24
-----				
Tissue/Observation	Group/Sex:	1/M	2/M	3/M
	Number of Animals:	10	10	10
-----				
Stomach, Glandular	Number Examined:	10	10	10
	Unremarkable:	8	8	10
Congestion/hemorrhage, mucosa	finding not present -	8	8	10
	minimal	1	2	0
	Total Incidence:	2	2	0
Stomach, Nonglandular	Number Examined:	10	10	10
	Unremarkable:	8	9	10
Degeneration, epithelium, stratum corneum	finding not present -	8	9	10
	minimal	1	1	0
	Total Incidence:	2	1	0

**Table 5.12: Summary of Severity of Microscopic Observations - Recovery Sacrifice 3 (Recovery Phase)**

Test Article	(dosage)	1M	2M	3M
TRV130	mg/kg/day	0	12	24
Tissue/ Observation	Group/Sex: Number of Animals:	1/M 10	2/M 10	3/M 10
Stomach, Glandular	Number Examined:	10	10	10
	Unremarkable:	9	9	10
Congestion/hemorrhage, mucosa	finding not present -	9	9	10
	minimal	1	1	0
	Total Incidence:	1	1	0
Stomach, Nonglandular	Number Examined:	10	10	10
	Unremarkable:	10	8	10
Degeneration, epithelium, stratum corneum	finding not present -	10	8	10
	minimal	1	2	0
	Total Incidence:	0	2	0

The study suggested that stomach findings were attributed to withdrawal-induced stress and were resolvable.

### Special Evaluation

NA

### Toxicokinetics

Analysis of plasma samples collected 4 hours post start of infusion on Days 1 and 4 hours post syringe change on Day 8 showed that steady state was achieved within 4 hours following the start of infusion. A dose-proportional increase in TRV130 exposure was observed, with mean  $C_{ss}$  values of 82.4 ng/mL and 160.7 ng/mL in animals dosed with 0.5 and 1 mg/kg/day (12 and 24 mg/kg/day), respectively

### Dosing Solution Analysis

All formulations were within  $\pm 10\%$  of the target concentrations (means ranging from 97.9 to 101.4% of theoretical). The test article was not detected in any vehicle control article formulation. Thus, all formulations met the acceptance criteria for study use.

### ***Study title: TRV130 (Oliceridine): 4-Week Continuous IV Infusion Toxicity and Toxicokinetic Study in Rats***

This study evaluated the toxicity and determined the toxicokinetics of the test article, TRV130, when administered 24 hours/day via continuous intravenous infusion to rats for 29 days. The animals were sacrificed within 45 minutes from the termination of the drug infusion.

Study no.: 8336088  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8336088\8336088-study-report.pdf>

Conducting laboratory and location:



Date of study initiation: 4/2016  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: The test article was TRV130 Fumarate.

Test Article	Storage	Lot No.	Retest Date	Purity
TRV130 Fumarate	Room temperature, protected from humidity with desiccant	FP-000326	(b) (4)	99.6% <sup>a</sup>

<sup>a</sup> Potency of 76.1%.

**Key Study Findings**

- TRV130-related clinical observations:
  - Limited to excessive biting of the cage in females administered  $\geq 6$  mg/kg/day and yellow or brown haircoat discoloration of the hind quarters, midline abdomen, or scrotum in males administered 24 mg/kg/day
  - Reduced body weight gain with more pronounced change in males than in females; Reduced body weight gain correlates with reduced food consumption.
- TRV130-related minor clinical pathology which may be related to dehydration, stress and inflammation:
  - Lower white blood cell and absolute lymphocyte counts, higher urea nitrogen, higher total serum protein, albumin, and calcium, and lower alkaline phosphatase activity.
- TRV130-related macroscopic and microscopic findings:
  - Increased adrenal weight parameters in males administered 24 mg/kg/day correlated with the increased incidence and severity of the microscopic finding of hypertrophy of the adrenal cortex (minimal to slight) in this group, which was considered stress related.
  - A greater incidence and severity of minimal to slight apoptosis in the pancreas in males treated with the test article was considered secondary to decreased food consumption in this group, rather than a direct effect of TRV130, by the Applicant.
  - A dose-dependent increase in the incidence and/or severity of minimal to severe mixed cell inflammation at the infusion site in animals administered  $\geq 6$  mg/kg/day; this correlated with an increased incidence of the macroscopic observation of thickened infusion site and was considered a local rather than a systemic effect of TRV130.
- Collectively, the haircoat discoloration, substantial reductions in mean body weight change and food consumption in males administered 24 mg/kg/day, coupled with the increased incidence/severity of the infusion site observations, were considered dose-limiting by the

Applicant. The dose of 12 mg/kg/day was considered by the Applicant as the NOAEL given that neither the incidence nor severity of the local infusion site reaction were markedly different than those noted in controls. This dose level produced a mean TRV130 C<sub>ss</sub> of 81.2 and 74.9 ng/mL corresponding to an AUC<sub>0-24h</sub> of 1949 and 1798 ng\*h/mL in males and females, respectively, which is approximately 2 times the estimated total daily human exposure of 783 ng\*h/mL at MRHD of 40 mg/day.

**Methods**

Doses: 0, 6, 12, and 24 mg/kg/day (0, 0.25, 0.5 and 1 mg/kg/h)  
 Frequency of dosing: Continuous IV infusion for 4 weeks  
 Route of administration: IV  
 Dose volume: 1mL/kg/h  
 Formulation/Vehicle: (b) (4) mg/mL L-histidine and (b) (4) mg/mL mannitol in Sterile Water for Injection, USP, pH (b) (4)  
 Species/Strain: Crl:CD(SD) rats  
 Number/Sex/Group: 3.1.5 Study Design

Group <sup>a</sup>	Subgroup	No. of Animals		Dose Level <sup>b</sup> (mg/kg/day)	Dose Concentration <sup>c</sup> (mg/mL)
		Male	Female		
1 (Control)	1 (Toxicity)	10	10	0	0
	2 (Toxicokinetic)	4	4		
2 (Low)	1 (Toxicity)	10	10	6	0.25
	2 (Toxicokinetic)	4	4		
3 (Mid)	1 (Toxicity)	10	10	12	0.5
	2 (Toxicokinetic)	4	4		
4 (High)	1 (Toxicity)	10	10	24	1
	2 (Toxicokinetic)	4	4		

a Group 1 received the vehicle control article only ( (b) (4)mg/mL L-histidine and (b) (4)mg/mL mannitol in Sterile Water for Injection, USP, pH (b) (4)  
 b Dose levels were expressed as the free base. Concentrations were corrected for lot-specific potency using a correction factor of (b) (4)  
 c Animals were dosed at a dose rate of 1 mL/kg/hour continuously (approximately 24 hours/day) for at least 29 days.  
 Note: There was one extra toxicokinetic animal/sex/group available for use as a replacement animal, if needed.

Age: 8 to 9 weeks old at initiation of dosing  
 Weight: 273 to 356 g for males and 209 to 271 g for females at initiation of dosing  
 Satellite groups: TK group (see the table above)  
 Unique study design: No  
 Deviation from study protocol: No deviation from study protocol was identified to affect the data interpretation.

**Observations and Results**

**Mortality**

Six toxicity animals died or were sacrificed prior to the scheduled necropsy. It appears that these deaths were not related to the test article.

Applicant's justification for the mortality

Catheter-related mortality generally associated with marked or severe mixed cell inflammation and bacteria at the infusion and/or catheter site occurred in five toxicity animals sacrificed at an unscheduled interval or found dead. In general, clinical pathology findings in these animals were consistent with inflammation and resulting sequelae that correlated with minimal to severe mixed cell inflammation and bacteria observed microscopically at the infusion and/or catheter site and were not attributed to the test article. All other toxicity animals survived to the terminal sacrifice.

**Text Table 4.2: Unscheduled Sacrifices/Deaths**

Animal	Sex	Dose Level (mg/kg/day)	Subgroup	Day	Status Information	Noteworthy Observations
B62106	Male	0	Toxicity	16	Found Dead	None
B62167	Female	6	Toxicity	27	Moribund Sacrifice	Hunched posture; low carriage; piloerection
B62173	Female	6	Toxicity	16	Moribund Sacrifice	Limited use (left front leg); swollen midline abdomen; rough haircoat
B62178	Female	6	Toxicokinetic	8	Found Dead	Died after blood sampling
B62180	Female	6	Toxicokinetic	27	Moribund Sacrifice	Hunched posture; piloerection
B62145 <sup>a</sup>	Male	24	Toxicity	2	Moribund Sacrifice	Red discharge
B62199	Female	24	Toxicity	19	Moribund Sacrifice	Catheter retracted
B62200	Female	24	Toxicity	25	Moribund Sacrifice	Swollen left inguinal area and right front leg; squinted eyes
B62208	Female	24	Toxicokinetic	27	Moribund Sacrifice	Hunched posture; low carriage

a Animal was replaced on study and not examined microscopically.

*Reviewer's note: This Reviewer agrees with the Applicant that the mortality is likely related to the inflammation and infections originated from the infusion site. However, the mortality rate appears higher in test-article-treated groups. It has been constantly observed across studies that TRV130 treatment leads to loss of body weight, reduced total white blood cells and absolute lymphocyte counts as well as hypertrophy of the adrenal cortex. It can be speculated that opioid treatment-related stress and subsequently compromised immune function may contribute to the higher death rate after prolonged infusion of TRV130.*

**Clinical Signs**

TRV130-related clinical observations were limited to excessive biting of the cage in females administered  $\geq 6$  mg/kg/day and yellow or brown haircoat discoloration of the hind quarters, midline abdomen, or scrotum in males administered 24 mg/kg/day.

**Table 7.2: Summary of Clinical Observations**

Test Article	(dosage)	1	2	3	4					
TRV130 fumarate	mg/kg/day	0	6	12	24					
Phase: Dosing										
Category	Group/Subgroup/Sex:	1/1/M	2/1/M	3/1/M	4/1/M	1/1/F	2/1/F	3/1/F	4/1/F	
Observation	Number in Group:	10	10	10	10	10	10	10	10	
NORMAL										
No remarkable observations		10	10	10	10	10	10	10	10	
Appearance										
hunched		0	0	0	0	0	1	0	0	
limited use, left front leg		0	0	0	0	0	1	0	0	
limited use, left hind foot		1	0	0	0	0	0	0	0	
limited use, left hind leg		1	0	0	0	0	0	0	0	
limited use, right front foot		0	0	0	1	0	0	0	0	
low carriage		0	0	0	0	0	1	0	0	
swollen, hind legs		0	0	0	1	0	0	0	0	
swollen, left front foot		0	0	1	0	0	0	0	0	
swollen, left inguinal		0	0	0	0	0	0	0	1	
swollen, midline abdomen		0	0	0	0	0	1	0	0	
swollen, right front leg		0	0	0	0	0	0	0	1	
swollen, right hind leg		0	0	0	1	0	0	0	0	
Behavior										
animal struggled excessively		0	0	0	1	0	0	0	0	
excessive biting of cage		0	0	0	0	1	4	2	3	
hyperactive		0	0	0	0	0	0	0	1	
Discharge										
red, penis		0	0	0	1	0	0	0	0	
unknown, individual observation, red		0	0	0	1	0	0	0	1	
Excretion										
feces, nonformed, individual observation		0	1	0	0	0	1	0	0	

(b) (4) Study Number 8336088  
 Sponsor Reference Number MORIVCOV24

Table Summary of Clinical Observations										
Test Article	(dosage)	1	2	3	4					
TRV130 fumarate	mg/kg/day	0	6	12	24					
Phase: Dosing										
Category	Group/Subgroup/Sex:	1/1/M	2/1/M	3/1/M	4/1/M	1/1/F	2/1/F	3/1/F	4/1/F	
Observation	Number in Group:	10	10	10	10	10	10	10	10	
Eyes										
squinting, eyes		0	0	0	0	0	1	0	1	
Skin and pelage										
discolored haircoat, entire head, red		0	0	0	0	0	0	0	1	
discolored haircoat, hind quarters, yellow		0	0	0	1	0	0	0	0	
discolored haircoat, midline abdomen, brown		0	0	0	2	0	0	0	0	
discolored haircoat, midline abdomen, yellow		0	0	0	2	0	0	0	0	
discolored haircoat, nose, red		0	0	0	0	0	1	0	0	
discolored haircoat, perineal, red		0	0	0	1	0	0	0	0	
discolored haircoat, perineal, yellow		0	0	0	0	0	0	0	1	
discolored haircoat, rostral head, red		0	0	0	0	0	1	0	0	
discolored haircoat, scrotum, brown		0	0	0	2	0	0	0	0	
discolored haircoat, scrotum, red		0	0	0	1	0	0	0	0	
discolored haircoat, scrotum, yellow		0	0	0	5	0	0	0	0	
discolored skin, nose, red		0	0	0	1	0	0	0	0	
piloerection		0	0	0	0	0	1	0	0	
rough haircoat		0	0	0	0	0	1	0	0	
scaly skin, hind feet		0	0	0	1	0	0	0	0	
sore, left front foot		0	0	1	0	0	0	0	0	
thinning hair coat, front legs		0	0	0	0	0	1	0	0	

**Body Weights**

TRV130 administration significantly reduced body weight gain in the first week of treatment with more pronounced effect on males (the first table below) than on females (the second table below).

**Table 7.5: Summary of Body Weight Change**

		Test Article	(dosage)				
		TRV130 fumarate	mg/kg/day	0	6	12	24
Group/ Subgroup/ Sex	Phase Day	Data Presented in "g" Interval X through X DSNG					
		1 - 8	8 - 15	15 - 22	22 - 29	1 - 29	
1/1/M	Mean	44	35	32	28	144	
	SD	7.4	14.3	11.7	6.2	12.8	
	N	10	10	9	9	9	
	P(overall)	<0.0001	0.5273	0.2124	0.1749	0.0021	
2/1/M	Mean	41	38	27	21	127	
	SD	7.2	10.2	12.6	12.0	27.3	
	N	10	10	10	10	10	
	P(v1)	0.8457	-	-	-	0.2574	
3/1/M	Mean	28*	33	26	25	112*	
	SD	10.7	8.5	10.5	6.7	24.5	
	N	10	10	10	10	10	
	P(v1)	0.0003	-	-	-	0.0099	
4/1/M	Mean	18*	31	35	19	103*	
	SD	6.4	9.2	5.6	10.1	21.2	
	N	10	10	10	10	10	
	P(v1)	<0.0001	-	-	-	0.0011	
Statistics		A	A	A	A	A	

\* P<=0.05  
A = ANOVA and Dunnett's

		Test Article	(dosage)				
		TRV130 fumarate	mg/kg/day	0	6	12	24
Group/ Subgroup/ Sex	Phase Day	Data Presented in "g" Interval X through X DSNG					
		1 - 8	8 - 15	15 - 22	22 - 29	1 - 29	
1/1/F	Mean	25	16	15	13	70	
	SD	8.9	8.7	4.7	5.0	14.9	
	N	10	10	10	10	10	
	P(overall)	0.0816	0.3382	0.2537	0.1084	0.0103	
2/1/F	Mean	21	11	12	7	49*	
	SD	7.7	8.3	8.4	6.2	11.7	
	N	10	10	9	8	8	
	P(v1)	-	-	-	-	0.0027	
3/1/F	Mean	29	13	7	12	60	
	SD	5.7	6.1	7.2	4.8	9.4	
	N	10	10	10	10	10	
	P(v1)	-	-	-	-	0.2086	
4/1/F	Mean	28	9	14	12	62	
	SD	5.4	12.3	14.7	7.5	11.7	
	N	10	10	9	8	8	
	P(v1)	-	-	-	-	0.3706	
Statistics		A	A	A	A	A	

\* P<=0.05  
A = ANOVA and Dunnett's

**Food Consumption**

TRV130-related alteration in food consumption was limited to a 9.7% reduction compared with controls from Days 1-8 of the dosing phase in males administered

24 mg/kg/day (the first table below). Other instances of statistically significant differences in food consumption were considered incidental and within the normal variation of data due to the small magnitude of the change and lack of dose-response.

**Males:**

**Table 7.6: Summary of Food Consumption**

		Test Article	(dosage)				
		TRV130 fumarate	mg/kg/day	0	6	12	24
Group/ Subgroup/ Sex	Phase Day	Data Presented in "g/animal/day" DSNG				Interval X to X	
		1 - 8	8 - 15	15 - 22	22 - 29		
1/1/M	Mean	31	29	29	28		
	SD	2.7	2.7	2.4	2.1		
	N	10	10	9	9		
	P(overall)	0.0284	0.2191	0.7850	0.4910		
2/1/M	Mean	31	29	28	27		
	SD	2.3	1.9	2.9	3.8		
	N	10	10	10	10		
	P(v1)	0.9998	-	-	-		
3/1/M	Mean	28	29	28	29		
	SD	3.7	3.0	3.9	3.6		
	N	10	9	10	10		
	P(v1)	0.1093	-	-	-		
4/1/M	Mean	28*	27	27	27		
	SD	3.0	2.5	6.5	5.2		
	N	9	10	10	10		
	P(v1)	0.0498	-	-	-		
	Statistics	A	A	A	A		

\* P<=0.05  
A = ANOVA and Dunnett's

**Females:**

Table  
Summary of Food Consumption

		Test Article	(dosage)				
		TRV130 fumarate	mg/kg/day	0	6	12	24
Group/ Subgroup/ Sex	Phase Day	Data Presented in "g/animal/day" DSNG				Interval X to X	
		1 - 8	8 - 15	15 - 22	22 - 29		
1/1/F	Mean	25	24	24	24		
	SD	2.4	2.7	2.8	3.6		
	N	10	10	10	10		
	P(overall)	0.2542	0.0493	0.3726	0.1659		
2/1/F	Mean	24	21*	22	21		
	SD	2.2	2.4	2.9	2.8		
	N	10	9	9	8		
	P(v1)	-	0.0408	-	-		
3/1/F	Mean	25	24	22	23		
	SD	1.9	3.0	3.3	1.8		
	N	9	9	10	10		
	P(v1)	-	0.9995	-	-		
4/1/F	Mean	24	23	23	23		
	SD	2.7	2.1	2.4	3.3		
	N	9	10	9	8		
	P(v1)	-	0.7632	-	-		
	Statistics	A	A	A	A		

\* P<=0.05  
A = ANOVA and Dunnett's

**Ophthalmoscopy**

No TRV130-related ophthalmic observations were noted.

**ECG**

NA

**Hematology**

TRV130-related hematology findings on Day 30 were limited to moderately lower white blood cell and absolute lymphocyte counts in males administered 24 mg/kg/day. These findings were consistent with a stress response, also suggested by the increased incidence and severity of hypertrophy of the adrenal cortex noted in males in this group microscopically.

Table  
Summary of Hematology

Group/ Subgroup/ Sex	Phase Day	Test Article (dosage)				TRV130 fumarate	
		1 mg/kg/day	2 6	3 12	4 24	mg/kg/day	
		RETIC E3/uL Dosing	PLT E3/uL Dosing	WBC E3/uL Dosing	NEUT E3/uL Dosing	LYM E3/uL Dosing	MONO E3/uL Dosing
		30	30	30	30	30	30
1/1/M	Mean	259.2	987	12.09	1.82	9.76	0.22
	SD	48.84	202.0	1.968	0.901	1.499	0.098
	N	9	9	9	9	9	9
	P(overall)	0.5843	0.9242	0.0827	0.7160	0.0414	0.0630
2/1/M	Mean	272.7	1010	11.87	2.54	8.69	0.28
	SD	81.80	310.4	2.939	1.490	2.865	0.097
	N	10	10	10	10	10	10
	P(v1)	-	-	-	-	0.3334	-
3/1/M	Mean	250.2	939	11.21	1.99	8.71	0.23
	SD	42.62	144.1	3.647	1.529	2.755	0.131
	N	9	9	9	9	9	9
	P(v1)	-	-	-	-	0.4870	-
4/1/M	Mean	235.8	974	8.90	1.72	6.81*	0.14
	SD	38.49	208.1	1.582	0.534	1.179	0.046
	N	8	8	8	8	8	8
	P(v1)	-	-	-	-	0.0133	-
	Statistics	A	A	AT	AT	AT	A

\* P<=0.05  
A = ANOVA and Dunnett's  
T = Rank-transformed data

**Clinical Chemistry**

TRV130-related clinical chemistry findings on Day 30 are listed below. Due to the moderate changes, these effects were not considered adverse.

- Higher urea nitrogen in males administered 24 mg/kg/day and females administered ≥6 mg/kg/day
- Higher total serum protein in females administered ≥6 mg/kg/day
- Lower alkaline phosphatase activity in males administered ≥6 mg/kg/day and females administered ≥12 mg/kg/day

Table 5.2: Summary of Clinical Chemistry

		Test Article (dosage)		1	2	3	4
		TRV130 fumarate	mg/kg/day	0	6	12	24
Group/ Subgroup/ Sex	Phase Day	GLU mg/dL	UN mg/dL	CREA mg/dL	TP g/dL	ALB g/dL	GLOB g/dL
		Dosing	Dosing	Dosing	Dosing	Dosing	Dosing
		30	30	30	30	30	30
1/1/M	Mean	75	14	0.7	6.6	4.1	2.5
	SD	16.3	1.2	0.05	0.19	0.23	0.25
	N	9	9	9	9	9	9
	P(overall)	0.6924	0.0392	-	0.7075	0.3223	0.3708
2/1/M	Mean	83	15	0.7	6.6	3.9	2.7
	SD	15.0	2.5	0.07	0.19	0.41	0.41
	N	10	10	10	10	10	10
	P(v1)	-	0.7417	-	-	-	-
3/1/M	Mean	81	16	0.7	6.7	4.2	2.5
	SD	11.7	1.6	0.04	0.32	0.32	0.41
	N	10	10	10	10	10	10
	P(v1)	-	0.2791	-	-	-	-
4/1/M	Mean	79	18*	0.7	6.6	4.1	2.5
	SD	11.6	4.0	0.04	0.21	0.32	0.26
	N	10	10	10	10	10	10
	P(v1)	-	0.0167	-	-	-	-
Statistics		A	A	X2	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's  
X2 = Not analyzed (too few distinct values)

		Test Article (dosage)		1	2	3	4
		TRV130 fumarate	mg/kg/day	0	6	12	24
Group/ Subgroup/ Sex	Phase Day	GLU mg/dL	UN mg/dL	CREA mg/dL	TP g/dL	ALB g/dL	GLOB g/dL
		Dosing	Dosing	Dosing	Dosing	Dosing	Dosing
		30	30	30	30	30	30
1/1/F	Mean	106	13	0.7	7.5	5.0	2.6
	SD	9.0	1.2	0.07	0.47	0.53	0.42
	N	10	10	10	10	10	10
	P(overall)	0.3794	0.0085	-	0.0026	0.2053	0.3350
2/1/F	Mean	95	17*	0.7	8.2*	5.3	2.9
	SD	10.8	2.0	0.04	0.35	1.09	0.81
	N	8	8	8	8	8	8
	P(v1)	-	0.0086	-	0.0027	-	-
3/1/F	Mean	100	16	0.7	8.1*	5.6	2.6
	SD	17.5	2.9	0.07	0.24	0.48	0.29
	N	10	10	10	10	10	10
	P(v1)	-	0.0587	-	0.0073	-	-
4/1/F	Mean	97	17*	0.8	8.1*	5.5	2.6
	SD	15.4	3.2	0.08	0.48	0.47	0.17
	N	8	8	8	8	8	8
	P(v1)	-	0.0114	-	0.0110	-	-
Statistics		A	A	X2	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's  
X2 = Not analyzed (too few distinct values)

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1 2 3 4  
TRV130 fumarate mg/kg/day 0 6 12 24

Group/ Subgroup/ Sex	Phase Day	GLU mg/dL	UN mg/dL	CREA mg/dL	TP g/dL	ALB g/dL	GLOB g/dL
		Dosing	Dosing	Dosing	Dosing	Dosing	Dosing
		30	30	30	30	30	30
1/1/F	Mean	106	13	0.7	7.5	5.0	2.6
	SD	9.0	1.2	0.07	0.47	0.53	0.42
	N	10	10	10	10	10	10
	P(overall)	0.3794	0.0085	-	0.0026	0.2053	0.3350
2/1/F	Mean	95	17*	0.7	8.2*	5.3	2.9
	SD	10.8	2.0	0.04	0.35	1.09	0.81
	N	8	8	8	8	8	8
	P(v1)	-	0.0086	-	0.0027	-	-
3/1/F	Mean	100	16	0.7	8.1*	5.6	2.6
	SD	17.5	2.9	0.07	0.24	0.48	0.29
	N	10	10	10	10	10	10
	P(v1)	-	0.0587	-	0.0073	-	-
4/1/F	Mean	97	17*	0.8	8.1*	5.5	2.6
	SD	15.4	3.2	0.08	0.48	0.47	0.17
	N	8	8	8	8	8	8
	P(v1)	-	0.0114	-	0.0110	-	-
Statistics		A	A	X2	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's  
X2 = Not analyzed (too few distinct values)

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1 2 3 4  
TRV130 fumarate mg/kg/day 0 6 12 24

Group/ Subgroup/ Sex	Phase Day	ALP U/L	GGT U/L	Ca mg/dL	PHOS mg/dL	Na mmol/L	K mmol/L
		Dosing	Dosing	Dosing	Dosing	Dosing	Dosing
		30	30	30	30	30	30
1/1/M	Mean	154	<3	11.2	7.4	146	5.7
	SD	23.8	0.0	0.35	0.31	1.0	0.43
	N	9	9	9	9	9	9
	P(overall)	0.0033	-	0.0666	0.7734	0.7474	0.2768
2/1/M	Mean	112*	<3	11.1	7.5	147	5.7
	SD	24.1	0.0	0.36	0.43	1.3	0.28
	N	10	10	10	10	10	10
	P(v1)	0.0010	-	-	-	-	-
3/1/M	Mean	131	<3	11.0	7.5	147	5.4
	SD	22.5	0.0	0.48	1.08	2.6	0.50
	N	10	10	10	10	10	10
	P(v1)	0.1046	-	-	-	-	-
4/1/M	Mean	123*	<3	10.7	7.3	147	5.4
	SD	22.5	0.0	0.22	0.76	1.9	0.41
	N	10	10	10	10	10	10
	P(v1)	0.0175	-	-	-	-	-
Statistics		A	X5	A	AT	A	A

\* P<=0.05  
A = ANOVA and Dunnett's  
X5 = Not analyzed (values above/below the limit of quantitation)  
T = Rank-transformed data

Table  
Summary of Clinical Chemistry  
Test Article (dosage) 1 2 3 4  
TRV130 fumarate mg/kg/day 0 6 12 24

Group/ Subgroup/ Sex	Phase Day	ALP U/L	GGT U/L	Ca mg/dL	PHOS mg/dL	Na mmol/L	K mmol/L
		Dosing	Dosing	Dosing	Dosing	Dosing	Dosing
		30	30	30	30	30	30
1/1/F	Mean	80	<3	11.8	6.2	146	5.2
	SD	45.0	0.0	0.33	0.48	2.8	0.26
	N	10	10	10	10	10	10
	P (overall)	0.2464	-	0.2359	0.6272	0.7663	0.7410
2/1/F	Mean	93	<3	12.0	5.9	146	5.3
	SD	114.1	0.7	0.55	0.70	2.8	0.50
	N	8	8	8	8	8	8
	P (v1)	-	-	-	-	-	-
3/1/F	Mean	59	<3	12.1	5.9	146	5.3
	SD	7.4	0.0	0.37	0.82	1.8	0.39
	N	10	10	10	10	10	10
	P (v1)	-	-	-	-	-	-
4/1/F	Mean	53	<3	12.0	5.8	145	5.1
	SD	7.3	0.0	0.29	0.81	1.8	0.22
	N	8	8	8	8	8	8
	P (v1)	-	-	-	-	-	-
Statistics		AT	X5	A	A	A	A

A = ANOVA and Dunnett's  
T = Rank-transformed data  
X5 = Not analyzed (values above/below the limit of quantitation)

*Reviewer's note: The mild effects observed in hematology and clinical chemistry have been considered as responses to stress or dehydration by the Applicant. The Applicant hypothesized that the lower alkaline phosphatase activity may have been related to transient reduction in food consumption observed in some of these groups. However, the reduced alkaline phosphatase activity appears more robust in females, while the food intake in females appears to be minimally affected.*

**Urinalysis**

TRV130-related urinalysis findings on Day 30 included mildly lower urine volume and higher urine specific gravity in males administered ≥6 mg/kg/day. In the absence of histologic changes in the kidney, these findings likely reflected dehydration (reduced glomerular filtration rate).

**Males:**

**Table 5.3: Summary of Urinalysis**

Test Article		(dosage)	1	2	3	4
TRV130 fumarate		mg/kg/day	0	6	12	24
Group/ Subgroup/ Sex	Phase Day	UVOL mL	SPGR		UpH	
		Dosing	Dosing		Dosing	
		30	30		30	
1/1/M	Mean	25.2	1.019		6.9	
	SD	7.88	0.0051		0.22	
	N	9	9		9	
	P (overall)	0.0017	-		-	
2/1/M	Mean	16.6*	1.026		6.6	
	SD	5.87	0.0077		0.32	
	N	10	10		10	
	P (v1)	0.0174	-		-	
3/1/M	Mean	15.9*	>1.029		6.6	
	SD	7.07	0.0109		0.28	
	N	10	10		10	
	P (v1)	0.0096	-		-	
4/1/M	Mean	12.8*	1.034		6.4	
	SD	5.00	0.0094		0.32	
	N	10	10		10	
	P (v1)	0.0006	-		-	
Statistics		A	X5		X2	

\* P<=0.05  
 A = ANOVA and Dunnett's  
 X5 = Not analyzed (values above/below the limit of quantitation)  
 X2 = Not analyzed (too few distinct values)

**Females:**

Table  
Summary of Urinalysis

Test Article		(dosage)	1	2	3	4
TRV130 fumarate		mg/kg/day	0	6	12	24
Group/ Subgroup/ Sex	Phase Day	UVOL mL	SPGR		UpH	
		Dosing	Dosing		Dosing	
		30	30		30	
1/1/F	Mean	19.2	1.022		6.5	
	SD	7.73	0.0094		0.33	
	N	10	10		10	
	P (overall)	0.1018	-		-	
2/1/F	Mean	9.4	>1.035		6.3	
	SD	4.28	0.0088		0.37	
	N	8	8		8	
3/1/F	Mean	17.0	>1.028		6.4	
	SD	12.77	0.0148		0.24	
	N	10	10		10	
4/1/F	Mean	15.4	>1.032		6.3	
	SD	16.16	0.0177		0.53	
	N	8	8		8	
Statistics		AT	X5		X2	

A = ANOVA and Dunnett's  
 T = Rank-transformed data  
 X5 = Not analyzed (values above/below the limit of quantitation)  
 X2 = Not analyzed (too few distinct values)

*Reviewer's note: Similar effects were observed in the previous 14-day rat studies.*

## Terminal Procedure

In this study, rats were euthanized within 45 minutes after the discontinuation of infusion on Day 30. The following tissues from each animal were preserved in 10% neutral-buffered formalin, unless otherwise indicated.

Organ/Tissue		Organ/Tissue	
adrenal (2)	W P,E	muscle, biceps femoris	P,E
aorta	P,E	optic nerve (2) <sup>a</sup>	P,E
brain <sup>b</sup>	W P,E	ovary (2)	W P,E
catheterization site	P,E	pancreas	P,E
cecum	P,E	pituitary gland	W P,E
cervix	P,E	prostate	W P,E
colon	P,E	rectum	P,E
duodenum	P,E	salivary gland (mandibular [2])	W P,E
epididymis (2)	W P,E	sciatic nerve	P,E
esophagus	P,E	seminal vesicle	W P,E
eye (2) <sup>a</sup>	P,E	skin/subcutis	P,E
femur with bone marrow (articular surface of the distal end)	P,E	spinal cord (cervical, thoracic, and lumbar)	P,E
Harderian gland <sup>a</sup>	P,E	spleen	W P,E
heart	W P,E	sternum with bone marrow	P,E
ileum	P,E	stomach	P,E
infusion site(s)	P,E	testis (2) <sup>a</sup>	W P,E
jejunum	P,E	thymus	W P,E
kidney (2)	W P,E	thyroid (2 lobes) with parathyroid	W P,E
liver	W P,E	tongue	P,E
lesions	P,E	trachea	P,E
lungs with large bronchi	W P,E	urinary bladder	P,E
lymph nodes (mandibular)	P,E	uterus	W P,E
lymph nodes (mesenteric)	P,E	vagina	P,E
mammary glands (females)	P,E		

E = Examined microscopically; P = Processed; W = Weighed.

a Collected in modified Davidson's fixative and stored in 10% neutral-buffered formalin.

b Brain will be sectioned into seven sections, according to published recommendations (Bolton et al., 2013), to include the olfactory bulb.

The following animals had tissues embedded in paraffin, sectioned, and slides were prepared and stained with hematoxylin and eosin:

- Toxicity animals in control and high-dose groups
- Toxicity animals that died or were sacrificed at an unscheduled interval
- Lungs, stomachs, macroscopic lesions, infusion sites and pancreas (males only) from toxicity animals in the low- and mid-dose groups

## Gross Pathology

At the terminal sacrifice, the increased incidence of the macroscopic observations of thickened infusion site in animals administered TRV130 was considered TRV130-related and correlated with the increased incidence and/or severity of the microscopic finding of minimal to severe mixed cell inflammation.

**Organ Weights**

No direct TRV130-related changes in organ weight parameters occurred at the terminal sacrifice.

- Increased adrenal weight parameters in males administered 24 mg/kg/day correlated with the increased incidence and severity of the microscopic finding of hypertrophy of the adrenal cortex in this group, which was considered stress related.
- Decreased liver weights in males administered 12 or 24 mg/kg/day lacked a microscopic correlate or a dose response and were considered secondary to the reduction in body weight change and trend toward decreased terminal body weights in these groups.

Table  
Summary of Organ Weights and Organ Weight Ratios  
Terminal Sacrifice (Dosing phase)  
Test Article (dosage) 1 2 3 4  
TRV130 fumarate mg/kg/day 0 6 12 24

Group/ Subgroup/ Sex	Terminal Body Weight (g)	Adrenal			Thyroid/Parathyroid			
		Unadjusted (g)	Body Weight (%)	Brain Weight (%)	Unadjusted (g)	Body Weight (%)	Brain Weight (%)	
1/1/M	Mean	420	0.0644	0.0153	3.0012	0.0255	0.0060	1.1924
	SD	22.3	0.01018	0.00191	0.41760	0.00598	0.00125	0.30205
	N	9	9	9	9	9	9	9
	P(overall)	0.1776	0.0869	0.0146	0.1040	0.1078	0.0474	0.1150
2/1/M	Mean	401	0.0728	0.0183	3.3081	0.0352	0.0087	1.5833
	SD	39.9	0.01230	0.00388	0.58770	0.01187	0.00283	0.50525
	N	10	10	10	10	10	10	10
	P(v1)	-	-	0.1400	-	-	0.0599	-
3/1/M	Mean	390	0.0733	0.0189	3.2595	0.0318	0.0084	1.4141
	SD	38.5	0.01329	0.00322	0.70054	0.01067	0.00339	0.49153
	N	10	10	10	10	10	10	10
	P(v1)	-	-	0.0693	-	-	0.1193	-
4/1/M	Mean	387	0.0791	0.0206*	3.6857	0.0356	0.0091*	1.6547
	SD	35.7	0.01175	0.00397	0.59212	0.00896	0.00175	0.38917
	N	10	10	10	10	10	10	10
	P(v1)	-	-	0.0044	-	-	0.0261	-
	Statistics	A	A	A	A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's

Table 5.1: Summary of Organ Weights and Organ Weight Ratios - Terminal Sacrifice (Dosing Phase)

Group/ Subgroup/ Sex	Terminal Body Weight (g)	Liver			Kidney			
		Unadjusted (g)	Body Weight (%)	Brain Weight (%)	Unadjusted (g)	Body Weight (%)	Brain Weight (%)	
1/1/M	Mean	420	10.3808	2.4713	484.2510	2.4504	0.5832	114.1595
	SD	22.3	0.59805	0.10808	19.34076	0.25199	0.05494	8.75336
	N	9	9	9	9	9	9	9
	P(overall)	0.1776	0.0293	0.0080	0.0024	0.6609	0.6929	0.1124
2/1/M	Mean	401	9.9698	2.4854	452.0767	2.4163	0.6027	109.5370
	SD	39.9	1.08072	0.08546	42.84922	0.28161	0.04175	11.16015
	N	10	10	10	10	10	10	10
	P(v1)	-	0.7112	0.9775	0.2543	-	-	-
3/1/M	Mean	390	9.1524*	2.3427*	406.3671*	2.3035	0.5931	102.1688
	SD	38.5	1.19033	0.10013	59.12163	0.18973	0.04059	9.28112
	N	10	10	10	10	10	10	10
	P(v1)	-	0.0352	0.0387	0.0010	-	-	-
4/1/M	Mean	387	9.1644*	2.3701	425.7059*	2.3738	0.6158	110.2655
	SD	35.7	1.09626	0.21620	38.75885	0.32998	0.09330	12.63825
	N	10	10	10	10	10	10	10
	P(v1)	-	0.0373	0.0761	0.0145	-	-	-
	Statistics	A	A	AT	A	A	A	A

\* P<=0.05  
A = ANOVA and Dunnett's  
T = Rank-transformed data

**Histopathology****Adequate Battery: Yes****Peer Review: No**

- TRV130-related microscopic finding was a dose-dependent increase in the incidence and/or severity of minimal to severe mixed cell inflammation at the infusion site in animals administered  $\geq 6$  mg/kg/day; this correlated with an increased incidence of the macroscopic observation of thickened infusion site and was considered a local rather than a systemic effect of TRV130.
- Minimal or slight hypertrophy of the adrenal cortex in males administered 24 mg/kg/day, which correlated with increased adrenal weight parameters
- Greater incidence and severity of increased apoptosis in the pancreas in males administered 24 mg/kg/day

The Applicant considered the pancreas and adrenal changes secondary to decreased food consumption or stress rather than direct effects of TRV130.

**Text Table 4.3: Incidence and Severity of Selected Microscopic Findings - Terminal Sacrifice**

Dose Level (mg/kg/day)	Sex	TRV130							
		Males				Females			
		0	6	12	24	0	6	12	24
Infusion Site									
	Number Examined	9	10	10	10	10	8	10	8
Inflammation, mixed cell									
	Minimal	1	2	2	1	2	1	0	0
	Slight	0	2	1	0	2	2	1	0
	Moderate	3	0	3	3	0	1	2	2
	Marked	1	3	2	6	1	0	2	4
	Severe	0	0	1	0	0	1	0	2
Bacteria									
	Present	0	1	1	0	0	1	1	0
Pancreas									
	Number Examined	9	10	10	10	10	0	0	8
Apoptosis, increased									
	Minimal	1	1	3	3	2	NE	NE	2
	Slight	0	0	0	1	0	NE	NE	0

NE = Not examined.

Table 5.4: Summary of Severity of Microscopic Observations - Terminal Sacrifice (Dosing Phase)

Tissue/ Observation	Group/Subgroup/Sex: Number of Animals:	Test Article (dosage)				1 2 3 4					
		TRV130 fumarate	mg/kg/day	0	6	12	24	10	8	10	8
Adrenal, Cortex	Number Examined:	9	0	0	10	10	0	0	8		
	Unremarkable:	8	0	0	3	8	0	0	6		
Hypertrophy	finding not present -	8	0	0	4	8	0	0	6		
	minimal 1	1	0	0	2	2	0	0	2		
	slight 2	0	0	0	4	0	0	0	0		
	Total Incidence:	1	0	0	6	2	0	0	2		
Inflammation, blood vessel	finding not present -	9	0	0	9	10	0	0	8		
	minimal 1	0	0	0	1	0	0	0	0		
	Total Incidence:	0	0	0	1	0	0	0	0		
Adrenal, Medulla	Number Examined:	9	0	0	9	10	0	0	8		
	Unremarkable:	9	0	0	9	10	0	0	7		
Infiltrate, mononuclear cell	finding not present -	9	0	0	9	10	0	0	7		
	minimal 1	0	0	0	0	0	0	0	1		
	Total Incidence:	0	0	0	0	0	0	0	1		
Aorta	Number Examined:	9	0	0	10	10	0	0	8		
	Unremarkable:	9	0	0	10	10	0	0	8		

## Special Evaluation

NA

## Toxicokinetics

Blood samples (approximately 0.5 mL) were collected from nonfasted toxicokinetic animals via a jugular vein as indicated in the following table. Plasma analysis for TRV130 and TRV0109662 (metabolite) were conducted.

Group	Subgroup	Set	Dosing Phase Day	Time Points <sup>a</sup>
1	2	three/sex/group	1, 8, 15, 22, and 29	4 hours postdose
2, 3, 4	2	three/sex/group	1 8 and 29	2 hour postdose 4 hours postdose
2, 3, 4	2	three/sex/group	1 15	4 hours postdose 4 hours postdose
2, 3, 4	2	three/sex/group	1 22	8 hours postdose 4 hours postdose

a Blood collection times were approximate. Day 1 times were based on the start of infusion for each animal. Times on remaining days were based on the time of syringe change for each animal.

No sex differences in TRV130 or TRV0109662 (metabolite) mean  $C_{ss}$  values were observed; therefore, results and discussion were based on combined sex values. Exposure, as assessed by mean  $C_{ss}$  values, increased with the increase in dose level from 6 to 24 mg/kg/day; the increases in mean TRV130  $C_{ss}$  values were roughly dose proportional, while the increase in mean TRV0109662  $C_{ss}$  values were less than dose proportional. Mean TRV130 CL values ranged from 5270 to 6430 mL/h/kg. The mean  $C_{ss}$  metabolite to parent ratios ranged from 0.00695 to 0.0135.

**Table 21: Summary of Mean TRV130 C<sub>ss</sub> and CL and Mean TRV0109662 C<sub>ss</sub> in Rat Plasma**

Group	TRV130 Dose Level (mg/kg/hr)	Sex	TRV130 C <sub>ss</sub> (ng/mL)	TRV130 CL (mL/hr/kg)	TRV0109662 C <sub>ss</sub> (ng/mL)
2	0.25	Male	43.0	5850	0.670
		Female	43.5	5780	0.502
		Combined	43.3	5820	0.586
3	0.5 (NOAEL)	Male	81.2	6170	1.24
		Female	74.9	6690	0.735
		Combined	78.0	6430	0.989
4	1.0	Male	213	4730	1.54
		Female	175	5820	1.16
		Combined	194	5270	1.35

CL = Clearance; C<sub>ss</sub> = Steady state concentration; NOAEL = No observed adverse effect level

### Dosing Solution Analysis

All formulations were within  $\pm 10\%$  of the target concentrations (means ranging from 95.5 to 101.5% of theoretical). The test article was not detected in any vehicle control article formulation. Thus, all formulations met the acceptance criteria for study use.

### Study title: TRV130A: 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Study in Cynomolgus Monkeys

This study evaluated the toxicity and determined the toxicokinetics of TRV130 when administered 24 hours/day via continuous IV infusion to cynomolgus monkeys for at least 14 days. The animals were sacrificed with 45 minutes after cessation of drug infusion.

*Note: The review of this study was adapted from Dr. Armaghan Emami's review of IND 113537.*

Study no.: 8242809  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8242807\8242807-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: 25 May 2011  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: TRV130A (HCL salt), Lot CMLW-423/11-TV3, purity: 99.1%

### Key Study Findings

- Test article-related clinical observations in animals given  $\geq 0.2$  mg/kg/h:

- Low or no food consumption, hunched posture, tremors, red skin, and skin scabs. Red nasal discharge, thin appearance, and skin sores were also noted in HD (1 mg/kg/h) animals.
  - These clinical observations were attributed to the class of compound (i.e., stereotypic behavior such as repetitive skin picking or scratching associated with agonists at the mu-opioid receptor).
  - Hunched posture was also noted on Day 15 of the dosing phase in animals given  $\geq 0.2$  mg/kg/h, but this finding occurred after dosing was completed and animals were no longer exposed to the test article, suggesting the finding was a response due to cessation of TRV130A administration.
  - The QTc interval was significantly longer on Day 11 of the dosing phase in males (mean QTc interval = 348 msec compared with control males (331 msec) given 1 mg/kg/h. However, there was no dose dependency given that QTc interval was shorter on Day 11 of the dosing phase in males given 0.05 mg/kg/h or 0.2 mg/kg/h. Therefore, the statistical finding in QTc interval on Day 11 of the dosing phase in males given 1 mg/kg/h was considered incidental and not attributed to TRV130A.
- Test article-related macroscopic findings:
  - Sores and scabs were noted in the skin/subcutis of the shoulders, distal tail, or hind foot of some animals given  $\geq 0.2$  mg/kg/h and correlated with some microscopic findings.
    - These findings were attributed to the class of compound.
- Test article-related microscopic findings:
  - Minimal to marked skin findings (erosion/ulceration, chronic-active inflammation, and acanthosis/hyperkeratosis) in animals given  $\geq 0.2$  mg/kg/h
    - These findings are attributed to the class of compound (opioids).
  - Minimal thymic atrophy observed in 3/6 MD and 2/6 of animals given 1 mg/kg/day.
    - Considered as a consequence of opioid-induced stress
- The Applicant concluded that the NOAEL for the test article is 1 mg/kg/h, given that the test-article related clinical observations and macroscopic and microscopic findings at this dose level were not indicative of systemic toxicity and not dose limiting within the context of this study. This reviewer considered the skin ulceration/erosion adverse. However, given that skin ulceration/erosion commonly occurs in opioid-users and is related to the class of compound and is monitorable, this reviewer agrees that the 1 mg/kg/day can be used to establish the safety margin from this study. The average  $C_{ss}$  plasma concentration in monkeys given 1 mg/kg/h in the 14-day study was approximately 356 ng/mL corresponding to  $AUC_{0-24h}$  of 8562 ng\*hour/mL that is 11 times the estimated total daily human exposure of 783 ng\*h/mL at MRHD of 40 mg/day.

**Methods**

Doses: 0, 0.05, 0.2, or 1 mg/kg/h (0, 1.2, 4.8 and 24 mg/kg/day)  
 Frequency of dosing: Continuous IV infusion for 14 days  
 Route of administration: Intravenous infusion  
 Dose volume: at a dose rate of 1 mL/kg/h  
 Formulation/Vehicle: TRV130A (HCl salt) suspended in the vehicle [0.2 mM sodium phosphate buffer in 5% w/v Dextrose Injection, USP (D5W)]  
 Species/Strain: Cynomolgus monkeys

Group	No. of Animals		Dose Level (mg/kg/hour)	Dose Cor (mg)
	Male	Female		
1 (Control) <sup>b</sup>	3	3	0	0
2 (Low)	3	3	0.05	0
3 (Mid)	3	3	0.2	0
4 (High)	3	3	1	1

a Concentrations were corrected for salt content using a correction factor of (b) (4)  
 b Group 1 received vehicle control article only.

Age: 2-4-year-old  
 Weight: 2.5 to 3.2 kg for males and 2.4 to 3.2 kg for females  
 Satellite groups: No  
 Unique study design: No  
 Deviation from study protocol: None of the deviations affected the results of the study.

**Observations and Results**

**Mortality**

None

**Clinical Signs**

Test article-related clinical observations in mid- and high-dose groups included low or no food consumption, hunched posture, tremors, red skin, and skin scabs. Red nasal discharge, thin appearance, and skin sores were also noted in HD animals. The Applicant considers these clinical changes were not adverse, given that they were attributed to the class of compound (i.e., stereotypic behavior such as repetitive skin picking, or scratching associated with agonists at the mu-opioid receptor). were generally transient, occurred at a relatively low incidence, and were of minimal severity, they were not considered adverse. *This Reviewer agrees with the Applicant's conclusion that these clinical changes can be considered not adverse, although the food reduction in the high-dose group does not appear to be minimal with low frequency.*

Summary of Clinical Observations

Test Article	(dosage)	1	2	3	4					
TRV130A (HCl salt)	mg/kg/hour	0	0.05	0.20	1					
Phase: Dosing										
Category	Group/Sex:	1/M	2/M	3/M	4/M	1/F	2/F	3/F	4/F	
Observation	Number in Group:	3	3	3	3	3	3	3	3	3
NORMAL										
No remarkable observations		3	3	3	3	3	3	3	2	
Appearance										
hunched posture		0	0	0	1	0	0	1	1	
thin		0	0	0	1	0	0	0	0	
tremors, all legs, intermittent		0	0	0	1	0	0	0	0	
tremors, arms, intermittent		0	0	0	1	0	0	0	0	
tremors, entire body, continuous		0	0	0	0	0	0	1	0	
Discharge										
red, nose		0	0	0	0	0	0	0	1	
Discharge - unknown source										
found in pan, red		0	0	0	0	0	0	0	1	
Excretion										
feces, nonformed		0	0	0	0	0	0	0	1	
Qualitative food consumption										
low		2	2	3	3	3	3	3	3	
none		0	0	0	3	0	0	1	2	

Phase: Dosing										
Category	Group/Sex:	1/M	2/M	3/M	4/M	1/F	2/F	3/F	4/F	
Observation	Number in Group:	3	3	3	3	3	3	3	3	3
Skin and pelage										
alopecia, entire body		0	0	0	0	1	0	0	0	
discolored haircoat, left shoulder, red		0	0	0	1	0	0	0	0	
discolored haircoat, right shoulder, red		0	0	0	1	0	0	0	0	
discolored haircoat, tail distal, red		0	0	0	0	0	0	0	1	
discolored skin, left shoulder, red		0	0	0	0	0	0	0	1	
discolored skin, nose, red		0	0	0	2	0	0	0	1	
discolored skin, right shoulder, red		0	0	0	0	0	0	2	1	
discolored skin, tail distal, red		0	0	0	0	0	0	0	1	
scab, left shoulder		0	0	0	1	0	0	0	0	
scab, right shoulder		0	0	0	0	0	0	2	1	
scab, tail distal		0	0	0	1	0	0	0	0	
scab, ventral thorax		0	0	0	0	0	0	0	1	
sore, left foot		0	0	0	0	0	0	0	1	
sore, left hind foot		0	0	0	0	0	0	0	1	
sore, left periorbital		0	0	0	0	0	0	0	1	
sore, nose		0	0	0	1	0	0	0	1	
sore, right shoulder		0	0	0	1	0	0	0	0	
sore, tail distal		0	0	0	0	0	0	0	1	

Reviewer’s note: The tremor was observed in 1/6 monkeys and only on Day 8. It was transit and likely stress-related. Therefore, it is not considered adverse.

Body Weights

No significant changes were noted in body weight or body weight gain, except that a statistically significant reduction of body weight was observed in male animals in the high dose group (1 mg/kg/day) at the end of the treatment period. Note that because animals given 0.2 or 1 mg/kg/h were noted with multiple days of low or no food consumption, all animals were provided with additional food supplements beginning on Day 4 of the dosing phase for the remainder of the study.

**Summary of Body Weight**

Test Article		(dosage)				
TRV130A (HCl salt)		mg/kg/hour	0	0.05	0.20	1
-----						
Data Presented in "kg"						
Group/ Sex	Phase	DSNG				
		Day	1	8	15	
-----						
1/M	Mean	2.8	2.8	2.9		
	SD	0.32	0.36	0.06		
	N	3	3	3		
2/M	Mean	2.7	2.8	2.7		
	SD	0.21	0.21	0.20		
	N	3	3	3		
3/M	Mean	2.8	2.8	2.6		
	SD	0.25	0.20	0.25		
	N	3	3	3		
	P(DR1)	-	-	0.2067		
4/M	Mean	2.6	2.6	2.4*		
	SD	0.12	0.10	0.15		
	N	3	3	3		
	P(DR1)	0.3935	0.2235	0.0072		
	Statistics	L	L	L		

\* P<=0.05

DR1 = Dose response test (Control group 1)  
L = Linear regression for dose response

**Food Consumption**

Test article-related clinical observations in the mid- and high-dose groups included low or no food consumption.

Test Article		(dosage)							
TRV130A (HCl salt)		mg/kg/hour	0	0.05	0.20	1			
-----									
Phase: Dosing									
-----									
Category	Group/Sex:	1/M	2/M	3/M	4/M	1/F	2/F	3/F	4/F
Observation	Number in Group:	3	3	3	3	3	3	3	3
-----									
Qualitative food consumption									
low		2	2	3	3	3	3	3	3
none		0	0	0	3	0	0	1	2

**Ophthalmoscopy**

No remarkable ophthalmic observations were noted.

**ECG**

Electrocardiograms were collected twice during the predose phase and on Day 11 of the dosing phase. Recordings were performed on animals anesthetized with ketamine. At each time point, six lead ECGs were recorded for at least 30 continuous seconds.

The QTc interval was significantly longer on Day 11 of the dosing phase in males given 1 mg/kg/h (mean QTc interval = 348 msec) compared with control males (331 msec). However, QTc interval was shorter on Day 11 of the dosing phase in males given 0.05 mg/kg/h (325 msec) or 0.2 mg/kg/h (323 msec). Additionally, QTc interval was identical on Day 11 of the

dosing phase in females given 1 mg/kg/h and control females (330 msec). Taken together, the statistical finding in QTc interval on Day 11 of the dosing phase in males given 1 mg/kg/h was considered incidental and not attributed to TRV130A. No test article-related changes in PR interval, QRS duration, QT interval, RR interval, or heart rate were observed on Day 11 of the dosing phase in any treatment animals. No rhythm abnormalities or qualitative ECG changes attributed to TRV130A were observed on Day 11 of the dosing phase as part of the qualitative assessment of the ECGs.

### Hematology

On Day 14 of the dosing phase, eosinophil count was significantly and moderately decreased in females treated with the high dose and a similar trend was present in males. A mild decrease in lymphocyte count was also present in animals treated with the high dose. The Applicant considered these changes likely represented stress due to procedures and handling and are not considered directly test article-related.

### Clinical Chemistry

No test article related changes.

### Urinalysis

No test article related changes.

### Terminal Procedure

On Day 15 of the dosing phase following the completion of dosing, all surviving animals were anesthetized with sodium pentobarbital, exsanguinated, and necropsied. All tissues from all animals were embedded in paraffin, stained with hematoxylin and eosin, and examined microscopically.

### Gross Pathology

TRV130A-related macroscopic findings of sores and scabs were noted in the skin/subcutis of some animals in the mid- and high-dose group. These lesions correlated microscopically with erosion/ulceration, chronic-active inflammation, and/or acanthosis/hyperkeratosis.

Test Article	Incidence of Macroscopic Observations								
	(dosage)		1	2	3	4			
TRV130A (HCl salt)	mg/kg/hour		0	0.05	0.20	1			
Tissue/ Observation No.	Group/Sex: No. of Animals Examined:	1/M 3	2/M 3	3/M 3	4/M 3	1/F 3	2/F 3	3/F 3	4/F 3
	Unremarkable:	2	2	3	0	1	2	0	0
Skin/Subcutis									
Discolored		0	0	0	0	0	0	0	1
Scab		0	0	0	1	0	0	2	1
Sore		0	0	0	2	0	0	0	2

**Organ Weights**

No significant organ weights or organ weight ratio changes

**Histopathology**

**Adequate Battery: Yes**

**Peer Review: Yes**

TRV130A-related microscopic findings were noted in the skin/subcutis and thymus:

- Skin/subcutis, erosion/ulceration and acanthosis/hyperkeratosis:
  - Higher incidence in females than males; Severity ranged from slight to marked
    - Mid-dose group: 2/3 females
    - High-dose group: 2/3 males; 3/3 females
  - These changes were consistent with the class of opioid compounds. Skin findings suggestive of excessive grooming and/or stereotypic behavior included red skin, scabs, and sores and one animal with excessive picking at the skin on the heel. Skin findings correlated microscopically with erosion/ulceration, chronic-active inflammation, and/or acanthosis/hyperkeratosis.
  
- Thymus atrophy:
  - Rated minimal
    - Mid-dose group: 1/3 male; 2/3 females
    - High-dose group: 1/3 male; 1/3 female.
  - Considered as a consequence of opioid-induced stress. It was characterized by attenuation of the cortex and/or blurring of the corticomedullary junction.

Sex	Male				Female			
Continuous Daily Dose (mg/kg/hour)	0 (Control)	0.05 (Low)	0.2 (Mid)	1 (High)	0 (Control)	0.05 (Low)	0.2 (Mid)	1 (High)
Number of Animals Examined	3	3	3	3	3	3	3	3
Microscopic Observations								
Skin/Subcutis								
Erosion/Ulceration								
Slight	0	0	0	0	0	0	1	0
Moderate	0	0	0	1	0	0	1	3
Marked	0	0	0	1	0	0	0	0
Inflammation, chronic-active								
Slight	0	0	0	0	0	0	1	2
Moderate	0	0	0	0	0	0	1	1
Marked	0	0	0	1	0	0	0	0
Acanthosis/Hyperkeratosis								
Slight	0	0	0	1	0	0	1	0
Moderate	0	0	0	1	0	0	1	2
Marked	0	0	0	0	0	0	0	1
Thymus								
Atrophy								
Minimal	0	0	1	1	0	0	2	1

- = No noteworthy findings; C<sub>ss</sub> = Steady state concentration; CL = Total plasma clearance; GLP = Good Laboratory Practices; NA = Not applicable.

*Reviewer's note: The Applicant did not consider the histopathological changes adverse in the context of this study. This reviewer considers erosion/ulceration as adverse event given its frequency and slight-marked severity.*

**Special Evaluation**

N/A

## Toxicokinetics

Steady state was generally achieved by 4 hours post the start of infusion on Day 1 of the dosing phase. Exposure to TRV130 free base increased with the increase in dose level from 0.05 to 1 mg/kg/h. Sex differences were less than 2-fold in TRV130 free base  $C_{ss}$  values. Increases in  $C_{ss}$  for males and females were roughly dose proportional.

Summary of Mean Toxicokinetic Parameters for TRV130 Free Base in Monkey Plasma

Group	Dose Level (mg/kg/hour)	Sex		$C_{ss}$ (ng/mL)	CL (mL/hr/kg)
2	0.05	M	Mean	30.7	1685
			SD	7.0	367
			N	3	3
		F	Mean	26.2	1923
			SD	2.7	212
			N	3	3
3	0.2	M	Mean	143	1463
			SD	38	354
			N	3	3
		F	Mean	149	1365
			SD	25	210
			N	3	3
4	1	M	Mean	710	1428
			SD	106	200
			N	3	3
		F	Mean	717	1403
			SD	68	141
			N	3	3

F= Female; M = Male; N = Number; SD = Standard deviation.

## Dosing Solution Analysis

All formulations were within +10% of the target concentrations (means ranged from 97.0 to 99.5% of theoretical). TRV130A was not detected in any vehicle control article formulation. Thus, all formulations met the acceptance criteria for study use, and animals received the intended dose.

## 7 Genetic Toxicology of Oliceridine

The following reviews of genetic toxicology studies are reproduced verbatim from Dr. Emami's review of IND 113537.

- Study title: TRV130A: Reverse mutation study in four histidine-requiring strains of *Salmonella typhimurium* and one tryptophan-requiring strain of *Escherichia coli* (Study 8242829)
- TRV130A: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes (Study 8242830)
- TRV130A: Intravenous 24-Hour Continuous Infusion Micronucleus Study Using Bone Marrow from Rats (Study 8242831)
- TRV 130A: Detection of DNA damage in the liver and blood of treated rats using the Comet assay (Study 8254795)

## 7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

**Study title: TRV130A (Hydrochloride Salt Form): Reverse Mutation Study in Four Histidine-requiring Strains of *Salmonella typhimurium* and One Tryptophan-requiring Strain of *Escherichia coli***

**Reviewed by Dr. Emami under IND 113537**

Study no.:	8242829
Study report location:	\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\8242829\8242829-study-report.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	28 June, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TRV130A, Lot CMLW-423/11-TV3, purity: 99.13%

### **Key Study Findings**

- TRV130A was tested in the Ames Reverse Mutation Assays at concentrations of 0.32 to 5000 mcg/plate.
- In the initial mutagenicity assay (plate incorporation method, Experiment 1) with and without S9, the test article was tested at concentration levels of 0.32, 1.6, 8, 40, 200, 1000, and 5000 mcg/plate. The evidence of toxicity was observed in all strains at 5000 mcg/plate, with the exception of strain WP2 uvrA in the presence of S9, where no evidence of toxicity was observed. No positive mutagenic response was observed.
- In the confirmatory mutagenicity assay (plate incorporation method, Experiment 2) with and without S9, the test article was tested at concentration levels of 156.3, 312.5, 635, 1250, 2500, and 5000 mcg/plate. The toxicity was observed in all strains at 5000 mcg/plate, with the exception of strain WP2 uvrA in the presence of S9, where no evidence of toxicity was observed. No positive mutagenic response was observed. Under the conditions of the study, TRV130A was concluded to be negative in the bacterial reverse mutation assay when tested up to maximum limit of 5000 mcg/plate.
- Under the conditions of the study, TRV130A was negative in the bacterial reverse mutation assay when tested up to maximum limit of 5000 mcg/plate.

