



# 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 and 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.



*Developing innovative therapies for patients with CNS conditions.*

---

Carrie Bourdow

President and Chief Executive Officer

# Trevena Overview

**Focused on Innovative Medicines  
For CNS Disorders**

**Detailed in Following Slides**

## **Olinvyk IV\***

**Approved NCE for the  
management of acute pain in  
adults\***

Proven track record of Trevena  
internal discovery and  
development through approval

## **S1P Modulator Program**

**Novel S1P<sub>1</sub>R modulator with  
differentiated MOA (lead  
asset: TRV045)**

Preliminary data from proof-of-  
concept studies for  
CNS disorders

## **Innovative CNS Pipeline**

**Based on Nobel-prize  
winning biased ligand  
technology**

NCEs addressing acute /  
neuropathic pain, epilepsy,  
acute migraine, OUD<sup>1</sup>

\* 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](http://www.OLINVYK.com).

# Key Highlights

---

## TRV045 Proof-of-Concept Study Program – 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



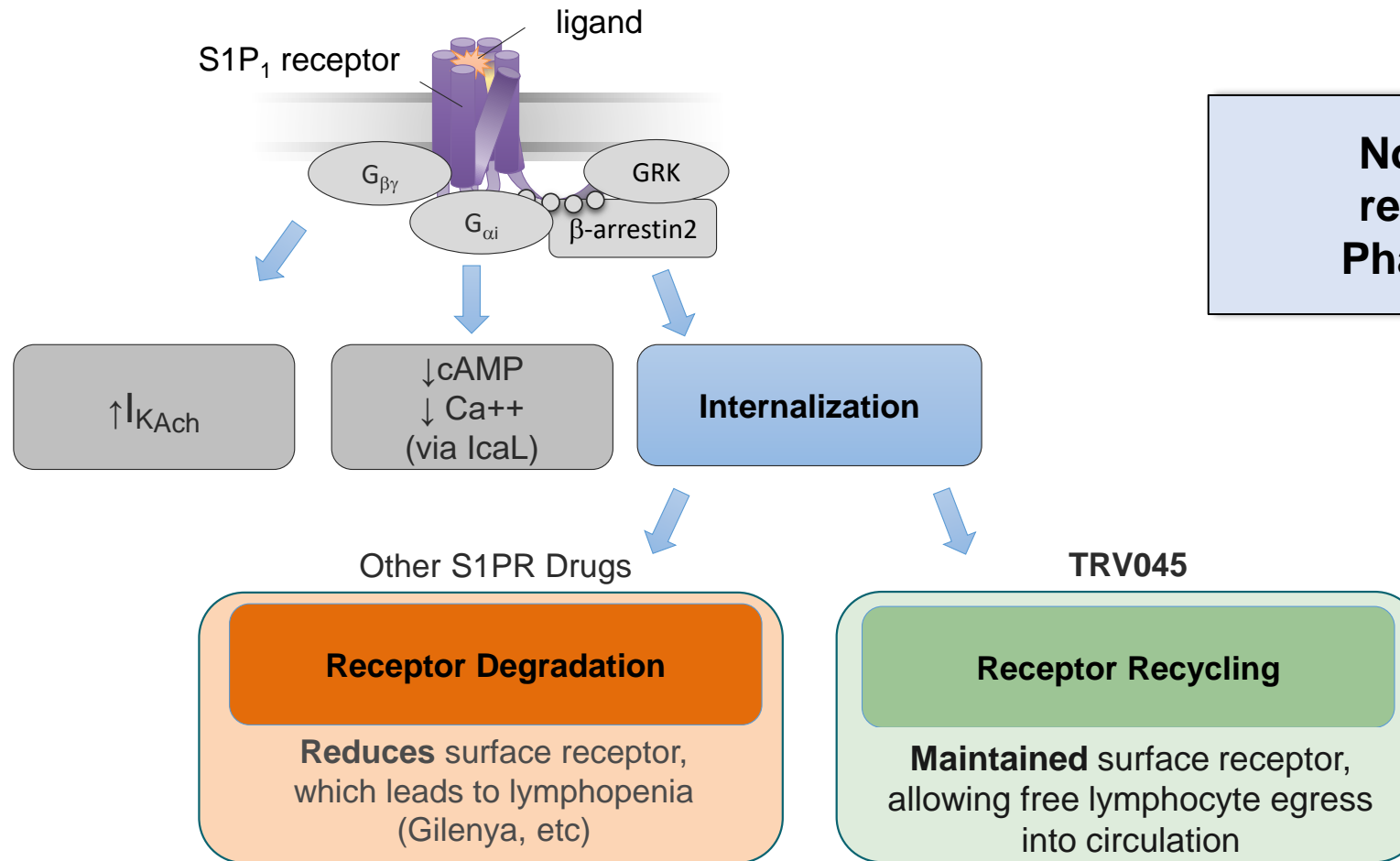
*Developing innovative therapies for patients with CNS conditions.*

---

Mark Demitrack, M.D.  
Chief Medical Officer

# TRV045 MOA: Rapid Receptor Recycling

Maintained (rather than degraded) S1P receptors on cell surface



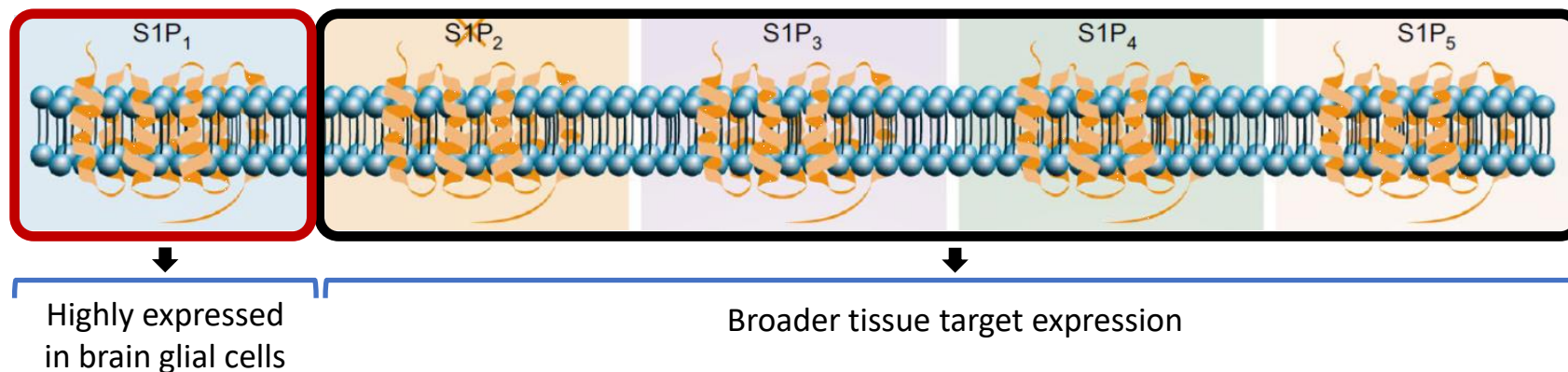
No lymphopenia reported in prior Phase 1 FIH study

# 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<sub>1-5</sub>)
- TRV045 is **potent and selective for S1P subtype-1 receptor**
  - S1P<sub>1</sub>R 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



# Overall Objectives

---

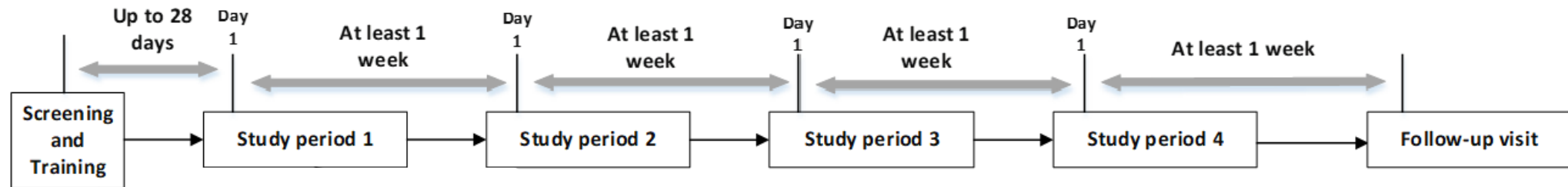
## TRV045 Proof of Concept Study Program\*

- Provide evidence of CNS penetration and target engagement via pharmacodynamic effects on validated experimental study endpoints in humans, using:
  - Battery of acute and chronic pain models (characterize ‘analgesic phenotype’ for TRV045)
  - EEG and EMG measures of changes in resting state brain electrical activity on and off drug and TMS-stimulated brain cortical excitability
- Provide PK-PD exposure data to guide future formulation development efforts and dose range selection for future Phase 2 studies
  - Prior phase 1 data demonstrated PK profile consistent with anticipated once-daily dosing
- Provide additional safety and tolerability data to support results of initial Phase 1 FIH study
  - No lymphopenia
  - No cardiovascular signals of concern
  - No evidence of ophthalmologic, pulmonary adverse effects

\* Complete safety and tolerability data expected early 4Q 2023  
Studies were conducted outside the United States and not under the IND for TRV045  
Source: Trevena data on file

# Target Engagement (PainCart®) POC Study Design

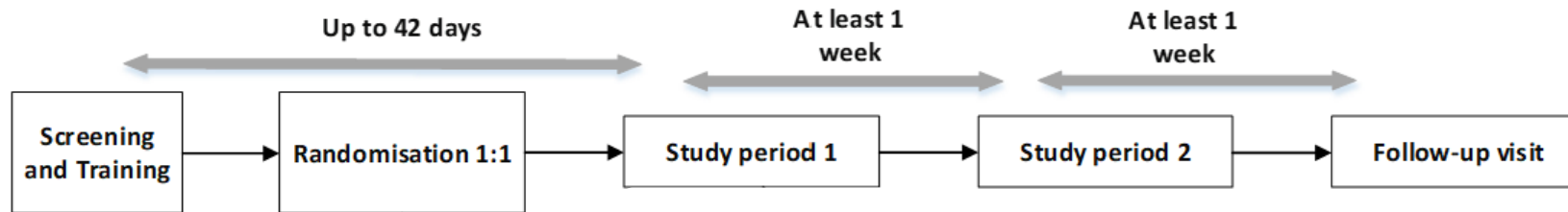
- **Design:** Randomized, double-blind, placebo-controlled, single dose, four-way cross-over (N=25 subjects; 8F/17M, mean age 37.6 years, range 18-53)
  - Placebo or TRV045 (50/150/300mg)



- Pharmacodynamic Endpoints:
  - 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 ( $C_{max}$ ,  $t_{1/2}$ )
- Safety and tolerability

# 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



*Developing innovative therapies for patients with CNS conditions.*

---

# TRV045 POC Data Update

## September 6, 2023

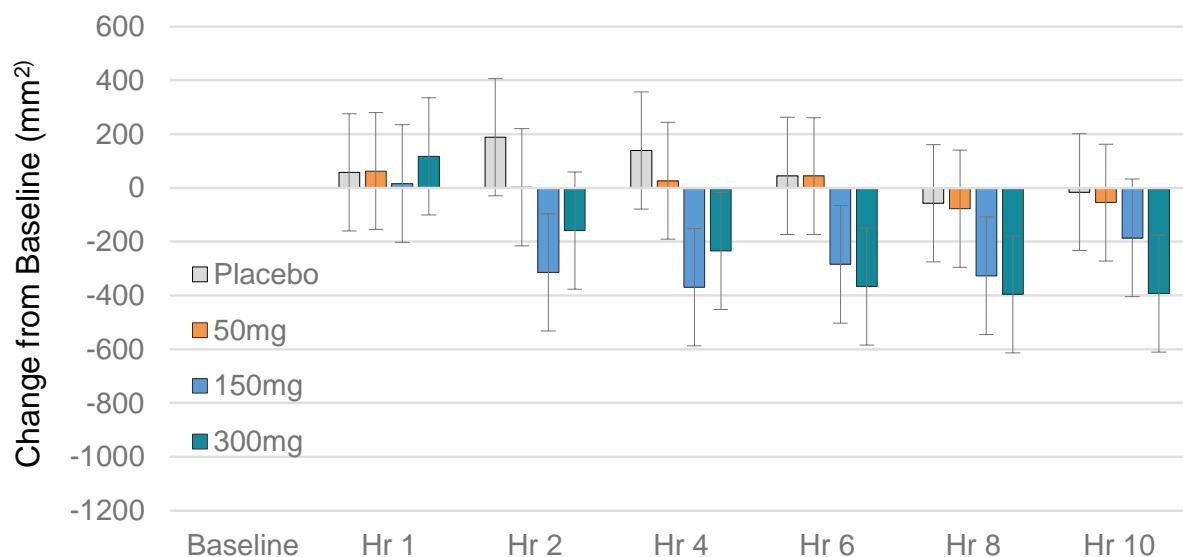
# TRV045 Significantly Reduced Mechanical Allodynia

1% Capsaicin-treated dominant volar forearm – Von Frey filament allodynic area (CFB, mm<sup>2</sup>)

300mg TRV045 v Placebo; P=0.0023

150mg TRV045 v Placebo; P=0.0022

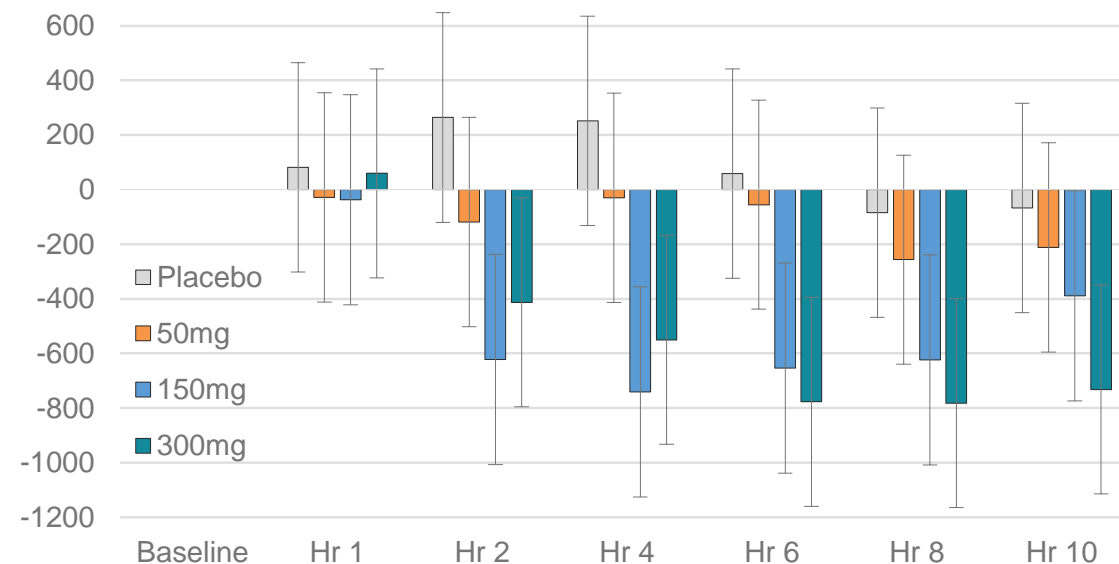
Secondary Allodynic Area



300mg TRV045 v Placebo; P=0.0001

150mg TRV045 v Placebo; P=0.0002

Total Allodynic Area



# Preliminary Conclusions

---

## Target Engagement (PainCart®) Study

- 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; full safety and tolerability data expected early 4Q 23



*Developing innovative therapies for patients with CNS conditions.*

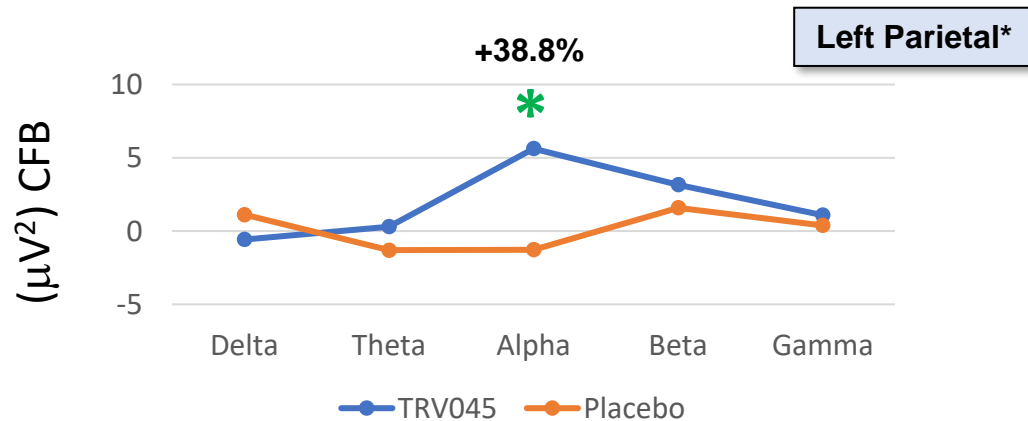
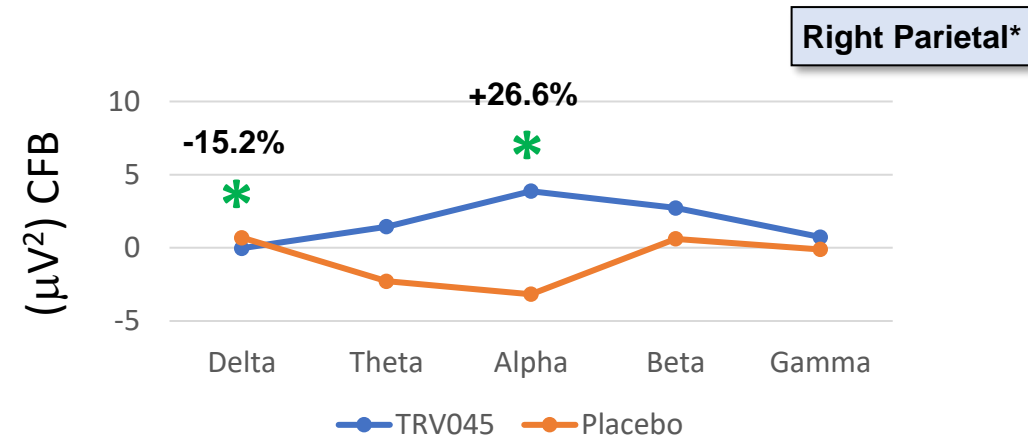
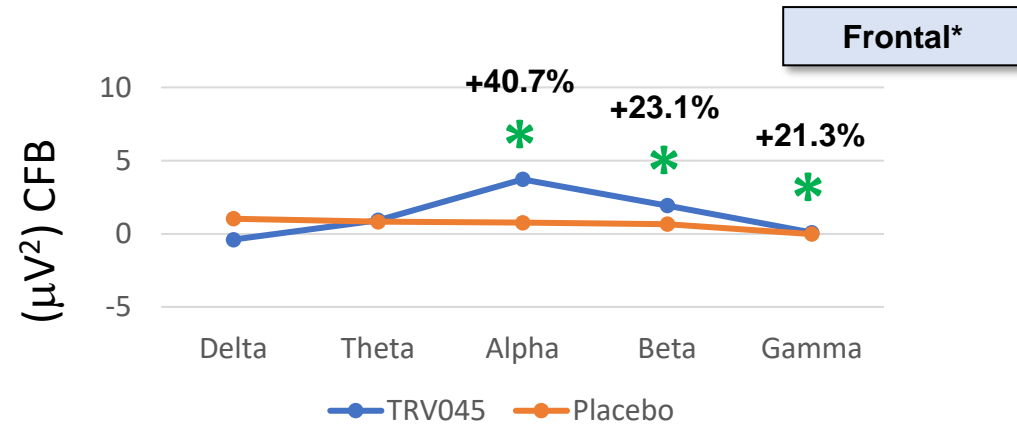
---

# TRV045 POC Data Update

## September 6, 2023

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

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



**Alpha:** Significant increase across all regions

**Beta/Gamma:** Significant increase in frontal region

**Delta:** Significant reduction in right parietal region

**Theta:** No significant difference

associated with  
alertness / arousal  
memory / learning

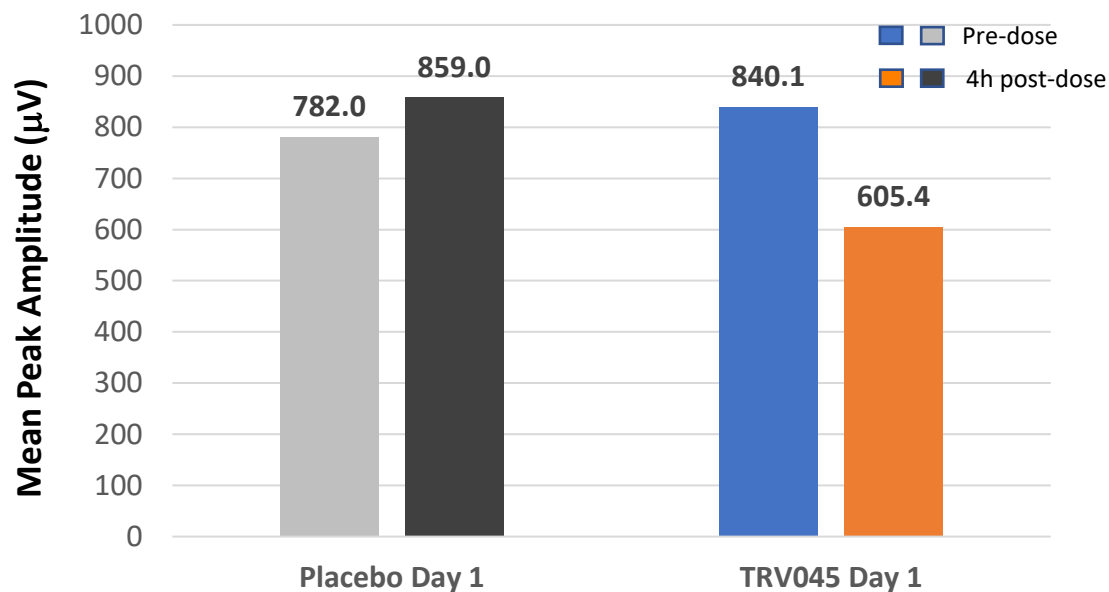
associated with  
sedation / sleep

\* 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

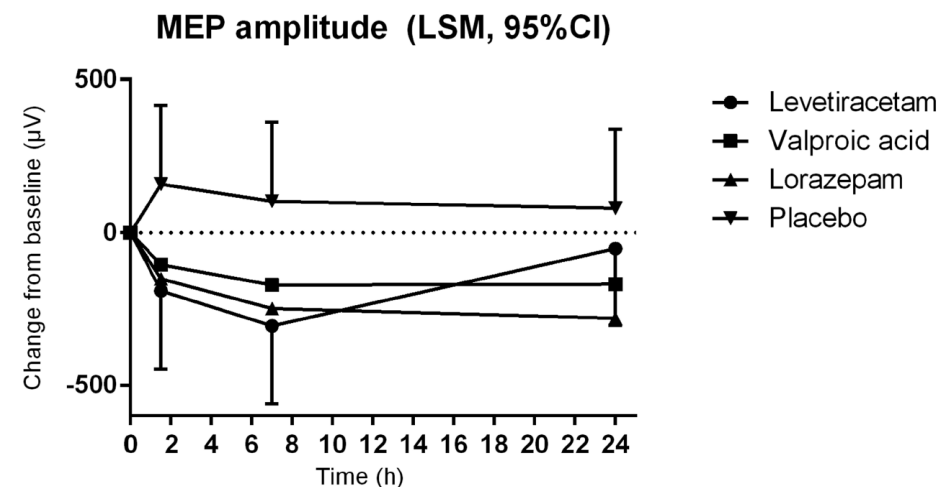
# TRV045 Effect on Cortical Excitability vs AEDs\*

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

# 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
- **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, which are both associated with sedation / sleep

- **Cortical Excitability.** Promising evidence of early reduction in cortical excitability



*Developing innovative therapies for patients with CNS conditions.*

---

# Trevena – TRV045 POC Data Update

## Q&A

### September 6, 2023



# 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<sub>2</sub> retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO<sub>2</sub> 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.
- 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<sub>2</sub> retention, such as those with evidence of increased intracranial pressure or brain tumors, as a reduction in respiratory drive and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy.
- As with all opioids, OLINVYK may cause spasm of the sphincter of Oddi, and may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.
- OLINVYK may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in vulnerable patients. Monitor patients with a history of seizure disorders for worsened seizure control.
- Do not abruptly discontinue OLINVYK in a patient physically dependent on opioids. Gradually taper the dosage to avoid a withdrawal syndrome and return of pain. Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving OLINVYK, as they may reduce the analgesic effect and/or precipitate withdrawal symptoms.
- OLINVYK may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
- Although self-administration of opioids by patient-controlled analgesia (PCA) may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression. Health care providers and family members monitoring patients receiving PCA analgesia should be instructed in the need for appropriate monitoring for excessive sedation, respiratory depression, or other adverse effects of opioid medications.

## ADVERSE REACTIONS

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

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

**PLEASE see [www.OLINVYK.com](http://www.OLINVYK.com) for full prescribing information including BOXED warning and important safety information**