



Forward-Looking Statements

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Innovative Pipeline in Areas with Significant Unmet Needs

	PRE-CLIN	PHASE 1	PHASE 2	PHASE 3	NDA	POST-APPR	EXPECTED CATALYSTS
TRV045 Selective S1P receptor modulator		PoC – pain / target engagement > PoC - epilepsy > Epilepsy > NIH/ETSP Infantile Spasm > NY Med College	Chronic, non-opioid pain. Epilepsy indications.				• Data reported • Data reported • Multiple studies reported • Data reported
		Acute decompensated heart failure > COVID-19 ARDS > Pediatric HF > Shinshu University, Tokyo Japan COVID-19 Biomarker PoC study > Imperial College London collab.	NIH ACTIV collab. Imperial College London collab.				• Ph2 data reported • Topline data 2H '22 • Non-clinical studies ongoing • Topline data announced
		Acute migraine >					• IND-enabling activities (oral)
		Opioid use disorder > NIH / NIDA collab.					• POC Study Ongoing

TRV250, TRV734, TRV027, and TRV045 are investigational products and are not approved by the FDA or any other regulatory agency.; ARDS = Acute Respiratory Distress Syndrome; ACTIV = Accelerating COVID-19 Therapeutic Interventions and Vaccines; NDA = New Drug Application, PoC = Proof-of-Concept, DNP = Diabetic Neuropathic Pain

Trevena: Innovative CNS Company



TRV045: Selective S1PR1 Agonist

S1PR: Validated target for blockbusters (fingolimod / siponimod / ozanimod / ponesimod)
New chemical entity; potent & selective for subtype 1; developed in-house with strong IP (2038)
Unique profile (with potential for no lymphopenia) for new indications; oral once-daily dosing



TRV045: Compelling Data

POC human study: Stat sig. EEG changes & evidence of early reduction in cortical excitability
New nonclinical data: Additional evidence of statistically significant acute anticonvulsant effect
New nonclinical data in infantile spasm: Stat. sig., dose-dependent reduction in NDMA-triggered spasms



Novel CNS pipeline

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



TRV045 Overview

TRV045: S1P₁ Receptor – A Novel Target for CNS Indications

S1P₁ receptors are highly expressed on key central nervous system cells involved in neuroinflammation

Potential therapeutic role in seizures and pain signaling

Epilepsy

- Neuroprotective effects¹
- Modulates anti-inflammatory effects^{2,3}



Neuropathic pain

- Inhibits pain sensation⁴
- Inhibits excitatory neuronal signaling⁵



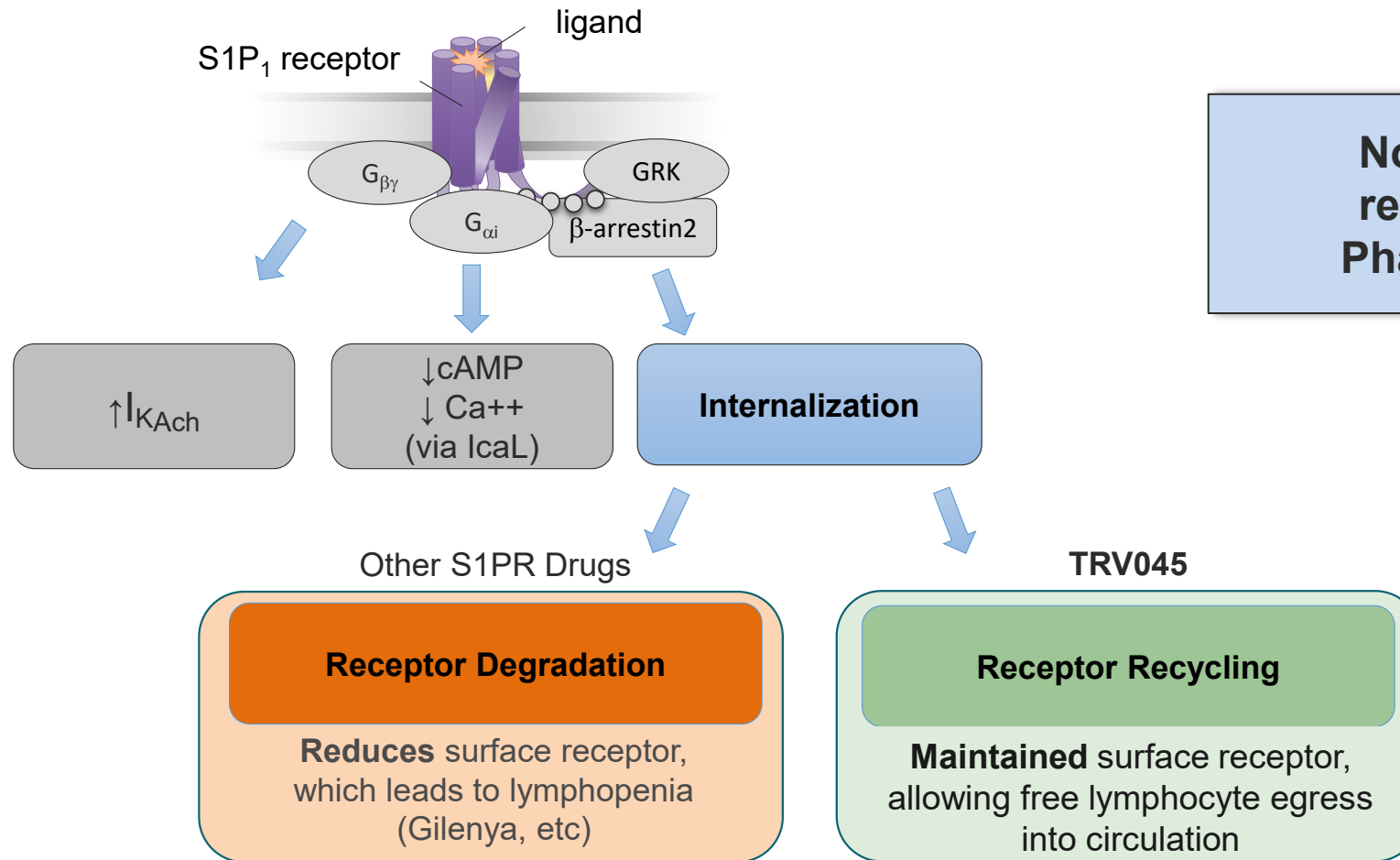
Existing S1PR-targeted drugs, however, are ill-suited for CNS indications due to known:

Lymphopenia
Cardiac AEs

Pulmonary AEs
Ophthalmologic AEs

TRV045 MOA: Rapid Receptor Recycling

Maintained (rather than degraded) S1P receptors on cell surface



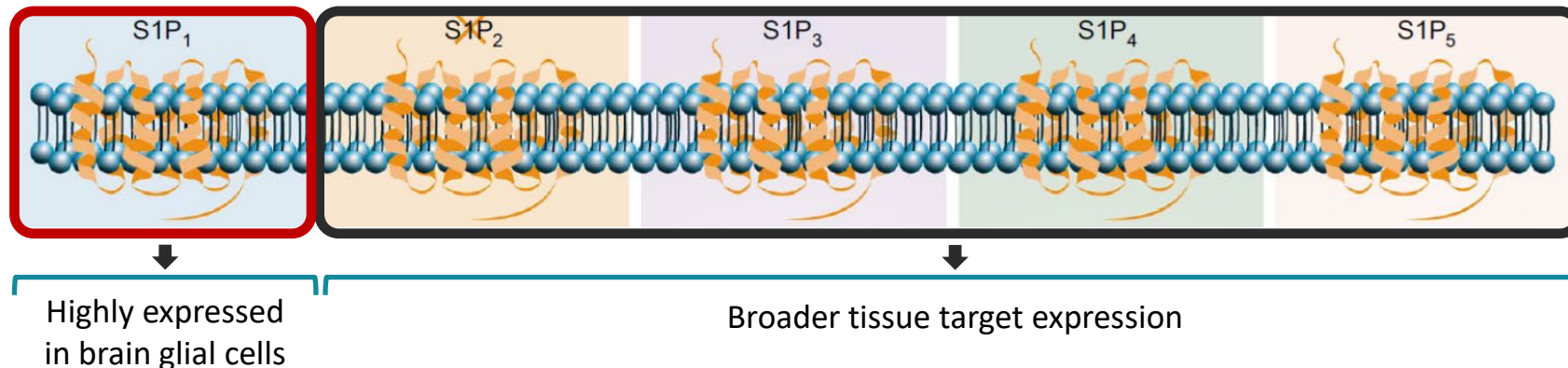
No lymphopenia reported in prior Phase 1 FIH study

