IV Oliceridine for the Management of Moderate-to-Severe Acute Pain in Hospital or Controlled Clinical Settings

October 11, 2018
Trevena, Inc.
Meeting of the Anesthetic and Analgesic Drugs Products Advisory Committee
Introduction

Maxine Gowen, PhD
Founding President and CEO
Trevena, Inc.
Overview of IV Oliceridine for Management of Moderate-to-Severe Acute Pain

- New chemical entity with novel mechanism of action
- Designed to deliver pain relief of conventional IV opioid with fewer opioid-related adverse events (ORAEs)
  - Improving benefit-risk profile for patients
- First new opioid molecule in decades
Oliceridine Scientific History

- Trevena founded in 2008 to translate GPCR discoveries into better medicines
- Lab of Robert Lefkowitz, Duke University
  - 2012 Nobel Prize in Chemistry for work on GPCRs
Prior Theory on GPCRs, Including μ-Opioid Receptor

- Operated like light switch
  - ON by agonist like morphine
  - OFF by antagonists like naloxone
- Beneficial and adverse effects inseparable
- Opioid analgesia only obtained with associated ORAEs
New Hypothesis: GPCRs Have Distinct Signaling Pathways

Conventional Opioids

- µ-opioid receptor
- G protein
- β-arrestin

- Analgesia
- Respiratory Depression
- Nausea/Vomiting
- Liking/Dependence

Respiratory Depression
Nausea/Vomiting

Oliceridine

- µ-opioid receptor
- G protein
- β-arrestin

Hypothesis (vs Conventional Opioids):
- Similar Analgesia
- Similar Liking/Dependence
- Less Respiratory Depression
- Less Nausea/Vomiting

IV Oliceridine: G-Protein Biased Ligand at μ-Opioid Receptor (MOR)

- Novel MoA designed to optimize MOR pharmacology
- New chemical entity; not derivative of opium

Oliceridine

Morphine

Hydromorphone
Optimizing multimodal therapy and ERAS protocols
  ▪ Reduced need for IV opioids for many procedures

IV opioids still often necessary
  ▪ Pain more severe, deep/visceral, longer duration

45 million patients received IV opioids in US hospitals

1. IQVIA Hospital Charge Detail Master Database, 2017.

IV Opioids Essential Treatment Option for Moderate-to-Severe Acute Pain in Hospital or Controlled Setting
Limitations of Conventional IV Opioids

- ORAEs
  - Nausea, vomiting, and respiratory depression
- Narrow therapeutic windows
  - Small dose range effective without leading to ORAEs
- Active metabolites
  - Complicates analgesic and side effect profile
IV Oliceridine in Context of Ongoing Opioid Crisis

- Schedule II product with same mandatory restrictions as other IV opioids
- Reversible by naloxone
- Not expected to affect opioid abuse crisis
  - Short-term IV use only
  - Used only in hospital or other controlled clinical setting
  - Substitute for current IV opioids
Unique Features of Oliceridine Development Program

- IV oliceridine studied in >1,800 individuals in 17 clinical trials
- Included IV morphine as active comparator
- Used as needed (PRN) dosing
- Studied respiratory safety
  - Experimental gold standard VRH test
  - No accepted clinical endpoint for respiratory depression
    - Variety of different measures

VRH: ventilatory response to hypercapnia
IV Oliceridine Key Efficacy and Safety Findings

- Met efficacy requirements for approval
  - Superior to placebo in both Phase 3 studies
- Safe for intended use
  - Evaluated full safe and efficacious dose range
  - Expert review found no clinically significant hepatic or cardiac safety issues
- Delivered sufficient analgesia similar to morphine
- Supportive evidence of safety benefit vs morphine across multiple safety measures, studies, and interventions
  - Not seeking label claim
Oliceridine Proposed Indication

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

- Administration supervised by trained medical personnel
  - Acute use only
  - Hospital or other controlled setting
Oliceridine Proposed Dosing

**Initial Dose**
- Initial Loading Dose
  - 1 to 2 mg bolus

**Maintenance Doses**
- Bolus Doses
  - 1 to 2 mg every 1 to 3 hours
- PCA Demand Doses
  - Range: 0.1 to 0.35 mg (6-min lockout)

- Maximum single bolus dose of 3 mg
- Maximum daily dose of 40 mg
# Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>Efficacy and Safety</td>
<td><strong>Mark A Demitrack, MD</strong></td>
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<td>Chief Medical Officer</td>
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<td>Trevena, Inc.</td>
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<tr>
<td>Special Safety Topics</td>
<td><strong>Paul Watkins, MD</strong></td>
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<tr>
<td></td>
<td>Professor of Medicine, Toxicology, and</td>
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<td>Experimental Therapeutics</td>
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<td></td>
<td>University of North Carolina at Chapel</td>
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<td>Hill</td>
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<td>Opioid-Related Adverse Events</td>
<td><strong>Robert B Kleiman, MD</strong></td>
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<td>Chief Medical Officer, Vice President</td>
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<td>Global Cardiology eResearch Technology</td>
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<td>Clinical Perspective</td>
<td><strong>Jonathan Violin, PhD</strong></td>
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<td>Co-founder and Senior Vice President</td>
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<td>of Scientific Affairs</td>
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<td>Trevena, Inc.</td>
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<td><strong>Gregory Hammer, MD</strong></td>
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<tr>
<td></td>
<td>Professor of Anesthesiology, Perioperative</td>
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<td>and Pain Medicine and of Pediatrics</td>
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<tr>
<td></td>
<td>(Critical Care)</td>
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<td>Stanford University Medical Center</td>
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# Additional Experts

<table>
<thead>
<tr>
<th>Statistics</th>
<th>David Burt, PhD</th>
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<tr>
<td></td>
<td>Senior Director, Biostatistics</td>
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<td></td>
<td>Trevena, Inc.</td>
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<tr>
<td>Clinical Pharmacology</td>
<td>Michael Fossler, PharmD, PhD</td>
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<td>Vice President, Clinical Operations &amp; Quantitative Sciences</td>
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<td>Trevena, Inc.</td>
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<td>Human Abuse Liability</td>
<td>Lynn Webster, MD</td>
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<tr>
<td>Opioid-induced Respiratory Depression</td>
<td>Vice President, Scientific Affairs</td>
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<td>PRA Health Sciences</td>
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Efficacy and Safety

