FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

Oliceridine

MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations and Definition of Terms

AC	Active-comparator
AD	Adaptive
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASA	American Society of Anesthesiologists
AUC	Area under the concentration curve
$AUC_{0-\infty}$	Area under the concentration curve extrapolated to infinity
AUC_{0-24}	Area under the concentration curve through 24 hours
BOCF	Baseline observation carried forward
BMI	Body mass index
BSEP	Bile salt export pump
cAMP	Cyclic adenosine monophosphate
CL	Clearance
C_{max}	Maximum observed plasma concentration
CYP450	Cytochrome P450
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DB	Double-blind
DILI	Drug-induced liver injury
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
ED	Emergency department
eDISH	Evaluation of drug-induced serious hepatoxicity
EM	Extensive metabolizer
ESRD	End stage renal disease
FAS	Full analysis set
FDA	Food and Drug Administration
GI	Gastrointestinal
GPCR	G protein-coupled receptor
GSH	Glutathione
HAL	Human abuse liability
IC_{50}	Half maximal inhibitory concentration
IV	Intravenous
ITZ	Itraconazole
LDH	Lactate dehydrogenase
LFT	Liver function test
LOCF	Last observation carried forward

LSM	Least squares mean
M22	TRV130 glucuronide
M6G	Morphine-6-glucuronide
MC	Multi-center
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum recommended human dose
MOR	μ-opioid receptor
MRPSS	Moline Roberts Pharmacologic Sedation Scale
NCE	New chemical entity
NDA	New Drug Application
NI	Non-inferiority
NOAEL	No-observed-adverse-effect-level
NPRS	Numeric pain rating scale
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drugs
OL	Open-label
ORAE	Opioid-related adverse event
PACU	Post-anesthesia care unit
PC	Placebo-controlled
PCA	Patient-controlled analgesia
PD	Pharmacodynamics
PID	Pain intensity difference
PK	Pharmacokinetics
PM	Poor metabolizer
PO	Per os (oral administration)
PRN	As needed
PT	Prothrombin time
qxh	Every x hours (eg; q3h is every 3 hours)
QTcF	Fridericia- corrected QT interval
ΔΔQTcF	Change from baseline in QTcF
R	Randomized
RSB	Respiratory safety burden
RSE	Respiratory safety event
SAE	Serious adverse event
SD	Standard deviation
SOWS	Subjective Opiate Withdrawal Scale
SPID	Sum of pain intensity difference
SPID-24/48	Sum of pain intensity differences from baseline to 24 or 48 hours
$t_{½}$	Half-life
t_{max}	Time to peak concentration
tQT	Thorough QT

TWA	Time-weighted average
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
VRH	Ventilatory response to hypercapnia
Vz	Volume of distribution

1 EXECUTIVE SUMMARY

1.1 Introduction

Oliceridine is the first of a new class of μ-opioid receptor (MOR) ligands biased towards G protein and away from β-arrestin post-receptor signaling. Oliceridine, with this novel mechanism of action, was designed to optimize MOR pharmacology with the goal of delivering the pain relief of a conventional intravenous (IV) opioid with fewer opioid-related adverse events (ORAEs), thereby improving the benefit-risk profile for patients who require acute IV pain therapy. As proposed, oliceridine is indicated for the management of moderate to severe acute pain in adult patients for whom an IV opioid is warranted. The administration of oliceridine is to be supervised by trained medical personnel for acute use only within a hospital or other controlled clinical setting.

Background on G Protein-Coupled Receptors

G protein-coupled receptors (GPCRs) are located on the surface of cells and bind to hormones and neurotransmitters, translating extracellular information into cellular responses. GPCR activation engages broad networks of signaling pathways, which are typically mediated by both G proteins and β-arrestins (DeWire et al 2007; Wei et al 2003). Distinct pharmacological responses, such as specific beneficial or adverse effects, are often linked to these different signaling pathways.

Previously, it was thought that GPCRs operated in a binary fashion, like a light switch, which could be turned "on" by agonists or "off" by antagonists. Thus, it was thought that the beneficial and adverse effects associated with activation of a particular GPCR were pharmacologically inseparable. Standard agonists and antagonists of GPCRs (eg, beta blockers, opioid analgesics, antihistamines), which account for more than 30% of all medicines, work by either activating or inactivating the entirety of a GPCR's signaling network (Hauser et al 2017).

Recent Advances in GPCR Pharmacology and Rationale for Oliceridine Development

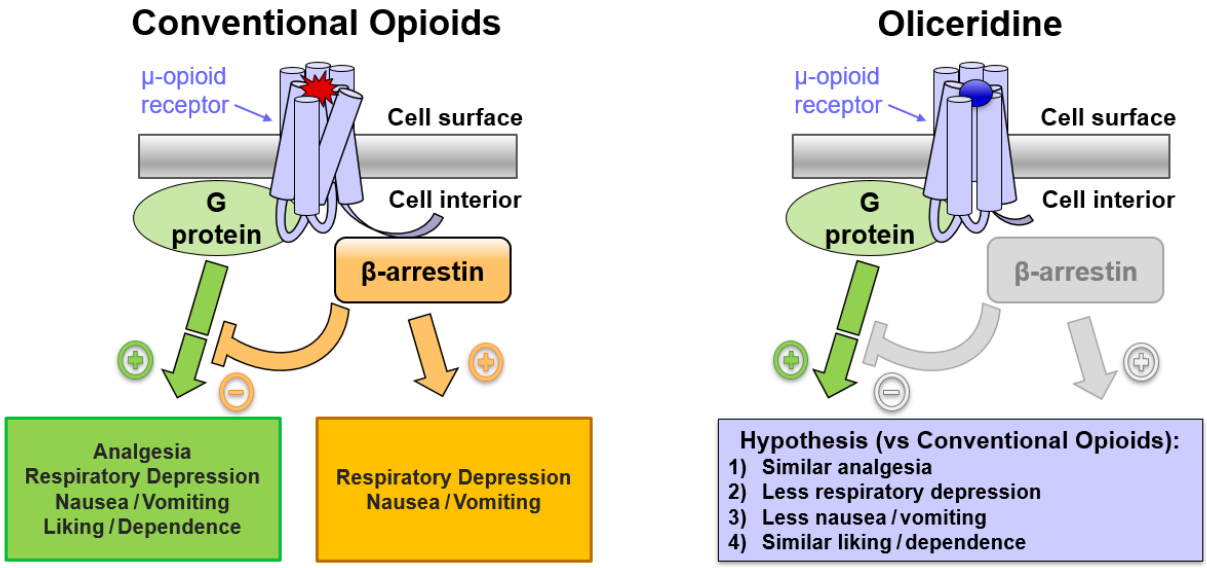
In the last several years, researchers have found that "biased" ligands could selectively engage some signaling pathways while avoiding, or even inactivating, other signaling pathways mediated by the same receptor (DeWire et al 2013; DeWire & Violin 2011; Kenakin 2007; Kenakin 2013; Violin & Lefkowitz 2007). Trevena, Inc. (Trevena) was founded to translate these discoveries into developing new GPCR-targeted medicines that could offer improved benefit-risk profiles over existing therapies. One of the researchers primarily responsible for the work that led to the understanding of GPCR function and biased ligands, Dr. Robert Lefkowitz, was awarded the Nobel Prize for Chemistry for his work in 2012 and is an academic co-founder of Trevena.

The scientific rationale for the discovery and development of oliceridine stemmed from findings that mice lacking β-arrestin-2 expression treated with morphine demonstrated enhanced analgesia and reduced respiratory and gastrointestinal (GI) dysfunction compared with wild-type animals (Bohn et al 1999; Raehal et al 2005). These results suggested that analgesia and ORAEs are mediated by two distinct signaling pathways:

- G protein: responsible for analgesia; partial contribution to ORAEs
- β-arrestin: contributes to ORAEs and attenuation of the analgesic response

Conventional IV opioids (eg, morphine, fentanyl, hydromorphone) are standard agonists that activate both G protein and β-arrestin pathways. In contrast, oliceridine is a G protein-biased ligand at the MOR with reduced activation of the β-arrestin pathway (Figure 1). It was hypothesized that this novel mechanism of action would provide the rapid and systemic analgesia of an IV opioid with an attenuation – but not an elimination – of ORAEs. This hypothesis and the initiation of clinical development was supported by nonclinical studies in which reduced respiratory and GI dysfunction were observed in oliceridine-treated rodents at doses providing equivalent analgesic activity compared with morphine (DeWire et al 2013; Violin et al 2014).

Figure 1: μ-Opioid Receptor Binding of Conventional Opioids and Oliceridine



1.2 Current Pain Management Paradigm

Management of Moderate to Severe Acute Pain in the Hospital or Other Controlled Setting

Contemporary postoperative pain management guidelines recommend a multimodal approach, which is the concurrent use of two or more analgesics with different mechanisms of action that work at different sites in the central and peripheral nervous system (Chou et al 2016). Multimodal analgesia is used to provide further reductions in pain than could be achieved with a single analgesic agent and to reduce the adverse events (AEs) of all the agents used by reducing the doses needed.

The components of a treatment plan to manage moderate to severe acute pain are tailored to the patient, clinical setting, and surgical procedure. Opioid-sparing regimens often work well in procedures that are less invasive or when pain can be well-controlled with an epidural or a local or regional nerve block. However, for surgical procedures associated with pain of moderate to severe intensity, extended duration, or deep/visceral pain (eg, open colectomy, total joint replacement, abdominal hysterectomy, spine and thoracic procedures), IV opioids remain a critical component of multimodal pain management in hospitals and other controlled clinical

settings (Chou et al 2016). In 2017, approximately 45 million patients in the United States (US) were administered IV opioids in hospital settings, demonstrating the need for the high level of analgesic efficacy that this class of medicines provides (IQVIA Hospital Charge Detail Master Database 2017).

Challenges of Opioid Use in the Context of the Ongoing Opioid Overdose Epidemic

While opioid analgesics remain a necessary medication for the treatment of moderate to severe pain when alternative treatment options are inadequate, their overuse in clinical settings, diversion, and abuse has led to a difficult public health issue – balancing the needs of patients in pain with the public health safety risks.

Most opioid overdose deaths in the US occur from illicit heroin, fentanyl, and fentanyl analogs; however, prescription opioid medications are also a major source of morbidity and mortality (CDC 2017). A majority of the prescription opioids misused or abused in the community are oral medications that are dispensed directly to patients (SAMHSA 2017). Thus, there is currently an ongoing effort to reduce the number and size of prescriptions for oral opioid medications.

While the diversion and abuse of IV opioids from controlled settings is low relative to oral opioids that are dispensed directly to individuals in the community, Trevena believes that any new entrant into the class of IV opioid medications should not expand the population exposed to these powerful medicines or introduce a greater risk of abuse. As described in Section 5.2, a human abuse liability (HAL) study showed that oliceridine has similar abuse liability to equianalgesic doses of IV morphine. In addition, as described in Section 4.2, oliceridine has very low oral bioavailability. Thus, Trevena is requesting that oliceridine be a Schedule II product under the Controlled Substances Act and carry the same mandatory precautions as other IV opioid medications. It is important to note that nonclinical data suggest that oliceridine can be reversed by naloxone in the case of an accidental overdose.

The approval of oliceridine as a treatment option for the management of moderate to severe acute pain in hospitals or other controlled settings would not be expected to affect the ongoing opioid overdose epidemic. However, it does offer the potential to provide a new option which may improve care for patients who require IV opioid therapy.

Unmet Needs in Acute Pain Management with IV Opioids

The primary limitations of conventional IV opioid analgesics are their associated safety risks and relatively narrow therapeutic windows (ie, efficacious dose range without associated toxicity). ORAEs such as nausea, vomiting, and respiratory depression occur on a continuum of severity, ranging from common and transient (eg, mild nausea) to rare and fatal (eg, respiratory arrest). While life-threatening respiratory complications with conventional IV opioids are relatively uncommon in a controlled setting, earlier signs of reduced respiratory function, such as decreased oxygen saturation and CO_2 retention, are more common, often require intervention, and may delay the ability of a patient to progress toward ambulation and hospital discharge.

Achieving adequate analgesia while avoiding ORAEs can be clinically challenging. Due to safety concerns, opioids are often titrated slowly, which can leave patients with substantial pain

early in treatment. Furthermore, even when titrated quickly, lag in onset of meaningful pain relief can result in more dosing than is needed ("dose stacking") to achieve pain relief, which can then cause more ORAEs, unintentionally overshooting the therapeutic window. Titration can also be complicated by the formation of active metabolites that accumulate over time (eg, morphine-6-glucuronide [M6G] with morphine) and by compromised renal or hepatic function, all of which can contribute to unpredictable analgesic efficacy and increase the risk of developing ORAEs.

1.3 Goals of Development Program

The oliceridine clinical development program was designed with three primary aims:

- to provide the data required to demonstrate analgesic efficacy (including two adequate and well-controlled clinical trials demonstrating superiority to placebo in both hard and soft tissue pain models)
- to adequately characterize oliceridine safety and establish an overall favorable benefit/risk profile
- to explore the effects of oliceridine on ORAEs in relation to a conventional IV opioid

1.4 Dosing and Administration

As with all IV opioids, the dosing regimen for oliceridine should be individualized for each patient and titrated to effect with the goal of reaching a sufficient level of analgesia with a minimal emergence of ORAEs. As needed (PRN) dosing can be achieved by either patient-controlled analgesia (PCA) or practitioner-administered intermittent bolus dosing.

Based on results from the clinical studies, the initial dose of oliceridine should be 1 to 2 mg. Onset of analgesic effect is expected within 5 minutes of the initial dose. 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 of analgesia is generally achieved with bolus doses of 1 to 2 mg every 1 to 3 hours as needed, or as PCA demand doses of 0.1 to 0.35 mg as needed. Bolus doses of 3 mg may be used for maintenance in patients with more severe pain. The maximum proposed daily dose of oliceridine is 40 mg.

1.5 Efficacy

As a G protein-biased ligand, it was hypothesized that oliceridine would provide IV opioid analgesia in a dose-dependent manner. This hypothesis was confirmed during development in 4 randomized, double-blind, placebo-controlled trials with an active IV morphine comparator arm. Each study used validated hard tissue (ie, bunionectomy) or soft tissue (ie, abdominoplasty) models in accordance with current Food and Drug Administration (FDA) Guidance (FDA 2014).

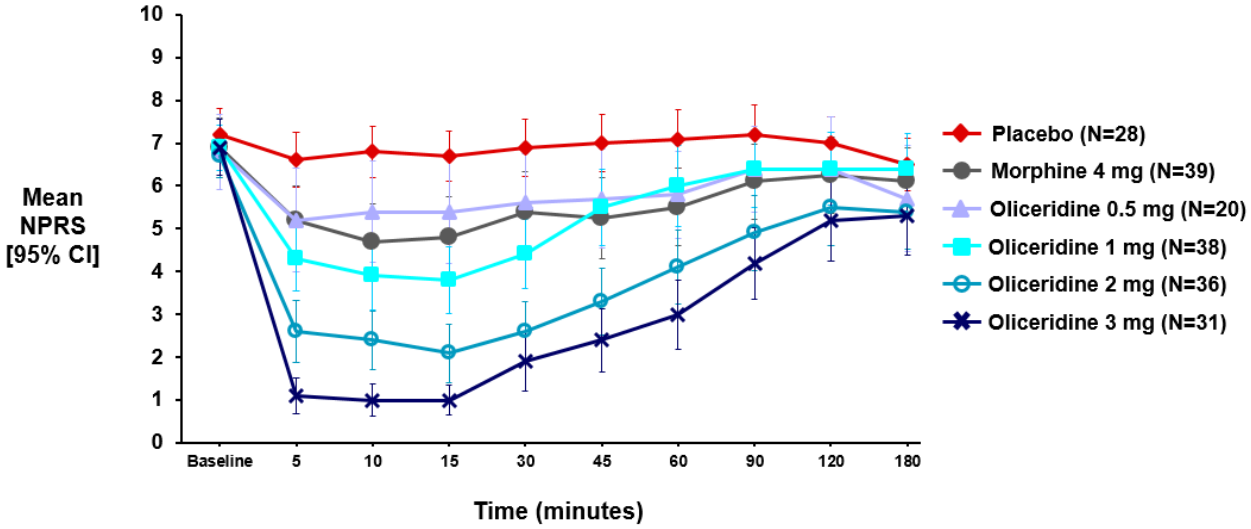
Study 2001: Phase 2a Study in Bunionectomy

Study 2001 was a fixed-dose, randomized, double-blind study designed to explore a range of dose strengths and dosing intervals for oliceridine compared to fixed-dose placebo and IV morphine regimens. Although not reflective of clinical practice, fixed dosing provided a clear

assessment of onset, magnitude, and duration of discrete oliceridine doses and allowed for an evaluation of the dose-response and dose-interval relationships. In addition, fixed dosing allowed an assessment of the relative potency of the first dose of oliceridine and morphine. Rescue analgesia was provided as needed by first-line acetaminophen 650 mg q4h, then second-line intramuscular or IV ketorolac 15 to 30 mg q6h. This study randomized and treated 333 patients to receive one of several oliceridine doses, morphine 4 mg, or placebo the day after bunionectomy.

In the first 3 hours after dosing, patients who received IV morphine 4 mg had significantly lower numeric pain rating scores (NPRS) than placebo (Figure 2). The pain scores of the oliceridine 0.5 mg and 1 mg groups overlapped with those of the morphine 4 mg group throughout the first dosing interval, indicating that in this study, oliceridine was approximately 5 times more potent than IV morphine at the first dose. Patients who received higher doses of oliceridine (2 mg and 3 mg) experienced greater reductions in pain intensity in a dose-dependent manner that were also superior to placebo. With repeated dosing, the relative potency is difficult to ascertain due to the accumulation of active metabolites with morphine.

Figure 2: Mean NPRS over First 3 Hours in Study 2001



Subsequent doses in this 48-hour trial showed that oliceridine elicited a repeated analgesic effect. The results of the study were used to inform the design of the subsequent Phase 2b and Phase 3 studies, which studied oliceridine in the more clinically relevant context of PRN dosing regimens.

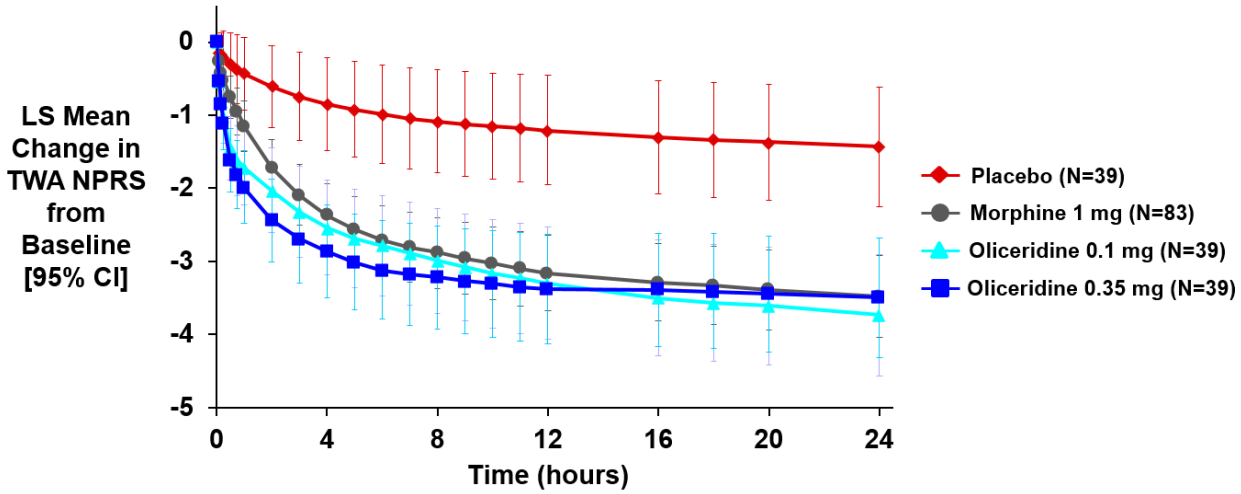
Study 2002: Phase 2b Study in Abdominoplasty

Study 2002 was a two-part randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of PRN oliceridine dosing regimens. PRN dosing was used to better simulate clinical practice and allow patients to achieve sufficient analgesic efficacy with any active regimen, and enable comparisons of relative safety and tolerability. Rescue analgesia was provided as needed with first-line ibuprofen 400 mg PO (per os [oral administration]) every 6 hours (q6h) followed by second-line oxycodone 5 mg PO q2h.

The study randomized and treated 200 patients in a 2:2:1 ratio to oliceridine, morphine, or placebo regimens after abdominoplasty. For the first part of the study, the oliceridine regimen was a 1.5 mg loading dose followed by 0.1 mg demand doses delivered via PCA. Following a pre-specified interim analysis, the oliceridine demand dose was increased to 0.35 mg for the second part of the study to further explore the oliceridine dose range. The morphine comparator regimen was a standard PCA regimen – a 4 mg loading dose with 1 mg demand doses. All demand doses had a 6-minute lockout interval. For efficacy analyses, the last observation carried forward (LOCF) imputation method was used for patients who utilized rescue pain medication.

Study 2002 met the primary endpoint by demonstrating that oliceridine provided reductions in time-weighted average (TWA) NPRS that were significantly greater than placebo over the 24-hour treatment period (both oliceridine treatments $p < 0.001$). The efficacy of oliceridine 0.1 mg and 0.35 mg dosing regimens were similar to the IV morphine 1 mg dosing regimen, confirming the hypothesis that patients could dose themselves to achieve analgesia with a range of on-demand doses (Figure 3). Although the primary endpoint showed similar effects with the 0.1 mg and 0.35 mg oliceridine regimens, a higher incidence of rescue analgesia use in the 0.1 mg regimen (31%) than the 0.35 mg regimen (21%) suggested a dose-related effect on efficacy.

Figure 3: Change in TWA NPRS Over 24 Hours in Study 2002



APOLLO 1 and APOLLO 2: Phase 3 Studies in Bunionectomy and Abdominoplasty

Two randomized, multicenter, double-blind, placebo-controlled Phase 3 studies were conducted to fulfill the FDA requirements for two successful adequate and well-controlled trials in validated and standardized clinical settings of acute nociceptive pain (one in soft tissue/visceral pain and one in hard tissue/nonvisceral pain) demonstrating superiority over placebo:

- APOLLO 1 evaluated 389 patients with moderate to severe pain after bunionectomy over a 48-hour treatment period.
- APOLLO 2 evaluated 401 patients with moderate to severe pain after abdominoplasty over a 24-hour treatment period.

In both studies, patients were randomized in an equal ratio to 1 of 3 oliceridine PCA regimens, a morphine PCA regimen, or placebo PCA regimen (Table 1). As in Phase 2b, oliceridine demand doses of 0.1 mg and 0.35 mg were included. Although pharmacokinetic/pharmacodynamic (PK/PD) modeling suggested no additional efficacy with demand doses above 0.35 mg, a 0.5 mg regimen was also included to confirm this prediction. The morphine group received the same standard regimen that was used in the Phase 2b study. Blinded clinician-administered supplemental doses were permitted if the PCA demand doses were inadequate. Use of blinded supplemental doses was recommended prior to the administration of rescue pain medication. Protocol-specified rescue pain medication (etodolac 200 mg PO q6h PRN) was permitted if study medication was inadequate.

Table 1: APOLLO 1 and APOLLO 2 Dosing Paradigm

<table>
<tr><th>Randomized Group</th><th>Loading Dose</th><th>Demand Dose (PCA)</th><th>Lockout</th><th>Clinician-Administered Supplemental Dose (q1h PRN)</th></tr>
<tr><td>Oliceridine 0.1 mg</td><td rowspan="3">1.5 mg</td><td>0.1 mg</td><td rowspan="4">6 minutes</td><td rowspan="3">0.75 mg</td></tr>
<tr><td>Oliceridine 0.35 mg</td><td>0.35 mg</td></tr>
<tr><td>Oliceridine 0.5 mg</td><td>0.5 mg</td></tr>
<tr><td>Placebo</td><td>Volume-matched placebo solution</td><td>Volume-matched placebo solution</td><td>Volume-matched placebo solution</td></tr>
<tr><td>Morphine 1 mg</td><td>4 mg</td><td>1 mg</td><td>2 mg</td></tr>
</table>

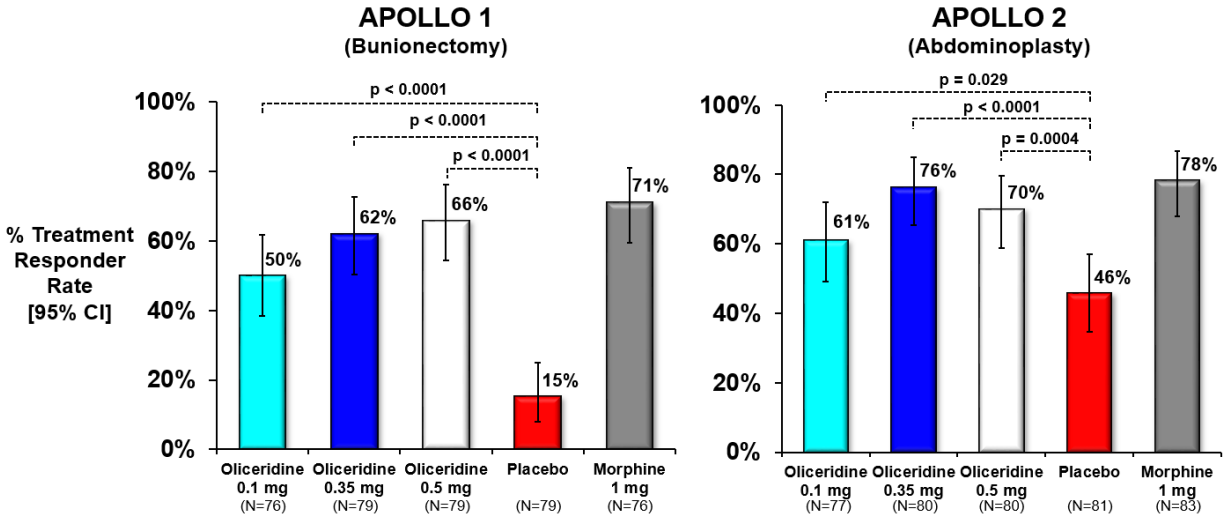
Both controlled Phase 3 studies utilized a treatment responder primary endpoint, in part to mitigate confounding effects of differential rescue medication utilization and early termination events that require statistical imputation of pain scores. The use of a categorical responder definition in these studies conforms to the current FDA Analgesic Development guidance document, which notes that a responder definition, which can include multiple components such as pain intensity, use of rescue, and ability to complete the study, may serve as an acceptable primary outcome metric (FDA 2014). In the APOLLO studies, a patient was declared to be a responder only if they met all of the following criteria:

- at least a 30% improvement in final time-weighted sum of pain intensity difference (SPID) from baseline at 48 hours (for APOLLO 1) or 24 hours (for APOLLO 2);
- without use of rescue pain medication during the randomized treatment period;
- without early discontinuation of study medication for any reason;
- without reaching the study medication volume-based dosing limit.

All oliceridine treatment regimens met the pre-specified primary endpoint and demonstrated analgesic efficacy (ie, superiority to placebo) in both controlled Phase 3 studies (Figure 4). The treatment responder rate was lower for the 0.1 mg oliceridine regimen than the other active regimens in both APOLLO 1 and APOLLO 2. The responder rates for the 0.35 and 0.5 mg oliceridine regimens were not significantly different from morphine. Since the plateau in efficacy with the 0.35 mg regimen was consistent with the prediction of the PK/PD model and indicated little, if any, additional benefit of the 0.5 mg regimen over the 0.35 mg regimen, the 0.5 mg regimen will not be sought for approval. A sensitivity analysis evaluating the analgesic efficacy

of oliceridine using SPID scores with imputation for rescue medication and early discontinuation yielded results consistent with the primary endpoint, with all three oliceridine regimens statistically superior to placebo in both studies (see Appendix 10.7).

Figure 4: Primary Endpoint Results in APOLLO 1 and APOLLO 2

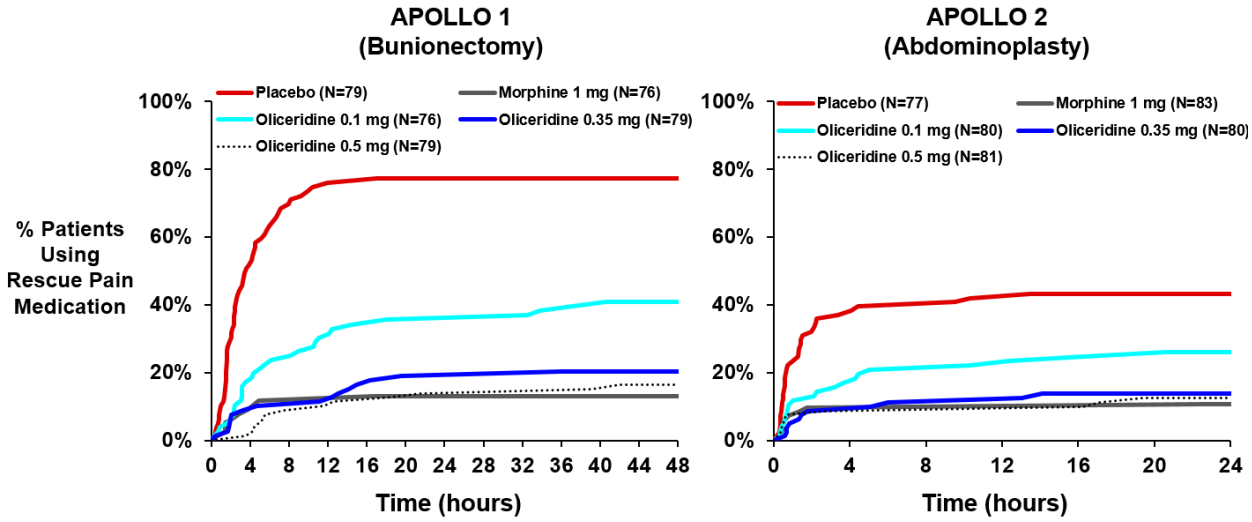


While the oliceridine regimens consistently demonstrated IV opioid-level analgesia in both Phase 3 studies, mean SPID values were numerically higher with the morphine regimen (higher SPID scores indicate greater reduction in pain scores – the magnitude of efficacy; see Appendix 10.7). Since morphine has active metabolites which accumulate over time, patients have the potential to receive *more* analgesia than necessary due to the delayed onset of morphine's metabolite effects.

Receiving more analgesia than necessary conflicts with the therapeutic goal of giving patients only as much IV opioid as they need. Furthermore, higher IV opioid doses are also associated with overshooting the therapeutic window, which can lead to more ORAEs and need for clinical interventions (eg, dosing interruptions, supplemental oxygen, administration of rescue antiemetics). Thus, efficacy should also be evaluated in terms of its sufficiency, through use of rescue pain medication, to interpret the relevance of the magnitude of efficacy.

Consistent with the results of the primary endpoint, all active regimens had lower utilization of rescue pain medication during the study compared with the placebo regimen. The oliceridine 0.1 mg regimen had a higher use of rescue pain medication than the other active regimens, while the use of rescue medication was similar in the other oliceridine and morphine regimens (Figure 5). This suggests that while the effect on pain was numerically greater with the morphine regimen, a similar proportion of patients were able to achieve a level of analgesia that they found to be sufficient with access to the oliceridine 0.35 mg and 0.5 mg PCA regimens.

Figure 5: Time to First Use of Rescue Pain Medication in APOLLO 1 and APOLLO 2



1.6 Opioid-Related Adverse Events

The primary hypothesized benefit of oliceridine as a G protein-biased ligand over conventional IV opioids was that it would attenuate, though not eliminate, the incidence of ORAEs such as respiratory depression, nausea, and vomiting. One of the goals of the development program was to identify dosing regimens that meaningfully reduced ORAEs while also providing opioid-level analgesic efficacy.

1.6.1 Respiratory Effects

For more than 40 years, the gold standard for evaluating opioid-induced respiratory depression has been the ventilatory response to hypercapnia (VRH) (Weil et al 1975). These studies are conducted among subjects in experimental settings who are administered an opioid and breathe a gas mixture enriched with CO_2 to experimentally increase respiratory drive. This method allows for a direct and well-controlled evaluation of the relative impact of different drugs on depressing respiratory drive. However, this approach is not amenable to the constraints of a clinical pain study.

To date, there are no validated measures of opioid-induced respiratory depression in clinical trials. Therefore, Trevena explored the relative clinical impact of oliceridine relative to morphine using a variety of standard and novel complementary endpoints throughout development. In addition to performing the "gold standard" VRH test in Phase 1, pre-specified respiratory endpoints were also evaluated in Phase 2 and Phase 3 studies.

Ventilatory Response to Hypercapnia

Study 1003 was a randomized, double-blind, placebo-controlled, five-period crossover study conducted to evaluate the effects of oliceridine on analgesia and on respiratory drive compared to morphine in 30 healthy volunteers. All participants received each of five treatments (placebo, morphine 10 mg, and oliceridine 1.5, 3, and 4.5 mg as two-minute IV infusions) in a random

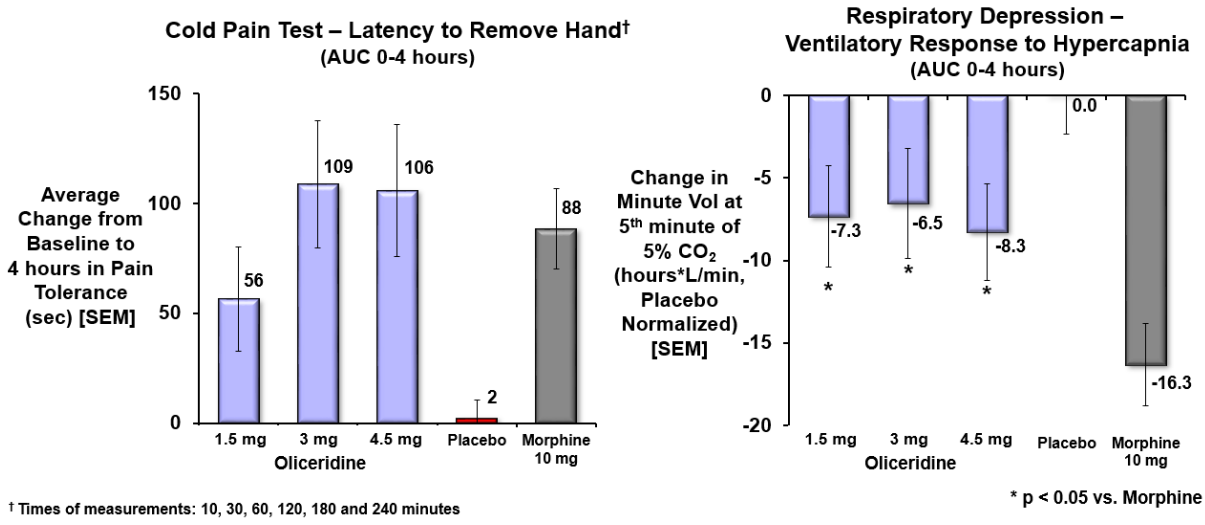
order. The effects on analgesia and respiratory drive were evaluated with the following methodologies:

- Cold pain test: At various time points after study drug administration, participants immersed one hand into water cooled to 2°C and kept their hand immersed for as long as could be tolerated up to a maximum of 180 seconds. Analgesic activity (ie, pain tolerance) was measured as the amount of time participants kept their hand in the cold water.
- Ventilatory response to hypercapnia: Subjects breathed a hypercapnic gas mixture through a facemask for 5 minutes at various time points after study drug administration. Depression of respiratory drive was measured as the change from pre-dose baseline in minute ventilation during hypercapnic exposure.

All active treatments showed greater analgesic activity than placebo; oliceridine 3 mg and 4.5 mg had similar analgesic activity to morphine 10 mg (Figure 6; left panel). All oliceridine doses had a significantly lower impact on respiratory depression than morphine 10 mg (Figure 6; right panel).

Thus, using the gold standard model for opioid-induced respiratory depression, oliceridine caused significantly less depression of respiratory drive than morphine at doses providing at least as much analgesic activity.

Figure 6: Latency to Hand Removal and Respiratory Depression in Study 1003

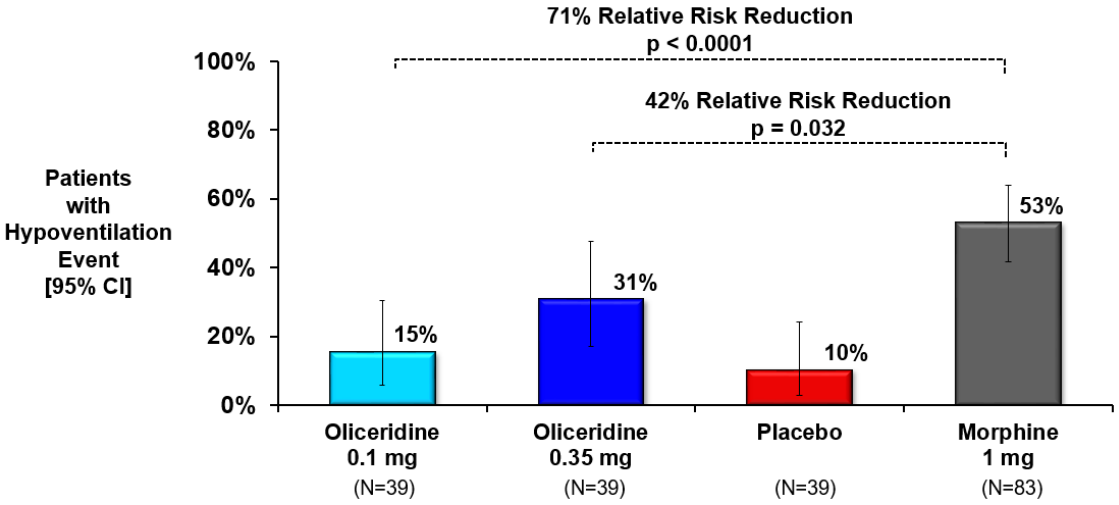


Respiratory Safety in Phase 2

In the Phase 2b study (Study 2002), respiratory-related AEs were measured using a pre-specified definition for *hypoventilation events*: clinically apparent and persistently decreased respiratory rate, respiratory effort, or oxygen saturation. Hypoventilation events were captured by investigators blinded to study treatment in the context of standard clinical monitoring. To ensure patient safety, clinical judgment was used to determine the significance of the events as "clinically apparent" or "persistently decreased", rather than using fixed thresholds for respiratory parameters.

