

A photograph of an older couple walking away from the camera in a park. The woman is on the left, wearing a white t-shirt and blue jeans. The man is on the right, wearing a light blue button-down shirt and khaki shorts, pushing a blue bicycle with a basket. The background is a lush green park with trees and a path.

 **Trevena**[®]
INNOVATING FOR PATIENTS

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



Mark A. Demitrack, M.D.

SVP, Chief Medical Officer



Patricia Drake

SVP, Chief Commercial Officer



Barry Shin

SVP, Chief Financial Officer



PiperJaffray

Robert T. Yoder

SVP, Chief Business Officer & Head of Commercial Operations



BOARD OF DIRECTORS

Leon O. Moulder, Jr. Chairman



Marvin H. Johnson, Jr.



Carrie L. Bourdow



Jake R. Nunn



Scott Braunstein, M.D.



Anne M. Phillips, M.D.



Michael R. Dougherty



Barbara Yanni



Trevena: Innovative CNS Company



IV OLINVYK: Differentiated profile

NCE approved for the management of acute pain in adults
Launch in Q1 2021; additional supportive studies vs. IV morphine with near-term data



Large market, targeted launch

45M+ US hospital patients; 9M procedures is initial core focus
\$1.5B+ market opportunity for core focus



TRV045: Selective S1PR modulator

Novel candidate for diabetic neuropathic pain (with potential broader applicability)
Phase 1 study completed; proof-of-concept study planned for early 2023



Novel CNS pipeline

New mechanisms for acute / neuropathic pain, epilepsy, acute migraine, opioid use disorder
NCEs targeting significant unmet needs



Solid financial position

\$40.4M cash / equivalents / marketable securities @ Q3
Funds operations into 3Q 2023

OLINVYK is indicated in adults for the management of acute pain severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate. Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.
NCE = New Chemical Entity; MOA = Mechanism of Action; NIH = National Institutes of Health;

Multiple Expected Catalysts

	PRE-CLIN	PHASE 1	PHASE 2	PHASE 3	NDA	POST-APPR	EXPECTED CATALYSTS
OLINVYK® New chemical entity (mu-opioid receptor)	IV acute pain*					APPROVED	<ul style="list-style-type: none"> Commercial launch ongoing
				Leiden UMC collab.		Respiratory physiology	<ul style="list-style-type: none"> Topline data released March 2022
			Center for Human Drug Research, Leiden			Cognitive function	<ul style="list-style-type: none"> Topline data released July 2022
			Cleveland Clinic / Wake Forest Baptist Health collab.			Clinical outcomes	<ul style="list-style-type: none"> Enrollment complete 2H 22
					Nhwa NDA Submission in China		<ul style="list-style-type: none"> NDA Submitted
TRV045 Selective S1P receptor modulator	DNP						<ul style="list-style-type: none"> Phase 1 complete
		Epilepsy	NIH collab.				<ul style="list-style-type: none"> Epilepsy data announced
TRV250 G-protein selective agonist (delta receptor)	Acute migraine						<ul style="list-style-type: none"> IND-enabling activities (oral)
TRV734 G-protein selective agonist (mu-opioid receptor)	Opioid use disorder		NIH / NIDA collab.				<ul style="list-style-type: none"> POC study ongoing

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

Ex-US Royalty-Based Financing Highlights

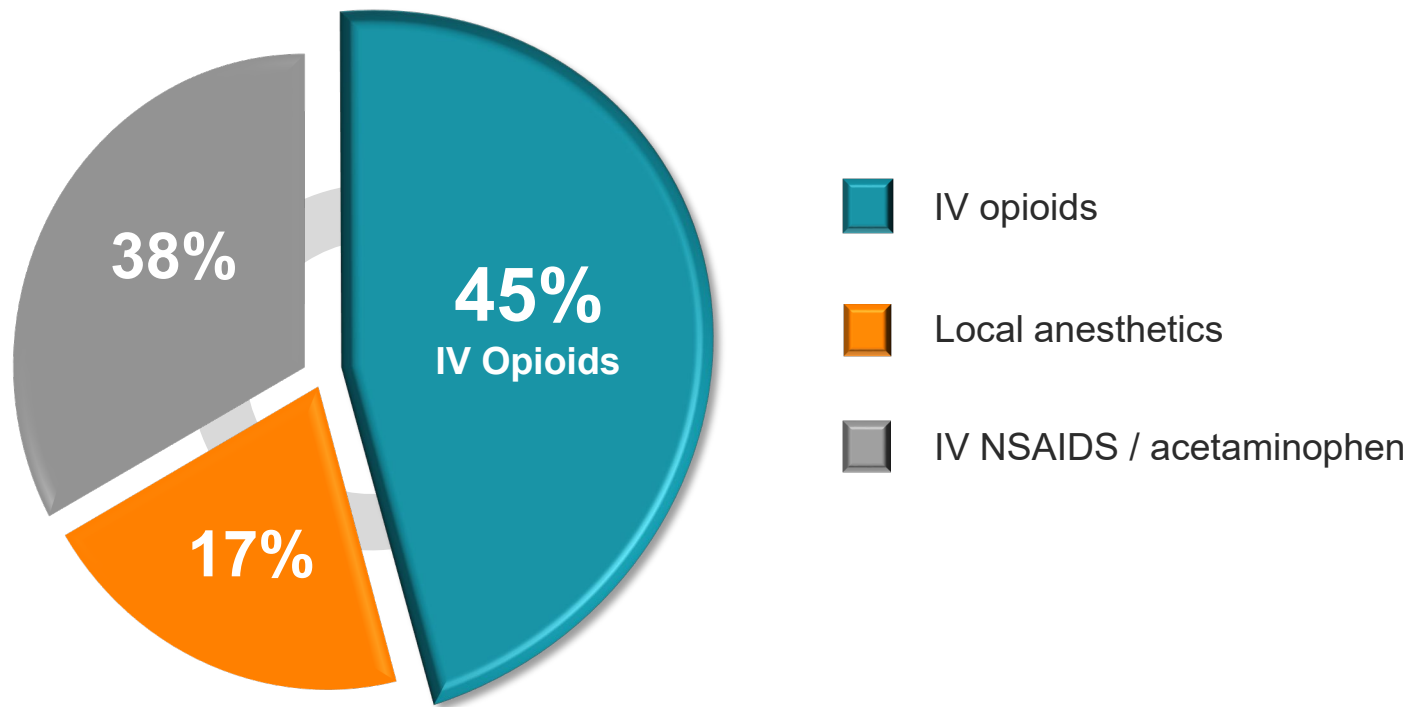
Blue Chip Investor	<p>R-Bridge Healthcare Fund affiliate of CBC Group (one of the largest and most active healthcare-dedicated investment firms in Asia)</p>
\$40M Total Financing	<p>\$15M upfront (received April 2022) \$10M on commercial or financing milestone \$15M on first commercial sale in China <hr/> \$40M total</p>
Flexible Payments*	<ul style="list-style-type: none"> • Chinese Royalties. All royalties from Nhwa partnership, TRVN retains milestones • Capped US Royalty. 4% royalty on US OLINVYK net sales, with \$10M cap**
Constructive Terms	<ul style="list-style-type: none"> • No financial covenants • Negative pledge only until Chinese approval • Flexibility for additional business development opportunities

* R-Bridge will receive a 1.5% fee and warrants for 5M shares at a strike price of \$0.82 / sh (75% premium to 30-day VWAP)

**Potential increase to 7% (with combined US/China cap) if not approved by YE-23

Large Market Opportunity – Acute Pain

US injectable analgesic hospital market unit volume¹



45M patients receive IV opioids annually to treat acute pain¹

IV opioids have unrivalled analgesic efficacy

Top surgeries:
Total knee arthroplasty,
colectomy, hernia repair,
spine fusion, C-section²

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

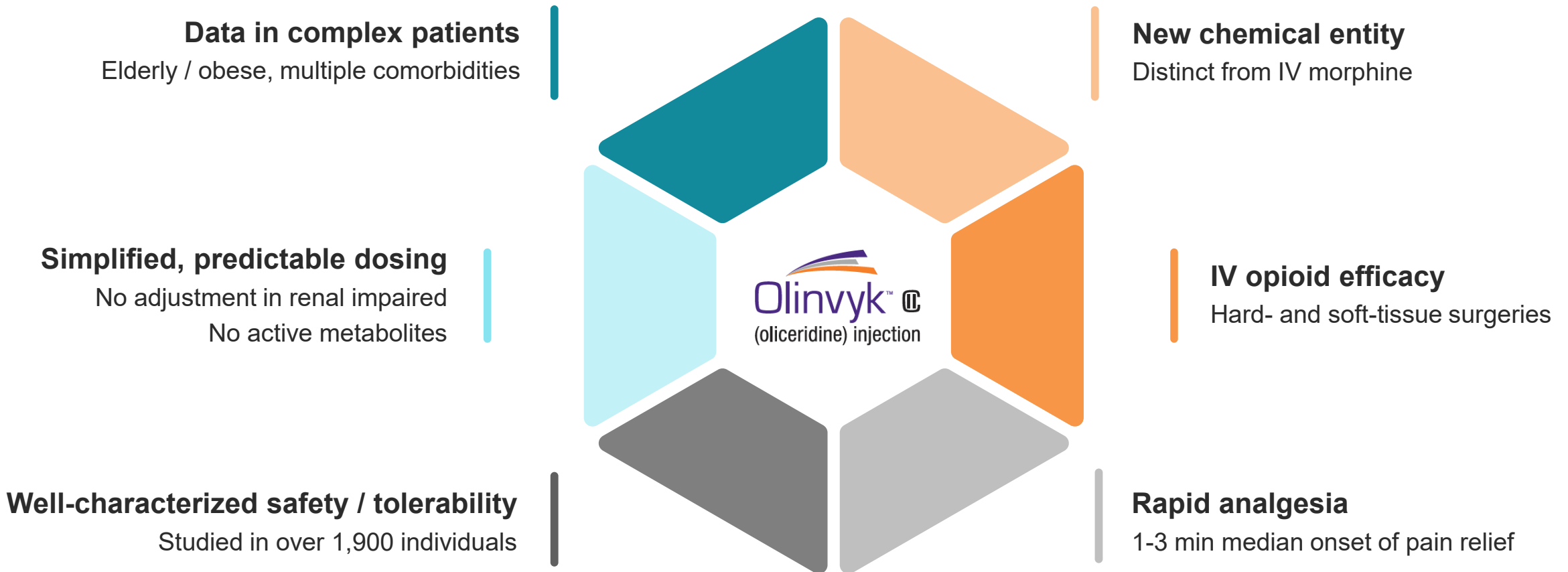
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

Opioids are associated with serious, potentially life-threatening adverse reactions.

