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): **March 9, 2021**

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 March 9, 2021, Trevena, Inc. (the "Company") issued a press release announcing its financial results for the quarter and year ended December 31, 2020 and provided an overview of its 2020 and 2021 year-to-date operational highlights. A copy of the press release is furnished hereto as Exhibit 99.1 and incorporated herein by reference.

The information under this caption and contained in the press release attached hereto as Exhibit 99.1 is furnished by the Company in accordance with Securities Exchange Commission Release No. 33-8216. This information 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 7.01 Regulation FD Disclosure

On March 9, 2021, 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 on this Item 7.01 and furnished hereto as Exhibit 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 March 9, 2021
99.2	Updated Corporate Presentation Deck dated March 9, 2021
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: March 9, 2021

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

Exhibit 99.1

Trevena, Inc. Reports Fourth Quarter and Full Year 2020 Results

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OLINVYK™ approved in U.S.; customer-facing teams now fully deployed

Primary study completion for TRV027 in COVID-19 patients expected in 1H 2021

IND for TRV045 ($S1P_1$ receptor modulator) on track for 1H 2021; focus in epilepsy and neuropathic pain

Year-end cash of $109.4M funds operations through YE 2022

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Company to host conference call today, March 9th, 2021, at 8:00 a.m. ET

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CHESTERBROOK, PA., Mar. 9, 2021 (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 fourth quarter and full year ended December 31, 2020, and provided an overview of its 2020 and 2021 year-to-date operational highlights.

"2020 was a year of unprecedented achievement for Trevena. We secured U.S. approval of OLINVYK, laid the groundwork for a successful field launch, and partnered with leading institutions to significantly advance our pipeline – all while navigating the challenges that COVID-19 posed to our industry and our communities," said Carrie Bourdow, President and Chief Executive Officer of Trevena, Inc. "We enter 2021 with focus and resilience, as we look to deliver a successful first year of launch for OLINVYK and achieve multiple milestone events across our pipeline."

2020 and 2021 YTD Corporate Highlights:

OLINVYK™ (oliceridine) injection Milestones

- **Obtained FDA approval and DEA scheduling.** In August 2020, the U.S. FDA approved OLINVYK in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. In October 2020 the U.S. DEA classified oliceridine as a Schedule II controlled substance.

  The Company is reiterating its commitment to the ethical promotion of OLINVYK. OLINVYK is a novel and differentiated alternative to existing IV analgesics. In those patients for whom an IV opioid is necessary to manage their acute pain, the Company's goal is to replace conventional IV opioids, not to increase opioid usage.

- **Launched commercial and field medical teams in February.** The Company today announced it has recently completed full deployment of its customer-facing team, including Medical Science Liaisons, Regional Sales Managers, Key Account Managers, and sales representatives. Multiple institutions and ambulatory surgery centers are in the process of reviewing OLINVYK for formulary inclusion. The Company has set a target of 100 formulary acceptances by year-end.

- **Completed foundational launch activities.** Following DEA scheduling, the Company made OLINVYK commercially available across all three vial presentations (1 mg/1 mL and 2 mg/2 mL single-dose vials; 30 mg/30 mL single-patient-use vials for patient-controlled analgesia) and announced contracts in place with the three major wholesalers covering the majority of the acute care business.

  In January 2021, the Company completed a comprehensive product dossier for OLINVYK, including head-to-head data versus IV morphine and health economic models, for use by hospital formulary committees. The Company also finalized all J- and C-code submissions with the Centers for Medicare and Medicaid (CMS) and completed market access resources for customers to facilitate reimbursement of OLINVYK.

- **Continued to expand body of published peer-reviewed literature.** In 2020, the Company announced four new publications of OLINVYK data, with the number of publications from the development program now totaling 24. These findings provide additional insight into the differentiated safety and tolerability profile of OLINVYK and are available to healthcare providers as they consider the use of OLINVYK in their patients.

- **Supported development progress made by ex-U.S. partner.** In June 2020, the Company announced that Jiangsu Nhwa Pharmaceutical Co., its partner in China, was approved by the Chinese National Medical Products Administration (NMPA) to initiate clinical trials for OLINVYK. Jiangsu Nhwa holds an exclusive license agreement for the development and commercialization of OLINVYK in China.

Pipeline Milestones

- **Announced new pipeline asset: TRV027 for COVID-19 patients.** In June 2020, the Company entered into a collaboration with Imperial College London (ICL) to investigate TRV027, a novel AT_1 receptor selective agonist, as a potential treatment for acute lung damage / abnormal clotting associated with COVID-19. TRV027's mechanism of action received significant scientific interest, including a publication in *Circulation*, highlighting its hypothesized reparative effects in the lungs and other major organs.

  ICL initiated a 60-person study with a primary objective of assessing the effect of TRV027 on abnormal clotting in COVID-19 patients. ICL expects the primary completion date to be in 1H 2021.

- **Commenced partnership with NIH to evaluate TRV045 for epilepsy and chronic neuropathic pain; IND filing on track for 1H 2021.** In March 2020, the Company announced that the National Institutes of Health (NIH) had begun evaluating TRV045, a novel S1P receptor modulator in nonclinical animal models, as a potential treatment for epilepsy. In May 2020, NIH also began evaluating TRV045 in nonclinical animal models as a treatment for various pain conditions, including inflammatory and neuropathic pain. Data demonstrating efficacy in animal models of neuropathic pain and epilepsy were presented in December 2020 at the 59th Annual Meeting for the American College of Neuropsychopharmacology (ACNP).

- **Identified novel oral dose formulation for delta receptor selective agonist, TRV250.** The Company today announced that following the pause of clinical activity in 2020 due to COVID-19, it advanced formulation work for TRV250 that has yielded a novel oral dose form. This differentiated formulation could extend the Company's market exclusivity an additional five years to 2041. The Company has initiated IND-enabling activities with this oral dosage form, which it believes offers significant advantages for exploring multiple CNS disease states.

Financial Milestones

- **Strengthened balance sheet.** The Company significantly bolstered its financial position in 2020, including a successful $57.5 million public offering of common stock following approval of OLINVYK, and receipt of a $3 million milestone payment from its partner in China in connection with this approval. The Company today reported $109.4 million in cash and cash equivalents as of December 31, 2021.