Mark A Demitrack, MD
Chief Medical Officer
Trevena, Inc.
# Efficacy and Safety Supported by Phase 2 and Phase 3 Studies

<table>
<thead>
<tr>
<th>Study (Phase)</th>
<th>Pain Model (Design)</th>
<th>N Treated</th>
<th>Dosing</th>
</tr>
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<tbody>
<tr>
<td>Study 2001 (Phase 2a)</td>
<td>Bunionectomy (RCT)</td>
<td>333</td>
<td>Fixed</td>
</tr>
<tr>
<td>Study 2002 (Phase 2b)</td>
<td>Abdominoplasty (RCT)</td>
<td>200</td>
<td>As Needed (PRN)</td>
</tr>
<tr>
<td>APOLLO 1 (Phase 3)</td>
<td>Bunionectomy (RCT)</td>
<td>389</td>
<td></td>
</tr>
<tr>
<td>APOLLO 2 (Phase 3)</td>
<td>Abdominoplasty (RCT)</td>
<td>401</td>
<td></td>
</tr>
<tr>
<td>ATHENA (Phase 3)</td>
<td>Diverse settings (Open-label)</td>
<td>768</td>
<td>PRN</td>
</tr>
</tbody>
</table>

- IV morphine comparator in controlled studies
Phase 2a Bunionectomy Study (Study 2001)

- 333 randomized and treated patients
- Explored range of oliceridine dose strengths and intervals
  - Placebo and morphine 4 mg comparators
- Clearest assessment of onset, magnitude, and duration
Phase 2a (Bunionectomy): Fixed Doses of Oliceridine Provided Efficacy for Moderate-to-Severe Acute Pain

Mean Numeric Pain Rating Scale [95% CI]

First Dosing Interval

Baseline 5 10 15 30 45 60 90 120 180

- Placebo (N=28)
- Morphine 4 mg (N=39)
- Oliceridine 0.5 mg (N=20)
- Oliceridine 1 mg (N=38)
- Oliceridine 2 mg (N=36)
- Oliceridine 3 mg (N=31)
Phase 2b Abdominoplasty Study (Study 2002)

- 200 patients randomized and treated
- PRN dosing to reflect clinical practice
  - Oliceridine: 1.5 mg loading with 0.1 or 0.35 mg demand doses
  - Morphine: 4 mg loading with 1 mg demand dose
  - Placebo
- 6-minute lockout intervals
Phase 2b (Abdominoplasty): Oliceridine Statistically Significant Pain Reductions vs Placebo, Similar to Morphine

**Graph:**
- LS Mean Change in TWA NPRS from Baseline [95% CI]
- Time (hours): 0, 4, 8, 12, 16, 20, 24
- Placebo (N=39)
- Morphine 1 mg (N=83)
- Oliceridine 0.1 mg (N=39)
- Oliceridine 0.35 mg (N=39)

**Table:**
<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Placebo</th>
<th>Oliceridine 0.1 mg</th>
<th>Oliceridine 0.35 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>4</td>
<td>-1</td>
<td>-2</td>
<td>-2</td>
</tr>
<tr>
<td>8</td>
<td>-2</td>
<td>-3</td>
<td>-3</td>
</tr>
<tr>
<td>12</td>
<td>-3</td>
<td>-4</td>
<td>-4</td>
</tr>
<tr>
<td>16</td>
<td>-4</td>
<td>-5</td>
<td>-5</td>
</tr>
<tr>
<td>20</td>
<td>-5</td>
<td>-6</td>
<td>-6</td>
</tr>
<tr>
<td>24</td>
<td>-6</td>
<td>-7</td>
<td>-7</td>
</tr>
</tbody>
</table>

**Notes:**
- Last observation carried forward (LOCF) imputation for rescue medication
- TWA NPRS: time-weighted average in numeric pain rating scale
Phase 3 Bunionectomy (APOLLO 1) and Abdominoplasty (APOLLO 2) Studies

Studies 3001 and 3002
# APOLLO 1 and APOLLO 2 Study Designs

<table>
<thead>
<tr>
<th>Design Element</th>
<th>APOLLO 1</th>
<th>APOLLO 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pain model</td>
<td>Bunionectomy (hard tissue)</td>
<td>Abdominoplasty (soft tissue)</td>
</tr>
<tr>
<td>N randomized and treated</td>
<td>389</td>
<td>401</td>
</tr>
<tr>
<td>Treatment period</td>
<td>48 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>Regional (popliteal sciatic nerve block)</td>
<td>General</td>
</tr>
<tr>
<td>Pain entry criteria</td>
<td>NRS ≥ 4 within 9 hours after discontinuation of regional anesthesia</td>
<td>NRS ≥ 5 within 4 hours from end of surgery</td>
</tr>
</tbody>
</table>
# APOLLO 1 and APOLLO 2: Treatment Regimens

<table>
<thead>
<tr>
<th>Nominal Dose</th>
<th>Clinician-administered Loading Dose</th>
<th>Patient-administered Demand Dose</th>
<th>Clinician-administered Supplemental Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliceridine 0.1 mg</td>
<td>0.1 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliceridine 0.35 mg</td>
<td>1.5 mg</td>
<td>0.35 mg</td>
<td>0.75 mg q1h PRN</td>
</tr>
<tr>
<td>Oliceridine 0.5 mg</td>
<td>0.5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>4 mg</td>
<td>1 mg</td>
<td>2 mg q1h PRN</td>
</tr>
<tr>
<td>Placebo</td>
<td>Volume-matched solution</td>
<td>Volume-matched solution</td>
<td>Volume-matched solution</td>
</tr>
</tbody>
</table>

- Monotherapy protocol: multimodal therapy not allowed
- Rescue pain medication: etodolac 200 mg q6h PRN
Considerations for Analysis of IV Opioid Efficacy with PRN Dosing

- Treatment paradigm with opioid analgesics
  - Patients should receive what they need and no more
- Sufficiency, not magnitude, of efficacy most clinically relevant
- Efficacy greater than adequate should not be considered benefit
  - Reflects unnecessary opioid exposure and added risk
- Analyses focused on magnitude alone may bias towards treating patients with more opioid than needed
- Pre-specified treatment responder primary endpoint that measures both efficacy and tolerability
Section 11a – Demonstrating efficacy

“A responder analysis, in which the outcome for each subject is summarized as a success or a failure based on a single cut-off point (e.g., 30 percent reduction in pain (with early discontinuation counted as a failure)), can be used… such analyses are easy for clinicians to interpret, and they can greatly mitigate the problems of missing data.”