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

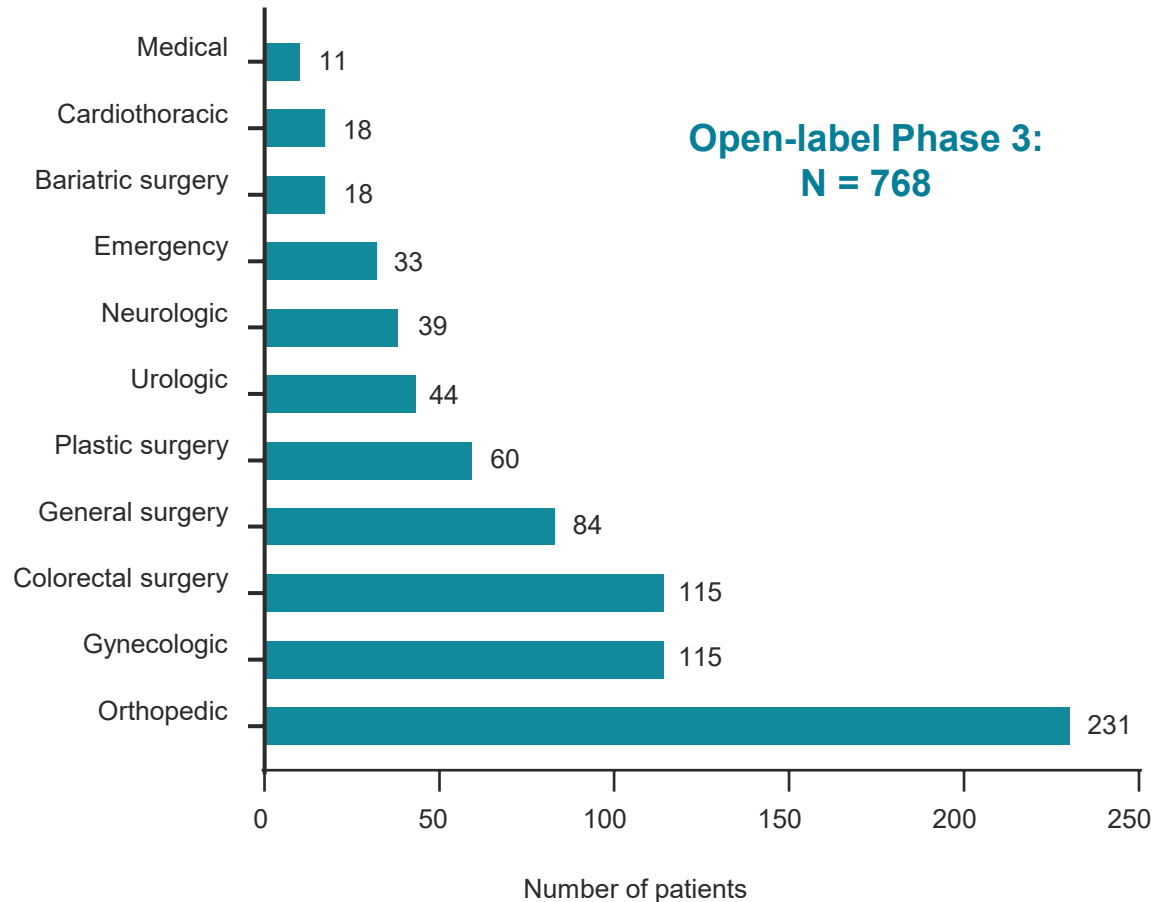
OLINVYK: Differentiated Profile for Acute Pain

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



OLINVYK Studied in Complex Surgeries & Patients

Broad range of surgeries / medical procedures



Complex patients included

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

Multiple inpatient and hosp outpatient settings

- Hospital recovery
- Emergency department
- Critical care
- Ambulatory surgical centers

Low discontinuation for AEs / lack of efficacy

- 2% for adverse events
- 4% for lack of efficacy

OLINVYK: Well-Characterized Safety / Tolerability

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

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

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

Key cost-drivers associated with IV opioids:

Vomiting

Can result in significant health risks and compromise recovery

Somnolence

Significant patient safety concern, can lead to respiratory depression

O₂ saturation < 90%

Independent predictor of early post-op respiratory complications

Respiratory Physiology Study

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

Assessment of Respiratory Function:

- Increase inhaled CO₂ to experimentally induce respiratory drive
- Impact of drug measured as change in minute ventilation
- Greater reductions in minute ventilation indicate more respiratory depression
- Validated method to estimate the impact of a drug on respiratory drive



Ventilatory Response to Hypercapnia

Assessment of Pain Threshold:

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

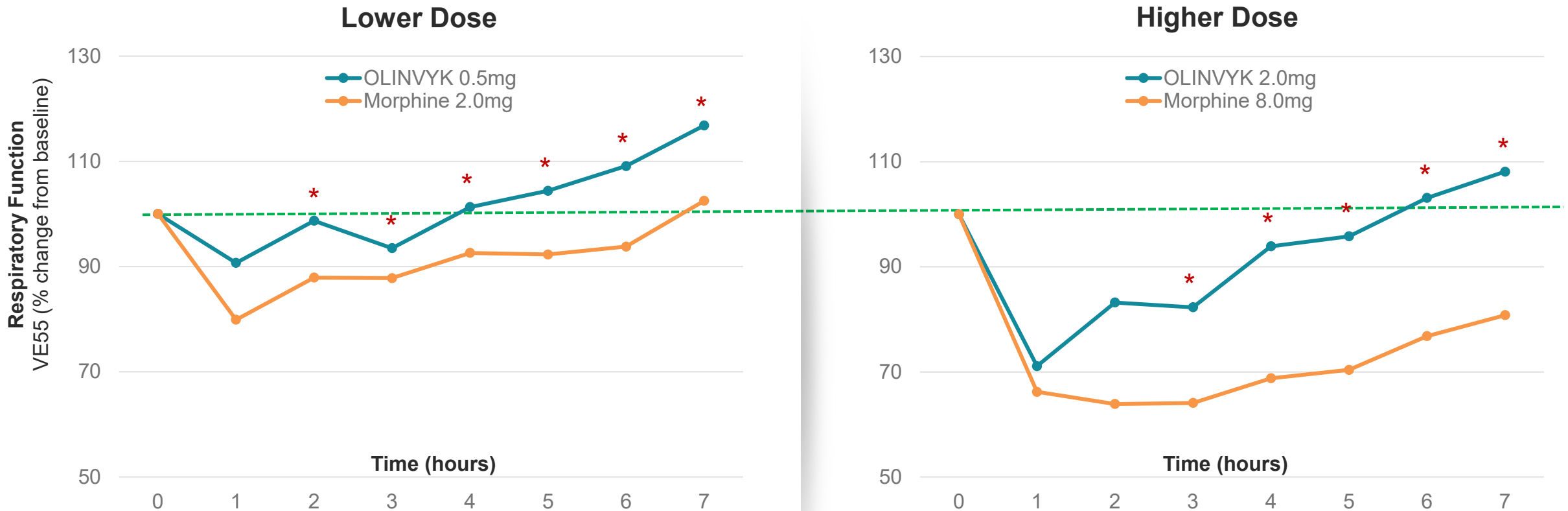


Analgesia Assessment

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

Respiratory Physiology Study: Elderly / Overweight Subjects

OLINVYK demonstrated reduced impact on respiratory function vs IV morphine



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

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

Respiratory Physiology Study Observations

- Study population comprised elderly individuals (56 to 87 years, mean = 71.2) with BMI ranging from 20 to 34 (mean = 26.3)
- Both OLINVYK and IV morphine achieved comparable levels of pain relief. A statistically significant reduced impact on respiratory function was observed in patients treated with OLINVYK as measured by the mean respiratory ventilation profiles over time ($P < 0.0001$)
- The study replicates the results from the earlier study in younger subjects using a similar methodology¹. The findings extend our knowledge to patients who are at higher risk for the development of respiratory depression with the use of opioids, namely the elderly and overweight patients

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

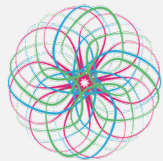
¹. Soergel DG, et al. *Pain*. 2014;155:1829-1835

Top Line Data: OLINVYK vs IV Morphine Cognitive Function Study

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

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

Cognitive function assessment: NeuroCart



CHDR
Centre for Human Drug Research

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

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

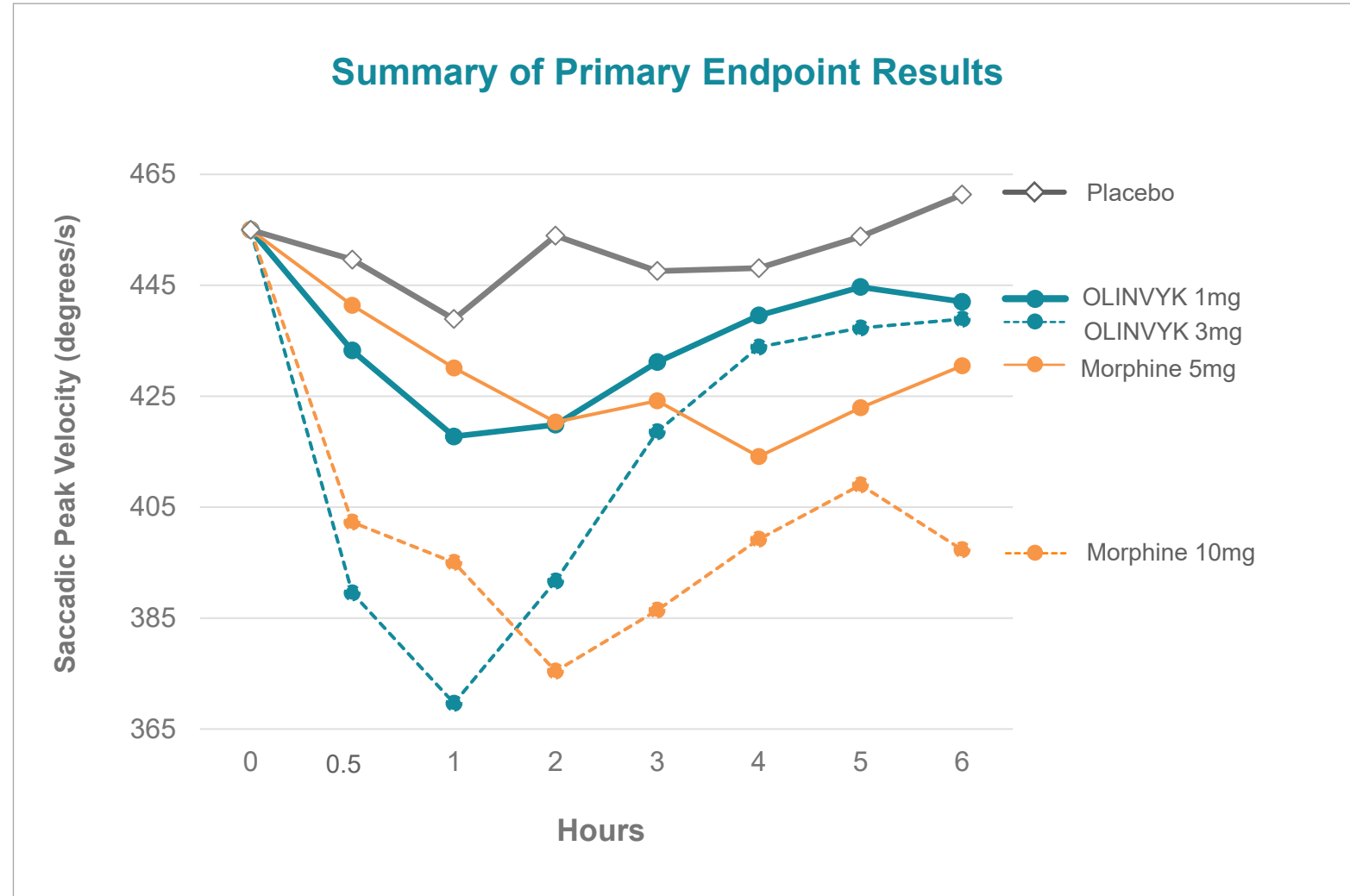
OLINVYK Showed Evidence of Reduced Impact on Neurocognitive Function Compared to IV Morphine

