Biased Ligands. Better Drugs.

Maxine Gowen, Ph.D., CEO

November 19, 2015
Forward looking statements and other important cautions

To the extent that statements contained in this presentation are not descriptions of historical facts regarding Trevena, Inc., 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 and potential payments under our agreements with Allergan plc.

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, changes in the regulatory environment for our drug candidates and our need for future capital, 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.
Phase 2b programs target large underserved markets.

Differentiated “biased ligand” receptor modulation; long patent lives.

Multiple potential high-value breakthrough medicines.

Productive platform

Portfolio of potential first-in-class NCEs

Novel GPCR science based on Nobel Prize-winning research

GPCR = G protein-coupled receptor
NCE = new chemical entity
Trevena’s platform productivity: 4 NCEs in 8 years

<table>
<thead>
<tr>
<th>Target</th>
<th>Indication</th>
<th>Lead Op.</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Ownership</th>
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<tbody>
<tr>
<td><strong>CNS Portfolio</strong></td>
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<tr>
<td>Oliceridine</td>
<td>Moderate to severe pain</td>
<td>Intravenous</td>
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<td>(TRV130)</td>
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<tr>
<td>TRV734</td>
<td>Moderate to severe pain</td>
<td>Oral</td>
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<td>Wholly owned</td>
</tr>
<tr>
<td>TRV250</td>
<td>Migraine</td>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wholly owned</td>
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</tbody>
</table>

| **Cardiovascular Program** |           |            |             |         |         |         |           |
| TRV027           | Angiotensin II type 1 receptor | Acute Heart Failure | Intravenous |         |         |         | Collaborator |

U.S. composition of matter and method of use patents issued for TRV130 and TRV734 (expire 2032)
U.S. and ex-U.S. composition of matter and method of use patents issued for TRV027 (expire 2031)
OLICERIDINE (TRV130)

Novel intravenous $\mu$-receptor modulator for acute moderate to severe pain
IV opioids are the foundation of pain management in the hospital.

### Annual Hospital IV Opioid Standard Units* (US)

*Dispensing Units = vials, ampules, syringes

* Source: IMS MIDAS (2014)
The challenges of IV opioid use

• Tolerability: most frequently nausea/vomiting
  – High prevalence (30%)\(^4\)
  – Also sedation, constipation, pruritis, and others

• Safety: primarily respiratory depression
  – Low prevalence (0.5-2%)\(^1\) but large number (~175K patients/year)\(^2\)
  – Can be fatal, contributing to ~46K annual deaths from post-op pulmonary complications\(^2,3\)

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(2) Shander et al, Clinical and economic burden of postop pulmonary complications... Crit. Care Med. 2011; V.39, No.9.
The danger of IV opioids
The danger of IV opioids
Oliceridine: a new mechanism of action

Mechanism of action hypothesis based on preclinical research
2) Raehal KM et al JPET 2005 Sep;314(3):1195-201
3) Dewire SM et al JPET 2013 Mar;344(3):708-17
Oliceridine differentiation is well documented

A G Protein-Biased Ligand at the μ-Opioid Receptor in Analgesic with Reduced Gastrointestinal and Respiratory Dysfunction Compared with Morphine

Scott M. DeWire, Dennis S. Yamashita, David H. Rominger, Guodong Liu, Conrad L. Cowan, Thomas M. Graczyk, Xia-Tao Chen, Philip M. Pitsis, Dimitar Gotchev, Catherine Yuan, Michael Koblish, Michael W. Lark, and Jonathan D. Violin
Trevena Inc, King of Prussia, Pennsylvania
Received November 5, 2012; accepted January 7, 2013

Xiao-Tao Chen, Philip Pitsis, Guodong Liu, Catherine Yuan, Dimitar Gotchev, Conrad L. Cowan, David H. Rominger, Michael Koblish, Scott M. DeWire, Aimee L. Crombie, Jonathan D. Violin, and Dennis S. Yamashita

First Clinical Experience With TRV130: Pharmacokinetics and Pharmacodynamics in Healthy Volunteers
David G. Soergel, MD, Ruth Ann Subach, PharmD, BCPS, Brian Sadler, PhD, John Connell, PhD, Alan S. Marion, MD, PhD, Conrad L. Cowan, PhD, Jonathan D. Violin, PhD, and Michael W. Lark, PhD

Biased agonism of the μ-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects versus morphine: A randomized, double-blind, placebo-controlled, crossover study in healthy volunteers
David G. Soergel, MD, Ruth Ann Subach, Nancy Burnham, Michael W. Lark, Ian E. James, Brian M. Sadler, Franck Skobieranda, Jonathan D. Violin, Lynn R. Webster

