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): **July 28, 2022**

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 2.02 Results of Operations and Financial Condition.

On July 28, 2022, Trevena, Inc. (the "Company") issued a press release reporting, among other things, cash and cash equivalents for the quarter ended June 30, 2022. A copy of the press release is furnished herewith as Exhibit 99.1 and incorporated herein by reference.

Item 8.01 Other Events.

On July 28, 2022, the Company updated its website to include an updated corporate presentation deck. A copy of the updated corporate presentation deck is attached hereto as Exhibit 99.2. Additionally, on July 28, 2022, the Company issued a press release announcing, among other things, top-line data from its cognitive function study, successful negotiation of a contract with a large group purchasing organization to support OLINVYK commercialization efforts and also provided a general business update that included a realignment of company resources and advancement of the Phase 1 study for TRV045. A copy of the press release is furnished herewith as Exhibit 99.1 to this Current Report on Form 8-K and incorporated herein by reference.

The information set forth on this Item 8.01 and furnished hereto as Exhibits 99.1 and 99.2 shall not be deemed "filed" for purposes of Section 18 of the Exchange Act or incorporated by reference into any of the Company's filings under the Securities Act or the Exchange Act, whether made before or after the date of this Current Report, except as shall be expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Number	Description
99.1	Press Release dated July 28, 2022
99.2	Updated Corporate Presentation Deck dated July 28, 2022
104	The cover page from this Current Report on Form 8-K, formatted in Inline XBRL

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: July 28, 2022

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

Exhibit 99.1

Trevena Announces Positive Topline OLINVYK Cognitive Function Data and Provides General Business Update

OLINVYK demonstrated statistically significant reduced impact on neurocognitive functioning vs IV morphine on primary endpoint

Successfully negotiated OLINVYK contract with a large group purchasing organization (GPO) serving over 50% of US acute care providers and 20% of US ambulatory care providers

Novel S1P receptor modulator TRV045 for diabetic neuropathic pain on track for completion of Phase 1 in 2H 2022

Strategic allocation of resources and cost reductions reinforce key focus areas and extends cash runway to mid-2023

CHESTERBROOK, Pa., July 28, 2022 (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 reported positive topline results from its post-approval study designed to assess the impact on cognitive function in subjects treated with OLINVYK compared to IV morphine. The Company also provided a general business update including recent realignment of resources and cost reductions, as well as progress on the US commercial launch of OLINVYK and the Company's pipeline assets.

"We are pleased to announce the positive topline cognitive function data and a major contract win for OLINVYK," said Carrie Bourdow, President and CEO of Trevena. "We also remain focused on advancing the clinical studies for TRV045, our novel S1P receptor modulator, and our recent corporate realignment will help us increase financial flexibility to drive forward our strategic priorities."

Cognitive Function Study

OLINVYK was studied in a randomized, double-blind, placebo-controlled, dose-ranging design, in collaboration with the Netherlands-based Center for Human Drug Research. Subjects received single intravenous doses of OLINVYK 1 mg and 3 mg, or morphine 5 mg and 10 mg, or placebo, using a partial-block crossover design. A comprehensive battery of neurocognitive and motor assessments was obtained following each blinded dose, which included measures of Sedation/Reaction Time, Visual Tracking, Higher-order Cognitive Processing, Motor Function and Eye-Hand Coordination. Twenty-three healthy subjects participated in the study, including 13 males and 10 females, with a median age of 26.

Overall, OLINVYK showed evidence of a reduced impact on neurocognitive function compared to IV morphine.

Key Findings:

- **Primary Endpoint.** OLINVYK showed a statistically significant reduction in sedation versus IV morphine, measured by saccadic eye movement peak velocity, a sensitive laboratory measure of sedating action of medications. The prespecified mixed-model repeated measures ANOVA highlighted a difference between treatments (main effect of treatment, P<0.0001), driven by a reduced impact of OLINVYK versus IV morphine (P=0.0236).

- **Secondary Endpoints.** On several of the prespecified secondary outcome measures, OLINVYK showed a statistically significant difference or trend compared to IV morphine, despite the relatively small sample size, across a range of neurocognitive measures and motor performance:
    - *Reaction Time.* Reduced impact on saccadic eye movement reaction time (main effect, P=0.0201) (OLINVYK vs IV morphine, P=0.0273)
    - *Postural Stability (Motor Function).* Reduced body sway, a measure of motor function (main effect, P=0.0314) (OLINVYK vs IV morphine, P=0.0951)
    - *Eye-Hand Coordination*. Reduced performance accuracy on the adaptive tracking test, a measure of eye-hand coordination (main effect, P=0.0011), (OLINVYK vs IV morphine, P=0.1303)
    - *Target Engagement (Pupillometry and Analgesia).* Across the dose ranges studied, both OLINVYK and IV morphine demonstrated expected effects on opioid-induced pupillary constriction, and analgesia in response to cold pain testing

Other secondary outcome measures, including visual tracking and higher-order cognitive processing did not show statistical differences between OLINVYK and IV morphine. No serious adverse events were observed in the study, and adverse events were generally assessed as mild.

"Neurocognitive function including sedation and postural instability may have important consequences in the clinical care setting with the use of opioid medications." said Mark Demitrack, M.D. Chief Medical Officer of Trevena. "Mitigating the impact of these adverse events may have important implications for length of stay and other health economic outcomes."

Trevena General Business Updates

- **Executed a contract in July with a leading hospital group purchasing organization (GPO), which will allow for broad OLINVYK access for member hospitals.**The hospital GPO has coverage across US academic medical centers, acute care hospitals and ambulatory surgical centers.

- **Implemented a realignment of Company resources in July to maintain focus on key value drivers and extend cash runway to mid-2023.** The Company implemented a ~25% reduction in full-time employees and terminated its contract sales force agreement with Syneos. Trevena maintains a focused internal commercial and medical affairs team supporting OLINVYK. The Company effected other general expense reductions that the Company believes will collectively help reduce operating expenses and extend the cash runway to mid-2023. The Company believes these decisions allow Trevena to continue to sufficiently resource its key strategic priorities of driving commercial adoption of OLINVYK and developing TRV045.

- **Continued to advance Phase 1 study of TRV045, our novel S1P receptor modulator, for diabetic neuropathic pain; on track for completion 2H 22.**TRV045 is a novel, selective sphingosine-1 phosphate subtype 1 (S1P1) receptor modulator being developed as a potential treatment for acute and chronic neuropathic pain secondary to diabetic peripheral neuropathy. Through a preclinical collaboration with the National Institutes of Health, Trevena is also exploring TRV045 as a potential treatment for epilepsy, with possible application in refractory epilepsy and other rare or orphan seizure disorders.

- **Maintained approximately $49.5 million in cash and equivalents at June 30, 2022**, which the Company believes will be sufficient to fund the Company's operating expenses and capital expenditure requirements to mid-2023. There were no net sales of OLINVYK for the quarter ended June 30, 2022. The cash balance includes net proceeds in April from the first $15 million tranche of the royalty-based financing agreement with an affiliate of R Bridge Healthcare Fund.

About OLINVYK® (oliceridine) injection

OLINVYK is a new chemical entity approved by the FDA in August 2020. OLINVYK contains oliceridine, an opioid, which is a Schedule II controlled substance with a high potential for abuse similar to other opioids. It 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. OLINVYK is available in 1 mg/1 mL and 2 mg/2 mL single-dose vials, and a 30 mg/30 mL single-patient-use vial for patient-controlled analgesia (PCA). Approved PCA doses are 0.35 mg and 0.5 mg and doses greater than 3 mg should not be administered. The cumulative daily dose should not exceed 27 mg. Please see Important Safety Information, including the BOXED WARNING, and full prescribing information at www.OLINVYK.com.

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.

INDICATIONS AND USAGE

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

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.

- 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 CO_2 retention, such as those with evidence of increased intracranial pressure or brain tumors, as

- a reduction in respiratory drive and the resultant CO_2 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.

- OLINVYK may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in vulnerable patients. Monitor patients with a history of seizure disorders for worsened seizure control.

