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 "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "objective," "predict," "project," "suggest," "target," "potential," "will," "would," "could," "should," "continue," "ongoing," or the negative of these terms or similar expressions. 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.

Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the commercialization of any approved drug product, the status, timing, costs, results and interpretation of our clinical trials or any future trials of any of our investigational drug candidates; the uncertainties inherent in conducting clinical trials; expectations for regulatory interactions, submissions and approvals, including our assessment of the discussions with the FDA or other regulatory agencies about any and all of our programs; uncertainties related to the commercialization of OLINVYK; available funding; uncertainties related to our intellectual property; uncertainties related to the ongoing COVID-19 pandemic, other matters that could affect the availability or commercial potential of our therapeutic candidates; and other factors discussed in the Risk Factors set forth in our Annual Report on Form 10-K and Quarterly Reports on Form 10-Q filed with the Securities and Exchange Commission (SEC) and in other filings we make with the SEC from time to time. In addition, the forward-looking statements included in this presentation represent our views only as of the date hereof. We anticipate that subsequent events and developments may cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we specifically disclaim any obligation to do so, except as may be required by law.
# Trevena’s Experienced Leadership Team

## SENIOR MANAGEMENT

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrie L. Bourdow</td>
<td>President &amp; Chief Executive Officer</td>
<td>Cubist, Merck</td>
</tr>
<tr>
<td>Scott Applebaum</td>
<td>SVP, Chief Legal &amp; Regulatory Officer</td>
<td>Shire, Vitae, Bristol Myers Squibb</td>
</tr>
<tr>
<td>Mark A. Demitrack, M.D.</td>
<td>SVP, Chief Medical Officer</td>
<td>Neuronetics, Lilly, Roivant</td>
</tr>
<tr>
<td>Barry Shin</td>
<td>SVP, Chief Financial Officer</td>
<td>Mizuho, Guggenheim, PiperJaffray</td>
</tr>
<tr>
<td>Robert T. Yoder</td>
<td>SVP, Chief Commercial Officer</td>
<td>Merck, Cresset, Inc.</td>
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## BOARD OF DIRECTORS

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Leon O. Moulder, Jr.</td>
<td>Tesaro, MG</td>
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<td>Carrie L. Bourdow</td>
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<td>Julie H. McHugh</td>
<td>Centocor, Johnson &amp; Johnson, Endo</td>
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<td>Scott Braunstein, M.D.</td>
<td>Marinus Pharmaceuticals, Aisling Capital, Pacira</td>
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<td>Jake R. Nunn</td>
<td>NEA.</td>
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<td>Michael R. Dougherty</td>
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<td>Anne M. Phillips, M.D.</td>
<td>Meridian, Guggenheim</td>
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<td>Maxine Gowen, Ph.D.</td>
<td>Merck</td>
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<tr>
<td>Barbara Yanni</td>
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<tr>
<td><strong>Trevena: Innovative CNS Company</strong></td>
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| **IV OLINVYK:** Differentiated profile | NCE approved for the management of acute pain in adults  
Commercial launch in Q1 2021 |
|----------------------------------------|-------------------------------------------------|
| **Large market, targeted launch**     | 45M+ US hospital patients; 9M procedures is initial core focus  
$1.5B+ market opportunity for core focus |
| **Novel CNS pipeline**                | New mechanisms for acute migraine, opioid use disorder, epilepsy, pain  
NCEs targeting significant unmet needs |
| **TRV027 for COVID-19**              | Novel MOA to treat COVID-19 acute lung injury / abnormal clotting  
PoC study in collab with Imperial College London; primary completion date expected in 1H 2021 |
| **Strong financial position**        | $112.7M cash and cash equivalents as of 9/30/2020  
Funds operations through Q4 2022 |

OLINVYK is indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at [www.OLINVYK.com](http://www.OLINVYK.com).
## Multiple Expected Catalysts

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<th>PRE-CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
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<td>New chemical entity</td>
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<td>(mu-opioid receptor)</td>
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<td>Opioid use disorder</td>
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<td>Collaboration with National Institute on Drug Abuse</td>
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<td>Novel S1P receptor modulator</td>
<td>CNS disorders</td>
<td>oral</td>
<td></td>
<td></td>
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</tbody>
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*ARDS = Acute Respiratory Distress Syndrome; IND = Investigational New Drug; PoC = Proof-of-Concept.*
OLINVYK: Differentiated Profile for Acute Pain

OLINVYK is indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.