TRV045 MOA: 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 (S1P₁₋₅)
- TRV045 is **potent and selective for S1P subtype-1 receptor**
 - EC₅₀ ~32 nM for G-protein signaling; EC₅₀ ~2 μM for β-arrestin signaling at human S1P1 receptor
 - Highly selective compared to S1P2-5 subtypes
 - S1P₁R 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**

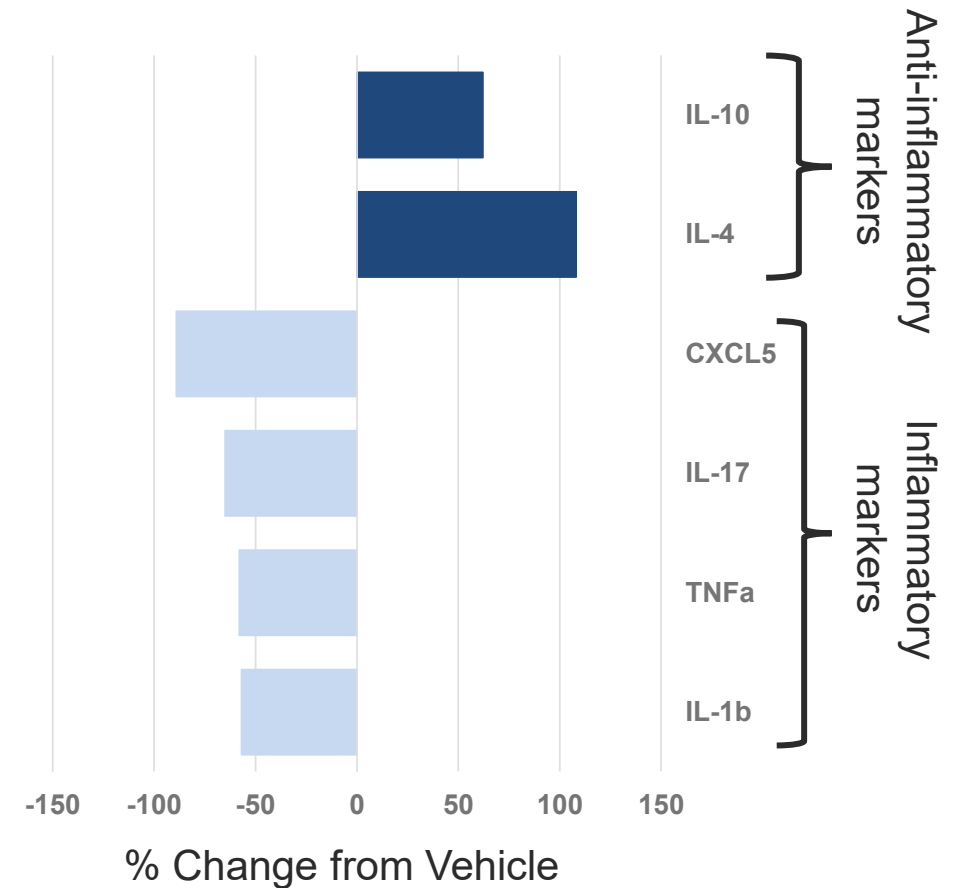


TRV045 MOA: Anti-Inflammatory Effect (nonclinical)

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 measured¹
 - Reduced all **inflammatory** markers measured¹
- **Method:** Primary mouse astrocytes in monolayer cell culture, incubated for 24hrs w/ 5 μ M TRV045
 - 17 cytokines / chemokines² 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)

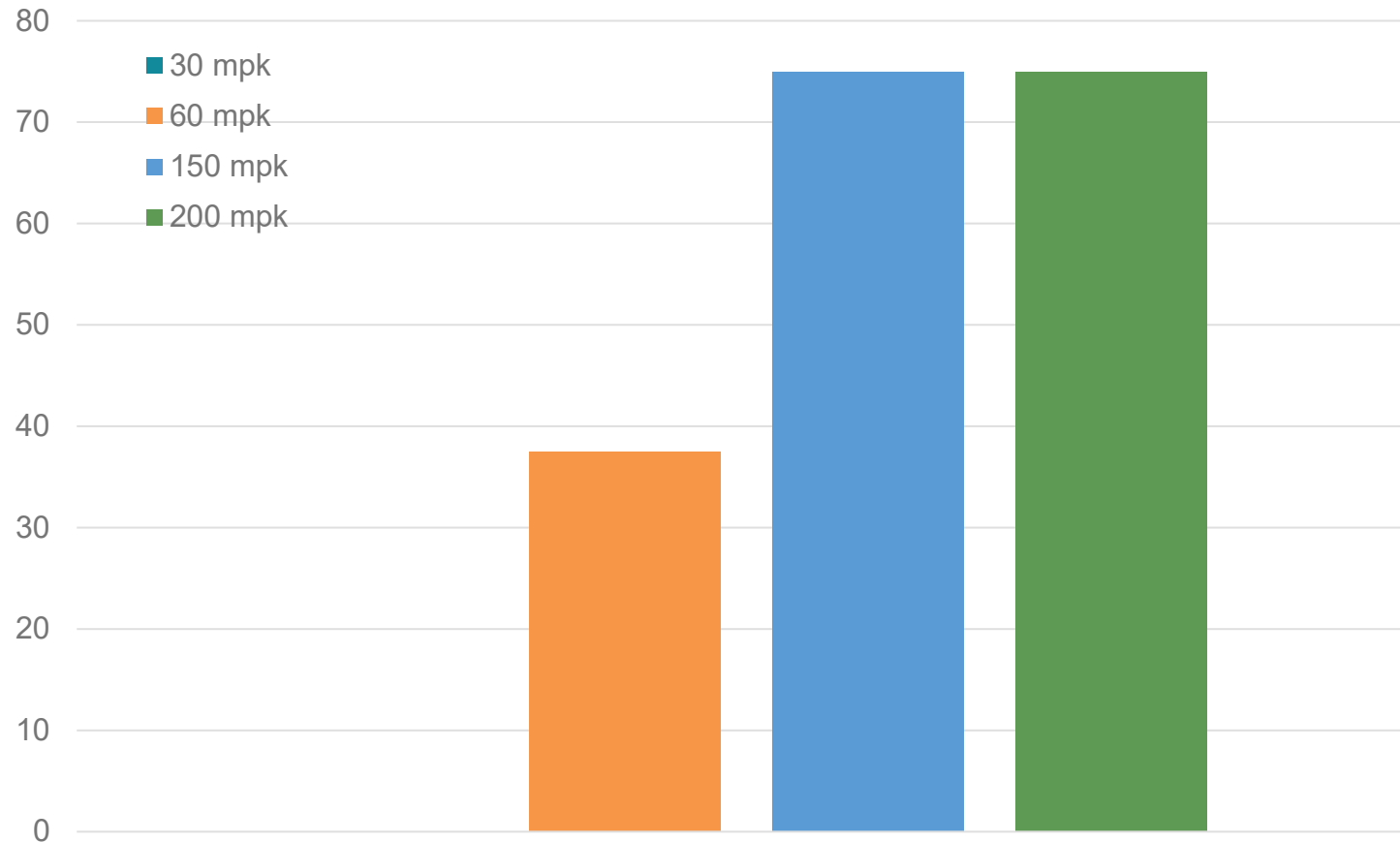
NIH Epilepsy Therapy Screening Program (ETSP) Study Results – New Data

Summary and Main Findings

- TRV045 has completed a broad range of ETSP anticonvulsant screening studies
 - Identification and Differentiation phase work largely complete
 - Data provide replicated evidence of TRV045 as an acute anticonvulsant with a novel mechanism of action and support future development as a human anti-seizure medication
- New data provide additional evidence of statistically significant acute anticonvulsant effect
 - Mouse: 6Hz Electrical Stimulation Model
 - Rat: Maximal Electroshock Model
- New data provide additional statistically significant anticonvulsant protection in disease-state animal models with subchronic administration
 - Mouse: Intra-amygdala kainic acid spontaneous seizure model

