Trevena®

Developing innovative therapies for patients with CNS disorders

Nasdaq: TRVN
November 2019
Forward-Looking Statements

To the extent that statements contained in this presentation are not descriptions of historical facts regarding Trevena, Inc. (the “Company” or “we”), they are forward-looking statements reflecting management’s current beliefs and expectations. Forward-looking statements are subject to known and unknown risks, uncertainties, and other factors that may cause our or our industry’s actual results, levels of activity, performance, or achievements to be materially different from those anticipated by such statements. You can identify forward-looking statements by terminology such as “may,” “will,” “should,” “expects,” “plans,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “intends,” or “continue,” or the negative of these terms or other comparable terminology. Forward-looking statements contained in this presentation include, but are not limited to, (i) statements regarding the timing of anticipated clinical trials for our product candidates; (ii) the timing of receipt of clinical data for our product candidates; (iii) our expectations regarding the potential safety, efficacy, or clinical utility of our product candidates; (iv) the size of patient populations targeted by our product candidates and market adoption of our potential drugs by physicians and patients; (v) the timing or likelihood of regulatory filings and approvals; and (vi) our cash needs.

Various factors may cause differences between our expectations and actual results, including: unexpected safety or efficacy data, unexpected side effects observed during preclinical studies or in clinical trials; lower than expected enrollment rates in clinical trials; changes in expected or existing competition; uncertainties regarding the regulatory submission and approval process; changes in the regulatory environment for our drug candidates; changes in our need for future capital; unexpected manufacturing or other supply disruptions; the inability to protect our intellectual property; and the risk that we become a party to unexpected litigation or other disputes. You should read our filings with the Securities and Exchange Commission, including the Risk Factors set forth in our Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q filed with the Securities and Exchange Commission and other filings the Company makes with the Securities and Exchange Commission from time to time, completely and with the understanding that our actual future results may be materially different from what we expect. Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.
# Trevena’s Experienced Leadership Team

## Senior Management

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
<tr>
<td>Carrie L. Bourdow</td>
<td>President &amp; Chief Executive Officer</td>
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<tr>
<td>Mark A. Demitrack, M.D.</td>
<td>SVP, Chief Medical Officer</td>
</tr>
<tr>
<td>Barry Shin</td>
<td>SVP, Chief Financial Officer</td>
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<tr>
<td>Robert T. Yoder</td>
<td>SVP, Chief Business Officer</td>
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</tbody>
</table>

## Board of Directors

<table>
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<tr>
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<tr>
<td>Leon O. Moulder, Jr.</td>
<td>Chairman of the Board</td>
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<tr>
<td>Carrie L. Bourdow</td>
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<tr>
<td>Scott Braunstein, M.D.</td>
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<tr>
<td>Michael R. Dougherty</td>
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<tr>
<td>Maxine Gowen, Ph.D.</td>
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<tr>
<td>Julie H. McHugh</td>
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<td>Jake R. Nunn</td>
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<tr>
<td>Anne M. Phillips, M.D.</td>
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<td>Barbara Yanni</td>
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Trevena: Innovative CNS Company

Lead asset
IV oliceridine
- New MOA designed to improve on IV morphine for acute pain

Clear regulatory
pathway
- NDA resubmission expected Q1 2020
- All items completed to address CRL

Large market,
targeted launch
- 45M+ US hospital patients; 9M at higher risk for AEs (initial focus)
- Focused launch plan, supported by market research/publications

Novel
CNS pipeline
- New mechanisms: acute migraine, opioid use disorder, pain
- Large markets with significant unmet medical need

Strong financial
position
- $44.7M in cash / marketable securities (9/30/19)
- Funds operations into Q3 2020
### Near-Term Catalysts Across Pipeline

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<th>Product</th>
<th>Stage</th>
<th>Indication</th>
<th>Expected Catalysts</th>
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<td><strong>OLICERIDINE</strong></td>
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<td>Moderate-to-severe acute pain (IV)</td>
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<td>Ph3</td>
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<td>NDA</td>
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Oliceridine, TRV250, TRV734, and TRV045 are investigational products and are not approved by the FDA or any other regulatory agency.