In the context of similar analgesia to morphine (Figure 3), significantly fewer patients who received oliceridine experienced hypoventilation events compared with the morphine regimen (Figure 7).

Figure 7: Hypoventilation Events in Phase 2b in Study 2002



Respiratory Safety in Phase 3

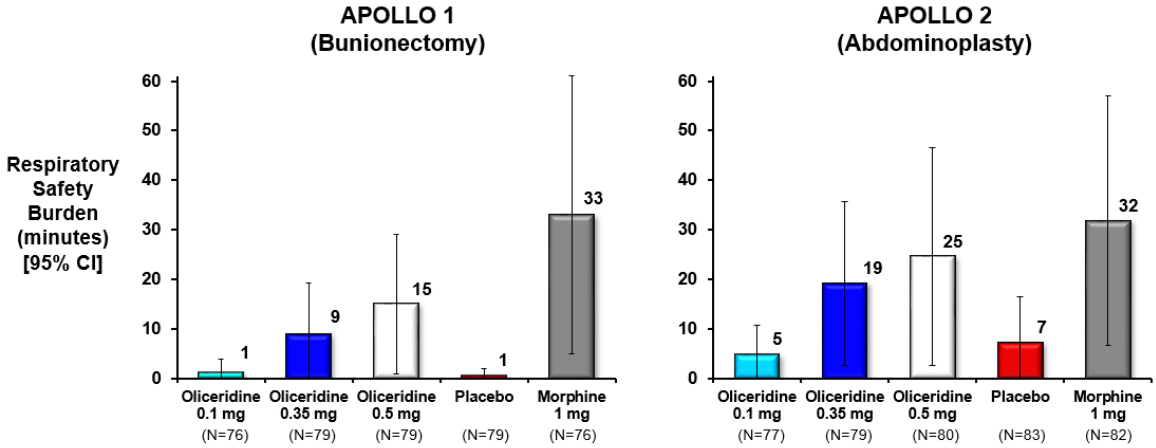
As the first novel IV opioid specifically designed to improve respiratory safety, and at the recommendation of the FDA, Trevena established a formal approach to closely monitor signs, symptoms, and duration of respiratory safety events (RSEs) and captured clinical interventions used to manage respiratory safety in the Phase 3 studies. Similar to the "hypoventilation event" definition used in the Phase 2b study, RSEs were prospectively defined as "a clinically relevant worsening in oxygen saturation, respiratory rate or sedation," the latter of which replaced the event of decreased respiratory effort. Trevena also attempted to capture an additional aspect of respiratory safety by combining the *incidence* of RSEs with the cumulative *duration* of the events using a new composite index called Respiratory Safety Burden (RSB). RSB was calculated by multiplying the incidence of RSEs by the cumulative duration of the events. RSB was prespecified as a key secondary endpoint in the APOLLO studies. It is important to note that this endpoint was not previously validated and, thus, could not be used to support a comparative FDA labeling claim.

As this approach relied heavily on clinical judgement, only trained anesthesiologists or certified registered nurse anesthetists could perform these respiratory evaluations. Patients were monitored at least every 2 hours for the presence of RSEs, and at least every 30 minutes once a respiratory event was identified. Monitoring of respiratory safety included concurrent assessment of continuous O_2 saturation, stopwatch-timed respiratory rate for a full minute, and completion of the Moline Roberts Pharmacologic Sedation Scale (MRPSS).

The results for RSB are shown in Figure 8. RSB can be interpreted as the expected amount of time a patient would experience an RSE. In both Phase 3 APOLLO studies, the RSB showed a dose regimen-dependent increase across the three oliceridine regimens. The RSB was numerically lower in all oliceridine regimens compared with the morphine regimen, however, none of these contrasts reached threshold levels of statistical significance. A contributing factor to this outcome was an unexpectedly lower number of RSEs across all groups, which was

approximately 50% lower in Phase 3 as compared with Phase 2. The lower incidence of RSEs is presumed to be, in part, due to the more rigorous and operationally formalized monitoring of respiratory safety used in the Phase 3 studies.

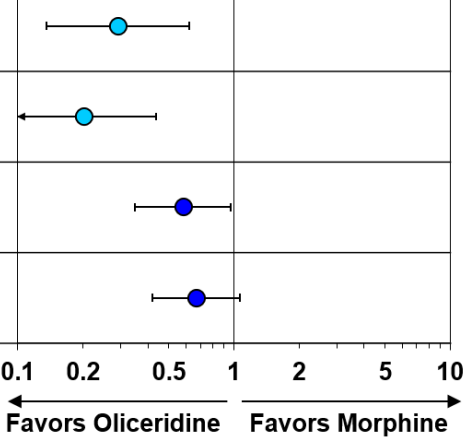
Figure 8: Respiratory Safety Burden in APOLLO 1 and APOLLO 2



Analyses of the components of the RSB endpoint, as well as associated clinical interventions, were pooled across the two Phase 3 studies to further evaluate respiratory safety signals. Despite the lower event rates in Phase 3, the relative risk reductions in RSEs compared to morphine were consistent across development phases for the range of demand dosing regimens (0.1 mg to 0.35 mg) being considered for regulatory approval (Figure 9).

Figure 9: Summary of Respiratory Safety Events in Phase 2b and Phase 3 Studies

Oliceridine Dosing Regimen	Phase	% of Patients Experiencing Respiratory Safety Event: Oliceridine	% of Patients Experiencing Respiratory Safety Event: Morphine	Relative Risk Reduction vs Morphine
0.1 mg	2b	15	53	71%
	3	5	23	80%
0.35 mg	2b	31	53	42%
	3	15	23	33%



The clinical relevance of the relative incidence of RSEs is further supported by the data collected on oxygen desaturations and interventions necessary to maintain respiratory safety in the Phase 3 studies (Table 2). The magnitude of relative risk reductions for oliceridine compared with

morphine for clinically objective measures of respiratory event detection (i.e., pulse oximeter detection of oxygen saturation falling below 90%) and for clinical interventions (i.e., need for supplemental oxygen rescue and dosing interruption for patient safety) were consistent with the relative risk reductions observed for the recording of RSEs themselves.

Table 2: Oxygen Desaturations and Clinician Interventions in Controlled Phase 3 Studies

Safety Parameter/Intervention	Incidence (%)				Relative Risk Reduction (p-value)	
	Oliceridine			Morphine 1 mg (N=158)	0.1 mg vs Morphine	0.35 mg vs Morphine
	0.1 mg (N=153)	0.35 mg (N=158)	0.5 mg (N=159)			
O_2 saturation < 90%	5.9	14.6	17.0	22.2	73% (< 0.001)	34% (0.11)
Dosing interruption	3.9	14.6	17.6	24.7	83% (< 0.001)	41% (0.033)
Supplemental O_2	4.6	14.6	17.6	22.8	80% (< 0.001)	36% (0.083)

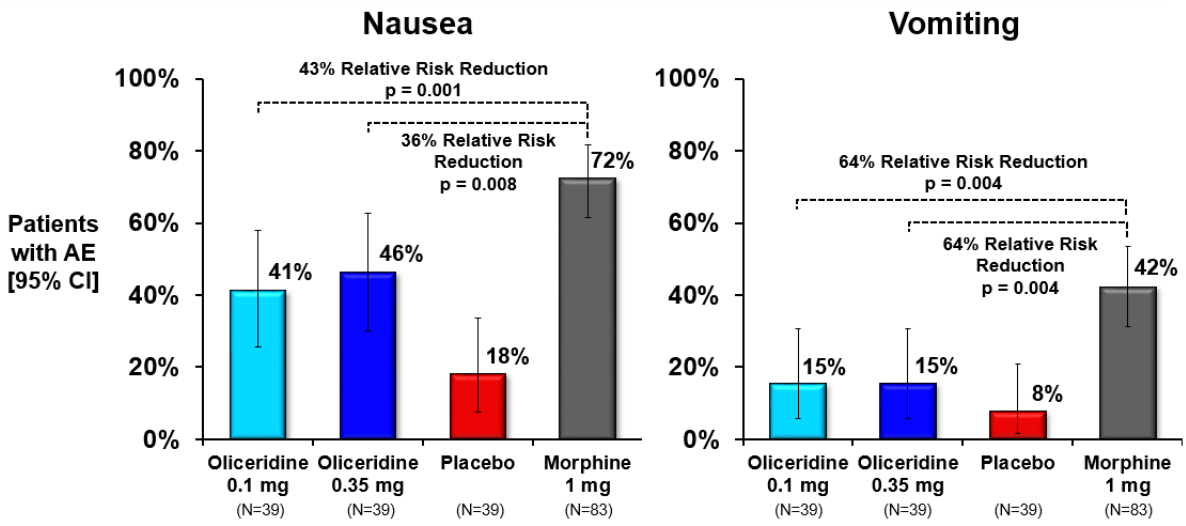
Conclusions

In summary, the respiratory safety effects of oliceridine were thoroughly evaluated throughout clinical development. Using the gold standard VRH model for evaluating opioid-induced respiratory depression, oliceridine caused significantly less respiratory depression than morphine at doses providing at least as much analgesia. In the Phase 2b study, oliceridine 0.1 mg and 0.35 mg regimens were associated with significantly fewer hypoventilation events than the morphine 1 mg regimen. In the Phase 3 studies, the novel composite measure of RSB did not achieve statistical significance due to lower-than-expected RSE rates in all treatment groups, which reduced statistical power. However, the magnitude of relative risk reductions for oliceridine compared with morphine in the incidence of RSEs, oxygen desaturation events, and clinical interventions for respiratory safety were consistent in Phase 2b and Phase 3. Taken together, these findings provide evidence that oliceridine's novel mechanism of action imparts a favorable respiratory safety profile compared with conventional IV opioids.

1.6.2 Nausea and Vomiting

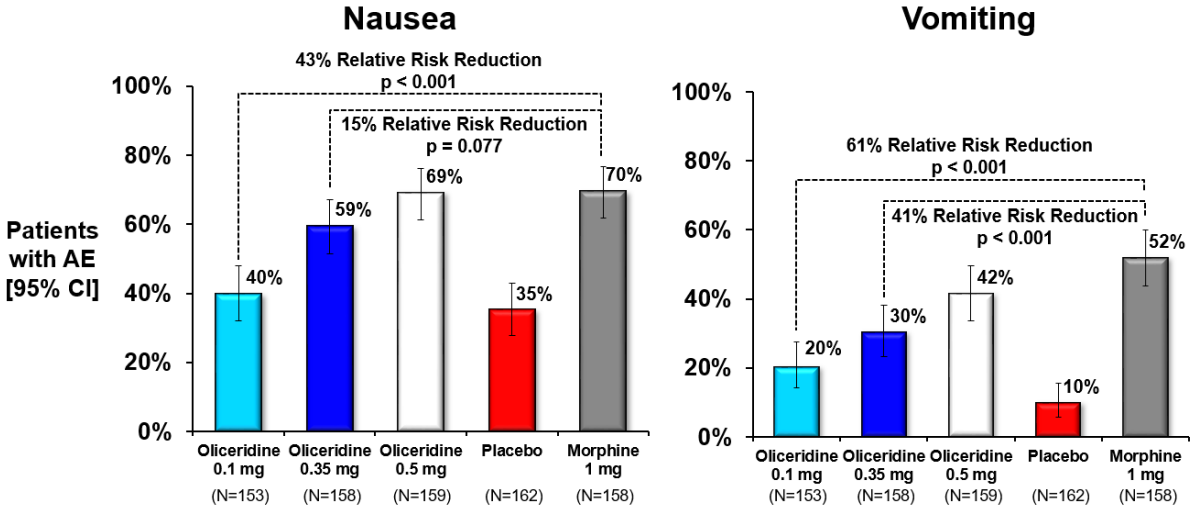
In the Phase 2b study, postoperative nausea and vomiting were explored by analysis of the spontaneously-reported Medical Dictionary for Regulatory Activities (MedDRA) adverse event Preferred Terms of "nausea" and "vomiting". The reported incidence of these AEs was significantly lower in both oliceridine regimens than the morphine regimen (Figure 10).

Figure 10: Postoperative Nausea and Vomiting in Study 2002



In Phase 3, postoperative nausea and vomiting were again evaluated by comparing the spontaneously reported incidence of MedDRA adverse event Preferred Terms for nausea and vomiting. In general, a regimen-dependent effect for oliceridine was observed where higher demand doses were associated with higher AE rates. The incidence of nausea was significantly lower in the 0.1 mg regimen compared to morphine, and the incidence of vomiting was significantly lower for both the 0.1 mg and 0.35 mg regimens (Figure 11).

Figure 11: Postoperative Nausea and Vomiting in Controlled Phase 3 Studies



The findings regarding the lower observed event rates in postoperative nausea and vomiting were consistent across the Phase 2b and Phase 3 studies. Figure 12 illustrates the incidence, relative risk, and relative risk reductions for nausea for the two oliceridine regimens bracketing the demand dose range being considered for approval compared with the morphine regimen; Figure 13 illustrates the corresponding statistics for the incidence of vomiting.

Figure 12: Summary of Incidence of Postoperative Nausea in Phase 2b and Phase 3 Studies

Oliceridine Dosing Regimen	Phase	% of Patients Experiencing Nausea: Oliceridine	% of Patients Experiencing Nausea: Morphine	Relative Risk Reduction vs Morphine
0.1 mg	2b	41	72	43%
	3	40	70	43%
0.35 mg	2b	46	72	36%
	3	59	70	15%

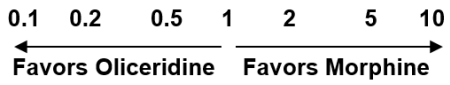
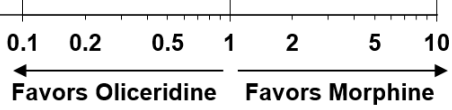


Figure 13: Summary of Incidence of Postoperative Vomiting in Phase 2b and Phase 3 Studies

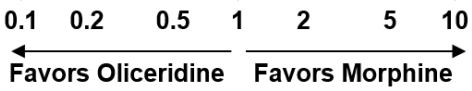
Oliceridine Dosing Regimen	Phase	% of Patients Experiencing Vomiting: Oliceridine	% of Patients Experiencing Vomiting: Morphine	Relative Risk Reduction vs Morphine
0.1 mg	2b	15	42	64%
	3	20	52	61%
0.35 mg	2b	15	42	64%
	3	30	52	41%



Consistent with the reported incidence of nausea and vomiting, the use of protocol-permitted antiemetics also increased in a regimen-dependent manner. (Note: use of prophylactic antiemetics was not allowed in the Phase 2b or Phase 3 APOLLO studies.) The proportion of patients requiring rescue antiemetics was lower in both the oliceridine 0.1 mg and 0.35 mg regimens compared with morphine (Figure 14).

Figure 14: Summary of Rescue Antiemetic Use in Phase 2b and Phase 3 Studies

Oliceridine Dosing Regimen	Phase	% of Patients Receiving Rescue Antiemetics		Relative Risk Reduction vs Morphine	Relative Risk [95% CI]
		Oliceridine	Morphine		
0.1 mg	2b	49	65	25%	
	3	26	63	59%	
0.35 mg	2b	38	65	41%	
	3	46	63	28%	



Conclusions

In summary, the lower incidence of postoperative nausea and vomiting and use of rescue antiemetics in the Phase 2b and Phase 3 clinical studies are consistent with the hypothesis underlying oliceridine's novel mechanism of action, suggesting that ORAEs should be attenuated with oliceridine compared to a conventional IV opioid, though not completely eliminated.

1.7 Other Safety Findings

Adverse Event Summary

In the pooled APOLLO 1 and APOLLO 2 studies, most subjects in all groups experienced at least one AE during the study. As expected, the rate of serious AEs (SAEs) was low in all treatment regimens and all SAEs resolved without sequelae. No subjects in the placebo regimen or the oliceridine 0.1 mg regimen had an AE leading to early study medication discontinuation; the rate was 3% to 6% in the other active regimens. No deaths were reported. A full evaluation of safety in Phase 3 is provided in Section 7.3.

ATHENA: Phase 3 Open-label Safety Study

The primary objective of the open label ATHENA study was to evaluate the safety and tolerability of oliceridine in a broad population of patients with moderate to severe acute pain in diverse clinical settings, including inpatient hospitals, outpatient hospital departments, ambulatory surgical care centers, and emergency departments. The study was conducted simultaneously with and in parallel to the APOLLO 1 and 2 studies and included 768 patients who received oliceridine administered as needed by PCA, as a bolus by the clinician, or both for moderate to severe pain following a variety of surgical procedures (eg, orthopedic, GI, gynecologic) and certain medical conditions.

Compared to the Phase 3 controlled APOLLO studies, ATHENA had fewer patient exclusions, allowed the use of multimodal analgesia, and enrolled a heterogeneous patient population. In general, the ATHENA patient population was older, with a higher body mass index (BMI), and had a higher number of medical comorbidities. The average baseline NRS pain score was 6. The mean reduction in pain scores was approximately 2 points at the 20-to-30-minute measurement timepoint and was maintained throughout the treatment period, suggesting a clinically meaningful magnitude of pain relief. Correspondingly, only 4.3% of all patients discontinued use of oliceridine due to lack of efficacy.

The pattern and type of safety observations was similar to that observed in the controlled trials. Most AEs were mild to moderate in severity; the most common events were typical ORAEs such as nausea, vomiting, and constipation. AEs leading to discontinuation occurred in 2.2% of patients. SAEs occurred in 3.4% of patients, most of which were secondary to complications associated with surgical procedures. All SAEs resolved or were resolving by the end of the study. There were no deaths in the study. Overall, no new AE signals were observed in this larger, more diverse group of general acute pain patients with more complications and comorbidities. A full evaluation of results from the ATHENA study is provided in Section 7.4.

Safety Topics of Special Interest

Hepatic Safety: Trevena performed nonclinical and clinical evaluations of hepatic safety throughout the development program. No evidence of hepatic toxicity was observed in the nonclinical studies. During the clinical studies, elevations in liver enzymes were observed in the placebo, morphine, and oliceridine groups. Overall, based on the available data, it was the unanimous consensus of a panel of expert hepatologists that there was no evidence of a clinically significant liver safety signal with oliceridine treatment. A full evaluation of nonclinical and clinical information on hepatic safety with oliceridine is provided in Section 7.5.1.

Cardiac Safety: Trevena performed nonclinical studies, a thorough QT (tQT) study, and extensive electrocardiogram (ECG) monitoring during the Phase 3 program. The tQT study identified a transient effect at a supratherapeutic dose of oliceridine (6 mg), which is twice the maximum proposed single oliceridine dose (3 mg), with a brief extension of the Fridericia-corrected QT interval (QTcF). At the request of FDA, Trevena implemented additional ECG monitoring in the Phase 3 studies at the time points of interest identified in the tQT study. ECG monitoring during the controlled Phase 3 studies showed no meaningful differences in the incidence of potentially clinically significant ECG results for any of the oliceridine groups, morphine, or placebo. Overall, the data suggest that oliceridine does not present a clinically meaningful risk on the cardiac safety of patients under the proposed conditions of use and dosing recommendations. A full evaluation of the nonclinical and clinical information on cardiac safety is provided in Section 7.5.2.

1.8 Conclusions

Oliceridine is the first of a new class of biased ligands with a novel mechanism of action at the MOR. This novel pharmacology was designed to selectively activate the G protein pathway, which is primarily associated with analgesia, with substantially reduced activation of the β-arrestin pathway, which contributes to respiratory depression and GI dysfunction. The clinical

and regulatory goals of the development program were tailored to thoroughly evaluate this investigational product: (1) to provide the efficacy data required for FDA approval, including two adequate and well-controlled trials demonstrating superiority over placebo, (2) to adequately characterize oliceridine safety to establish an overall benefit/risk profile, and (3) to explore the effects of oliceridine on ORAEs in relation to a conventional IV opioid.

Across nonclinical studies and all phases of clinical development, oliceridine has shown a clinical profile that is consistent with its differentiated pharmacology:

- With onset of analgesia within 5 minutes, duration of effect of 1-3 hours, and no known active metabolites, oliceridine addresses the need for a rapidly acting, titratable IV analgesic in managing moderate to severe acute pain. These features may help avoid the administration of more dosing than is needed ("dose stacking") early in therapy to achieve adequate pain relief, which can then cause more ORAEs later in therapy, unintentionally overshooting the therapeutic window.
- In terms of efficacy, all oliceridine regimens met the primary endpoint in both pivotal Phase 3 studies, meeting FDA's efficacy requirement for approval. Throughout development, oliceridine has demonstrated opioid-level analgesia for the treatment of moderate to severe pain, as expected given its selective activation of the G protein pathway.
- In terms of safety, the development program successfully explored the attenuating effects of oliceridine on ORAEs in relation to a conventional IV opioid and showed an overall favorable safety profile. Consistent with its substantially reduced activation of the β-arrestin pathway, the safety data collected provide evidence that oliceridine is associated with a reduced burden of respiratory effects and reduced incidence of nausea and vomiting compared with morphine. While clinically differentiated from the IV opioid comparator used in the development program, any formal labeling claim of safety superiority to conventional IV opioid therapy would require confirmation in the post-approval setting.
- In terms of benefit-risk, the positive efficacy and safety data from the controlled studies are supported by a large Phase 3 open-label study, which found that a diverse patient population experienced significant pain relief and a favorable safety profile across a wide range of procedures. Thus, the benefit-risk profile for oliceridine has been well characterized across a comprehensive dose range in diverse clinical settings.

2 PRODUCT DESCRIPTION AND DEVELOPMENT PROGRAM

Summary

- Oliceridine is a new chemical entity proposed for the management of moderate to severe acute pain in adult patients for whom an IV opioid is warranted.
- Conventional opioid analgesics activate both G protein and β-arrestin pathways at the MOR. G protein signaling is primarily responsible for analgesia while β-arrestin contributes to ORAEs and attenuation of analgesic response.
- Oliceridine is a biased G protein-selective modulator that was designed to provide opioid-level analgesia with less β-arrestin recruitment to reduce or attenuate ORAEs.
- The proposed dosing recommendations for oliceridine are consistent with IV analgesic use in clinical practice (ie, titration to effect).
  - The initial dose of oliceridine should be 1 to 2 mg IV. Onset of analgesic effect is expected within 5 minutes of the initial dose.
  - Maintenance of analgesia is generally achieved with bolus doses of 1 to 2 mg every 1 to 3 hours as needed, or as PCA demand doses of 0.1 to 0.35 mg as needed. Bolus doses of 3 mg may be used for maintenance in patients with more severe pain. The maximum daily dose of oliceridine should not exceed 40 mg.
- The clinical program was developed in accordance with relevant FDA guidance documents and incorporated specific feedback from the FDA throughout development.
- As a novel, first-in-class G protein-biased ligand for the MOR, the clinical development program was designed to provide the data required for approval, to characterize the overall benefit/risk profile of oliceridine for use in clinical practice, and to explore the attenuating effects of oliceridine on ORAEs:
  - All controlled Phase 2 and Phase 3 studies included an IV morphine treatment group to provide a clinically relevant comparator.
  - The Phase 2a study used fixed dosing regimens of study medications to evaluate dose-response and dose-interval relationships.
  - The Phase 2b and the Phase 3 APOLLO 1 and APOLLO 2 studies used PRN dosing to simulate clinical practice and allow patients to achieve similar analgesic efficacy with any active regimen to enable comparisons of relative safety and tolerability.
  - The open-label ATHENA study used PRN dosing in surgical, medical, and emergency department patients for whom an IV opioid was warranted to evaluate whether the safety and tolerability of oliceridine observed in controlled clinical studies was maintained in a broader patient population.

2.1 G Protein-Coupled Receptors

G protein-coupled receptors, which sit on the surface of cells and bind to hormones, neurotransmitters, and other extracellular stimuli, translate extracellular information into cellular responses (Lefkowitz 2004). Although GPCRs were originally thought to function as binary

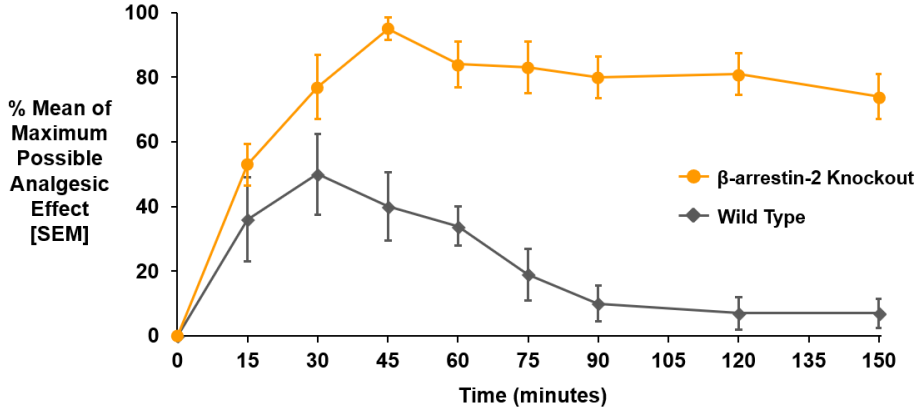
"on/off switches" with inseparable pharmacological effects, multiple signaling pathways linked to separate biological responses have been discovered. Typically, GPCR activation engages broad networks of signaling pathways, which for most receptors are mediated by both G proteins and β-arrestins (DeWire et al 2007; Wei et al 2003). Distinct pharmacological responses, such as specific beneficial or adverse effects, are often linked to these different signaling pathways. Standard agonists and antagonists of GPCRs (eg, beta blockers, opioid analgesics, antihistamines), which account for 30% of all medicines, work by either activating or inactivating the entirety of a GPCR's signaling network (Hauser et al 2017).

In the 1990's and 2000's, molecules were discovered that selectively stimulated subsets of the signaling pathways associated with specific receptors. The pharmacology of these compounds demonstrated a new model of receptor function in which these compounds stabilized different sets of receptor conformations, thereby defining a new mechanism of action. These findings led to the concept of biased ligands, which selectively activate specific signaling pathways downstream of GPCRs to elicit novel biological effects (Violin & Lefkowitz 2007; Violin et al 2014). Two researchers responsible for many of these scientific discoveries on GPCRs received the Nobel Prize for Chemistry in 2012; one of whom, Dr. Robert Lefkowitz, is an academic co-founder of Trevena.

The MOR was one of the first GPCRs to demonstrate a potential for translating the advances in GPCR pharmacology into the development of a biased ligand to improve the benefit-risk profile of existing analgesics. When activated by endorphins or opioids, the MOR triggers activation of two pathways inside the cell: G protein coupling, primarily associated with analgesic effects, and β-arrestin coupling, primarily associated with respiratory and GI effects.

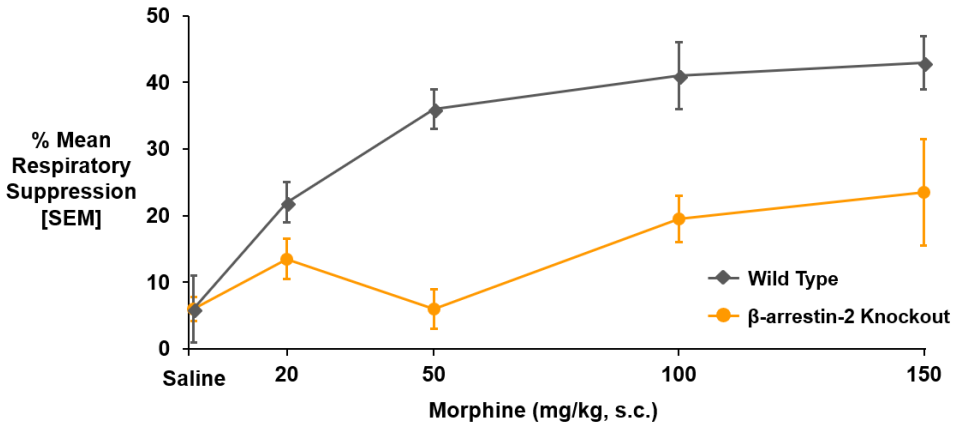
In preclinical studies, β-arrestin-2 knockout mice receiving morphine demonstrated enhanced analgesic effects (Figure 15), about 50% less respiratory depression (Figure 16), and less GI dysfunction compared with morphine-treated wild-type animals (Bohn et al 1999; Raehal et al 2005). Importantly, the pre-clinical studies suggested that elimination of β-arrestin recruitment could *reduce or attenuate*, but *not eliminate* ORAEs such as respiratory depression and GI dysfunction.

Figure 15: Analgesic Effect of Morphine in β-arrestin-2 Knockout Mice in Hot Plate Assay



Morphine dose: 10 mg/kg s.c.
Adapted from Bohn et al. *Science*, 1999

Figure 16: Morphine-induced Respiratory Depression Reduced in β-arrestin-2 Knockout Mice



Source: Raehal et al *J Pharmacol Exp Ther*, 2005

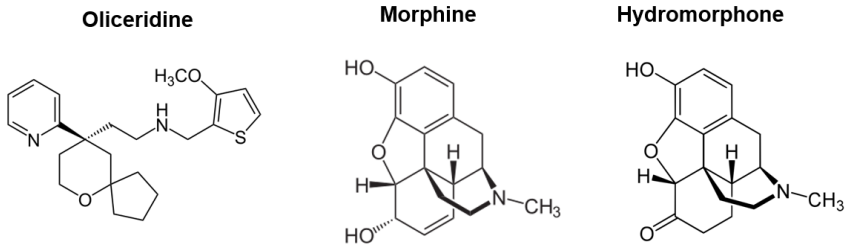
These effects are all mediated by MOR expressed on neurons, either centrally (contributing to analgesia and respiratory depression) or peripherally (contributing to nausea, vomiting, and constipation). Beta-arrestin is expressed ubiquitously and is thought to regulate the MOR in all tissues where it is expressed (DeWire et al 2007). Because morphine is systemically distributed to central and peripheral compartments, the effects of morphine in β-arrestin-2 knockout mice led to the hypothesis that analgesia and ORAEs are largely mediated by two distinct signaling pathways. This implied that a molecule that engaged with the MOR with a different mechanism of action, triggering G protein coupling with less β-arrestin coupling, could widen the therapeutic window compared to conventional IV opioids like morphine (Violin & Lefkowitz 2007).

2.2 Product Characteristics and Mechanism of Action

Oliceridine is the first of a new class of MOR ligands biased towards G protein and away from β-arrestin post-receptor signaling, defining it as a G protein-biased MOR agonist. The rationale for developing oliceridine was that this mechanism may offer opioid-level analgesia with a more favorable benefit-risk profile than conventional IV opioids.

Oliceridine was discovered by Trevena scientists in 2010. As shown by its chemical structure in Figure 17, oliceridine is a new chemical entity (NCE) that is structurally distinct from natural opiates (eg, morphine) or its semi-synthetic derivatives (eg, hydromorphone).

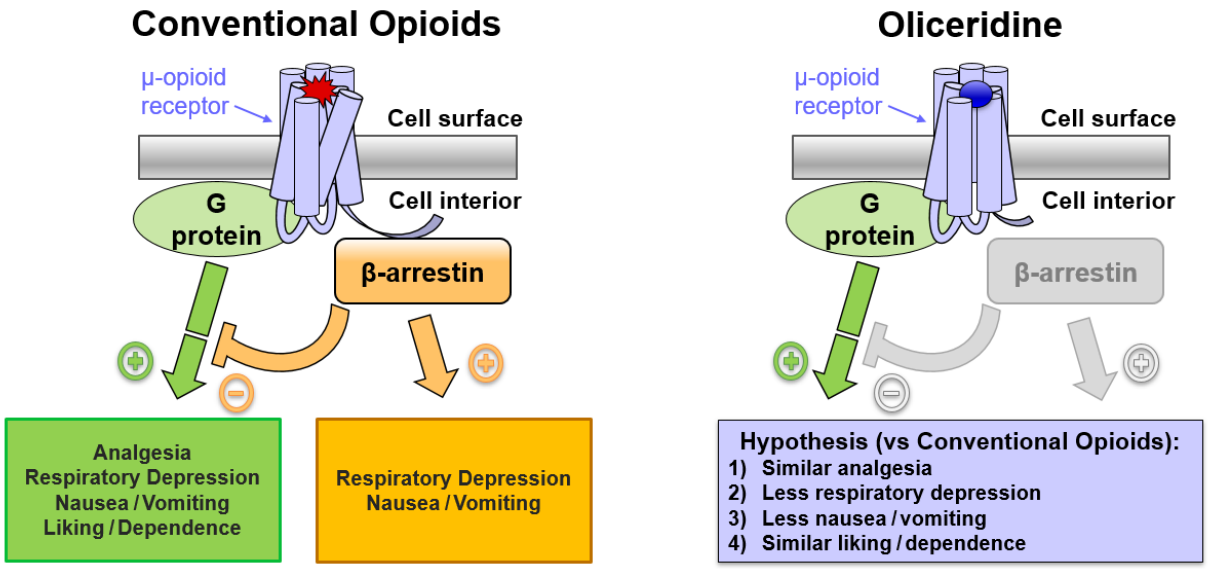
Figure 17: Chemical Structure of Oliceridine and Conventional Opioids



Nonclinical evidence suggests oliceridine exerts its actions at both central and peripheral sites in a naloxone-reversible manner, and that the differential signaling stimulated by oliceridine results from stabilization of receptor conformations distinct from those triggered by conventional opioids like morphine.

Unlike conventional opioids that activate both the G protein and β-arrestin pathways, oliceridine stimulates G protein signaling with markedly reduced β-arrestin-2 recruitment (Figure 18 provides a simplified diagram; see Section 3.1.1 for details). Thus, it was hypothesized that oliceridine would be able to provide the rapid and systemic analgesia of an opioid, but with reduced incidence of ORAEs.

Figure 18: μ-Opioid Receptor Binding of Conventional Opioids and Oliceridine



2.3 Proposed Indication and Dosing

Trevena is proposing the following indication for the prescribing information for oliceridine, 1 mg/mL:

Oliceridine is a G protein-biased ligand at the μ-opioid receptor indicated for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted.

Oliceridine (1 mg/mL) is a clear, colorless, sterile, preservative-free solution in a glass vial for IV use. The dosing regimen for each patient should be initiated individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and comorbidities.

2.3.1 Dosing Paradigms Evaluated During Development

Oliceridine is intended to be administered as needed, as is standard for injectable opioids, to deliver the minimum required cumulative dose. As needed dosing can be achieved by either PCA

or practitioner-administered intermittent bolus dosing. PCA dosing was used in the Phase 3 controlled studies with demand doses of 0.1, 0.35, and 0.5 mg; all three regimens demonstrated efficacy vs. placebo, but the 0.5 mg regimen did not provide any benefit beyond that of the 0.35 mg regimen. In addition to these trials, an open label safety study evaluated PCA 0.5 mg on demand and bolus doses of 1, 2, and 3 mg given every 1-3 hours. When administered as needed, adequate efficacy was achieved with oliceridine in the Phase 2 and Phase 3 trials, with an average cumulative dose of approximately 1 mg/hr regardless of PCA or bolus dosing paradigm. Typically, patients require more doses in the initial hours of treatment, and fewer doses to maintain analgesia once pain is adequately controlled; the majority of patients achieved adequate analgesia with daily doses less than 40 mg.

2.3.2 Proposed Dosing

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 of analgesia is generally achieved with oliceridine administered as 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 PCA administration, 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 dose. 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 bolus 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.

Oliceridine is an IV formulation that will only be administered by trained medical personnel for IV use within a controlled clinical setting.

2.4 Regulatory Milestones

Trevena has worked collaboratively with the FDA throughout the clinical development program.

Following submission of the results for the Phase 2 studies to the FDA, which showed that oliceridine led to statistically significantly fewer hypoventilation, nausea, and vomiting AEs in the context of similar efficacy to morphine, FDA granted Fast Track designation and Breakthrough Therapy designation on December 2, 2015 and February 19, 2016, respectively. Fast Track designation is “a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need” (FDA 2018). Breakthrough Therapy designation is “designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy” (FDA 2018).

Prior to submission of the New Drug Application (NDA) for oliceridine, Trevena and the FDA agreed upon an initial pediatric study plan, which includes studies to collect efficacy, safety, tolerability, and PK data to establish the appropriate dose in all pediatric age groups. The

planned clinical studies to support pediatric development are summarized in Appendix 10.1. The submission of the oliceridine NDA was accepted on January 2, 2018.