<b>Methods</b>	
Strains:	S. typhimurium TA98, TA100, TA1535, TA1537, and E. coli WP2 uvrA.
Concentrations in initial mutagenicity study	0.32, 1.6, 8, 40, 200, 1000 and 5000 µg/plate
Concentrations in definitive study (confirmatory assay) :	156.3, 312.5, 635, 1250, 2500 and 5000 µg/plate
Basis of concentration selection:	Maximum recommended concentrations of test article
Negative control:	Water for test article
Positive control:	2-nitrofluorene (2NF) Sodium azide (NaN <sub>3</sub> ) 9-aminoacridine (AAC) 4-nitroquinoline 1-oxide (NQO) Benzo[a]pyrene (B[a]P) 2-aminoanthracene (AAN)
Formulation/Vehicle:	TRV130A/ water
Incubation & sampling time:	incubated at 37±1°C in the dark for 3 days
Protocol Deviation:	Deviation did not have an adverse impact on the integrity of the data or the validity of the study.

### **Study Validity**

All positive and vehicle control values were within acceptable ranges, and all criteria for a valid study was met.

### **Results**

The test article did not produce any increases in the number of revertants in any tester stain under the current conditions at concentrations up to 5000 mcg/plate in the absence and in the presence of a rat liver metabolic activation system (S-9). This is in concurrence with the Applicant's conclusions. See the Applicant's tables.

#### **Plate incorporation for initial assay (Experiment 1)**

The evidence of toxicity was observed in all strains at 5000 mcg/plate, with the exception of strain WP2 uvrA in the presence of S-9, where no evidence of toxicity was observed.

Metabolic Activation	Test Article	Concentration (µg/plate)	Experiment 1				
			Revertants/Plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2 uvrA
Without Activation	Purified water	100 µL	31.0 ± 1.0	130.8 ± 8.7	20.6 ± 6.5	6.4 ± 1.8	12.6 ± 3.4
	TRV130A	0.32	18.3 ± 11.0	132.7 ± 5.9	23.7 ± 4.7	9.3 ± 3.1	11.0 ± 3.5
	TRV130A	1.6	23.0 ± 5.2	131.3 ± 9.2	11.7 ± 2.5	7.0 ± 3.0	11.3 ± 0.6
	TRV130A	8	28.0 ± 6.1	135.3 ± 0.6	19.0 ± 7.0	10.0 ± 5.0	15.0 ± 4.0
	TRV130A	40	31.7 ± 4.9	143.0 ± 14.8	15.7 ± 0.6	7.7 ± 1.2	14.0 ± 2.0
	TRV130A	200	34.7 ± 6.4	137.7 ± 12.6	18.3 ± 2.9	8.3 ± 2.1	10.7 ± 3.5
	TRV130A	1000	29.0 ± 5.0	128.7 ± 13.7	24.3 ± 2.9	7.7 ± 1.2	12.3 ± 2.5
	TRV130A	5000	8.3 ± 4.9 <sup>S</sup>	76.7 ± 25.8 <sup>S</sup>	T	2.0 ± 2.6 <sup>S</sup>	5.7 ± 2.9 <sup>S</sup>
	2-Nitrofluorene (2NF)	5	592.7 ± 167.5	NT	NT	NT	NT
	Sodium azide (NaN <sub>3</sub> )	2	NT	651.0 ± 57.0	269.3 ± 78.9	NT	NT
	9-Aminoacridine (AAC)	50	NT	NT	NT	212.7 ± 54.8	NT
	4-nitroquinoline 1-oxide (NQO)	2	NT	NT	NT	NT	638 ± 26.7

S: Slight thinning of background bacterial lawn  
T: Toxic, no revertant colonies  
NT: Not tested

Metabolic Activation	Test Article	Concentration (µg/plate)	Experiment 1				
			Revertants/Plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2 uvrA
With Activation	Purified water	100 µL	35.2 ± 4.5	130.8 ± 12.5	16.8 ± 3.1	10.8 ± 5.4	16.6 ± 2.9
	TRV130A	0.32	39.0 ± 5.0	141.7 ± 4.5	20.3 ± 5.5	11.7 ± 2.1	14.7 ± 3.2
	TRV130A	1.6	32.0 ± 4.4	130.3 ± 33.6	19.0 ± 6.2	9.7 ± 5.0	8.7 ± 2.9
	TRV130A	8	30.3 ± 8.1	134.0 ± 14.7	15.7 ± 5.7	9.0 ± 3.0	22.3 ± 4.0
	TRV130A	40	36.0 ± 4.0	129.3 ± 18.3	20.0 ± 2.6	6.0 ± 2.6	12.0 ± 7.5
	TRV130A	200	40.7 ± 8.5	131.0 ± 10.8	16.7 ± 2.9	9.3 ± 0.6	12.3 ± 1.5
	TRV130A	1000	43.7 ± 7.5	131.7 ± 5.7	21.0 ± 2.6	8.7 ± 2.5	15.3 ± 3.5
	TRV130A	5000	7.3 ± 6.1 <sup>S</sup>	89.3 ± 8.3 <sup>S</sup>	7.3 ± 4.7 <sup>S</sup>	0.3 ± 0.6 <sup>S</sup>	10.7 ± 4.0
	Benzo[a]pyrene (B[a]P)	10	349.3 ± 72.4	NT	NT	NT	NT
	2-Aminoanthracene (AAN)	5	NT	568.3 ± 232.2	97.7 ± 24.1	34.7 ± 4.5	NT
	2-Aminoanthracene (AAN)	15	NT	NT	NT	NT	237.0 ± 34.0

S: Slight thinning of background bacterial lawn  
NT: Not tested

### Plate incorporation for confirmatory assay (Experiment 2)

The maximum test concentration of 5000 mcg/plate was retained for all strains. Narrowed concentration intervals were employed in this experiment (156.3 - 5000 mcg/plate). The toxicity was observed in all strains at 5000 mcg/plate, with the exception of strain WP2 uvrA in the presence of S9, where no evidence of toxicity was observed.

Metabolic Activation	Test Article	Concentration (µg/plate)	Experiment 2				
			Revertants/Plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2 uvrA
Without Activation	Purified water	100 µL	29.4 ± 9.4	129.2 ± 9.8	17.8 ± 4.7	13.6 ± 2.1	10.2 ± 2.7
	TRV130A	156.3	24.3 ± 9.0	123.0 ± 6.2	16.3 ± 5.1	13.7 ± 3.5	11.0 ± 5.6
	TRV130A	312.5	25.0 ± 4.6	135.3 ± 15.3	16.3 ± 7.5	15.0 ± 4.6	9.70 ± 2.3
	TRV130A	625	25.7 ± 1.2	130.3 ± 21.5	18.3 ± 6.7	12.0 ± 3.6	13.7 ± 6.4
	TRV130A	1250	23.7 ± 4.2	119.3 ± 3.1	14.3 ± 3.8	11.0 ± 1.0	13.3 ± 5.8
	TRV130A	2500	28.7 ± 6.4	120.0 ± 6.1	15.3 ± 3.5	11.3 ± 2.3	9.3 ± 2.9
	TRV130A	5000	10.3 ± 1.5 <sup>S</sup>	79.0 ± 13.5 <sup>S</sup>	4.0 ± 2.0 <sup>S</sup>	1.3 ± 2.3 <sup>S</sup>	9.7 ± 1.2 <sup>S</sup>
	2-Nitrofluorene (2NF)	5	849.7 ± 70.7	NT	NT	NT	NT
	Sodium azide (NaN <sub>3</sub> )	2	NT	596.0 ± 52.2	631.3 ± 25.7	NT	NT
	9-Aminoacridine (AAC)	50	NT	NT	NT	233.3 ± 45.7	NT
	4-nitroquinoline 1-oxide (NQO)	2	NT	NT	NT	NT	508.0 ± 46.2

S: Slight thinning of background bacterial lawn  
NT: Not tested

Metabolic Activation	Test Article	Concentration (µg/plate)	Experiment 2				
			Revertants/Plate (Mean ± SD)				
			TA98	TA100	TA1535	TA1537	WP2 <i>uvrA</i>
With Activation	Purified water	100 µL	36.8 ± 7.4	136.6 ± 14.9	23.2 ± 2.8	19.2 ± 7.0	17.2 ± 4.2
	TRV130A	156.3	36.7 ± 9.5	138.7 ± 3.2	27.3 ± 9.1	21.3 ± 3.2	12.3 ± 4.6
	TRV130A	312.5	42.0 ± 4.4	142.3 ± 17.9	24.3 ± 4.6	19.3 ± 4.0	13.7 ± 2.3
	TRV130A	625	48.7 ± 7.6	148.7 ± 1.2	27.3 ± 4.7	20.7 ± 5.7	15.7 ± 4.5
	TRV130A	1250	33.7 ± 14.2	142.3 ± 12.9	24.0 ± 6.2	18.0 ± 2.6	17.7 ± 4.0
	TRV130A	2500	22.3 ± 9.1	145.0 ± 11.4	27.7 ± 8.3	12.3 ± 6.1	12.7 ± 5.5
	TRV130A	5000	22.7 ± 9.0 <sup>S</sup>	128.7 ± 7.4 <sup>S</sup>	9.0 ± 2.0 <sup>S</sup>	4.3 ± 0.6 <sup>S</sup>	10.7 ± 1.5
	Benzo[a]pyrene (B[a]P)	10	283.3 ± 27.2	NT	NT	NT	NT
	2-Aminoanthracene (AAN)	5	NT	883.7 ± 172.4	237.3 ± 22.5	101.0 ± 12.2	NT
	2-Aminoanthracene (AAN)	15	NT	NT	NT	NT	154.3 ± 34.0

S: Slight thinning of background bacterial lawn  
 NT: Not tested

**Study title: TRV130 Fumarate: Bacterial Reverse Mutation Study**

In order to qualify an alternative TRV130 salt form, TRV130 fumarate was evaluated in this GLP study for its ability to induce reverse mutations at the histidine locus in four strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and at the tryptophan locus of *Escherichia coli* (*E. coli*) strain WP2 *uvrA* in the presence or absence of an exogenous metabolic activation system (S9) in two separate assays.

Study No. 8292857  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\8292857\8292857-study-report.pdf>

Conducting laboratory and location:  (b) (4)

Date of study initiation: 12/10/2013  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: TRV130 (fumarate); 2417-14-1; 99.3%

**Key Study Findings**

The study indicates that TRV130 fumarate is negative in the Bacterial Reverse Mutation Assay when tested up to 5000 mcg/plate in the presence and absence of S9 under the conditions of this protocol.

**Methods**

Strains: Four strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and at the tryptophan locus of *Escherichia coli* (*E. coli*) strain WP2 *uvrA*

Concentrations in definitive study: 5.00, 16.0, 50.0, 160, 500, 1600, and 5000 mcg/plate

Basis of concentration selection: Maximum recommended concentration

Negative control: Water

Positive control:

Tester Strain(s)	S9	Positive Control Articles			
		Positive Control	Dose (µg/plate)	CAS No.	Lot No.
TA98	-	2-nitrofluorene	1.0	607-57-8	S43858
TA100, TA1535	-	sodium azide	2.0	26628-22-8	MKBF6507V
TA1537	-	ICR-191	2.0	17070-45-0	031M1947V
WP2 <i>uvrA</i>	-	4-nitroquinoline-N-oxide	1.0	56-57-5	A0305157
TA98	+	benzo[a]pyrene	2.5	50-32-8	090M1400V
TA100, TA1535, TA1537	+	2-aminoanthracene	2.5	613-13-8	STBB1901
WP2 <i>uvrA</i>	+	2-aminoanthracene	25.0	613-13-8	STBD3302V STBB1901

Formulation/Vehicle: Water

Incubation & sampling time: The test system was exposed to the test article via the plate incorporation methodology. There were 3 plates per dose in the presence and absence of metabolic activation. The metabolic activation system consisted of an S9 fraction prepared from livers obtained from Aroclor 1254 pretreated male Sprague-Dawley rats. The S9 percentage was 10%, which is within the acceptable range. Plates were incubated at 37°C for 52 ± 4 hours. Plates that were not counted immediately following the incubation period were stored at 2-8°C until colony counting could be conducted. The condition of the bacterial background lawn was evaluated for evidence of test article toxicity by using a dissecting microscope. Precipitate was evaluated after the incubation period by visual examination without magnification. As appropriate, colonies were enumerated either by hand or by machine.

### Study Validity

- Selection of bacterial tester strains was adequate based upon guideline for industry: *ICH S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (April 1996).
- Positive controls produced expected responses. In the initial assay, a suitable (≥3 fold) response was not produced by the positive control in TA1535 in the presence of S9. The assay was repeated (Initial 3) with this tester strain in the presence of S9 using the same dose levels as in the initial assay. Concurrent vehicle and positive controls were used. The positive control produced expected responses in the repeat studies.
- Dose selection for the plate incorporation method was adequate based upon use of the limit dose of 5000 mcg/plate.
- The S9 concentration was within acceptable limits.

**Results**

- No precipitate was observed at any tested dose level.
- Cytotoxicity (decrease in the mean number of revertant colonies and/or reduced background lawn):
  - Observed at 5000 mcg/plate in TA100 and TA1535 in the presence and absence of S9 and WP2uvrA in the presence of S9.
  - Observed at  $\geq 500$  mcg/plate in TA1537 and at  $\geq 1600$  mcg/plate in WP2uvrA in the absence of S9.
- In the Initial study (as shown in the table below), no increase in the number of revertant colonies was observed at any tested dose level with any tester strain in the initial or repeat assay in the presence or absence of S9. With the exception of TA1535 (2AA) in the presence of S9, all positive and vehicle control values were within acceptable ranges, and all criteria for a valid study were met.

**Table 14.1: Mutagenicity Assay Results with S9**

Study No.: 8292857  
 Trial No.: 8292857 Initial  
 Plating Method: Plate incorporation assay

Date Plated: 12/17/2013

Strain	Compound	Dose level (µg/plate)	Mean revertants per plate	SD	Ratio treated/vehicle	Individual revertant colony counts
TA98	TRV130 (fumarate)	5000	13.7	3.1	0.9	13 N, 17 N, 11 N
		1600	14.3	6.7	0.9	10 N, 22 N, 11 N
		500	17.7	5.9	1.1	11 N, 22 N, 20 N
		160	11.3	1.5	0.7	13 N, 11 N, 10 N
		50.0	13.7	3.5	0.9	17 N, 14 N, 10 N
		16.0	15.3	1.2	1.0	14 N, 16 N, 16 N
		5.00	15.3	3.1	1.0	16 N, 12 N, 18 N
		Reverse Osmosis Water		16.0	6.1	
TA100	TRV130 (fumarate)	5000	42.3	9.0	0.4	32 N, 48 N, 47 N
		1600	99.7	9.6	0.9	110 N, 98 N, 91 N
		500	110.0	6.0	1.0	110 N, 104 N, 116 N
		160	131.3	24.7	1.1	148 N, 103 N, 143 N
		50.0	105.3	15.6	0.9	120 N, 89 N, 107 N
		16.0	94.0	15.7	0.8	108 N, 77 N, 97 N
		5.00	109.7	6.5	1.0	103 N, 110 MN, 116 N
		Reverse Osmosis Water		114.7	6.1	
TA1535	TRV130 (fumarate)	5000	3.0	2.6	0.3	6 N, 1 N, 2 N
		1600	10.7	3.2	1.1	12 N, 13 N, 7 N
		500	16.0	3.0	1.6	16 N, 19 N, 13 N
		160	11.0	3.0	1.1	14 N, 11 N, 8 N
		50.0	11.3	1.5	1.1	11 N, 10 N, 13 N
		16.0	9.0	1.7	0.9	7 N, 10 N, 10 N
		5.00	11.7	0.6	1.2	12 N, 12 N, 11 N
		Reverse Osmosis Water		10.0	2.6	
TA1537	TRV130 (fumarate)	5000	3.3	1.2	0.7	4 N, 2 N, 4 N
		1600	4.7	0.6	0.9	5 N, 4 N, 5 N
		500	6.7	1.5	1.3	7 N, 5 N, 8 N
		160	3.7	2.5	0.7	6 N, 4 N, 1 N
		50.0	7.0	1.7	1.4	8 MN, 5 N, 8 N
		16.0	6.3	3.2	1.3	4 N, 5 N, 10 N
		5.00	5.3	1.5	1.1	7 N, 4 MN, 5 N
		Reverse Osmosis Water		5.0	2.6	

**Key to Plate Postfix Codes**

N	Normal background bacterial lawn
M	Plate counted manually
R	Reduced background bacterial lawn

Table 14.1 (Continued): Mutagenicity Assay Results with S9

Study No.: 8292857  
 Trial No.: 8292857 Initial  
 Plating Method: Plate incorporation assay

Date Plated: 12/17/2013

Strain	Compound	Dose level (µg/plate)	Mean revertants per plate	SD	Ratio treated/ vehicle	Individual revertant colony counts
WP2uvrA	TRV130 (fumarate)	5000	7.0	5.0	0.5	12 R, 7 R, 2 R
		1600	12.0	1.0	0.9	11 N, 13 N, 12 N
		500	15.3	5.0	1.1	16 N, 10 N, 20 N
		160	14.7	2.1	1.1	17 N, 13 N, 14 N
		50.0	16.3	4.7	1.2	20 N, 11 N, 18 N
		16.0	16.7	4.2	1.2	12 N, 20 N, 18 N
		5.00	16.0	2.6	1.2	18 N, 13 N, 17 N
		Reverse Osmosis Water		13.7	4.7	
TA98	BP	2.5	423.7	47.6	26.5	415 N, 381 N, 475 N
TA100	2AA	2.5	1122.3	39.6	9.8	1168 N, 1102 N, 1097 N
TA1535	2AA	2.5	10.3	2.1	1.0	8 N, 12 N, 11 N
TA1537	2AA	2.5	82.7	6.5	16.5	83 MN, 89 N, 76 N
WP2uvrA	2AA	25.0	300.7	27.8	22.0	279 N, 332 N, 291 N

Key to Positive Controls

BP	Benzo(a)pyrene	N	Normal background bacterial lawn
2AA	2-aminoanthracene	M	Plate counted manually
		R	Reduced background bacterial lawn

Key to Plate Postfix Codes

- Given that the positive control in TA1535 (2AA) in the presence of S9 did not induce a suitable ( $\geq 3$  fold) response in the initial assay. The assay was repeated again (Initial 3) with tester strain TA1535 in the presence of S9 using the same dose levels as in the initial assay with concurrent vehicle and positive controls (See the table below). The positive and vehicle control values were within acceptable ranges, and no increase in the mean number of revertant colonies was observed.

Study No.: 8292857

Trial No.: 8292587 Initial 3

Date Plated: 1/28/2014

Plating Method: Plate incorporation assay

Strain	Compound	Dose level (µg/plate)	Mean revertants per plate	SD	Ratio treated/ vehicle	Individual revertant colony counts
TA1535	TRV130 (fumarate)	5000	6.7	3.1	0.5	10 N, 4 N, 6 N
		1600	15.0	3.6	1.2	12 N, 14 N, 19 N
		500	13.7	2.9	1.1	12 N, 12 N, 17 N
		160	10.3	2.5	0.8	8 N, 13 N, 10 N
		50.0	13.3	4.5	1.1	13 N, 18 N, 9 N
		16.0	13.3	0.6	1.1	13 N, 13 N, 14 N
		5.00	10.7	1.2	0.8	10 N, 10 N, 12 N
		Reverse Osmosis Water		12.7	4.0	
TA1535	2AA	2.5	168.7	40.5	13.3	122 N, 194 N, 190 N

2AA	2-aminoanthracene	N	Normal background bacterial lawn
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Table 14.2: Mutagenicity Assay Results without S9

Study No.: 8292857  
 Trial No.: 8292857 Initial  
 Plating Method: Plate incorporation assay

Date Plated: 12/17/2013

Strain	Compound	Dose level ( $\mu\text{g}/\text{plate}$ )	Mean revertants per plate	SD	Ratio treated/vehicle	Individual revertant colony counts
TA98	TRV130 (fumarate)	5000	10.7	4.2	0.9	12 N, 6 N, 14 N
		1600	9.0	3.5	0.8	5 N, 11 N, 11 N
		500	13.0	5.6	1.1	8 N, 19 N, 12 N
		160	9.7	3.5	0.8	6 N, 13 N, 10 N
		50.0	11.3	6.1	1.0	6 N, 18 N, 10 N
		16.0	11.3	6.7	1.0	13 N, 4 N, 17 N
		5.00	8.3	1.5	0.7	10 N, 7 N, 8 N
		Reverse Osmosis Water		11.7	2.1	
TA100	TRV130 (fumarate)	5000	42.0	6.0	0.5	36 N, 42 N, 48 N
		1600	88.0	15.4	0.9	101 N, 92 N, 71 N
		500	95.3	12.9	1.0	90 N, 110 N, 86 N
		160	103.0	24.0	1.1	95 N, 130 N, 84 N
		50.0	86.3	13.2	0.9	89 N, 98 N, 72 N
		16.0	76.3	3.5	0.8	76 N, 73 N, 80 N
		5.00	88.0	23.4	0.9	115 N, 73 N, 76 N
		Reverse Osmosis Water		93.0	17.1	
TA1535	TRV130 (fumarate)	5000	3.7	1.5	0.3	5 N, 2 N, 4 N
		1600	7.0	5.6	0.7	6 N, 2 N, 13 N
		500	12.7	6.7	1.2	17 N, 16 N, 5 N
		160	7.7	0.6	0.7	8 N, 8 N, 7 N
		50.0	10.3	2.5	1.0	10 N, 13 N, 8 N
		16.0	8.7	2.1	0.8	11 N, 8 N, 7 N
		5.00	12.7	2.9	1.2	11 N, 16 N, 11 N
		Reverse Osmosis Water		10.7	4.2	
TA1537	TRV130 (fumarate)	5000	2.0	2.0	0.4	0 N, 4 N, 2 N
		1600	2.3	1.5	0.5	2 N, 4 N, 1 N
		500	2.0	2.0	0.4	2 N, 4 N, 0 N
		160	4.0	2.0	0.8	2 N, 4 N, 6 N
		50.0	7.3	2.3	1.5	6 N, 10 N, 6 N
		16.0	3.7	3.2	0.7	0 N, 6 N, 5 N
		5.00	4.7	3.2	0.9	7 N, 1 N, 6 N
		Reverse Osmosis Water		5.0	1.0	

Key to Plate Postfix Codes

N	Normal background bacterial lawn
R	Reduced background bacterial lawn

(b) (4) Study No. 8292857  
 Sponsor Reference No. MORIVCOV19

**Table 14.2 (Continued): Mutagenicity Assay Results without S9**

Study No.: 8292857  
 Trial No.: 8292857 Initial  
 Plating Method: Plate incorporation assay

Date Plated: 12/17/2013

Strain	Compound	Dose level (µg/plate)	Mean revertants per plate	SD	Ratio treated/ vehicle	Individual revertant colony counts
WP2uvrA	TRV130 (fumarate)	5000	7.0	4.6	0.5	8 R, 11 R, 2 R
		1600	5.7	3.2	0.4	2 N, 7 N, 8 N
		500	11.3	5.8	0.8	8 N, 18 N, 8 N
		160	14.7	4.2	1.0	10 N, 16 N, 18 N
		50.0	12.7	4.2	0.9	16 N, 8 N, 14 N
		16.0	9.7	3.5	0.7	13 N, 10 N, 6 N
		5.00	14.3	10.7	1.0	12 N, 5 N, 26 N
	Reverse Osmosis Water		14.3	2.3		13 N, 13 N, 17 N
TA98	2NF	1.0	289.7	31.0	24.8	259 N, 289 N, 321 N
TA100	SA	2.0	939.0	88.2	10.1	858 N, 926 N, 1033 N
TA1535	SA	2.0	756.0	35.4	70.9	794 N, 724 N, 750 N
TA1537	ICR	2.0	383.7	19.9	76.7	392 N, 361 N, 398 N
WP2uvrA	4NQO	1.0	183.7	13.6	12.8	168 N, 191 N, 192 N
Key to Positive Controls			Key to Plate Postfix Codes			
2NF	2-nitrofluorene		N	Normal background bacterial lawn		
SA	sodium azide		R	Reduced background bacterial lawn		
ICR	ICR-191					
4NQO	4-nitroquinoline-N-oxide					

**7.2 In Vitro Assays in Mammalian Cells**

**Study title: TRV130A: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes**

**Reviewed by Dr. Emami in IND 113537**

Study no.: 8242830  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\8242830\8242830-study-report.pdf>  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: 28 June, 2011  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: TRV130A, Lot CMLW-423/11-TV3, purity: 99.1%

### Key Study Findings

- TRV130A was tested in the Chromosomal Aberration assay in cultured human peripheral blood lymphocytes (HPBL).
- The test article concentrations for chromosome analysis were selected by evaluating the effect of TRV130A on mitotic index. Maximum concentrations analyzed in all treatment regimens were limited by cytotoxicity (range of 50-63%).
- The concentrations chosen for the chromosome aberration assay ranged from 200 to 850/900 mcg/mL for the 3-hour exposure groups with and without S9, and from 25 to 140 mcg/mL for the nonactivated 20-hour exposure groups.
- The percentage of cells with structural or numerical aberrations in the nonactivated 4-hour exposure group was statistically increased in high concentrations tested in Experiments 1 and 2 (3.5% at 900 mcg/mL and 140 mcg/mL, giving 58% and 50% cytotoxicity, respectively) relative to the solvent control (0.5%). The percentage of cells with structural aberrations or numerical in historical vehicle control was 0-3%. These increases over historical controls at slightly higher than necessary cytotoxicity levels are small and only were seen in high dose, therefore, is considered little biological importance.
- The percentage of cells with structural aberrations in the S9-activated 4-hour exposure group was statistically increased (up to 7%) relative to the solvent control in Experiment 1 (600, 700, and 850 mcg/mL, giving 14%, 35%, and 63% cytotoxicity, respectively) and in Experiment 2 (600, 800, and 850 mcg/mL, giving 26%, 40%, and 52% cytotoxicity, respectively). The aberrant cell frequency (excluding gaps) exceeded the historical vehicle control range (0-3%). However, there was no concentration related response.
- TRV130A showed evidence of inducing chromosome aberrations in cultured human peripheral blood lymphocytes when tested up to the limit of cytotoxicity following 3+17 hours treatment in the presence of a rat liver metabolic activation system (S-9), in two independently conducted Experiments. Therefore, the test article, TRV130A, is considered **positive** for inducing chromosomal aberrations in cultured human lymphocytes with metabolic activation.

*Reviewer's note of Dr. Zhang: TRV130 concentrations that produced evidence of inducing chromosome aberrations in this study ( $\geq 600$  mcg/mL or  $\geq 1.6$  mM) exceed the current recommended maximum concentration for testing in mammalian cell assays [1 mM per ICH S2(R1) 2011]. Additionally, it appears the effect is not always concentration dependent. Therefore, the biological importance of these observations is questionable. The applicant conducted additional chromosomal aberration studies with both HCL and fumarate salts (See the review of the study) and did not see similar effects when the concentrations were tested up to 1 mM in the 3-hour treatment in the presence and absence of S9 and up to the limit of cytotoxicity in the 24-hour treatment in the absence of S9. Because the study tested concentrations in excess of the current recommended maximum concentrations, although technically positive, this study will not be used to inform labeling.*

Methods	
Cell line:	cultured human peripheral blood lymphocytes
Concentrations in definitive study:	<ul style="list-style-type: none"> <li>• 200, 600, 800, 850 and 900 µg/mL, without metabolic activation (3-hour treatment)</li> <li>• 200, 600, 700 and 850 µg/mL, with metabolic activation (3-hour treatment)</li> <li>• 25, 70, 90 and 140 µg/mL without metabolic activation (20-hour treatment),</li> </ul>
Basis of concentration selection:	Cytotoxicity (range of 50-63%)
Negative control:	water
Positive control:	4-Nitroquinoline 1-oxide (NQO), Cyclophosphamide (CPA)
Formulation/Vehicle:	TRV130A/ water
Incubation & sampling time:	With and without S9 activation: 3 hours incubation Without S9 activation: 20 hours incubation
Protocol deviation:	This deviation has no impact on the validity of the study.

### Treatment scheme

Treatment	S-9	Number of cultures				
		Cytotoxicity Range-Finder		Experiment 1	Experiment 2	
		3+17*	20+0*	3+17*	3+17*	20+0*
Vehicle control	-	2	2	4		4
	+	2		4	4	
Test article	-	1	1	2		2
	+	1		2	2	
Positive controls	-			2		2
	+			2	2	

\* Hours treatment + hours recovery

### Study Validity

The following criteria for a valid assay were met: 1) the dose selection based upon mitotic index was acceptable for both non-activated and activated system; 2) the percentage of cells with aberrations in the negative and vehicle control did not exceed 5%, 3) the positive control produced significant chromosomal aberrations of the cells; 4) a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations.

However, the study did test concentrations that exceeded the maximum recommended concentration of 1 mM, as such the positive findings have questionable clinical relevance.

## Results

TRV130A showed evidence of inducing chromosome aberrations in cultured human peripheral blood lymphocytes when tested up to the limit of cytotoxicity following 3+17 hours treatment in the presence of a rat liver metabolic activation system (S-9), in two independently conducted Experiments. See below the Applicant's table

### Mitotic Index Determinations - Experiment 1

Treatment (µg/mL)	Mitotic index (%)					
	3+17 hours, -S-9			3+17 hours, +S-9		
A/C	B/D	MIH*	A/C	B/D	MIH*	
Vehicle	8.5/10.2	9.3/8.8	-	9.4/10.5	8.7/9.8	-
200.0	10.1	9.4	0 #	9.3	8.9	5 #
400.0	7.1	8.3	16	8.2	6.6	23
600.0	7.0	8.2	17 #	7.7	8.8	14 #
700.0	6.8	8.9	15	6.0	6.4	35 #
800.0	7.6	6.7	22 #	4.9	6.9	39
850.0	6.0	5.7	36**	4.2	2.9	63 #
900.0	3.6	4.1	58 #	2.1	4.6	65
950.0	1.9	1.8	80	1.8	1.2	84
1000	1.3	1.2	86	0.7	1.0	91
1050	0.5	0.2	96	0.5	0.8	93
1100	0.2	0.3	97	0	0.2	99
1200	0	0	100	0	0	100

\*Mitotic inhibition (%) =  $[1 - (\text{mean MI}_T / \text{mean MI}_C)] \times 100\%$   
(where T = treatment and C = negative control)

# Highlighted concentrations were analysed

\*\* Additional concentration along with concurrent re-analysis of concurrent vehicle controls subsequently requested by the Sponsor to aid in clarifying the -S-9 data.

### Mitotic Index Determinations - Experiment 2

Treatment (µg/mL)	Mitotic index (%)					
	20+0 hours, -S-9			3+17 hours, +S-9		
	A/C	B/D	MIH*	A/C	B/D	MIH*
Vehicle	9.5/7.3	8.8/9.3	-	105/10.7	12.4/11.5	-
10.00	8.4	8.2	4	NT	NT	-
25.00	8.7	9.9	0 #	NT	NT	-
50.00	7.2	8.1	12	NS	NS	-
60.00	9.4	8.2	0	NT	NT	-
70.00	6.5	5.3	32 #	NT	NT	-
80.00	6.0	7.7	21	NT	NT	-
90.00	4.7	4.8	46 #	NT	NT	-
100.0	5.7	2.9	51	12.3	13.6	0
120.0	3.2	2.7	66	NT	NT	-
140.0	4.2	4.6	50 #	NT	NT	-
160.0	2.7	3.8	63	NT	NT	-
180.0	2.9	2.2	71	NT	NT	-
200.0	2.9	1.9	72	14.9	12.4	0
225.0	2.8	0.8	79	NT	NT	-
250.0	2.6	1.7	75	NT	NT	-
300.0	1.5	2.1	79	NT	NT	-
400.0	NT	NT	-	12.9	10.6	0 #
600.0	NT	NT	-	7.2	9.5	26 #
700.0	NT	NT	-	5.5	7.6	42
750.0	NT	NT	-	8.7	6.0	35
800.0	NT	NT	-	6.5	7.0	40 #
825.0	NT	NT	-	6.3	5.5	48
850.0	NT	NT	-	6.5	4.3	52 #
875.0	NT	NT	-	2.7	3.3	73
900.0	NT	NT	-	2.9	3.6	71 H
1000	NT	NT	-	1.0	1.9	87 H

NS = Not scored

NT = Not tested

H = Precipitation observed at harvest

\*Mitotic inhibition (%) = [1 - (mean MI<sub>T</sub>/mean MI<sub>C</sub>)] x 100%  
(where T = treatment and C = negative control)

# Highlighted concentrations were analysed

**Table 1: Experiment 1 – Results summary**

Treatment	Concentration (µg/mL)	Cytotoxicity (%)	% Cells with Chromosome Aberrations (Excluding Gaps)	Historical Control Range (%) <sup>#</sup>	Statistical significance
3+17 hour -S-9	Vehicle <sup>a</sup>	-	0.50	0-3	-
	200.0	0	0.50		NP
	600.0	17	0.50		NP
	800.0	22	2.50		NP
	850.0**	36	0.00		NP
	900.0	58	3.50		NP
	*NQO, 5.00	ND	24.49		p ≤ 0.001
3+17 hour +S-9	Vehicle <sup>a</sup>	-	0.00	0-3	-
	200.0	5	0.00		NS
	600.0	14	3.50		p ≤ 0.01
	700.0	35	3.00		p ≤ 0.01
	850.0	63	5.00		p ≤ 0.001
	*CPA, 12.5	ND	53.33		p ≤ 0.001

<sup>a</sup> Vehicle control was purified water

\* Positive control // \*\* concentration subsequently analysed

<sup>#</sup> 95<sup>th</sup> percentile of the observed range

NP = Not presented as there were no concentrations analysed where both cultures demonstrated aberrant cell frequencies (excluding gaps) that exceeded historical ranges

NS = Not significant / ND = Not determined

**Table 2: Experiment 2 – Results summary**

Treatment	Concentration (µg/mL)	Cytotoxicity (%)	% Cells with Chromosome Aberrations (Excluding Gaps)	Historical Control Range (%) <sup>#</sup>	Statistical significance
20+0 hour -S-9	Vehicle <sup>a</sup>	-	0.50	0-3	-
	25.00	0	1.50		NP
	70.00	32	2.00		NP
	90.00	46	2.00		NP
	140.0	50	3.50		NP
	*NQO, 5.00	ND	32.50		p ≤ 0.001
3+17 hour +S-9	Vehicle <sup>a</sup>	-	0.00	0-3	-
	400.0	0	1.00		NS
	600.0	26	7.22		p ≤ 0.001
	800.0	40	3.50		p ≤ 0.01
	850.0	52	5.08		p ≤ 0.001
	*CPA, 12.5	ND	58.82		p ≤ 0.001

<sup>a</sup> Vehicle control was purified water

\* Positive control

<sup>#</sup> 95<sup>th</sup> percentile of the observed range

NP = Not presented as there were no concentrations analysed where both cultures demonstrated aberrant cell frequencies (excluding gaps) that exceeded historical ranges.

NS = Not significant

ND = Not determined

**Historical vehicle control ranges for human peripheral blood lymphocyte chromosome aberration (HLC) assay**

**Table 27: Historical vehicle control ranges - Females**

		Structural aberrations observed on 100 cells scored		Numerical aberrations observed during scoring of structural aberrations	
		Structural aberrations including gaps	Structural aberrations excluding gaps	Polyploid cells	Numerical aberrations (H+E+P)
-S-9	Number of studies	32	32	32	32
	Number of cultures	164	164	164	164
	Median	1	1	0	0
	Mean	1.20	0.82	0.21	0.41
	SD	1.19	0.94	0.59	0.81
	Observed range	0 - 5	0 - 4	0 - 4	0 - 5
	95% reference range	0 - 4	0 - 3	0 - 2	0 - 2
+S-9	Number of studies	33	33	33	33
	Number of cultures	146	146	146	146
	Median	1	0	0	0
	Mean	1.13	0.72	0.23	0.42
	SD	1.17	0.91	0.48	0.67
	Observed range	0 - 6	0 - 4	0 - 2	0 - 3
	95% reference range	0 - 4	0 - 3	0 - 2	0 - 2

H = Hyperdiploid, E=Endoreduplicated, P = Polyploid  
Reference ranges are calculated from percentiles of the observed distributions.

Calculated in April 2010 by (b) (4), from audited report data of studies started between January 2008 and August 2009

**Cytotoxic Effects:** Concentration related cytotoxicity (in terms of mitotic inhibition).  
**Genotoxic Effects:** Evidence of biologically relevant increases in cells with structural chromosome aberrations following test article treatments in the presence of S-9.

**Experiment 1**

Metabolic Activation	Test Article	Concentration (µg/mL)	Cytotoxicity (%) †	Aberrant Cells Mean %	Total Abs/Cell	Total Polyploid cells
Without Activation	Purified water	0	-	0.50 NP	0.0050	0
	TRV130A	200.0	0	0.50 NP	0.0050	0
	TRV130A	600.0	17	0.50 NP	0.0050	4
	TRV130A	800.0	22	2.50 NP	0.0250	3
	TRV130A	850.0	36	0.00 NP	0.0000	2
	TRV130A	900.0	58	3.50 NP	0.0400	2
	4-Nitroquinoline (NQO)	5.00	ND	24.49***	0.4082	0
With Activation	Purified water	0	-	0.00	0.0000	1
	TRV130A	200.0	5	0.00	0.0000	0
	TRV130A	600.0	14	3.50**	0.0400	1
	TRV130A	700.0	35	3.00**	0.0350	2
	TRV130A	850.0	63	5.00***	0.0550	4
	Cyclophosphamide (CPA)	12.50	ND	53.33***	0.8267	0

Fisher's exact test \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001

† Mitotic inhibition (%) = [1 - (mean MI<sub>T</sub>/mean MI<sub>C</sub>)] x 100% (where T = treatment and C = negative control)

ND = Not determined // NP = Statistics not presented as there were no concentrations analysed where both cultures demonstrated aberrant cell frequencies (excluding gaps) that exceeded historical range

Experiment 2

Metabolic Activation	Test Article	Concentration (µg/mL)	Cytotoxicity (%) †	Aberrant Cells Mean %	Total Abs/Cell	Total Polyploid cells
	Purified water	0	-	0.50	0.0050	2
Without Activation	TRV130A	25.00	0	1.50 NP	0.0150	0
	TRV130A	70.00	32	2.00 NP	0.0200	0
	TRV130A	90.00	46	2.00 NP	0.0200	1
	TRV130A	140.0	50	3.50 NP	0.0400	1
	4-Nitroquinoline (NQO)	5.00	ND	32.50***	0.4917	0
With Activation	Purified water	0	-	0.00	0.0000	0
	TRV130A	400.0	0	1.00	0.0150	3
	TRV130A	600.0	26	7.22***	0.0778	9
	TRV130A	800.0	40	3.50**	0.0350	6
	TRV130A	850.0	52	5.08***	0.0558	2
	Cyclophosphamide (CPA)	12.5	ND	58.82***	0.8382	0

Fisher's exact test \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001

† Mitotic inhibition (%) = [1 - (mean MI<sub>T</sub>/mean MI<sub>C</sub>)] x 100% (where T = treatment and C = negative control)

ND = Not determined

NP = Statistics not presented as there were no concentrations analysed where both cultures demonstrated aberrant cell frequencies (excluding gaps) that exceeded historical range

**Study title: TRV130 Fumarate and TRV130 HCl: Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes**

In order to qualify an alternative TRV130 salt form, the ability of TRV130 fumarate and TRV130 HCl to induce chromosomal aberrations in cultured human peripheral blood lymphocytes with and without an exogenous metabolic activation system (S9) was evaluated in this in vitro GLP study.

Study no.: 8292858  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\8292858\8292858-study-report.pdf>

Conducting laboratory and location: Trevena, Inc.  
 1018 West 8th Avenue, Suite A  
 King of Prussia, Pennsylvania 19406  
 United States of America

Date of study initiation: 12/10/2013

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

Test Article	Lot No.	Storage	Purity	Re-test Date
TRV130 (fumarate) <sup>a</sup>	2417-14-1			(b) (4)
TRV130A	(b) (4)			(b) (4)
TRV110130 and TRV0110130	(b) (4)			(b) (4)

<sup>a</sup> A correction factor of (b) (4) used during preparation.

<sup>b</sup> A correction factor of (b) (4) used during preparation.

**Key Study Findings**

As per the study report, “TRV130 fumarate and TRV130 HCl were considered negative for inducing chromosomal aberrations, polyploidy, and endoreduplication in cultured human lymphocytes when tested up to a 1 mM concentration in the 3-hour treatment in the presence and absence of S9 and up to the limit of cytotoxicity (65.5 mcg/mL for TRV130 fumarate and 93.6 mcg/mL for TRV130 HCl) in the 24-hour treatment in the absence of S9.” This reviewer agrees with the conclusion that the fumarate salt was not clastogenic in the study.

**Methods**

Cell line: Human peripheral blood lymphocytes  
 Concentrations in definitive study: Both test articles were tested for cytotoxicity at concentrations of 2.65, 3.78, 5.40, 7.71, 11.0, 15.7, 22.5, 32.1, 45.9, 65.5, 93.6, 134, 191, 273, and 390 mcg/mL for a 3-hour treatment in the presence and absence of S9 and for an approximate 24-hour treatment in the absence of S9.

The doses analyzed for chromosomal aberrations:

- 3-hour treatment with dose selection based upon limit concentration of 1 mM: 191, 273, and 390 mcg/mL in the presence and absence of S9 in both test articles, except TRV130 HCl in the presence of S9, where the lowest dose analyzed was 134 mcg/mL.
- 24-hour treatment with dose selection based upon cytotoxicity:
  - TRV130 fumarate: 15.7, 32.1, and 65.5 mcg/mL
  - TRV130 HCl: 45.9, 65.5, and 93.6 mcg/mL

Basis of concentration selection: Top dose produced approximately 50% cytotoxicity; 1 mM was selected as the top dose if no cytotoxicity was observed.

Negative control: RO (reverse osmosis) water

Positive control:

Control Article	CAS No.	Supplier	Lot No.
Mitomycin C (MMC)	50-07-7	(b) (4)	SLBF5285V
Cyclophosphamide (CP)	6055-19-2		120M1253V

Formulation/Vehicle: RO water

- Incubation & sampling time:
- Duplicate cultures were used at each test article concentration, for vehicle controls, and for the positive controls.
  - With and without S9 activation: 3-hour treatment time  
 Without S9 activation: 24-hour treatment time
  - All cultures were harvested approximately 24 hour after the initiation of treatment. This harvest time corresponds to 1.5 times a cell cycle time of approximately 15 hours after the lymphocytes are

induced to divide by the addition of phytohemagglutinin M (PHA-M).

### Study Validity

The following criteria for a valid assay were met:

- The dose selection based upon mitotic index or limit of acceptable dose (1 mM) was acceptable for both non-activated and activated system.
- The percentage of cells with aberrations in the negative and vehicle control did not exceed 5%.
- The positive control produced significant chromosomal aberrations of the cells.
- A minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations.

### Results

- No precipitate was observed in any test condition at the time of treatment, wash, or harvest with either TRV130 fumarate or TRV130 HCL.
- 3-hour treatment study:
  - In the presence and absence of S9, less than 50% cytotoxicity was observed at the highest tested dose for either TRV130 fumarate or TRV130 HCL.
  - The top three doses ( $\geq 191$  mcg/mL) were analyzed for chromosomal aberrations in the 3-hour treatment in the presence and absence of S9 in both test articles, except TRV130 HCl in the presence of S9, where the lowest dose analyzed was 134 mcg/mL.
  - No statistically significant increases ( $p \leq 0.01$ ) in the number of cells with chromosomal aberrations, polyploidy, or endoreduplication were observed in the cultures analyzed for any test condition in the presence or absence of S9 in either TRV130 fumarate or TRV130 HCl. Treatment of cultures with the vehicle (RO water) and positive control articles were consistent with historical data, meeting assay acceptance criteria.

**Table 17.2: Chromosomal Aberrations in Human Lymphocytes - Without Metabolic Activation - 3-Hour Treatment, ~24-Hour Harvest**

Study No.: 8292858      Trial No.: B1      Date: 18 December 2013      Test Article: TRV130 (fumarate)

Treatment		# Cells Scored for Aberrations	% Mitotic Index Reduction <sup>a</sup>	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge-ment (+/-) <sup>b</sup>	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations					Totals <sup>c</sup>		Judge-ment (+/-) <sup>d</sup>
								gaps	simple breaks	chte	chre	mab	-g	+g	
								Vehicle:	RO Water	100 µL/mL	A 100 B 100 Total 200 Average %	100 100 200	0 0 0.0	0 0 0.0	
Positive:	MMC	1.00 µg/mL	A 50 B 50 Total 100 Average %	100 100 200	0 0 0.0	0 0 0.0	-	5 5 10.0	30 26 56.0	6 5 11.0		32 28 60.0	35 31 66.0	+	
Test Article		191 µg/mL	A 100 B 100 Total 200 Average %	100 100 200	0 0 0.0	0 0 0.0	-	1 1 0.5				0 1 0.5	1 1 1.0	-	
		273 µg/mL	A 100 B 100 Total 200 Average %	100 100 200	0 0 0.0	0 0 0.0	-		1 1 0.5			1 0 0.5	1 0 0.5	-	
		390 µg/mL	A 100 B 100 Total 200 Average %	100 100 200	0 1 0.5	0 0 0.0	-		1 1 0.5			1 0 0.5	1 0 0.5	-	

chte: chromatid exchange    chre: chromosome exchange    mab: multiple aberrations, greater than 4 aberrations    pp: polyploidy    er: endoreduplication  
<sup>a</sup>% Mitotic index reduction as compared to the vehicle control.  
<sup>b</sup>Significantly greater in % polyploidy and % endoreduplication than the vehicle control, p ≤ 0.01.  
<sup>c</sup>-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.  
<sup>d</sup>Significantly greater in -g than the vehicle control, p ≤ 0.01.    RO Water = Reverse Osmosis Water    MMC = Mitomycin C

**Table 17.6: Chromosomal Aberrations in Human Lymphocytes - With Metabolic Activation - 3-Hour Treatment, ~24-Hour Harvest**

Study No.: 8292858      Trial No.: B1      Date: 18 December 2013      Test Article: TRV130 (fumarate)

Treatment		# Cells Scored for Aberrations	% Mitotic Index Reduction <sup>a</sup>	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge-ment (+/-) <sup>b</sup>	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations					Totals <sup>c</sup>		Judge-ment (+/-) <sup>d</sup>
								gaps	simple breaks	chte	chre	mab	-g	+g	
								Vehicle:	Water	100 µL/mL	A 100 B 100 Total 200 Average %	100 100 200	0 0 0.0	0 0 0.0	
Positive:	CP	25.0 µg/mL	A 50 B 50 Total 100 Average %	100 100 200	0 0 0.0	0 0 0.0	-	4 4 8.0	27 27 54.0	2 2 4.0	1 1 1.0	27 28 55.0	30 30 60.0	+	
Test Article		191 µg/mL	A 100 B 100 Total 200 Average %	100 100 200	0 0 0.0	0 0 0.0	-	1 1 0.5				0 0 0.0	1 0 0.5	-	
		273 µg/mL	A 100 B 100 Total 200 Average %	100 100 200	1 0 0.5	0 0 0.0	-		1 1 0.5			0 0 0.0	1 0 0.5	-	
		390 µg/mL	A 100 B 100 Total 200 Average %	100 100 200	0 0 0.0	0 0 0.0	-	1 1 0.5	1 1 0.5			1 0 0.5	2 0 1.0	-	

chte: chromatid exchange    chre: chromosome exchange    mab: multiple aberrations, greater than 4 aberrations    pp: polyploidy    er: endoreduplication  
<sup>a</sup>% Mitotic index reduction as compared to the vehicle control.  
<sup>b</sup>Significantly greater in % polyploidy and % endoreduplication than the vehicle control, p ≤ 0.01.  
<sup>c</sup>-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.  
<sup>d</sup>Significantly greater in -g than the vehicle control, p ≤ 0.01.    RO Water = Reverse Osmosis Water    CP = Cyclophosphamide

**Table 17.8: Chromosomal Aberrations in Human Lymphocytes - Without Metabolic Activation - 3-Hour Treatment, ~24-Hour Harvest**

Study No.: 8292858      Trial No.: B1      Date: 18 December 2013      Test Article: TRV130A (HCl)

Treatment		# Cells Scored for Aberrations	% Mitotic Index Reduction <sup>a</sup>	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge-Ment (+/-) <sup>b</sup>	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations						Judge-ment (+/-) <sup>d</sup>	
								gaps	simple breaks	chte	chre	mab	Totals <sup>c</sup>		
													-g		+g
Vehicle: RO Water	100 µL/mL	A	100	100	0	0						0	0		
		B	100	100	0	0		1				0	1		
		Total	200	200				1				0	1		
		Average %		0	0.0	0.0		0.5				0.0	0.5		
Positive: MMC	1.00 µg/mL	A	50	100	0	0		3	22	8		28	30		
		B	50	100	0	0		1	18	11	1	28	29		
		Total	100	200				4	40	19	1	56	59		
		Average %		54	0.0	0.0	-	4.0	40.0	19.0	1.0	56.0	59.0	+	
Test Article	191 µg/mL	A	100	100	0	0						0	0		
		B	100	100	0	0						0	0		
		Total	200	200								0	0		
		Average %		7	0.0	0.0	-					0.0	0.0	-	
	273 µg/mL	A	100	100	0	0			1			1	1		
		B	100	100	0	0						0	0		
		Total	200	200					1			1	1		
		Average %		17	0.0	0.0	-		0.5			0.5	0.5	-	
	390 µg/mL	A	100	100	0	0		2	1			1	2		
		B	100	100	1	0		2				0	2		
		Total	200	200				4	1			1	4		
		Average %		5	0.5	0.0	-	2.0	0.5			0.5	2.0	-	

chte: chromatid exchange    chre: chromosome exchange    mab: multiple aberrations, greater than 4 aberrations    pp: polyploidy    er: endoreduplication  
<sup>a</sup>% Mitotic index reduction as compared to the vehicle control.  
<sup>b</sup>Significantly greater in % polyploidy and % endoreduplication than the vehicle control, p ≤ 0.01.  
<sup>c</sup>-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.  
<sup>d</sup>Significantly greater in -g than the vehicle control, p ≤ 0.01.    RO Water = Reverse Osmosis Water    MMC = Mitomycin C

**Table 17.12: Chromosomal Aberrations in Human Lymphocytes - With Metabolic Activation - 3-Hour Treatment, ~24-Hour Harvest**

Study No.: 8292858      Trial No.: B1      Date: 18 December 2013      Test Article: TRV130A (HCl)

Treatment		# Cells Scored for Aberrations	% Mitotic Index Reduction <sup>a</sup>	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge-Ment (+/-) <sup>b</sup>	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations						Judge-ment (+/-) <sup>d</sup>	
								gaps	simple breaks	chte	chre	mab	Totals <sup>c</sup>		
													-g		+g
Vehicle: RO Water	100 µL/mL	A	100	100	0	0						0	0		
		B	100	100	0	0						0	0		
		Total	200	200								0	0		
		Average %		0	0.0	0.0						0.0	0.0		
Positive: CP	25.0 µg/mL	A	50	100	0	0		2	25	2		26	28		
		B	50	100	0	0		5	19	2		21	22		
		Total	100	200				7	44	4		47	50		
		Average %		53	0.0	0.0	-	7.0	44.0	4.0		47.0	50.0	+	
Test Article	134 µg/mL	A	100	100	0	0		1	2			2	3		
		B	100	100	0	0		1				0	1		
		Total	200	200				2	2			2	4		
		Average %		25	0.0	0.0	-	1.0	1.0			1.0	2.0	-	
	273 µg/mL	A	100	100	0	0		1				0	1		
		B	100	100	0	0		1				0	1		
		Total	200	200				2				0	2		
		Average %		15	0.0	0.0	-	1.0				0.0	1.0	-	
	390 µg/mL	A	100	100	0	0						0	0		
		B	100	100	0	0						0	0		
		Total	200	200								0	0		
		Average %		22	0.0	0.0	-					0.0	0.0	-	

chte: chromatid exchange    chre: chromosome exchange    mab: multiple aberrations, greater than 4 aberrations    pp: polyploidy    er: endoreduplication  
<sup>a</sup>% Mitotic index reduction as compared to the vehicle control.  
<sup>b</sup>Significantly greater in % polyploidy and % endoreduplication than the vehicle control, p ≤ 0.01.  
<sup>c</sup>-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.  
<sup>d</sup>Significantly greater in -g than the vehicle control, p ≤ 0.01.    RO Water = Reverse Osmosis Water    CP = Cyclophosphamide

- 24-hour treatment study in the absence of S9:

- TRV130 fumarate produced 49% cytotoxicity at 65.5 mcg/mL. This dose along with two lower doses (15.7 and 32.1 mcg/mL) producing 15 and 39% cytotoxicity were selected for chromosomal aberrations analysis. No statistically significant increases ( $p \leq 0.01$ ) in the number of cells with chromosomal aberrations, polyploidy, or endoreduplication were observed.
- TRV130 HCl produced 46% cytotoxicity at 93.6 mcg/mL. This dose along with two lower doses (45.9 and 65.5 mcg/mL) producing 22 and 36% cytotoxicity, respectively, were selected for chromosomal aberrations analysis. No statistically significant increases ( $p \leq 0.01$ ) in the number of cells with chromosomal aberrations, polyploidy, or endoreduplication were observed.

**Table 17.4: Chromosomal Aberrations in Human Lymphocytes - Without Metabolic Activation - ~24-Hour Treatment, ~24-Hour Harvest**

Study No.: 8292858      Trial No.: B1      Date: 18 December 2013      Test Article: TRV130 (fumarate)

Treatment	Vehicle	Concentration	# Cells Scored for Aberrations	% Mitotic Index Reduction <sup>a</sup>	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge-Ment (+/-) <sup>b</sup>	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations					Judge-ment (+/-) <sup>d</sup>		
									gaps	simple breaks	chte	chre	mab		Totals <sup>c</sup>	
															-g	+g
	RO Water	100 µL/mL	A 100		100	0	0						1	1		
			B 100		100	0	0						1	1		
			Total 200		200	0	0						2	2		
			Average %	0		0.0	0.0						1.0	1.0		
Positive:	MMC	0.300 µg/mL	A 50		100	0	0		3	28	3		30	31		
			B 50		100	0	0		6	29	7		31	33		
			Total 100		200	0	0		9	57	10		61	64		
			Average %	58		0.0	0.0	-	9.0	57.0	10.0		61.0	64.0	+	
Test Article		15.7 µg/mL	A 100		100	0	0						0	1		
			B 100		100	0	0						0	0		
			Total 200		200	0	0						0	1		
			Average %	15		0.0	0.0	-	0.5				0.0	0.5	-	
		32.1 µg/mL	A 100		100	0	0						0	3		
			B 100		100	0	0						0	0		
			Total 200		200	0	0						0	3		
			Average %	39		0.0	0.0	-	1.5				0.0	1.5	-	
		65.5 µg/mL	A 100		100	0	0						0	1		
			B 100		100	0	0						0	4		
			Total 200		200	0	0						0	5		
			Average %	49		0.0	0.0	-	2.5				0.0	2.5	-	

chte: chromatid exchange    chre: chromosome exchange    mab: multiple aberrations, greater than 4 aberrations    pp: polyploidy    er: endoreduplication  
<sup>a</sup>% Mitotic index reduction as compared to the vehicle control.  
<sup>b</sup>Significantly greater in % polyploidy and % endoreduplication than the vehicle control,  $p \leq 0.01$ .  
<sup>c</sup>-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.  
<sup>d</sup>Significantly greater in -g than the vehicle control,  $p \leq 0.01$ .    RO Water = Reverse Osmosis Water    MMC = Mitomycin C

**Table 17.10: Chromosomal Aberrations in Human Lymphocytes - Without Metabolic Activation - ~24-Hour Treatment, ~24-Hour Harvest**

Study No.: 8292858

Trial No.: B1

Date: 18 December 2013

Test Article: TRV130A (HCl)

Treatment	Vehicle	RO Water	100 µL/mL	# Cells Scored for Aberrations	% Mitotic Index Reduction <sup>a</sup>	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judge-ment (+/-) <sup>b</sup>	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations					Judge-ment (+/-) <sup>d</sup>		
										gaps	simple breaks	chte	chre	mab		Totals <sup>c</sup>	
																-g	+g
				A 100		100	0	0					0	0			
				B 100		100	0	0					1	1			
				Total 200		200							1	1			
				Average %	0		0.0	0.0					0.5	0.5			
	Positive:	MMC	0.300 µg/mL	A 50		100	0	0		1	19	6	23	24			
				B 50		100	0	0		2	27	3	28	29			
				Total 100		200				3	46	9	51	53			
				Average %	66		0.0	0.0	-	3.0	46.0	9.0	51.0	53.0	+		
	Test Article		45.9 µg/mL	A 100		100	0	0		2			0	2			
				B 100		100	0	0		2	1		1	3			
				Total 200		200				4	1		1	5			
				Average %	22		0.0	0.0	-	2.0	0.5		0.5	2.5	-		
			65.5 µg/mL	A 100		100	0	0		2			2	2			
				B 100		100	0	0					0	0			
				Total 200		200				2			2	2			
				Average %	36		0.0	0.0	-	1.0			1.0	1.0	-		
			93.6 µg/mL	A 100		100	0	0			3	1	4	4			
				B 100		100	0	0		1	2		2	3			
				Total 200		200				1	5	1	6	7			
				Average %	46		0.0	0.0	-	0.5	2.5	0.5	3.0	3.5	-		

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication

<sup>a</sup>% Mitotic index reduction as compared to the vehicle control.

<sup>b</sup>Significantly greater in % polyploidy and % endoreduplication than the vehicle control, p ≤ 0.01.

<sup>c</sup>-g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.

<sup>d</sup>Significantly greater in -g than the vehicle control, p ≤ 0.01. RO Water = Reverse Osmosis Water MMC = Mitomycin C

- Treatment of cultures with the vehicle (RO water) and positive control articles were consistent with historical data, meeting assay acceptance criteria.
- According to the historical control data provided in the study report, 22-hour incubation without metabolic activation results in 0-2.0 % of cells with chromosomal aberrations without gaps (-g) and a range of 0-11.0% when gaps are included (+g). As such, the reported level of 3.0% (-g) appears to be outside of historical control levels whereas (+g) is within historical control levels. Nonetheless, as chromosomal aberrations in the fumarate salt groups were not increased, these effects may be an artifact of the culture conditions.