OLINVYK showed a statistically significant reduction in sedation versus IV morphine

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

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

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



Secondary Endpoint Results

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

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

OLINVYK Safety Outcomes Study w/ Cleveland Clinic

Further characterizes potential respiratory, GI and cognitive outcomes

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

Respiratory Safety



**Predefined capnography
and oximetry measures**

Assessment via continuous
respiratory monitoring

GI Tolerability



**Complete GI response
endpoint**

No vomiting and no antiemetic use
through study period

Cognitive Function



**Somnolence, delirium,
and sedation**

Validated, standardized
assessment scales

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

OLINVYK: Ease of Dosing and Administration

3 vials allow for flexible and tailored IV dosing

- **Bolus Dosing:** 1 mg and 2 mg vials (single dose)
- **PCA Dosing:** 30 mg vial (single patient use)
- **OLINVYK 1 mg \approx morphine 5 mg¹**

27 mg cumulative daily dose limit

Do not administer single doses greater than 3 mg

No refrigeration / reconstitution



1 mg / 1mL

WAC:

\$17.50



2 mg / 2mL

\$25.75



30 mg / 30 mL

\$110.00

~\$100 / day

(estimated avg cost across procedures)

OLINVYK vs IV Morphine Health Economic Models

Published¹ and available to formulary committees

Representative Inputs:

AE rates*

Ph3 trials

Placebo (N = 162)	OLINVYK ≤ 27 mg (N = 516)	Morphine (N = 159)
73	86	96
35	52	70
10	26	32
30	26	30
11	18	25
9	14	14
3	12	17
8	9	19
5	7	15
4	6	10
4	6	6
4	4	8
1	2	10

Vomiting
Somnolence / sedation
O₂ saturation <90%

Cost of AEs

Gov't sources /
Publications

\$8k nausea / vomiting²
\$28k critical resp event³
+7 days hospital stay³

Drug cost



OLINVYK
IV morphine

HECON
model



Key Outputs:

>10x

Cost savings
for hospitals⁴

Due to improved
patient outcomes

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

1) Simpson KN, et al., J Comp Eff Res, 2021; 10:1107-1119 and Simpson KN, et al. Expert Rev Pharmacoecon Outcomes Res; 2022

2) Oderda, GM, J Pain Palliative Care Pharm, 2019; data based on 5 surgical procedure categories including Cardiothoracic / vascular, General / Colorectal, Ob / Gyn, Orthopedic, and Urologic. 3) Overdyk FJ, PLoS One, 2016. More conservative inputs were used in the model. 4) Calculated based on total costs of Tx and average total costs of care. Image: flaticon.com.



Customer Engagement Strategy

Targeted Account Launch

Health Care Practitioners (HCPs)

Anesthesiology, Colorectal, Critical Care physicians

Targeted Accounts

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

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

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

Expanded Targets: ~150 Burn Center Accounts

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

Targeted market opportunity

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

Key considerations

Need for rapid, long-lasting acute pain relief

Many patients have renal injury

Need to avoid dose-stacking

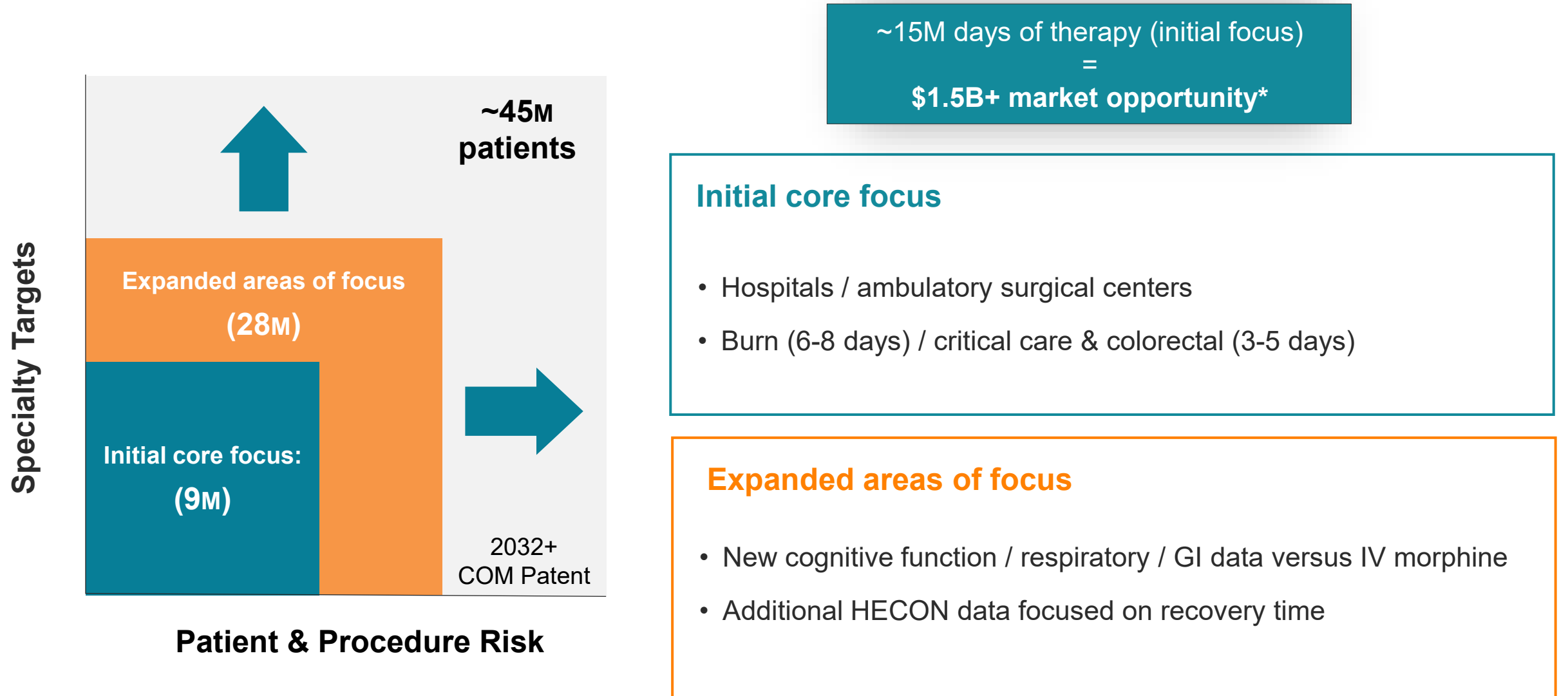
OLINVYK attributes

1-3 minute onset of action
~3 hour duration

No dose adjustment for patients with renal impairment

No active metabolites

OLINVYK: Significant Opportunity in Acute Pain Market





TRV045
S1P Receptor Modulator
Novel MOA for Diabetic Neuropathic Pain

TRV045: Novel MOA for CNS Indications

Selective S1P₁R modulator with no lymphopenia – Phase 1 study complete

S1P₁ receptors are highly expressed on key CNS cell targets (astrocytes) involved in the perpetuation of neuroinflammation
Potential therapeutic role in seizures, epileptogenesis and pain signaling

Epilepsy

- Neuroprotective effects³
- Modulates permeability of BBB, anti-inflammatory effects^{4,6}



Neuropathic pain

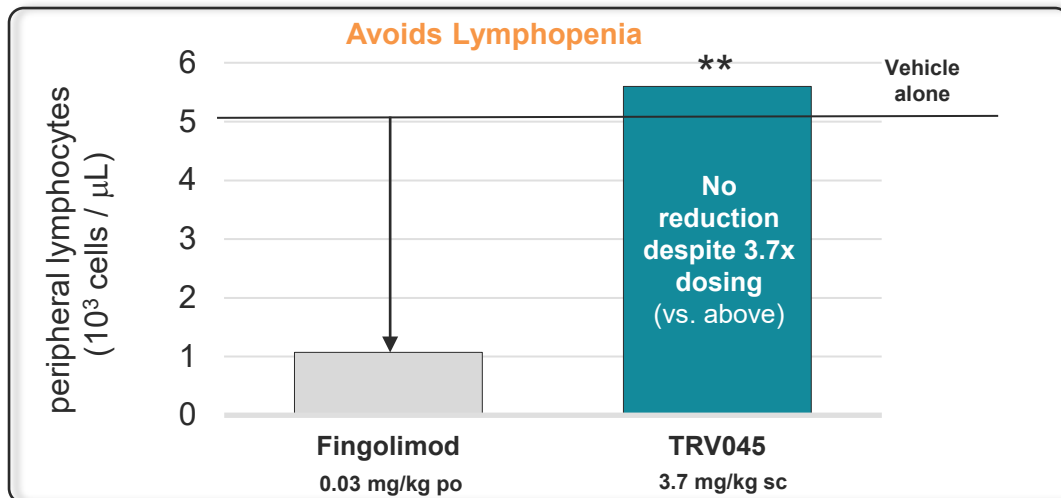
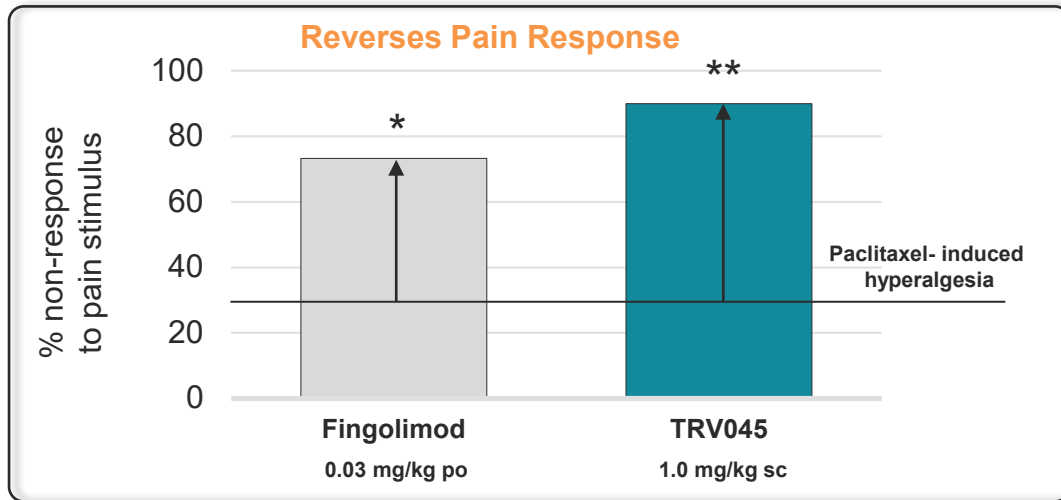
- Inhibits pain sensation¹
- Inhibits excitatory neuronal signaling²



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

Potential to also avoid known safety issues associated with S1P receptor subtypes 2, 3, 4, 5:
Including pulmonary, cardiac, and cancer-related effects⁵

TRV045: Novel MOA, Selective S1PR



- In animals, TRV045 reversed neuropathic pain without immune-suppressing activity¹
- Novel mechanism with broad potential for CNS indications
 - Phase 1 study completed
 - Targeted proof-of-concept study planned for early 2023