2.5 Clinical Development Program

The oliceridine clinical development program was designed with three primary aims:

- to provide the data required to demonstrate analgesic efficacy (including two adequate and well-controlled clinical trials demonstrating superiority to placebo in both hard and soft tissue pain conditions)
- to adequately characterize oliceridine safety and establish an overall favorable benefit/risk profile
- to explore the effects of oliceridine on ORAEs in relation to a conventional IV opioid

To meet these goals, the oliceridine development program included 17 clinical studies:

- seven (7) Phase 1 safety and PK studies in healthy volunteers (including a Phase 1, randomized, double-blind, placebo-controlled, crossover study that evaluated experimental models of analgesic activity and respiratory safety)
- one (1) Phase 1 tQT study in healthy volunteers
- one (1) Phase 1 PK and safety study in patients with and without hepatic impairment
- one (1) Phase 1 PK and safety study in patients with and without end stage renal disease (ESRD)
- one (1) HAL study in recreational, nondependent opioid users
- one (1) Phase 2 open-label study in patients with long-bone fracture (terminated due to lack of enrollment after 1 subject enrolled)
- two (2) Phase 2 placebo-controlled studies with a morphine comparator group (one study each in bunionectomy and abdominoplasty) to establish proof of efficacy and evaluate dose strengths and dosing intervals
- two (2) Phase 3 placebo-controlled studies with a morphine comparator group (APOLLO 1 in patients undergoing bunionectomy and APOLLO 2 in patients undergoing abdominoplasty)
- one (1) Phase 3 open-label multi-procedure safety study (ATHENA) in patients with moderate to severe acute pain.

Table 3 provides a summary of the objectives and designs of the completed Phase 2 and Phase 3 studies. (Note: Phase 2 Study 2004 is omitted from the table; only one patient was screened and enrolled.)

Table 3: Description of Completed Phase 2 and Phase 3 Studies in Oliceridine Clinical Development Program

Study	Evaluation(s)	Study Design (N Randomized and Treated)	Treatment Regimen(s)
Adequate and Well-Controlled Phase 3 Studies			
APOLLO 1 (3001)	Efficacy, Safety	MC, R, DB, PC, AC in patients undergoing bunionectomy (N=389)	PRN dosing via PCA: IV oliceridine: 1.5 mg loading dose and 0.1, 0.35, or 0.5 mg demand doses IV morphine: 4 mg loading dose and 1 mg demand dose IV placebo: volume- and time-matched treatments • 6-minute lockout interval • Supplemental doses (0.75 mg oliceridine, 2 mg morphine) permitted PRN q1h after loading dose • Treatment period: 48 hours
APOLLO 2 (3002)	Efficacy, Safety	MC, R, DB, PC, AC in patients undergoing abdominoplasty (N=401)	PRN dosing via PCA: IV oliceridine: 1.5 mg loading dose and 0.1, 0.35, or 0.5 mg demand doses IV morphine: 4 mg loading dose and 1 mg demand dose IV placebo: volume- and time-matched treatments • 6-minute lockout interval • Supplemental doses (0.75 mg oliceridine, 2 mg morphine) permitted PRN q1h after loading dose • Treatment period: 24 hours
Open-label Phase 3 Study			
ATHENA (3003)	Safety, Effectiveness	MC, OL in surgical and medical patients (N=768 treated)	IV oliceridine: administered either by clinician-administered bolus, PCA, or both bolus and PCA, according to the clinical situation. • Clinician-administered bolus dosing: 1-2 mg initial dose; 1 mg supplemental dose PRN, as early as 15 minutes after the initial dose; subsequent doses 1-3 mg every 1-3 hours PRN • In settings where rapid analgesia is targeted (eg, ED or PACU): 1-3 mg initial dose; 1-3 mg supplemental doses every 5 minutes PRN; subsequent doses 1-3 mg every 1-3 hours PRN • PCA Regimen: 1.5 mg loading dose, 0.5 mg demand dose, 6-minute lockout interval • Supplemental 1 mg doses permitted PRN • Treatment period: Duration of treatment based on clinical need for IV opioid therapy
Adequate and Well-Controlled Phase 2 Studies			
2001	Efficacy, safety, PK	MC, R, DB, PC, AC, AD in patients undergoing bunionectomy (N=333)	IV oliceridine: Stage A: 1, 2, 3, or 4 mg q4h; Stage B: 0.5, 1, 2, or 3 mg q3h IV morphine: 4 mg q4h IV placebo: volume- and time-matched treatment • Treatment Period: 48 hours
2002	Efficacy, safety	R, DB, PC, AC in patients undergoing abdominoplasty (N=200)	IV oliceridine: 1.5 mg loading dose (administered as 0.75 mg at T0 and 0.75 mg at T10 minutes) and 0.1 mg demand dose with up-titration to 0.15 mg (Stage 1) or 0.35 mg (Stage 2) IV morphine: 4 mg loading dose (administered as 2 mg at T0 and 2 mg at T10 minutes) and 1 mg demand dose with up-titration to 1.5 mg in Stage 1 IV placebo: volume and time matched treatment • 6-minute lockout interval • Treatment Period: 24 hours

MC = multi-center; R = randomized; DB = double-blind; PC = placebo-controlled; AC = active-comparator; OL = open-label; AD = adaptive; ED = Emergency Department; PACU = Post-anesthesia care unit.

2.6 Treatment Exposures

A total of 1,853 unique individuals have been exposed to oliceridine: 221 healthy subjects in Phase 1 studies, 97 special population subjects in Phase 1 studies, and 1,535 patients with moderate to severe acute pain in Phase 2 and Phase 3 studies. As is appropriate for the treatment of acute pain, most patients in the Phase 2 and Phase 3 studies (1317/1535 patients [86%]) received oliceridine PRN. Table 4 provides an overview of the number of treatment exposures in the Phase 2 and 3 studies.

Table 4: Exposure in Phase 2 and Phase 3 Oliceridine Clinical Studies

Study	Oliceridine	Placebo	Morphine	Total
Phase 2 Study 2004	1	-	-	1
Phase 2a Study 2001	218	51	64	333
Phase 2b Study 2002	78	39	83	200
Phase 3 APOLLO 1	234	79	76	389
Phase 3 APOLLO 2	236	83	82	401
Phase 3 ATHENA	768	-	-	768
Overall	**1,535**	**252**	**305**	**2,092**

3 NONCLINICAL PHARMACOLOGY

Summary

- Oliceridine is a G protein-biased ligand with substantially reduced β-arrestin coupling compared with morphine.
- Consistent with its differential pharmacology, oliceridine was associated with less respiratory depression and GI dysfunction than equianalgesic doses of morphine in nonclinical studies.
- Nonclinical studies provide evidence that naloxone can reverse the effects of oliceridine.
- Oliceridine is metabolized by the liver into non-active metabolites.
- General toxicity, genotoxicity, and developmental and reproductive toxicology studies did not identify any unique issues beyond those seen in prior studies with conventional MOR agonists.

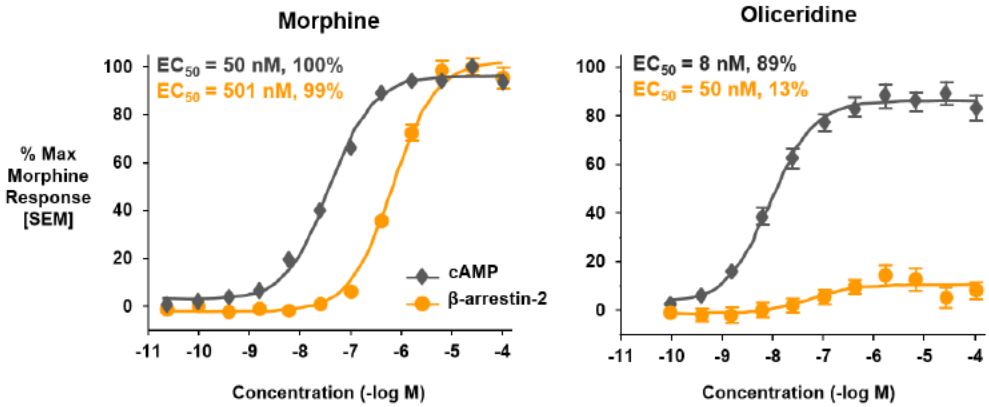
3.1 Nonclinical Pharmacology

3.1.1 G Protein-Biased Signaling with Oliceridine

A nonclinical model in human embryonic kidney cells was used to evaluate the comparative G protein and β-arrestin signaling of oliceridine and morphine (DeWire et al 2013). The study measured cyclic adenosine monophosphate (cAMP) activity, a measure of G protein signaling, and β-arrestin-2 activity at various concentrations of both study drugs.

Increasing concentrations of morphine yielded strong activity for both G protein and β-arrestin-2 coupling, which would be expected for a conventional opioid agonist (Figure 19; left panel). In contrast, oliceridine showed G protein activity similar to morphine and higher potency than morphine, but with markedly reduced β-arrestin-2 coupling (Figure 19; right panel). Thus, oliceridine was shown to be a G protein-biased ligand at the MOR.

Figure 19: G Protein and β-arrestin-2 Activity of Morphine and Oliceridine in Human Embryonic Kidney Cells Expressing Human MOR



Source: Adapted from DeWire et al. *J Pharmacol Exp Ther*, 2013

3.1.2 Analgesic Efficacy and Gastrointestinal and Respiratory Effects in Nonclinical Studies

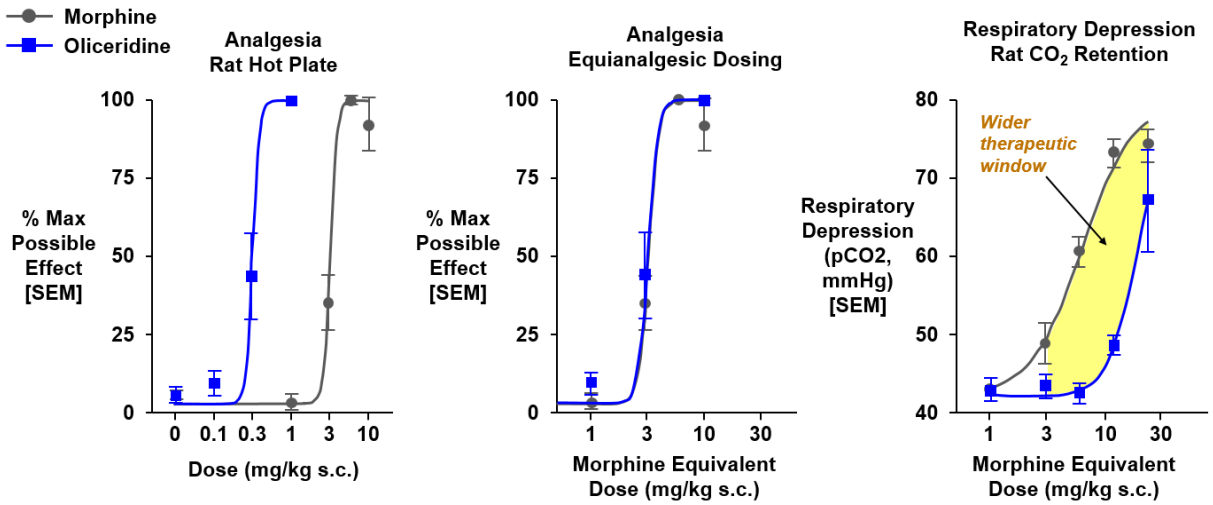
Nonclinical studies of oliceridine were consistent with prior research in β-arrestin-2 knockout mice. In mice and rats, oliceridine elicited potent and robust analgesia in multiple models of spinal reflexive and supraspinal affective nociceptive pain (potency 3- to 10-times that of morphine) with significantly less respiratory depression and constipation compared with equianalgesic doses of morphine (DeWire et al 2013; Violin et al 2014).

Figure 20 shows dose-response curves for morphine and oliceridine from these nonclinical studies.

- The left panel shows the dose-response relationship for analgesic activity in the rat hot plate model, a standard preclinical model for assessing the potential efficacy of analgesics. Oliceridine and morphine both achieved maximal analgesic efficacy, with oliceridine showing approximately 10-fold greater potency in the rat model.
- The middle panel shows the analgesic dose-response curves dose-normalized to morphine. Dose-normalization by analgesic potency allows for an evaluation of the therapeutic window – the relative safety profile at equianalgesic doses.
- The right panel shows the dose-response curves for respiratory depression displayed using morphine-equivalent doses. Partial pressure of CO_2 in arterial blood was used as the model of opioid-induced respiratory depression. At equianalgesic doses, oliceridine was associated with a substantial decrease in respiratory depression and had a wider therapeutic window compared with morphine, which is illustrated with the yellow highlighting.

An improved therapeutic window was also observed for constipation and GI motility (DeWire et al 2013; Violin et al 2014).

Figure 20: Log-Transformed Oliceridine and Morphine Dose-Response Curves for Analgesic Activity and Respiratory Depression in Rats



Source: Adapted from Violin et al. *Trends Pharmacol Sci*, 2014

The preclinical studies predicted that oliceridine would be expected to display an optimum dose (ie, where doses too low would have few AEs but modest efficacy and doses too high would provide efficacy similar to morphine with little to no difference in AEs). Thus, the clinical studies were designed to explore a range of doses to maximize the benefit-risk compared with a clinically appropriate morphine dose.

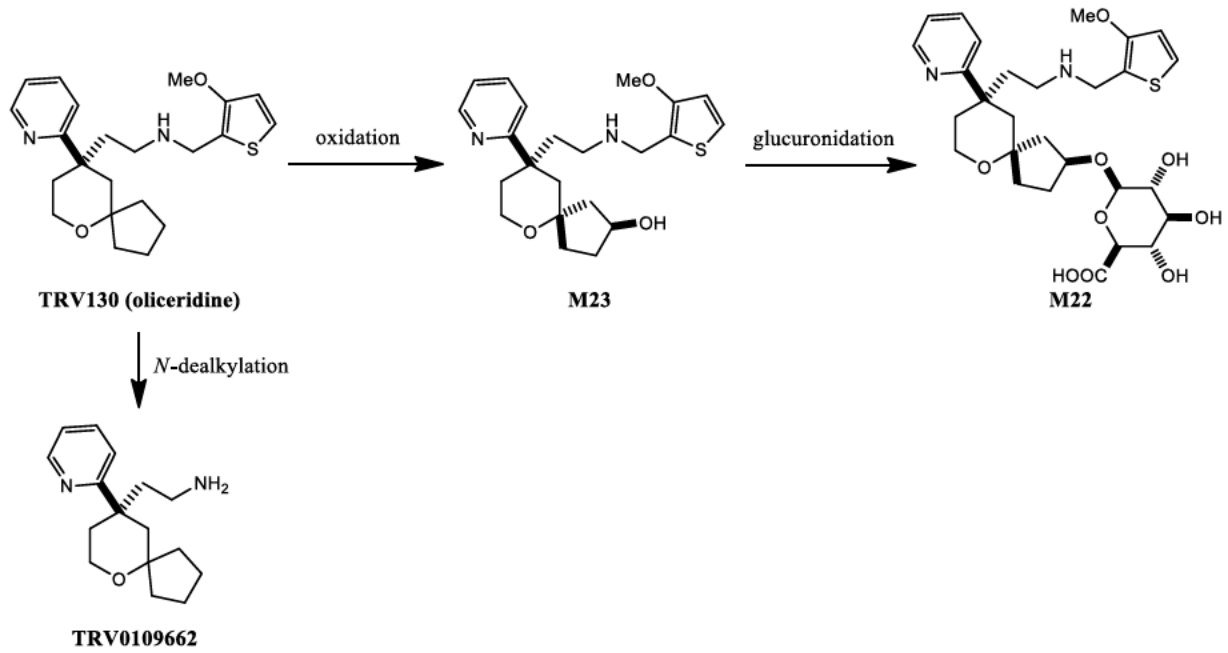
3.1.3 Oliceridine Binding and Reversibility with Naloxone

Cell-based assays showed that oliceridine binds competitively with respect to conventional opioids and naloxone, and that oliceridine has a short receptor residence time comparable to morphine. Consistent with the assay results, oliceridine pharmacology was rapidly reversed by naloxone in rodents (DeWire et al 2013).

3.1.4 Metabolism and Excretion

Oliceridine is extensively metabolized by oxidation and subsequent glucuronidation or by *N*-dealkylation (Figure 21). In vitro, oliceridine is a substrate of both cytochrome P450 2D6 (CYP2D6) and cytochrome P450 3A4 (CYP3A4), with each enzyme contributing approximately 50% to its metabolism. Oliceridine and its major metabolites had no effects on the major human uptake and efflux transporters, including bile salt export pump (BSEP), at clinically relevant concentrations.

Figure 21: Proposed Metabolic Pathways of Oliceridine



The metabolic activation of oliceridine was tested in vitro using human liver microsomes fortified with glutathione (GSH). Hepatocyte incubates from several animal species, and plasma and urine from animals and humans dosed with oliceridine were also profiled by mass spectrometry for the presence of metabolites including glutathione conjugates or subsequent metabolites of any glutathione conjugates. No isomeric GSH conjugates were formed after

oxidation of 10 uM oliceridine in human microsomes and were noted only at higher concentrations of 50 uM, compared with a mean maximum observed unbound plasma concentration (C_{max}) of 0.172 µM following a single supratherapeutic 6 mg bolus dose (see Section 7.5.2). No GSH conjugates were found after profiling rat or human plasma, urine and feces collected after a single IV dose of ^{14}C-oliceridine (ie, radiolabeled oliceridine). In addition, no metabolism dependent CYP inhibition was found after incubation of oliceridine with human liver microsomes (see Section 4.2.2), unlike reference compounds that do have reactive intermediates or metabolites, supporting the conclusion that metabolic activation of oliceridine with subsequent reactivity with tissue or soluble (GSH) nucleophiles is negligible.

The major routes of excretion for oliceridine and total radioactivity were determined following IV dosing of radiolabeled oliceridine. In humans, 70% of an IV dose was excreted renally (primarily as metabolites), with 18% in the feces. Excretion of intact oliceridine was negligible, confirming that clearance is primarily via metabolism.

Analysis of human plasma following IV dosing of radiolabeled oliceridine identified oxy-TRV130 glucuronide (M22) as the main circulating radioactive component, accounting for a mean of 61.9% of total radiolabeled drug-related plasma exposure (area under the concentration curve [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). Overall, these data indicate that oliceridine undergoes extensive metabolism in humans, primarily by oxidation of the pyridine or oxaspirodecane moiety with subsequent glucuronidation.

3.1.5 Oliceridine Metabolites

The two major metabolites of oliceridine, TRV0109662 and M22, are 500- and 800-fold less potent than oliceridine at the MOR, respectively, and show minimal activity for β-arrestin-2 recruitment at all opioid receptors. In addition, TRV0109662 and M22 showed negligible binding to more than 130 common drug targets tested in vitro. Therefore, these major metabolites are not expected to contribute to the pharmacologic activity of oliceridine at relevant human exposures.

The fact that oliceridine has no known active metabolites contrasts with morphine, where analgesic efficacy and ORAEs are driven in part by an active metabolite (M6G) that may accumulate over time. These attributes of oliceridine may provide a clinical advantage in dosing, titration, and predictability of analgesic response.

3.2 Nonclinical Toxicology

Trevena performed a comprehensive set of nonclinical toxicology studies. The key findings from these studies are summarized below:

- Nonclinical toxicology studies with up to 28 days of continuous IV infusion of oliceridine in rats and up to 14 days of continuous IV infusion in monkeys identified no unique oliceridine-induced toxicity other than prototypical changes seen after opioid administration (decreased food consumption and body weights, decreased activity, decreased mean blood pressure, decreased body temperature, and stereotypic behavioral changes).

- Total daily exposure at the no-observed-adverse-effect-level (NOAEL) dose of 0.5 mg/kg/hr in rats and 1 mg/kg/hr in monkeys was approximately 3-times (rats) and 22-times (monkeys) the daily exposure at the 40 mg/day maximum recommended human dose (MRHD) on an AUC basis.
- Oliceridine was also tested for genotoxicity in a comprehensive battery of in vitro and in vivo genetic toxicity assays. Results from these studies indicate that the risk of clastogenicity in humans, if any, is minimal.
- Developmental and reproductive toxicology studies did not identify any unique issues beyond those seen in prior studies with conventional MOR agonists. The effects of oliceridine have not been evaluated in pregnant women; therefore, oliceridine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

4 CLINICAL PHARMACOLOGY

Summary

- Oliceridine is metabolized by the liver, primarily by CYP3A4 and CYP2D6 isozymes. It has no known active metabolites, which may provide a clinical advantage in dosing and titration.
- Oliceridine C_{max} and AUC generally increased in a dose-proportional or slightly greater than dose-proportional manner across the dose range of 0.15 to 7 mg when administered IV.
- The mean half maximal effective concentration (EC_{50}) for oliceridine's effect on pain scores after bunionectomy was estimated to be 10.1 ng/mL (90% confidence interval [CI]: 8.41-12.1 ng/mL).
- In CYP2D6 poor metabolizers (PMs), clearance (CL) was reduced by approximately 50% and C_{max} was in the upper range of the C_{max} values in extensive metabolizers (EMs).
- Oliceridine exhibited a half-life ($t_{½}$) of approximately 1.5 to 3 hours when administered IV over 1 minute to 1 hour. In CYP2D6 PMs, oliceridine tended to have a longer $t_{½}$ than in EMs. The data suggest that, because oliceridine is intended to be administered as needed, CYP2D6 PMs do not need different dosing instructions.
- In vitro, oliceridine or its metabolites TRV0109662 and M22 did not cause direct, time, or metabolism-dependent inhibition of any of the major P-450 enzymes at clinically relevant concentrations.
- Administration of a strong CYP3A4 inhibitor with oliceridine in PMs decreased clearance by about 44%, with a similar proportional increase in the AUC. The mean C_{max} was not significantly affected. These patients may require less frequent dosing.
- Data in subjects with end stage renal disease (ESRD) suggests that no dose adjustment is needed in patients with renal impairment. In patients with mild to moderate hepatic impairment, no adjustment of the initial dose of oliceridine is needed; however, these patients will likely require less frequent dosing.

4.1 Relevant Background and CYP2D6 Pharmacogenomics

Approximately 80% of all therapeutic drugs used today are metabolized by one of the cytochrome P450 (CYP450) enzymes (Zanger & Schwab 2013). Two of these enzymes, CYP3A4 and CYP2D6, are responsible for the metabolism of oliceridine. Approximately 7-10% of US Caucasians and 2-7% of African-Americans have one of several functional polymorphisms, which causes a loss in metabolic function for CYP2D6. These so-called "poor metabolizers" (PMs) will exhibit decreased clearance and therefore increased exposure to drugs metabolized by CYP2D6 compared with "extensive metabolizers" (EMs) with normal metabolic function (Bernard et al 2006).

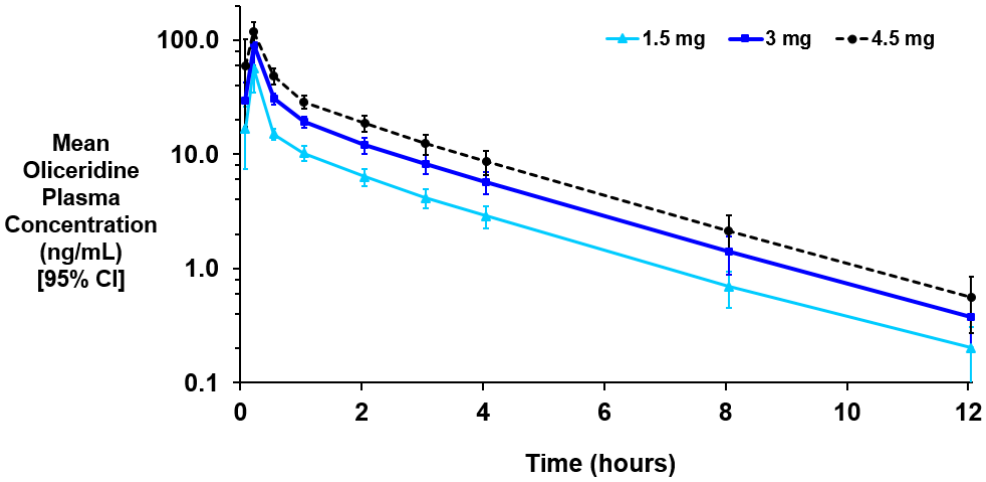
4.2 Oliceridine Pharmacokinetics

The PK profile of oliceridine and its metabolites was consistent across the clinical pharmacology program. Refer to Appendix 10.5 for a full list of Phase 1 pharmacology studies. The main conclusions of these studies are presented below:

- The increase in exposure (C_{max} and AUC) was somewhat greater than proportional as the dose was increased from 0.15 to 7 mg, deviating from linearity, on average, by approximately 15%.
- In CYP2D6 PMs, clearance (CL) was reduced by approximately 50% and C_{max} was in the upper range of the C_{max} values in EMs. Reduced CL in CYP2D6 PMs was consistent across all of the studies in the Phase 1 program, and this finding is consistent with previous in vitro studies that demonstrated that oliceridine CL is primarily mediated by CYP2D6 and CYP3A4 oxidation.
- Oliceridine exhibited a half-life ($t_{½}$) of approximately 1.5 to 3 hours when administered IV over 1 minute to 1 hour. CYP2D6 PMs tended to have a longer $t_{1/2}$ than EM subjects (see Appendix 10.5, Table 33 for cross-study results).
- Renal clearance of oliceridine is low (2.2 – 5.1% of total clearance). Renal impairment has no effect on the clearance of oliceridine; therefore, no dose adjustment of oliceridine is needed in patients with renal impairment.
- Plasma protein binding in humans is low (77%).
- The oral bioavailability of oliceridine is low (5.77%).

Figure 22 shows a representative mean plasma concentration vs. time plot for oliceridine from Study 1003 (see Appendix 10.5 for a cross-summary of single-dose oliceridine PK).

Figure 22: Mean Oliceridine Plasma Concentration over Time for Three IV Doses of Oliceridine in Study 1003



4.2.1 Population Pharmacokinetics/Pharmacodynamics

Extensive population PK/PD modeling and simulation studies were carried out prior to the start of the Phase 3 studies. The initial modeling effort used the PK data from the Phase 1 program along with data collected from the Phase 2a bunionectomy study. Pain score data from this trial was utilized to build a PK/PD model relating the change in NPRS score to oliceridine plasma concentration. The PK model incorporated the effects of covariates such as body weight, CYP2D6 status, and the presence of concomitant CYP3A4 inhibitors. Sex and age did not have any clinically significant effect on the pharmacokinetics of oliceridine. Body weight had a small effect on clearance that would not be expected to be clinically significant in the context of titration to analgesic effect in clinical treatment settings. The PD portion of the model related plasma oliceridine concentrations to change in pain score and incorporated a model of the placebo effect. This model was then used in several simulation studies which yielded important insights into the expected PK/PD relationships of oliceridine:

- Simulations were performed in which simulated doses were only given to simulated patients when their pain score was ≥ 4, thus mimicking what would ordinarily occur in the actual clinical context. The simulations showed that as oliceridine was titrated to an effective level of analgesia for a patient, CYP2D6 PMs received less frequent doses, and their drug exposure was therefore predicted to be similar to EM patients, thus obviating the need to adjust the oliceridine dose based on CYP2D6 status. This finding from the simulations was confirmed in the Phase 3 studies (Table 5).
- The mean half maximal effective concentration (EC_{50}) for oliceridine's effect on pain score after bunionectomy was estimated to be 10.1 ng/mL (90% CI: 8.41-12.1 ng/mL), indicating that oliceridine is a potent analgesic at relatively low plasma concentrations.
- The PK/PD model was further updated with data from the Phase 2b study. The resulting updated model was similar to the previous model, yielding an EC_{50} of 10.6 ng/mL. PK/PD simulations were then performed using PCA demand doses of 0.1 mg, 0.35 mg, and 0.5 mg. The 0.5 mg demand dose had not been studied in any clinical trial to date. The simulations suggested that no significant additional efficacy benefit would be seen with demand doses greater than 0.35 mg. The 0.5 mg demand dose was studied in Phase 3 to confirm this prediction.
- The simulations also indicated that supplemental doses may be helpful during the course of therapy with oliceridine. As a result, the option for clinicians to give 0.75 mg supplemental oliceridine doses during PCA therapy was incorporated into the Phase 3 program.

Sparse population PK samples were collected in the APOLLO studies as well in as the ATHENA study, which allowed the estimation of peak and total exposure from the Phase 3 trials (Table 5). These data confirmed that the oliceridine C_{max} and AUC values would be similar in EM and PM patients when titrated to clinical analgesic effect, despite the significantly decreased oliceridine clearance in PM patients.

Table 5: Comparison of Estimated Peak and Total Oliceridine Plasma Exposure in Extensive (EM) and Poor (PM) Metabolizers in the Phase 3 Program

Exposure Parameter	Geometric Mean (95% CI)	
	Extensive Metabolizers (N=564)	Poor Metabolizers (N=88)
C_{max} (ng/mL)	90.1 (15.7 - 517.8)	92.1 (24.3 - 349.2)
AUC_{0-24} (ng*hr/mL)	223.8 (16.4 - 3061.2)	250.3 (35.2 - 1781.7)

4.2.2 Drug Interactions

In vitro, oliceridine or its metabolites TRV0109662 and M22 did not cause direct, time-, or metabolism-dependent inhibition of CYP1A2, 2B6, 2C8, 2D6, 2C9, 2C19 or 3A4/5 at clinically relevant concentrations. Oliceridine was not a substrate when tested against a standard panel of eight human uptake and three human efflux transporters. Oliceridine, TRV0109662, and M22 did not inhibit any of the transporters at clinically relevant concentrations. These data suggest that drug interactions mediated by uptake or efflux transporters are unlikely at clinically relevant plasma concentrations of oliceridine and metabolites.

Because both CYP2D6 and CYP3A4 contribute equally to the clearance of oliceridine, a strong inhibitor of either enzyme would be expected to decrease oliceridine clearance by about 50% in EMs. Physiologically-based pharmacokinetic modeling has shown that a strong CYP3A4 inhibitor might be expected to increase oliceridine exposure by 1.3- to 1.5-fold in CYP2D6 EMs and 1.7- to 2.2-fold in CYP2D6 PMs. Using a strong CYP2D6 inhibitor in the model might be expected to increase oliceridine exposure by approximately 1.5-fold in EMs. No effect would be seen in PMs, since they have little CYP2D6 to inhibit.

To determine the effect of a concomitantly administered strong CYP3A4 inhibitor on the clearance of oliceridine in CYP2D6 poor metabolizers, healthy CYP2D6 PM subjects (N=4) received a single dose of 0.25 mg oliceridine followed by five doses of itraconazole, a strong CYP3A4 inhibitor, 200 mg once a day in Study 1005. On the last day of itraconazole dosing, a single dose of 0.25 mg oliceridine was given.

Administration of itraconazole in CYP2D6 PMs in this study decreased oliceridine clearance by approximately 44%, with a similar proportional increase in the AUC (Table 6). The mean C_{max} was not significantly affected by the administration of itraconazole. The mean $t_{½}$ was increased 2.4-fold with itraconazole as compared to oliceridine given alone. Since oliceridine is titrated to effect, these patients will need less frequent doses than patients not on a CYP3A4 inhibitor; however, since C_{max} is not affected, no adjustment of the initial dose is needed. Patients taking both a CYP3A4 and a CYP2D6 inhibitor should be closely monitored.

Table 6: Effect of a Strong CYP3A4 Inhibitor (Itraconazole) on Oliceridine PK in CYP2D6 Poor Metabolizers

Parameter	Geometric Mean (% Coefficient of Variation)	
	Oliceridine (N=4)	Oliceridine + Itraconazole (N=4)
C_{max} (ng/mL)	4.8 (44.4)	5.2 (51.7)
T_{max} (hrs)	0.16*	0.16*
$AUC_{0-\infty}$ (ng*hr/mL)	10.6 (24.9)	19.0 (20.7)
CL (L/hr)	23.5 (24.9)	13.2 (20.6)
$t_{½}$ (hrs)	2.8 (15.3)	6.6 (39.3)

* Median

4.2.3 Hepatic Impairment

Study 1010 was an open-label study to evaluate the PK, safety, and tolerability of a single 2-minute IV infusion of oliceridine in healthy adult subjects and subjects with mild, moderate, or severe hepatic impairment. Hepatic function was assessed at screening using the Child-Pugh scoring system. Healthy adults were administered oliceridine 1 mg, and subjects with hepatic impairment were administered oliceridine 0.5 mg.

A summary of the plasma oliceridine PK parameters is presented in Table 7, with dose-normalized C_{max} and AUC values to allow for comparisons across the groups. Clearance and AUC were generally similar across individuals with and without hepatic impairment of any severity. Both volume of distribution (V_z) and $t_{½}$ increased with the severity of hepatic impairment. Among individuals with mild or moderate hepatic impairment, the initial dose of oliceridine does not require adjustment since the peak concentration is similar to that seen in individuals with normal hepatic function; however, given the observed increase in $t_{½}$, these individuals will likely require longer dosing intervals.

The increases in $t_{½}$ and V_z (indicating increased tissue distribution) in patients with severe hepatic impairment are consistent with the presence of ascites in these patients, as well as an increased free fraction of plasma oliceridine, due to the hypoalbuminemia typically observed in hepatically-impaired patients; therefore, oliceridine should be used with caution since these patients are likely to require fewer doses.

Table 7: Summary of Oliceridine PK Parameters by Hepatic Impairment in Study 1010

PK Parameter	Geometric Mean (% Coefficient of Variation)			
	Normal N=8	Mild N=8	Moderate N=8	Severe N=6
Dose-normalized C_{max} (ng/mL)	34.8 (110.0)	41.4 (78.4)	41.9 (41.6)	8.4 (89.5)
Dose-normalized $AUC_{0\text{-}inf}$ (ng*hr/mL)	23.7 (30.5)	22.5 (33.9)	29.5 (37.0)	23.9 (41.6)
Dose-normalized $AUC_{0\text{-}24}$ (ng*hr/mL)	23.6 (30.5)	22.5 (33.9)	28.5 (32.3)	22.1 (36.0)
$t_{1/2}$ (h)	2.1 (11.3)	2.6 (20.0)	4.3 (44.1)	5.8 (41.2)
CL (L/h)	42.3 (27.2)	44.5 (48.9)	33.9 (32.1)	41.8 (36.5)
V_z (L)	126.1 (21.6)	167.3 (44.8)	211.5 (18.2)	347.9 (35.2)

$t_{1/2}$: half-life; CL: clearance; V_z: volume of distribution.

4.2.4 Renal Impairment

Study 1012 was an open-label study to evaluate the PK, safety, and tolerability of a single 2-minute IV infusion of oliceridine in subjects who regularly undergo hemodialysis as part of their treatment regimen for end stage renal disease (ESRD) compared with healthy subjects. Healthy adults were administered oliceridine 1 mg and subjects with ESRD were administered 0.5 mg.

A summary of the plasma oliceridine PK parameters is presented in Table 8 with dose-normalized C_{max} and AUC values to allow comparisons across the groups. All PK parameters were similar between healthy individuals and those with ESRD; therefore, dosage adjustment of oliceridine in patients with renal impairment is not required.

Table 8: Summary of Oliceridine PK Parameters by ESRD Status in Study 1012

PK Parameter	Geometric Mean (% Coefficient of Variation)	
	ESRD Subjects N=8	Healthy Subjects N=8
Dose-normalized C_{max} (ng/mL)	9.9 (14.8)	8.8 (22.4)
T_{max} (hr)	0.25 (0.25 – 0.25)*	0.25 (0.25 – 0.25)*
Dose-normalized $AUC_{0\text{-}last}$ (ng*hr/mL)	19.1 (27.3)	17.8 (17.8)
Dose-normalized $AUC_{0\text{-}\infty}$ (ng*hr/mL)	20.3 (28.3)	18.1 (17.8)
$t_{1/2}$ (hr)	3.0 (31.9)	2.3 (31.9)
CL (L/hr)	49.2 (28.3)	55.3 (17.8)
V_z (L/hr)	212.0 (27.8)	187.0 (34.5)

$t_{1/2}$: half-life; CL: clearance; V_z: volume of distribution.
*Data are median (range).

4.2.5 Comparison to Other IV Opioids

Table 9 summarizes the key PK and PD parameters of oliceridine and the conventional IV opioids morphine, hydromorphone, and fentanyl.

Table 9: Comparison between Oliceridine and Conventional IV Opioids

Attributes	Oliceridine	Morphine	Hydromorphone	Fentanyl
β-arrestin recruitment (max response compared to morphine)[a]	14%	Reference (100%)	89%	478%
Onset of First Perceptible Effect	1-2 min[b]	5-10 min	~5 min	Immediate
Peak Effect	0.1-0.2 hours[b]	0.5-10 hours	0.17 – 0.33 hours	ND
Half-life	1.5-3 hours[c]	2-4 hours	2-3 hours	2-4 hours
Duration of Effect	1-3 hours[b]	3-4 hours[e]	3-4 hours	0.5-1 hours
Potency[e]	1 mg	5 mg	0.75 mg	0.1 mg
Metabolism	Hepatic CYP3A4:CYP2D6	Hepatic Glucuronidation M6G: Renal[d]	Hepatic Glucuronidation	Hepatic CYP3A4
Active metabolites	No	Yes (M6G)	No	No
Dose Adjustment in Renal Impairment	No	Yes[f]	Yes[f]	No[f]
Dose Adjustment in Hepatic Impairment	Mild/Moderate: No Severe: Yes	Yes[f]	Yes[f]	Yes[f]

M6G: morphine-6-glucoronide; ND: no data
Source except where noted: Opioid Analgesics: Adult Pharmacokinetics. Facts and Comparisons [database online], 2017.
[a]DeWire et al 2013. [b]Study 2001. [c]Study 1003. [d]Lotsch & Geisslinger 2001. [e]Kishner 2018. [f]Product Labeling

4.2.6 Conclusions

Oliceridine is the first of a new class of MOR ligands biased towards G protein and away from β-arrestin-2 post-receptor signaling. The novel mechanism of action was designed to reduce or attenuate respiratory effects and GI dysfunction relative to conventional IV opioids. Nonclinical studies showed that oliceridine was associated with a wider therapeutic window than morphine at equianalgesic doses and provided support for clinical development.