### 7.3 In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

#### TRV130A: Intravenous 24-Hour Continuous Infusion Micronucleus Study Using Bone Marrow from Rats

Reviewed by Dr. Emami in IND 113537

Study no: 8242831  
Study report location: <\\cdsesub1\levsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42332-in-vivo\8242831\8242831-study-report.pdf>  
Conducting laboratory and location: (b) (4)  
Date of study initiation: 30 June 2011  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: TRV130A,  
Lot CMLW-423/11-TV3, purity: 99.1%

### **Key Study Findings**

- Based on the range-findings results, 1 mg/kg/h of TRV130A, administered by continuous infusion for approximately 24 hours, was considered an appropriate estimate of the MTD and used as the maximum dose for the pivotal micronucleus experiment. Two lower doses of 0.25 and 0.50 mg/kg/h were also tested. As no substantial difference in toxicity was observed between males and females in the range-finding experiment, only male animals were used in the micronucleus assay.
- At the highest test dose of 1 mg/kg/h clinical signs including; decreased activity, bulging of the eyeballs, staining around the mouth and snout, persistent licking/chewing, piloerection and hunched posture were observed. Clinical signs were also noted at 0.5 mg/kg/h though these were less marked. Increased activity over part of the dosing period was noted in the majority of animals dosed at 0.25 mg/kg/h with no clinical signs observed over the recovery period.
- TRV130A did not induce micronuclei in the polychromatic erythrocytes (MN PCE) of the bone marrow of male rats treated via 24-hour continuous infusion up to 1 mg/kg/h (an estimate of the maximum tolerated dose for this study, under the experimental conditions employed).
- No evidence of bone marrow suppression as measured by a change in PCE/NCE ratio (polychromatic erythrocytes/ normochromatic erythrocytes) was detected up MTD level.
- Therefore, under the conditions of this assay, TRV130A is not considered to be an in vivo clastogen in the mouse.

Methods	
Doses in definitive study:	0.25, 0.50 and 1.00 mg/kg/hour
Frequency of dosing:	A single dose
Route of administration:	Intravenous Infusion (24 hours)
Dose volume:	1 mL/kg/hour
Formulation/Vehicle:	TRV130A/ 0.2 mM sodium phosphate buffer in 5% (w/v) Dextrose (D5W).
Species/Strain:	Sprague Dawley (CD) rats
Number/Sex/Group:	6 Males/group (as no marked gender differences noted in a preliminary dose-range finding toxicity study) see below
Satellite groups:	12 males for bioanalysis, see below
Basis of dose selection:	Maximum Tolerated dose
Negative control:	vehicle
Positive control:	CPA 20 mg/kg, single i.v bolus administration, given 24 hours prior to bone marrow harvest.

**Table 1: Dose Levels - Range-Finder Experiment**

Group Number	Treatment	Dose rate (mL/kg/hour)	Dose (mg/kg/hour)	No. of animals
1	TRV130A	1	1.5	3M 3F
2	TRV130A	1	2.5	3M 3F
3	TRV130A	1	1.0	3M 3F

M Male  
F Female

In dose range finding TRV130 was administered as a continuous intravenous infusion for 24 hours.

**Table 2: Dose Levels - Micronucleus Experiment**

Group No.	Group Description	Dose level (mg/kg/hour)	Animal Numbers		Sample time (hours after start of infusion)
			Main Experiment animals		
			Male		
1	Vehicle control	0	1-6		24
2	TRV130A	0.25	7-12		24
3	TRV130A	0.50	13-18		24
4	TRV130A	1.00	19-24		24
5	Positive control♦	20	25-30		24
6	Vehicle control	0	31-36		48
7	TRV130A	0.25	37-42		48
8	TRV130A	0.50	43-48		48
9	TRV130A	1.00	49-54		48
			Satellite animals for blood level determination		
		Dose level (mg/kg/hour)	Male		
10	Vehicle control	0	100-102		4*
11	TRV130A	0.25	103-105		4*
12	TRV130A	0.50	106-108		4*
13	TRV130A	1.00	109-111		4*

♦ Cyclophosphamide (CPA) positive control animals received a single i.v. bolus administration at 20 mg/kg approximately 24 hours prior to bone marrow harvest.

\*Blood taken via jugular vein (TK samples for analysis were taken from satellite animals only).

#### Mean Concentrations of TRV130 Free Base at Approximately 4 Hours After Infusion Start in the Pivotal Rat Micronucleus Study

Group	Dose Level (mg/kg/hr)	Sex	N	Mean TRV130 Free Base Concentration (ng/mL)
10	0	M	3	0
11	0.25	M	2 <sup>a</sup>	58 <sup>a</sup>
12	0.5	M	3	146
13	1.0	M	3	366

Data Source: Study No. 8242831, Table 2.6.7.9A

a Results from Animal No. 104 (<2.00, BQL) were not included in the calculation of the mean from this group.

BQL: below quantitation limit; M: male.

#### Study Validity

The study is considered valid based on the following criteria:

- 1) Dosing appeared to be adequate based upon the results of the dose-ranging study.
- 2) Blood plasma was sampled from satellite dosed animals at 4 hours post start of infusion (at all dose levels) and confirmed exposure to the test article.

- 3) Positive controls exhibited appropriate responses. With the exception of one animal (Number 28) all individual MN PCE values were clearly elevated above historical vehicle control ranges.
- 4) The % micronucleated PCEs and the PCE/NCE ratio in the negative control and the positive control groups were within the historical data range for the testing laboratory.
- 5) The proportion of immature erythrocytes among total erythrocytes was not less than 20% of the control value (indicating no bone marrow suppression).

## Results

### • Range-Finder Experiment:

- Group 1, 1.5 mg/kg/h: One female animal (1016) was euthanized in extremis at the time of necropsy (Day 3) showing signs of rapid respiration, agitation with tail cuff, red discharge (both eyes) and red staining of the snout. One male animal was euthanized early (1004) due to problems with the surgical tail cuff. Clinical signs included protrusion of eyes, rigid posture, stereotypical behaviors such as persistent gnawing/chewing of bedding and food pellets, distended abdomen, lethargy, piloerection, chromodacryorrhea (red discharge from the eyes), and excessive drinking. Clinical signs were similar between the sexes.
- Group 2, 2.5 mg/kg/h: No mortality was observed. Clinical signs were severe over the dosing period with poor recovery over the post-dose observation period. Clinical signs were same as Group 1 with additional observations of periods of lethargy with short bursts of uncoordinated movement, hunched posture, ataxia, licking, chewing motions, bradypnea, and decreased activity.
- Group 3, 1 mg/kg/h: Clinical signs over the dose infusion which included protrusion of eyes, rigid posture, licking and chewing motions, lethargy with short bursts of uncoordinated movement, eating/gnawing constantly at pellets and/or bedding, decreased activity, staining around the snout, piloerection, and soft feces. No marked differences in toxicity were observed between sexes and although the clinical signs recorded over the dosing period were similar between dose groups, the severity was less at 1 mg/kg/h with animals recovering well post the end of the test article infusion period. No clinical signs were noted in any animal on Day 3.

Group bodyweight changes (percentage change) from Day of Infusion (Day 1) to Necropsy (Day 3) were as follows:

Dose Group 1: 1.5 mg/kg/hour

Male = -12% // Females = -9%

Dose Group 2: 2.5 mg/kg/hour

Male = -12% // Females = -8%

Dose Group 3: 1.0 mg/kg/hour

Male = -9% // Females = -10%.

The Applicant chose the dose level of 1 mg/kg/h as an MTD under the assay conditions employed and used as the maximum dose for the micronucleus experiment.

- **Micronucleus Experiment :**

There was no difference in toxicity between males and females in the range-finder experiment; thus, male animals only were used in the micronucleus experiment. Bone marrow sampled 24 hours or 48 hours after the start of infusion.

**Clinical sign:**

24-hour sample time animals: At the highest test dose of 1 mg/kg/h, decreased activity, bulging of the eyeballs and pink/red fluid in the eyes, persistent licking/chewing, and snout staining was observed. Hunched posture was also observed on Day 2, 24 hours after dosing commenced. No body weight changes were observed.

48-hour sample time animals: At the highest test dose of 1 mg/kg/h, decreased activity, bulging of the eyeballs, staining around the mouth and snout, persistent licking/chewing, and piloerection was observed. Hunched posture was observed in two animals 24 hours after dosing commenced. One animal (50) was found to be self-mutilating and was killed in extremis. Body weight changes (measured from Day 1 to Day 3) were noted as -0.51%, -8.0%, and -13.8% for dose groups of 0.25, 0.5, and 1.0 mg/kg/h respectively as compared to a +2.2% change for the concurrent vehicle control.

**Analysis of micronucleus data**

Rats treated with TRV130A at all doses exhibited group mean %PCE that were similar to vehicle control groups and which fell within the laboratory's historical vehicle control (normal, 36% to 53% PCE) range, therefore there was no evidence of test article related bone marrow toxicity.

There were no statistically significant increases in micronucleus frequency for any of the groups (24- and 48-hour sample times) receiving the test article as compared to the concurrent vehicle control values.

See below tables, summary and statistical analysis of micronucleus data by the Applicant

**24 hours**

Treatment (mg/kg/hour)	Cell Total	% PCE	Total MN PCE	Mean MN PCE/2000 PCE	% MN PCE	SD	Heterogeneity		Contingency	
							X <sup>2</sup>	S	X <sup>2</sup> C	S
Vehicle	12000	35.45	8	1.33	0.07	0.07	7.00	NS		
0.25	12000	43.05	12	2.00	0.10	0.09	8.01	NS	0.45	NS
0.5	12000	39.70	9	1.50	0.08	0.09	10.34	NS	0.00	NS
1	12000	40.38	6	1.00	0.05	0.03	2.00	NS	0.07	NS
CPA, 20+	12000	35.20	134	22.33	1.12	0.48			110.69	P ≤ 0.001

Linear trend: z = -0.829, NS

NS Not significant

MN Micronucleated

+ Administered as a single dose

SD Standard deviation

S Significance

**48 hours**

Treatment (mg/kg/hour)	Cell Total	% PCE	Total MN PCE	Mean MN PCE/2000 PCE	% MN PCE	SD	Heterogeneity		Contingency	
							X <sup>2</sup>	S	X <sup>2</sup> C	S
Vehicle	12000	39.85	8	1.33	0.07	0.07	7.00	NS		
0.25	12000	37.87	4	0.67	0.03	0.06	11.00	NS	0.75	NS
0.5	12000	39.80	9	1.50	0.08	0.05	3.67	NS	0.00	NS
1	10000	41.92	7	1.40	0.07	0.03	0.86	NS	0.03	NS

Linear trend: z = 0.493, NS

NS Not significant

MN Micronucleated

+ Administered as a single dose

SD Standard deviation

S Significance

TRV130A did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats treated via 24-hour continuous infusion up to 1 mg/kg/h (the highest dose tested and the estimated MTD).

**7.4 In Vivo Rat Comet Study**

***Study Title: TRV 130A: Detection of DNA damage in the liver and blood of treated rats using the Comet assay***

***Reviewed by Dr. Emami in IND 113537***

<b>Study title: TRV130A: Detection of DNA damage in the liver and blood of treated rats using the Comet assay</b>	
Study no:	8254795
Study report location:	eCTD 0003 (4) 4.2.3.3.2.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	30 June 2011
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	TRV130A, lot # CMLW-423/11-TV3, purity: 99.1%

### Key Study Findings

- In order to further evaluate the in vitro chromosome aberration assay positive findings, a comet assay was performed.
- Six male rats were given a single continuous 24-hour infusion of TRV130A at doses of 0.25, 0.50, and 1 mg/kg/h. Maximum tolerated dose was based on data generated in (b) (4) 8242831 (rat micronucleus test).
- Liver and blood sampled at necropsy for comet analysis.
- Histopathology data indicate that in the liver, there was a generally dose-related reduction in the level of glycogen vacuolation in all treated groups related to treatment with TRV130A. According to the Applicant Glycogen vacuolation was characterized by generally perinuclear, clear, variably sized, indistinctly defined, vacuoles.
- In Comet assay,
  - There was no dose-related increase in % clouds or % diffused cells in liver and blood following treatment with TRV130A.
  - There was a concentration-dependent reduction of tail length/intensity in liver cells (not blood cells) that may indicate a cross-linking effect of TRV130. Therefore, although the Sponsor considers the study negative since there was no dose-responsive increase in tail length in the assay which would indicate direct DNA damage, the results are considered questionable by this reviewer.

Methods	
Doses in definitive study:	0.25, 0.50 and 1.00 mg/kg/hour
Frequency of dosing:	A single dose
Route of administration:	Intravenous Infusion (24 hours)
Dose volume:	1 mL/kg/hour
Formulation/Vehicle:	TRV130A/ 0.2 mM sodium phosphate buffer in 5% (w/v) Dextrose (D5W).
Species/Strain:	Sprague Dawley (CD) rats
Number/Sex/Group:	6 Males/group (as no marked gender differences noted in a preliminary dose-range finding toxicity study 88242831)
Satellite groups:	12 males for bioanalysis, see below
Basis of dose selection:	Maximum Tolerated dose
Negative control:	vehicle
Positive control:	EMS 250 mg/kg, single oral administration, given 3 hours prior to necropsy.

## Dose levels for Comet assay:

Group No.	Group Description	Dose level (mg/kg/hr)	Animal ID Numbers
1	Vehicle control <sup>a</sup>	0	1-6M
2	TRV130A	0.25	7-12M
3	TRV130A	0.5	13-18M
4	TRV130A	1.0	19-24M
5	Positive control <sup>b</sup>	250 mg/kg	25-30M
<b>Satellite animals<sup>c</sup></b>			
1	Vehicle control <sup>a</sup>	0	101-103M
2	TRV130A	0.25	104-106M
3	TRV130A	0.5	107-109M
4	TRV130A	1.0	110-112M

a 0.2 mM sodium phosphate buffer in 5% (w/v) Dextrose (D5W)

b Ethyl Methanesulfonate (EMS) administered once only at 21 hours by oral gavage

c Animals were sampled approximately 4 hours after initiation of dosing (equivalent to C<sub>ss</sub>)

M Male

**Study Validity**

- Negative vehicle control data were comparable with laboratory's historical data. However, the historical data for rat liver is from 8 studies and seems too broad to be useful (see below)
- Positive control resulted in a marked increase in comet parameters compared to vehicle control.

- Bioanalysis confirmed exposure to the test article.

## Results

### Clinical sign:

Lethargy, excessive gnawing/grooming or self mutilation were observed in all animals dose at 0.5 or 1 mg/kg/h during the infusion period. Similar clinical signs were observed in animals dosed at 0.25 mg/kg/h, although these were generally shorter in duration.

### Histopathology:

In the liver, there was a dose-related reduction in the level of glycogen vacuolation in all treated groups related to treatment with TRV130A. According to the Applicant findings seen in the liver were generally consistent with the usual pattern of findings in animals of this strain and age.

Group incidence of selected microscopic findings: liver					
		Males			
Tissue and finding	Level (mg/kg/hr)	1M 0	2M 0.25	3M 0.5	4M 1.0
Liver glycogen vacuolation	No. examined:	6	6	6	6
	Grade -	0	2	3	5
	1	0	0	3	1
	2	2	3	0	0
	3	4	1	0	0

Key: "--" = finding not present, 1 = minimal, 2 = slight, 3 = moderate.

Note: Morphological and biochemical investigations showed that cytoplasmic vacuolation of liver cells following low doses of toxins was due to excess accumulation of glycogen, predominantly of the monoparticulate form. These observations on animal and human livers that many of the vacuolated hepatocytes seen in liver injury are cells adaptively altered to resist further insult rather than cells undergoing hydropic degeneration, (Nayak NC, 1996)

### Comet assay

TRV130A: Summary of group mean data -Liver

Group / Treatment (mg/kg/hr)	Total no. cells scored	Tail Intensity		Tail Moment		Mean % clouds	Mean %Diffused cells
		Mean	SEM	Mean	SEM		
1 / Vehicle	600	1.76	0.28	0.17	0.02	2.50	2.67
2 / TRV130A (0.25)	600	1.76	0.23	0.17	0.02	1.75	2.17
3 / TRV130A (0.5)	600	1.03	0.26	0.12	0.02	2.00	2.67
4 / TRV130A (1.0)	600	0.77	0.13	0.08	0.01	2.83	3.00
5 / EMS (250)	600	17.37	0.80	2.15	0.12	3.50	3.50

SEM Standard error of mean

EMS Ethyl methanesulfonate, administered at 250 mg/kg by oral gavage

Note: There is a concentration-dependent reduction of tail length/intensity in liver cells that may indicate a cross-linking effect of TRV130.

#### Evaluation criteria

For valid data, the test article was considered to induce DNA damage if:

1. A dose related change in tail moment or tail intensity was observed in any tissue between the vehicle and test article groups, or
2. A marked change in tail moment or tail intensity is observed in any tissue between the vehicle and at least a single dose group.

The test article was considered positive in this assay if at least one of the above criteria were met.

The test article was considered negative in this assay if none of the above criteria were met.

#### TRV130A: Summary of group mean data – Blood

Group / Treatment (mg/kg/hr)	Total no. cells scored	Tail Intensity		Tail Moment		Mean % clouds	Mean %Diffused cells
		Mean	SEM	Mean	SEM		
1 / Vehicle	600	0.84	0.19	0.08	0.01	1.67	1.33
2 / TRV130A (0.25)	500	1.13	0.23	0.10	0.02	1.50	1.40
3 / TRV130A (0.5)	600	1.23	0.32	0.12	0.03	1.08	0.50
4 / TRV130A (1.0)	600	1.02	0.22	0.09	0.02	1.58	1.50
5 / EMS (250)	600	14.82	0.77	1.60	0.12	3.75	2.50

SEM Standard error of mean

EMS Ethyl methanesulfonate, administered at 250 mg/kg by oral gavage

There was no dose-related increase in % clouds or % diffused cells in liver and blood following treatment with TRV130A.

The Applicant's conclusion:

There was no dose-related increase in % clouds or % diffused cells in liver and blood following treatment with TRV130A, thus demonstrating that treatment with TRV130A did not cause excessive DNA damage that could have interfered with comet analysis. Comet analysis of liver and blood provided tail intensities and tail moment values that were considered generally consistent with or slightly lower than the concurrent vehicle control group. The absence of any clear increases or decreases in comet parameters observed in test article treated groups was considered indicative of an absence of DNA damage or cross-linking effects. It is concluded that, under the conditions of this Comet assay, TRV130A did not induce DNA damage in the liver and blood of rats treated up to 1 mg/kg/h, when analyzed after 24-hours continuous infusion.

The reviewer's conclusion (Dr. Emami):

There is a concentration-dependent reduction of tail length/intensity in liver cells that may indicate a cross-linking effect of TRV130. The Sponsor should provide a persuasive scientific justification or provide evidence from experimental results on the chemical reactivity of the two centers (the oxygen and amine functional groups) of the drug substance that would support a weight-of-evidence argument against a crosslinking effect of the drug substance (See the recommendation to the Sponsor)

Reviewer's note (Dr. Zhang):

*In the IND review, Dr. Emami communicated with the Applicant, asking for persuasive scientific justification or evidence from experimental results on the chemical reactivity of the two centers (the oxygen and amine functional groups) of the drug substance that would support a weight-of-evidence argument against a crosslinking effect of the drug substance. In response to Dr. Emami's comments, the Applicant provided the following justifications:*

- *TRV130 is not a bis-functional electrophile and would not cross-link DNA from a chemical standpoint.*
- *The COMET assay is not routinely run to detect DNA cross-linking agents as these agents are readily detectable in an in vivo micronucleus assay (Morita et al, 1997). TRV130 was clearly not genotoxic in the in vivo micronucleus test (Study 8242831). Therefore, it is unlikely that TRV130 is a DNA cross-linker.*

*The reduced tail intensity observed in the liver in the in vivo COMET assay with TRV130 was seen in only a few animals and was not robust. All group means as well as values for all individual animals were within the laboratory's historical range for vehicle controls (n=59) for both median tail moment and median tail intensity, although the historical data for rat liver is from 8 studies and seems too broad to be useful. Overall, Dr. Emami agreed with the Applicant's scientific justifications that TRV130 is not a DNA cross-linker in the in vivo Comet assay.*

## 7.5 Other Genetic Toxicology Studies

The proposed specifications for four impurities/degradation products exceed ICH qualification thresholds. In order to support specification levels above ICH qualification thresholds, the Applicant qualified these four impurities/degradation products in accordance with ICH Q3A(R2) and ICH Q3B(R2) in in vitro genotoxicity assays (bacterial reverse mutation assay and in vitro micronucleus assay) up to the assay limit dose or up to the limit of cytotoxicity. These studies have been reviewed in Section 9.1.1.

## 8 Reproductive and Developmental Toxicology of Oliceridine

### 8.1 Fertility and Early Embryonic Development

#### ***Study title: A Continuous Infusion Study of the Effects of TRV130 on Fertility in Male Sprague-Dawley Rats***

Study no.: (b) (4)-141505  
Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev\141505\141505-study-report.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: 19-Dec-2014  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: TRV130 Fumarate, Lot FP-000016 (b) (4) ID 140347); 99.6%

#### ***Key Study Findings***

- Male systemic toxicity: No adverse effects were observed up to 24 mg/kg/day. The NOAEL for male systemic toxicity was 24 mg/kg/day.
- Male reproductive toxicity:
  - No treatment-related effects on spermatogenic endpoints, male mating, fertility or copulation indices and intrauterine survival were observed at any dosage level. The mean number of days between pairing and coitus were comparable across all groups.
  - There were no treatment-related macroscopic or microscopic findings or changes in organ weights at any dose level.
  - The NOAEL for male reproductive toxicity was considered to be 24 mg/kg/day.

- The TK data showed average steady state plasma concentration in male rats dosed with 24 mg/kg/day TRV130 was 184 ng/mL, with an AUC<sub>0-24h</sub> of 4416 ng\*hour/mL that is 6 times the estimated total daily human exposure of 783 ng\*h/mL at MRHD of 40 mg/day.

**Methods**

Doses: 0, 6, 12, and 24 mg/kg/day (0, 0.25, 0.5 and 1 mg/kg/h) administered at an infusion flow rate of 1 mL/kg/h.

The following table presents the study group assignment:

Group Number	Treatment	Dosage Level (mg/kg/day)	Infusion Flow		Number of Males	Number of Females <sup>a</sup>
			Rate (mL/kg/hr)			
1	Vehicle Control	0	1		25	25
2	TRV130	6	1		25 <sup>b</sup>	25
3	TRV130	12	1		25	25
4	TRV130	24	1		25 <sup>b</sup>	25

<sup>a</sup> = Females were not administered the vehicle or test article and were used for breeding purposes only.

<sup>b</sup> = One male each in the 6 and 24 mg/kg/day groups were found dead on study day 0 and 1 male was added to each group to maintain 25 animals/group (see [Deviations from the Protocol](#)).

Frequency of dosing: Continuous infusion  
 Treatment duration: Males were dosed for 28 days prior to cohabitation (Study Days 0-27), throughout the mating period and up to the time of scheduled necropsy for a total of 64-65 days of dosing.  
 Dose volume: 1 mL/kg/h  
 Route of administration: Continuous IV infusion  
 Formulation/Vehicle: 0.2 mM sodium phosphate buffer in 5% (w/v) dextrose injection, USP, pH 6.4 ± 0.2  
 Species/Strain: Crl:CD (SD) Sprague-Dawley  
 Number/Sex/Group: 25 males/group; Only males were dosed.  
 TK groups (Not satellite): For toxicokinetic evaluation, blood samples were collected from 4 males/group approximately 2, 4, and 8 hours after the initiation of infusion on Study Day 0 and approximately 4 hours following the daily syringe change on Study Days 7, 14, 21, and 27.  
 Dose selection rational: The dose selection was based upon a previously conducted 14-day toxicology study in rats ( (b) (4) Study 8242808). The NOAEL in that study is 0.5 mg/kg/h based upon decreases in food consumption and body weight at doses ≥ 1 mg/kg/h. Therefore, a high dosage level of 1 mg/kg/h was selected for the current study.  
 Deviation from study protocol: One male each in the 6 and 24 mg/kg/day groups were found dead on Study Day 0 and 1 male was added to each group to maintain 25 animals/group. None of these deviations impacted the integrity or interpretations of the study.

## **Observations and Results**

### **Mortality**

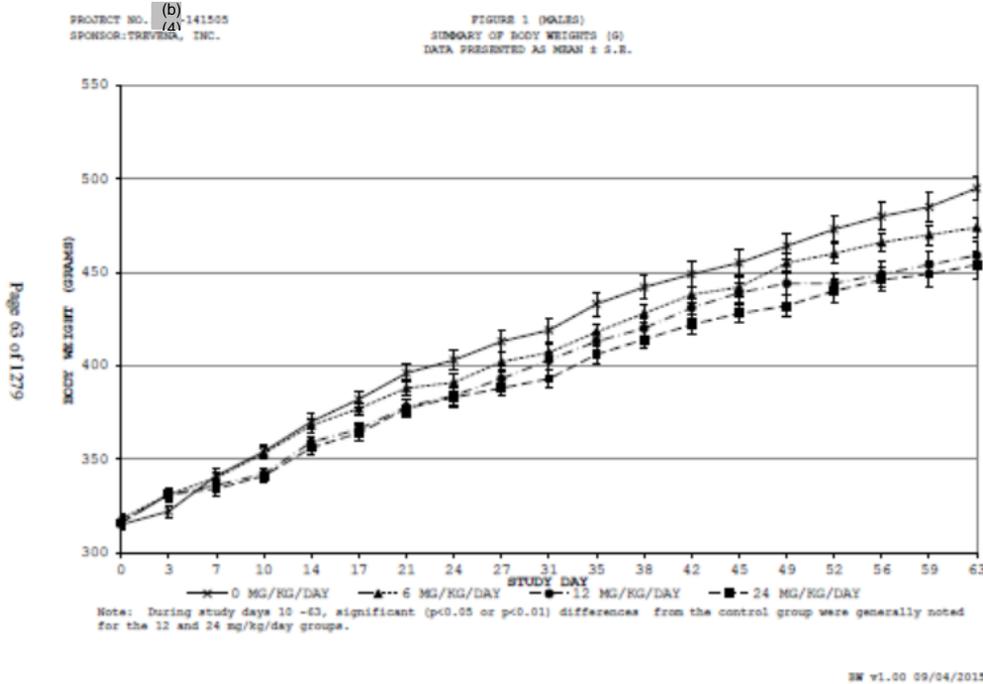
There were no test article-related effects on survival. A total of 3, 5, 3, and 3 males in the control, 6, 12, and 24 mg/kg/day groups, respectively, were found dead, euthanized in extremis or removed from study. These unscheduled events were not considered test article related because they were due to infection, an error in the blood collection procedure, or the inability to continue dose administration due to catheter issues.

### **Clinical Signs**

A slightly increased incidence of red material around the eyes and nose was noted for the 24 mg/kg/day group throughout the treatment period. No other test article-related clinical findings were noted at any dosage level.

### **Body Weight and Food Consumption**

As shown in the figure below, there were transiently higher mean body weight gains in TRV130-treatment groups compared to the control group during Study Days 0-3 followed by a dose-dependent reduction of body weight in these groups compared to control. Mean body weights were lower for the 12 and 24 mg/kg/day groups during Study Days 10-63 compared to the control group (up to 7.3% and 8.3%, respectively). Mean food consumption in the 12 and 24 mg/kg/day groups was lower than the control group throughout the treatment period. The reduction of body weight was correlated to the reduction of food consumption. These decrements in body weight and food consumption in the 12 and 24 mg/kg/day groups were considered test article related, but not adverse because they were pharmacological effects of the mu-opioid receptor agonist and mean body weights in all groups were no more than 8.3% less than the control group throughout the treatment period.



### Toxicokinetics

Steady-state plasma concentration ( $C_{ss}$ ) was generally achieved within 8 hours after the start of infusion. TRV130 plasma exposure was generally dose proportional, increasing with the increase in dosage level from 6 to 24 mg/kg/day. Average total plasma CL values ranged from approximately 5.2 to 5.9 L/kg/h and were not dose-dependent. All TRV130 concentration values in the control group were below the lower limit of quantitation (2.0 ng/mL).

**Table 32: Toxicokinetic Parameters for TRV130 in Male Rat Plasma**

Group	Dose Level (mg/kg/hr)	Sex	$C_{ss}$ (ng/mL)	CL (mL/hr/kg)
2	0.25	Male	47.6	5290
3	0.5	Male	85.4	5940
4	1 (NOAEL)	Male	184	5470

CL = Clearance;  $C_{ss}$  = Steady state concentration; NOAEL = No observed adverse effect level

### Dosing Solution Analysis

TRV130 formulations in the vehicle at concentrations ranging from 0.01 to 4.5 mg/mL have been shown to be solutions and are stable for 37 days at room temperature or when stored refrigerated at 2°C to 8°C (Fritz, 2012; (b) (4) Study 8242808). Therefore, homogeneity and stability analyses were not conducted in this study. The analyzed dosing formulations were within (b) (4) SOP range for solutions

(90% to 110%). The test article was not detected in the vehicle formulation that was administered to the control group (Group 1).

### Necropsy

There were no test article-related macroscopic or microscopic findings in the examined tissues (coagulating, pituitary, and prostate glands, seminal vesicles, testis with epididymis, and vas deferens) at all dose levels. Brain, epididymides (total and cauda), pituitary gland and testes that were weighed at the scheduled necropsy. Slightly lower epididymis (right, right cauda, and left) and pituitary gland weights were noted. No histological changes were noted in the epididymis or pituitary gland which correlated with the decreased weights in these organs. Although these values were statistically significant compared to the control animals, all organ weight values were within the range of the normal (b) (4) historical control database, attributed to 1 or 2 animals, and were not considered test article related.

### Reproductive Performance

No test article-related effects on spermatogenic endpoints were observed at any dosage level. No test article-related effects on male mating, fertility, and copulation indices were observed at any dosage level. The mean number of days between pairing and coitus were comparable across all groups. No test article-related effects on intrauterine survival of embryos were noted in the 6, 12, and 24 mg/kg/day groups.

### ***Study title: A Continuous Infusion Study of the Effects of TRV130 on Fertility and Early Embryonic Development in Female Sprague-Dawley Rats***

Study no.: (b) (4) -141506

Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev\141506\141506-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: 19-Dec-2014

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: TRV130 (fumarate), FP-000016, 99.6%

### ***Key Study Findings***

- Maternal toxicity: Lower mean body weight gains (16% decrease in body weight gain) were noted in the 24 mg/kg/day group during the gestation period (GD 0-15), indicating that maternal toxicity was achieved, and an appropriate high-dose was selected. A dosage level of 24 mg/kg/day was considered to be the NOAEL for female systemic toxicity. Mean

$C_{ss}$  at the NOAEL dose of 24 mg/kg/day was 148 ng/mL, with an  $AUC_{0-24h}$  of 3552 ng\*hour/mL that is 4.5 times the estimated total daily human exposure of 783 ng\*h/mL at MRHD of 40 mg/day.

- Female reproductive and early embryonic toxicity:
  - There were no test article-related effects on mating, fertility, and conception indices and the number of days between pairing and mating at any dosage level.
  - A longer estrous cycle length was noted in the 12 and 24 mg/kg/day groups.
  - Lower mean numbers of implantation sites and viable embryos and higher mean litter proportions of pre-implantation loss were noted at 12 and 24 mg/kg/day.
  - There were no treatment-related macroscopic findings noted at the GD 15 necropsy and female reproductive organ weights.
  - Based on these results, 6 mg/kg/day was considered to be the NOAEL for reproductive and early embryonic toxicity. Mean  $C_{ss}$  at the NOAEL dose of 6 mg/kg/day was 32.1 ng/mL, with an  $AUC_{0-24h}$  of 770 ng\*hour/mL that is 1 times the estimated total daily human exposure of 783 ng\*h/mL at the proposed MRHD of 40 mg/day.

## Methods

Doses	0, 6, 12, and 24 mg/kg/day
Treatment Duration:	The females were dosed for 14 days prior to cohabitation (Study Days 0-13) and were dosed through Gestation Day 15 for a total of 29-42 days of dosing.
Frequency of dosing:	Continuous IV Infusion
Dose volume:	1mL/kg/h
Route of administration:	IV
Formulation/Vehicle:	0.2 mM sodium phosphate buffer in 5% (w/v) dextrose injection, USP, pH 6.4 ± 0.2
Species/Strain:	Crl:CD(SD) Sprague-Dawley
Number/Sex/Group:	25 females/dose group
TK groups (not satellite):	For toxicokinetic evaluation, blood samples were collected from 4 females per group approximately 2, 4, and 8 hours after the initiation of infusion on Study Day 0 and approximately 4 hours following the daily syringe change on Study Days 7 and 13.
Dose selection rationale:	The dose selection was based upon a previously conducted 14-day toxicology study in rats ( (b) (4) Study 8242808). The NOAEL in the study was 0.5 mg/kg/h based upon decreases in food consumption and body weight at doses ≥ 1 mg/kg/h. Therefore, a high dosage level of 1 mg/kg/h was selected for the current study.
Deviation from study protocol:	None of the deviations affected the results of the study.

## Observations and Results

### Mortality

There were mortalities in the control, 6, and 24 mg/kg/day groups. These mortalities were not considered test article related.

### Clinical Signs

The following observations were considered test article-related but not adverse due to the transient nature of the effects:

- A slight increase in the incidence of red material around the nose was noted for females in the 24 mg/kg/day group compared to the control group at the scheduled daily examinations throughout the treatment period.
- There was a slight increase in the incidence of swollen forelimbs or digits on the forelimbs and facial area in the 12 and/or 24 mg/kg/day groups. Swelling of the paws was noted in a

previous 14-day study (Fritz, 2012; (b) (4) Study 8242808) and is commonly noted in rats given opioids.

### Body Weight and Food Consumption

No toxicologically significant effects were observed on body weight, body weight gain, or food consumption:

- Transient higher mean body weight gains and corresponding higher mean food consumption were noted immediately following the initiation of infusion (Study Days 0-4) for females at all dosage levels. Acute increases in food consumption and delayed gastric motility are known effects of mu-opioid receptor agonists. These initial effects were considered test article related but not adverse. Mean body weights in the 6, 12, and 24 mg/kg/day groups remained slightly (not statistically significant) higher than the control group throughout the remainder of the pre-mating period.
- A statistically significantly ( $p < 0.01$ ) lower mean body weight gain (16.2%) was noted in the 24 mg/kg/day group when the entire gestation treatment period (Gestation Days 0-15) was evaluated compared to the control group. However, mean body weights in the 24 mg/kg/day group were similar to the control group throughout gestation, and therefore the deficits in mean body weight gain were considered test article-related but not necessarily be adverse. Mean maternal food consumption, evaluated as g/animal/day and g/kg/day, was unaffected by test article administration during gestation.

### Toxicokinetics

Steady-state plasma concentration ( $C_{ss}$ ) was generally achieved within 8 hours after the start of infusion. TRV130 plasma exposure was approximately dose proportional, increasing with the increase in dosage level from 6 to 24 mg/kg/day. Average total plasma CL values ranged from approximately 7.1 to 7.8 L/kg/h and were not dose-dependent. All TRV130 concentration values in the control group were below the lower limit of quantitation (2.0 ng/mL).

**Table 36: Toxicokinetic Parameters for TRV130 in Female Rat Plasma**

Group	Dose Level (mg/kg/hr)	Sex	$C_{ss}$ (ng/mL)	CL (mL/hr/kg)
2	0.25 (NOAEL)	Female	32.1	7830
3	0.5	Female	71.0	7080
4	1	Female	148	7250

CL = Clearance;  $C_{ss}$  = Steady state concentration; NOAEL = No observed adverse effect level

### Dosing Solution Analysis

TRV130 formulations in the vehicle at concentrations ranging from 0.01 to 4.5 mg/mL

have been shown to be solutions and are stable for 37 days at room temperature or when stored refrigerated at 2°C to 8°C (Fritz, 2012 (b) (4) Study 8242808). Therefore, homogeneity and stability analyses were not conducted in this study. The analyzed dosing formulations were within (b) (4) SOP range for solutions (90% to 110%). The test article was not detected in the vehicle formulation that was administered to the control group.

## Necropsy

There were no test article-related macroscopic findings noted at the Gestation Day 15 necropsy for females with evidence of mating. In addition, female reproductive organ weights (absolute and relative to brain weight) were unaffected by test article administration at all dosage levels.

## Reproductive Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

### Mating/Fertility Index and Estrous Cycle:

As shown in the table below, no test article-related effects were noted on female mating, fertility, and conception indices or the number of days between pairing and mating at any dosage level. A test article-related longer mean estrous cycle length was noted in the 12 and 24 mg/kg/day groups compared to the control group. The mean length of the estrous cycle in the 24 mg/kg/day group was significantly ( $p < 0.05$ ) longer than the concurrent control group and the maximum mean value in the (b) (4) historical control data. This difference was driven by 5 females in this group with estrous cycles ranging from 6 to 13 days in length and in combination with the preimplantation loss. These findings were considered test article-related and adverse. The mean length of the estrous cycle in the 12 mg/kg/day group was also slightly longer than the concurrent control group. Although the difference was not statistically significant and the group mean was within the (b) (4) historical control data range, 3 females in the 12 mg/kg/day group were noted with estrous cycles that were  $\geq 8$  days in length and there was a dose-response relationship. Therefore, the higher mean estrous cycle length in the 12 mg/kg/day group was considered test article-related. It is worthwhile to notice that  $\geq 12$  mg/kg/day groups also had increased pre-implantation loss.

**Text Table 4. Results of Reproductive Performance**

Parameter	Dosage Level (mg/kg/day)				(b) (4) HC <sup>a</sup>
	0	6	12	24	Mean (Range)
Female Mating Index (%)	100.0	96.0	100.0	100.0	99.3 (92.0-100.0)
Female Fertility Index (%)	91.7	92.0	100.0	95.8	96.5 (84.0-100.0)
Female Conception Index (%)	91.7	95.8	100.0	95.8	97.3 (85.0-100.0)
Estrous Cycle Length (days)	4.2	4.4	4.8	5.5*	4.2 (3.6-5.1)
Pre-Coital Interval (days)	4.2	5.0	4.0	4.3	2.8 (2.0-3.8)

<sup>a</sup> = (b) (4) historical control data

\* = Significantly different from the control group at  $p < 0.05$

**Fertility Parameters:**

- There were no test article-related effects on the mean numbers of corpora lutea or postimplantation loss in the 12 and 24 mg/kg/day groups.
- The following changes are considered test article-related and adverse:
  - A higher (not statistically significant) mean litter proportion of pre-implantation loss was noted in the 12 and 24 mg/kg/day groups (18.6% and 12.5% per litter, respectively) compared to the concurrent control group (7.5% per litter) and the maximum mean value in the (b) (4) historical control data (10.8% per litter).
  - The increased preimplantation lose resulted in a lower mean number of implantation sites noted in the 12 and 24 mg/kg/day groups (12.1 and 12.2 per litter, respectively) compared to the concurrent control group (13.5 per litter) and the minimum mean value in the (b) (4) historical control data (13.9 per litter); the difference from the concurrent control group was significant (p<0.05) at 12 mg/kg/day.
  - Consequently, the mean number of viable embryos in the 12 and 24 mg/kg/day groups (10.9 and 11.6 per litter, respectively) was lower than the concurrent control group (12.8 per litter); the difference was significant (p<0.01) at 12 mg/kg/day.
  - Although these changes did not occur in a clear dose-related manner, they were considered test article-related and adverse because they were outside of the (b) (4) historical control ranges and correlated with the longer estrous cycle lengths in these same dosage groups, particularly at 24 mg/kg/day.
- Intrauterine survival of the embryos was unaffected by test article administration at 6 mg/kg/day.

GROUP:	0 MG/KG/DAY	6 MG/KG/DAY	12 MG/KG/DAY	24 MG/KG/DAY
<b>PRE-IMPLANTATION LOSS (%)</b>				
MEAN	7.5	8.4	18.6	12.5
S.D.	8.56	10.17	19.50	10.68
S.E.	1.83	2.12	3.90	2.33
N	22	23	25	21
<b>POST-IMPLANTATION LOSS (%)</b>				
MEAN	4.6	6.0	10.0	5.1
S.D.	7.92	10.65	13.43	4.81
S.E.	1.69	2.22	2.69	1.05
N	22	23	25	21
<b>IMPLANTATION SITES</b>				
MEAN	13.5	12.8	12.1*	12.2
S.D.	1.74	1.27	2.53	1.22
S.E.	0.37	0.26	0.51	0.27
N	22	23	25	21
<b>CORPORA LUTEA</b>				
MEAN	14.7	14.2	15.2	14.2
S.D.	2.55	2.17	3.14	2.74
S.E.	0.54	0.45	0.63	0.60
N	22	23	25	21

PROPORTIONAL (%) DATA COMPARED USING DUNN'S TEST  
 CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST  
 MODIFIED STATISTICS USED. \* INDICATES PARAMETRIC ANALYSIS AND + INDICATES NON-PARAMETRIC ANALYSIS.  
 \* = Significantly different from the control group at 0.05

## 8.2 Embryonic Fetal Development

### **Study title: A Continuous Infusion Embryo/Fetal Development-Study of TRV130 in Sprague-Dawley Rats**

Study no.: (b) (4)-141503  
Study report location: <\\cdsesub1\levsprod\nda210730\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\141503\141503-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: 03-Nov-2014  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: TRV130 fumarate; 2417-21-1; 99.1%

### **Key Study Findings**

- Maternal toxicity:
  - Slightly increased incidences of red material around the nose were noted in 24 mg/kg/day group throughout the treatment period as well as low occurrences of pale extremities, hunched posture and hypoactivity in 24 mg/kg/day group. These findings were considered treatment related but not adverse due to the low incidence or transient nature of the finding.
  - Mean body weight loss (~1.7% at 24 mg/kg/day in GD 7-8 only), reduced body weight gain, and lower mean food consumption were observed early in the dosing period, mostly in the 12 and 24 mg/kg/day groups. These changes were considered treatment-related, but not adverse.
  - One female in both the 12 and 24 mg/kg/day main study groups were identified as nongravid at the terminal necropsy.
  - No test article-related maternal macroscopic findings were noted at the scheduled laparohysterectomy.
  - Based on the lack of clear adverse effects at any dosage level, 24 mg/kg/day, the highest dosage level evaluated, was considered to be the NOAEL for maternal toxicity, approximately 5 times the human daily exposure at MRHD of 40 mg/day.
- Embryo/fetal development toxicity:

- Intrauterine growth and survival were unaffected by maternal test article administration at all dosage levels.
- Mean number of corpora lutea, implantation sites and the mean litter proportions of preimplantation loss were similar across groups. A slightly higher (not statistically significant) proportion of post-implantation loss was observed in the 24 mg/kg/day group; however, the value was within the range of laboratory historical control data and the effect was considered secondary to maternal toxicity associated with infection.
- The numbers of fetuses (litters) available for morphological evaluation were 325 (24), 333 (25), 309 (24), and 287 (23) in the control, 6, 12 and 24 mg/kg/day groups, respectively. Malformations were observed in 2 (2), 0 (0), 4 (4), and 1 (1) fetuses (litters) in these same respective dose groups and were considered spontaneous in origin. When the total malformations and developmental variations were evaluated on a proportional basis, no statistically significant differences from the control group were noted. Fetal malformations and developmental variations in the TRV130-treated groups occurred infrequently or at a frequency similar to that in the control group, did not occur in a dose-related manner, and/or were within the testing laboratory's historical control data ranges.
- The percent of litters with reduced ossification of the vertebral arches was increased in the HD group (5.2%) compared to controls and outside the historical control range of up to 2%. Reduced ossification of the skull was also higher in the HD group compared to control (2% of litters in HD vs. 0% in controls), suggesting a potential developmental delay at this dose. Reduced ossification could be considered a developmental delay or a direct structural alteration. Given the lack of overt evidence of malformations or skeletal abnormalities in the pre- and postnatal study, this may be more of a developmental delay (inhibition of growth) and not necessarily adverse.
- Based on these data, no other fetal malformations or developmental variations were attributed to the TRV130. The HD could be considered a NOAEL.
- The TK study showed mean  $C_{ss}$  at the NOAEL dose of 24 mg/kg/day was 164 ng/mL, with an  $AUC_{0-24h}$  of 3936 ng\*h/mL that is 5 times the estimated total daily human exposure of 783 ng\*h/mL at MRHD of 40 mg/day.

## Methods

Doses:	0, 6, 12, and 24 mg/kg/day (0, 0.25, 0.5 and 1 mg/kg/h)
Frequency of dosing:	Continuous infusion from Gestation Day (GD) 6 through 20
Dose volume:	1 mL/kg/h
Route of administration:	IV
Formulation/Vehicle:	0.2 mM sodium phosphate buffer in 5% [w/v] dextrose injection, USP, pH 6.4 ± 0.2

Species/Strain: Crl:CD(SD) Sprague-Dawley rats  
 Number/Sex/Group: 25 pregnant females/dose

Group Number	Treatment	Dosage Level (mg/kg/day)	Infusion Flow Rate (mL/kg/hr)	Number of Females	
				Embryo/Fetal Development Phase (b) (4) 141503	Toxicokinetic Phase (b) (4) 141503T
1	Vehicle control	0	1	25	6
2	TRV130	6	1	25	6
3	TRV130	12	1	25	6
4	TRV130	24	1	25	6

Satellite groups: 6 pregnant females/dose; Blood samples were collected from each rat approximately 2, 4, and 8 hours after the initiation of infusion on GD 6 and approximately 4 hours following the daily syringe change on GD 10, 14, and 20. All toxicokinetic phase animals were euthanized on GD 20, and pregnancy status was determined for each female.

Dose selection rationale: The dosage levels were selected based on the results of a dose range-finding study in pregnant rats conducted at 6, 12, and 24 mg/kg/day (Edwards, 2015, (b) (4) 141501) and a 14-day continuous infusion toxicology study in rats (Fritz, 2012; (b) (4) Study 8242808). In the range-finding study in pregnant rats, there was a slight reduction in mean body weight gains and food consumption in rats dosed from GD 6 through 20 at 24 mg/kg/day. The NOAEL in the study was 12 mg/kg/day based upon decreases in food consumption and body weight at doses ≥ 1 mg/kg/h. Therefore, based on these previously collected data, a high dosage level of 24 mg/kg/day was selected for the current study.

Deviation from study protocol: Female 31720 in the 6 mg/kg/day group was removed from the study on GD 7 due to the catheter being lost below the exteriorization site and the inability to continue dosing; no internal findings were noted for this female at necropsy. This female was replaced with Female 31776.

**Observations and Results**

**Mortality**

All females survived to the scheduled laparohysterectomy on GD 20.

**Clinical Signs**

A slightly increased incidence of red material around the nose was noted for females in the 24 mg/kg/day as well as occurrences of pale extremities (3 females in 24 mg/kg/day group) and hunched posture and hypoactivity (1 female in 24 mg/kg/day group). Because the increase in the incidence of red material around the nose was slight and the findings of pale extremities, hunched posture, and hypoactivity were transient and limited to only a few animals, these findings were considered test article-related but not adverse.

**Body Weight and Food Consumption**

- A transient increase in mean body weight gain was noted in all the test article-treated groups following the initial 24 hours of test article administration, GD 6-7, compared to the control group. The body weight gain was 0, 9, 14 and 18 g in vehicle, 6, 12 and 24 mg/kg/day group, respectively (see the table below). The Applicant stated that this finding may result from delayed gastric motility, a known side effect of mu-opioid receptor agonists.
- As shown in the table below, immediately following the increase in mean body weight gain, test article-related mean body weight loss or reduced mean body weight gains were noted beginning on GD 7-8 (12 and 24 mg/kg/day) or GD 8-9 (6 mg/kg/day) through GD 10. Mean body weight gains at all dosage levels were generally similar to the control group throughout the remainder of the treatment period.

PROJECT NO. (b) 141503 TABLE S5 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS PAGE 1  
 SPONSOR: TREVENA, INC. SUMMARY OF BODY WEIGHT CHANGES DURING GESTATION [G]

GROUP:		0 MG/KG/DAY	6 MG/KG/DAY	12 MG/KG/DAY	24 MG/KG/DAY
DAY	0- 6				
	MEAN	29.	27.	26.	23.*
	S.D.	6.1	7.1	6.8	9.5
	S.E.	1.2	1.4	1.4	1.9
	N	25	26	24	24
DAY	6- 7				
	MEAN	0.	9.**	14.**	18.**
	S.D.	3.0	6.2	5.6	8.2
	S.E.	0.6	1.2	1.1	1.7
	N	25	26	24	24
DAY	7- 8				
	MEAN	4.	3.	0.*	-3.**
	S.D.	4.8	4.4	5.5	8.6
	S.E.	1.0	0.9	1.1	1.7
	N	25	25	24	24
DAY	8- 9				
	MEAN	3.	1.	1.	0.
	S.D.	3.6	5.4	8.9	12.9
	S.E.	0.7	1.1	1.8	2.6
	N	25	25	24	24
DAY	9- 10				
	MEAN	7.	2.	2.	1.
	S.D.	4.1	6.9	7.5	11.9
	S.E.	0.8	1.4	1.5	2.4
	N	25	25	24	24

\* = Significantly different from the control group at 0.05 using Dunnett's test  
 \*\* = Significantly different from the control group at 0.01 using Dunnett's test  
 MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES  
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

PROJECT NO. (b) 141503 TABLE S5 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS PAGE 2  
 SPONSOR: TREVENA, INC. SUMMARY OF BODY WEIGHT CHANGES DURING GESTATION [G]

GROUP:		0 MG/KG/DAY	6 MG/KG/DAY	12 MG/KG/DAY	24 MG/KG/DAY
DAY	10- 11				
	MEAN	6.	6.	5.	7.
	S.D.	4.5	6.1	3.1	8.7
	S.E.	0.9	1.2	0.6	1.8
	N	25	25	24	24
DAY	11- 12				
	MEAN	7.	7.	3.	4.
	S.D.	3.7	3.5	5.5	7.7
	S.E.	0.7	0.7	1.1	1.6
	N	25	25	24	24
DAY	12- 13				
	MEAN	4.	5.	6.	4.
	S.D.	4.0	3.7	3.9	5.1
	S.E.	0.8	0.7	0.8	1.0
	N	25	25	24	24
DAY	13- 14				
	MEAN	6.	7.	6.	5.
	S.D.	3.6	4.4	5.4	3.6
	S.E.	0.7	0.9	1.1	0.7
	N	25	25	24	24
DAY	14- 15				
	MEAN	8.	6.	7.	8.
	S.D.	3.6	3.7	5.9	4.5
	S.E.	0.7	0.7	1.2	0.9
	N	25	25	24	24

None significantly different from control group  
 MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES  
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

PROJECT NO.: (b) (4) 141503  
 SPONSOR: TREVENA, INC. TABLE S5  
 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS  
 SUMMARY OF BODY WEIGHT CHANGES DURING GESTATION [G] PAGE 3

GROUP:	0 MG/KG/DAY	6 MG/KG/DAY	12 MG/KG/DAY	24 MG/KG/DAY
DAY 15- 16				
MEAN	11.	11.	11.	8.
S.D.	3.6	4.5	4.6	3.6
S.E.	0.7	0.9	0.9	0.7
N	25	25	24	24
DAY 16- 17				
MEAN	12.	12.	11.	13.
S.D.	4.5	8.0	5.8	4.1
S.E.	0.9	1.6	1.2	0.8
N	25	25	24	24
DAY 17- 18				
MEAN	17.	18.	18.	15.
S.D.	5.6	5.6	5.9	5.2
S.E.	1.1	1.1	1.2	1.1
N	25	25	24	24
DAY 18- 19				
MEAN	17.	18.	17.	17.
S.D.	5.6	5.3	5.1	6.6
S.E.	1.1	1.1	1.0	1.4
N	25	25	24	24
DAY 19- 20				
MEAN	16.	17.	17.	17.
S.D.	5.7	4.3	5.1	5.6
S.E.	1.1	0.9	1.0	1.1
N	25	25	24	24

None significantly different from control group  
 MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES  
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

- As shown in the table below, total body weight gain during the treatment period (GD 6-GD 20) was similar across the treatment groups. The female rats treated with 24 mg/kg/day only gained 2.5% less than the vehicle treated rats. Therefore, the changes in body weight gain were considered test article-related but not adverse.

PROJECT NO.: (b) (4) 141503  
 SPONSOR: TREVENA, INC. TABLE S5  
 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS  
 SUMMARY OF BODY WEIGHT CHANGES DURING GESTATION [G] PAGE 4

GROUP:	0 MG/KG/DAY	6 MG/KG/DAY	12 MG/KG/DAY	24 MG/KG/DAY
DAY 6- 9				
MEAN	7.	14.*	15.**	16.**
S.D.	4.4	6.0	8.4	12.5
S.E.	0.9	1.2	1.7	2.6
N	25	25	24	24
DAY 9- 12				
MEAN	20.	14.*	11.**	11.**
S.D.	4.7	3.9	9.2	12.5
S.E.	0.9	0.8	1.9	2.5
N	25	25	24	24
DAY 12- 15				
MEAN	18.	17.	18.	17.
S.D.	5.8	5.2	5.7	8.5
S.E.	1.2	1.0	1.2	1.7
N	25	25	24	24
DAY 15- 20				
MEAN	72.	76.	74.	71.
S.D.	15.6	9.7	14.9	17.4
S.E.	3.1	1.9	3.0	3.6
N	25	25	24	24
DAY 6- 20				
MEAN	118.	121.	117.	115.
S.D.	17.0	13.9	16.7	23.1
S.E.	3.4	2.8	3.4	4.7
N	25	25	24	24

\* = Significantly different from the control group at 0.05 using Dunnett's test  
 \*\* = Significantly different from the control group at 0.01 using Dunnett's test  
 MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES  
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

*Reviewer's note: Although the total body weight gain during the treatment period was not affected by the test article, this Reviewer considers the doses were adequately tested for the characterization of embryonic-fetal effects given that significantly less body weight gain*

*(45% less body weight gain vs. the vehicle group) was observed in GD 9-12 across the treatment groups, suggesting a minimal adverse maternal effect has been achieved.*

- Lower mean food consumption was noted for females at all dosage levels during GD 6-7 and in the 12 and 24 mg/kg/day groups in general throughout the remainder of the treatment period, resulting in lower food consumption at 6 (mg/kg/day only), 12, and 24 mg/kg/day during the overall dosing period, GD 6-20. Given that the changes in food consumption did not result in changes in total body weight gain, the changes in food consumption were considered test article related but not adverse.

### Toxicokinetics

The individual concentrations and mean concentration-time profiles show that mean steady state concentration ( $C_{ss}$ ) levels were generally achieved within 8 hours post-start of infusion. Plasma concentrations were approximately dose proportional, with mean  $C_{ss}$  values of 34.9, 78.3, and 164 ng/mL for doses of 6, 12, and 24 mg/kg/day, respectively. Average total plasma clearance (CL) values ranged from approximately 6.2 to 7.2 L/h/kg and were not dose-dependent. All TRV130 concentration values in the control group were below the lower limit of quantitation (2.0 ng/mL).

**Table 40: Mean TRV130 Toxicokinetic Parameters in Pregnant Rats**

Group	Dose Level (mg/kg/hr)	$C_{ss}$ <sup>a</sup> (ng/mL)	CL <sup>a</sup> (mL/hr/kg)
2	0.25	34.9	7190
3	0.5	78.3	6600
4	1.0 (NOAEL)	164	6150

<sup>a</sup>Data from non-pregnant animals was excluded from group mean calculations

CL = Clearance;  $C_{ss}$  = Steady state concentration; NOAEL = No observed adverse effect level

### Dosing Solution Analysis

The analyzed dosing formulations were within  <sup>(b) (4)</sup> SOP range for solutions (90% to 110%).

### Necropsy

No test article-related maternal macroscopic findings were noted at the scheduled Laparohysterectomy on GD 20. Macroscopic findings observed in the test article-treated groups occurred infrequently, at similar frequencies in the control group, and/or in a manner that was not dose-related.

### Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Intrauterine growth and survival and fetal morphology were unaffected by maternal test

article administration at all dosage levels. Parameters evaluated included post-implantation loss, live litter size, mean fetal body weights, and fetal sex ratios.

- A slightly (not statistically significant) higher litter proportion of post-implantation loss was noted for females in the 24 mg/kg/day group (11.2% vs 7.8% in the control group); however, this value was within the range of values in the (b) (4) historical control data. Additionally, there is no increase in the number of dams with 3 or more resorptions compared to the vehicle control group and the increase of post-implantation was considered to be related to maternal toxicity observed in 2 females. Taken together, the increased post-implantation loss in the high-dose group is not considered test-article related reproductive and developmental effect.
  - 3 females (31695, 31659, and 31772, see the table below) from the 24 mg/kg/day group contributed to the notable increase in post-implantation loss (100%, 50%, and 47.4%, respectively). Two of these 3 females (31696, 31659) had macroscopic findings at necropsy including pale, enlarged, and/or swollen spleen, dark red discoloration of the adrenal glands, and/or white areas of the kidneys. In addition, both of these females were noted with clinical findings of pale extremities and red vaginal discharge. The effects on post-implantation loss of these two females were considered secondary to the maternal toxicity associated with signs of infection. No clinical signs and macroscopic findings were observed in Female 31772, which also exhibited increased post-implantation loss.

PROJECT NO. (b) (4) 141503 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS  
 SPONSOR: TREVENA, INC. INDIVIDUAL FETAL DATA AT SCHEDULED NECROPSY [% PER LITTER]

DAMS FROM GROUP 4: 24 MG/KG/DAY

DAM #	CORPORA LUTEA		IMPLANTATION SITES		FETUSES		RESORPTIONS			PRE-IMPLANTATION LOSS	POST-IMPLANTATION LOSS	MALES	FEMALES
	#	%	#	%	VIABLE	DEAD	EARLY	LATE	TOTAL	%	%	%	%
31624	16.0		14.0	92.9	0.0	0.0	7.1	0.0	7.1	12.5	7.1	38.5	61.5
31625	12.0		11.0	90.9	0.0	0.0	9.1	0.0	9.1	8.3	9.1	50.0	50.0
31627	16.0		13.0	100.0	0.0	0.0	0.0	0.0	0.0	18.8	0.0	53.8	46.2
31659	16.0		12.0	50.0	33.3	0.0	0.0	16.7	16.7	25.0	50.0	50.0	50.0
31662	15.0		14.0	100.0	0.0	0.0	0.0	0.0	0.0	6.7	0.0	28.6	71.4
31666	16.0		14.0	92.9	0.0	0.0	7.1	0.0	7.1	12.5	7.1	69.2	30.8
31673	14.0		14.0	92.9	0.0	0.0	7.1	0.0	7.1	0.0	7.1	76.9	23.1
31680	13.0		13.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	61.5	38.5
31695	15.0		15.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	0.0
31697	17.0		14.0	100.0	0.0	0.0	0.0	0.0	0.0	17.6	0.0	50.0	50.0
31699	13.0		13.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	69.2	30.8
31704	17.0		15.0	93.3	0.0	0.0	6.7	0.0	6.7	11.8	6.7	42.9	57.1
31705	17.0		14.0	100.0	0.0	0.0	0.0	0.0	0.0	17.6	0.0	64.3	35.7
31709	17.0		16.0	93.8	0.0	0.0	6.3	0.0	6.3	5.9	6.3	66.7	33.3
31718	13.0		13.0	92.3	0.0	0.0	7.7	0.0	7.7	0.0	7.7	50.0	50.0
31731	12.0		12.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	41.7	58.3
31732	15.0		14.0	92.9	0.0	0.0	7.1	0.0	7.1	6.7	7.1	38.5	61.5
31734	13.0		12.0	100.0	0.0	0.0	0.0	0.0	0.0	7.7	0.0	66.7	33.3
31749	13.0		10.0	100.0	0.0	0.0	0.0	0.0	0.0	23.1	0.0	10.0	90.0
31750	12.0		12.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	50.0	50.0
31753	13.0		13.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	53.8	46.2
31772	30.0		19.0	52.6	0.0	0.0	47.4	0.0	47.4	36.7	47.4	50.0	50.0
31775	17.0		16.0	87.5	0.0	0.0	12.5	0.0	12.5	5.9	12.5	35.7	64.3
31783	15.0		14.0	100.0	0.0	0.0	0.0	0.0	0.0	6.7	0.0	78.6	21.4
MEAN	15.3		13.6	88.8	1.4	0.0	9.1	0.7	9.8	9.3	11.2	52.0	48.0
S.D.	3.61		1.84	23.16	6.80	0.00	21.72	3.41	21.68	9.74	23.16	16.18	16.18
S.E.	0.74		0.37	4.73	1.39	0.00	4.43	0.70	4.43	1.99	4.73	3.37	3.37
N	24		24	24	24	24	24	24	24	24	24	23	23

Reviewer's note: There were no visceral and skeletal findings in the dead fetus.