Ease of use in clinical practice
Bolus / PCA; no active metabolites

New chemical entity
Distinct from IV morphine

Data in complex patients
Elderly, obese, renal impaired

IV opioid efficacy
Hard- and soft-tissue surgeries

Well-characterized safety / tolerability
IV morphine data included in label

Rapid analgesia
2-5 min onset of pain relief

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.
OLINVYK: Broad Indication for Acute Pain

Large acute market opportunity

US injectable analgesic hospital market unit volume\(^1\)

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

45M patients receive IV opioids annually to treat acute pain\(^1\)

- Unrivalled analgesic efficacy
- Top surgeries: Total knee arthroplasty, colectomy, hernia repair, spine fusion, C-section\(^2\)

OLINVYK is indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

NSAIDs = nonsteroidal anti-inflammatory drugs. 1) IMS MIDAS sales audit 2017; IV NSAIDs and Ofirmev\(^\circledR\). 2) Definitive database, and National Vital Statistics report, CDC 2018.
OLINVYK: Distinct From IV Morphine / Hydromorphone

Studied in >1,900 individuals

IV morphine included as active comparator

NCE with 2032+ COM patent\(^1\)

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

\(^1\) 2032 composition of matter patent expiration does not include potential patent extensions.
OLINVYK: IV Opioid Efficacy and Rapid Onset

- Efficacy achieved in hard tissue & soft tissue models
- Rapid onset: perceptible pain relief within 2-5 minutes
- OLINVYK efficacy data in peer-reviewed journals
  
  *The Journal of Pain Research*¹ and *Pain Practice*²

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Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at [www.OLINVYK.com](http://www.OLINVYK.com).

OLINVYK: Well-Characterized Safety / Tolerability

<table>
<thead>
<tr>
<th>Patients with any TEAE (%)</th>
<th>Placebo (N = 162)</th>
<th>OLINVYK ≤ 27 mg (N = 316)</th>
<th>Morphine (N = 158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>73</td>
<td>86</td>
<td>96</td>
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<tr>
<td>Vomiting</td>
<td>35</td>
<td>52</td>
<td>70</td>
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<tr>
<td>Headache</td>
<td>10</td>
<td>26</td>
<td>52</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>9</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Sedation</td>
<td>6</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Hot flush</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Pruritus gen.</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

Adverse drug reactions reported in ≥5% of OLINVYK-treated patients stratified by daily dose (Phase 3 pivotal trials pooled)¹

Key cost-drivers associated with IV opioids:

- **Vomiting**
  - Can result in significant health risks and compromise recovery

- **Somnolence**
  - Significant patient safety concern, can lead to respiratory depression

- **O₂ saturation < 90%**
  - Independent predictor of early post-op respiratory complications

---

1) OLINVYK Prescribing Information. Not an adequate basis for comparison of rates between the OLINVYK treatment group and the morphine treatment group.

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.
Data in “Real World Use”: Complex Surgeries & Patients

Broad range of surgeries / medical procedures

Complex patients were included

- 32% ≥ 65 years; 46% BMI ≥ 30
- Co-morbidities: diabetes, obstructive sleep apnea, COPD, chronic / cancer pain
- Concomitant medications: antiemetics, antibiotics

Multiple inpatient and outpatient settings

- Hospital recovery
- Critical care
- Emergency department
- Ambulatory surgical centers

Low discontinuation for AEs / lack of efficacy

- 2% for adverse events
- 4% for lack of efficacy

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

See FDA draft guidance for Industry Distributing Scientific and Medical Publications on Unapproved New Uses.
OLINVYK: Ease of Dosing and Administration

3 vials allow for flexible and tailored IV dosing

- **Bolus Dosing:** 1 mg and 2 mg vials (single dose)

- **PCA Dosing:** 30 mg vial (single patient use)

- **OLINVYK 1 mg ≈ morphine 5 mg\(^1\)**

27 mg cumulative daily dose limit

Do not administer single doses greater than 3 mg

No refrigeration / reconstitution

WAC:
- 1 mg / 1mL: $17.50
- 2 mg / 2mL: $25.75
- 30 mg / 30 mL: $110.00

~$100 / day (estimated avg cost across procedures)

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

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1) For an initial dose. PCA = Patient-Controlled Analgesia
Customer Engagement Strategy
Comprehensive Data Available at Launch

Will support future commercialization and hospital formulary uptake

Health Care Practitioners (HCPs)
- New chemical entity
- Fast, effective IV opioid pain relief
- Clinical data in complex patients / targeted surgeries

Hospital Formulary Committees
- Published head-to-head trials vs. IV morphine
- Published health economic / cost offset data*

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVK.com.