With no known active metabolites and an onset of analgesia within 5 minutes, the PK/PD profile of oliceridine suggests that it may be easier to titrate and provide a more predictable analgesic response than morphine, which has active metabolites that can accumulate over time. The presence of active metabolites and lag in onset of meaningful pain relief can result in more dosing than is needed ("dose stacking") early in therapy to achieve pain relief, which can then cause more ORAEs later in therapy, unintentionally overshooting the therapeutic window.

Extensive population PK modeling found no significant impact of key intrinsic factors such as age, body weight, and sex. Patients receiving strong CYP3A4 or CYP2D6 inhibitors, or patients who are CYP2D6 PMs, may require less frequent dosing; however, no initial dose adjustments should be required. Data in ESRD subjects suggests that no dose adjustment is needed in patients with renal impairment. In patients with mild to moderate hepatic impairment, no adjustment of the initial dose of oliceridine is needed; however, these patients will likely require fewer doses.

5 HUMAN PHARMACODYNAMICS

Summary

- The Phase 1 proof-of-concept study used ventilatory response to hypercapnia (VRH), the gold standard method for evaluating opioid-induced respiratory depression, to compare the relative effects of oliceridine and morphine on respiratory drive. The study demonstrated that oliceridine caused significantly less depression in respiratory drive than morphine at doses providing at least as much analgesic activity.
- In the human abuse liability (HAL) study, oliceridine had drug liking scores similar to equianalgesic doses of morphine. Oliceridine is proposed to be a Schedule II drug under the Controlled Substances Act and administered only in a controlled clinical setting.

5.1 Pharmacologic Proof-of-Concept Study

In order to test the hypothesis in a human model that oliceridine would attenuate the incidence of respiratory depression compared to conventional opioids, a proof-of-concept study was done using VRH, to measure respiratory drive. This method was selected as it represents the "gold standard" for evaluating the impact of different medications on opioid-induced respiratory depression (Weil et al 1975).

Study 1003 was a randomized, double-blind, placebo-controlled, five-period crossover proof-of-concept study in healthy volunteers. Thirty participants received a single 2-minute IV infusion of each of five treatments in a randomized and blinded fashion: placebo, oliceridine (1.5, 3, and 4.5 mg) and morphine 10 mg. The dose range of oliceridine was based on doses found to be safe and well-tolerated in the first-in-human study (Study 1001). The morphine dose of 10 mg was chosen based on literature support for this dose across the major pharmacodynamic endpoints of VRH, cold pressor test, and drug effect questionnaires (Romberg et al 2003; Yancey-Wrona et al 2011).

In each treatment period, the study used experimental models to evaluate analgesia and drug-induced depression of respiratory drive in the same subjects. This design facilitates the comparison of respiratory effects at equianalgesic doses in a well-controlled setting. The two models used were:

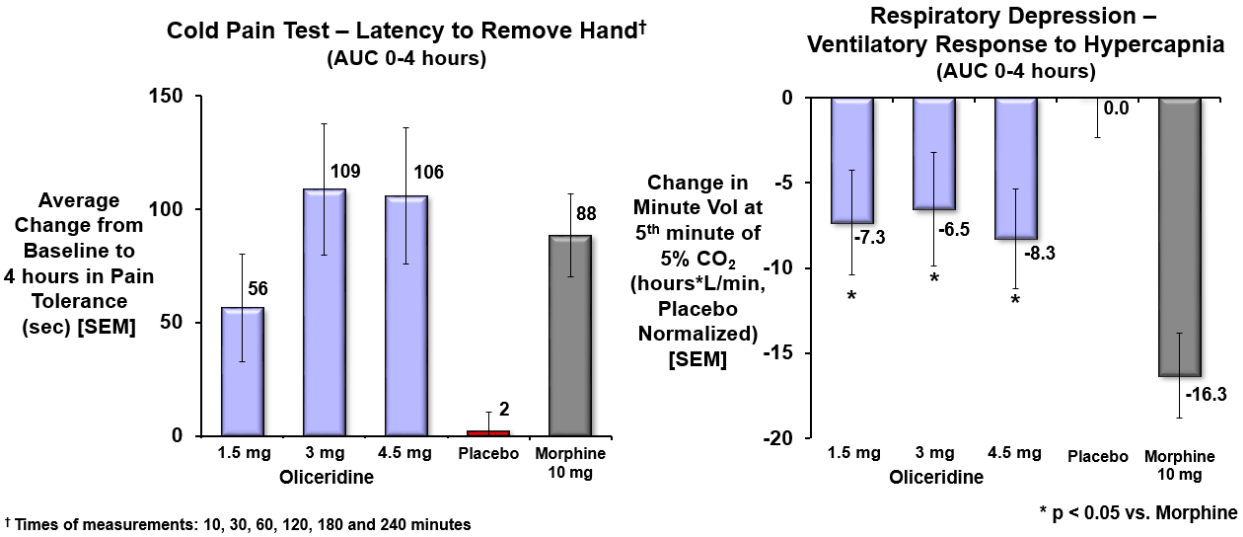
- Cold pressor test: At various time points after study drug administration, participants immersed one hand into water cooled to 2°C for as long as could be tolerated up to 180 seconds. Analgesic activity (ie, pain tolerance) was measured as the amount of time the participants kept their hand in the cold water.
- Ventilatory response to hypercapnia: Subjects breathed a hypercapnic gas mixture of 5% CO_2 through a facemask for 5 minutes at various time points after study drug administration. Depression in respiratory drive was measured as the change from pre-dose baseline in minute ventilation during hypercapnic exposure.

Figure 23 illustrates the average effect of study drugs through 4 hours post-dose.

- The left panel shows the average change from baseline through 4 hours in pain tolerance in the cold pressor test. All active treatments showed greater pain tolerance after study drug administration than placebo. Oliceridine 3 mg and 4.5 mg showed similar analgesic activity to morphine 10 mg. Therefore, the 3 mg and 4.5 mg oliceridine doses are the appropriate comparators for morphine 10 mg to evaluate the relative effects on respiratory drive.
- The right panel shows the average placebo-normalized hypercapnic minute volume over the same 4-hour time period as the cold pressor test. All oliceridine doses, including the equianalgesic 3 mg and 4.5 mg doses, had a statistically lower suppressant impact on respiratory drive than morphine 10 mg ($p < 0.05$).

Thus, the controlled Phase 1 study suggests that oliceridine was associated with significantly less depression of respiratory drive than morphine at equianalgesic doses, which is consistent with oliceridine's novel mechanism of action and prior pharmacologic and nonclinical data.

Figure 23: Analgesic Activity and Respiratory Drive in Study 1003



† Times of measurements: 10, 30, 60, 120, 180 and 240 minutes

* $p < 0.05$ vs. Morphine

5.2 Human Abuse Liability

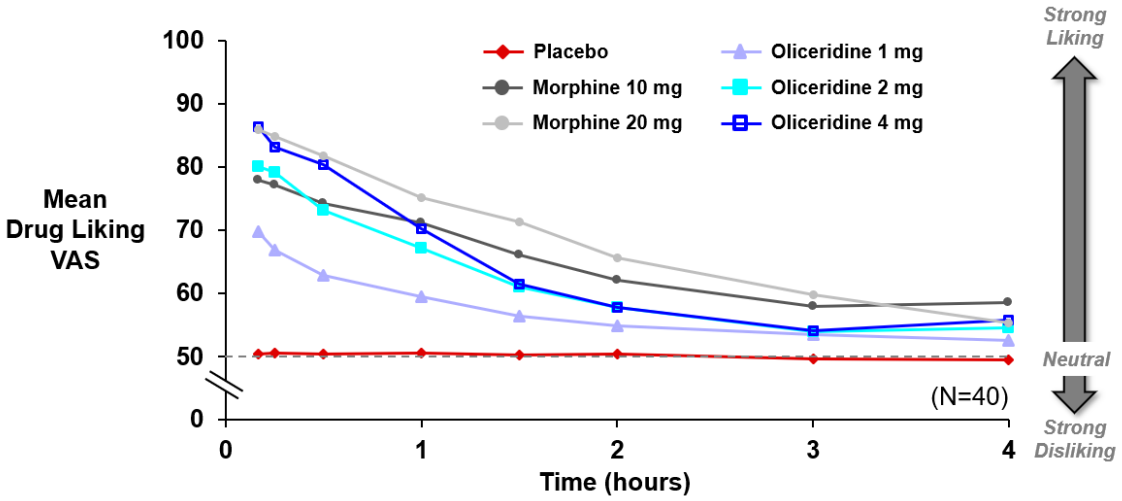
A Drug Abuse Liability Assessment was conducted to adhere to guidelines outlined in the FDA Guidance "Guidance for Industry: Assessment of Abuse Potential of Drugs" (FDA 2017). The abuse potential assessment of oliceridine is comprised of nonclinical and clinical data, including clinical PD and PK results from a HAL study, to evaluate the abuse potential of oliceridine.

Chemical and nonclinical data related to the assessment of abuse potential – including oliceridine's MOR agonist pharmacology, PK profile, full generalization to morphine, and reinforcing effects similar to morphine in animal abuse potential studies – suggest that oliceridine is similar to conventional Schedule II opioids.

Study 1011 was a single-dose, randomized, double-blind crossover study that was conducted to assess the abuse potential of IV oliceridine compared with IV morphine and placebo in 60 healthy, non-dependent, recreational opioid users. Subjects received each of six blinded treatments in a random order as 1-minute IV infusions: oliceridine 1 mg, 2 mg, or 4 mg, morphine 10 mg or 20 mg, or placebo. Based on the results from a prior dose escalation study (Phase A of Study 1011), it was anticipated that the effect of oliceridine 2 mg would be similar to morphine 10 mg and oliceridine 4 mg would be similar to morphine 20 mg. During each period, standard abuse liability endpoints were assessed, such as Drug Liking, Take Drug Again, and Overall Drug Liking. Adverse event data were also collected.

The study found that equianalgesic doses of oliceridine and morphine had similar abuse potential. As hypothesized, the Drug Liking visual analog scale (VAS) scores following IV infusion were similar between oliceridine 2 mg and morphine 10 mg, as well as oliceridine 4 mg and morphine 20 mg (Figure 24). The more rapid reductions in mean Drug Liking scores with oliceridine compared with morphine is consistent with oliceridine's shorter $t_{½}$ and lack of active metabolites.

Figure 24: Mean "At the Moment" Drug Liking VAS



Overall, the pharmacological profile, abuse potential, and physical dependence potential of oliceridine is similar to that of equianalgesic doses of morphine. Therefore, Trevena has proposed that, if approved, oliceridine be designated a Schedule II drug under the Controlled Substances Act, which would provide the same controls and precautions that currently exist for conventional IV opioid medications administered in a hospital or controlled setting.

6 PHASE 2 STUDIES

Summary

- The Phase 2 clinical studies were designed to evaluate the efficacy and safety of various doses and dosing regimens of oliceridine relative to placebo and a conventional IV opioid. Thus, all controlled Phase 2 studies during development included IV morphine as a clinically relevant comparator group.
- The Phase 2a fixed-dose study evaluated 333 patients treated following bunionectomy. The study was designed to explore a range of fixed dose strengths and dose intervals of oliceridine and to compare them to fixed-dose placebo and IV morphine regimens.
  - Oliceridine produced dose-dependent reductions in pain scores.
  - Oliceridine was approximately five times more potent than morphine.
- The Phase 2b study utilized PRN dosing to evaluate the efficacy, safety, and tolerability of oliceridine when titrated to effect. PRN dosing allows patients to achieve analgesia with any active regimen, enabling comparisons of relative safety and tolerability.
  - Patients achieved similar analgesic efficacy with oliceridine and morphine dosing regimens.
  - Consistent with its differentiated pharmacology and the Phase 1 proof-of-concept study, oliceridine regimens were associated with statistically significant, regimen-dependent reductions in the incidence of hypoventilation events, nausea, and vomiting compared with the morphine regimen.
- The results from the Phase 2 studies were used to inform the design of the two pivotal Phase 3 randomized, placebo-controlled trials.

6.1 Study 2001: Phase 2a, Fixed-Dose Bunionectomy Study

6.1.1 Study Design

Study 2001 was a multicenter, double-blind, randomized, placebo-controlled study with an active comparator in the validated clinical setting of moderate to severe acute pain following bunionectomy. This fixed-dose study was designed to evaluate the analgesic efficacy of IV oliceridine compared with placebo in patients with acute postoperative pain over 48 hours and provide information on dose-response and onset and duration of action independent of the confounding influence of dosing to effect. A fixed-dose study design also allowed for an assessment of the relative potency of oliceridine and morphine. Additionally, Study 2001 evaluated the tolerability and therapeutic index of oliceridine compared with a typical IV morphine bolus dose. All regimens were volume-matched and double-blinded.

The study was conducted in two stages:

- In Stage A of the study (the pilot phase), patients were randomized equally to one of six treatment regimens:
  - placebo
  - oliceridine 1 mg, 2 mg, 3 mg, or 4 mg q4h
  - morphine 4 mg q4h
- Following a pre-specified interim analysis, oliceridine doses and dosing intervals were optimized for Stage B (the primary phase). The dose-related decrease in pain intensity that was evident early in the dosing interval for oliceridine was essentially absent by the end of the dosing interval, consistent with oliceridine PK, so the dosing interval for oliceridine was shortened, and the doses were adjusted accordingly. In Stage B, patients were randomized to one of six treatment regimens:
  - placebo
  - oliceridine 0.5 mg, 1 mg, 2 mg, or 3 mg q3h
  - morphine 4 mg q4h

Study 2001 randomized and treated 333 patients (141 Stage A, 192 Stage B) with moderate to severe acute pain, defined as a numeric rating scale (NRS) ≥ 4 within 9 hours after discontinuation of the regional anesthetic block. The primary efficacy endpoint was the time-weighted average change from baseline in the NRS pain intensity rating over 48 hours (NRS TWA_{0-48}).

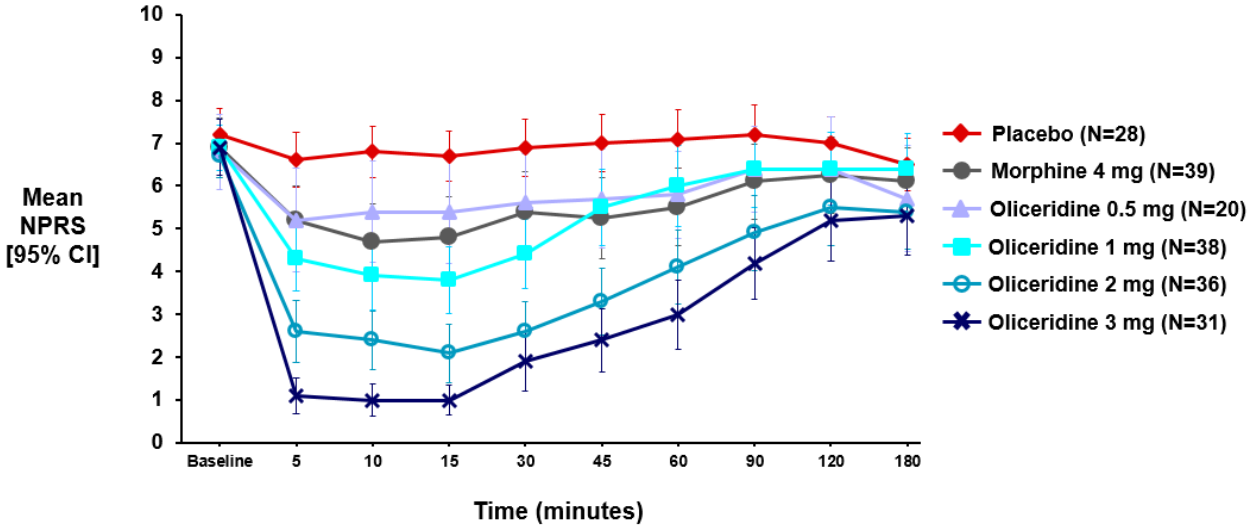
During the treatment period, patients could receive rescue pain medication if their study medication did not provide sufficient pain relief. First-line rescue was acetaminophen 650 mg PO q4h PRN. Second-line rescue was intramuscular or IV ketorolac 30 mg q6h PRN.

6.1.2 Results

In Stage B, the two highest doses of oliceridine, 2 mg q3h (total daily dose 16 mg, N = 36) and 3 mg q3h (total daily dose 24 mg, N = 31) significantly reduced pain intensity over 48 hours compared with placebo (N = 28), achieving the primary endpoint and demonstrating proof-of-concept for analgesic efficacy of oliceridine (both $p < 0.003$). The IV morphine 4 mg q4h regimen also showed statistically significant reductions in pain compared with placebo (N = 39; $p = 0.002$).

Consistent with the results of the nonclinical and Phase 1 studies, in which pain scores were highest early in the study, patients who received the higher fixed doses of oliceridine had greater and more rapid pain relief than morphine in a dose-dependent manner, providing 2- to 6-point mean reductions by 5 minutes after dosing (Figure 25). The efficacy results showed that after a single dose, oliceridine was approximately five times more potent than morphine. Relative potency is difficult to ascertain with subsequent doses due to the accumulation of active metabolites with morphine. These findings were used to inform dosing regimens for the subsequent studies.

Figure 25: Mean NPRS over First 3 Hours in Study 2001



6.2 Study 2002: Phase 2b, PRN-Dosing Abdominoplasty Study

6.2.1 Design

Study 2002 was a randomized, double-blind, placebo-controlled study with an active comparator to evaluate the analgesic efficacy of oliceridine compared to placebo and morphine following abdominoplasty, a validated clinical setting to evaluate treatment of moderate to severe acute pain. Therapy was administered PRN via PCA with 6-minute lockout intervals for demand doses. Using PRN dosing allowed for evaluation of both efficacy and tolerability and allowed for the study results to be more easily generalized to clinical practice.

The oliceridine PRN regimen was determined based on initial efficacy and tolerability results from the prior Phase 2a study; the morphine PRN regimen is a standard PRN regimen. All regimens were volume-matched and double-blinded.

The study was conducted in two stages:

- In Stage 1, patients were randomized 1:2:2 to one of three treatment regimens:
    - placebo
    - oliceridine: 1.5 mg loading dose and 0.1 mg demand doses
    - morphine: 4 mg loading dose and 1 mg demand doses
- As oliceridine had not been previously administered in a PRN regimen, a prespecified interim analysis was planned to adjust the oliceridine regimen, if needed, after review of Stage 1 efficacy, safety, tolerability, and utilization data. The oliceridine 0.1 mg demand dose was found to be safe and well tolerated in Stage 1. In order to further explore the dose range for oliceridine, the demand dose was increased to 0.35 mg in Stage 2.

The study randomized and treated 200 patients with moderate to severe pain, defined as an NRS ≥ 5 within 4 hours after the end of their abdominoplasty procedure. The primary efficacy

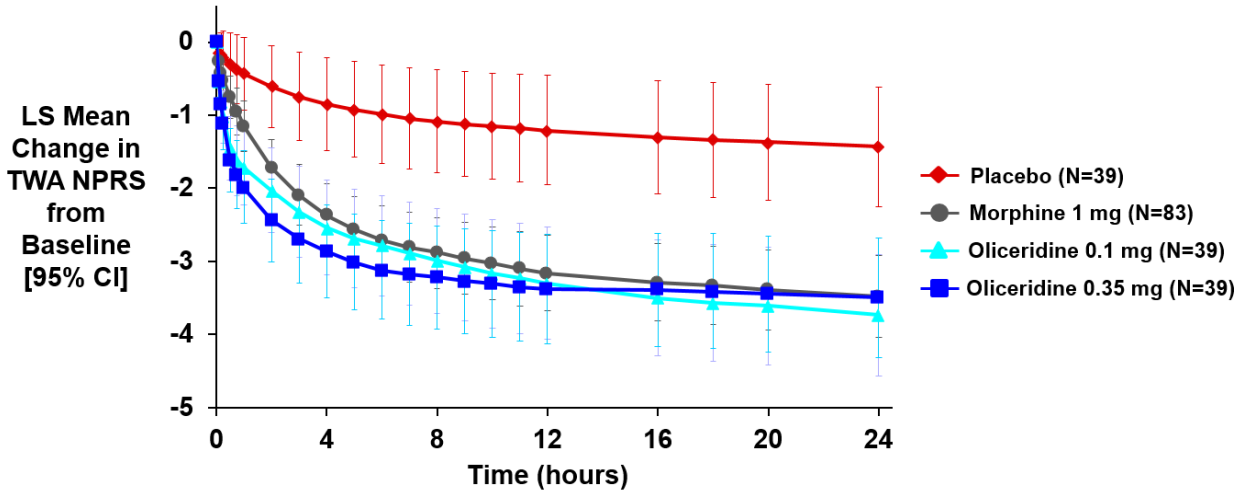
endpoint was the TWA change from baseline in the NRS over the 24-hour treatment period (NRS TWA_{0-24}). Lower NRS TWA_{0-24} values correspond to greater reductions in pain.

During the treatment period, patients could receive rescue pain medication if the study medication was insufficient. Initial rescue medication was ibuprofen 400 mg PO q6h PRN. If pain was still not adequately controlled, patients received oxycodone 5 mg PO q2h PRN.

6.2.2 Efficacy Results

The respective efficacy and safety profiles of placebo and morphine were similar in both stages of the study, so results for these groups were pooled for the analysis. Both oliceridine treatment regimens (0.1 mg [N = 39] and 0.35 mg [N = 39] demand doses) met the primary efficacy endpoint, providing significant pain reductions from baseline compared to placebo (N = 39) through 24 hours (Figure 26). The mean cumulative dose (SD) of the active treatment regimens was 7.6 mg (4.6), 14.8 mg (8.4), and 26.4 mg (16.0) for the oliceridine 0.1 mg, 0.35 mg, and morphine treatment regimens, respectively. The study confirmed the hypothesis that patients could dose themselves to achieve analgesia with a range of on-demand doses. Although the primary endpoint showed similar effects of 0.1 mg and 0.35 mg oliceridine regimens, a higher incidence of rescue analgesia use in the 0.1 mg regimen (31%) than the 0.35 mg regimen (21%) suggested a dose-related effect on analgesic efficacy.

Figure 26: Change in TWA NPRS Over 24 Hours in Study 2002



6.2.3 Safety Results

All treatments were generally well tolerated. Fewer than 5% of patients in each group discontinued for an AE. The most commonly reported AEs were nausea, vomiting and headache.

Respiratory Safety

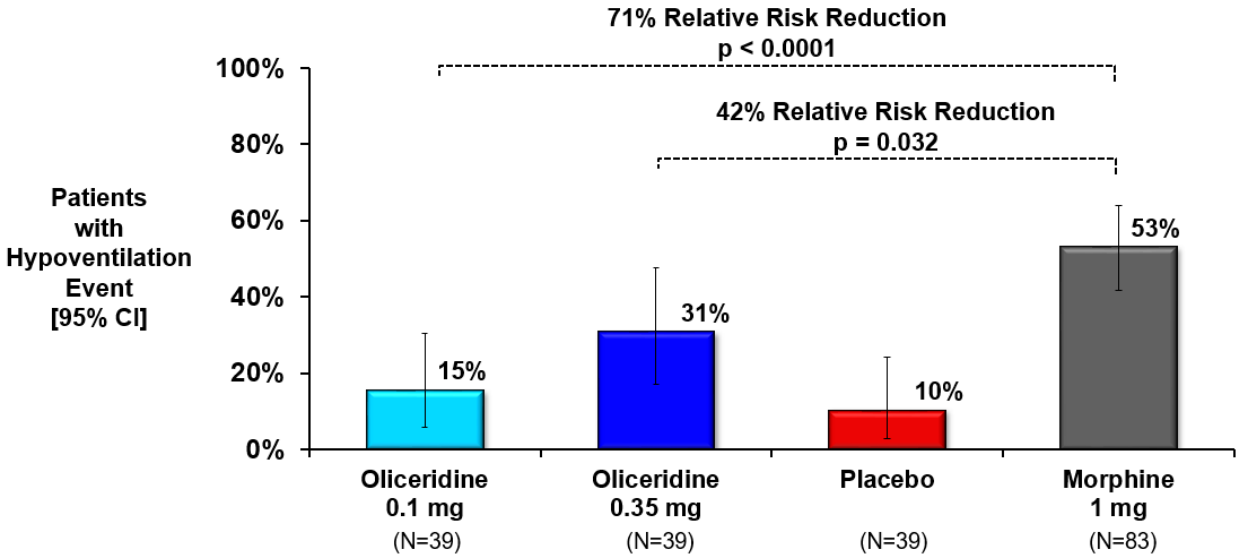
The measurement of respiratory safety is complex in the setting of a clinical therapeutic trial. There is no consensus standard method comparable to the human experimental model of VRH, which can be studied as an experimental paradigm of drug effect on minute ventilation.

Therefore, in both the Phase 2 and 3 trials, Trevena used endpoints that could be evaluated clinically. Evaluation of respiratory safety in the Phase 2b study included prospective evaluation of hypoventilation events. Hypoventilation events were defined in the protocol as clinically apparent and persistently decreased respiratory rate, respiratory effort, or oxygen saturation as determined by the treating clinician. Because opioid-induced respiratory depression can begin with any one or more of these signs, no specific threshold for oxygen saturation or respiratory rate were prespecified to qualify as hypoventilation. Instead, to ensure patient safety, the measure depended on an integrated clinical assessment.

In the context of similar analgesic efficacy, significantly fewer patients on the oliceridine 0.1 mg and 0.35 mg regimens experienced hypoventilation events compared to patients who received the morphine 1 mg regimen (Figure 27). Compared to the morphine 1 mg regimen, the relative risk of a hypoventilation event was reduced by 71% for the oliceridine 0.1 mg regimen ($p < 0.0001$) and by 42% for the oliceridine 0.35 mg regimen ($p = 0.032$). This finding of improved respiratory safety with oliceridine was consistent with its differential pharmacology, prior nonclinical results, and the Phase 1 proof-of-concept study.

In addition to the lower incidence of hypoventilation events in the oliceridine regimens, the average duration of the events, as measured by the time from onset to resolution, was approximately 40 to 50% shorter with oliceridine compared with morphine. These positive findings were used to inform the respiratory safety endpoint in the Phase 3 studies.

Figure 27: Hypoventilation Events in Study 2002

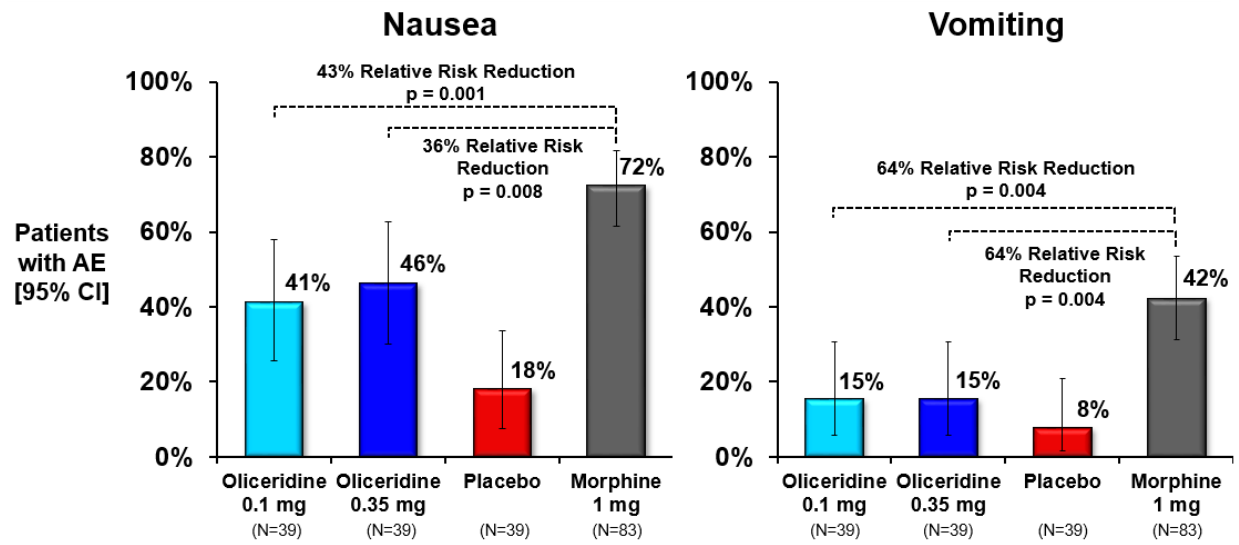


Postoperative Nausea and Vomiting

The effects of the study drugs on postoperative nausea and vomiting were assessed as an analysis of the MedDRA-coded Preferred Terms “nausea” and “vomiting.” In the context of similar analgesia, the incidence of these AEs was statistically significantly lower in the oliceridine regimens than the morphine regimen (Figure 28). Compared to the morphine 1 mg regimen, the incidence of nausea was 43% lower for the oliceridine 0.1 mg regimen ($p = 0.001$) and 36%

lower for the 0.35 mg regimen (p = 0.008). For vomiting, the incidence was 64% lower than morphine for both oliceridine regimens (both p = 0.004). The proportion of patients who received rescue antiemetics was also lower for both oliceridine regimens (49% for 0.1 mg and 38% for 0.35 mg) than for the morphine regimen (65%).

Figure 28: Postoperative Nausea and Vomiting in Study 2002



6.2.4 Conclusions from Phase 2 Studies

The findings of the Phase 2 studies provided additional evidence in support of the hypothesis that the differentiated pharmacology of oliceridine could be expected to attenuate, but not eliminate, the incidence of ORAEs compared with equianalgesic doses of conventional IV opioids. Findings from the Phase 2 studies were used to inform dosing regimens and endpoints for the subsequent studies.

7 PHASE 3 STUDIES

Summary

- The Phase 3 studies were designed to meet the regulatory requirements to establish analgesic efficacy: two positive, adequate, and well-controlled clinical trials – one in soft tissue/visceral pain and one in hard tissue/nonvisceral pain.
- To explore the relative effects of oliceridine on ORAEs and inform clinical practice, all controlled Phase 3 studies included three oliceridine dosing regimens and an IV morphine regimen as a clinically relevant comparator group.
- Consistent with the goals of PRN dosing, the Phase 3 studies utilized a treatment responder primary endpoint that incorporated measures of both efficacy and tolerability.
- All oliceridine treatment regimens met the primary endpoint, demonstrating superiority to placebo in the percentage of subjects who were treatment responders; efficacy was maximized with the 0.35 mg regimen.
- The respiratory safety burden (RSB) endpoint was not met, due in part to a lower-than-anticipated event rate. However, the favorable respiratory safety signal was maintained with the 0.1 and 0.35 mg regimens on all respiratory safety parameters, which is consistent with Phase 2 studies.
- Nausea and vomiting, the most common ORAEs, occurred less frequently with the oliceridine 0.1 mg and 0.35 mg regimens than the morphine regimen.
- The safety and tolerability of oliceridine observed in the Phase 3 APOLLO controlled clinical studies were also observed in the ATHENA open-label safety study, which was conducted in diverse clinical settings in a patient population with more comorbidities.
- Overall, oliceridine has shown a favorable benefit-risk profile when administered to adult patients with moderate to severe acute pain.

7.1 APOLLO 1 and APOLLO 2 Study Designs

Two pivotal Phase 3, multicenter, randomized, double-blind, placebo-controlled studies evaluated oliceridine administered PRN in validated hard and soft tissue models to provide primary evidence for efficacy and safety in accordance with FDA guidance:

- APOLLO 1: bunionectomy (hard tissue model) study with a 48-hour randomized treatment period
- APOLLO 2: abdominoplasty (soft tissue model) study with a 24-hour randomized treatment period

The APOLLO 1 and 2 studies were similar in design; however, each surgical pain model involved different anesthetic methods, different time from surgery to the first dose of study medication, and different temporal courses of pain after discontinuation of anesthesia. In APOLLO 1, prior to surgery, patients received a popliteal sciatic nerve block with local

anesthetic, which was maintained using a continuous infusion via catheter until early on the first postoperative day. General anesthesia was used in APOLLO 2.

Additionally, the qualifying NRS pain intensity score and the duration of the randomized treatment period differed between the two studies. Despite their differences in study methods, these trials were designed to generate reproducible data in support of the efficacy and safety of oliceridine in the acute pain settings of soft tissue and hard tissue models.

7.1.1 PRN Dosing Regimens

In both APOLLO studies, patients were randomized equally to one of three oliceridine treatment regimens (demand doses of 0.1 mg, 0.35 mg, or 0.5 mg), morphine (demand dose of 1 mg), or placebo (Table 10).

For oliceridine, the loading dose for all regimens was 1.5 mg (based on safety and efficacy findings from Phase 2b). As in the Phase 2b study, the APOLLO studies included oliceridine demand dose regimens of 0.1 and 0.35 mg. Simulations using a PK/PD model developed using data from Phase 1 and both Phase 2 studies suggested that the optimal demand dosing range for oliceridine ranged between 0.1 to 0.5 mg, with a plateau in efficacy predicted at doses ≥ 0.35 mg. Therefore, a 0.5 mg demand dose regimen was included in the APOLLO studies in order to confirm this plateau in efficacy and provide a comprehensive characterization of the appropriate dose range for oliceridine in routine clinical use. The morphine group received the same standard regimen as used in Phase 2b.

Demand doses were delivered, as needed, beginning 10 minutes after loading dose, and with a 6-minute lockout interval. Clinician-administered, blinded supplemental doses were permitted 1 hour after the loading dose and hourly thereafter, as needed; there was no continuous background infusion of study medication. All regimens were volume-matched and double-blind.

Table 10: APOLLO 1 and APOLLO 2 Dosing Paradigm

<table>
<tr><th>Randomized Group</th><th>Loading Dose</th><th>Demand Dose (PCA)</th><th>Lockout</th><th>Clinician-Administered Supplemental Dose (q1h PRN)</th></tr>
<tr><td>Oliceridine 0.1 mg</td><td rowspan="3">1.5 mg</td><td>0.1 mg</td><td rowspan="4">6 minutes</td><td rowspan="3">0.75 mg</td></tr>
<tr><td>Oliceridine 0.35 mg</td><td>0.35 mg</td></tr>
<tr><td>Oliceridine 0.5 mg</td><td>0.5 mg</td></tr>
<tr><td>Placebo</td><td>Volume-matched placebo solution</td><td>Volume-matched placebo solution</td><td>Volume-matched placebo solution</td></tr>
<tr><td>Morphine 1 mg</td><td>4 mg</td><td>1 mg</td><td>2 mg</td></tr>
</table>

In order to reduce variability and avoid confounding effects of other analgesic treatments, the use of multimodal therapy was not permitted in APOLLO 1 and APOLLO 2. However, rescue pain medication (etodolac 200 mg PO q6h PRN) was permitted during the treatment period if study medication was inadequate. Patients who received rescue pain medication continued to be treated with study medication PRN but were classified as non-responders for the primary responder analysis (see Section 7.1.3.1).

7.1.2 Enrollment Criteria

To participate in APOLLO 1 or APOLLO 2, patients had to meet all of the following inclusion criteria:

- age ≥ 18 and ≤ 75 years at screening
- ≥ 40 kg in body weight or a body mass index (BMI) of ≤ 35 kg/m^2, and
- scheduled to undergo primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation (hard tissue model; APOLLO 1) or an abdominoplasty procedure with no additional collateral procedures (soft tissue model; APOLLO 2).

Key exclusion criteria included current diagnosis of sleep apnea or suspicion of sleep apnea. Additionally, patients must have rated their pain intensity (via the NRS) as ≥ 4 within 9 hours after discontinuation of regional anesthesia (APOLLO 1) or ≥ 5 within 4 hours after the end of surgery (APOLLO 2). See Appendix 10.2 and 10.3 for a full list of inclusion and exclusion criteria.

7.1.3 Clinical Endpoints

7.1.3.1 Primary Endpoint: Treatment Responder Rate versus Placebo

Both controlled Phase 3 studies utilized a treatment responder primary endpoint, in part, to mitigate confounding effects of differential rescue medication utilization and early termination events that require statistical imputation of pain scores. The use of a categorical responder definition in these studies conforms to the current FDA Analgesic Development guidance document, which notes that a responder definition – which can include multiple components such as pain intensity, use of rescue, and ability to complete the study – may serve as an acceptable primary outcome metric (FDA 2014). A patient was considered a treatment responder if all the following conditions were met:

- at least a 30% improvement in their final time-weighted sum of pain intensity difference (SPID from baseline at 48 hours (for APOLLO 1) or 24 hours (for APOLLO 2);
- 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.

If any of these criteria were not met, the patient was considered a non-responder. Therefore, no imputation procedures were needed for rescue pain medication use or early discontinuation of study medication for the primary endpoint.

The time-weighted SPID from baseline was calculated by the sum of the time-weighted pain intensity difference (PID = difference between current pain and pain at baseline) multiplied by the interval between ratings.

7.1.3.2 Key Secondary Safety Endpoint: Respiratory Safety Burden versus Morphine

To date, there is currently no validated endpoint to measure respiratory safety of medications in a Phase 3 clinical trial, and many factors complicate that measurement. For instance, this assessment is made more complex by the fact that clinical factors such as thoracic or abdominal pain may alter respiratory effort, and the need to intervene clinically in response to changes in respiratory status may impede the ability to detect a respiratory safety signal itself. As the first NCE IV opioid analgesic designed, in part, to improve respiratory safety, Trevena established a protocol with a structured, operational approach intended to closely monitor signs, symptoms, and duration of respiratory effects. Additionally, all clinical interventions implemented for respiratory events in the controlled Phase 3 studies were captured. As this approach relied heavily on clinical judgement, the monitoring and ascertainment of these respiratory evaluations were performed only by trained anesthesiologists or certified nurse anesthetists who were blinded to study medication.