APOLLO 1 and APOLLO 2 Primary Endpoint

- Treatment responder if all 4 criteria met
  - $\geq 30\%$ improvement in SPID
  - Without rescue pain medication
  - Without early discontinuation
  - Without reaching study medication dosing limit
- No imputation required for rescue medication or discontinuation
- Primary efficacy analysis vs placebo
- Analysis considerations incorporated at FDA request
  - Account for use of analgesics outside of rescue pain medication
  - Multiple imputation for missing data

SPID: sum of pain intensity differences
All Oliceridine Regimens Met Primary Endpoint

**APOLLO 1**
(Bunionectomy)

- Mean Baseline Pain Score = 6.7

**APOLLO 2**
(Abdominoplasty)

- Mean Baseline Pain Score = 7.3

- **Oliceridine 0.1 mg (N=76)**
- **Oliceridine 0.35 mg (N=79)**
- **Oliceridine 0.5 mg (N=79)**
- **Placebo (N=76)**
- **Morphine 1 mg (N=76)**

- **Oliceridine 0.1 mg (N=80)**
- **Oliceridine 0.35 mg (N=81)**
- **Oliceridine 0.5 mg (N=83)**
- **Placebo (N=81)**
- **Morphine 1 mg (N=83)**

- **Treatment Responder Rate [95% CI]**
  - **APOLLO 1**
    - Oliceridine 0.1 mg: 49% ± 5%
    - Oliceridine 0.35 mg: 59% ± 5%
    - Oliceridine 0.5 mg: 61% ± 5%
    - Placebo: 16% ± 5%
    - Morphine 1 mg: 63% ± 5%

  - **APOLLO 2**
    - Oliceridine 0.1 mg: 58% ± 5%
    - Oliceridine 0.35 mg: 70% ± 5%
    - Oliceridine 0.5 mg: 68% ± 5%
    - Placebo: 41% ± 5%
    - Morphine 1 mg: 76% ± 5%

- *p < 0.001*
- *p = 0.014*
Time to First Use of Rescue Medication Consistent with Results of Primary Endpoint

APOLLO 1
(Bunionectomy)

- Placebo (N=79)
- Morphine 1 mg (N=76)
- Oliceridine 0.1 mg (N=76)
- Oliceridine 0.35 mg (N=79)
- Oliceridine 0.5 mg (N=79)

APOLLO 2
(Abdominoplasty)

- Placebo (N=77)
- Morphine 1 mg (N=83)
- Oliceridine 0.1 mg (N=80)
- Oliceridine 0.35 mg (N=80)
- Oliceridine 0.5 mg (N=81)
Efficacy Analyses
Evaluating Sufficiency vs Magnitude
# Clinical Meaningfulness of Efficacy Analyses

<table>
<thead>
<tr>
<th>Efficacy Consideration</th>
<th>Treatment Responder</th>
<th>SPID with Imputations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Pain Score</td>
<td>&gt; 30% is adequate</td>
<td>Greater is better</td>
</tr>
<tr>
<td>Rescue Pain Medication for Lack of Efficacy</td>
<td></td>
<td>LOCF for duration of labeled dosing interval</td>
</tr>
<tr>
<td>Discontinue Study Medication for AE</td>
<td>Non-responder</td>
<td>Not accounted for</td>
</tr>
<tr>
<td>Discontinue Study Medication for Lack of Efficacy</td>
<td>(inadequate analgesia or lack of tolerability)</td>
<td>Not accounted for</td>
</tr>
<tr>
<td>Discontinue Study for Lack of Efficacy</td>
<td></td>
<td>LOCF to end of treatment period</td>
</tr>
<tr>
<td>Discontinue Study for AE</td>
<td></td>
<td>BOCF to end of treatment period</td>
</tr>
<tr>
<td>What does it measure?</td>
<td>Sufficiency, Comfort</td>
<td>Magnitude, Intensity</td>
</tr>
</tbody>
</table>

BOCF: baseline observation carried forward
Focus on Magnitude of Efficacy Alone Favors Higher Opioid Doses

<table>
<thead>
<tr>
<th>APOLLO 1 Efficacy Measure</th>
<th>Placebo</th>
<th>Oliceridine 0.35 mg</th>
<th>Oliceridine 0.5 mg</th>
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<tbody>
<tr>
<td>SPID48-LOCF-6hr (placebo-corrected)</td>
<td>0</td>
<td>27</td>
<td>51</td>
</tr>
<tr>
<td>Primary endpoint (treatment responder)</td>
<td>16%</td>
<td>59%</td>
<td>61%</td>
</tr>
<tr>
<td>Did not use rescue medication</td>
<td>23%</td>
<td>80%</td>
<td>84%</td>
</tr>
<tr>
<td>Discontinuation for lack of efficacy</td>
<td>34%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Patient dissatisfied (mostly/completely)</td>
<td>47%</td>
<td>10%</td>
<td>11%</td>
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<tr>
<td>Clinician dissatisfied (mostly/completely)</td>
<td>46%</td>
<td>8%</td>
<td>11%</td>
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SPID-LOCF suggests 0.5 mg twice as efficacious as 0.35 mg

Additional efficacy measures suggest 0.35 and 0.5 mg offer comparably sufficient analgesia

SPID-LOCF
- Favors higher doses
- As primary efficacy measure, misaligned with goal of minimizing opioid exposure

Focus on Magnitude of Efficacy Alone Favors Higher Opioid Doses

- SPID-LOCF suggests 0.5 mg twice as efficacious as 0.35 mg
- Additional efficacy measures suggest 0.35 and 0.5 mg offer comparably sufficient analgesia