Financial Results for Fourth Quarter and Full Year 2020

For the fourth quarter of 2020, the Company reported a net loss attributable to common stockholders of $11.9 million, or $0.08 per share, compared to $6.4 million, or $0.07 per share, for the fourth quarter of 2019. For the full year ended December 31, 2020, net loss attributable to common stockholders was $29.4 million, or $0.23 per share, compared to $24.9 million, or $0.27 per share, for the year ended December 31, 2019. This increase is primarily due to activities in preparation for commercial launch of OLINVYK.

Cash and cash equivalents were $109.4 million as of December 31, 2020, which the Company believes will be sufficient to fund the Company's operating expenses and capital expenditure requirements through the fourth quarter of 2022.

Conference Call and Webcast Information

The Company will host a conference call and webcast with the investment community on March 9, 2021, at 8:00 a.m. Eastern Time featuring remarks by Carrie Bourdow, President and Chief Executive Officer, Bob Yoder, Senior Vice President and Chief Commercial Officer, Mark Demitrack, M.D., Senior Vice President and Chief Medical Officer, Barry Shin, Senior Vice President and Chief Financial Officer, and Gregory Hammer, M.D., Professor of Anesthesiology, Stanford University Medical Center.

Title:	Trevena Fourth Quarter 2020 & Full Year 2019 Financial Results Conference Call and Webcast
Date:	Tuesday, March 9, 2021
Time:	8:00 a.m. ET
Conference Call Details:	Toll-Free: (855) 465-0180 International: (484) 756-4313 Conference ID: 7276985
Webcast:	https://www.trevena.com/investors/events-presentations/ir-calendar

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About OLINVYK™ (oliceridine) injection

OLINVYK is a new chemical entity approved by the FDA in August 2020. OLINVYK contains oliceridine, 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.

About Trevena

Trevena, Inc. is a biopharmaceutical company focused on the development and commercialization of novel medicines for patients with CNS disorders. The Company has 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 also has four novel and differentiated investigational drug candidates: TRV250 for the acute treatment of migraine, TRV734 for maintenance treatment of opioid use disorder, and TRV027 for acute lung injury / abnormal blood clotting in COVID-19 patients. The Company has also identified TRV045, a novel S1P receptor modulator that may offer a new approach to treating a variety of CNS disorders.

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, commercialization of approved drug products and other statements containing the words "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, 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 commercialization of any approved drug product, the status, timing, costs, results and interpretation of the Company's clinical trials or any future trials of any of the Company's investigational drug candidates; the uncertainties inherent in conducting clinical trials; expectations for regulatory interactions, submissions and approvals, including the Company's assessment of the discussions with the FDA or other regulatory agencies about any and all of its programs; uncertainties related to the commercialization of OLINVYK; available funding; uncertainties related to the Company's intellectual property; uncertainties related to the ongoing COVID-19 pandemic, other matters that could affect the availability or commercial potential of the Company's therapeutic candidates; and other factors discussed in the Risk Factors set forth in the Company's Annual Report on Form 10-K and Quarterly Reports on Form 10-Q filed with the Securities and Exchange Commission (SEC) and in other filings the Company makes with the SEC from time to time. In addition, the forward-looking statements included in this press release represent the Company's views only as of the date hereof. The

Company anticipates that subsequent events and developments may cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so, except as may be required by law.

For more information, please contact:

Investor Contact:

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

Company Contact:

Bob Yoder
SVP and Chief Commercial Officer
Trevena, Inc.
(610) 354-8840

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

	Three Months Ended December 31,		Year Ended December 31,	
	2020	2019	2020	2019
Product revenue	$ 69	$ -	$ 69	$ -
License revenue	-	31	3,000	31
Total revenue	69	31	3,069	31
Operating expenses:				
Cost of goods sold	182	-	182	-
General and administrative	8,227	3,640	19,248	13,212
Research and development	3,674	2,861	13,124	13,291
Impairment of property and equipment	-	-	-	108
Total operating expenses	12,083	6,501	32,554	26,611
Loss from operations	(12,014)	(6,470)	(29,485)	(26,580)
Other income	143	25	416	1,709
Loss before income tax expense	(11,871)	(6,445)	(29,069)	(24,871)
Foreign income tax expense	-	-	(300)	-
Net loss	$ (11,871)	$ (6,445)	$ (29,369)	$ (24,871)
Per share information:				
Net loss per share of common stock, basic and diluted	($0.08)	($0.07)	($0.23)	($0.27)
Weighted average shares outstanding, basic and diluted	158,012,954	92,777,480	127,623,859	91,677,963

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

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 109,403	$ 32,305
Accounts receivable, net	71	-
Marketable securities	-	3,500
Insurance recovery	9,000	-
Prepaid expenses and other current assets	570	1,683
Total current assets	119,044	37,488
Restricted cash	1,310	1,309
Property and equipment, net	2,253	2,705
Right-of-use lease assets	5,119	5,472
Other assets	13	20
Total assets	$ 127,739	$ 46,994
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable, net	$ 1,693	$ 1,047
Accrued expenses and other current liabilities	5,168	2,403
Estimated settlement liability	9,000	-
Current portion of loans payable, net	-	5,037
Current portion of lease liabilities	703	620
Total current liabilities	16,564	9,107
Leases, net of current portion	7,101	7,804
Warrant liability	6	5
Total liabilities	23,671	16,916
Common stock	160	94
Additional paid-in capital	546,422	443,129
Accumulated deficit	(442,514)	(413,145)
Total stockholders' equity	104,068	30,078
Total liabilities and stockholders' equity	$ 127,739	$ 46,994

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
Scott Applebaum	SVP, Chief Legal & Regulatory Officer	Shire, vitae, Bristol Myers Squibb
Mark A. Demitrack, M.D.	SVP, Chief Medical Officer	NEURONETICS, Lilly, ROIVANT
Barry Shin	SVP, Chief Financial Officer	MIZUHO, GUGGENHEIM, PiperJaffray
Robert T. Yoder	SVP, Chief Commercial Officer	MERCK, OREXIGEN

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

Trevena: Innovative CNS Company

IV OLINVYK: Differentiated profile	NCE approved for the management of acute pain in adults Commercial launch in Q1 2021; targeting 100 formulary wins by year-end
Large market, targeted launch	45M+ US hospital patients; 9M procedures is initial core focus $1.5B+ market opportunity for core focus
Novel CNS pipeline	New mechanisms for acute migraine, opioid use disorder, epilepsy, pain NCEs targeting significant unmet needs
TRV027 for COVID-19	Novel MOA to treat COVID-19 acute lung injury / abnormal clotting PoC study in collab with Imperial College London; primary completion date expected in 1H 2021
Strong financial position	$109.4M cash and cash equivalents as of YE 2020 Funds operations through Q4 2022