*Expected to be published at time of launch
Robust Set of Peer-Reviewed Publications

Comprehensive overview of OLINVYK development program

OLINVYK nonclinical / Phase 1 / Phase 2 data

- 15 publications
  - 4 head-to-head studies vs. IV morphine
    - IV opioid efficacy
    - Well-characterized safety and tolerability
  - Data in complex patients / surgery types
  - Respiratory safety data in elderly / obese
  - Respiratory safety profile measured by dosing interruptions
  - Clinical utility vs. IV morphine - benefit-risk analysis
  - Reduced risk of N / V - complete GI response analysis

OLINVYK Phase 3 trials & secondary analyses

- 9 publications

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com. See www.trevena.com for full manuscripts and abstracts. These publications will be used in a manner consistent with FDAMA sections 114 and 401 and the FDA Guidances thereunder.
Positive Feedback from Formulary Stakeholders¹

~75% of formulary stakeholders find OLINVYK’s published data clinically meaningful:²

<table>
<thead>
<tr>
<th>Key Endpoint (vs. IV morphine)</th>
<th>Pharmacist (n=50)</th>
<th>Physician (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Safety Events and GI Tolerability</td>
<td>72%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Majority of stakeholders view IV morphine as likely to be replaced by OLINVYK:

- IV morphine (66)
- IV hydromorphone (41)
- IV fentanyl (23)
- Ofirmev (14)
- Exparel (13)
- Other (2)

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

1) Qualitative Pricing research, Charles River Associates, April 2020. 2) “Are the improvements in respiratory safety events and GI tolerability clinically meaningful?” Based on OLINVYK Ph3 clinical trial data.
Hospital Formulary Considerations for New Products

Cost Burden of Adverse Events

- **$8,826** in hospital costs per patient for nausea / vomiting\(^1\)
- **$28,000** per critical respiratory event / sequelae\(^2\)
- Increased hospital length of stay: ~7 additional days\(^2\)

Why OLINVYK?

- Compelling clinical data
  - Differentiated acute pain profile
  - Head-to-head peer-reviewed clinical evidence versus IV morphine\(^3\)
- Compelling health economic model
  - >10x net savings for hospitals\(^4\)

---

1) Oderda, GM, J Pain Palliative Care Pharm, 2019; data based on 5 surgical procedure categories including Cardiothoracic / vascular, General / Colorectal, Ob / Gyn, Orthopedic, and Urologic. 2) Overdyk FJ, PLoS One, 2016. 3) These publications will be used in a manner consistent with FDAMA sections 114 and the FDA Guidance thereunder. 4) Data on file.
Targeted Account Launch

Initial focus: complex patients in 3 key surgical areas

Physician specialties

~4 specialties
- Anesthesiology
- Orthopedic
- Colorectal
- Gynecologic

Inpatient & hospital outpatient

~550 hospitals
- Community
- Large regional systems
- Hospital outpatient
- Ambulatory surgical centers

~500 ASCs

40 customer-facing roles
- Hospital Account Executives
- Medical Science Liaisons

Includes virtual HCP engagement

Medical Education programs
Customer Facing Organization

Partnering with Syneos Health to provide “best in class” commercial support

- Allows for execution speed and flexibility in deployment
- Full range support: source, hire, train and deploy customer-facing roles
- Ability to flex as business needs evolve

40 Customer-Facing Roles

- **Sales**: Institutional Account Managers
- **Trade & Access**: Regional Account Managers
- **Medical**: Medical Science Liaisons
Principles for Deploying Commercial Resources

**Strategic priorities**

- Expand awareness of OLINVYK
- Initiate appropriate trials of OLINVYK
- Expand use among targeted procedures and patients

**Put the right resource**

- MSLs
- KAMs
- Reps

**In the right location**

- Tele-sales

**At the right time**

- Digital engagement
- Peer-to-peer education

**Data-driven decisions**

- Leverage Syneos call data
- Definitive Health – ICD-10 codes for labs
- IQVIA claims data
- Year-over-year utilization data (DDD)
Multi-Channel Strategy for HCP Engagement