SPID-LOCF
- Favors higher doses
- As primary efficacy measure, misaligned with goal of minimizing opioid exposure
Differences in Pain Scores May Not Represent Clinically Meaningful Differences in Efficacy

**Average NRS Pain Score**

- Oliceridine 0.1 mg
- Oliceridine 0.35 mg
- Oliceridine 0.5 mg
- Placebo
- Morphine 1 mg

**LOCF/BOCF (6-hour imputation)**

- Additional magnitude did not translate into meaningful benefit
- May be due to delayed onset of accumulating active metabolites

**First Use of Rescue Medication**

- % Patients Using Rescue Pain Medication

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**APOLLO 1**
Summary of Efficacy Findings

- Oliceridine is efficacious IV opioid
- Evaluated broad range of doses and regimens
- Met primary endpoint vs placebo in pivotal studies
- Secondary endpoints support sufficiency of 0.1 and 0.35 mg regimens
  - No added benefit of 0.5 mg regimen
- PCA dosing regimens sought for approval
  - Initial loading dose 1 to 2 mg
  - Range of demand doses 0.1 to 0.35 mg
Safety
## Incidence (%) of AEs by Treatment Regimen

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Oliceridine</th>
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<th></th>
<th>Placebo N=162</th>
<th>Morphine N=158</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0.1 mg N=153</td>
<td>0.35 mg N=158</td>
<td>0.5 mg N=159</td>
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<tr>
<td>Any AE</td>
<td>82</td>
<td>90</td>
<td>93</td>
<td>73</td>
<td>97</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>0</td>
<td>3.2</td>
<td>5.7</td>
<td>0</td>
<td>5.1</td>
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<tr>
<td>SAE</td>
<td>0</td>
<td>0.6</td>
<td>2.5</td>
<td>0</td>
<td>0.6</td>
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<tr>
<td>Severe AE</td>
<td>5.9</td>
<td>6.3</td>
<td>6.9</td>
<td>3.1</td>
<td>8.9</td>
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<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

Pooled APOLLLO Studies
Phase 3 Open-Label ATHENA Study

Study 3003
Broad Surgical, Medical, and Emergency Department Patient Population Treated in ATHENA

Study design features:
- N=768
- PRN dosing by PCA or bolus, clinician choice
- Multimodal analgesia permitted

Median cumulative dose:
- 19.3 mg (0.9 to 223.5 mg)

Median duration:
- 20.3 hours (< 1 to 142.7 hours)
Key Findings from ATHENA Consistent with APOLLO Studies

- ATHENA patients older with more comorbidities (32% ≥ 65 years)
- Safety and tolerability similar to APOLLO studies
  - 91% completed study using oliceridine
  - 4.3% discontinued for lack of efficacy
  - 2.2% discontinued for AE
  - 3.4% experienced an SAE
  - No deaths
- No differences in safety between bolus and PCA treatment conditions
- No new safety signal in larger, more diverse general acute pain patient population with more comorbid conditions
Special Safety Topics

Hepatic Safety
Cardiac Safety
Clinical Interpretation of Hepatic Findings

Paul Watkins, MD
Howard Q Ferguson Distinguished Professor
Schools of Medicine, Pharmacy and Public Health
Director, Institute for Drug Safety Sciences
University of North Carolina at Chapel Hill
Expert Panel of Hepatologists Convened to Assess Causality

Paul B Watkins, MD (Chair)
Howard Q Ferguson Distinguished Professor
Schools of Medicine, Pharmacy and Public Health
Director, Institute for Drug Safety Sciences
University of North Carolina

Neil Kaplowitz, MD
Thomas H Brem Professor
Chief, Division of Gastroenterology and Liver Diseases
Keck School of Medicine
University of Southern California

Hans Tillmann, MD
Clinical Associate Professor
East Carolina University
Brody School of Medicine

Donald C Rockey, MD
Chair, Department of Medicine
Medical University of South Carolina
eDISH Plots for Controlled Phase 2 and 3 Studies

- **eDISH Plots for Placebo in Controlled Phase 2 and 3 Studies (N=252)**
- **eDISH Plots for Morphine in Controlled Phase 2 and 3 Studies (N=305)**
- **eDISH Plots for Oliceridine in Controlled Phase 2 and 3 Studies (N=767)**
eDISH Plot for Oliceridine in Open-Label ATHENA Study (N=706)

Maximum Alanine Aminotransferase (X/ULN) vs. Maximum Total Bilirubin (X/ULN)

- **Aortic arch repair**: aortic cross-clamping
- **Hiatal hernia repair**: Only 6 mg received
- **Total knee replacement**: > 50% hemoglobin loss

ALT ≥ 3X ULN, Bilirubin ≤ 2X ULN: 1.0%
Additional Considerations for Hepatic Safety

- No preclinical liver safety signal
- No relationship between dose of oliceridine received and liver events
- Total dose of oliceridine received low and duration of treatment too short to cause DILI
- Similar events were seen in placebo and morphine cases
  - Suggesting population or procedure-related risk factors
Current Data Do Not Suggest Clinically Significant Hepatic Safety Risk of Oliceridine

- Unanimous consensus of expert hepatologist panel
  - No liver events likely result of treatment with oliceridine
  - No evidence of clinically significant liver safety signal with oliceridine
Cardiac Safety

Robert B Kleiman, MD
Chief Medical Officer, Vice President Global Cardiology
eResearch Technology
Expert Cardiologists Convened to Evaluate Oliceridine’s Cardiac Safety

Robert B Kleiman, MD  
Chief Medical Officer,  
Vice President Global Cardiology  
eResearch Technology

Peter R Kowey, MD  
Professor of Medicine and Clinical Pharmacology  
Jefferson Medical College of Thomas Jefferson University

Emeritus Chair, Lankenau Heart Institute  
William Wikoff Smith Chair for CV Research  
Lankenau Institute for Medical Research
Overview of Evidence for Cardiac Safety of Oliceridine

- No preclinical signal
- Minor QT effect for supratherapeutic dose in tQT Study
- No QT prolongation in Phase 3 studies
No Clinically Relevant Effect of Oliceridine or Metabolites on Cardiac Ion Channels