- Mean numbers of corpora lutea and implantation sites and the mean litter proportions of pre-implantation loss were similar across all groups; differences from the control group were slight and not statistically significant. No effects were observed in live litter size, mean fetal body weights, and fetal sex ratios.

**Offspring (Malformations, Variations, etc.)**

The numbers of fetuses (litters) available for morphological evaluation were 325 (24), 333 (25), 309 (24), and 287 (23) in the control, 6, 12 and 24 mg/kg/day groups, respectively. Malformations were observed in 2 (2), 0 (0), 4 (4), and 1 (1) fetuses (litters) in these same respective dose groups and were considered spontaneous in origin.

(b) PROJECT NO.: (b)(4) 141503 SPONSOR: TREVENA, INC. TABLE S12 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS SUMMARY OF FETUSES AND LITTERS WITH MALFORMATIONS [ABSOLUTE NO.] PAGE 1 DAY 20

DOSE GROUP:	FETUSES				LITTERS			
	1	2	3	4	1	2	3	4
NUMBER EXAMINED EXTERNALLY	325	333	309	287	24	25	24	23
MANDIBULAR MICROGNATHIA	1	0	0	0	1	0	0	0
MICROPTHALMIA AND/OR ANOPHTHALMIA	1	0	0	1	1	0	0	1
NUMBER EXAMINED VISCERALLY	325	333	309	287	24	25	24	23
RIGHT-SIDED AORTIC ARCH	0	0	1	0	0	0	1	0
NUMBER EXAMINED SKELETALLY	325	333	309	287	24	25	24	23
COSTAL CARTILAGE ANOMALY	0	0	1	0	0	0	1	0
RIB ANOMALY	0	0	2	0	0	0	2	0
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY ONLY 12 PAIRS OF RIBS PRESENT	1	0	0	0	1	0	0	0
TOTAL NUMBER WITH MALFORMATIONS								
EXTERNAL :	1	0	0	1	1	0	0	1
SOFT TISSUE :	0	0	1	0	0	0	1	0
SKELETAL :	1	0	3	0	1	0	3	0
COMBINED :	2	0	4	1	2	0	4	1

1- 0 MG/KG/DAY 2- 6 MG/KG/DAY 3- 12 MG/KG/DAY 4- 24 MG/KG/DAY

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02/11/2015

(b)(4) PROJECT NO.: (b)(4) 141503 SPONSOR: TREVENA, INC. TABLE S13 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS SUMMARY OF LITTER PROPORTIONS OF MALFORMATIONS % PER LITTER PAGE 4 DAY 20

DOSE GROUP:	1	2	3	4
NUMBER OF LITTERS EXAMINED	24	25	24	23
TOTAL MALFORMATIONS				
PERCENT PER LITTER WITH EXTERNAL MALFORMATIONS	MEAN 0.3	0.0	0.0	0.3
	S.D. 1.57	0.00	0.00	1.49
	S.E. 0.32	0.00	0.00	0.31
PERCENT PER LITTER WITH SOFT TISSUE MALFORMATIONS	MEAN 0.0	0.0	0.3	0.0
	S.D. 0.00	0.00	1.46	0.00
	S.E. 0.00	0.00	0.30	0.00
PERCENT PER LITTER WITH SKELETAL MALFORMATIONS	MEAN 0.3	0.0	1.3	0.0
	S.D. 1.28	0.00	3.83	0.00
	S.E. 0.26	0.00	0.78	0.00
TOTAL PERCENT PER LITTER WITH MALFORMATIONS	MEAN 0.6	0.0	1.6	0.3
	S.D. 1.98	0.00	4.00	1.49
	S.E. 0.40	0.00	0.82	0.31

1- 0 MG/KG/DAY 2- 6 MG/KG/DAY 3- 12 MG/KG/DAY 4- 24 MG/KG/DAY  
MODIFIED STATISTICS USED.  
None significantly different from control group

**External Malformations and Variations:**

No treatment related external malformation or variations were noted for fetuses.

PROJECT NO. (b) (4) 141503  
SPONSOR: TREVENA, INC.

TABLE S13  
A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS  
SUMMARY OF LITTER PROPORTIONS OF MALFORMATIONS  
% PER LITTER

PAGE 1  
DAY 20

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED EXTERNALLY		24	25	24	23
MANDIBULAR MICROGNATHIA	MEAN	0.3	0.0	0.0	0.0
	S.D.	1.57	0.00	0.00	0.00
	S.E.	0.32	0.00	0.00	0.00
MICROPTHALMIA AND/OR ANOPHTHALMIA	MEAN	0.3	0.0	0.0	0.3
	S.D.	1.57	0.00	0.00	1.49
	S.E.	0.32	0.00	0.00	0.31

1- 0 MG/KG/DAY    2- 6 MG/KG/DAY    3- 12 MG/KG/DAY    4- 24 MG/KG/DAY  
MODIFIED STATISTICS USED.  
None significantly different from control group

**Visceral Malformations and Variations:**

**Visceral Malformation:**

- There were no test-article related visceral malformations at any of the dosage level. Fetus no. 31675-08 in the 12 mg/kg/day group had right-sided aortic arch which was noted in a single fetus and was not noted in a dose-related manner.

PROJECT NO. (b) (4) 141503  
SPONSOR: TREVENA, INC.

TABLE S13  
A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS  
SUMMARY OF LITTER PROPORTIONS OF MALFORMATIONS  
% PER LITTER

PAGE 2  
DAY 20

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED VISCERALLY		24	25	24	23
RIGHT-SIDED AORTIC ARCH	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.46	0.00
	S.E.	0.00	0.00	0.30	0.00

1- 0 MG/KG/DAY    2- 6 MG/KG/DAY    3- 12 MG/KG/DAY    4- 24 MG/KG/DAY  
MODIFIED STATISTICS USED.  
None significantly different from control group

**Visceral Variations:**

- The visceral variations include renal papilla(e) not developed and/or distended ureter(s), pale or small spleen, major blood vessel variation, and short brachiocephalic trunk. These findings were noted infrequently, at similar frequencies in the concurrent control group without statistical significance, in a manner that was not dose-related and were within the ranges of values in the (b) (4) historical control data; therefore, these variations were not considered test article related.

**Skeletal Malformations and Variations:**

**Skeletal Malformation:**

- No test article-related skeletal malformations were identified:
  - Three fetuses in the 12 mg/kg/day group were noted with skeletal malformations. These findings occurred infrequently and/or in a manner that was not dose-related. In addition, the mean litter proportions of these findings were not statistically significantly different from the control group and/or were within the ranges of values in the (b) (4) historical control data. Note that Fetus 31740-06 in the control group also had vertebral anomaly with associated rib anomaly consisting of fused, small, or misshapen thoracic arches and fused and forked ribs. Therefore, the findings in 12 mg/kg/day were not considered test article-related.

TABLE S13  
A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS  
SUMMARY OF LITTER PROPORTIONS OF MALFORMATIONS  
% PER LITTER

PROJECT NO. (b) (4) 141503  
SPONSOR: TREVENA, INC. PAGE 3  
DAY 20

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED SKELETALLY		24	25	24	23
COSTAL CARTILAGE ANOMALY	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.57	0.00
	S.E.	0.00	0.00	0.32	0.00
RIB ANOMALY	MEAN	0.0	0.0	1.0	0.0
	S.D.	0.00	0.00	3.58	0.00
	S.E.	0.00	0.00	0.73	0.00
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	MEAN	0.3	0.0	0.0	0.0
	S.D.	1.28	0.00	0.00	0.00
	S.E.	0.26	0.00	0.00	0.00
ONLY 12 PAIRS OF RIBS PRESENT	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.28	0.00
	S.E.	0.00	0.00	0.26	0.00

1- 0 MG/KG/DAY    2- 6 MG/KG/DAY    3- 12 MG/KG/DAY    4- 24 MG/KG/DAY  
 MODIFIED STATISTICS USED.  
 None significantly different from control group

**Skeletal Variation:**

- An increased incidence of reduced ossification of the vertebral arches was noted in the 24 mg/kg/day group (5.2% vs. 0% in the control group) and the value is outside the historical control range of 0-2%. Other variations were not considered test article related since the incidences were low and comparable to those observed in the control group.

*Reviewer’s note: Increased incidence of reduced bone ossification is a common finding in embryo-fetal development studies and usually associated with maternal toxicity and can be due to decreased maternal food intake and/or malnutrition. The reader is referred to an excellent review by Carney and Kimmel (Carney & Kimmel, 2007). Food intake and body weights were slightly altered in this study; although a clear cause and effect cannot be delineated as the body weight differences are less later in gestation. Fetal skeletal ossification is closely linked to overall fetal growth and as such this finding may be due to a delay in growth of the fetus. Fetal reduced ossification generally does not persist, and the normal ossification patterns are typically noted in post-natal animals. Further, there is not a clear relationship between reduced ossification and malformations, as such the clinical significance is not always clear. If the finding were due to a generalized delay, additional common “fingerprint” may be expected with bones undergoing ossification at the same period likely impacted (such as phalanges, sternbrae and vertebrae). In this case, the delayed ossification does not exactly appear to follow a generalized delay pattern, is present with minimal maternal toxicity more noted at times less relevant to ossification events, and no clear effect on fetal weights were noted. As such, the effect, if real, may not be readily dismissed as a clear developmental delay. However, review of the individual animal data does suggest that the high-dose effect is largely driven by one litter, which does support the conclusion that the finding is not likely treatment related. As such, we concur with the Applicant’s conclusion and the finding need not be included in labeling or impact the NOAEL.*

TABLE G15  
 PROJECT NO. (b) (4) 41503 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS PAGE 3  
 SPONSOR: TREVENA, INC. SUMMARY OF LITTER PROPORTIONS OF VARIATIONS DAY 20  
 % PER LITTER

DOSE GROUP:	1	2	3	4
NUMBER OF LITTERS EXAMINED SKELETALLY	24	25	24	23
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	MEAN 8.2 S.D. 15.44 S.E. 3.15	MEAN 7.3 S.D. 9.70 S.E. 1.94	MEAN 6.9 S.D. 11.89 S.E. 2.43	MEAN 9.1 S.D. 12.86 S.E. 2.68
14TH RUDIMENTARY RIB(S)	MEAN 6.5 S.D. 9.56 S.E. 1.95	MEAN 5.1 S.D. 12.47 S.E. 2.49	MEAN 8.3 S.D. 14.43 S.E. 2.94	MEAN 10.7 S.D. 17.78 S.E. 3.71
CERVICAL CENTRUM #1 OSSIFIED	MEAN 15.1 S.D. 17.17 S.E. 3.50	MEAN 18.1 S.D. 20.07 S.E. 4.01	MEAN 18.9 S.D. 18.60 S.E. 3.80	MEAN 17.2 S.D. 23.31 S.E. 4.86
UNCO-OSSIFIED VERTEBRAL CENTRA	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.8 S.D. 4.00 S.E. 0.80	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.0 S.D. 0.00 S.E. 0.00
REDUCED OSSIFICATION OF THE 13TH RIB(S)	MEAN 0.9 S.D. 2.45 S.E. 0.50	MEAN 1.4 S.D. 3.34 S.E. 0.67	MEAN 0.5 S.D. 2.55 S.E. 0.52	MEAN 0.6 S.D. 2.98 S.E. 0.62
BENT RIB(S)	MEAN 2.2 S.D. 5.75 S.E. 1.17	MEAN 1.0 S.D. 3.61 S.E. 0.72	MEAN 6.3 S.D. 11.87 S.E. 2.42	MEAN 2.9 S.D. 9.97 S.E. 2.08
HYOID UNOSSIFIED	MEAN 2.4 S.D. 4.48 S.E. 0.91	MEAN 1.0 S.D. 3.66 S.E. 0.73	MEAN 1.3 S.D. 5.21 S.E. 1.06	MEAN 1.3 S.D. 3.66 S.E. 0.76
25 PRESACRAL VERTEBRAE	MEAN 0.3 S.D. 1.28 S.E. 0.26	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.3 S.D. 1.28 S.E. 0.26	MEAN 0.0 S.D. 0.00 S.E. 0.00

1- 0 MG/KG/DAY 2- 6 MG/KG/DAY 3- 12 MG/KG/DAY 4- 24 MG/KG/DAY  
 MODIFIED STATISTICS USED.  
 None significantly different from control group

TABLE G15  
 PROJECT NO. (b) (4) 41503 A CONTINUOUS INFUSION EMBRYO/FETAL DEV. STUDY OF TRV130 IN RATS PAGE 4  
 SPONSOR: TREVENA, INC. SUMMARY OF LITTER PROPORTIONS OF VARIATIONS DAY 20  
 % PER LITTER

DOSE GROUP:	1	2	3	4
NUMBER OF LITTERS EXAMINED SKELETALLY	24	25	24	23
7TH CERVICAL RIB(S)	MEAN 1.7 S.D. 5.39 S.E. 1.10	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.6 S.D. 1.98 S.E. 0.40	MEAN 1.4 S.D. 3.14 S.E. 0.65
REDUCED OSSIFICATION OF THE SKULL	MEAN 0.9 S.D. 2.49 S.E. 0.51	MEAN 0.6 S.D. 1.99 S.E. 0.40	MEAN 0.3 S.D. 1.57 S.E. 0.32	MEAN 2.0 S.D. 6.61 S.E. 1.38
STERNEBRA(E) MALALIGNED (SLIGHT OR MODERATE)	MEAN 1.3 S.D. 2.90 S.E. 0.59	MEAN 0.3 S.D. 1.67 S.E. 0.33	MEAN 0.4 S.D. 1.86 S.E. 0.38	MEAN 0.6 S.D. 2.98 S.E. 0.62
REDUCED OSSIFICATION OF THE VERTEBRAL ARCHES	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 5.2 S.D. 17.69 S.E. 3.69
BENT SCAPULA	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.6 S.D. 2.07 S.E. 0.43
27 PRESACRAL VERTEBRAE	MEAN 0.7 S.D. 2.26 S.E. 0.46	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.6 S.D. 2.14 S.E. 0.45
14TH FULL RIB(S)	MEAN 0.3 S.D. 1.70 S.E. 0.35	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.0 S.D. 0.00 S.E. 0.00	MEAN 0.3 S.D. 1.60 S.E. 0.33

1- 0 MG/KG/DAY 2- 6 MG/KG/DAY 3- 12 MG/KG/DAY 4- 24 MG/KG/DAY  
 MODIFIED STATISTICS USED.  
 None significantly different from control group

**Study title: A Continuous Infusion Embryo/Fetal Development Study of TRV130 in New Zealand White Rabbits**

Study no.: (b) (4)-141504  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\141504\141504-study-report.pdf>  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: 24-Nov-2014  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: TRV130 fumarate; Lot 2417-21-1; 99.1%

### Key Study Findings

- Maternal toxicity:
  - Clinical findings (decreased defecation and cool extremities), body weight deficits, and corresponding reduced food consumption were noted at 6 mg/kg/day.
  - Based on these results, a dosage level of 3 mg/kg/day was considered to be the NOAEL for maternal toxicity. This dosage level corresponded to a  $C_{ss}$  value of 95.8 ng/mL, with an  $AUC_{0-24h}$  of 2299.2 ng\*h/mL that is 3 times the estimated total daily human exposure of 783 ng\*h/mL at MRHD of 40 mg/day.
- Embryo and fetal development:
  - The numbers of fetuses (litters) available for morphological evaluation were 167 (20), 165 (20), 149 (19), and 179 (21) in the control, 1.5, 3, and 6 mg/kg/day groups, respectively. Malformations were observed in 5 (2), 7 (4), 2 (2), and 3 (3) fetuses (litters) in these same respective dose groups and were considered spontaneous in origin. When the total malformations and developmental variations were evaluated on a proportional basis, no statistically significant differences from the control group were noted. Fetal malformations and developmental variations in the TRV130-treated groups occurred infrequently or at a frequency similar to that in the control group, did not occur in a dose-related manner, and/or were within the testing laboratory's historical control data ranges. Based on these data, no fetal malformations or developmental variations were attributed to the TRV130.
  - No clear evidence of developmental toxicity was observed at any dosage level; therefore, a dosage level of 6 mg/kg/day, the highest dosage level evaluated, was considered to be the NOAEL for embryo/fetal development in this study. This dosage level corresponded to a  $C_{ss}$  value of 173 ng/mL, with an  $AUC_{0-24h}$  of 4152 ng\*h/mL that is 5.3 times the estimated total daily human exposure of 783 ng\*h/mL at the proposed MRHD of 40 mg/day.

## Methods

- Doses: 0, 1.5, 3, and 6 mg/kg/day (0, 0.0625, 0.125 and 0.25 mg/kg/h) administered by continuous infusion via an indwelling catheter implanted in the femoral vein
- Frequency of dosing: Continuous infusion from Gestation Days (GD) 7 through 29 in female rabbits. Although dosing normally ends on GD 19 in standard rabbit embryo-fetal development studies, dosing was continued up to the time of scheduled laparohysterectomy (GD 29) to avoid the potential for withdrawal-induced stress.
- Dose volume: 0.3 mL/kg/h
- Route of administration: IV
- Formulation/Vehicle: 0.2 mM sodium phosphate buffer in 5% [w/v] dextrose injection, USP, pH 6.4 ± 0.2
- Species/Strain: New Zealand White [Hra:(NZW)SPF] rabbits
- Number/Sex/Group: 21 or 23 females/group

The following table presents the study group assignment:

Group Number	Treatment	Dosage Level (mg/kg/day)	Infusion Flow Rate (mL/kg/hr)	Number of Females	
				Embryo/Fetal Development Phase (b) (4) 141504	Toxicokinetic Phase (b) (4) 141504T
1	Vehicle Control	0	0.3	21	4
2	TRV130	1.5	0.3	21	4
3	TRV130	3	0.3	21	4
4	TRV130	6	0.3	21	4

- Satellite groups: For toxicokinetic evaluation, 4 or 5 additional rabbits/group were administered the vehicle or test article on a regimen comparable to the embryo/fetal development phase females. Blood samples were collected from each rabbit approximately 1, 4, and 8 hours after the initiation of infusion on Gestation Day 7 and approximately 4 hours following the daily syringe change on GD 14, 20, and 28.
- Dose Selection Rational: Dosage levels were selected based on the results of a previously conducted range-finding study in pregnant rabbits (Edwards, 2015, (b) (4) 141502); dosage levels were 2.4, 6, and 12 mg/kg/day. In the range-finding study, reduced food consumption and body weight gains were noted primarily during the first 2 weeks of dose administration at 6 and 12 mg/kg/day in a dose-related manner. Food consumption improved toward the end of the dosing regimen and all females survived until

the scheduled necropsy. Therefore, 6 mg/kg/day was chosen as the high dose for the current study.

Deviation from study protocol: Two females in the embryo/fetal development phase 1.5 mg/kg/day group were removed from study on GD 9 due to incorrect volume of test material being delivered based on inaccurate body weight data. Two additional females were added to the study to replace these females.

## **Observations and Results**

### **Mortality**

There was no mortality observed in this study.

### **Clinical Signs**

- Test article-related decreased defecation was noted at the daily examinations for the majority of females in the 6 mg/kg/day group beginning as early as Gestation Day (GD) 8 and generally continuing throughout the treatment period.
- Cool extremities were noted at approximately 1 hour following syringe change for 3 females in the 6 mg/kg/day group on 1-2 occurrences sporadically throughout the gestation treatment period.
- No test article-related clinical findings were noted in the 1.5 or 3 mg/kg/day groups.

### **Body Weight and Food Consumption**

- Test article-related mean body weight losses and corresponding reduced food consumption were noted in the 6 mg/kg/day group during GD 7-10 and 10-13; these deficits correlated with the decreased defecation noted in this group. Mean body weight gain and food consumption in this group were similar to the control group during the remainder of the treatment period (GD 13-20 and 20-29). However, mean body weight gain and food consumption in the 6 mg/kg/day group were lower than the control group when the entire treatment period (GD 7-29) was evaluated. As a result, mean body weight gain (up to 31%), mean body weights in this group were lower (up to 5.9%) than the control group during the treatment period.
- In the 1.5 and 3 mg/kg/day groups, mean body weight gains and food consumption were generally similar to the control group when the entire treatment period was evaluated, although there was an initial reduction of body weight gain and food consumption. The initial changes in body weight gain and food consumption were considered test article-related but not adverse.



PROJECT NO.: (b)(4) 141504  
 SPONSOR: TREVENA, INC.

TABLE S10  
 INFUSION STUDY OF TRV130 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS  
 SUMMARY OF FETAL DATA AT SCHEDULED NECROPSY

PAGE 1

GROUP	SEX		VIABLE FETUSES	DEAD FETUSES	RESORPTIONS EARLY	RESORPTIONS LATE	POST IMPLANTATION LOSS	IMPLANTATION SITES	CORPORA LUTEA	PRE IMPLANTATION LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES	
	M	F											
1	TOTAL	83	84	167	0	7	2	9	176	194	18	NA	20
	MEAN	4.2	4.2	8.4	0.0	0.4	0.1	0.5	8.8	9.7	0.9	41.7	
	S.D.	1.35	1.82	1.46	0.00	0.59	0.31	0.76	1.32	1.38	1.33	5.17	
	S.E.	0.30	0.41	0.33	0.00	0.13	0.07	0.17	0.30	0.31	0.30	1.16	
2	TOTAL	77	88	165	0	8	1	9	174	190	16	NA	20
	MEAN	3.9	4.4	8.3	0.0	0.4	0.1	0.5	8.7	9.5	0.8	42.1	
	S.D.	1.60	2.06	1.89	0.00	0.82	0.22	0.83	1.98	1.76	0.95	5.62	
	S.E.	0.36	0.46	0.42	0.00	0.18	0.05	0.18	0.44	0.39	0.21	1.26	
3	TOTAL	81	68	149	0	5	6	11	160	176	16	NA	20
	MEAN	4.1	3.4	7.5	0.0	0.3	0.3	0.6	8.0	8.8	0.8	43.6	
	S.D.	1.99	1.60	2.58	0.00	0.72	1.13	1.28	2.27	2.57	1.54	4.06	
	S.E.	0.44	0.36	0.58	0.00	0.16	0.25	0.29	0.51	0.57	0.34	0.93	
4	TOTAL	93	86	179	0	13	1	14	193	208	15	NA	21
	MEAN	4.4	4.1	8.5	0.0	0.6	0.0	0.7	9.2	9.9	0.7	40.3	
	S.D.	2.29	1.45	1.86	0.00	0.86	0.22	0.91	1.54	1.48	0.78	4.43	
	S.E.	0.50	0.32	0.41	0.00	0.19	0.05	0.20	0.34	0.32	0.17	0.97	

None significantly different from control group  
 NA = NOT APPLICABLE  
 MEAN NUMBER OF VIABLE FETUSES, MEAN NUMBER OF IMPLANTATION SITES, MEAN NUMBER OF CORPORA LUTEA, FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

1- 0 MG/KG/DAY    2- 1.5 MG/KG/DAY    3- 3 MG/KG/DAY    4- 6 MG/KG/DAY

PROJECT NO.: (b)(4) 141504  
 SPONSOR: TREVENA, INC.

TABLE S11  
 INFUSION STUDY OF TRV130 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS  
 SUMMARY OF FETAL DATA AT SCHEDULED NECROPSY [% PER LITTER]

PAGE 2

GROUP:	0 MG/KG/DAY	1.5 MG/KG/DAY	3 MG/KG/DAY	6 MG/KG/DAY
LATE RESORPTIONS (%)				
MEAN	1.2	0.6	3.0	0.5
S.D.	3.64	2.80	10.50	2.42
S.E.	0.81	0.63	2.35	0.53
N	20	20	20	21
TOTAL RESORPTIONS (%)				
MEAN	5.1	4.7	9.1	7.5
S.D.	9.12	8.41	23.92	10.22
S.E.	2.04	1.88	5.35	2.23
N	20	20	20	21
PRE-IMPLANTATION LOSS (%)				
MEAN	8.7	8.8	7.5	7.1
S.D.	12.42	11.36	13.96	7.43
S.E.	2.78	2.54	3.12	1.62
N	20	20	20	21
POST-IMPLANTATION LOSS (%)				
MEAN	5.1	4.7	9.1	7.5
S.D.	9.12	8.41	23.92	10.22
S.E.	2.04	1.88	5.35	2.23
N	20	20	20	21
MALES (%)				
MEAN	51.0	47.1	53.6	50.0
S.D.	16.92	20.50	17.63	20.07
S.E.	3.78	4.58	4.04	4.38
N	20	20	19	21

PROPORTIONAL (%) DATA COMPARED USING DUNN'S TEST MODIFIED STATISTICS USED. \* INDICATES PARAMETRIC ANALYSIS AND + INDICATES NON-PARAMETRIC ANALYSIS.  
 None significantly different from control group

**Offspring (Malformations, Variations, etc.)**

Malformations were observed in 5(2), 7(4), 2(2), and 3(3) fetuses (litters) in the control, 1.5, 3 and 6 mg/kg/day groups and were considered spontaneous in origin.

PROJECT NO. (b) (4) 141504  
SPONSOR: TREVENA, INC.

TABLE S12  
INFUSION STUDY OF TRV130 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS  
SUMMARY OF FETUSES AND LITTERS WITH MALFORMATIONS [ABSOLUTE NO.]

PAGE 1  
DAY 29

DOSE GROUP:	F E T U S E S				L I T T E R S			
	1	2	3	4	1	2	3	4
NUMBER EXAMINED EXTERNALLY	167	165	149	179	20	20	19	21
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0
NUMBER EXAMINED VISCERALLY	167	165	149	179	20	20	19	21
KIDNEYS- FUSED	0	1	0	0	0	1	0	0
LUNGS- LOBULAR AGENESIS	5	2	0	2	2	1	0	2
LUNGS- LOBULAR DYSGENESIS	0	1	0	0	0	1	0	0
NUMBER EXAMINED SKELETALLY	167	165	149	179	20	20	19	21
STERNEBRA (E) MALALIGNED (SEVERE)	0	0	0	1	0	0	0	1
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	0	2	0	0	0	1	0	0
VERTEBRAL CENTRA ANOMALY	0	1	0	0	0	1	0	0
COSTAL CARTILAGE ANOMALY	0	0	1	0	0	0	1	0
SKULL ANOMALY	0	0	1	0	0	0	1	0
TOTAL NUMBER WITH MALFORMATIONS								
EXTERNAL :	0	0	0	0	0	0	0	0
SOFT TISSUE :	5	4	0	2	2	3	0	2
SKELETAL :	0	3	2	1	0	1	2	1
COMBINED :	5	7	2	3	2	4	2	3

1- 0 MG/KG/DAY    2- 1.5 MG/KG/DAY    3- 3 MG/KG/DAY    4- 6 MG/KG/DAY

PROJECT NO. (b) (4) 141504  
SPONSOR: TREVENA, INC.

TABLE S13  
INFUSION STUDY OF TRV130 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS  
SUMMARY OF LITTER PROPORTIONS OF MALFORMATIONS  
% PER LITTER

PAGE 4  
DAY 29

DOSE GROUP:				
	1	2	3	4
NUMBER OF LITTERS EXAMINED	20	20	19	21
TOTAL MALFORMATIONS				
PERCENT PER LITTER WITH EXTERNAL MALFORMATIONS	MEAN 0.0	0.0	0.0	0.0
	S.D. 0.00	0.00	0.00	0.00
	S.E. 0.00	0.00	0.00	0.00
PERCENT PER LITTER WITH SOFT TISSUE MALFORMATIONS	MEAN 3.1	2.5	0.0	1.3
	S.D. 11.38	6.54	0.00	4.04
	S.E. 2.54	1.46	0.00	0.88
PERCENT PER LITTER WITH SKELETAL MALFORMATIONS	MEAN 0.0	1.5	1.6	0.6
	S.D. 0.00	6.71	5.12	2.73
	S.E. 0.00	1.50	1.18	0.60
TOTAL PERCENT PER LITTER WITH MALFORMATIONS	MEAN 3.1	4.0	1.6	1.9
	S.D. 11.38	8.94	5.12	4.71
	S.E. 2.54	2.00	1.18	1.03

1- 0 MG/KG/DAY    2- 1.5 MG/KG/DAY    3- 3 MG/KG/DAY    4- 6 MG/KG/DAY

MODIFIED STATISTICS USED.  
None significantly different from control group

**External Malformations and Variations:**

There were no external malformations or developmental variations noted for fetuses in this study.

PROJECT NO. (b) (4) 141504  
SPONSOR: TREVENA, INC.

TABLE S13  
INFUSION STUDY OF TRV130 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS  
SUMMARY OF LITTER PROPORTIONS OF MALFORMATIONS  
% PER LITTER

PAGE 1  
DAY 29

DOSE GROUP:				
	1	2	3	4
NUMBER OF LITTERS EXAMINED EXTERNALLY	20	20	19	21
NUMBER OF LITTERS WITH FINDINGS	0	0	0	0

1- 0 MG/KG/DAY    2- 1.5 MG/KG/DAY    3- 3 MG/KG/DAY    4- 6 MG/KG/DAY

MODIFIED STATISTICS USED.  
None significantly different from control group

**Visceral Malformations and Variations:**

**Visceral Malformations:**

Visceral malformations were observed in 5(2), 4(3), 0(0), and 2(2) fetuses (litters) in the control, 1.5, 3, and 6 mg/kg/day groups, respectively. These findings were noted infrequently, at similar frequencies in the concurrent control group, or in a manner that was not dose-related. Therefore, these findings were not considered test article-related.

TABLE S15  
INFUSION STUDY OF TRV130 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS  
SUMMARY OF LITTER PROPORTIONS OF MALFORMATIONS  
% PER LITTER

PAGE 2  
DAY 29

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED VISCERALLY		20	20	19	21
KIDNEYS- FUSED	MEAN	0.0	0.6	0.0	0.0
	S.D.	0.00	2.80	0.00	0.00
	S.E.	0.00	0.62	0.00	0.00
LUNGS- LOBULAR AGENESIS	MEAN	3.1	1.3	0.0	1.3
	S.D.	11.38	5.59	0.00	4.04
	S.E.	2.54	1.25	0.00	0.88
LUNGS- LOBULAR DYSGENESIS	MEAN	0.0	0.6	0.0	0.0
	S.D.	0.00	2.80	0.00	0.00
	S.E.	0.00	0.62	0.00	0.00

1- 0 MG/KG/DAY    2- 1.5 MG/KG/DAY    3- 3 MG/KG/DAY    4- 6 MG/KG/DAY  
MODIFIED STATISTICS USED.  
None significantly different from control group

- Lobular agenesis of the lungs (right accessory lobe absent) was noted for 5(2), 2(1), and 2(2) fetuses (litters) in the control, 1.5, and 6 mg/kg/day groups, respectively.
- In the 1.5 mg/kg/day group, Fetus 73915-04 was noted with lobular dysgenesis (right diaphragmatic and right accessory lobes fused and only 1 left lobe present).
- In the 1.5 mg/kg/day group, Fetus 73850-02 was observed with fused and malpositioned kidneys (medial).

**Visceral Variations:**

The visceral variations are listed below. The findings were noted infrequently, at similar frequencies in the concurrent control group, and/or in a manner that was not dose-related. In addition, the mean litter proportions of these findings were not statistically significantly different from the concurrent control group and/or were within the ranges of values in the (b) (4) historical control data. Therefore, these findings were not considered test article-related.

- Major blood vessel variation (left carotid artery arose from the brachiocephalic trunk or right subclavian artery coursed retroesophageal and joined the aortic arch adjacent to ductus arteriosus [no brachiocephalic trunk]), accessory spleen(s), extra papillary muscle or only 2 papillary muscles in the heart, small gallbladder or spleen, renal papilla(e) not developed and distended ureter(s), hemorrhagic ring around the iris, and retrocaval ureter

**Skeletal Malformations and Variations**

**Skeletal Malformations:**

Skeletal malformations were observed in 3(1), 2(2), and 1(1) fetuses (litters) in the 1.5, 3, and 6 mg/kg/day groups, respectively (see below). The Applicant considered these findings not treatment related, given that the findings were noted infrequently and/or in a manner that was not dose related. In addition, the mean litter proportions of these malformations were not statistically significantly different from the concurrent control group and/or were within the ranges of values in the (b) (4) historical control data.

PROJECT NO. (b) (4) 141504  
SPONSOR: TREVENA, INC.

TABLE S13  
INFUSION STUDY OF TRV130 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS  
SUMMARY OF LITTER PROPORTIONS OF MALFORMATIONS  
% PER LITTER

PAGE 3  
DAY 29

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED SKELETALLY		20	20	19	21
STERNEBRA(E) MALALIGNED (SEVERE)	MEAN	0.0	0.0	0.0	0.6
	S.D.	0.00	0.00	0.00	2.73
	S.E.	0.00	0.00	0.00	0.60
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	MEAN	0.0	1.0	0.0	0.0
	S.D.	0.00	4.47	0.00	0.00
	S.E.	0.00	1.00	0.00	0.00
VERTEBRAL CENTRA ANOMALY	MEAN	0.0	0.5	0.0	0.0
	S.D.	0.00	2.24	0.00	0.00
	S.E.	0.00	0.50	0.00	0.00
COSTAL CARTILAGE ANOMALY	MEAN	0.0	0.0	0.6	0.0
	S.D.	0.00	0.00	2.55	0.00
	S.E.	0.00	0.00	0.58	0.00
SKULL ANOMALY	MEAN	0.0	0.0	1.1	0.0
	S.D.	0.00	0.00	4.59	0.00
	S.E.	0.00	0.00	1.05	0.00

1- 0 MG/KG/DAY    2- 1.5 MG/KG/DAY    3- 3 MG/KG/DAY    4- 6 MG/KG/DAY  
MODIFIED STATISTICS USED.  
None significantly different from control group

- In the 6 mg/kg/day group, Fetus 73972-01 was observed with severely malaligned sternebra(e) consisting of fused and/or malpositioned sternebra(e). The incidence of this finding was within the historical control range.
- In the 3 mg/kg/day group, Fetus 73901-09 was noted with a costal cartilage anomaly (costal cartilage arose from 7th cervical rib; fused to costal cartilage no. 1 bilateral).
- In the 3 mg/kg/day group, Fetus 73858-01 was observed with a skull anomaly (frontal bones fused along frontal suture).
- In the 1.5 mg/kg/day group, Fetus 73955-03 and 73955-04 were noted with vertebral anomalies with or without associated rib anomalies (extra rib or arch; malpositioned arch, rib, and/or centra; malproportioned centrum; absent centrum; and fused ribs).
- In the 1.5 mg/kg/day group, a vertebral centra anomaly (absent, malpositioned, or malproportioned centra) was noted for Fetus 73955-11.

**Skeletal Variations:**

The skeletal variations noted in the study are listed in the table below. These findings did not occur in a dose-related manner, were noted similarly in the concurrent control group, and/or the mean litter proportions were within the ranges of the (b) (4) historical control data, and therefore were not considered test article-related.

		TABLE 11			
PROJECT NO. (b) (4) 141504		INFUSION STUDY OF TRV130 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS		PAGE 4	
SPONSOR: TREVENA, INC.		SUMMARY OF LITTER PROPORTIONS OF VARIATIONS		DAY 29	
		% PER LITTER			
DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED SKELETALLY		20	20	19	21
13TH FULL RIB(S)	MEAN	49.7	45.3	60.1	57.5
	S.D.	32.56	28.36	28.79	30.95
	S.E.	7.28	6.34	6.61	6.75
27 PRESACRAL VERTEBRAE	MEAN	14.7	17.5	14.8	13.4
	S.D.	21.08	20.28	19.49	16.66
	S.E.	4.71	4.53	4.47	3.63
HYOID ARCH(ES) BENT	MEAN	3.4	3.3	6.3	5.6
	S.D.	9.18	6.08	12.24	11.34
	S.E.	2.05	1.36	2.81	2.48
13TH RUDIMENTARY RIB(S)	MEAN	17.8	18.0	16.2	16.7
	S.D.	15.46	16.16	12.54	14.88
	S.E.	3.46	3.61	2.88	3.25
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	MEAN	5.3	8.8	5.4	5.5
	S.D.	8.02	15.70	9.57	8.39
	S.E.	1.79	3.51	2.20	1.83
STERNEBRAE WITH THREAD-LIKE ATTACHMENT	MEAN	0.6	0.7	0.0	0.0
	S.D.	2.48	3.19	0.00	0.00
	S.E.	0.56	0.71	0.00	0.00
EXTRA SITE OF OSSIFICATION ANTERIOR TO STERNEBRA #1	MEAN	2.6	1.3	2.8	2.2
	S.D.	9.16	4.13	8.70	7.12
	S.E.	2.05	0.92	2.00	1.55
VERTEBRAL CENTRA UNOSSIFIED	MEAN	0.0	0.4	0.0	0.0
	S.D.	0.00	1.86	0.00	0.00
	S.E.	0.00	0.42	0.00	0.00

1- 0 MG/KG/DAY 2- 1.5 MG/KG/DAY 3- 3 MG/KG/DAY 4- 6 MG/KG/DAY  
 MODIFIED STATISTICS USED.  
 None significantly different from control group

### 8.3 Prenatal and Postnatal Development

**Study title: A Continuous Infusion Study of the Effects of TRV130 (Oliceridine) on Pre- and Postnatal Development, Including Maternal Function in Rats**

Study no.: (b) (4) 141509  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42353-pre-postnatal-dev\141509\141509-study-report.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: 6/08/2016  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: TRV130 Fumarate, FP-000326, 99.6%

#### Key Study Findings

In the definitive rat pre- and postnatal study, pregnant rats were treated with 0, 0.6, 2.4, and 6.0 mg/kg/day (0, 0.025, 0.1 and 0.25 mg/kg/h) and the following key study findings were noted:

- Based on the lack of any adverse effects on the F<sub>0</sub> generation, the NOAEL for F<sub>0</sub> maternal systemic toxicity was considered to be 6.0 mg/kg/day when TRV130 was administered via intravenous infusion to female Crl:CD(SD) rats from Gestation Day (GD) 6 through Lactation Day (LD) 21.
- Reduced live litter size relative to total number born was noted at 6 mg/kg/day on PND 0. Statistically significant reduction of percentage survival per litter between birth and PND 4, and lower mean F<sub>1</sub> male and female body weights on PND 1 were noted at 6.0 mg/kg/day. The numbers of F<sub>1</sub> pups (litters) found dead or euthanized in extremis from PND 0 through the selection of the F<sub>1</sub> generation were 7(7), 9(7), 27(14), and 69(18) in the control, 0.6, 2.4, and 6.0 mg/kg/day groups, respectively; therefore, a dosage level of 0.6 mg/kg/day was considered to be the NOAEL for F<sub>1</sub> neonatal/developmental toxicity.
- No toxicity was observed in F<sub>1</sub> animals during the post-weaning period or in the F<sub>2</sub> pups. Therefore, the NOAEL for F<sub>1</sub> parental systemic toxicity, F<sub>1</sub> reproductive toxicity, and F<sub>2</sub> neonatal/early postnatal toxicity was considered to be 6.0 mg/kg/day.
- Oliceridine plasma concentrations were not measured in this study, but based on female plasma concentrations measured in Study (b) (4) 141503 (the embryo-fetal development toxicity study in rats), and assuming dose-linear exposures, total daily exposures at 0.6 mg/kg/day, 2.4 mg/kg/day and 6 mg/kg/day were estimated to be 83.8 ng\*h/mL, 335 ng\*h/mL and 837 ng\*h/mL, respectively, approximately, 0.1 times, 0.4 times and 1.1 times the plasma exposure at the proposed MRHD of 40 mg/day on an AUC basis.

**Methods**

Doses: 0, 0.6, 2.4, and 6.0 mg/kg/day (0, 0.025, 0.1 and 0.25 mg/kg/h) administered by continuous infusion via an indwelling catheter implanted in the femoral vein.

Frequency of dosing: Continuous IV infusion from Gestation Day 6 to Lactation Day 21 for a total of 36 to 38 days. Females that failed to deliver were dosed through Post-Mating Day 24 for a total of 19 days.

Dose volume: 1 mL/kg/h

Route of administration: IV

Formulation/Vehicle: (b) (4) mg/mL L-histidine and (b) (4) mg/mL mannitol in sterile water for injection, USP, pH (b) (4)

Species/Strain: Crl:CD(SD) Sprague-Dawley rats

Number/Sex/Group: 25/females/dose group

Text Table 3  
Study Group Assignments

Group Number	Treatment	Dosage Level (mg/kg/day)	Infusion Flow Rate (mL/kg/hr)	Number of Females
1	Vehicle Control	0	1	25
2	TRV130	0.6	1	25
3	TRV130	2.4	1	25
4	TRV130	6.0	1	26

Satellite groups: No

Dose selection rationale: Dosage levels were selected based on results from a previously conducted range-finding pre- and postnatal developmental toxicity study (Study (b) (4) 141508), that included dosage levels of 2.4, 12, and 24 mg/kg/day. In this range-finding study, postnatal survival was 0% at 24 mg/kg/day (all pups were found dead or euthanized in extremis by PND 1), and 20.1% by PND 1 at 12 mg/kg/day. Postnatal survival was unaffected at 2.4 mg/kg/day. There was no adverse maternal toxicity noted at dosage levels up to 12 mg/kg/day. Based on the effects on postnatal survival at 12 and 24 mg/kg/day, a dosage level of 6.0 mg/kg/day was selected as the high-dosage level for the current study.

Deviation from study protocol: No deviations have negative impact on the quality or integrity of the data or the outcome of the study.

Others: To reduce variability among the litters, 8 pups/litter, 4 pups/sex when possible, were randomly selected on PND 4. Standardization of litter size was not performed on litters with fewer than 8 pups.

**Observations and Results (Optional Table)**

**F<sub>0</sub> Dams**

- Survival:
- One, 3, 2, and 1 F<sub>0</sub> females in the control, 0.6, 2.4, and 6.0 mg/kg/day groups, respectively, were found dead or euthanized in extremis between Gestation Day 14 and Lactation Day 13.
    - All of the F<sub>0</sub> females found dead or euthanized in extremis were noted with similar clinical observations (pale and cool body, swollen abdominal area, red material findings, and/or an unkempt appearance) at the daily examinations and/or signs of possible infection (thickened areas, masses, and/or thick green contents) around the infusion site at necropsy.
    - In the absence of other signs of toxicity in the test article-treated groups, the apparent lack of a dose-response relationship and the occurrence of similar findings in a control group female, the mortality and moribundity were likely due to secondary infections at the infusion site, and not directly attributed to the test article.

Clinical signs: No test article-related clinical findings were noted for surviving animals at the daily examinations or approximately 1-hour post-syringe change at any dosage level.

Body weight and food consumption

Gestation: No test article-related effects were noted for F<sub>0</sub> females at any dosage level.

Lactation: Slightly lower mean body weight gains and food consumption were noted for F<sub>0</sub> females in the 6.0 mg/kg/day group generally throughout lactation; the differences were not statistically significant. The Applicant considered these effects secondary to the reduced nutritional demand of the dams and need for milk production based on the reduced live litter sizes and decreased postnatal survival.

Uterine content: No effects on the mean number of former implantation sites and unaccounted-for sites were noted at any dosage level. No test article-related effects on gestation lengths or the process of parturition were noted for F<sub>0</sub> females.

Necropsy observation: No test article-related macroscopic findings

Toxicokinetics: Not done

Dosing Solution Analysis: The analyzed dosing formulations were within (b) (4) SOP range for solutions (90% to 110%). The test article was not detected in the analyzed vehicle formulation that was administered to the control group (Group 1).

Other: NA

**F<sub>1</sub> Generation**

Survival: Test article-related effects on F<sub>1</sub> postnatal survival were noted in the 6.0 mg/kg/day group from birth to PND 4 (pre-selection), with a corresponding lower mean live litter size on PND 0 and increased number of pups found dead, euthanized in extremis, and missing prior to weaning (total of 96 pups) compared to the control group (10 pups). It is suspected by the Applicant that the pup deaths noted within the first 24 hours after delivery may be related to the effects of opioids on milk let-down. Milk let-down is controlled by oxytocin, and oxytocin levels are reduced by opioids. However, milk let-down is also stimulated by the act of suckling, so by nursing, the milk let-down does occur, but is delayed, leading to early postnatal deaths, but normal survival and growth following the first 24 hours. Although a possible explanation, there were no data provided to support this hypothesis.

- Litter size: As shown in the table below, a lower mean live litter size on PND 0 (10.3 per dam) were noted in the 6.0 mg/kg/day group compared to the control group (12.7 per dam). The difference was significant (p < 0.05), and the value was below the minimum mean value in the (b) (4) historical control data (12.3 per dam). No effect was observed on the number of total pups born.

PROJECT NO. (b) 41509  
SPONSOR: TREVENA, INC.

TABLE S20 (F1)  
INFUSION STUDY OF TRV130 ON PRE- AND POSTNATAL DEV IN RATS  
SUMMARY OF PND 0 LITTER DATA

GROUP :	1	2	3	4
<b>NUMBER BORN</b>				
MEAN	12.8	12.3	12.9	11.4
S.D.	1.68	3.05	1.75	2.74
S.E.	0.36	0.65	0.36	0.57
N	22	22	24	23
<b>SEX AT BIRTH (% MALES PER LITTER)</b>				
MEAN	47.6	64.0++	45.9	56.8
S.D.	15.92	15.13	14.94	18.77
S.E.	3.39	3.23	3.05	3.91
N	22	22	24	23
<b>LIVE LITTER SIZE (PND 0)</b>				
MEAN	12.7	12.2	12.7	10.3*
S.D.	1.76	3.15	1.90	3.78
S.E.	0.37	0.67	0.39	0.79
N	22	22	24	23

1- 0 MG/KG/DAY    2- 0.6 MG/KG/DAY    3- 2.4 MG/KG/DAY    4- 6.0 MG/KG/DAY  
SEX COMPARED USING DUNN'S TEST, NUMBER BORN, AND LIVE LITTER SIZE COMPARED USING DUNNETT'S MODIFIED STATISTICS USED. \* INDICATES PARAMETRIC ANALYSIS AND + INDICATES NON-PARAMETRIC ANALYSIS.  
\* = Significantly different from the control group at 0.05  
++ = Significantly different from the control group at 0.01

- Postnatal survival: As shown in the table below, a lower (not statistically significant) mean litter proportion of postnatal survival was noted at birth (PND 0) in the 6.0 mg/kg/day group compared to the control group. A lower mean litter proportion of postnatal survival continued to be noted in this group during PND 0-1 compared to the control group. The difference from the control group was significant (p < 0.01), and the values in the 6.0 mg/kg/day group were below the minimum mean litter proportion values in the (b) (4) historical control data. A

similar effect on postnatal survival was observed in the dose-range finding study.

PROJECT NO (b) (4) 141509  
SPONSOR: TREVENA, INC.

TABLE S21 (F1)  
INFUSION STUDY OF TRV130 ON PRE- AND POSTNATAL DEV IN RATS  
SUMMARY OF POSTNATAL SURVIVAL [% PER LITTER]

GROUP :	1	2	3	4
-----				
PND 0 (RELATIVE TO NUMBER BORN)				
MEAN	98.9	98.9	98.3	86.2
S.D.	2.89	3.84	3.50	28.20
S.E.	0.62	0.82	0.71	5.88
N	22	22	24	23
PND 0 TO PND 1				
MEAN	100.0	96.0	95.9	72.2++
S.D.	0.00	11.28	9.24	27.99
S.E.	0.00	2.40	1.89	5.97
N	22	22	24	22
PND 1 TO PND 4 (PRE-SELECTION)				
MEAN	98.4	98.4	98.1	95.5
S.D.	4.12	4.70	3.44	10.98
S.E.	0.88	1.00	0.70	2.40
N	22	22	24	21
PND 4 (POST-SELECTION) TO PND 7				
MEAN	99.4	99.4	98.4	99.3
S.D.	2.67	2.67	7.65	3.12
S.E.	0.57	0.57	1.56	0.68
N	22	22	24	21
PND 7 TO PND 14				
MEAN	99.4	95.2	98.6	95.8
S.D.	3.05	21.82	4.82	19.09
S.E.	0.65	4.76	1.00	4.17
N	22	21	23	21
-----				
GROUP :	1	2	3	4
PND 14 TO PND 21				
MEAN	99.4	100.0	99.5	100.0
S.D.	2.67	0.00	2.61	0.00
S.E.	0.57	0.00	0.54	0.00
N	22	20	23	21
BIRTH TO PND 4 (PRE-SELECTION)				
MEAN	97.3	93.4	92.5	63.2++
S.D.	4.65	12.65	10.60	31.07
S.E.	0.99	2.70	2.16	6.48
N	22	22	24	23
PND 4 (POST-SELECTION) TO PND 21				
MEAN	98.3	94.6	96.7	95.2
S.D.	5.84	21.86	10.80	19.19
S.E.	1.25	4.77	2.25	4.19
N	22	21	23	21
-----				
1- 0 MG/KG/DAY    2- 0.6 MG/KG/DAY    3- 2.4 MG/KG/DAY    4- 6.0 MG/KG/DAY				
STATISTICS PERFORMED USING DUNN'S TEST				
MODIFIED STATISTICS USED.				
++ = Significantly different from the control group at 0.01				

The chronic administration of opioids has been shown to inhibit the synthesis and excretion of oxytocin, the hormone responsible for milk let-down, providing a possible explanation for early pup deaths (Clarke & Wright, 1984; Lincoln & Paisley, 1982; Rayner, Robinson, & Russell, 1988; Vuong, Van Uum, O'Dell, Lutfy, & Friedman, 2010).

Necropsies of pups found dead or euthanized in extremis: As shown in the table below, the numbers of F<sub>1</sub> pups (litters) found dead or euthanized in extremis from PND 0 through the selection of the F<sub>1</sub> generation were 7(7), 9(7), 27(14), and 69(18) in the control, 0.6, 2.4, and 6.0 mg/kg/day groups, respectively. According to the study report, “No internal findings that could be attributed to F<sub>0</sub> maternal administration to the test article were noted at the necropsies of F<sub>1</sub> pups that were found dead or euthanized in extremis. Aside from the absence of milk in the stomach, internal findings were observed for single pups in all test article-treated groups.” As noted below, the apparent decrease in post-natal survival through weaning was associated with the observation of decreased milk present in the stomach of the pups that either died or were sacrificed moribund. This may be the result of decreased milk production by the mother, decreased maternal care/behavior, of failure to suckle. Though not a standard predefined endpoint, the data raise concerns that the MD is not a NOAEL, as proposed by the Applicant.

PROJECT NO. (b) (4) 41509  
SPONSOR: TREVENA, INC.

TABLE S25 (F1 - UNSCHEDULED DEATHS)  
INFUSION STUDY OF TRV130 ON PRE- AND POSTNATAL DEV IN RATS  
SUMMARY OF PUP NECROPSY FINDINGS

PAGE 1

FOUND DEAD OR EUTHANIZED MORIBUND OR IN EXTREMIS

DOSE GROUP:	P U P S				L I T T E R S			
	1	2	3	4	1	2	3	4
NUMBER EXAMINED VISCERALLY	7	9	27	69	7	7	14	18
STOMACH MILK NOT PRESENT	3	3	14	31	3	3	7	13
KIDNEY								
RENAL PAPILLA(E) NOT FULLY DEVELOPED (WOO AND HOAR GRADE 1)	0	0	0	1	0	0	0	1
MALFORMATION								
LOCALIZED EDEMA	0	0	0	1	0	0	0	1
VARIATION								
MAJOR BLOOD VESSEL VARIATION	0	0	0	1	0	0	0	1
LIVER- ACCESSORY LOBULE(S)	0	0	0	2	0	0	0	2
HEMORRHAGIC RING AROUND THE IRIS	0	0	0	1	0	0	0	1
ACCESSORY SPLEEN(S)	0	1	0	0	0	1	0	0
RENAL PAPILLA(E) NOT DEVELOPED AND/OR DISTENDED URETER(S)	0	0	1	0	0	0	1	0
1- 0 MG/KG/DAY	2- 0.6 MG/KG/DAY	3- 2.4 MG/KG/DAY	4- 6.0 MG/KG/DAY					

- Clinical signs: The general physical condition (defined as the occurrence and severity of clinical findings) of all surviving F<sub>1</sub> pups in this study was unaffected by F<sub>0</sub> maternal test article administration.
- Body weight: Mean F<sub>1</sub> male and female pup weights on PND 1 in the 6.0 mg/kg/day group were 8.1% and 8.5% lower, respectively, compared to the control group. However, higher mean body weight gains were noted for the F<sub>1</sub> males and females in this group during PND 1–4, resulting in mean male and female body weights on PND 4 that were similar to the control group. Mean F<sub>1</sub> pup body weights and body weight gains in the 6.0 mg/kg/day group were similar to the control group during the remainder of the pre-weaning period (PND 4–21).
- No test article-related effects on survival, clinical condition, or mean body weights and body weight gains were noted during the adult F<sub>1</sub> generation at any dosage level.
- Feed consumption: Not measured
- Physical development: No test article-related effects on developmental landmarks (balanopreputial separation and vaginal patency) were observed.
- Neurological assessment: No test-article related effects on startle response, motor activity or learning and memory (Biel maze) were observed.
- Reproduction: F<sub>1</sub> reproductive endpoints (pre-coital intervals, estrous cycle lengths, and mating, fertility, and copulation/conception indices), gestation lengths, and the process of parturition were unaffected by F<sub>0</sub> maternal test article administration. There were no test article-related macroscopic findings in the F<sub>1</sub> males and females or effects on the mean numbers of former implantation sites, unaccounted-for sites, and corpora lutea.
- Other: NA

## F<sub>2</sub> Generation

- Survival: No test article-related effects were observed.
- Body weight: No test article-related effects were observed.
- External evaluation: No test article-related effects were observed.
- Male/Female ratio: No test article-related effects were observed.
- Other: NA

## 9 Other Nonclinical Studies

### 9.1 Safety Qualification of Impurities

The specifications of four impurities/degradation products ICH qualification thresholds for qualification. In order to support specification levels above ICH qualification thresholds, the

Applicant attempted to qualify the four impurities/degradation products according to ICH Q3A(R2) and ICH Q3B(R2) in a 14-day continuous IV infusion toxicology study in rats and in *in vitro* genotoxicity assays (bacterial reverse mutation assay and *in vitro* micronucleus assay) up to the assay limit dose or up to the limit of cytotoxicity.

### 9.1.1 Repeat-Dose Toxicity

#### **Study title: Oliceridine (TRV130): 14-Day Continuous Intravenous Infusion Toxicity and Toxicokinetic Bridging Study in Rats**

TRV130 (oliceridine) drug product solution that was fortified with impurities/degradation products by accelerated degradation of drug product solution and addition of isolated impurities was evaluated in a 14-day continuous IV infusion toxicology study in rats, which tested a TRV130 dose (12 mg/kg/day) that was previously established as a NOAEL of a previously conducted 14-day repeat-dose toxicity study. The drug product solution included

(b) (4)

area in the study report).

Study no.: 8354309

Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\8354309\8354309-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: 11/28/2016 (Protocol review)

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: For Group 2: TRV130 fumarate, FP-000326, 99.6%

For Group 3: TRV130 fumarate with enriched degradants and spiked impurities, Batch No 4948-1-1, 99.5%

### Key Study Findings

- Continuous IV infusion of TRV130, alone or with enriched degradants and spiked impurities, to rats produced responses in clinical observations, body weights, food consumption, and clinical and anatomical pathology that were generally similar. Therefore, TRV130 fortified with (b) (4) impurity, (b) (4), and (b) (4) did not produce any clear difference in responses compared to animals administered TRV130 alone.

- Minimal to slight subacute inflammation of cecum was observed in animals administered TRV130 alone or with degradants and impurities, but it was not present in controls. The incidence was higher in males treated with TRV130 with enriched impurities and degradants (5/10 vs 2/10 in males treated with TRV130 alone). In contrast, the incidence was the same in females treated with either TRV130 alone or with enriched degradants though the severity was slightly higher in the TRV130 alone group. In addition, cecum subacute inflammation has not been observed in the other general toxicity studies. Rats possess a larger and more fully developed cecum that serves as a fermentation chamber to digest cellulose (Snipes, 1981). The cecum is largely a vestigial organ in humans, and as a result, inflammation in the rat cecum is likely to have low relevance to human safety. Taken together, this reviewer does not consider the cecum finding to be toxicologically significant.
- The excess of the four impurities administered to rats in this study compared to the maximum exposure to these impurities in humans is presented in the table below. The calculated human exposure to impurities is based on the acceptance criterion proposed in finished API or DP specification and an oliceridine maximum daily dose of 40 mg. It appears that adequate level for each of the four impurities has been tested and their safety is qualified from a general toxicity perspective.

Table 20. Impurity Dose Levels in Rats During a 14-Day Toxicology Study Compared to the Maximum Dose in Humans

Impurity	Concentration of Impurity in Fortified TRV130DP	Dose in the Animal Study (mg/kg/day)	HED Based upon BSA (mg/day)	Proposed Specifications	Maximum Human Exposure* (mg/day)	HED/Maximum Human Exposure
	(b) (4)		(b) (4)			(b) (4)

\*Based upon proposed MRHD of 40 mg/day

**Methods**

Doses: 0, 12 mg/kg/day

Group	Subgroup	No. of Animals		Dose Level a,b (mg/kg/day)	Dose Concentration <sup>a</sup> (mg/mL)
		Male	Female		
1 (Control) <sup>c</sup>	1 (Toxicity)	10	10	0	0
	2 (Toxicokinetic)	3	3	0	0
2 TRV130	1 (Toxicity)	10	10	12	0.5
	2 (Toxicokinetic)	3	3	12	0.5
3 TRV130 (with degradants and impurities) <sup>d</sup>	1 (Toxicity)	10	10	12	0.5
	2 (Toxicokinetic)	3	3	12	0.5

a Dose levels were expressed as the free base. Concentrations were corrected for lot-specific potency using a correction factor of (b) (4) for TRV130 (Group 2).

b Animals were dosed at a dose rate of 1 mL/kg/hour continuously (24 hours/day) for at least 14 days.

c Group 1 was administered vehicle control article only.

d TRV130 drug product containing (b) (4)

RRT (b) (4): It is also named as (b) (4) in the NDA submission.

- Frequency of dosing: Continuous infusion for 14 days
- Route of administration: IV
- Dose volume: 1 mL/kg/h
- Formulation/Vehicle: (b) (4) mg/mL L-histidine and (b) (4) mg/mL mannitol in Sterile Water for Injection, USP, pH (b) (4).
- Species/Strain: Rat/SD
- Number/Sex/Group: 10/sex/dose group
- Age: 8-9-week-old
- Weight: 270-326 g for males; 159-222 g for females
- Satellite groups: 3 rats/sex/dose group (See the table above) for the TK group
- Rational of dose selection: The TRV130 doses for this study were selected based on results from previously conducted 14-day continuous intravenous infusion studies in rats (b) (4) Studies 8242808 and 8253529). The 12 mg/kg/day dose level was well-tolerated in Study 8242808, with TRV130-related findings limited to nonadverse clinical pathology effects consistent with dehydration and stress/inflammation and indirect stress-related microscopic findings at necropsy.
- Deviation from study protocol: No deviation from the study protocol impacted the data interpretation

**Observations and Results**

**Mortality**

No test article-related mortality was observed.

**Clinical Signs**

Detailed observations were conducted for each toxicity animal twice during the predose phase, prior to dosing on Day 1, and on Days 8 and 14 of the dosing phase. Detailed observations were also collected for each toxicity animal on days of scheduled sacrifice (all surviving animals). Cage side observations were conducted for each toxicity animal once daily during the dosing phase, except on days when detailed observations were conducted.

Abnormal clinical observations occurred at a low frequency in the study (two or fewer animals/sex/group) and were of minimal severity (e.g., gnawing of digits, discolored skin or haircoat, audible respiration). No evidence was apparent to conclude the presence of impurities and degradants in TRV130 formulations altered the incidence or occurrence of abnormal clinical observations.

### **Body Weights**

Body weights for all toxicity and toxicokinetic animals were recorded twice during the predose phase, before dosing on Day 1, and on Days 8 and 14 of the dosing phase.

Administration of TRV130 alone or with degradants resulted in similar effects on body weight or body weight change in comparison to control animals.