TRV045 Phase 1 Study – Safety / Tolerability / PK

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

Well Tolerated

- Favorable tolerability profile with no SAEs

Target Exposure

- Calculated free plasma concentrations exceeded targeted efficacy range¹

Attractive PK Profile

- Half-life consistent with anticipated once-daily dosing

Highly Differentiated

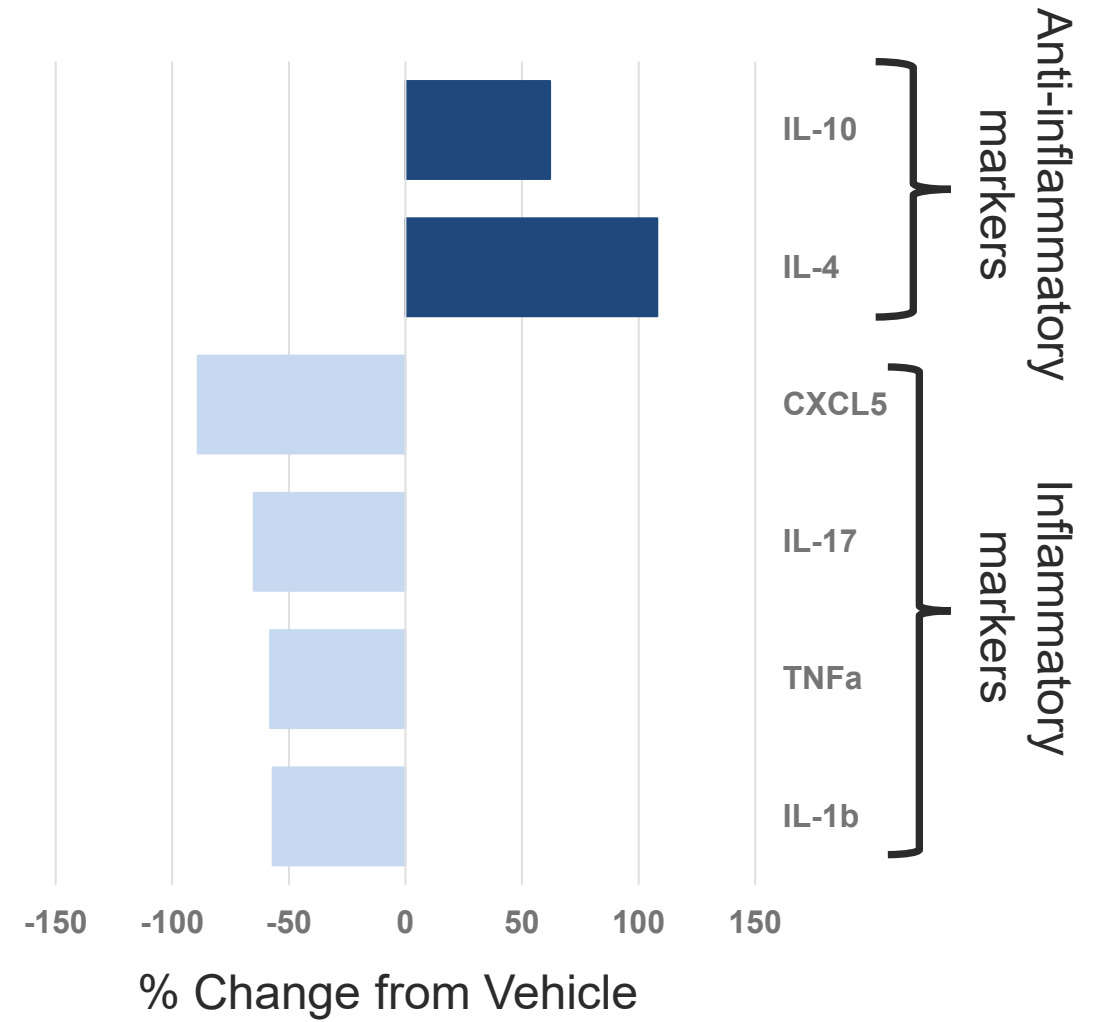
- No lymphopenia and no reported cardiac / pulmonary / ophthalmologic AEs (AEs commonly associated with currently marketed S1P-targeted compounds)

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

Effect of TRV045 on Cytokine / Chemokine Release

Anti-inflammatory actions on astrocytes in cell culture

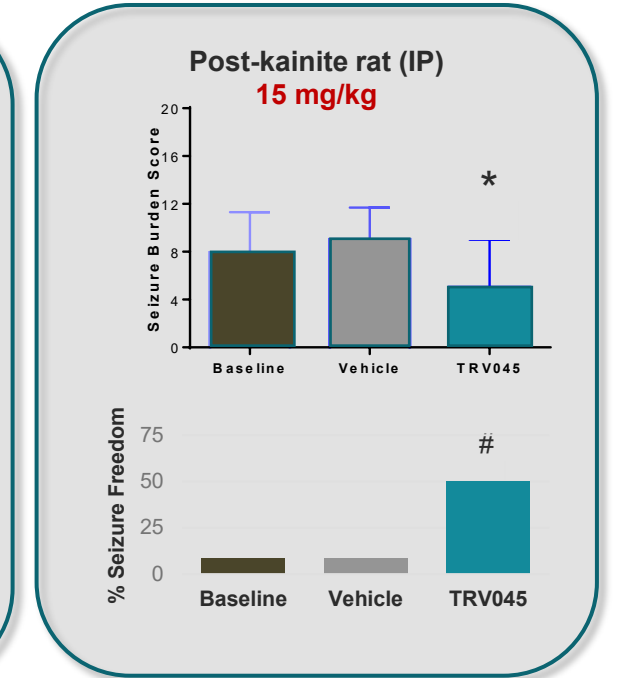
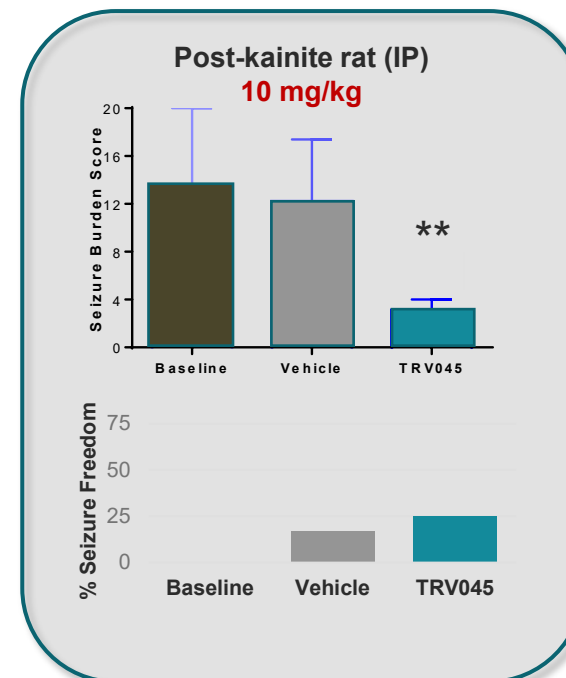
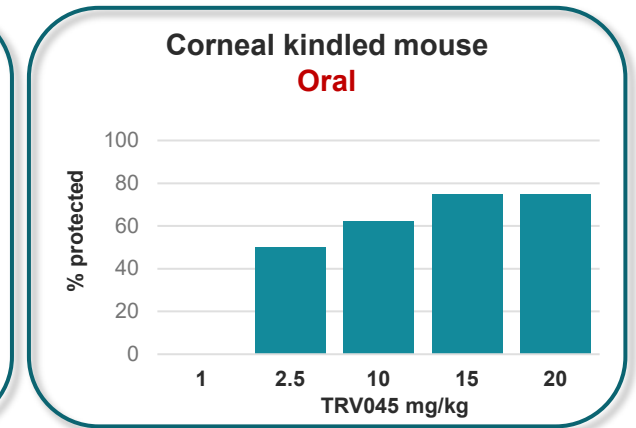
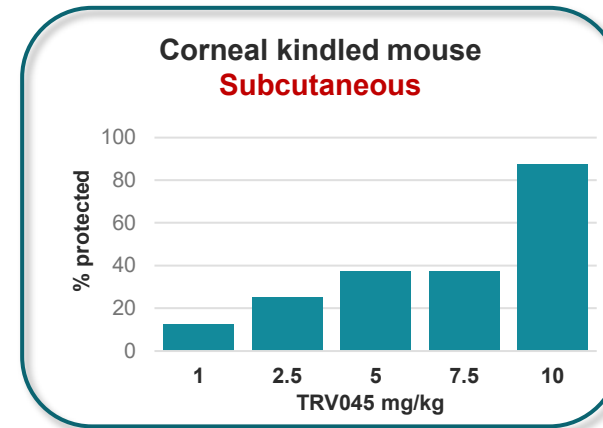
- Methods:
 - Primary mouse astrocytes in monolayer cell culture; incubated for 24 hrs w/ 5 μ M TRV045
 - Panel of 17 cytokines / chemokines * assessed by ELISA
- Main Findings:
 - Net anti-inflammatory action on astrocyte cytokine / chemokine release in culture
 - Increase in release of all anti-inflammatory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



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

TRV045 Demonstrates Efficacy in Nonclinical Epilepsy Models

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





**TRV250: New MOA for Acute Treatment
of Migraine**

**TRV734: Maintenance Therapy for
Opioid Use Disorder**

TRV250: New MOA for Acute Treatment of Migraine

Delta receptor: Untapped potential in CNS space

Migraine represents a large market opportunity; total migraine drug market = ~\$3.5B

Delta receptors have
unique distribution
throughout the brain

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

Every year in the US¹:



**650M migraines
treated each year**



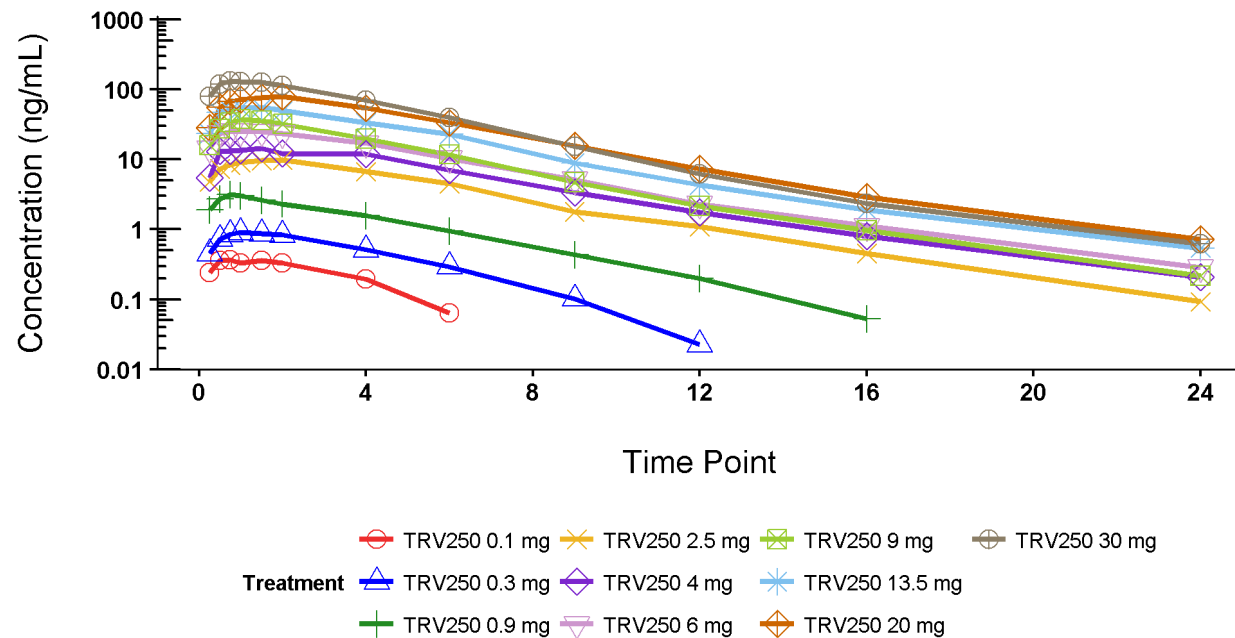
**1.2M ER visits
due to migraines**

- **20-30%** of migraine sufferers do not respond to / cannot tolerate the market-leading triptan drug class
- Approx. **50%** of migraineurs also suffer from anxiety²