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

NCE = New Chemical Entity; MOA = Mechanism of Action; PoC = Proof-of-Concept

Multiple Expected Catalysts

	PRE-CLINICAL / PHASE 1 / PHASE 2 / PHASE 3 / NDA	EXPECTED CATALYSTS
OLINVYK™ New chemical entity (mu-opioid receptor)	Acute pain IV — APPROVED	**Q1 21:** Commercial launch
TRV027 Novel AT_1 receptor selective agonist	ARDS / abnormal clotting (COVID-19) IV — Collaboration with Imperial College London	**1H 21:** Primary completion date (ICL)
TRV250 G-protein selective agonist (delta receptor)	Acute migraine oral/subcutaneous	**1H 21:** IND-enabling activities (oral)
TRV734 G-protein selective agonist (mu-opioid receptor)	Opioid use disorder oral — Collaboration with National Institute on Drug Abuse	PoC study data (NIDA)
TRV045 Novel S1P receptor modulator	CNS disorders oral — Collaboration with National Institutes of Health	**1H 21:** IND filing

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

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TRV250, TRV734, TRV027, and TRV045 are investigational products and are not approved by the FDA or any other regulatory agency.
ARDS = Acute Respiratory Distress Syndrome; IND = Investigational New Drug; PoC = Proof-of-Concept

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
IV morphine data included in label

Rapid analgesia
1-3 min median onset of pain relief

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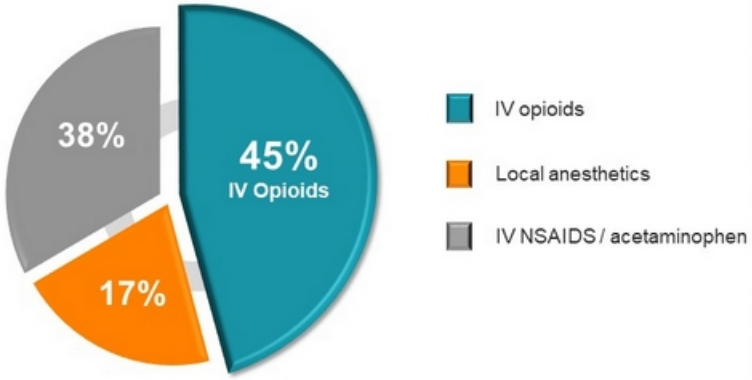
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

OLINVYK: Broad Indication for Acute Pain

Large acute market opportunity

US injectable analgesic hospital market unit volume[1]



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

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

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

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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: 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

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

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

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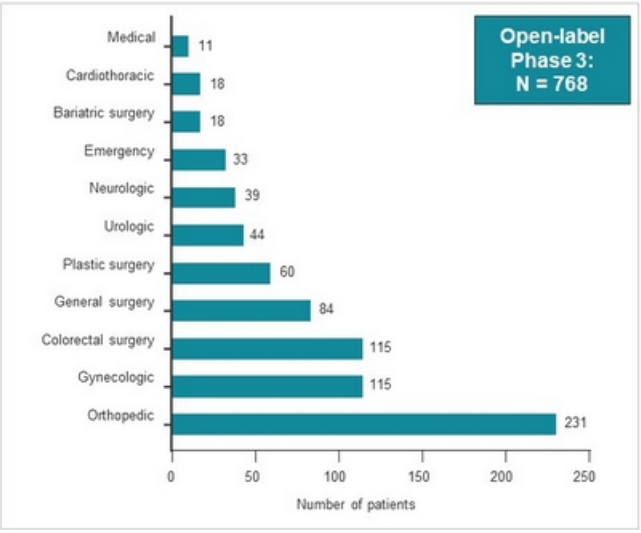
1) OLINVYK Prescribing Information. Not an adequate basis for comparison of rates between the OLINVYK treatment group and the morphine treatment group.

Real World Use: 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

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

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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: 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)

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

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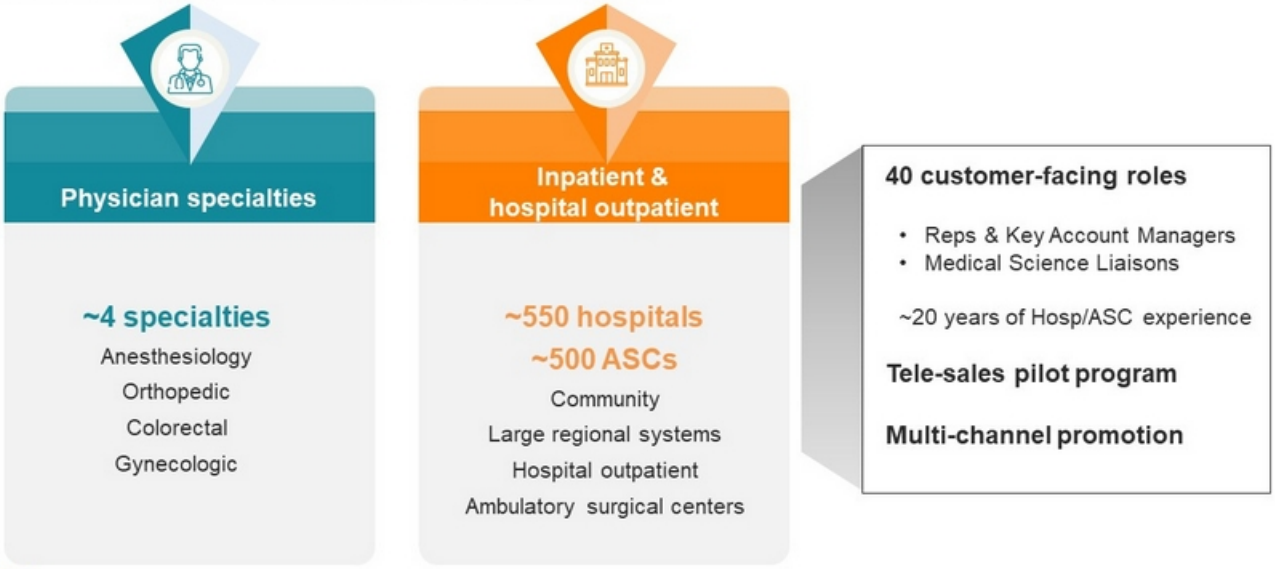
1) For an initial dose. PCA = Patient-Controlled Analgesia

Customer Engagement Strategy

Targeted Account Launch

Initial focus: complex patients in 3 key surgical areas



ASCs = ambulatory surgical centers

Targeted Messaging and Resources

Key OLINVYK attributes focused on key customers

Health Care Practitioners (HCPs)

- OLINVYK: NCE, distinct from IV morphine
- Fast pain relief & no active metabolites
- Safety data in complex patients / surgeries

Targeted Accounts

- OLINVYK published safety data vs. IV morphine
- Published health economic / cost offset data*

Trevena

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

*Published by 1H 2021. Images: flaticon.com.