The monitoring clinicians were trained according to a standardized protocol to ensure that all relevant observations and all clinical interventions were systematically recorded. The study case report forms were designed to quantify the incidence, severity, and duration of the relevant clinical events. Specific minimum periodic observation schedules were also predefined in the protocol; monitoring for respiratory safety occurred every 2 hours, or every 30 minutes if a patient was experiencing a respiratory event.

Similar to the definition of hypoventilation events in the Phase 2b study, RSEs were prospectively defined as a clinically relevant worsening in oxygen saturation, respiratory rate, or sedation. These criteria were similar to those defining the hypoventilation endpoint used in Phase 2b, except that sedation, assessed by Moline Roberts Pharmacologic Sedation Scale, was used instead of respiratory effort in an attempt to rely on standardized, quantifiable measures. Compared to Phase 2b, Trevena expanded the detail of information captured in the Phase 3 studies to characterize an additional aspect of respiratory safety by combining both the incidence of RSEs (as measured in Phase 2b) along with their duration. The composite index, the RSB, was calculated by multiplying the *incidence* of RSEs with the cumulative *duration* of the events. Thus, the RSB, reported in minutes, can be interpreted as the expected average duration of a RSE for a patient within a particular treatment regimen. Patients who did not experience a RSE were considered to have a RSB of 0 hours. RSB was analyzed using a zero-inflated gamma model with baseline NRS score, study site, and BMI as covariates.

Given the importance of respiratory safety, a superiority assessment of oliceridine to morphine on the RSB measure was prespecified as a key secondary endpoint in the APOLLO studies. However, it is important to note that the RSB endpoint, as defined in this study, had no precedent in the published scientific literature, and hence was not previously validated. Therefore, even if demonstrated to be a sensitive measure of respiratory safety, it was not anticipated by Trevena or FDA to provide sufficient level of evidence to justify a comparative labeling claim. There currently is no validated endpoint for the assessment of respiratory safety that would qualify for a formal labeling claim.

7.1.3.3 Key Secondary Efficacy Endpoint: Treatment Responder Rate Versus Morphine

The proportion of treatment responders for all oliceridine groups was to be compared to morphine in key secondary efficacy endpoint analyses for non-inferiority (NI) and then superiority. The NI margin was pre-specified as 50% of the analgesic effect of morphine. The NI margin was selected based on the historical precedent in other clinical applications of retaining statistically greater than 50% of the effect of an efficacious agent as well as practical implications for sample size, as outlined in FDA guidance on NI trial designs (FDA 2016).

7.1.3.4 Other Secondary Efficacy Endpoints

Other secondary efficacy variables included time to first meaningful pain relief, time to onset of analgesia, and the proportion of patients using rescue pain medication. These analyses were not formally controlled for type-I error.

7.1.3.5 Statistical Analyses

The full analysis set (FAS), which included all randomized patients from both studies who received study medication, was used for all summaries and analyses conducted on the efficacy data. For efficacy analyses, patients in the APOLLO studies were analyzed according to their randomized treatment group.

The Phase 3 studies were powered to demonstrate superiority of all oliceridine treatment regimens to placebo for the primary endpoint. The primary and key secondary efficacy endpoints were powered and controlled for multiplicity using the Hochberg tree structured multiplicity adjustment. The gatekeeping hierarchy to preserve each study's type-I error rate is shown in Table 11. Within each gate, all oliceridine regimens that had passed the prior gate were to be analyzed with p-values adjusted using Hochberg's method. The superiority assessment for the primary endpoint was conducted using a logistic regression model that contained the treatment regimen as a fixed factor, and baseline NRS score and study site as covariates.

Table 11: Hierarchy of Primary and Key Secondary Endpoints

Gate	Endpoint	Comparator	Test
Primary Endpoint			
1	Responder Rate	Placebo	Superiority
Key Secondary Endpoints			
2	Respiratory Safety Burden	Morphine 1 mg	Superiority
3	Responder Rate	Morphine 1 mg	Non-inferiority
4	Responder Rate	Morphine 1 mg	Superiority

7.1.4 Patient Disposition

In general, the disposition of patients was similar in APOLLO 1 and APOLLO 2 (Table 12 and Table 13, respectively). In APOLLO 1, early discontinuation of study medication was highest in the placebo regimen, due primarily to lack of efficacy. The next highest rate of discontinuation of study medication was with the morphine regimen, where the most common reason for discontinuation was an AE. For oliceridine, the only notable reason for discontinuation of study medication was due to lack of efficacy in the 0.1 mg regimen.

In APOLLO 2, early discontinuation of study medication was highest with placebo, primarily due to lack of efficacy. Rates of study medication discontinuation were similar for the active regimens; the most common reasons for discontinuation were lack of efficacy with the oliceridine 0.1 mg regimen, and either AEs or lack of efficacy with the oliceridine 0.35 mg and 0.5 mg and morphine 1 mg regimens.

Table 12: Subject Disposition in APOLLO 1

Disposition	Oliceridine			Placebo	Morphine 1 mg
	0.1 mg	0.35 mg	0.5 mg		
Randomized, n	82	86	82	84	84
Treated (FAS), n (%)	76 (92.7)	79 (91.9)	79 (96.3)	79 (94.0)	76 (90.5)
Completed study, n (%)	75 (91.5)	78 (90.7)	75 (91.5)	76 (90.5)	74 (88.1)
Discontinued study medication, n (%)	8 (9.8)	4 (4.7)	10 (12.2)	29 (34.5)	12 (14.3)
Reasons for discontinuation of study medication, n					
Adverse event	0	1	4	0	6
Withdrawal by patient	0	0	1	1	2
Lack of efficacy	7	3	4	27	3
Other	1	0	1	1	1

Table 13: Subject Disposition in APOLLO 2

Disposition	Oliceridine			Placebo	Morphine 1 mg
	0.1 mg	0.35 mg	0.5 mg		
Randomized, n	78	82	82	82	83
Treated (FAS), n (%)	77 (98.7)	80 (97.6)	80 (97.6)	81 (98.8)	83 (100)
Completed study, n (%)	76 (97.4)	79 (96.3)	79 (96.3)	79 (96.3)	80 (96.4)
Discontinued study medication, n (%)	10 (12.8)	6 (7.3)	9 (11.0)	20 (24.4)	8 (9.6)
Reasons for discontinuation of study medication, n					
Adverse event	0	4	4	0	2
Withdrawal by patient	1	0	1	1	0
Lack of efficacy	9	2	4	18	6
Other	0	0	0	1	0

7.1.5 Demographics and Baseline Characteristics

For both APOLLO studies, the treatment regimens were generally balanced for patient demographics and baseline characteristics.

In APOLLO 1, most patients were female with an average age of 45 years. Nearly 70% of patients in each regimen were Caucasian, and approximately 25% of patients were African-American. The average BMI was 27 kg/m^2. The mean NRS pain intensity score at baseline ranged from 6.5 to 7.0 across the regimens (Table 14).

Table 14: Demographic and Baseline Characteristics in APOLLO 1 (FAS)

Disposition	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	Placebo N=79	Morphine 1 mg N=76
Age (years)					
Mean (SD)	48 (13)	44 (14)	47 (14)	44 (13)	43 (14)
Min, Max	19, 74	19, 74	19, 71	19, 67	20, 69
Sex, n (%)					
Male	12 (16)	14 (18)	13 (17)	9 (11)	11 (15)
Female	64 (84)	65 (82)	66 (84)	70 (89)	65 (86)
Race, n (%)					
Caucasian	47 (62)	56 (71)	61 (77)	56 (71)	50 (66)
African American	22 (29)	17 (22)	13 (17)	21 (27)	21 (28)
Other	7 (9)	6 (8)	5 (6)	2 (3)	5 (7)
Hispanic or Latino Ethnicity, n (%)	17 (22)	25 (32)	19 (24)	17 (22)	18 (24)
BMI (kg/m^2), Mean (SD)	26 (4)	26 (4)	27 (4)	26 (4)	27 (5)
CYP2D6 metabolizer status, n (%)					
Extensive metabolizer (EM)	65 (88)	69 (90)	71 (93)	58 (82)	56 (82)
Poor metabolizer (PM)	9 (12)	8 (10)	5 (7)	13 (18)	12 (18)
Baseline pain intensity, Mean (SD)	6.8 (1.8)	6.6 (1.9)	6.5 (1.7)	7.0 (1.5)	6.7 (1.6)

In APOLLO 2, nearly all patients in the study were female with an average age of 41 years, consistent with the patient population undergoing abdominoplasty. Approximately two-thirds of patients were Caucasian, and approximately one-third were African-American. The mean BMI across the randomized groups was 27 kg/m^2. The mean NRS pain intensity scores at baseline ranged from 7.2 to 7.5 (Table 15).

Table 15: Demographic and Baseline Characteristics in APOLLO 2 (FAS)

Disposition	Oliceridine			Placebo	Morphine
	0.1 mg N=77	0.35 mg N=80	0.5 mg N=80	N=81	1 mg N=83
Age (years)					
Mean (SD)	42 (11)	42 (10)	40 (10)	42 (10)	40 (10)
Min, Max	21, 69	23, 67	23, 71	24, 67	20, 69
Sex, n (%)					
Male	1 (1)	0	0	0	2 (2)
Female	76 (99)	80 (100)	80 (100)	81 (100)	81 (98)
Race, n (%)					
Caucasian	45 (58)	55 (69)	50 (63)	52 (64)	55 (66)
African American	24 (31)	22 (28)	28 (35)	27 (33)	24 (29)
Other	8 (10)	3 (4)	2 (3)	2 (2)	4 (5)
Hispanic or Latino Ethnicity, n (%)	28 (36)	24 (30)	24 (30)	27 (33)	29 (35)
BMI (kg/m^2), Mean (SD)	28 (3)	28 (3)	27 (3)	27 (3)	27 (3)
CYP2D6 metabolizer status, n (%)					
Extensive metabolizer (EM)	58 (81)	63 (84)	67 (87)	68 (88)	66 (83)
Poor metabolizer (PM)	14 (19)	12 (16)	10 (13)	9 (12)	14 (18)
Baseline pain intensity, Mean (SD)	7.4 (1.4)	7.4 (1.6)	7.5 (1.6)	7.2 (1.4)	7.3 (1.5)

7.2 APOLLO 1 and APOLLO 2 Efficacy Results

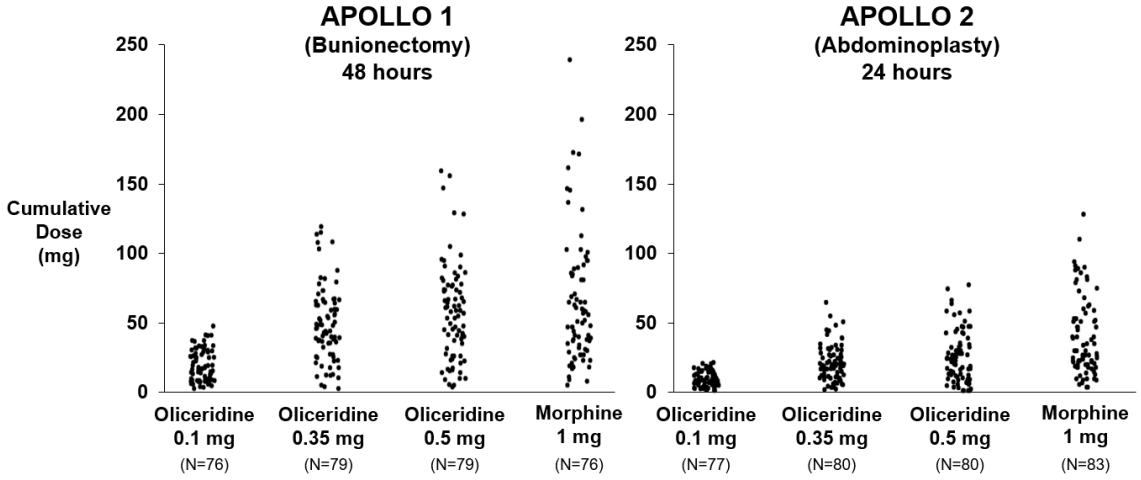
7.2.1 Exposure to Active Study Medication

Since patients could self-administer study medication with PCA as needed for pain control, patients within each demand dose regimen could potentially receive a variable range of cumulative dose of study medication, which is aligned with the goal of giving patients only as much IV opioid as they require.

Figure 29 shows the cumulative exposure to active study medications for each patient in the two APOLLO studies; each dot represents the cumulative dose for each individual patient. As would be expected, the average cumulative exposure was higher in APOLLO 1 than APOLLO 2 due to the longer randomized treatment period.

In APOLLO 1, the mean cumulative dose (SD) of the active treatment regimens was 19.2 mg (11.2), 49.4 mg (27.2), 57.4 mg (34.7), and 68.1 mg (52.5) for the oliceridine 0.1 mg, 0.35 mg, 0.5 mg, and morphine treatment regimens, respectively. The mean cumulative dose (SD) of the active treatment regimens in APOLLO 2 was 9.7 mg (5.1), 21.2 mg (12.9) mg, 26.3 mg (18.2), and 39.7 mg (27.6) for the oliceridine 0.1 mg, 0.35 mg, 0.5 mg, and morphine treatment regimens, respectively.

Figure 29: Cumulative Dose of Study Medication in APOLLO 1 and APOLLO 2



7.2.2 Primary Endpoint Results: Responder Analysis Versus Placebo

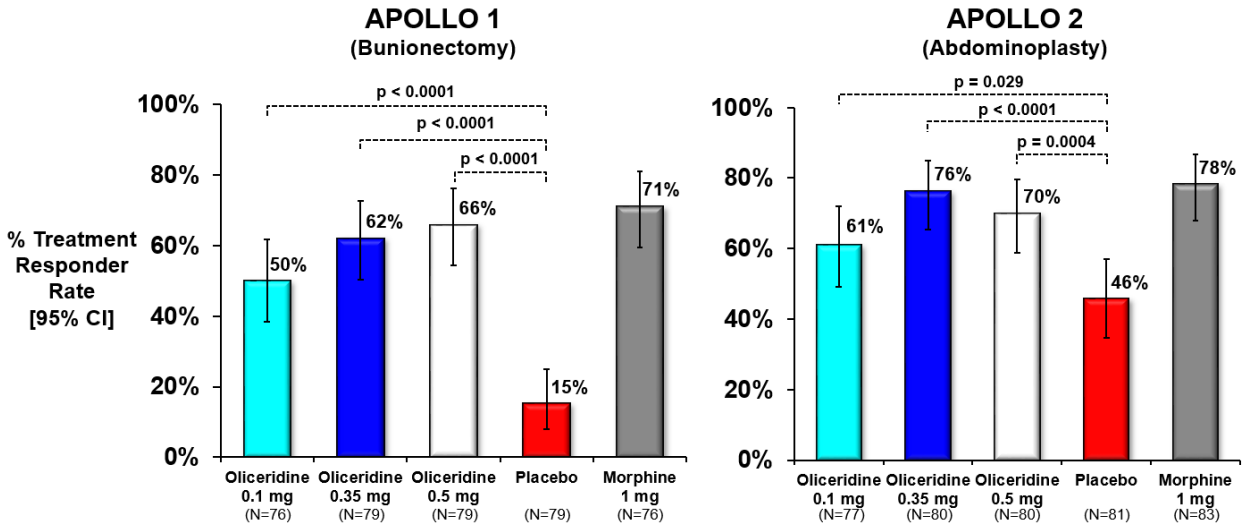
In each APOLLO study, all oliceridine treatment regimens met the primary endpoint demonstrating superior analgesic efficacy to placebo (Figure 30). In APOLLO 1, statistically significantly greater proportions of responders were observed in the oliceridine 0.1 mg, 0.35 mg, and 0.5 mg regimens compared with the placebo regimen at 48 hours. The morphine 1 mg regimen had a treatment responder rate which was significantly higher than the oliceridine 0.1 mg regimen and not statistically different than the oliceridine 0.35 mg and 0.5 mg regimens.

In APOLLO 2, the proportions of responders for all the oliceridine regimens were statistically significantly greater than the placebo regimen at 24 hours. Similar to APOLLO 1, the proportion of treatment responders in the morphine 1 mg regimen was significantly higher than the oliceridine 0.1 mg regimen and not significantly different from the oliceridine 0.35 mg and 0.5 mg regimens.

In both studies, no clinically meaningful difference in efficacy was observed between the 0.35 mg and 0.5 mg regimens. The plateau in efficacy with the 0.35 mg regimen was consistent with the prediction of the PK/PD model and indicated little, if any, additional benefit of the 0.5 mg regimen over the 0.35 mg regimen in these patients. Therefore, Trevena is not seeking approval for the 0.5 mg regimen. (Appendix 10.6 provides results for each regimen by component of the treatment responder definition.)

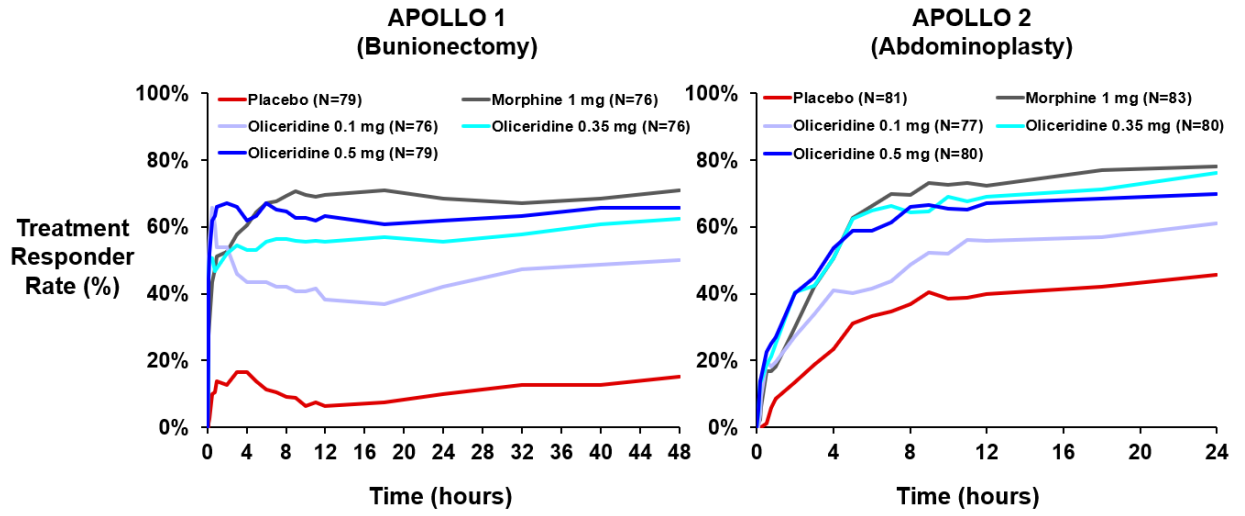
A sensitivity analysis evaluating the analgesic efficacy of oliceridine using SPID scores with imputation for rescue medication and early discontinuation yielded results consistent with the primary endpoint, with all three oliceridine regimens statistically superior to placebo in both studies (see Appendix 10.7).

Figure 30: Primary Endpoint Results in APOLLO 1 and APOLLO 2



An analysis of the proportion of treatment responders over time illustrates signals of efficacy in all active treatments throughout the duration of the dosing period (Figure 31). The results of treatment responder status over time are consistent with the primary endpoint results (at 48 and 24 hours for APOLLO 1 and APOLLO 2, respectively).

Figure 31: Proportion of Treatment Responders over Time in APOLLO 1 and APOLLO 2



While the oliceridine regimens consistently demonstrated IV opioid-level analgesia in both Phase 3 studies, mean SPID values were numerically higher with the morphine regimen (higher

SPID scores indicate greater reduction in pain scores – the magnitude of efficacy; see Appendix 10.7). Since morphine has active metabolites which accumulate over time, patients have the potential to receive *more* analgesia than necessary due to the delayed onset of morphine's metabolite effects.

Receiving more analgesia than necessary conflicts with the therapeutic goal of giving patients only as much IV opioid as they need. Furthermore, higher IV opioid doses are also associated with overshooting the therapeutic window, which can lead to more ORAEs and need for clinical interventions (eg, dosing interruptions, supplemental oxygen, administration of rescue antiemetics). Thus, efficacy should also be evaluated in terms of its sufficiency, through use of rescue pain medication, to interpret the relevance of the magnitude of efficacy (see Section 7.2.4).

7.2.3 Key Secondary Endpoint Results

7.2.3.1 Respiratory Safety Burden (RSB) Versus Morphine

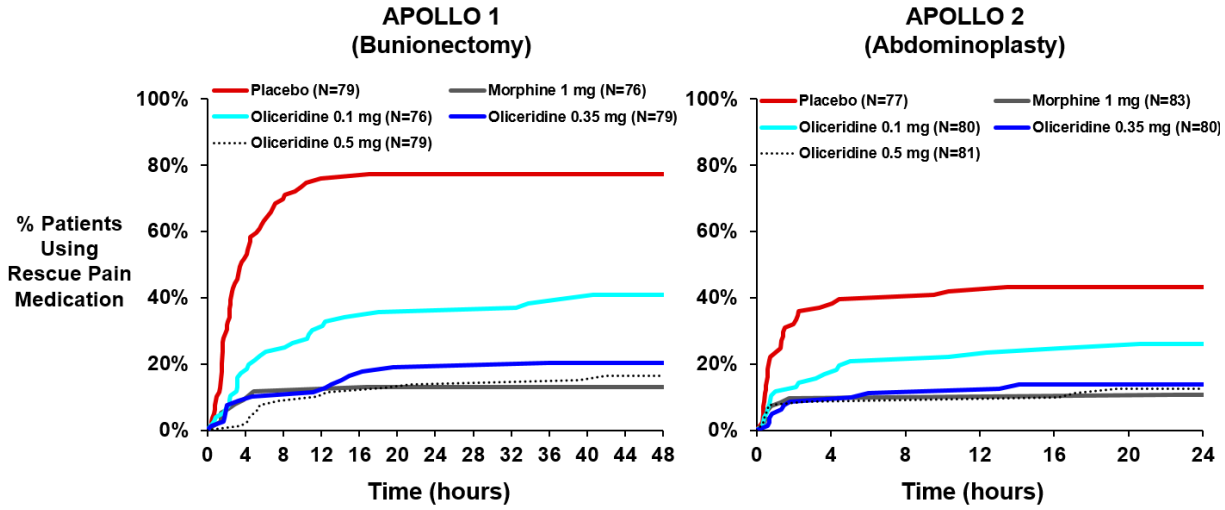
Analyses of the RSB (Section 7.3.5.1) indicated a dose regimen-dependent improvement in respiratory safety of oliceridine over morphine in both studies; however, these results were not statistically significantly superior to morphine. As such, the subsequent key secondary endpoints in the gatekeeping hierarchy, evaluating noninferiority and superiority of the treatment responder rate for oliceridine compared to morphine (described in Section 7.1.3.5), were not formally assessed.

7.2.4 Use of Rescue Pain Medication

In accordance with the FDA guidance, the use of rescue medication was analyzed as a secondary outcome measure (FDA 2014) and provides a useful measure of the sufficiency of analgesic efficacy. This measure is complementary to efficacy measures based on numeric pain rating scales (eg, SPID), which assess the magnitude of efficacy.

In both APOLLO studies, the only protocol-specified rescue analgesic was the nonsteroidal anti-inflammatory drug (NSAID), etodolac. Results by treatment group on the use of rescue pain medication were consistent with the results of the primary endpoint. All active regimens had lower rates of rescue medication than placebo (Figure 32). The use of rescue was similar in the oliceridine 0.35 mg and 0.5 mg regimens and morphine 1 mg regimen, providing additional support for the conclusion that the 0.5 mg regimen does not meaningfully increase efficacy beyond the 0.35 mg regimen.

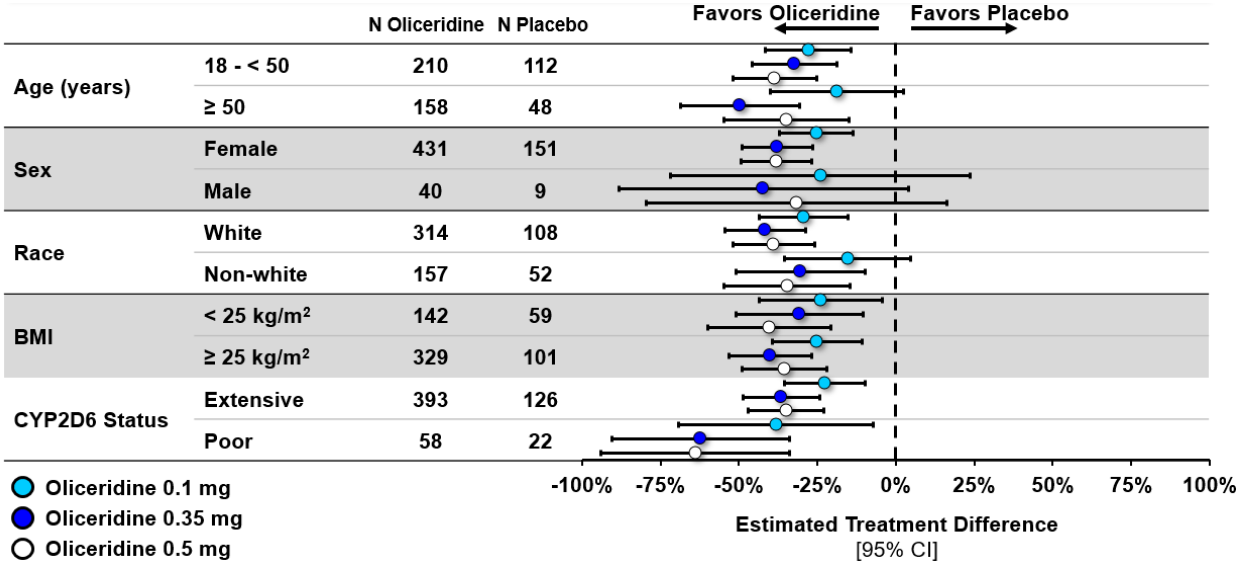
Figure 32: Time to First Use of Rescue Pain Medication in APOLLO 1 and APOLLO 2



7.2.5 Efficacy in Subgroups

Pooled data for the primary endpoint were summarized by the following subgroups: age group, sex, race, BMI category, and CYP2D6 metabolizer phenotype (Figure 33). The results illustrate consistency of the observed treatment effect across subgroups, with a greater percentage of treatment responders in all oliceridine regimens compared with the placebo regimen.

Figure 33: Primary Endpoint by Subgroup in Pooled APOLLO Studies



7.2.6 Efficacy Conclusions

Across the Phase 2 and Phase 3 studies, oliceridine consistently demonstrated opioid-level efficacy for the treatment of moderate to severe acute pain. In both pivotal Phase 3 studies, all oliceridine regimens met the primary endpoint by demonstrating superiority to placebo in the

proportion of treatment responders. In both APOLLO studies, the efficacy was maximized with the 0.35 mg regimen, and thus, Trevena is not seeking approval for the 0.5 mg regimen. The Phase 3 studies also demonstrated a consistent effect across subgroups of clinical interest.

7.3 APOLLO 1 and APOLLO 2 Safety Results

The results from the pooled controlled Phase 3 studies were used to characterize the safety and tolerability of oliceridine compared with placebo and morphine. Safety data for oliceridine were analyzed by randomized treatment regimen (demand dose of 0.1 mg, 0.35 mg, or 0.5 mg), which represented an *opportunity* for exposure. Thus, the cumulative exposure of patients in any treatment regimen could vary due to PRN dosing (also see Section 7.2.1).

On average, the cumulative exposure to oliceridine was greater with the higher demand dose regimens (Table 16), though the mean cumulative dose was not statistically different between the 0.35 mg and 0.5 mg demand dose regimens. The average number of supplemental doses was low for all treatment regimens but was highest with placebo and the oliceridine 0.1 mg dosing regimen. As expected, the average number of demand doses with oliceridine decreased as the demand dose increased.

Table 16: Summary of Exposure by Treatment Regimen in the Controlled Phase 3 Studies

Parameter	Oliceridine			Placebo	Morphine
	0.1 mg N=153	0.35 mg N=158	0.5 mg N=159	N=162	1 mg N=158
Number of demand doses					
Mean (SD)	110 (80)	94 (69)	79 (62)	81 (72)	48 (43)
Median (Min, Max)	87 (2, 314)	74 (2, 317)	62 (0, 305)	61 (0, 295)	35 (0, 246)
Number of supplemental doses					
Mean (SD)	2.6 (3.6)	1.3 (2.5)	0.8 (2.1)	1.8 (1.9)	0.5 (1.0)
Median (Min, Max)	1 (0, 20)	0 (0, 17)	0 (0, 13)	1 (0, 9)	0 (0, 9)
Cumulative exposure (mg)					
Mean (SD)	14 (10)	35 (25)	42 (32)	0	53 (44)
Median (Min, Max)	11 (2, 48)	27 (2, 120)	33 (2, 160)	0	40 (4, 268)

7.3.1 Overview of Adverse Events (AEs)

A summary of AEs for the controlled Phase 3 studies by treatment regimen is shown in Table 17. Most subjects experienced at least one AE during the study. The rate of SAEs was low in all regimens, and all resolved without sequelae. No subjects in the placebo regimen or the oliceridine 0.1 mg regimen had an AE leading to early study medication discontinuation; the rate was 3 to 6% in the other active regimens. No deaths were reported in any treatment regimen.

Table 17: Summary of Adverse Events (AEs) by Treatment Regimen in the Controlled Phase 3 Studies

Type of AE, n (%)	Oliceridine			Placebo	Morphine
	0.1 mg N=153	0.35 mg N=158	0.5 mg N=159	N=162	1 mg N=158
Any AE	125 (81.7)	142 (89.9)	148 (93.1)	119 (73.5)	153 (96.8)
Severe AE	9 (5.9)	10 (6.3)	11 (6.9)	5 (3.1)	14 (8.9)
SAE	0	1 (0.6)	4 (2.5)	0	1 (0.6)
AE Leading to Discontinuation of Study Medication	0	5 (3.2)	9 (5.7)	0	8 (5.1)
Deaths	0	0	0	0	0

7.3.2 Common Adverse Events

The common AEs with an incidence of ≥ 5% in any treatment regimen in the controlled Phase 3 studies are provided in Table 18. AEs were collected until the follow-up visit or seven days after the last dose of study medication. The most frequently reported AEs were the most common ORAEs, nausea and vomiting (see Section 7.3.6 for detail).

Table 18: Most Common AEs (≥ 5% of Patients) in the Controlled Phase 3 Studies

Type of AE, n (%)	Oliceridine			Placebo	Morphine
	0.1 mg N=153	0.35 mg N=158	0.5 mg N=159	N=162	1 mg N=158
Any AE	125 (81.7)	142 (89.9)	148 (93.1)	119 (73.5)	153 (96.8)
Nausea	61 (39.9)	94 (59.5)	110 (69.2)	57 (35.2)	110 (69.6)
Vomiting	31 (20.3)	48 (30.4)	66 (41.5)	16 (9.9)	82 (51.9)
Headache	31 (20.3)	43 (27.2)	47 (29.6)	48 (29.6)	47 (29.7)
Dizziness	32 (20.9)	32 (20.3)	35 (22.0)	17 (10.5)	39 (24.7)
Constipation	20 (13.1)	22 (13.9)	20 (12.6)	15 (9.3)	22 (13.9)
Pruritus	12 (7.8)	25 (15.8)	12 (7.5)	10 (6.2)	30 (19.0)
Hypoxia	6 (3.9)	20 (12.7)	21 (13.2)	4 (2.5)	26 (16.5)
Somnolence	6 (3.9)	15 (9.5)	14 (8.8)	6 (3.7)	16 (10.1)
Sedation	7 (4.6)	15 (9.5)	10 (6.3)	8 (4.9)	21 (13.3)
Hot flush	4 (2.6)	9 (5.7)	11 (6.9)	7 (4.3)	12 (7.6)
Back pain	3 (2.0)	11 (7.0)	10 (6.3)	6 (3.7)	9 (5.7)
Anxiety	2 (1.3)	8 (5.1)	9 (5.7)	3 (1.9)	6 (3.8)
Hyperhidrosis	5 (3.3)	8 (5.1)	4 (2.5)	4 (2.5)	5 (3.2)
Pruritus generalized	1 (0.7)	4 (2.5)	8 (5.0)	1 (0.6)	16 (10.1)
Dry mouth	2 (1.3)	5 (3.2)	5 (3.1)	1 (0.6)	14 (8.9)
Oxygen saturation decreased	1 (0.7)	4 (2.5)	5 (3.1)	0	10 (6.3)

7.3.3 Adverse Events Leading to Early Discontinuation of Study Medication

In the Phase 3 APOLLO 1 and APOLLO 2 studies, no patients in the placebo or oliceridine 0.1 mg regimens reported an AE leading to early study medication discontinuation. The incidence of AEs leading to discontinuation ranged between 3 and 6% in the other active regimens. The most common AE leading to early discontinuation of study medication was oxygen saturation decreased in the morphine 1 mg regimen and hypoxia in the oliceridine 0.35 mg and 0.5 mg regimens (Table 19).

Table 19: AEs Leading to Early Study Medication Discontinuation in the Controlled Phase 3 Studies

Type of AE, n (%)	Oliceridine			Placebo	Morphine
	0.1 mg N=153	0.35 mg N=158	0.5 mg N=159	N=162	1 mg N=158
AE Leading to Discontinuation of Study Medication	0	5 (3.2)	9 (5.7)	0	8 (5.1)
Oxygen saturation decreased	0	1 (0.6)	2 (1.3)	0	5 (3.2)
Hypoxia	0	3 (1.9)	3 (1.9)	0	0
Nausea	0	0	2 (1.3)	0	0
Vomiting	0	0	0	0	1 (0.6)
Dizziness	0	0	1 (0.6)	0	0
Sedation	0	0	1 (0.6)	0	0
Non-cardiac chest pain	0	0	0	0	1 (0.6)
Post-procedural hemorrhage	0	0	1 (0.6)	0	0
Syncope/Presyncope	0	0	1 (0.6)	0	1 (0.6)
Hypotension	0	1 (0.6)	0	0	0

7.3.4 Serious Adverse Events

There were no treatment-emergent SAEs reported in any treatment regimen in APOLLO 1. In APOLLO 2, 7 treatment-emergent SAEs were reported in six patients (none in the placebo or oliceridine 0.1 mg regimens; Table 20). All SAEs resolved without sequelae by the end of the study, and most SAEs were assessed by the investigator as unrelated to study medication.

Table 20: SAEs in Controlled Phase 3 Studies

Preferred Term	Treatment	Cumulative Dose at Time of SAE	Causality
Abdominal wall hematoma	Oliceridine 0.35 mg	9.2 mg	Not related
Post-procedural hemorrhage	Oliceridine 0.5 mg	10.5 mg	Not related
Lethargy	Oliceridine 0.5 mg	20.5 mg	Possibly related
Syncope	Oliceridine 0.5 mg	7.75 mg	Possibly related
Deep vein thrombosis	Oliceridine 0.5 mg	17.25 mg	Not related
Pulmonary embolism*	Morphine 1 mg	10.0 mg	Not related
Respiratory failure*	Morphine 1 mg	10.0 mg	Not related

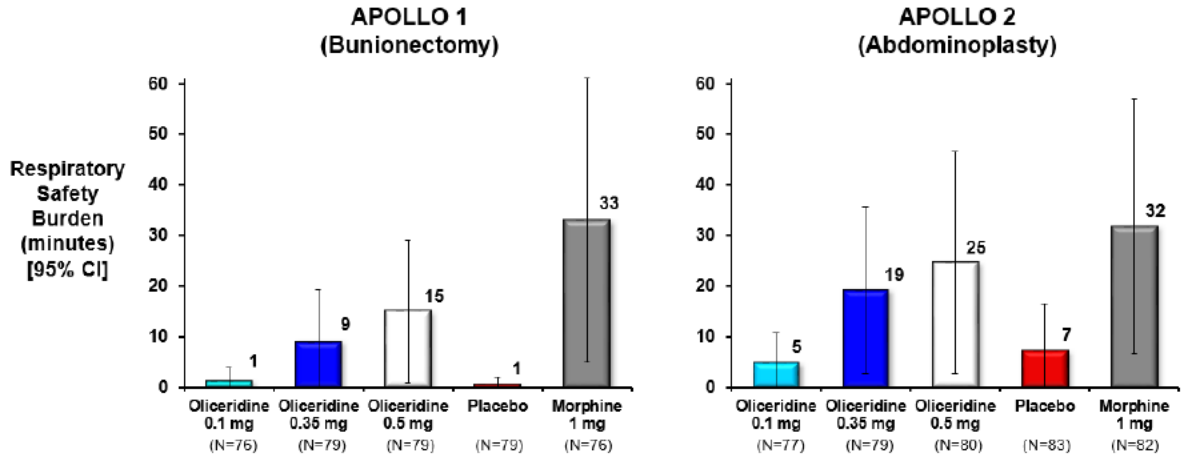
* SAEs occurred in same patient

7.3.5 Respiratory Safety

7.3.5.1 Key Secondary Safety Endpoint: Respiratory Safety Burden

In both APOLLO studies, the RSB showed a dose-dependent increase across the three oliceridine demand dose regimens, and in all instances was numerically lower than the RSB values measured in the morphine regimen; however, none of these contrasts reached threshold levels of statistical significance (Figure 34). As shown below, the confidence intervals are very wide due to a lower-than-expected overall event rate (approximately 50% lower than Phase 2b in all active and placebo groups), which reduced the statistical power to detect a significant effect.