- Mean body weight change was significantly decreased in Group 2 males (TRV130 only) between Days 1 and 8 and between Days 1 and 14 relative to controls, leading to a significant decrease in mean absolute body weights on Day 14 (-7%). Similar body weight change was observed in Group 3 males treated with TRV130 with degradants and impurities.
- The only statistically significant change in female body weights occurred between Days 8 and 14 in Group 3, where females had a lower mean body weight change (4 g) compared to respective controls (9 g) and compared to Group 2 (TRV130 only) (10 g).

### **Food Consumption**

The amount of food consumed by each toxicity animal was measured quantitatively from Days 1 to 8 and Days 8 to 14 of the dosing phase.

Administration of TRV130 alone or with degradants resulted in similar effects on food consumption in comparison to control animals. Between Days 8 and 14, significant differences in mean food consumption in males administered TRV130 alone were noted in comparison to the control group (-18%) and to the TRV130 with degradants and impurities group (-15%). Female food consumption was similar in all groups.

### **Ophthalmoscopy**

Ophthalmic examinations were conducted once during the predose phase for all animals and once for all toxicity animals during Week 2 of the dosing phase within 3 days of the scheduled necropsy.

No abnormal findings were reported.

### **ECG**

Not done

### **Clinical Pathology**

Blood samples for hematology, coagulation, and clinical chemistry were collected on the

day of scheduled sacrifice from fasted toxicity animals via a jugular vein. Urine samples for urinalysis were collected chilled during the overnight period before blood collection on the day of scheduled sacrifice from toxicity animals fasted overnight. See the tables below for the parameters measured:

### 3.5.1.2 Hematology Tests

red blood cell (erythrocyte) count	platelet count
hemoglobin	white blood cell (leukocyte) count
hematocrit	differential blood cell count
mean corpuscular volume	blood smear
mean corpuscular hemoglobin	reticulocyte count
mean corpuscular hemoglobin concentration	red blood cell distribution width

### 3.5.1.3 Coagulation Tests

prothrombin time	activated partial thromboplastin time
fibrinogen	

### 3.5.1.4 Clinical Chemistry Tests

glucose	alkaline phosphatase
urea nitrogen	gamma glutamyltransferase
creatinine	aspartate aminotransferase
total protein	calcium
albumin	inorganic phosphorus
globulin	sodium
albumin/globulin ratio	potassium
cholesterol	chloride
total bilirubin	triglycerides
alanine aminotransferase	creatine kinase

### 3.5.1.5 Urinalysis Tests

appearance (clarity and color)	pH
bilirubin	protein
blood	specific gravity
glucose	volume
ketones	

TRV130 administration produced several minor, non-adverse clinical pathology effects that were not generally affected by the presence of TRV130 degradants and impurities.

- Minimally to mildly increased urea nitrogen, electrolytes (chloride and/or sodium), and/or protein (albumin, total protein, and/or albumin: globulin ratio) concentrations.
- Decreased urine volume, with accompanying increased urine specific gravity and urine protein, which were supportive of dehydration.
- Minimally decreased red cell mass (red blood cell count, hemoglobin concentration, and hematocrit), with minimally decreased absolute reticulocyte count and minimally increased

red blood cell distribution and mean corpuscular hemoglobin concentration, which were supportive of decreased erythropoiesis.

- Minimally to mildly decreased enzymes (aspartate and alanine aminotransferase, alkaline phosphatase, and creatine kinase activities) and minimally decreased globulin concentration. This probably was associated with decreased food consumption and body weight.

### **Gross Pathology**

On Day 15 of the dosing phase, the toxicity animals were anesthetized and necropsied. No effect on organ weight parameters occurred for either sex administered TRV130 alone or with degradants and impurities, compared with controls.

- Discoloration of the cecum, observed at necropsy in one male administered TRV130 alone and one male and one female administered TRV130 with degradants and impurities was correlated with the microscopic observation of subacute inflammation and was considered related to the administration of TRV130 alone or with degradants and impurities.

### **Organ Weights**

For a list of organs that were weighed see Applicant's tissue list below. No direct test article-related effects on organ weight parameters occurred for terminal sacrifice animals.

(b) (4) Study Number S354309  
 Sponsor Reference Number MORIVCOV27

The following tissues (when present) from each animal were preserved in 10% neutral-buffered formalin, unless otherwise indicated.

Organ/Tissue		Organ/Tissue	
adrenal (2)	W P,E	lymph nodes (mesenteric)	P,E
animal identification		mammary glands (females)	P,E
aorta	P,E	muscle, biceps femoris	P,E
bone, femur with bone marrow (articular surface of distal end to include stifle joint)	P,E	optic nerve (2) <sup>c</sup>	P,E
bone, sternum with bone marrow	P,E	ovary (2) <sup>b</sup>	W P,E
brain <sup>a</sup>	W P,E	oviduct (2) <sup>b</sup>	W P,E
cecum	P,E	pancreas	P,E
cervix <sup>b</sup>	W P,E	pituitary gland	W P,E
coagulating gland [intact with seminal vesicles (2)]	P,E	prostate	W P,E
colon	P,E	rectum	P,E
duodenum	P,E	salivary gland (mandibular [2])	P,E
epididymis (2)	W P,E	sciatic nerve	P,E
esophagus	P,E	seminal vesicle	P,E
eye (2) <sup>c</sup>	P,E	skin/subcutis	P,E
GALT (Peyer's Patch)	P,E	spinal cord (cervical, thoracic, and lumbar)	P,E
Harderian gland <sup>c</sup>	P,E	spleen	W P,E
heart	W P,E	stomach	P,E
ileum	P,E	testis (2) <sup>c</sup>	W P,E
infusion site	P,E	thymus	W P,E
catheterization site	P,E	thyroid (2 lobes) with parathyroid	W P,E
jejunum	P,E	tongue	P,E
kidney (2)	W P,E	trachea	P,E
lesions	P,E	urinary bladder	P,E
liver	W P,E	uterus <sup>b</sup>	W P,E
lungs with large bronchi	P,E	vagina	P,E
lymph nodes (mandibular)	P,E		

E = Examined microscopically; P = Processed; W = Weighed.

- a Include olfactory bulb (collected intact in skull), piriform cortex, amygdala, and entorhinal cortex.
- b Organs weighed together; ovary with oviduct and uterus with cervix
- c Collected in modified Davidson's fixative and stored in 10% neutral-buffered formalin.

Bone marrow smears (two slides) were prepared from the femur of each animal at scheduled sacrifices.

**Histopathology**

**Adequate Battery: Yes**

**Peer Review: No**

Tissues indicated in the table above from all animals were examined microscopically. Minimal to slight subacute inflammation of the cecum was observed in animals administered TRV130 alone or with degradants and impurities, but it was not present in controls. The subacute inflammation was characterized by thinning of the mucosa, with slight edema and congestion of the lamina propria and an infiltration mixed inflammatory cells in the lamina propria; in addition, loss of the surface epithelium occurred, with accumulation of cellular debris in the lumen of the cecum was noted. The incidence and severity of the subacute inflammation in the cecum are summarized in the table below:

**Text Table 4.2: Incidence and Severity of Test Article-Related Microscopic Findings - Cecum**

		TRV130					
		Sex	Males			Females	
TRV130 Dose Level (mg/kg/day)		0	12	0	0	12	0
TRV130 with degradants and impurities Dose Level (mg/kg/day)		0	0	12	0	0	12
Cecum							
	Number Examined	10	10	10	10	10	10
Inflammation, subacute							
	Minimal	0	1	1	0	3	4
	Slight	0	1	4	0	1	0

*Reviewer's note: In this study, it appears that the effect on cecum is test article related and the incidence appears higher in males treated with TRV130 plus fortified impurities/degradants. However, the minimal to slight subacute inflammation of the cecum observed in the current study was not observed in the other four repeat-dose toxicity studies which evaluated a full battery of tissues for histopathology after a treatment duration of 14 days or longer in rats or monkeys. In addition, the incidence was the same in females treated with either TRV130 alone or with enriched degradants in this study, and the severity was slightly higher in the TRV130 alone group. As a response (dated July 26, 2018) to our IR, the Applicant conducted a statistical analysis on the histopathology data from this study. A Chi-Square test of association ( $p = 0.1596$ ) and a Fisher's exact two-sided test ( $p = 0.3498$ ) showed that there was no statistical difference in total incidence among male rats between the TRV130 alone and TRV130 with impurities and degradation products groups. Further, an exact ordered categorical permutation test ( $p = 0.2107$ ) showed no statistical difference between the severity of inflammation in male rats in the TRV130 alone group compared with the TRV130 with impurities and degradation products group. The Applicant also pointed out that rats possess a larger and more fully developed cecum that serves as a fermentation chamber to digest cellulose (Snipes, 1981). The cecum is largely a vestigial organ in humans, and as a result, inflammation in the rat cecum is not likely to have any relevance to human safety. All other regions of the gastrointestinal tract (duodenum, jejunum, ileum and colon) were normal in this study. This Reviewer agrees that the totality of evidence across the nonclinical toxicity program indicates that the minimal to slight inflammation observed in the cecum in this single 14-day rat study does not pose a risk to patient safety.*

All other microscopic findings were considered spontaneous and/or incidental because

they occurred at a low incidence, were randomly distributed across groups (including concurrent controls), and/or their severity was as expected for young Hsd:Sprague Dawley® SD® rats; therefore, they were considered not test article related.

No significant difference in findings was observed at the catheter (section taken at the entrance into the femoral vein) or infusion site (section taken at the catheter tip) of animals administered the vehicle control article or TRV130 alone or with degradants and impurities. The most common finding at the catheter site was thrombi formation surrounding or adjacent to the catheter. The most common finding present at the infusion site was minimal to slight hyperplasia of the endothelium lining the vein. These findings were considered associated with the infusion procedure and were not directly related to vehicle control article or TRV130 alone or with degradants and impurities.

### **Special Evaluation**

No

### **Toxicokinetics**

Blood samples were collected from all toxicokinetic animals on Day 1 at approximately 2, 4, and 8 hours post the start of infusion (based on the start of infusion for each animal), and on Days 4, 8, and 14 at approximately 4 hours post the daily syringe change (76, 172, and 316 hours post the start of the infusion, respectively). Plasma samples were assayed for TRV130 and (b) (4).

TRV130 and (b) (4) mean concentration-time profiles show that steady state was generally achieved within 8 hours post the start of infusion. Mean (b) (4) and CL values were similar in animals dosed with TRV130 alone (96.7 ng/mL  $C_{ss}$  and 5330 mL/h/kg CL) and TRV130 with degradants and impurities ((b) (4)). Due to the presence of (b) (4) in the Group 3 dosing solution, mean (b) (4) values were approximately (b) (4) fold higher in animals dosed with TRV130 with degradants and impurities ((b) (4) ng/mL) compared to animals dosed with TRV130 alone ((b) (4) ng/mL).

### **Dosing Solution Analysis**

The evaluation of stability of the test solution showed the solution used in Group 2 was stable over the duration of the dosing phase.

TRV130 formulations (used for Group 2) were within  $\pm 10\%$  of the target concentrations (see the table below). The test article was not detected in the vehicle control.

**Table 7.1: Results of Concentration Verification Analyses**

Method Reference: 11001/11528

		TRV130 (also known as oliceridine) in (b) (4) mg/mL L-histidine and (b) (4) mg/mL mannitol in Sterile Water for Injections, (b) (4)			
		0 mg/mL		0.5 mg/mL	
Interval	Replicate	Actual	% of Target	Actual	% of Target
Day 1 <sup>a</sup>	1	DNS	-	(b) (4)	(b) (4)
	2	-	-	(b) (4)	(b) (4)
	3	-	-	(b) (4)	(b) (4)
	Mean	-	-	-	97.8
	RSD (%)	-	-	-	2.2
Day 8 <sup>b</sup>	1	DNS	-	(b) (4)	(b) (4)
	2	-	-	(b) (4)	(b) (4)
	3	-	-	(b) (4)	(b) (4)
	Mean	-	-	-	94.2
	RSD (%)	-	-	-	2.2

- = Not applicable

DNS = Detection not significant

RSD = Relative standard deviation

a Method 11001 used for Day 1 analyses.

b Method 11528 used for Day 8 analyses.

The (b) (4) study report states that the test article formulation for Group 3 was used as provided by the Applicant without additional formulation. (b) (4) retained a sample of TRV130 DP (Lot 4948-1-1) with the enriched degradants and spiked impurities, and after completion of the dosing phase, the formulation was retested to determine if the extended storage affected the composition of the formulation. Data are presented in the table below in the report entitled *Spiking, Intentional Degradation, and Analysis of TRV130 Fumarate Injection, 0.5 mg/mL, Free base, Tox Batch* (see End of Use Stability Summary). It appears the API concentration in the drug formulation for Group 3 was comparable to that in the drug formulation for Group 2.

Table 5. Release and End of Study Analysis Results from TRV130 BATCH NO. 4948-1-1

Test	Release Results	End of Study Results
Appearance	Clear, colorless solution essentially free of particulate matter	Clear, colorless solution essentially free of particulate matter
pH	7.1	7.1
Chiral Purity	TRV130 (b) (4) w/w	(b) (4)
Assay	TRV130 0.48 mg/mL 95.5% LC of 0.5 mg/mL	0.47 mg/mL 94.8% LC of 0.5 mg/mL (b) (4)
Related Substances	(b) (4)	
ID by RT	Conforms	Conforms
ID by UV (PDA)	Conforms	Conforms

RRT=(b) (4) is also called (b) (4)

### 9.1.2 Genetic Toxicity

**9.1.2.1 In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)**

**Study title:** (b) (4) : **Bacterial Reverse Mutation Assay**

Study no.: AE85CE.502ICH.BTL  
Study report location: <\\cdsesub1\levsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\ae85ce-502ich-btl\ae85ce-502ich-btl-study-report.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: 3/2017  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: (b) (4); (b) (4); % assigned purity as free base= (b) (4) %  
Dose formulations were adjusted to compensate for the potency ( (b) (4) %) of the test article, using a correction factor of (b) (4).

**Key Study Findings**

The results of the study indicate that (b) (4) was negative for the ability to induce reverse mutations at selected loci of several strains of *Salmonella typhimurium* and at the tryptophan locus of *Escherichia coli* strain WP2 *uvrA* in the presence and absence of an exogenous metabolic activation system.

**Methods**

Strains: TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA*  
Concentrations in definitive study: 15.0, 50.0, 150, 500, 1500, and 5000 mcg per plate  
Basis of concentration selection: Maximum dose level; no precipitation and cytotoxicity were observed at 5000 mcg/plate in a preliminary dose range finding study.  
Negative control: Sterile water  
Positive control: See the table below:

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4)	1.0
TA100, TA1537			2.0
WP2 <i>uvrA</i>		Lot No. STBD3302V Exp. Date 31-Jul-2017 CAS No. 613-13-8 Purity 97.5%	15
TA98	None	2-nitrofluorene (b) (4)	1.0
		Lot No. S43858V Exp. Date 31-Mar-2019 CAS No. 607-57-8 Purity 99.4%	
TA100, TA1535		sodium azide (b) (4)	1.0
		Lot No. MKBT8080V Exp. Date Jan-2020 CAS No. 26628-22-8 Purity 99.8%	
TA1537		9-aminoacridine (b) (4)	
WP2 <i>uvrA</i>	methyl methanesulfonate (b) (4)	1,000	
	Lot No. MKBR6050V Exp. Date 31-Mar-2018 CAS No. 66-27-3 Purity 100.0%		

- Formulation/Vehicle:
- Sterile water for the test article
  - All positive controls were diluted in dimethyl sulfoxide (DMSO) except for sodium azide, which was diluted in sterile water.

Incubation & sampling time: The test system was exposed to the test article via the plate incorporation methodology. There were 3 plates per dose in the presence and absence of metabolic activation. The metabolic activation system consisted of an S9 fraction prepared from livers obtained from Aroclor 1254 pretreated male Sprague-Dawley rats. The S9 percentage was 10%, which is within the acceptable range. Plates were incubated at 37°C for 2-3 days. Plates that were not counted immediately following the incubation period were stored at 2-8°C until colony counting could be conducted. The condition of the bacterial background lawn was evaluated for evidence of test article toxicity by using a dissecting microscope. Precipitate was evaluated after the incubation period by visual examination without magnification. As appropriate, colonies were enumerated either by hand or by machine.

### Study Validity

- Selection of bacterial tester strains was adequate based upon Guideline for Industry: *Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (ICH S2A, April 1996).
- Positive controls produced expected responses.
- Dose selection for the plate incorporation method was adequate based upon use of the limit dose of 5000 mcg/plate.
- The S9 concentration was within acceptable limits.

### Results

- Neither precipitate nor toxicity were observed.
- As shown in the table below, all positive and vehicle control values were within acceptable ranges, and all criteria for a valid assay were met.

TABLE 3 (CONT.)  
Mutagenicity Assay without S9 activation

Study Number: AE85CE.502ICH.BTL			Study Code: AE85CE			
Experiment: Mutagenicity Assay (B1)			Date Plated: 4/25/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 4/27/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	2NF	1.00 µg	53	3	3.8	52 <sup>A</sup> , 56 <sup>A</sup> , 51 <sup>A</sup>
TA100	SA	1.00 µg	581	12	6.8	593 <sup>A</sup> , 581 <sup>A</sup> , 570 <sup>A</sup>
TA1535	SA	1.00 µg	397	31	30.5	405 <sup>A</sup> , 362 <sup>A</sup> , 423 <sup>A</sup>
TA1537	9AAD	75.0 µg	590	84	98.3	641 <sup>A</sup> , 636 <sup>A</sup> , 493 <sup>A</sup>
WP2uvrA	MMS	1000 µg	316	32	12.2	333 <sup>A</sup> , 336 <sup>A</sup> , 280 <sup>A</sup>

#### Key to Positive Controls

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

#### Key to Automatic Count Flags

<sup>A</sup>: Automatic count

**TABLE 4 (CONT.)**  
**Mutagenicity Assay with S9 activation**

Study Number: AE85CE.502ICH.BTL			Study Code: AE85CE			
Experiment: Mutagenicity Assay (B1)			Date Plated: 4/25/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 4/27/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
<b>TA98</b>	<b>2AA</b>	1.00 µg	192	22	10.1	181 <sup>A</sup> , 177 <sup>A</sup> , 217 <sup>A</sup>
<b>TA100</b>	<b>2AA</b>	2.00 µg	1080	166	12.1	942 <sup>A</sup> , 1264 <sup>A</sup> , 1035 <sup>A</sup>
<b>TA1535</b>	<b>2AA</b>	1.00 µg	74	5	6.2	78 <sup>A</sup> , 76 <sup>A</sup> , 69 <sup>A</sup>
<b>TA1537</b>	<b>2AA</b>	2.00 µg	40	7	5.7	40 <sup>A</sup> , 47 <sup>A</sup> , 33 <sup>A</sup>
<b>WP2uvrA</b>	<b>2AA</b>	15.0 µg	286	36	11.9	260 <sup>A</sup> , 272 <sup>A</sup> , 327 <sup>A</sup>

Key to Positive Controls

2AA 2-aminoanthracene

Key to Automatic Count Flags

<sup>A</sup>: Automatic count

- As shown in the table below, the test article elicited no positive mutagenic responses in any of the tester strains in either the presence or absence of S9 activation.

**TABLE 3**  
**Mutagenicity Assay without S9 activation**

Study Number: AE85CE.502ICH.B.TL			Study Code: AE85CE			
Experiment: Mutagenicity Assay (B1)			Date Plated: 4/25/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 4/27/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	(b) (4)	5000 µg	13	8	0.9	21 <sup>A</sup> , 6 <sup>A</sup> , 11 <sup>A</sup>
		1500 µg	9	3	0.6	11 <sup>A</sup> , 5 <sup>A</sup> , 11 <sup>A</sup>
		500 µg	12	4	0.9	14 <sup>A</sup> , 7 <sup>A</sup> , 14 <sup>A</sup>
		150 µg	14	3	1.0	10 <sup>A</sup> , 16 <sup>A</sup> , 16 <sup>A</sup>
		50.0 µg	11	2	0.8	14 <sup>A</sup> , 10 <sup>A</sup> , 10 <sup>A</sup>
		15.0 µg	15	2	1.1	14 <sup>A</sup> , 17 <sup>A</sup> , 14 <sup>A</sup>
	Water	100 µL	14	3		15 <sup>A</sup> , 10 <sup>A</sup> , 16 <sup>A</sup>
TA100	(b) (4)	5000 µg	71	15	0.8	87 <sup>A</sup> , 58 <sup>A</sup> , 67 <sup>A</sup>
		1500 µg	85	13	1.0	87 <sup>A</sup> , 72 <sup>A</sup> , 97 <sup>A</sup>
		500 µg	87	9	1.0	77 <sup>A</sup> , 93 <sup>A</sup> , 90 <sup>A</sup>
		150 µg	82	3	1.0	79 <sup>A</sup> , 82 <sup>A</sup> , 85 <sup>A</sup>
		50.0 µg	83	18	1.0	103 <sup>A</sup> , 74 <sup>A</sup> , 71 <sup>A</sup>
		15.0 µg	89	4	1.0	90 <sup>A</sup> , 92 <sup>A</sup> , 85 <sup>A</sup>
	Water	100 µL	85	12		99 <sup>A</sup> , 77 <sup>A</sup> , 80 <sup>A</sup>
TA1535	(b) (4)	5000 µg	12	2	0.9	14 <sup>A</sup> , 11 <sup>A</sup> , 10 <sup>A</sup>
		1500 µg	12	3	0.9	9 <sup>A</sup> , 14 <sup>A</sup> , 12 <sup>A</sup>
		500 µg	7	0	0.5	7 <sup>A</sup> , 7 <sup>A</sup> , 7 <sup>A</sup>
		150 µg	9	2	0.7	10 <sup>A</sup> , 10 <sup>A</sup> , 7 <sup>A</sup>
		50.0 µg	11	1	0.8	10 <sup>A</sup> , 12 <sup>A</sup> , 11 <sup>A</sup>
		15.0 µg	12	6	0.9	16 <sup>A</sup> , 5 <sup>A</sup> , 14 <sup>A</sup>
	Water	100 µL	13	2		12 <sup>A</sup> , 12 <sup>A</sup> , 15 <sup>A</sup>
TA1537	(b) (4)	5000 µg	3	2	0.5	5 <sup>A</sup> , 2 <sup>A</sup> , 2 <sup>A</sup>
		1500 µg	7	3	1.2	11 <sup>A</sup> , 5 <sup>A</sup> , 5 <sup>A</sup>
		500 µg	8	1	1.3	7 <sup>A</sup> , 7 <sup>A</sup> , 9 <sup>A</sup>
		150 µg	7	3	1.2	10 <sup>A</sup> , 4 <sup>A</sup> , 6 <sup>A</sup>
		50.0 µg	5	1	0.8	6 <sup>A</sup> , 5 <sup>A</sup> , 4 <sup>A</sup>
		15.0 µg	6	0	1.0	6 <sup>A</sup> , 6 <sup>A</sup> , 6 <sup>A</sup>
	Water	100 µL	6	1		5 <sup>A</sup> , 7 <sup>A</sup> , 6 <sup>A</sup>
WP2uvrA	(b) (4)	5000 µg	20	5	0.8	25 <sup>A</sup> , 19 <sup>A</sup> , 15 <sup>A</sup>
		1500 µg	32	3	1.2	30 <sup>A</sup> , 31 <sup>A</sup> , 36 <sup>A</sup>
		500 µg	29	6	1.1	24 <sup>A</sup> , 36 <sup>A</sup> , 28 <sup>A</sup>
		150 µg	32	5	1.2	28 <sup>A</sup> , 31 <sup>A</sup> , 37 <sup>A</sup>
		50.0 µg	24	3	0.9	25 <sup>A</sup> , 27 <sup>A</sup> , 21 <sup>A</sup>
		15.0 µg	32	4	1.2	28 <sup>A</sup> , 31 <sup>A</sup> , 36 <sup>A</sup>
	Water	100 µL	26	5		27 <sup>A</sup> , 20 <sup>A</sup> , 30 <sup>A</sup>

Key to Automatic Count Flags

<sup>A</sup>: Automatic count

**TABLE 4**  
**Mutagenicity Assay with S9 activation**

Study Number: AE85CE.502ICH.BTL			Study Code: AE85CE			
Experiment: Mutagenicity Assay (B1)			Date Plated: 4/25/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 4/27/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	(b) (4)	5000 µg	21	3	1.1	20 <sup>A</sup> , 24 <sup>A</sup> , 19 <sup>A</sup>
		1500 µg	23	2	1.2	25 <sup>A</sup> , 24 <sup>A</sup> , 21 <sup>A</sup>
		500 µg	18	7	0.9	19 <sup>A</sup> , 11 <sup>A</sup> , 25 <sup>A</sup>
		150 µg	18	4	0.9	17 <sup>A</sup> , 15 <sup>A</sup> , 22 <sup>A</sup>
		50.0 µg	21	6	1.1	27 <sup>A</sup> , 20 <sup>A</sup> , 16 <sup>A</sup>
		15.0 µg	18	10	0.9	7 <sup>A</sup> , 21 <sup>A</sup> , 26 <sup>A</sup>
	Water	100 µL	19	4		17 <sup>A</sup> , 17 <sup>A</sup> , 24 <sup>A</sup>
TA100	(b) (4)	5000 µg	93	10	1.0	83 <sup>A</sup> , 94 <sup>A</sup> , 103 <sup>A</sup>
		1500 µg	81	7	0.9	87 <sup>A</sup> , 84 <sup>A</sup> , 73 <sup>A</sup>
		500 µg	98	1	1.1	97 <sup>A</sup> , 98 <sup>A</sup> , 98 <sup>A</sup>
		150 µg	98	11	1.1	110 <sup>A</sup> , 89 <sup>A</sup> , 94 <sup>A</sup>
		50.0 µg	116	5	1.3	119 <sup>A</sup> , 118 <sup>A</sup> , 110 <sup>A</sup>
		15.0 µg	107	16	1.2	115 <sup>A</sup> , 89 <sup>A</sup> , 118 <sup>A</sup>
	Water	100 µL	89	1		90 <sup>A</sup> , 88 <sup>A</sup> , 89 <sup>A</sup>
TA1535	(b) (4)	5000 µg	12	5	1.0	12 <sup>A</sup> , 16 <sup>A</sup> , 7 <sup>A</sup>
		1500 µg	11	6	0.9	10 <sup>A</sup> , 17 <sup>A</sup> , 6 <sup>A</sup>
		500 µg	10	6	0.8	10 <sup>A</sup> , 16 <sup>A</sup> , 5 <sup>A</sup>
		150 µg	11	2	0.9	11 <sup>A</sup> , 9 <sup>A</sup> , 12 <sup>A</sup>
		50.0 µg	13	3	1.1	17 <sup>A</sup> , 11 <sup>A</sup> , 12 <sup>A</sup>
		15.0 µg	12	4	1.0	9 <sup>A</sup> , 16 <sup>A</sup> , 11 <sup>A</sup>
	Water	100 µL	12	3		9 <sup>A</sup> , 12 <sup>A</sup> , 15 <sup>A</sup>
TA1537	(b) (4)	5000 µg	10	2	1.4	10 <sup>A</sup> , 12 <sup>A</sup> , 9 <sup>A</sup>
		1500 µg	6	2	0.9	6 <sup>A</sup> , 7 <sup>A</sup> , 4 <sup>A</sup>
		500 µg	9	2	1.3	10 <sup>A</sup> , 10 <sup>A</sup> , 6 <sup>A</sup>
		150 µg	8	1	1.1	7 <sup>A</sup> , 9 <sup>A</sup> , 7 <sup>A</sup>
		50.0 µg	8	2	1.1	10 <sup>A</sup> , 7 <sup>A</sup> , 6 <sup>A</sup>
		15.0 µg	8	2	1.1	6 <sup>A</sup> , 7 <sup>A</sup> , 10 <sup>A</sup>
	Water	100 µL	7	2		5 <sup>A</sup> , 9 <sup>A</sup> , 7 <sup>A</sup>
WP2uvrA	(b) (4)	5000 µg	21	5	0.9	21 <sup>A</sup> , 26 <sup>A</sup> , 16 <sup>A</sup>
		1500 µg	28	6	1.2	30 <sup>A</sup> , 33 <sup>A</sup> , 21 <sup>A</sup>
		500 µg	30	5	1.3	35 <sup>A</sup> , 31 <sup>A</sup> , 25 <sup>A</sup>
		150 µg	28	8	1.2	35 <sup>A</sup> , 30 <sup>A</sup> , 19 <sup>A</sup>
		50.0 µg	28	4	1.2	32 <sup>A</sup> , 28 <sup>A</sup> , 24 <sup>A</sup>
		15.0 µg	27	9	1.1	37 <sup>A</sup> , 19 <sup>A</sup> , 24 <sup>A</sup>
	Water	100 µL	24	5		27 <sup>A</sup> , 27 <sup>A</sup> , 19 <sup>A</sup>

**Key to Automatic Count Flags**

<sup>A</sup>: Automatic count

**Study title:** (b) (4) : **Bacterial Reverse Mutation Assay**

Study no.: AE95MG.502ICH.BTL  
Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\ae95mg-502ich-btl\ae95mg-502ich-btl-study-report.pdf>

Conducting laboratory and location:

(b) (4)

Date of study initiation: 7/2017  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: (b) (4); % Assigned purity = (b) (4) %

Dose formulations were adjusted to compensate for the purity ((b) (4) %) of the test article, using a correction factor of (b) (4) .

### Key Study Findings

The results of the study indicate that (b) (4) was negative for the ability to induce reverse mutations at selected loci of several strains of *Salmonella typhimurium* and at the tryptophan locus of *Escherichia coli* strain WP2 *uvrA* in the presence and absence of an exogenous metabolic activation system.

**Methods**

Strains: TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA*  
 Concentrations in definitive study: 100, 333, 1000, 3333, and 5000 mcg per plate.  
 Basis of concentration selection: No precipitation and cytotoxicity were observed at 5000 mcg/plate in a preliminary dose range-finding study; however, a reduction in revertant count was observed at 5000 mcg per plate with tester strain TA1535 in the presence of S9 activation. Based upon these results, the maximum dose tested in the mutagenicity assay was 5000 mcg per plate.  
 Negative control: DMSO  
 Positive control: See the table below:

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4)	1.0
TA100, TA1537		Lot No. STBD3302V Exp. Date 31-Jul-2017 CAS No. 613-13-8 Purity 97.5%	2.0
WP2 <i>uvrA</i>			15
TA98	None	2-nitrofluorene (b) (4)	1.0
		Lot No. S43858V Exp. Date 31-Mar-2019 CAS No. 607-57-8 Purity 99.4%	
TA100, TA1535		sodium azide (b) (4)	1.0
		Lot No. MKBT8080V Exp. Date Jan-2020 CAS No. 26628-22-8 Purity 99.8%	
TA1537		9-aminoacridine (b) (4)	75
	Lot No. BCBK1177V Exp. Date 31-Mar-2019 CAS No. 52417-22-8 Purity 99.5%		
WP2 <i>uvrA</i>	methyl methanesulfonate (b) (4)	1,000	
	Lot No. MKBR6050V Exp. Date 31-Mar-2018 CAS No. 66-27-3 Purity 100.0%		

Formulation/Vehicle: 

- DMSO for the test article
- All positive controls were diluted in dimethyl sulfoxide (DMSO) except for sodium azide, which was diluted in sterile water.

Incubation & sampling time: The test system was exposed to the test article via the plate incorporation methodology. There were 3 plates per dose in the presence and absence of metabolic activation. The metabolic activation system consisted of an S9 fraction prepared from livers obtained from Aroclor 1254 pretreated male Sprague-Dawley rats. The S9 percentage was 10%, which is within the acceptable range. Plates

were incubated at 37°C for 2-3 days. Plates that were not counted immediately following the incubation period were stored at 2-8°C until colony counting could be conducted. The condition of the bacterial background lawn was evaluated for evidence of test article toxicity by using a dissecting microscope. Precipitate was evaluated after the incubation period by visual examination without magnification. As appropriate, colonies were enumerated either by hand or by machine.

### Study Validity

- Selection of bacterial tester strains was adequate based upon ICH guideline for industry: *Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A, April 1996)*.
- Positive controls produced expected responses.
- Dose selection for the plate incorporation method was adequate based upon use of the limit dose of 5000 mcg/plate.
- The S9 concentration was within acceptable limits.

### Results

- Neither precipitate nor toxicity were observed.
- As shown in the table below, all positive and vehicle control values were within acceptable ranges, and all criteria for a valid assay were met.

**TABLE 3 (CONT.)**  
**Mutagenicity Assay without S9 activation**

Study Number: AE95MG.502ICH.BTL			Study Code: AE95MG			
Experiment: B1			Date Plated: 7/19/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 7/30/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
<b>TA98</b>	<b>2NF</b>	1.00 µg	109	17	6.4	98 <sup>A</sup> , 100 <sup>A</sup> , 128 <sup>A</sup>
<b>TA100</b>	<b>SA</b>	1.00 µg	585	45	6.9	547 <sup>A</sup> , 635 <sup>A</sup> , 572 <sup>A</sup>
<b>TA1535</b>	<b>SA</b>	1.00 µg	551	51	34.4	569 <sup>A</sup> , 591 <sup>A</sup> , 494 <sup>A</sup>
<b>TA1537</b>	<b>9AAD</b>	75.0 µg	679	105	75.4	766 <sup>A</sup> , 562 <sup>A</sup> , 708 <sup>A</sup>
<b>WP2uvrA</b>	<b>MMS</b>	1000 µg	331	19	10.7	339 <sup>A</sup> , 309 <sup>A</sup> , 344 <sup>A</sup>

Key to Positive Controls

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

Key to Automatic Count Flags

<sup>A</sup>: Automatic count

**TABLE 4**  
**Mutagenicity Assay with S9 activation**

Study Number: AE95MG.502ICH.BTL			Study Code: AE95MG			
Experiment: B1			Date Plated: 7/19/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 7/30/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
<b>TA98</b>	<b>2AA</b>	1.00 µg	241	16	10.5	222 <sup>A</sup> , 251 <sup>A</sup> , 250 <sup>A</sup>
<b>TA100</b>	<b>2AA</b>	2.00 µg	690	102	6.2	792 <sup>A</sup> , 588 <sup>A</sup> , 689 <sup>A</sup>
<b>TA1535</b>	<b>2AA</b>	1.00 µg	71	11	4.7	60 <sup>A</sup> , 72 <sup>A</sup> , 82 <sup>A</sup>
<b>TA1537</b>	<b>2AA</b>	2.00 µg	64	17	5.3	48 <sup>A</sup> , 63 <sup>A</sup> , 82 <sup>A</sup>
<b>WP2uvrA</b>	<b>2AA</b>	15.0 µg	337	127	10.5	193 <sup>A</sup> , 383 <sup>A</sup> , 434 <sup>A</sup>

Key to Positive Controls

Key to Plate Postfix Codes

2AA	2-aminoanthracene	2	Slightly reduced background
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Key to Automatic Count Flags

<sup>A</sup>: Automatic count

- As shown in the table below, the test article elicited no positive mutagenic responses in any of the tester strains in either the presence or absence of S9 activation.

**TABLE 3**  
**Mutagenicity Assay without S9 activation**

Study Number: AE95MG.502ICH.BTL  
Experiment: B1  
Exposure Method: Plate incorporation assay

Study Code: AE95MG  
Date Plated: 7/19/2017  
Evaluation Period: 7/30/2017

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
<b>TA98</b>	(b) (4)	5000 µg	16	6	0.9	11 <sup>A</sup> , 22 <sup>A</sup> , 15 <sup>A</sup>
		3333 µg	15	4	0.9	18 <sup>A</sup> , 10 <sup>A</sup> , 17 <sup>A</sup>
		1000 µg	18	6	1.1	13 <sup>A</sup> , 17 <sup>A</sup> , 25 <sup>A</sup>
		333 µg	20	2	1.2	21 <sup>A</sup> , 18 <sup>A</sup> , 21 <sup>A</sup>
		100 µg	14	4	0.8	16 <sup>A</sup> , 17 <sup>A</sup> , 10 <sup>A</sup>
	<b>DMSO</b>	50.0 µL	17	6		22 <sup>A</sup> , 11 <sup>A</sup> , 18 <sup>A</sup>
<b>TA100</b>	(b) (4)	5000 µg	78	5	0.9	73 <sup>A</sup> 2, 82 <sup>A</sup> 2, 78 <sup>A</sup> 2
		3333 µg	83	4	1.0	84 <sup>A</sup> , 86 <sup>A</sup> , 79 <sup>A</sup>
		1000 µg	90	13	1.1	86 <sup>A</sup> , 79 <sup>A</sup> , 104 <sup>A</sup>
		333 µg	85	6	1.0	83 <sup>A</sup> , 80 <sup>A</sup> , 92 <sup>A</sup>
		100 µg	88	8	1.0	86 <sup>A</sup> , 97 <sup>A</sup> , 82 <sup>A</sup>
	<b>DMSO</b>	50.0 µL	85	5		81 <sup>A</sup> , 91 <sup>A</sup> , 83 <sup>A</sup>
<b>TA1535</b>	(b) (4)	5000 µg	15	4	0.9	17 <sup>A</sup> , 10 <sup>A</sup> , 17 <sup>A</sup>
		3333 µg	16	3	1.0	13 <sup>A</sup> , 19 <sup>A</sup> , 15 <sup>A</sup>
		1000 µg	16	5	1.0	13 <sup>A</sup> , 21 <sup>A</sup> , 13 <sup>A</sup>
		333 µg	16	3	1.0	15 <sup>A</sup> , 13 <sup>A</sup> , 19 <sup>A</sup>
		100 µg	18	5	1.1	15 <sup>A</sup> , 15 <sup>A</sup> , 23 <sup>A</sup>
	<b>DMSO</b>	50.0 µL	16	2		14 <sup>A</sup> , 17 <sup>A</sup> , 17 <sup>A</sup>
<b>TA1537</b>	(b) (4)	5000 µg	9	2	1.0	7 <sup>A</sup> , 11 <sup>A</sup> , 10 <sup>A</sup>
		3333 µg	8	6	0.9	3 <sup>A</sup> , 6 <sup>A</sup> , 14 <sup>A</sup>
		1000 µg	7	6	0.8	2 <sup>A</sup> , 7 <sup>A</sup> , 13 <sup>A</sup>
		333 µg	7	1	0.8	6 <sup>A</sup> , 8 <sup>A</sup> , 6 <sup>A</sup>
		100 µg	6	0	0.7	6 <sup>A</sup> , 6 <sup>A</sup> , 6 <sup>A</sup>
	<b>DMSO</b>	50.0 µL	9	5		14 <sup>A</sup> , 5 <sup>A</sup> , 7 <sup>A</sup>
<b>WP2uvr.A</b>	(b) (4)	5000 µg	26	3	0.8	25 <sup>A</sup> , 24 <sup>A</sup> , 30 <sup>A</sup>
		3333 µg	30	12	1.0	17 <sup>A</sup> , 34 <sup>A</sup> , 39 <sup>A</sup>
		1000 µg	35	1	1.1	34 <sup>A</sup> , 36 <sup>A</sup> , 36 <sup>A</sup>
		333 µg	34	12	1.1	33 <sup>A</sup> , 23 <sup>A</sup> , 46 <sup>A</sup>
		100 µg	27	4	0.9	24 <sup>A</sup> , 27 <sup>A</sup> , 31 <sup>A</sup>
	<b>DMSO</b>	50.0 µL	31	2		30 <sup>A</sup> , 30 <sup>A</sup> , 33 <sup>A</sup>

Key to Plate Postfix Codes

2 Slightly reduced background

Key to Automatic Count Flags

<sup>A</sup>: Automatic count

**TABLE 4**  
**Mutagenicity Assay with S9 activation**

Study Number: AE95MG.502ICH.BTL

Study Code: AE95MG

Experiment: B1

Date Plated: 7/19/2017

Exposure Method: Plate incorporation assay

Evaluation Period: 7/30/2017

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
<b>TA98</b>	(b) (4)	5000 µg	24	8	1.0	25 <sup>A</sup> , 16 <sup>A</sup> , 32 <sup>A</sup>
		3333 µg	28	3	1.2	25 <sup>A</sup> , 29 <sup>A</sup> , 30 <sup>A</sup>
		1000 µg	27	5	1.2	29 <sup>A</sup> , 31 <sup>A</sup> , 22 <sup>A</sup>
		333 µg	30	5	1.3	35 <sup>A</sup> , 29 <sup>A</sup> , 26 <sup>A</sup>
		100 µg	26	4	1.1	23 <sup>A</sup> , 24 <sup>A</sup> , 30 <sup>A</sup>
		<b>DMSO</b>	50.0 µL	23	6	
<b>TA100</b>	(b) (4)	5000 µg	96	11	0.9	88 <sup>A</sup> 2, 91 <sup>A</sup> 2, 108 <sup>A</sup> 2
		3333 µg	102	11	0.9	115 <sup>A</sup> , 99 <sup>A</sup> , 93 <sup>A</sup>
		1000 µg	110	5	1.0	113 <sup>A</sup> , 113 <sup>A</sup> , 104 <sup>A</sup>
		333 µg	101	7	0.9	106 <sup>A</sup> , 103 <sup>A</sup> , 93 <sup>A</sup>
		100 µg	112	4	1.0	112 <sup>A</sup> , 108 <sup>A</sup> , 115 <sup>A</sup>
		<b>DMSO</b>	50.0 µL	111	12	
<b>TA1535</b>	(b) (4)	5000 µg	17	4	1.1	15 <sup>A</sup> , 22 <sup>A</sup> , 14 <sup>A</sup>
		3333 µg	13	4	0.9	10 <sup>A</sup> , 11 <sup>A</sup> , 18 <sup>A</sup>
		1000 µg	12	2	0.8	11 <sup>A</sup> , 14 <sup>A</sup> , 10 <sup>A</sup>
		333 µg	14	8	0.9	13 <sup>A</sup> , 23 <sup>A</sup> , 7 <sup>A</sup>
		100 µg	10	8	0.7	18 <sup>A</sup> , 3 <sup>A</sup> , 10 <sup>A</sup>
		<b>DMSO</b>	50.0 µL	15	5	
<b>TA1537</b>	(b) (4)	5000 µg	9	1	0.8	9 <sup>A</sup> , 10 <sup>A</sup> , 9 <sup>A</sup>
		3333 µg	11	3	0.9	13 <sup>A</sup> , 13 <sup>A</sup> , 7 <sup>A</sup>
		1000 µg	14	6	1.2	7 <sup>A</sup> , 16 <sup>A</sup> , 18 <sup>A</sup>
		333 µg	11	3	0.9	8 <sup>A</sup> , 13 <sup>A</sup> , 11 <sup>A</sup>
		100 µg	8	3	0.7	10 <sup>A</sup> , 9 <sup>A</sup> , 5 <sup>A</sup>
		<b>DMSO</b>	50.0 µL	12	3	
<b>WP2uvrA</b>	(b) (4)	5000 µg	36	6	1.1	39 <sup>A</sup> , 40 <sup>A</sup> , 29 <sup>A</sup>
		3333 µg	28	5	0.9	25 <sup>A</sup> , 25 <sup>A</sup> , 34 <sup>A</sup>
		1000 µg	39	7	1.2	34 <sup>A</sup> , 47 <sup>A</sup> , 35 <sup>A</sup>
		333 µg	31	11	1.0	19 <sup>A</sup> , 41 <sup>A</sup> , 33 <sup>A</sup>
		100 µg	31	2	1.0	29 <sup>A</sup> , 31 <sup>A</sup> , 32 <sup>A</sup>
		<b>DMSO</b>	50.0 µL	32	14	

**Study title: TRV130 (b) (4) : Bacterial Reverse Mutation Assay**

Study no.: AE85CG.502ICH.BTL  
Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\ae85cg-502ich-bt\ae85cg-502ich-btl-study-report.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: 3/2017  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: TRV130- (b) (4); % Assigned purity = (b) (4) %  
Dose formulations were adjusted to compensate for the purity ( (b) (4) %) of the test article, using a correction factor of (b) (4).

**Key Study Findings**

The results of the study indicate TRV130 (b) (4) was negative for the ability to induce reverse mutations at selected loci of several strains of *Salmonella typhimurium* and at the tryptophan locus of *Escherichia coli* strain WP2 *uvrA* in the presence and absence of an exogenous metabolic activation system.

**Methods**

Strains: TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA*  
 Concentrations in definitive study: 15.0, 50.0, 150, 500, 1500 and 5000 mcg per plate.  
 Basis of concentration selection: No precipitation and cytotoxicity were observed at 5000 mcg/plate in a preliminary dose range finding study; however, a reduction in revertant count was observed at 5000 mcg per plate with tester strain TA1535 in the presence of S9 activation. Based upon these results, the maximum dose tested in the mutagenicity assay was 5000 mcg per plate.  
 Negative control: DMSO  
 Positive control: See the table below:

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4)	1.0
TA100, TA1537		Lot No. STBD3302V Exp. Date 31-Jul-2017 CAS No. 613-13-8 Purity 97.5%	2.0
WP2 <i>uvrA</i>			15
TA98	None	2-nitrofluorene (b) (4)	1.0
TA100, TA1535		Lot No. S43858V Exp. Date 31-Mar-2019 CAS No. 607-57-8 Purity 99.4%	
		sodium azide (b) (4)	1.0
TA1537		Lot No. MKBT8080V Exp. Date Jan-2020 CAS No. 26628-22-8 Purity 99.8%	
		9-aminoacridine (b) (4)	
WP2 <i>uvrA</i>	methyl methanesulfonate (b) (4)	1,000	
	Lot No. MKBR6050V Exp. Date 31-Mar-2018 CAS No. 66-27-3 Purity 100.0%		

Formulation/Vehicle: 

- DMSO for the test article
- All positive controls were diluted in dimethyl sulfoxide (DMSO) except for sodium azide, which was diluted in sterile water.

Incubation & sampling time: The test system was exposed to the test article via the plate incorporation methodology. There were 3 plates per dose in the presence and absence of metabolic activation. The metabolic activation system consisted of an S-9 fraction prepared from livers obtained from Aroclor 1254 pretreated male Sprague-Dawley rats. The S-9 percentage was 10%, which is within the acceptable range.

Plates were incubated at 37°C for 2-3 days. Plates that were not counted immediately following the incubation period were stored at 2-8°C until colony counting could be conducted. The condition of the bacterial background lawn was evaluated for evidence of test article toxicity by using a dissecting microscope. Precipitate was evaluated after the incubation period by visual examination without magnification. As appropriate, colonies were enumerated either by hand or by machine.

### Study Validity

- Selection of bacterial tester strains was adequate based upon Guideline for Industry: *Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (ICH S2A, April 1996).
- Positive controls produced expected responses.
- Dose selection for the plate incorporation method was adequate based upon use of the limit dose of 5000 mcg/plate.
- The S9 concentration was within acceptable limits.

### Results

- Neither precipitate nor toxicity were observed.
- As shown in the table below, all positive and vehicle control values were within acceptable ranges, and all criteria for a valid assay were met.
- As shown in the table below, the test article elicited no positive mutagenic responses in any of the tester strains in either the presence or absence of S9 activation.

**TABLE 3**  
**Mutagenicity Assay without S9 activation**

Study Number: AE85CG.502ICH.BTL  
Experiment: Mutagenicity Assay (B1)  
Exposure Method: Plate incorporation assay

Study Code: AE85CG  
Date Plated: 4/26/2017  
Evaluation Period: 4/29/2017

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
<b>TA98</b>	<b>TRV130</b> (b) (4)	5000 µg	17	2	0.9	19 <sup>A</sup> , 18 <sup>A</sup> , 15 <sup>A</sup>
		1500 µg	16	6	0.9	22 <sup>A</sup> , 11 <sup>A</sup> , 16 <sup>A</sup>
	<b>DMSO</b>	500 µg	18	3	1.0	15 <sup>A</sup> , 21 <sup>A</sup> , 17 <sup>A</sup>
		150 µg	19	5	1.1	13 <sup>A</sup> , 21 <sup>A</sup> , 23 <sup>A</sup>
		50.0 µg	19	0	1.1	19 <sup>A</sup> , 19 <sup>A</sup> , 19 <sup>A</sup>
		15.0 µg	21	8	1.2	30 <sup>A</sup> , 17 <sup>A</sup> , 17 <sup>A</sup>
		50.0 µL	18	1		17 <sup>A</sup> , 19 <sup>A</sup> , 18 <sup>A</sup>
<b>TA100</b>	<b>TRV130</b> (b) (4)	5000 µg	72	7	0.9	64 <sup>A</sup> 2, 76 <sup>A</sup> 2, 76 <sup>A</sup> 2
		1500 µg	92	8	1.1	96 <sup>A</sup> , 97 <sup>A</sup> , 82 <sup>A</sup>
	<b>DMSO</b>	500 µg	88	10	1.0	86 <sup>A</sup> , 79 <sup>A</sup> , 99 <sup>A</sup>
		150 µg	93	16	1.1	105 <sup>A</sup> , 75 <sup>A</sup> , 100 <sup>A</sup>
		50.0 µg	87	15	1.0	104 <sup>A</sup> , 81 <sup>A</sup> , 75 <sup>A</sup>
		15.0 µg	85	8	1.0	76 <sup>A</sup> , 90 <sup>A</sup> , 88 <sup>A</sup>
		50.0 µL	84	3		83 <sup>A</sup> , 87 <sup>A</sup> , 81 <sup>A</sup>
<b>TA1535</b>	<b>TRV130</b> (b) (4)	5000 µg	14	1	0.8	14 <sup>A</sup> , 15 <sup>A</sup> , 13 <sup>A</sup>
		1500 µg	15	6	0.8	16 <sup>A</sup> , 21 <sup>A</sup> , 9 <sup>A</sup>
	<b>DMSO</b>	500 µg	14	4	0.8	10 <sup>A</sup> , 14 <sup>A</sup> , 18 <sup>A</sup>
		150 µg	19	5	1.1	14 <sup>A</sup> , 24 <sup>A</sup> , 19 <sup>A</sup>
		50.0 µg	19	6	1.1	19 <sup>A</sup> , 14 <sup>A</sup> , 25 <sup>A</sup>
		15.0 µg	13	2	0.7	11 <sup>A</sup> , 13 <sup>A</sup> , 14 <sup>A</sup>
		50.0 µL	18	1		18 <sup>A</sup> , 17 <sup>A</sup> , 18 <sup>A</sup>
<b>TA1537</b>	<b>TRV130</b> (b) (4)	5000 µg	9	3	1.0	6 <sup>A</sup> , 11 <sup>A</sup> , 11 <sup>A</sup>
		1500 µg	6	1	0.7	5 <sup>A</sup> , 6 <sup>A</sup> , 7 <sup>A</sup>
	<b>DMSO</b>	500 µg	9	0	1.0	9 <sup>A</sup> , 9 <sup>A</sup> , 9 <sup>A</sup>
		150 µg	10	0	1.1	10 <sup>A</sup> , 10 <sup>A</sup> , 10 <sup>A</sup>
		50.0 µg	7	4	0.8	10 <sup>A</sup> , 3 <sup>A</sup> , 8 <sup>A</sup>
		15.0 µg	10	1	1.1	9 <sup>A</sup> , 9 <sup>A</sup> , 11 <sup>A</sup>
		50.0 µL	9	2		7 <sup>A</sup> , 11 <sup>A</sup> , 10 <sup>A</sup>

Key to Plate Postfix Codes

2 Slightly reduced background

Key to Automatic Count Flags

<sup>A</sup>: Automatic count

**TABLE 3 (CONT.)**  
**Mutagenicity Assay without S9 activation**

Study Number: AE85CG.502ICH.BTL  
 Experiment: Mutagenicity Assay (B1)  
 Exposure Method: Plate incorporation assay

Study Code: AE85CG  
 Date Plated: 4/26/2017  
 Evaluation Period: 4/29/2017

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA	TRV130 (b) (4)	5000 µg	16	5	0.7	19 <sup>A</sup> , 11 <sup>A</sup> , 19 <sup>A</sup>
		1500 µg	24	3	1.0	26 <sup>A</sup> , 21 <sup>A</sup> , 24 <sup>A</sup>
	DMSO	500 µg	24	2	1.0	23 <sup>A</sup> , 23 <sup>A</sup> , 26 <sup>A</sup>
		150 µg	20	5	0.9	19 <sup>A</sup> , 26 <sup>A</sup> , 16 <sup>A</sup>
		50.0 µg	28	1	1.2	29 <sup>A</sup> , 29 <sup>A</sup> , 27 <sup>A</sup>
		15.0 µg	30	6	1.3	36 <sup>A</sup> , 29 <sup>A</sup> , 24 <sup>A</sup>
		50.0 µL	23	4		26 <sup>A</sup> , 19 <sup>A</sup> , 25 <sup>A</sup>
TA98	2NF	1.00 µg	83	11	4.6	95 <sup>A</sup> , 73 <sup>A</sup> , 81 <sup>A</sup>
TA100	SA	1.00 µg	687	33	8.2	666 <sup>A</sup> , 725 <sup>A</sup> , 670 <sup>A</sup>
TA1535	SA	1.00 µg	648	30	36.0	617 <sup>A</sup> , 651 <sup>A</sup> , 677 <sup>A</sup>
TA1537	9AAD	75.0 µg	680	126	75.6	624 <sup>A</sup> , 592 <sup>A</sup> , 824 <sup>A</sup>
WP2uvrA	MMS	1000 µg	339	47	14.7	381 <sup>A</sup> , 288 <sup>A</sup> , 348 <sup>A</sup>

Key to Positive Controls

2NF 2-nitrofluorene  
 SA sodium azide  
 9AAD 9-Aminoacridine  
 MMS methyl methanesulfonate

Key to Automatic Count Flags

<sup>A</sup>: Automatic count

**TABLE 4**  
**Mutagenicity Assay with S9 activation**

Study Number: AE85CG.502ICH.BTL  
Experiment: Mutagenicity Assay (B1)  
Exposure Method: Plate incorporation assay

Study Code: AE85CG  
Date Plated: 4/26/2017  
Evaluation Period: 4/29/2017

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes	
TA98	TRV130 (b) (4) (u) (4)	5000 µg	29	6	1.0	30 <sup>A</sup> , 35 <sup>A</sup> , 23 <sup>A</sup>	
		1500 µg	23	4	0.8	27 <sup>A</sup> , 19 <sup>A</sup> , 24 <sup>A</sup>	
	DMSO	500 µg	32	1	1.1	31 <sup>A</sup> , 33 <sup>A</sup> , 31 <sup>A</sup>	
		150 µg	26	7	0.9	22 <sup>A</sup> , 34 <sup>A</sup> , 23 <sup>A</sup>	
		50.0 µg	26	5	0.9	21 <sup>A</sup> , 25 <sup>A</sup> , 31 <sup>A</sup>	
		15.0 µg	29	6	1.0	35 <sup>A</sup> , 29 <sup>A</sup> , 24 <sup>A</sup>	
		DMSO	50.0 µL	30	4		29 <sup>A</sup> , 27 <sup>A</sup> , 34 <sup>A</sup>
TA100	TRV130 (b) (4) (u) (4)	5000 µg	109	11	1.0	121 <sup>A</sup> 2, 100 <sup>A</sup> 2, 106 <sup>A</sup> 2	
		1500 µg	107	27	1.0	138 <sup>A</sup> , 89 <sup>A</sup> , 93 <sup>A</sup>	
	DMSO	500 µg	114	5	1.0	111 <sup>A</sup> , 111 <sup>A</sup> , 119 <sup>A</sup>	
		150 µg	112	12	1.0	101 <sup>A</sup> , 124 <sup>A</sup> , 112 <sup>A</sup>	
		50.0 µg	120	17	1.1	109 <sup>A</sup> , 112 <sup>A</sup> , 139 <sup>A</sup>	
		15.0 µg	103	14	0.9	108 <sup>A</sup> , 87 <sup>A</sup> , 114 <sup>A</sup>	
		DMSO	50.0 µL	112	5		116 <sup>A</sup> , 114 <sup>A</sup> , 106 <sup>A</sup>
TA1535	TRV130 (b) (4) (u) (4)	5000 µg	12	9	0.6	5 <sup>A</sup> , 22 <sup>A</sup> , 10 <sup>A</sup>	
		1500 µg	14	2	0.7	16 <sup>A</sup> , 13 <sup>A</sup> , 13 <sup>A</sup>	
	DMSO	500 µg	17	5	0.9	22 <sup>A</sup> , 15 <sup>A</sup> , 13 <sup>A</sup>	
		150 µg	15	7	0.8	23 <sup>A</sup> , 10 <sup>A</sup> , 13 <sup>A</sup>	
		50.0 µg	12	3	0.6	10 <sup>A</sup> , 11 <sup>A</sup> , 16 <sup>A</sup>	
		15.0 µg	14	3	0.7	17 <sup>A</sup> , 14 <sup>A</sup> , 11 <sup>A</sup>	
		DMSO	50.0 µL	19	7		18 <sup>A</sup> , 13 <sup>A</sup> , 27 <sup>A</sup>
TA1537	TRV130 (b) (4) (u) (4)	5000 µg	9	6	0.9	3 <sup>A</sup> , 11 <sup>A</sup> , 14 <sup>A</sup>	
		1500 µg	10	4	1.0	15 <sup>A</sup> , 8 <sup>A</sup> , 7 <sup>A</sup>	
	DMSO	500 µg	8	4	0.8	6 <sup>A</sup> , 13 <sup>A</sup> , 6 <sup>A</sup>	
		150 µg	12	4	1.2	15 <sup>A</sup> , 7 <sup>A</sup> , 13 <sup>A</sup>	
		50.0 µg	9	1	0.9	10 <sup>A</sup> , 8 <sup>A</sup> , 10 <sup>A</sup>	
		15.0 µg	10	4	1.0	11 <sup>A</sup> , 5 <sup>A</sup> , 13 <sup>A</sup>	
		DMSO	50.0 µL	10	4		6 <sup>A</sup> , 10 <sup>A</sup> , 13 <sup>A</sup>

**Key to Automatic Count Flags**

<sup>A</sup>: Automatic count



**Key Study Findings**

The results of the study indicate that TRV130 (b) (4) impurity was negative for the ability to induce reverse mutations at selected loci of several strains of *Salmonella typhimurium* and at the tryptophan locus of *Escherichia coli* strain WP2 *uvrA* in the presence and absence of an exogenous metabolic activation system. Toxicity was observed beginning at 1500 or at 5000 mcg per plate with some of the tester strains in the presence and absence of S9 activation.

**Methods**

- Strains: TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA*
- Concentrations in definitive study: 15.0, 50.0, 150, 500, 1500, and 5000 mcg per plate.
- Basis of concentration selection: In a dosing-range finding study, no precipitate was observed up to 5000 mcg/plate and toxicity was observed beginning at 3333 mcg per plate with tester strains TA100 and TA1535 in the presence and absence of S9 activation. A 1.9-fold maximum increase was observed with tester strain TA98 in the presence of S9 activation. Based upon these results, the maximum dose tested in the mutagenicity assay was 5000 mcg per plate.
- Negative control: DMSO
- Positive control: See the table below:

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4)	1.0
TA100, TA1537		Lot No. STBD3302V Exp. Date 31-Jul-2017 CAS No. 613-13-8 Purity 97.5%	2.0
WP2 <i>uvrA</i>			15
TA98	None	2-nitrofluorene (b) (4)	1.0
		Lot No. S43858V Exp. Date 31-Mar-2019 CAS No. 607-57-8 Purity 99.4%	
TA100, TA1535		sodium azide (b) (4)	1.0
		Lot No. MKBT8080V Exp. Date Jan-2020 CAS No. 26628-22-8 Purity 99.8%	
TA1537		9-aminoacridine (b) (4)	75
	Lot No. BCBK1177V Exp. Date 31-Mar-2019 CAS No. 52417-22-8 Purity 99.5%		
WP2 <i>uvrA</i>	methyl methanesulfonate (b) (4)	1,000	
	Lot No. MKBR6050V Exp. Date 31-Mar-2018 CAS No. 66-27-3 Purity 100.0%		

- Formulation/Vehicle:
- DMSO for the test article
  - All positive controls were diluted in dimethyl sulfoxide (DMSO) except for sodium azide, which was diluted in sterile water.