Mouse 6Hz Electrical Stimulation Model (IP Administration) – NEW

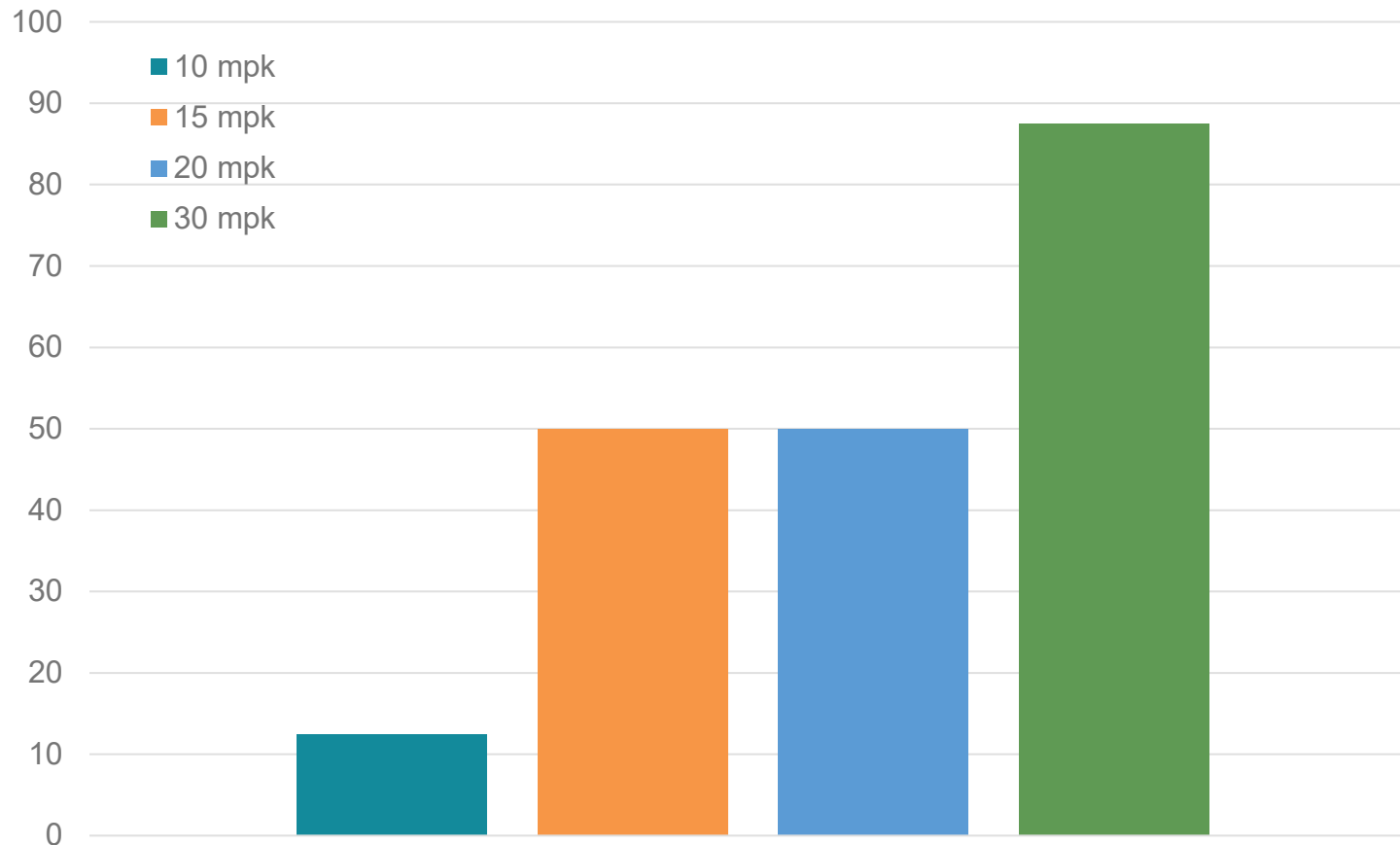
Positive dose-effect relationship – ED50 = 98.13 mg/kg



- TRV045 administered by IP route
 - N=8 animals / group
 - Tested 1 hr post dose
- ED50 est. 98.13 mpk
- ED50 for toxicologic dose >500 mpk
- IP formulation determined to be preferred route of administration across species

Rat MES Model (IP administration) – NEW

Positive dose-effect relationship – ED50 = 17.47 mg/kg

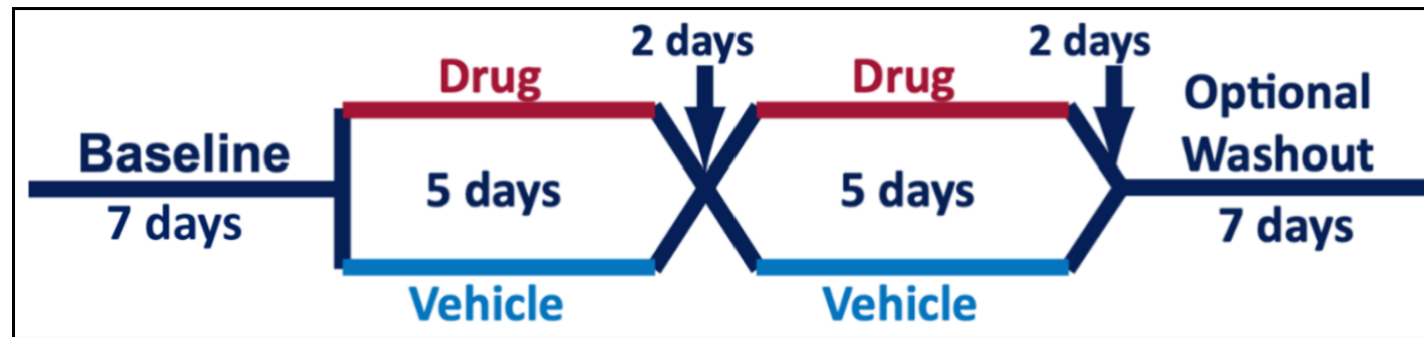


- TRV045 administered by IP route
 - N=8 animals / group
 - Peak effect 1 hr post dose
- ED50 est. 17.47 mpk
- ED50 for toxicologic dose >500 mpk
- IP formulation determined to be preferred route of administration across species

Study Design: Intra-amygdala kainate (IAK) model (IP, mouse) – NEW

Differentiation model of mesial temporal lobe epilepsy (MTLE)

- Late stage ETSP model used to screen for drug-resistant seizures and disease prevention/modification
 - Microinjection of kainic acid into amygdala; results in emergence of spontaneous recurrent seizures (SRS)
 - Key endpoints: Reduction in seizure burden, % seizure-free
 - Conducted as cross-over design, with 5-day dosing interval during test periods (20 mg/kg IP)

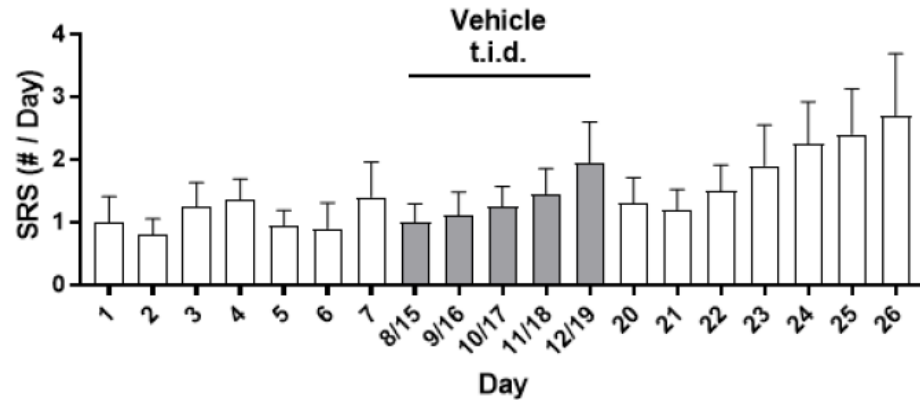


- In acute drug-resistant seizure model, many compounds are not active:
 - Only diazepam shows statistically significant reduction in *both* seizure burden and seizure freedom in this model
 - Carbamazepine, phenytoin both show NS reduction in seizure burden
 - Carbamazepine, phenytoin, valproic acid and phenobarbital all show NS reduction in seizure freedom

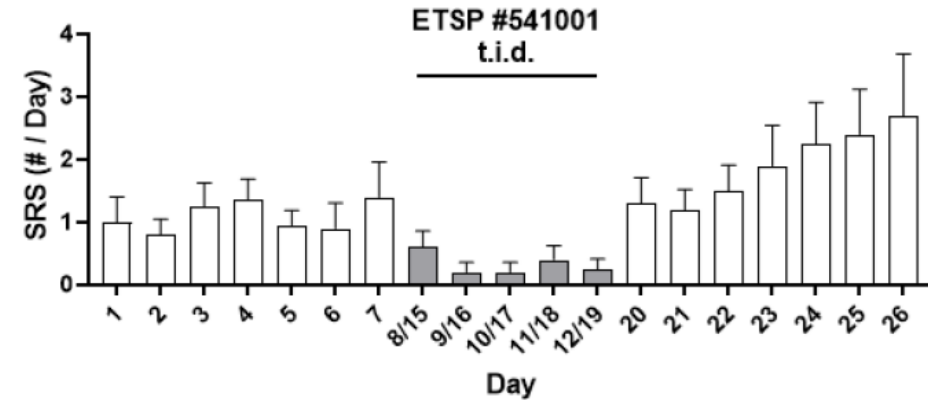
Study Design: Intra-amygdala kainate (IAK) model (IP, mouse)