POC = Proof of Concept; NIDA = National Institute on Drug Abuse
IV Oliceridine Value Proposition

IV opioids are necessary for effective acute pain management

**US injectable analgesic hospital market unit volume**

- 45% IV Opioids
- 38% Local anesthetics
- 17% IV NSAIDs/acetaminophen

**Conventional IV opioids**

- e.g. IV morphine, IV hydromorphone

**Primary advantages:**
- Unrivalled analgesic efficacy

**Primary disadvantages:**
- Respiratory depression
- Nausea, vomiting, ileus

---

1) IMS MIDAS sales audit 2017; IV NSAIDs and Ofirmev®. 2) Healogix hospital physician market research (N=91), August ‘16.
Designed to Improve on Conventional IV Opioids

If approved, oliceridine is expected to be a CII controlled substance, as defined in the Controlled Substances Act of 1970.  
1) 2032 composition of matter expiration does not include potential patent extension.

4 head to head clinical studies vs. morphine
Clinical data in at-risk patient populations
Long patent life (2032)¹

1) 2032 composition of matter expiration does not include potential patent extension.
IV Oliceridine: Compelling Product Profile

- Unique MOA
- Demonstrated safety & tolerability
- No dosage adjustment for elderly or renally impaired
- IV opioid-level efficacy
- Rapid onset
- No known active metabolites

If approved, oliceridine is expected to be a CII controlled substance, as defined in the Controlled Substances Act of 1970. Data based on Phase 1-3 clinical trials including comparisons of oliceridine to IV morphine.
Oliceridine achieved IV opioid-level efficacy & fast onset

### Ph3: Hard Tissue Surgery

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>0.1</th>
<th>0.35</th>
<th>0.5</th>
<th>Morphine (1 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic Responder Rate (%)</td>
<td><img src="graph1.png" alt="Graph" /></td>
<td><img src="graph2.png" alt="Graph" /></td>
<td><img src="graph3.png" alt="Graph" /></td>
<td><img src="graph4.png" alt="Graph" /></td>
<td><img src="graph5.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

P = 0.0001

Published in *The Journal of Pain Research*¹

### Ph3: Soft Tissue Surgery

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>0.1</th>
<th>0.35</th>
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<td><img src="graph5.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

P = 0.0004

Published in *Pain Practice*²

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Morphine regimen: 4 mg loading bolus, with 1 mg available on demand as often as every 6 minutes. Oliceridine regimens: 1.5 mg loading bolus, with 0.1, 0.35, or 0.5 mg available on demand every 6 minutes. Displayed p-values are for oliceridine vs. placebo with Hochberg multiplicity adjustment.

#p < 0.05 vs. placebo (unadjusted)

Consistent Respiratory Safety Profile

Phase 1:
• **Reduced** impact on hypercapnic respiratory drive vs. morphine\(^1\)

Phase 2:
• **Decreased** incidence of hypoventilation events vs. morphine\(^2\)

Phase 3:
• **Reduced** overall respiratory safety burden
• **Reduced** underlying respiratory safety events and treatment interruptions\(^3,4\)

\(^*p < 0.05\) vs. morphine. Hypoventilation: clinically apparent and persistently decreased respiratory rate, respiratory effort, or oxygen saturation.

