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): **November 9, 2022**

TREVENA, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-36193**	**26-1469215**
(State or other jurisdiction of incorporation)	(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 November 9, 2022, Trevena, Inc. (the "Company") issued a press release announcing its financial results for the quarter ended September 30, 2022. A copy of the press release is furnished hereto as Exhibit 99.1 and incorporated herein by reference.

The information set forth in this Item 2.02 and furnished hereto as Exhibit 99.1 shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or incorporated by reference in any filing under the Securities Act of 1933, as amended, 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 8.01 Other Events.

Additionally, on November 9, 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.

The information set forth in this Item 8.01 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"), or incorporated by reference in any filing under the Securities Act of 1933, as amended, 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 November 9, 2022
99.2	Updated Corporate Presentation Deck dated November 9, 2022
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

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: November 9, 2022

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

Exhibit 99.1

Trevena Reports Third Quarter 2022 Results and Provides Business Update

OLINVYK commercialization progresses with Vizient contract and receipt of CMS outpatient pass-through reimbursement

Positive Phase 1 topline results for TRV045, a novel S1P receptor modulator; no serious adverse events and PK profile supports anticipated once daily dosing

Targeted TRV045 proof-of-concept study to assess CNS activity planned for early 2023

Cash balance of $40.4 million at Q3 funds operations into Q3 2023

Company to host conference call today, November 9, 2022 at 8:00 a.m. ET

CHESTERBROOK, Pa., November 9, 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 its financial results for the third quarter ended September 30, 2022, and provided an overview of its recent operational highlights.

"We are pleased that OLINVYK received CMS pass-through reimbursement for ambulatory surgical centers and hospital outpatient settings. Our recently announced relationship with Vizient is advancing, which enables us to efficiently manage and allocate resources in this challenging hospital environment," said Carrie Bourdow, President and CEO of Trevena. "We are also excited to report positive topline Phase 1 data for our novel S1P receptor modulator, TRV045. The results of the study support potential advancement of TRV045 in CNS areas such as non-opioid chronic pain and epilepsy. Based on this promising clinical data, we plan to move forward with a targeted proof-of-concept study with near term expected data."

Third Quarter 2022 and Recent Corporate Highlights

- **Received CMS pass-through designation for OLINVYK® (oliceridine) injection:** Trevena received CMS pass-through designation for OLINVYK, effective October 1. CMS's pass-through status will allow ambulatory surgery centers and outpatient hospital facilities to be reimbursed by Medicare and other insurance providers for OLINVYK using the unique C-code, which opens the opportunity for potential expanded utilization in the outpatient setting. These pass-through payments can be made for the next 3 years.

- **Progressed OLINVYK commercialization:** In July, Trevena entered into a multi-year agreement with Vizient, Inc., a leading hospital performance improvement company, which will allow for broad OLINVYK access to enhanced savings for member hospitals. Trevena continues to work with Vizient to educate its members on the clinical and health economic benefits of OLINVYK as an alternative to IV morphine. OLINVYK is currently on formulary in 172 institutions, which includes a recent contract with a large ambulatory surgical center (ASC) provider.

- **Advanced differentiating clinical data for OLINVYK:** Presented respiratory physiology data in elderly/overweight subjects at annual American Society of Anesthesiologist (ASA) meeting. At ASA, Dr. Albert Dahan and his research team at Leiden University Medical Center (LUMC) presented a poster abstract titled, "A Randomized Double-blind Trial Comparing Oliceridine And Morphine On Ventilation In An Elderly Population." Separately, the Company expects enrollment in the collaborative real-world outcomes study, VOLITION, to be completed by the end of 2022. The VOLITION trial is being led by clinical outcomes research experts from the Cleveland Clinic and Wake Forest Baptist Health Medical Center. The study assesses the potential impact of OLINVYK on respiratory, gastrointestinal (GI) and cognitive function outcomes in the postoperative setting.

- **Announced positive topline Phase 1 and non-clinical data for TRV045, a novel S1P receptor modulator for diabetic neuropathic pain and epilepsy.** The Phase 1 study evaluated single-ascending and multiple dose phases, as well as a food effect study. There were no serious adverse events, and TRV045 was generally well tolerated. The observed PK profile was consistent with anticipated once-daily dosing. Consistent with prior nonclinical safety data, there was no evidence of reduction in lymphocytes, and no adverse event reports of cardiac, pulmonary or ophthalmologic events which are known to be associated with S1P modulators. The Company also announced the results of a nonclinical study of the effects of TRV045 on primary mouse astrocytes in cell culture. These data support the potential for TRV045 to play a role as a disease-modifying agent in the treatment of epilepsy.

Financial Results for Third Quarter 2022

For the third quarter of 2022, the Company reported a net loss attributable to common stockholders of $15.3 million, or $0.09 per share, compared to $13.8 million, or $0.08 per share in the third quarter of 2021.

Results for the third quarter of 2022 include a $2.2 million non-cash valuation adjustment for slow-moving or obsolete inventory due to the uncertainty of commercial activities underlying OLINVYK sales, which is recognized as a cost of goods expense. The results also include a $0.4 million non-cash adjustment in reserves for potential returns of OLINVYK held at wholesalers, which results in negative product revenue.

Cash, cash equivalents and marketable securities totaled $40.4 million as of September 30, 2022, which the Company believes will be sufficient to fund the Company's operating expenses and capital expenditure requirements into the third quarter of 2023.

Conference Call and Webcast Information

The Company will host a conference call and webcast with the investment community on November 9, 2022, at 8:00 a.m. Eastern Time featuring remarks by Carrie Bourdow, President and Chief Executive Officer, Patricia Drake, Chief Commercial Officer, Mark Demitrack, M.D., Senior Vice President and Chief Medical Officer, and Barry Shin, Chief Financial Officer.

Title:	Trevena Third Quarter 2022 Financial Results Conference Call & Webcast
Date:	Wednesday, November 9, 2022
Time:	8:00 a.m. ET
Conference Call Details:	Toll-Free: 1-800-954-0687 International: 1-212-231-2935 Conference ID: 22021290

The conference call will be webcast live from the Company's website and will be available via the following links:

Webcast: https://viavid.webcasts.com/starthere.jsp?ei=1572499&tp_key=b8766e3409

The webcast should be accessed 15 minutes prior to the conference call start time. A replay of the webcast will be available following the conclusion of the live broadcast and will be accessible on the Company's website.

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 TRV045

TRV045 is a novel, selective sphingosine-1-phosphate subtype 1 ($S1P_1$) receptor modulator being developed as a potential treatment for acute and chronic neuropathic pain secondary to diabetic peripheral neuropathy. Through a collaboration with the National Institutes of Health, Trevena is also exploring TRV045 as a potential treatment for epilepsy.

