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Monograph

Oliceridine, a G protein-selective ligand at the μ-opioid receptor, for the management of moderate to severe acute pain

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Summary

Oliceridine is a next-generation investigational intravenous opioid that is a G protein-selective agonist at the μ-opioid receptor. The G protein selectivity of this compound results in potent analgesia with substantially reduced recruitment of β-arrestin, a signaling pathway associated with opioid-related adverse events. In randomized, placebo- and active-controlled clinical studies, use of oliceridine for the management of moderate to severe acute pain provided potent analgesic effect superior to that observed with placebo, with lower incidence of adverse events, including respiratory events and gastrointestinal events of nausea and vomiting, compared with morphine. Here, we provide a review of the preclinical and clinical data of intravenous oliceridine, a selective agonist, which has the potential to offer a wider therapeutic window than conventional opioids.

Key words: Oliceridine – Opioid analgesics – μ-Opioid receptor agonists – Opioid-related adverse events – Breakthrough pain – Acute pain

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Background

Acute pain following surgery or trauma is a normal physiological response to tissue insult or injury (1, 2). The prevalence of acute postoperative pain reported varies depending on the type of surgery, anesthesia used and time of data collection, but a U.S. national survey reported a rate as high as 86%, with 75% of patients reporting moderate to severe pain during the immediate postoperative period (3). Likewise, acute pain in prehospital emergency medicine is reported to affect 48% of patients, with at least 71% of these patients reporting moderate to severe pain (4).

Inadequately managed acute pain is associated with negative clinical outcomes, including prolonged hospitalization, increased morbidity with impaired functional recovery and delayed mobilization, and potential development of a chronic pain state requiring prolonged use of analgesics (2, 5-7). These negative clinical outcomes also have a significant health economic impact, with a considerable increase in direct costs resulting from excess healthcare resource utilizations, as well as increases in indirect societal costs due to reduced patient functionality and productivity (2). Thus, adequate management of postoperative pain is an important aspect of patient recovery. Despite this, treatment of moderate to severe acute pain remains a challenge (5, 8).

In the clinical management of moderate to severe acute pain, opioids remain an important component of pharmacotherapeutic planning (5, 9). However, adverse events (AEs) associated with opioids can limit their use and thereby impede their clinical effectiveness (5, 10). In addition, when prescribing opioids, clinicians must consider the potential for misuse or development of opioid use disorder in patients (10).

Common opioid-related adverse events (ORAEs) in the acute setting are respiratory events, with a recent study reporting occurrence among 49% of patients (including severe acute respiratory failure in 20% and use of ventilator in 48% of these patients) (9). Other common events were gastrointestinal effects, 23% (including paralytic ileus/postoperative ileus nausea/vomiting and constipation); central nervous system (CNS) effects, 7% (including delirium or confusion of moderate severity); bradycardia, 48%; or pruritus/dermatitis, 25% (9). Urinary retention as a complication of opioid use as a postoperative analgesic has been reported in 3% to as high as 17% of patients (5, 11). Renal toxicity associated with opioids appears in the context of the use of higher than needed doses (e.g., in patients with renal dysfunction) or preexisting dehydration (12). In patients with preexisting impairment of renal function, the accumulation of both drug and active metabolites can result in unwanted AEs, so that most opioids require careful dose adjustment in renally impaired patients (12, 13). Considering the ORAEs that limit the clinical utility of opioids for moderate to severe pain, there is a significant need for analgesic regimens that improve safety and tolerability while maintaining efficacy (5).

In an effort to reduce the potential AEs associated with opioids, a joint task force of the American Pain Society and American Academy of Pain Medicine put forth guidelines focusing on the judicious use of opioids by introducing multimodal analgesia (14, 15). Inclusion of analgesics with different mechanisms of action, in addition to opioids, with resultant additive and/or synergistic effects while potentially reducing side effects, is the goal of the "multimodal" approach (16).

Measures to enhance the recovery phase after surgery gave rise to the concept of "enhanced recovery after surgery" (ERAS), which is a protocol-driven clinical algorithm that utilizes multimodal evidence-based strategies at every step of preoperative, perioperative and postoperative care (17). The use of opioids in many ERAS protocols is usually carefully circumscribed only for use in managing "breakthrough" pain on an as-needed basis. There is emerging evidence suggesting that the implementation of ERAS protocols may lead to a reduction in unnecessary opioid use (14, 17). While opioids will likely remain an important component of acute pain control, the use of ERAS pathways will combine quality improvement techniques to improve the safe use of opioids as part of multimodal analgesia (9). It is hoped that this will contribute positively to efforts to address the opioid crisis.

Other novel strategies to reduce ORAEs are the development of next-generation opioids that selectively

bind to receptor sites to provide an analgesic effect while reducing AEs associated with μ-receptor agonism (18). Conventional opioid agonists bind to the μ-opioid receptor (MOR), a type of G protein-coupled receptor, leading to G protein post-receptor signaling and analgesia, but they also activate the β-arrestin pathway, leading to unwanted effects including respiratory depression and gastrointestinal-related effects (19). Opioids that selectively confer preferential activation through the G protein signaling pathway over the β-arrestin pathway, or providing "functional selectivity" (biased agonism), offer potential for full analgesic effects with less AEs (20, 21).

Oliceridine (also referred to as TRV-130; Trevena Inc., Chesterbrook, Pennsylvania, U.S.) is the first of a new class of MOR ligands that are pharmacologically biased towards preferential G protein post-receptor signaling, with markedly reduced β-arrestin post-receptor activation (22, 23). In this article we review the development of oliceridine for the management of moderate to severe acute pain in hospital settings.

Nonclinical Pharmacology

Mechanism of action

Oliceridine is a novel, small-molecule, G protein-biased (or selective) ligand targeting the MOR (22, 24-26). Oliceridine is structurally distinct from natural opiates (e.g., morphine) or its semi-synthetic derivatives (e.g., hydromorphone) (Fig. 1).

Oliceridine potently stimulates G protein signaling downstream from binding to the MOR but is much less effective at recruiting β-arrestin 2 than traditional opioids such as morphine, fentanyl or hydromorphone (Fig. 2). Due to its preferential activation of G protein signaling over β-arrestin 2 recruitment, oliceridine would be predicted to provide rapid systemic analgesic effect while attenuating the ORAEs (21, 22, 27, 28), suggesting an improved therapeutic window compared with conventional, parenterally administered opioids such as fentanyl and hydromorphone.

Oliceridine has shown remarkable selectivity for the MOR with approximately 400-fold preference for MOR over κ- and δ-opioid receptors (morphine is only 10-fold selective for the MOR vs. κ- and δ-opioid receptors) (22, 29). In human embryonic kidney (HEK)-293 cells, oliceridine had ~3 times the preference for G protein signaling over β-arrestin recruitment, stimulating around 14% of the β-arrestin recruitment observed with morphine and correlating with minimal MOR internalization (22).

