Trevena®

INNOVATING FOR PATIENTS

Nasdaq TRVN | June 2021

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

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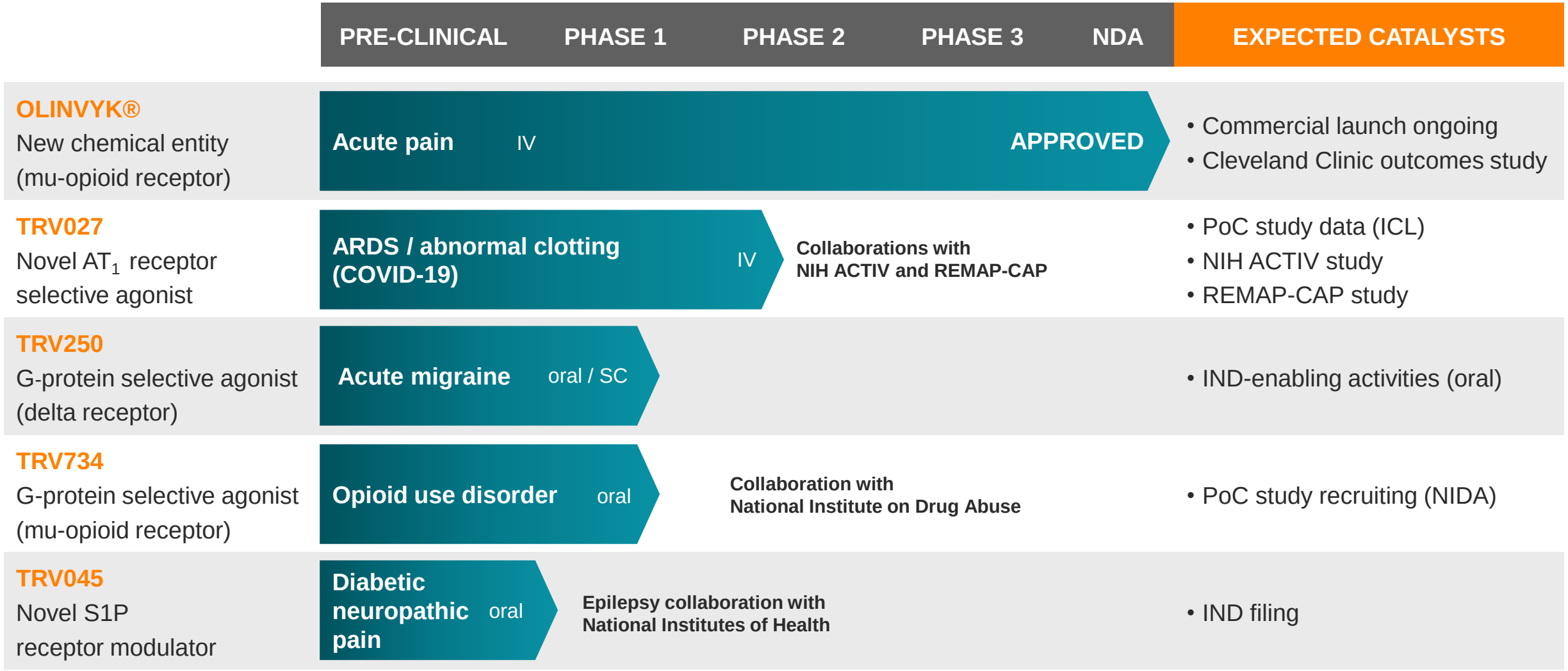
Trevena: Innovative CNS Company

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, diabetic neuropathic pain, epilepsy, opioid use disorder NCEs targeting significant unmet needs
TRV027 for COVID-19	Novel MOA to treat COVID-19 acute lung injury / abnormal clotting Selected for NIH ACTIV and REMAP-CAP trials; up to 600 COVID-19 patients on TRV027
Strong financial position	$97.7M cash and cash equivalents as of 3/31/2021 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; NIH = National Institutes of Health; ACTIV = Accelerating COVID-19 Therapeutic Interventions and Vaccines; REMAP-CAP = Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

Multiple Expected Catalysts



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

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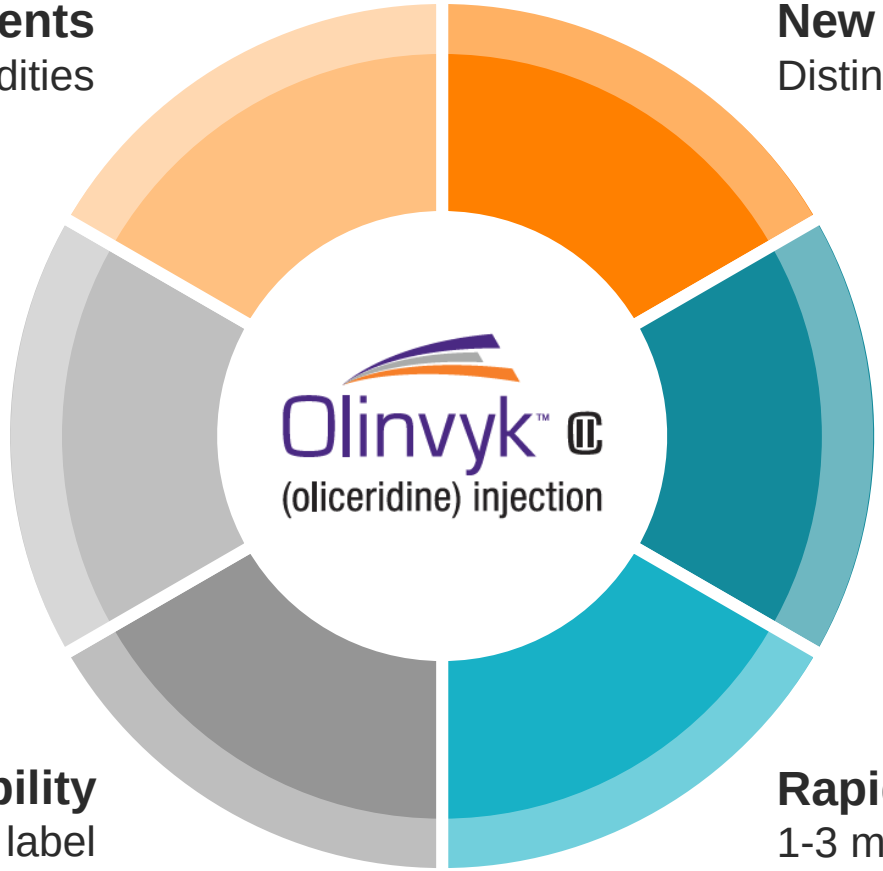
TRV250, TRV734, TRV027, and TRV045 are investigational products and are not approved by the FDA or any other regulatory agency.
ARDS = Acute Respiratory Distress Syndrome; ACTIV = Accelerating COVID-19 Therapeutic Interventions and Vaccines;
REMAP-CAP = Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia; 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

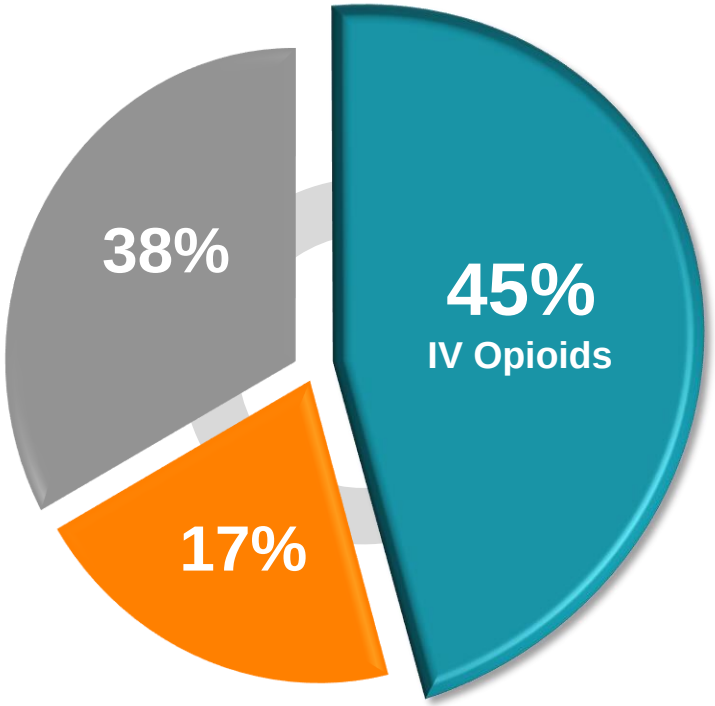
Rapid analgesia
1-3 min median onset of pain relief

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]



- IV opioids
- Local anesthetics
- IV NSAIDS / acetaminophen

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]