S1P receptors are located throughout the body, including the central nervous system, where they are believed to play a role in modulating neurotransmission and membrane excitability.

Trevena's discovery efforts have identified a family of compounds that are highly selective for the $S1P_1$ receptor. TRV045 reversed thermal hyperalgesia, a measure of neuropathic pain, in nonclinical models of diabetic peripheral neuropathy and chemotherapy-induced peripheral neuropathy. TRV045 was not associated with lymphopenia and produced no changes in blood pressure, heart rate, or respiratory function at or above pharmacologically active doses in nonclinical studies. TRV045 is an investigational product and is not yet approved by the FDA.

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.

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TREVENA, INC.
Condensed Statements of Operations
(Unaudited, in thousands except share and per share data)

	Three Months Ended Sep 30,		Nine Months Ended Sep 30,	
	2022	2021	2022	2021
Product revenue	$ minus(438)	$ 112	$ minus(438)	$ 499
License revenue	-	69	20	69
Total revenue	minus(438)	181	minus(418)	568
Operating expenses:				
Cost of goods sold	2,368	199	2,791	620
Selling, general and administrative	7,683	10,438	29,003	28,351
Research and development	5,266	3,404	14,816	9,489
Total operating expenses	15,317	14,041	46,610	38,460
Loss from operations	minus(15,755)	minus(13,860)	minus(47,028)	minus(37,892)
Other income	460	89	363	257
Net loss	minus(15,295)	minus(13,771)	minus(46,665)	minus(37,635)
Unrealized gain (loss) on marketable securities	$ 32	$ -	$ minus(28)	$ -
Comprehensive loss	$ minus(15,263)	$ minus(13,771)	$ minus(46,693)	$ minus(37,635)
Per share information:				
Net loss per share of common stock, basic and diluted	$ minus(0.09)	$ minus(0.08)	$ minus(0.28)	$ minus(0.23)
Weighted average shares outstanding, basic and diluted	170,725,392	164,510,570	167,276,563	162,811,136

TREVENA, INC.
Condensed Balance Sheets
(Unaudited, in thousands)

	Sep 30, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 22,431	$ 66,923
Marketable securities	17,961	-
Inventories	785	2,352
Prepaid expenses and other current assets	1,363	1,448
Total current assets	42,540	70,723
Restricted cash	2,557	1,311
Property and equipment, net	1,570	1,841
Right-of-use lease assets	4,352	4,706
Other assets	-	1,543
Total assets	$ 51,019	$ 80,124
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable, net	$ 1,416	$ 4,547
Accrued expenses and other current liabilities	6,794	3,847
Current portion of loans payable, net	174	-
Current portion of lease liabilities	873	792
Total current liabilities	9,257	9,186
Loans payable, net	13,359	-
Leases, net of current portion	5,672	6,309
Warrant liability	868	-
Total liabilities	29,156	15,495
Common stock	174	165
Additional paid-in capital	562,484	558,566
Subscription receivable	-	-
Accumulated deficit	minus(540,767)	minus(494,102)
Accumulated other comprehensive income (loss)	minus(28)	-
Total stockholders' equity	21,863	64,629
Total liabilities and stockholders' equity	$ 51,019	$ 80,124

Exhibit 99.2


Trevena®
INNOVATING FOR PATIENTS
Nasdaq: TRVN I November 2022

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 PHARMACEUTICALS, 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, INC.	**Anne M. Phillips, M.D.**	novo nordisk, GSK GlaxoSmithKline
Michael R. Dougherty	Adolor, centocor	**Barbara Yanni**	MERCK

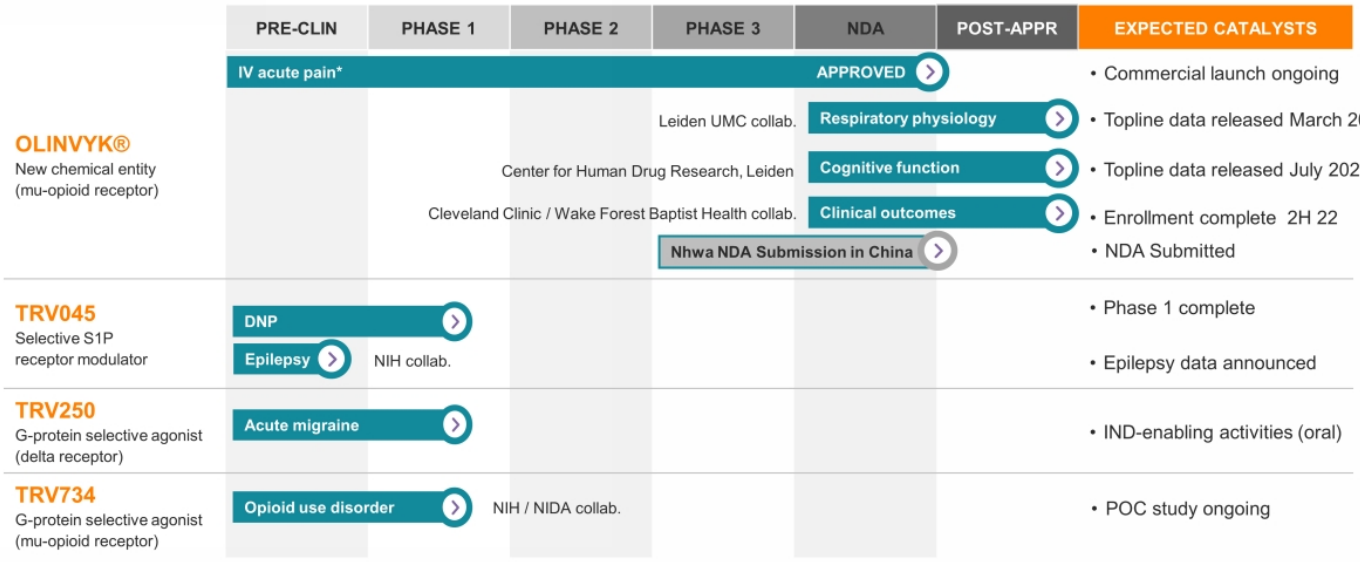
Trevena: Innovative CNS Company

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 for diabetic neuropathic pain (with potential broader applicability) Phase 1 study completed; proof-of-concept study planned for early 2023
Novel CNS pipeline	New mechanisms for acute / neuropathic pain, epilepsy, acute migraine, opioid use disorder NCEs targeting significant unmet needs
Solid financial position	$40.4M cash / equivalents / marketable securities @ Q3 Funds operations into 3Q 2023