1) Soergel, et al. (2014).  
4) Singla, et al. (2019)
Strong Support in “Real World Use” Study

Safety and tolerability demonstrated in broad range of surgeries with at-risk patients

Multiple inpatient and outpatient settings
- hospital recovery
- critical care
- emergency department
- ambulatory surgical centers (bolus and PCA dosing)

At-risk patients were well represented
- ~30% > 65 years; ~50% BMI > 30
- Co-morbidities: diabetes, chronic / cancer pain, obstructive sleep apnea
- Concomitant medications: antiemetics, antibiotics

Low discontinuation for AEs / lack of efficacy
- 2% for adverse events
- 4% for lack of efficacy

Trial modeled real-world use: usual patient care with oliceridine instead of standard IV opioid
Overview of Cardiac Safety Data

- **Max proposed dose (3mg):** No clinically significant effect on QTc
- **Supratherapeutic dose (6mg):** Small transient increase in QTc interval, peak at one hour
- **Pivotal studies (n=790):** No differences seen between oliceridine, morphine and placebo
- **Open label study (n=768):** 22 pts with QT prolongation in “real world” study
  - Many with confounding factors, QT prolongation at baseline
  - No patients with ventricular arrhythmias

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1) Design based on FDA E14 Guidance: Clinical Evaluation of QT / QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
Multi-Dose tQT Study

No Accumulation Despite Repeated Dosing

Key results

- **No accumulation through 24 hrs**
  Mean QTcI <10ms at 22 of 24 points

- **No categorical QTc outliers**
  $\Delta >60$ ms; $>500$ ms absolute

- **Well tolerated, no SAEs***
  92% reached max daily dose

*N = 68 healthy volunteers

---

*3 subjects not dosed due to lack of venous access

1 discontinuation due to a non-serious adverse event (asymptomatic non-sustained ventricular tachycardia) with confounding hypokalemia and no meaningful QT prolongation during dosing

1 subject completed dosing but not evaluable due to equipment malfunction

---

Primary endpoint: $\Delta \Delta$ QTcI (hourly); secondary endpoints: categorical QTc outliers, mean change in QTcI (24 hrs)
Clear Regulatory Path to NDA Resubmission

NDA resubmission expected Q1 2020

All activities to address CRL now complete

- Completed healthy volunteer QT study
- Safety database supports maximum daily dose of 27mg
- PK study characterized exposure of inactive metabolite (‘9662)
- Completed drug product validation reports
Focused Hospital Launch Plan

Initial focus: at-risk patients in 3 key surgical areas

Patients

~45M patients in the US

~9M at-risk patients
  - Co-morbidities
  - Obese
  - Renal impairment
  - Elderly

Physician specialties

~12 specialties across settings

~4 specialties
  - Anesthesiology
  - Orthopedic
  - Colorectal
  - Cardiothoracic

Hospitals

~5,800 hospitals in the US

~600 hospitals
  - Community
  - Large Regional Systems
  - Hospital outpatient
  - Ambulatory surgical centers
Hospital Outpatient Will Accelerate Early Uptake

Physician trial in outpatient can accelerate inpatient uptake

Hospital Outpatient

Target:
At-risk ("CORE") patients

Ambulatory Surgical Center

Target:
Ortho and colorectal
Positive Feedback from Formulary Stakeholders\textsuperscript{1,2,3}

Majority of formulary stakeholders believe that oliceridine pivotal data is clinically meaningful:

<table>
<thead>
<tr>
<th>Key Endpoint (vs. IV morphine)</th>
<th>Pharmacy (n=160)</th>
<th>Physicians (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in Respiratory Safety Events</td>
<td>74%</td>
<td>90%</td>
</tr>
<tr>
<td>Reduction in Vomiting</td>
<td>70%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Hospital pharmacy will consider:

- Robust peer-reviewed clinical evidence
- Price: $60-$100/day range identified in market research with formulary stakeholders
- Compelling health economic model

1) Source: Quantitative Price-Access Survey (n=200), Charles River Associates 2017. 2) “Are the improvements in the following respiratory/GI safety endpoints clinically meaningful?” Based on oliceridine Ph3 clinical trial data. 3) Source: Quantitative Price-Access Survey (n=200), Charles River Associates 2017. Average acquisition cost per full day across dose and mode of administration range.
Hospital Focus: Improve Outcomes and Decrease Costs