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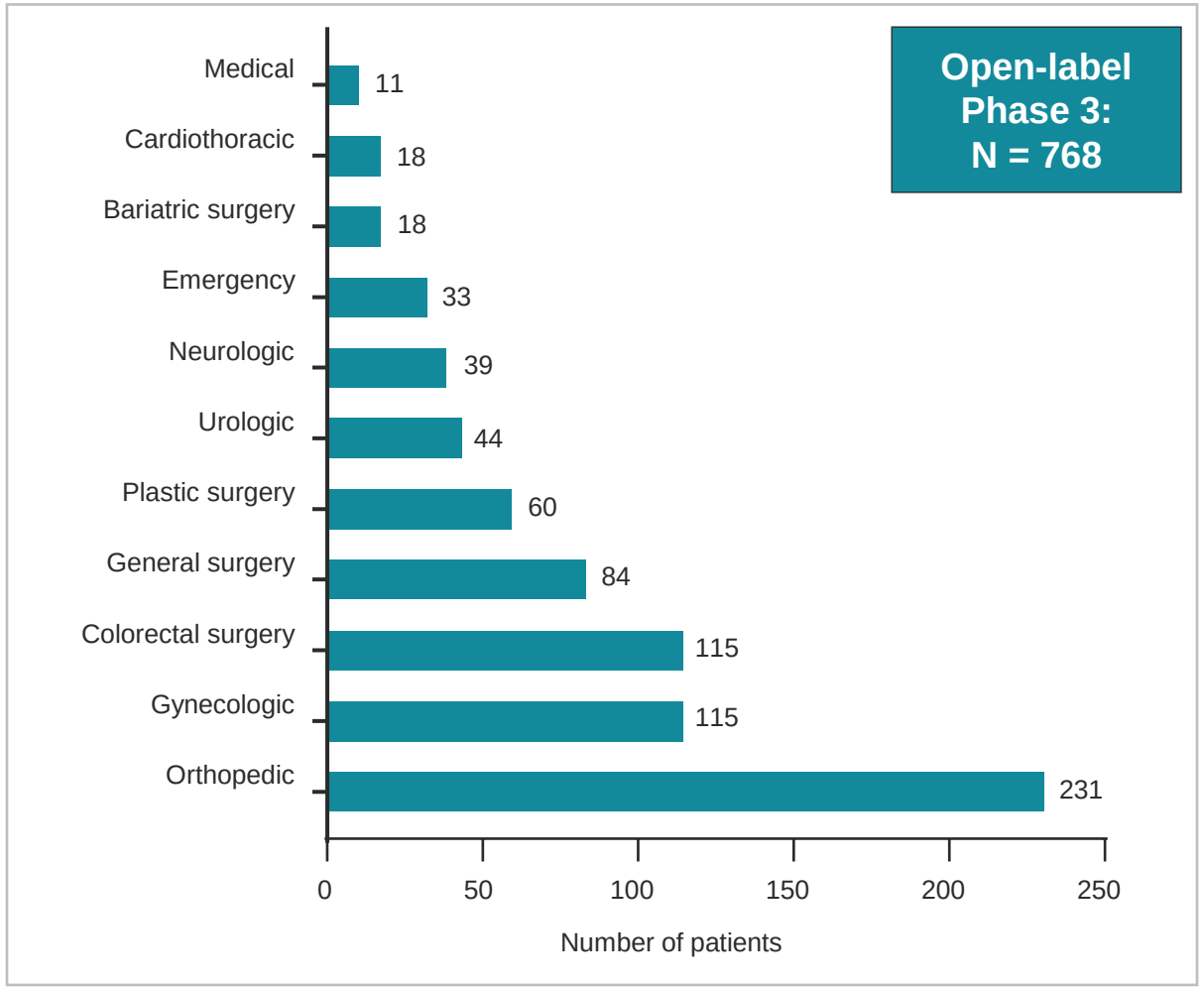
NSAIDs = nonsteroidal anti-inflammatory drugs. 1) IMS MIDAS sales audit 2017; IV NSAIDs and Ofirmev®. 2) Definitive database, and National Vital Statistics report, CDC 2018.

OLINVYK 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

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: 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

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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.

OLINVYK Safety Differentiation Study w/ Cleveland Clinic

Further characterizes potential respiratory, GI and cognitive outcomes

- Open-label, multi-site study led by experts at Cleveland Clinic
- N = ~200 adults undergoing major non-cardiac surgery
- Patient enrollment to begin in Q3 2021

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

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.

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

OLINVYK vs IV Morphine Health Economic Models

Models presented at AMCP 2021[1] and available to formulary committees

Representative Inputs:

AE rates

Ph3 trials

Placebo (N = 162)	OLINVYK ≤ 27 mg (N = 316)	Morphine (N = 158)
73	86	96
35	52	70
10	26	52
30	26	30
11	18	25
9	14	14
3	12	17
6	9	19
5	7	13
4	6	10
4	6	6
4	4	8
1	2	10

Vomiting
Somnolence / sedation
O_2 saturation <90%

Cost of AEs

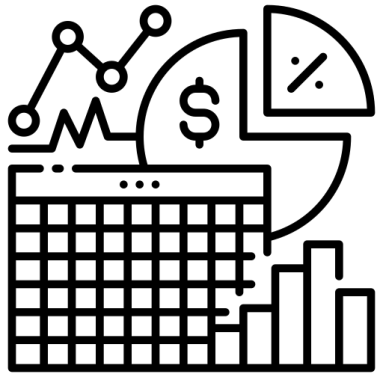
Gov't sources /
Publications

$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

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1) https://www.trevena.com/publications. 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.

Customer Engagement Strategy

Targeted Account Launch as of Q1 2021

~40 account reps / MSLs deployed Q1 2021

Health Care Practitioners (HCPs)

Anesthesiology, Orthopedic, Colorectal, Gynecologic

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

Targeted Accounts

550 hospitals and 500 ambulatory surgery centers

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

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MSL = Medical Science Liaison; NCE = New Chemical Entity. Images: flaticon.com.

Hospital Formulary Review Process

Physician

Submits request for drug review

Pharmacy Department

Conducts formal assessment of the drug

P&T Committee

Reviews assessment / votes to revise formulary

Approval

APPROVED

Pharmacy Department

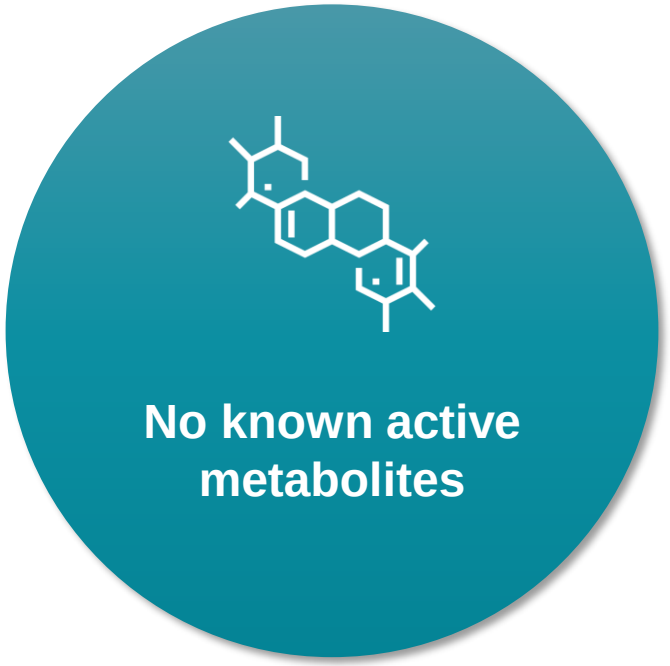
Updates formulary, protocols / order sets

YE 2021 target: 100 formulary wins

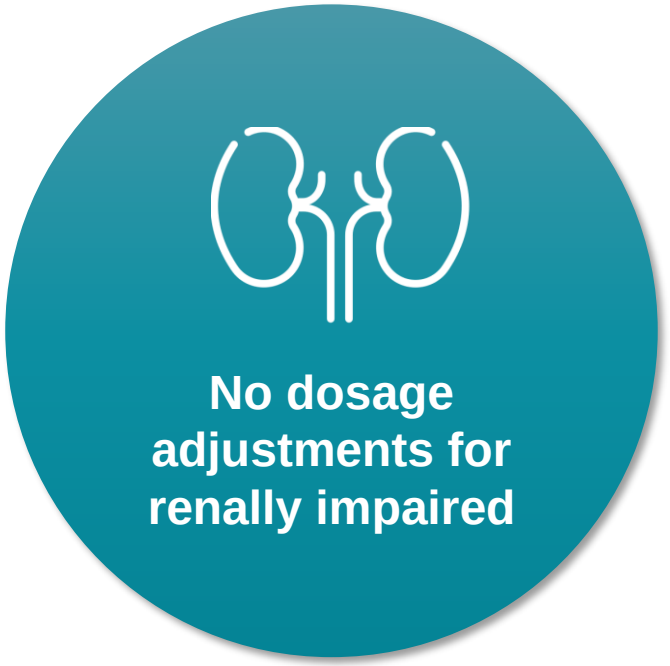
Differentiated Profile For Use in Hosp Outpatient & ASCs

