Nasdaq: TRVN **I** **January 2024**

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

BOARD OF DIRECTORS

Carrie L. Bourdow	Trevena	**Jake R. Nunn**	NEA · SR One
Scott Braunstein, M.D. Lead Independent Director	MARINUS PHARMACEUTICALS · AISLING CAPITAL · PACIRA BIOSCIENCES, INC.	**Anne M. Phillips, M.D.**	novo nordisk · gsk GlaxoSmithKline
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Marvin H. Johnson, Jr.	MERCK		

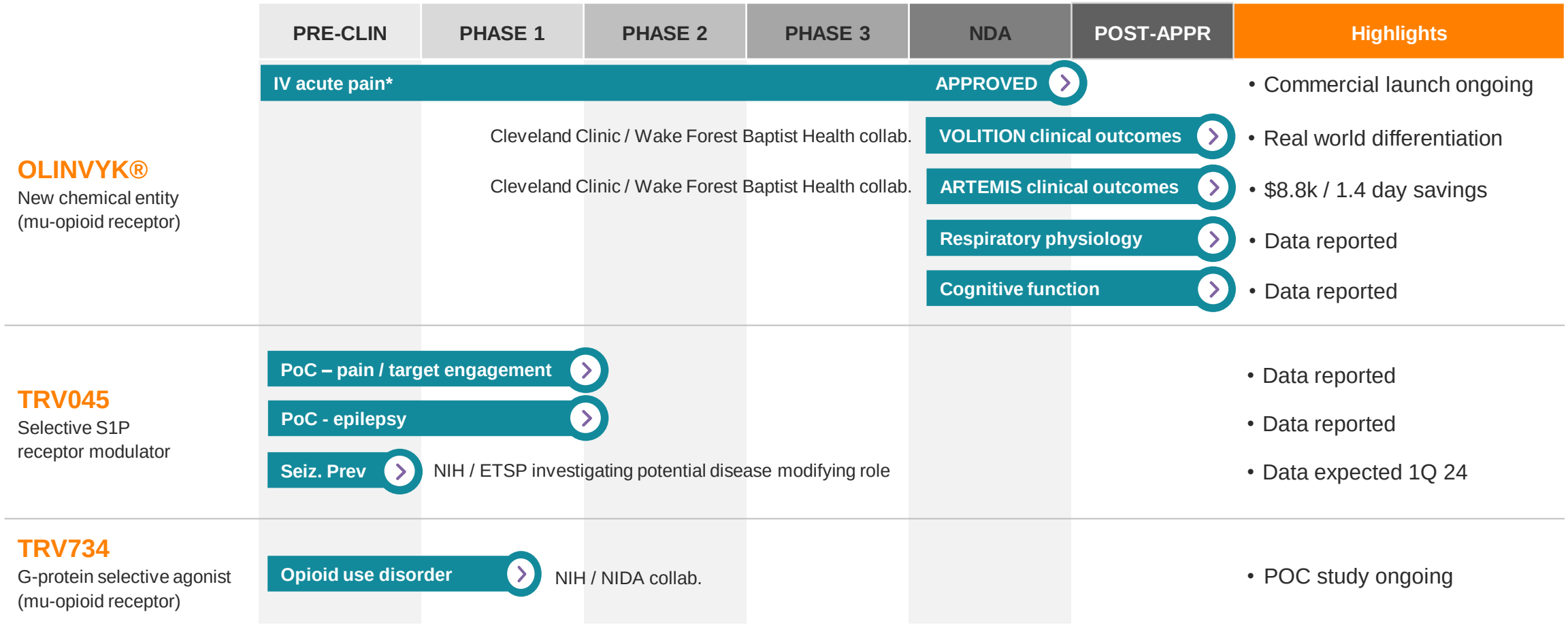
Trevena: Innovative CNS Company

IV OLINVYK: Differentiated profile	NCE approved for the management of acute pain in adults* Significant cost savings / differentiation shown in ‘real world’ post-approval studies
TRV045: Selective S1PR modulator	**S1PR:** Validated target for blockbusters (fingolimod / siponimod / ozanimod / ponesimod) **TRV045:** Unique profile (with potential for no lymphopenia) for new indications
TRV045: Compelling PoC Data	Statistically significant, dose-dependent effect in validated model of neuropathic pain Statistically significant EEG changes and evidence of early reduction in cortical excitability
Novel CNS pipeline	New mechanisms for acute / neuropathic pain, epilepsy, acute migraine, opioid use disorder NCEs targeting significant unmet needs
Financial position	$35.0M cash / equivalents / marketable securities @ 3Q 23 Recent financing extends cash runway into 4Q 24

*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; PoC = Proof of concept

Multiple Expected Catalysts



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Full Prescribing Information at www.OLINVYK.com

TRV045 and TRV734 are investigational products and are not approved by the FDA or any other regulatory agency
NDA = New Drug Application; PoC = Proof-of-Concept

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OLINVYK Overview

OLINVYK: Differentiated Profile for Acute Pain

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

Data in complex patients
Elderly / obese, multiple comorbidities

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

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

New chemical entity
Distinct from IV morphine

IV opioid efficacy
Hard- and soft-tissue surgeries

Rapid analgesia
1-3 min median onset of pain relief

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

VOLITION Clinical Outcomes Study w/ Cleveland Clinic

Further characterizes respiratory, GI and cognitive outcomes

- Open-label, multi-site study led by experts at Cleveland Clinic and Wake Forest Baptist Health
- N = 203 adults undergoing major non-cardiac surgery treated with IV OLINVYK

GI Tolerability

52.7%
complete GI response[1]

defined as no vomiting / no antiemetic use through study period

[1] In pooled Phase 3 data for OLINVYK, GI complete response rate was 46.2% (0.35mg) and 39.7% (0.5mg)

Respiratory Outcomes

22.8% respiratory compromise

defined as any one of five respiratory events[2] over **48hrs** of continuous monitoring

[2] End-tidal PCO_2 ≤ 15 mmHg for ≥3 min; RR ≤ 5 breaths/min for ≥3 min; SpO_2 ≤ 85% for ≥3 min; apnea episode >30 sec; any serious respiratory event