Figure 34: Respiratory Safety Burden in APOLLO 1 and APOLLO 2



To put the clinical significance of these events into perspective, the average oxygen saturation for patients during a RSE was compared with the average oxygen saturation while not experiencing a RSE. In APOLLO 1, the average oxygen saturation was 86% and 84% for oliceridine and morphine during RSEs and 97% and 96% at other time points, respectively. In

APOLLO 2, the average oxygen saturation was 87% and 88% for oliceridine and morphine during RSEs and 97% and 97% at other time points, respectively. These data underscore that when RSEs were identified by the study methods used, they represented clinically significant medical events.

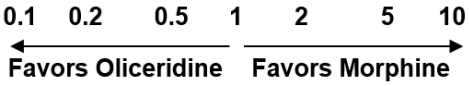
7.3.5.2 Exploratory Summary of Respiratory Safety Event Incidence and Clinical Interventions in Response to Respiratory Safety Events

Safety analyses of the components of the RSB endpoint, as well as associated clinical interventions, were pooled across the two Phase 3 studies to evaluate additional respiratory safety signals. These analyses focused on: 1) the incidence and duration of respiratory safety events (RSEs), which together determine RSB; 2) the criteria upon which RSEs were declared; and 3) clinical interventions implemented in response to respiratory safety events.

1) Consistent with the results of the Phase 2b study, a regimen-related pattern of benefit in RSEs was observed, with the 0.1 mg and 0.35 mg oliceridine regimens (ie, the regimens being considered for approval) showing the greatest difference compared to morphine. The oliceridine 0.1 mg regimen, which was efficacious but less so than the morphine regimen, was associated with 71 to 80% relative risk reductions in RSEs. The oliceridine 0.35 mg regimen, which was similarly efficacious to the morphine regimen, was associated with 33 to 42% relative risk reductions for RSEs. In contrast to the incidence of events, the duration of RSEs showed no difference across treatment groups in the Phase 3 studies (Figure 35).

Figure 35: Summary of Respiratory Safety Events in Phase 2b and Phase 3 Studies

Oliceridine Dosing Regimen	Phase	% of Patients Experiencing Respiratory Safety Event		Relative Risk Reduction vs Morphine	Relative Risk [95% CI]
		Oliceridine	Morphine		
0.1 mg	2b	15	53	71%	
	3	5	23	80%	
0.35 mg	2b	31	53	42%	
	3	15	23	33%	



2) Of the three prespecified criteria that were integrated to determine the presence or absence of an RSE, oxygen desaturation was the strongest contributor, with clear correlation of incidence of oxygen desaturation with RSEs: 91% of RSE cases had

desaturations below 90%. Incidence of desaturations across treatment group was consistent with the incidence of RSEs.

3) Interventions for respiratory safety (dosing interruption and supplemental rescue oxygen), made at clinicians' discretion, were consistent with the patterns seen for incidence of RSEs and desaturations below 90% O_2 (Table 21).

Table 21: Oxygen Desaturations and Clinician Interventions in Controlled Phase 3 Studies

Safety Parameter	Incidence (%)				Relative Reduction (p-value)	
	Oliceridine			Morphine 1 mg N=158	0.1 mg vs Morphine	0.35 mg vs Morphine
	0.1 mg N=153	0.35 mg N=158	0.5 mg N=159			
O_2 saturation < 90%	5.9	14.6	17.0	22.2	73% (< 0.001)	34% (0.11)
Dosing interruption	3.9	14.6	17.6	24.7	83% (< 0.001)	41% (0.033)
Supplemental O_2	4.6	14.6	17.6	22.8	80% (< 0.001)	36% (0.083)

The aggregate findings characterizing respiratory safety and the associated clinical interventions implemented in response to an RSE in the Phase 3 studies are consistent with the results from the Phase 2b study, the Phase 1 proof-of-concept study using the gold standard VRH model, the nonclinical studies, and the differentiated pharmacology of oliceridine. These results support the hypothesis that oliceridine shows a clinically important and distinguishable respiratory safety and tolerability profile compared to a conventional opioid comparator.

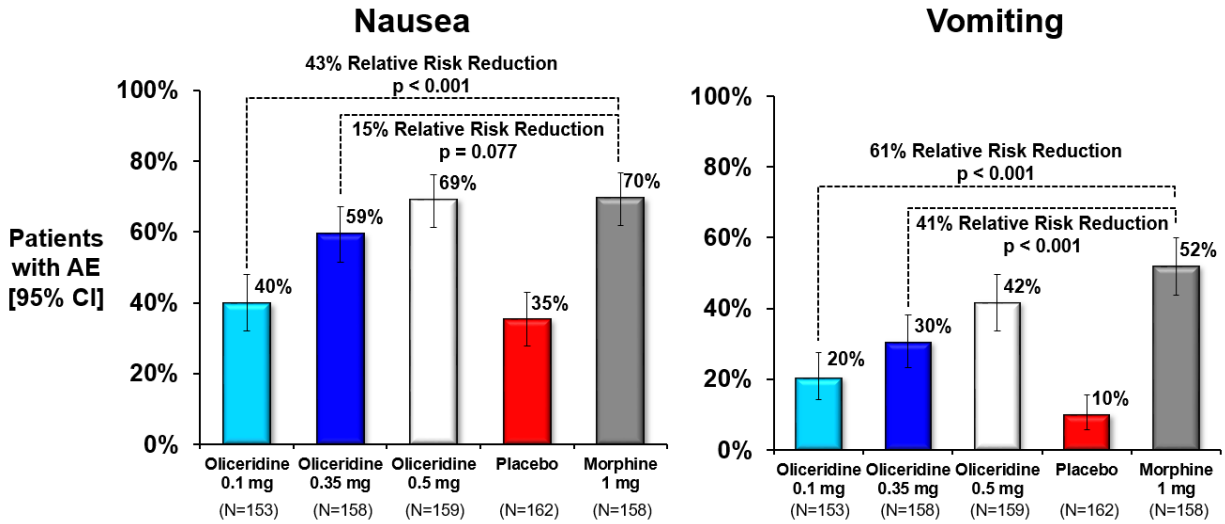
The absence of a statistically significant result on the protocol-specified key secondary outcome using the composite index of RSB underscores the methodologic challenges of differentiating respiratory safety outcomes in controlled therapeutic trials across treatment conditions. Nevertheless, the differences on the underlying measure of RSE and respiratory safety interventions provide important clinical and scientific information to inform Trevena's future work in this area.

7.3.6 Postoperative Nausea and Vomiting

As in the Phase 2b study, postoperative nausea and vomiting were assessed using MedDRA-coded Preferred Terms for the AEs of nausea and vomiting. In addition, the Phase 3 studies recorded the use of rescue antiemetics. In the APOLLO studies, prophylactic antiemetics were not allowed; however, rescue antiemetics were allowed if the patient was vomiting or reported moderate to severe nausea. Given that the 0.5 mg dosing regimen is not being sought for marketing, the analyses focus on the two regimens that represent the range of dosing regimens being considered for approval (0.1 mg and 0.35 mg).

In general, regimen-dependent effects for oliceridine were observed where higher demand doses were associated with higher rates of nausea and vomiting. The incidence of nausea was significantly lower in the oliceridine 0.1 mg regimen compared to the morphine 1 mg regimen, and the incidence of vomiting was significantly lower for both 0.1 mg and 0.35 mg regimens (Figure 36).

Figure 36: Postoperative Nausea and Vomiting in Controlled Phase 3 Studies



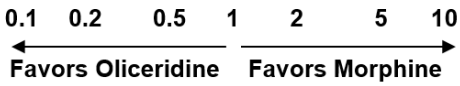
The findings regarding the lower observed rates of postoperative nausea and vomiting AEs, as assessed by MedDRA Preferred Terms, were consistent across the Phase 2b and Phase 3 studies. Figure 37 illustrates the incidence, relative risk, and relative risk reductions for the oliceridine 0.1 mg and 0.35 mg regimens compared with the morphine regimen; Figure 38 shows the same statistics for vomiting.

Figure 37: Summary of Postoperative Nausea in Phase 2b and Phase 3 Studies

Oliceridine Dosing Regimen	Phase	% of Patients Experiencing Nausea		Relative Risk Reduction vs Morphine	Relative Risk [95% CI]
		Oliceridine	Morphine		
0.1 mg	2b	41	72	43%	
	3	40	70	43%	
0.35 mg	2b	46	72	36%	
	3	59	70	15%	

Figure 38: Summary of Postoperative Vomiting in Phase 2b and Phase 3 Studies

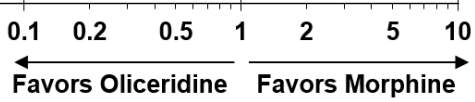
Oliceridine Dosing Regimen	Phase	% of Patients Experiencing Vomiting		Relative Risk Reduction vs Morphine	Relative Risk [95% CI]
		Oliceridine	Morphine		
0.1 mg	2b	15	42	64%	
	3	20	52	61%	
0.35 mg	2b	15	42	64%	
	3	30	52	41%	



Consistent with the incidence of nausea and vomiting, the use of rescue antiemetics was also lower with the oliceridine regimen than the morphine regimen in the Phase 2b and Phase 3 studies (Figure 39).

Figure 39: Summary of Incidence of Rescue Antiemetic Use in Phase 2b and Phase 3 Studies

Oliceridine Dosing Regimen	Phase	% of Patients Receiving Rescue Antiemetics		Relative Risk Reduction vs Morphine	Relative Risk [95% CI]
		Oliceridine	Morphine		
0.1 mg	2b	49	65	25%	
	3	26	63	59%	
0.35 mg	2b	38	65	41%	
	3	46	63	28%	



Overall, the favorable reductions in nausea and vomiting with oliceridine in the controlled Phase 3 studies are consistent with the prior results from the Phase 2b study and with the novel pharmacology of oliceridine.

7.4 Phase 3 Open-label Safety Study (ATHENA)

7.4.1 Study Design

Study 3003, ATHENA, was an open-label safety study that evaluated the safety and tolerability of oliceridine in 768 patients at 41 sites in the US with any moderate to severe acute pain for which IV opioid therapy was warranted in diverse clinical settings, including inpatient hospitals, outpatient hospital departments, ambulatory surgical care centers, and emergency departments (EDs). To support the goal of evaluating oliceridine in a realistic clinical setting, concomitant non-opioid pain medication (ie, multimodal analgesia) was permitted in the study. Enrollment criteria were intentionally more inclusive for ATHENA compared with the APOLLO studies (see Appendix 10.4 for full list of inclusion and exclusion criteria); for instance, there were no limitations on eligible BMI or age, and patients with obstructive sleep apnea were allowed to enroll in the study.

In ATHENA, oliceridine was administered either by clinician-administered bolus, PCA, or both bolus and PCA. Oliceridine dosing was permitted in a manner to achieve sufficient cumulative dose exposure to complete the required safety exposure requirements for the data in support of the NDA for oliceridine. The dosing regimens were as follows:

- clinician-administered bolus dosing
    - 1-2 mg initial dose
    - 1 mg supplemental dose PRN, as early as 15 minutes after the initial dose
    - subsequent doses 1-3 mg every 1-3 hours PRN
- in settings where rapid analgesia is targeted (eg, ED or post-anesthesia care unit)
    - 1-3 mg initial dose
    - 1-3 mg supplemental doses every 5 minutes PRN
    - subsequent doses 1-3 mg every 1-3 hours PRN
- PCA regimen
    - 1.5 mg loading dose, 0.5 mg demand dose, 6-minute lockout interval
    - supplemental 1 mg doses permitted PRN

The duration of the treatment period was based on the medical needs of individual patients. Doses were not permitted to exceed 60 mg in the first 12 hours.

7.4.2 Patient Disposition

A total of 768 patients were treated with oliceridine, and 698 patients (90.9%) completed the study. The most common reasons for early discontinuation were lack of efficacy (4.3%), AEs (2.2%), and lost to follow-up or withdrawal by patient (0.8% each).

7.4.3 Patient Characteristics and Exposure to Study Medication

Patients in ATHENA represent the general targeted patient population for IV opioids, namely, adult patients with moderate to severe acute pain for whom IV opioid therapy was warranted. Medical and surgical specialties represented in the ATHENA population are shown in Table 22.

Table 22: Patient Population in ATHENA

Specialty	Patients, n (%)	Specialty	Patients, n (%)
Orthopedic	231 (30.1)	Neurologic	39 (5.1)
Colorectal Surgery	115 (15.0)	Bariatric Surgery	18 (2.3)
Gynecologic	115 (15.0)	Cardiothoracic Surgery	18 (2.3)
General Surgery	84 (10.9)	Emergency	33 (4.3)
Plastic Surgery	60 (7.8)	Medical	11 (1.4)
Urologic	44 (5.7)		

The most common reasons for receiving oliceridine (by procedure) were:

- knee arthroplasty (n=127, 16.5%)
- hysterectomy (n=72, 9.4%)
- hip arthroplasty (n=58, 7.6%)
- colectomy (n=54, 7.0%)
- mammoplasty (n=46, 6.0%).

As an open-label safety study in which all patients were treated with oliceridine, results are summarized by five pre-specified cumulative dose exposure groups. In comparison to the APOLLO studies, patients in ATHENA were older, had a higher BMI, and had more underlying comorbidities.

The mean age in ATHENA was 54.1 years old (ranging from 18-89 years old). 32% of patients were age 65 or older and 8% of patients were age 75 or older. Approximately two-thirds of patients were female, three-quarters of patients were white, and the mean BMI was 30.5 kg/m^2 (Table 23). 13% of patients had a diagnosis of sleep apnea syndrome. Across oliceridine cumulative dose groups, mean ages increased with increasing cumulative dose.

Table 23: Demographic and Baseline Characteristics in ATHENA by Cumulative Oliceridine Dose

Characteristic	Oliceridine					
	≤ 4 mg (N=156)	> 4 to 8 mg (N=85)	> 8 to 16 mg (N=121)	> 16 to 36 mg (N=168)	> 36 mg (N=238)	Overall (N=768)
Age, mean (SD)	51.6 (15.0)	52.9 (15.4)	53.3 (15.4)	54.8 (16.3)	56.0 (17)	54.1 (16.1)
Age range	19-84	20-82	19-86	20-84	18-89	18-89
Female sex, n (%)	93 (60)	52 (61)	78 (65)	117 (70)	158 (66)	498 (65)
Race, n (%)						
Caucasian	120 (77)	70 (82)	95 (79)	133 (79)	178 (75)	596 (78)
African American	29 (19)	10 (12)	22 (18)	26 (15)	50 (21)	137 (18)
Other	7 (4)	5 (6)	4 (3)	9 (5)	8 (3)	33 (4)
Hispanic/Latino ethnicity, n (%)	11 (7)	9 (11)	10 (8)	12 (7)	19 (8)	61 (8)
BMI (kg/m^2), mean (SD)	30.1 (7.2)	29.9 (6.8)	30.6 (6.9)	30.8 (6.8)	30.8 (8.2)	30.5 (7.4)
Baseline pain intensity, mean (SD)	6.1 (1.8)	6.0 (2.0)	6.3 (2.1)	6.2 (2.0)	6.3 (2.4)	6.3 (2.1)
CYP2D6 metabolizer status, n (%)						
Extensive metabolizer (EM)	110 (87)	72 (97)	92 (85)	138 (87)	175 (83)	587 (87)
Poor metabolizer (PM)	16 (13)	2 (3)	16 (15)	20 (13)	35 (17)	89 (13)

Oliceridine could be administered as needed by PCA or as a bolus by the clinician. Patients with less exposure tended to receive oliceridine by bolus dosing only, while those patients with greater cumulative dose exposure tended to receive oliceridine predominantly by PCA. As would be expected, the average duration of exposure increased with higher cumulative dosing (Table 24). The median cumulative dose was 19.3 mg, with a range from 0.9 mg to 223.5 mg. The median duration of exposure was 20.3 hours, with a range of < 1 hour to 142.7 hours or about 6 days.

Table 24: Exposure to Study Medication in ATHENA

Characteristic	Oliceridine					
	≤ 4 mg (N=156)	> 4 to 8 mg (N=85	> 8 to 16 mg (N=121)	> 16 to 36 mg (N=168)	> 36 mg (N=238)	Overall (N=768)
Method of administration, n (%)						
Bolus	148 (95)	66 (78)	71 (59)	70 (42)	65 (27)	420 (55)
PCA	8 (5)	19 (22)	50 (41)	98 (58)	173 (73)	348 (45)
Exposure to oliceridine (hours)						
Mean (SD)	1.5 (3.6)	10.5 (12.3)	19.2 (16.8)	35.9 (20.5)	53.7 (22.9)	28.7 (26.9)
Median (Min, Max)	0.2 (0, 26.8)	4.5 (0.3, 51.7)	16.4 (0.2, 73.9)	36.3 (0.6, 93.1)	52.3 (6, 142.7)	20.3 (0, 142.7)
Cumulative oliceridine dose (mg)						
Mean (SD)	2.5 (1.0)	6.2 (1.2)	12.3 (2.3)	25.7 (5.5)	67.5 (28.6)	29.7 (31.1)
Median (Min, Max)	3 (0.9, 4)	6 (4.5, 8)	12 (8.5, 16)	25.5 (17, 36)	59 (36.5, 223.5)	19.3 (0.9, 223.5)

7.4.4 ATHENA Safety Results

Despite the notable differences in study design and patient population between the Phase 3 APOLLO 1 and APOLLO 2 studies and ATHENA, the safety and tolerability profile seen in the APOLLO studies was maintained in the target patient population of adult patients with moderate to severe acute pain for whom IV opioid therapy was warranted (Table 25). AEs leading to discontinuation occurred in 2.2% of patients. SAEs occurred in 3.4% of patients; most events were secondary to complications associated with the surgical procedure. All SAEs resolved or were resolving by the end of the study. There were no deaths. The rate of AEs was lowest in the ≤ 4 mg group; with the higher oliceridine cumulative doses, the incidence of AEs increased and then plateaued.

Table 25: Summary of AEs in ATHENA

Type of AE, n (%)	Oliceridine					
	≤ 4 mg (N=156)	> 4 to 8 mg (N=85)	> 8 to 16 mg (N=121)	> 16 to 36 mg (N=168)	> 36 mg (N=238)	Overall (N=768)
Any AE	60 (38.5)	52 (61.2)	79 (65.3)	125 (74.4)	174 (73.1)	490 (63.8)
Severe AE	2 (1.3)	3 (3.5)	5 (4.1)	3 (1.8)	2 (0.8)	15 (2.0)
SAE	1 (0.6)	4 (4.7)	5 (4.1)	7 (4.2)	9 (3.8)	26 (3.4)
AE Leading to Early Discontinuation	5 (3.2)	1 (1.2)	3 (2.5)	7 (4.2)	1 (0.4)	17 (2.2)
Deaths	0	0	0	0	0	0

Compared with the controlled Phase 3 studies, the incidence of overall AEs and severe AEs was lower in the ATHENA patient population. The incidence of SAEs and AEs leading to study

discontinuation was similar in the controlled and open-label studies. Importantly, no new AE signals were observed in this larger, more diverse group of general acute pain patients with more medical complications and illness comorbidities, which more closely resembles the intended real-world circumstances of use of oliceridine.

7.4.4.1 Common AEs

Similar to the controlled Phase 3 studies, the most common AEs in ATHENA (≥ 5% of patients in any oliceridine cumulative dose group) were typical ORAEs: nausea, vomiting, and constipation (Table 26). As expected, there was a strong relationship between cumulative oliceridine dose and the duration of exposure. Differences between exposure groups in the incidence of AEs are consistent with the differences in the duration of exposure.

Table 26: Most Common AEs (≥ 5% in any Exposure Group) in ATHENA

	Oliceridine					
Type of AE, n (%)	**≤ 4 mg (N=156)**	**> 4 to 8 mg (N=85)**	**> 8 to 16 mg (N=121)**	**> 16 to 36 mg (N=168)**	**> 36 mg (N=238)**	**Overall (N=768)**
Exposure to oliceridine (hours)						
Mean (SD)	1.5 (3.6)	10.5 (12.3)	19.2 (16.8)	35.9 (20.5)	53.7 (22.9)	28.7 (26.9)
Any AE, n (%)	60 (38.5)	52 (61.2)	79 (65.3)	125 (74.4)	174 (73.1)	490 (63.8)
Nausea	17 (10.9)	22 (25.9)	41 (33.9)	63 (37.5)	96 (40.3)	239 (31.1)
Constipation	3 (1.9)	5 (5.9)	19 (15.7)	25 (14.9)	32 (13.4)	84 (10.9)
Vomiting	5 (3.2)	4 (4.7)	11 (9.1)	17 (10.1)	43 (18.1)	80 (10.4)
Pruritus	1 (0.6)	4 (4.7)	9 (7.4)	7 (4.2)	17 (7.1)	38 (4.9)
Hypokalemia	2 (1.3)	2 (2.4)	2 (1.7)	6 (3.6)	24 (10.1)	36 (4.7)
Dizziness	3 (1.9)	5 (5.9)	8 (6.6)	8 (4.8)	10 (4.2)	34 (4.4)
Headache	3 (1.9)	3 (3.5)	6 (5.0)	8 (4.8)	14 (5.9)	34 (4.4)
Hypotension	4 (2.6)	1 (1.2)	5 (4.1)	9 (5.4)	9 (3.8)	28 (3.6)
Insomnia	1 (0.6)	2 (2.4)	5 (4.1)	12 (7.1)	8 (3.4)	28 (3.6)
Pyrexia	2 (1.3)	0	5 (4.1)	9 (5.4)	9 (3.8)	25 (3.3)
Hypocalcemia	1 (0.6)	1 (1.2)	2 (1.7)	5 (3.0)	15 (6.3)	24 (3.1)
Hypophosphatemia	0	2 (2.4)	1 (0.8)	7 (4.2)	13 (5.5)	23 (3.0)
Procedural nausea	7 (4.5)	6 (7.1)	4 (3.3)	2 (1.2)	2 (0.8)	21 (2.7)
Flatulence	1 (0.6)	2 (2.4)	10 (8.3)	6 (3.6)	1 (0.4)	20 (2.6)

7.4.5 ATHENA Conclusions

Overall, no new AE signals were observed in this larger, more diverse group of general acute pain patients with more complications and comorbidities. The overall safety profile of oliceridine was shown to be favorable for its intended use in this broader safety patient population.

7.5 Safety Topics of Special Interest

7.5.1 Hepatic Safety

7.5.1.1 Nonclinical Evaluations

Nonclinical toxicology studies with up to 28 days of continuous IV infusion of oliceridine in rats and up to 14 days of continuous IV infusion in monkeys identified no evidence of oliceridine-induced hepatic toxicity (see Section 3.2 for details). Additional nonclinical studies evaluated metabolic activation, an important mechanism of potential drug induced liver injury (DILI), and found no evidence of risk from reactive metabolites or intermediates (see Section 3.1.4 for details). Furthermore, oliceridine and its major metabolites had no effects on the major human uptake and efflux transporters, including bile salt export pump (BSEP), at clinically relevant concentrations.

7.5.1.2 Controlled Phase 2 and Phase 3 Studies

The incidence of liver enzyme elevations observed in the controlled Phase 2 and Phase 3 studies, for which randomized comparisons can be made across treatment conditions, is presented in Table 27. Across the pooled groups, the incidence of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations of at least 3 times more than the upper limit of normal (≥ 3× upper limit of normal [ULN]) was 1.6% with placebo, 2.6% with oliceridine, and 2.0% with morphine (post-hoc chi-square p=0.591). Elevations ≥3× ULN are recognized as a sensitive, but nonspecific, measure of DILI (FDA 2009). Two patients in the controlled studies, both allocated to the oliceridine group, experienced an elevation in AST or ALT ≥ 20× ULN. No patients had a concomitant rise in AST or ALT ≥ 3× ULN and total bilirubin ≥ 2× ULN. An evaluation of drug-induced serious hepatotoxicity (eDISH) plot for the controlled Phase 2 and Phase 3 clinical studies is shown in Appendix 10.8.

Table 27: Number and Proportion of Patients with Elevated Liver Enzymes in Controlled Phase 2 and 3 Studies

Test Result, n (%)	Oliceridine N=767	Placebo N=252	Morphine N=305
AST or ALT ≥ 3× ULN	20 (2.6)	4 (1.6)	6 (2.0)
AST or ALT ≥ 5× ULN	12 (1.6)	1 (0.4)	4 (1.3)
AST or ALT ≥ 10× ULN	5 (0.7)	1 (0.4)	1 (0.3)
AST or ALT ≥ 20× ULN	2 (0.3)	0	0
Bilirubin ≥ 2× ULN	0	0	0
AST or ALT ≥ 3× ULN and bilirubin ≥ 2× ULN	0	0	0

7.5.1.3 Open-label Phase 3 Study

In the open-label Phase 3 ATHENA study, 12 patients (1.6%) had an AST or ALT elevation ≥ 3× ULN, and 2 patients (0.3%), noted below, had an elevation ≥ 20× ULN (Table 28). Two

patients (0.3%) experienced AST or ALT elevations ≥ 3× ULN with a concomitant rise in bilirubin ≥ 2× ULN, without clinical jaundice. A single patient, who had also developed transaminase elevations ≥ 20× ULN, experienced substantial post-operative blood loss and subsequently experienced the serious adverse events of transient hepatic failure and renal failure, which resolved within two to three weeks. There did not appear to be a correlation between total dose of oliceridine received and incidence of elevations in serum aminotransferases at any cut-off level. An eDISH plot for the open-label Phase 3 study is shown in Appendix 10.8.

Table 28: Number and Proportion of Patients with Elevated Liver Enzymes in ATHENA Study

	Oliceridine					
Type of AE, n (%)	≤ 4 mg N=156	> 4 to 8 mg N=85	> 8 to 16 mg N=121	> 16 to 36 mg N=168	> 36 mg N=238	Overall N=768
AST or ALT ≥ 3× ULN	1 (0.7)	1 (1.2)	3 (2.5)	3 (1.8)	4 (1.7)	12 (1.6)
AST or ALT ≥ 5× ULN	1 (0.7)	1 (1.2)	0	2 (1.2)	1 (0.4)	5 (0.7)
AST or ALT ≥ 10× ULN	0	1 (1.2)	0	1 (0.6)	1 (0.4)	3 (0.4)
AST or ALT ≥ 20× ULN	0	1 (1.2)	0	1 (0.6)	0	2 (0.3)
Bilirubin ≥ 2× ULN	1 (0.7)	5 (5.9)	1 (0.8)	1 (0.6)	2 (0.8)	10 (1.3)
AST or ALT ≥ 3× ULN and bilirubin ≥ 2× ULN	0	1 (1.2)	0	1 (0.6)	0	2 (0.3)

7.5.1.4 Review of Liver Events by Expert Hepatologists

An external panel of hepatologists with expertise in DILI was convened to perform causality assessment on each of the 22 cases of elevations in serum ALT or AST exceeding 5× ULN. The reviewers were provided with case summaries and summary tables of liver enzymes changes for each of the 22 cases. The reviewers assessed each case for the likelihood of the occurrence of DILI and conducted a separate assessment for the probable causality of the contribution of oliceridine to the liver enzyme changes. The causality assessment followed the five-tiered general causality methodology used by the DILI Network, and all cases were assessed in an unblinded manner.

External Hepatologist Panel Members

Paul B. Watkins, MD (Chair)
Howard Q. Ferguson Distinguished Professor
Schools of Medicine, Pharmacy and Public Health
Director, UNC Institute for Drug Safety Sciences
University of North Carolina
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Neil Kaplowitz, MD
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University of Southern California
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Hans Tillmann, MD
Clinical Associate Professor
East Carolina University
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Greenville, NC

Donald C. Rockey, MD
Chair, Department of Medicine
Medical University of South Carolina
Charleston, SC

Among the 22 cases reviewed, this causality assessment included five cases noted by the FDA to be of special interest, which may appear as outliers from the overall pattern of similar incidence of hepatic laboratory abnormalities across oliceridine, morphine and placebo groups noted above. Detailed clinical vignettes and graphical summaries of the hepatic laboratory test results over time on these five cases are located in the Appendix 10.9.1.

The panel members individually assessed the possible role of study medication in each liver event for all 22 cases. A subsequent teleconference with all members present was held where individual cases were discussed, and consensus adjudication of case causality was ascertained. It was the unanimous consensus of the panel that none of the liver events in any of the 22 cases could be considered probably related (ie, indicating a confidence in causal likelihood > 50%) to treatment with study medication. Furthermore, there were more likely etiologies than study drug in the two patients, both from the ATHENA study, experiencing concomitant elevations in serum ALT or AST ≥ 3× ULN and serum bilirubin ≥ 2× ULN. In these two cases, and in a third ATHENA study patient who experienced substantial postoperative blood loss and developed hepatic impairment and renal failure, it was the unanimous opinion of the panel that these cases were considered unlikely (ie, indicating a causal likelihood of < 25%) to be related to exposure to oliceridine.

The panel also achieved consensus on the following conclusions:

- The majority (>75%) of cases had a short latency to onset usually within two to four days following the first exposure to oliceridine, were transient in duration, with AST and ALT levels falling at the rates of their clearance from the circulation, and all patients experienced complete resolution of the noted abnormalities without further clinical sequelae.
- The generally low doses of oliceridine administered, the early latency to liver event onset, the time course of enzyme elevations and duration of abnormalities, were not generally characteristic of DILI, which is more commonly associated with a delayed onset and more protracted fall in liver enzyme levels. Rather, most cases are highly consistent with the pattern of liver chemistry changes seen in the setting of transient liver ischemia and provide strong circumstantial support for a perioperative ischemic event as a contributing cause of the observed abnormalities.
- Of note, liver events observed among the placebo and morphine treated patients were similar to those associated with oliceridine treatment in terms of latency to onset, time course of enzyme elevations and duration of abnormalities. This suggests a background incidence of liver events in this patient population, presumably related to the perioperative and concomitant medications, the surgical procedures, and/or other unknown common clinical risk factors within this patient group. (The placebo and morphine cases with transaminase elevations exceeding 10× ULN are also included in the Appendix).
- The majority of cases reviewed by the consultant panel were asymptomatic and were only discovered due to the protocol-driven laboratory testing.

In summary, based on the available data, it was the unanimous consensus of the panel of hepatologists that there was no evidence of a clinically significant liver safety signal with oliceridine treatment.

7.5.2 Cardiac Safety

7.5.2.1 Effect of Oliceridine on Cardiac Ion Channels

Oliceridine and its two major metabolites, TRV0119662 and M22, were evaluated for their *in vitro* effects on calcium, potassium, and sodium ion channels. TRV0109662 and M22 had little effect on hERG, hCav1.2, peak hNav1.5, or late hNav1.5 ion channel currents when tested at concentrations up 300 µM, resulting in half maximal inhibitory concentrations (IC_{50}'s) > 300 µM at all channels. Oliceridine had an observed IC_{50} of 4.3 µM at the hERG ion channel and 8.8 µM at the late hNav1.5 ion channel, with IC_{50}'s > 10 µM at all other channels. These results establish large safety margins compared to the projected free C_{max} concentrations in humans of 37 nM, 6 nM, and 50 nM for oliceridine, TRV0109662 and M22, respectively. These ion channel data indicate that oliceridine is a weak hERG blocker at very high supratherapeutic concentrations with some multi-channel effects that may abrogate inhibition of hERG current. Additionally, oliceridine's major metabolites have no estimable activity at the calcium, potassium and sodium ion channels.

7.5.2.2 Nonclinical Cardiac Safety Study

Oliceridine was administered to eight cynomolgus monkeys at dose levels of 0.05, 0.2 and 1.0 mg/kg/hour in a continuous 10-hour IV infusion to evaluate the effects on corrected QT (QTc). No abnormal ECG waveforms or arrhythmias were observed. Based on the hemodynamic changes, the no-observed-adverse-effect-level (NOAEL) in this cardiovascular safety study was 0.2 mg/kg/hr, with extrapolated plasma concentrations (143 ng/mL) that were approximately 2.3 times the projected median human C_{max} (61 ng/mL) at the maximum recommended human dose (MRHD) of 40 mg/day. At the NOAEL dose, oliceridine was associated with a decrease of approximately 15% in mean systolic, diastolic, and mean arterial pressure, along with similar reductions in mean arterial pulse pressure and mean body temperature. All changes were of similar magnitude to effects known to occur with conventional opioid agonists in animals.

Estimated unbound plasma concentrations at the 1 mg/kg/hour dose level in this study were 0.76 µM, which is more than 4 times higher than the unbound C_{max} (0.172 µM) observed in humans at the 6 mg dose used in the tQT study.

7.5.2.3 General Indices of Cardiac Safety in All Phase 2 and Phase 3 Clinical Studies

Vital signs were obtained at baseline and at various post-baseline timepoints in the Phase 2 and Phase 3 studies. Mean change from baseline to worst post-baseline observations were assessed for systolic and diastolic blood pressure, pulse rate, respiratory rate, and oxygen saturation. In general, there were no clinically meaningful changes in these measures of vital sign function within or between treatment groups.

7.5.2.4 Thorough QT Study

Study 1008 was a randomized, four-period crossover tQT study to assess the effect of therapeutic and supratherapeutic doses of oliceridine on the QTc interval in healthy adults. 58 subjects were randomized and received at least one active dose in a treatment sequence that included a single IV bolus of placebo over 5 minutes, a single oral dose of moxifloxacin (400 mg) as a positive

control, a single therapeutic IV bolus of oliceridine (3 mg) over 5 minutes, and a single supratherapeutic IV bolus of oliceridine (6 mg) over 5 minutes. The study assessed PK and the electrocardiographic effects over the course of 24 hours.

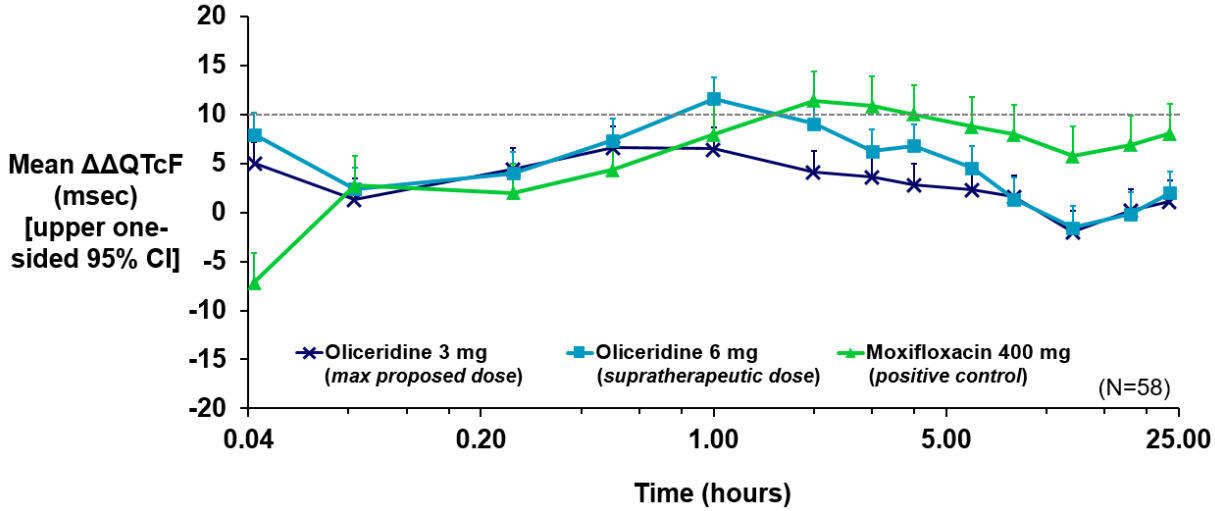
The 3 mg dose of oliceridine was chosen as it is the highest proposed clinical dose of oliceridine. The supratherapeutic dose of 6 mg oliceridine was chosen to mimic the expected exposure of a patient getting the maximum clinical dose while taking an interacting drug which would decrease the clearance of oliceridine. The 400 mg dose of moxifloxacin is a standard single dose used in tQT studies, which has been shown to reliably prolong the QTc interval (as calculated by Fridericia's correction[QTcF]) in healthy volunteers.

The results of the primary analysis found no evidence of any clinically significant effect of oliceridine at the highest proposed clinical dose (3 mg) on cardiac repolarization. At the supratherapeutic dose (6 mg), there was a minor, transient effect shown by a brief extension of the QTcF observed at three time points (Figure 40). The upper one-sided 95% confidence limit of the mean placebo-adjusted change from baseline in QTcF (ΔΔQTcF) exceeded the 10 msec, the threshold level of regulatory interest (FDA 2005), at 2.5 minutes, 1 hour, and 2 hours post-dose. An analysis of the relationship between plasma concentrations of oliceridine and cardiac repolarization showed no evidence of a concentration-mediated effect (Figure 41).

In both oliceridine treatments, there was a small increase in heart rate at 2.5 and 5 minutes post-dose (7.6-9.4 bpm) which resolved by 15 minutes post-dose. There were no clinically relevant changes in the PR and QRS intervals in either oliceridine dose group.