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

TRV734: Maintenance Therapy for Opioid Use Disorder

Selective agonism at μ receptor: nonclinical evidence of improved tolerability

Ongoing collaboration with National Institute on Drug Abuse (NIDA)

NIDA study demonstrated reduced drug-seeking behavior in animal model of relapse²

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



>2.5M
people in
U.S. suffer from
opioid use disorder¹

Trevena: Innovative CNS Company



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\$1.5B+ market opportunity for core focus



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New mechanisms for acute / neuropathic pain, epilepsy, acute migraine, opioid use disorder
NCEs targeting significant unmet needs



Solid financial position

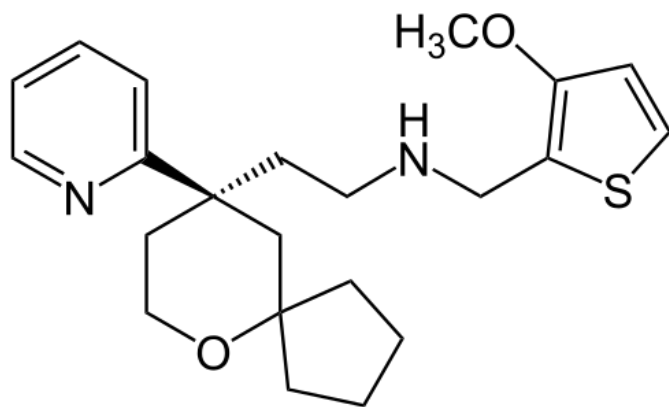
\$40.4M cash / equivalents / marketable securities @ Q3
Funds operations into 3Q 2023

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

Appendix

OLINVYK: Distinct From IV Morphine / Hydromorphone

OLINVYK



Studied in >1,900 individuals

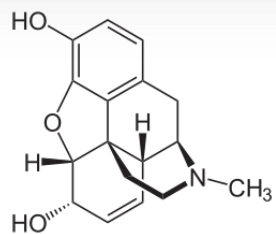


IV morphine included as active comparator

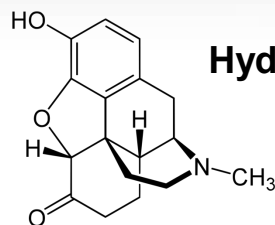


NCE with
2032+ COM patent¹

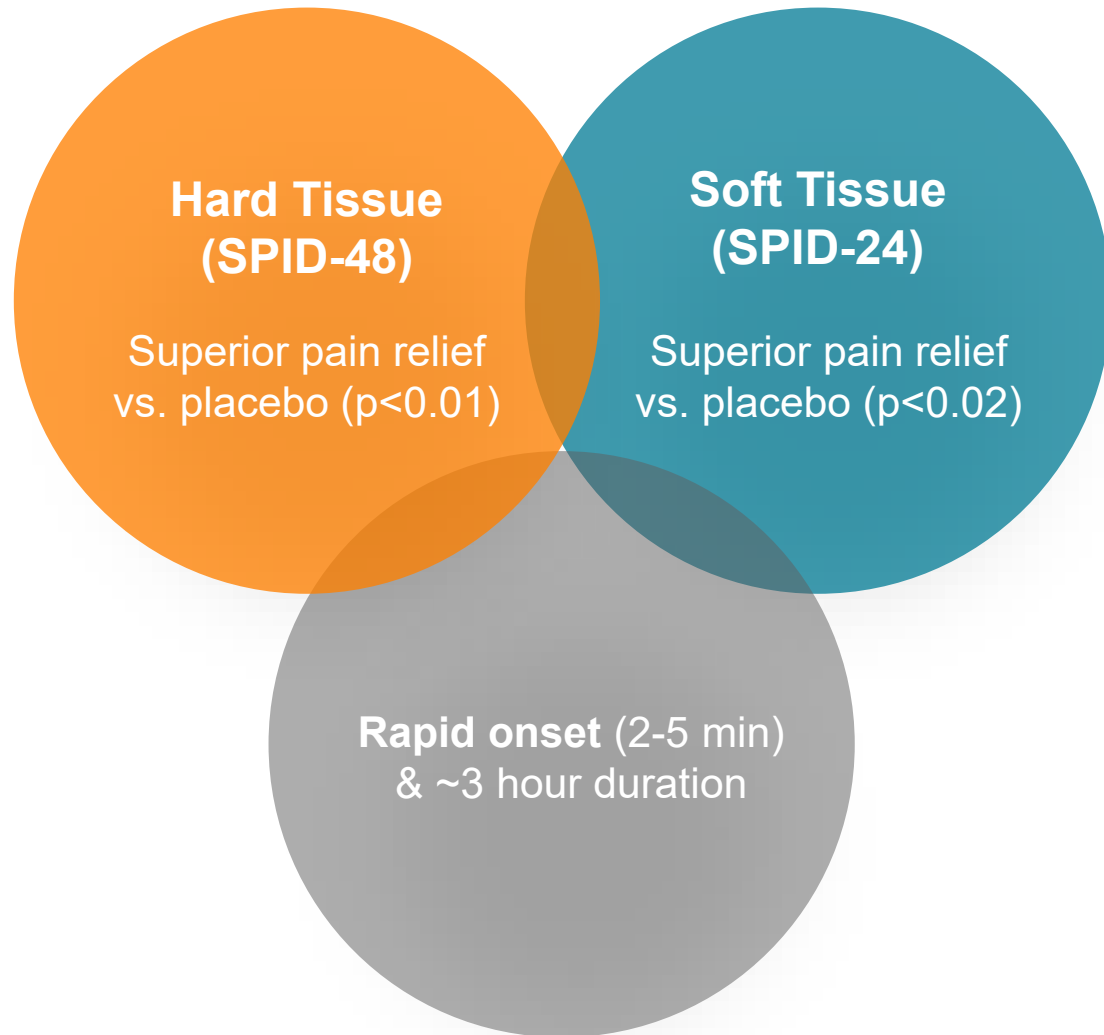
Morphine



Hydromorphone



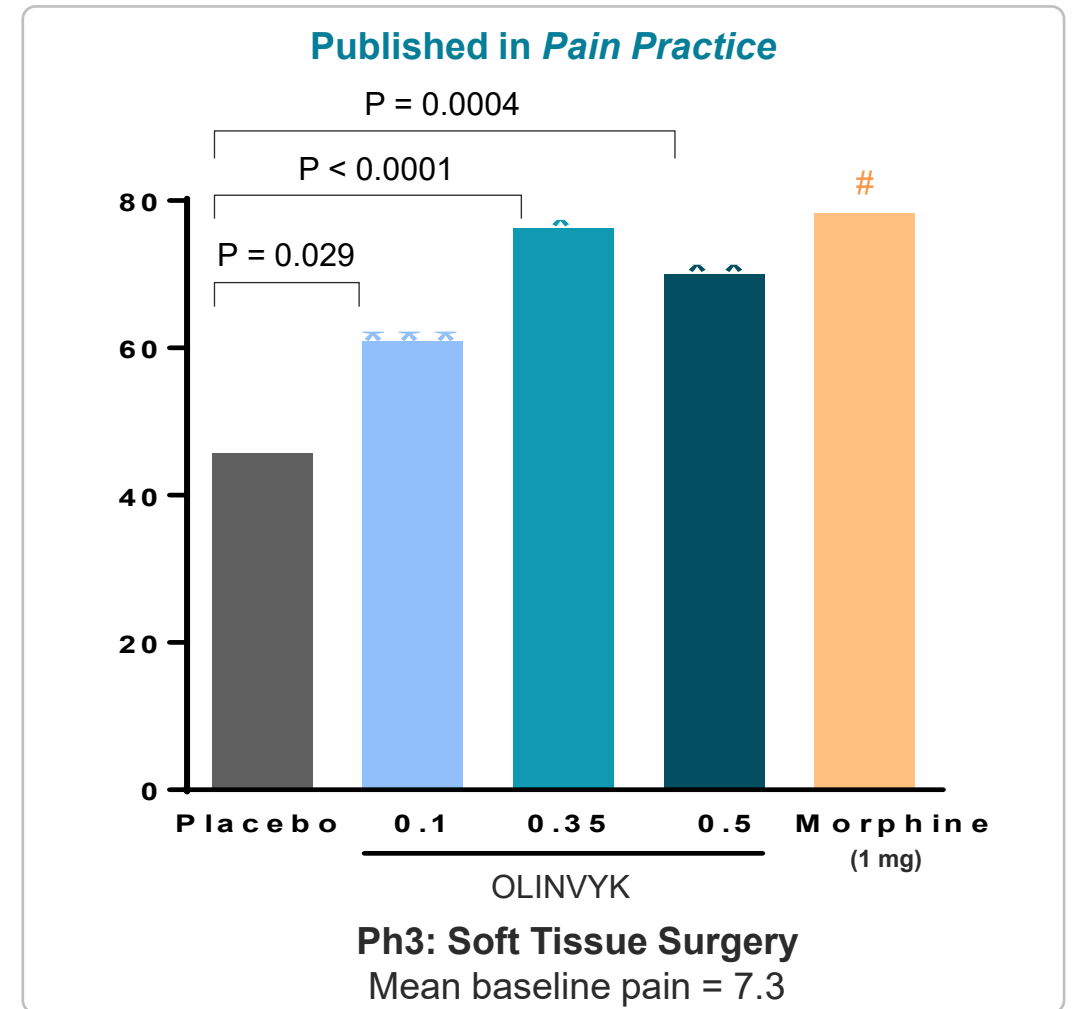
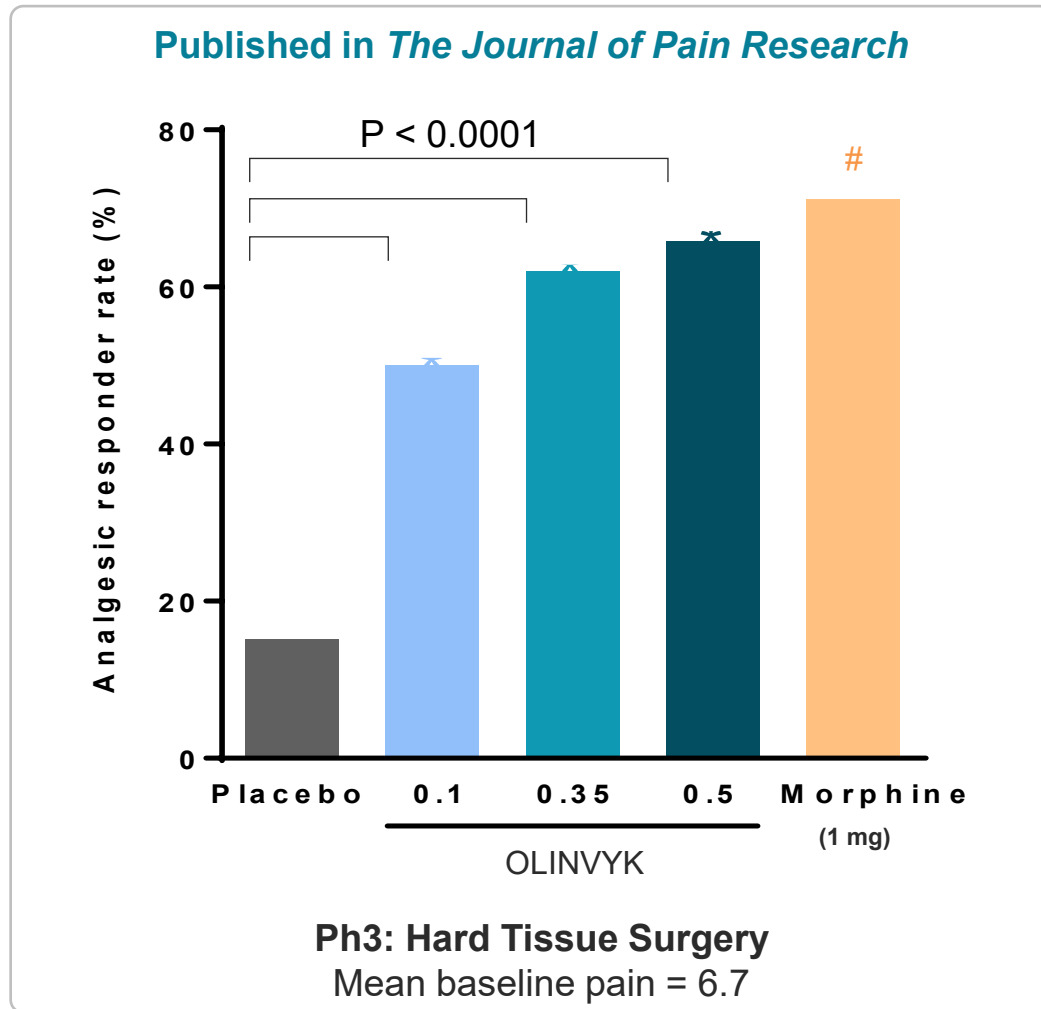
OLINVYK: IV Opioid Efficacy and Rapid Onset