Incubation & sampling time: The test system was exposed to the test article via the plate incorporation methodology. There were 3 plates per dose in the presence and absence of metabolic activation. The metabolic activation system consisted of an S-9 fraction prepared from livers obtained from Aroclor 1254 pretreated male Sprague-Dawley rats. The S-9

percentage was 10%, which is within the acceptable range. Plates were incubated at 37°C for 2-3 days. Plates that were not counted immediately following the incubation period were stored at 2-8°C until colony counting could be conducted. The condition of the bacterial background lawn was evaluated for evidence of test article toxicity by using a dissecting microscope. Precipitate was evaluated after the incubation period by visual examination without magnification. As appropriate, colonies were enumerated either by hand or by machine.

### **Study Validity**

- Selection of bacterial tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A, April 1996).
- Positive controls produced expected responses.
- Dose selection for the plate incorporation method was adequate based upon use of the limit dose of 5000 mcg/plate.
- The S9 concentration was within acceptable limits.

### **Results**

- No precipitate was observed. Toxicity was observed beginning at 1500 or at 5000 mcg per plate with tester strains TA100, TA1535, and TA1537 in the presence and absence of S9 activation.
- As shown in the table below, all positive and vehicle control values were within acceptable ranges, and all criteria for a valid assay were met.
- As shown in the table below, the test article elicited no positive mutagenic responses in any of the tester strains in either the presence or absence of S9 activation.

**TABLE 3**  
Mutagenicity Assay without S9 activation

Study Number: AE85CF.502ICH.BTL			Study Code: AE85CF			
Experiment: Mutagenicity Assay (B1)			Date Plated: 4/25/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 4/29/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	(b) (4)	5000 µg	17	0	1.1	17 <sup>A</sup> , 17 <sup>A</sup> , 17 <sup>A</sup>
		1500 µg	17	8	1.1	24 <sup>A</sup> , 19 <sup>A</sup> , 9 <sup>A</sup>
		500 µg	16	2	1.0	13 <sup>A</sup> , 17 <sup>A</sup> , 17 <sup>A</sup>
		150 µg	15	2	0.9	13 <sup>A</sup> , 16 <sup>A</sup> , 16 <sup>A</sup>
		50.0 µg	17	3	1.1	19 <sup>A</sup> , 14 <sup>A</sup> , 18 <sup>A</sup>
		15.0 µg	22	4	1.4	19 <sup>A</sup> , 26 <sup>A</sup> , 22 <sup>A</sup>
TA100	(b) (4)	5000 µg	0	0	0.0	0 <sup>M</sup> 4, 0 <sup>M</sup> 4, 0 <sup>M</sup> 4
		1500 µg	65	6	0.7	68 <sup>A</sup> 3, 70 <sup>A</sup> 3, 58 <sup>A</sup> 3
		500 µg	89	12	1.0	82 <sup>A</sup> , 103 <sup>A</sup> , 83 <sup>A</sup>
		150 µg	92	8	1.0	100 <sup>A</sup> , 91 <sup>A</sup> , 84 <sup>A</sup>
		50.0 µg	90	11	1.0	93 <sup>A</sup> , 99 <sup>A</sup> , 78 <sup>A</sup>
		15.0 µg	97	17	1.1	99 <sup>A</sup> , 113 <sup>A</sup> , 80 <sup>A</sup>
TA1535	(b) (4)	5000 µg	0	0	0.0	0 <sup>M</sup> 4, 0 <sup>M</sup> 4, 0 <sup>M</sup> 4
		1500 µg	13	2	0.8	13 <sup>A</sup> 2, 15 <sup>A</sup> 2, 11 <sup>A</sup> 2
		500 µg	19	6	1.2	17 <sup>A</sup> , 14 <sup>A</sup> , 26 <sup>A</sup>
		150 µg	13	4	0.8	17 <sup>A</sup> , 10 <sup>A</sup> , 13 <sup>A</sup>
		50.0 µg	14	4	0.9	17 <sup>A</sup> , 14 <sup>A</sup> , 10 <sup>A</sup>
		15.0 µg	14	3	0.9	15 <sup>A</sup> , 17 <sup>A</sup> , 11 <sup>A</sup>
TA1537	(b) (4)	5000 µg	4	2	0.5	3 <sup>A</sup> 3, 6 <sup>A</sup> 3, 3 <sup>A</sup> 3
		1500 µg	10	1	1.3	10 <sup>A</sup> , 9 <sup>A</sup> , 11 <sup>A</sup>
		500 µg	13	4	1.6	16 <sup>A</sup> , 14 <sup>A</sup> , 9 <sup>A</sup>
		150 µg	12	2	1.5	10 <sup>A</sup> , 14 <sup>A</sup> , 11 <sup>A</sup>
		50.0 µg	9	0	1.1	9 <sup>A</sup> , 9 <sup>A</sup> , 9 <sup>A</sup>
		15.0 µg	9	3	1.1	5 <sup>A</sup> , 14 <sup>A</sup> , 8 <sup>A</sup>
DMSO	(b) (4)	100 µL	8	3		5 <sup>A</sup> , 10 <sup>A</sup> , 8 <sup>A</sup>

Key to Plate Postfix Codes	
4	Extremely reduced background
3	Moderately reduced background
2	Slightly reduced background

Key to Automatic & Manual Count Flags	
<sup>M</sup>	Manual count
<sup>A</sup>	Automatic count

**TABLE 3 (CONT.)**  
**Mutagenicity Assay without S9 activation**

Study Number: AE85CF.502ICH.BTL			Study Code: AE85CF			
Experiment: Mutagenicity Assay (B1)			Date Plated: 4/25/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 4/29/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA		5000 µg	32	3	1.0	34 <sup>A</sup> , 29 <sup>A</sup> , 34 <sup>A</sup>
		1500 µg	29	5	0.9	35 <sup>A</sup> , 26 <sup>A</sup> , 27 <sup>A</sup>
	TRV130 impurity (b) (4)	500 µg	31	5	1.0	34 <sup>A</sup> , 25 <sup>A</sup> , 34 <sup>A</sup>
		150 µg	33	8	1.0	24 <sup>A</sup> , 39 <sup>A</sup> , 35 <sup>A</sup>
		50.0 µg	28	6	0.9	25 <sup>A</sup> , 35 <sup>A</sup> , 24 <sup>A</sup>
	DMSO	15.0 µg	31	6	1.0	30 <sup>A</sup> , 38 <sup>A</sup> , 26 <sup>A</sup>
		100 µL	32	8		29 <sup>A</sup> , 27 <sup>A</sup> , 41 <sup>A</sup>
TA98	2NF	1.00 µg	80	29	5.0	109 <sup>A</sup> , 51 <sup>A</sup> , 80 <sup>A</sup>
TA100	SA	1.00 µg	920	75	10.5	936 <sup>A</sup> , 986 <sup>A</sup> , 838 <sup>A</sup>
TA1535	SA	1.00 µg	816	31	51.0	807 <sup>A</sup> , 850 <sup>A</sup> , 791 <sup>A</sup>
TA1537	9AAD	75.0 µg	675	116	84.4	693 <sup>A</sup> , 552 <sup>A</sup> , 781 <sup>A</sup>
WP2uvrA	MMS	1000 µg	384	17	12.0	390 <sup>A</sup> , 365 <sup>A</sup> , 398 <sup>A</sup>

**Key to Positive Controls**

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

**Key to Automatic Count Flags**

<sup>A</sup>: Automatic count

**TABLE 4**  
Mutagenicity Assay with S9 activation

Study Number: AE85CF.502ICH.BTL			Study Code: AE85CF			
Experiment: Mutagenicity Assay (B1)			Date Plated: 4/25/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 4/29/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98		5000 µg	26	3	1.0	25 <sup>A</sup> , 30 <sup>A</sup> , 24 <sup>A</sup>
		1500 µg	26	9	1.0	35 <sup>A</sup> , 17 <sup>A</sup> , 26 <sup>A</sup>
	TRV130 impurity (b) (4)	500 µg	28	3	1.1	32 <sup>A</sup> , 26 <sup>A</sup> , 26 <sup>A</sup>
		150 µg	23	4	0.9	26 <sup>A</sup> , 18 <sup>A</sup> , 25 <sup>A</sup>
		50.0 µg	30	4	1.2	34 <sup>A</sup> , 26 <sup>A</sup> , 30 <sup>A</sup>
	DMSO	15.0 µg	27	5	1.0	27 <sup>A</sup> , 23 <sup>A</sup> , 32 <sup>A</sup>
		100 µL	26	3		29 <sup>A</sup> , 24 <sup>A</sup> , 25 <sup>A</sup>
TA100		5000 µg	0	0	0.0	0 <sup>M</sup> 4, 0 <sup>M</sup> 4, 0 <sup>M</sup> 4
		1500 µg	106	9	1.0	116 <sup>A</sup> 3, 101 <sup>A</sup> 3, 100 <sup>A</sup> 3
	TRV130 impurity (b) (4)	500 µg	116	20	1.0	138 <sup>A</sup> , 111 <sup>A</sup> , 100 <sup>A</sup>
		150 µg	114	5	1.0	120 <sup>A</sup> , 111 <sup>A</sup> , 112 <sup>A</sup>
		50.0 µg	101	6	0.9	105 <sup>A</sup> , 95 <sup>A</sup> , 104 <sup>A</sup>
	DMSO	15.0 µg	120	5	1.1	125 <sup>A</sup> , 115 <sup>A</sup> , 120 <sup>A</sup>
		100 µL	111	5		105 <sup>A</sup> , 115 <sup>A</sup> , 113 <sup>A</sup>
TA1535		5000 µg	0	0	0.0	0 <sup>M</sup> 4, 0 <sup>M</sup> 4, 0 <sup>M</sup> 4
		1500 µg	15	2	0.9	16 <sup>A</sup> 3, 13 <sup>A</sup> 3, 16 <sup>A</sup> 3
	TRV130 impurity (b) (4)	500 µg	13	2	0.8	15 <sup>A</sup> , 13 <sup>A</sup> , 11 <sup>A</sup>
		150 µg	18	3	1.1	18 <sup>A</sup> , 21 <sup>A</sup> , 15 <sup>A</sup>
		50.0 µg	17	3	1.0	19 <sup>A</sup> , 13 <sup>A</sup> , 18 <sup>A</sup>
	DMSO	15.0 µg	19	2	1.1	18 <sup>A</sup> , 22 <sup>A</sup> , 18 <sup>A</sup>
		100 µL	17	1		18 <sup>A</sup> , 17 <sup>A</sup> , 17 <sup>A</sup>
TA1537		5000 µg	10	2	0.9	11 <sup>A</sup> 3, 10 <sup>A</sup> 3, 8 <sup>A</sup> 3
		1500 µg	10	2	0.9	11 <sup>A</sup> , 11 <sup>A</sup> , 8 <sup>A</sup>
	TRV130 impurity (b) (4)	500 µg	12	2	1.1	13 <sup>A</sup> , 14 <sup>A</sup> , 10 <sup>A</sup>
		150 µg	11	2	1.0	13 <sup>A</sup> , 10 <sup>A</sup> , 9 <sup>A</sup>
		50.0 µg	14	3	1.3	16 <sup>A</sup> , 16 <sup>A</sup> , 11 <sup>A</sup>
	DMSO	15.0 µg	13	3	1.2	17 <sup>A</sup> , 11 <sup>A</sup> , 11 <sup>A</sup>
		100 µL	11	4		15 <sup>A</sup> , 8 <sup>A</sup> , 9 <sup>A</sup>

Key to Plate Postfix Codes

- 4 Extremely reduced background
- 3 Moderately reduced background

Key to Automatic & Manual Count Flags

- <sup>M</sup>: Manual count
- <sup>A</sup>: Automatic count

**TABLE 4 (CONT.)**  
**Mutagenicity Assay with S9 activation**

Study Number: AE85CF.502ICH.BTL			Study Code: AE85CF			
Experiment: Mutagenicity Assay (B1)			Date Plated: 4/25/2017			
Exposure Method: Plate incorporation assay			Evaluation Period: 4/29/2017			
Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA		5000 µg	30	3	0.8	27 <sup>A</sup> , 32 <sup>A</sup> , 32 <sup>A</sup>
		1500 µg	32	3	0.9	29 <sup>A</sup> , 33 <sup>A</sup> , 34 <sup>A</sup>
	TRV130 impurity <sup>(b) (4)</sup>	500 µg	32	8	0.9	24 <sup>A</sup> , 39 <sup>A</sup> , 33 <sup>A</sup>
		150 µg	38	3	1.1	40 <sup>A</sup> , 35 <sup>A</sup> , 39 <sup>A</sup>
		50.0 µg	33	10	0.9	21 <sup>A</sup> , 40 <sup>A</sup> , 38 <sup>A</sup>
	DMSO	15.0 µg	32	3	0.9	34 <sup>A</sup> , 32 <sup>A</sup> , 29 <sup>A</sup>
100 µL		36	6		39 <sup>A</sup> , 40 <sup>A</sup> , 29 <sup>A</sup>	
TA98	2AA	1.00 µg	274	14	10.5	272 <sup>A</sup> , 261 <sup>A</sup> , 288 <sup>A</sup>
TA100	2AA	2.00 µg	926	26	8.3	944 <sup>A</sup> , 938 <sup>A</sup> , 897 <sup>A</sup>
TA1535	2AA	1.00 µg	131	8	7.7	136 <sup>A</sup> , 122 <sup>A</sup> , 136 <sup>A</sup>
TA1537	2AA	2.00 µg	59	3	5.4	58 <sup>A</sup> , 62 <sup>A</sup> , 57 <sup>A</sup>
WP2uvrA	2AA	15.0 µg	471	42	13.1	428 <sup>A</sup> , 475 <sup>A</sup> , 511 <sup>A</sup>

Key to Positive Controls

2AA 2-aminoanthracene

Key to Automatic Count Flags

<sup>A</sup>: Automatic count

**9.1.2.2 In Vitro Assays in Mammalian Cells**

**Study Title:** (b) (4) : *In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)*

Study no.: AE85CE.348ICH.BTL  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\ae85ce-348ich-bt\ae85ce-348ich-btl-study-report.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: 3/2017  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: (b) (4); % assigned purity as free base= (b) (4) %  
 Dose formulations were adjusted to compensate for the potency ( (b) (4) %) of the test article, using a correction factor of (b) (4).

**Key Study Findings**

The results of the study indicate (b) (4) was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system up to the limit dose.

**Methods**

Cell line: Human peripheral blood lymphocytes  
 Concentrations in definitive study: 15, 35, 65, 130, and 260 mcg/mL  
 Basis of concentration selection: In the preliminary toxicity assay, the doses tested ranged from 0.026 to 260 mcg/mL (1 mM) which is the limit dose for this assay. Cytotoxicity [ $\geq$  45% cytokinesis-blocked proliferation index (CBPI) relative to the vehicle control] was not observed at any dose in any of the treatment conditions. Based upon these results, the doses chosen for the micronucleus assay ranged from 15 to 260 mcg/mL for all three treatment conditions.  
 Negative control: Sterile water  
 Positive control:
 

- Vinblastine (VB) for the test system without S9; Dissolved and diluted in sterile water for a final concentration of 5, 7.5, and 10 ng/mL

- Cyclophosphamide (CP) for the test system with S9; Dissolved and diluted in sterile water for a final concentration of 2.5, 5 and 7.5 mcg/mL
- Since the non-activated and S9-activated treatments were tested concurrently, the positive control for the non-activated 4-hour exposure groups was eliminated.

Formulation/Vehicle: Sterile Water

Incubation & sampling time: Exposure conditions used in the study is shown in the table below:

Treatment Condition	Treatment Time	Recovery Time	Doses (µg/mL)
Non-activated	4 hr	20 hr	15, 35, 65, 130, 260
	24 hr	0 hr	15, 35, 65, 130, 260
S9-activated	4 hr	20 hr	15, 35, 65, 130, 260

After the 4-hour treatment in the non-activated and the S9-activated studies, the cells were centrifuged, the treatment medium was aspirated, the cells were then washed with calcium and magnesium free phosphate buffered saline (CMF-PBS), re-fed with complete medium containing cytoB at 6.0 mcg/mL and returned to the incubator under standard conditions. For the 24-hour treatment in the non-activated study, cytoB (6.0 mcg/mL) was added at the beginning of the treatment and cells were collected after being exposed to cyto B for 24 hours ( $\pm$  30 minutes), 1.5 to 2 normal cell cycles, to ensure identification and selective analysis of micronucleus frequency in cells that have completed one mitosis evidenced by binucleated cells. The cyto B exposure time for the 4-hour treatment in the non-activated and the S9-activated studies was 20 hours ( $\pm$  30 minutes).

### Study Validity

The study is valid based on the following criteria:

- The appropriate positive and negative controls were employed according OECD guidelines 487.
- The S9 concentration was within acceptable limits.
- The dose selection criteria used are acceptable.
- The test article doses selected for scoring showed appropriate toxicities and the slides were scored blind.

- The appropriate number of cells was evaluated from two replicates of each test concentrations in accordance with the current practice (at least 2000 binucleated cells per concentration or at least 1000 binucleated cells per culture; two cultures per concentration were scored blind).
- The frequencies of micronuclei in the concurrent negative and positive controls were within the historical control ranges.

## Results

- In the micronucleus assay, cytotoxicity ( $\geq 45\%$  CBPI relative to the vehicle control) was not observed at any dose in any of the treatment conditions.
- As shown in the table below, no significant or dose-dependent increases in micronuclei induction were observed in treatment groups with or without S9 ( $p > 0.05$ ; Fisher's Exact and Cochran-Armitage tests).

TABLE 7  
MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
WITH (b) (4) IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment $\mu\text{g/mL}$	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
Water	A	1000	0.40%	0.30%
	B	1000	0.20%	
(b) (4) 65	A	1000	0.20%	0.25%
	B	1000	0.30%	
130	A	1000	0.20%	0.20%
	B	1000	0.20%	
260	A	1000	0.20%	0.15%
	B	1000	0.10%	

TABLE 8  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH (b) (4) IN THE PRESENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
Water	A	1000	0.50%	0.35%
	B	1000	0.20%	
(b) (4) 65	A	1000	0.10%	0.20%
	B	1000	0.30%	
130	A	1000	0.30%	0.25%
	B	1000	0.20%	
260	A	1000	0.10%	0.15%
	B	1000	0.20%	
CP, 7.5	A	1000	1.10%	1.15%**
	B	1000	1.20%	

\*\* p ≤ 0.01, Fisher's exact test, relative to the solvent control.

TABLE 9  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH (b) (4) IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 24-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
Water	C	1000	0.20%	0.20%
	D	1000	0.20%	
(b) (4) 65	C	1000	0.10%	0.15%
	D	1000	0.20%	
130	C	1000	0.30%	0.30%
	D	1000	0.30%	
260	C	1000	0.30%	0.25%
	D	1000	0.20%	
VB, 10 ng/mL	C	1000	1.80%	1.70%**
	D	1000	1.60%	

\*\* p ≤ 0.01, Fisher's exact test, relative to the solvent control.

**Study Title:** (b) (4) : *In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)*

Study no.: AE95MG.348ICH.BTL  
Study report location: <\\cdsesub1\levsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\ae95mg-348ich-btl\ae95mg-348ich-btl-study-report.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: 7/2017  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: (b) (4); % Assigned purity = (b) (4) %  
Dose formulations were adjusted to compensate for the purity ((b) (4) %) of the test article, using a correction factor of (b) (4) .

**Key Study Findings**

The results of the study indicate (b) (4) was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system up to the limit dose.

**Methods**

Cell line: Human peripheral blood lymphocytes  
Concentrations in definitive study: 1, 13, and 114 mcg/mL  
Basis of concentration selection: In the preliminary toxicity assay, the doses tested ranged from 0.0114 to 114 mcg/mL (1 mM) which is the limit dose for this assay. Cytotoxicity [ $\geq$  45% cytokinesis-blocked proliferation index (CBPI) relative to the vehicle control] was not observed at any dose in the non-activated and S9-activated 4-hour exposure groups. Cytotoxicity was observed at 114 mcg/mL in the non-activated 24-hour exposure group. Based upon these results, the doses chosen for the micronucleus assay ranged from 0.3 to 114 mcg/mL for all three treatment groups.  
Negative control: DMSO

- Positive control:
- Vinblastine (VB) for the test system without S9; Dissolved and diluted in sterile water for a final concentration of 5, 7.5, and 10 ng/mL
  - Cyclophosphamide (CP) for the test system with S9; Dissolved and diluted in sterile water for a final concentration of 2.5, 5 and 7.5 mcg/mL
  - Since the non-activated and S9-activated treatments were tested concurrently, the positive control for the non-activated 4-hour exposure groups was eliminated.

Formulation/Vehicle: DMSO

Incubation & sampling time: Exposure conditions used in the study is shown in the table below:

Treatment Condition	Treatment Time	Recovery Time	Doses ( $\mu\text{g/mL}$ )
Non-activated	4 hr	20 hr	15, 35, 65, 130, 260
	24 hr	0 hr	15, 35, 65, 130, 260
S9-activated	4 hr	20 hr	15, 35, 65, 130, 260

After the 4-hour treatment in the non-activated and the S9-activated studies, the cells were centrifuged, the treatment medium was aspirated, the cells were then washed with calcium and magnesium free phosphate buffered saline (CMF-PBS), re-fed with complete medium containing cytoB at 6.0 mcg/mL and returned to the incubator under standard conditions. For the 24-hour treatment in the non-activated study, cytoB (6.0 mcg/mL) was added at the beginning of the treatment and cells were collected after being exposed to cyto B for 24 hours ( $\pm 30$  minutes), 1.5 to 2 normal cell cycles, to ensure identification and selective analysis of micronucleus frequency in cells that have completed one mitosis evidenced by binucleated cells. The cyto B exposure time for the 4-hour treatment in the non-activated and the S9-activated studies was 20 hours ( $\pm 30$  minutes).

### Study Validity

The study is valid based on the following criteria.

- The appropriate positive and negative controls were employed according OECD guidelines 487.
- The S9 concentration was within acceptable limits.
- The dose selection criteria used are acceptable.

- The test article doses selected for scoring showed appropriate toxicities and the slide were scored blind.
- The appropriate number of cells was evaluated from two replicates of each test concentrations in accordance with the current practice (at least 2000 binucleated cells per concentration or at least 1000 binucleated cells per culture; two cultures per concentration were scored blind).
- The frequencies of micronuclei in the concurrent negative and positive controls were within the historical control ranges.

### **Results**

- In the micronucleus assay, cytotoxicity ( $\geq 45\%$  CBPI relative to the vehicle control) was not observed at any dose in any of the three treatment conditions.
- As shown in the table below, no significant or dose-dependent increases in micronuclei induction were observed in treatment groups with or without S9 ( $p > 0.05$ ; Fisher's Exact and Cochran-Armitage tests).

TABLE 7

MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED WITH (b) (4) IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment $\mu\text{g/mL}$	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.50%	0.40%
	B	1000	0.30%	
(b) (4) 1	A	1000	0.40%	0.40%
	B	1000	0.40%	
13	A	1000	0.50%	0.55%
	B	1000	0.60%	
114	A	1000	0.60%	0.55%
	B	1000	0.50%	

TABLE 8  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH (b) (4) IN THE PRESENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.50%	0.50%
	B	1000	0.50%	
(b) (4) 1	A	1000	0.20%	0.25%
	B	1000	0.30%	
13	A	1000	0.40%	0.35%
	B	1000	0.30%	
114	A	1000	0.20%	0.25%
	B	1000	0.30%	
CP, 2.5	A	1000	1.30%	1.45%**
	B	1000	1.60%	

\*\*  $p \leq 0.01$ , Fisher's exact test, relative to the solvent control.

TABLE 9  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH (b) (4) IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 24-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.50%	0.60%
	B	1000	0.70%	
(b) (4) 1	A	1000	0.20%	0.25%
	B	1000	0.30%	
13	A	1000	0.40%	0.40%
	B	1000	0.40%	
114	A	1000	0.60%	0.55%
	B	1000	0.50%	
VB, 7.5 ng/mL	A	1000	1.70%	1.55%**
	B	1000	1.40%	

\*\* p ≤ 0.01, Fisher's exact test, relative to the solvent control.

**Study Title: TRV130 (b) (4): In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)**

Study no.: AE85CG.348ICH.BTL  
Study report location: [\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\ae85cg-348ich-btl\ae85cg-348ich-btl-study-report.pdf](#)

Conducting laboratory and location: (b) (4)

Date of study initiation: 2/2017  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: TRV130 (b) (4); % Assigned purity = (b) (4) %  
Dose formulations were adjusted to compensate for the purity ( (b) (4) %) of the test article, using a correction factor of (b) (4) .

**Key Study Findings**

The results of the study indicate TRV130 (b) (4) was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system up to the limit dose or the highest evaluated dose that induced approximately 45% cytotoxicity relative to the vehicle control group.

**Methods**

- Cell line: Human peripheral blood lymphocytes
- Concentrations in definitive study:
- 75, 150, and 387 mcg/mL for the non-activated 4-hour exposure group
  - 25, 75, and 387 mcg/mL for the S9-activated 4-hour exposure group
  - 5, 100, and 200 mcg/mL for the non-activated 24-hour exposure group

Basis of concentration selection: In the preliminary toxicity assay, the doses tested ranged from 0.0387 to 387 mcg/mL (1 mM) which is the limit dose for this assay. Cytotoxicity [≥ 45% cytokinesis-blocked proliferation index (CBPI) relative to the vehicle control] was not observed at any dose in the non-activated and S9-activated 4-hour exposure groups. Cytotoxicity (88% CBPI relative to the vehicle control) was observed at 387 mcg/mL in the non-activated 24-hour exposure group. Based upon these

results, the doses chosen for the micronucleus assay ranged from 1 to 387 mcg/mL for the non-activated and S9-activated 4-hour exposure groups, and from 0.1 to 300 mcg/mL for the non-activated 24-hour exposure group.

Negative control: DMSO

- Positive control:
- Vinblastine (VB) for the test system without S9; Dissolved and diluted in sterile water for a final concentration of 5, 7.5, and 10 ng/mL
  - Cyclophosphamide (CP) for the test system with S9; Dissolved and diluted in sterile water for a final concentration of 2.5, 5 and 7.5 mcg/mL
  - Since the non-activated and S9-activated treatments were tested concurrently, the positive control for the non-activated 4-hour exposure groups was eliminated.

Formulation/Vehicle: DMSO

Incubation & sampling time: Exposure conditions used in the study is shown in the table below:

Treatment Condition	Treatment Time	Recovery Time	Doses ( $\mu\text{g/mL}$ )
Non-activated	4 hr	20 hr	15, 35, 65, 130, 260
	24 hr	0 hr	15, 35, 65, 130, 260
S9-activated	4 hr	20 hr	15, 35, 65, 130, 260

After the 4-hour treatment in the non-activated and the S9-activated studies, the cells were centrifuged, the treatment medium was aspirated, the cells were then washed with calcium and magnesium free phosphate buffered saline (CMF-PBS), re-fed with complete medium containing cytoB at 6.0 mcg/mL and returned to the incubator under standard conditions. For the 24-hour treatment in the non-activated study, cytoB (6.0 mcg/mL) was added at the beginning of the treatment and cells were collected after being exposed to cyto B for 24 hours ( $\pm 30$  minutes), 1.5 to 2 normal cell cycles, to ensure identification and selective analysis of micronucleus frequency in cells that have completed one mitosis evidenced by binucleated cells. The cytoB exposure time for the 4-hour treatment in the non-activated and the S9-activated studies was 20 hours ( $\pm 30$  minutes).

### Study Validity

The study is valid based on the following criteria.

- The appropriate positive and negative controls were employed according OECD guidelines 487.
- The S9 concentration was within acceptable limits.

- The dose selection criteria used are acceptable.
- The test article doses selected for scoring showed appropriate toxicities and the slide were scored blind.
- The appropriate number of cells was evaluated from two replicates of each test concentrations in accordance with the current practice (at least 2000 binucleated cells per concentration or at least 1000 binucleated cells per culture; two cultures per concentration were scored blind).
- The frequencies of micronuclei in the concurrent negative and positive controls were within the historical control ranges.

## Results

- In the micronucleus assay, cytotoxicity ( $\geq 45\%$  CBPI relative to the vehicle control) was observed as following:

Treatment Condition	Treatment Time	Highest Evaluated Dose ( $\mu\text{g/mL}$ )	Cytotoxicity (%)
Non-activated	4 hr	387	19
	24 hr	200	54
S9-activated	4 hr	387	4

- As shown in the table below, no significant or dose-dependent increases in micronuclei induction were observed in treatment groups with or without S9 ( $p > 0.05$ ; Fisher's Exact and Cochran-Armitage tests).

TABLE 7  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH TRV130 (b) (4) THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment µg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.40%	0.35%
	B	1000	0.30%	
TRV130 (b) (4) 75	A	1000	0.30%	0.30%
	B	1000	0.30%	
150	A	1000	0.40%	0.35%
	B	1000	0.30%	
387	A	1000	0.40%	0.35%
	B	1000	0.30%	

TABLE 8  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH TRV130 (b) (4) THE PRESENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.30%	0.35%
	B	1000	0.40%	
TRV130 (b) (4) 25	A	1000	0.40%	0.30%
	B	1000	0.20%	
75	A	1000	0.40%	0.45%
	B	1000	0.50%	
387	A	1000	0.30%	0.30%
	B	1000	0.30%	
CP, 7.5	A	1000	1.50%	1.55%**
	B	1000	1.60%	

\*\*  $p \leq 0.01$ , Fisher's exact test, relative to the solvent control.

TABLE 9  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH TRV130 (b) (4) THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 24-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.40%	0.35%
	B	1000	0.30%	
TRV130 (b) (4) 5	A	1000	0.30%	0.30%
	B	1000	0.30%	
100	A	1000	0.30%	0.40%
	B	1000	0.50%	
200	A	1000	0.40%	0.35%
	B	1000	0.30%	
VB, 10 ng/mL	A	1000	1.70%	2.20%**
	B	1000	2.70%	

\*\* p ≤ 0.01, Fisher's exact test, relative to the solvent control.

**Study Title: TRV130 (b) (4) Impurity: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)**

Study no.: AE85CF.348ICH.BTL  
 Study report location: <\\cdsesub1\evsprod\nda210730\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\ae85cf-348ich-btl\ae85cf-348ich-btl-study-report.pdf>

Conducting laboratory and location: (b) (4)

Date of study initiation: 2/2017  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: TRV130 (b) (4) impurity; (b) (4) %  
 Dose formulations were adjusted to compensate for the purity ( (b) (4) %) of the test article, using a correction factor of (b) (4).

**Key Study Findings**

The results of the study indicate TRV130 (b) (4) impurity was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system up to the highest evaluated dose that induced approximately 45% cytotoxicity relative to the vehicle control group.

**Methods**

Cell line: Human peripheral blood lymphocytes  
 Concentrations in definitive study:

Treatment Condition	Treatment Time	Recovery Time	Doses (µg/mL)
Non-activated	4 hr	20 hr	5, 75, 150, 200, 250, 275, 300, 350, 400, 500
	24 hr	0 hr	10, 20, 40, 60, 80, 100, 130, 150
S9-activated	4 hr	20 hr	5, 75, 150, 200, 250, 275, 300, 350, 400, 500

Basis of concentration selection: In the preliminary toxicity assay, the doses tested ranged from 0.05 to 500 mcg/mL (1 mM) that is the limit dose for this assay. Cytotoxicity [≥ 45% cytokinesis-blocked proliferation index (CBPI) relative to the vehicle control] was observed at 500 mcg/mL in the non-activated and S9-activated 4-hour exposure groups, and at doses ≥ 150 mcg/mL in the non-activated 24-hour exposure group. Based upon these results, the doses chosen for the micronucleus assay ranged from 5 to 500 mcg/mL for the non-activated and S9-activated 4-hour exposure groups, and from 10 to 150 mcg/mL for the non-activated 24-hour exposure group.

Negative control: DMSO

- Positive control:
- Vinblastine (VB) for the test system without S9; Dissolved and diluted in sterile water for a final concentration of 5, 7.5, and 10 ng/mL
  - Cyclophosphamide (CP) for the test system with S9; Dissolved and diluted in sterile water for a final concentration of 2.5, 5 and 7.5 mcg/mL
  - Since the non-activated and S9-activated treatments were tested concurrently, the positive control for the non-activated 4-hour exposure groups was eliminated.

Formulation/Vehicle: DMSO

Incubation & sampling time: Exposure conditions used in the study is shown in the table below:

Treatment Condition	Treatment Time	Recovery Time	Doses (µg/mL)
Non-activated	4 hr	20 hr	15, 35, 65, 130, 260
	24 hr	0 hr	15, 35, 65, 130, 260
S9-activated	4 hr	20 hr	15, 35, 65, 130, 260

After the 4-hour treatment in the non-activated and the S9-activated studies, the cells were centrifuged, the treatment medium was aspirated, the cells were then washed with calcium and magnesium free phosphate buffered saline (CMF-PBS), re-fed with complete medium containing cytoB at 6.0 mcg/mL and returned to the incubator under standard conditions. For the 24-hour treatment in the non-activated study, cytoB (6.0 mcg/mL) was added at the beginning of the treatment and cells were collected after being exposed to cytoB for 24 hours ( $\pm$  30 minutes), 1.5 to 2 normal cell cycles, to ensure identification and selective analysis of micronucleus frequency in cells that have completed one mitosis evidenced by binucleated cells. The cyto B exposure time for the 4-hour treatment in the non-activated and the S9-activated studies was 20 hours ( $\pm$  30 minutes).

### Study Validity

The study is valid based on the following criteria.

- The appropriate positive and negative controls were employed according OECD guidelines 487.
- The S9 concentration was within acceptable limits.
- The dose selection criteria used are acceptable.
- The test article doses selected for scoring showed appropriate toxicities and the slide were scored blind.

- The appropriate number of cells was evaluated from two replicates of each test concentrations in accordance with the current practice (at least 2000 binucleated cells per concentration (at least 1000 binucleated cells per culture; two cultures per concentration were scored blind).
- The frequencies of micronuclei in the concurrent negative and positive controls were within the historical control ranges.

## Results

- In the micronucleus assay, cytotoxicity (CBPI relative to the vehicle control) was observed as follows:

<b>Treatment Condition</b>	<b>Treatment Time</b>	<b>Highest Evaluated Dose (<math>\mu\text{g/mL}</math>)</b>	<b>Cytotoxicity (%)</b>
Non-activated	4 hr	200	55
	24 hr	80	49
S9-activated	4 hr	200	53

- As shown in the table below, no significant or dose-dependent increases in micronuclei induction were observed with or without S9 ( $p > 0.05$ ; Fisher's Exact and Cochran-Armitage tests) up to the highest evaluated dose (see table above) under the test conditions.

TABLE 7  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH TRV130 (b) (4) IMPURITY IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment µg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.60%	0.45%
	B	1000	0.30%	
TRV130 (b) (4) impurity 5	A	1000	0.30%	0.35%
	B	1000	0.40%	
75	A	1000	0.20%	0.35%
	B	1000	0.50%	
200	A	1000	0.40%	0.35%
	B	1000	0.30%	

TABLE 8  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH TRV130 (b) (4) IMPURITY IN THE PRESENCE OF  
 EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.40%	0.35%
	B	1000	0.30%	
TRV130 (b) (4) impurity 5	A	1000	0.40%	0.35%
	B	1000	0.30%	
150	A	1000	0.30%	0.30%
	B	1000	0.30%	
200	A	1000	0.30%	0.45%
	B	1000	0.60%	
CP, 7.5	A	1000	1.70%	1.65%**
	B	1000	1.60%	

\*\* p ≤ 0.01, Fisher's exact test, relative to the solvent control.

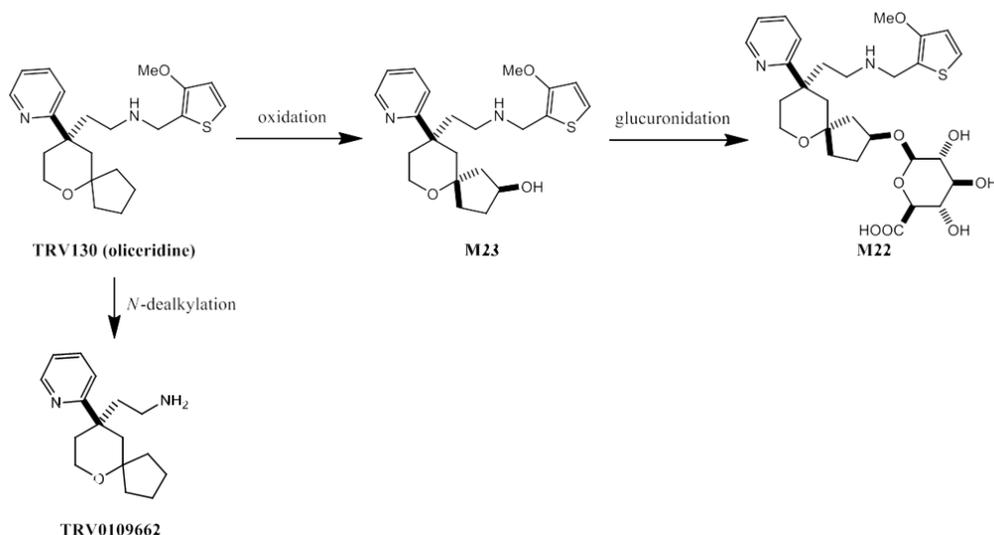
TABLE 9  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH TRV130 (b) (4) IMPURITY IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
 DEFINITIVE ASSAY: 24-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.40%	0.40%
	B	1000	0.40%	
TRV130 (b) (4) impurity 10	A	1000	0.40%	0.30%
	B	1000	0.20%	
40	A	1000	0.40%	0.35%
	B	1000	0.30%	
80	A	1000	0.30%	0.35%
	B	1000	0.40%	
VB, 10 ng/mL	A	1000	4.30%	4.60%**
	B	1000	4.90%	

\*\*  $p \leq 0.01$ , Fisher's exact test, relative to the solvent control.

## 9.2 Safety Evaluation of Major Human Metabolites:

Oliceridine is metabolized primarily by CYP3A4 and 2D6. *N*-dealkylation forms the primary amine, TRV0109662, and oxidation of the spirocycle ring forms M23 with subsequent glucuronidation to form the ether glucuronide, M22 (TRV0306954). Radiochemical and mass spectrometric profiling of plasma collected from clinical Study CP130-1007 (a single IV dose of [14C]-TRV130 administered to six healthy volunteers) showed that mean AUC values for M22 (61.9%) and TRV0109662 (17.4%) were greater than 10% of total drug-related material.

**Figure 8: Proposed Metabolic Pathways of TRV130 (Oliceridine)**

### 9.2.1 TRV0109662

TRV0109662 is the primary amine metabolite of TRV130. Radiochemical and mass spectrometric profiling of plasma collected from Clinical Study CP130-1007 showed that this metabolite accounts for 17.4% of total drug-related exposure. It was synthesized and tested in a battery of *in vitro* pharmacology and drug disposition assays.

The completed studies and reports are listed in the table below, and the key findings are discussed in greater detail following the table.

Table 21: Completed Studies Characterizing TRV0109662

Study Type	Study Number	Study Title
In Vitro Primary Pharmacology—Metabolite	TRV130-20	Characterization of TRV0109662 Activity in Cyclic AMP and $\beta$ -arrestin2 Assays at Human Mu-, Delta-, Kappa- and Nociceptin-Opioid Receptors
In Vitro Safety Pharmacology-FASTPatch Assay	180724.USF	Effects of Three Test Articles on Ion Channels Expressed in Mammalian Cells
Secondary Pharmacodynamics—Metabolite	100022039	In Vitro Pharmacology: Study of Compound TRV0109662
Distribution (Plasma Protein Binding)—Metabolite	TRE-R6505	In Vitro Protein Binding of TRV0109662 in Sprague-Dawley Rat, Cynomolgus Monkey and Human Plasma
Pharmacodynamic Drug Interaction—Metabolite	XT155061	In Vitro Evaluation of TRV0109662 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
Pharmacodynamic Drug Interaction—Metabolite	XT153041	In Vitro Evaluation of TRV130 and TRV0109662 as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes

Pharmacodynamic Drug Interaction—Metabolite	Trevena-03-01Sep2016	In vitro Interaction Studies of TRV0109662 with the Human BSEP, BCRP and MDR1 Efflux (ABC) Transporters, and with the Human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters
<b>Study Type</b>	<b>Study Number</b>	<b>Study Title</b>
Pharmacodynamic Drug Interaction—Metabolite	<a href="#">Trevena-03-01Sep2016</a>	In vitro Interaction Studies of TRV0109662 with the Human BSEP, BCRP and MDR1 Efflux (ABC) Transporters, and with the Human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters
Bioanalytical Method Validation—Metabolite	<a href="#">8334540</a>	Validation of a Method for the Determination of TRV110130 and TRV0109662 in Rat Plasma by HPLC with MS/MS Detection
Bioanalytical Method Validation—Metabolite	<a href="#">8334538</a>	Validation of a Method for the Determination of TRV110130 and TRV0109662 in Human Plasma by HPLC with MS/MS Detection
Single-Dose Pharmacokinetics—Metabolite	<a href="#">8346251</a>	Determination of TRV0109662 in Human Plasma Samples from CP130-1008 by HPLC with MS/MS Detection
Repeat-Dose Pharmacokinetics—Metabolite	<a href="#">XT150020</a>	Quantitation of TRV0109662 in Sprague-Dawley Rat, Cynomolgus Monkey and Human Plasma
(b) (4)		
Repeat-Dose Toxicology	<a href="#">8336088</a>	TRV130 (Oliceridine): 4-Week Continuous IV Infusion Toxicity and Toxicokinetic Study in Rats

### Pharmacological Characterization

- Primary pharmacology: The Applicant has characterized TRV0109662 as a selective, weak, partial agonist of the human MOR.
  - Study TRV130-20 showed that TRV0109662 stimulates G protein activation as measured by inhibition of forskolin-stimulated cAMP accumulation with an EC<sub>50</sub> at the human MOR of 5 mcM with low efficacy (span = 25% compared to reference full agonist ligand).
  - TRV0109662 shows negligible activity (not quantifiable) for β-arrestin2 recruitment at all receptors tested.

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Table 22: Summary of TRV0109622 Potency and Efficacy at Human Opioid Receptors

		cAMP					β-arrestin2				
		EC <sub>50</sub> (nM)	pEC <sub>50</sub>	SEM	Span	N	EC <sub>50</sub> (nM)	pEC <sub>50</sub>	SEM	Span	N
hMOR	TRV0109662	5012	5.3	0.11	25	32	N.Q.	N.Q.	N.Q.	N.Q.	32
	DAMGO	16	7.8	0.14	94	8	631	6.2	0.09	110	8
hKOR	TRV0109662	50119	4.3	0.24	12	32	N.Q.	N.Q.	N.Q.	N.Q.	32
	U69,593	2.5	8.6	0.07	91	8	631	6.2	0.03	117	8
hDOR	TRV0109662	63096	4.2	0.06	31	32	N.Q.	N.Q.	N.Q.	N.Q.	32
	DPDPE	0.3	9.5	0.09	95	8	50	7.3	0.02	104	8
hNOP	TRV0109662	6310	5.2	0.35	5	16	N.Q.	N.Q.	N.Q.	N.Q.	32
	Nociceptin	1	9	0.09	96	4	1000	6	0.03	121	8

- Secondary pharmacology:  
TRV0109662 showed negligible activity (i.e., <50% displacement of prototypical ligands) against a panel of 135 typical counter screen enzymes, receptors, channels, and neurotransmitter uptake transporters at concentrations up to 10 mcM (Study 100022039). The only significant interaction was at the human MOR, where 10 mcM TRV0109662 inhibited binding by 85%.

#### ***In Vitro Drug-Drug Interaction (DDI) Potential of TRV0109662***

- TRV0109662 is not a direct or time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 with half maximal inhibitory concentration (IC<sub>50</sub>) values >30 mcM (Study XT155061).
- There was no metabolism-dependent inhibition (>2-fold IC<sub>50</sub> shift after 30-minute preincubation with nicotinamide adenine dinucleotide phosphate [NADPH]) of any CYP isozyme; a 24% increase in inhibition of CYP2D6 was observed at the highest concentration tested (30 mcM).
- TRV0109662 did not increase CYP1A2, 2B6, or 3A4 messenger ribonucleic acid (mRNA) after incubation with three lots of human hepatocytes for 3 days at concentrations of up to 30 mcM (Study XT153041). Concentration-dependent increases in CYP2B6 activity were observed at 10 and 30 mcM TRV0109662; the significance of increased CYP2B6 activity in

the absence of increased mRNA is unclear, but the Applicant concluded that increased CYP2B6 activity at concentrations greater than 10  $\mu\text{M}$  is unlikely to be clinically relevant.

- TRV0109662 did not inhibit the transport of prototypical substrates for organic anion transporters (OAT1, OAT3, OATP1B1, OATP1B3), organic cation transporters (OCT1 and OCT2), multidrug and toxin extrusion proteins (MATE1 and MATE2-K), bile salt export pump (BSEP), breast cancer resistance protein (BCRP), or multidrug resistance protein 1 (MDR1) at concentrations of up to 300 nM (50-fold of the projected mean clinical  $C_{\text{max}}$  stated by the Applicant), the highest concentration tested (Study Trevena-03-01Sep2016).
- Although not determined directly, the concentrations used for the in vitro metabolism assays likely reflect the free (unbound) concentrations because TRV0109662 was not bound in plasma, ranging from 85% to 88% free in cynomolgus monkey to 95% to 101% free in humans and Sprague-Dawley rats at concentrations of 1 to 10 nM (Study TRE-R6505).

### ***Bioanalytical Assay Validations and Plasma Exposure (AUC) of TRV0109662***

From the NDA submission:

Initially, a fit-for-purpose high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) method was developed and utilized to quantify TRV0109662 concentrations in plasma collected from human subjects and rat and monkey samples collected from 14-day toxicology studies (Study XT150020). Subsequently, bioanalytical methods were validated in compliance with the 2001 FDA Guidance for Industry, Bioanalytical Method Validation (FDA 2001) and the 2012 European Medicines Agency (EMA) Guideline for Bioanalytical Method Validation (EMA 2012) and used to analyze human plasma samples (Study CP130-1008) and rat samples collected from two GLP-compliant toxicology studies (b) (4) 28-day toxicology study (Study 8336088). In these PK studies, plasma concentrations were measured with sensitive and selective HPLC-MS/MS assays validated to quantitate both TRV130 and TRV0109662 from the same sample using a stable isotope-labeled ( $^{13}\text{C}$  and  $^2\text{H}$ ) analog of oliceridine as the internal standard. The lower limit of quantification (LLOQ) in human plasma was 0.050 ng/mL for both analytes and the method was linear over the range of 0.050 to 50.0 ng/mL (Study 8334538), a range sufficient to capture the PK for both parent and metabolite. A bioanalytical assay was also validated for the concurrent quantitation of TRV130 and TRV0109662 in Sprague Dawley rat plasma, with a range of 0.100 to 100 ng/mL (Study 8334540).

The validated bioanalytical assay described above was subsequently used to quantify TRV0109662 plasma concentrations in human subjects dosed IV with a therapeutic (3 mg) or supratherapeutic (6 mg) dose of oliceridine in a thorough corrected QT interval (QTc) study (Study CP130-1008). Plasma  $C_{\text{max}}$  values ranged from 0.284 to 1.47 ng/mL following a 3-mg dose of oliceridine and 0.582 to 3.30 ng/mL following a 6 mg dose (Study 8346251).

These data were used to project TRV0109662 relative daily exposure ( $\text{AUC}_{0-24\text{h}}$ ). As shown in the Table 23 below, these exposure data were compared with data from the two rat toxicology studies to confirm that exposures (AUC) in at least one nonclinical toxicology species were greater than one-half of human exposure as recommended in the *ICH M3(R2) Guidance, Questions and Answers (FDA 2012)*.

Table 23. In Vivo Exposure to TRV0109662 in Human and GLP Toxicology Studies

	Mean AUC <sub>0-24h</sub> (ng*h/mL)	PK Source	Exposure Multiples (AUC animal/AUC human at MRHD of 40 mg)
28-day Rat Study 8336088	31.7	8336088	
Rat, embryo-fetal develop (b) (4) 141503	27.8	Extrapolated from 8336088	55%
Human (1.5 mg loading, 0.35 mg Q 0.2 h; MRHD of 43.5 mg/day) *	56		
Human: MRHD of 40 mg/day**	51		

## Note:

\*In response to the Agency's information request, the Applicant conducted another PK simulation based upon Phase 3 study dosing regimens, which resulted in plasma exposures to this metabolite approximately 34% higher than the original PK simulation data based upon a dose scheme of 1-3 mg/h.

\*\* Calculated proportionally from exposures at MRHD of 43.5 mg/day; The Applicant has assumed linearity in their PK simulations.

The validated rat bioanalytical assay was used to quantitate TRV0109662 in plasma samples from a 28-day continuous infusion toxicology study (Study 8336088) (b) (4)

(b) (4)

Mean daily exposure to TRV0109662 in a rat embryofetal development study (Study (b) (4) 141503) was 27.8 ng\*h/mL (PK data extrapolated from a 28-day rat toxicology study; Study 8336088), an exposure that was 55% of the projected maximum human exposure. As outlined in the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions and Answers*, it is appropriate for exposure to the metabolite in animals to be at least 50% the exposure seen in humans, and in some cases to exceed that in human when a metabolite composes the majority of the total human exposure. This metabolite constitutes 17.4% of the total drug exposure, thus reaching 50% of the human exposure in the animal toxicology samples would qualify this metabolite for safety. As summarized in Table 23, mean total exposure in rats was at least 50% of projected human exposure, thus qualifying TRV0109662 in one species used for general and developmental and reproductive toxicology endpoints if the measured plasma exposures are valid.

Incurred sample reanalysis (ISR) was successful for Study (b) (4) with **83%** of ISR samples met the acceptance criteria. However, ISR of samples from Study 8346251 (human) and 8336088 (rat) failed, with **62%** of the human ISR samples and **17%** of the rat ISR samples (4 out of 24 samples) meeting the acceptance criteria. The Study Reports (Study 8334538 and 8334540) from (b) (4) have indicated that the analytical methods are suitable for the determination of the parent and TRV0109662 in human and rat plasma, over the calibration range of 0.05 to 50 ng/mL for human plasma and 0.1 to 100 ng/mL for rat plasma. For the ISR samples, initial reported human concentrations ranged from 0.144 to 3.30 ng/mL, while rat concentrations ranged from 0.607 to 2.04 ng/mL. This suggests that the ISR failures were not attributed to metabolite levels being below the limit of quantitation. An IR was sent to the Applicant for more information about what caused the ISR failures and for a justification for

why the Applicant believes that the ISR failures do not negatively impact the integrity of the PK/TK data and the safety qualification of the metabolite, including the potential for embryo-fetal toxicity.

Applicant's Justification for ISR failures:

"The potential causes for the failed ISR studies were thoroughly investigated at the time they were observed", and "no methodological, procedural, or human errors were identified. No additional experimental data are available." "The most likely explanation for the failing ISR with rat plasma (Study 8336088) remains a species-selective matrix interference in rat plasma that may lead to ion suppression and lower concentrations, especially at concentrations between the LLOQ (0.100 ng/mL) and the LQC (0.300 ng/mL) testing limit. In a second rat study (Study (b) (4)) 83% of ISR samples met the acceptance criteria.

(b) (4) plasma concentrations were significantly higher in this study, (b) (4)

"In contrast to the rat results, the ISR performance for the human samples was more robust, with 62% (Study CP130-1008) and 64% (Study CP130-1010) of samples passing (vs the 67% acceptance criteria); the difference between passing and failing is 2 plasma samples (Study CP130-1008) or 1 plasma sample (Study CP130-1010). No matrix effects were observed in the validation study nor in a prospective pre- and post-HPLC infusion study conducted during the ISR failure investigation." "The most likely explanation for the failure of the human ISR studies is a combination of statistical chance (e.g. relatively low sample number available where passing or failing is driven by 2 samples) and the low concentrations of TRV0109662 contained in the samples."

"Plasma concentrations of TRV0109662 in humans are very low, approximately 3 ng/mL or less depending on the olliceridine dose. The human PK data for TRV0109662 calculated from the original plasma concentrations and the interpretation of the human exposure to this metabolite is not adversely impacted by the ISR failure because the effect of individual plasma sample concentrations differing by up to 2-fold at these low levels, especially at the later sampling times, is minimal. Moreover, the general correlation between the original and ISR concentrations for the majority of the samples containing measurable concentrations of TRV0109662 supports the validity of the data originally used in the PK calculations."

"The safety qualification of TRV0109662 is supported by the rat TK data because the impact of any single plasma concentration difference on the aggregate mean TK is minimal."

"TRV0109662 AUC<sub>0-24</sub> exposure in the rat embryo-fetal development study ((b) (4) 141503) was 27.8 ng\*hr/mL, determined by extrapolating female TK data from the 28-day toxicity study (Study 8336088). Daily exposure in this study was approximately 73% of human exposure at the MRHD of 40 mg/day." AUC<sub>0-24</sub> exposure in rat Study (b) (4) of the projected human exposure at the maximum

recommended human oliceridine dose (MRHD) of 40 mg/day. “In all cases, TRV0109662 exposures are well above the minimal metabolite qualification threshold of 50% at the maximum recommended human exposure of 40 mg/day.”

Reviewer’s assessment:

This Reviewer agrees that ISR failures due to two more failed samples may not change the mean value much for human plasma concentration. The impact on rat plasma sample concentration from the 28-day rat study (Study 8336088) may not be negligible given that majority of the samples failed to meet the acceptance criteria.

The impact of ISR failures on the establishment of adequate general toxicity assessment for this metabolite is likely minimal given that the impact of ISR failures on human plasma samples is negligible (as discussed above) and ISR was successful on the rat plasma samples (b) (4) of human exposure at the MRHD of 40 mg/day, well above the human exposure at MRHD and therefore, the general toxicity evaluation is considered adequate for this metabolite.

The Applicant reported that the daily exposure to TRV0109662 in the rat embryo-fetal study, whose exposure data was extrapolated from the rat 28-day study (Study 8336088) study, was approximately 55% of human exposure at the MRHD of 40 mg/day. The number of 55% is questionable considering the data from 20/24 plasma samples from the study were irreproducible. The Applicant speculated that the cause of ISR failures is related to low concentration of the metabolite in the samples, small sample size and species-selective matrix interference. The data of human plasma concentrations does suggest the exposure to this metabolite is low in human. TRV0109662 did not show pharmacological activity when screened against over 100 receptors, enzymes, transporters and channels at a high concentration of 10 mcM, except a weak partial mu agonism activity. It is negative in the in vitro genotoxicity assessment up to the limit concentration. In the (b) (4) study with the elevated TRV0109662, no evident additional (b) (4) was observed compared to oliceridine alone. Considering the totality of the data, this Reviewer speculates the likelihood for this metabolite to contribute to embryo-fetal toxicity is relatively low for an acute indication. However, given the concerns on the validity of the PK data from rat embryo-fetal developmental study, the safety characterization of this metabolite on embryo-fetal development should be considered inadequate.

**9.2.2 M22 (TRV0306954):**

M22 was identified by high resolution nuclear magnetic resonance and chemical synthesis as a non-acyl ether glucuronide conjugate of hydroxylated TRV130. As mentioned above, radiochemical and mass spectrometric profiling of plasma collected from clinical Study CP130-1007 showed that M22 accounts for 61.9% total drug-related exposure.

The Applicant conducted the following studies listed in the table below to characterize the pharmacology, pharmacokinetics, genetic toxicity and the exposures from human and nonclinical study samples as an attempt for safety qualification.

**Table 50: Completed Studies Characterizing M22 (TRV0306954)**

Study Type	Study Number	Study Title
In vitro Primary Pharmacology—Metabolite	<a href="#">TRV130-21</a>	Characterization of TRV0306954 Activity in Cyclic AMP and $\beta$ -arrestin2 Assays at Human Mu-, Delta-, Kappa- and Nociceptin-Opioid Receptors
Secondary Pharmacodynamics—Metabolite	<a href="#">100040220</a>	In Vitro Pharmacology: Study of Compound TRV0306954
Pharmacodynamic Drug Interaction—Metabolite	<a href="#">XT165110</a>	In Vitro Evaluation of TRV0306954 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes

Study Type	Study Number	Study Title
Pharmacodynamic Drug Interaction—Metabolite	<a href="#">Trevena-04-01Sep2016</a>	In Vitro Interaction Studies of TRV0306954 with the Human BSEP, BCRP and MDR1 Efflux (ABC) Transporters, and with the Human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters
Distribution (Plasma Protein Binding)—Metabolite	<a href="#">TRE-R6804</a>	In Vitro Protein Binding of TRV0306954 in Sprague-Dawley Rat, Cynomolgus Monkey and Human Plasma
Bioanalytical Method Validation—Metabolite	<a href="#">TRE-R7531</a>	Validation of Method BTM-2386-R0: Determination of TRV0306954 (M22) in K <sub>2</sub> EDTA New Zealand White Rabbit Plasma by LC-MS/MS Detection
Bioanalytical Method Validation—Metabolite	<a href="#">TRE-R7537</a>	Validation of Method BTM-2385-R0: Determination of TRV0306954 (M22) in K <sub>2</sub> EDTA Cynomolgus Monkey Plasma by LC-MS/MS Detection
Bioanalytical Method Validation—Metabolite	<a href="#">TRE-R7572</a>	Validation of Method BTM-2387-R0: Determination of TRV0306954 (M22) in K <sub>2</sub> EDTA Human Plasma by LC-MS/MS Detection
Repeat-Dose Toxicology	<a href="#">TRE-R7676</a>	LC-MS/MS Analysis for the Determination of TRV0306954 (M22) in Rabbit (WIL-141504) and Monkey (8242809) Plasma
Single-Dose Pharmacokinetics--Metabolite	<a href="#">TRE-R7642</a>	LC-MS/MS Analysis for the Determination of TRV0306954 (M22) in Human Plasma Samples from Study CP130-1008

In addition to the studies listed in the table above, the Applicant submitted two genetic toxicity studies and an in vitro study evaluating the effects of the both of the major metabolites on hERG, hCav1.2, peak hNav1.5 or late hNav1.5 ion channel currents during the review cycle:

- TRV0306954 (M22): Bacterial Reverse Mutation Assay in 6-Well Plates (AF16PD.502008.BTL)
- TRV0306954 (M22): *In Vitro* Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL) (AF16PD.348ICH.BTL)

- Effects of Three Test Articles on Ion Channels Expressed in Mammalian Cells (180724.USF).

### **M22 is Nonreactive without Structural Alerts**

Following a request from the Agency during the Pre-NDA meeting, the Applicant conducted a literature review to support their conclusion that M22, an ether glucuronide, is unreactive and chemically stable from the perspective of chemical rational. It has been well accepted that highly polar glucuronides cross membranes with difficulty and distribute poorly to extravascular sites, minimizing potential tissue distribution. Their literature search did not identify examples of toxicity mediated by high concentrations of ether glucuronides. Additionally, the Applicant conducted Derek and VEGA-QSAR analysis of M22 that did not predict mutagenicity in Ames assay. During the review cycle, the Applicant submitted two *in vitro* genetic toxicology studies, demonstrating M22 was negative for mutagenicity in a 6-well bacterial reverse mutation assay (Study AF16PD.502008.BTL) and negative for clastogenicity in an *in vitro* micronucleus assay (Study AF16PD.348ICH.BTL).

### **Study Title: TRV0306954 (M22): Bacterial Reverse Mutation Assay in 6-Well Plates**

Study no.: AF16PD.502008.BTL

Study report location: <\\cdsesub1\evsprod\nda210730\0028\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\af16pd.502008.bt\af16pd502008btl.pdf>

Conducting laboratory and location:



(b) (4)

Date of study initiation: 29 January 2018

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Lot TRV0306954:5

Purity: 97.78 and 97.79% (per Certificate of Analysis)

### **Key Study Findings**

M22 was negative in the Bacterial Reverse Mutation Assay when tested up to 5000 mcg/plate in the presence and absence of S9 under the conditions of this protocol.