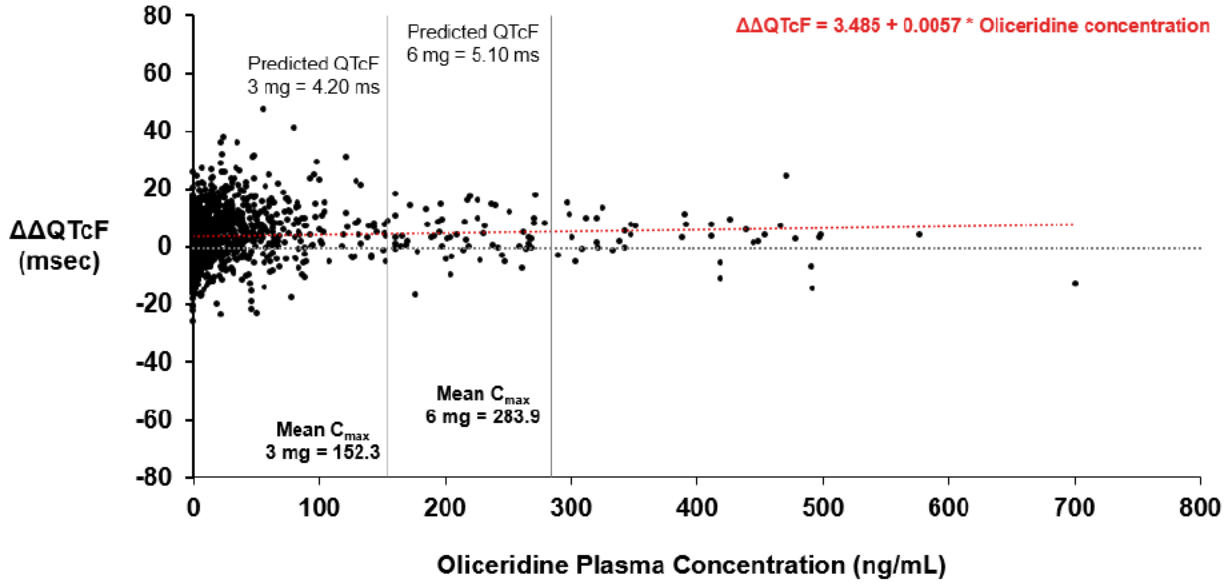
Based on the results of the tQT study, and at the request of FDA, the cardiac safety of oliceridine was carefully monitored in subsequent clinical studies (see Section 7.5.2.5).

Figure 40: Placebo-Adjusted Change from Baseline QTcF vs Time in tQT Study



Note: The dashed line at 10 msec represents the threshold level of regulatory interest (FDA 2005).

Figure 41: Placebo-Adjusted Change from Baseline QTcF vs. Oliceridine Plasma Concentration in tQT Study



7.5.2.5 Phase 3 Monitoring of Electrocardiograms

Based on the observations in the tQT study, the FDA recommended that Trevena incorporate clinical safety ECG monitoring in the Phase 3 studies. The FDA suggested obtaining measures at baseline, following the first dose, and then periodically at later time points to provide a comprehensive assessment of any potential delayed onset of a QT effect. Trevena obtained measures at baseline, and 1, 24, and 48 hours after the initial dose to address this request.

ECG monitoring during the controlled Phase 3 studies showed no meaningful differences in the incidence of potentially clinically significant ECG results for any of the oliceridine groups, morphine, or placebo (Table 29).

Table 29: Potentially Clinically Significant ECG Results by Treatment Regimen in Controlled Phase 3 Studies

Measure, n (%)	Oliceridine			Placebo N=162	Morphine 1 mg N=158
	0.1 mg N=153	0.35 mg N=158	0.5 mg N=159		
QTcF >500 msec	0	0	0	0	0
QTcF change from baseline >30 msec	15 (9.8)	11 (7.0)	13 (8.2)	12 (7.5)	13 (8.2)
QTcF change from baseline >60 msec	1 (0.7)	0	0	0	0
QT interval > 450 msec	19 (12.4)	9 (5.7)	17 (10.7)	21 (13.0)	14 (8.9)
QT interval change from baseline > 30 msec	25 (16.3)	10 (6.3)	18 (11.4)	22 (13.8)	21 (13.4)

In the open-label Phase 3 ATHENA study, ECGs were performed at baseline, 60 minutes after the first dose of oliceridine, and every 24 hours of oliceridine treatment. The patients included in the ATHENA study represented a broader population of patients with more intrinsic risk factors such as obesity, obstructive sleep apnea, and older age, and more medical illness comorbidities than the patients in the controlled Phase 3 studies (see Section 7.4 for details). No patients in either the ATHENA or the APOLLO studies had any AEs or ECG assessments indicating the presence of ventricular extrasystoles, premature ventricular contractions or premature ventricular complexes, or evidence of ventricular tachycardia.

In summary, oliceridine was not associated with a clinically meaningful increase in risk for ventricular arrhythmia or other indices of cardiovascular safety under the proposed conditions for clinical use.

7.5.3 Safety by Subgroups

No meaningful differences were observed in the safety profile of oliceridine based on subgroup evaluations by age, sex, race, BMI, and CYP2D6 metabolizer status in the Phase 2 and 3 studies.

7.5.4 Overdose

In the Phase 3 open-label study ATHENA, patients were not to receive a dose of oliceridine that exceeded 3 mg; however, in one patient, a single 10 mg dose was inadvertently administered as a bolus. The patient did not receive an opioid reversal agent, nor was assisted ventilation required. No overdoses were reported with oliceridine in the Phase 1, Phase 2, or Phase 3 controlled studies, and no patient was administered naloxone while receiving oliceridine.

As with any opioid, there is a risk that oliceridine will be involved in intentional or unintentional overdose situations, which may result in injury or death. However, based on the safety profile observed following administration of high/supratherapeutic doses of oliceridine in a controlled hospital setting, this risk is not expected to be greater than that of conventional Schedule II opioid products. In addition, given that all doses of oliceridine are administered in a medical setting, the risk of overdose with oliceridine is considered to be low.

Nonclinical data show that oliceridine binds reversibly to the MOR, is competitive with naloxone, and oliceridine pharmacology can be quickly reversed in rodents.

7.5.5 Opioid Withdrawal

The pharmacological profile and available PK data indicate that the physical dependence potential of oliceridine is similar to other Schedule II full MOR agonists used for the treatment of acute pain. This is supported by data from the clinical assessments of physical withdrawal. In clinical studies, post-discontinuation AEs associated with withdrawal were minimal; additionally, mean scores on the Subjective Opiate Withdrawal Scale (SOWS) were associated with zero to minimal withdrawal and were consistent with symptoms reported following the acute administration of morphine. These data indicate that oliceridine is expected to be associated with physical dependence similar to other Schedule II opioids.

8 CONCLUSIONS

IV opioids are an essential medication for the management of moderate to severe acute pain in the hospital and other controlled settings. Last year, 45 million patients in the US received an IV opioid in these settings to manage their acute pain. While effective, these powerful medicines are limited by their relatively narrow therapeutic windows and their associated liability for ORAEs such as respiratory depression, nausea, and vomiting. Unfortunately, in the last several decades, there have been few, if any, advancements to improve the inherent safety profile of IV opioids.

Based on the latest scientific understanding of MOR pharmacology, Trevena developed oliceridine, the first G protein-biased MOR agonist, with the goal of providing an efficacious IV opioid that reduces or attenuates the incidence of ORAEs.

The clinical and regulatory goals of the development program were tailored to thoroughly evaluate oliceridine: (1) to provide the data required for FDA approval, including two adequate and well-controlled trials demonstrating superiority over placebo, (2) to adequately characterize oliceridine safety to establish an overall benefit/risk profile, and (3) to explore the differential effects on ORAEs relative to a conventional IV opioid. As summarized in Table 30, the goals of the clinical development program were achieved.

Table 30: Overview of Oliceridine Clinical Program Goals and Outcomes

Development Goals	Action	Key Oliceridine Findings
Meet efficacy requirements for approval	• Two Phase 3 randomized controlled trials	• Superior to placebo in APOLLO 1 and APOLLO 2
Characterize benefit-risk profile	• Included IV morphine as active comparator in all controlled clinical studies • Phase 3 open-label study	• Efficacy consistent with IV opioid analgesic • Favorable safety profile for intended use • Favorable safety profile maintained in more diverse patient population in large, open-label study
Explore effects on ORAEs	• Included IV morphine as active comparator in all controlled clinical studies • Performed gold standard VRH assessment for opioid-induced respiratory depression • Measured complementary respiratory safety endpoints in Phase 2b and Phase 3 studies	• Significantly less nausea and vomiting than morphine • Produced less depression of respiratory drive than morphine at equianalgesic doses using gold standard VRH method • Consistent signal of reduced respiratory impact vs morphine in Phase 2b and Phase 3

From an efficacy perspective, oliceridine has been studied when administered as either PCA or bolus dosing, across a range of dosing regimens, to provide support for its clinical use in a variety of controlled clinical settings. With 2 positive, adequate, and well-controlled trials demonstrating analgesic efficacy, oliceridine has met the regulatory efficacy threshold for approval for its proposed indication for the management of moderate to severe acute pain in adult patients for whom an IV opioid is warranted.

Consistent with its novel mechanism of action, the totality of data across the development program suggest that oliceridine can attenuate, but not eliminate, ORAEs, and has an overall favorable safety profile as an IV analgesic.

- **Opioid Abuse:** The administration of oliceridine is to be supervised by trained medical personnel for acute use only within a hospital or other controlled clinical setting. A HAL study demonstrated that oliceridine was associated with similar drug liking to equianalgesic doses of morphine. These findings support Trevena's proposal that, if approved, oliceridine should be designated a Schedule II drug under the Controlled Substances Act, which would provide the same controls and precautions that currently exist for conventional IV opioid medications.
- **Respiratory Safety:** Results from VRH, the gold standard methodology for evaluating opioid-induced respiratory depression, demonstrated that oliceridine caused significantly less depression of respiratory drive than morphine at equianalgesic doses. While no validated endpoint exists for evaluating respiratory safety in the context of clinical trials for the treatment of acute pain, Trevena used complementary endpoints and methodologies to characterize the relative respiratory safety profile of oliceridine compared with morphine, the prototypical IV opioid. The relative risk reductions observed for clinically relevant events were consistent across phases of development for the 2 dosing regimens representing the dosing range considered for approval. While the Phase 3 studies were ultimately underpowered for the statistical evaluation of the novel composite measure of RSB, a comprehensive appraisal of the respiratory safety data provides evidence that oliceridine attenuates the respiratory impact of an IV opioid. While clinically differentiated from morphine, the current data are not sufficient to warrant a formal labeling claim of safety superiority to conventional opioid therapy.
- **Nausea and Vomiting:** Oliceridine was associated with significant reductions in the incidence of nausea, vomiting, and the use of rescue antiemetics compared with IV morphine. Common ORAEs such as nausea and vomiting diminish the quality of postoperative recovery for the patient and put a greater burden on the clinical team managing the patient's care. Vomiting, in particular, can cause postsurgical complications such as wound dehiscence, esophageal rupture, and dehydration. The 41% to 64% relative risk reductions in vomiting compared with morphine observed in the Phase 2b and Phase 3 studies suggest that oliceridine could offer advantages over conventional IV opioids in this important aspect of patient care.
- **Hepatic Safety:** Trevena performed nonclinical and clinical evaluations of hepatic safety throughout the development program. Liver enzyme elevations occurred in all treatment groups (oliceridine, placebo, and morphine) during the clinical studies. Trevena convened an expert group of hepatologists to review all available data on patients who experienced

a significant liver enzyme elevation. Based on a comprehensive review of the available data, it was the unanimous consensus of the expert panel that there was no evidence of a clinically significant liver safety signal with oliceridine.

- **Cardiac Safety:** A tQT study found that a supratherapeutic dose of oliceridine produced a transient prolongation of the QT interval beyond the regulatory threshold of interest, which prompted enhanced ECG monitoring in the Phase 3 studies. Based on a comprehensive review of cardiac ion channel data, nonclinical studies, analyses of changes in vital signs, extensive ECG monitoring, and review from outside experts, oliceridine does not appear to be associated with a clinically relevant cardiac safety issue.
- **Safety in Diverse Patient Population:** The positive efficacy and safety data from the controlled studies is supported by a large Phase 3 open-label study which found that a diverse patient population experienced clinically meaningful pain relief and a favorable safety profile across a wide range of procedures. Thus, the benefit-risk profile for oliceridine has been well characterized across a comprehensive dose range in diverse clinical settings.

Overall, oliceridine has a favorable benefit/risk profile for its intended use in a controlled clinical setting and would provide physicians with a valuable treatment option for patients who require IV opioid therapy.

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10 APPENDIX

10.1 Planned Pediatric Studies

Table 31: Planned Clinical Studies to Support Oliceridine Pediatric Development

Age Group	Type of Study	Study Objective
6 to <17years	Phase 3 R, DB, PC Dose (Exposure) Response	Primary: To evaluate the efficacy of oliceridine vs placebo (added to standard-of care analgesia and rescue) using the cumulative amount of background pain medication administered. Secondary: To describe the safety, tolerability, and PK of oliceridine; To evaluate the exposure-response for efficacy of oliceridine. Exploratory: To describe the relationship between exposure and safety.
3 to <6 years	Phase 3 R, DB, PC Dose (Exposure) Response	Primary: To evaluate the efficacy of oliceridine vs placebo (added to standard-of care analgesia and rescue) using the cumulative amount of background pain medication administered. Secondary: To describe the safety, tolerability, and PK of oliceridine; To evaluate the exposure-response for efficacy of oliceridine with moderate to severe post-surgical pain. Exploratory: To describe the relationship between exposure and safety.
2 months to <3years	Phase 1b DB, PC Dose Escalation	Primary: To describe the relationship between oliceridine exposure vs placebo (added to standard-of care analgesia and rescue) using the cumulative amount of background pain medication administered. Secondary: To describe the safety, tolerability, and PK of oliceridine. Exploratory: To describe efficacy of oliceridine and the relationship between oliceridine exposure and safety.
2 months to <3years	Phase 3 R, DB, PC	Primary: To evaluate the efficacy of oliceridine vs placebo (added to standard-of care analgesia and rescue) using the cumulative amount of background pain medication administered. Secondary: To assess safety and tolerability of oliceridine.
Birth to <2 months	Phase 1b DB, PC Dose Escalation	Primary: To describe the relationship between oliceridine exposure vs placebo (added to standard-of care analgesia and rescue) and the cumulative amount of background pain medication administered. Secondary: To describe the safety, tolerability and PK of oliceridine Exploratory: To describe efficacy of oliceridine and the relationship between oliceridine exposure and safety
Birth to <2 months	Phase 3 R, DB, PC	Primary: To evaluate the efficacy of oliceridine vs. placebo (added to standard-of care analgesia and rescue) using the cumulative amount of background pain medication administered. Secondary: To assess safety and tolerability of oliceridine

R = randomized; DB = double-blind; PC = placebo-controlled

10.2 APOLLO 1 Inclusion and Exclusion Criteria

Preoperative Entry Criteria

Preoperative entry criteria were evaluated at Screening and during the Presurgical Period.

Inclusion Criteria

Patients must have met all of the following inclusion criteria:

1. Age ≥18 and ≤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

Patients must not have met any of the following 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 had been clinically stable and fully excised in a curative procedure).
6. Current painful condition that could have confounded the interpretation of efficacy, safety, or tolerability data in the study.
7. Body weight <40 kg or body mass index (BMI) >35 kg/m^2.
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 >1 month, within 12 months before surgery.
13. Used any analgesic medication within five half-lives (or, if half-life was unknown, within 48 hours) before surgery, or used chronic nonsteroidal anti-inflammatory drug (NSAID) therapy, defined as daily use for >2 weeks within 6 months before surgery (aspirin ≤325 mg daily was permitted for cardiovascular prophylaxis if the patient had been on a stable regimen for ≥30 days before surgery).
14. Used agents that could have affected the analgesic response (such as central alpha-adrenergic agents [clonidine and tizanidine], antiepileptic drugs, neuroleptic agents, antidepressants and other antipsychotic agents) that had 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 were 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 × upper limit of normal [ULN], aspartate aminotransferase [AST] ≥1.5×ULN AND alanine aminotransferase [ALT] ≥1.5×ULN) or renal impairment (estimated glomerular filtration rate [eGFR] ≤29 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease equation) at Screening.
18. Clinically significantly abnormal clinical laboratory value at Screening.
19. Positive human immunodeficiency virus (HIV) antibody, hepatitis B virus surface antigen, or hepatitis C virus antibody status at Screening.
20. Clinically significant abnormality on electrocardiogram (ECG), 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 Criteria

Inclusion Criteria

Patients must have met all of the following 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 ≥4 within 9 hours after discontinuation of regional anesthesia.

Exclusion Criteria

Patients must not have met any of the following exclusion criteria:

1. Duration of surgical event from incision to skin closure >90 minutes.
2. Surgical, postsurgical, or anesthetic complication that could have confounded the interpretation of efficacy, safety, or tolerability data in the study.
3. Deviation from the surgical, postsurgical, or anesthetic protocol that could have confounded the interpretation of efficacy, safety, or tolerability data in the study.
4. Evidence of hemodynamic instability or respiratory insufficiency.

10.3 APOLLO 2 Inclusion and Exclusion Criteria

Preoperative Entry Criteria

Preoperative entry criteria were evaluated at Screening and during the Presurgical Period.

Inclusion Criteria

Patients must have met all of the following inclusion criteria:

1. Age ≥18 and ≤75 years at Screening.
2. Scheduled to undergo abdominoplasty procedure with no additional collateral procedures.
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

Patients must not have met any of the following 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 had been clinically stable and fully excised in a curative procedure).
6. Current painful condition that could have confounded the interpretation of efficacy, safety, or tolerability data in the study.
7. Body weight <40 kg or body mass index (BMI) >35 kg/m2.
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 >1 month, within 12 months before surgery.
13. Used any analgesic medication within five half-lives (or, if half-life was unknown, within 48 hours) before surgery, or used chronic nonsteroidal anti-inflammatory drug (NSAID) therapy, defined as daily use for >2 weeks within 6 months before surgery (aspirin ≤325 mg daily was permitted for cardiovascular prophylaxis if the patient had been on a stable regimen for ≥30 days before surgery).
14. Used agents that could have affected the analgesic response (such as central alpha-adrenergic agents [clonidine and tizanidine], antiepileptic drugs, neuroleptic agents, antidepressants and other antipsychotic agents) that had 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 were 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 × upper limit of normal [ULN], aspartate aminotransferase [AST] ≥1.5×ULN AND alanine aminotransferase [ALT] ≥1.5×ULN) or renal impairment (estimated glomerular filtration rate [eGFR] ≤29 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease equation) at Screening.
18. Clinically significantly abnormal clinical laboratory value at Screening.
19. Positive human immunodeficiency virus (HIV) antibody, hepatitis B virus (HBV) surface antigen, or hepatitis C virus (HCV) antibody status at Screening.
20. Clinically significant abnormality on electrocardiogram (ECG), 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 Criteria

Inclusion Criteria

Patients must have met all of the following 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 end of surgery.
3. NRS ≥5 within 4 hours after end of surgery.

Exclusion Criteria

Patients must not have met any of the following exclusion criteria:

1. Duration of surgical event from incision to end of surgery >2.5 hours.
2. Surgical, postsurgical, or anesthetic complication that could have confounded the interpretation of efficacy, safety, or tolerability data in the study.
3. Deviation from the surgical, postsurgical, or anesthetic protocol that could have confounded the interpretation of efficacy, safety, or tolerability data in the study.
4. Evidence of hemodynamic instability or respiratory insufficiency.

10.4 ATHENA Inclusion and Exclusion Criteria

Inclusion Criteria

Patients were eligible for study inclusion of they met all of the following inclusion criteria:

1. Age =18 years at Screening.
2. Moderate to severe acute pain for which parenteral opioid therapy was warranted, defined as NRS pain intensity of =4 during the predose period.
3. Able to understand and comply with the procedures and study requirements, and to provide written informed consent before any study procedure.
4. If it was anticipated that the patient would be treated with oliceridine in the ED with subsequent discharge or transfer to another facility, the patient was to remain under the care of the investigator for at least 3 hours after the last dose of oliceridine.

Exclusion Criteria

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

Patients were excluded from study participation for any one of the following reasons:

1. Participating in another oliceridine clinical study.
2. Clinically significant medical, surgical, postsurgical, psychiatric, or substance abuse condition or history of such condition that would have confounded the interpretation of safety, tolerability, or efficacy data in the study.
3. Hemodynamic instability or respiratory insufficiency; or required a tracheostomy or mechanically assisted ventilation.
4. If a surgical or medical patient, an American Society of Anesthesiologists (ASA) Physical Status Classification System score of IV or worse (American Society of Anesthesiologists 2017); if an ED patient, an ESI triage score of 1 (Gilboy 2011).
5. If an ED patient, alcohol intoxication, acute substance impairment, or positive urine or serum toxicology screen.
6. Advanced cancer in palliative or end-of-life care.
7. Concurrent use of chemotherapeutic or biologic agents for the treatment of cancer.
8. Another current painful condition (other than acute pain for which parenteral opioid therapy was warranted) that would have confounded the interpretation of safety, tolerability, or efficacy data in the study.
9. Clinically significant, immune-mediated hypersensitivity reaction to opioids.
10. Pregnancy, breastfeeding, or positive urine or serum pregnancy test at Screening.
11. Hepatic impairment (total bilirubin >2 × upper limit of normal [ULN], aspartate aminotransferase [AST] =1.5×ULN AND alanine aminotransferase [ALT] =1.5×ULN) or renal impairment (estimated Glomerular Filtration Rate =29 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease equation), known or obtained at Screening (Levey 2009).
12. History of human immunodeficiency virus, hepatitis B, or hepatitis C.

13. Clinically significant abnormal clinical laboratory values, known or obtained at Screening.
14. Clinically significant abnormal ECG, including a QTcF interval of >450 msec in males and >470 msec in females, known or obtained at Screening.

10.5 Additional Clinical Pharmacology Tables

Table 32: Overview of Phase 1 Clinical Pharmacology Studies

Study	Population and Number of Subjects/Patients Treated	Treatment Arms	Mode of Administration	Frequency of Administration
1001 (first-in-human, Phase 1, multipart, randomized, single-blind, placebo-controlled, parallel group, SAD study)	Population: healthy adults, CYP2D6 EMs and PMs Number of subjects: Total: 74 Oliceridine: 58 Placebo: 16	Part A: 0.15, 0.25, 0.4, 0.7, 1.2, 2.2, 4, and 7 mg oliceridine; placebo Part B (PMs): 0.25 mg oliceridine Part C: 1.5 mg oliceridine	Part A: IV over 1 hour Part B: IV over 1 hour Part C: IV over 1, 5, 15, and 30 minutes	Part A: Single dose Part B: Single dose Part C: 4 single doses separated by approximately 24 hours
1002 (Phase 1, open-label, nonrandomized, four-day crossover, SAD study)	Population: healthy adults, CYP2D6 EMs and PMs Number of subjects: 6	2, 2.5, 3, or 3.5 mg oliceridine	IV over 2 minutes	Single dose
1003 (Phase 1, randomized, double-blind, placebo-controlled, five-period crossover study)	Population: healthy adults, CYP2D6 EMs and PMs Number of subjects: 30	1.5, 3, and 4.5 mg of oliceridine; 10 mg of morphine; placebo	IV over 2 minutes	Single dose
1004 (Phase 1, open-label, nonrandomized, single oral dose study)	Population: healthy adults, CYP2D6 EMs and PMs Number of subjects: 8	100 µg of oliceridine	Oral	Single dose

Study	Population and Number of Subjects/Patients Treated	Treatment Arms	Mode of Administration	Frequency of Administration
1005 (Phase 1, multipart, MAD [randomized, double-blind, placebo-controlled], and DDI study)	Population: healthy adults, CYP2D6 EMs and PMs Number of subjects: Total: 51 Oliceridine: 40 Placebo: 11	Part A: Treatment Group A: 1.5 mg oliceridine Treatment Group B: 3 mg oliceridine Treatment Group C: 4.5 mg oliceridine Treatment Group D: 4 mg oliceridine Placebo Part B: Multiple dose phase: 0.4 mg DDI phase: 0.25 mg	IV over 2 minutes IV over 10 minutes	Part A: Treatment Group A, B, and C: q6h x 5 doses Treatment Group D: q4h x7 doses Part B: Multiple dose phase: q6h x 6 doses DDI phase: single dose
1006 (Phase 1, open-label, single-sequence, crossover DDI study)	Population: healthy adults, CYP2D6 EMs Number of subjects: 11	2 mg oliceridine alone, followed by 2 mg oliceridine with 200 mg ketoconazole	IV over 2 minutes	2 doses, 12 hours apart
1007 (Phase 1, single-dose, ^{14}C-oliceridine study)	Population: healthy adults Number of subjects: 6	2 mg oliceridine combined with 100 µCi ^{14}C-oliceridine	IV over 2 minutes	Single dose
1008 (Phase1, multipart, single dose [therapeutic or supratherapeutic], fixed sequence, cross-over study [two-period in Part A or four-period in Part B])	Population: healthy adults, CYP2D6 EMs and PMs Number of subjects: 72	3 and 6 mg of oliceridine; 400 mg moxifloxacin; or placebo	IV over 5 minutes	Single dose
1010 (Phase 1, open-label, parallel group, single dose, hepatic function study)	Population: healthy adults and adults with mild, moderate, or severe hepatic impairment Number of subjects: 34	0.5 and 1 mg oliceridine	IV over 2 minutes	Single dose

Study	Population and Number of Subjects/Patients Treated	Treatment Arms	Mode of Administration	Frequency of Administration
1011 (Phase 1, randomized, double-blind, crossover, abuse potential study)	Population: healthy adults, CYP2D6 EMs and PMs Number of subjects: Total: 60 Part A: Oliceridine: 6 Placebo: 2 Part B: Oliceridine: 52	Part A: 3 mg and 5 mg oliceridine; placebo Part B: 1 mg, 2 mg, and 4 mg oliceridine; 10 mg and 20 mg morphine; placebo	IV over 1 minute	Single dose
1012 (Phase 1, open-label, parallel group, two-part, single dose, renal function study)	Population: healthy adults and adults with end-stage renal disease Number of subjects: 17	0.5 and 1 mg oliceridine	IV over 2 minutes	Single dose

Table 33: Cross-study Summary of Single-dose PK of Oliceridine in EMs and PMs

Study Number	Dose (mg)	Infusion Time (min)	CYP2D6 Status	N	Geometric Mean (Coefficient of Variation)				
					CL (L/hr)	$AUC_{0-\infty}$ (µg*hr/L)	C_{max} (µg/L)	t_{max}* (hr)	$t_{½}$ (hr)
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)
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)
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)
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)
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)
1008	6	5	EM	44	35.0 (26.3)	171.6 (26.3)	239.7 (77.8)	0.09 (0.06 - 0.60)	3.64 (42.1)
			PM	5	24.7 (22.2)	243.0 (22.2)	183.8 (120.4)	0.09 (0.09 - 0.60)	4.07 (13.6)

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

* Median (minimum - maximum).

10.6 Results of Primary Endpoint Treatment Responder Definition by Component

Table 34: Components of Primary Endpoint Treatment Responder Rate in APOLLO 1

Primary Endpoint Component	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	Morphine 1 mg N=76
Treatment Responder	15%	50%	62%	66%	71%
≥ 30% improvement in SPID	63%	70%	72%	79%	88%
No Rescue Medication	23%	59%	80%	84%	87%
No Early Discontinuation	63%	90%	95%	87%	84%
Did Not Meet Dosing Limit	100%	95%	100%	100%	100%

Table 35: Components of Primary Endpoint Treatment Responder Rate in APOLLO 2

Primary Endpoint Component	Placebo N=81	Oliceridine 0.1 mg N=77	Oliceridine 0.35 mg N=80	Oliceridine 0.5 mg N=80	Morphine 1 mg N=83
Treatment Responder	46%	61%	76%	70%	78%
≥ 30% improvement in SPID	75%	74%	84%	85%	90%
No Rescue Medication	57%	74%	86%	88%	89%
No Early Discontinuation	75%	87%	93%	89%	90%
Did Not Meet Dosing Limit	99%	100%	100%	100%	100%

10.7 Sum of Pain Intensity Differences (SPID) in APOLLO 1 and APOLLO 2

Note, for both tables below, pain scores following rescue pain medication administration were imputed from the time of first rescue pain medication use to the end of the randomized treatment period using the last observation carried forward (LOCF). For patients who discontinued due to lack of efficacy the pain scores were imputed from the time of discontinuation until the end of the randomized treatment period using LOCF. For patients who discontinued due to any reason other than lack of efficacy (eg, due to an AE), the baseline pain scores (BOCF) were used to impute missing pain scores from the time of discontinuation until the end of the randomized treatment period.

Table 36: SPID at 48 Hours in APOLLO 1

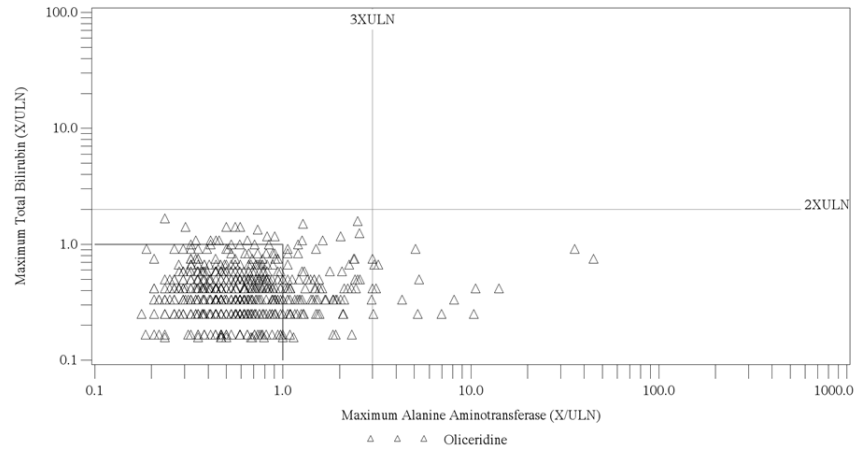
Statistic	Oliceridine			Placebo	Morphine
	0.1 mg N=76	0.35 mg N=79	0.5 mg N=79	N=79	1 mg N=76
Mean (SD)	89.4 (135.5)	117.0 (114.8)	133.8 (124.7)	-19.4 (101.4)	155.4 (116.2)
LS Mean (SE)	88.7 (12.9)	120.5 (12.6)	139.5 (12.7)	-25.3 (12.7)	156.9 (12.9)
LS Mean Difference vs Placebo (SE)	114.1 (18.01)	145.8 (17.9)	164.9 (17.9)	--	182.2 (18.1)
p-value	<0.0001	<0.0001	<0.0001	--	<0.0001
LS Mean Difference vs Morphine (SE)	-68.1 (18.1)	-36.4 (18.0)	-17.4 (18.0)	-182.2 (18.1)	--
p-value	0.0002	0.043	0.34	<0.0001	--

Table 37: SPID at 24 Hours in APOLLO 2

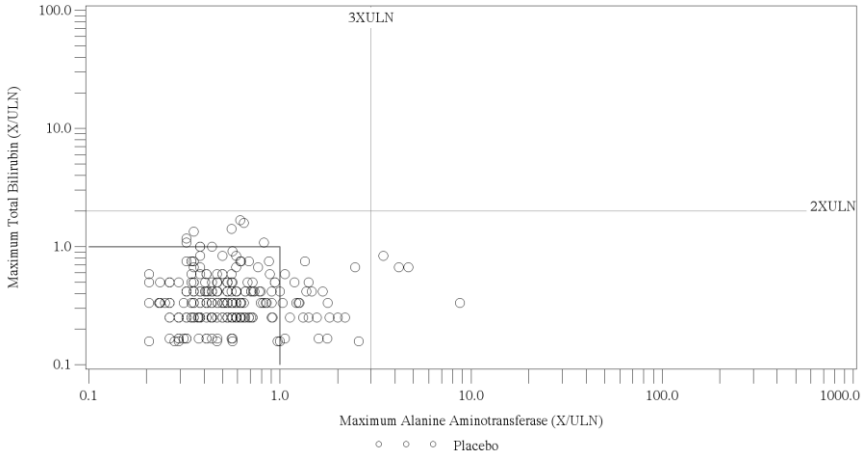
Statistic	Oliceridine			Placebo	Morphine
	0.1 mg N=77	0.35 mg N=80	0.5 mg N=78	N=81	1 mg N=81
Mean (SD)	63.3 (56.9)	82.8 (51.4)	82.2 (53.0)	42.4 (55.8)	91.7 (56.7)
LS Mean (SE)	69.1 (6.1)	87.9 (6.0)	87.5 (6.1)	49.5 (6.0)	97.5 (6.0)
LS Mean Difference vs Placebo (SE)	19.6 (8.1)	38.4 (8.1)	38.0 (8.2)	--	48.0 (8.0)
p-value	0.017	<0.0001	<0.0001	--	<0.0001
LS Mean Difference vs Morphine (SE)	-28.4 (8.1)	-9.6 (8.1)	-10.0 (8.2)	-48.0 (8.0)	--
p-value	0.0005	0.23	0.22	<0.0001	--

10.8 Evaluation of Drug-induced Serious Hepatotoxicity (eDISH) Plots

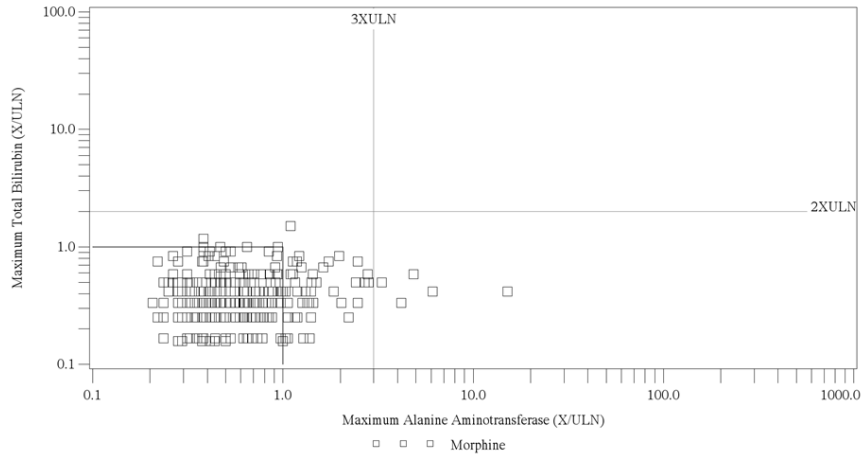
Figure 42: eDISH Plots for Controlled Phase 2 and Phase 3 Studies



Oliceridine (N=767)

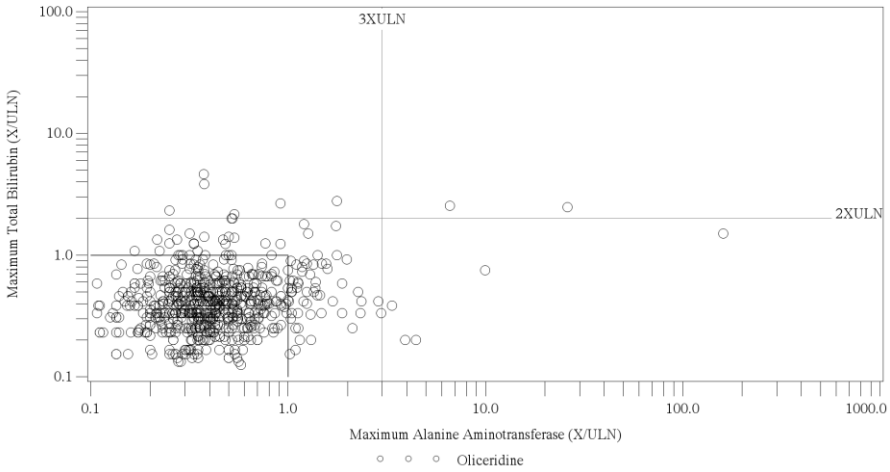


Placebo (N=252)



Morphine (N=305)

Figure 43: eDISH Plot for Open-Label ATHENA Study



10.9 Clinical Case Vignettes and Graphical Liver Enzyme Laboratory Results for Cases of Interest with Transaminase Elevations ≥10× ULN

10.9.1 Liver Events among Patients Who Received Oliceridine

Case 1: ATHENA Patient (b) (6) is a 70-year-old white male (101.9 kg, 182.9 cm) in the oliceridine >4 to 8 mg cumulative dose group. He was enrolled in the ATHENA study to treat acute pain following hiatal hernia repair with general anesthesia.

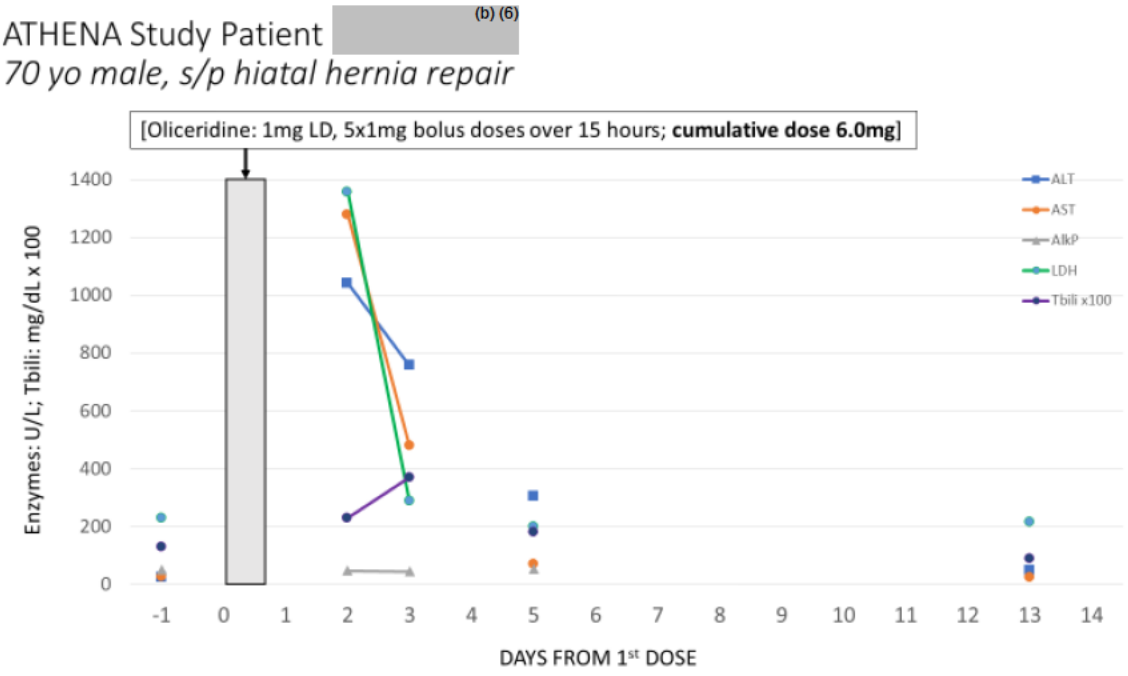
The patient received a loading dose of oliceridine (1 mg) on Relative Day 1 at 15:37 and subsequently received 5 bolus administrations of oliceridine 1 mg (for a cumulative dose of 6 mg) over the 15-hour Treatment Period.