- Do not abruptly discontinue OLINVYK in a patient physically dependent on opioids. Gradually taper the dosage to avoid a withdrawal syndrome and return of pain. Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving OLINVYK, as they may reduce the analgesic effect and/or precipitate withdrawal symptoms.

- OLINVYK may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

- Although self-administration of opioids by patient-controlled analgesia (PCA) may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression. Health care providers and family members monitoring patients receiving PCA analgesia should be instructed in the need for appropriate monitoring for excessive sedation, respiratory depression, or other adverse effects of opioid medications.

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.

MEDICAL INFORMATION

For medical inquiries or to report an adverse event, other safety-related information or product complaints for a company product, please contact the Trevena Medical Information Contact Center at **1-844-465-4686** or email **MedInfo@Trevena.com**.

You are encouraged to report suspected adverse events of prescription drugs to the FDA. Visit**www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please see Full Prescribing Information, including Boxed Warning.

About Trevena

Trevena, Inc. is a biopharmaceutical company focused on the development and commercialization of innovative medicines for patients with CNS disorders. The Company has one approved product in the United States, OLINVYK® (oliceridine) injection, indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. The Company's novel pipeline is based on Nobel Prize winning research and includes three differentiated investigational drug candidates: TRV045 for diabetic neuropathic pain and epilepsy, TRV250 for the acute treatment of migraine and TRV734 for maintenance treatment of opioid use disorder.

For more information, please visit www.Trevena.com

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 discussions with FDA; 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 approved product; 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.

For more information, please contact:

Investor Contact:

Dan Ferry
Managing Director
LifeSci Advisors, LLC
daniel@lifesciadvisors.com
(617) 430-7576

PR & Media Contact:

Sasha Bennett
Associate Vice President
Clyde Group
Sasha.Bennett@clydegroup.com
(239) 248-3409

Company Contact:

Bob Yoder
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 "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

Carrie L. Bourdow	President & Chief Executive Officer	CUBIST, MERCK
Mark A. Demitrack, M.D.	SVP, Chief Medical Officer	NEURONETICS, Lilly, ROIVANT SCIENCES
Patricia Drake	SVP, Chief Commercial Officer	MERCK, sesen bio
Barry Shin	SVP, Chief Financial Officer	MIZUHO, GUGGENHEIM, PiperJaffray
Robert T. Yoder	SVP, Chief Business Officer & Head of Commercial Operations	MERCK, OREXIGEN

BOARD OF DIRECTORS

Leon O. Moulder, Jr. Chairman	TESARO, MGI PHARMA	Marvin H. Johnson, Jr.	MERCK
Carrie L. Bourdow	Trevena	Jake R. Nunn	NEA
Scott Braunstein, M.D.	MARINUS PHARMACEUTICALS, AISLING CAPITAL, PACIRA BIOSCIENCES	Anne M. Phillips, M.D.	novo nordisk, GSK
Michael R. Dougherty	Adolor, centocor	Barbara Yanni	MERCK

Trevena: Innovative CNS Company

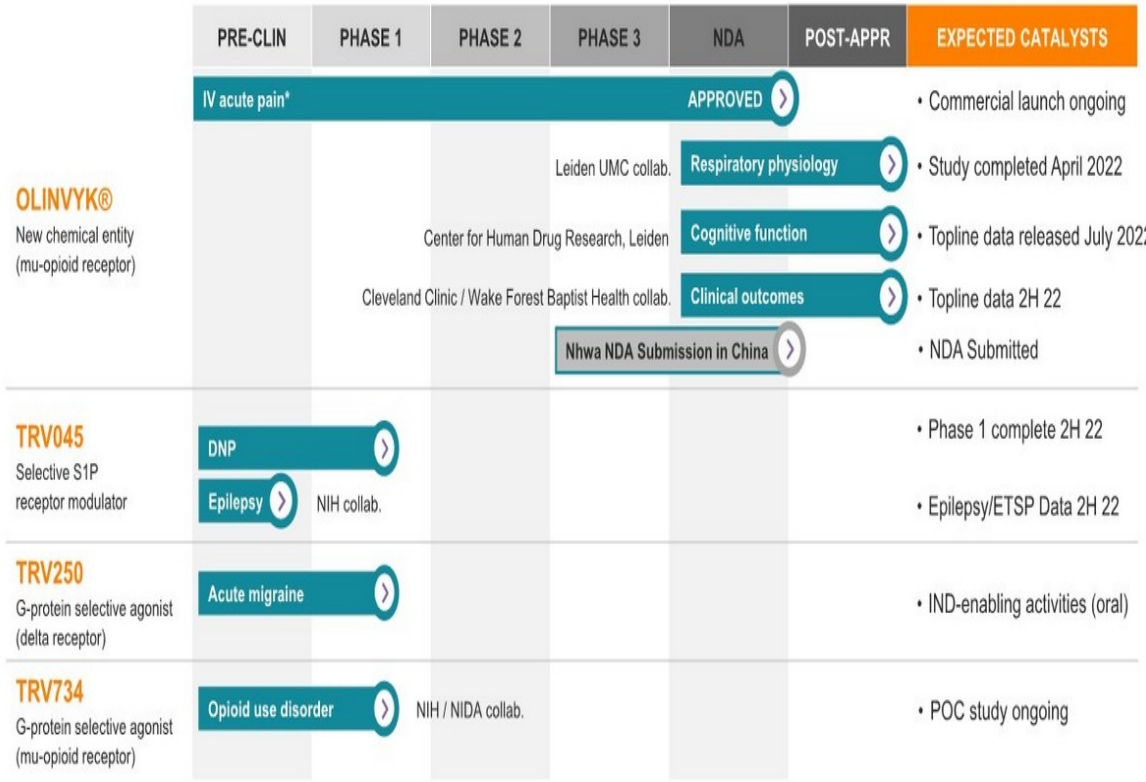
IV OLINVYK: Differentiated profile	NCE approved for the management of acute pain in adults Launch in Q1 2021; additional supportive studies vs. IV morphine with near-term data
Large market, targeted launch	45M+ US hospital patients; 9M procedures is initial core focus $1.5B+ market opportunity for core focus
TRV045: Selective S1PR modulator	Novel candidate in Phase 1 for diabetic neuropathic pain (with potential broader applicability) NIH collaboration exploring TRV045 potential for epilepsy
Novel CNS pipeline	New mechanisms for acute / neuropathic pain, epilepsy, acute migraine, opioid use disorder NCEs targeting significant unmet needs
Solid financial position	$48.7M cash / equivalents @ Q1 (not including R-Bridge $15M tranche received April)

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.

NCE = New Chemical Entity; MOA = Mechanism of Action; NIH = National Institutes of Health;

Trevena

Multiple Expected Catalysts



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.
TRV250, TRV734 and TRV045 are investigational products and are not approved by the FDA or any other regulatory agency.; NDA = New Drug Application, PoC = Proof-of-Concept, DNP = Diabetic Neuropathic Pain

Trevena®

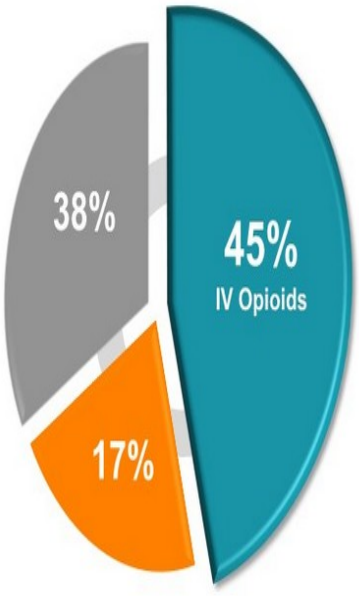
Ex-US Royalty-Based Financing Highlights

Blue Chip Investor	**R-Bridge Healthcare Fund** affiliate of CBC Group (one of the largest and most active healthcare-dedicated investment firms in Asia)
$40M Total Financing	**$15M** upfront (received April 2022) **$10M** on commercial or financing milestone **$15M** on first commercial sale in China **$40M total**
Flexible Payments*	• **Chinese Royalties.** All royalties from Nhwa partnership, TRVN retains milestones • **Capped US Royalty.** 4% royalty on US OLINVYK net sales, with $10M cap**
Constructive Terms	• No financial covenants • Negative pledge only until Chinese approval • Flexibility for additional business development opportunities