<table>
<thead>
<tr>
<th>Channel</th>
<th>IC$_{50}$ (Concentration blocking 50% of flow through channel)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oliceridine</td>
</tr>
<tr>
<td>hERG</td>
<td>4.3 µM</td>
</tr>
<tr>
<td>hCav1.2</td>
<td>&gt; 10 µM</td>
</tr>
<tr>
<td>hNav1.5 (tonic)</td>
<td>&gt; 10 µM</td>
</tr>
<tr>
<td>hNav1.5 (phasic)</td>
<td>&gt; 10 µM</td>
</tr>
<tr>
<td>Late hNav1.5</td>
<td>8.8 µM</td>
</tr>
</tbody>
</table>

- Oliceridine’s major metabolites have no measurable activity at the tested channels.
- IC$_{50}$ for oliceridine at 4.3 µM (116x greater than maximum human exposure).
- Additional studies also showed no QT effect:
  - Isolated rabbit wedge preparation
  - Cynomolgus monkeys at 8x maximum human exposure
TQT Study Evaluated ECG Effects of Therapeutic and Supratherapeutic Oliceridine Doses

- Randomized, double-blind, placebo- and active-controlled four-period crossover study
- 58 healthy adults randomized and received at least 1 active dose
- Randomized treatment sequence
  - Placebo IV bolus over 5 min
  - Oliceridine 3 mg (max proposed dose) IV bolus over 5 min
  - Oliceridine 6 mg (supratherapeutic dose) IV bolus over 5 min
  - Moxifloxacin 400 mg PO (positive control)
No Clinically Significant Effect of Maximum Proposed Oliceridine Dose on Cardiac Repolarization

![Graph showing the effect of different doses of Oliceridine on cardiac repolarization compared to a positive control (Moxifloxacin 400 mg). The graph includes the mean ΔΔQTcF (msec) [90% CI] over time (hours) for Oliceridine 3 mg (max proposed dose) and Oliceridine 6 mg (supratherapeutic dose).]

- Oliceridine 3 mg (max proposed dose): Mean Cmax: 152 ng/mL
- Oliceridine 6 mg (supratherapeutic dose): Mean Cmax: 284 ng/mL
- Moxifloxacin 400 mg (positive control)
FDA suggested ECG measurements at baseline, following first dose, and periodically at later time points
  ▪ Sought to capture potential delayed QT effect
Trevena incorporated ECGs for > 1,500 patients in Phase 3
  ▪ Baseline
  ▪ 1 hour (peak effect in tQT study)
  ▪ 24 hours (potential delayed effects)
  ▪ Every 24 hours thereafter (potential delayed effects)
24-Hour ECG Assessment Captures Maximum Levels of Oliceridine and Its Inactive Metabolites

Theoretical maximum dosing
- 1.5 mg loading dose
- 0.35 mg demand dose every 6 minutes
No Clinically Meaningful Differences in Incidence of QT Prolongation in Controlled Phase 3 Studies

<table>
<thead>
<tr>
<th>Threshold ECG Criteria, %</th>
<th>Oliceridine</th>
<th>Placebo</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 mg N=153</td>
<td>0.35 mg N=158</td>
<td>0.5 mg N=159</td>
</tr>
<tr>
<td>QTcF &gt; 500 msec</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QTcF change from baseline &gt; 60 msec</td>
<td>0.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QTcF change from baseline &gt; 30 msec</td>
<td>9.8</td>
<td>7.0</td>
<td>8.2</td>
</tr>
</tbody>
</table>
ECG Assessments in ATHENA

- No control group and not designed for QT testing
- Few patients experienced QT prolongation
  - Many with QT prolongation at baseline
  - No ventricular arrhythmias
- Among patients who did not experience QT prolongation
  - 1 patient undergoing aortic valve replacement had non-sustained ventricular tachycardia
Summary of Oliceridine Cardiac Safety

- Comprehensive nonclinical program revealed no QT concerns
- tQT study: small QTc increase for supratherapeutic dose
  - Prompted enhanced ECG monitoring in Phase 3
- No differences in ECG findings in controlled Phase 3 studies
- Totality of data
  - Small QTc effect in tQT study not clinically relevant
  - Oliceridine does not pose clinically meaningful risk for drug-induced ventricular arrhythmia
Opioid-Related Adverse Events

Jonathan Violin, PhD
Co-founder and Senior Vice President of Scientific Affairs
Trevena, Inc.
Clinical Program Explored Biased Ligand Hypothesis

- Hypothesis for oliceridine
  - Provide opioid-level efficacy
  - *Attenuate*, but not *eliminate*, incidence of ORAEs

- No precedent for how to explore impact of novel MoA in clinical setting
  - Attempted to capture safety in variety of ways
  - Assessed experimental gold standard, clinically-relevant events, interventions for safety, MedDRA Preferred Terms, novel endpoints

- Goal to identify dosing regimens
  - Meaningfully reduced ORAEs
  - Provided sufficient analgesic efficacy
Respiratory Safety

- Phase 1: Gold standard VRH test for opioid-induced respiratory depression
- Phase 2 and 3: Standard and novel complementary endpoints
Phase 1 Pharmacologic Proof-of-Concept Study

- Randomized, double-blind, placebo-controlled crossover study
- 30 healthy volunteers randomized and received study drug
- 5 study periods with 2-minute IV infusions
  - Placebo, morphine 10 mg, oliceridine 1.5, 3, and 4.5 mg
- Assessed experimental models
  - Analgesic effects – cold pressor test
  - Opioid-induced respiratory depression – VRH
Cold Pressor Test Measures Analgesic Effects via Pain Tolerance

- Hand immersed in 2°C water for as long as possible (up to 180 sec)
- Analgesic effect measured as duration of hand in cold water
VRH Measures Respiratory Impact via Change in Ventilation

- Inhaled 5% CO$_2$ to experimentally induce respiratory drive
- Opioid-induced respiratory depression measured as change in minute ventilation
Oliceridine Produced Significantly Less Opioid-Induced Respiratory Depression than Morphine