A liver function test (LFT) time course plot for this patient is provided in Figure 44.

The patient experienced a high, clinically significant (by the investigator) ALT >26xULN (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 high but not clinically significant bilirubin >1xULN (2.3 mg/dL [normal range 0-1.5 mg/dL]). The ALT, AST and bilirubin values had been within the normal range at Baseline (25 and 27 U/L, and 1.3 mg/dL, respectively). On Relative Day 3, AST and ALT remained clinically significant by the investigator (758 and 480 U/L, respectively), bilirubin was high ≥2xULN (3.7 mg/dL) but not considered clinically significant by the investigator. By relative Day 5 the ALT, AST and bilirubin were 305 (clinically significant by the investigator), and 69 U/L, and 1.8 mg/dL, respectively. On Day 13 ALT continued to decline, remaining high ≥1xULN (49U/L) while AST and bilirubin were within normal range (23 U/L and 0.9 mg/dL, respectively) ALP remained within normal range during the study.

His relevant past medical history included coronary artery disease, dyslipidemia, hypertension, hypothyroidism, sleep apnea syndrome, and colon cancer. He received heparin, cefazolin, propofol, desflurane, ondansetron, and labetalol as relevant perioperative medications. Other concomitant medications included docusate, acetylsalicylic acid, metoprolol, levothyroxine, lisinopril, oxycodone, and pravastatin. Other than the laboratory AEs of hepatic enzyme increased (nonserious, moderate, unlikely related, resolved; no treatment was received) and blood LDH increased (1359 U/L on Day 2; nonserious, moderate, unlikely related, resolved; no treatment was received), no relevant clinical AEs were reported. On Day 13 Final ALT was ≥1xULN, and AST, ALP and total bilirubin values were within normal range.

Figure 44: Liver Enzymes in ATHENA Study Patient (b) (6)



Expert Hepatologist Panel Comments: Total dose of 6 mg is too small to cause sudden, severe liver necrosis. This is most consistent with a perioperative ischemic episode as is the very rapid resolution of injury as indicated by with serum aminotransferases falling at their serum half-lives.

Case 2: ATHENA Patient (b) (6) is a 54-year-old white male (105.4 kg, 181.6 cm) in the oliceridine >16 to 36 mg cumulative dose group. He was enrolled in the ATHENA study to treat acute pain following aortic arch repair with general anesthesia.

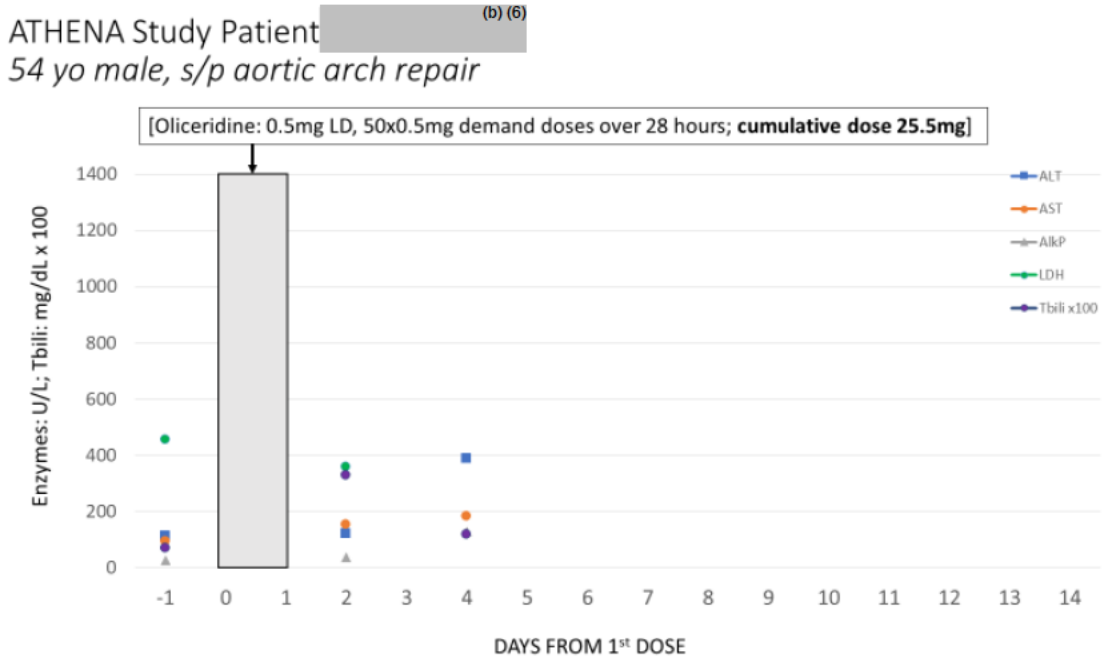
The patient received a loading dose of oliceridine (0.5 mg) on Relative Day 1 at 08:01 and subsequently self-administered 50 demand doses of oliceridine 0.5 mg (for a cumulative dose of 25.5 mg) over the 28-hour Treatment Period.

An LFT time course plot for this patient is provided in Figure 45.

The patient experienced abnormal, not clinically significant by the investigator ALT ≥1xULN (114 U/L [normal range: 0-59 U/L]), ALP (28 U/L [normal range: 40-130 U/L]) and AST ≥2xULN (95 U/L [normal range: 0-39 U/L]) during Baseline on Relative Day -1 while bilirubin was within normal range (0.7 mg/dL [normal range: 0-1.3 mg/dL]). On Relative Day 2, ALT and ALP were abnormal, not clinically significant by the investigator (123 and 39 U/L, respectively) while AST and bilirubin were high, clinically significant by the investigator (154 U/L, and 3.3 mg/dL, respectively). On Relative Day 4, ALT, ALP and AST remained high (389, 131 and 184

U/L, respectively [ALT and AST clinically significant by the investigator, ALP not clinically significant by the investigator), while bilirubin was within normal range (1.2 mg/dL). Additional laboratory results were not provided. His relevant past medical history included aortic coarctation, atrial fibrillation, atrial flutter, and hypertension. He received acetylsalicylic acid, atorvastatin, eplerenone, lisinopril, amlodipine, metoprolol, propofol, sevoflurane, cefazolin, vancomycin, heparin, amiodarone, famotidine, and as relevant perioperative medications. Of note, the patient had received a concomitant medication containing acetaminophen (paracetamol 650 mg QID [between Relative Day -1 and Day 3]). Other concomitant medications included docusate, furosemide, insulin, oxycodone, and oxygen. His lowest observed SBP was 85 mmHg and his lowest observed DBP was 49 mmHg. In addition to the TEAEs of ALT increased, AST increased, and hyperbilirubinemia (all nonserious, mild, and not related; no treatment received), he experienced the relevant clinical TEAEs of post procedural hemorrhage (nonserious, severe, not related, resolved; aminocalproic acid and red blood cells were administered as treatment), blood pressure decreased (nonserious, moderate, not related, resolved; no treatment received), metabolic acidosis (nonserious, moderate, not related, resolved; sodium bicarbonate administered as treatment), and hypokalemia (nonserious, moderate, not related, resolved; potassium chloride administered as treatment), all occurring on Day -1. No subsequent ALT, AST, or bilirubin values were reported after Day 4. This patient also experienced a TEAE leading to early discontinuation of QT prolongation (nonserious, moderate, unlikely related, resolving).

Figure 45: Liver Enzymes in ATHENA Study Patient (b) (6)



Expert Hepatologist Panel Comments: Elevations in aminotransferases are relatively modest and likely attributed to the perioperative complications and medications. Transient elevation in serum bilirubin is likely to reflect hemolysis and not liver dysfunction.

Case 3: ATHENA Patient (b) (6) is a 55-year-old white male. He experienced treatment-emergent SAEs of hepatic failure and renal failure (both severe, possibly related, resolved, required or prolonged hospitalization).

An LFT time course plot for this patient is provided in Figure 46.

His relevant medical history included hypertension, hypercholesterolemia, type II diabetes, hypothyroidism, left knee osteoarthritis, alcohol use consisting of "3-6 beers and 1-3 whiskeys daily for > 30 years" (admitted by the patient upon re-hospitalization for liver and kidney failure) and tobacco use. The patient had no prior history of hepatic disease or renal disease. His ongoing medications since 2015 included lisinopril, simvastatin, metformin, and levothyroxine.

On (b) (6), his screening laboratory tests included: blood urea nitrogen 16 mg/dL, creatinine 0.9 mg/dL, protein 7.5 g/dL, albumin 3.7 g/dL, total bilirubin 0.4 mg/dL, AST 27 U/L, ALT 54 U/L, alkaline phosphatase 83 U/L, LDH 164 U/L, hemoglobin 14.7 g/dL, and hematocrit 43.5%.

On (b) (6) at 13:41, the patient underwent total left knee arthroplasty. Perioperative medications included acetaminophen (1000 mg), celecoxib, dexamethasone, gabapentin, ropivacaine, bupivacaine, ketorolac intra-articular injection, fentanyl, propofol, midazolam, cefazolin, vancomycin, epinephrine, clonidine, warfarin, insulin lispro, ondansetron, docusate senna, lactated ringers, sodium chloride 0.9%, tranexamic acid, and oxygen. Post-operatively on (b) (6), the patient received a bolus dose of oliceridine (1.5 mg) at 00:13. The patient subsequently received 43 PCA doses of oliceridine (0.5 mg each; cumulative dose of 23 mg) until (b) (6) at 07:22 (approximately 30 hours) for a cumulative dose of 23 mg. Operative and post-operative periods were uneventful and the patient did not receive perioperative blood transfusions. No perioperative hypoperfusion event was reported.

On (b) (6), laboratory test results included: blood urea nitrogen 13 mg/dL, creatinine 1.0 mg/dL, protein 5.6 g/dL, albumin 2.8 g/dL, total bilirubin 0.3 mg/dL, AST 16 U/L, ALT 29 U/L, alkaline phosphatase 59 U/L, LDH 144 U/L, hemoglobin 9.0 g/dL, hematocrit 27.2%, and platelets 154 x 10^3/µL.

On (b) (6) the patient experienced nausea, was treated with ondansetron, and was subsequently discharged from the hospital. After discharge, the patient continued to experience "vomiting which worsened after going home" from the original hospitalization; on (b) (6), he presented to the ED with the chief complaint of nausea and vomiting. The patient denied using alcohol after discharge. ED laboratory test results included: BUN 31, creatinine 3.8, protein 6.5, albumin 2.9, total bilirubin 1.3, AST 16509, ALT 6845, alkaline phosphatase 94, hemoglobin 8.4, hematocrit 26.6, international normalized ratio (INR) 4.7, prothrombin time (PT) 53.8 and platelets 131; LDH not reported. A repeat AST and ALT result included: AST >21000 and ALT 8989. Hepatitis B surface antigen, Hep B C IgM, HIV-1 and HIV-2 were all nonreactive. Additional laboratory test results included: iron 327, ferritin >40000, CMV <390, blood toxicology ethanol < 3 and salicylate < 1.7 (reference ranges not known), haptoglobin 161,

ANA titer 1 <1.40 and acetaminophen level 3.9 (reference range not known). Hepatic ultrasound revealed hepatic steatosis. He was re-hospitalized on (b) (6).

Later on (b) (6), laboratory test results included alkaline phosphatase 126, AST 19018, ALT 7847, direct bilirubin 0.5, and total bilirubin 1.4. Hematology laboratory tests included platelets 91, PT 47.7, INR 4.2, and hemoglobin 6.7 and hematocrit 20.0, for which the patient was transfused. Additional laboratory test results included: C3 complement 27 and C4 complement < 2.0, ETOH level-negative and salicylate level-negative. On (b) (6), LDH was 5740 U/L.

On (b) (6), a liver biopsy was performed which demonstrated "massive centrilobular necrosis with cholestasis and increased iron deposition." On the same day, a renal ultrasound was obtained to rule out venous or arterial thrombosis; findings noted that "flow was seen in both kidneys, with no evidence of renal artery stenosis." LDH was 135 U/L.

On (b) (6), laboratory test results included BUN 78, creatinine 10.6, protein 5.2, albumin 2.3, total bilirubin 1.4, AST 678, ALT 2348, alkaline phosphatase 147, hemoglobin 9.7, hematocrit 29.7, INR 2.5, PT 28.8, and platelets 99.

On (b) (6) laboratory test results included BUN 74, creatinine 11.1, protein 5.3, albumin 2.1, total bilirubin 1.3, AST 111, ALT 1027, and alkaline phosphatase 121.

On (b) (6), laboratory test results included BUN 40, creatinine 7.7, protein 6.7, albumin 2.3, total bilirubin 1.25, AST 41, ALT 426, alkaline phosphatase 91, hemoglobin 9.6, hematocrit 29.4, and platelets 117. The patient underwent hemodialysis; the final dialysis occurred on (b) (6).

On (b) (6), the patient was discharged when his renal function began to improve after dialysis was stopped.

On (b) (6), the patient underwent nephrology consultation. At that visit, the patient reported slight nausea; this was considered to be not likely related to his renal status.

On (b) (6), the patient was tolerating food and liquids and improving, having had one episode of vomiting early that day, for which he declined treatment.

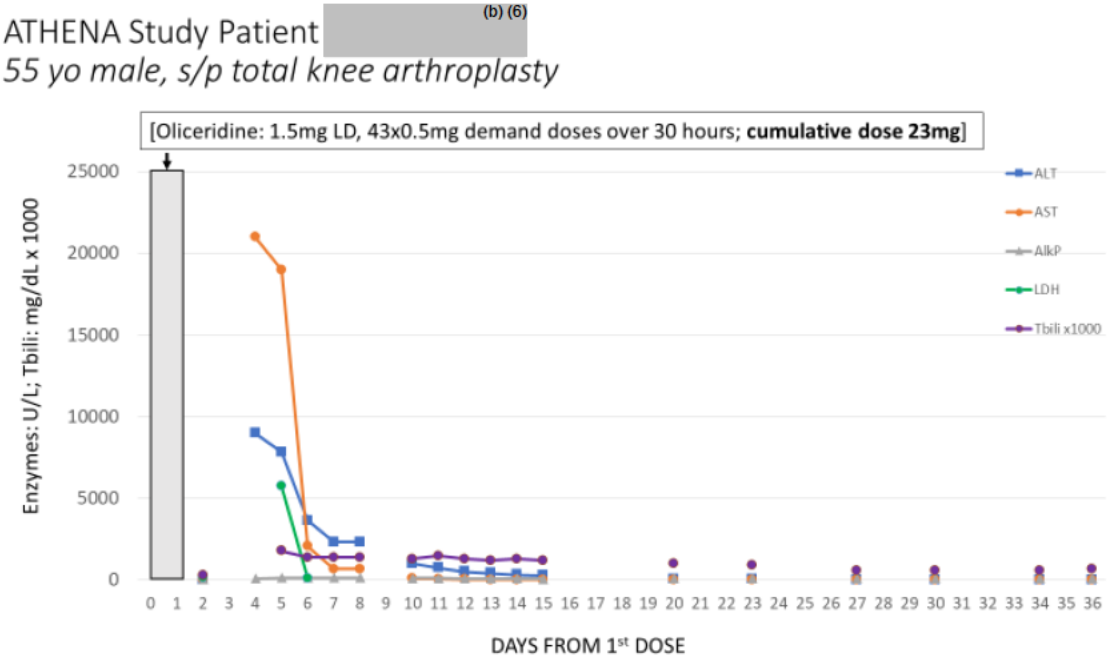
On (b) (6), the patient was doing well, with no further episodes of vomiting. Laboratory test results included: BUN 31, creatinine 1.89, bilirubin 0.6, AST 23 and ALT 30.

On (b) (6), laboratory test results included: BUN 30, creatinine 1.37, total bilirubin 0.6, ALT 27 and AST 21.

On (b) (6), the patient underwent follow-up nephrology consultation. His overall kidney function "was continuing to improve, with near full recovery expected." At this visit, the patient was being treated for a urinary tract infection.

As of (b) (6), the patient was recovering from the events of liver and kidney failure. The SAEs of hepatic failure and renal failure were considered to be unexpected.

Figure 46: Liver Enzymes in ATHENA Study Patient (b) (6)



Expert Hepatologist Panel Comments: Liver chemistries were unremarkable the day after the last dose of oliceridine when this drug should no longer be in the body (~3-hour serum half-life). The liver biopsy, towering elevations in serum aminotransferases, and rapid recovery are most consistent with an ischemic episode post-discharge likely related to blood loss (note hemoglobin falling to 6.7 g/L).

Case 4: CP130-2001 Patient (b) (6) (b) (6) in study listings) is a 32-year-old white female (83.4 kg, 171 cm) allocated to the oliceridine 2mg Q4hours treatment group, following bunionectomy surgery with regional anesthesia, who received a cumulative dose of 24 mg of oliceridine over the 48-hour Randomized Treatment Period. She received 7 doses of rescue pain medication (4 doses of acetaminophen 650 mg and 3 doses of ketorolac) between Relative Days 1 and 2.

An LFT time course plot for this patient is provided in Figure 47.

The patient experienced elevated levels of ALT ≥4xULN (160 U/L [normal range: 0-33 U/L]) and AST ≥1xULN (44 U/L [normal range: 14-34 U/L]) on Relative Day 3 while ALP was within normal range (67 U/L [normal range: 42-98 U/L]). ALT, ALP and AST had been normal at Screening (30, 59 and 28 U/L, respectively) ALT, ALP and AST were high at Follow-up on Relative Day 7 (1433, 144 and 676 U/L, respectively) and peaked on this day (≥43xULN,

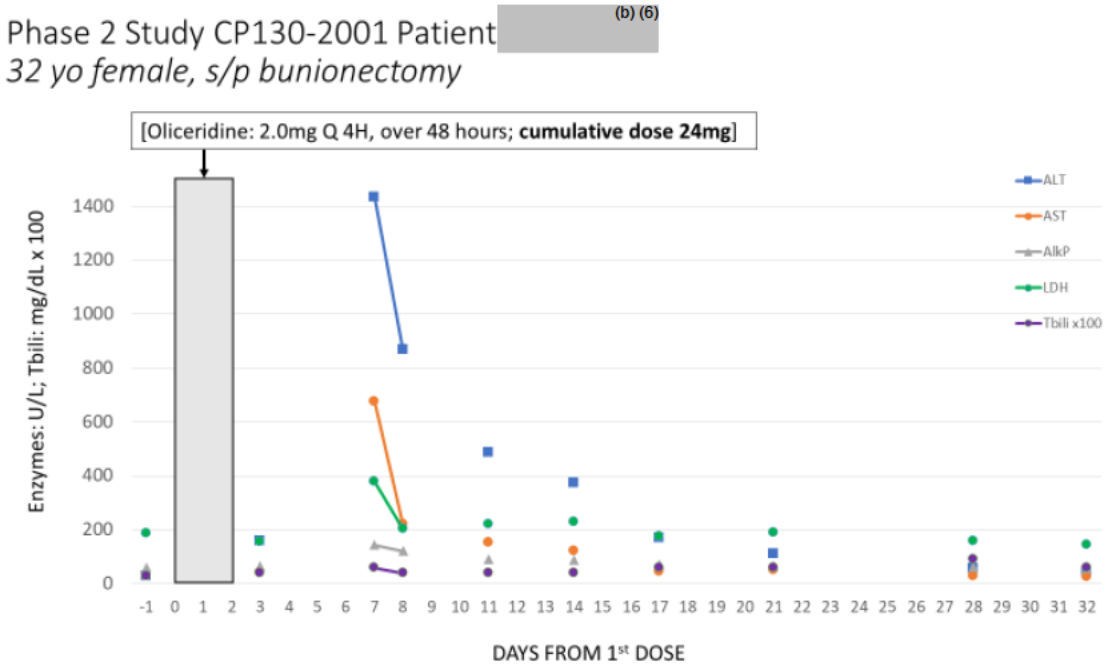
≥1xULN and ≥19xULN, respectively). ALP was within normal range on Relative Day 11 (92 U/L) while ALT and AST remained high (488 and 152 U/L, respectively). AST was within normal range on Relative Day 28 (30 U/L) while ALT remained high (58 U/L). ALT remained high at the final assessment on Relative Day 32 (45 U/L). Bilirubin remained within normal range during the study.

Screening hepatitis serology was negative for HBV Surface antigen and HCV antibody. Postbaseline hepatitis serology (on Relative Day 8) was negative for HAV antibody IgM, HBV core IgM antibody, HBV Surface antigen, and HCV antibody. HEV IgM antibody was not detected and Liver kidney microsomal type 1 antibody was <20. On Relative Day 32, Hepatitis C RNA was not detected.

Relevant past medical history included headaches, cholecystectomy and cholelithiasis.
Her prior medications included ibuprofen, thomapyrin N, midazolam, propofol, lidocaine, ropivacaine, cefazolin, mepivacaine, and Vicodin (1 tablet). Concomitant medications included cefalexin, ketorolac and paracetamol (a total dose of 3250 mg through Relative Day 3).

In addition to the TEAE hepatic enzyme increased (nonserious, severe, unrelated, resolved; no treatment received), she experienced the clinically relevant TEAE of nausea (nonserious, mild, possibly related, resolved; no treatment received) on Relative Day 4.

Figure 47: Liver Enzymes in Study CP130-2001 (b) (6)



Expert Hepatologist Panel Comments: Liver chemistries were unremarkable the day after the last dose of oliceridine when this drug should have been entirely excreted from the body. The towering elevations in serum aminotransferases and rapid recovery are most consistent with an ischemic episode although the cause of such an event is not evident.

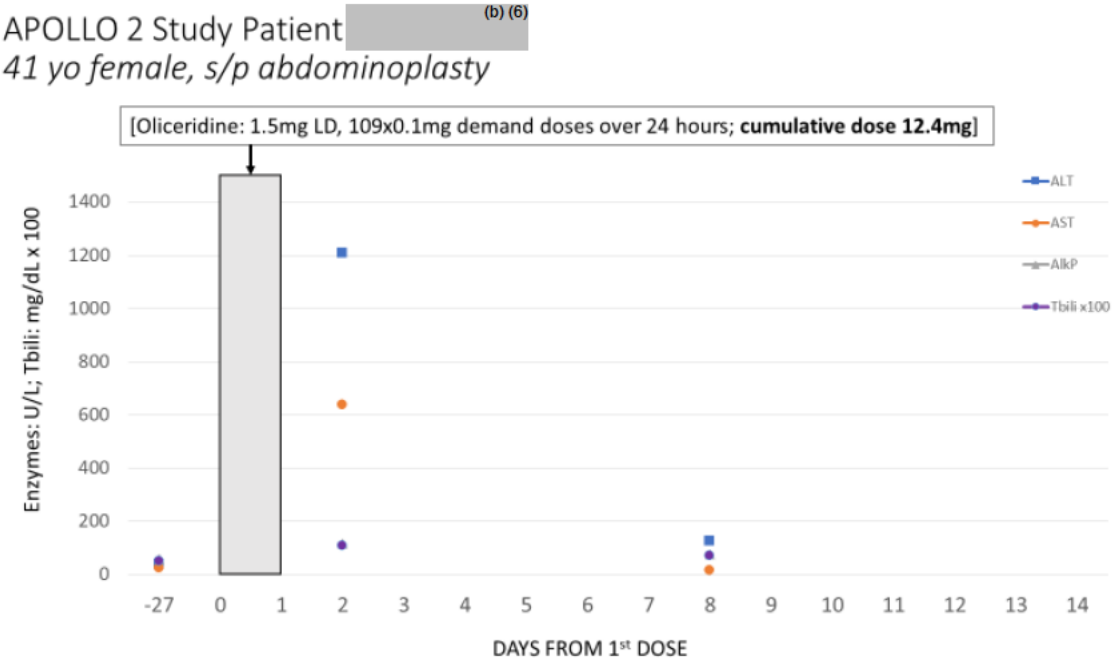
Case 5: APOLLO 2 Patient (b) (6) is a 41-year-old black female (97.9 kg, 170.1 cm) in the oliceridine 0.1 mg PCA treatment regimen following abdominoplasty surgery with general anesthesia.

The patient received a loading dose of oliceridine (1.5 mg) on Relative Day 1 at 15:05 and subsequently self-administered 109 demand doses of oliceridine 0.1 mg and received no supplemental doses of oliceridine (for a cumulative dose of 12.4 mg) prior to discontinuing study medication in the 24-hour Randomized Treatment Period due to lack of efficacy. The patient did not receive any rescue pain medication.

An LFT time course plot for this patient is provided in Figure 48.

The patient experienced a clinically significant (per the investigator) ALT ≥35xULN (1209 U/L [normal range: 6-34 U/L]), ALP (118 U/L [normal range: 31-106 U/L]), and AST ≥18xULN (638 U/L [normal range: 9-34 U/L]) during the Predischarge Period on Relative Day 2 that peaked on this day. Her relevant past medical history included cholecystectomy in 2005. Baseline HIV antibody, HBV surface antigen, and HCV antibody were negative. The ALT value had been high during the Screening Phase [39 U/L] and high-normal during the Presurgical Period [34 U/L), peaked at Day 2, declined but remained elevated, though no longer considered clinically significant by the investigator, at follow-up on Relative Day 8 (125 U/L). The ALP and AST values had been normal during the Screening Phase (61 and 24 U/L, respectively), and Presurgical Period (63 and 23 U/L, respectively), and returned to normal by follow-up on Relative Days 8 (76 and 16 U/L, respectively). Bilirubin remained within normal range during the study. She received propofol and sevoflurane as surgical medications. Of note, the patient had received a concomitant medication containing acetaminophen (paracetamol [total of 9000 mg between Relative Day 3 and 8]). Other than the TEAEs of AST increased, ALT increased, and blood ALP increased (all nonserious, mild, possibly related, resolved; action taken of laboratory sample redrawn), she experienced the relevant clinical TEAEs of nausea (nonserious, mild, probably related, resolved; ondansetron received as treatment) on Relative Day 1, vomiting (nonserious, mild, probably related, resolved; ginger ale and ondansetron received as treatment) on Relative Day 1 and 2, drug withdrawal syndrome (nonserious, mild, possibly related, resolved; no treatment was received) between Relative Day 2 and 17 (SOWS scale relevant responses: bones and muscles ache - a little; feel nauseous - a little; feel like vomiting - a little; have stomach cramps - a little), and headache (nonserious, moderate, resolved; con med received as treatment) on Relative Day 2, 3, and 4. On Relative Day 8, final ALT value was >3xULN but <5xULN while AST was within normal range. Screening hepatitis serology was negative for HBV Surface antigen and HCV antibody. No post-Baseline hepatitis serology was reported.

Figure 48: Liver Enzymes in APOLLO 2 Study Patient (b) (6)



Expert Hepatologist Panel Comments: Dose of oliceridine is low to cause toxicity. Relatively high elevations in serum aminotransferases and rapid recovery are consistent with a perioperative ischemic episode or possibly toxicity due to perioperative medications.

10.9.2 Liver Events among Patients Who Received Placebo or Morphine

Case 6: CP130-2001 Patient (b) (6) is a 38-year-old white female (72.3 kg, 161 cm) allocated to the placebo treatment group, following bunionectomy surgery with regional anesthesia. She received 6 doses of rescue pain medication (3 doses of acetaminophen 650 mg and 3 doses of ketorolac) between Relative Days 1 and 2.

An LFT time course plot for this patient is provided in Figure 49.

The patient experienced elevated levels of ALT (279 U/L [normal range: 0-33 U/L]), ALP (130 U/L [normal range: 42-98 U/L]), and AST (431 U/L [normal range: 14-34 U/L]) at Follow-up on Relative Day 7 that peaked on this day. ALT, ALP and AST had been normal at Screening on Relative Day -28 (20, 96 and 29 U/L, respectively), at re-screening on Relative Day -21 (18, 71 and 23 U/L, respectively) on Relative Day -1 (13, 71 and 17 U/L, respectively), and on Relative Day 3 (11, 70 and 20 U/L, respectively). ALT remained high on Relative Days 13 and 15 (57 and 38 U/L, respectively) and was within normal range on Relative Day 17 (30 U/L) while ALP and AST were in normal range on Relative Day 13 (89 and 26 U/L, respectively). Bilirubin remained within normal range during the study.

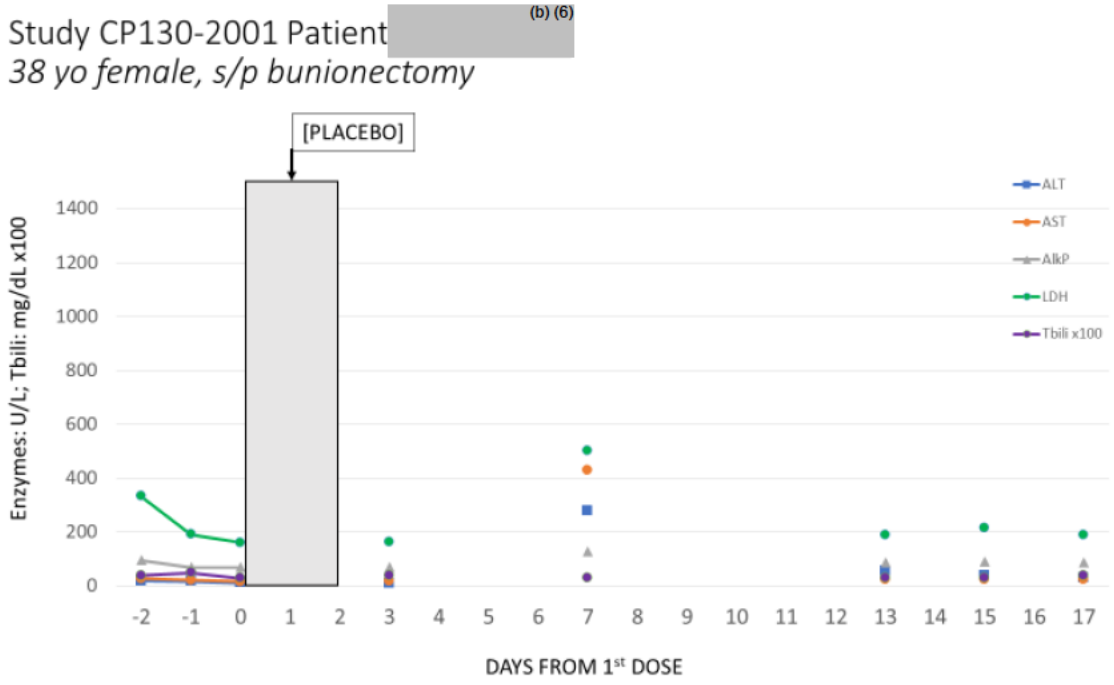
Screening hepatitis serology was negative for HBV Surface antigen and HCV antibody. Postbaseline hepatitis serology (on Relative Day 13) was negative for HAV antibody IgM, HBV core IgM antibody, and HBV Surface antigen. HEV IgM antibody was not detected and Liver kidney microsomal type 1 antibody was <20.

Relevant past medical history included headaches, cholecystectomy and cholecystitis.

Her prior medications included ibuprofen, midazolam, lidocaine, propofol, ropivacaine, cefazolin, and mepivacaine. Concomitant medications included cefalexin, ketorolac, oxycodone/acetaminophen (11 doses between Relative Days 3 and 6) and paracetamol (a total of 1950 mg through Relative Day 2).

In addition to the TEAE of hepatic enzyme increased (nonserious, moderate, unlikely related, resolved; no treatment received), there were no clinically relevant TEAEs reported.

Figure 49: Liver Enzymes in Study CP130-2001 Patient (b) (6)



Expert Hepatologist Panel Comments: Delayed rise in serum aminotransferases is similar to events observed in oliceridine-treated subjects and supports a background incidence of such liver events.

Case 7: APOLLO 1 Patien (b) (6) is a 27-year-old female (84.4 kg, 162.5 cm) allocated to the morphine PCA treatment regimen following bunionectomy surgery with regional anesthesia. The patient received a loading dose of morphine (4 mg) on Relative Day 1 at 04:28 and subsequently self-administered 246 demand doses of morphine 1 mg and received 9 supplemental doses of morphine 2 mg over the 48-hour Randomized Treatment Period (for a cumulative dose of 268 mg). The patient received a total of three doses of rescue pain medication (etodolac 200 mg PO), one at 21:08 on Relative Day 1 and one at 05:57 and 20:47 on Relative Day 2.

An LFT time course plot for this patient is provided in Figure 50.

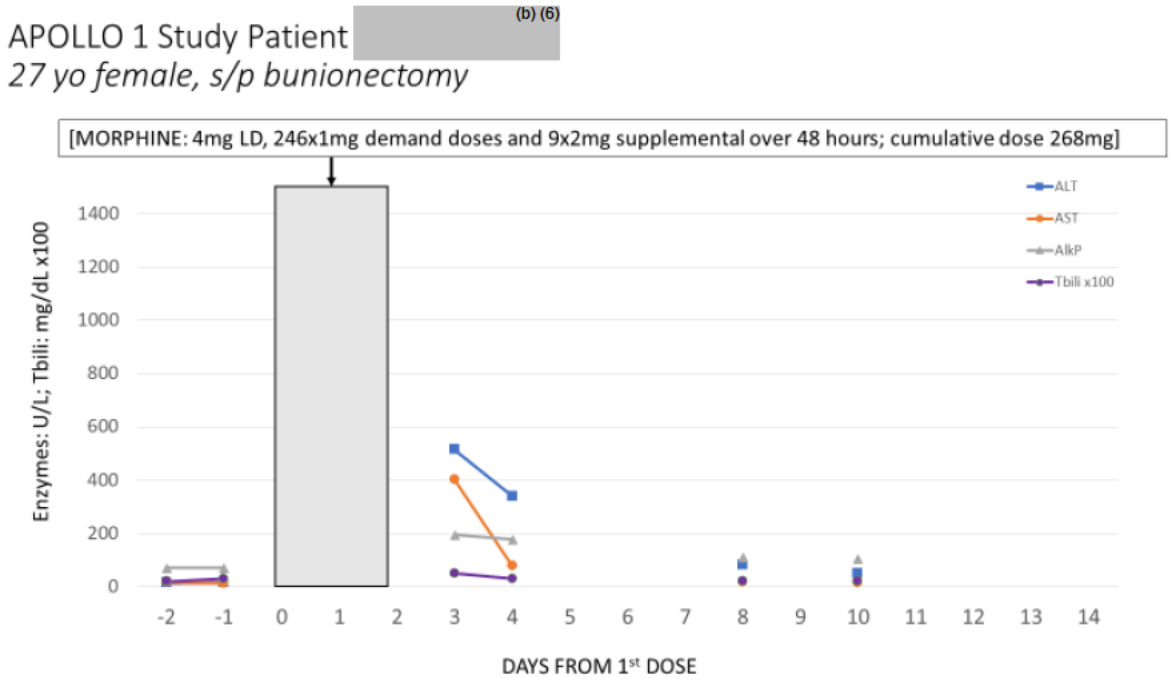
The patient experienced a clinically significant (as assessed by the investigator) ALT ≥15xULN (515 U/L [normal range: 6-34 U/L]), ALP ≥1xULN (195 U/L [normal range: 31-106 U/L]), and

AST ≥11xULN (401 U/L [normal range: 9-34 U/L]), with normal bilirubin levels during the Predischarge Period on Relative Day 3. The patient had a TEAE of transaminases increased reported on the same day. The TEAE was nonserious, severe, possibly related, and resolved; no treatment was received. The ALT, ALP and AST values had been within the normal range at the Screening Phase (14, 71, and 17 U/L, respectively) and Presurgical Period (15, 70, and 12 U/L, respectively), however they remained high on Relative Day 4 (339, 177, and 78 U/L, respectively), with ALT and AST elevations declining but still clinically significant as assessed by the investigator. At follow-up on Relative Day 8, ALT (80 U/L) and ALP (111 U/L) remained high, with AST (17 U/L) within the normal range. The ALT values continued to decline towards the normal range on Relative Day 10 (49 U/L [≥1xULN]), with both ALP and AST within the normal range by this time (105 U/L and 14 U/L, respectively).

Bilirubin remained within normal range at all time points during the study. Screening hepatitis serology and post-baseline measurements (on Relative Day 4) were negative for HBV Surface antigen and HCV antibody.

Of note, the patient received concomitant medication containing acetaminophen (verbatim percocet [5/325 mg]: one dose on Relative Day 3 and one dose on Relative Day 4). Other concomitant medications included oxycodone and ibuprofen. Relevant medical history included nausea, vomiting, gastric bypass surgery, ovarian cyst, asthma, and ovarian cystectomy.

Figure 50: Liver Enzymes in APOLLO 1 Study Patient (b) (6)



Expert Hepatologist Panel Comments: Early rise in serum aminotransferases similar to that observed in oliceridine-treated subjects supports a background incidence of such liver events.