Physician trial in outpatient can accelerate inpatient uptake

Improves patient throughput / time to discharge



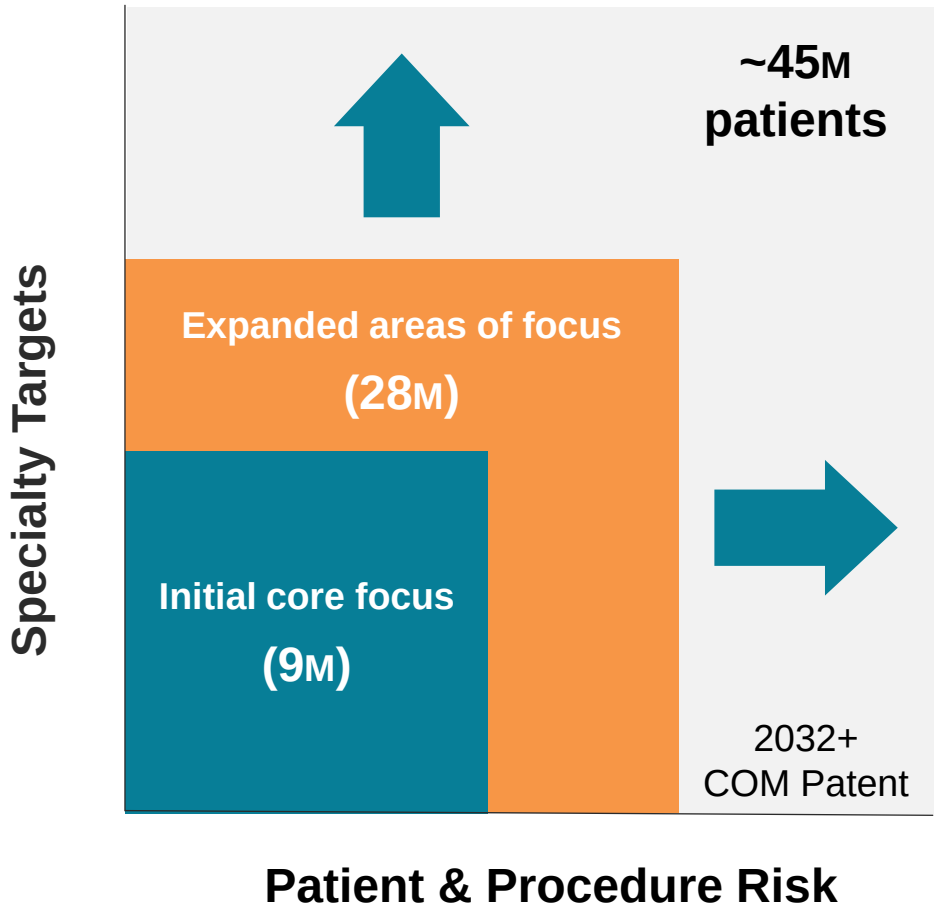
Streamlines dosing for short-term setting of care



Addresses shift to complex patients

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

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

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

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

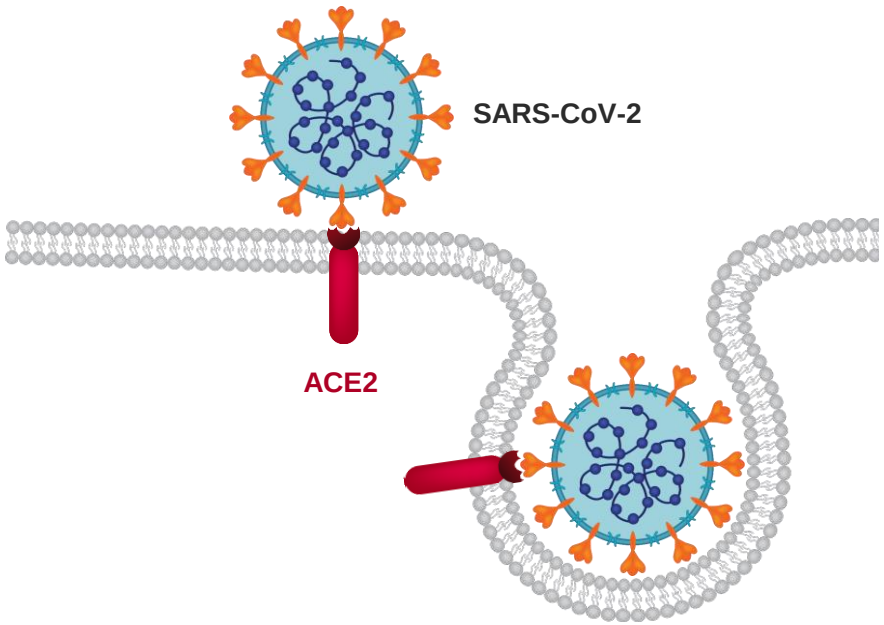
TRV027

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]

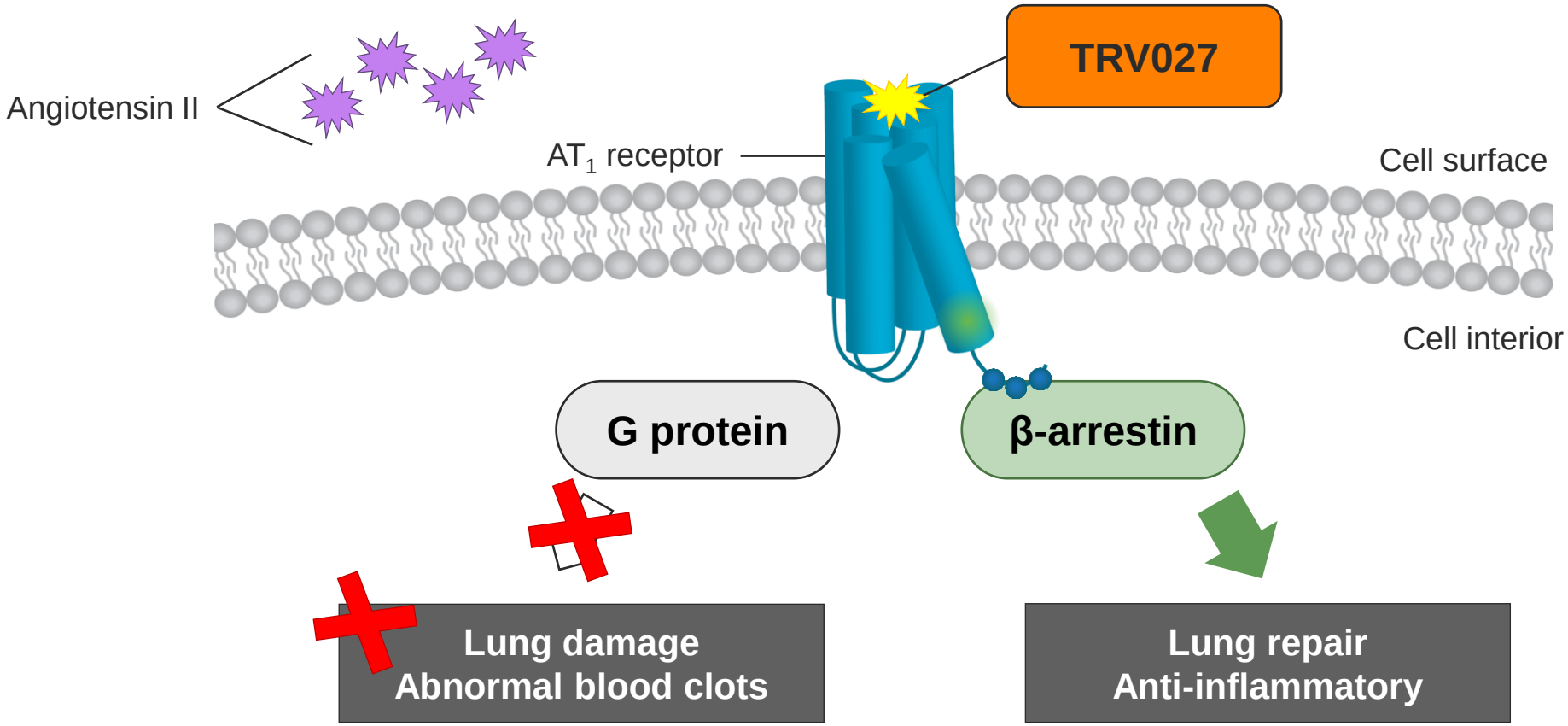


- Leads to accumulation of angiotensin II:
  - Acute lung injury and abnormal blood clots
  - Can lead to ARDS / pulmonary embolism / stroke
- 66% - 94% mortality rate for COVID-19 related ARDS[2*]
- ~1/3 of hospitalized COVID-19 patients develop clotting complications[3]

*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

Interim review by DMSC supports transition to REMAP-CAP trial

- Randomized, double-blind, placebo-controlled proof-of-concept study
- N = 30 COVID-19 patients
  - Hospitalized, non-ventilated
  - ≥18 years old
- IV infusion of placebo or TRV027 for 7 days (12 mg/hr)
- Review of interim data by DMSC found no safety concerns and supported advancement to more extensive study with clinical efficacy outcomes

Transition to REMAP-CAP
ICL to publish topline data

Primary ICL endpoint:
Reduction of abnormal clotting associated with COVID-19[1]

Imperial College London

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DMSC = Data Monitoring & Safety Committee; 1) Primary endpoint: D-dimer levels. https://clinicaltrials.gov/ct2/show/record/NCT04419610.