Communication across a full range of channels to maximize reach and impact

Customize mix across channels with targeted HCPs

- Olinvyk.com
- Field directed: live, virtual & email
- Virtual “on demand” Medical Education programs
- Professional Society Meetings & Congresses
- HCP social media
“Now Available” Campaign

“Now Available” Website
- Order/Reimbursement/Dosing Guides
- Connect with Medical Affairs and/or Sales Rep

“Now Available” Drivers
- Programmatic Banner Ads
  - Banner ad messaging to connect HCPs through digital journey
- Journal Ads
  - Ads will run in *American Journal of Health-System Pharmacy, Pharmacy Purchasing & Products*
- Select Emails to Key Health Care Professionals
  - Emails to provide online introduction to OLINVYK
OLINVYK Approval Strategy Allows for Growth

Initial core focus (9M)
- Broad indication & dosing / admin
- IV opioid efficacy & fast onset
- Complex patients: elderly, obese, renal

~15M days of therapy (initial core focus) = $1.5B+ market opportunity*

Expanded areas of focus (28M)
- Leverage respiratory and GI safety vs. IV morphine to expand surgical procedures
- Cognitive function & additional HECON

Source: Definitive Healthcare; American Hospital Association. *Assumes ~$100 / day price for oliceridine

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.
TRV027

NCE targeting the AT$_1$ receptor in COVID-19
Multi-Organ Damage From Coronavirus

Elimination of ACE2 protein leads to critical hormonal imbalances

Coronavirus binds to and eliminates ACE2

- Leads to accumulation of angiotensin II:
  - Acute lung injury and abnormal blood clots
  - Can lead to ARDS / pulmonary embolism / stroke
- 66% - 94% mortality rate for COVID-19 related ARDS
- ~1/3 of hospitalized COVID-19 patients develop clotting complications

TRV027: New MOA for COVID-19

Mechanism targeted to improve lung function and prevent abnormal clotting

Angiotensin II → AT₁ receptor → G protein → β-arrestin

TRV027

Cell surface

Cell interior

Lung damage
Abnormal blood clots

Lung repair
Anti-inflammatory

TRV027 is the only selective AT₁ receptor agonist
Safety / tolerability established in ~700 patients
TRV027 COVID-19 Study - Imperial College London

Investigate effect of TRV027 on blood clotting, lung function, and other clinical outcomes

- Randomized, double-blind, placebo-controlled proof-of-concept study

- N = ~60 (30 per arm) COVID-19 patients
  - Hospitalized, non-ventilated
  - ≥18 years old

- IV infusion of placebo or TRV027 for 7 days (12 mg/hr)

- Study currently ongoing, primary completion date expected in 1H 2021

Primary endpoint:

Reduction of abnormal clotting associated with COVID-19*

Indicator of TRV027’s effect on health outcomes associated with increased mortality in COVID-19

## Multiple Expected Catalysts

<table>
<thead>
<tr>
<th>Expected Catalyst</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
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TRV250, TRV734, TRV027, and TRV045 are investigational products and are not approved by the FDA or any other regulatory agency.

ARDS = Acute Respiratory Distress Syndrome; IND = Investigational New Drug; PoC = Proof-of-Concept
TRV250: New MOA for Acute Treatment of Migraine

Delta receptor: Untapped potential in CNS space
Migraine represents a large market opportunity; total migraine drug market = ~$3.5B

Delta receptors have unique distribution throughout the brain
Play important role in regulation of pain, mood, and anxiety

Every year in the US¹:

- 650M migraines treated each year
- 1.2M ER visits due to migraines

- 20-30% of migraine sufferers do not respond to / cannot tolerate the market-leading triptan drug class
- Approx. 50% of migraineurs also suffer from anxiety²

¹ Data from Decision Resources, Pharmacor migraine market landscape and forecast 2018. ² Moven et al., J Neurol Neurosurg Psychiatry, 2016.
Icons made by Freepik from www.flaticon.com
TRV250: Well-Tolerated in Ph1 Healthy Volunteer PK Study

Subcutaneous doses up to 30 mg studied; no SAEs observed

- Well tolerated, with no SAEs across broad range of doses
- Predictable PK: dose-proportional between 0.1 mg to 30 mg SC
- Half-life consistent across all doses
- No EEG findings observed in any subject