Robust Set of Peer-Reviewed Publications

Comprehensive overview of OLINVYK development program

OLINVYK nonclinical / Phase 1 / Phase 2 data

15 publications

OLINVYK Phase 3 trials & secondary analyses

9 publications

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

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See www.trevena.com for full manuscripts and abstracts. These publications will be used in a manner consistent with FDAMA sections 114 and 401 and the FDA Guidances thereunder.

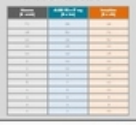
HECON Model Driven by Compelling Clinical Data

Publication of base and high-risk patient models expected 1H 2021

Representative Inputs:

AE rates

Ph3 trials



Vomiting
Somnolence / sedation
O_2 saturation <90%

Cost of AEs

Gov't sources / Publications

$8k nausea / vomiting[1]
$28k critical resp event[2]
+7 days hospital stay[2]

Drug cost

OLINVYK
Generic IV opioids

HECON model

Key Outputs:

>10x
Cost savings for hospitals[4]

Due to improved patient outcomes

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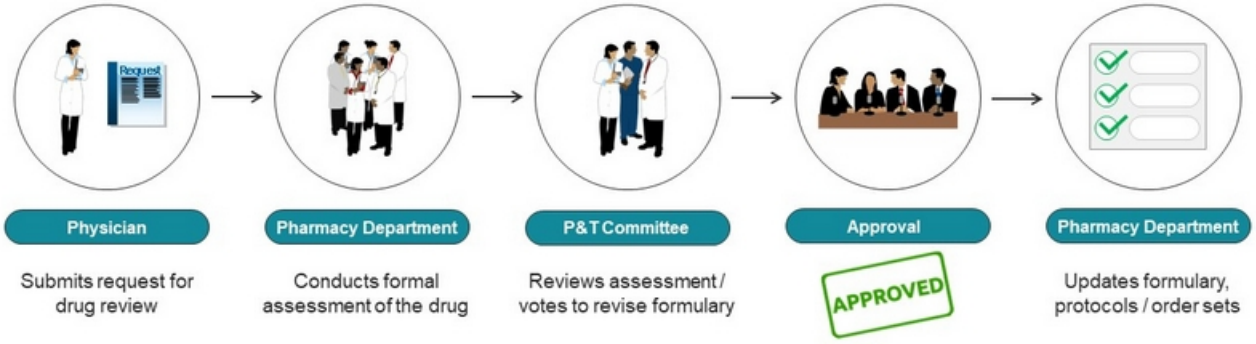
1) Oderda, GM, J Pain Palliative Care Pharm, 2019; data based on 5 surgical procedure categories including Cardiothoracic / vascular, General / Colorectal, Ob / Gyn, Orthopedic, and Urologic. 2) Overdyk FJ, PLoS One, 2016. More conservative inputs were used in the model. 4) Calculated based on total costs of Tx and total costs of care. Image: flaticon.com.

Hospital Formulary Review Process



Submits request for drug review

Conducts formal assessment of the drug

Reviews assessment / votes to revise formulary

Updates formulary, protocols / order sets

YE 2021 target: 100 formulary wins

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Differentiated Profile For Use in Hosp Outpatient & ASCs

Separate reimbursement may provide lower access hurdle

Physician trial in outpatient can accelerate inpatient uptake

Improves patient throughput / time to discharge

Streamlines dosing for short-term setting of care

Addresses shift to complex patients

ASC = ambulatory surgery center. PK = pharmacokinetic. Images: www.flaticon.com

We Continue to Learn from and Adapt to COVID-19 Challenges

Transitioned into commercial organization with minimal business interruption

- No delays in regulatory timelines; approval and DEA scheduling in 2H 2020
- Commercial supply of all 3 presentations made available to customers

What we learned from our customers

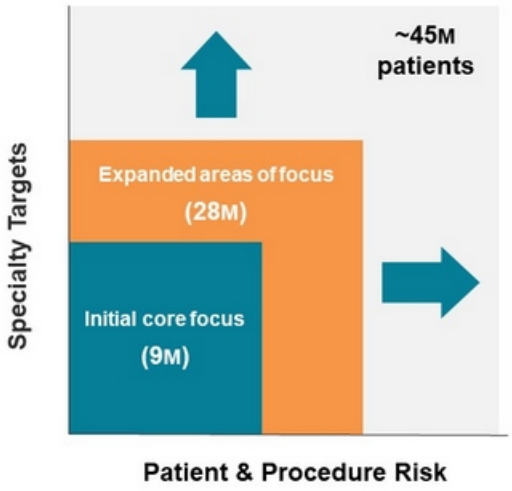
- Procedure volumes may be slow to recover; backlog of elective surgeries building[1]
- IV drug shortages, increase in patient acuity continue to pressure healthcare systems

Considerations for a successful field launch in 2021

- COVID-19 will continue impacting our customers; OLINVYK's value proposition remains relevant
- We will be making informed resource deployment decisions throughout first year of launch

1) Kaufman Hall 2020 State of Healthcare Performance Improvement Report: The Impact of COVID-19, October 2020.