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

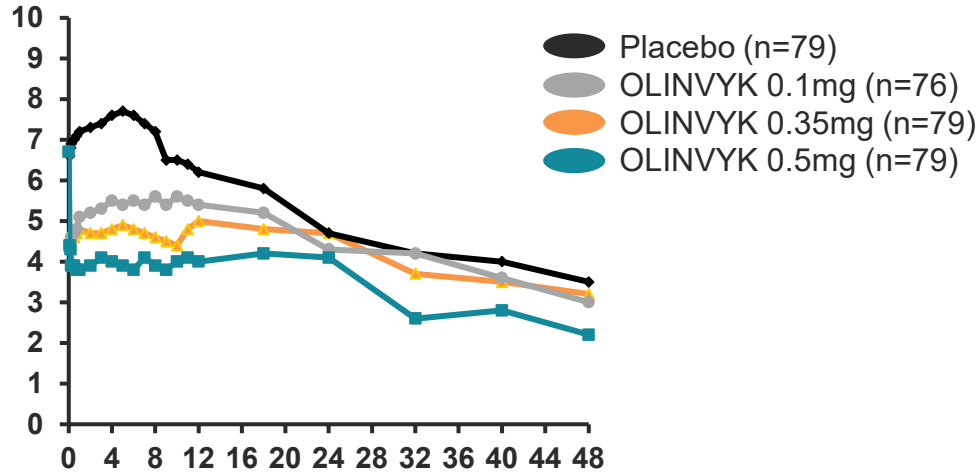
Primary Efficacy Endpoint Achieved in Two Pivotal Studies

OLINVYK achieved IV opioid efficacy



OLINVYK: IV Opioid Efficacy in 2 Phase 3 RCTs

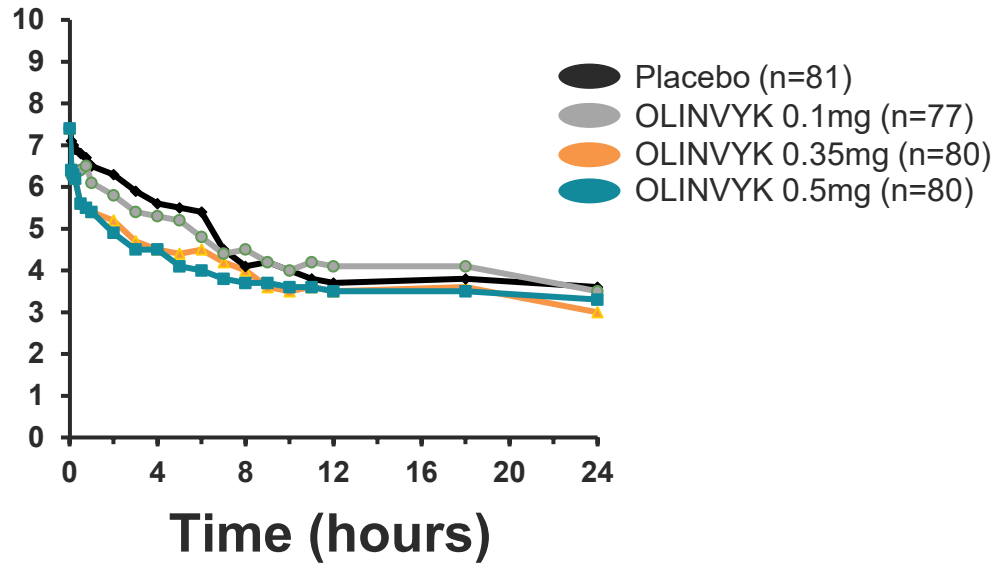
Average NRS Pain Score



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

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



Study 2 (Plastic Surgery – Soft Tissue)

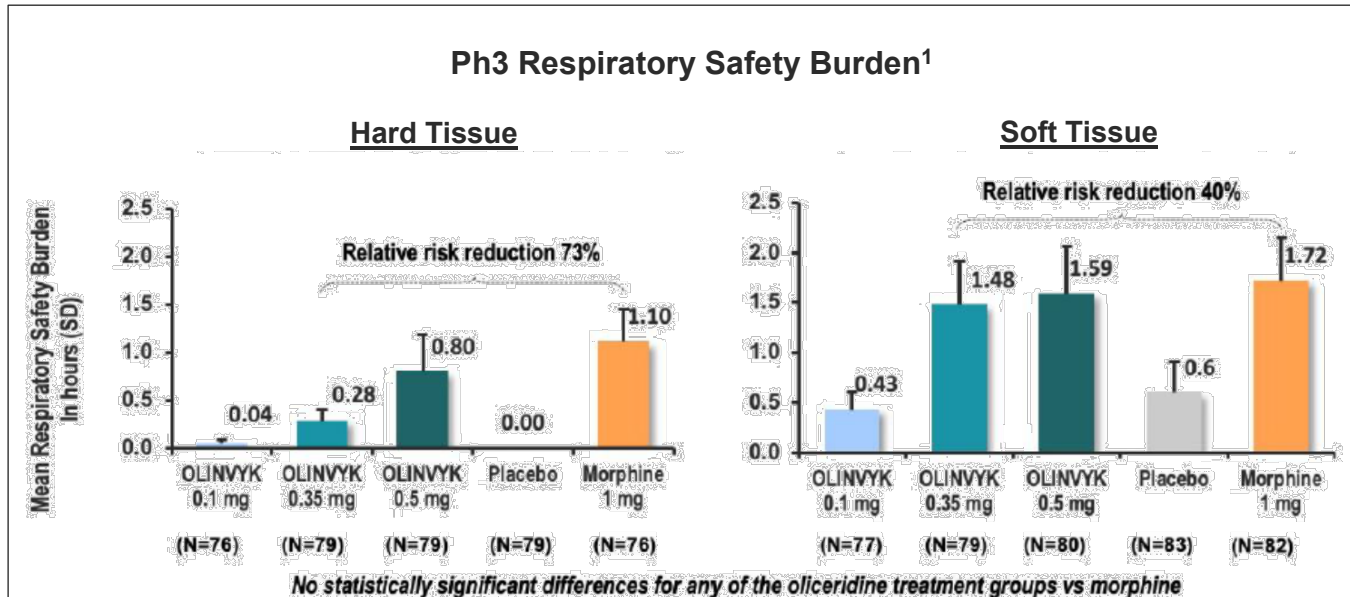
3 PCA regimens studied (0.1, 0.35, 0.5 mg) vs. placebo;
0.35 / 0.5 mg doses P<0.02 vs. placebo

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

Robust Assessment of Respiratory Safety in Phase 3 RCTs

Data included in AMCP dossier used in formulary review

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



Ph3 Respiratory Safety Events² (Components of the RSB calculation)

Hard Tissue

Orthopedic Surgery-Bunionectomy Study	Placebo (N=79)	Demand Dose OLINVYK			Morphine 1 mg (N=76)
		0.1 mg (N=76)	0.35 mg (N=79)	0.5 mg (N=79)	
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			Morphine 1 mg (N=82)
		0.1 mg (N=77)	0.35 mg (N=79)	0.5 mg (N=80)	
Components of the respiratory safety burden					
≥1 respiratory safety event, n (%)	5 (6.0)	6 (7.8)	17 (21.5)	18 (22.5)	22 (26.8)
Odds ratio vs morphine	0.15	0.19	0.61	0.68	-
P value vs morphine	0.0003	0.0007	0.20	0.32	-
Duration of event, mean hours (SD)	9.88 (7.0)	5.51 (1.91)	6.88 (5.66)	7.07 (6.56)	6.40 (5.09)
P value vs morphine	0.52	0.29	0.78	0.76	-
Respiratory safety event measures					
Oxygen saturation <90%, n (%)	7 (8.4)	6 (7.8)	15 (19.0)	16 (20.0)	20 (24.4)
P value vs morphine	0.02	0.01	0.57	0.76	-
Respiratory rate ≤8 bpm, n (%)	1 (1.2)	0	4 (5.1)	6 (7.5)	8 (9.8)
P value vs morphine	0.054	0.95	0.38	0.84	-
Sedation (MRPSS ≥3), n (%)	15 (18.1)	8 (10.4)	19 (24.1)	18 (22.5)	21 (25.6)
P value vs morphine	0.25	0.02	0.83	0.65	-