Efficacy in animal in vivo/in vitro models

In mouse and rat analgesic models, oliceridine was 3-10 times more potent in its analgesic efficacy than morphine (22). In a tail-flick assay, oliceridine showed a 4-fold more potent analgesic effect than morphine, with less tolerance and opioid-induced hyperalgesia than morphine after 4 days of ascending-dose administration (30). A recent study in rodents reported robust antinociception after acute treatment with oliceridine that was prolonged during a 3-day repeated administration, indicative of lack of tolerance development to the analgesic effect (31).

In mice models that examined the effects of oliceridine versus morphine on recovery from tibial fracture, oliceridine did not worsen allodynia or gait disturbances after tibial fractures, while morphine appeared to significantly impair the recovery from nociceptive sensitization and gait after tibial fracture (30).

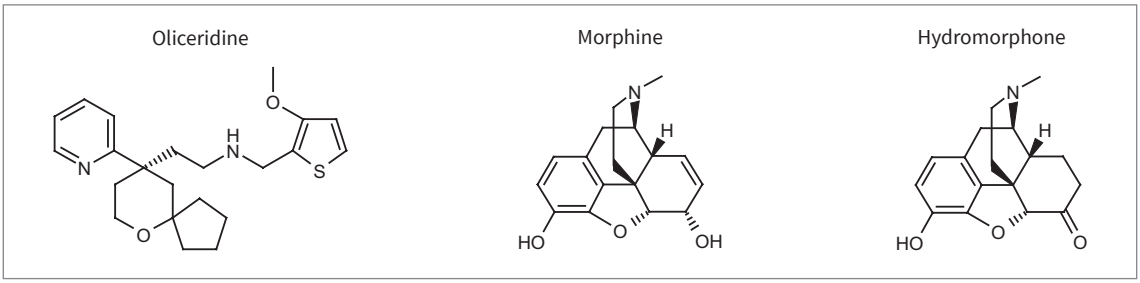

Figure 1. Structure of oliceridine (in comparison with conventional opioids).

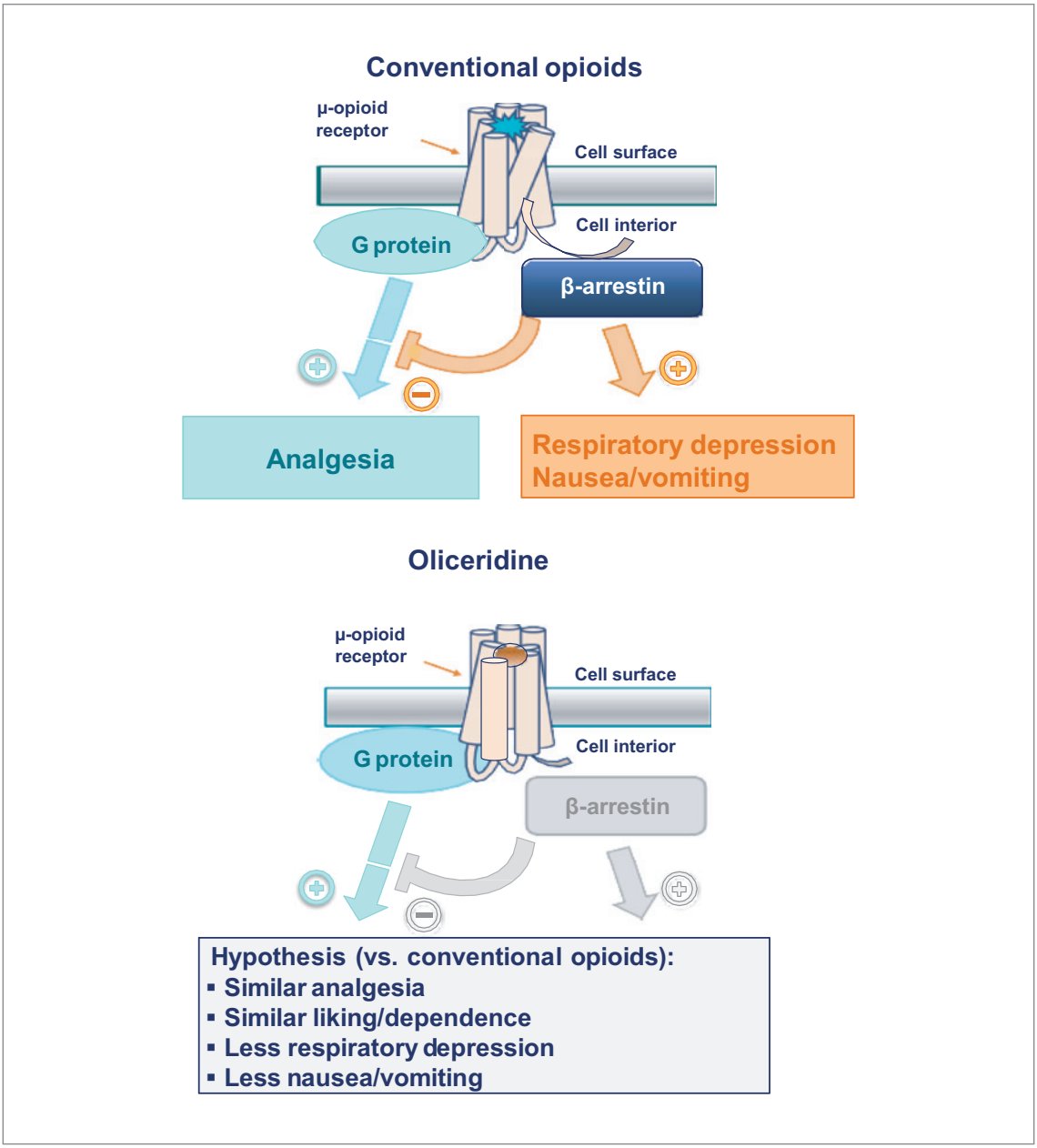

Figure 2. Mechanism of action of oliceridine. Oliceridine selectively binds to the G protein, with less recruitment of β-arrestin (23).

Naloxone rapidly and completely reversed oliceridine-induced analgesia in a mouse hot plate assay, suggesting that its effects are solely mediated by MOR agonism (22). In vitro studies also showed that naloxone shifted the EC_{50} of oliceridine-evoked G protein coupling in a concentration-dependent manner, further confirming the competitive mechanism of action (22).

Safety in animal models

In mice, oliceridine caused less constipation, less gastrointestinal dysfunction and less respiratory

depression than morphine at single equianalgesic doses (22). Respiratory depression (pCO_2 > 50 mmHg) was observed with morphine at doses 4-fold above the analgesic dose while oliceridine produced no changes at 8-fold over the analgesic dose (22), demonstrating an increased therapeutic window for analgesia versus respiratory depression.

However, a study utilizing repeated administration of oliceridine showed constipating effects in mice and abuse potential similar to that of morphine and other MOR agonists (31). Signs of naloxone-induced withdrawal were similar in oliceridine- and morphine-treated mice, but oliceridine produced less conditioned place preference at equianalgesic doses (30). A recent study investigated the abuse potential of oliceridine, assessing the relative reinforcing effects of oliceridine in comparison with oxycodone in rats self-administering the drugs under a progressive-ratio schedule of reinforcement (32). The findings from this study showed that both oxycodone and oliceridine functioned as reinforcers in a dose-dependent manner. In addition, oliceridine and oxycodone were equipotent and equally effective in self-administration and thermal antinociception, suggesting that G protein selectivity does not necessarily reduce abuse potential (32).

Data from nonclinical studies indicate that oliceridine has little or no potential to produce significant QT prolongation, Torsades de Pointes, or other abnormal electrocardiogram (ECG) waveforms or arrhythmias.

Continuous infusion of oliceridine for up to 28 days in rats and 14 days in monkeys produced no unique oliceridine-induced toxicity other than prototypical changes seen after opioid administration (decreased food consumption and body weight, reduced activity, mean blood pressure and body temperature, and stereotypic behavioral changes). Oliceridine plasma concentrations in these studies were 9 times and 32 times the expected human exposure at the maximum recommended dose of 27 mg/day (33).

Oliceridine was tested for genotoxicity in a comprehensive battery of in vitro and in vivo genetic toxicity assays. Results from these studies identified no definitive signs of mutagenicity or clastogenicity (33). Findings in reproductive toxicology studies were consistent with the known pharmacological effects of opioids.

Clinical Pharmacokinetics and Metabolism

Oliceridine exhibited a half-life ($t_{½}$) of approximately 1.5 to 3 hours when administered intravenously over 1 minute to 1 hour. The increase in exposure (C_{max} and AUC) was slightly greater than proportional as the dose was increased from 0.15 to 7 mg, deviating from linearity by approximately 15%. Commensurate with this increase in half-life, when administered intravenously over 1 hour oliceridine clearance decreased with increasing dosing from 47.2 L/h at a dose of 0.25 mg to 34 L/h at a dose of 7 mg (33).

Oliceridine is extensively hepatically metabolized by both cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4, with each enzyme contributing equally. Approximately 7-10% of Caucasians and 2-7% of African-Americans have one of several CYP2D6 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 (34). In PMs, the clearance of oliceridine is reduced by about 50% as compared with EMs. Since oliceridine, like most opioids used for the treatment of acute pain, is given “as needed”, with no fixed dose or dosing interval, this reduction in clearance is not expected to have any clinical significance.

A human ^{14}C mass balance and excretion study showed that oliceridine is extensively metabolized, with two major metabolites, M22 and TRV0109662, which are pharmacologically inactive. Renal clearance is a minor pathway (2.2-5.1%) of the total clearance for elimination of oliceridine. There is no clinically significant difference between men and women in the disposition of oliceridine. As oliceridine is hepatically metabolized, it is unlikely that its pharmacokinetics would be significantly affected by age (33).

In patients with mild to moderate hepatic impairment, the peak concentration was similar to that

seen in individuals with normal hepatic function. However, volume of distribution (V_z) and $t_{½}$ increased with severity of hepatic impairment, although clearance was within the range of control subjects (35). In patients with end-stage renal disease, the pharmacokinetics of oliceridine was similar to that observed in healthy individuals (35).

Pharmacodynamics

Oliceridine elicited marked pupil constriction (miosis) lasting for 2 hours after discontinuation of infusion. Furthermore, there was a strong correlation between dose-and exposure-related pupil constriction, confirming central compartment of MOR activity (36).

Drug Interactions

There are no clinically significant drug interactions specific to oliceridine or its metabolites. Since 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. These data suggest that patients on concomitant medications known to inhibit the CYP2D6 enzyme (e.g., paroxetine, fluoxetine, quinidine, bupropion) will have a similar reduction in oliceridine clearance. Likewise, administration of itraconazole (a strong CYP3A4 inhibitor) in CYP2D6 PMs resulted in an additional 44% reduction in oliceridine clearance. Oliceridine does not inhibit any CYP enzymes to any clinically significant extent, and thus is not expected to cause any drug interactions (33).

A comparison between oliceridine and conventional intravenous opioids is shown in Table I.

Dosing Considerations

Patients receiving strong CYP3A4 inhibitors (e.g., clarithromycin, indinavir, itraconazole, ritonavir, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole) or CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion), or patients who are CYP2D6 PMs, may require less frequent dosing; however, no initial dose adjustments should be required (33).

As discussed earlier, in patients with mild to moderate hepatic impairment, no adjustment of the initial dose of oliceridine is needed (35); however, these patients will likely require fewer doses. Oliceridine

Table I. *Comparison of intravenous oliceridine to conventional intravenous opioids.*

Attributes	Oliceridine	Morphine	Hydromorphone	Fentanyl
β-Arrestin recruitment (max. response compared to morphine) (22)	14%	Reference (100%)	89%	478%
Onset of first perceptible effect	1-2 min (33)	5-10 min	~5 min	Immediate
Peak effect	0.1-0.2 hours (33)	0.5-10 hours	0.17-0.33 hours	ND
Half-life	1.5-3 hours (33)	2-4 hours	2-3 hours	2-4 hours
Duration of effect	1-3 hours (33)	3-4 hours (48)	3-4 hours	0.5-1 hours
Potency (48)	1 mg	5 mg	0.75 mg	0.1 mg
Metabolism	Hepatic CYP3A4:CYP2D6	Hepatic glucuronidation M6G: renal (49)	Hepatic glucuronidation	Hepatic CYP3A4
Active metabolites	No	Yes (M6G)	No	No
Dose adjustment in renal impairment	No	Yes	Yes	No
Dose adjustment in hepatic impairment	Mild/moderate: no Severe: yes	Yes	Yes	Yes

CYP, cytochrome P450; M6G, morphine-6-glucoronide; ND, no data.
Source except where noted: Opioid Analgesics: Adult Pharmacokinetics. Facts and Comparisons [database online], 2017.

should be used with caution in patients with severe hepatic impairment. Dosing in these patients should be initiated with a reduced dose, and subsequent doses should be administered only after a careful review of the patient's severity of pain and overall clinical status. In patients with renal dysfunction as well as with end-stage renal disease, there was no clinically significant change in oliceridine clearance versus healthy, age- and sex-matched control subjects. Thus, no dose adjustment is needed in patients with renal impairment.

There is no significant difference in oliceridine clearance in younger patients as compared to the elderly (≥ 65 years), and the recommended dosing for elderly patients is the same as for younger adult patients; however, considerations for individualized dosing should be applied and reassessed frequently. Oliceridine has not been studied in patients younger than 18 years (data on file).

The effects of oliceridine have not been evaluated in pregnant women or during lactation. Use in these cases is justified only if the potential benefit outweighs the potential risk to the fetus or baby (33).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared with the use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risks with the concomitant use of other CNS-depressant drugs with oliceridine. Oliceridine should not be administered concurrently with benzodiazepines or other CNS depressants, or serotonergic drugs. If required, caution is advised. Oliceridine should also not be administered to patients with acute or severe bronchial asthma, unless in a setting with monitoring and resuscitative equipment (data on file).

Clinical Experience

Phase I studies

During the development of oliceridine, a total of 11 phase I studies were conducted. A total of 318 healthy subjects have been exposed to single and multiple intravenous doses of oliceridine in phase I studies.

In addition to evaluating the pharmacokinetics and pharmacodynamics of oliceridine in healthy subjects and those with hepatic or renal impairment, as well as potential drug interactions (findings discussed in the section of clinical pharmacokinetics), phase I studies evaluated AEs in special population healthy subjects (n = 97), including oliceridine's effect on the QTc interval, its effect on respiratory depression compared to morphine, and a drug abuse liability assessment in nonaddicted recreational drug users.

In a dose-ranging safety and tolerability study in 30 healthy volunteers, the most commonly reported AEs included dizziness, nausea, vomiting, somnolence, pruritus, feeling hot, and headache of mild to moderate intensity. Nausea and vomiting were considered dose-limiting at a (supratherapeutic) 7-mg dose with 9 subjects experiencing severe nausea (vs. 7 subjects in the morphine group), but no subjects experienced nausea with a single intravenous 1.5-mg dose, and only 1 subject receiving the 3-mg dose experienced nausea (23, 36). In this study, oliceridine at all doses (including the equianalgesic doses of 3 and 4.5 mg) had statistically less reduction in parameters of respiratory drive than morphine at 10 mg (−15.9 for morphine vs. −7.3, −7.6 and −9.4 h·min/L, $P < 0.05$) (23).

In a study of thorough QT (tQT) in 58 healthy volunteers, there was no evidence of any clinically significant effect of oliceridine on cardiac repolarization at the highest proposed clinical dose of 3 mg (33). However, at the supratherapeutic dose of 6 mg, there was a minor, transient effect, with the upper one-sided 95% confidence interval of the mean placebo-adjusted change from baseline in QTcF exceeding 10 ms at 2.5 min, 1 hour and 2 hours after dosing. An analysis of the relationship between plasma concentrations of oliceridine and cardiac repolarization showed no evidence of a concentration-mediated effect (33). An additional tQT multidose study in healthy volunteers has been recently completed.

In assessing abuse liability, the dose-ranging safety and tolerability study in 30 healthy volunteers assessed ORAEs using the Drug Effects Questionnaire (DEQ). This consisted of a series of subject self-administered visual analog scales, measuring a range of subjective opioid CNS effects, including

"liking" (23). Oliceridine at equianalgesic doses of 3 mg produced a similar DEQ CNS effect as morphine 10 mg (23). Subsequently, in a single-dose intravenous, randomized, double-blind, placebo- and active-controlled crossover study that evaluated the abuse potential of oliceridine compared to morphine, equianalgesic doses of oliceridine (2 and 4 mg), compared with morphine (10 and 20 mg), had similar abuse potential (33). If approved, oliceridine is expected to be a schedule II-controlled substance under the Controlled Substances Act. Oliceridine is intended for short-term intravenous use in the hospital or ambulatory surgical center, for the management of moderate to severe acute pain and will be administered only by trained health professionals.

Phase II studies

Two phase II studies evaluated the efficacy and safety of various doses and dosing regimens of oliceridine compared to placebo and morphine in two surgical models of nonvisceral and visceral acute pain [bunionectomy (37) and abdominoplasty (38)].

The first of these studies was a phase IIa randomized, double-blind, adaptive-design, fixed-dose study in patients experiencing postoperative pain after bunionectomy, a hard-tissue postoperative pain model (ClinicalTrials.gov Identifier NCT02100748). It was designed to evaluate the analgesic efficacy of intravenous oliceridine compared with placebo (primary objective) and morphine (secondary objective) (37).

During the pilot phase of the study, 144 patients experiencing moderate to severe acute pain (numeric rating scale [NRS] ≥ 4) after bunionectomy were enrolled and 141 were treated with oliceridine 1, 2, 3 or 4 mg i.v. every 4 hours (q4h); placebo; or morphine 4 mg i.v. q4h; 134 patients (95%) completed the study. Although oliceridine at doses of 3 and 4 mg produced significant analgesia during the first 12 hours, the q4h dosing regimen resulted in loss of analgesia between doses, and the primary endpoint of time-weighted average change from baseline in pain NRS scores over 48 hours was not met. Subsequently, 195 patients were randomized to receive double-blind oliceridine 0.5, 1, 2 or 3 mg i.v. every 3 hours (q3h); placebo; or morphine 4 mg i.v. q4h. Oliceridine 2 and 3 mg (administered q3h) as well as morphine 4 mg (administered q4h) met the primary endpoint, with significantly greater reductions in NRS score than placebo over 48 hours ($P < 0.005$). Oliceridine 2 and 3 mg produced significantly greater categorical pain relief than morphine ($P < 0.005$) after the first dose, with meaningful pain relief occurring in less than 5 minutes. The proportion of patients achieving meaningful pain relief increased with higher doses of oliceridine and was 97% with oliceridine 3 mg versus 56% with morphine and 36% with placebo. No serious AEs were reported in either phase of the study (37).

Most frequently reported AEs were typical ORAEs, including nausea, dizziness, headache and vomiting in all active treatment groups. Dose regimens were fixed with no reductions or missed doses allowed. If a reduction was needed, or a dose was missed, the patient was required to discontinue from the study. Despite this, only 5 patients discontinued oliceridine due to AEs (hypotension [4, graded mild to moderate]; tachycardia [1, mild]) (37).

The second phase II study was a two-part phase IIb randomized, double-blind study, using patient-controlled analgesia (PCA). This study evaluated the efficacy, safety and tolerability of oliceridine compared with morphine and placebo in patients with moderate to severe pain following abdominoplasty, a soft-tissue (visceral) pain model (NCT02335294) (38). In each part of the study, eligible patients with moderate or severe pain, as indicated by a score of ≥ 5 on an 11-point NRS and by report of moderate or severe pain on a 4-point categorical rating scale (with categories of none, mild, moderate or severe), were randomized to postoperative analgesic regimens of intravenous oliceridine, morphine or volume-matched placebo, in a 2:2:1 ratio, within 4 hours after the end of surgery. In stage 1, the oliceridine regimen consisted of two 0.75-mg loading doses separated by 10 minutes, followed by 0.10-mg demand doses. In stage 2, following interim analysis, the oliceridine demand dose was increased from 0.10 to 0.35 mg. The morphine treatment regimen consisted of two 2-mg loading doses separated by 10 minutes, followed by 1-mg demand doses in both stages.

An important component of this study was to evaluate the comparative respiratory safety profile of

oliceridine as compared to an equianalgesic dose of morphine. In this study, a hypoventilation event was defined by any clinically apparent and persistent decreased respiratory rate, respiratory effort or oxygen saturation, as judged by an anesthesiologist blinded to treatment. Upon determining that a hypoventilation event was occurring, the clinician then either took away the demand dosing from the patient until the event was resolved, or discontinued the patient permanently from randomized treatment, based on clinical judgement (38).

Oliceridine 0.1- and 0.35-mg demand dose regimens and morphine 1-mg demand doses had similar reductions in pain scores that were significantly different as compared with placebo (2.3 and 2.1 points, respectively, $P = 0.0001$ and $P = 0.0005$ vs. placebo for oliceridine groups; and 2.1 points, $P < 0.0001$ vs. placebo for morphine regimen). The time to meaningful pain relief, per the stopwatch method, was numerically shorter for the oliceridine 0.35-mg regimen (0.3 hours) than with morphine (1.0 hours). The use of rescue analgesics (ibuprofen 400 mg orally every 6 hours as needed [p.r.n.] as first-line and oxycodone 5 mg orally every 2 hours p.r.n. as second-line), although similar in the active groups, was higher, as expected, in the placebo group (31% with oliceridine 0.1-mg regimen, 21% with oliceridine 0.35-mg regimen and 25% with morphine, compared with 64% with placebo; $P < 0.0005$ vs. placebo) (38).

AEs associated with oliceridine were largely opioid-related, and nausea, vomiting and headache were the most frequent events. Incidences of nausea and vomiting were lower with both demand dose regimens of oliceridine, 0.1 mg (nausea: 41%, vomiting: 15%) and 0.35 mg (nausea: 46%, vomiting: 15%), than with morphine (nausea: 72%, vomiting: 42%; $P < 0.01$ for both oliceridine demand dose regimens vs. morphine). Importantly, respiratory events (hypoventilation and respiratory depression) were also lower with both oliceridine regimens (0.1-mg demand dose: 15%, 0.35-mg demand dose: 31%) versus morphine (53%, $P < 0.05$ for both oliceridine regimens vs. morphine) (38).

The findings from these phase II studies thus provided additional evidence that the differentiated pharmacology of oliceridine could be expected to attenuate the incidence of ORAEs compared with equianalgesic doses of conventional intravenous opioids.

Phase III studies

The phase III programs were designed to meet the regulatory requirements and evaluated oliceridine in well-controlled clinical trials in models of hard-tissue/nonvisceral pain (bunionectomy) and soft-tissue/visceral pain (abdominoplasty). To evaluate the relative effects of oliceridine on ORAEs and inform clinical practice, oliceridine at 0.1, 0.35 and 0.5 mg PCA dosing regimens and a 1-mg i.v. morphine regimen as a clinically relevant comparator were included. In addition to the two controlled clinical trials, a phase III open-label study (ATHENA) evaluated the safety and effectiveness of oliceridine in patients with moderate to severe acute pain who underwent a wide range of surgical procedures, or with nonsurgical medical conditions warranting parenteral opioids, to represent intravenous opioid use in a broad "real-world setting".

Controlled clinical trials

The two pivotal studies, APOLLO-1 in hard tissue (39) (bunionectomy study with a 48-hour randomized treatment period) and APOLLO-2 in soft tissue (40) (abdominoplasty study with a 24-hour randomized treatment period), were similar in design; however, each surgical pain model involved different anesthetic methods, different time from surgery to the first dose of study medication, different temporal courses of pain after discontinuation of anesthesia, different qualifying NRS pain intensity score and duration of the randomized treatment period (Table II).

In both pivotal studies, patients were randomized equally to one of three oliceridine treatment regimens (demand doses of 0.1, 0.35 or 0.5 mg), morphine (demand dose of 1 mg) or placebo. The loading dose of oliceridine for all regimens was 1.5 mg. The loading dose of morphine was 4 mg. The PCA demand doses were delivered p.r.n. beginning 10 minutes after the 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, p.r.n. (Table III).

Table II. *Phase III pivotal studies APOLLO-1 (hard tissue) and APOLLO-2 (soft tissue) study design: key elements (39, 40).*

Design element	Hard tissue	Soft tissue
Acute pain model	Bunionectomy	Abdominoplasty
N receiving study medication	389	401
Treatment period	48 hours	24 hours
Anesthesia	Regional (popliteal sciatic nerve block)	General
Pain entry criteria	NRS ≥ 4 within 9 hours after discontinuation of regional anesthesia	NRS ≥ 5 within 4 hours from end of surgery

NRS, numeric rating scale.

Table III. *Dosing regimens in the two pivotal studies APOLLO-1 and APOLLO-2 (39, 40).*

Randomized group	Loading dose	Demand dose (PCA)	Lockout	Clinician-administered supplemental dose (q1h p.r.n.)
Oliceridine 0.1 mg	1.5 mg	0.1 mg	6 minutes	0.75 mg
Oliceridine 0.35 mg	1.5 mg	0.35 mg		0.75 mg
Oliceridine 0.5 mg	1.5 mg	0.5 mg		0.75 mg
Placebo	Volume-matched placebo solution	Volume-matched placebo solution		Volume-matched placebo solution
Morphine 1 mg	4 mg	1 mg		2 mg

Clinician-administered supplemental dosing could start 1 hour following the loading dose and be administered up to hourly, as needed. Further open-label rescue pain medication (oral etodolac 200 mg every 6 hours) was permitted, as needed. PCA, patient-controlled analgesia; p.r.n., as needed.

To reduce variability and avoid confounding effects of other analgesic treatments, multimodal analgesics were not permitted, although rescue pain medication with etodolac 200 mg p.o. q6h p.r.n. was allowed (39, 40).

Both studies utilized a treatment responder primary endpoint (in line with the current Food and Drug Administration [FDA] analgesic development guidance while also combining elements of safety and tolerability). This was defined as follows: a) patients with at least a 30% improvement in their final time-weighted sum of pain intensity difference (SPID) from baseline at 48 hours (for APOLLO-1, hard-tissue) or 24 hours (for APOLLO-2, soft-tissue); b) without receiving rescue pain medication during the randomized treatment period; c) without early discontinuation of study medication for any reason; d) without reaching the study medication dosing limit. Patients not meeting the criteria were considered nonresponders. The primary endpoint compared all oliceridine treatment regimens to placebo. This endpoint has the advantage of not "rewarding" greater analgesic efficacy at the expense of safety and does not require any imputation for rescue medication (39, 40).

Both pivotal studies evaluated respiratory safety using a novel assessment, termed the 'respiratory safety burden' (RSB). This endpoint was derived by multiplying the incidence of respiratory safety events (RSEs) with the cumulative duration of the events. RSEs were determined by clinical observations of changes in respiratory rate, oxygen saturation or sedation measured using the Moline-Roberts Pharmacologic Sedation Scale. The cumulative duration was defined as the mean sum of durations of each occurring RSE. The RSB, reported in minutes, can be interpreted as the expected average duration of an RSE for a patient within a particular treatment

regimen. The RSB of oliceridine versus morphine was a key secondary safety endpoint. Likewise, the proportion of treatment responders for all oliceridine groups was compared to morphine as a key secondary efficacy endpoint. Overall safety and tolerability of all treatment regimens were assessed using the incidence of treatment-emergent AEs reported during the treatment period and the 7-day follow-up period (39, 40).

In both studies, most patients were female (hard-tissue study: 85%; soft-tissue study: 99%) and Caucasians (hard-tissue study: 69%; soft-tissue study: 64%), with an average body mass index (BMI) of 27 kg/m^2. The mean NRS pain intensity score at baseline ranged from 6.5 to 7.0 across the regimens in the hard-tissue study and from 7.2 to 7.5 in the soft-tissue study (39, 40).

Primary endpoint: responder analysis

In both studies, all oliceridine treatment regimens (0.1, 0.35 and 0.5 mg) showed a significantly greater proportion of responders compared with placebo, meeting the primary endpoint (Fig. 3). The proportion of treatment responders in the morphine group was also significantly greater than placebo (39, 40).

In the secondary efficacy endpoint, the proportion of treatment responders over time and the mean pain scores over time were similar for the oliceridine 0.35- and 0.5-mg demand dose regimens and the morphine regimen. Furthermore, the use of rescue medication for pain was similar in the oliceridine 0.35- and 0.5-mg regimens and the morphine 1-mg regimen, indicating that the two oliceridine regimens were equianalgesic compared to the morphine regimen (39, 40).

RSB compared with morphine

The key secondary outcome of RSB for oliceridine was not statistically significant compared to morphine, although it indicated a dose regimen-dependent trend toward improvement in respiratory safety (Fig. 4). In an exploratory analysis, the incidence of RSEs was numerically lower with the oliceridine regimens, and the odds ratio of a dosing interruption or requirement of supplemental oxygen was also numerically lower with the oliceridine regimens than with morphine (Fig. 5) (39, 40).

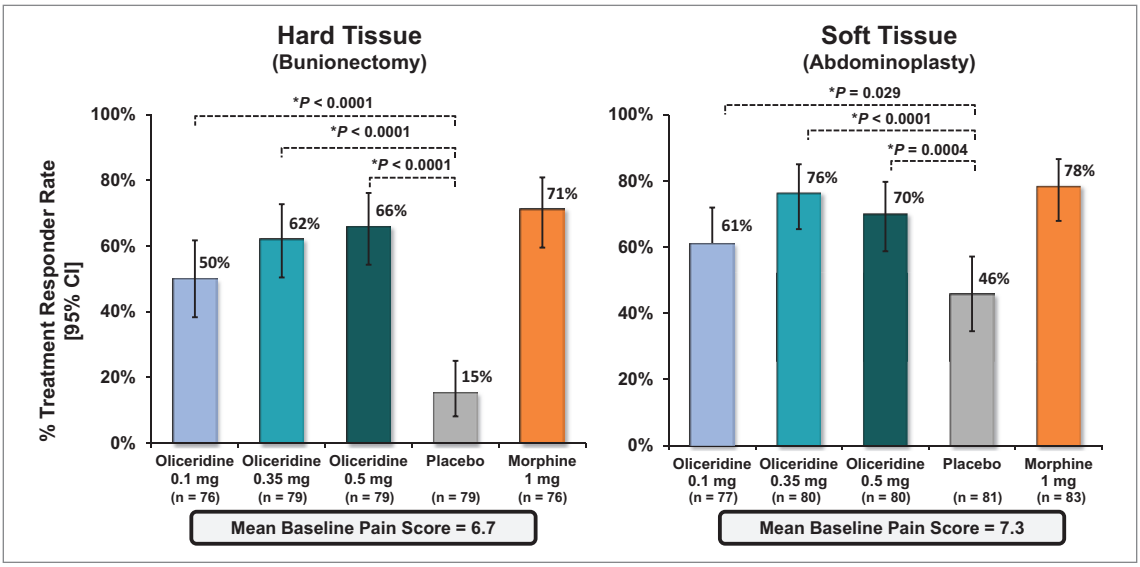

Figure 3. Primary treatment response: oliceridine compared with placebo in the pivotal studies (39, 40). The duration in the hard-tissue (bunionectomy) study (APOLLO-1) was 48 hours and in the soft-tissue (abdominoplasty) study (APOLLO-2) was 24 hours. Responders were patients who reached a ≥ 30% improvement in time-weighted sum of pain intensity difference (SPID-48 or SPID-24) from baseline, while a) not receiving rescue pain medication; b) not discontinuing study medication early; and c) without reaching dosing limits. *P < 0.0001 vs. placebo for the hard-tissue study and *P < 0.05 vs. placebo for the soft-tissue study (Hochberg-adjusted). CI, confidence interval.

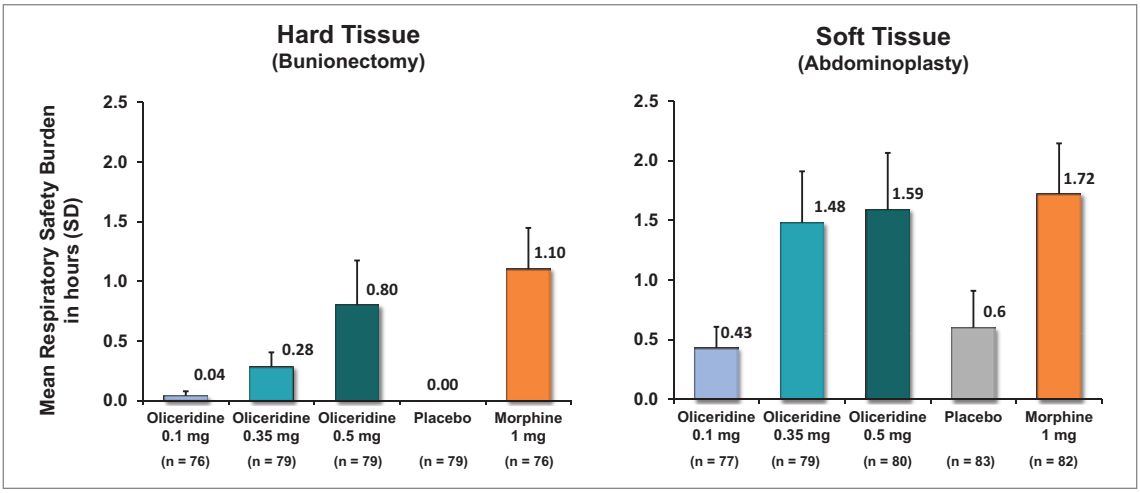

Figure 4. Respiratory safety burden (RSB) in the pivotal studies APOLLO-1 (hard tissue) and APOLLO-2 (soft tissue) (39, 40). During the randomized treatment period, patients were monitored on a protocol-defined schedule by either a certified registered nurse anesthetist or an anesthesiologist, blinded to study medication assignment. The monitoring professional intervened when clinically indicated and determined the onset and resolution of each respiratory safety event (RSE). RSB was defined as the expected cumulative duration of RSEs in a particular treatment group and was calculated as the mathematical product of the incidence of RSEs and the mean duration of such events in affected patients. There were no statistically significant differences for this composite outcome measure for any of the oliceridine treatment groups compared to morphine. Mean RSB from model-based estimates was 1, 1, 9, 15 and 33 minutes in the hard-tissue study and 7, 5, 19, 25 and 32 minutes in the soft-tissue study for the placebo, oliceridine 0.1 mg, oliceridine 0.35 mg, oliceridine 0.5 mg and morphine groups, respectively. SD, standard deviation.

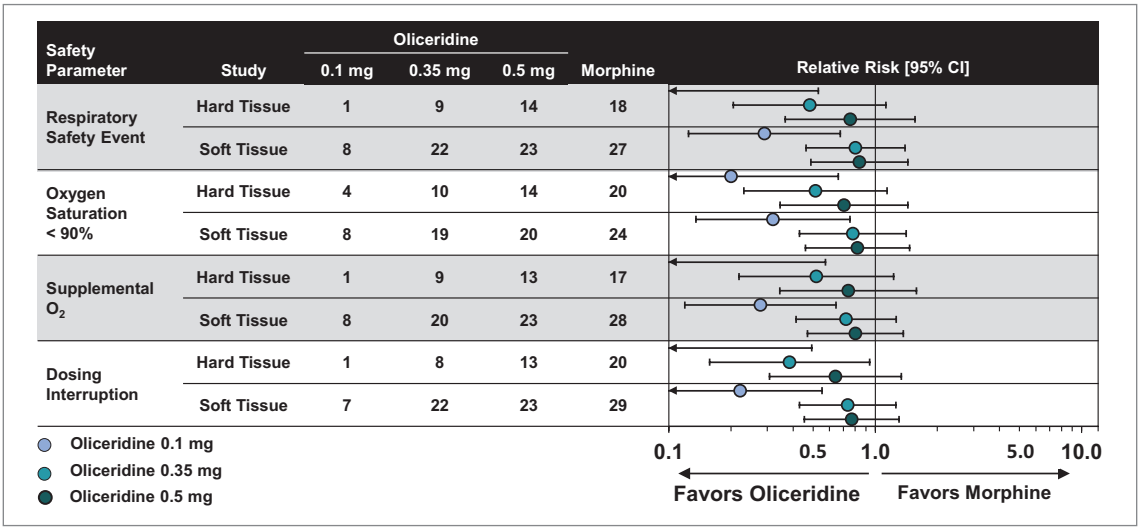

Figure 5. Respiratory safety events (RSEs) and clinical interventions in the pivotal studies APOLLO-1 and APOLLO-2 (39, 40). RSEs included clinical observations of changes in respiratory rate, oxygen saturation or sedation measured using the Moline-Roberts Pharmacologic Sedation Scale.

There are no standard accepted and validated endpoints for measuring respiratory safety with opioids. RSB was a novel concept and as designed proved to be a challenging endpoint to measure due to reliance on subjective clinical assessments of both RSEs and their duration. In a recent narrative review, it was discussed that utilization of single-measure readings of respiratory function to characterize RSEs is known to have serious limitations (41). Comprehensive and reliable approaches that allow for standardized respiratory safety assessment to make comparisons among different therapeutic agents are currently under development (41).

Adverse events

No serious adverse events (SAEs) were reported in APOLLO-1 (hard-tissue study). In APOLLO-2 (soft-tissue study), SAEs were reported in 5 patients (4 patients in the oliceridine treatment regimens and 1 patient in the morphine treatment regimen) (40). In the oliceridine treatment group, postprocedural hemorrhage, syncope and lethargy were reported with the 0.5-mg regimen, and abdominal wall hematoma with the 0.35-mg regimen. Among these, only syncope and lethargy were considered possibly related to oliceridine. In the morphine group, pulmonary embolism and respiratory failure were reported as SAEs in 1 patient, and were deemed not related to treatment. All SAEs resolved without sequelae by the end of the study (40). The incidence of AEs leading to discontinuation ranged from 3% to 6%, and was comparable between the oliceridine 0.5-mg regimen (9/159; 5.7%) and the morphine regimen (8/158; 5.1%). The most common AE leading to early discontinuation of study medication was reduction in oxygen saturation in the morphine 1-mg regimen (n = 5, 3.2%) and hypoxia in the oliceridine 0.35-mg (n = 3, 1.9%) and 0.5-mg (n = 3, 1.9%) regimens (39, 40).

The most frequently reported AEs for oliceridine, based on the data pooled from the pivotal trials, were nausea and vomiting (Table IV). The proportion of patients experiencing nausea/vomiting in patients receiving an oliceridine demand dose of

Table IV. *Most common adverse events (AEs) (≥ 5% of patients) in the phase III controlled clinical trials (APOLLO-1 and APOLLO-2) (39, 40).*

Type of AE, n (%)	Oliceridine			Placebo	Morphine 1 mg
	0.1 mg N = 153	0.35 mg N = 158	0.5 mg N = 159	N = 162	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)

0.35 mg (or lower), was numerically lower than in those receiving morphine (Table IV). No prophylactic antiemetics were allowed in either trial; however, rescue antiemetics were allowed if the patient was vomiting or reported moderate to severe nausea. The use of rescue antiemetics was numerically lower with the oliceridine dose regimens (0.1 mg: 18.4% in hard-tissue study, 32.5% in soft-tissue study; 0.35 mg: 35.4% in hard-tissue study, 55% in soft-tissue study; 0.5 mg: 41.8% in hard-tissue study, 61.3% in soft-tissue study) than with the morphine regimen (61% in hard-tissue study; 65% in soft-tissue study) (39, 40).

In either pivotal study, no meaningful differences in the incidence of potentially clinically significant ECG results were observed for any of the oliceridine groups, morphine or placebo (39, 40).

The findings from these pivotal studies suggest that oliceridine provides rapid analgesia compared with placebo in the management of moderate to severe acute postoperative pain. In addition, at dosing regimens equianalgesic to morphine, oliceridine was associated with a lower incidence of most AEs, in particular RSEs and gastrointestinal events of nausea/vomiting (39, 40).

Open-label study (ATHENA)

The phase III, multicenter, open-label clinical study ATHENA (NCT02656875) was conducted at 41 sites in the United States, including ambulatory surgical centers, hospital-based outpatient and inpatient settings and emergency departments (42). The objective of the study was to evaluate the safety and effectiveness of oliceridine in patients with moderate to severe acute pain undergoing a wide range of surgical procedures, or with nonsurgical medical conditions, warranting the use of a parenteral opioid in either setting. ATHENA was designed to be less restrictive (compared with the APOLLO studies) for patient eligibility criteria, treatment protocol requirements, patient population and mode of administration to accurately represent intravenous opioid use in a broad, "real-world" setting.

Adult patients with a score ≥ 4 on the 11-point NRS for pain intensity received intravenous oliceridine either by bolus or PCA. In this study, multimodal analgesia was permitted. For intravenous bolus dosing, a loading dose of 1 to 2 mg was administered, and a supplemental dose of 1 mg was given within 15 minutes if needed. Subsequent doses of 1 to 3 mg were administered every 1 to 3 hours p.r.n. (42).

In settings where rapid analgesia was required (e.g., emergency departments, postanesthesia care units), loading doses of 1 to 3 mg were administered and supplemental doses of 1 to 3 mg every 5 minutes p.r.n. were allowed. Subsequent doses of 1 to 3 mg every 1 to 3 hours were used if clinically indicated (42).

For PCA, a loading dose of 1.5 mg and a demand dose of 0.5 mg were administered using a 6-minute lockout interval. If clinically indicated, 1-mg supplemental doses were allowed p.r.n. throughout the remainder of the treatment period. 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 (42).

The mean age of patients enrolled in the ATHENA study was 54.1 years, with 32% of patients aged 65 or older, and the mean BMI was 30.5 kg/m^2. Of the 768 patients enrolled, 94% were in surgical settings, with orthopedic (30%), colorectal (15%) or gynecologic (15%) procedures as the most common surgical procedures. All enrolled patients had at least one comorbid condition, with hypertension (44%), gastroesophageal reflux disease (36%), osteoarthritis (28%), depression (18%), anxiety (16%), hyperlipidemia (15%), hypercholesterolemia (13%), sleep apnea syndrome (13%), obesity (12%) and type 2 diabetes mellitus (12%) as the most common comorbidities. Thus, in contrast to the pivotal studies (APOLLO-1 and -2), patients enrolled in ATHENA were older, had a higher BMI, and had more underlying comorbidities. Overall, 84% of the patients received multimodal analgesic therapy concomitantly with oliceridine (42).

The median cumulative dose of oliceridine 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 from < 1 hour to 142.7 hours or about 6 days (42).

Compared with the APOLLO studies, the incidence of overall AEs and severe AEs was lower in the ATHENA patient population. Overall, 64% of patients reported at least 1 AE during the study. The most

frequent AEs reported were nausea (31%), constipation (11%) and vomiting (10%). The incidence of SAEs (3.4%) and AEs leading to study discontinuation (2.2%) was similar to those in the pivotal studies. AEs "probably" or "possibly" related to oliceridine were reported in 33.3% of patients, with low incidence of nausea (18%), vomiting (7%) and constipation (6%). Oxygen saturation < 90% was reported in 6% and none of the patients required use of naloxone (42).

Findings from the ATHENA trial suggest that oliceridine administered alone or as a component of multimodal analgesia was safe and well tolerated in surgical and nonsurgical patients experiencing moderate to severe acute pain. Importantly, no new AE signals were observed in this larger, more diverse group of general acute pain patients with more medical complications and underlying medical comorbidities (42).

Collectively, the findings from the phase III studies suggest that oliceridine, a novel centrally acting, G protein pathway-selective MOR agonist optimizes analgesic effect with lower incidences of ORAEs and may represent a potential new treatment option for patients requiring intravenous opioid therapy.

Current Status

A new drug application (NDA) submission for oliceridine was completed in November 2017. In November 2018, the FDA issued a complete response letter (CRL) to Trevena requesting additional QT data, nonclinical data confirming levels of an inactive metabolite, and drug product validation reports. In a follow-up Type A meeting, the FDA agreed with the labeling at a maximum daily dose of 27 mg based on the current safety database and clarified conducting a study in healthy volunteers for the additional QT data. No additional efficacy data were requested (43).

The multidose QT study was completed in November 2019 and the results show no evidence of an accumulating effect of oliceridine on the QT interval when administered in repeated doses to the 27-mg proposed maximum daily dose over 24 hours. No SAEs were reported. Resubmission of the NDA for oliceridine was completed on February 10, 2020 (44).

The Future: Oliceridine as a Part of ERAS Protocol

Within an ERAS protocol, the approach to treating pain is multifaceted, including a combination of techniques as well as multimodal intravenous and oral analgesia (45). The goal is to deliver "optimal analgesia," defined as a technique that optimizes patient comfort and facilitates functional recovery with the fewest medication side effects (45). Although many ERAS protocols have a goal of "opioid minimization", opioids are still an important analgesic option for use on an "as needed basis" (46). On the basis of findings from the pivotal trials in models of hard tissue and soft tissue, oliceridine provided rapid analgesia with fewer ORAEs than morphine. Furthermore, in an open-label trial approximating a "real-world" setting, oliceridine administered alone or as a component of multimodal analgesia was generally safe and well tolerated.

Unlike conventional opioids, oliceridine has a unique pharmacology, with a half-life that allows for adequate drug concentrations to provide efficacy without drug accumulation or development of active metabolites. In addition, oliceridine does not require dosing adjustment in the elderly or in patients with renal dysfunction. Elderly individuals have physiologically reduced kidney function and functional reserve with the appearance of global glomerulosclerosis, but also more comorbidity than do young adults, all of which heighten older persons' susceptibility to nephrotoxic medicines or drug accumulation (47). This could be important in situations where acute kidney injury may develop during the early postoperative period. Evaluating oliceridine as part of the analgesic regimen in ERAS protocols will be an important step in the future.

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Disclosures

At the time of preparation and submission of this manuscript, oliceridine, an investigational intravenous opioid, was not yet approved by the FDA or any other governmental agency. T.J. Gan has been a consultant for Trevena, Inc. and has no other conflicts of interest. L. Wase is a full-time employee of Trevena, Inc. and owns stock in Trevena, Inc.

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