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;

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

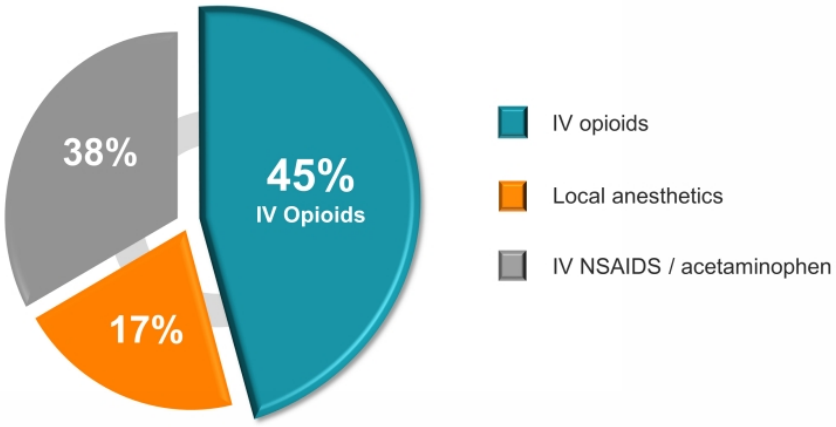
Ex-US Royalty-Based Financing Highlights

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]



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]

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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.

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

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

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

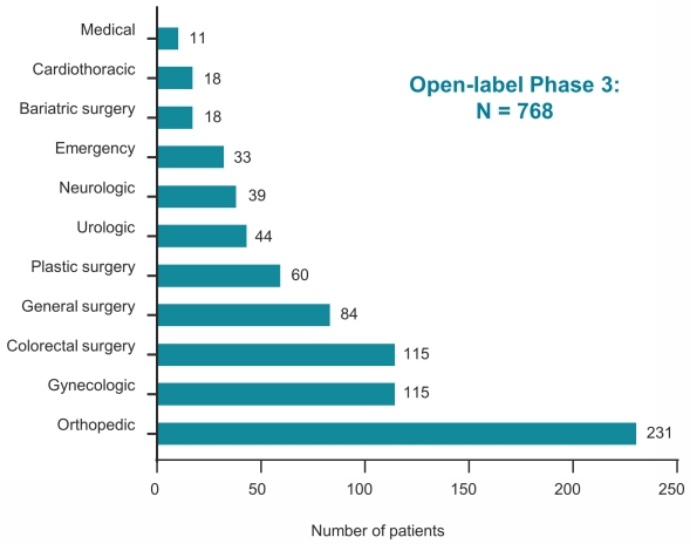
New chemical entity
Distinct from IV morphine

IV opioid efficacy
Hard- and soft-tissue surgeries

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

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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

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1) OLINVYK Prescribing Information.

Respiratory Physiology Study

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

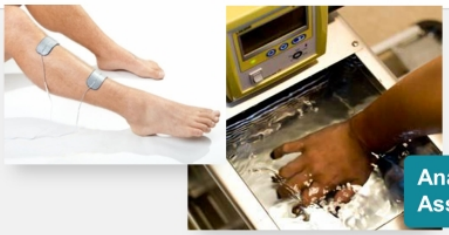
Assessment of Respiratory Function:

- 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

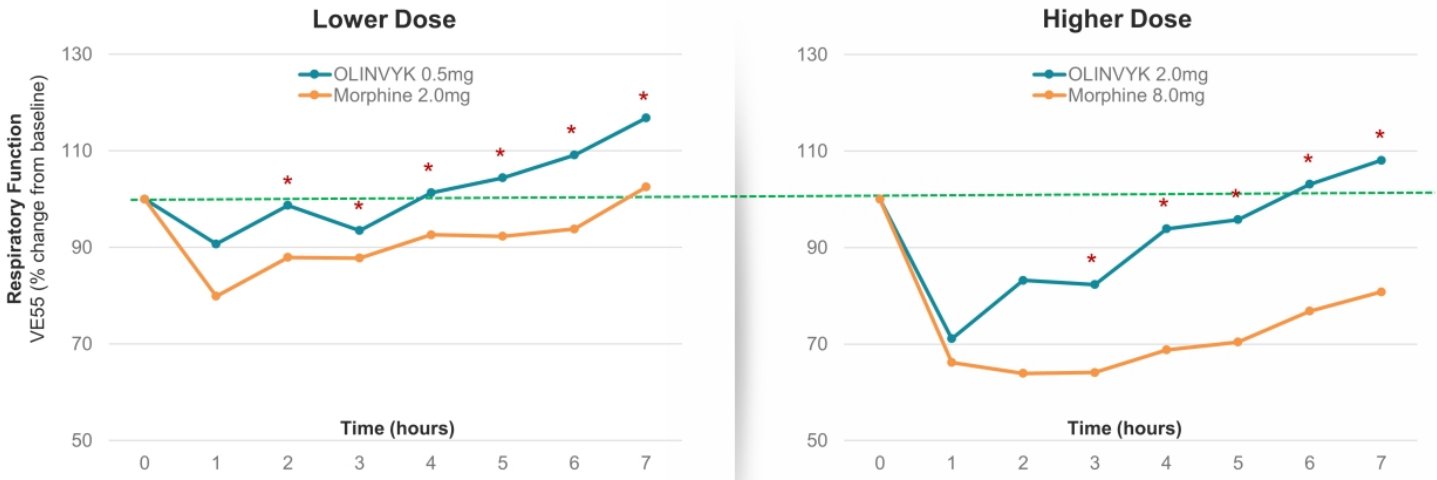


Analgesia Assessment

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.

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

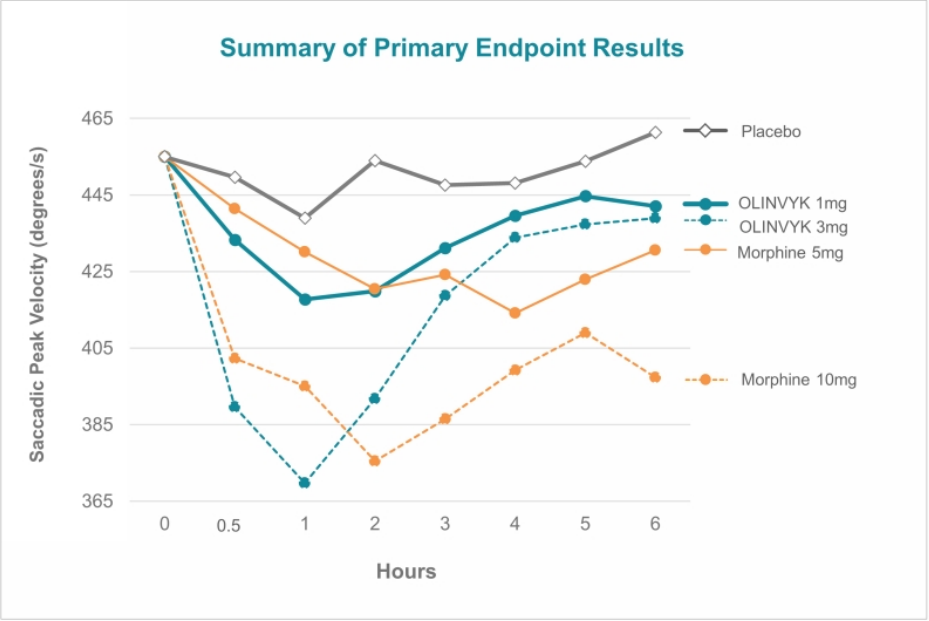
OLINVYK Showed Evidence of Reduced Impact on Neurocognitive Function Compared to IV Morphine