* R-Bridge will receive a 1.5% fee and warrants for 5M shares at a strike price of $0.82 / sh (75% premium to 30-day VWAP)
**Potential increase to 7% (with combined US/China cap) if not approved by YE-23

Large Market Opportunity – Acute Pain

US injectable analgesic hospital market unit volume[1]



- IV opioids
- Local anesthetics
- IV NSAIDS / acetaminophen

45M patients receive IV opioids annually to treat acute pain[1]

IV opioids have unrivalled analgesic efficacy

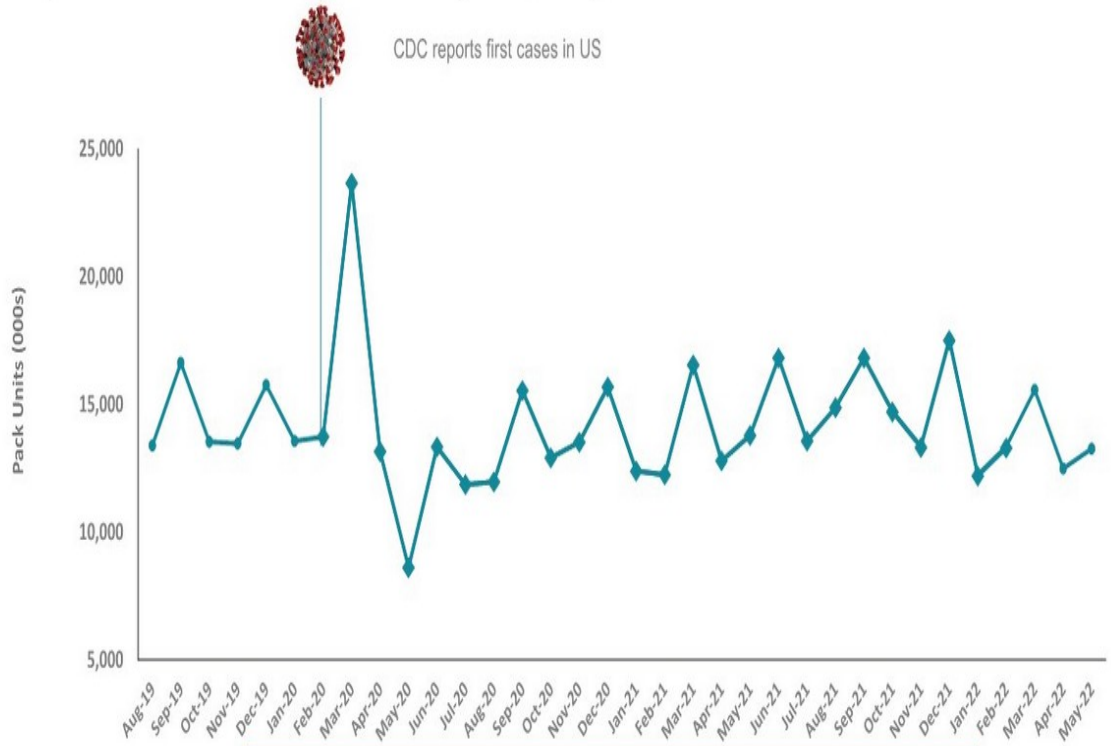
Top surgeries:
Total knee arthroplasty, colectomy, hernia repair, spine fusion, C-section[2]

Trevena®

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.
Opioids are associated with serious, potentially life-threatening adverse reactions.
NSAIDs = nonsteroidal anti-inflammatory drugs. 1) IMS MIDAS sales audit 2017; IV NSAIDs and Ofirmev®. 2) Definitive database, and National Vital Statistics report, CDC 2018.

Stable IV Opioid Market Performance

Despite the 20% decline in elective surgeries, IV opioid volume remained stable



Declines due to COVID-19 across top surgical procedures:
Total knee, Total hip, Hernia repair, Hysterectomy, Bariatric

Trevena

SOURCE: IQVIA DDD Data May 2022

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

Data in complex patients
Elderly / obese, multiple comorbidities

New chemical entity
Distinct from IV morphine

Simplified, predictable dosing
No adjustment in renal impaired
No active metabolites

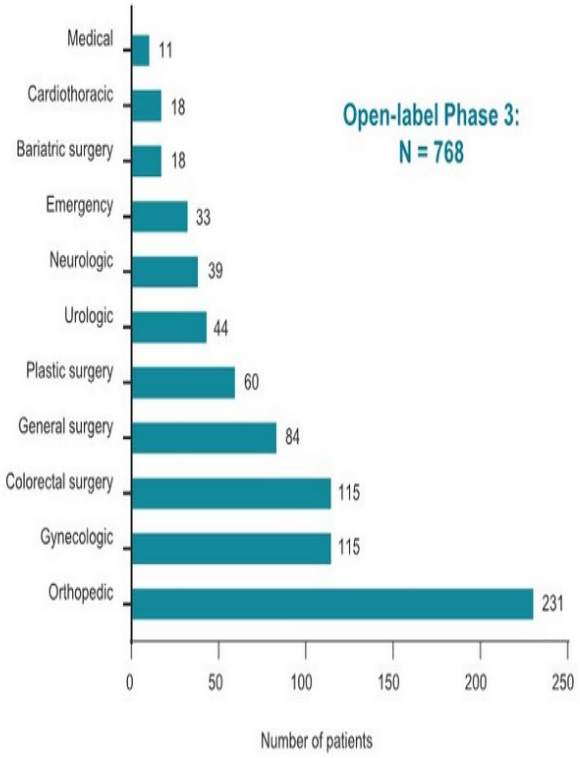
IV opioid efficacy
Hard- and soft-tissue surgeries

Well-characterized safety / tolerability
Studied in over 1,900 individuals

Rapid analgesia
1-3 min median onset of pain relief

OLINVYK Studied in Complex Surgeries & Patients

Broad range of surgeries / medical procedures



Complex patients included

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

Multiple inpatient and hosp 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

Trevena®

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.
Bergese SD et al. J Pain Research, 2019. Trial modeled real-world use: usual patient care with OLINVYK instead of standard IV opioid.
See FDA draft guidance for Industry Distributing Scientific and Medical Publications on Unapproved New Uses.

OLINVYK: Well-Characterized Safety / Tolerability

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

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

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

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

O_2 saturation < 90%
Independent predictor of early post-op respiratory complications

Trevena®

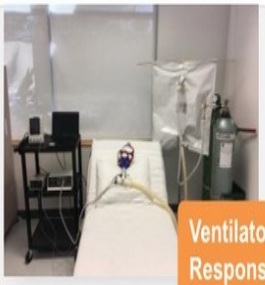
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.
1) OLINVYK Prescribing Information.

Respiratory Physiology Study

Head-to-Head Comparison of OLINVYK and IV morphine in Elderly/Overweight Subjects (N=18)

Assessment of Respiratory Function:

- Increase inhaled CO_2 to experimentally induce respiratory drive
- Impact of drug measured as change in minute ventilation
- Greater reductions in minute ventilation indicate more respiratory depression
- Validated method to estimate the impact of a drug on respiratory drive



Ventilatory Response to Hypercapnia

Assessment of Pain Threshold:

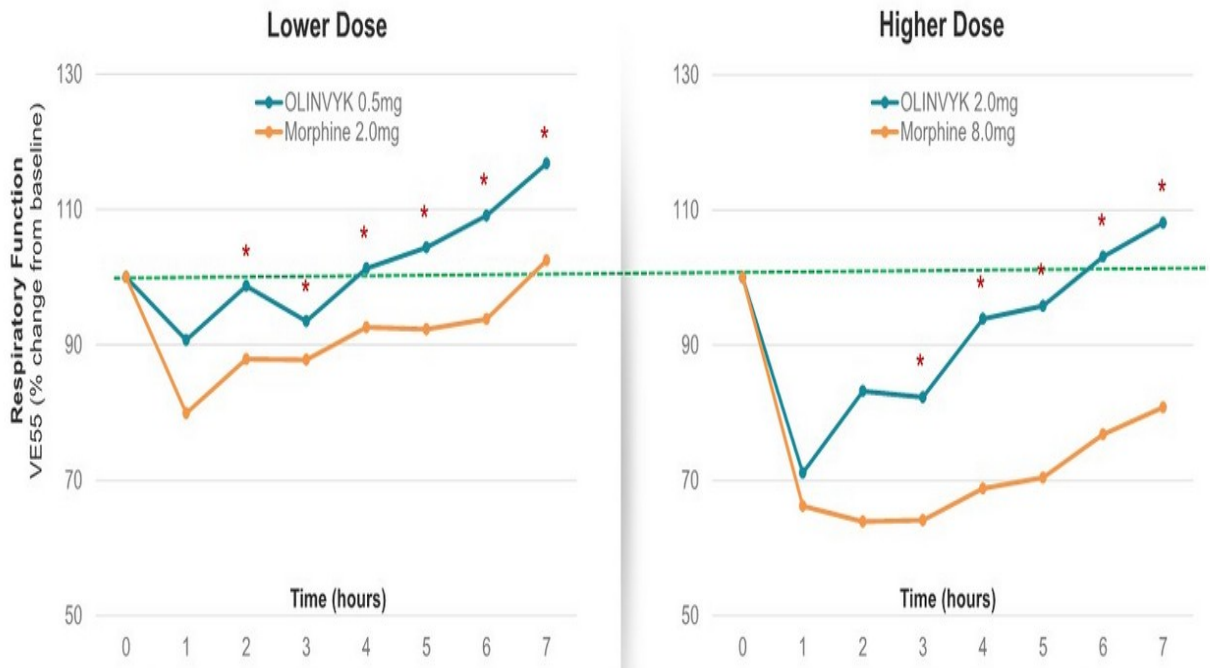
- Analgesic comparison measured using valid models of induced cold and electrical pain

Analgesia Assessment

As with all opioids, serious, life-threatening, or fatal respiratory depression may occur in patients treated with OLINVYK.

Respiratory Physiology Study: Elderly / Overweight Subjects

OLINVYK demonstrated reduced impact on respiratory function vs IV morphine



* Represents P < 0.05 (statistically significant) in pairwise comparison between treatments
Treatments differ over time: main effect P < 0.0001 using a linear mixed effects model

As with all opioids, serious, life-threatening, or fatal respiratory depression may occur in patients treated with OLINVYK.

Trevena

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

Respiratory Physiology Study Observations

- Study population comprised elderly individuals (56 to 87 years, mean = 71.2) with BMI ranging from 20 to 34 (mean = 26.3)
- Both OLINVYK and IV morphine achieved comparable levels of pain relief. A statistically significant reduced impact on respiratory function was observed in patients treated with OLINVYK as measured by the mean respiratory ventilation profiles over time (P<0.0001)
- The study replicates the results from the earlier study in younger subjects using a similar methodology[1] . The findings extend our knowledge to patients who are at higher risk for the development of respiratory depression with the use of opioids, namely the elderly and overweight patients.

As with all opioids, serious, life-threatening, or fatal respiratory depression may occur in patients treated with OLINVYK.

1. *Soergel DG, et al. Pain. 2014;155:1829-1835*

Top Line Data: OLINVYK vs IV Morphine Cognitive Function Study

Clinical assessment of OLINVYK's potential impact on cognitive function vs. IV morphine

- Randomized, double-blind, placebo-controlled, crossover study
- N = 23 subjects, 19-53 years old (median age 26), 13 females & 10 males
- Topline data received July 2022

Cognitive function assessment: NeuroCart

CHDR
Centre for Human Drug Research

- Comprehensive CNS test battery, used in testing a wide range of CNS drugs for 30 years
- Cognitive outcome measures include major domains of motor performance, attention, reaction time, memory, and executive function

Study will also include pain model testing (cold pressor test) and PK assessment

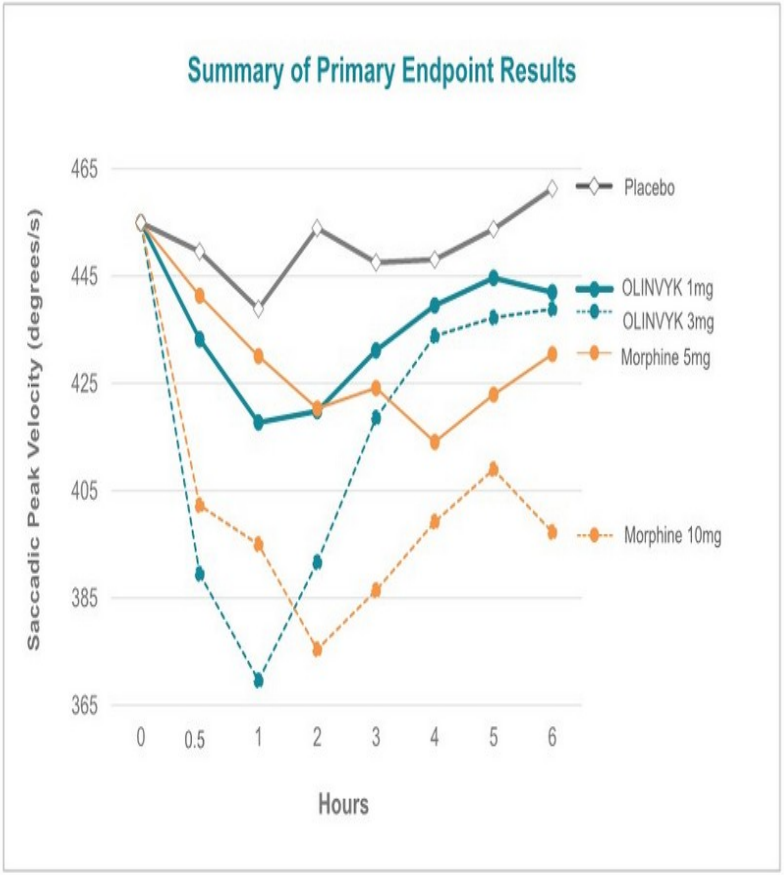
OLINVYK Showed Evidence of Reduced Impact on Neurocognitive Function Compared to IV Morphine

OLINVYK showed a statistically significant reduction in sedation versus IV morphine

- Measured by saccadic eye movement peak velocity (a sensitive measure of sedating action of medications)

The prespecified mixed-model repeated measures ANOVA highlighted a difference between treatments:

- Main effect of treatment: P<0.0001
- OLINVYK versus IV morphine: P=0.0236



Secondary Endpoint Results

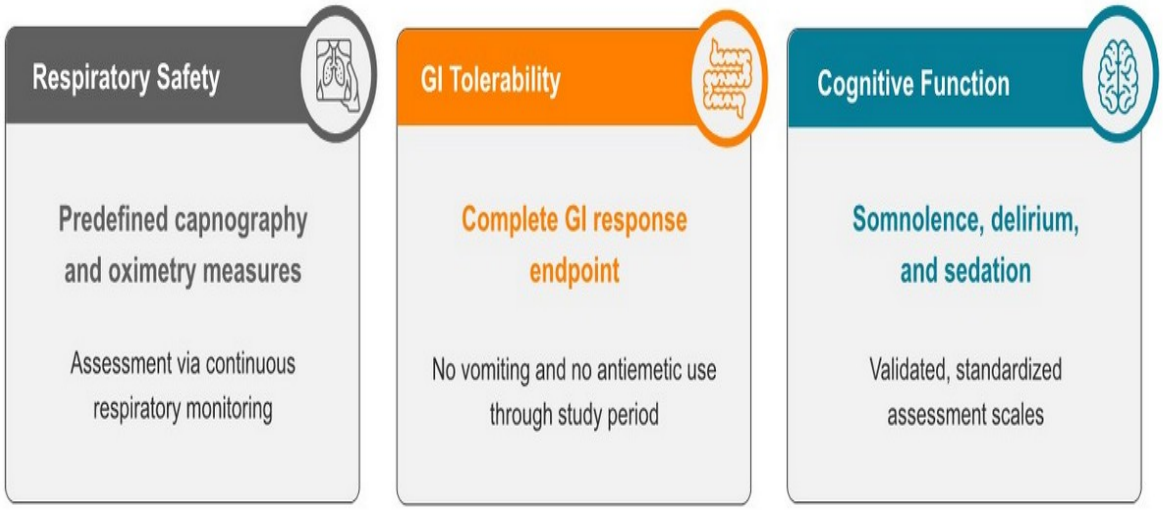
OLINVYK showed a statistically significant difference or trend (vs IV morphine) on several prespecified secondary endpoints, despite the relatively small sample size, across a range of neurocognitive measures and motor performance:

- ***Reaction Time.*** Reduced impact on saccadic eye movement reaction time
  - Main effect, P=0.0201 OLINVYK vs IV morphine, P=0.0273
- ***Postural Stability (Motor Function).*** Reduced body sway, a measure of motor function
  - Main effect, P=0.0314 OLINVYK vs IV morphine, P=0.0951
- ***Eye-Hand Coordination.*** Reduced performance accuracy on the adaptive tracking test, a measure of eye-hand coordination
  - Main effect, P=0.0011 OLINVYK vs IV morphine, P=0.1303
- Neurocognitive function including impaired sedation and postural instability may have potentially important consequences in clinical care settings with the use of opioid medications, and consequent benefits in length of stay and other health economic outcomes
- Other secondary outcome measures, including visual tracking and higher-order cognitive processing did not show statistical differences between OLINVYK and IV morphine
- No serious adverse events were observed in the study, and adverse events were generally assessed as mild

OLINVYK Safety Outcomes Study w/ Cleveland Clinic

Further characterizes potential respiratory, GI and cognitive outcomes

- Open-label, multi-site study led by experts at Cleveland Clinic and Wake Forest Baptist Health
- N = ~200 adults undergoing major non-cardiac surgery
- Topline data expected in 2H 2022



As with all opioids, serious, life-threatening, or fatal respiratory depression may occur in patients treated with OLINVYK

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

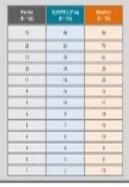
	1 mg / 1mL	2 mg / 2mL	30 mg / 30 mL
WAC:	$17.50	$25.75	$110.00

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

OLINVYK vs IV Morphine Health Economic Models

Published[1] and available to formulary committees

Representative Inputs:

AE rates*
Ph3 trials

Vomiting
Somnolence / sedation
O_2 saturation <90%

Cost of AEs
Gov't sources / Publications
$8k nausea / vomiting[2]
$28k critical resp event[3]
+7 days hospital stay[3]

Drug cost

OLINVYK
IV morphine

HECON model

Key Outputs:

>10x
Cost savings for hospitals[4]

Due to improved patient outcomes

*** As stated in the lable, these data are not an adequate basis for comparison of rates between OLINVYK treatment group and the morphine treatment group. The OLINVYK and morphine dosing regimens studied are not considered equipotent.**

1) Simpson KN, et al., J Comp Eff Res, 2021; *10:1107-1119* and *Simpson KN, et al. Expert Rev Pharmacoecon Outcomes Res; 2022*
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. More conservative inputs were used in the model. 4) Calculated based on total costs of Tx and average total costs of care. Image: flaticon.com.

Trevena


Trevena
Customer
Engagement Strategy

Targeted Account Launch

Health Care Practitioners (HCPs)

Anesthesiology, Colorectal, Critical Care physicians

1. OLINVYK: NCE, distinct from IV morphine
2. 1-3 min onset & no active metabolites
3. Safety data in complex patients / surgeries

Targeted Accounts

Over 50% of IV opioid volume covered by customer facing team

1. OLINVYK published safety data
2. Published health economic / cost offset data

Expanded Targets: ~150 Burn Center Accounts

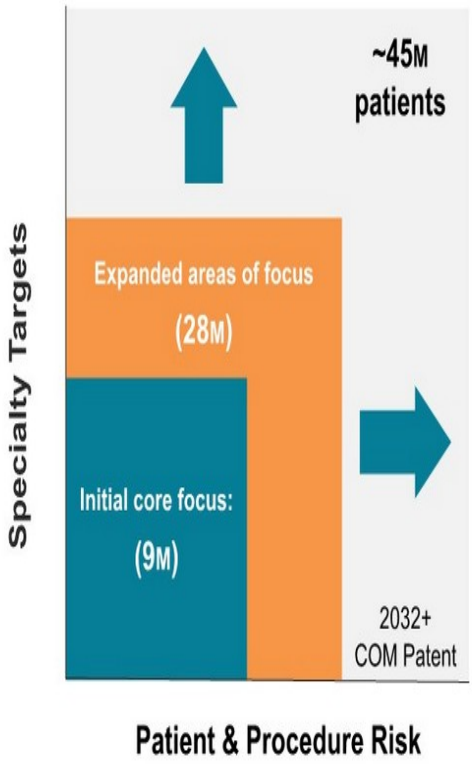
Critical care / burn patients experience severe pain and are at higher risk for AEs

Targeted market opportunity

- ~40k burn-related hospitalizations each year across 150 burn centers in US
- Longer average in-patient stay: 8-9 days
- Burn guidelines recommend use of IV opioids

Key considerations	OLINVYK attributes
Need for rapid, long-lasting acute pain relief	1-3 minute onset of action ~3 hour duration
Many patients have renal injury	No dose adjustment for patients with renal impairment
Need to avoid dose-stacking	No active metabolites

OLINVYK: Significant Opportunity in Acute Pain Market



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

Initial core focus

- Hospitals / ambulatory surgical centers
- Burn (6-8 days) / critical care & colorectal (3-5 days)

Expanded areas of focus

- New cognitive function / respiratory / GI data versus IV morphine
- Additional HECON data focused on recovery time

Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.
Source: Definitive Healthcare; American Hospital Association. *Assumes ~$100 / day price for OLINVYK
2032 composition of matter patent expiration does not include potential patent extensions.

Trevena

TRV045

S1P Receptor Modulator

Novel MOA for Diabetic Neuropathic Pain

TRV045: Novel MOA for Diabetic Neuropathic Pain

Selective S1PR with no lymphopenia – Expected Completion of Phase 1 2H 2022

$S1P_1$ receptors are expressed broadly in the CNS

Potential role in the treatment of:

Neuropathic pain

- Inhibits pain sensation[1]
- Inhibits excitatory neuronal signaling[2]

Epilepsy

- Neuroprotective effects[3]
- Modulates permeability of BBB, anti-inflammatory effects[4]

Selective for S1P-subtype 1 receptor:
Potential to avoid known safety issues associated with S1P receptor subtypes 2, 3, 4, 5:

Potential pulmonary, cardiac, and cancer-related effects[5]

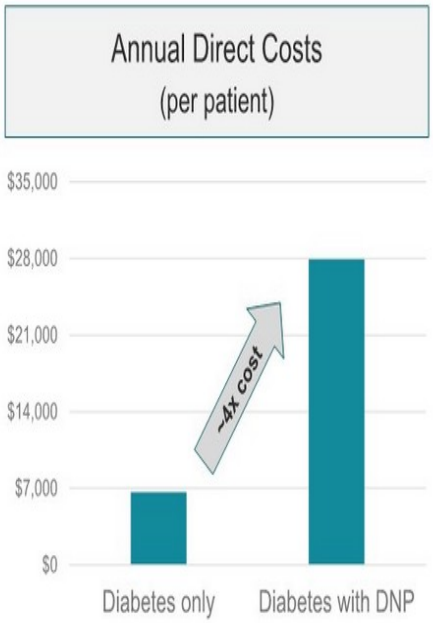
Trevena

1) Sim-Selley et al., Journal of Pharmacology & Experimental Therapeutics, 2018. 2) Sim-Selley et al, Journal of Neurochemistry, 2008. 3) Gol et al., European Journal of Pharmaceutical Sciences, 2017. 4) Leo et al., CNS & Neurological Disorders - Drug Targets, 2017. 5) Lymphopenia, bradycardia, vascular leakage, macular edema. BBB = blood-brain barrier. Images: flaticon.com.