~50% higher costs associated with IV opioid adverse events

- Inpatients with opioid-related AEs have **3.4x risk** of mortality
- Opioid-induced nausea / vomiting can add hospital costs up to **$8,826** per patient
- One critical **respiratory event** or its sequelae can add up to **$28,000** per event
  - 4 days in ICU
  - 7 additional days in hospital

ORAE = opioid-related adverse event; costs are per hospital stay
Hospital Trends: Potential Drivers for Oliceridine

Hospitals

Penalized for readmission and hospital acquired infections

Patient care

Increase in patients at high-risk for adverse events

- ~40% elderly patients\(^1\)
- 30%+ US adults are obese\(^2\)
- 37M Americans have chronic kidney disease\(^3\)
- ~40-50% incidence of respiratory depression\(^4\)

Surgical practice

Increase in complex, painful surgeries\(^5\)

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1) CDC, National Hospital Discharge Survey 2010. 2) AHRQ HCUP statistical brief #137. 3) CDC Fact Sheet, Chronic Kidney Disease in the United States, 2019. 4) In patients receiving IV morphine; Khanna, A. et al., Critical Care Medicine, 2018 via continuous monitoring. 5) SG2 Healthcare Intelligence. Icons made by Freepik from www.flaticon.com
Comprehensive Data Available at Launch
Will support future commercialization and hospital formulary uptake

**Health Care Practitioners (HCPs)**
- First-in-class new mechanism of action
- Fast, effective IV opioid-level pain relief
- Clinical data in at-risk patients / targeted surgeries

**Hospital Formulary Committees**
- Published head-to-head trials vs. IV morphine
- Published data in at-risk patients & target surgeries
- Published health economic / cost offset data*

*Will be published at time of approval / launch*
Focused Launch Strategy Allows for Growth

Patient risk factors, e.g.
- Co-morbidities
- Obese
- Renal impairment
- Elderly

Procedure risk factors, e.g.
- Severe / prolonged pain
- Ortho, colorectal, cardiothoracic

45M patients

~9M patients
(initial launch years)
### Near-Term Catalysts Across Pipeline

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<th></th>
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<th>Ph1</th>
<th>Ph2</th>
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<th>Expected catalysts</th>
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<tr>
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<td>Moderate-to-severe acute pain</td>
<td>IV</td>
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<td>Q1 20: NDA resubmission</td>
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<tr>
<td>G protein-selective agonist (mu-opioid receptor)</td>
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<td><strong>TRV734</strong></td>
<td>Opioid use disorder</td>
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<td>Novel S1P receptor modulator</td>
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Delta receptor: Untapped potential in CNS space

Delta receptors have unique distribution throughout the brain

Play important role in regulation of pain, mood, and anxiety

Acute migraine proof-of-concept study initiated

• Validated biomarker model (NTG infusion)
• Test dose: 20 mg subcutaneous TRV250 vs. placebo (n=~120 migraineurs)
• Primary outcome: reduction of sustained NTG-induced headaches
• Secondary outcomes: reduction of symptomatic anxiety, general safety
• Topline data expected in 2H 2020
TRV734: Maintenance Therapy for Opioid Use Disorder

Selective agonism at $\mu$ receptor: Potential for improved tolerability

Ongoing collaboration with National Institute on Drug Abuse (NIDA)

- Nonclinical evidence of improved tolerability with TRV734
- NIDA study demonstrated reduced drug-seeking behavior in animal model of relapse
- Current therapies not well tolerated, can hinder patient adherence

>2.5M people in U.S. suffer from opioid use disorder\textsuperscript{1}

NIDA-funded proof of concept patient study expected to initiate in Q4 2019

\textsuperscript{1} Center for Behavioral Health Statistics and Quality
TRV045: Non-Opioid Chronic Pain Relief

New MOA at S1P receptor without associated lymphopenia
IND-enabling activities planned for 2H 2019

• S1P receptors in the CNS play unique role in modulating neurotransmission/membrane excitability