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



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

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
- Enrollment complete 2H 2022

Respiratory Safety

Predefined capnography and oximetry measures

Assessment via continuous respiratory monitoring

GI Tolerability

Complete GI response endpoint

No vomiting and no antiemetic use through study period

Cognitive Function

Somnolence, delirium, and sedation

Validated, standardized assessment scales

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)

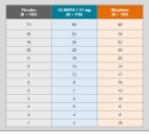
OLINVYK vs IV Morphine Health Economic Models

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.

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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

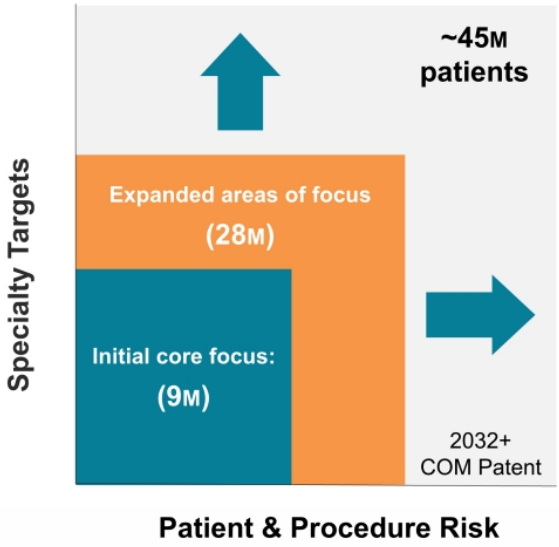
Critical care / burn patients experience severe pain and are at higher risk for AEs

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.

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TRV045

S1P Receptor Modulator
Novel MOA for Diabetic Neuropathic Pain

TRV045: Novel MOA for CNS Indications

Selective $S1P_1R$ modulator with no lymphopenia – Phase 1 study complete

$S1P_1$ receptors are highly expressed on key CNS cell targets (astrocytes) involved in the perpetuation of neuroinflammation

Potential therapeutic role in seizures, epileptogenesis and pain signaling

Epilepsy

- Neuroprotective effects[3]
- Modulates permeability of BBB, anti-inflammatory effects[4,6]

Neuropathic pain

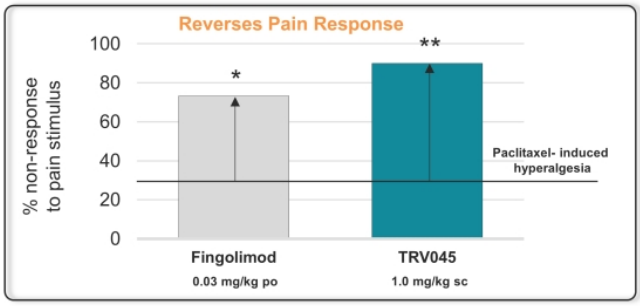
- Inhibits pain sensation[1]
- Inhibits excitatory neuronal signaling[2]

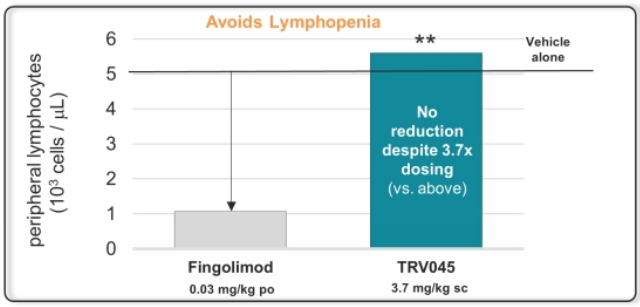
Selective for S1P-subtype 1 receptor, with more rapid receptor recycling (*no lymphopenia*)

Potential to also avoid known safety issues associated with S1P receptor subtypes 2, 3, 4, 5: Including pulmonary, cardiac, and cancer-related effects[5]

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. 6) Choi, et al. PNAS 2011

TRV045: Novel MOA, Selective S1PR





- In animals, TRV045 reversed neuropathic pain without immune-suppressing activity[1]
- Novel mechanism with broad potential for CNS indications
  - Phase 1 study completed
  - Targeted proof-of-concept study planned for early 2023

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1) 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

TRV045 Phase 1 Study – Safety / Tolerability / PK

Randomized, double-blinded, placebo-controlled study
3-parts: single dose (n=53), food effect (n=27), multiple dose (n=9)

Well Tolerated	• Favorable tolerability profile with no SAEs
Target Exposure	• Calculated free plasma concentrations exceeded targeted efficacy range[1]
Attractive PK Profile	• Half-life consistent with anticipated once-daily dosing
Highly Differentiated	• No lymphopenia and no reported cardiac / pulmonary / ophthalmologic AEs (AEs commonly associated with currently marketed S1P-targeted compounds)

Targeted CNS proof-of-concept study planned for early 2023

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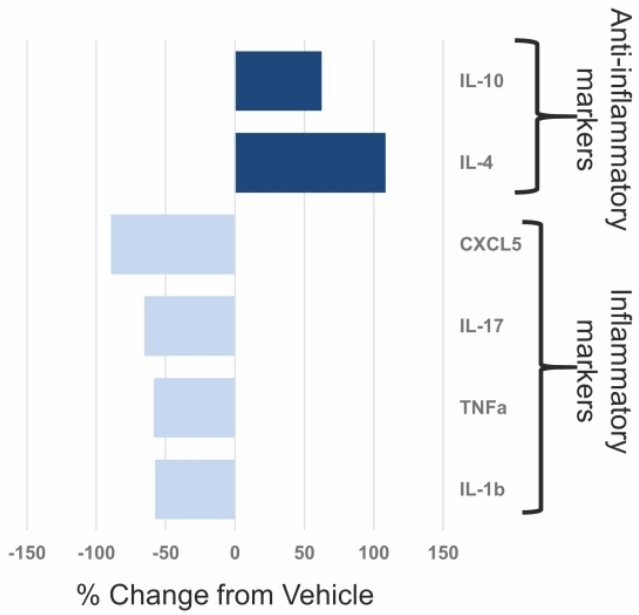
[1] Based on nonclinical measures of in vitro and in vivo PD