### **Methods**

Strains: *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA97a and *Escherichia coli* tester strain WP2 *uvrA*

Concentrations in definitive study: 0.300, 1.00, 3.00, 10.0, 30.0, 100, 300, and 1000 mcg per well

Basis of concentration selection: Concentration limit

Negative control: Water

Positive control:

Strain	S9 Activation	Positive Control	Concentration (µg/well)
TA98, TA1535, TA100, TA97a	Rat	2-aminoanthracene (b) (4)	0.4
WP2 <i>uvrA</i>		Lot No. STBD3302V Exp. Date 30-Nov-2019 CAS No. 613-13-8 Purity 97.5%	3.0
TA98	None	2-nitrofluorene (b) (4)	0.2
		Lot No. S43858V Exp. Date 31-Mar-2019 CAS No. 607-57-8 Purity 99.4%	
TA100, TA1535		sodium azide (b) (4)	0.2
		Lot No. MKBT8080V Exp. Date Jan-2020 CAS No. 26628-22-8 Purity 99.8%	
TA97a		ICR 191 (b) (4)	0.5
		Lot No. SLBV4070 Exp. Date 31-Dec-2020 Purity: Not provided	
WP2 <i>uvrA</i>	methyl methanesulfonate (b) (4)	200	
	Lot No. MKBR6050V Exp. Date 13-Mar-2018 CAS No. 66-27-3 Purity 100.0%		

Formulation/Vehicle: Water

Incubation & sampling time: In the modified 6-well plate incorporation method, one-tenth (0.100) mL of S9 or sham mix, 20.0 mL of tester strain (cells seeded) and 10.0 mL of vehicle or M22 dilution were added to 0.4 mL of molten selective top agar at 45±2°C. When plating the positive controls, M22 aliquot was replaced by a 10.0 mL aliquot of appropriate positive control. The mixture was vortex-mixed and overlaid onto the surface of each appropriate well containing 5 mL of minimal bottom agar. After the overlay had solidified, the plates were inverted and incubated for 48 to 72 hours at 37±2°C.

### **Study Validity**

- Selection of bacterial tester strains was adequate based upon Guideline for Industry: *Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (ICH S2A, April 1996).
- Positive controls produced expected responses.
- Dose selection for the modified plate incorporation method was adequate based upon use of the limit dose of 5000 mcg/plate.

- The S9 concentration was within acceptable limits.

### **Results**

- The mutagenicity assay via the modified plate incorporation method in 6-well plates was used to evaluate the mutagenic potential of the test article.
- Neither precipitate nor toxicity was observed. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation.
- The study indicates that M22 is negative in the Bacterial Reverse Mutation Assay when tested up to 1000 mcg/well in the presence and absence of S9 under the conditions of this protocol. The maximum dose level of 1000 mcg per well is mathematical equivalent to the 5000 mcg per plate in the regular Bacterial Reverse Mutation Assay. This is based on 5 times smaller area in the 6-well plates when compared to the 100 mm plates used in the regular Bacterial Reverse Mutation Assay.

**TABLE 1**  
Mutagenicity Assay without S9 activation

Study Number: AF16PD.502008.BTL			Study Code: AF16PD			
Experiment: B1			Date Plated: 2/6/2018			
Exposure Method: Plate incorporation assay-6 well assay			Evaluation Period: 2/9/2018			
Strain	Article	Dose level per well	Mean revertants per well	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	TRV0306954 (M22)	1000 µg	4	1	0.8	4 <sup>M</sup> , 3 <sup>M</sup>
		300 µg	6	3	1.2	4 <sup>M</sup> , 8 <sup>M</sup>
		100 µg	6	2	1.2	7 <sup>M</sup> , 4 <sup>M</sup>
		30.0 µg	7	2	1.4	8 <sup>M</sup> , 5 <sup>M</sup>
		10.0 µg	6	1	1.2	5 <sup>M</sup> , 6 <sup>M</sup>
		3.00 µg	4	0	0.8	4 <sup>M</sup> , 4 <sup>M</sup>
		1.00 µg	7	1	1.4	6 <sup>M</sup> , 7 <sup>M</sup>
		0.300 µg	5	1	1.0	5 <sup>M</sup> , 4 <sup>M</sup>
		Water	10.0 µL	5	3	
TA100	TRV0306954 (M22)	1000 µg	14	2	0.9	12 <sup>M</sup> , 15 <sup>M</sup>
		300 µg	14	1	0.9	15 <sup>M</sup> , 13 <sup>M</sup>
		100 µg	16	3	1.0	18 <sup>M</sup> , 14 <sup>M</sup>
		30.0 µg	16	3	1.0	14 <sup>M</sup> , 18 <sup>M</sup>
		10.0 µg	16	1	1.0	15 <sup>M</sup> , 16 <sup>M</sup>
		3.00 µg	14	1	0.9	14 <sup>M</sup> , 13 <sup>M</sup>
		1.00 µg	15	4	0.9	17 <sup>M</sup> , 12 <sup>M</sup>
		0.300 µg	15	5	0.9	18 <sup>M</sup> , 11 <sup>M</sup>
		Water	10.0 µL	16	1	
TA1535	TRV0306954 (M22)	1000 µg	2	1	0.7	1 <sup>M</sup> , 3 <sup>M</sup>
		300 µg	2	1	0.7	3 <sup>M</sup> , 1 <sup>M</sup>
		100 µg	3	1	1.0	2 <sup>M</sup> , 4 <sup>M</sup>
		30.0 µg	3	0	1.0	3 <sup>M</sup> , 3 <sup>M</sup>
		10.0 µg	2	1	0.7	1 <sup>M</sup> , 3 <sup>M</sup>
		3.00 µg	2	0	0.7	2 <sup>M</sup> , 2 <sup>M</sup>
		1.00 µg	4	1	1.3	3 <sup>M</sup> , 4 <sup>M</sup>
		0.300 µg	3	1	1.0	2 <sup>M</sup> , 4 <sup>M</sup>
		Water	10.0 µL	3	1	
TA97a	TRV0306954 (M22)	1000 µg	12	1	0.9	11 <sup>M</sup> , 12 <sup>M</sup>
		300 µg	15	1	1.1	15 <sup>M</sup> , 14 <sup>M</sup>
		100 µg	11	1	0.8	10 <sup>M</sup> , 12 <sup>M</sup>
		30.0 µg	13	5	0.9	9 <sup>M</sup> , 16 <sup>M</sup>
		10.0 µg	14	1	1.0	13 <sup>M</sup> , 14 <sup>M</sup>
		3.00 µg	14	2	1.0	15 <sup>M</sup> , 12 <sup>M</sup>
		1.00 µg	13	4	0.9	16 <sup>M</sup> , 10 <sup>M</sup>
		0.300 µg	12	1	0.9	11 <sup>M</sup> , 12 <sup>M</sup>
		Water	10.0 µL	14	1	

Key to Manual Count Flags

<sup>M</sup>: Manual count

TABLE 1 (CONT.)  
Mutagenicity Assay without S9 activation

Study Number: AF16PD.502008.BTL

Study Code: AF16PD

Experiment: B1

Date Plated: 2/6/2018

Exposure Method: Plate incorporation assay-6 well assay

Evaluation Period: 2/9/2018

Strain	Article	Dose level per well	Mean revertants per well	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA	TRV0306954 (M22)	1000 µg	5	1	0.8	4 <sup>M</sup> , 6 <sup>M</sup>
		300 µg	7	1	1.2	6 <sup>M</sup> , 7 <sup>M</sup>
		100 µg	5	1	0.8	4 <sup>M</sup> , 6 <sup>M</sup>
		30.0 µg	6	4	1.0	3 <sup>M</sup> , 9 <sup>M</sup>
		10.0 µg	6	1	1.0	7 <sup>M</sup> , 5 <sup>M</sup>
		3.00 µg	4	3	0.7	2 <sup>M</sup> , 6 <sup>M</sup>
		1.00 µg	5	2	0.8	3 <sup>M</sup> , 6 <sup>M</sup>
		0.300 µg	5	1	0.8	6 <sup>M</sup> , 4 <sup>M</sup>
	Water	10.0 µL	6	1		7 <sup>M</sup> , 5 <sup>M</sup>
TA98	2NF	0.2µg/wel 1	22	1	4.4	21 <sup>M</sup> , 23 <sup>M</sup>
TA100	SA	0.2µg/wel 1	65	4	4.1	62 <sup>M</sup> , 67 <sup>M</sup>
TA1535	SA	0.2µg/wel 1	62	18	20.7	49 <sup>M</sup> , 75 <sup>M</sup>
TA97a	ICR-191	0.5µg/wel 1	88	4	6.3	90 <sup>M</sup> , 85 <sup>M</sup>
WP2uvrA	MMS	200µg/we ll	50	6	8.3	54 <sup>M</sup> , 46 <sup>M</sup>

## Key to Positive Controls

2NF 2-nitrofluorene

SA sodium azide

ICR-191 ICR-191

MMS methyl methanesulfonate

## Key to Manual Count Flags

<sup>M</sup>: Manual count

**TABLE 2**  
Mutagenicity Assay with S9 activation

Study Number: AF16PD.502008.BTL

Study Code: AF16PD

Experiment: B1

Date Plated: 2/6/2018

Exposure Method: Plate incorporation assay-6 well assay

Evaluation Period: 2/9/2018

Strain	Article	Dose level per well	Mean revertants per well	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes	
TA98	TRV0306954 (M22)	1000 µg	3	1	0.6	4 <sup>M</sup> , 2 <sup>M</sup>	
		300 µg	5	1	1.0	6 <sup>M</sup> , 4 <sup>M</sup>	
		100 µg	7	4	1.4	4 <sup>M</sup> , 9 <sup>M</sup>	
		30.0 µg	6	1	1.2	5 <sup>M</sup> , 6 <sup>M</sup>	
		10.0 µg	6	1	1.2	5 <sup>M</sup> , 7 <sup>M</sup>	
		3.00 µg	5	1	1.0	4 <sup>M</sup> , 6 <sup>M</sup>	
		1.00 µg	6	1	1.2	6 <sup>M</sup> , 5 <sup>M</sup>	
		0.300 µg	7	0	1.4	7 <sup>M</sup> , 7 <sup>M</sup>	
		Water	10.0 µL	5	1		6 <sup>M</sup> , 4 <sup>M</sup>
		TA100	TRV0306954 (M22)	1000 µg	20	1	1.2
300 µg	19			0	1.1	19 <sup>M</sup> , 19 <sup>M</sup>	
100 µg	22			0	1.3	22 <sup>M</sup> , 22 <sup>M</sup>	
30.0 µg	15			1	0.9	14 <sup>M</sup> , 15 <sup>M</sup>	
10.0 µg	15			3	0.9	17 <sup>M</sup> , 13 <sup>M</sup>	
3.00 µg	16			4	0.9	13 <sup>M</sup> , 18 <sup>M</sup>	
1.00 µg	17			4	1.0	14 <sup>M</sup> , 19 <sup>M</sup>	
0.300 µg	14			0	0.8	14 <sup>M</sup> , 14 <sup>M</sup>	
Water	10.0 µL			17	7		22 <sup>M</sup> , 12 <sup>M</sup>
TA1535	TRV0306954 (M22)			1000 µg	3	1	1.0
		300 µg	2	1	0.7	3 <sup>M</sup> , 1 <sup>M</sup>	
		100 µg	3	0	1.0	3 <sup>M</sup> , 3 <sup>M</sup>	
		30.0 µg	2	1	0.7	1 <sup>M</sup> , 3 <sup>M</sup>	
		10.0 µg	2	0	0.7	2 <sup>M</sup> , 2 <sup>M</sup>	
		3.00 µg	3	1	1.0	2 <sup>M</sup> , 3 <sup>M</sup>	
		1.00 µg	3	1	1.0	4 <sup>M</sup> , 2 <sup>M</sup>	
		0.300 µg	3	2	1.0	4 <sup>M</sup> , 1 <sup>M</sup>	
		Water	10.0 µL	3	1		2 <sup>M</sup> , 3 <sup>M</sup>
		TA97a	TRV0306954 (M22)	1000 µg	11	1	0.8
300 µg	15			1	1.2	16 <sup>M</sup> , 14 <sup>M</sup>	
100 µg	13			2	1.0	11 <sup>M</sup> , 14 <sup>M</sup>	
30.0 µg	16			1	1.2	16 <sup>M</sup> , 15 <sup>M</sup>	
10.0 µg	12			6	0.9	16 <sup>M</sup> , 8 <sup>M</sup>	
3.00 µg	14			6	1.1	18 <sup>M</sup> , 9 <sup>M</sup>	
1.00 µg	15			1	1.2	16 <sup>M</sup> , 14 <sup>M</sup>	
0.300 µg	17			2	1.3	18 <sup>M</sup> , 15 <sup>M</sup>	
Water	10.0 µL			13	1		12 <sup>M</sup> , 14 <sup>M</sup>

Key to Manual Count Flags

<sup>M</sup>: Manual count

(b) (4) Study No. AF16PD.502008.BTL

**TABLE 2 (CONT.)**  
Mutagenicity Assay with S9 activation

Study Number: AF16PD.502008.BTL			Study Code: AF16PD			
Experiment: B1			Date Plated: 2/6/2018			
Exposure Method: Plate incorporation assay-6 well assay			Evaluation Period: 2/9/2018			
Strain	Article	Dose level per well	Mean revertants per well	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA	TRV0306954 (M22)	1000 µg	4	1	0.6	3 <sup>M</sup> , 5 <sup>M</sup>
		300 µg	5	1	0.7	4 <sup>M</sup> , 6 <sup>M</sup>
		100 µg	6	2	0.9	7 <sup>M</sup> , 4 <sup>M</sup>
		30.0 µg	6	1	0.9	5 <sup>M</sup> , 6 <sup>M</sup>
		10.0 µg	6	1	0.9	7 <sup>M</sup> , 5 <sup>M</sup>
		3.00 µg	7	0	1.0	7 <sup>M</sup> , 7 <sup>M</sup>
		1.00 µg	7	2	1.0	8 <sup>M</sup> , 5 <sup>M</sup>
		0.300 µg	8	1	1.1	7 <sup>M</sup> , 9 <sup>M</sup>
	Water	10.0 µL	7	1		7 <sup>M</sup> , 6 <sup>M</sup>
TA98	2AA	0.4µg/wel 1	75	9	15.0	81 <sup>M</sup> , 68 <sup>M</sup>
TA100	2AA	0.4µg/wel 1	119	16	7.0	108 <sup>M</sup> , 130 <sup>M</sup>
TA1535	2AA	0.4µg/wel 1	18	3	6.0	20 <sup>M</sup> , 16 <sup>M</sup>
TA97a	2AA	0.4µg/wel 1	64	14	4.9	54 <sup>M</sup> , 74 <sup>M</sup>
WP2uvrA	2AA	3.0µg/wel 1	47	3	6.7	45 <sup>M</sup> , 49 <sup>M</sup>
<b>Key to Positive Controls</b>						
2AA	2-aminoanthracene					
<b>Key to Manual Count Flags</b>						
<sup>M</sup> : Manual count						

**Study Title: TRV0306954 (M22): *In Vitro* Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)**

Study no: AF16PD.348ICH.BTL  
 Study report location: <\\cdsesub1\evsprod\nda210730\0028\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\af16pd.348ich.bt\af16ppd-348ich-btl.pdf>

Conducting laboratory and location:



(b) (4)

Date of study initiation: 13 February 2018  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: Lot #: TRV0306954:5  
 Purity: 97.8% (provided by Sponsor)

**Key Study Findings**

No significant or dose-dependent increases in micronuclei induction were observed in treatment groups with or without S9 ( $p > 0.05$ ; Fisher's Exact and Cochran-Armitage tests). These results indicate TRV0306954 (M22) was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system.

**Methods**

Cell line: Human peripheral blood lymphocytes (HPBL)

Concentrations in definitive study:

Treatment Condition	Treatment Time	Recovery Time	Doses ( $\mu\text{g/mL}$ )
Non-activated	4 hr	20 hr	31.3, 62.5, 125, 250, 500
	24 hr	0 hr	31.3, 62.5, 125, 250, 500
S9-activated	4 hr	20 hr	31.3, 62.5, 125, 250, 500

Basis of concentration selection: Limit dose for the assay

Negative control: Water

Positive control:

Vehicle	Supplier	CAS No.	Lot No.	Exp. Date
Cyclophosphamide (CP)	(b) (4)	6055-19-2	MKBX1822V	31 Dec 2018
Vinblastine (VB)		143-67-9	107M4057V	31 Aug 2019
Sterile water		7732-18-5	1933762	30 Nov 2019

Formulation/Vehicle: Water

Incubation & sampling time: After the 4-hour treatment in the non-activated and the S9-activated studies, the cells were centrifuged, the treatment medium was aspirated, the cells were washed with calcium and magnesium free phosphate buffered saline (CMF-PBS), re-fed with complete medium containing cytoB at 6.0 mcg/mL and returned to the incubator under standard conditions. For the 24-hour treatment in the non-activated study, cytoB (6.0 mcg/mL) was added at the beginning of the treatment.

Cells were collected after being exposed to cytoB for 24 hours ( $\pm 30$  minutes), 1.5 to 2 normal cell cycles, to ensure identification and selective analysis of micronucleus frequency in cells that have completed one mitosis evidenced by binucleated cells. The cytoB exposure time for the 4-hour treatment in the non-activated and the S9-activated studies was 20 hours ( $\pm 30$  minutes).

**Study Validity**

The following criteria for a valid assay were met:

- The dose selection based upon limit of acceptable dose (1 mM or 500 mcg/mL) was acceptable for both non-activated and activated system.
- Positive control significantly increased the percentage of micronucleated cells as expected. In addition, the cytotoxicity response did not exceed the upper limit for the assay (55%).

- At least 2000 binucleated cells from at least three appropriate M22 concentrations were evaluated.

### **Results**

- In the preliminary toxicity assay, the doses tested ranged from 0.05 to 500 mcg/mL, which was the limit dose for this assay. Cytotoxicity [ $\geq 45\%$  cytokinesis-blocked proliferation index (CBPI) relative to the vehicle control] was not observed at any dose in any of the three treatment groups. Based upon these results, the doses chosen for the micronucleus assay ranged from 31.3 to 500 mcg/mL for all three exposure groups.
- In the micronucleus assay, cytotoxicity ( $\geq 45\%$  CBPI relative to the vehicle control) was not observed at any dose in any of the three treatment groups. The doses selected for evaluation of micronuclei were 125, 250, and 500 mcg/mL for all three exposure groups.
- No significant or dose-dependent increases in micronuclei induction were observed in treatment groups with or without S9 ( $p > 0.05$ ; Fisher's Exact and Cochran-Armitage tests). The results for the positive and vehicle controls indicate that all criteria for a valid assay were met.
- These results indicate M22 was negative for the induction of micronuclei in the presence and absence of the exogenous metabolic activation system.

TABLE 7

MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED WITH TRV0306954 (M22) IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
MICRONUCLEUS ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment µg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
Water	A	1000	0.40%	0.40%
	B	1000	0.40%	
TRV0306954 (M22) 125	A	1000	0.40%	0.35%
	B	1000	0.30%	
250	A	1000	0.20%	0.30%
	B	1000	0.40%	
500	A	1000	0.70%	0.60%
	B	1000	0.50%	

TABLE 8

MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED WITH TRV0306954 (M22) IN THE PRESENCE OF EXOGENOUS METABOLIC ACTIVATION  
MICRONUCLEUS ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment µg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
Water	A	1000	0.40%	0.45%
	B	1000	0.50%	
TRV0306954 (M22) 125	A	1000	0.40%	0.35%
	B	1000	0.30%	
250	A	1000	0.50%	0.40%
	B	1000	0.30%	
500	A	1000	0.30%	0.30%
	B	1000	0.30%	
CP, 7.5	A	1000	1.80%	1.55%**
	B	1000	1.30%	

\*\*  $p \leq 0.01$ , Fisher's exact test, relative to the solvent control.

TABLE 9  
 MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED  
 WITH TRV0306954 (M22) IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION  
 MICRONUCLEUS ASSAY: 24-HOUR TREATMENT, 24-HOUR HARVEST

Treatment μg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
Water	A	1000	0.50%	0.50%
	B	1000	0.50%	
TRV0306954 (M22)	125	A	0.30%	0.35%
		B	0.40%	
	250	A	0.60%	0.50%
		B	0.40%	
500	A	0.40%	0.45%	
	B	0.50%		
VB, 7.5 ng/mL	A	1.40%	1.35%**	
	B	1.30%		

\*  $p \leq 0.05$ ; \*\*  $p \leq 0.01$ , Fisher's exact test, relative to the solvent control.

**Pharmacological Characterization: Lack pharmacological interaction except weak interacting with mu-opioid receptors**

**Primary Pharmacology**

The in vitro functional assays evaluating the potency and efficacy of M22 against the human mu, kappa, delta, and nociception opioid receptors (Study TRV130-21) showed that M22 only has low potency at the mu ( $EC_{50}$  of 6310 nM) receptors. Similar to the parent molecule, oliceridine, M22 shows negligible activity (not quantifiable) in recruiting  $\beta$ -arrestin2 at these opioid receptors.

The potency and efficacy values of TRV0306954 on human opioid receptors to inhibit forskolin-stimulated cAMP accumulation and to recruit  $\beta$ -arrestin2 are summarized in the table below:

**Table 1 Summary of potency and efficacy at human opioid receptors.**  
TRV0306954 exhibits lower potency and efficacy at human MOR (DAMGO), KOR (U69,593), DOR (DPDPE) and NOP (Nociceptin) compared to respective standard reference compounds.

		cAMP					$\beta$ -arrestin2				
		EC <sub>50</sub> (nM)	pEC <sub>50</sub>	SEM	Span	n	EC <sub>50</sub> (nM)	pEC <sub>50</sub>	SEM	Span	n
hMOR	TRV0306954	6310	5.2	0.13	13	8	N.Q.	N.Q.		N.Q.	8
	DAMGO	31	7.5	0.03	98	8	810	6.1	0.06	105	8
hKOR	TRV0306954	N.Q.	N.Q.		N.Q.	8	N.Q.	N.Q.		N.Q.	8
	U69,593	1.5	8.8	0.03	97	8	570	6.2	0.06	101	8
hDOR	TRV0306954	63096	4.2	0.08	44	8	N.Q.	N.Q.		N.Q.	8
	DPDPE	0.36	9.4	0.04	93	8	38	7.4	0.05	102	8
hNOP	TRV0306954	N.Q.	N.Q.		N.Q.	8	N.Q.	N.Q.		N.Q.	8
	Nociceptin	2.5	8.6	0.04	94	8	898	6	0.04	110	8

N.Q. = not quantifiable

## Secondary Pharmacology

The selectivity of M22 (radio-ligand binding) was determined by screening against a panel of 132 enzymes, channels, receptors, and transporters (Study 100040220). The study showed that M22 at concentration of 10 mcM had 75% inhibition of control (DMSO) specific binding. % inhibition or % simulation of control at other receptors, channels, enzymes and transporters were less than 50%. The data are in line with the primary pharmacology data that demonstrated M22 has a weak interaction with mu-opioid receptor. The Applicant concluded that M22 did not have clinically meaningful interaction with any receptor, channel, enzyme or transporter at clinical concentration.

### ***Pharmacokinetic Drug-Drug Interaction: Lack drug-drug interaction potential***

The Applicant has submitted data (Study Trevena-04-01Sep2016) demonstrating that M22 is not an inhibitor of 14 major human uptake and efflux transporters MDR1, BCRP, BSEP, MRP2, MRP3, and MRP4; OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE, and MATE2-K at concentrations of up to 3 mcM (highest concentration tested).

The potential for M22 to inhibit (Study XT165110) the major human CYP isozymes was also studied. At concentrations of M22 ranging from 0.003 to 3.0 mcM, there was no direct, time-dependent or metabolism-dependent inhibition of any CYP enzyme (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 [testosterone 6 $\beta$ -hydroxylation and midazolam 1'-hydroxylation]) and IC<sub>50</sub> values of > 3 mcM were reported.

### **Characterization of M22 Exposure from Toxicological Study Samples**

The in vitro metabolism Study QBRMU10130 TRV01 suggested that M22 may only be produced in human and monkey, but not in rats. Although M22 represents a large majority of the total drug-related exposure in human, it was not initially measured in any toxicological studies. As per the Agency's request, the Applicant developed bioanalytical assays which were validated to comply with GLP regulations and were used to measure M22 concentrations in human plasma samples and in available plasma samples from completed rabbit and monkey toxicology studies. The validated assays were used to measure M22 concentrations in pooled rabbit samples from a GLP embryo-fetal development study (Study (b) (4) 141504) and pooled monkey plasma samples from a GLP 14-day toxicology study (Study 8242809) to confirm that M22 is not a human-specific metabolite. Plasma samples for analysis were collected following multiple days of continuous (24 hour) IV infusion of 0.25 mg/kg/h oliceridine in the rabbit embryo-fetal development study and 1 mg/kg/h oliceridine in the monkey 14-day toxicology study; therefore, M22 was at steady state in the samples. Because differences in M22 concentrations in male and female monkeys were less than 2-fold, data from males and females were combined when calculating mean exposure.

The measured plasma exposure to M22 in the nonclinical samples and the estimated human exposure to M22 are presented in the tables below. Mean M22 plasma exposure in the 14-day monkey study was 530% of the projected human exposure at the proposed MRHD of 40 mg/day. Mean total daily exposure to M22 in rabbits dosed with oliceridine in the embryofetal development toxicology study was 53% of the projected maximum human exposure.

Table 24: In Vivo Exposure to M22 in Human and GLP Toxicology Studies

	<b>Mean AUC<sub>0-24h</sub> (ng*h/mL)</b>	<b>PK Source</b>	<b>Exposure Multiples (AUC animal/AUC Human at MRHD of 40 mg)</b>
Rabbit EFD Study (b) (4) 141504 (Day 28)	1423	TRE-R7676	53%
14-day Monkey Study 8242809 (Day 14)	14304	TRE-R7676	530%
Human (1.5 mg loading, 0.35 mg Q 0.2 h; daily MRHD=43.5 mg) *	2901	QS130-3004	
Human: daily MRHD=40 mg**	2667		

Note:

\*In response to the Agency's information request, the Applicant conducted another PK simulation based upon Phase 3 study dosing regimens, which resulted in plasma exposures approximately 50% higher than the original PK simulation data based upon a dose scheme of 1-3 mg/h.

\*\* Calculated proportionally from exposures at MRHD of 43.5 mg/day; The Applicant has assumed linearity in their PK simulations.

As per the ICH guidance for industry: *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions and Answers*, it is appropriate for exposure to the metabolite in animals to be at least 50% the exposure seen in humans, and in some cases to exceed that in human when a metabolite composes the majority of the total human exposure. This metabolite had formed enough in the monkey general toxicology study to be considered qualified from a general toxicology perspective. As shown in the table above, M22 in the embryo-fetal study only reached 53% of the estimated total human exposure at the proposed MRHD of 40 mg/day, suggesting this metabolite formed disproportionately in rabbits, therefore the embryofetal study in rabbits did not adequately characterize the reproductive toxicology potential of M22. However, M22 is an ether glucuronide metabolite with no intrinsic toxicity which has been supported by the Applicant's genetic toxicity studies demonstrating no genetic toxicity concerns. In addition, M22 did not have significant pharmacology activity in a secondary pharmacology screen, was negative for hERG inhibition in in vitro studies, and showed a benign safety profile in the monkey 14-day study in which exposure to M22 was much higher than the estimated human exposure at the proposed MRHD of 40 mg/day. These data are in line with what has been noted in the *Safety Testing of Drug Metabolites* guidance that "Phase II conjugation reactions generally render a compound more water soluble and pharmacologically inactive, thereby eliminating the need for further evaluation. However, if the conjugate forms a toxic compound such as acylglucuronide, additional safety assessment may be needed." Taking into consideration the totality of the data, this Reviewer concluded that the likelihood for this metabolite to contribute to embryofetal toxicity in human is low at the proposed MRHD of 40 mg/day for an acute indication; therefore, this metabolite is considered qualified for safety at the proposed MRHD.

## 10 Special Toxicology Studies

### ***Study Title: TRV130: Evaluation of the Potential to Cause Hemolysis in Human Blood (Study 0725XT44.002)***

The purpose of this GLP study was to assess the hemolytic potential of TRV130 (TRV11 0130 HCl; Lot CMLW-423/11-TV3; Purity: 99.1%) in human blood. TRV130 at a concentration of 1 mg/mL, the vehicle (0.2 mM sodium phosphate buffer in 5% w/v dextrose), the negative control (saline) and the positive control (water) were mixed with a dilution of human whole blood. Samples were incubated for 1 hour at 37°C. The red cells were removed from the samples by centrifugation and the amount of hemoglobin in the supernatant was measured spectrophotometrically by determining the optical density at 540 nm (OD<sub>540</sub>). The percent hemolysis was determined. The assay was run twice.

The analysis of the initial dose formulation verified the homogeneity of the sample. However, the TRV130 concentration was 1.2 mg/mL which is 20% higher than nominal. This level of variability was deemed acceptable for valid interpretation of the findings.

A series of dilutions (1:2, 1:3, 1:4, 1:5, and 1:10) of the human blood sample was prepared. When added to de-ionized water, a 1:3 dilution of the human blood sample resulted in OD<sub>540</sub> values of 0.910, and 1.009 for the retest. This dilution was used as the blood substrate.

The results for the vehicle compatibility test indicated that the vehicle was compatible with

blood. The OD with the vehicle was 0.008 compared to the OD with saline which was 0.016. In the first run of the assay, incubation of TRV130 at 1.0 mg/mL mixed with the blood substrate resulted in 19.81% hemolysis. However, the vehicle also caused 13.87% hemolysis. The OD for the vehicle with blood was 0.151, which was higher than what was seen in the vehicle compatibility test; therefore, the main study was repeated.

**B. Table 2: Initial Test**

Treatment	Final Concentration (mg/ml)	OD <sub>540</sub> without Blood	OD <sub>540</sub> with Blood	% Hemolysis
Saline	-	-	0.018	0
Water	-	-	0.977	100
Vehicle	-	-0.000	0.151	13.87
TRV130 free base	1	0.008	0.216	19.81

For the retest, the analysis of the dose formulations verified the homogeneity and concentration of the samples. The final mean TRV130 concentration was 1.02 mg/mL, which was 102% of the nominal concentration. Homogeneity was also acceptable.

In the retest, incubation of TRV130 at 1.0 mg/mL with the blood substrate resulted in -2.91% hemolysis. The vehicle was also negative resulting in -0.43% hemolysis. Based on the results of this study, TRV130 was found to be compatible with human blood at a concentration of 1 mg/mL.

**C. Table 3: Retest**

Treatment	Final Concentration (mg/ml)	OD <sub>540</sub> without Blood	OD <sub>540</sub> with Blood	% Hemolysis
Saline	-	-	0.008	0
Water	-	-	0.937	100
Vehicle	-	0.058	0.062	-0.43
TRV130 free base	1	0.103	0.084	-2.91

***Study Title: TRV130: Evaluation of the Potential to Cause Flocculation in Human Plasma and Serum (Study 0726XT44.002)***

The purpose of this GLP study was to assess the compatibility in human serum and plasma of TRV130 (TRV11 0130 HCl; Lot CMLW-423/11-TV3; Purity: 99.1%) in its formulation. A test article dosing solution (TRV130 at 2 mg/mL in 0.2 mM sodium phosphate buffer in 5% w/v dextrose) and vehicle (0.2 mM sodium phosphate buffer in 5% w/v dextrose) were mixed with

equal volumes of human plasma and serum from a single donor. The final concentration of test article was 1 mg/mL free base. Samples were incubated for 30 minutes at room temperature. After incubation the tubes were examined macroscopically and microscopically for precipitation or coagulation.

No precipitation or coagulation was observed either macroscopically or microscopically in the human plasma or serum when mixed with the TRV130 at 2 mg/mL in 0.2 mM sodium phosphate buffer in 5% w/v dextrose or with 0.2 mM sodium phosphate buffer in 5% w/v dextrose. When these samples were centrifuged, no pellet formation was observed.

The analysis of the dose formulations verified the homogeneity and concentration of the samples. The final mean TRV130 concentration was 1.91 mg/mL, which was 95.5% of the nominal concentration. Homogeneity was also acceptable.

Based on the results of this study, TRV130 is compatible with human plasma and serum at a concentration of 2 mg/mL in 0.2 mM sodium phosphate buffer in 5% w/v dextrose (final TRV130 concentrations of 1 mg/mL).

## 11 Integrated Summary and Safety Evaluation

The Applicant, Trevena Inc, is seeking to market oliceridine, a G protein-biased mu-opioid receptor (MOR) agonist, for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted. This is the first G protein-biased mu-opioid agonist seeking market approval from FDA. In order to support the hypothesized therapeutic benefits that G protein-biased mu-opioid would provide an opioid analgesic with an increased therapeutic window compared with conventional opioids, the Applicant conducted nonclinical pharmacology studies in animal models of pain, constipation, and respiratory depression. These animal studies showed that oliceridine elicited potent and robust analgesia in multiple models of spinal reflexive and supraspinal affective nociceptive pain (potency 3- to 10 times that of morphine) with less respiratory depression and constipation in rodents compared to equianalgesic doses of morphine (see Table 11 in Section 4.1.2). However, the final determination of therapeutic benefits of G protein-biased MOR agonists can only be concluded by human experience.

### Determination of Maximum Recommended Human Dose (MRHD) for Nonclinical Safety Assessment

Given that the drug product is intended to be administered “as needed”, which generates wide range of doses and potential clinical exposures. The Agency advised at End-of-Phase 2 and pre-NDA meetings that the safety database needed to include at least 350 patients exposed to the highest doses for the longest expected duration of use. The Applicant evaluated the exposure in the 350 patients with the highest doses over the first 24 hours of treatment with oliceridine injection and reported a mean cumulative dose of 40.3 mg, and a median of 37.5 mg (range 27-88.5 mg). The Applicant believes the mean cumulative dose is most representative of the analgesic needs of this patient population and thus proposed to lower the MRHD from 100 mg daily to 40 mg daily. However, based on discussions with the review team, it does not appear that the Division will consider a proposed MRHD at 40 mg/day to be adequately supported based on the current safety database, though an MRHD of 27 mg may

be supported. Because of the challenge in determining the MRHD, this Reviewer attempted to summarize the nonclinical safety assessment based upon the two possible MRHD doses, 40 mg/day with projected total daily exposure of 786 ng\*h/mL and 27 mg/day with projected daily exposure of 531 ng\*h/mL. The Clinical Pharmacology review team has concurred with the Applicant's projection.

## Pharmacology and ADME Summary

The pharmacological profile of oliceridine as a G protein-biased MOR agonist is conserved across human, rat, and mouse orthologues of the MOR. Oliceridine elicits less receptor phosphorylation and receptor internalization than morphine, consistent with its reduced engagement of  $\beta$ -arrestin 2. Oliceridine is selective for the MOR based on selectivity screening results examining greater than 100 receptors, channels, transporters and 33 different enzymes. In vitro data show that oliceridine exhibits 220-fold selectivity for MOR over the kappa opioid receptor (KOR) and 375-fold for MOR over the delta opioid receptor (DOR). The major metabolites of oliceridine TRV0109662 and TRV0306954 (M22) are weak mu-opioid partial agonist, 500- and 800-fold less potent at the MOR than TRV130, respectively. No significant pharmacological interactions have been identified when these two metabolites were screened against over 100 receptors, channels, transporters and enzymes. Therefore, the two major metabolites are not expected to contribute to the pharmacologic activity of oliceridine at relevant human exposures.

The half-life of oliceridine in animals was short, approximately 1 hour. Steady-state was achieved rapidly, generally within 4 hours of the start of the infusion. Oliceridine was not extensively bound to plasma protein(s) in any species with free (unbound) fractions ranging from 11% in dogs to 42% in monkeys, with 23% free in human plasma. Total radioactivity (parent and metabolites) is distributed widely after IV dosing of oliceridine in rats, with  $^{14}\text{C}$ -concentrations found in well-perfused (liver, kidney) and poorly-perfused (skin, skeletal muscle) tissues. There was no unexpected accumulation or retention of radioactivity in any tissue. There were no sex differences (< 2-fold differences) in toxicokinetic (TK) parameters. Exposure levels ( $C_{\text{ss}}$  or  $\text{AUC}_{0-24}$ ) were generally proportional to increasing dose in rats, rabbits, and monkeys. There was no accumulation of oliceridine after continuous IV infusion of oliceridine for 14 to 28 days.

Oliceridine is extensively metabolized by oxidation and subsequent glucuronidation. Two major metabolites have been identified. The primary amine metabolite TRV0109662, a *N*-dealkylated human metabolite comprising approximately 17% of total drug-related material in human plasma, is essentially free in plasma, with free unbound ( $f_u$ ) >90% in rats and humans and >85% in monkeys. M22, an unreactive and chemically stable ether glucuronide comprising approximately 62% of the total drug-related material, has negligible plasma binding. It has been well accepted that highly polar glucuronides cross membranes with difficulty and distribute poorly to extravascular sites, minimizing potential tissue distribution.

## Safety Pharmacology Summary

Safety pharmacology studies were conducted to evaluate the effects of oliceridine on the cardiovascular, respiratory, and central nervous systems. These systems are known to be affected by MOR activation and the findings are summarized in the tables below:

Table 25. Summary of In Vivo Safety Pharmacology and Safety Margin Based upon Projected Human  $C_{max}$  at MRHD

	Study	Doses mg/kg/h	Key Findings	NOAEL/LOAEL		Projected Human $C_{max}$ (ng/mL)at MRHD (mg/kg/day)		Projected Exposure Multiples*	
				Doses mg/kg/h	$C_{max}$ ng/mL	40	27	40	27
Cardiovascular System	Male Monkeys; 10-hour IV infusion (Study 8242813)	0, 0.05, 0.2 and 1	↓blood pressures and body temperature and heart rate; reversible	0.2 (LOAEL)	120	86	58	1.4	2.1
			No effect on QTc interval	1	600			7	10
Respiratory System	Male rats; 6-hour IV infusion (Study 8242815)	0, 0.25, 0.5 and 1	No effect on tidal volume, respiration rate and minute volume	1	176			2	3
CNS	Male rats; 6-hour IV infusion (Study 8242814)	0, 0.25, 0.5 and 1	↓forelimb grip strength; cranial reflexes; reversible	1 (LOAEL)	176			2	3

\*Projected exposure Multiples=NOAEL or LOAEL/projected human  $C_{max}$

As shown in the table above, the effects of oliceridine on cardiovascular and CNS systems are generally expected with opioid agonists. The opioid agonist-related risk on cardiovascular, respiratory, and CNS are informed in the proposed label as drug class effects. Although administration of many MOR receptor agonists cause respiratory depression, a 6-hour infusion of oliceridine did not cause any changes in respiratory parameters (tidal volume, respiration rate, and minute volume) in the GLP rat respiratory study at doses up to 1 mg/kg/h, the highest dose tested (Study 8242815). Extrapolated plasma concentrations at the NOAEL dose of 1 mg/kg/h in these studies were approximately 2 and 3 times the projected human  $C_{max}$  at the MRHDs of 40 mg and 27 mg, respectively. Given that there is no head-to-head comparison in

this GLP study, no definitive conclusion can be drawn from this study on whether oliceridine would carry a lower risk for respiratory depression compared to other approved opioid agonists. In a non-GLP rat study that measured pCO<sub>2</sub> levels in the blood, oliceridine had an increased therapeutic window for analgesia vs. respiratory depression (see Table 11 in Section 4.1.2 of this review), but significant increase of pCO<sub>2</sub> was still observed at high doses. In a dose-range finding study (Study 8242806), irregular respiration was observed in rats dosed with oliceridine at 4.5 mg/kg/h. These studies suggest that oliceridine may have an improved therapeutic window, but it still likely carries a risk for respiratory depression.

Potential effects of oliceridine on the cardiovascular system were also evaluated in a GLP in vitro hERG assay, non-GLP studies with QPatch automated patch clamp platform assessing effects of oliceridine on hCav1.2 and hNav1.5, an ex vivo rabbit left ventricular wedge preparation and an in vivo monkey cardiovascular safety study. As shown in the table below, the IC<sub>50</sub> for oliceridine in the hERG assay (Study 110520.USF) is 2.2 mcM, approximately 367 times the K<sub>i</sub> at MOR, 27 times the free C<sub>max</sub> after 3 mg IV infusion, and 43 and 65 times the estimated free C<sub>max</sub> at MRHDs of 40 mg/day and 27 mg/day, respectively. These comparisons suggested that the test article may have weak inhibition of hERG at clinical doses. Weak inhibition of hCav 1.2 (IC<sub>50</sub> of 39.6 mcM) and of hNav1.5 (IC<sub>50</sub> of 19.5 mcM for tonic and IC<sub>50</sub> of 9 mcM for phasic) were also identified. However, in the rabbit wedge preparation (Study 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 mcM. As mentioned above, no effects on QTc interval have been observed in monkeys up to exposure of 7-10 times the projected human MRHDs. The Applicant concluded that oliceridine is a weak hERG blocker with some multi-channel effects that may abrogate inhibition of hERG current. However, dose-dependent QTc prolongations during the drug infusion period and at a delayed timepoint have been observed in a human study after single 3 mg and 6 mg infusion. Following discussions with the Agency, the Applicant performed a full ion channel evaluation of oliceridine and the two major metabolites, as described for a comprehensive in vitro proarrhythmia assay (CiPA) evaluation. TRV0109662 and M22 had no effect on hERG, hCav1.2, peak hNav1.5 or late hNav1.5 ion channel currents when tested at concentrations up to 300 mcM, resulting in IC<sub>50</sub>'s > 300 mcM at all channels. Both metabolites appear to form adequately in monkeys to cover the QT assessment in monkeys. The Applicant has proposed language to reflect the human QT prolongation risk in the label.

Table 26: Reviewer's Interpretation of hERG Results Copied from Section 4.3.1

PD or PK Parameters	PD or PK Values	Calculations	Result (Exposure Margin)
hERG IC <sub>50</sub> :	2.2 mcM		
K <sub>i</sub> at MOR	6 nM	2.2 mcM/6 nM	367
C <sub>max</sub> after 3 mg Infusion (CP130-1008):	132.9 ng/mL (Total) 30.6 ng/mL (Unbound)* =79 nM	2.2 mcM/79 nM	27
Projected C <sub>max</sub> at MRHD of 40 mg/day	86 ng/mL (Total) 19.8 ng/mL (Unbound)* =51 nM	2.2 mcM/51 nM	43

## Toxicology Summary

The toxicological profile of oliceridine was evaluated in a series of GLP studies that characterized general, genetic, and reproductive toxicological effects. Most of the effects are opioid-related drug-class effects, or secondary to stress, dehydration or substantial food reduction. Lung thrombosis, subchronic inflammation in cecum and injection site inflammation are considered as treatment-related adverse findings. The major findings and exposure margin assessment are summarized in the tables below.

Table 27: General Toxicology Summary

Study Type	Doses mg/kg/h	Test Article-Related Key Findings	NOAEL/LOAEL		Projected Human AUC <sub>(0-24h)</sub> (ng*h/mL) at MRHD (mg/kg/day)		Projected Exposure Multiples**	
			Doses	AUC <sub>(0-24h)</sub> ng*h/mL	40	27	40	27
14-day rat (Study 8242808)  Sacrificed 24 hours after termination of treatment	0, 0.25, 0.5 and 1	Minimal to marked stomach lesions  (Considered opioid-withdrawal related)	NOAEL not established  LOAEL: 0.25 mg/kg/h	1008	783	529	1.3	1.9
		Lung thrombosis found at 1 mg/kg/h group; No lower doses were tested except one in 0.25 mg/kg/h group.	NOAEL not established  LOAEL: 1 mg/kg/h	4224				
		Others: - Minimal to slight adrenal cortical hypertrophy - Atrophy of seminal vesicles and prostate - Decreased lymphocytes in immune organs  Considered opioid and/or opioid-withdrawal/stress-related						
14-day rat (oliceridine fumarate) (Study 8292859)  Sacrificed within 45 min after termination of treatment	0 and 0.5	Moderate to marked pulmonary arterial thrombosis	NOAEL not established  LOAEL: 0.5 mg/kg/mL	1884			2.4	3.6
14-day rat (oliceridine with degradants and impurities) (Study (b) (4))  Sacrificed within	0 and 0.5	Minimal to slight subacute inflammation of cecum	NOAEL not established  LOAEL: 0.5 mg/kg/h	2328			3	4.4

(b) (4)								
14-day rat with 28-day recovery (Study 8347111)  Sacrificed at different timepoints after termination of treatment	0, 0.5	Minimal to marked stomach lesion when sacrificed 24 hours after termination of treatment; resolved after 7 days	LOAEL: 0.5 mg/kg/h	1968			2.5	3.7
28-day rat (Study 8336088)  Sacrificed within 45 min after termination of treatment	0, 0.25, 0.5 and 1	-Dosing site inflammation -Substantial reduction of body weight  Others: -Minimal to slight hypertrophy of adrenal cortex (stress related) -Minimal to slight apoptosis in pancreas (related to reduced food consumption) -Higher catheter-related mortality in test-article group.	NOAEL: 0.5 mg/kg/h	1872			2.4	3.5
14-day monkey (Study 8242809)  Sacrificed within 45 min after termination of treatment	0, 0.05, 0.2 and 1	Minimal-marked skin findings (erosion/ulceration, etc)  Considered secondary to repetitive skin picking or scratching  Others: Minimal thymic atrophy (Stress-related)	NOAEL: 0.05 mg/kg/h	682			0.9	1.3

Projected Exposure Multiples\*\*: NOAEL or LOAEL/human AUC

Table 28: Developmental and Reproductive Toxicity Summary

Study Type	Doses mg/kg/h	Test-Article Related Key Findings	NOAEL/LOAEL		Projected Human AUC <sub>(0-24h)</sub> (ng*h/mL) at MRHD		Projected Exposure Multiples**	
			Doses	AUC <sub>(0-24h)</sub> (ng*h/mL)	40 mg/ kg/day	27 mg/ kg/day	40	27
Rat fertility, male (b) (4) 141505)	0, 0.25, 0.5, and 1	No adverse findings	NOAEL: 1 mg/kg/h	4416	783	529	6	8
Rat fertility, female (b) (4) 141506)	0, 0.25, 0.5, and 1	<b>-Longer estrous cycle length -Lower mean number of implantation sites and increased preimplantation loss; Lower viable embryos</b>	NOAEL 0.25 mg/kg/h	768			1	1.5
Rat teratology (b) (4) 141503)	0, 0.25, 0.5, and 1	No adverse findings	NOAEL 1 mg/kg/h	3936			5	7.4
Rabbit teratology (b) (4) 141504)	0, 0.0625, 0.15, and 0.25	No adverse findings	NOAEL 0.25	4152			5.3	7.8
Rat pre- & postnatal Development (b) (4) 141509)	0, 0.025, 0.1, and 0.25	F <sub>0</sub> : No adverse finding for F <sub>0</sub> maternal toxicity	NOAEL: 0.25 mg/kg/h	837			1.1	1.6
		F <sub>1</sub> : <b>-Reduced live litter size relative to total number born -Lower mean postnatal survival PND0- PND4 -Lower body weight on PND 1</b>	NOAEL: 0.025 mg/kg/h	84	0.1	0.15		
		F <sub>2</sub> : No adverse finding for F <sub>2</sub> neonatal/early postnatal toxicity	0.25 mg/kg/h	837	1.1	1.6		

### **General Toxicity Summary**

The key general toxicity findings have been summarized in Table 27.

#### **Drug class- or Stress- or Dehydration- Related Safety Findings:**

Oliceridine treatment resulted in clinical observations that are typically observed with opioid drugs such as decreased food consumption and body weights, decreased activity, hunched postures, haircoat discoloration, increased stereotypic behavior, swelling paws, decreased mean blood pressure and decreased body temperature in rats or monkeys. In the 14-day general toxicity monkey study, skin sores and scabs were noted with 1 mg/kg/h oliceridine treatment due to repetitive picking or scratching associated with MOR agonists. Skin scores and scabs were associated with minimal to marked microscopic skin tissue findings of erosion/ulceration, chronic-active inflammation and acanthosis/hyperkeratosis. Higher oliceridine doses up to 4.5 mg/kg/h in a rat dose range-finding study produced additional clinical signs that included rigid stance, swollen nose or perioral area, decreased reactivity to stimulus, sensitivity to touch, and audible or irregular respiration, in conjunction with decreases in food consumption and body weight.

Mild to moderate clinical pathology changes in rats or monkeys such as lower white blood cell and absolute lymphocyte counts, higher total serum protein, higher urea nitrogen, lower alkaline phosphatase correlated with treatment-related dehydration, stress/inflammation, and reduced food consumption. The reversibility of the changes has been demonstrated.

In monkeys (Study 8242809), 14 days of drug infusion at 1 mg/kg/h elicited minimal thymic atrophy that is considered as a consequence of opioid treatment-induced stress. Increased adrenal weight parameters and corresponding minimal to slight hypertrophy of the adrenal cortex in male rats administered 1 mg/kg/h have been observed as changes in response to treatment-related stress after 28 days of drug infusion (Study 8336088). A greater incidence and severity of minimal to slight apoptosis in the pancreas observed in male rats after 28 days of drug infusion is considered to be attributed to substantial reduction of food intake and not associated with any evidence of an inflammatory response in that tissue. The changes described above were observed in animals sacrificed within 45 minutes after the termination of oliceridine infusion. A higher mortality rate was observed in rats after prolonged infusion of oliceridine in the 28-day repeat dose study. The mortality was considered secondary to the infusion site inflammation/infection. Opioids have been conventionally considered immunosuppressive. Exogenous opioids such as morphine and fentanyl have been found to impair the function of macrophages, natural killer cells and T-cells and to weaken the gut barrier in vitro and in animal studies (Plein & Rittner, 2018). Reduced total white cells, reduced lymphocytes in immune organs and thymic atrophy have also been observed with oliceridine in the studies conducted by the Applicant. In epidemiological studies, high doses and the initiation of opioid therapy for non-malignant pain have been correlated with a higher risk of infectious diseases such as pneumonia (Plein & Rittner, 2018). Therefore, the higher death rate in the test article groups may be associated with compromised immune systems after prolonged treatment of oliceridine. No test article-associated increased mortality has been observed in the 14-day treatment studies in rats or monkeys, suggesting a much lower risk for shorter-term use which is intended for this product.

Opioid withdrawal-stress-related histopathological changes have been observed in rats sacrificed 24 hours after termination of 14-day infusion of oliceridine (Study 8242808 and Study 8347111). The changes include minimal to marked stomach lesions such as erosions/ulcers in the glandular stomach, mucosal congestion/hemorrhage and degeneration/necrosis in the nonglandular stomach, as well as minimal to slight adrenal cortical hypertrophy and atrophy of the seminal vesicles and prostate and decreased lymphocytes in the spleen, thymus, mesenteric and mandibular lymph nodes. The effects on stomach were observed at doses at 0.25 mg/kg/h and higher, approximately  $\geq 1.3$  and 1.9 times the projected human daily exposure at MRHDs of 40 mg and 27 mg, respectively. No NOAEL has been established for this adverse finding. The stomach lesions resolved 7 days after the termination of drug infusion. The stomach lesions were not observed after 14 days or 28 days of treatment if the rats or monkeys were sacrificed within 45 minutes after the termination of infusion as shown in Table 27. In the 14-day rat studies (Study 8242808 and Study 8347111), the incidence of stomach lesion appears to correlate with the clinical observations reflecting withdrawal symptoms such as hunched posture, nonformed feces and cold to the touch. The oliceridine-treated rats (Study 8242808) also had substantial elevations in serum corticosterone, findings consistent with stress. In a rat drug dependence study (Study 8317097), decreased food consumption and changes in behavior peaked within the first 24-48 hours during the withdrawal phase and then diminished with time, returning to baseline values by the end of the 1-week observation period. The timing of stomach lesions in rat studies where necropsies were conducted 24 hours after the discontinuation of dosing correlates with the peak symptoms of withdrawal observed in this drug dependence study. The resolution of stomach lesions (reported in Study 8347111) also appears to correlate with the disappearance of withdrawal symptoms in rats. Gastric erosion and ulceration can occur as a response to stress in laboratory animals (Greaves, 2007) and severe gastric ulceration can occur in morphine-dependent rats stressed during spontaneous or naloxone-precipitated withdrawal (Glavin, Kiernan, Hnatowich, & Labella, 1986). To further address the clinical relevance of this finding, the Applicant conducted a search using the Standardized MedDRA query “Gastrointestinal perforation, haemorrhage or obstruction” on the Controlled Phase 3, ATHENA, and All Phase 2 and Phase 3 populations. Results showed seven cases of potential interest captured among the dictionary-derived terms “hematochezia” (3 cases), “haemorrhoidal hemorrhage” (1 case), “abdominal discomfort” (2 cases), and “gastric ulcer” (1 case). These seven patients either went through GI-related surgery or invasive GI diagnostic procedure or had medical history of gastric ulcers or was in the placebo group. Therefore, these cases did not provide strong evidence suggesting an increased risk for gastric erosion or other potentially ulcerative lesions associated with the administration of oliceridine in the clinical studies. Nevertheless, attempting to evaluate the potential for drug-related gastric lesions in clinical studies may pose challenges given that patients do not undergo routine endoscopy or might be asymptomatic. In consideration of all these data and literature, the gastric lesion identified in animals after withdrawal from the drug treatment represents a risk associated with drug withdrawal rather than a direct effect from the drug. Therefore, tapering the doses would be expected to help mitigate the gastric lesion risk. The Applicant has proposed the following standard language in the drug labeling for discontinuation which is the same language for other opioids.

*When a patient who has been taking opioids regularly and may be physically dependent no longer requires therapy with [BRANDNAME], taper the dose gradually while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more (b) (4). Do not abruptly discontinue [BRANDNAME] in a physically-dependent patient [see Warnings and Precautions (**Error! Reference source not found.**), Drug Abuse and Dependence (**Error! Reference source not found.**)].*

Given that the Division has not observed the same degree of gastric lesions with other opioid drugs, this Reviewer proposes to include language describing these gastric lesions under 13.2 of the drug labeling to further inform physicians of this risk.

In summary, the effects described above are either those expected with an opioid agonist drug or secondary to stress or dehydration. These effects are monitorable or reversibility has been demonstrated after termination of the treatment. The gastric lesion was only observed after abrupt termination of the continuous infusion of the product. Tapering the doses as recommended in the label is expected to effectively mitigate the risk.

### ***Oliceridine-Specific Toxicity Findings***

A notable oliceridine-related microscopic finding was a dose-dependent increase in inflammation at the infusion site in the 28-day rat general toxicity study with a NOAEL of 0.5 mg/kg/h at 0.5 mg/mL concentration (Study 8336088), a concentration lower than the clinical concentration of 1 mg/mL. No increased inflammation at the infusion site was observed up to 1 mg/kg/h oliceridine (up to 1 mg/mL) infusion for 14 days in rats. These studies suggest a low risk of local infusion site inflammation when the IV infusion is given for a short period (e.g., ≤14 days) for treating acute pain.

In addition, an increased incidence of lung thrombi was observed in two 14-day continuous IV infusion rat studies (see the table below). Pulmonary thrombosis was observed in one vehicle-dosed male and three males and one female dosed with 1 mg/kg/h oliceridine in Study 8242808. In a rat 14-day continuous IV infusion bridging study conducted to qualify oliceridine fumarate (Study 8292859), a variable increase in the incidence of moderate or marked thrombus in pulmonary arteries was observed in animals administered oliceridine HCl or oliceridine fumarate. The Applicant stated that "*Pulmonary thrombosis is a common finding associated with IV infusion studies (Morton, et al., 1997); therefore, the apparent increased incidence and severity of thrombi in the lung may have resulted from random variation secondary to the dosing procedure and was of uncertain direct relationship to oliceridine. As a result of these findings in the 14-day infusion studies, histopathology was performed on the lungs from all animals in a 28-day continuous IV infusion study (Study 8336088) as well as a 14-day continuous IV infusion bridging study conducted to qualify oliceridine impurities (Study 8354309). No incidence of lung thrombi was observed in either study, confirming that findings in the initial 14-day studies were most likely related to random variation associated with the dosing procedure, and not a direct oliceridine effect.*" There is no observation of lung thrombi in the 14-day monkey study either. This Reviewer agrees that the lung thrombi may be associated with IV infusion given that it has been observed in vehicle-treated rats. However,

the increased incidence in oliceridine treated groups (12% for 0.5 mg/kg/h, 10.8 % for 1 mg/kg/h vs 2.5% for vehicle in the combined four rat studies) and the fact that the increased incidence only happened when there was a lung thrombosis observation in the control group appear to suggest that oliceridine treatment may exacerbate the formation of lung thrombosis originated from IV administration. There is no apparent correlation with other findings. In one of the two positive studies, a moderate reduction of platelets (around 20% reduction) was observed (Study 8292859) in males not in females, which appears to correlate with greater incidence of lung thrombosis in the males. However, this is likely not a causal relationship given that platelet increase, rather than platelet reduction, is attributable to thrombosis. Additionally, there is no change of platelets in the other lung thrombosis-positive study (Study 8242808). In these two studies the incidence of local inflammation and thrombus around the dosing site were similar to the vehicle-treated group. There is no increased lung inflammation identified in the test article-treated groups in these two studies. The preclinical studies suggest that oliceridine does not have the potential to cause hemolysis (Study 0725XT44.002) in human blood or flocculation in human plasma and serum (Study 0726XT44.002). NOAELs for lung thrombi were not established in the two positive studies where lower doses were not examined for this findings except for only one female rat in the 0.25 mg/kg/h group.

**Table 58: Incidence of Lung Thrombosis in Rat Toxicology Studies**

Study 8242808 Dose Level (mg/kg/hr)	Male				Female			
	0	0.25	0.5	1	0	0.25	0.5	1
Number Examined	10	0	0	10	10	1	0	9
Present	1	NA	NA	3	0	0	NA	1
Study 8292859 Dose Level (mg/kg/hr)	0	0.5 <sup>a</sup>	0.5 <sup>b</sup>		0	0.5 <sup>a</sup>	0.5 <sup>b</sup>	
Number Examined	10	10	10		10	10	10	
Minimal	1	0	0		0	0	0	
Slight	0	0	3		0	0	0	
Moderate	0	3	2		0	1	1	
Marked	0	0	1		0	0	1	
Study 8336088 Dose Level (mg/kg/hr)	0	0.25	0.5	1	0	0.25	0.5	1
Number Examined	9	10	10	10	10	8	10	8
Present	0	0	0	0	0	0	0	0
Study (b) (4) Dose Level (mg/kg/hr)	0	0.5 <sup>c</sup>	0.5 <sup>a</sup>		0	0.5 <sup>c</sup>	0.5 <sup>d</sup>	
Number Examined	10	10	10		10	10	10	
Minimal	0	0	0		0	0	0	

<sup>a</sup> Oliceridine fumarate

<sup>b</sup> Oliceridine HCl

<sup>c</sup> Oliceridine fumarate

<sup>d</sup> Oliceridine fumarate with degradation products and impurities

NA: not applicable

In response to our information request, the Sponsor submitted a summary of historical control data on the incidence of lung thrombosis from (b) (4) where the rat studies were conducted. The historical control data illustrated in the table below are from six rat studies of 1 to 4 weeks of duration at the (b) (4) site from January 2011 through December 2017. Four of the six studies included in the table are the Applicant's oliceridine studies, indicating a relatively small number of rat infusion studies conducted at (b) (4) over the past 7 years. Comparing to the historical control data, oliceridine in both of Study 8242808 and Study 8292859 for both sexes except females in Study 8242808 elicited lung thrombosis with an

incidence outside the high end of the historical control range. However, these historical control data are limited as 4 of the 6 studies were completed for this drug development program.

**Table 1: Incidence and Range of Selected Lung Finding in Hsd:Sprague Dawley Rats<sup>a</sup>**

Sex	Male		Female	
	Incidence (%)	Range %	Incidence (%)	Range %
Lung				
Thrombus <sup>b</sup>	5/84 (6.0)	0.0-20.0	5/84(6.0)	0.0- 13.3

<sup>a</sup>Data from 6 continuous and/or intermittent infusion studies, 1 to 4 weeks in duration conducted at (b) (4) from Jan 2011-Dec 2017.

<sup>b</sup>Includes synonym "Thrombosis".