TRV045 for Diabetic Neuropathic Pain

Diabetic neuropathic pain (DNP) represents a large market opportunity

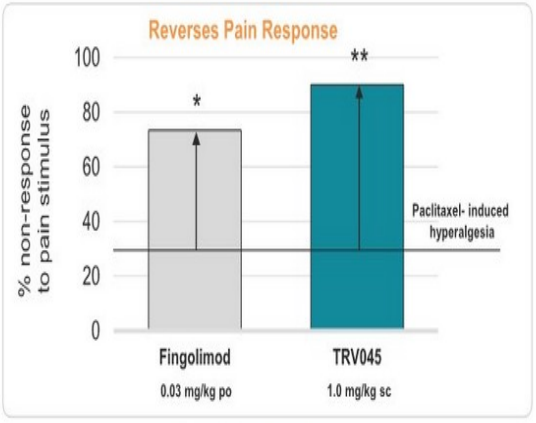
- 30M+ US adults with diabetes (500M+ worldwide)[1,2]
- DNP affects up to 25% of patients with diabetes[3,8]
- Significant need for efficacious medicines for DNP [4-5]
  - Only ~50% of patients experience a clinical response with currently approved therapies
- Direct costs for patients with DNP were ~4x that of patients with only diabetes (no DNP)[6]

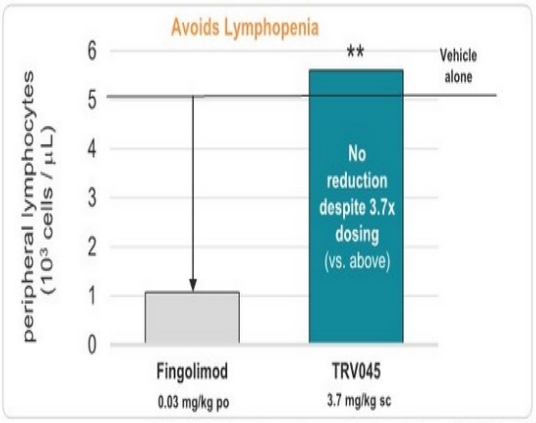


1) IDF, www.diabetesatlas.org 2) Economic Costs of Diabetes in the U.S. in 2017, Diabetes Care 2018;41:917–928. 3) Shillo et al., Current Diabetes Reports, 2019 4) Pritchett, YL et al. Pain Medicine 2007 5) Freeman R et al., Diabetes Care 2008 6) Sadosky et. al., J Diabetes Complications 2015. 7) Datamonitor 8) Hicks, et al. Current Diabetes Reports, 2019

TRV045: Novel MOA for Diabetic Neuropathic Pain

5M+ people (US) suffer from DNP, with limited therapeutic options[1]





- DNP affects ~25% of people w/ diabetes[2]
  - Approved agents inadequate for ~50% of patients[3,4]
  - ~4x direct costs for DNP patients (vs diabetes alone)[5]
- In animals, TRV045 reversed neuropathic pain without immune-suppressing activity[6]
- Non-opioid MOA with broad potential for CNS indications
  - Phase 1 for DNP underway
  - Epilepsy evaluation (NIH) ongoing

Trevena

1) Rosenberger et al., Journal of Neural Transmission, 2020 and CDC National Diabetes Statistics Report, 2020. 2) Shillo et al., Current Diabetes Reports, 2019. 3) American Diabetes Association. 4) FDA product labels for Lyrica, Lyrica CR, Cymbalta, Nucynta ER, and Qutenza, Tesfaye et.al. Pain (2013). 5) Sadosky et. al., J Diabetes Complications 2015. 6) 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

TRV250: New MOA for Acute Treatment of Migraine

TRV734: Maintenance Therapy for Opioid Use Disorder

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 US[1]:

650M migraines treated each year

1.2M ER visits due to migraines

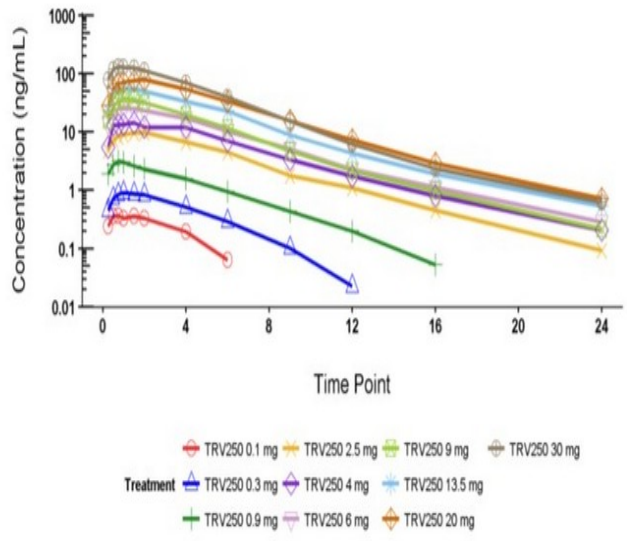
- **20-30%** of migraine sufferers do not respond to / cannot tolerate the market-leading triptan drug class
- Approx. **50%** of migraineurs also suffer from anxiety[2]

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

Single dose pharmacokinetics of TRV250 given by SC injection



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

IND-enabling activities initiated for new oral dose form

Trevena

SC = subcutaneous. Fossler MJ et al., CNS Drugs, Aug 2020;34(8):853-865.

TRV734: Maintenance Therapy for Opioid Use Disorder

Selective agonism at μ receptor: nonclinical evidence of improved tolerability

Ongoing collaboration with National Institute on Drug Abuse (NIDA)

NIDA study demonstrated reduced drug-seeking behavior in animal model of relapse[2]

NIDA-funded proof-of-concept patient study initiated

- Randomized, double-blind, placebo- and positive-controlled study
- N = ~50 opioid-dependent patients undergoing stable methadone maintenance therapy
- **Primary endpoint:** suppression of withdrawal symptoms as measured by the Subjective Opioid Withdrawal Scale
- **Secondary outcomes:** assessments of safety, tolerability, and neurocognitive changes

Trevena

1) Center for Behavioral Health Statistics and Quality. 2) NIDA data on file.

Trevena: Innovative CNS Company

IV OLINVYK: Differentiated profile	NCE approved for the management of acute pain in adults Launch in Q1 2021; additional supportive studies vs. IV morphine with near-term data
Large market, targeted launch	45M+ US hospital patients; 9M procedures is initial core focus $1.5B+ market opportunity for core focus
TRV045: Selective S1PR modulator	Novel candidate in Phase 1 for diabetic neuropathic pain (with potential broader applicability) NIH collaboration exploring TRV045 potential for epilepsy
Novel CNS pipeline	New mechanisms for acute / neuropathic pain, epilepsy, acute migraine, opioid use disorder NCEs targeting significant unmet needs
Solid financial position	$48.7M cash / equivalents @ Q1 (not including R-Bridge $15M tranche received April)

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.

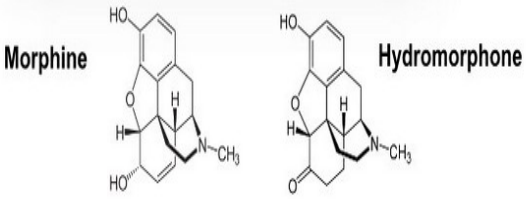
NCE = New Chemical Entity; MOA = Mechanism of Action; NIH = National Institutes of Health;