Cognitive Function

90%+
alert / calm at all points[3]

<4% symptoms of delirium[4]

[3] Richmond Agitation-Sedation Scale
[4] 3D-CAM screening tool

As reflected in the OLINVYK label, nausea and vomiting were two of the most common AEs reported in the controlled clinical trials

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

Sedation is an established risk of opioids including OLINVYK

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

ARTEMIS EMR-Based Clinical Outcomes Study

Statistically significant differentiation on a range of meaningful endpoints

- **201 OLINVYK-treated patients** at Cleveland Clinic and Wake Forest Baptist Health VOLITION sites
- **982 matched patients** undergoing similar surgical procedures, treated with other IV opioids, at same sites during VOLITION study

	Matched Patients Treated w/ other IV Opioids (N=982)		OLINVYK-Treated VOLITION Patients (N=201)	
Cost per Admission (avg)	$45.9k	**$8.8k** savings →	$37.1k	P<0.0001
Hospital Length of Stay (avg)	7.1 days	**1.4 days** shorter →	5.7 days	P<0.0001
Numerical Pain Score (1-10)				
24hr mean score	4.5	**15.0%** lower score →	3.9	P<0.0001
48hr mean score	4.3	**14.8%** lower score →	3.7	P<0.0001

As with all opioids, addiction, abuse and misuse, which can lead to overdose and death may occur in patients treated with OLINVYK as indicated in the boxed warning

EMR analysis does not provide definitive data of group differences as seen in a prospectively randomized study

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

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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

Trevena®

TRV045
S1P Receptor Modulator
Novel MOA for Diabetic Neuropathic Pain

$S1P_1$ Receptor – Novel Target for CNS Indications

$S1P_1$ receptors are highly expressed on key CNS cells involved in neuroinflammation

Potential therapeutic role in seizures, epileptogenesis and pain signaling

Epilepsy

- Neuroprotective effects[3]
- Modulates BBB permeability, anti-inflammatory effects[4,5]

Neuropathic pain

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

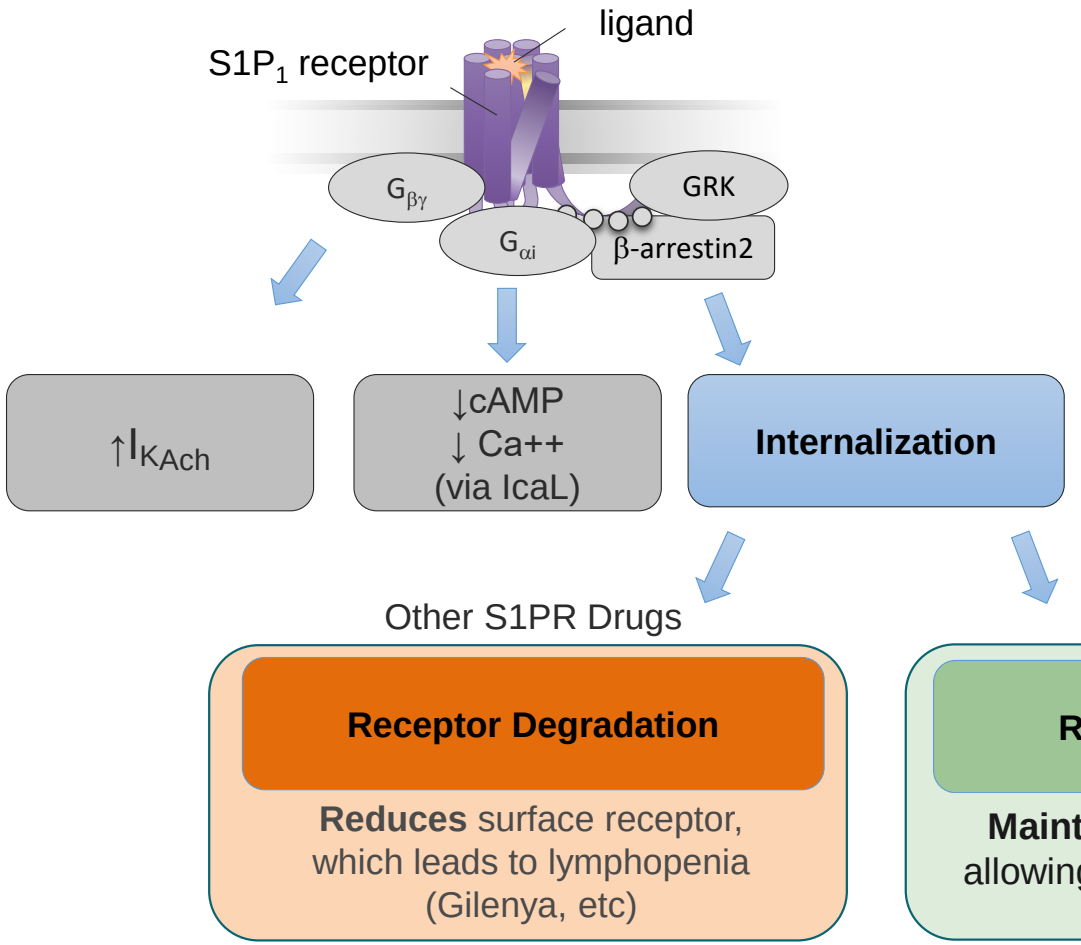
Existing S1PR-targeted drugs, however, are ill-suited for CNS indications due to known:

Lymphopenia
Cardiac AEs
Pulmonary AEs
Ophthalmologic AEs

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) Choi, et al. PNAS 2011.