Effect of TRV045 on Cytokine / Chemokine Release

Anti-inflammatory actions on astrocytes in cell culture

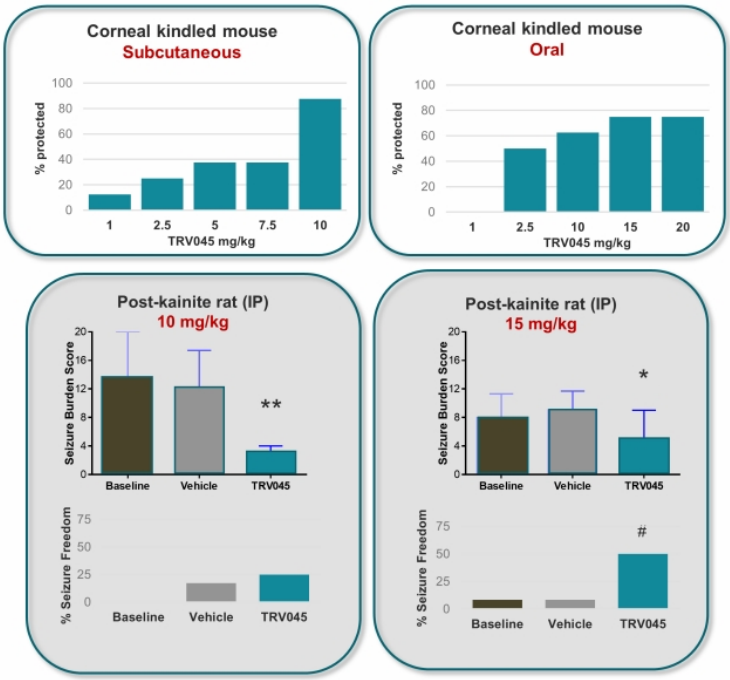
- Methods:
  - Primary mouse astrocytes in monolayer cell culture; incubated for 24 hrs w/ 5 μM TRV045
  - Panel of 17 cytokines / chemokines * assessed by ELISA
- Main Findings:
  - Net anti-inflammatory action on astrocyte cytokine / chemokine release in culture
    - Increase in release of all anti-inflammatory cytokines measured (P<0.05 v vehicle)
    - Reduction in release of all inflammatory cytokines measured (P<0.05 v vehicle)



** Full cytokine / chemokine panel studied: (Inflammatory markers) – TNFα, IL-6, IL-1b, IL-17, IL-23, IL-33, CCL1, CCL2, CCL20, CXCL5, CXCL12, CX3CL1, IFNγ, Csf2, Substance P; (Anti-inflammatory markers) – IL-10, IL-4. [Trevena, Inc., data on file]*

TRV045 Demonstrates Efficacy in Nonclinical Epilepsy Models

- NIH-supported Epilepsy Therapy Screening Program
- Acute seizure protection in max. electroshock model
  - Replicated in 3 independent experiments using either subcutaneous or oral administration
- Efficacy demonstrated in two different preclinical models of epilepsy (*data shown at right*)
  - Corneal-kindled seizure model (SC, PO)
    - Dose-dependent protection in seizure risk across two studies
  - Post-kainite spontaneous recurrent seizure model (IP*)
    - Dose-dependent reduction in seizure burden and increase in seizure freedom endpoints across two studies



Trevena Data on file, Trevena, Inc., 2022; * IP = intraperitoneal

* p<0.05 v vehicle, ** p<0.05 v baseline; Wilcoxon rank sum
# p<0.05 v baseline and vehicle; Fisher's exact test

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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

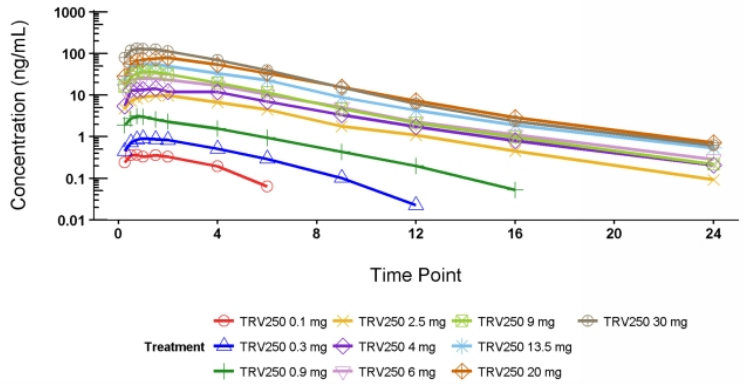
- **20-30%** of migraine sufferers do not respond to / cannot tolerate the market-leading triptan drug class
- Approx. **50%** of migraineurs also suffer from anxiety[2]

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

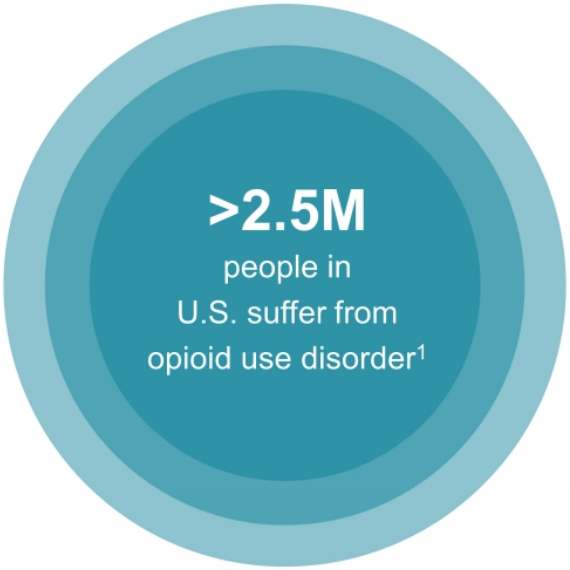
No EEG findings observed in any subject

IND-enabling activities initiated for new oral dose form

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

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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 for diabetic neuropathic pain (with potential broader applicability) Phase 1 study completed; proof-of-concept study planned for early 2023
Novel CNS pipeline	New mechanisms for acute / neuropathic pain, epilepsy, acute migraine, opioid use disorder NCEs targeting significant unmet needs
Solid financial position	$40.4M cash / equivalents / marketable securities @ Q3 Funds operations into 3Q 2023

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;

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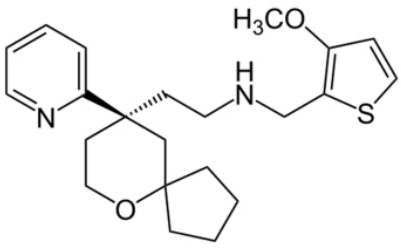
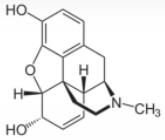
Appendix

OLINVYK: Distinct From IV Morphine / Hydromorphone

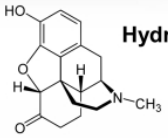
OLINVYK



Morphine



Hydromorphone

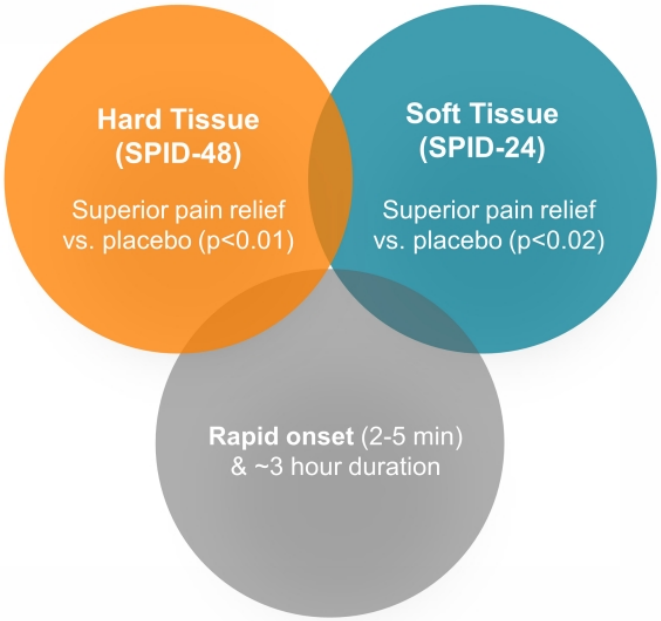


- Studied in >1,900 individuals
- IV morphine included as active comparator
- NCE with 2032+ COM patent[1]

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



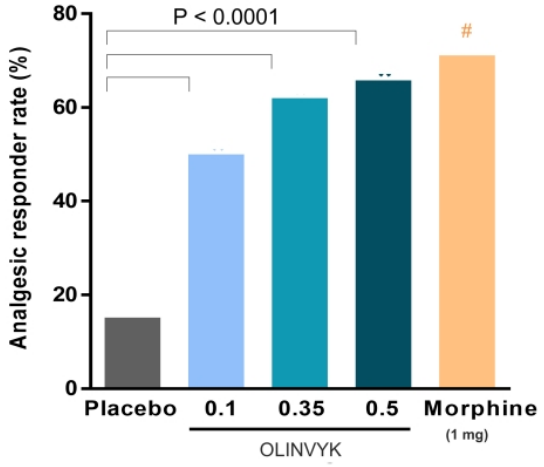
- Efficacy achieved in hard tissue & soft tissue models
- Rapid onset: perceptible pain relief within 1-3 minutes
- OLINVYK efficacy data in peer-reviewed journals
  The Journal of Pain Research[1] and *Pain Practice*[2]

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

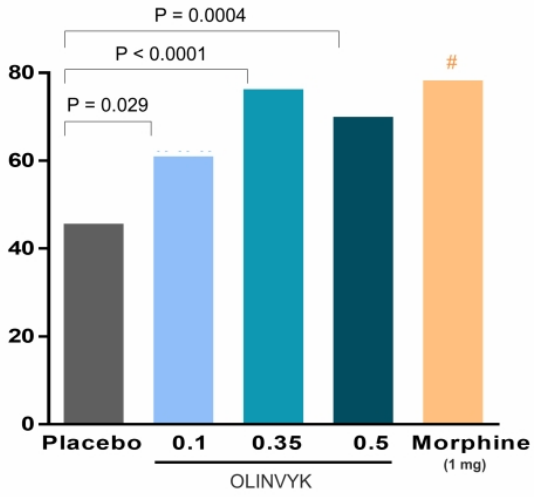
OLINVYK achieved IV opioid efficacy

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

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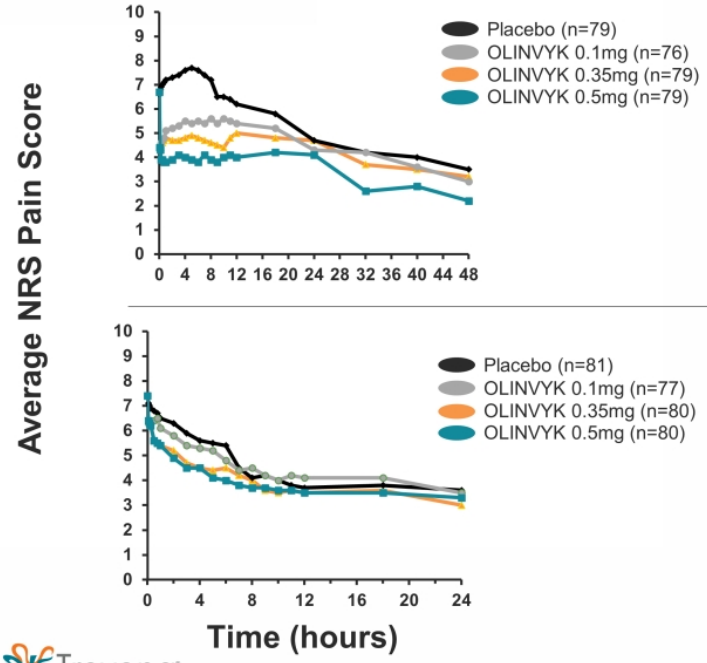
These analyses were the prespecified primary endpoints for both studies. Section 14 of the Prescribing Information includes the SPID-24 and SPID-48 efficacy analyses that were the basis for approval.

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

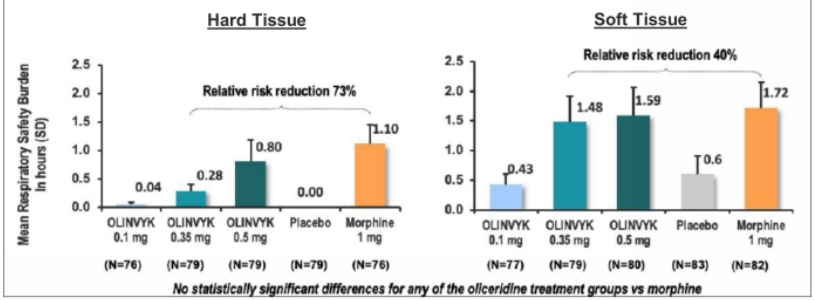
	OLINVYK			
Outcome	**0.1 mg**	**0.35 mg**	**0.5 mg**	**Placebo**
% Completed	86%	90%	87%	74%
% D/C LOE	11%	3%	5%	22%
% Rescue Meds	31%	21%	18%	49%

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]



No statistically significant differences for any of the oliceridine treatment groups vs morphine

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

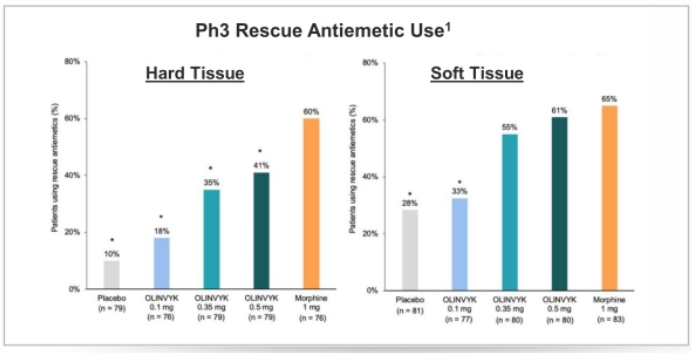
Plastic Surgery-Abdominoplasty Study	Placebo (N=83)	Demand Dose OLINVYK 0.1 mg (N=77)	OLINVYK 0.35 mg (N=79)	OLINVYK 0.5 mg (N=80)	Morphine 1 mg (N=82)
Components of the respiratory safety burden					
≥1 respiratory safety event, n (%)	5 (6.0)	6 (7.8)	17 (21.5)	18 (22.5)	22 (26.8)
Odds ratio vs morphine	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	–

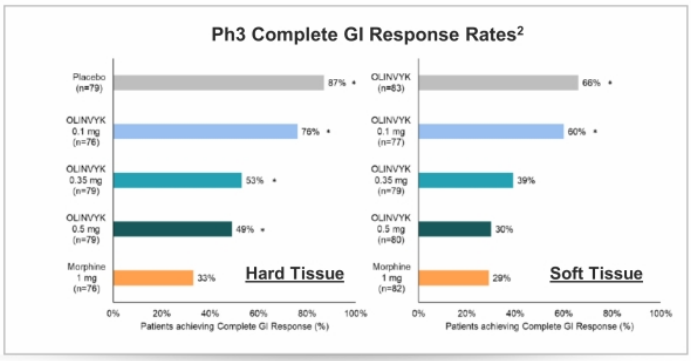
bpm = breaths per minute; MRPSS = Moline-Roberts Pharmacologic Sedation Scale

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

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

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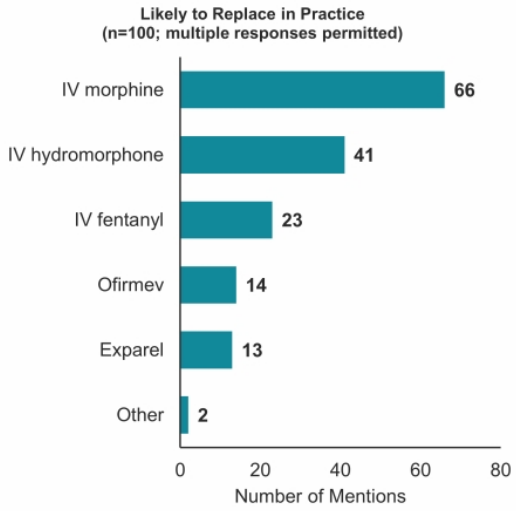
P < 0.05 vs. morphine.1) Figure 2-10, Section 2.2, OLINVYK Evidence Dossier for Formulary Consideration. 2) Figure 2-11, Section 2.2, OLINVYK Evidence Dossier for Formulary Consideration. 3) GI complete response defined as the proportion of patients who did not experience the AE of vomiting and did not 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]

Pharmacist (n=50)	Physician (n=50)
	
72%	76%

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



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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.

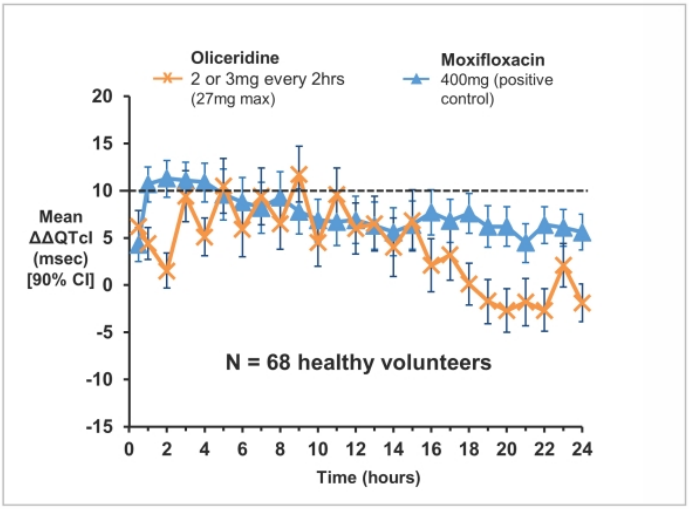
Omni-channel Approach for HCP Engagement

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.

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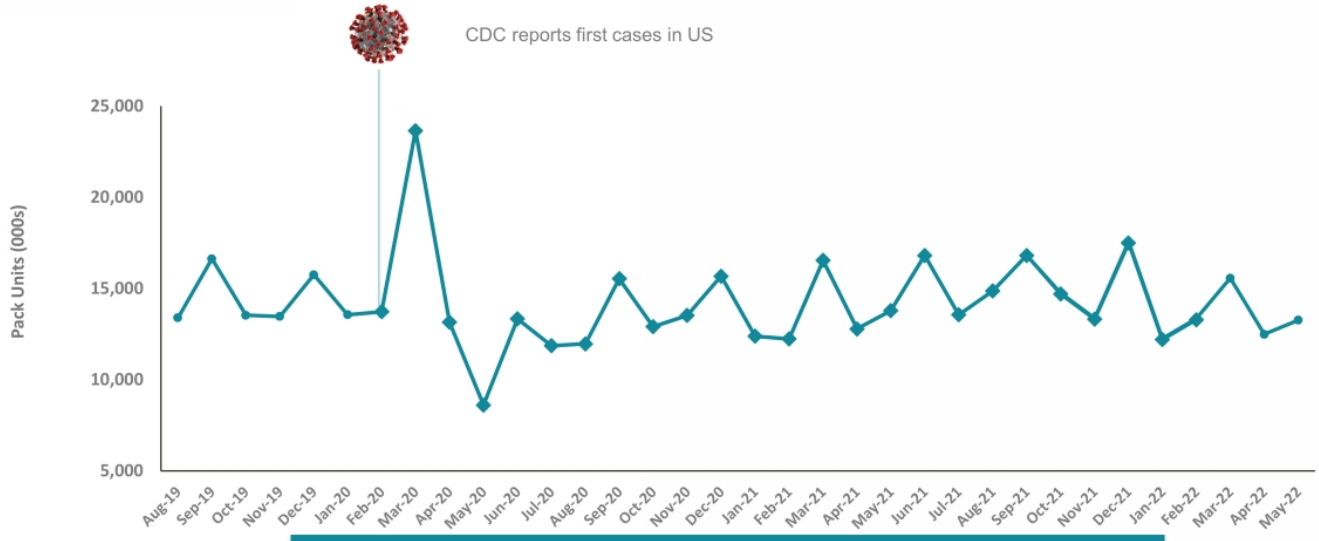
3 subjects not dosed due to lack of venous access: 1 discontinuation due to a non-serious adverse event (asymptomatic non-sustained ventricular tachycardia) with confounding hypokalemia and no meaningful QT prolongation during dosing, 1 subject completed dosing but not evaluable due to equipment malfunction

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

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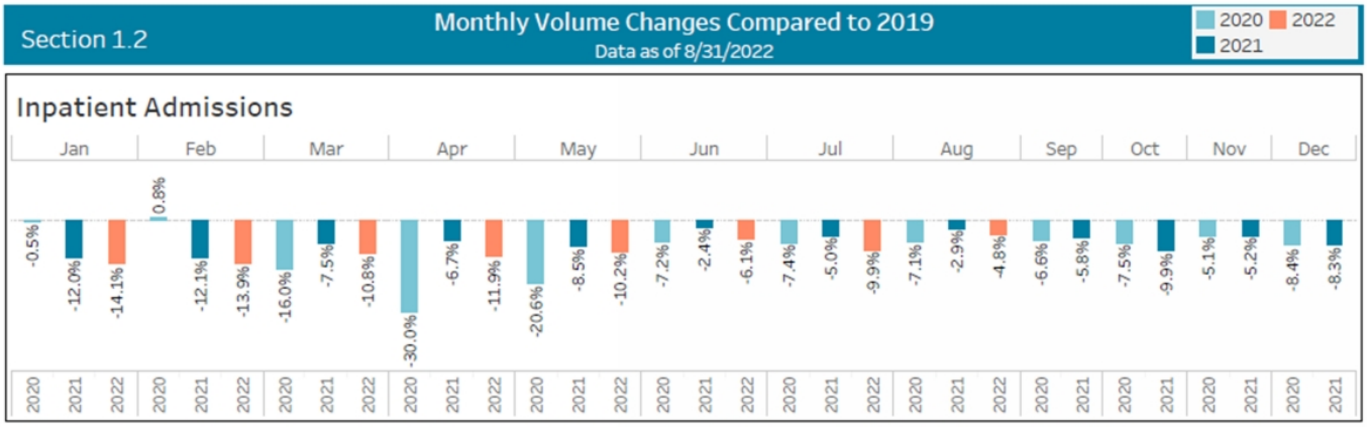
SOURCE: IQVIA DDD Data May 2022

Hospital Inpatient Visits Below Pre-Pandemic Levels

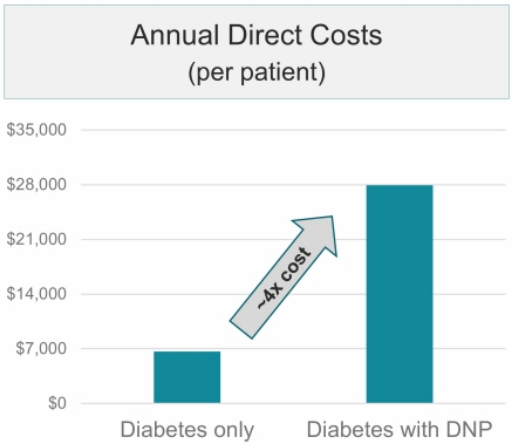


- Monthly Volume Changes in 2022 remain below 2019 levels for each month of the year.
- Through August each month in 2022 has shown a decline greater than was seen in 2021

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

Epilepsy

One of the most common neurological diseases in the world[1]

Disease Overview

- Epilepsy is a chronic disorder characterized by recurrent seizures[1].
- Epilepsy is defined as having two or more unprovoked seizures separated by at least 24 hours or after one seizure with a high risk of more[2].
  - A seizure is a sudden surge of electrical activity in the brain caused by complex chemical changes that occur in nerve cells[3].
  - Usually, there is a balance of cells that either encourage or stop other brain cells from sending messages[3].
  - A seizure occurs when there may be too much or too little electrical activity in the brain causing an imbalance[3].
  - Seizures are a symptom of many different disorders that can affect the brain[3].

Market Opportunity

- Nearly 50 million people suffer from epilepsy worldwide, including 3 million adults and 470,000 children in the U.S[1,4,5].
- 150,000 new cases of epilepsy are reported in the United States each year[6].
- According to the CDC, 56% of adults living with diagnosed epilepsy continue to have seizures[7].

1. World Health Organization. Epilepsy. https://www.who.int/news-room/fact-sheets/detail/epilepsy. Accessed November, 2021. 2. Epilepsy Foundation. About Epilepsy: The Basics. https://www.epilepsy.com/learn/about-epilepsy-basics. Accessed November, 2021. 3. Epilepsy Foundation. What is a Seizure? https://www.epilepsy.com/learn/about-epilepsy-basics/what-seizure. Accessed November, 2021.4. CURE Epilepsy. What is epilepsy? https://www.cureepilepsy.org/about-epilepsy/what-is-epilepsy. Accessed November, 2021. 5. Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy—United States, 2015. MMWR Morb Mortal Wkly Rep. 2017;66(31):821-825. 6. Epilepsy Foundation. What is Epilepsy? https://www.epilepsy.com/learn/about-epilepsy-basics/what-epilepsy. Accessed November, 2021. 7. Tian N, Boring M, Kobau R, Zack MM, Croft JB. Active Epilepsy and Seizure Control in Adults — United States, 2013 and 2015. MMWR Morb Mortal Wkly Rep 2018; 67:437–442. DOI: http://dx.doi.org/10.15585/mmwr.mm6715a1

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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.
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- 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.