Trevena

Trevena

Appendix

OLINVYK: Distinct From IV Morphine / Hydromorphone



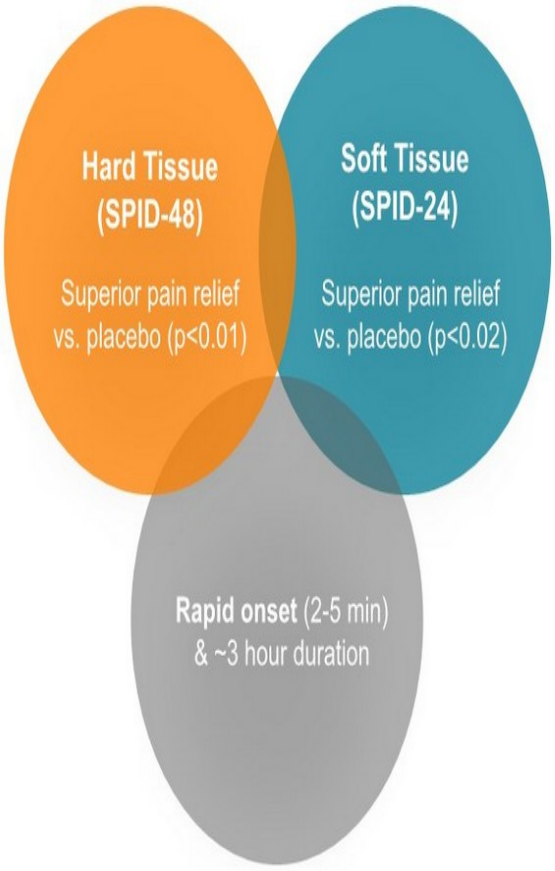
Studied in >1,900 individuals

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



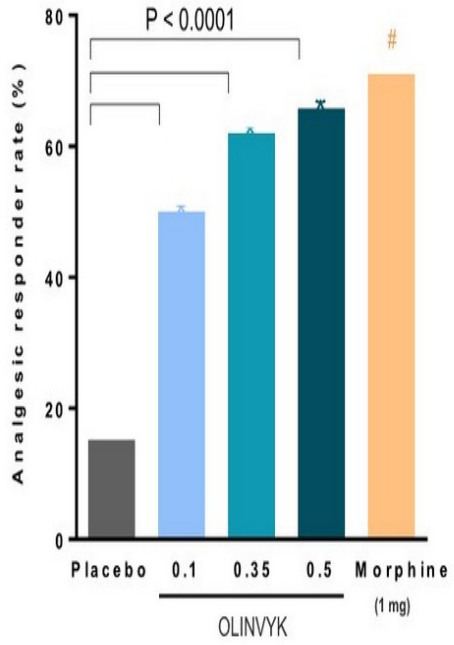
- Efficacy achieved in hard tissue & soft tissue models
- Rapid onset: perceptible pain relief within 1-3 minutes
- OLINVYK efficacy data in peer-reviewed journals *The Journal of Pain Research*[1] and *Pain Practice*[2]

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

Primary Efficacy Endpoint Achieved in Two Pivotal Studies

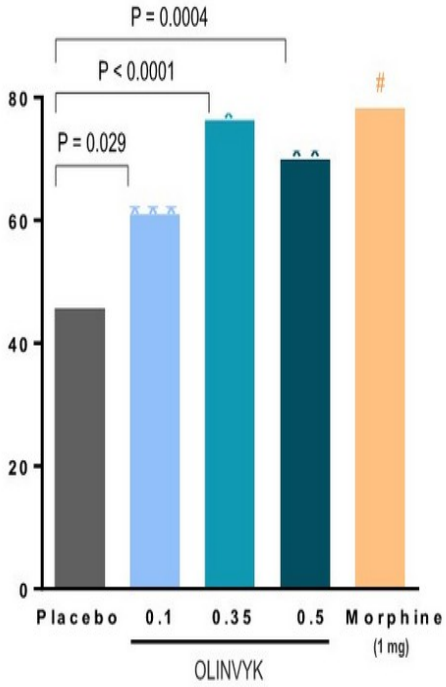
OLINVYK achieved IV opioid efficacy

Published in *The Journal of Pain Research*



Ph3: Hard Tissue Surgery
Mean baseline pain = 6.7

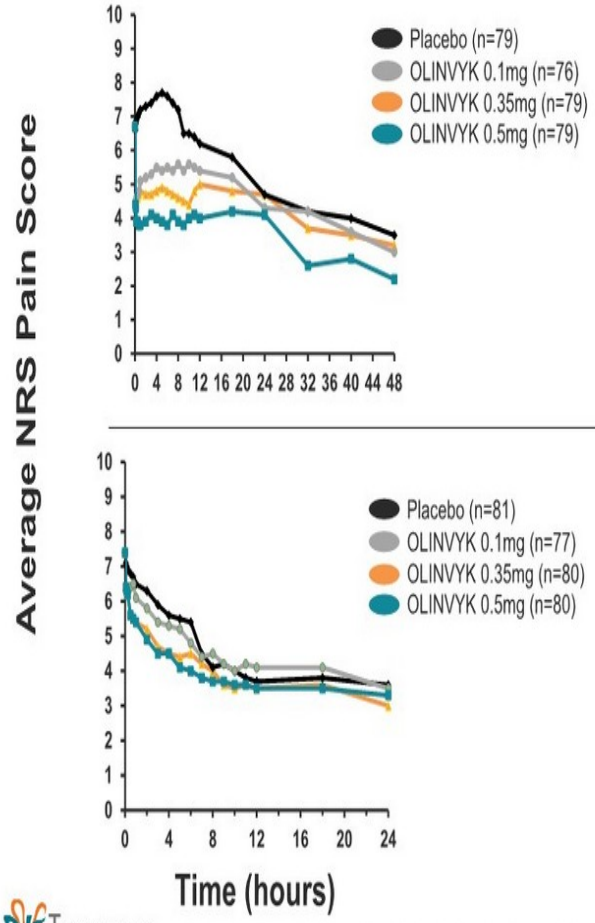
Published in *Pain Practice*



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.
These analyses were the prespecified primary endpoints for both studies. Section 14 of the Prescribing Information includes the SPID-24 and SPID-48 efficacy analyses that were the basis for approval.
Viscusi ER et al. J Pain Res. 2019;12:927–943. Published 2019 Mar 11. Singla NK et al. Pain Pract. 2019;19:715-731. Published 2019 Jun 04. #p < 0.05 vs. placebo (unadjusted).

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

	OLINVYK			
Outcome	0.1 mg	0.35 mg	0.5 mg	Placebo
% Completed	83%	87%	84%	60%
% D/C LOE	9%	4%	5%	34%
% Rescue Meds	41%	20%	17%	77%

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

	OLINVYK			
Outcome	0.1 mg	0.35 mg	0.5 mg	Placebo
% Completed	86%	90%	87%	74%
% D/C LOE	11%	3%	5%	22%
% Rescue Meds	31%	21%	18%	49%

Trevena®

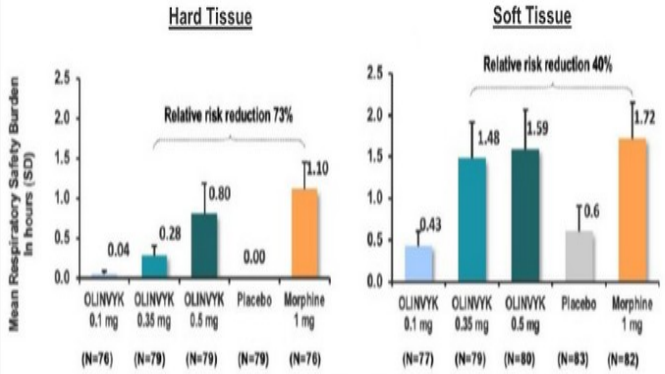
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

Robust Assessment of Respiratory Safety in Phase 3 RCTs

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 Burden[1]



Ph3 Respiratory Safety Events[2]
(Components of the RSB calculation)

Hard Tissue

Orthopedic Surgery-Bunionectomy Study	Placebo (N=79)	Demand Dose OLINVYK 0.1 mg (N=76)	OLINVYK 0.35 mg (N=79)	OLINVYK 0.5 mg (N=79)	Morphine 1 mg (N=76)
Components of the respiratory safety burden					
≥1 respiratory safety event, n (%)	0	1 (1.3)	7 (8.9)	11 (13.9)	14 (18.4)
P-value vs morphine	0.006	0.002	0.050	0.364	–
Duration of event, mean hours (SD)	0 (N/E)	2.88 (N/E)	3.21 (2.24)	5.72 (7.44)	5.96 (4.67)
P-value vs morphine	0.102	0.140	0.260	0.186	–
Respiratory safety event measures					
Oxygen saturation <90%, n (%)	1 (1.3)	3 (3.9)	8 (10.1)	11 (13.9)	15 (19.7)
P value vs morphine	0.005	0.006	0.100	0.352	–
Respiratory rate ≤8 bpm, n (%)	0	0	1 (1.3)	1 (1.3)	4 (5.3)
P value vs morphine	0.956	0.956	0.188	0.185	–
Sedation (MRPSS ≥3), n (%)	10 (2.7)	14 (18.4)	16 (20.3)	13 (16.5)	15 (19.7)
P value vs morphine	0.242	0.838	0.926	0.610	–

Soft Tissue

Plastic Surgery-Abdominoplasty Study	Placebo (N=83)	Demand Dose OLINVYK 0.1 mg (N=77)	OLINVYK 0.35 mg (N=79)	OLINVYK 0.5 mg (N=80)	Morphine 1 mg (N=82)
Components of the respiratory safety burden					
≥1 respiratory safety event, n (%)	5 (6.0)	6 (7.8)	17 (21.5)	18 (22.5)	22 (26.8)
Odds ratio vs morphine	0.15	0.19	0.61	0.68	—
P value vs morphine	0.0003	0.0007	0.20	0.32	
Duration of event, mean hours (SD)	9.88 (7.0)	5.51 (1.91)	6.88 (5.66)	7.07 (6.56)	6.40 (5.09)
P value vs morphine	0.52	0.29	0.78	0.76	—
Respiratory safety event measures					
Oxygen saturation <90%, n (%)	7 (8.4)	6 (7.8)	15 (19.0)	16 (20.0)	20 (24.4)
P value vs morphine	0.02	0.01	0.57	0.76	–
Respiratory rate ≤8 bpm, n (%)	1 (1.2)	0	4 (5.1)	6 (7.5)	8 (9.8)
P value vs morphine	0.054	0.95	0.38	0.84	–
Sedation (MRPSS ≥3), n (%)	15 (18.1)	8 (10.4)	19 (24.1)	18 (22.5)	21 (25.6)
P value vs morphine	0.25	0.02	0.83	0.65	–

bpm = breaths per minute; MRPSS = Moline-Roberts Pharmacologic Sedation Scale

As with all opioids, serious, life-threatening, or fatal respiratory depression may occur in patients treated with OLINVYK

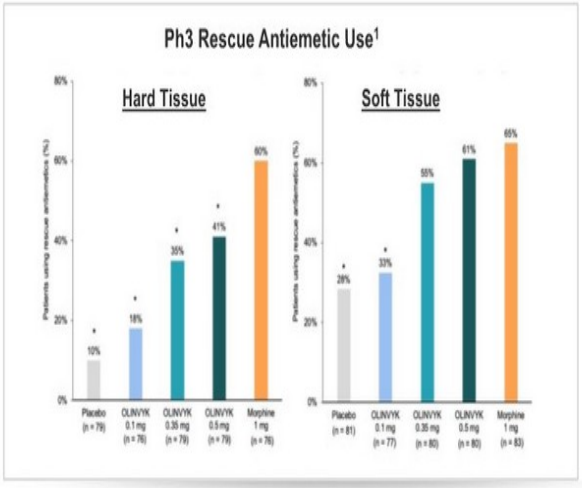
Trevena®

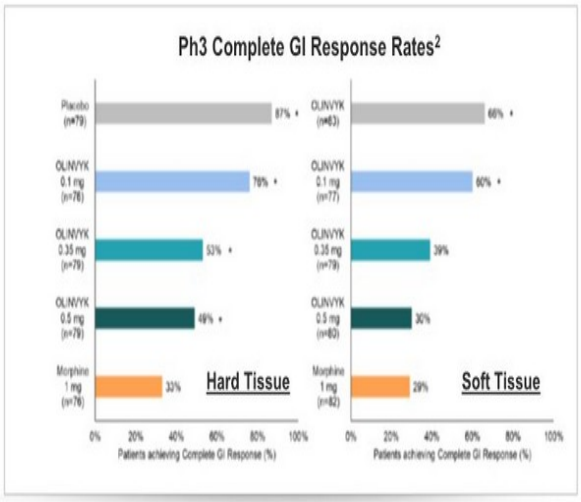
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

1) Figure 2-8, Section 2.2, OLINVYK Evidence Dossier for Formulary Consideration. 2) Figures 3-4 and 3-8, Section 3.1, OLINVYK Evidence Dossier for Formulary Consideration.

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[3]
- 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

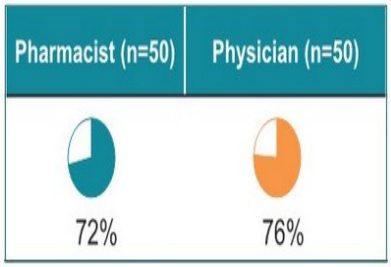
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

Trevena®

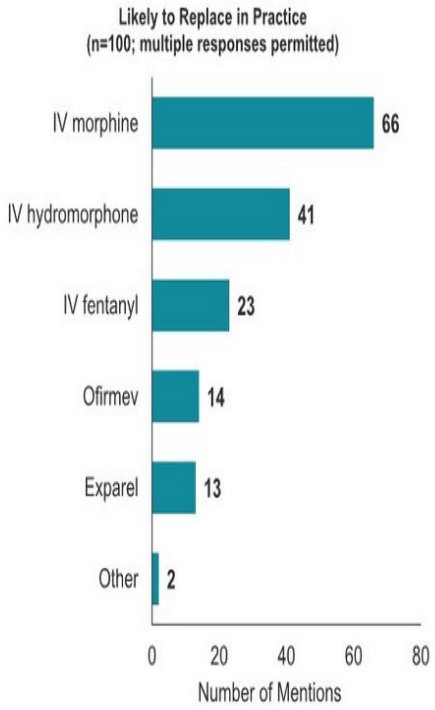
P < 0.05 vs. morphine.1) Figure 2-10, Section 2.2, OLINVYK Evidence Dossier for Formulary Consideration. 2) Figure 2-11, Section 2.2, OLINVYK Evidence Dossier for Formulary Consideration. 3) GI complete response defined as the proportion of patients who did not experience the AE of vomiting and did not use rescue antiemetic medication throughout their allocated treatment period in the study.

Positive Feedback from Formulary Stakeholders[1]

~75% of formulary stakeholders find OLINVYK's published data clinically meaningful:[2]



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



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.

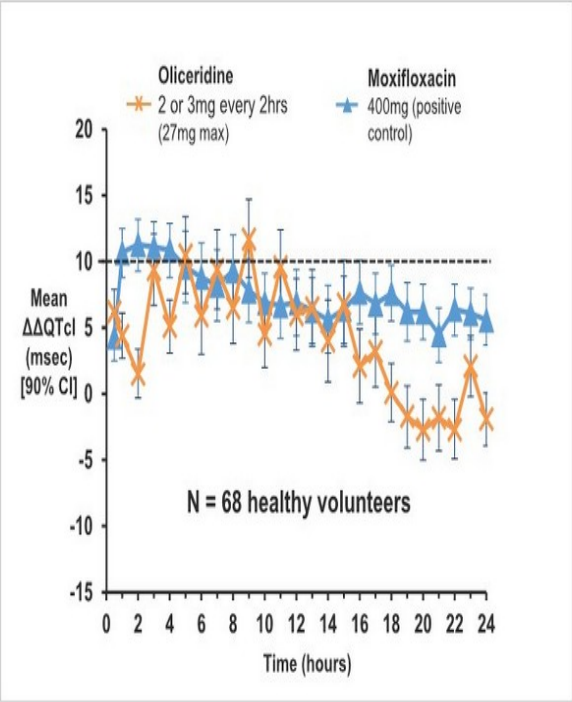
Omni-channel Approach for HCP Engagement

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

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

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

*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.

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

Trevena

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.

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.

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.

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 CO_2 retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO_2 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.
- 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 CO_2 retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO_2 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.
- OLINVYK may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in vulnerable patients. Monitor patients with a history of seizure disorders for worsened seizure control.
- Do not abruptly discontinue OLINVYK in a patient physically dependent on opioids. Gradually taper the dosage to avoid a withdrawal syndrome and return of pain. Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving OLINVYK, as they may reduce the analgesic effect and/or precipitate withdrawal symptoms.
- OLINVYK may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
- Although self-administration of opioids by patient-controlled analgesia (PCA) may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression. Health care providers and family members monitoring patients receiving PCA analgesia should be instructed in the need for appropriate monitoring for excessive sedation, respiratory depression, or other adverse effects of opioid medications.

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.