The PharmTox review team has noticed from experience that rats have much stronger foreign body reactions compared to other species. No lung thrombi were observed in the 14-day monkey study. A very aggressive IV dosing regimen was employed in animal studies. Therefore, it is likely the risk of lung thrombosis has been overpredicted in rat studies. The lung thrombosis was not observed in 2/4 rat studies including the one that employed continuous drug infusion for 28 days and the lung thrombosis was observed in oliceridine-treated groups only when the vehicle-treated rats exhibited the finding in the study, suggesting a procedure-related low overall incidence in a sensitive species. The fact that no lung thrombosis was observed in oliceridine-treated groups if there was no lung thrombosis observed in the vehicle-treated group suggests the incidence can be prevented if the IV procedure is performed appropriately. Taken together, this Reviewer speculates the finding may have low human relevance, particularly for this acute indication.

The other microscopic findings attributed to oliceridine in rats were subacute inflammation in the cecum in Study 8354309 (14-days of infusion). Compared to humans, rats possess a larger and more fully developed cecum that serves as a fermentation chamber to digest cellulose. The cecum is largely a vestigial organ in humans, and as a result, inflammation in the rat cecum is expected to have little relevance to human safety. All other regions of the gastrointestinal tract (duodenum, jejunum, ileum and colon) were normal in this study. Inflammation of the cecum was not identified in any individual animal from two other 14-day rat infusion studies, the 28-day rat infusion study, or the 14-day monkey infusion study. The totality of evidence across the nonclinical toxicity program indicates that the minimal to slight inflammation observed in the cecum in this single 14-day rat study does not pose a significant risk to patient safety.

### ***Reproductive and Developmental Toxicity Summary***

The reproductive and developmental toxicity key findings have been summarized in Table 28. The effects on male and female fertility were evaluated in separate studies with continuous IV infusion of oliceridine. Male Sprague-Dawley rats were infused with oliceridine at doses up to 1 mg/kg/h beginning 28 days prior to cohabitation with females, throughout the mating period, and through the day of euthanasia, for a total of 64-65 days of dosing (Study (b) (4) 141505). Reproductive performance and intrauterine survival were unaffected by any dosage level in the

study, resulting in a NOAEL of 1 mg/kg/h for male reproductive toxicity and early embryonic toxicity. Total daily exposure in this study (4416 ng\*h/mL) at the NOAEL was approximately 6 and 8 times the estimated daily human exposure at MRHDs of 40 mg and 27 mg, respectively, on an AUC basis.

Female Sprague-Dawley rats were infused with oliceridine at doses up to 1 mg/kg/h beginning 14 days prior to cohabitation, continuing through the day of euthanasia on Gestation Day (GD) 15 (Study (b) (4) 141506). Oliceridine had no effect on reproductive performance (mating, fertility, and conception indices) at any dosage level. However, a longer estrous cycle length, increased pre-implantation loss, and a lower number of implantation sites and viable embryos were observed in females in the 0.5 and 1 mg/kg/h groups, resulting in a NOAEL of 0.25 mg/kg/h for female reproductive toxicity and early embryonic toxicity. The average steady-state plasma concentration in female rats dosed with 0.25 mg/kg/h oliceridine was 32 ng/mL. Total daily exposure in this study (768 ng\*h/mL) at the NOAEL was approximately 1 and 1.5 times the estimated daily human plasma exposure at MRHDs of 40 mg and 27 mg, respectively, on an AUC basis.

Following range-finding studies in rats (Study (b) (4) 141501) and rabbits (Study (b) (4) 141502), GLP studies were conducted to evaluate the effects of oliceridine on embryo-fetal development. Female Sprague-Dawley rats were continuously infused with oliceridine from the time of implantation (GD 6) to 1 day prior to expected parturition (GD 20) at doses up to 1 mg/kg/h (Study (b) (4) 141503). No adverse maternal toxicity was observed in the study and intrauterine growth and survival and fetal morphology were unaffected by oliceridine dosing, resulting in a NOAEL of 1 mg/kg/h for teratogenic effects in rats. In the rat study, the percent of litters with reduced ossification of the vertebral arches was increased in the high-dose group (5.2%) compared to controls and outside the historical control range of up to 2%. Reduced ossification of the skull was also higher in the high-dose group compared to control (2% of litters in HD vs. 0% in controls), suggesting a potential developmental delay at this dose. Reduced ossification could be considered as a developmental delay or a direct structural alteration. Given the lack of overt evidence of malformations or skeletal abnormalities in the pre- and postnatal study, this may be more of a developmental delay (inhibition of growth) and not necessarily adverse. The average steady state plasma concentration in female rats dosed with 1 mg/kg/h oliceridine was 164 ng/mL. Total daily exposure in this study (3936 ng\*h/mL) at the NOAEL was approximately 5 and 7.4 times the estimated daily human exposure at the MRHDs of 40 mg and 27 mg, respectively, on an AUC basis.

Female New Zealand White rabbits were continuously infused with oliceridine from the time of implantation (GD 7) to 1 day prior to expected parturition (GD 29) at doses up to 0.25 mg/kg/h (Study (b) (4) 141504). Maternal adverse effects that included reduced food consumption and corresponding reductions in mean body weights were observed in rabbits dosed with 0.25 mg/kg/h. Intrauterine growth and survival and fetal morphology were unaffected by oliceridine dosing, resulting in a NOAEL of 0.25 mg/kg/h for teratogenic effects in rabbits. The average steady state plasma concentration in female rabbits dosed with 0.25 mg/kg/h oliceridine was 173 ng/mL. Total daily exposure in this study (4152 ng\*h/mL) at the NOAEL was approximately 5 and 8 times the estimated daily human exposure at the MRHDs of 40 mg and 27 mg, respectively, on an AUC basis.

The effects on pre- and postnatal development were assessed in Sprague-Dawley rats administered oliceridine via continuous IV infusion from implantation to weaning (Study (b) (4) 141509) at doses up to 0.25 mg/kg/h. Oliceridine administration to F<sub>0</sub> dams produced no F<sub>0</sub> or F<sub>1</sub> maternal toxicity, had no effect on F<sub>1</sub> developmental landmarks or memory and learning, had no effect on F<sub>1</sub> reproductive endpoints, gestation lengths or the process of parturition, and produced no F<sub>2</sub> neonatal/early postnatal toxicity, resulting in a NOAEL of 0.25 mg/kg/h for these parameters. However, oliceridine F<sub>0</sub> maternal dosing did produce a dose-related decrease in F<sub>1</sub> pup survival from birth to PND 4 in the 0.1 mg/kg/h group, with lower mean surviving pup weights on PND 1 compared to controls; therefore, a dose level of 0.025 mg/kg/h was the NOAEL for F<sub>1</sub> neonatal/developmental toxicity. Oliceridine plasma concentrations were not measured in this study but based on female plasma concentrations measured in Study (b) (4) 141506, and assuming dose-linear exposures, total daily exposures at the NOAEL of 0.25 mg/kg/h for F<sub>0</sub>/F<sub>2</sub> and 0.025 mg/kg/h for F<sub>1</sub> in this study were 837 ng\*h/mL and 84 ng\*h/mL, respectively. These exposures result in approximately 1 and 2 times the estimated daily human plasma exposure at the MRHDs of 40 mg and 27 mg, respectively, for F<sub>0</sub> maternal toxicity and F<sub>2</sub> neonatal/early postnatal toxicity; approximately 0.1 and 0.15 times the estimated daily human plasma exposure at the MRHD of 40 mg and 27 mg, respectively, on an AUC basis for F<sub>1</sub> neonatal developmental toxicity.

The effects of oliceridine characterized in developmental and reproductive toxicology studies have been illustrated in the proposed label under Session 8.1 Pregnancy, 8.3 Females and Males of Reproductive Potential, and 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.

### **Genetic Toxicology Summary**

Genetic toxicity testing of oliceridine revealed no evidence of mutagenicity in a bacterial reverse mutation assay (Study 8242829) in the absence or presence of a rat metabolic activation system at concentrations up to 5000 mcg/plate, and no evidence of clastogenicity in an in vivo rat micronucleus assay (Study 8242831) when dosed up to the maximally tolerated IV infusion dose of 1 mg/kg/h (oliceridine plasma concentrations in rats at the 1 mg/kg/h dose level were 366 ng/mL, approximately 4 and 6 times the daily exposure at the MRHDs of 40 mg and 27 mg, respectively, on an AUC basis.

Oliceridine showed evidence of weak clastogenicity in cultured human peripheral blood lymphocytes in two experiments when incubated with high concentrations of oliceridine for 3 hours in the presence of a rat liver metabolic activation system (+S9) up to the limit of cytotoxicity (2.2 mM; cytotoxicity range of 50-63%) (Study 8242830). There was no clear evidence of a concentration-related response and only concentrations >1.6 mM (concentrations that induced high cytotoxicity) demonstrated aberrant cell frequencies that exceeded the 95<sup>th</sup> percentile of the normal range for both replicate cultures. An additional chromosome aberration study (Study 8292858) conducted to qualify an alternative oliceridine salt form (oliceridine fumarate) showed that both oliceridine salt forms were negative for inducing chromosomal aberrations, polyploidy, and endoreduplication in cultured human lymphocytes when tested up the limit dose of the assay (1 mM) or the limit of cytotoxicity in the

presence and absence of metabolic activation. In order to further evaluate the in vitro chromosome aberration assay findings, a comet assay was performed (Study 8254795) in rats following a 24-hour continuous IV infusion up to the maximally tolerated dose of 1 mg/kg/h. Results from this assay showed that oliceridine did not induce DNA damage in the liver and blood of rats administered a 24-hour continuous IV infusion of 1 mg/kg/h oliceridine. Results from these studies indicate that the risk of clastogenicity in humans, if any, is minimal.

### ***Safety Evaluation of Major Human Metabolites***

As mentioned above, radiochemical and mass spectrometric profiling of plasma collected from a human metabolism and excretion study (Study CP130-1007) with IV administration of [<sup>14</sup>C]-TRV130 identified two human metabolites with mean plasma AUC values greater than 10% of total drug-related material—M22 (61.9%) and TRV0109662 (17.4%).

Although TRV0109662 binds to the human MOR, it is approximately 500-fold less potent (function) and approximately half as efficacious at mediating GPCR activation than oliceridine as a MOR agonist. TRV0109662 showed negligible activity against a panel of 135 typical counterscreen enzymes, receptors, channels, and neurotransmitter uptake transporters at concentrations up to 10 mcM. TRV0109662 was negative for mutagenicity in a bacterial reverse mutation assay (Study AE85CE.502ICH.BTL) and negative for clastogenicity in an in vitro micronucleus assay (Study AE85CE.348ICH.BTL). These data indicate that it is not very likely that TRV0109662 will contribute to either to the pharmacologic or toxicologic profile of oliceridine.

Validated bioanalytical methods were developed and utilized to measure TRV0109662 concentrations in rat and human plasma. As summarized in Table 23 in Section 9.2.1, mean total exposure in the Study (b) (4) of the estimated daily human plasma exposure, thus qualifying TRV0109662 in one species for general toxicity. The rat samples from Study 8336088 used to extrapolate for the exposure in the rat embryo-fetal study failed significantly in Incurred Sample Reanalysis (ISR). Therefore, the stated 55% of the human exposure reached in the rat embryo-fetal study is considered questionable. The Applicant speculated that the cause of ISR failures is related to low concentration of the metabolite in the samples, small sample size and species-selective matrix interference. The data of human plasma concentrations does suggest the exposure to this metabolite is low in human. TRV0109662 did not show pharmacological activity when screened against over 100 receptors, enzymes, transporters and channels at a high concentration of 10 mcM, except a weak partial mu agonism activity. It is negative in the in vitro genotoxicity assessment up to the limit concentration. In the 14-day general toxicity study with the elevated TRV0109662, no evident additional toxicity was observed compared to oliceridine alone. Considering the totality of the data, this Reviewer speculates the likelihood for this metabolite to contribute to embryo-fetal toxicity is relatively low for an acute indication. However, given the concerns on the validity of the PK data for rat embryo-fetal developmental study, the safety characterization of this metabolite on embryo-fetal development should be considered inadequate.

M22 in the embryo-fetal study only reached 53% of the estimated total human exposure at the MRHD of 40 mg/day, suggesting this metabolite formed disproportionately in rabbits, therefore the embryo-fetal study in rabbits did not adequately characterize the toxicology of M22.

However, M22 is an ether glucuronide metabolite with no intrinsic toxicity which has been supported by the Applicant's genetic toxicity studies demonstrating no genetic toxicity concerns. M22 does not have significant pharmacology activities and showed a benign safety profile in the monkey 14-day study in which exposure to M22 was much higher than the estimated human exposure at the proposed MRHD of 40 mg/day. These data are in line with what has been noted in the *Safety Testing of Drug Metabolites* guidance that "Phase II conjugation reactions generally render a compound more water soluble and pharmacologically inactive, thereby eliminating the need for further evaluation. However, if the conjugate forms a toxic compound such as acylglucuronide, additional safety assessment may be needed." Taking into consideration the totality of the data, this metabolite is considered qualified for safety at the proposed MRHD.

### **Qualification of Alternative Salt Form**

Initial nonclinical and clinical development studies were conducted with oliceridine HCl. In order to qualify an alternative oliceridine salt form, oliceridine fumarate was evaluated in a bacterial reverse mutation assay (Study 8292857), a chromosome aberration study in cultured human peripheral blood lymphocytes (Study 8292858), and a 14-day continuous IV infusion toxicity study in Sprague-Dawley rats (Study 8292859). Oliceridine fumarate produced no evidence of mutagenicity or clastogenicity in the two genotoxicity studies. The 14-day infusion study did not identify clear difference between oliceridine HCL and oliceridine fumarate in toxicology profile. TRV130 fumarate has been tested in the longer-term, 28-day, general toxicity study and in all the reproductive and developmental toxicology studies. This Reviewer concluded the safety and toxicology profile of oliceridine fumarate have been adequately characterized.

### **Evaluation of Related Substance**

The proposed specifications for four drug substance impurities and drug product degradants exceed ICH thresholds for identification/qualification based on a 40 mg daily maximum dose of oliceridine. The list includes one process impurity/degradation product (b) (4), two API process impurities (b) (4), and one regulatory starting material/degradation product (b) (4). The Applicant has qualified the four impurities/degradation products according to ICH Q3A(R2) and ICH Q3B(R2) (b) (4) and in vitro battery of genetic toxicology studies up to the limit dose.

For mutagenicity potentials, the Applicant conducted QSAR prediction studies with Derek and VEGA-QSAR assessment on all the specified impurities and unspecified impurities likely to arise during synthesis and storage of oliceridine fumarate drug substance and drug product, except two mutagenic/carcinogenic impurities (b) (4). The assessments predicted that all the impurities would be negative in the bacterial reverse mutation test. (b) (4) was identified as a possible impurity introduced during an (b) (4) manufacturing step and (b) (4) is a likely impurity formed during drug product degradation. The Applicant did risk assessment on these two carcinogenic impurities in a worst-case scenario assuming a maximum daily oliceridine dose of 100 mg. The worst-case scenario risk assessment estimated maximal level of (b) (4) in human plasma

from the drug product accounts for negligible (b) (4) % of the endogenous turnover of (b) (4) at 100 mg/day. The percentage will be further reduced based on the proposed MRHD of 40 mg/day or 27 mg/day. The worst-case scenario risk assessment on (b) (4) estimated the highest (b) (4) intake calculated from oliceridine drug product at 100 mg/day will not exceed (b) (4) mcg/day which is far below 120 mcg/day acceptable intake for a mutagenic impurity according to ICH M7(R1). The Applicant has proposed to reduce the MRHD from 100 mg/day to 40 mg/day and, therefore, the risk would further be minimized. This Reviewer agrees that the risk of (b) (4) from the oliceridine drug product with the proposed specification is low to humans.

The five primary registration batches of oliceridine met the proposed specifications for (b) (4) set according to ICH Q3C(R6) limits, indicating that no further safety assessment is required. Elemental impurities are controlled at levels not more than 30% of the permitted daily exposure identified in ICH Q3D; therefore, no further safety assessment is required.

Analytical evaluation thresholds (AET) were established based on preliminary extraction studies to identify potential leachable compounds present in the oliceridine drug product at concentrations (b) (4) based upon daily MRHD of 100 mg in 100 mL originally proposed by the Applicant). A toxicological risk assessment was performed on volatile and semi-volatile leachables that were shown to exceed the AET. In all cases, the maximum potential daily exposure following a 100 mg daily oliceridine dose was either well below the calculated PDE or well below the qualification threshold as per ICH Q3C(R6), indicating a minimal risk to patient safety even at 100 mg daily. The safety margin would be widened further with a lower MRHD such as that proposed at 40 mg/day. No elemental leachables have been identified with the improved analytical methods with LOQ capable of identifying elemental compounds exceeding PDE indicated in ICH Q3D for specific elements. Therefore, the safety of the container closure system has been adequately justified.

There are no novel excipients used in the drug product.

## 12 Appendix/Attachments

Carney, E. W., & Kimmel, C. A. (2007). Interpretation of skeletal variations for human risk assessment: delayed ossification and wavy ribs. *Birth Defects Res B Dev Reprod Toxicol*, 80, 473-496.

Chung, Y. H., Shin, S. H., Han, J. H., & Lee, Y. H. (2016). Subacute Inhalation Toxicity of 3-Methylpentane. *Toxicol Res*, 32, 245-250.

Clarke, G., & Wright, D. M. (1984). A comparison of analgesia and suppression of oxytocin release by opiates. *Br J Pharmacol*, 83, 799-806.

European Food Safety Authority, E. (2014). Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources. *EFSA Journal*, 12, 3550.

Glavin, G. B., Kiernan, K., Hnatowich, M. R., & Labella, F. S. (1986). Effects of morphine and naloxone on stress ulcer formation and gastric acid secretion. *Eur J Pharmacol*, 124, 121-127.

Greaves, P. (2007). *Histopathology of preclinical toxicity studies : interpretation and relevance in drug safety evaluation*: Academic Press: Amsterdam; New York.

Heck, H. D., Casanova-Schmitz, M., Dodd, P. B., Schachter, E. N., Witek, T. J., & Tosun, T. (1985). Formaldehyde (CH<sub>2</sub>O) concentrations in the blood of humans and Fischer-344 rats exposed to CH<sub>2</sub>O under controlled conditions. *Am Ind Hyg Assoc J*, 46, 1-3.

(b) (4)

Morton, D., Safron, J. A., Glosson, J., Rice, D. W., Wilson, D. M., & White, R. D. (1997). Histologic lesions associated with intravenous infusions of large volumes of isotonic saline solution in rats for 30 days. *Toxicol Pathol*, 25, 390-394.

Plein, L. M., & Rittner, H. L. (2018). Opioids and the immune system - friend or foe. *Br J Pharmacol*, 175, 2717-2725.

Rayner, V. C., Robinson, I. C., & Russell, J. A. (1988). Chronic intracerebroventricular morphine and lactation in rats: dependence and tolerance in relation to oxytocin neurones. *J Physiol*, 396, 319-347.

Snipes, R. L. (1981). Anatomy of the cecum of the laboratory mouse and rat. *Anat Embryol (Berl)*, 162, 455-474.

Subramaniam, S., Patel, D., Davit, B. M., & Conner, D. P. (2015). Analysis of imprecision in incurred sample reanalysis for small molecules. *AAPS J*, 17, 206-215.

(b) (4)

Vuong, C., Van Uum, S. H., O'Dell, L. E., Lutfy, K., & Friedman, T. C. (2010). The effects of opioids and opioid analogs on animal and human endocrine systems. *Endocr Rev*, 31, 98-132.

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/s/  
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MIN ZHANG  
10/04/2018

JAY H CHANG  
10/04/2018

RICHARD D MELLON  
10/04/2018  
I concur.



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

# Statistical Review and Evaluation

## CLINICAL STUDIES

**NDA/Serial Number:** 210730/0001  
**Drug Name:** Oliceridine (injection)  
**Indication:** Acute Pain, Opioid (5030350)  
**Study number:** CP130-1011  
**Applicant:** TREVENA INC  
**Date(s):** Date of Document: 11/02/2017  
PDUFA date: 11/02/2018  
Completion date: 3/15/2018  
**Review Priority:** S  
**Biometrics Division:** DB VI  
**Statistical Reviewer:** Ling Chen, Ph.D., Expert Mathematical Statistician, CSS supporting team/DBVI/OB  
**Concurring Reviewers:** Qianyu Dang, Ph.D., Lead Statistician, CSS supporting team/DBVI/OB  
**Medical Division:** Controlled Substance Staff  
**The CSS Team:** Katherine Bonson, Ph.D., Pharmacologist, OD/CSS  
Dominic Chiapperino, Ph.D., Acting Director, OD/CSS  
**Project Manager:** Sandra Saltz, OD/CSS  
**Keywords:** Crossover design; Human abuse potential study; Self-reported endpoint; Stimulants

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## 1. Executive Summary

The applicant, Trevena Inc., submitted the results from the human abuse potential study CP130-1011 for the assessment of abuse potential of oliceridine.

Study CP130-1011 was a single-dose, randomized, double-blind, placebo- and active-controlled crossover study. The primary objective was to evaluate the abuse potential of single intravenous (IV) doses (1 mg, 2 mg and 4 mg) of oliceridine compared to IV morphine (10 mg and 20 mg) and IV placebo in healthy, non-dependent, recreational, opioid users. Forty-two subjects were randomized to the Treatment Phase. Of these, 40 subjects completed the study.

The primary endpoint was Drug Liking Emax. The secondary endpoints included in the reviewer's secondary analysis were Good Effects Emax and High Emax.

As with morphine, all 3 doses of oliceridine showed large increases in mean of VAS scores with peak effects occurring by 5 minutes post-dose. Compared to the morphine's effects which lasted approximately 4 hours, oliceridine had a shorter duration of effects, lasting for approximately 2 to 3 hours.

The results from the reviewer's primary analysis show that

- oliceridine 1 mg had significantly lower maximum liking than each dose of morphine, but had significantly greater maximum liking than placebo;
- there was no significant difference in maximum liking between oliceridine 2 mg and morphine 10 mg;
- there was no significant difference in maximum liking between oliceridine 4 mg and morphine 20 mg.

The significant difference in maximum liking between each dose of morphine and placebo validated the study.

The results from the secondary analysis on Good Effects Emax and High Emax echo those from the primary analysis.

In conclusion, the positive effects (drug liking, good effects and high) of oliceridine 2 mg and 4 mg may be comparable with morphine 10 mg and 20 mg, respectively. The positive effects of Oliceridine 1 mg were lower than both doses of morphine but greater than placebo.

## **2. Review report on Study CP130-1011**

### **2.1. Overview**

Study CP130-1011 was a single-dose, randomized, double-blind, placebo- and active-controlled crossover study to evaluate the abuse potential of oliceridine compared to morphine and placebo when administered intravenously in healthy, non-dependent, recreational, opioid users.

#### **2.1.1. Objectives of the study**

Primary Objective:

- To evaluate the abuse potential of single intravenous (IV) doses of oliceridine compared to IV morphine and IV placebo in healthy, non-dependent, recreational, opioid users.

Secondary Objective:

- To evaluate the safety and tolerability of IV oliceridine in healthy, non-dependent, recreational opioid users.

#### **2.1.2. Study design**

The study consisted of a Dose Escalation Phase (Part A) and the Main Study (Part B).

##### Dose Escalation Phase (Part A)

Part A utilized a randomized, double-blind, placebo-controlled, dose escalation design that planned to include up to 3 separate cohorts of subjects to evaluate escalating oliceridine doses. Planned dose levels of oliceridine included 3 mg, 5 mg, and 7 mg. Following dosing in each cohort, the Sponsor and Investigator reviewed the blinded safety and pharmacodynamic data prior to initiating the next cohort. Based on results from the 3 mg and 5 mg dose cohorts, the 7 mg dose cohort was ultimately not completed.

Part A consisted of 3 visits: an outpatient screening visit (Day -28 to Day -1); an inpatient treatment visit (Day -1 to Day 2), and a Follow-up visit (3 to 7 days after discharge). Subjects were admitted on Day -1, dosed with study drug on Day 1, and discharged after completion of study assessments on Day 2. All subjects who participated in the treatment visit returned within 3 to 7 days of discharge for a follow-up visit.

##### Main Study (Part B)

Part B consisted of 3 visits: an outpatient screening visit (Day -28 to Day -1); an inpatient Qualification and Treatment Phase visit (Day -1 to Day 15), and a Follow-up visit (7 to 14 days after discharge). The Qualification Phase comprised a Naloxone Challenge Test to confirm subjects were not opioid-dependent, and a Drug Discrimination Test (subjects received IV morphine and matching placebo in a randomized-sequence, double-blind, crossover manner, separated by approximately 24 hours) to ensure subjects could discriminate and show positive subjective effects of morphine. Subjects who met the Drug Discrimination Test criteria entered the Treatment Phase. A minimum washout interval of approximately 48 hours was required between last study drug

administration in the Qualification Phase (Day 2) and first study drug administration in the Treatment Phase (Day 4).

Following confirmation of eligibility in the Qualification Phase, subjects were randomized to 1 of 6 treatment sequences including single doses of oliceridine 1, 2, and 4 mg; morphine 10 and 20 mg (doses were selected based on Part A results); and placebo according to a  $6 \times 6$  Williams square in the Treatment Phase. Each treatment was separated by a 48-hour washout period.

*Reviewer's comments: This review is for the main study Part B. Therefore, from now on any information, analysis, results and conclusion are based on Part B of the study.*

### **2.1.3. Qualification Phase Eligibility Criteria**

Maximum effect (Emax) score in response to IV morphine greater than that of placebo on the bipolar Drug Liking VAS (difference of at least 15 points) and Emax score of at least 65 points for IV morphine within 1 hour post-dose, and acceptable overall responses to morphine on all other subjective measures, as judged by the Investigator or designee.

- Acceptable placebo response based on Drug Liking VAS (score between 40 and 60 points, inclusive). Acceptable placebo response on all other subjective measures.
- Subject was able to tolerate the dose of IV morphine, as judged by the Investigator, including ability to complete all pharmacodynamic assessments within 1 hour postdose.
- General behavior suggested that the subject could successfully complete the study (eg, following clinic rules, compliance, etc), as judged by the CRU staff.

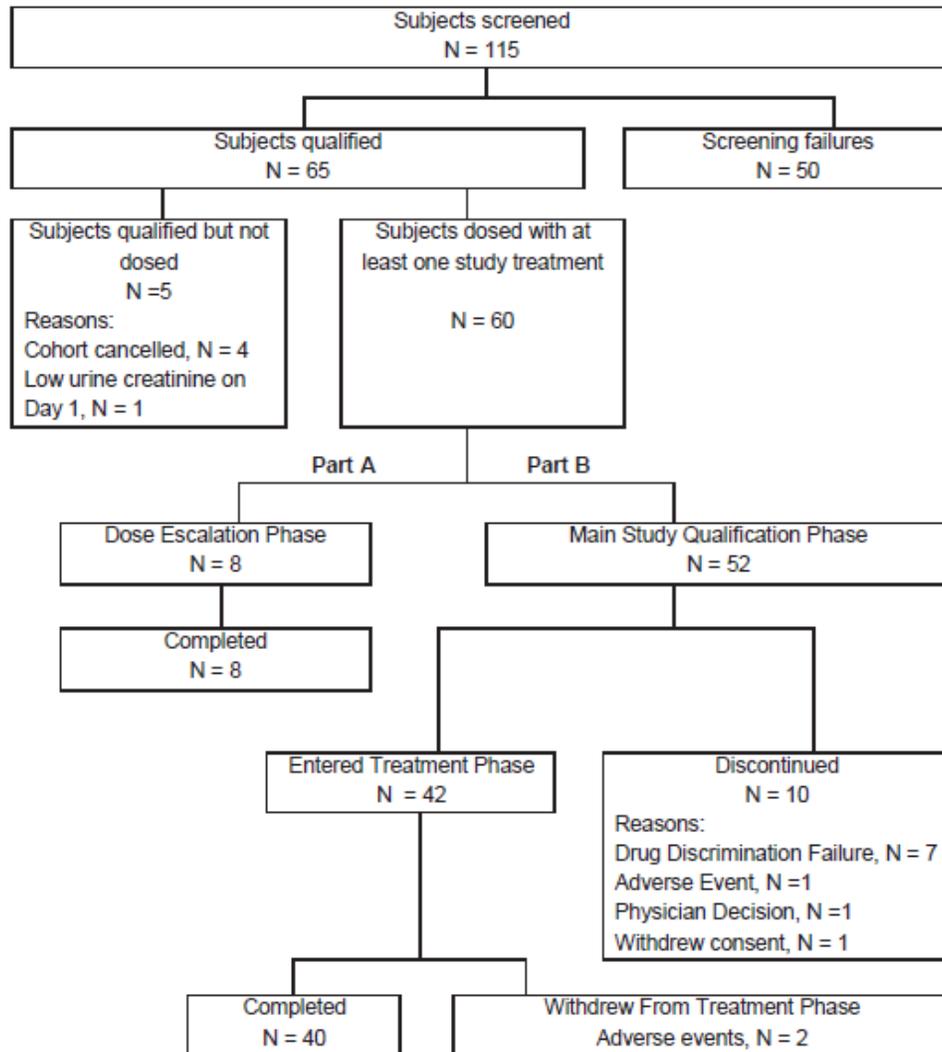
### **2.1.4. Number of Subjects**

Fifty-two subjects entered the Main Study Qualification Phase and received at least one dose of the Drug Discrimination Test treatments (Qualification Population). Twenty-six subjects were randomized to the XY (10 mg morphine, followed by placebo) sequence and 26 subjects to the YX sequence (placebo followed by 10 mg morphine). Ten subjects discontinued in this phase: 7 subjects were drug discrimination failures, 1 subject was discontinued due to physician decision, 1 withdrew consent, and 1 discontinued due to an AE.

Forty-two subjects were thus randomized to the Treatment Phase (Part B Randomized Population), with 7 subjects randomized to each sequence. Each of these subjects was dosed with at least 1 dose of oliceridine, morphine, or placebo, and was included in the Safety Population. Two subjects discontinued the Treatment Phase prematurely due to adverse events after receiving the first treatment of their assigned sequence (Treatment E, morphine 20 mg); 40 subjects thus completed and were included in the Completer Population. Of the completers, 2 had major protocol deviations; thus, the Per Protocol Population consisted of 38 subjects.

The following figure shows the overall subject disposition (Sponsor's Figure 1 on page 64 of the report)

**Figure 1 Overall Subject Disposition**



Source: Subject enrolment log, data on file; Listing 16.2.1.1

### 2.1.5. Abuse potential Endpoints

Drug Liking (Emax, TEmax, Emin, TEmin, TA\_AUE<sub>0-8</sub>), bipolar VAS

Overall Drug Liking (Emax, Emin), bipolar VAS

Take Drug Again (Emax), bipolar VAS

Good Effects (Emax, TEmax, TA\_AUE<sub>0-8</sub>), unipolar VAS

Bad Effects (Emax, TEmax, TA\_AUE<sub>0-8</sub>), unipolar VAS

Any Effects (Emax, TEmax, TA\_AUE<sub>0-8</sub>), unipolar VAS

High (Emax, TEmax, TA\_AUE<sub>0-8</sub>), unipolar VAS

Alertness/Drowsiness (E<sub>max</sub>, T<sub>E<sub>max</sub></sub>, TA\_AUE0-8), unipolar VAS  
Drug Similarity (E<sub>max</sub>, T<sub>E<sub>max</sub></sub>, TA\_AUE0-8), 8-hour score  
Pupillometry (MPC, PAOC<sub>0-8</sub>)

The primary endpoint is Drug Liking E<sub>max</sub>.

### **2.1.6. Statistical methodologies used in the Sponsor's analyses**

All statistical analyses were performed on the Treatment Phase using the Completer Population. The treatment comparisons to assess the abuse potential of IV oliceridine included the following:

- Each dose of morphine vs placebo (study validity)
- Each dose of oliceridine vs each dose of morphine (relative abuse potential)
- Each dose of oliceridine vs placebo (absolute abuse potential)

For primary endpoint Drug Liking E<sub>max</sub>, the following tests are performed:

#### Carryover Effect Test

The SAS mixed effects linear model procedure (PROC MIXED) was used to construct an analysis of variance model for the primary endpoint, Drug Liking VAS E<sub>max</sub>. The model included terms for treatment, period, sequence, and first-order carryover effect as fixed effects, with subject nested within sequence as a random effect.

#### Normality Test

The residuals of the primary endpoint were investigated for normality using the Shapiro-Wilk W-test. As the probability value was  $\geq 0.01$  and the residuals appeared relatively unskewed and moderately symmetric, Drug Liking E<sub>max</sub> was analyzed as having a normal distribution and the results of the mixed effects model were reported. Least squares means, the difference between the means, and corresponding 95% confidence intervals (CIs) were provided for the treatment comparisons. No adjustments were made for multiplicity.

#### Validity Test

Study validity was to be concluded if there was a statistically significant difference between morphine and placebo in the primary endpoint for at least one of the two doses of morphine, with the other dose being at least numerically in the correct rank versus placebo (ie, mean E<sub>max</sub> for both morphine doses should be in the same direction relative to placebo). If one of the doses of morphine was not statistically different from placebo, it was not to be included in the comparisons with oliceridine to assess abuse potential relative to morphine.

The primary endpoint analyses were to be repeated with the Per Protocol Population if the size of the Completer Population was greater than the Per Protocol Population by more than 10%. The same analysis method chosen for the primary endpoint, Drug Liking VAS E<sub>max</sub>, of the Completer Population was to be used for the Per Protocol Population analysis.

All secondary PD parameters were analyzed using the same method chosen for the primary endpoint, Drug Liking VAS Emax, ie, a linear mixed effects model with treatment, period, sequence, and carryover as fixed effects and subject nested within sequence as a random effect. No adjustments were made for multiplicity.

## 2.2. Data Location

The datasets used in the reviewer's analysis are located at

<\\cdsesub1\evsprod\nda210730\0001\m5\datasets\cp130-1011\analysis\adam\datasets>

## 2.3. Summary of Sponsor Reported Analysis Results

- Study validity was demonstrated by the statistically significant difference between both doses of morphine and placebo on the primary endpoint of Drug Liking VAS Emax. A positive dose-effect relationship was observed with morphine, as the morphine 20 mg dose had numerically higher scores than that of the 10 mg dose on the majority of measures, although morphine 20 mg was also associated with higher scores than placebo on the Bad Effects VAS, suggesting greater negative effects at the higher dose.
- As with morphine, all 3 doses of oliceridine showed large increases in VAS scores, with peak effects occurring by 5 minutes post-dose. In contrast to morphine's effects which lasted approximately 4 hours, oliceridine had a shorter duration of effects, lasting for approximately 2 to 3 hours. Oliceridine also showed a positive dose-effect relationship, with scores for the oliceridine 2 mg dose numerically higher than those of the 1 mg dose, and for the 4 mg dose numerically higher than those of the 2 mg dose on the majority of measures.
- In terms of absolute abuse potential, there were statistically significant differences between all 3 oliceridine doses and placebo on the primary endpoint of Drug Liking VAS Emax, as well as majority of secondary measures and endpoints.
- With respect to relative abuse potential, oliceridine 1 mg was associated with weaker subjective effects compared to 2 mg and 4 mg doses; however, oliceridine 1 mg was still associated with greater subjective effects compared to placebo. On the majority of subjective measures, including the primary endpoint, Drug Liking VAS Emax, comparisons between similar dose-match levels of oliceridine and morphine (ie, 2 mg and 10 mg and 4 mg and 20 mg) were not significantly different.

## 2.4. Reviewer's Assessment

In this report, the reviewer used the following notations for treatments in Study CP130-1011.

MPH10 – morphine 10 mg

MPH20 – morphine 20 mg

OLIC1 – oliceridine 1 mg  
 OLIC2 – oliceridine 2 mg  
 OLIC4 – oliceridine 3 mg  
 P – Placebo

## 2.4.1. Primary Analysis

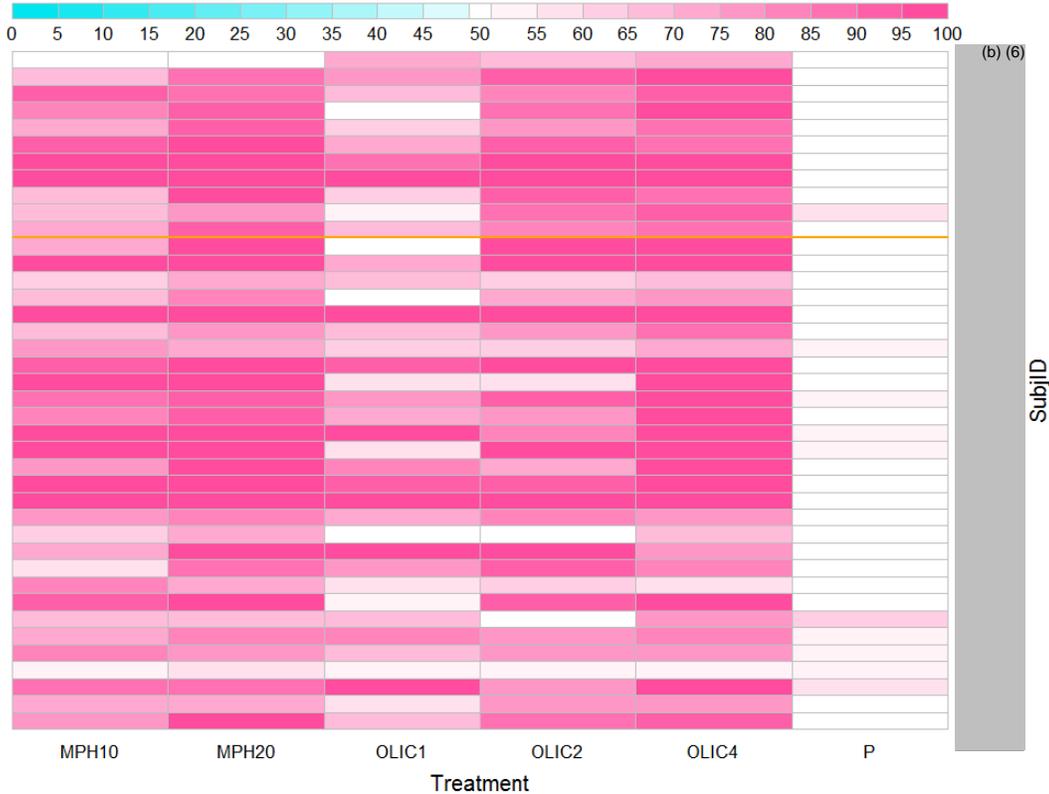
### 2.4.1.1. Descriptive statistics

Table 1 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 6 treatments in the study for the primary endpoint Drug Liking Emax.

**Table 1: Summary statistics for Drug Liking Emax (N=40)**

TRT	Mean	SD	Min	Q1	Med	Q3	Max
MPH10	80.7	14.5	50	70	79.5	95	100
MPH20	88.5	13.1	50	79.3	94	100	100
OLIC1	72.2	16.6	50	58.3	70	84	100
OLIC2	82.6	14.9	50	74.5	83	95	100
OLIC4	88.4	12.9	53	78.3	92.5	100	100
P	50.9	2.4	50	50	50	50.8	61

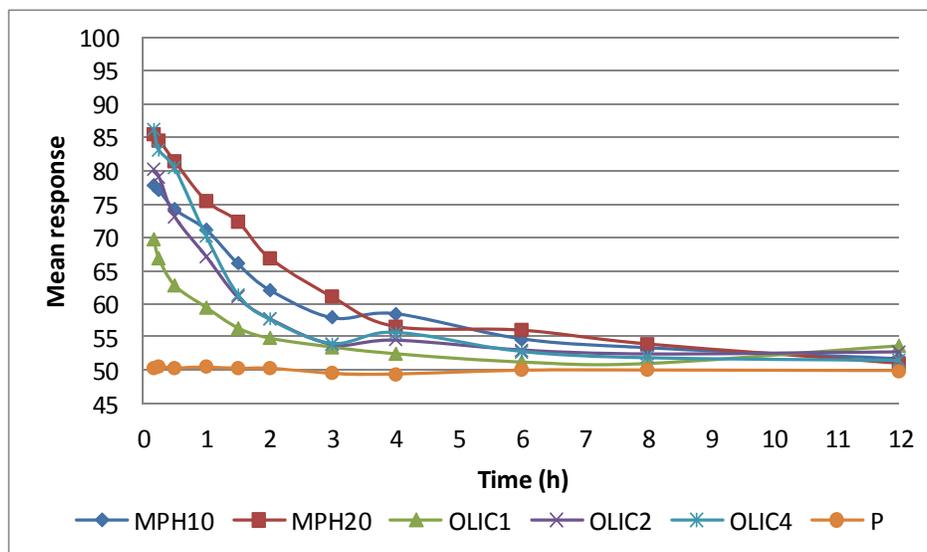
As summarized in Table 1, there was no much difference in means of maximum liking between oliceridine 2 mg and morphine 10 mg, and between oliceridine 4 mg and morphine 20 mg. Figure 1 is the heat map by treatment for the primary endpoint.



**Figure 1: Heat Map by Treatment for Drug Liking Emax**

The heat map presents maximum liking in color for each subject by each treatment. The orange line on the heat map separates females from males. Note that Subject # (b) (6) had maximum liking 50 to both morphine 20 mg and morphine 40. This means that the subject did not respond to morphine at all.

Figure 2 is the mean time course profiles by treatment for Drug Liking VAS. Data were collected at hours 0.083, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 12.0. The peak mean responses for morphine 20 mg and 40 mg were 77.9 and 85.5, respectively. Similarly, the peak mean responses for oliceridine 2 mg and 4 mg were 80.1 and 86.3, respectively. As with morphine, all 3 doses of oliceridine showed large increases in VAS scores with peak effects occurring by 5 minutes post dose. The peak mean of drug liking of oliceridine dropped quickly within 2 hour postdose and last for two hours, while the effect of morphine last for 3 to 4 hours.



**Figure 2: The mean time course profiles in 12 hours on Drug Liking VAS by treatment (N=40)**

#### 2.4.1.2. Statistical Testing

To evaluate abuse potential of oliceridine, the following comparisons were performed for the primary endpoint, Drug Liking Emax.

1. MPH20 versus P
2. MPH40 versus P
3. MPH20 versus OLIC1
4. MPH40 versus OLIC1
5. OLIC1 versus P
6. MPH20 versus OLIC2
7. MPH40 versus OLIC2
8. OLIC2 versus P
9. MPH20 versus OLIC4
10. MPH40 versus OLIC4
11. OLIC3 versus P

The comparisons #1 and #2 were for the study validation. If the comparison of a dose of oliceridine did not have a statistically significantly lower mean than any dose of morphine, the comparison between the dose of oliceridine and placebo would not be performed,.

The statistical model used in the reviewer's primary analysis was a mixed-effects model which included sequence, period and treatment as fixed effects, and subject as a random effect. With heteroscedasticity adjustment, the Shapiro-Wilk W-test on the residual was not statistically significant for Drug Liking VAS with a p-value greater than 0.01.

The FDA 2017 Guidance recommends the following hypotheses:

1.  $H_0 : \mu_C - \mu_P \leq \delta_1$  versus  $H_a : \mu_C - \mu_P > \delta_1$ ,
2.  $H_0 : \mu_C - \mu_T \leq \delta_2$  versus  $H_a : \mu_C - \mu_T > \delta_2$ , and
3.  $H_0 : \mu_T - \mu_P \geq \delta_3$  versus  $H_a : \mu_T - \mu_P < \delta_3$ ,

where  $C$ ,  $T$  and  $P$  denote morphine, or oliceridine and placebo. The sponsor did not pre-specify  $\delta$ s. The  $\delta_1=15$ ,  $\delta_2=0$  and  $\delta_3=11$  were used in the reviewer's analysis.

Table 3 summarizes the least square means by treatment. The statistical analysis results are listed in Table 4.

**Table 2: Least square means for Drug Liking Emax (N=40)**

TRT	LSMean	StdErr	95% CI	
			LCL	UCL
MPH10	80.7	2.2	77.1	84.3
MPH20	88.8	1.9	85.6	91.9
OLIC1	72.3	2.8	67.7	76.9
OLIC2	82.6	2.2	78.9	86.3
OLIC4	88.6	1.9	85.4	91.7
P	51.0	2.3	47.1	54.9

**Table 3: Statistical analysis results for Drug Liking Emax (N=40)**

Pairwise Comparison	LSMean Diff	StdErr	Test Value	p-value	95% CI	
					LCL	UCL
MPH10-P	29.7	2.2	15	<.0001	26.0	Infty
MPH20-P	37.7	2.0	15	<.0001	34.4	Infty
MPH20-OLIC1	16.5	2.5	0	<.0001	12.3	Infty
MPH10-OLIC1	8.5	2.7	0	0.0014	3.9	Infty
OLIC1-P*	21.3	2.8	11	0.9997	-Infty	26.0
MPH20-OLIC2	6.1	1.9	0	0.001	3.0	Infty
MPH10-OLIC2	-1.9	2.1	0	0.811	-5.4	Infty
MPH20-OLIC4	0.2	1.4	0	0.4476	-2.3	Infty

The reviewer's primary analysis showed that for Drug Liking Emax,

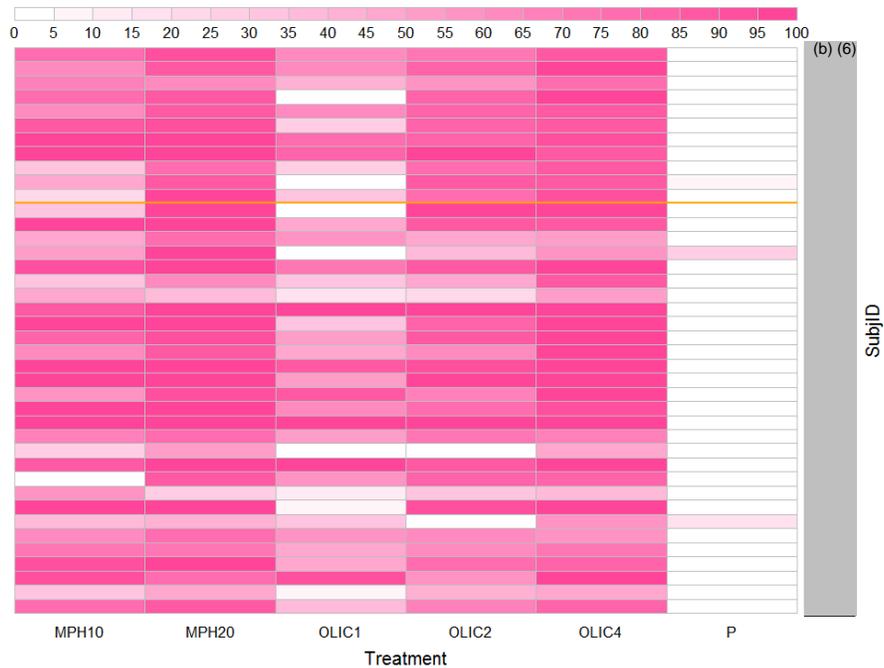
- both doses of morphine had means statistically significantly greater than placebo;
- oliceridine 1 mg had statistically significantly smaller mean than both doses of morphine, but had statistically significantly greater mean compared to placebo;
- oliceridine 2 mg had statistically significantly smaller mean compared to morphine 20 mg. There was no statistically significant difference in means between oliceridine 2 mg and morphine 10 mg;
- there was on statistically significant difference in means between oliceridine 4 mg and morphine 20 mg.

### 2.4.2. Secondary Analysis

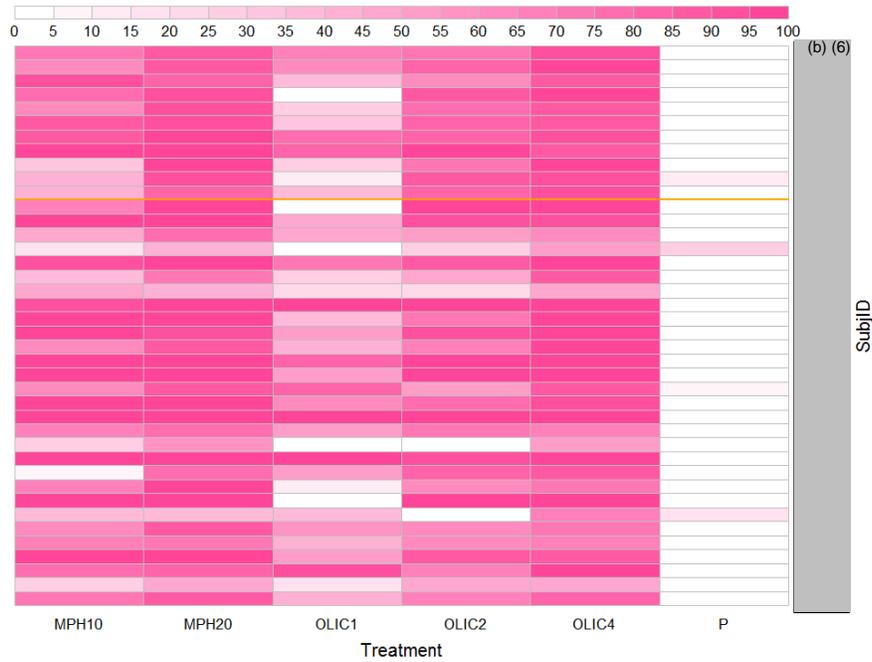
Because this was a human abuse potential study, secondary endpoints used in the reviewer's analysis were High Emax, and Good Effects Emax.

#### 2.4.2.1. Descriptive Statistics

Figures 3 and 4 are the heat maps by treatment for Good Effects Emax and High Emax.



**Figure 3: Heat map by treatment for Good Effects Emax**



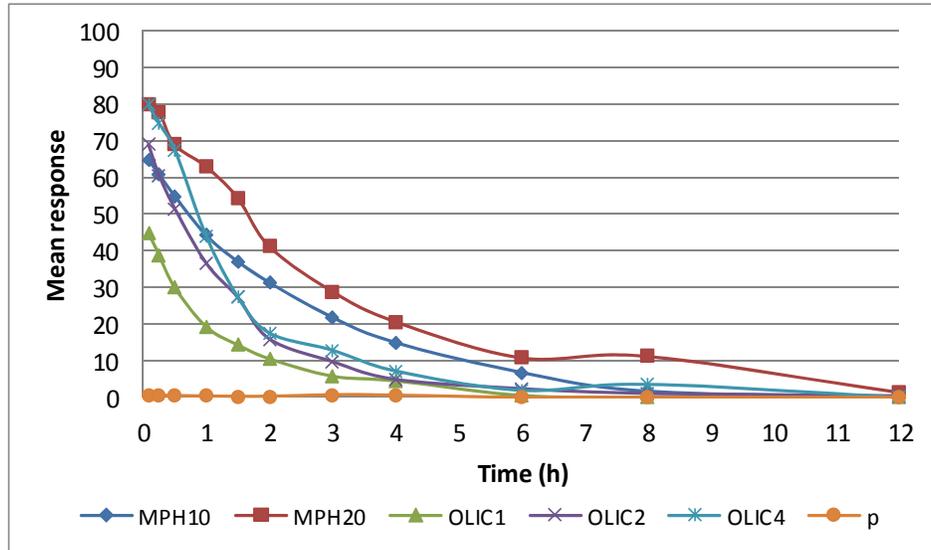
**Figure 4: Heat map by treatment for High Emax**

Table 4 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 6 treatments in the study for the secondary endpoints Good Effects Emax and High Emax.

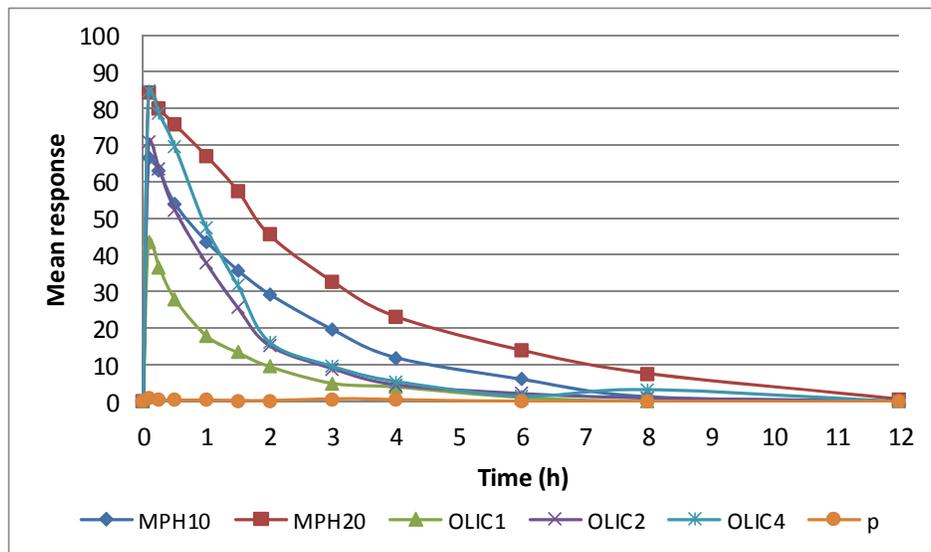
**Table 4: Summary statistics for Good Effects Emax, and High Emax (N=40)**

Measure	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Good Effects	MPH10	68.7	26.8	0	48	70	94.5	100
	MPH20	84.9	19.4	27	77.3	90.5	100	100
	OLIC1	47.7	30.4	0	27.8	49	64.8	100
	OLIC2	71.2	25.2	0	58.3	79	89	100
	OLIC4	84.2	18.3	38	73.3	89.5	100	100
	P	1.6	5.4	0	0	0	0	28
High	MPH10	70.1	26.8	6	49.3	72	97.5	100
	MPH20	86.7	17.5	39	80.8	93.5	100	100
	OLIC1	46.8	29.3	0	28.5	46	66.5	100
	OLIC2	72.3	25.5	0	63.3	78.5	92	100
	OLIC4	86.4	16.2	49	75	91.5	100	100
	P	1.8	5.7	0	0	0	0	29

The mean time course profiles by treatment for Good Effects VAS and High VAS are presented in Figures 3, and 4, respectively. These figures show that both morphine and oliceridine had a quick on set at 5 minutes. The oliceridine effect last up to hour 2, while morphine effect could last up to hour 3 or 4. The separation of profiles between oliceridine and placebo are evident.



**Figure 5: Mean Time Course Profiles by Treatment for Good Effects VAS (N=40)**



**Figure 6: Mean Time Course Profiles by Treatment for High VAS (N=40)**

All descriptive statistics for Good Effects Emax, and High Emax have the same pattern as those of the primary endpoint Drug Liking Emax.

### 2.4.2.2. Statistical Testing

The statistical model used in the reviewer's secondary analysis was the mixed-effects model which included sequence, period and treatment as fixed effects, and subject as a random effect. The model was adjusted heteroscedasticity. Pre-dose responses supposed to be collected for High VAS and included in the model as a covariate. However, all subjects had predose 0 except 4 subjects who had predose 1. Therefore, the predose response was not included as a covariate in the model in this analysis. The p-values of the Shapiro-Wilk W-test on the residuals were less than 0.0001. Therefore, the normality of distributions of paired differences was further examined. The results are presented in Table 5.

**Table 5: Results from the W Test on paired differences (N=40)**

Measure	Comparison	Skewness	W Statistic	p-value
Good Effects	MPH10-P	-0.52	0.9168	0.0061
	MPH10-OLIC1	-0.07	0.9877	0.9352
	MPH10-OLIC2	-1.34	0.8914	0.0011
	MPH10-OLIC4	-1.14	0.8958	0.0014
	MPH20-P	-1.48	0.7973	0.0000
	MPH20-OLIC1	0.66	0.9459	0.0547
	MPH20-OLIC2	1.50	0.8731	0.0003
	MPH20-OLIC4	0.78	0.9417	0.0393
	OLIC1-P	-0.17	0.9758	0.5369
	OLIC2-P	-1.50	0.8564	0.0001
	OLIC4-P	-1.18	0.8062	0.0000
High	MPH10-P	-0.80	0.9025	0.0023
	MPH10-OLIC1	0.27	0.9756	0.5294
	MPH10-OLIC2	-1.29	0.9077	0.0032
	MPH10-OLIC4	-1.19	0.8920	0.0011
	MPH20-P	-1.95	0.7359	0.0000
	MPH20-OLIC1	0.41	0.9636	0.2216
	MPH20-OLIC2	1.10	0.9106	0.0040
	MPH20-OLIC4	-0.08	0.9694	0.3437
	OLIC1-P	-0.14	0.9808	0.7204
	OLIC2-P	-1.55	0.8417	0.0001
	OLIC4-P	-1.54	0.7947	0.0000

In Table 5, the p-values less than 0.01 were colored. The p-values in red, green and purple denote that the paired distribution was negatively skewed and the test would be an upper-tailed test, the paired distribution was positively skewed and the test would be an upper-tailed test, and the paired distribution was negatively skewed and the test would be a lower-tailed test, respectively. For the

cases with p-values in black or red, the paired t-test was performed. Otherwise, the sign test was used. Test value zero was used for all tests. For the comparison between oliceridine and placebo, a two-sided test with the type I error rate of 0.05 was performed.

Tables 6 and 7 show the results from reviewer's statistical analysis for Good Effects Emax and High Emax, respectively.

**Table 6: Statistical analysis results for Good Effects Emax (N=40)**

Pairwise Comparison	Mean /Med Diff	StdErr /IQR	Test Value	p-value	95% CI	
					LCL	UCL
MPH10-P	67.2	4.5	0	<.0001	59.6	Infty
MPH20-P	83.3	3.3	0	<.0001	77.8	Infty
MPH20-OLIC1	37.2	4.5	0	<.0001	29.5	Infty
MPH10-OLIC1	21.0	4.6	0	<.0001	13.3	Infty
OLIC1-P	46.1	5.1	0	<.0001	37.5	54.7
MPH20-OLIC2*	9.5	3, 20.8	0	<0.001	6.0	Infty
MPH10-OLIC2	-2.5	4.0	0	0.729	-9.3	Infty
MPH20-OLIC4	0.7	1.9	0	0.3587	-2.5	Infty

\*: The Sign test was performed. The median difference and the interquartile range as well as the distribution free 95% confidence interval of the median difference were listed.

**Table 7: Statistical analysis results for High Emax (N=40)**

Pairwise Comparison	Mean /Med Diff	StdErr /IQR	Test Value	p-value	95% CI	
					LCL	UCL
MPH10-P	68.3	4.7	0	<.0001	60.4	Infty
MPH20-P	84.9	3.3	0	<.0001	79.3	Infty
MPH20-OLIC1	39.9	4.4	0	<.0001	32.4	Infty
MPH10-OLIC1	23.3	4.5	0	<.0001	15.7	Infty
OLIC1-P	45.0	4.9	0	<.0001	36.7	53.3
MPH20-OLIC2*	14.0	3, 22	0	<.0001	5.0	Infty
MPH10-OLIC2	-2.2	3.5	0	0.7386	-8.0	Infty
MPH20-OLIC4	0.3	1.6	0	0.4248	-2.3	Infty

\*: The Sign test was performed. The median difference and the interquartile range as well as the distribution free 95% confidence interval of the median difference were listed.

The reviewer's secondary analysis showed that for both Good Effects Emax and High Emax,

- both doses of morphine had means statistically significantly greater than placebo ( $p < 0.0001$ );
- oliceridine 1 mg had statistically significantly smaller mean than both doses of morphine, but had statistically significantly greater mean compared to placebo ( $p < 0.0001$ );
- the median difference between oliceridine 2 mg and morphine 20 mg was statistically significantly smaller than 0 ( $p < 0.0001$ ). There was no statistically significant difference in means between oliceridine 2 mg and morphine 10 mg ( $p = 0.0729$ );
- there was no statistically significant difference in means between oliceridine 4 mg and morphine 20 mg.

### **3. Conclusion**

The positive effects (drug liking, good effects and high) of oliceridine 2 mg and 4 mg may be comparable with those of morphine 10 mg and 20 mg, respectively. The positive effects of oliceridine 1 mg were lower than those of both doses of morphine but greater than placebo.

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/s/  
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LING CHEN  
07/11/2018

QIANYU DANG  
07/11/2018