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

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

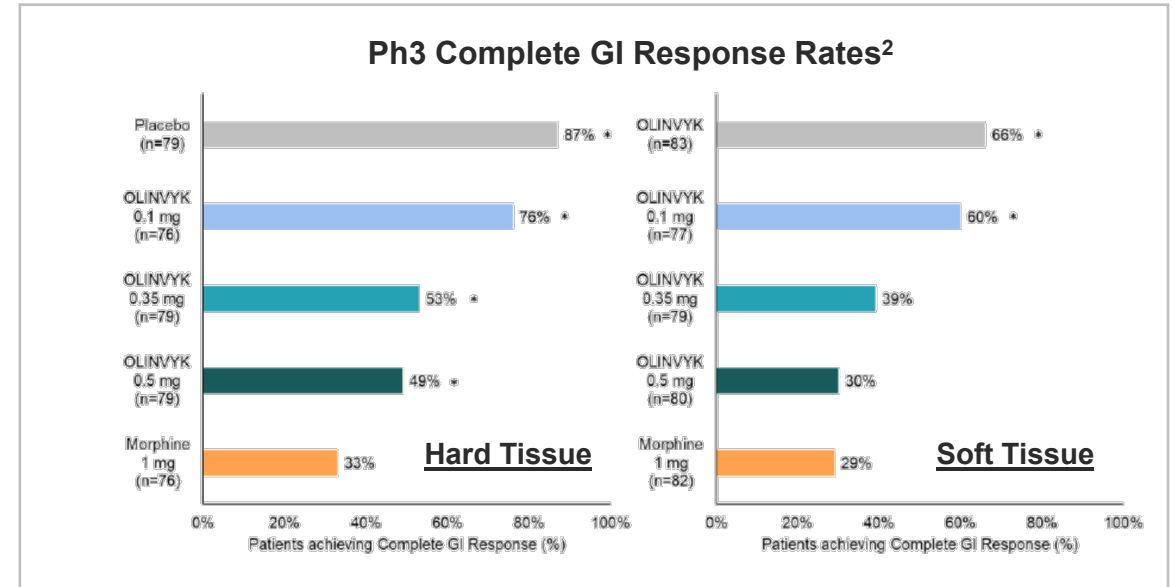
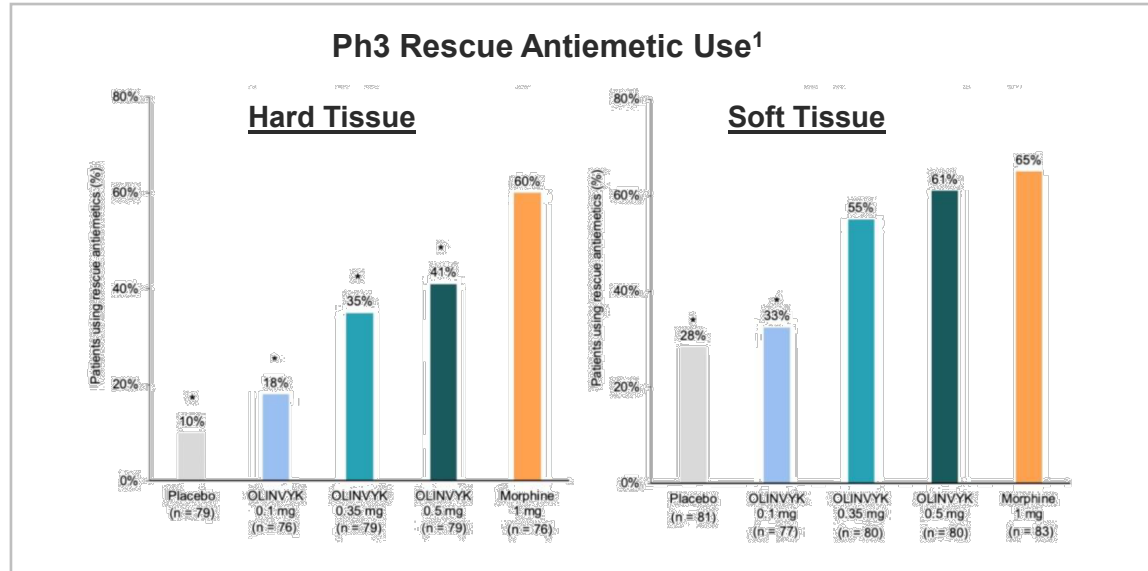


Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

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

Robust Assessment of GI Tolerability in Phase 3 RCTs

Data included in AMCP dossier used in formulary review

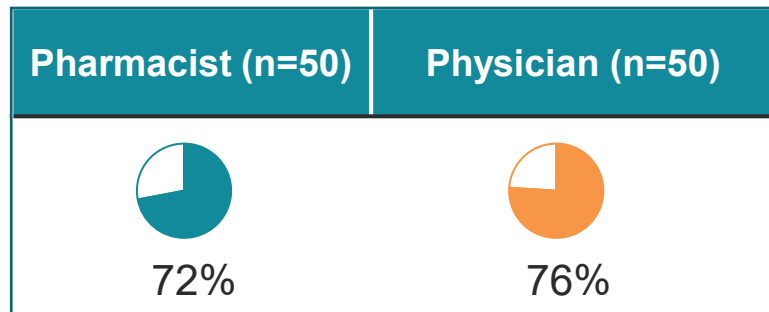


- Phase 3 pivotal trials included measurements of nausea / vomiting rates and rescue antiemetic use
- Additional exploratory post-hoc analysis was conducted using a “complete GI response” endpoint³
- Full characterization of GI tolerability has been made available to HCPs and formulary decision makers
 - Data can be found in OLINVYK AMCP dossier and published literature

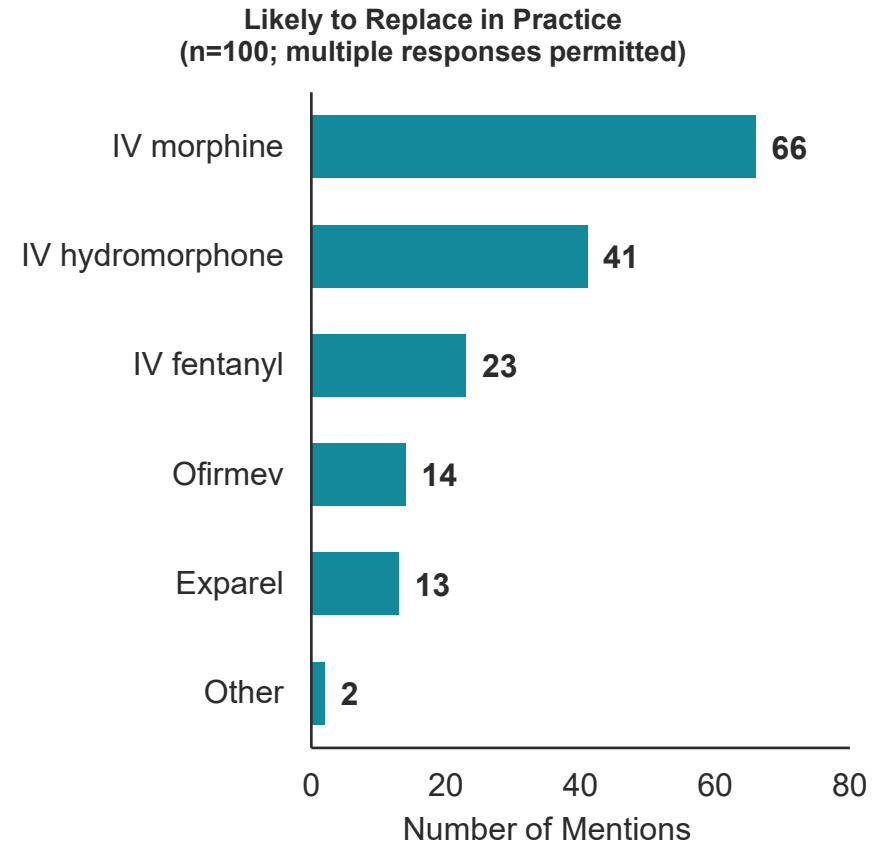
Please see Important Safety Information including BOXED WARNING at the end of presentation. Full Prescribing Information at www.OLINVYK.com.