TRV027 COVID-19 Study - Vanderbilt UMC (ACTIV-4d)

NIH-funded trial with Vanderbilt University Medical Center as lead coordinating site

- Part of NIH's ongoing ACTIV* public-private partnership
- Multi-site, multi-arm, placebo-controlled trial
- ~300 COVID-19 patients ≥18 years old treated with TRV027

Key outcomes to be studied:

Recovery

Supplemental O_2 use

Mechanical ventilation

Mortality

National Institutes of Health

VANDERBILT UNIVERSITY MEDICAL CENTER

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*ACTIV = Accelerating COVID-19 Therapeutic Interventions and Vaccines

TRV027 COVID-19 Study - REMAP-CAP

Funded by REMAP-CAP, a global clinical trial network led by experts in pandemic response

- Multi-site, adaptive, Phase 2 / 3 trial in hospitalized COVID-19 patients (≥18 years)*
- 200 - 300 COVID-19 patients treated with TRV027
- TRV027 administered (open label) in conjunction w/ACE inhibitor

Primary outcome:

In-hospital mortality +
Organ failure support in ICU
(21 days post-randomization)

Additional outcomes: ICU / hospital length of stay, ventilator-free days, organ failure-free days

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

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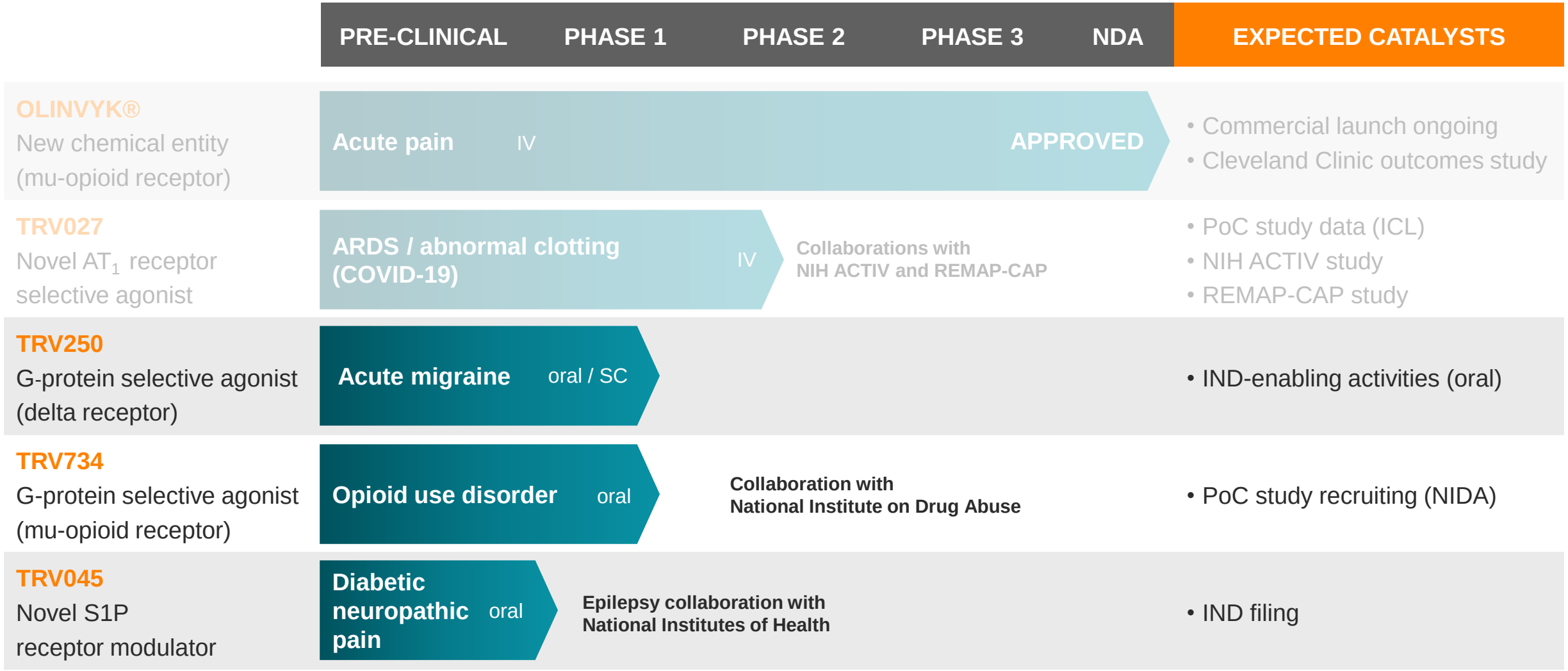
** Includes patients admitted to ICU*

Multiple Expected Catalysts



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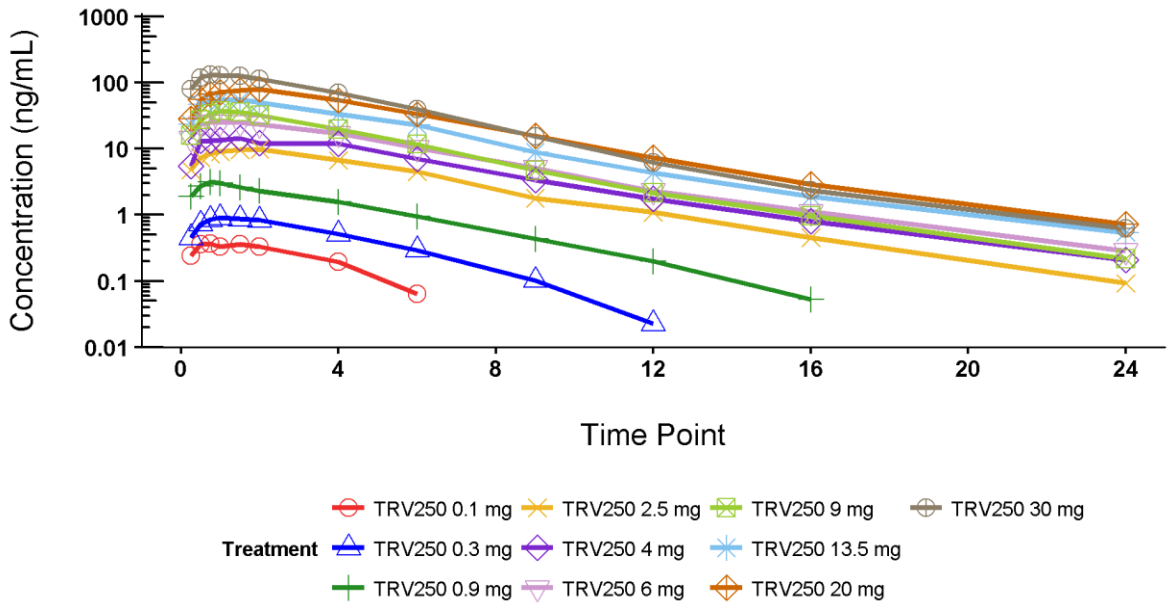
1) Data from Decision Resources, Pharmacor migraine market landscape and forecast 2018. 2) Moven et al., J Neurol Neurosurg Psychiatry, 2016.
Icons made by Freepik from www.flaticon.com

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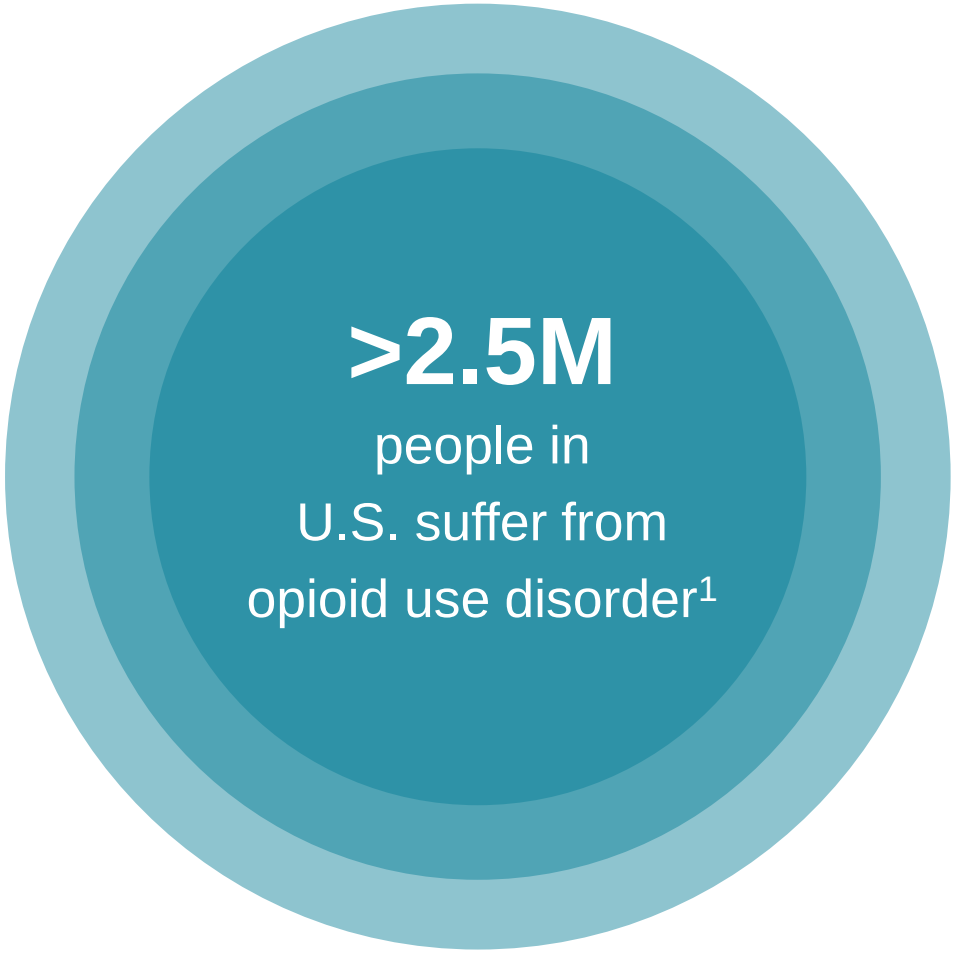
SC = subcutaneous. Fossler MJ et al., CNS Drugs, Aug 2020;34(8):853-865.

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]
- **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.