Differentiation model of mesial temporal lobe epilepsy (MTLE)

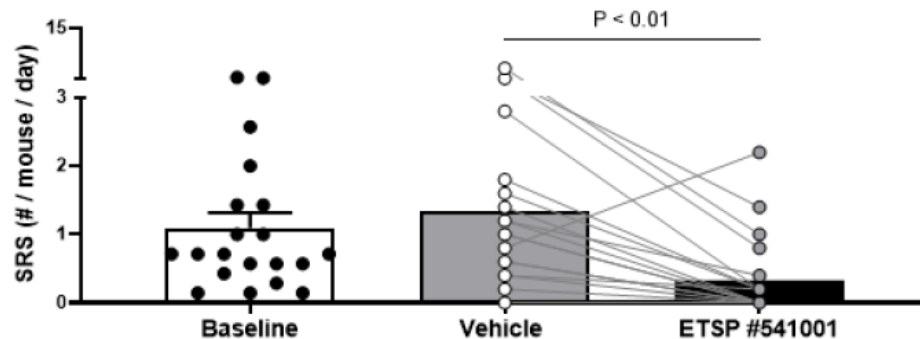
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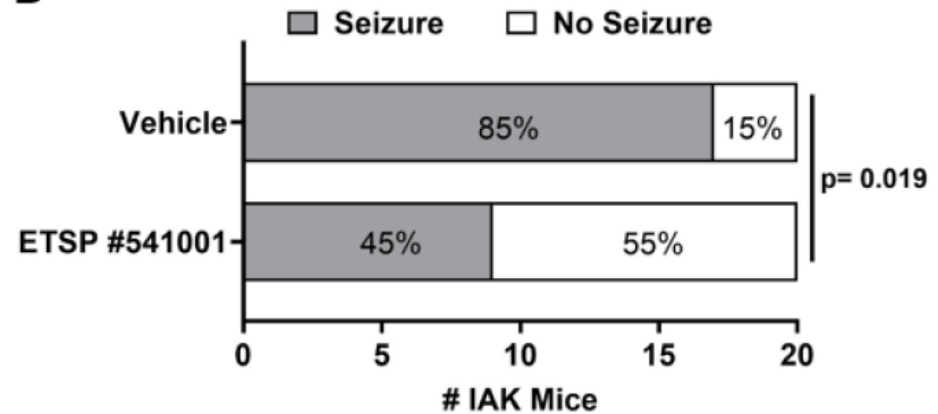
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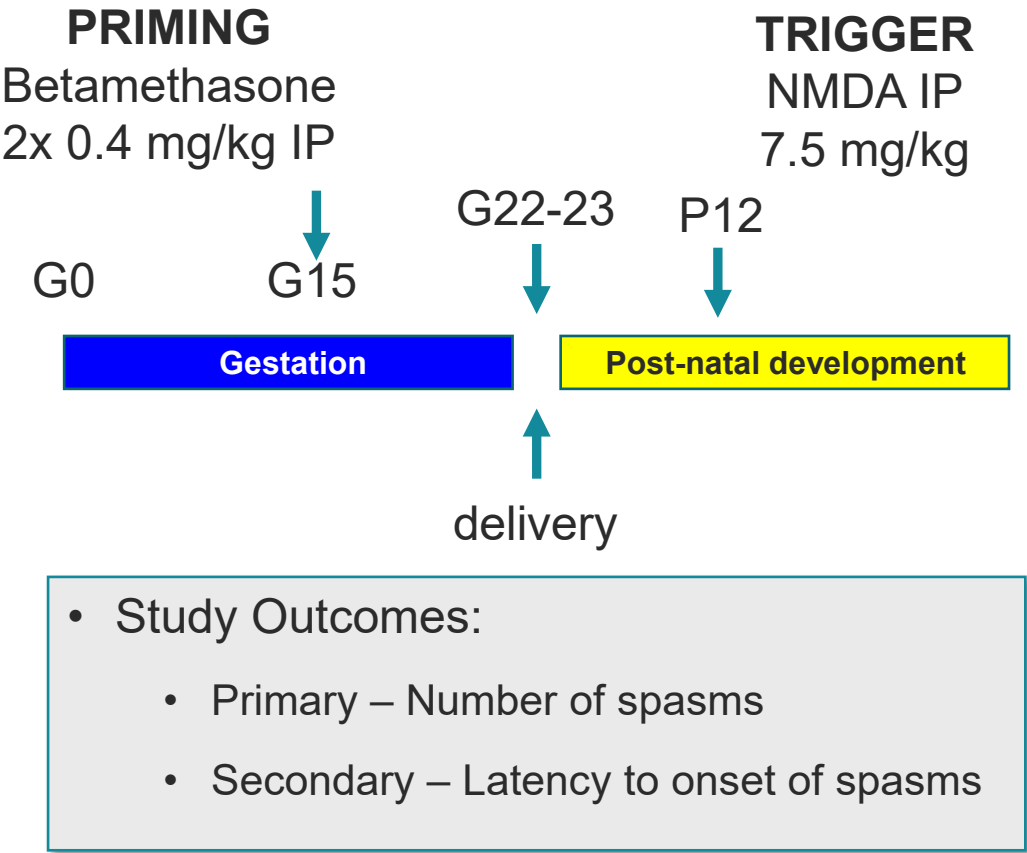
Statistically significant reduction in seizure frequency and seizure burden

NYMC Study Results – Cryptogenic Infantile Spasms Model (IP, rat)

Summary and Main Findings

- On the primary endpoint, final analysis shows that TRV045 demonstrates a statistically significant, dose-dependent reduction in the number of NDMA-triggered spasms at both 2 hours and 4 hours pre-treatment
 - Maximal reduction in number of spasms ranges from **70.5% (2 hours) to 50.3% (4 hours)**
 - Efficacy shown at doses of 30 mg/kg and 60 mg/kg
- On the secondary endpoint, statistically significant treatment effect on latency to onset of spasms seen at 4 hours, but no statistical significance in any pairwise comparisons at that time point

Efficacy of TRV045 in a Validated Model of Infantile Spasms



TRV045 Dosing Schedule
(Pretreatment time prior to NMDA spasm trigger)

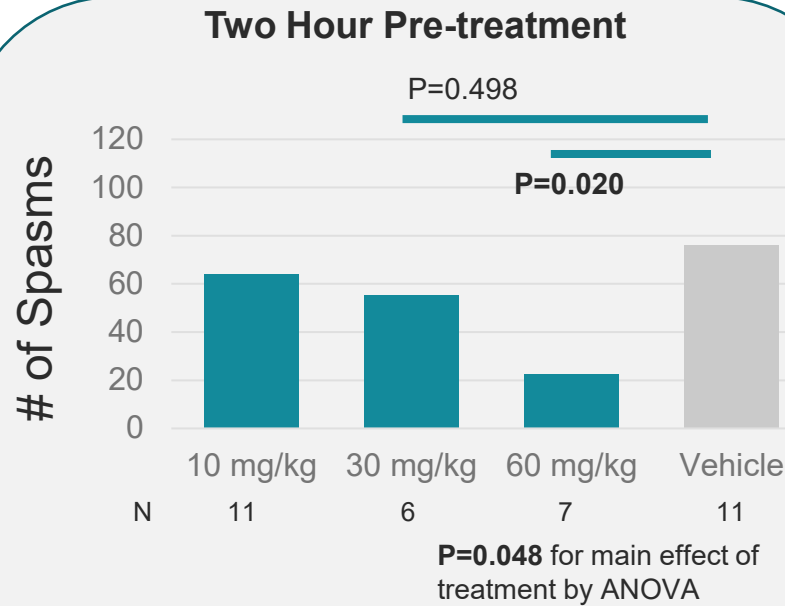
Test Compound	2 hour	4 hour
Vehicle*	X	X
TRV045 10 mg/kg	X	X
TRV045 30 mg/kg	X	X
TRV045 60 mg/kg	X	X

* carboxymethylcellulose

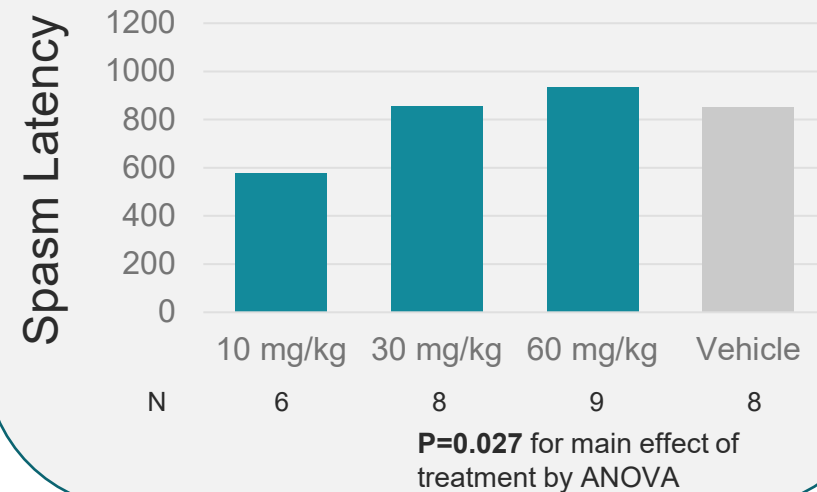
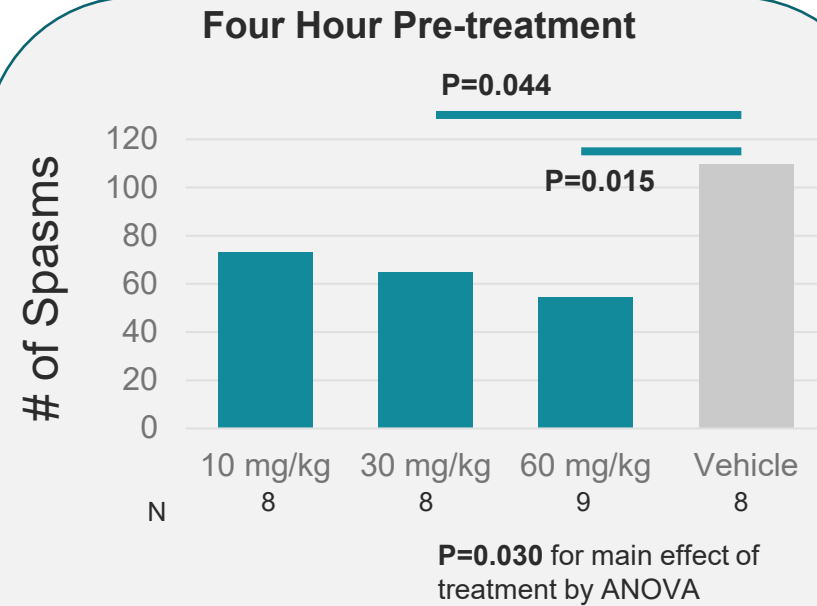
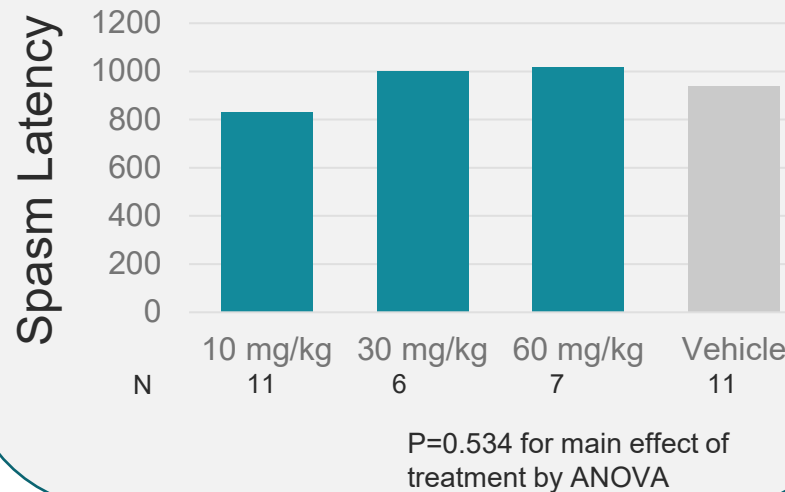
NOTE: “G” and “P” represent gestational and post-natal days, respectively

Efficacy of TRV045 in a Validated Model of Infantile Spasms

Primary Outcome:
Reduction in number
of spasms



Secondary Outcome:
Latency to onset of
spasms



TRV045 Proof-of-Concept Study Program – Highlights

Phase 1 Human Healthy Volunteers

- **Target Engagement.** Demonstrated CNS penetration and target engagement
- **EEG Spectral Power.** Statistically significant ***increases*** in brain waves (alpha, beta, gamma) associated with arousal, alertness, cognitive processing, learning and memory

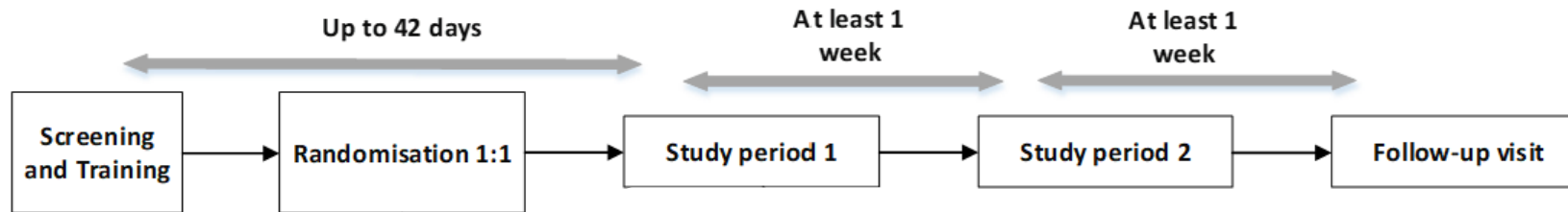
Statistically significant ***decrease*** in delta brain waves, and ***no significant change*** in theta brain waves, both of which are associated with sedation / sleep

- **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

TMS POC Study Design in Healthy Volunteers

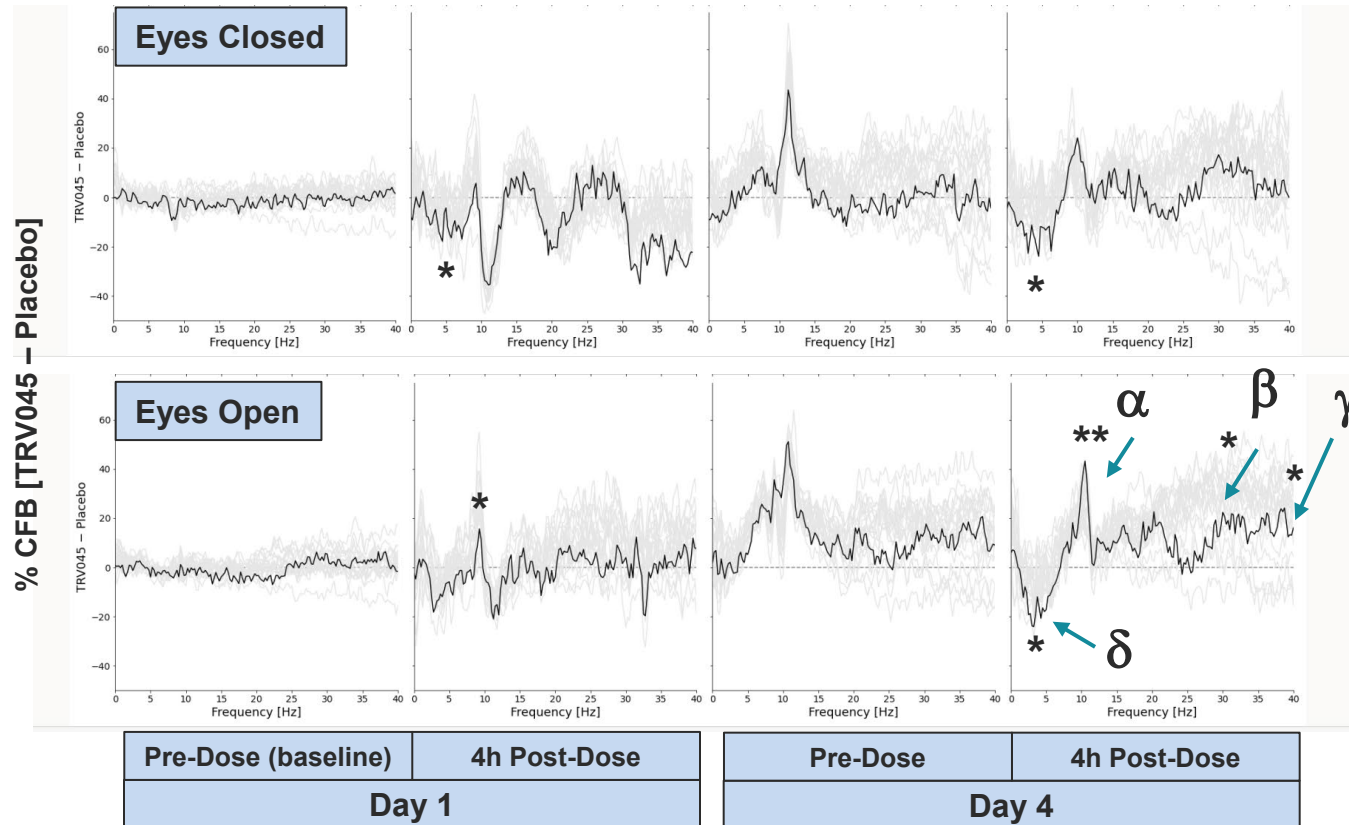
- **Design:** Randomized, double-blind, placebo-controlled, multiple dose, two-way cross-over (n=25 male subjects; mean age 31.5 years, range 21-55)
 - Placebo or TRV045 (250mg) for 4 days; post-dose assessments performed at 4 hours



- 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

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

qEEG Power Spectral Analysis (TRV045 minus placebo)



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

Associated with alertness / arousal / memory / learning

Delta: Significant reduction in right parietal region
Theta: No significant difference

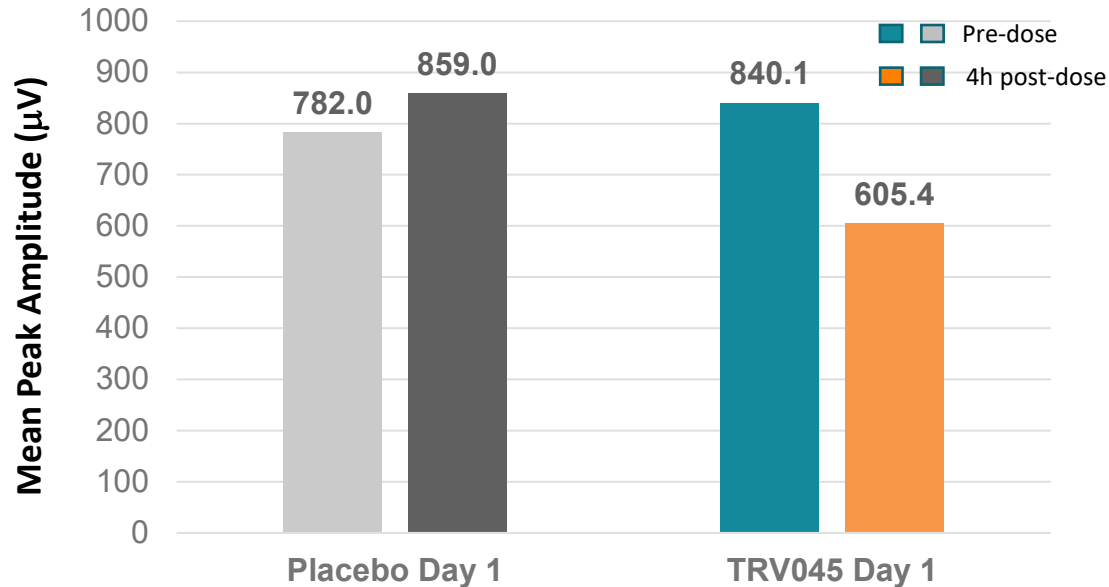
Associated with sedation / sleep

CFB = "Change from Baseline";

NOTE: Graphs display the difference between TRV045 and placebo average absolute power spectral densities (% change from baseline) at each study timepoint. Each grey line represents one channel with Cz as the black line. For biomarker analysis, * P < 0.05 ** P < 0.01 within the specified PSD bands.

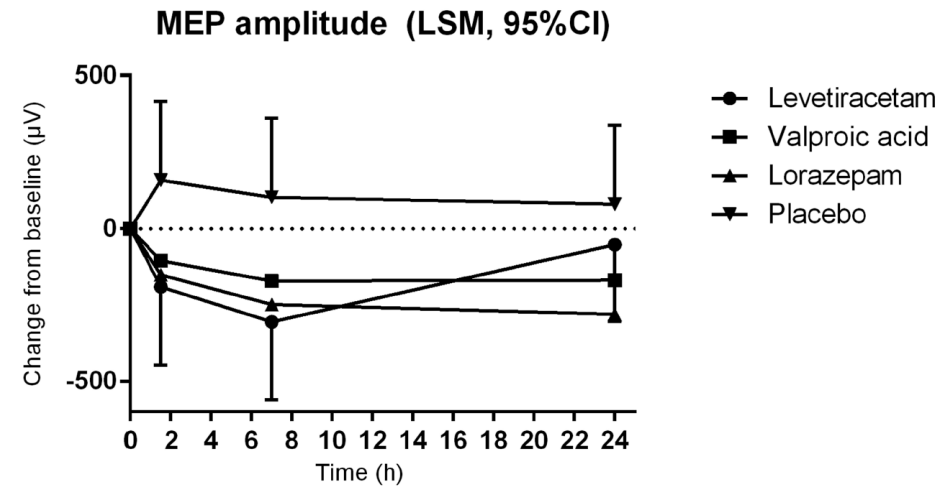
TRV045 Effect on Cortical Excitability vs AEDs*

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

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 $\geq 10\%$ 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 significant difference (vs placebo) in any AEs including:

Sedation

Balance Disorders

Attention Disturbances

Nausea

Dry Mouth

Blurred Vision

Overall Conclusions

TRV045 Proof-of-Concept Study Program

- **Target Engagement.** Demonstrated CNS penetration and target engagement
- **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

TRV045 Development Program: Key Milestones

- Nonclinical
 - DART studies; 3-month toxicology data (COMPLETE)
 - Nonclinical data package will support advancing to Phase 2 development
 - Strong support for epilepsy indications from ETSP (adult pharmaco-refractory epilepsy) and NYMC (orphan infantile spasms) study data
- CMC
 - API process optimization (GLP, GMP batch production) (COMPLETE)
 - Phase 2-ready formulation development (COMPLETE)
 - API/DP tech transfer (READY TO ADVANCE IN PREPARATION FOR PHASE 2)
- Clinical
 - Phase 1 Program (COMPLETE)
- Regulatory
 - IND available for diabetic neuropathic pain indication
 - Data package available to support advancing in epilepsy indications

Key milestones enable advancing to Phase 2

TRV045: Broad Potential Applicability

Unique MOA Produces Compelling Profile

Potent and selective S1P₁R 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)

Pain (DPN, CIPN)

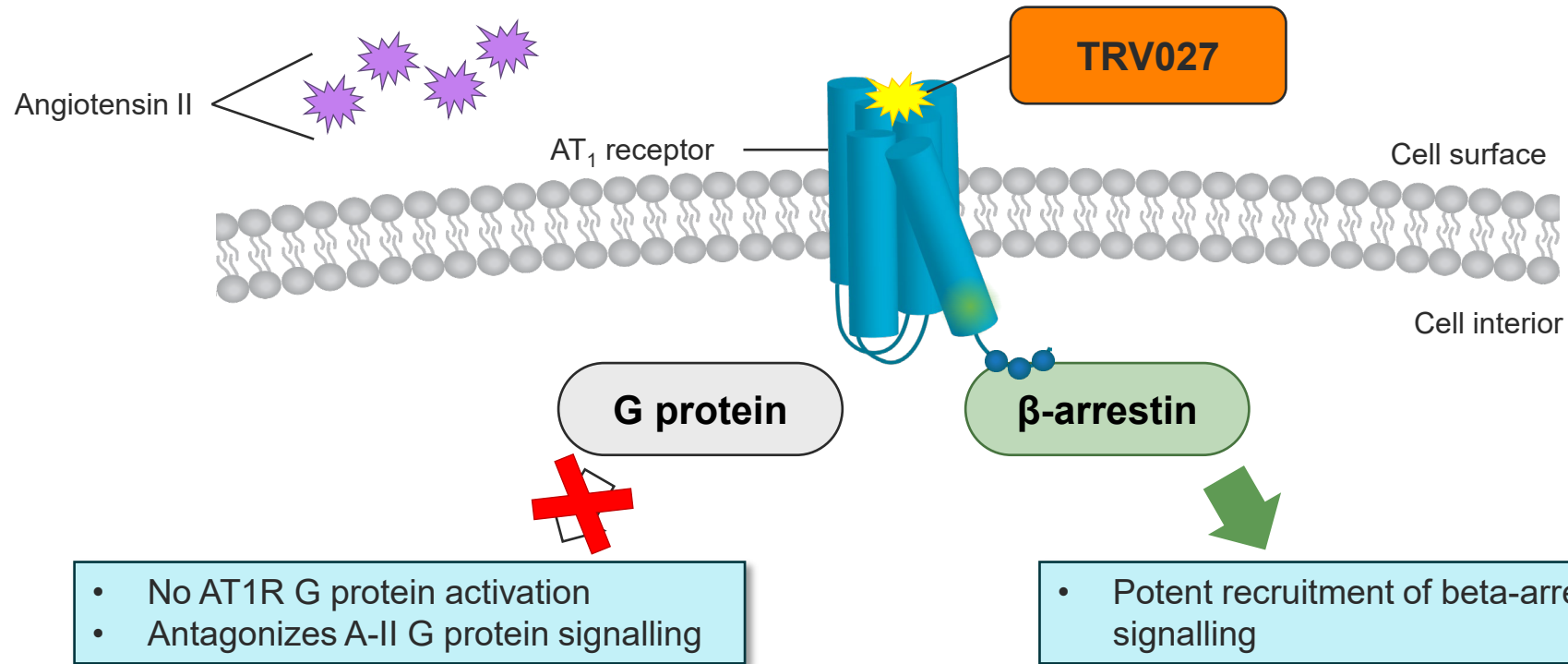
Autoimmune (MS, RA, UC, Crohn's Disease)

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

TRV027: New Chemical Entity Targeting the AT₁ Receptor

Beta-arrestin biased action, with no G-protein signalling



TRV027 is the only selective AT₁ receptor agonist
Safety / tolerability data in ~700 patients

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**



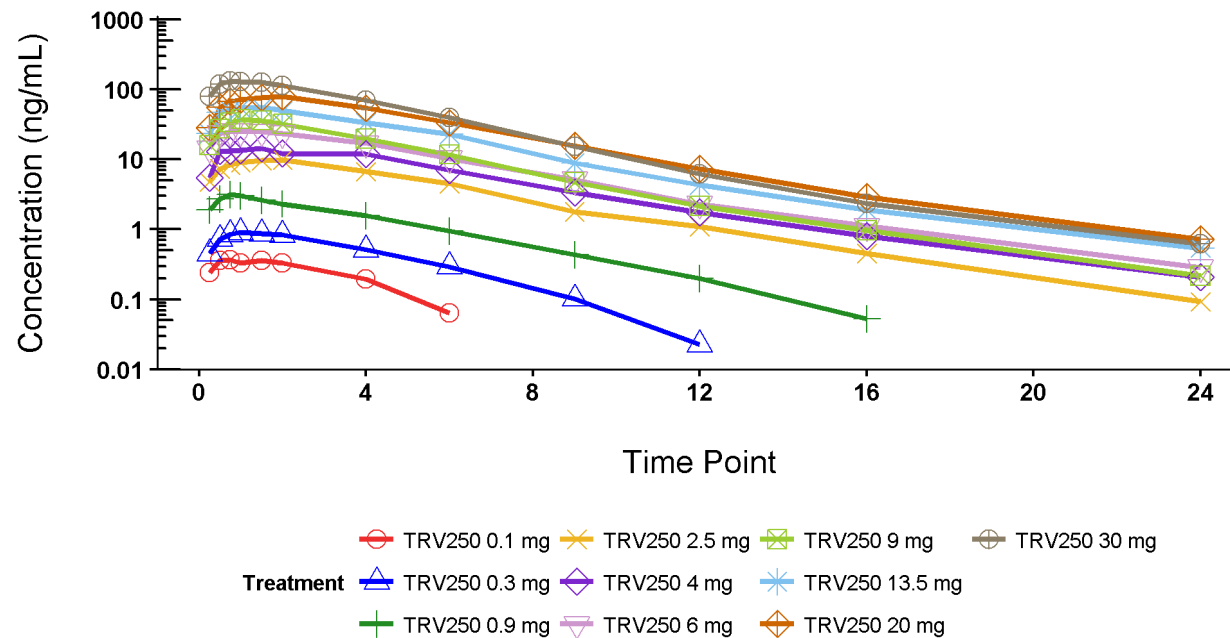
**1.2M ER visits
due to migraines**

- **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

TRV734: Maintenance Therapy for Opioid Use Disorder

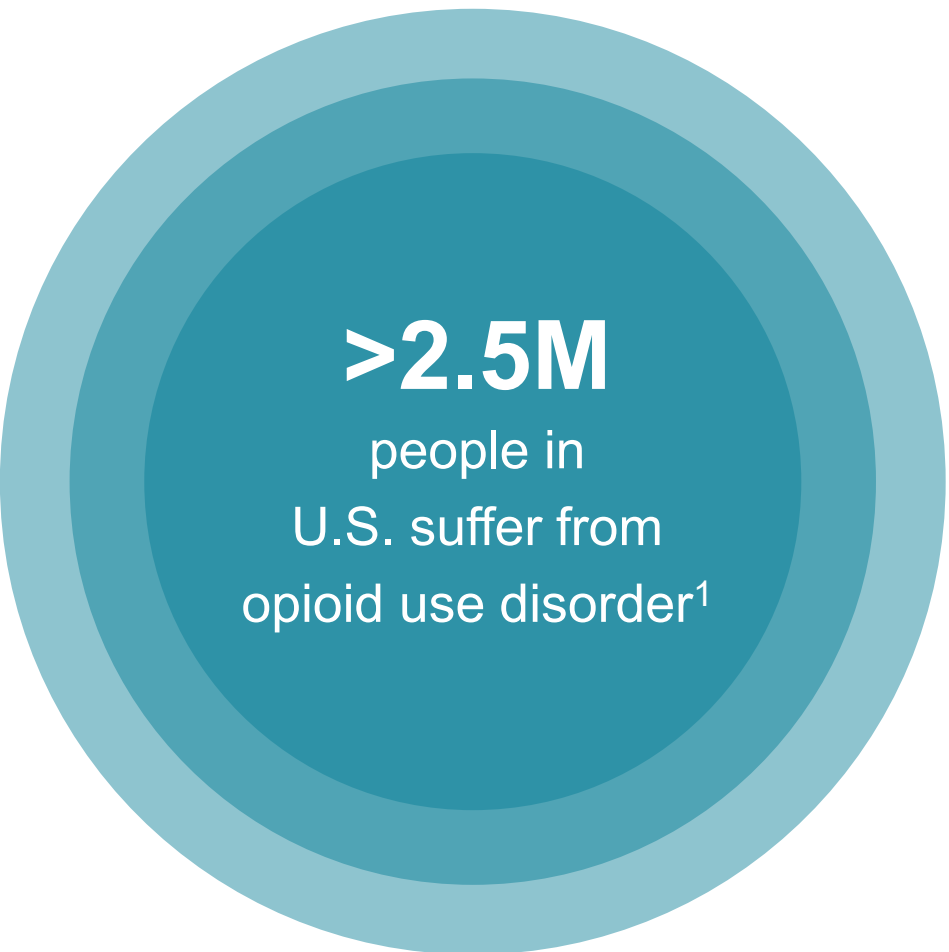
Selective agonism at μ receptor: nonclinical evidence of improved tolerability

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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S1PR: Validated target for blockbusters (fingolimod / siponimod / ozanimod / ponesimod)
New chemical entity; potent & selective for subtype 1; developed in-house with strong IP (2038)
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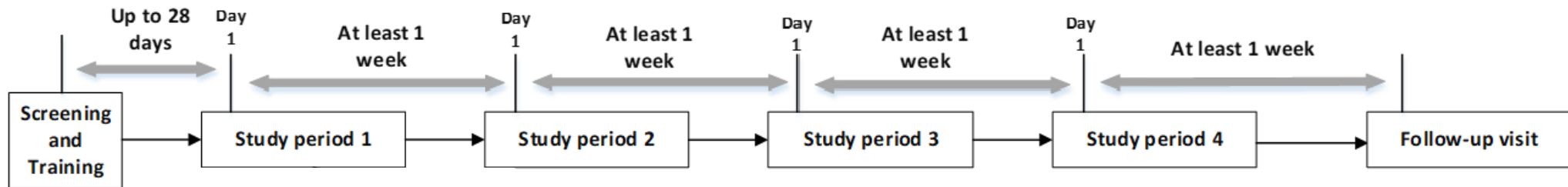
Novel CNS pipeline

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

Appendix

TRV045: PainCart® POC Study in Healthy Volunteers

- **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

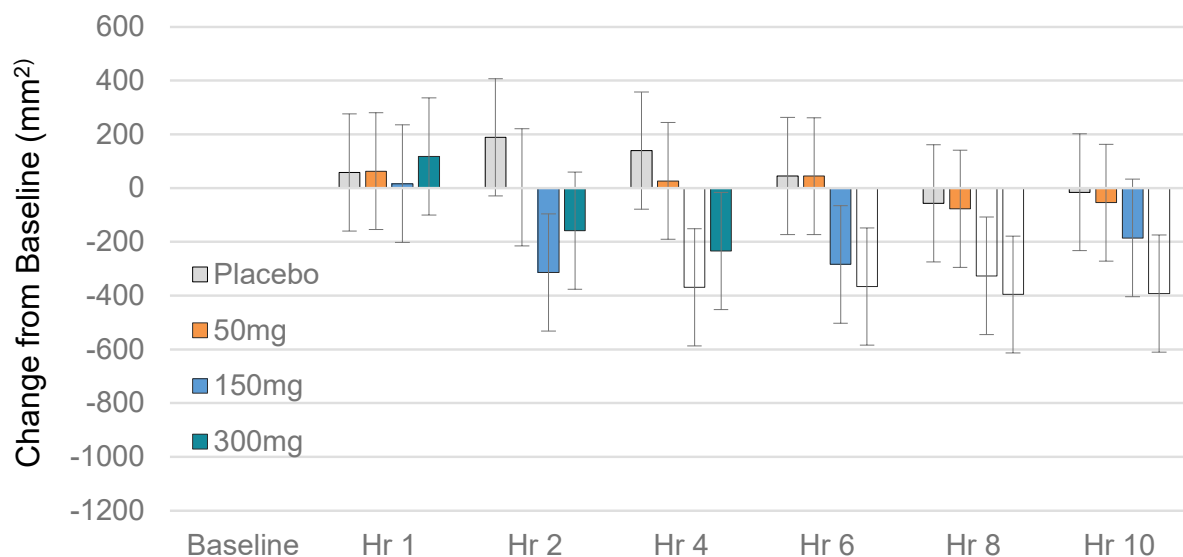
TRV045 Significantly Reduced Mechanical Allodynia

1% capsaicin-treated dominant volar forearm – Von Frey filament allodynic area (CFB, mm²)

300mg TRV045 v Placebo; P=0.0023

150mg TRV045 v Placebo; P=0.0022

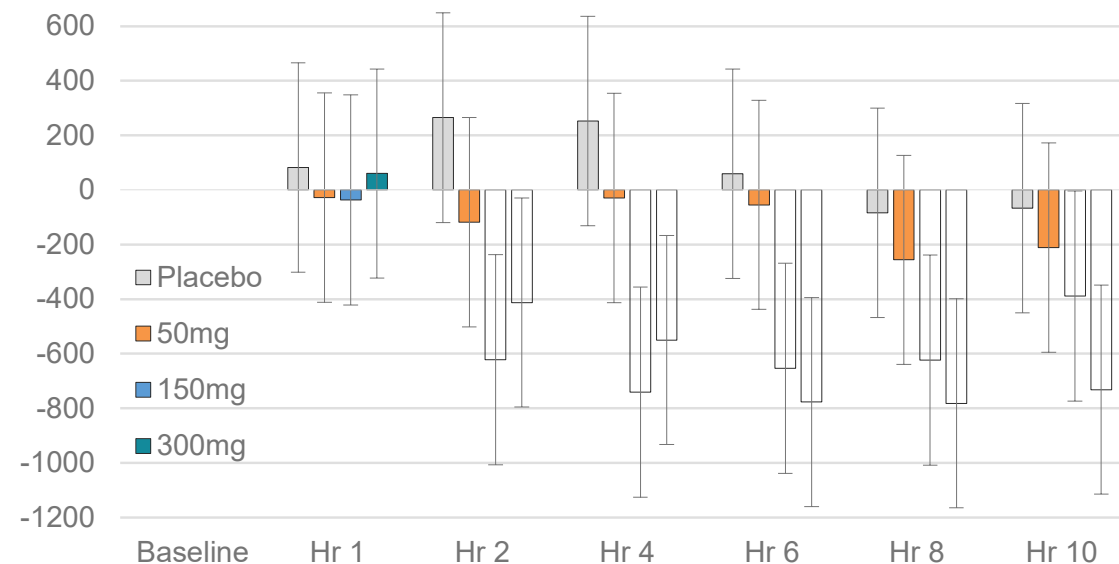
Secondary Allodynic Area



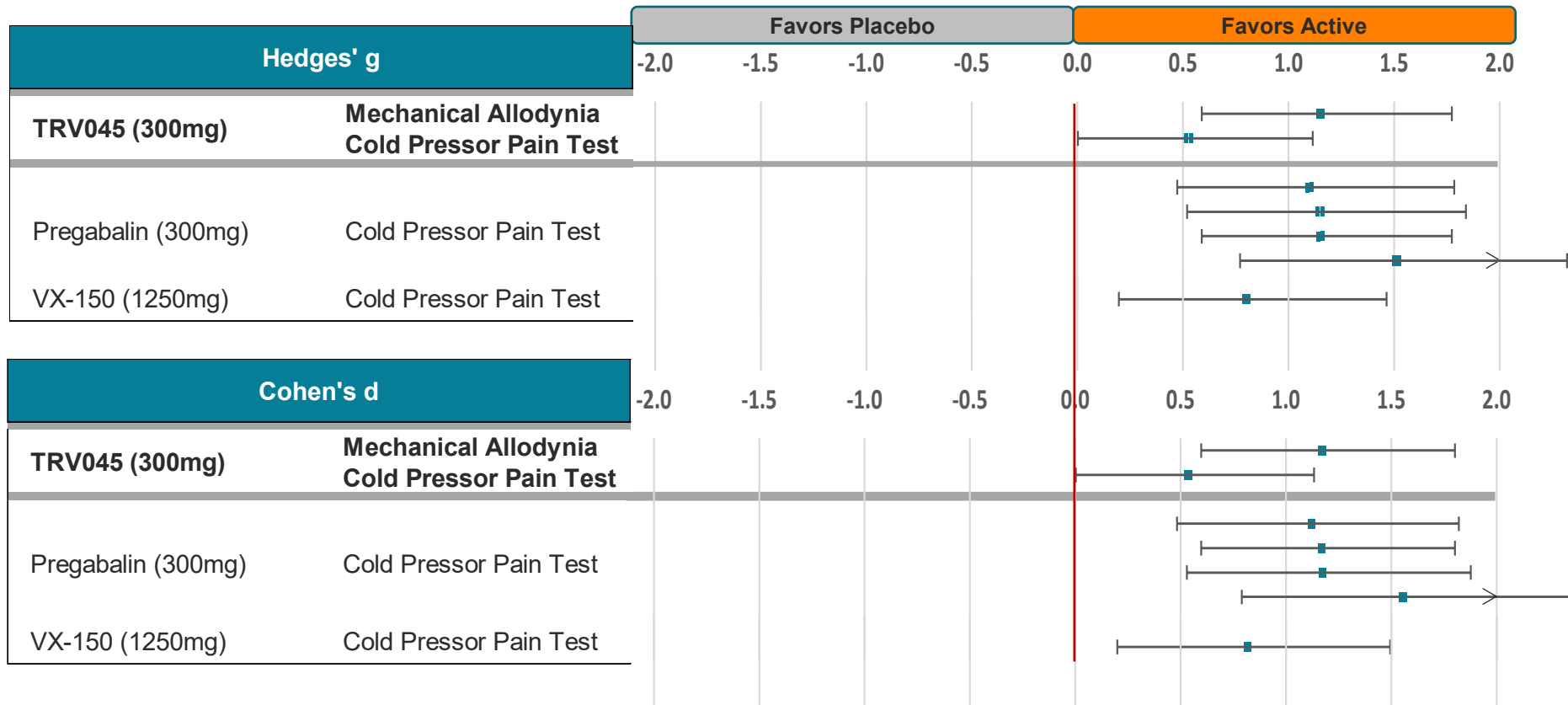
300mg TRV045 v Placebo; P=0.0001

150mg TRV045 v Placebo; P=0.0002

Total Allodynic Area



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

Summary: PainCart® Study in Healthy Volunteers

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