TRV045 MOA (1): Rapid Receptor Recycling

Maintained (rather than degraded) S1P receptors on cell surface



No lymphopenia reported in prior Phase 1 FIH study

FIH = First in human

Source: Trevena data on file

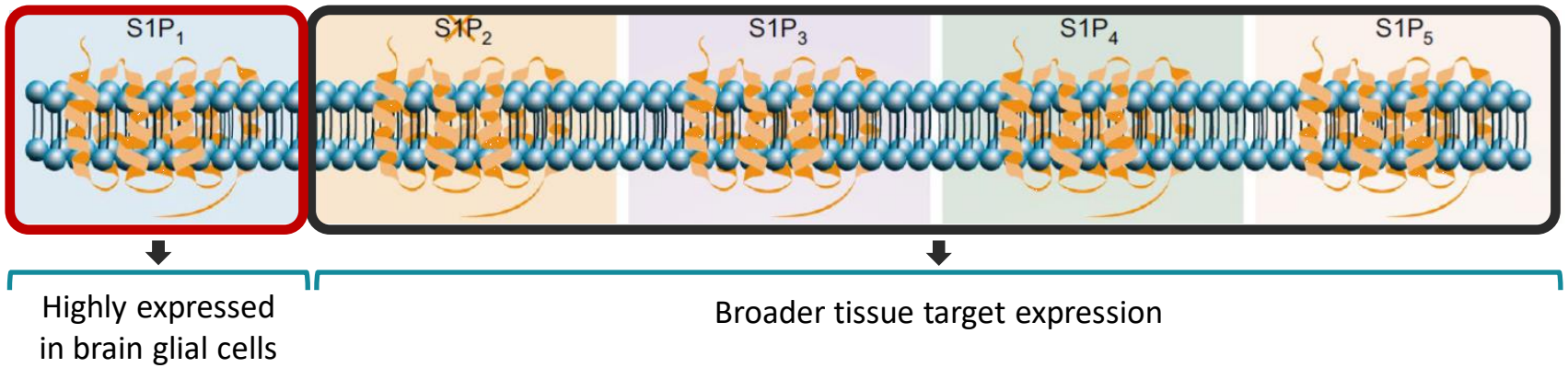
TRV045 MOA (2): S1PR Subtype-1 Selectivity

Subtype-1 is broadly expressed in the CNS and may avoid effects associated with other subtypes

- S1P acts on 5 distinct subtypes of receptors ($S1P_{1-5}$)

- TRV045 is **potent and selective for S1P subtype-1 receptor**
  - $S1P_1R$ is highly expressed on astrocytes / other glial cells
  - May play role in central pain signaling, as well as development and persistence of seizures

Highly expressed in key CNS / brain cells



Adapted from: Chun, J, et al., Drugs (2021) 81:207–231

TRV045 MOA (3): Anti-Inflammatory Effect (nonclinical)

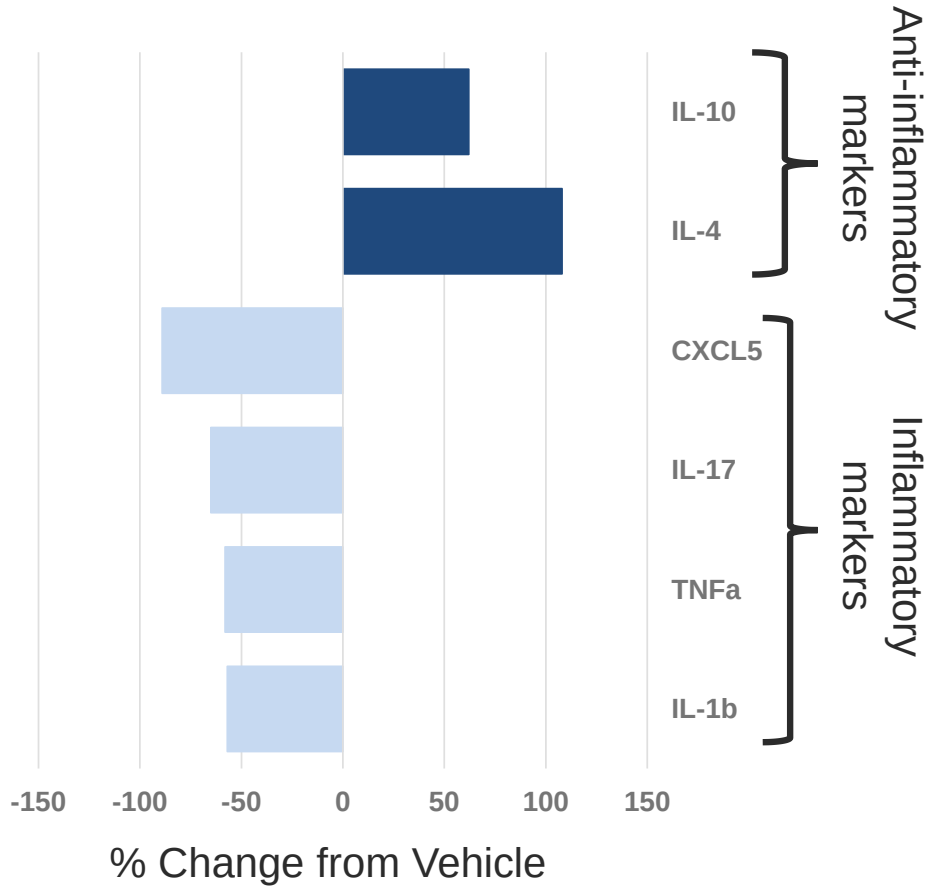
Anti-inflammatory actions (cytokines / chemokines) on astrocytes in cell culture

- **Main Findings:** Net anti-inflammatory action (statistically significant) on astrocyte cytokine / chemokine release
  - Increased all **anti-inflammatory** markers measured[1]
  - Reduced all **inflammatory** markers measured[1]

- **Method:** Primary mouse astrocytes in monolayer cell culture, incubated for 24hrs w/ 5 μM TRV045
  - 17 cytokines / chemokines[2] assessed by ELISA

TRV045-affected cytokines / chemokines play a role in many CNS disorders

(epilepsy, pain, neuropsych / neurodegen diseases)



1) P<0.05 v vehicle
2) Full cytokine / chemokine panel studied: (Inflammatory markers) – TNFa, IL-6, IL-1b, IL-17, IL-23, IL-33, CCL1, CCL2, CCL20, CXCL5, CXCL12, CX3CL1, IFNg, Csf2, Substance P; (Anti-inflammatory markers) – IL-10, IL-4. (Trevena, Inc., data on file)

TRV045 Proof-of-Concept Study Program – Highlights

Preliminary data*

- **Target Engagement.** Demonstrated CNS penetration and target engagement
- **Neuropathic Pain.** Statistically significant, dose-dependent effect in validated model of neuropathic pain
- **EEG Spectral Power.** Statistically significant ***increases*** in brain waves (alpha, beta, gamma) associated with arousal, alertness, cognitive processing, learning and memory

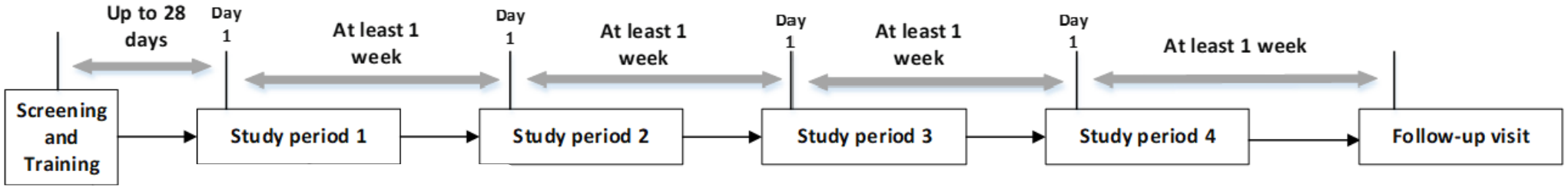
  Statistically significant ***decrease*** in delta brain waves, and ***no significant change*** in theta brain waves, both of which are associated with sedation / sleep
- **Cortical Excitability.** Directional evidence of early reduction in cortical excitability

Not all of the results were statistically significant;
details of the findings are presented on the following slides

Studies were conducted outside the United States and not under the IND for TRV045

Target Engagement (PainCart®) POC Study Design

- **Design:** Randomized, double-blind, placebo-controlled, single dose, four-way cross-over (N=25 subjects; 8F/17M, mean age 37.6 years, range 18-53)
  - Placebo or TRV045 (50/150/300mg)



- <u>Pharmacodynamic Endpoints</u>:
  - Mechanical allodynia (Von Frey hair testing on capsaicin-treated skin), pressure pain, heat pain (capsaicin-treated, UVB-exposed, and unexposed skin), cold pain (CPT), electrical pain (stair, burst conditions), conditioned pain modulation (electrical pain pre- and post-CPT)
- PK exposure parameters (C_{max}, t½)
- Safety and tolerability

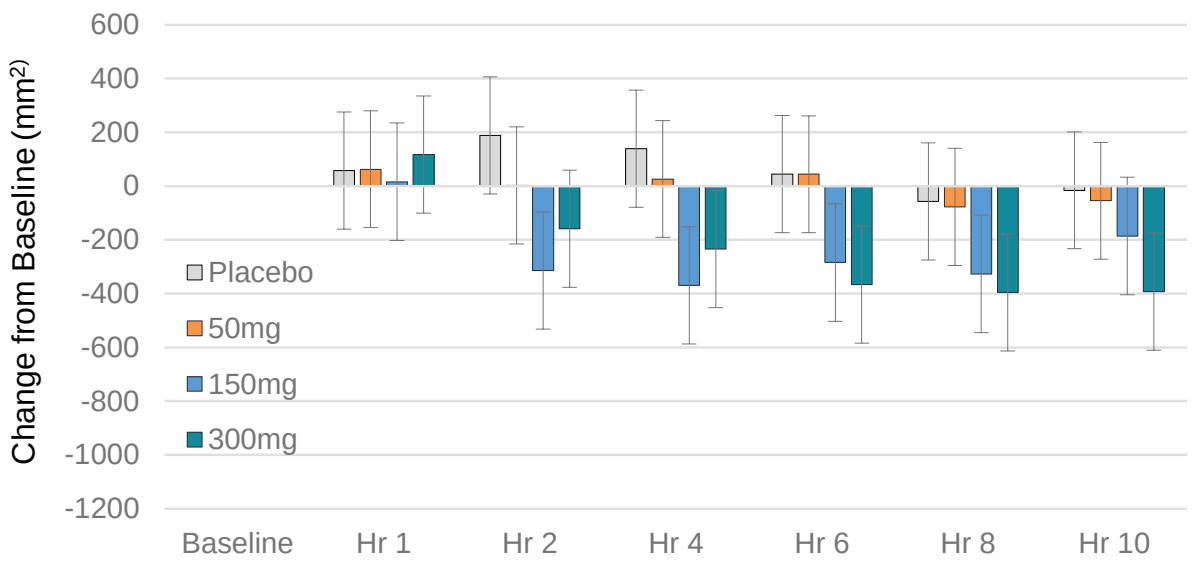
Studies were conducted outside the United States and not under the IND for TRV045
Source: Trevena data on file

TRV045 Significantly Reduced Mechanical Allodynia

1% capsaicin-treated dominant volar forearm – Von Frey filament allodynic area (CFB, mm^2)

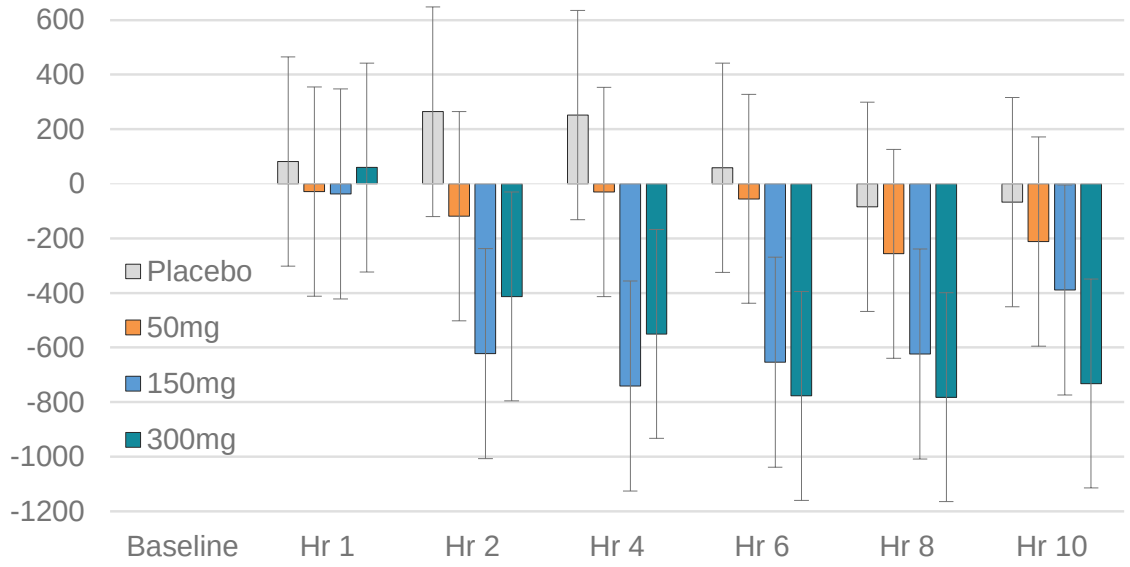
300mg TRV045 v Placebo; P=0.0023
150mg TRV045 v Placebo; P=0.0022

Secondary Allodynic Area



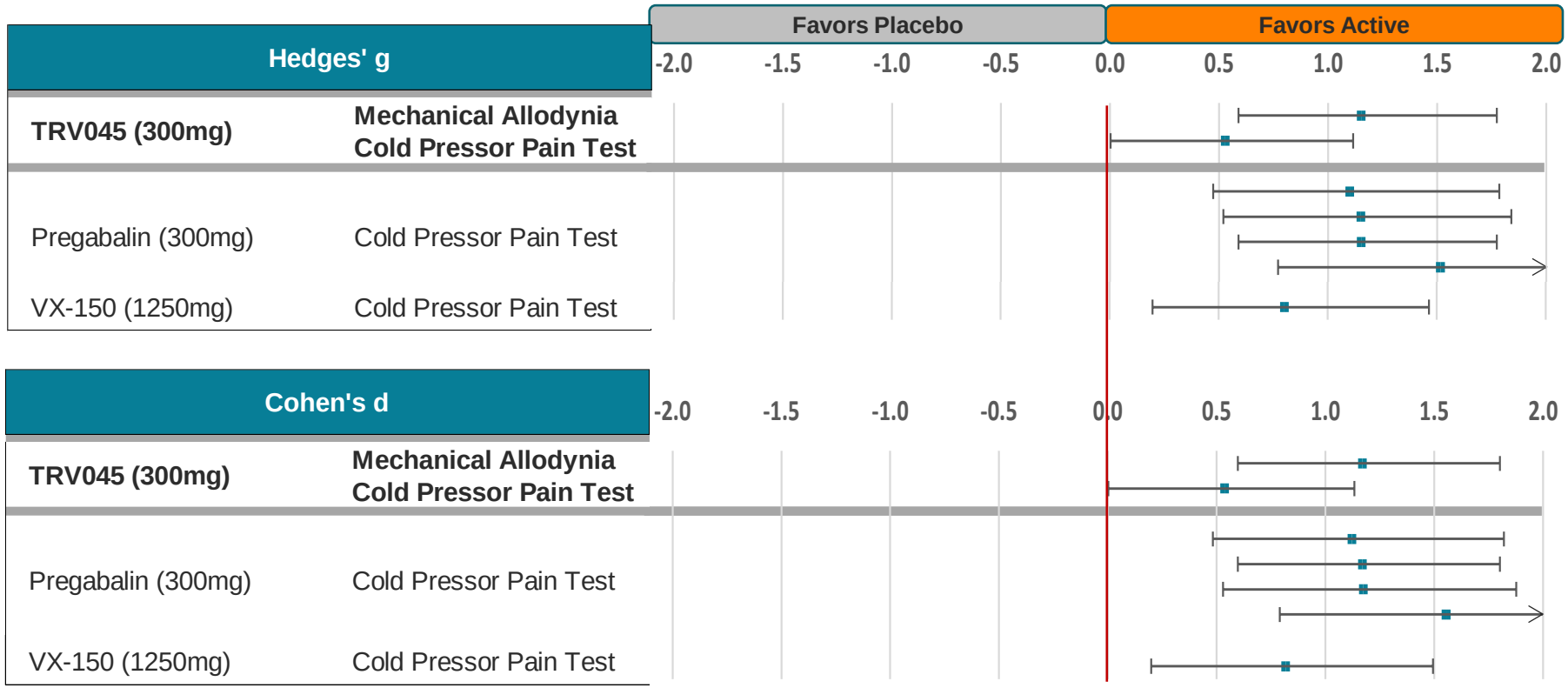
300mg TRV045 v Placebo; P=0.0001
150mg TRV045 v Placebo; P=0.0002

Total Allodynic Area



Source: Trevena data on file

Effect Size Comparison: TRV045 v Other Analgesics



Effect Size:

+0.2 – small effect

+0.5 – medium effect

+0.8 – large effect

- Studies for comparators conducted at **same** lab (CHDR) conducting TRV045 studies
- Single highest result for each comparator provided (cold pressor) from a battery of CHDR tests conducted
  - Mechanical allodynia test was not conducted on comparators

Target Engagement (PainCart®) Study

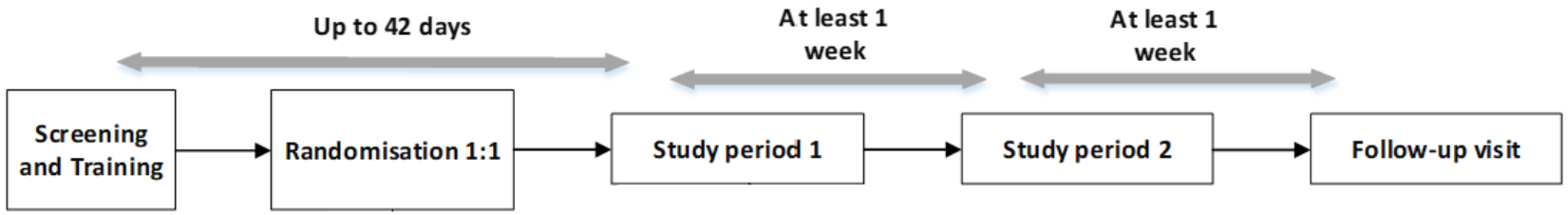
PainCart observations

- Statistically significant, dose-dependent, treatment effect in model of capsaicin-induced mechanical allodynia provides evidence of the therapeutic potential of TRV045 in neuropathic pain
  - Recognized and validated study index of central pain processing (‘central sensitization’)
  - Note that effect appeared similar with both 150mg and 300mg dose, potentially guiding future decisions on dose range for use in Phase 2
- Supportive evidence of analgesic action in select other nociceptive models
  - Other endpoints did not show trend / statistically significant results (pressure pain / conditioned pain modulation)
- Overall, strong support for CNS penetrance and engagement of pain signaling pathways in the brain
  - PK exposure consistent with parameters observed at comparable doses studied under fed conditions in Phase 1 FIH study
- No SAEs, no drug-related study discontinuations

Source: Trevena data on file

TMS POC Study Design

- **Design:** Randomized, double-blind, placebo-controlled, multiple dose, two-way cross-over (n=25 male subjects; mean age 31.5 years, range 21-55)
  - Placebo or TRV045 (250mg) for 4 days; post-dose assessments performed at 4 hours



- TMS-EEG Pharmacodynamic endpoints:
  - Resting qEEG power spectral analysis (eyes open/eyes closed): Alpha, Beta, Delta, Gamma, Theta bands
  - TMS-evoked EEG response (single and paired-pulse TMS)

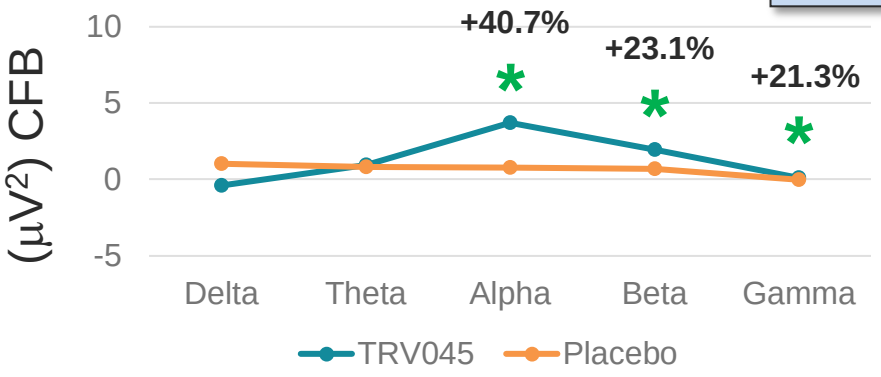
- TMS-EMG Pharmacodynamic endpoints:
  - Motor-evoked potential (MEP), resting motor threshold (single pulse TMS), paired-pulse TMS

Studies were conducted outside the United States and not under the IND for TRV045
TMS = Transcranial magnetic stimulation
Source: Trevena data on file

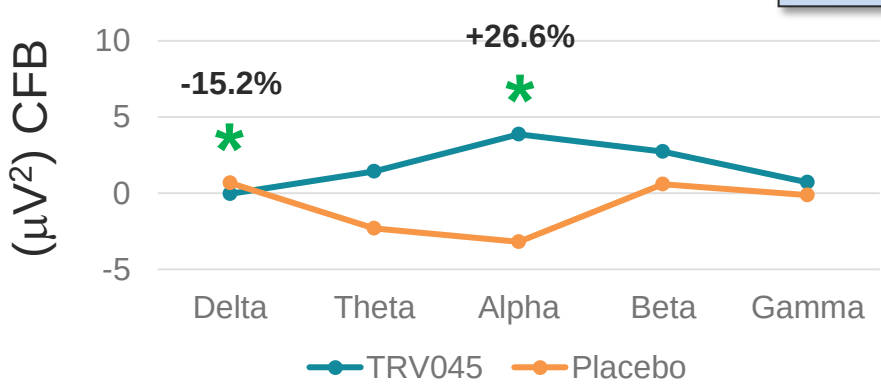
EEG Shifts in Alpha, Beta, Gamma, Delta Power Spectra

Resting qEEG Power Spectral Analysis – Eyes Open, Day 4 TRV045 v Placebo All Bands

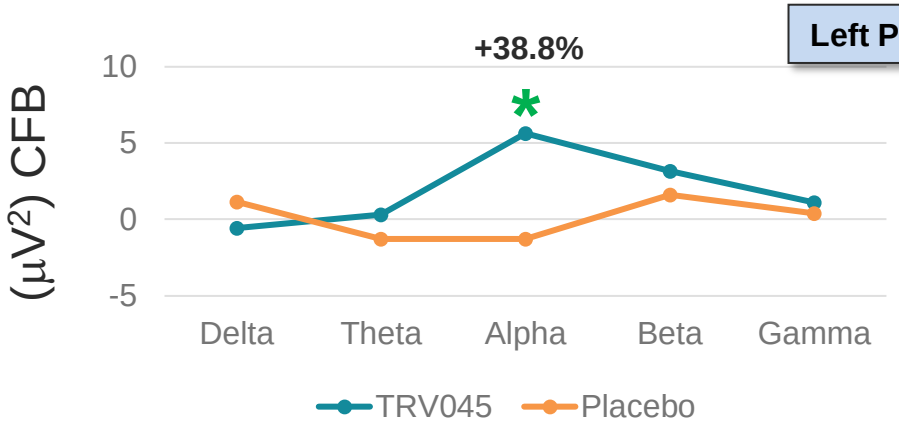
Frontal*



Right Parietal*



Left Parietal*



<u>Alpha</u>: Significant increase across all regions
<u>Beta</u>/<u>Gamma</u>: Significant increase in frontal region

associated with alertness / arousal memory / learning

<u>Delta</u>: Significant reduction in right parietal region
<u>Theta</u>: No significant difference

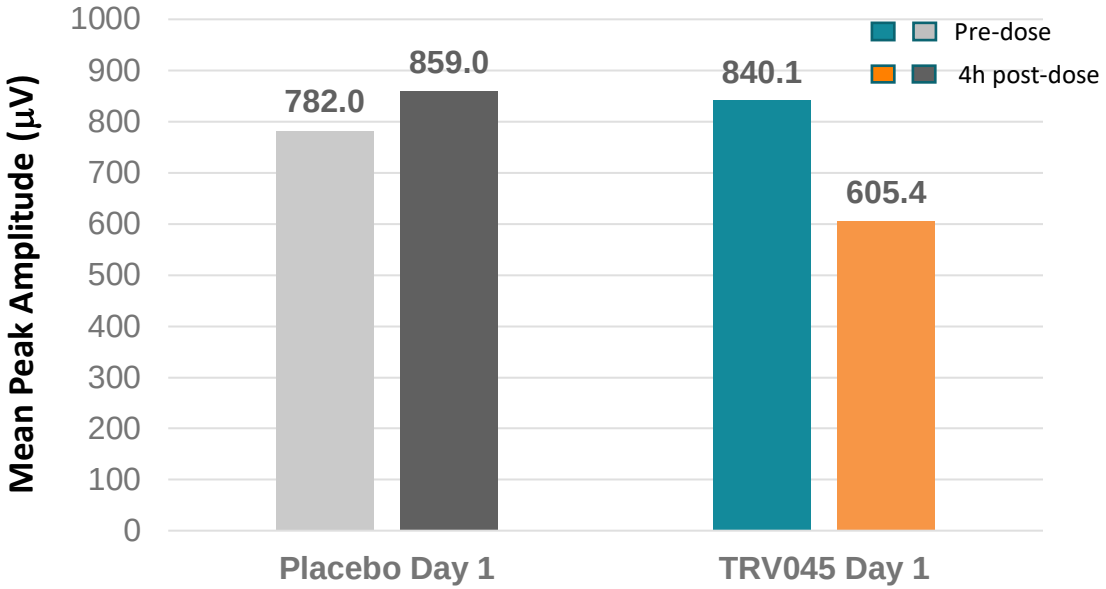
associated with sedation / sleep

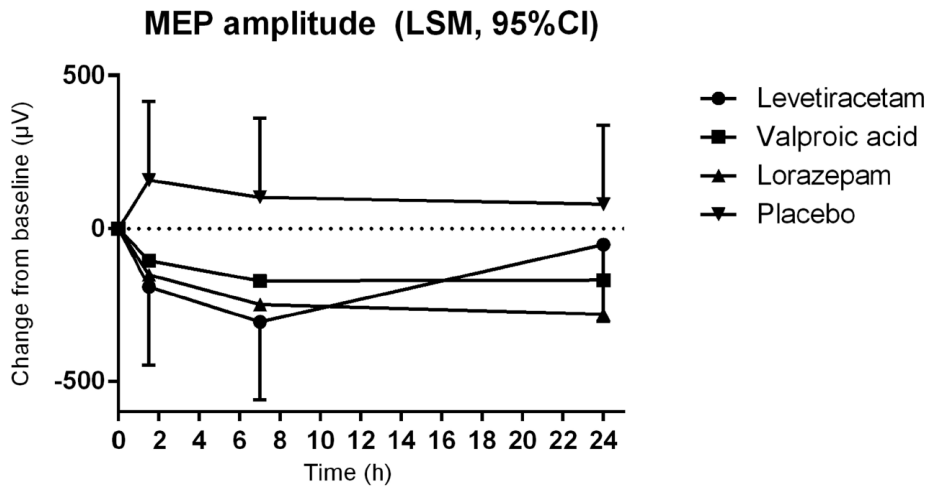
* Denotes pairwise comparison P < 0.05
Frontal = Fz-Cz; left parietal = Pz-O1; right parietal = PzO2
CFB = change from baseline; Source: Trevena data on file

Mantini, D, et al. PNAS (2007); Beste, C, et al. Nature Comm Biol (2023); Edwards, DJ and Trujillo, LT, Brain Sci (2021); Holler, Y, et al., CNS Drugs (2018)

TRV045 Effect on Cortical Excitability vs AEDs*

Mean change from baseline in motor-evoked potential (MEP) measured by peak-to-peak amplitude





Est. difference TRV045 v placebo (not stat. sig.)

- -304.14 µV, 95% CI -688.19 to 79.919 (P=0.1182)

Estimated difference vs placebo:

- Levetiracetam: -378.4 µV, 95% CI -644.3 to -112.5; P<0.01
- Valproic acid: -268.8 µV, 95% CI -532.9 to -4.6; P=0.047
- Lorazepam: -330.7.4 µV, 95% CI -595.6 to -65.8; P=0.02

Mean change from baseline in MEP on Day 1 with TRV045 comparable in magnitude to MEP reductions seen with known AEDs, including levetiracetam, valproic acid, and lorazepam, performed in the same laboratory

Trevena®

* AEDs = Antiepileptic drugs
Source: Trevena data on file

Ruijs, TQ, et al. BJCP (2022) 88:2926-2937

Safety and Tolerability Summary

POC data generally consistent with FIH study

- No AEs assessed as probably / definitely related to study drug; no AEs reported as severe; no SAEs
  - 98% of AEs (102 of 104) in PainCart® study reported as mild
  - 99% of AEs (79 of 80) in TMS study reported as mild
- Screening / follow-up physical exams (including ophthalmologic exams) with no clinically significant findings
- Lab results showed **no drug-related**:
  - Reduction in total lymphocyte count
  - Changes in heart rate or blood pressure
  - Changes in ECG interval measures (no prolongation of PR or QTcF intervals)

Safety and Tolerability Summary

Generally well tolerated and consistent with FIH study

- AEs with incidence of ≥10% for any TRV045 dose shown below (none deemed drug related)

PainCart Study		Placebo		TRV045 50mg		TRV045 150mg		TRV045 300mg	
		N (%)	Events	N (%)	Events	N (%)	Events	N (%)	Events
General Disorders	Fatigue	3 (12%)	3	1 (4%)	1	3 (12%)	3	2 (8%)	2
Nervous System Disorders	Dizziness	2 (8%)	2	0	0	3 (12%)	3	3 (12%)	3
	Headache	2 (8%)	2	3 (12%)	3	8 (32%)	9	8 (32%)	9
	Somnolence	2 (8%)	3	2 (8%)	2	5 (20%)	5	8 (32%)	8

TMS Study		Placebo		TRV045 250mg	
		N (%)	Events	N (%)	Events
General Disorders	Fatigue	1 (4%)	3	3 (12%)	5
Nervous System Disorders	Headache	6 (22%)	8	9 (36%)	12
	Somnolence	4 (15%)	3	3 (12%)	4

- No clinically signficant difference (vs placebo) in any AEs including:

Sedation	Balance Disorders	Attention Disturbances
Nausea	Dry Mouth	Blurred Vision

FIH = First in human

Overall Conclusions

TRV045 Proof-of-Concept Study Program

Taken together, these two POC studies provide
strong support and direction for future development of TRV045

- **Target Engagement.** Demonstrated CNS penetration and target engagement
- **Neuropathic Pain.** Statistically significant, dose-dependent effect in validated model of neuropathic pain
- **Epilepsy.** Promising evidence of early reduction in cortical excitability

  Statistically significant ***increases*** in brain waves (alpha, beta, gamma) associated with arousal, alertness, cognitive processing, learning and memory

  Statistically significant ***decrease*** in delta brain waves, and ***no significant change*** in theta brain waves, which are both associated with sedation / sleep
- **Differentiated Profile.** Novel MOA; expected once-daily oral dosing; potentially effective with favorable safety / tolerability

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Studies were conducted outside the United States and not under the IND for TRV045

TRV045: Broad Potential Applicability

Unique MOA Produces Compelling Profile

Potent and selective $S1P_1R$ target engagement
anti-inflammatory and nociceptive effects

No lymphopenia (in FIH study)
potentially limits other S1PR modulators

May avoid AEs associated with approved S1PR drugs
cardiac / pulmonary / ophthalmologic

Potential fields for development may include:

Seizure treatment (anticonvulsant)

Prevention of seizure (epileptogenesis) ← potential disease-modifying MOA

Pain (DPN, CIPN)

Autoimmune (MS, RA, UC, Crohn's Disease)

Neuropsychiatric / neurodegenerative (MDD, schizophrenia, AD, PD)

DPN: diabetic neuropathic pain; CIPN: chemotherapy-induced peripheral neuropathy; MS: multiple sclerosis; RA: rheumatoid arthritis; MDD: major depressive disorder; AD: Alzheimer's disease; PD: Parkinson's disease

Trevena: Innovative CNS Company

IV OLINVYK: Differentiated profile	NCE approved for the management of acute pain in adults* Significant cost savings / differentiation shown in ‘real world’ post-approval studies
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Novel CNS pipeline	New mechanisms for acute / neuropathic pain, epilepsy, acute migraine, opioid use disorder NCEs targeting significant unmet needs
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NCE = New Chemical Entity; PoC = Proof of concept

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IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS

Addiction, Abuse, and Misuse

OLINVYK exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing OLINVYK, and monitor all patients regularly for the development of behaviors or conditions.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OLINVYK. Monitor for respiratory depression, especially during initiation of OLINVYK or following a dose increase.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OLINVYK during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risk From Concomitant Use With Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

INDICATIONS AND USAGE

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

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OLINVYK for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

The cumulative total daily dose should not exceed 27 mg, as total daily doses greater than 27 mg may increase the risk for QTc interval prolongation.

CONTRAINDICATIONS

OLINVYK is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Known hypersensitivity to oliceridine (e.g., anaphylaxis)

WARNINGS AND PRECAUTIONS

- OLINVYK contains oliceridine, a Schedule II controlled substance, that exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OLINVYK. Assess risk, counsel, and monitor all patients receiving opioids.
- Serious, life-threatening respiratory depression has been reported with the use of opioids, even when used as recommended, especially in patients with chronic pulmonary disease, or in elderly, cachectic and debilitated patients. The risk is greatest during initiation of OLINVYK therapy, following a dose increase, or when used with other drugs that depress respiration. Proper dosing of OLINVYK is essential, especially when converting patients from another opioid product to avoid overdose. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status.
- Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia with risk increasing in a dose-dependent fashion. In patients who present with CSA, consider decreasing the dose of opioid using best practices for opioid taper.

WARNINGS AND PRECAUTIONS

- Prolonged use of opioids during pregnancy can result in withdrawal in the neonate that may be life-threatening. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using OLINVYK for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of OLINVYK with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, or alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate, prescribe the lowest effective dose, and minimize the duration.
- OLINVYK was shown to have mild QTc interval prolongation in thorough QT studies where patients were dosed up to 27 mg. Total cumulative daily doses exceeding 27 mg per day were not studied and may increase the risk for QTc interval prolongation. Therefore, the cumulative total daily dose of OLINVYK should not exceed 27 mg.
- Increased plasma concentrations of OLINVYK may occur in patients with decreased Cytochrome P450 (CYP) 2D6 function or normal metabolizers taking moderate or strong CYP2D6 inhibitors; also in patients taking a moderate or strong CYP3A4 inhibitor, in patients with decreased CYP2D6 function who are also receiving a moderate or strong CYP3A4 inhibitor, or with discontinuation of a CYP3A4 inducer. These patients may require less frequent dosing and should be closely monitored for respiratory depression and sedation at frequent intervals. Concomitant use of OLINVYK with CYP3A4 inducers or discontinuation of a moderate or strong CYP3A4 inhibitor can lower the expected concentration, which may decrease efficacy, and may require supplemental doses.
- Cases of adrenal insufficiency have been reported with opioid use (usually greater than one month). Presentation and symptoms may be nonspecific and include nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If confirmed, treat with physiologic replacement doses of corticosteroids and wean patient from the opioid.
- OLINVYK may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients.
- There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension. In patients with circulatory shock, avoid the use of OLINVYK as it may cause vasodilation that can further reduce cardiac output and blood pressure.
- Avoid the use of OLINVYK in patients with impaired consciousness or coma. OLINVYK should be used with caution in patients who may be susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy.
- As with all opioids, OLINVYK may cause spasm of the sphincter of Oddi, and may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

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

ADVERSE REACTIONS

Adverse reactions are described in greater detail in the Prescribing Information.

The most common (incidence ≥10%) adverse reactions in Phase 3 controlled clinical trials were nausea, vomiting, dizziness, headache, constipation, pruritus, and hypoxia.