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:

Neuropathic pain

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

Epilepsy

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

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

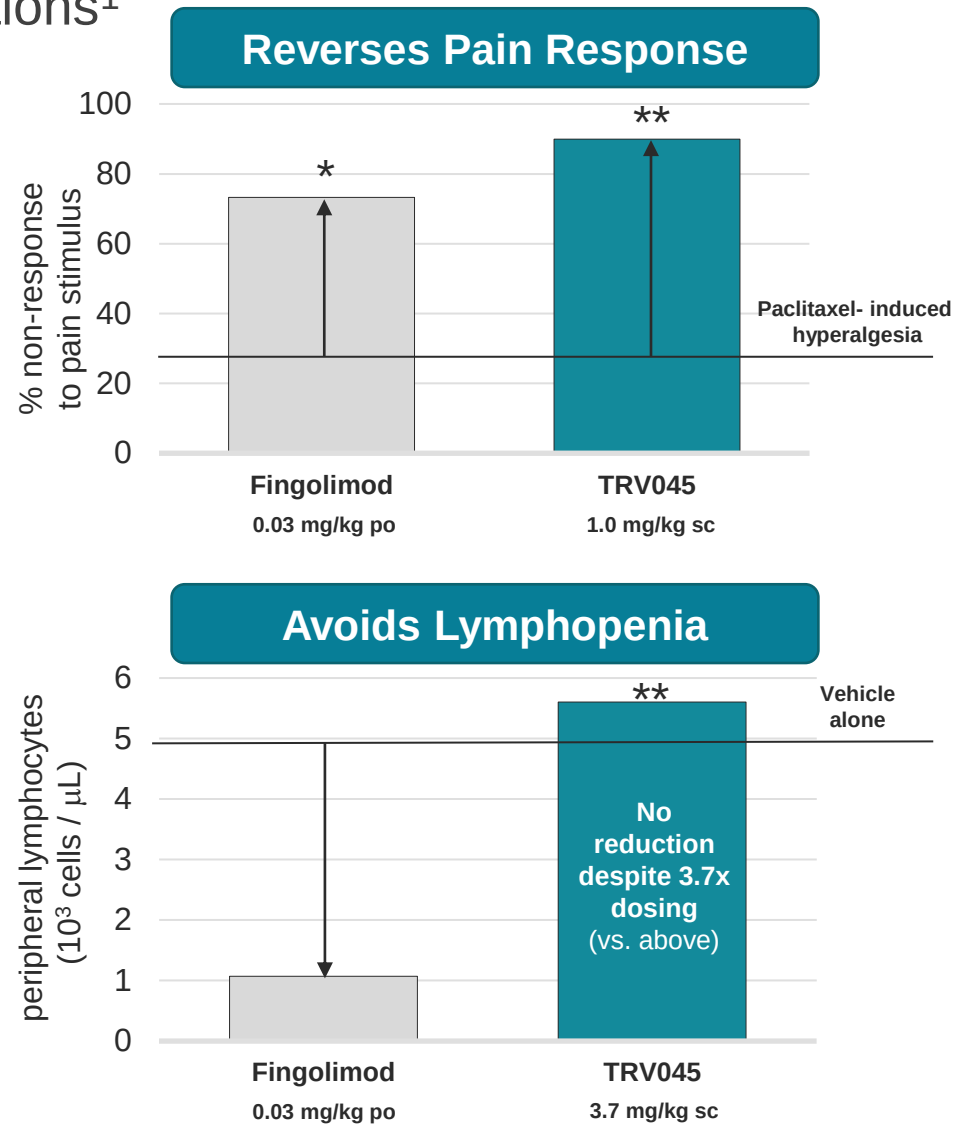
Pulmonary, cardiac, and cancer-related effects[5]

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.

TRV045: Novel MOA for Diabetic Neuropathic Pain

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

- DNP affects ~25% of people w/ diabetes[2]
  - Approved agents inadequate for ~50% of patients[3,4]
  - ~4x direct costs for DNP patients (vs diabetes alone)[5]
- In animals, TRV045 reversed neuropathic pain without immune-suppressing activity[6]
- Non-opioid MOA with broad potential for CNS indications
  - IND filing for DNP in Q3 2021
  - Epilepsy evaluation (NIH) ongoing



*1) Rosenberger et al., Journal of Neural Transmission, 2020 and CDC National Diabetes Statistics Report, 2020. 2) Shillo et al., Current Diabetes Reports, 2019. 3) American Diabetes Association. 4) FDA product labels for Lyrica, Lyrica CR, Cymbalta, Nucynta ER, and Qutenza, Tesfaye et.al. Pain (2013). 5) Sadosky et. al., J Diabetes Complications 2015. 6) CIPN mouse model: Paclitaxel 6 mg/kg, i.p. on Days 1, 3, 5, 7. Hyperalgesia measured as % non-response to 0.4 g Von Frey filament vs. baseline, tested 30' after dosing on Day 13. Lymphocytes measured after 3 days of dosing. Data are mean ± s.e.m. n=5-7 mice/group. *p<0.05 or **p<0.01 vs. control*

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Novel CNS pipeline	New mechanisms for acute migraine, diabetic neuropathic pain, epilepsy, opioid use disorder NCEs targeting significant unmet needs
TRV027 for COVID-19	Novel MOA to treat COVID-19 acute lung injury / abnormal clotting Selected for NIH ACTIV and REMAP-CAP trials; up to 600 COVID-19 patients on TRV027
Strong financial position	$97.7M cash and cash equivalents as of 3/31/2021 Funds operations through Q4 2022

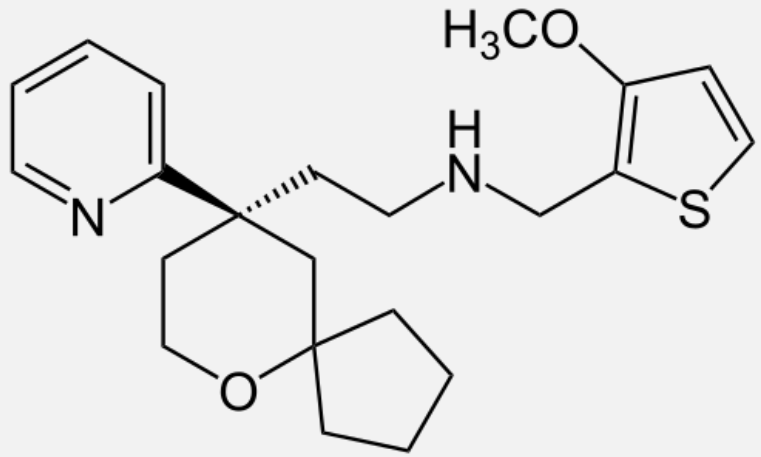
OLINVYK is indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

NCE = New Chemical Entity; MOA = Mechanism of Action; NIH = National Institutes of Health; ACTIV = Accelerating COVID-19 Therapeutic Interventions and Vaccines; REMAP-CAP = Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

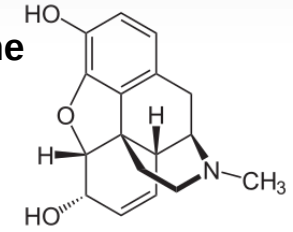
APPENDIX

OLINVYK: Distinct From IV Morphine / Hydromorphone

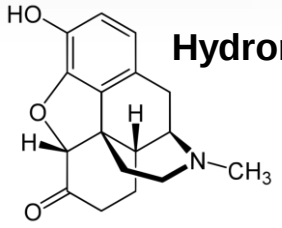
OLINVYK



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.

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

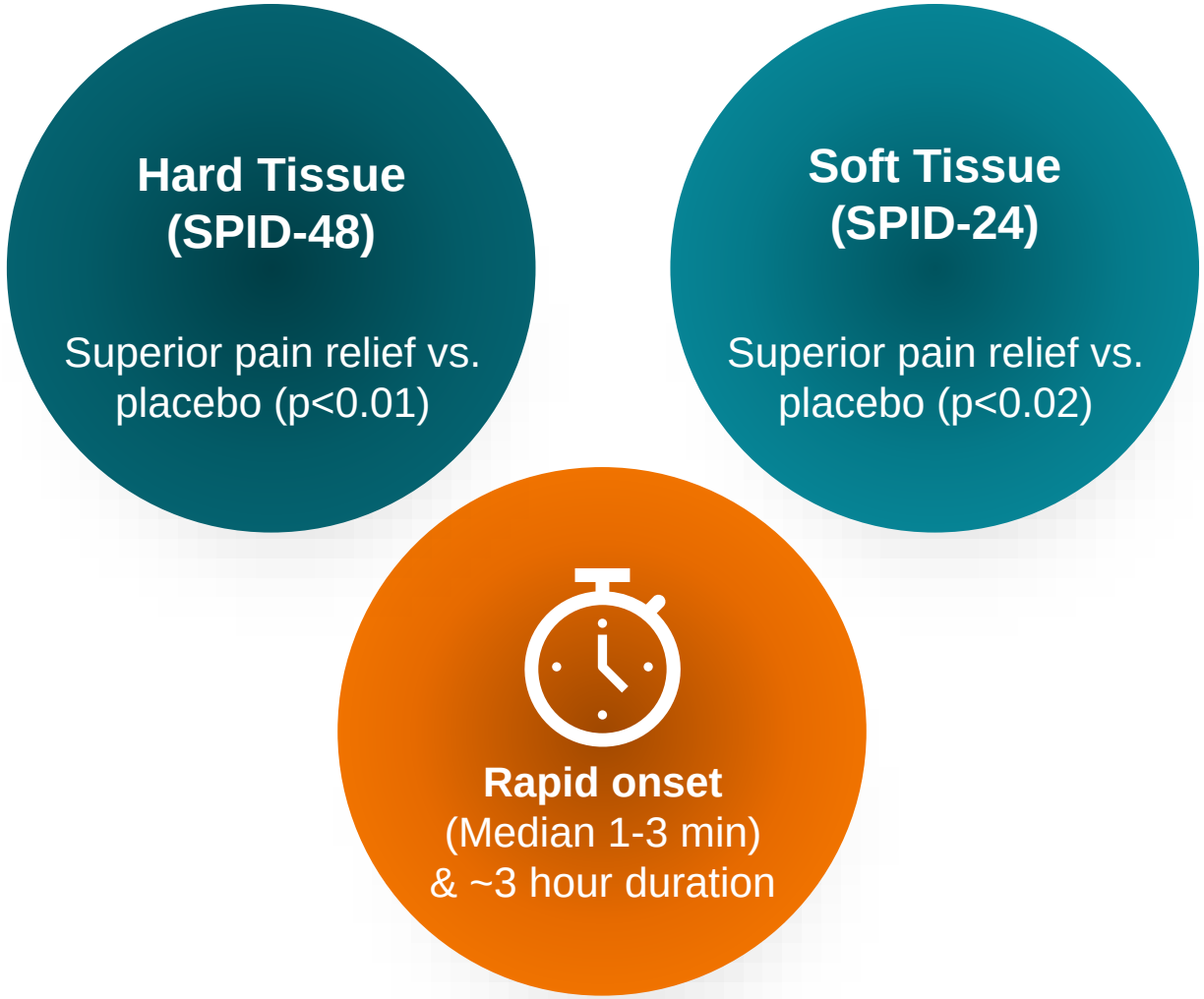
Large safety study:

- Real-world use in complex patients and target surgeries

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

 # 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 1-3 minutes (median onset of action)
- OLINVYK efficacy data in peer-reviewed journals
  The Journal of Pain Research[1] and *Pain Practice*[2]

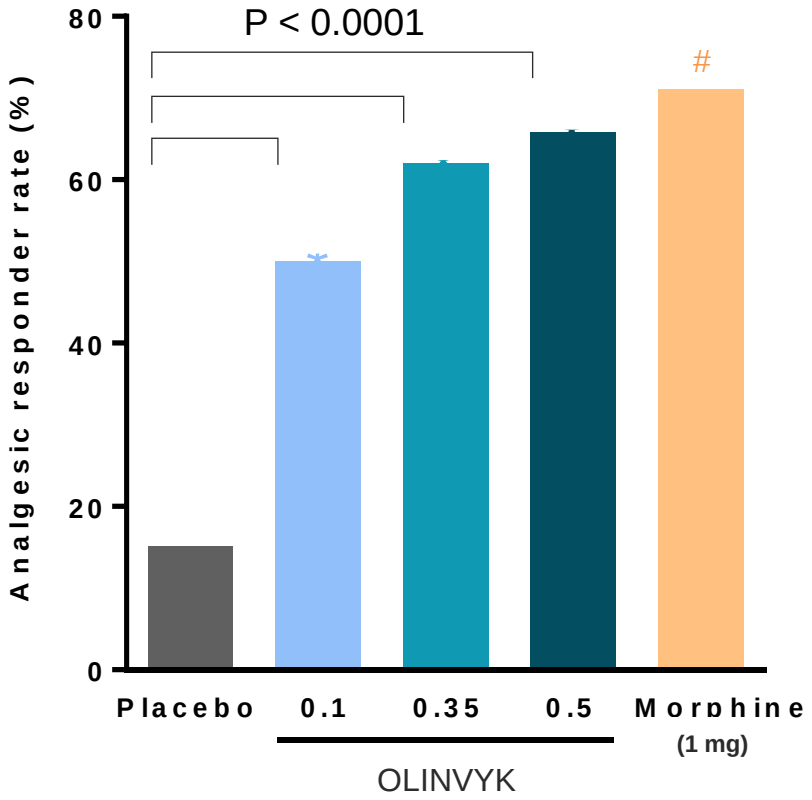
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

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

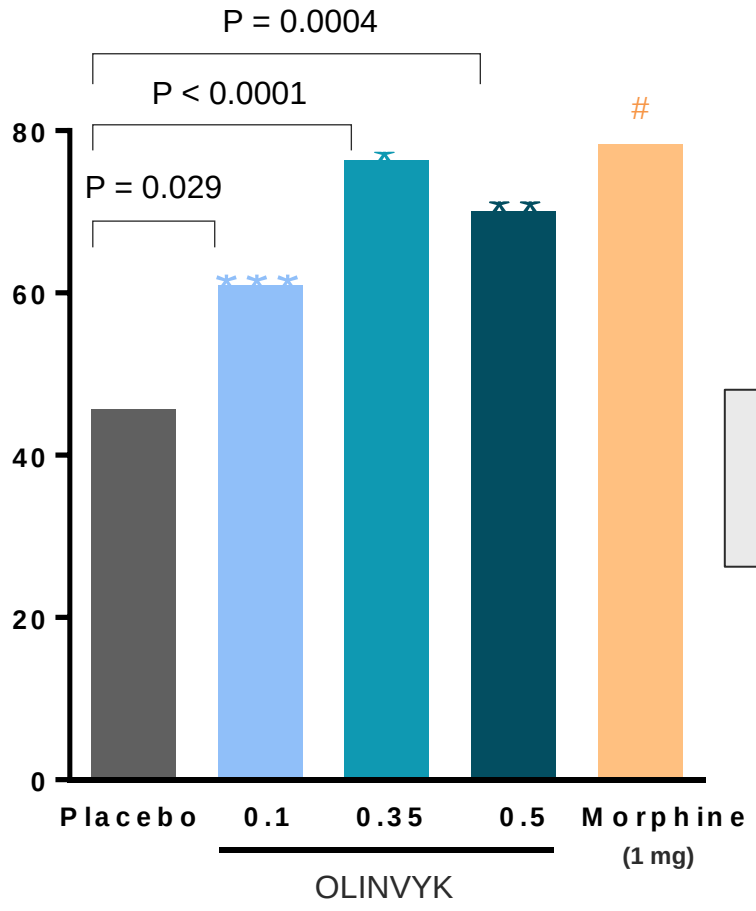
OLINVYK achieved IV opioid efficacy

Published in *The Journal of Pain Research*



Ph3: Hard Tissue Surgery

Mean baseline pain = 6.7



Ph3: Soft Tissue Surgery

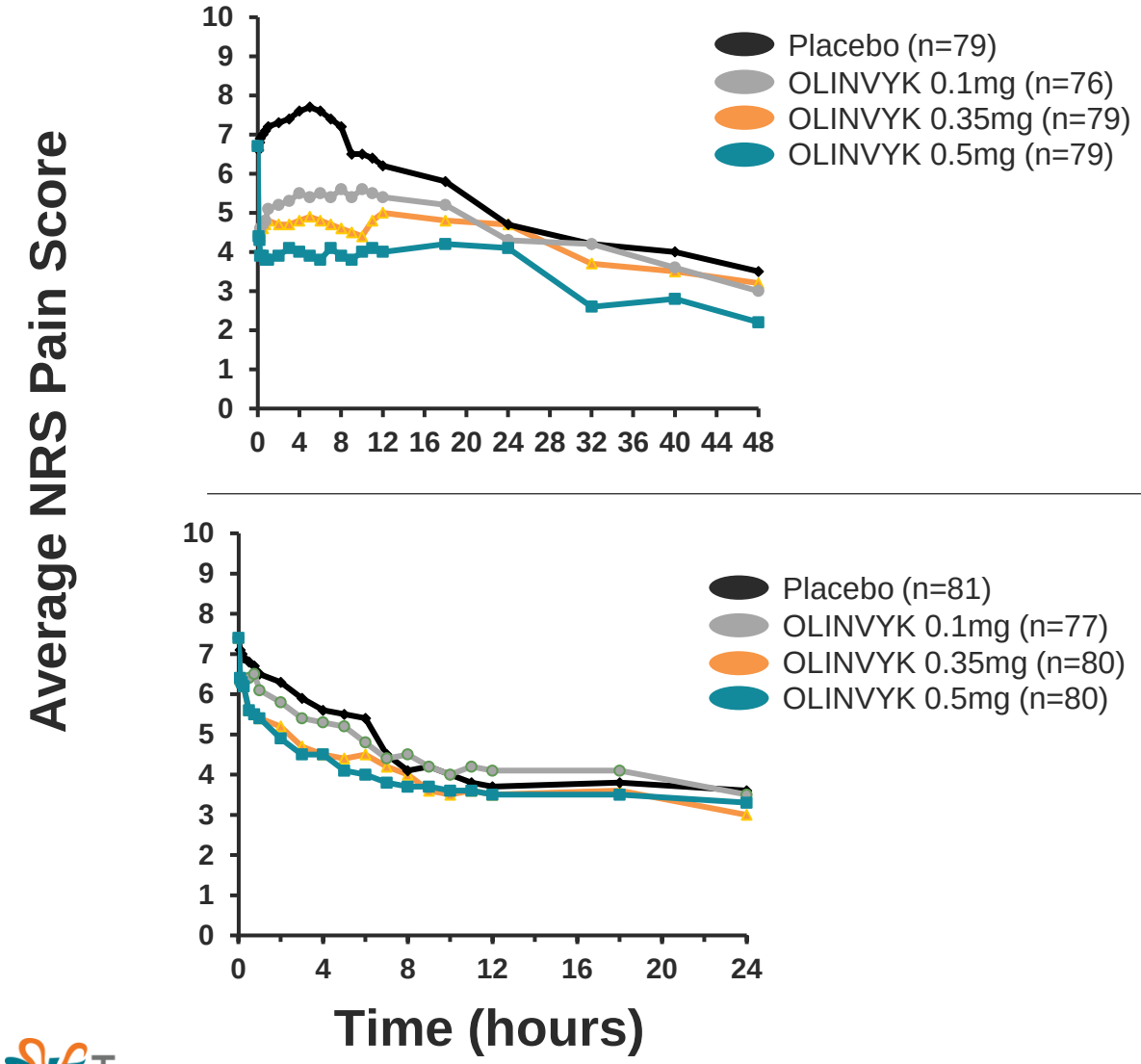
Mean baseline pain = 7.3

Published in *Pain Practice*

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

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

OLINVYK: IV Opioid Efficacy in 2 Phase 3 RCTs



Study 1 (Orthopedic – Hard Tissue)