TRV734: Maintenance Therapy for Opioid Use Disorder

Selective agonism at µ receptor: Potential for improved tolerability

Ongoing collaboration with National Institute on Drug Abuse (NIDA)

>2.5M people in U.S. suffer from opioid use disorder¹

- Nonclinical evidence of improved tolerability with TRV734
- NIDA study demonstrated reduced drug-seeking behavior in animal model of relapse²
- Current therapies not well tolerated, can hinder patient adherence

NIDA-funded proof-of-concept patient study initiated

1) Center for Behavioral Health Statistics and Quality. 2) NIDA data on file.
TRV045: Next-Generation S1P Modulator for CNS Disorders

New MOA at S1P, **without** associated lymphopenia

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

• In animals, TRV045 reversed paclitaxel-induced hyperalgesia without immune-suppressing activity
  - Fingolimod reduced lymphocytes by 78%
  - TRV045 had no effect on lymphocytes

• Non-opioid MOA with broad potential for CNS indications
  - Chronic pain, CIPN, diabetic neuropathy
  - Epilepsy, acute / chronic pain evaluations underway

CIPN mouse model: Paclitaxel 6 mg/kg, i.p. on Days 1, 3, 5, 7. Hyperalgesia measured as % non-response to 0.4 g Von Frey filament vs. baseline, tested 30’ after dosing on Day 13. Lymphocytes measured after 3 days of dosing. Data are mean ± s.e.m. n=5-7 mice/group. *p<0.05 or **p<0.01 vs. control.
### Trevena: Innovative CNS Company

| IV OLINVYK: Differentiated profile | NCE approved for the management of acute pain in adults
|                                 | Commercial launch in Q1 2021 |
| Large market, targeted launch     | 45M+ US hospital patients; 9M procedures is initial core focus
|                                 | $1.5B+ market opportunity for core focus |
| Novel CNS pipeline               | New mechanisms for acute migraine, opioid use disorder, epilepsy, pain
|                                 | NCEs targeting significant unmet needs |
| TRV027 for COVID-19              | Novel MOA to treat COVID-19 acute lung injury / abnormal clotting
|                                 | PoC study in collab with Imperial College London; primary completion date expected in 1H 2021 |
| Strong financial position        | $112.7M cash and cash equivalents as of 9/30/2020
|                                 | Funds operations through Q4 2022 |

OLINVYK is indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at [www.OLINVYK.com](http://www.OLINVYK.com).

**NCE** = New Chemical Entity; **MOA** = Mechanism of Action; **PoC** = Proof-of-Concept
Robust Clinical Development Program

OLINVYK studied in > 1,900 individuals

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

Phase 2
4 head-to-head trials vs. IV morphine:
- IV opioid efficacy
- Rapid onset of action
- Well-characterized respiratory safety / GI tolerability
- Low rates of vomiting and rescue antiemetic use

Phase 3
Large safety study:
- Real-world use in complex patients and target surgeries

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

# subjects exposed to OLINVYK in Ph1 = 318; # patients treated with OLINVYK in Ph2 and Ph3 = 1,535
Primary Efficacy Endpoint Achieved in Two Pivotal Studies

OLINVYK achieved IV opioid efficacy

Published in The Journal of Pain Research

Ph3: Hard Tissue Surgery
Mean baseline pain = 6.7

Published in Pain Practice

Ph3: Soft Tissue Surgery
Mean baseline pain = 7.3

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.
OLINVYK: IV Opioid Efficacy in 2 Phase 3 RCTs

Study 1 (Orthopedic – Hard Tissue)
3 PCA regimens studied (0.1, 0.35, 0.5 mg) vs. placebo; all doses P<0.01 vs. placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0.1 mg</th>
<th>0.35 mg</th>
<th>0.5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Completed</td>
<td>83%</td>
<td>87%</td>
<td>84%</td>
<td>60%</td>
</tr>
<tr>
<td>% D/C LOE</td>
<td>9%</td>
<td>4%</td>
<td>5%</td>
<td>34%</td>
</tr>
<tr>
<td>% Rescue Meds</td>
<td>41%</td>
<td>20%</td>
<td>17%</td>
<td>77%</td>
</tr>
</tbody>
</table>