Positive Feedback from Formulary Stakeholders¹

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



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

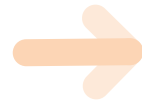


Omni-channel Approach for HCP Engagement

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



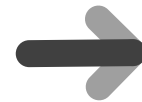
Field directed: live, virtual & email



HCP social media



Professional Society Meetings & Congresses



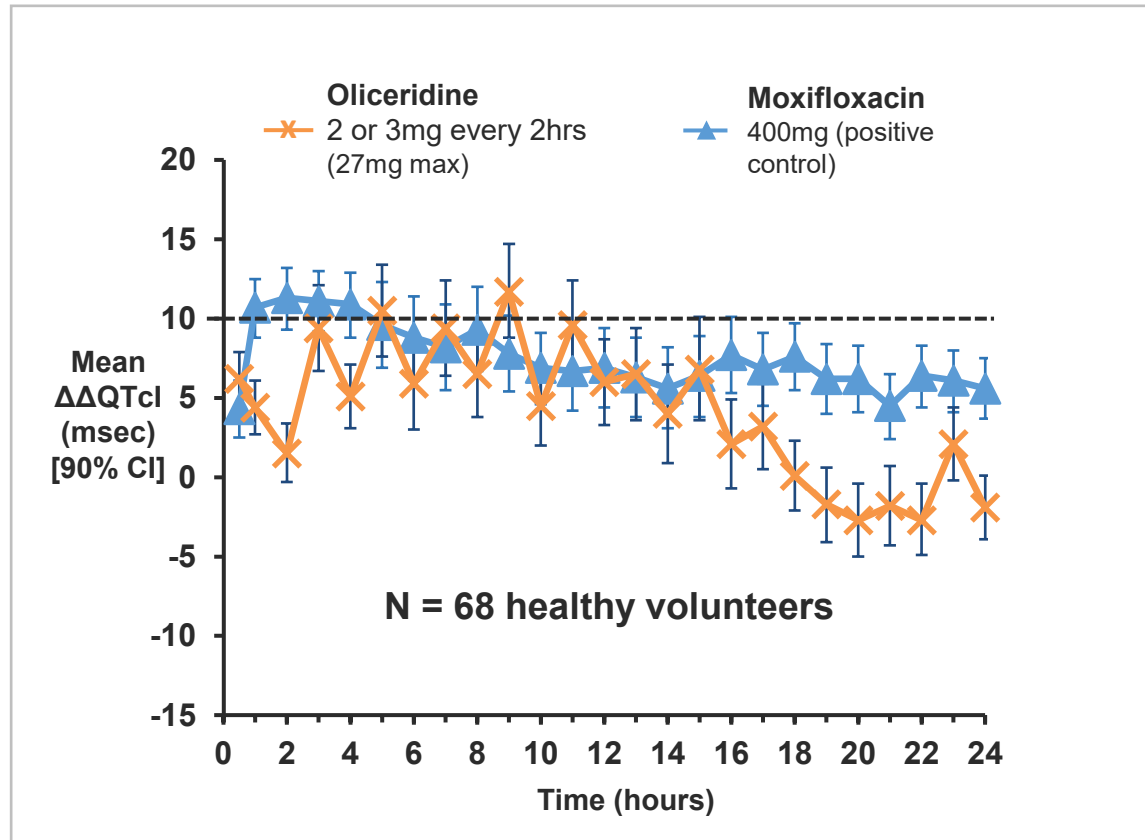
Olinvyk.com



Virtual “on demand” Medical Education programs

No Accumulation Despite Repeated Dosing

Multi-Dose tQT Study



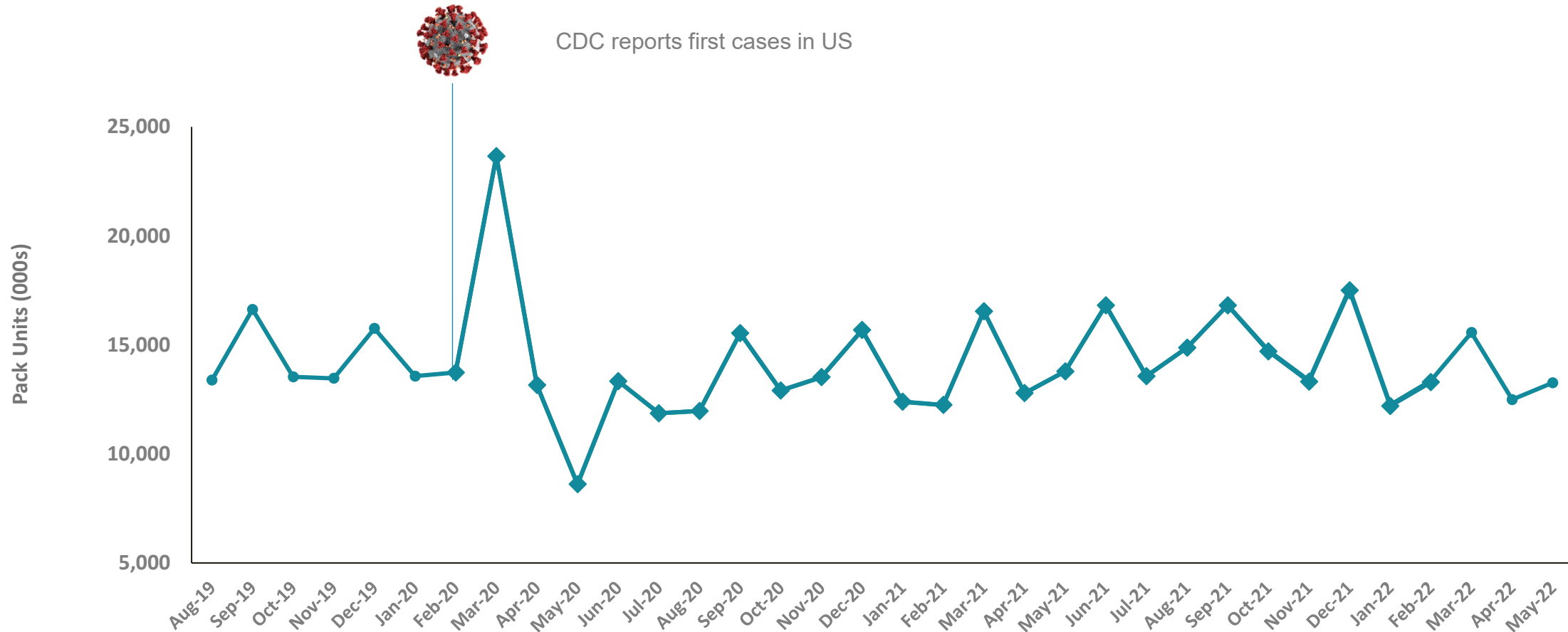
Key results

- **No accumulation through 24 hrs**
Mean QTcI <10ms at 22 of 24 points
- **No categorical QTc outliers**
 $\Delta >60$ 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.

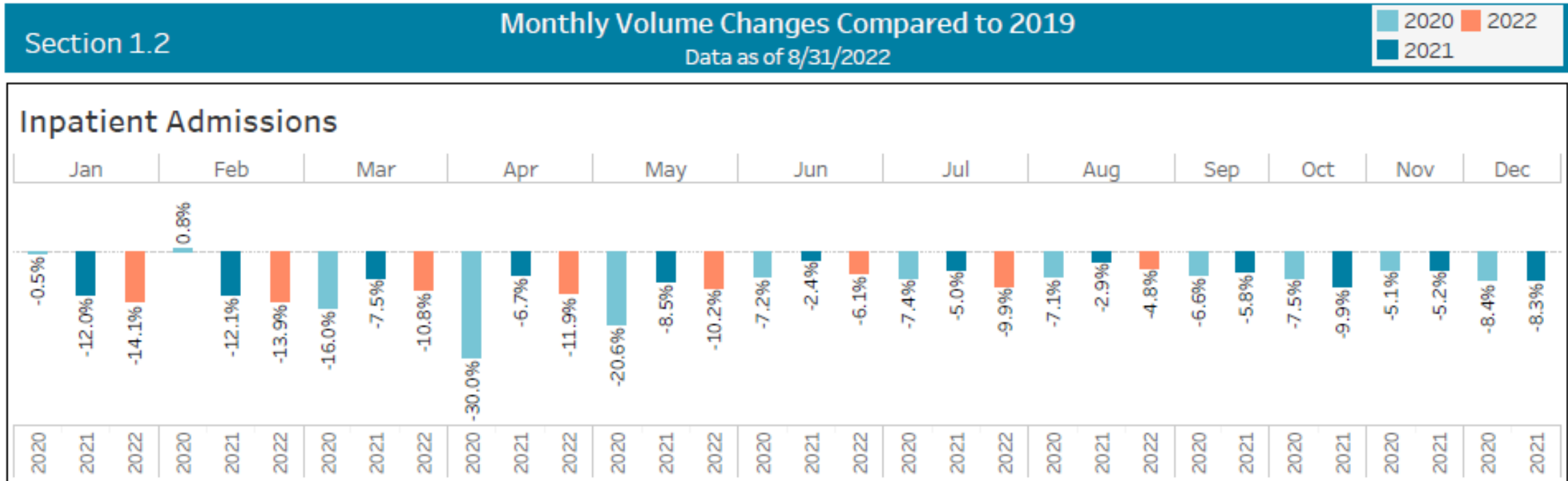
Stable IV Opioid Market Performance

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



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

Hospital Inpatient Visits Below Pre-Pandemic Levels

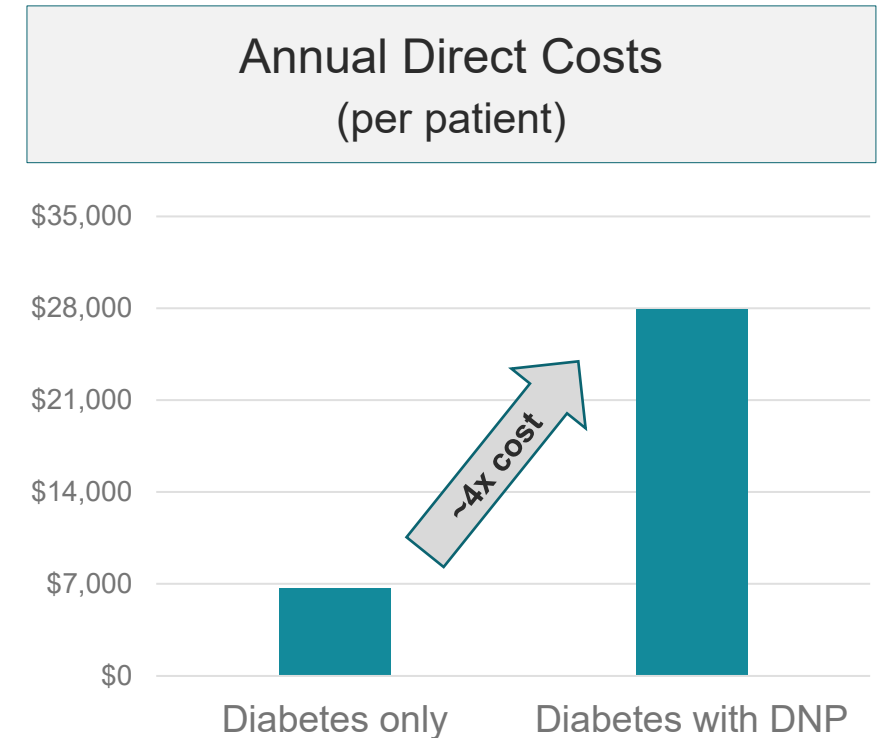


- Monthly Volume Changes in 2022 remain below 2019 levels for each month of the year.
- Through August each month in 2022 has shown a decline greater than was seen in 2021

Diabetic Neuropathic Pain

Diabetic neuropathic pain (DNP) represents a large market opportunity

- 30M+ US adults with diabetes (500M+ worldwide)^{1,2}
- DNP affects up to 25% of patients with diabetes^{3,8}
- Significant need for efficacious medicines for DNP⁴⁻⁵
 - Only ~50% of patients experience a clinical response with currently approved therapies
- Direct costs for patients with DNP were ~4x that of patients with only diabetes (no DNP)⁶



Epilepsy

One of the most common neurological diseases in the world¹

Disease Overview

- Epilepsy is a chronic disorder characterized by recurrent seizures¹.
- Epilepsy is defined as having two or more unprovoked seizures separated by at least 24 hours or after one seizure with a high risk of more².
 - A seizure is a sudden surge of electrical activity in the brain caused by complex chemical changes that occur in nerve cells³.
 - Usually, there is a balance of cells that either encourage or stop other brain cells from sending messages³.
 - A seizure occurs when there may be too much or too little electrical activity in the brain causing an imbalance³.
 - Seizures are a symptom of many different disorders that can affect the brain³.

Market Opportunity

- Nearly 50 million people suffer from epilepsy worldwide, including 3 million adults and 470,000 children in the U.S.^{1,4,5}.
- 150,000 new cases of epilepsy are reported in the United States each year⁶.
- According to the CDC, 56% of adults living with diagnosed epilepsy continue to have seizures⁷.

1. World Health Organization. Epilepsy. <https://www.who.int/news-room/fact-sheets/detail/epilepsy>. Accessed November, 2021. 2. Epilepsy Foundation. About Epilepsy: The Basics. <https://www.epilepsy.com/learn/about-epilepsy-basics>. Accessed November, 2021. 3. Epilepsy Foundation. What is a Seizure? <https://www.epilepsy.com/learn/about-epilepsy-basics/what-seizure>. Accessed November, 2021. 4. CURE Epilepsy. What is epilepsy? <https://www.cureepilepsy.org/about-epilepsy/what-is-epilepsy>. Accessed November, 2021. 5. Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy—United States, 2015. MMWR Morb Mortal Wkly Rep. 2017;66(31):821-825. 6. Epilepsy Foundation. What is Epilepsy? <https://www.epilepsy.com/learn/about-epilepsy-basics/what-epilepsy>. Accessed November, 2021. 7. Tian N, Boring M, Kobau R, Zack MM, Croft JB. Active Epilepsy and Seizure Control in Adults — United States, 2013 and 2015. MMWR Morb Mortal Wkly Rep 2018; 67:437–442. DOI: <http://dx.doi.org/10.15585/mmwr.mm6715a1>



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 CO₂ retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO₂ 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.

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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 $\geq 10\%$) adverse reactions in Phase 3 controlled clinical trials were nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia.

PLEASE see www.OLINVYK.com for full prescribing information including BOXED warning and important safety information