• New mechanism of S1P receptor stimulation without immune-suppressing activity

• Novel, non-opioid mechanism
  - e.g. chronic pain, chemotherapy-induced peripheral neuropathy, diabetic neuropathic pain, inflammatory pain

CIPN mouse model: Paclitaxel 6 mg/kg, i.p. on days 1, 3, 5, 7; fingolimod dosed p.o.; TRV compound dosed s.c. Hyperalgesia measured as % non-response to 0.4 g Von Frey filament vs. baseline, tested 30' after dosing.
*p<0.05 vs. control by ANOVA with Bonferroni correction. Data are mean ± s.e.m. n=7-8 rats/group.

Active in preclinical models of chronic pain
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<th>• New MOA designed to improve on IV morphine for acute pain</th>
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APPENDIX
Robust Clinical Development Program

oliceridine studied in > 1,800 individuals

Phase 1
- No dosage adjustments for elderly / renally impaired
- No known active metabolites

Phase 2
4 head-to-head trials vs. morphine:
- IV opioid-level efficacy with rapid onset of action
- Well-characterized respiratory safety profile
- Low rates of vomiting and rescue antiemetic use

Phase 3

Large safety study:
- Real-world use in at-risk patients and target surgeries

Proposed Indication:
Management of moderate to severe acute pain in adult patients for whom an IV opioid is warranted

# subjects exposed to oliceridine in Ph1 = 318
# patients treated with oliceridine in Ph2 and Ph3 = 1,535
Favorable GI Tolerability and Safety Profile

Phase 2:
- **Reduced** incidence of nausea and vomiting adverse events vs. morphine¹

![Graph showing reduced incidence of nausea and vomiting](image)

Phase 3:
- **Reduced** incidence of post-operative nausea and vomiting
- **Reduced** use of rescue antiemetics
- **Reduced** proportion of patients with vomiting or antiemetic use²,³

![Graph showing % experiencing NO vomiting and NO antiemetic use](image)

Superiority of the GI safety and tolerability of oliceridine vs. morphine has not been established in randomized controlled clinical trials.

GI = gastrointestinal
* p < 0.05 vs. morphine
Rapid Onset of Pain Relief

Consistent across Phase 2 and Phase 3 studies

• In as-needed dosing paradigms in Phase 3 trials, efficacy signal noted as soon as 5 minutes after first dose

• After a single IV bolus in a Phase 2 study, median meaningful pain relief was in 2-5 minutes

• Rapid equilibration across blood brain barrier reduces risk of dose-stacking and “over-shooting” effect

Time to meaningful pain relief
Phase 2 bunionectomy study

<table>
<thead>
<tr>
<th>Dose</th>
<th>50%</th>
<th>68%</th>
<th>81%</th>
<th>97%</th>
<th>56%</th>
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<tbody>
<tr>
<td>0.5 mg</td>
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<td>1 mg</td>
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<tr>
<td>2 mg</td>
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<tr>
<td>3 mg</td>
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<tr>
<td>Morphine 4 mg</td>
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</table>

% reporting meaningful pain relief after 1st dose

Data shown are from Phase 2 bunionectomy study; Viscusi et al, PAIN 2015
*p = 0.01 vs. morphine; **p < 0.0001 vs. morphine by Wald test from Cox-proportional regression
# APOLLO 1: Most Common TEAEs