3 PCA regimens studied (0.1, 0.35, 0.5 mg) vs. placebo;
all doses P<0.01 vs. placebo

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

Study 2 (Plastic Surgery – Soft Tissue)

3 PCA regimens studied (0.1, 0.35, 0.5 mg) vs. placebo;
0.35 / 0.5 mg doses P<0.02 vs. placebo

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

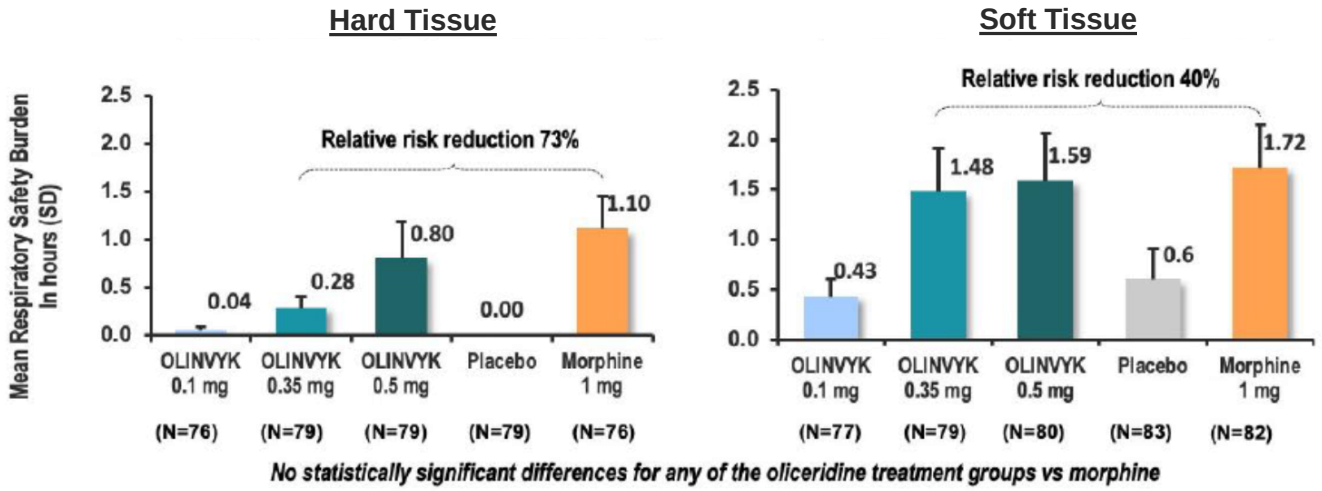
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

Robust Assessment of Respiratory Safety in Phase 3 RCTs

Data included in AMCP dossier used in formulary review

- Prespecified secondary endpoint: Respiratory Safety Burden (RSB)
  - Calculated based on incidence and cumulative duration of respiratory safety events
- Full characterization of respiratory safety profile has been made available to HCPs and formulary decision makers
  - Data can be found in OLINVYK AMCP dossier and published literature

Ph3 Respiratory Safety Burden[1]



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	–

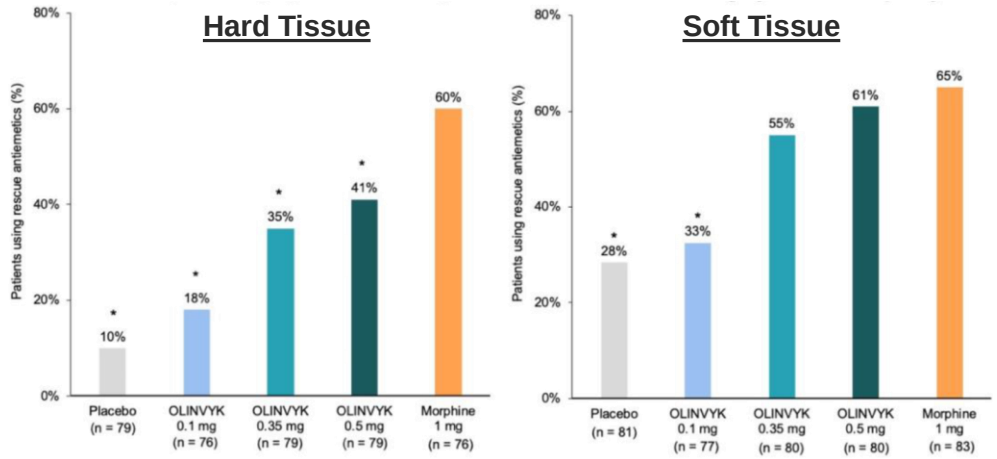
bpm = breaths per minute; MRPSS = Moline-Roberts Pharmacologic Sedation Scale

Robust Assessment of GI Tolerability in Phase 3 RCTs

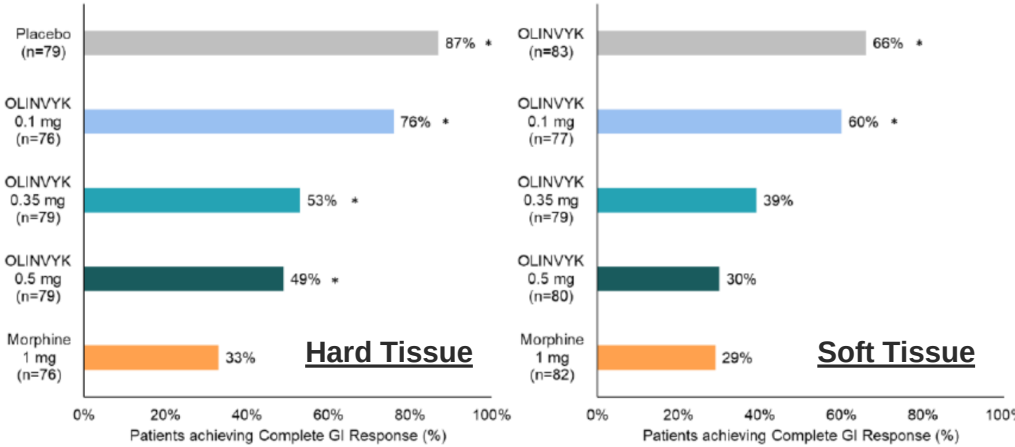
Data included in AMCP dossier used in formulary review

- 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

Ph3 Rescue Antiemetic Use[1]



Ph3 Complete GI Response Rates[2]



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

- 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

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

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

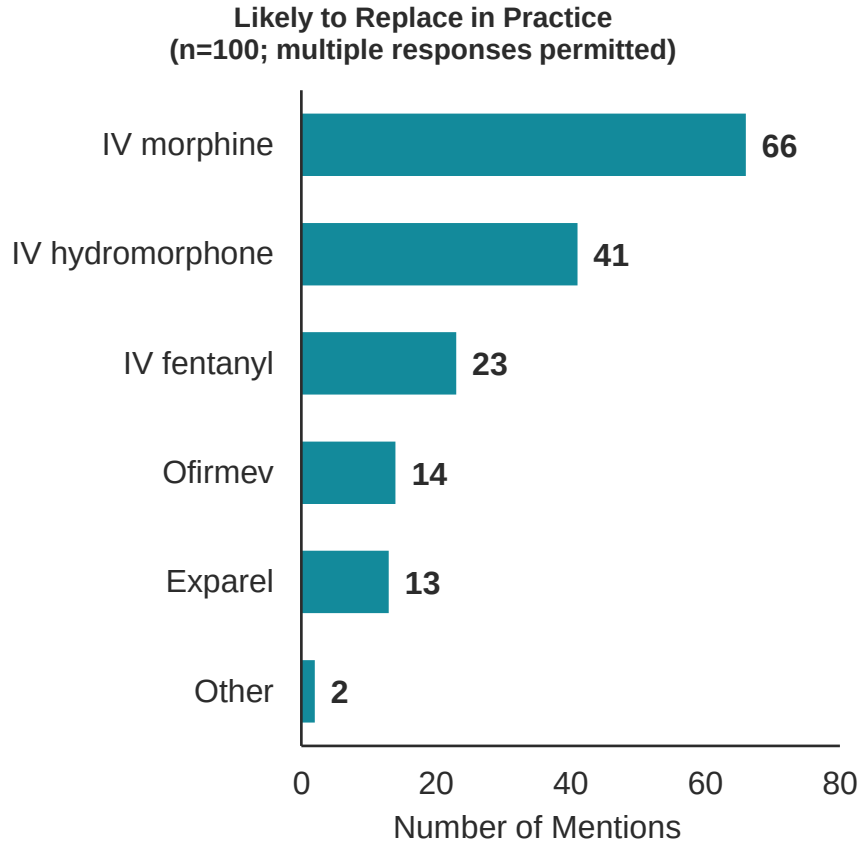
See www.trevena.com for full manuscripts and abstracts. These publications will be used in a manner consistent with FDAMA sections 114 and 401 and the FDA Guidances thereunder.