Biased ligands at G-protein-coupled receptors: promise and progress
Jonathan D. Violin, Aimee L. Crombie, David G. Soergel, and Michael W. Lark
Trevena Inc., 1018 West 8th Avenue, Suite A, King of Prussia, PA 19406, USA

A Randomized, Phase 2 Study Investigating TRV130, a Biased Ligand of the μ-opioid Receptor, for the Intravenous Treatment of Acute Pain
Eugene R. Viscusi, MD; Lynn Webster, MD; Michael Kuss, BS; Stephen Daniels, DO; James A. Bolognese, MS; Seth Zuckerman, MS; David G. Soergel, MD; Ruth Ann Subach, PharmD; Emily Cook, BA; Franck Skobieranda, MD
Summary of Phase 2b abdominoplasty flexible dosing study

• Two TRV130 regimens explored using adaptive trial design

• Standard morphine PCA regimen modeled “real world” use

• Primary endpoint: Time-weighted average change in numeric pain rating score over 24 hours (TWA 0-24), i.e. pain reduction over duration of study
  – Rescue pain medication available to all patients if needed
  – Using a standard methodology, pain scores were assessed before rescue use, with this value carried forward until the end of the study

• Secondary endpoints: efficacy, safety, and tolerability vs. morphine
  – Rescue pain medication use also assessed as a measure of efficacy
  – Pre-specified focus on respiratory safety risk and upper GI tolerability
    • Hypoventilation, nausea, and vomiting

PCA = patient-controlled analgesia
Study timeline and dosing arms

Pain measured with validated numeric pain rating scale (NPRS)

- Moderate-severe pain (NPRS ≥ 5)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>Loading dose (mg)</th>
<th>On-demand dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>39</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TRV130 0.1 mg</td>
<td>39</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>TRV130 0.35 mg</td>
<td>39</td>
<td>1.5</td>
<td>0.35</td>
</tr>
<tr>
<td>Morphine</td>
<td>83</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

On-demand doses were available as often as every 6 minutes
All regimens were volume matched
First-line rescue: ibuprofen 400 mg orally every 6 hours
Second-line rescue: oxycodone 5 mg orally every 2 hours
TRV130 reduced pain intensity over 24 hours

*Phase 2b flexible dosing abdominoplasty study*

Data on graph are least squares mean +/- s.e.m. of TWA NPRS change vs. baseline
TWA 0-24 is time-weighted average of NPRS change vs. baseline over 24 hours

<table>
<thead>
<tr>
<th>P-value vs. placebo for TWA NPRS Δ 0-24 hr (1° endpoint)</th>
</tr>
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<tbody>
<tr>
<td>TRV130 - 0.1 mg</td>
</tr>
<tr>
<td>TRV130 - 0.35 mg</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
</tbody>
</table>
Nausea and vomiting occurred in fewer olitliceridine patients than morphine patients

Phase 2b flexible dosing abdominoplasty study

**Nausea**

- Placebo
- TRV130 - 0.1 mg
- TRV130 - 0.35 mg
- Morphine

Proportion of patients with nausea (%)

* p<0.01 vs. placebo
# p<0.01 vs. morphine

**Vomiting**

- Placebo
- TRV130 - 0.1 mg
- TRV130 - 0.35 mg
- Morphine

Proportion of patients vomiting (%)

* p<0.001 vs. placebo
# p<0.01 vs. morphine

Post hoc statistics for pre-specified endpoint
Hypoventilation events occurred in fewer oliceridine patients than morphine patients

Phase 2b flexible dosing abdominoplasty study

Prevalence of hypoventilation

![Bar chart showing prevalence of hypoventilation with post hoc statistics]

Post hoc statistics for pre-specified endpoint
Hypoventilation (HV) events: clinically apparent and persistently decreased respiratory rate, respiratory effort, or oxygen saturation

* p<0.05 vs. placebo
** p<0.0001 vs. placebo
# p<0.05 vs. morphine
## p<0.0005 vs. morphine
Dynamics of as-needed analgesic use: rescue

- self-administered dose
- rescue: 400mg ibuprofen
- rescue: 5 mg oxycodone

New data from Ph2 PCA trial

<table>
<thead>
<tr>
<th>Placebo (n = 39)</th>
<th>Oliceridine 0.1 mg (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliceridine 0.35 mg (n = 39)</td>
<td>Morphine (n = 83)</td>
</tr>
</tbody>
</table>

Time after first dose (hours)
Dynamics of as-needed analgesic use: dose interruptions

New data from Ph2 PCA trial

- Placebo (n = 39)
- Oliceridine 0.1 mg (n = 39)
- Oliceridine 0.35 mg (n = 39)
- Morphine (n = 83)

* Self-administered dose
  - Dosing interruption duration

Time after first dose (hours)
Oliceridine delivered rapid onset of pain relief

*Phase 2a/b bunionectomy trial data*

Median time to meaningful pain relief

- 50%
- 68%
- 81%
- 97%
- 56%

**% reporting meaningful pain relief after 1st dose**

- TRV130 0.5 mg
- TRV130 1 mg
- TRV130 2 mg
- TRV130 3 mg
- Morphine 4 mg

Placebo onset not measurable

*p = 0.01 vs. Morphine

**p < 0.0001 vs. Morphine

Wald test from Cox-proportional regression
Oliceridine profile supports differentiating Phase 3 program

**Morphine**
- Narrow therapeutic window
- Slow brain entry
- Active metabolites (M6G, M3G)

  “Chasing pain”
  Prolonged and delayed adverse effects

**Oliceridine**
- Improved therapeutic window
- Rapid CNS entry
- No known active metabolites

  “Get ahead of pain”
  Fewer, less severe and/or briefer adverse effects

Oliceridine profile based on Phase 1 and Phase 2 data
Overview of Phase 3 planning
end of Phase 2 discussion with FDA expected 1Q 2016

• Proposed pivotal studies: as-needed dosing
  – Precedented 1º endpoint: change in pain scores over time vs. placebo
  – Does not capture clinical utility (trade-off between efficacy and AEs)

• Key secondary endpoints: built on Phase 2 successes vs. morphine
  – Onset of meaningful pain relief, upper GI tolerability, hypoventilation
    • Hypoventilation will include more detailed assessments, e.g. onset, duration, severity, interventions

Phase 1 & 2
~275 patients

Phase 3
Pivotal trials
~300-600 patients

• Phase 3 multi-procedure study (rate-limiting to NDA)
• Considering additional trials for label/publication
  ~600-900 patients

Guidance: 1,500 patients exposed to evaluate safety for an NME
Large potential opportunity for oliceridine

~50M IV Opioid Patient Visits in 2014

Inpatient & Outpatient Settings of Care

15M IV Opioid
Hospital Inpatient

Average 2 days
IV analgesic therapy

35M IV Opioid
Hospital Outpatient/ASC

Average 1-4 hours
IV analgesic therapy

(1) IMS Charge Detail Master Claims Database, 2014 US hospital data, surgical and medical cases.
(2) ASC = Ambulatory Surgical Center, Trevena estimates from Becker’s ASC Review data.
(3) CDC National Center for Health Statistics 2006; http://www.cdc.gov/nchs/data/nhsr/nhsr011.pdf
Oliceridine could capture significant market share across multiple settings of care.

<table>
<thead>
<tr>
<th>Health care providers</th>
<th>Post-Op. (PACU)</th>
<th>Medical/Surgical Floor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inpatient, outpatient, ASC</td>
<td>Less intensive monitoring</td>
</tr>
<tr>
<td></td>
<td><strong>Heavy monitoring</strong></td>
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</tr>
</tbody>
</table>

**Anesthesiologists**
- **Control pain quickly**
- **Discharge to floor/home**

**Surgeons**
- **Patient safety & satisfaction**
- **Discharge patient to home**

**Pain Specialists/Hospitalists**

**Nurses**
- **Respiratory safety**
- **GI tolerability**
- **Rapid & predictable titration**

**Primary goals**
- Fast onset
- Minimal complications

**Potential Oliceridine profile**

Source: Research Partnership 2014/2015; Trinity Partners 2015 (n=135)
Pharmacy directors recognize benefits of oliceridine profile

Pharmacy’s criteria for new treatments

Clinical profile
Efficacy and safety vs current therapies

Budget impact
Product price, LOS, PACU/ICU time, resource utilization

Quality metrics
Pain management, patient satisfaction, readmissions

Market access research findings

• Oliceridine profile compelling
  – Studies vs morphine meaningful

• Physician advocacy critical
  – Anesthesiologists & surgeons influential

• Published peer-reviewed data required
  – Primary input to P&T dossier

• Recognition of premium price for benefits
  – Branded product benchmarks

Source: Trevena Pharmacy Director Market Research, N=35,
Breakthrough potential of oliceridine vs. current IV opioids

**Power**
- Strong efficacy
- High potency

**Precision**
- Rapid onset
- No evidence of active metabolites

**Safety**
- Less hypoventilation
- Less nausea
- Less vomiting
TRV027

Novel therapy for acute heart failure
Acute heart failure (AHF) – poor patient outcomes with current treatment paradigm

- 2.6 MM hospitalizations in US, EU\(^{(2)}\)
  - $21bn\(^{(3)}\) annual costs in the US
- No significant advances in AHF therapy for decades
- 50%\(^{(4)}\) of patients are still symptomatic at discharge
  - 25%\(^{(5)}\) readmitted within 30 days
  - 30%\(^{(6)}\) die within one year

Notes:
1. Acute Heart Failure Pharmacor Report © 2009 - 2013 Decision Resources, LLC. All rights reserved
2. US data from the National Hospital Discharge Survey for 2010 - Europe data from the European Commission EUROSTAT database for 2010
3. American Heart Association, National Heart Lung and Blood Institute, 2012
4. Acute Decompensated Heart Failure National Registry (ADHERE) database, J Am Coll Cardiol 2006;47:76-84
5. Healthcare Cost and Utilization Project (H.CUP), Statistical Brief #153, April 2013
6. Yancy et al, 2013 ACCF/AHA Heart Failure Guidelines, JACC (2013), published online before print

Note: ARB = angiotensin receptor blocker; BB = beta blocker; ER = emergency room; ACEI = angiotensin converting enzyme inhibitor
CHF = chronic heart failure;
TRV027 – selective signaling potentially benefits the three key AHF-affected organ systems

- Decrease blood pressure
- Increase renal blood flow
- Enhanced contractility
- Cardioprotection

↓ blood pressure

↑ cardiac contractility

\[ \text{Angiotensin II} \]

\[ \text{AT1R} \]

\[ \beta\text{-arrestin} \]

\[ \text{G protein} \]

\[ \text{Telmisartan} \]

\[ \text{TRV027} \]
TRV027 – Phase 2b BLAST-AHF trial

- Randomized, double-blind, placebo-controlled trial in 620 AHF patients
  - Study drug administered as continuous IV infusion 48-96 hr as needed
  - Three TRV027 doses (1, 5, 25 mg/hr) and placebo

- Primary endpoint: composite of clinically important outcomes
  - Dyspnea
  - Worsening heart failure during hospitalization
  - Length of stay
  - 30-day readmission/mortality

- Trial Status: interim complete
  - Prespecified interim analysis conducted after 250 patients
  - Remaining enrollment focused on most promising dose of 5 mg/hr
  - Allergan fully funded increased target enrollment with $10M payment
  - Top-line data expected 2Q 2016

- Allergan option: potential $65M exercise after delivery of data
  Additional potential milestones of $365M and 10-20% royalties
## Milestones & Finances

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Target date</th>
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<tbody>
<tr>
<td>Oliceridine: FDA End of Phase 2 meeting</td>
<td>1Q 2016</td>
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<tr>
<td>Oliceridine: initiate Phase 3 multi-procedure safety study</td>
<td>1Q 2016</td>
</tr>
<tr>
<td>Oliceridine: initiate pivotal Phase 3 studies</td>
<td>2Q 2016</td>
</tr>
<tr>
<td>TRV027 Phase 2b data - $65M payment if option exercised</td>
<td>2Q 2016</td>
</tr>
<tr>
<td>TRV250 IND file</td>
<td>2016</td>
</tr>
<tr>
<td>Oliceridine top-line data from pivotal Phase 3 studies</td>
<td>1Q 2017</td>
</tr>
<tr>
<td>Oliceridine NDA submission</td>
<td>2H 2017</td>
</tr>
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</table>

$169.0M cash as of 9/30/15 funds:
- TRV130 through Phase 3, NDA filing, and initial launch preparations
- TRV027 through Allergan option decision ($65M payment)
- TRV250 through Phase 1
- Continued drug discovery in new therapy areas
Trevena is poised to reach new heights

Blockbuster potential in numerous indications

• Oliceridine: best-in-class IV analgesic
  – Phase 3 initiation expected in Q1 2016
  – NDA filing expected in 2017
  – Additional non-IV products planned

• TRV027: revolutionize AHF treatment
  – BLAST-AHF top-line data expected 2Q 2016
  – Positive data would drive Phase 3 planning

• TRV734: best-in-class oral analgesic
  – Seeking partner

• TRV250: first-in-class for migraine
  – Expected to enter the clinic in 2016
Biased Ligands. Better Drugs.