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=79)</th>
<th>Oliceridine 0.1mg (N=76)</th>
<th>Oliceridine 0.35mg (N=79)</th>
<th>Oliceridine 0.5mg (N=79)</th>
<th>Morphine 1mg (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (24.1)</td>
<td>27 (35.5)</td>
<td>44 (55.7)</td>
<td>50 (63.3)</td>
<td>49 (64.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (6.3)</td>
<td>13 (17.1)</td>
<td>31 (39.2)</td>
<td>32 (40.5)</td>
<td>38 (50.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (10.1)</td>
<td>21 (27.6)</td>
<td>25 (31.6)</td>
<td>28 (35.4)</td>
<td>26 (34.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>24 (30.4)</td>
<td>19 (25.0)</td>
<td>20 (25.3)</td>
<td>26 (32.9)</td>
<td>23 (30.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (11.4)</td>
<td>8 (10.5)</td>
<td>9 (11.4)</td>
<td>11 (13.9)</td>
<td>13 (17.1)</td>
</tr>
<tr>
<td>Somnolence, Sedation</td>
<td>6 (7.6)</td>
<td>6 (7.9)</td>
<td>19 (24.1)</td>
<td>13 (16.5)</td>
<td>12 (15.8)</td>
</tr>
<tr>
<td>Pruritus, Generalized pruritus</td>
<td>6 (7.6)</td>
<td>2 (2.6)</td>
<td>15 (19.0)</td>
<td>5 (6.3)</td>
<td>24 (31.6)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>4 (5.1)</td>
<td>4 (5.1)</td>
<td>12 (15.8)</td>
</tr>
</tbody>
</table>

**TEAE** = treatment-emergent adverse event

“Most common” refers to TEAEs occurring in ≥ 10% of patients in any treatment group

Discontinuations for safety/tolerability: 0 for placebo; 0, 1, and 4 for oliceridine 0.1, 0.35, and 0.5 mg; 6 for morphine
APOLLO 2: Most Common TEAEs

<table>
<thead>
<tr>
<th>Most common TEAEs, n (%) of patients</th>
<th>Placebo (N=83)</th>
<th>Oliceridine 0.1mg (N=77)</th>
<th>Oliceridine 0.35mg (N=79)</th>
<th>Oliceridine 0.5mg (N=80)</th>
<th>Morphine 1mg (N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>38 (45.8)</td>
<td>34 (44.2)</td>
<td>49 (62.0)</td>
<td>60 (75.0)</td>
<td>61 (74.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (13.3)</td>
<td>18 (23.4)</td>
<td>17 (21.5)</td>
<td>34 (42.5)</td>
<td>44 (53.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>24 (28.9)</td>
<td>12 (15.6)</td>
<td>23 (29.1)</td>
<td>21 (26.3)</td>
<td>24 (29.3)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>4 (4.8)</td>
<td>6 (7.8)</td>
<td>16 (20.3)</td>
<td>14 (17.5)</td>
<td>19 (23.2)</td>
</tr>
<tr>
<td>Pruritus, Generalized pruritus</td>
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<td>25 (30.5)</td>
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<tr>
<td>Dizziness</td>
<td>9 (10.8)</td>
<td>11 (14.3)</td>
<td>7 (8.9)</td>
<td>7 (8.8)</td>
<td>13 (15.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (6.0)</td>
<td>3 (3.9)</td>
<td>10 (12.7)</td>
<td>9 (11.3)</td>
<td>7 (8.5)</td>
</tr>
</tbody>
</table>

TEAE = treatment-emergent adverse event
“Most common” refers to TEAEs occurring in ≥ 10% of patients in any treatment group
Discontinuations for safety/tolerability: 0 for placebo; 0, 4, and 4 for oliceridine regimens 0.1, 0.35, and 0.5 mg; 2 for morphine
TRV250 PoC Study (acute migraine)

Study initiated 4Q19; Topline data expected 2H20

**Study Outline**

n = ~120 migraineurs w/o aura

- **NTG Infusion** (0.5μg/kg/min)
- **TRV250** 20mg SC
- **Placebo** (SC)

**Assessment of safety and effectiveness**

@ 60 min

**Recovery and final assessment**

20 mins

8 hrs

24hrs post-drug administration

**Primary endpoint:**
- reduction of sustained NTG-induced headaches @ 4hr

**Secondary Endpoints:**
- Pain response or pain freedom @ 6hr / 8hr
  - Anxiety symptom relief
  - Overall safety & tolerability