Study 2 (Plastic Surgery – Soft Tissue)
3 PCA regimens studied (0.1, 0.35, 0.5 mg) vs. placebo; 0.35/0.5 mg doses P<0.02 vs. placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0.1 mg</th>
<th>0.35 mg</th>
<th>0.5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Completed</td>
<td>86%</td>
<td>90%</td>
<td>87%</td>
<td>74%</td>
</tr>
<tr>
<td>% D/C LOE</td>
<td>11%</td>
<td>3%</td>
<td>5%</td>
<td>22%</td>
</tr>
<tr>
<td>% Rescue Meds</td>
<td>31%</td>
<td>21%</td>
<td>18%</td>
<td>49%</td>
</tr>
</tbody>
</table>
Data included in AMCP dossier used in formulary review

- Prespecified secondary endpoint: Respiratory Safety Burden (RSB)
  - Calculated based on incidence and cumulative duration of respiratory safety events
- Full characterization of respiratory safety profile has been made available to HCPs and formulary decision makers
  - Data can be found in OLINVYK AMCP dossier and published literature

### Ph3 Respiratory Safety Events

<table>
<thead>
<tr>
<th>Hard Tissue</th>
<th>Soft Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Components of the RSB calculation</strong></td>
<td><strong>Components of the RSB calculation</strong></td>
</tr>
<tr>
<td>Oxygen saturation &lt;90%, n (%)</td>
<td>Oxygen saturation &lt;90%, n (%)</td>
</tr>
<tr>
<td>P value vs morphine</td>
<td>P value vs morphine</td>
</tr>
<tr>
<td>Respiratory rate ≤ 8 bpm, n (%)</td>
<td>Respiratory rate ≤ 8 bpm, n (%)</td>
</tr>
<tr>
<td>Sedation (MRPSS ≥ 3), n (%)</td>
<td>Sedation (MRPSS ≥ 3), n (%)</td>
</tr>
<tr>
<td>P value vs morphine</td>
<td>P value vs morphine</td>
</tr>
</tbody>
</table>

bpm = breaths per minute; MRPSS = Moline-Roberts Pharmacologic Sedation Scale
Robust Assessment of GI Tolerability in Phase 3 RCTs

Data included in AMCP dossier used in formulary review

- Phase 3 pivotal trials included measurements of nausea / vomiting rates and rescue antiemetic use

- Additional exploratory post-hoc analysis was conducted using a “complete GI response” endpoint

- Full characterization of GI tolerability has been made available to HCPs and formulary decision makers
  - Data can be found in OLINVYK AMCP dossier and published literature

P < 0.05 vs. morphine.1) Figure 2-10, Section 2.2, OLINVYK Evidence Dossier for Formulary Consideration. 2) Figure 2-11, Section 2.2, OLINVYK Evidence Dossier for Formulary Consideration. 3) GI complete response defined as the proportion of patients who did not experience the AE of vomiting and did not use rescue antiemetic medication throughout their allocated treatment period in the study.
No Accumulation Despite Repeated Dosing

Multi-Dose tQT Study

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

*The effect on QT prolongation at total cumulative daily doses >27 mg has not been studied in a thorough QT study. Total cumulative daily doses exceeding 27 mg per day may increase the risk for QTc interval prolongation. Therefore, the cumulative total daily dose of OLINVYK should not exceed 27 mg.

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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.
Interaction Between the AT\textsubscript{1} Receptor and ACE2 in COVID-19

Downregulation of ACE2 by coronavirus indirectly promotes activation of the AT\textsubscript{1} receptor

- Coronavirus binds to and downregulates angiotensin converting enzyme 2 (ACE2)\textsuperscript{1}
- Decrease in ACE2 elevates angiotensin II levels
  - Angiotensin II activates AT\textsubscript{1} receptor
  - No breakdown of angiotensin II into Ang(1-7)
    - Normally, Ang(1-7) acts as a β-arrestin-biased ligand at the AT\textsubscript{1} receptor\textsuperscript{2}
    - Protective therapeutic benefits in the lungs\textsuperscript{3}

Delta Receptor Agonists Have Unique Benefits

Potential utility for a variety of CNS indications

**Triptans / Ditans**

- Target: serotonin receptors → mediate vascular excitability (associated CV risk)$^1$
- Migraine-specific treatment

**CGRPs**

- Target: CGRP receptors → regulate neuronal structures involved in pain signaling$^2$
- Migraine-specific treatment

**Delta receptor agonists**

- Target: delta receptors → located in pain pathways; also distributed throughout brain regions associated with sensory information, emotional processing, and reward / impulsivity$^3$
- Potential for broad therapeutic application

IMPORTANT SAFETY INFORMATION
WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS

**Addiction, Abuse, and Misuse**
OLINVYK exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing OLINVYK, and monitor all patients regularly for the development of behaviors or conditions.