OLINVYK: Significant Opportunity in Acute Pain



Initial core focus (9M)

- Hospitals / ambulatory surgical centers
- "CORES" patient focus: comorbid, obese, renal, elderly, sleep apnea

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

Expanded areas of focus (28M)

- Leverage respiratory and GI safety vs. IV morphine to expand surgical procedures
- Cognitive function & additional HECON

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

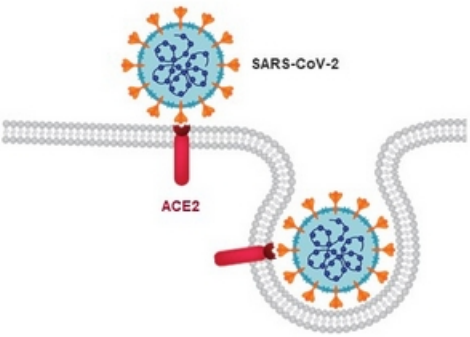
TRV027

NCE targeting the AT_1 receptor in COVID-19

Multi-Organ Damage From Coronavirus

Elimination of ACE2 protein leads to critical hormonal imbalances

Coronavirus binds to and eliminates ACE2[1]

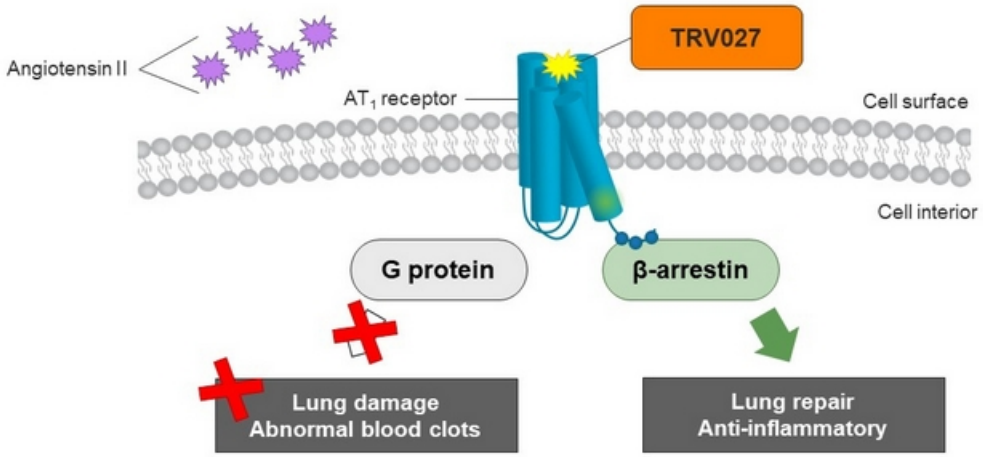


- Leads to accumulation of angiotensin II:
  - Acute lung injury and abnormal blood clots
  - Can lead to ARDS / pulmonary embolism / stroke
- 66% - 94% mortality rate for COVID-19 related ARDS[2*]
- ~1/3 of hospitalized COVID-19 patients develop clotting complications[3]

ARDS = Acute Respiratory Distress Syndrome. 1) Kuba K et al., Nat Med, 2005. 2) Gibson PG et al, Med J Aust, 2020. *In patients requiring ventilation. 3) Klok FA et al, Thromb Res, 2020.

TRV027: New MOA for COVID-19

Mechanism targeted to improve lung function and prevent abnormal clotting



TRV027 is the only selective AT_1 receptor agonist
Safety / tolerability established in ~700 patients

TRV027 COVID-19 Study - Imperial College London

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

- Randomized, double-blind, placebo-controlled proof-of-concept study
- N = ~60 (30 per arm) COVID-19 patients
  - Hospitalized, non-ventilated
  - ≥18 years old
- IV infusion of placebo or TRV027 for 7 days (12 mg/hr)
- Study currently ongoing, primary completion date expected in 1H 2021

Primary endpoint:

Reduction of abnormal clotting associated with COVID-19*

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

Imperial College London

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* Primary endpoint: D-dimer levels. https://clinicaltrials.gov/ct2/show/record/NCT04419610.

Multiple Expected Catalysts

	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	NDA	EXPECTED CATALYSTS
OLINVYK™ New chemical entity (mu-opioid receptor)	Acute pain IV				APPROVED	Q1 21: Commercial launch
TRV027 Novel AT_1 receptor selective agonist	ARDS / abnormal clotting (COVID-19) IV		Collaboration with Imperial College London			1H 21: Primary completion date (ICL)
TRV250 G-protein selective agonist (delta receptor)	Acute migraine oral/subcutaneous					1H 21: IND-enabling activities (oral)
TRV734 G-protein selective agonist (mu-opioid receptor)	Opioid use disorder oral		Collaboration with National Institute on Drug Abuse			PoC study data (NIDA)
TRV045 Novel S1P receptor modulator	CNS disorders oral		Collaboration with National Institutes of Health			1H 21: IND filing

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TRV250, TRV734, TRV027, and TRV045 are investigational products and are not approved by the FDA or any other regulatory agency.
ARDS = Acute Respiratory Distress Syndrome; IND = Investigational New Drug; PoC = Proof-of-Concept

TRV250: New MOA for Acute Treatment of Migraine

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

Delta receptors have unique distribution throughout the brain

Play important role in regulation of pain, mood, and anxiety

Every year in the 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]

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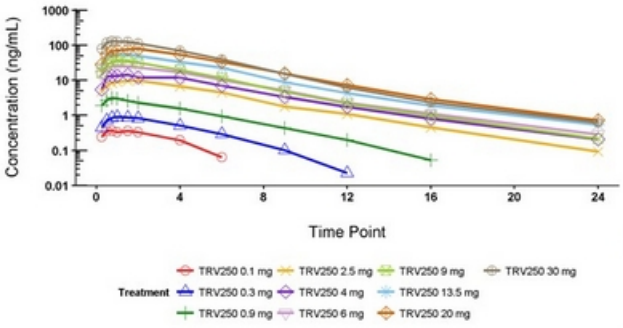
1) Data from Decision Resources, Pharmacor migraine market landscape and forecast 2018. 2) Moven et al., J Neurol Neurosurg Psychiatry, 2016.
Icons made by Freepik from www.flaticon.com

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

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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: Potential for improved tolerability

Ongoing collaboration with National Institute on Drug Abuse (NIDA)

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

NIDA-funded proof-of-concept patient study initiated

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

TRV045: Selective S1PR With No Lymphopenia

Uniquely selective for S1P-subtype 1 receptor

$S1P_1$ receptors are expressed broadly in the CNS

Potential role in the treatment of:

Epilepsy

- Neuroprotective effects[1]
- Modulates permeability of BBB, anti-inflammatory effects[2]

Chronic neuropathic pain

- Inhibits pain sensation[3]
- Inhibits excitatory neuronal signaling[4]

Avoids known safety issues associated with S1P receptor subtypes 2, 3, 4, 5:

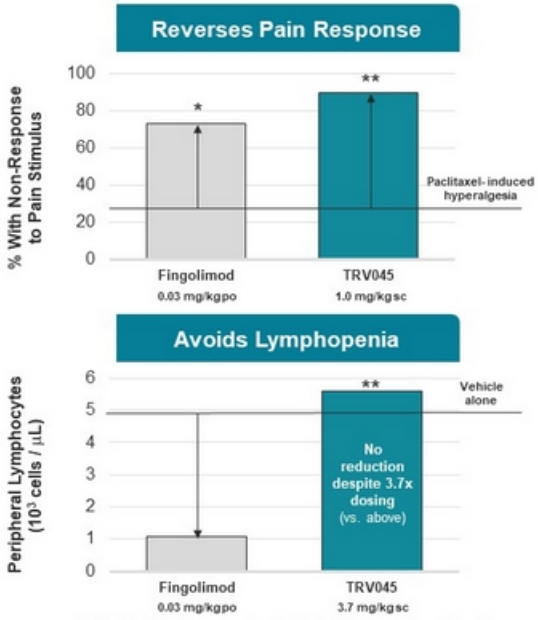
Pulmonary, cardiac, and cancer-related effects[5]

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

TRV045: Engages S1PR Without Lymphopenia in CIPN Model

S1P receptor activation conventionally associated with lymphopenia / immunosuppression

- In animals, TRV045 reversed paclitaxel-induced hyperalgesia without immune-suppressing activity
  - Fingolimod reduced lymphocytes by 78%
  - TRV045 had no effect on lymphocytes
- Non-opioid MOA with broad potential for CNS indications
  - Chronic pain, CIPN, diabetic neuropathy
  - Epilepsy, acute / chronic pain evaluations underway



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

Trevena: Innovative CNS Company

IV OLINVYK: Differentiated profile	NCE approved for the management of acute pain in adults Commercial launch in Q1 2021; targeting 100 formulary wins by year-end
Large market, targeted launch	45M+ US hospital patients; 9M procedures is initial core focus $1.5B+ market opportunity for core focus
Novel CNS pipeline	New mechanisms for acute migraine, opioid use disorder, epilepsy, pain NCEs targeting significant unmet needs
TRV027 for COVID-19	Novel MOA to treat COVID-19 acute lung injury / abnormal clotting PoC study in collab with Imperial College London; primary completion date expected in 1H 2021
Strong financial position	$109.4M cash and cash equivalents as of YE 2020 Funds operations through Q4 2022

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

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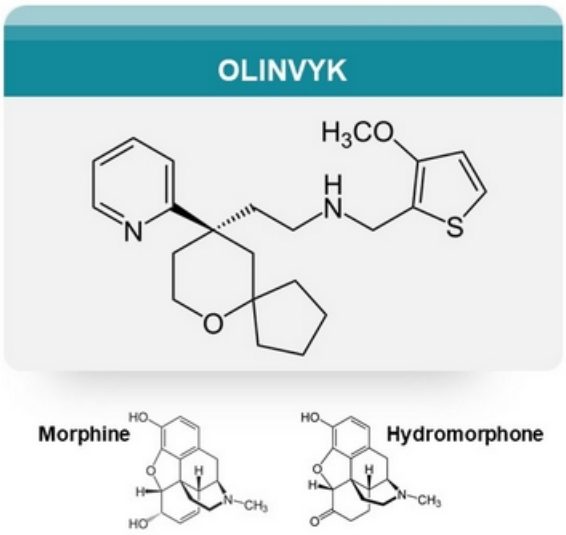
NCE = New Chemical Entity; MOA = Mechanism of Action; PoC = Proof-of-Concept

APPENDIX

OLINVYK: Distinct From IV Morphine / Hydromorphone



Studied in >1,900 individuals

IV morphine included as active comparator

NCE with 2032+ COM patent[1]

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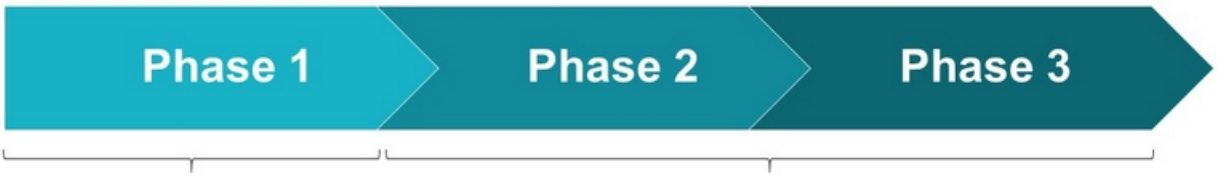
1) 2032 composition of matter patent expiration does not include potential patent extensions.

Robust Clinical Development Program

OLINVYK studied in > 1,900 individuals



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

4 head-to-head trials vs. IV morphine:

- IV opioid efficacy
- Rapid onset of action
- Well-characterized respiratory safety / GI tolerability
- Low rates of vomiting and rescue antiemetic use

Large safety study:

- Real-world use in complex patients and target surgeries

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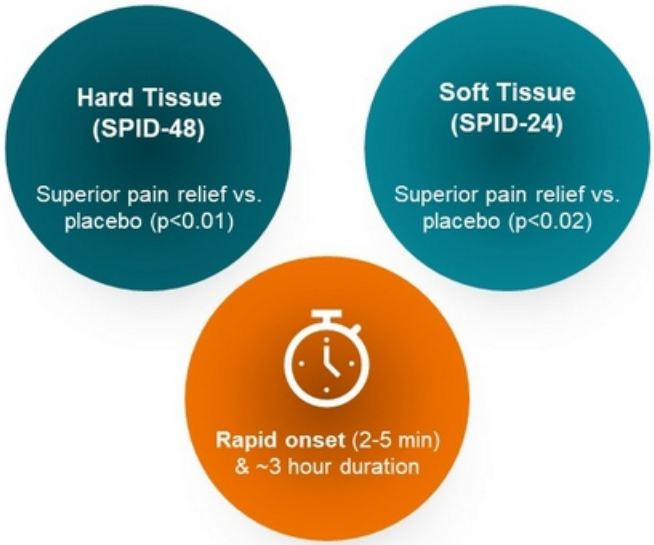
 # subjects exposed to OLINVYK in Ph1 = 318; # patients treated with OLINVYK in Ph2 and Ph3 = 1,535

OLINVYK: IV Opioid Efficacy and Rapid Onset



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

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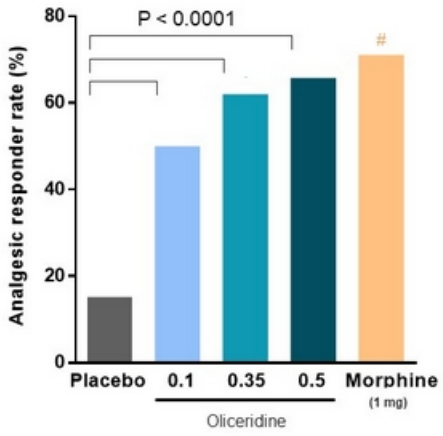
1) Viscusi ER et al. J Pain Res. 2019;12:927–943. Published 2019 Mar 11. 2) Singla NK et al. Pain Pract. 2019;19:715-731. Published 2019 Jun 04.

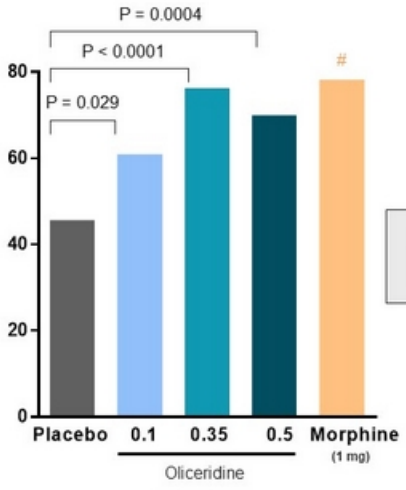
Primary Efficacy Endpoint Achieved in Two Pivotal Studies

OLINVYK achieved IV opioid efficacy

Published in *The Journal of Pain Research*



Ph3: Hard Tissue Surgery
Mean baseline pain = 6.7



Ph3: Soft Tissue Surgery
Mean baseline pain = 7.3

Published in *Pain Practice*

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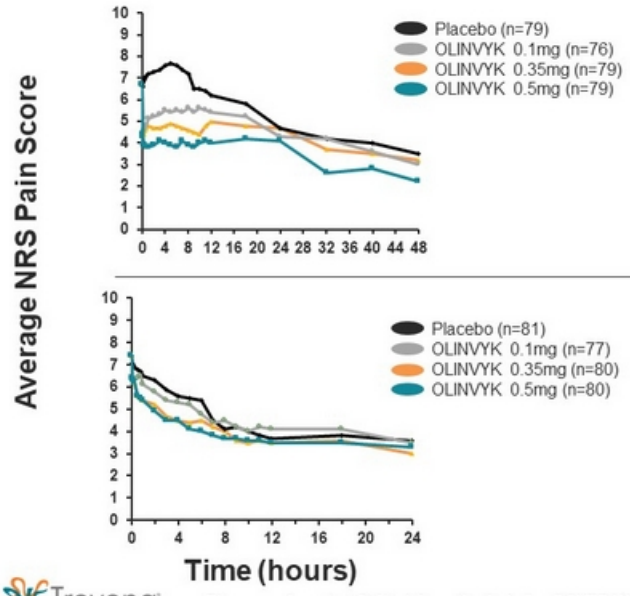
These analyses were the prespecified primary endpoints for both studies. Section 14 of the Prescribing Information includes the SPID-24 and SPID-48 efficacy analyses that were the basis for approval. Viscusi ER et al. J Pain Res. 2019;12:927–943. Published 2019 Mar 11. Singla NK et al. Pain Pract. 2019;19:715-731.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

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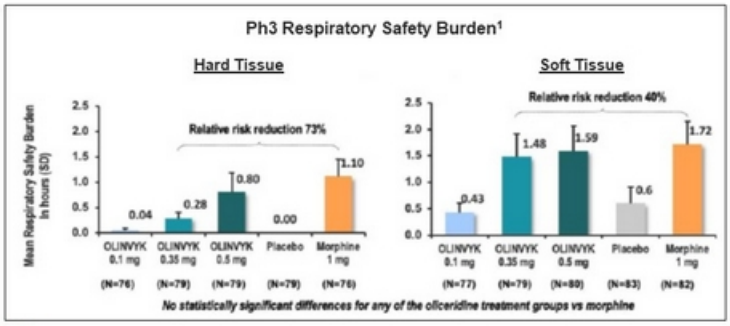
Robust Assessment of Respiratory Safety in Phase 3 RCTs

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 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	–

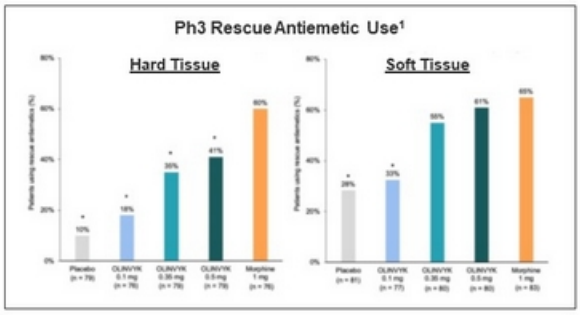
bpm = breaths per minute; MRPSS = Moline-Roberts Pharmacologic Sedation Scale

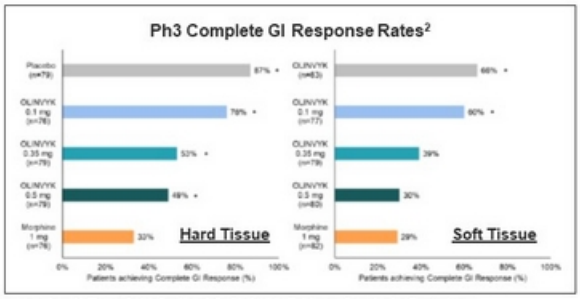
1) Figure 2-8, Section 2.2, OLINVYK Evidence Dossier for Formulary Consideration. 2) Figures 3-4 and 3-8, Section 3.1, OLINVYK Evidence Dossier for Formulary Consideration.

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





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.

Customer Facing Organization

Partnering with Syneos Health to provide "best in class" commercial support

Syneos Health

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

40 Customer-Facing Roles

- **Sales**: Institutional Account Managers
- **Trade & Access**: Regional Account Managers
- **Medical**: Medical Science Liaisons

Launch Team: Top Talent with Hospital Experience

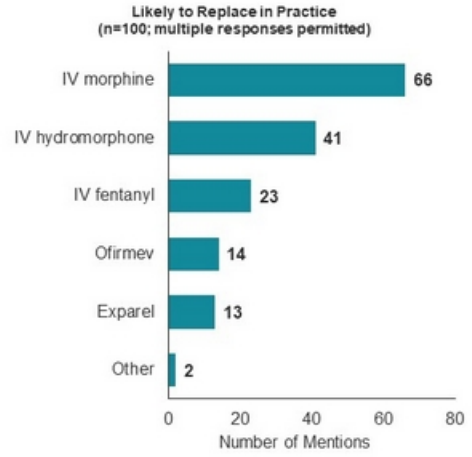
Role	Highlights
Medical Science Liaisons	100% with Advanced degrees 100% with Health Econ background 100% with hospital and launch experience
Regional Sales Managers	20+ Years experience Buy & Bill Hospital & ASC experience
Key Account Managers	21 years (avg) in Pharma 100% with GPO/IDN experience 100% with recent launch experience
Representatives	18 years experience 100% with recent launch experience 100% with Hospital experience Majority with therapeutic experience

Positive Feedback from Formulary Stakeholders[1]

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

Key Endpoint (vs. IV morphine)	Pharmacist (n=50)	Physician (n=50)
Respiratory Safety Events and GI Tolerability	72%	76%

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



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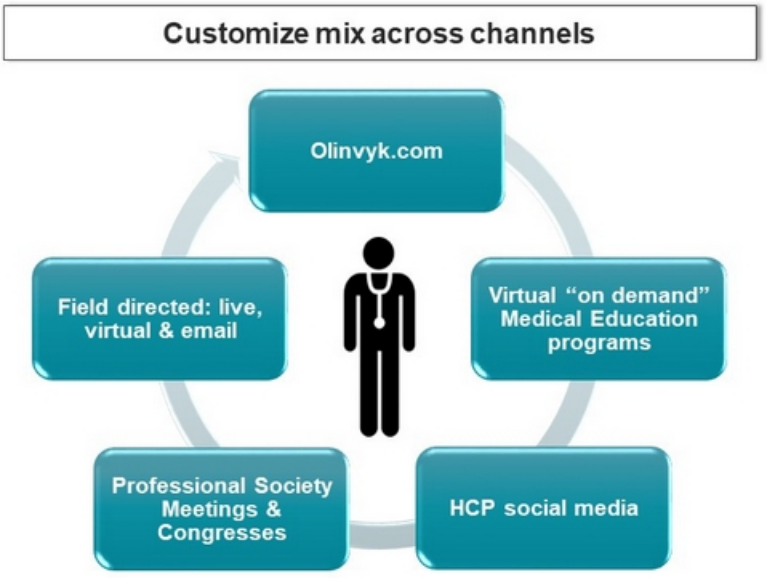
1) Qualitative Pricing research, Charles River Associates, April 2020. 2) "Are the improvements in respiratory safety events and GI tolerability clinically meaningful?" Based on OLINVYK Ph3 clinical trial data.

Omni-channel Approach for HCP Engagement

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



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"Now Available" Campaign

"Now Available" Website

- Order/Reimbursement/Dosing Guides
- Connect with Medical Affairs and/or Sales Rep

"Now Available" Drivers

- Programmatic Banner Ads
  - Banner ad messaging to connect HCPs through digital journey
- Journal Ads
  - Ads will run in *American Journal of Health-System Pharmacy, Pharmacy Purchasing & Products*
- Select Emails to Key Health Care Professionals
  - Emails to provide online introduction to OLINVYK

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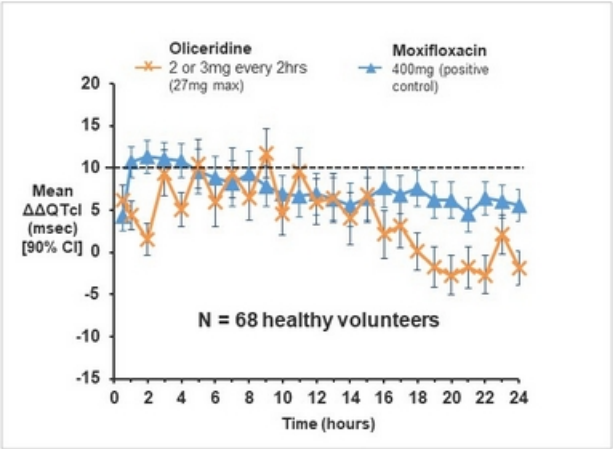
No Accumulation Despite Repeated Dosing

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.

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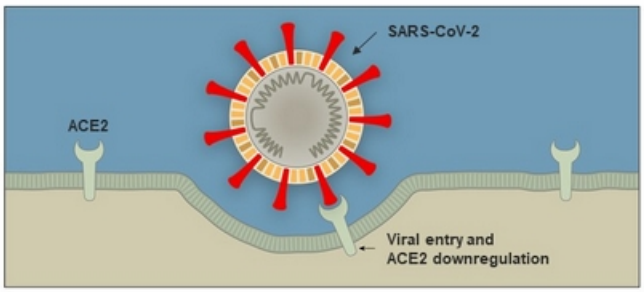
3 subjects not dosed due to lack of venous access; 1 discontinuation due to a non-serious adverse event (asymptomatic non-sustained ventricular tachycardia) with confounding hypokalemia and no meaningful QT prolongation during dosing; 1 subject completed dosing but not evaluable due to equipment malfunction

Interaction Between the AT_1 Receptor and ACE2 in COVID-19

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

- Coronavirus binds to and downregulates angiotensin converting enzyme 2 (ACE2)[1]
- Decrease in ACE2 elevates angiotensin II levels
  - Angiotensin II activates AT_1 receptor
  - No breakdown of angiotensin II into Ang(1-7)
    - Normally, Ang(1-7) acts as a β-arrestin-biased ligand at the AT_1 receptor[2]
    - Protective therapeutic benefits in the lungs[3]



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

Delta Receptor Agonists Have Unique Benefits

Potential utility for a variety of CNS indications

Triptans / Ditans

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

CGRPs

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

Delta receptor agonists

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

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

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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- 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.