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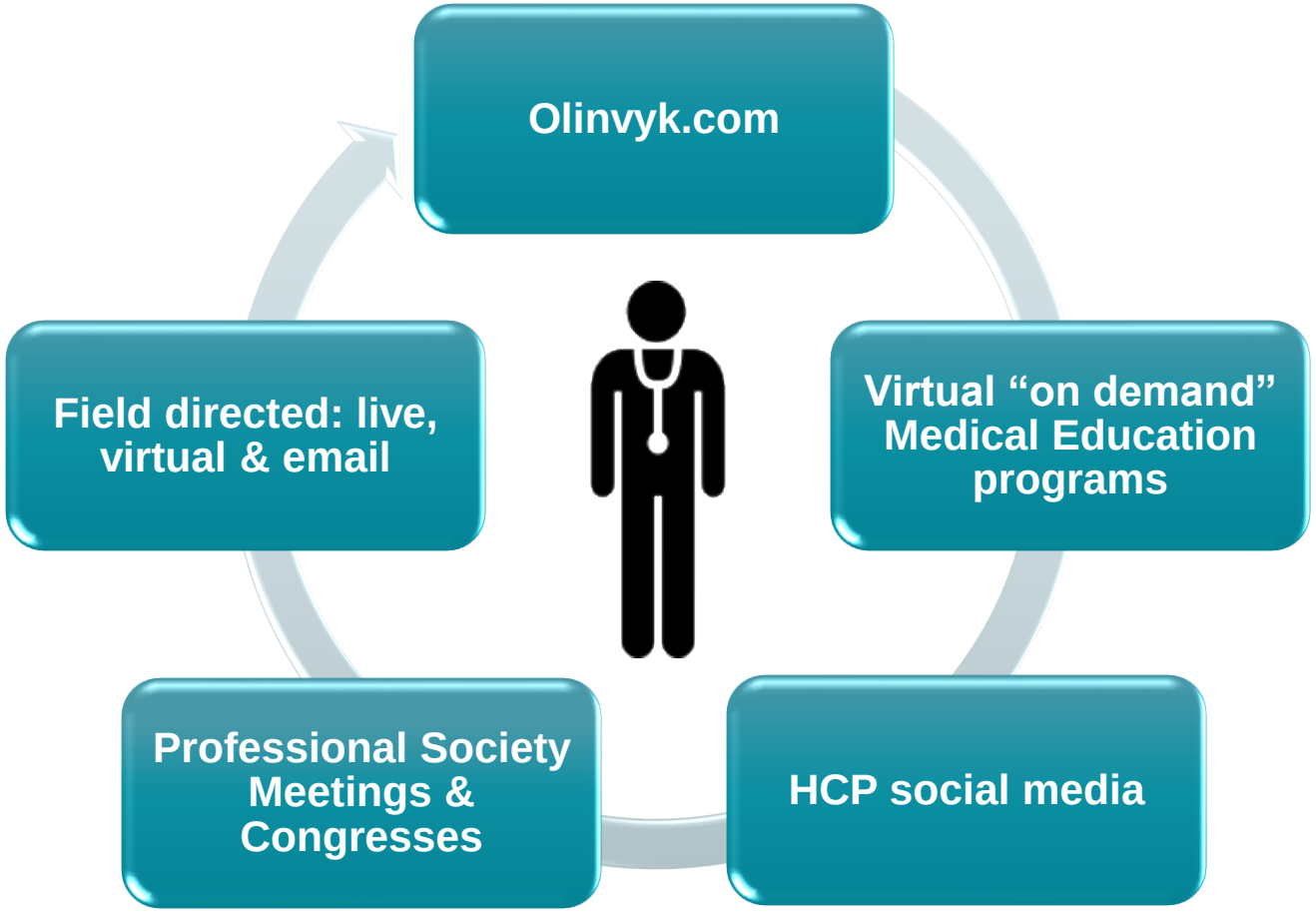
1) Qualitative Pricing research, Charles River Associates, April 2020. 2) "Are the improvements in respiratory safety events and GI tolerability clinically meaningful?" Based on OLINVYK Ph3 clinical trial data.

Omni-channel Approach for HCP Engagement

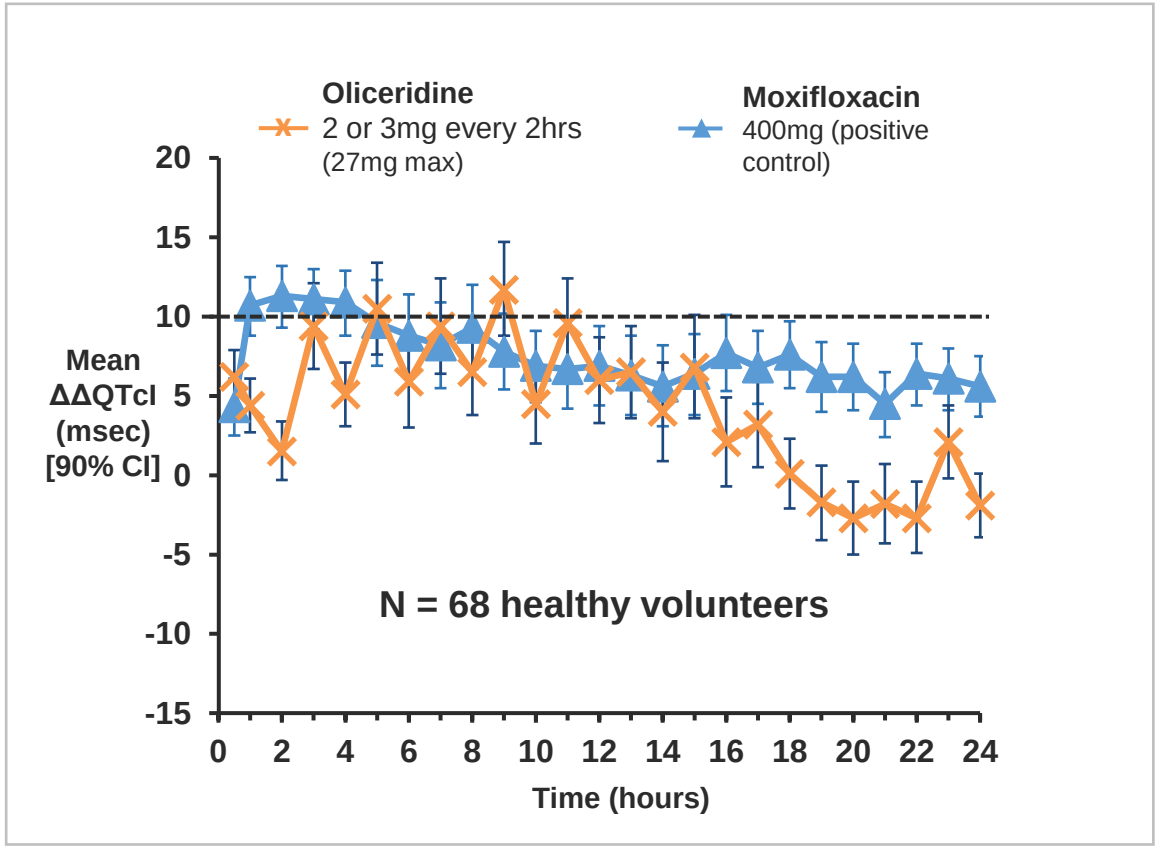
Communication across a full range of channels to maximize reach and impact

Customize mix across channels



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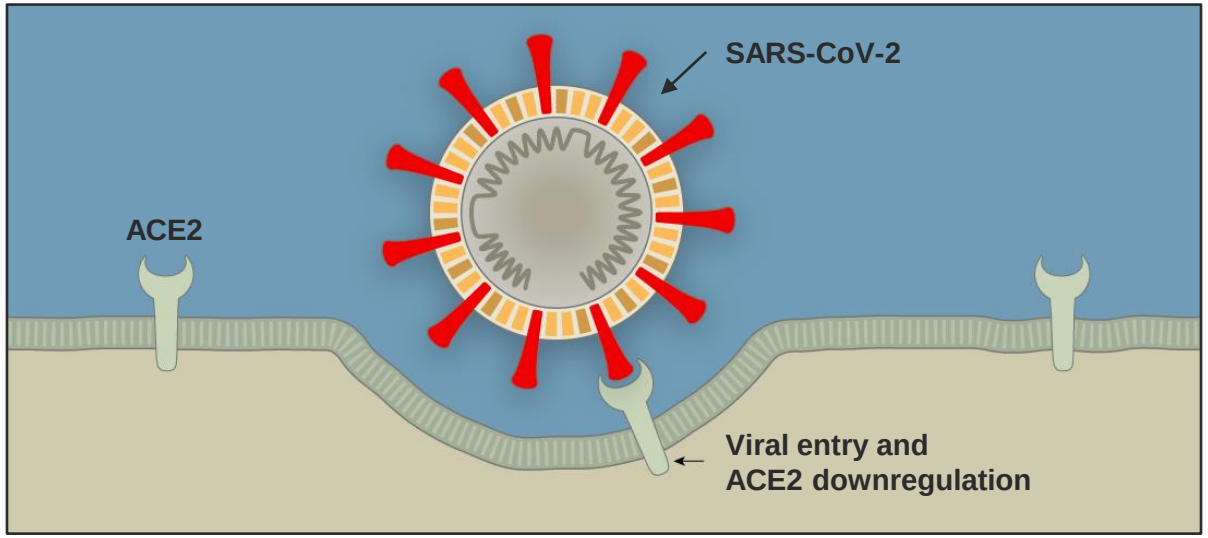
3 subjects not dosed due to lack of venous access: 1 discontinuation due to a non-serious adverse event (asymptomatic non-sustained ventricular tachycardia) with confounding hypokalemia and no meaningful QT prolongation during dosing, 1 subject completed dosing but not evaluable due to equipment malfunction

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]



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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

Trevena®

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.