**Life-Threatening Respiratory Depression**
Serious, life-threatening, or fatal respiratory depression may occur with use of OLINVYK. Monitor for respiratory depression, especially during initiation of OLINVYK or following a dose increase.

**Neonatal Opioid Withdrawal Syndrome**
Prolonged use of OLINVYK during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

**Risk From Concomitant Use With Benzodiazepines or Other CNS Depressants**
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

**Limitations of Use**
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OLINVYK for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:
- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.
The cumulative total daily dose should not exceed 27 mg, as total daily doses greater than 27 mg may increase the risk for QTc interval prolongation.

**CONTRAINDICATIONS**
OLINVYK is contraindicated in patients with:
- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Known hypersensitivity to oliceridine (e.g., anaphylaxis)

**WARNINGS AND PRECAUTIONS**
- OLINVYK contains oliceridine, a Schedule II controlled substance, that exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OLINVYK. Assess risk, counsel, and monitor all patients receiving opioids.
- Serious, life-threatening respiratory depression has been reported with the use of opioids, even when used as recommended, especially in patients with chronic pulmonary disease, or in elderly, cachectic and debilitated patients. The risk is greatest during initiation of OLINVYK therapy, following a dose increase, or when used with other drugs that depress respiration. Proper dosing of OLINVYK is essential, especially when converting patients from another opioid product to avoid overdose. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status.
- Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia with risk increasing in a dose-dependent fashion. In patients who present with CSA, consider decreasing the dose of opioid using best practices for opioid taper.

**INDICATIONS AND USAGE**
OLINVYK is a new chemical entity indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.
WARNINGS AND PRECAUTIONS

- Prolonged use of opioids during pregnancy can result in withdrawal in the neonate that may be life-threatening. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using OLINVYK for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OLINVYK with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, or alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate, prescribe the lowest effective dose, and minimize the duration.

- OLINVYK was shown to have mild QTc interval prolongation in thorough QT studies where patients were dosed up to 27 mg. Total cumulative daily doses exceeding 27 mg per day were not studied and may increase the risk for QTc interval prolongation. Therefore, the cumulative total daily dose of OLINVYK should not exceed 27 mg.

- Increased plasma concentrations of OLINVYK may occur in patients with decreased Cytochrome P450 (CYP) 2D6 function or normal metabolizers taking moderate or strong CYP2D6 inhibitors; also in patients taking a moderate or strong CYP3A4 inhibitor, in patients with decreased CYP2D6 function who are also receiving a moderate or strong CYP3A4 inhibitor, or with discontinuation of a CYP3A4 inducer. These patients may require less frequent dosing and should be closely monitored for respiratory depression and sedation at frequent intervals. Concomitant use of OLINVYK with CYP3A4 inducers or discontinuation of a moderate or strong CYP3A4 inhibitor can lower the expected concentration, which may decrease efficacy, and may require supplemental doses.

- Cases of adrenal insufficiency have been reported with opioid use (usually greater than one month). Presentation and symptoms may be nonspecific and include nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If confirmed, treat with physiologic replacement doses of corticosteroids and wean patient from the opioid.

- OLINVYK may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients.

- There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension. In patients with circulatory shock, avoid the use of OLINVYK as it may cause vasodilation that can further reduce cardiac output and blood pressure.

- Avoid the use of OLINVYK in patients with impaired consciousness or coma. OLINVYK should be used with caution in patients who may be susceptible to the intracranial effects of CO2 retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy.

- As with all opioids, OLINVYK may cause spasm of the sphincter of Oddi, and may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

- There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension. In patients with circulatory shock, avoid the use of OLINVYK as it may cause vasodilation that can further reduce cardiac output and blood pressure.

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ADVERSE REACTIONS

Adverse reactions are described in greater detail in the Prescribing Information. The most common (incidence ≥10%) adverse reactions in Phase 3 controlled clinical trials were nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia.