UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **June 1, 2020**

TREVENA, INC.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of incorporation)

001-36193	**26-1469215**
(Commission File No.)	(IRS Employer Identification No.)

955 Chesterbrook Boulevard, Suite 110
Chesterbrook, PA 19087
(Address of principal executive offices and zip code)

Registrant's telephone number, including area code: **(610) 354-8840**

Not applicable
(Former name or former address, if changed since last report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, $0.001 par value	TRVN	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter). Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure

On June 2, 2020, Trevena, Inc. (the "Company") updated its website to include an updated corporate presentation deck. A copy of the updated corporate deck is attached hereto as Exhibit 99.2.

The information set forth on this Item 7.01 and furnished hereto as Exhibit 99.2 shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and is not incorporated by reference into any of the Company's filings under the Securities Act of 1933, as amended, or the Exchange Act, whether made before or after the date hereof, except as shall be expressly set forth by specific reference in any such filing.

Cautionary Note on Forward Looking Statements

Any statements in Item 7.01 of this Current Report on Form 8-K, including within Exhibit 99.2 heretoabout future expectations, plans and prospects for the Company, including statements about the Company's strategy, future operations, clinical development and trials of its therapeutic candidates, plans for potential future product candidates and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "suggest," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the status, timing, costs, results and interpretation of the Company's clinical trials or any future trials of any of the Company's investigational drug candidates; the uncertainties inherent in conducting clinical trials; expectations for regulatory interactions, submissions and approvals, including the Company's assessment of the discussions with FDA, the timing of FDA's decision on the oliceridine NDA; available funding ; uncertainties related to the Company's intellectual property; uncertainties related to the ongoing COVID-19 pandemic, other matters that could affect the availability or commercial potential of the Company's therapeutic candidates; and other factors discussed in the Risk Factors set forth in the Company's 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 the Company makes with the SEC from time to time. In addition, the forward-looking statements included in this Current Report on Form 8-K, including Exhibit 99.2 hereto, represent the Company's views only as of the date hereof. The Company anticipates that subsequent events and developments may cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so, except as may be required by law.

Item 8.01 Other Events.

On June 2, 2020, the Company issued a press release announcing that it has entered into a collaboration with Imperial College London to evaluate the potential of TRV027, a novel AT_1 receptor selective agonist, to treat acute lung injury contributing to acute respiratory distress syndrome (ARDS) in COVID-19 patients. A copy of the press release is furnished herewith as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press Release dated June 2, 2020
99.2	Updated Corporate Presentation Deck dated June 2, 2020

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

TREVENA, INC.

Date: June 2, 2020

By: /s/ Barry Shin
Barry Shin
Senior Vice President & Chief Financial Officer

EXHIBIT 99.1

Trevena Announces Collaboration with Imperial College London to Evaluate TRV027 in COVID-19 Patients

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TRV027 is a novel AT_1 receptor selective agonist with the potential to treat acute lung injury and ARDS

Robust clinical development history with well-characterized PK and demonstrated safety in ~700 individuals

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CHESTERBROOK, Pa., June 2, 2020 (GLOBE NEWSWIRE) --**Trevena, Inc. (Nasdaq: TRVN)**, a biopharmaceutical company focused on the development and commercialization of novel medicines for patients with central nervous system (CNS) disorders, today announced it has entered into a collaboration with Imperial College London to evaluate the potential of TRV027, a novel AT_1 receptor selective agonist, to treat acute lung injury contributing to acute respiratory distress syndrome (ARDS) in COVID-19 patients. ARDS is a major complication leading to mortality associated with COVID-19. Imperial College London will be sponsoring and funding this study, with additional support through the British Heart Foundation Centre for Research Excellence Award.

“It is a great privilege to be working with Imperial College London, a global thought leader in this pandemic, as we join the urgent fight to deliver treatments to healthcare providers and COVID-19 patients in dire need,” said Carrie Bourdow, President and Chief Executive Officer of Trevena, Inc. “TRV027 may offer a new and innovative approach to treating acute lung injury, which poses a grave threat to patients’ lives.”

“We are very pleased to be partnering with Trevena in our endeavor to combat the global threat posed by this pandemic,” said David Owen, M.D., Ph.D., Faculty of Medicine, Imperial College London and Head of Clinical Studies, Imperial Clinical Research Facility. “I am excited for this opportunity to study the potential utility of TRV027 in treating COVID-19 patients.”

In a COVID-19 infection, the SARS-coronavirus-2 binds to and removes the ACE2 protein in the lungs, causing elevated levels of angiotensin II. This drives overactivation of the AT_1 receptor, which results in downstream acute lung injury. This often develops into ARDS, which can ultimately lead to mortality. TRV027 potentially counteracts the disproportionate levels of angiotensin II, by competitively binding to and rebalancing AT_1 receptor activation. Additionally, its unique mechanism of action preferentially engages the signaling pathway to promote reparative effects on lung tissue.

TRV027 is an investigational new drug that has previously been studied in 691 individuals. It has demonstrated efficacy, potency, and selectivity at the AT_1 receptor in nonclinical studies and has a well-characterized pharmacokinetic profile. In previous clinical trials, there was a low dropout rate associated with TRV027, and no significant safety issues were reported. In April 2020, the Company filed a provisional patent application with the United States Patent and Trademark Office covering the use of TRV027 to treat ARDS in COVID-19 patients.

About the Imperial College London COVID-19 Study
This will be a randomized, double-blind, placebo-controlled Phase 1b proof-of-concept study in approximately 60 hospitalized, non-ventilated patients aged 65 or older with a confirmed or suspected COVID-19 infection. The study will determine whether TRV027, a novel AT_1 receptor selective agonist, modulates pathways that contribute to COVID-19 pathology. The primary endpoint is a coagulation cascade biomarker, which serves as a surrogate for measuring the effect of TRV027 on adverse health outcomes associated with increased mortality in COVID-19 infections. Imperial College London will be sponsoring and funding this study, with additional support through the British Heart Foundation Centre for Research Excellence Award.

About TRV027
TRV027 is a novel AT_1 receptor selective agonist. It is an investigational new drug that was studied through a Phase 2b trial for acute heart failure. TRV027 is currently being investigated as a potential treatment for acute lung injury contributing to ARDS in COVID-19 patients. TRV027 may counteract overactivation of the AT_1 receptor caused by SARS-coronavirus-2, while simultaneously promoting reparative effects on lung tissue. The use of TRV027 in COVID-19 patients has been proposed by Nobel Laureate Robert J. Lefkowitz, M.D., and Howard A. Rockman, M.D., both Professors of Medicine at Duke University and scientific co-founders of the Company, along with two of their colleagues, Laura M. Wingler, Ph.D., Duke University and Aashish Manglik, M.D., Ph.D., University of California San Francisco.

About Trevena
Trevena, Inc. is a biopharmaceutical company focused on the development and commercialization of novel medicines for patients with CNS disorders. The Company has five novel and differentiated investigational drug candidates, including IV oliceridine, for the management of moderate to severe acute pain in hospitals, TRV250 for the acute treatment of migraine, TRV734 for maintenance treatment of opioid use disorder, and TRV027 for acute lung injury in COVID-19 patients. The Company has also identified TRV045, a novel S1P receptor modulator that may offer a new, non-opioid approach to treating a variety of CNS disorders.

Forward-Looking Statements
Any statements in this press release about future expectations, plans and prospects for the Company, including statements about the Company's strategy, future operations, clinical development and trials of its therapeutic candidates, plans for potential future product candidates and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "suggest," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the status, timing, costs, results and interpretation of the Company's clinical trials or any future trials of any of the Company's investigational drug candidates; the uncertainties inherent in conducting clinical trials; expectations for regulatory interactions, submissions and approvals, including the Company's assessment of the discussions with FDA, the timing of FDA's decision on the oliceridine NDA; available funding ; uncertainties related to the Company's intellectual property; uncertainties related to the ongoing COVID-19 pandemic, other matters that could affect the availability or commercial potential of the Company's therapeutic candidates; and other factors discussed in the Risk Factors set forth in the Company's 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 the Company makes with the SEC from time to time. In addition, the forward-looking statements included in this press release represent the Company's views only as of the date hereof. The Company anticipates that subsequent events and developments may cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so, except as may be required by law.

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SVP and Chief Business Officer
Trevena, Inc.
(610) 354-8840

EXHIBIT 99.2

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		
Carrie L. Bourdow	President & Chief Executive Officer	CUBIST, MERCK
Scott Applebaum	SVP, Chief Legal & Compliance Officer	context, vitae, Shire
Mark A. Demitrack, M.D.	SVP, Chief Medical Officer	NEURONETICS, Lilly, ROIVANT
Barry Shin	SVP, Chief Financial Officer	MIZUHO, GUGGENHEIM, PiperJaffray
Robert T. Yoder	SVP, Chief Business Officer	MERCK, OREXIGEN

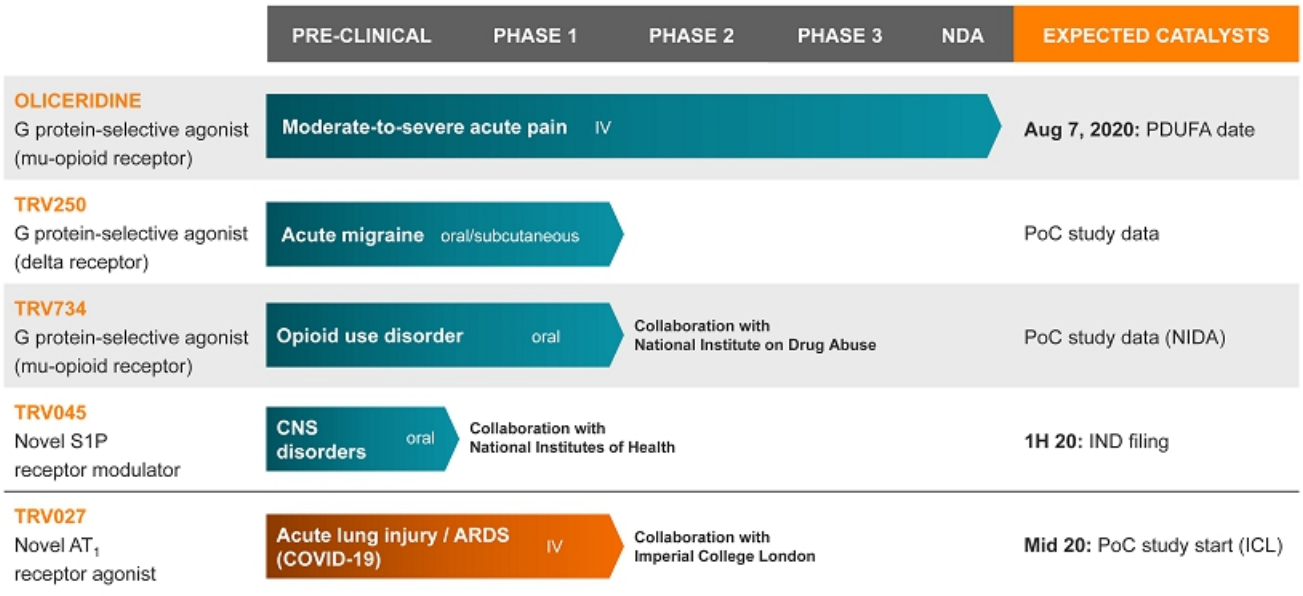
BOARD OF DIRECTORS			
Leon O. Moulder, Jr. *Chairman*	TESARO, MGI PHARMA		
Carrie L. Bourdow	Trevena	Julie H. McHugh	centocor, Johnson & Johnson, enda
Scott Braunstein, M.D.	MARINUS PHARMACEUTICALS, AISLING CAPITAL, J.P.Morgan	Jake R. Nunn	NEA
Michael R. Dougherty	Adolor, centocor	Anne M. Phillips, M.D.	novo nordisk, CSL
Maxine Gowen, Ph.D.	CSL, HUMAN GENOME SCIENCES, Trevena	Barbara Yanni	MERCK

Trevena: Innovative CNS Company

Lead asset IV Oliceridine	New MOA designed to improve intravenous (IV) moderate-to-severe acute pain management PDUFA date: August 7, 2020
Large market, targeted launch	45M+ US hospital patients; 9M at higher risk for AEs (initial focus) $1-1.5B market opportunity for higher-risk patient segment
Novel CNS pipeline	New mechanisms for acute migraine, opioid use disorder, epilepsy, pain NCEs targeting significant unmet needs
NCE for COVID-19	Novel MOA to treat COVID-19 acute lung injury POC study sponsored by Imperial College London
Solid financial position	$28.1M in cash as of 3/31/2020 Funds operations into Q1 2021

MOA = Mechanism of Action; PDUFA = Prescription Drug User Fee Act; NCE = New Chemical Entity

Multiple Expected Catalysts



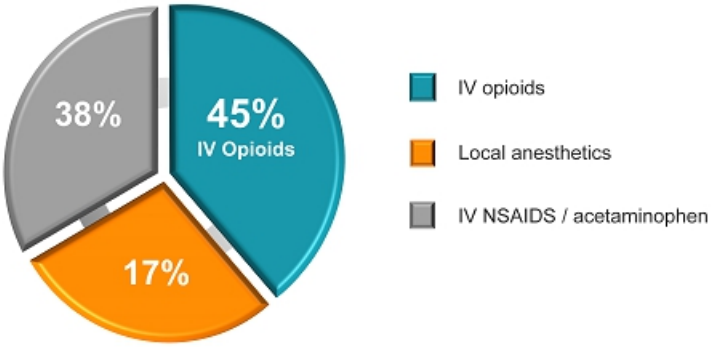
Trevena

Oliceridine, TRV250, TRV734, TRV027, and TRV045 are investigational products and are not approved by the FDA or any other regulatory agency.
PDUFA = Prescription Drug User Fee Act; PoC = Proof-of-Concept

IV Oliceridine Value Proposition

IV opioids are necessary for effective acute pain management

US injectable analgesic hospital market unit volume[1]



Conventional IV opioids

e.g. IV morphine, IV hydromorphone

Primary advantages

- Unrivalled analgesic efficacy

Primary disadvantages[2]

- Respiratory depression
- Nausea, vomiting, ileus

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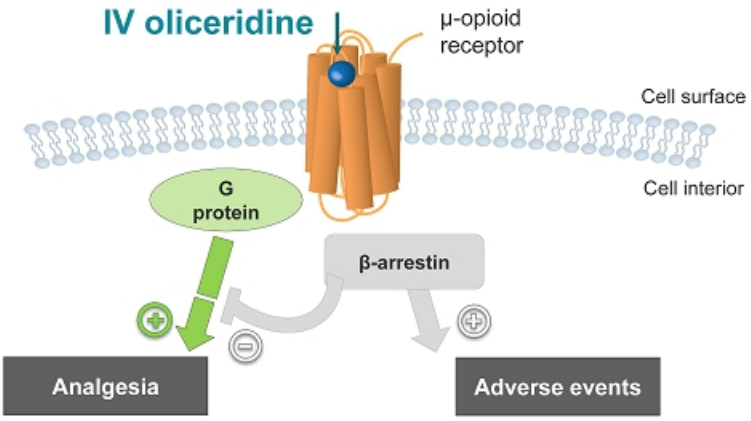
NSAIDs = nonsteroidal anti-inflammatory drugs

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

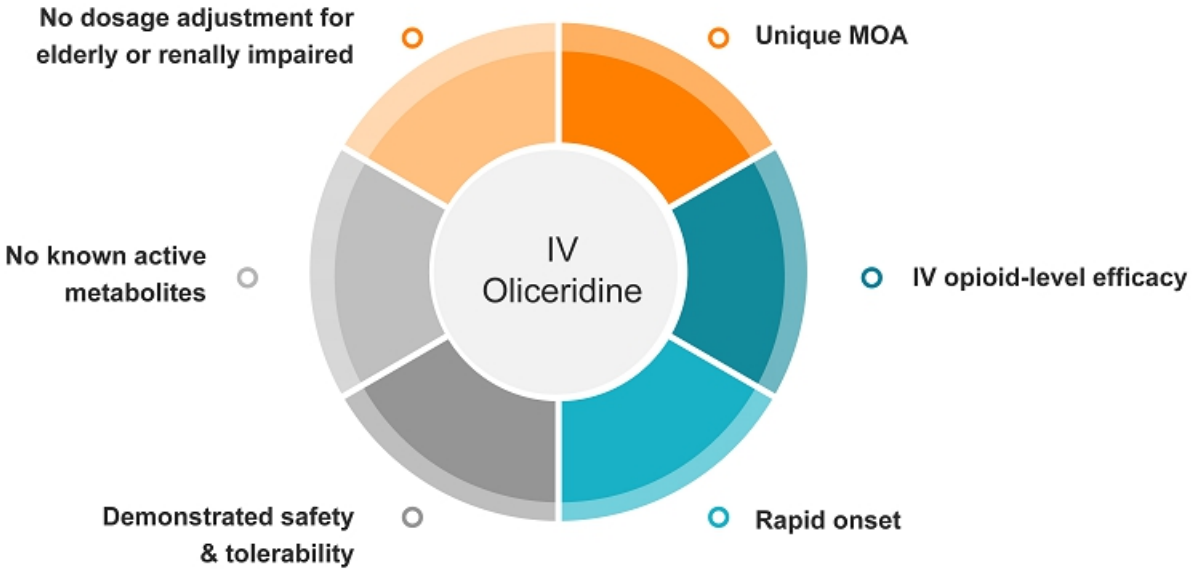


Unlike IV morphine, oliceridine's new technology enables preferential selection of the G-protein pathway for analgesia

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

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.

Compelling Product Profile



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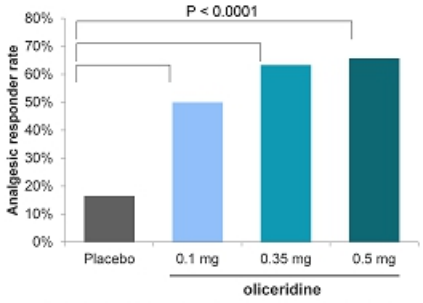
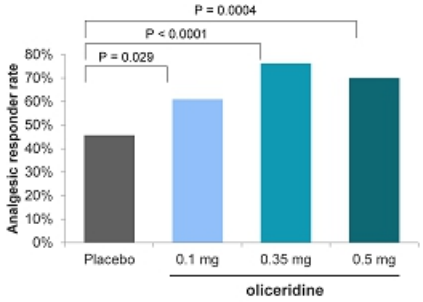
If approved, oliceridine is expected to be a CII controlled substance, as defined in the Controlled Substances Act of 1970.
Data based on Phase 1-3 clinical trials including comparisons of oliceridine to IV morphine.

Primary Efficacy Endpoint Achieved in Two Pivotal Studies

Hard tissue



Soft tissue



Oliceridine achieved IV opioid-level efficacy

- **Meets regulatory criteria for efficacy**
- **Efficacy comparable to IV morphine**
- **Head-to-head data published**

  The Journal of Pain Research[1] and *Pain Practice*[2]

Trevena®

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.

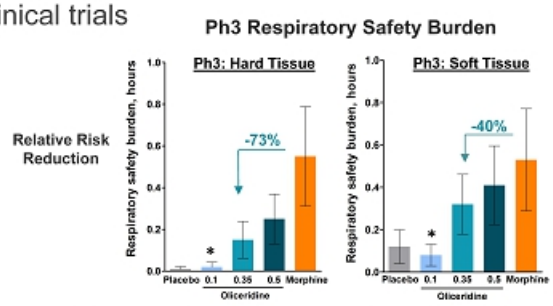
1) Viscusi ER et al. J Pain Res. 2019;12:927–943. Published 2019 Mar 11. 2) Singla NK et al. Pain Pract. 2019;19:715-731. Published 2019 Jun 04.

Well-Characterized Safety and Tolerability Profile

Phase 3 data consistent with findings from earlier clinical trials

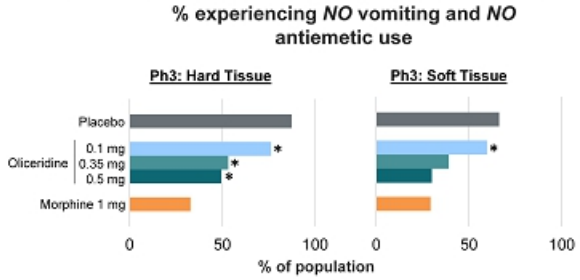
Respiratory safety vs. morphine

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



GI tolerability vs. morphine

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

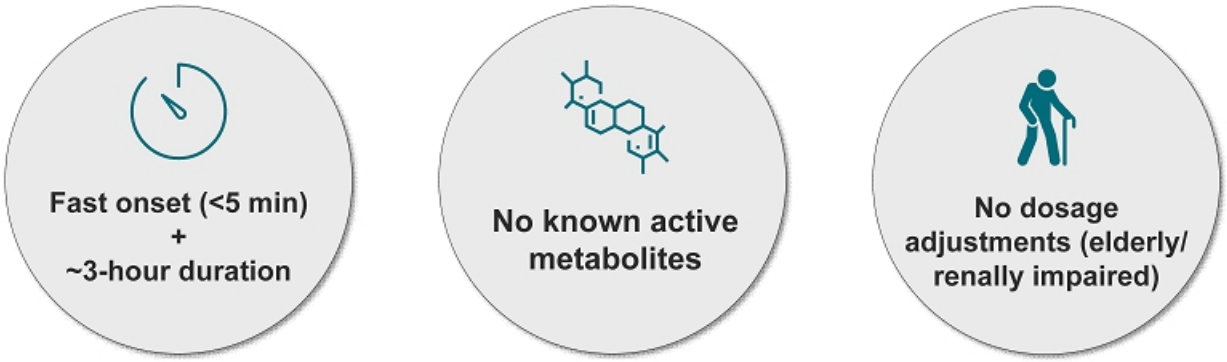


*GI = gastrointestinal; *p < 0.05 vs. morphine*

Phase 1 respiratory safety findings: oliceridine was associated with a reduced impact on hypercapnic drive vs. morphine (Soergel, et al. 2014). Phase 2 respiratory safety findings: oliceridine was associated with a decreased incidence of hypoventilation events vs. morphine (Singla, et al. 2017). Phase 2 GI tolerability findings: oliceridine was associated with a reduced incidence of nausea / vomiting vs. morphine (Singla, et al. 2017).

Unique and Differentiated PK Profile

IV oliceridine demonstrates:



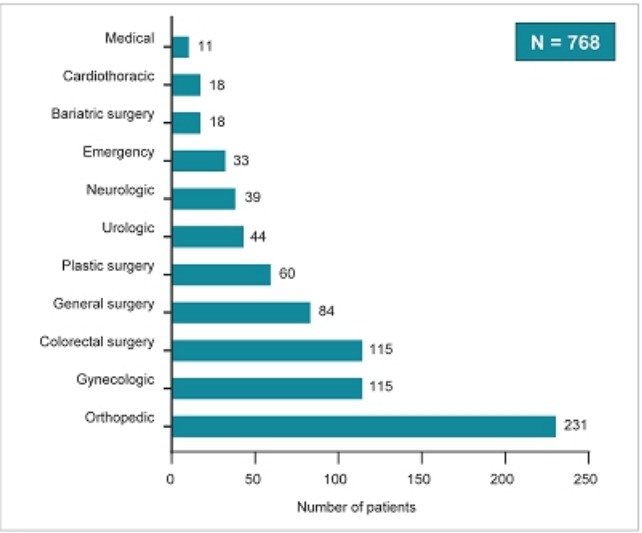
Attractive for ER, hospital floor, and surgery centers

Simplifies dosing for predictable pain control

New option for at-risk patients

Safety / Tolerability Demonstrated in “Real World Use” Study

Broad range of surgeries / medical procedures with at-risk patients



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

Multiple inpatient and outpatient settings

- hospital recovery
- critical care
- emergency department
- ambulatory surgical centers

(bolus and PCA dosing)

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 alfentanil instead of standard IV opioid

Positive Feedback from Formulary Stakeholders[1,2,3]

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

Key Endpoint (vs. IV morphine)	Pharmacy (n=160)	Physicians (n=40)
Reduction in Respiratory Safety Events	 **74%**	 **90%**
Reduction in Vomiting	 **70%**	 **87%**

Hospital pharmacy will consider:

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

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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

Formulary Focus: Improve Outcomes and Decrease Costs

~50% higher overall costs due to opioid-related AEs

~3.5x risk of mortality[1]

$8,826 in hospital costs per patient for nausea / vomiting[2]

$28,000 per critical respiratory event / sequelae[3]

Increased hospital length of stay

~7 additional days[3]

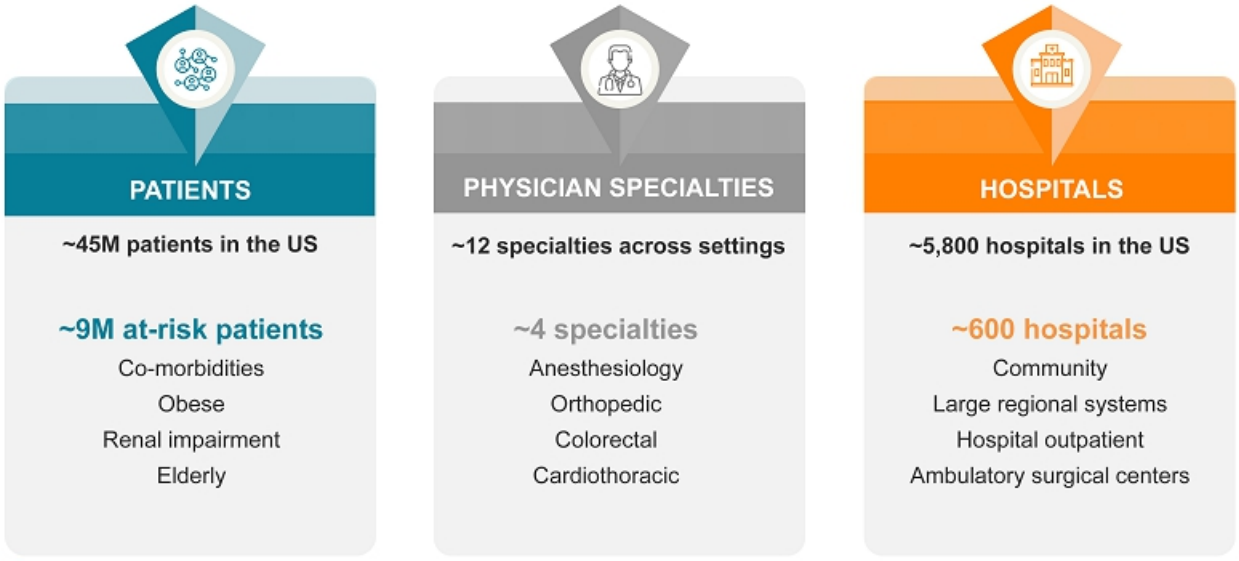
Growing number of at-risk patients in hospitals[4-7]

ORAE = opioid-related adverse event; costs are per hospital stay

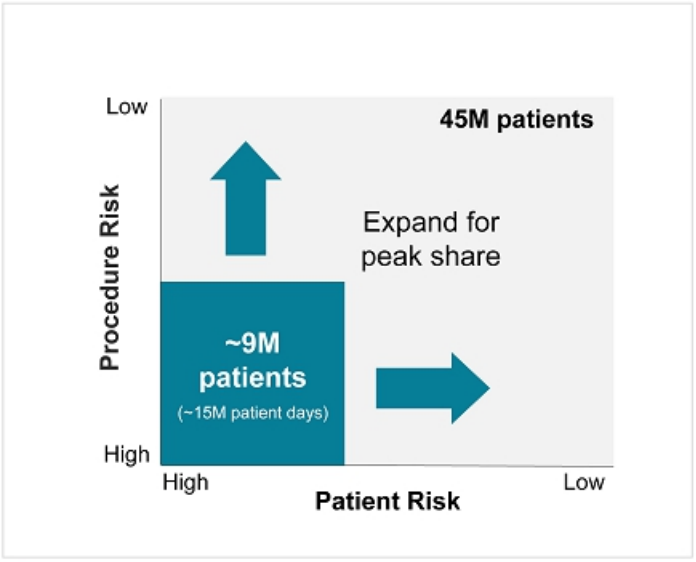
1) Kessler RE, Pharmacotherapy, 2013. 2) Oderda, GM, J Pain Palliative Care Pharm, 2019; data based on 5 surgical procedure categories including Cardiothoracic / vascular, General / Colorectal, Ob / Gyn, Orthopedic, and Urologic. 3) Overdyk FJ, PLoS One, 2016. 4) CDC, National Hospital Discharge Survey 2010. 5) AHRQ HCUP statistical brief #137. 6) CDC Fact Sheet, Chronic Kidney Disease in the United States, 2019. 7) In patients receiving IV morphine; Khanna, A. et al., Critical Care Medicine, 2018 via continuous monitoring.

Targeted Account Launch

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



Launch Strategy Allows for Growth



Patient risk factors, e.g.

- Co-morbidities
- Obese
- Renal impairment
- Elderly

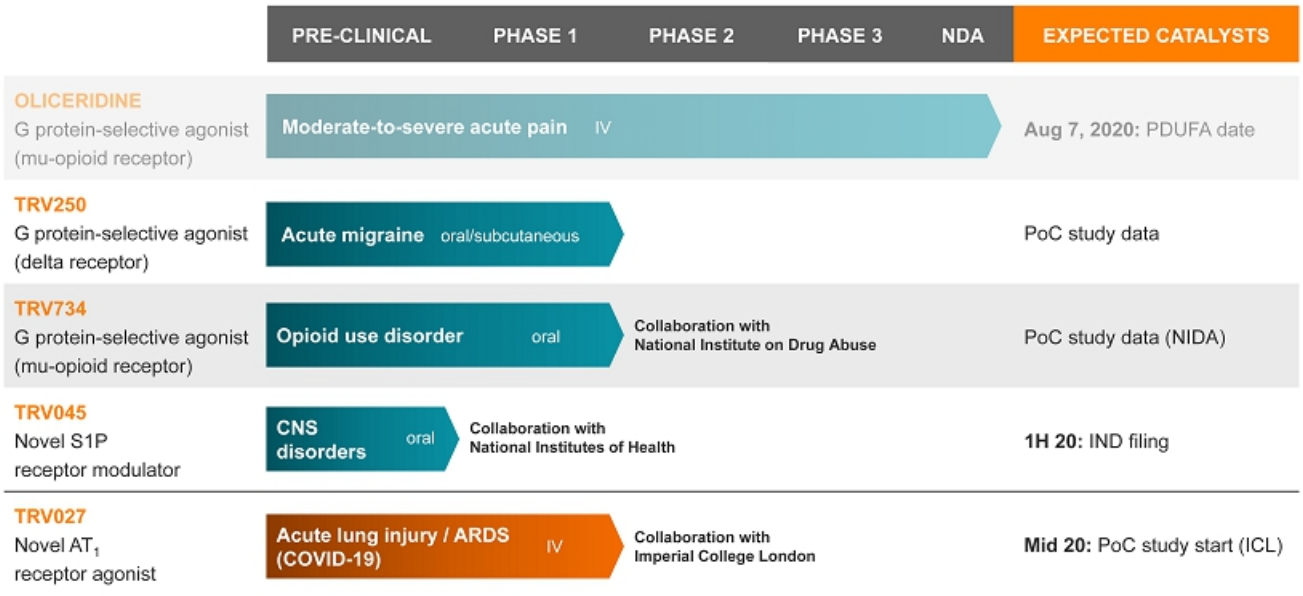
Procedure risk factors, e.g.

- Severe / prolonged pain
- Ortho, colorectal, cardiothoracic

15M patient days
=
$1B - $1.5B market opportunity*

* Assumes $60 - $100 / day price for alfentanil

Multiple Expected Catalysts



Trevena

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PDUFA = Prescription Drug User Fee Act; PoC = Proof-of-Concept

Migraine Represents A Large Market Opportunity

Total migraine drug market = ~$3.5B

Every year in the US:

20-30% of migraine sufferers do not respond to / cannot tolerate the market-leading triptan drug class

An estimated **50%** of migraineurs also suffer from anxiety[1]

Trevena

All data from Decision Resources, Pharmacor migraine market landscape and forecast 2018. 1) Maven et al., J Neurol Neurosurg Psychiatry, 2016.
Icons made by Freepik from www.flaticon.com

TRV250: New MOA for Acute Treatment of Migraine

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

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)

- Nonclinical evidence of improved tolerability with TRV734
- NIDA study demonstrated reduced drug-seeking behavior in animal model of relapse[2]
- Current therapies not well tolerated, can hinder patient adherence

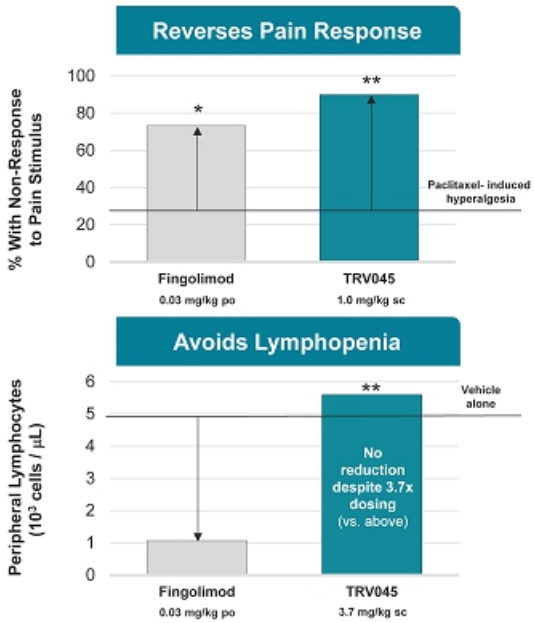
NIDA-funded proof-of-concept patient study initiated

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
- TRV045 reverses 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



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*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*

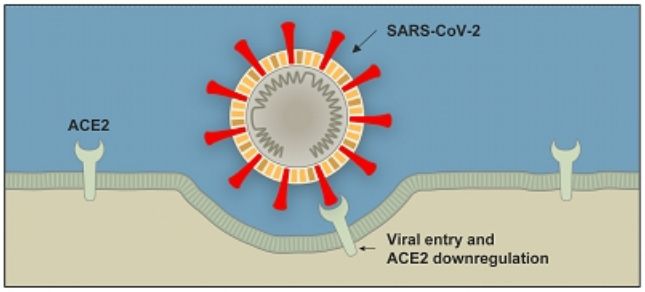
TRV027

NCE targeting the AT_1 receptor in COVID-19

Interaction Between the AT_1 Receptor and ACE2 in COVID-19

Downregulation of ACE2 by coronavirus indirectly promotes activation of the AT_1 receptor

- Coronavirus binds to and downregulates angiotensin converting enzyme 2 (ACE2)[1]
- Decrease in ACE2 elevates angiotensin II levels
  - Angiotensin II activates AT_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_1 receptor[2]
    - Protective therapeutic benefits in the lungs[3]

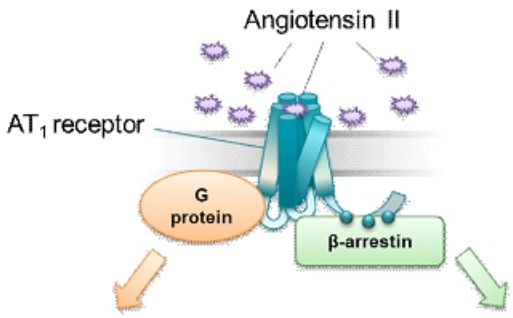


1) Kuba K et al., Nat Med, 2005. 2) Teixeira LB et al., Sci Rep, 2017. 3) Santos RAS et al., Physiol Rev, 2018.

AT_1 Receptor Integral to COVID-19 Morbidity

Coronavirus binds to and removes ACE2, elevating levels of angiotensin II

- High levels of angiotensin II overactivate AT_1 receptors, causing acute lung injury
  - Can lead to acute respiratory distress syndrome (ARDS)
- ARDS is a major complication leading to mortality
  - COVID-19-related ARDS is associated with a mortality rate of 66% - 94%[1*]



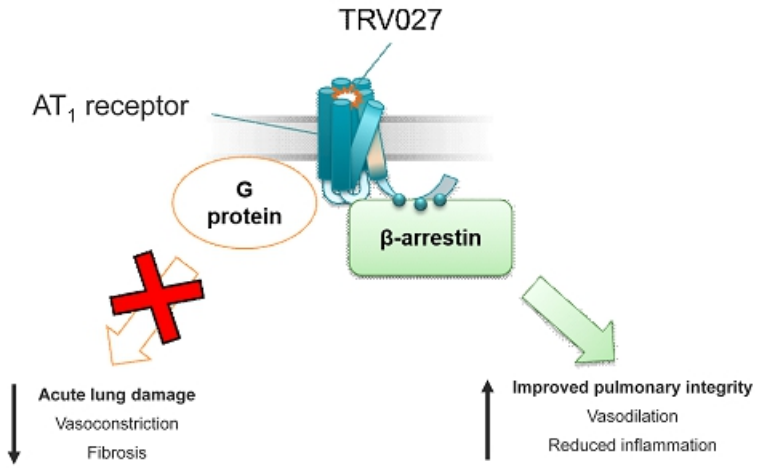
Acute lung damage
Vasoconstriction
Fibrosis

Improved pulmonary integrity
Vasodilation
Reduced inflammation

1) Gibson PG et al. Med J Aust, 2020. *In patients requiring ventilation.

TRV027: A New MOA at the AT_1 Receptor

TRV027 combats overactivation of AT_1 receptor while promoting reparative effects on lung tissue



TRV027 provides a selective and targeted approach to treating acute lung injury in COVID-19 patients

TRV027 is Ready to Enter Clinical Testing

Safety / tolerability has been established in large patient population

TRV027 clinical development history

- Advanced through Phase 2b for acute heart failure
- Studied in ~700 individuals
- Well-characterized pharmacology
- No significant safety issues during clinical trials

COVID-19 Study - Imperial College London

Investigate effect of TRV027 on pathways that contribute to COVID-19 pathology

- Randomized, double-blind, placebo-controlled proof-of-concept study
- N = ~60 (30 per arm) COVID-19 patients
  - Hospitalized, non-ventilated
  - ≥65 years old
- IV infusion of placebo or TRV027 for 7 days

Primary endpoint:

Coagulation biomarker
(predictor of COVID-19 mortality)

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

Imperial College London

Trevena: Innovative CNS Company

Lead asset IV Oliceridine	New MOA designed to improve intravenous (IV) moderate-to-severe acute pain management PDUFA date: August 7, 2020
Large market, targeted launch	45M+ US hospital patients; 9M at higher risk for AEs (initial focus) $1-1.5B market opportunity for higher-risk patient segment
Novel CNS pipeline	New mechanisms for acute migraine, opioid use disorder, epilepsy, pain NCEs targeting significant unmet needs
NCE for COVID-19	Novel MOA to treat COVID-19 acute lung injury POC study sponsored by Imperial College London
Solid financial position	$28.1M in cash as of 3/31/2020 Funds operations into Q1 2021

MOA = Mechanism of Action; PDUFA = Prescription Drug User Fee Act; NCE = New Chemical Entity

APPENDIX

NDA Resubmission Considered Complete

PDUFA date: August 7, 2020

Completed healthy volunteer QT study

- No accumulation of effect through 24 hrs despite repeated dosing
- No categorical QTc outliers with Δ > 60 ms or > 500 ms absolute

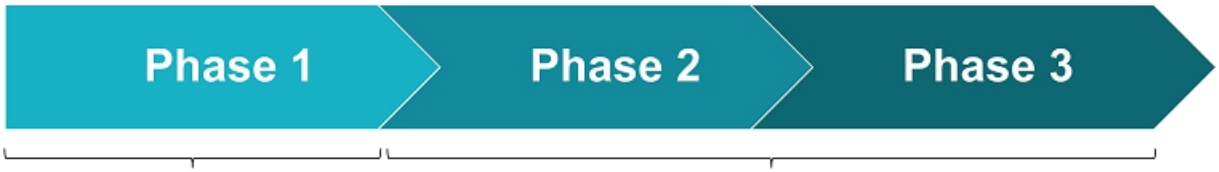
Confirmed safety database supports maximum daily dose of 27 mg

Validated bioassay and confirmed levels of inactive metabolite ('9662)

Completed drug product validation reports

Robust Clinical Development Program

IV oliceridine studied in > 1,800 individuals



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

4 head-to-head trials vs. morphine:

- IV opioid-level efficacy
- Rapid onset of action
- Well-characterized respiratory safety profile
- Low rates of vomiting and rescue antiemetic use

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**

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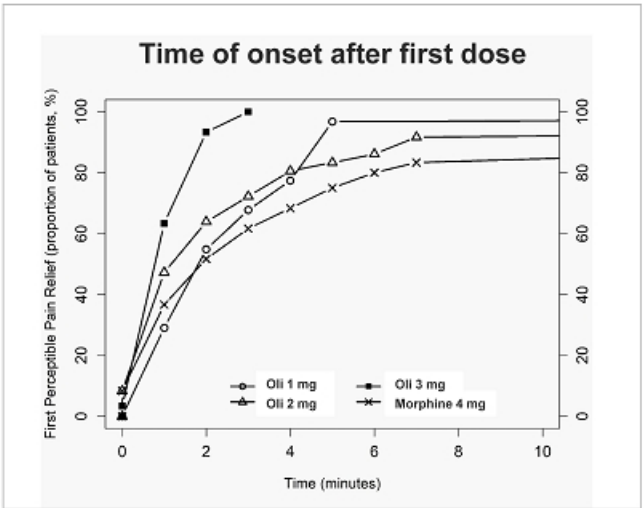
 # subjects exposed to oliceridine in Ph1 = 318
 # patients treated with oliceridine in Ph2 and Ph3 = 1,535

Oliceridine Delivers Rapid Analgesia

Fast onset measured by two-stopwatch method

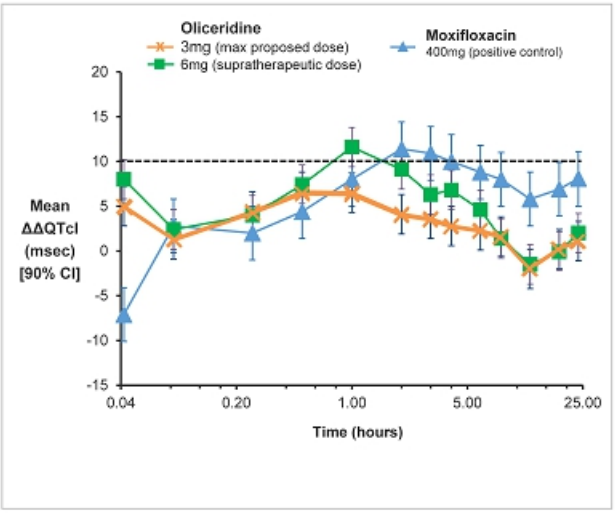


Majority of patients achieved perceptible pain relief within **2-5 minutes** after first dose[1]

1) Viscusi ER, Pain, 2016.

Overview of Cardiac Safety Data

Single-Dose tQT Study



Multiple inpatient and outpatient settings

- **Max proposed dose (3mg):** No clinically significant effect on QTc
- **Supratherapeutic dose (6mg):** Small transient increase in QTc interval, peak at one hour

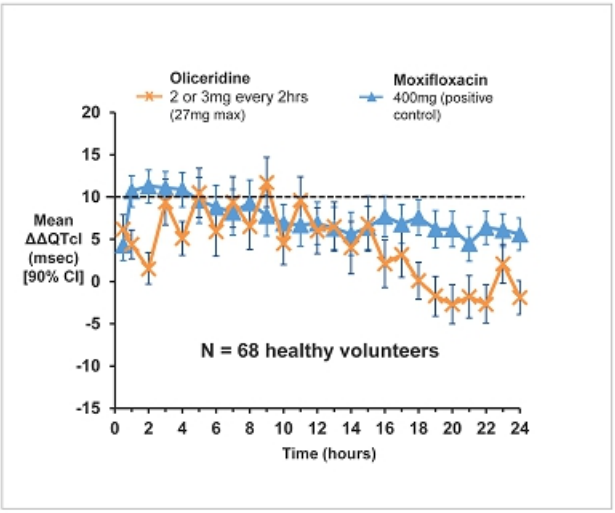
Phase 3 ECG monitoring

- **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

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

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**
  Δ >60 ms; >500 ms absolute
- **Well tolerated, no SAEs***
  92% reached max daily dose

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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

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*

Consistent Respiratory Safety Profile

Phase 1:

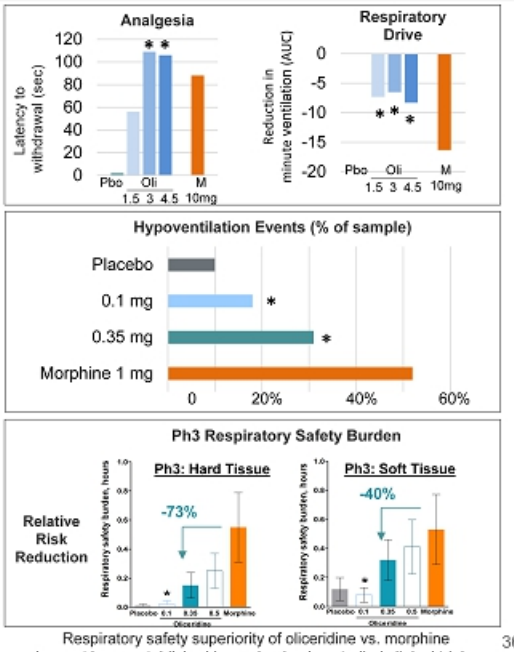
- **Reduced** impact on hypercapnic respiratory drive vs. morphine[1]

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]



Respiratory safety superiority of oliceridine vs. morphine has not been established in randomized controlled clinical trials.

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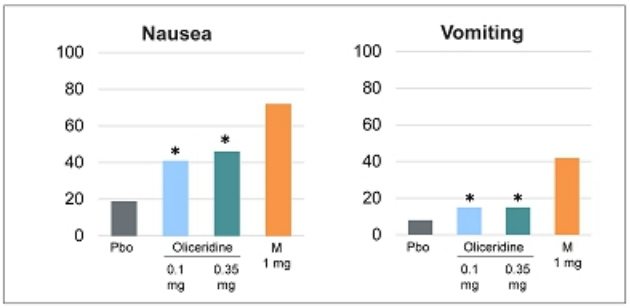
**p < 0.05 vs. morphine. Hypoventilation: clinically apparent and persistently decreased respiratory rate, respiratory effort, or oxygen saturation.*

1) Soergel, et al. (2014). 2) Singla, et al. (2017). 3) Viscusi, et al. (2019). 4) Singla, et al. (2019)

Favorable GI Tolerability and Safety Profile

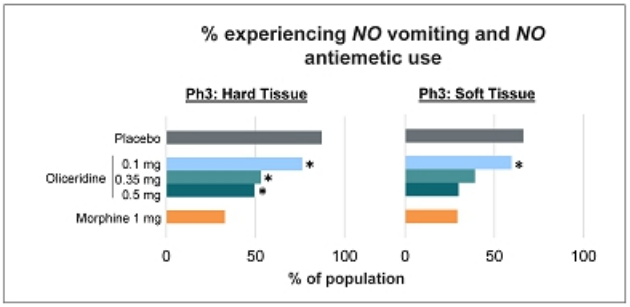
Phase 2:

- **Reduced** incidence of nausea and vomiting adverse events vs. morphine[1]



Phase 3:

- **Reduced** incidence of post-operative nausea and vomiting
- **Reduced** use of rescue antiemetics
- **Reduced** proportion of patients with vomiting or antiemetic use[2,3]



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

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*GI = gastrointestinal; *p < 0.05 vs. morphine*

1) Singla, et al. (2017). 2) Viscusi, et al. (2019). 3) Singla, et al. (2019)

APOLLO 1: Most Common TEAEs

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

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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

	Placebo	Oliceridine			Morphine
Most common TEAEs, n (%) of patients	(N=83)	**0.1mg** (N=77)	**0.35mg** (N=79)	**0.5mg** (N=80)	**1mg** (N=82)
Nausea	38 (45.8)	34 (44.2)	49 (62.0)	60 (75.0)	61 (74.4)
Vomiting	11 (13.3)	18 (23.4)	17 (21.5)	34 (42.5)	44 (53.7)
Headache	24 (28.9)	12 (15.6)	23 (29.1)	21 (26.3)	24 (29.3)
Hypoxia	4 (4.8)	6 (7.8)	16 (20.3)	14 (17.5)	19 (23.2)
Pruritus, Generalized pruritus	5 (6.0)	11 (14.3)	14 (17.7)	15 (18.8)	22 (26.8)
Constipation	6 (7.2)	12 (15.6)	13 (16.5)	9 (11.3)	9 (11.0)
Somnolence, Sedation	8 (9.6)	7 (9.1)	11 (13.9)	10 (12.5)	25 (30.5)
Dizziness	9 (10.8)	11 (14.3)	7 (8.9)	7 (8.8)	13 (15.9)
Back pain	5 (6.0)	3 (3.9)	10 (12.7)	9 (11.3)	7 (8.5)

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

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

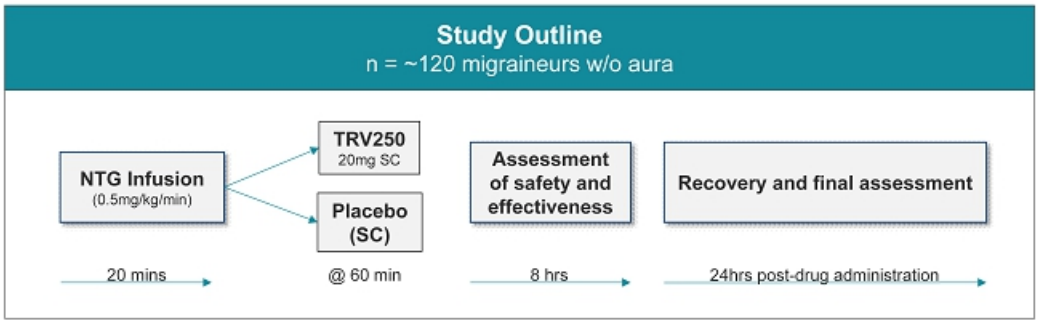
Delta receptor agonists

- 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

1) Rothrock JF & Friedman DI, American Headache Society website: https://americanheadachesociety.org/wp-content/uploads/2018/05/John_Rothrock_and_Deborah_Friedman_-_Triptans.pdf. 2) Durham PL, Headache, 2006. 3) Peppin JF & Raffa RB, Journal of Clinical Pharmacy and Therapeutics, 2015.

TRV250 PoC Study (acute migraine)

Study initiated Q4 2019



Primary endpoint:

- Reduction of sustained NTG-induced headaches @ 4hr

Secondary Endpoints:

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