**Cold Pain Test**
Latency to Remove Hand (AUC 0-4 hours)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Average Change from Baseline to 4 hours in Pain Tolerance (sec) [SEM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliceridine</td>
<td></td>
</tr>
<tr>
<td>1.5 mg</td>
<td>56</td>
</tr>
<tr>
<td>3 mg</td>
<td>109</td>
</tr>
<tr>
<td>4.5 mg</td>
<td>106</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
</tr>
<tr>
<td>Morphine 10 mg</td>
<td>88</td>
</tr>
</tbody>
</table>

**Ventilatory Response to Hypercapnia**
Respiratory Depression (AUC 0-4 hours)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Change in Minute Vol at 5th Minute of 5% CO₂ (hours*L/min, Placebo Normalized) [SEM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliceridine</td>
<td></td>
</tr>
<tr>
<td>1.5 mg</td>
<td>-7.3</td>
</tr>
<tr>
<td>3 mg</td>
<td>-6.5</td>
</tr>
<tr>
<td>4.5 mg</td>
<td>-8.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>-20</td>
</tr>
<tr>
<td>Morphine 10 mg</td>
<td>-16.3</td>
</tr>
</tbody>
</table>

* p < 0.05 vs Morphine
Phase 2b Study: Evaluated Incidence of Clinically Significant Respiratory Events

- Hypoventilation prospectively defined as clinically apparent and persistently decreased
  - Respiratory rate
  - Respiratory effort
  - Oxygen saturation
- Respiratory events ascertained using standard clinical monitoring in blinded fashion
Phase 2b Study: Significantly Fewer Hypoventilation Events with Oliceridine than Morphine

Patients with Hypoventilation Event [95% CI]

- Oliceridine 0.1 mg (N=39): 15%
- Oliceridine 0.35 mg (N=39): 31%
- Placebo (N=39): 10%
- Morphine 1 mg (N=83): 53%

71% Relative Risk Reduction
p < 0.0001

42% Relative Risk Reduction
p = 0.032

(N=39)
Phase 3 Studies Included Rigorous Monitoring and Assessment of Respiratory Events

- Trained anesthesiologists and certified registered nurse anesthetists (CRNA) performed all monitoring
  - Assessed signs, symptoms, and duration of respiratory effects
  - Administered clinical interventions
- Systematically captured incidence, severity, and duration
- Monitoring occurred every 2 hours or every 30 minutes during event in blinded fashion
Definitions of Respiratory Endpoints in Phase 3

- Respiratory Safety Event (RSE)
  - Clinical expertise used to declare clinically relevant worsening in $O_2$ desaturation, reduced respiratory rate, or sedation
- Respiratory Safety Burden (RSB) new composite index
  - Product of RSE incidence and duration
  - Key secondary endpoint
  - Not eligible for labeling claims
- Respiratory interventions
  - Supplemental $O_2$ administration, dosing interruption, and study medication discontinuations
Phase 3: Reductions in RSB Dose-Regimen Dependent and Numerically Lower than Morphine

**APOLLO 1**  
(Bunionectomy)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Respiratory Safety Burden (minutes) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliceridine 0.1 mg (N=76)</td>
<td>1 (4, 3)</td>
</tr>
<tr>
<td>Oliceridine 0.35 mg (N=79)</td>
<td>9 (6, 13)</td>
</tr>
<tr>
<td>Oliceridine 0.5 mg (N=79)</td>
<td>15 (13, 18)</td>
</tr>
<tr>
<td>Placebo (N=79)</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>Morphine 1 mg (N=76)</td>
<td>33 (32, 34)</td>
</tr>
</tbody>
</table>

**APOLLO 2**  
(Abdominoplasty)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Respiratory Safety Burden (minutes) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliceridine 0.1 mg (N=77)</td>
<td>5 (3, 7)</td>
</tr>
<tr>
<td>Oliceridine 0.35 mg (N=79)</td>
<td>19 (13, 24)</td>
</tr>
<tr>
<td>Oliceridine 0.5 mg (N=80)</td>
<td>25 (21, 28)</td>
</tr>
<tr>
<td>Placebo (N=83)</td>
<td>7 (4, 11)</td>
</tr>
<tr>
<td>Morphine 1 mg (N=82)</td>
<td>32 (30, 34)</td>
</tr>
</tbody>
</table>

Not statistically significant
Lower Incidence of Respiratory Safety Events in All Groups in Phase 3 vs Phase 2

Proportion with RSE [95% CI]

Phase 2b (Abdominoplasty)

- Oliceridine 0.1 mg: 15% (N=39)
- Oliceridine 0.35 mg: 31% (N=39)
- Placebo: 10% (N=39)
- Morphine: 53% (N=83)

APOLLO 1 (Bunionectomy)

- Oliceridine 0.1 mg: 1% (N=76)
- Oliceridine 0.35 mg: 9% (N=79)
- Oliceridine 0.5 mg: 14% (N=79)
- Placebo: 0% (N=79)
- Morphine: 18% (N=76)

APOLLO 2 (Abdominoplasty)

- Oliceridine 0.1 mg: 8% (N=77)
- Oliceridine 0.35 mg: 22% (N=79)
- Oliceridine 0.5 mg: 23% (N=80)
- Placebo: 6% (N=83)
- Morphine: 27% (N=82)
### Similar Relative Risk Reductions in Hypoventilation and Respiratory Safety Events

<table>
<thead>
<tr>
<th>Oliceridine Dosing Regimen</th>
<th>Phase</th>
<th>% of Patients Experiencing Respiratory Safety Event</th>
<th>Relative Risk Reduction vs Morphine</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oliceridine</td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>0.1 mg</td>
<td>2b</td>
<td>15</td>
<td>53</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>23</td>
<td>80%</td>
</tr>
<tr>
<td>0.35 mg</td>
<td>2b</td>
<td>31</td>
<td>53</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>15</td>
<td>23</td>
<td>33%</td>
</tr>
</tbody>
</table>

Favors Oliceridine  Favors Morphine

0.1  0.2  0.5  1  2  5  10
# Summary of Respiratory Safety Interventions

<table>
<thead>
<tr>
<th>Safety Parameter, %</th>
<th>Oliceridine</th>
<th>Morphine</th>
<th>Relative Risk Reduction (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 mg N=153</td>
<td>0.35 mg N=158</td>
<td>0.5 mg N=159</td>
</tr>
<tr>
<td><strong>O₂ Saturation &lt; 90%</strong></td>
<td>5.9</td>
<td>14.6</td>
<td>17.0</td>
</tr>
<tr>
<td><strong>Dosing Interruption</strong></td>
<td>3.9</td>
<td>14.6</td>
<td>17.6</td>
</tr>
<tr>
<td><strong>Supplemental O₂</strong></td>
<td>4.6</td>
<td>14.6</td>
<td>17.6</td>
</tr>
</tbody>
</table>

Pooled APOLLO Studies
Nausea and Vomiting

- MedDRA Preferred Terms for Nausea and Vomiting
Incidence of Nausea and Vomiting in Pivotal Phase 2b Study

**Nausea**

- **Oliceridine 0.1 mg** (N=39) 41%
- **Oliceridine 0.35 mg** (N=39) 46%
- **Placebo** (N=39) 18%
- **Morphine 1 mg** (N=83) 72%

43% Relative Risk Reduction  
**p = 0.001**

36% Relative Risk Reduction  
**p = 0.008**

**Vomiting**

- **Oliceridine 0.1 mg** (N=39) 15%
- **Oliceridine 0.35 mg** (N=39) 15%
- **Placebo** (N=39) 8%
- **Morphine 1 mg** (N=83) 42%

64% Relative Risk Reduction  
**p = 0.004**

64% Relative Risk Reduction  
**p = 0.004**
Incidence of Nausea and Vomiting in Pivotal Phase 3 Studies

### Nausea

- **Oliceridine 0.1 mg**: 40% (N=153)
- **Oliceridine 0.35 mg**: 59% (N=158)
- **Oliceridine 0.5 mg**: 69% (N=159)
- **Placebo**: 35% (N=162)
- **Morphine 1 mg**: 70% (N=158)

43% Relative Risk Reduction  
**p < 0.001**

### Vomiting

- **Oliceridine 0.1 mg**: 20% (N=153)
- **Oliceridine 0.35 mg**: 30% (N=158)
- **Oliceridine 0.5 mg**: 42% (N=159)
- **Placebo**: 10% (N=162)
- **Morphine 1 mg**: 52% (N=158)

61% Relative Risk Reduction  
**p < 0.001**

41% Relative Risk Reduction  
**p < 0.001**
## Oliceridine Associated with Clinically Relevant Reductions in Nausea and Vomiting

<table>
<thead>
<tr>
<th>Oliceridine Dosing Regimen</th>
<th>Phase</th>
<th>Nausea</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Relative Risk Reduction vs Morphine</td>
<td>Relative Risk [95% CI]</td>
</tr>
<tr>
<td>0.1 mg</td>
<td>2b</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>0.35 mg</td>
<td>2b</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>15%</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Favors Oliceridine vs Morphine.*
Benefit-Risk Assessment

- Summary of comparative ORAEs
- Sufficiency of analgesia vs risks
Clinical Results Provide Support for G Protein Biased Ligand Hypothesis

Oliceridine

<table>
<thead>
<tr>
<th>Hypothesis (vs Conventional Opioids):</th>
<th>Current Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similar Analgesia</td>
<td>Met primary endpoint for all doses in both Phase 3 studies</td>
</tr>
<tr>
<td>Similar Liking / Dependence</td>
<td>Similar liking to equianalgesic morphine</td>
</tr>
<tr>
<td>Less Respiratory Depression</td>
<td>50% less opioid-induced respiratory depression vs morphine (gold standard)</td>
</tr>
<tr>
<td></td>
<td>Consistent reductions in safety events and interventions</td>
</tr>
<tr>
<td>Less Nausea / Vomiting</td>
<td>Consistently reduced in Phase 2 and 3 studies</td>
</tr>
</tbody>
</table>
# Positive Benefit-Risk Profile of Oliceridine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APOLLO 1: Relative Risk [95% CI]</th>
<th>APOLLO 2: Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory safety event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation &lt; 90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing interruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplemental O₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rescue antiemetics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Oliceridine 0.1 mg**: Favors Oliceridine
- **Oliceridine 0.35 mg**: Favors Morphine

Graphical representation of relative risks and confidence intervals for each parameter.
Clinical Perspective

Gregory Hammer, MD
Professor of Anesthesiology, Perioperative and Pain Medicine and of Pediatrics (Critical Care)
Stanford University Medical Center
Need for Incremental Improvement in IV Opioid Therapy

- Most surgical inpatients require IV opioids
  - Adequate pain management may be challenging
- No significant advances in IV opioids over several decades
- Biased ligands first in new class of targeted pain therapies
  - Opioid-level efficacy with fewer adverse effects
- Need to embrace step-wise approach
Oliceridine: First Step in Biased Ligand Discovery

- Important incremental improvement in pain management
- Provides opioid-level analgesia with improved safety and tolerability profile
IV Opioid Safety: Nausea and Vomiting

- Nausea and vomiting common opioid side-effects
  - Patients would rather avoid nausea/vomiting than pain\(^1\)
- May mitigate with antiemetics but come with other side effects

Oliceridine Associated with Clinically Relevant Reductions in Nausea and Vomiting

Phase 2b

- 3 in 4 morphine patients had nausea
  - Oliceridine reduced incidence by 35-40%
- 2 in 5 morphine patients experienced vomiting
  - Oliceridine reduced incidence by 64%

Phase 3

- 2 in 3 morphine patients had nausea
  - Oliceridine reduced incidence by 15-40%
- 1 in 2 morphine patients experienced vomiting
  - Oliceridine reduced incidence by 40-60%
Opioid-Induced Respiratory Depression

- Minimize risk by titrating medications gradually to effect
- Conventional IV opioids have narrow therapeutic window
- Overshoot opioid dose
  - Discontinue opioid
  - Administer or increase supplemental oxygen, high-flow nasal cannula therapy, or CPAP
  - Rare cases may need naloxone reversal, positive pressure ventilation
IV Oliceridine Reduces Opioid-Induced Respiratory Depression

- VRH gold standard for respiratory depression since 1960s
- 50% less respiratory depression vs equianalgesic morphine dose
Respiratory Safety Benefit: Consistent Safety Signal Across Clinical Studies

Phase 2b
- 1 in 2 morphine patients had hypoventilation event
  - Oliceridine reduced incidence by 40-70%

Phase 3
- 1 in 4 morphine patients had respiratory safety event
  - Oliceridine reduced incidence by 33-80%
- 1 in 4 morphine patients had PCA taken away for respiratory issues
  - Oliceridine reduced incidence by 40-80%
Clinical Practice: Titrate Dose to Response

- Initial loading dose (1 to 2 mg)
- Analgesia maintained with demand doses
  - PCA dose range: 0.1 to 0.35 mg
- 0.1 mg demand dose
  - Smaller, more “fragile” patients
  - History of opioid sensitivity, PONV
  - Relatively minor procedures
  - Sufficient in many patients
- Titrate dose as needed
Summary of Clinical Perspective

- IV opioids important medications with many safety liabilities
- Need to move beyond current opioid formulations
  - Make potent analgesic molecules safer
- Oliceridine first potent analgesic pharmacology engineered to reduce ORAEs
  - Reduces respiratory events, nausea, and vomiting
  - Does not eliminate ORAEs or reduce drug liking
- Incremental improvements should be embraced
Trevena Perspective on FDA Questions

Jonathan Violin, PhD
Co-founder and Senior Vice President of Scientific Affairs
Trevena, Inc.
### Trevena Perspective on FDA Questions

<table>
<thead>
<tr>
<th>FDA Question</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Substantial evidence of efficacy</strong></td>
<td>Superior to placebo in all pivotal Phase 3 studies</td>
</tr>
<tr>
<td></td>
<td>Comparable analgesic efficacy to morphine</td>
</tr>
<tr>
<td><strong>2. Adequacy of safety profile</strong></td>
<td></td>
</tr>
<tr>
<td>a. Safety database</td>
<td>&gt; 1,800 individuals have received oliceridine</td>
</tr>
<tr>
<td></td>
<td>Max daily dose of 40 mg based on median of top 350 exposures</td>
</tr>
<tr>
<td>b. Hepatic safety</td>
<td>Expert panel found no evidence for clinical safety issue</td>
</tr>
<tr>
<td>c. Respiratory safety</td>
<td>~50% less opioid-induced respiratory depression vs morphine</td>
</tr>
<tr>
<td></td>
<td>Consistent relative risk reductions in clinical studies</td>
</tr>
<tr>
<td>d. QT prolongation</td>
<td>No clinically meaningful risk for drug-induced arrhythmia</td>
</tr>
<tr>
<td><strong>3. Impact on public health</strong></td>
<td>Acute use in controlled setting</td>
</tr>
<tr>
<td></td>
<td>Similar abuse potential to morphine</td>
</tr>
<tr>
<td><strong>4. Approvability</strong></td>
<td>Meets regulatory requirements for approval</td>
</tr>
<tr>
<td></td>
<td>Incremental improvement vs conventional IV opioids</td>
</tr>
</tbody>
</table>
IV Oliceridine for the Management of Moderate-to-Severe Acute Pain in Hospital or Controlled Clinical Settings

October 11, 2018
Trevena, Inc.
Meeting of the Anesthetic and Analgesic Drugs Products Advisory Committee
BACKUP SLIDES
APOLLO Studies: Rescue Antiemetic Use

**APOLLO 1**
(Bunionectomy)

- Oliceridine 0.1 mg: 18%
- Oliceridine 0.35 mg: 35%
- Oliceridine 0.5 mg: 42%
- Placebo: 10%
- Morphine 1 mg: 61%

**APOLLO 2**
(Abdominoplasty)

- Oliceridine 0.1 mg: 33%
- Oliceridine 0.35 mg: 55%
- Oliceridine 0.5 mg: 61%
- Placebo: 28%
- Morphine 1 mg: 65%

Rescue Antiemetic Use (%)
[95% CI]
ATHENA: Concomitant Antiemetics

- Propulsives: 6%
- Serotonin Antagonists: 40%
- Peripheral Opioid Receptor Antagonists: 10%
- Other Antiemetics: 18%
APOLLO 1: Clinician and Patient Satisfaction Self-Reported Global Outcomes

Clinician View

- Oliceridine 0.1 mg
- Oliceridine 0.35 mg
- Oliceridine 0.5 mg
- Placebo
- Morphine

Patient View

- Oliceridine 0.1 mg
- Oliceridine 0.35 mg
- Oliceridine 0.5 mg
- Placebo
- Morphine

NOTE: ‘Dissatisfied’ = Mostly/Completely Dissatisfied
‘Satisfied’ = Mostly/Completely Satisfied
ATHENA: Benefit/Risk Evaluation by Sex

NRS: Change from Baseline

Discontinuation for AE and Lack of Efficacy (LoE)

Adverse Events

Female (N=498)  Male (N=270)
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
Phase 1: Oliceridine Showed Favorable Balance Between Analgesia and Respiratory Safety

**Analgesic Activity (Cold Pain Test)**

**Respiratory Depression (VRH)**

- **Mean Time in Cold Water (seconds)**
- **Mean % Change in Hypercapnic Minute Volume**

**Study 1003**
Figure 29: Cumulative Dose of Study Medication in APOLLO 1 and APOLLO 2

**APOLLO 1**
(Bunionectomy)  48 hours

- Oliceridine 0.1 mg (N=76)
- Oliceridine 0.3 mg (N=79)
- Oliceridine 0.5 mg (N=79)
- Morphine 1 mg (N=76)

**APOLLO 2**
(Abdominoplasty)  24 hours

- Oliceridine 0.1 mg (N=77)
- Oliceridine 0.3 mg (N=80)
- Oliceridine 0.5 mg (N=80)
- Morphine 1 mg (N=83)
APOLLO 2: Clinician and Patient Satisfaction
Self-Reported Global Outcomes

Clinician View

Patient View

% Reporting

Oliceridine 0.1 mg  Oliceridine 0.35 mg  Oliceridine 0.50 mg  Placebo  Morphine  Oliceridine 0.1 mg  Oliceridine 0.35 mg  Oliceridine 0.50 mg  Placebo  Morphine

NOTE: ‘Dissatisfied’ = Mostly/Completely Dissatisfied
‘Satisfied’ = Mostly/Completely Satisfied
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