

Preclinical Efficacy of Elismetrep, a TRPM8 Blocker, as a Monotherapy and in Combination with Gepants or Triptans

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Disclosures: Justine Kupferman


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Learning Goals

- I. TRPM8 channel blockade is a mechanistically distinct therapeutic approach from current migraine treatments
- II. Elismetrep is a novel, oral, selective TRPM8 migraine-associated channel blocker (MACB) in late-stage clinical development
- III. Elismetrep prevents migraine-like pain in response to a variety of known migraine triggers in rats, suggesting potential for addressing heterogeneity in migraine
- IV. Elismetrep works in combination with gepants and triptans in a preclinical model relevant to migraine


Transient Receptor Potential Melastatin 8 (TRPM8)

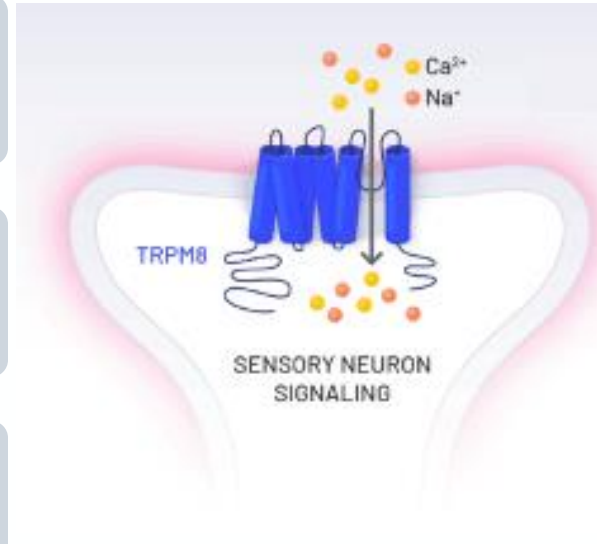
 TRPM8 is a non-selective cation channel activated by cool temperatures as well as agonists including menthol^{1,2,3}

 Expressed in peripheral sensory neurons including the trigeminal ganglia^{4,5}

 TRPM8 KO mice do not respond to migraine-inducing agents nitroglycerin and CGRP⁶

 TRPM8 gene is in a known migraine GWAS locus^{7,8}

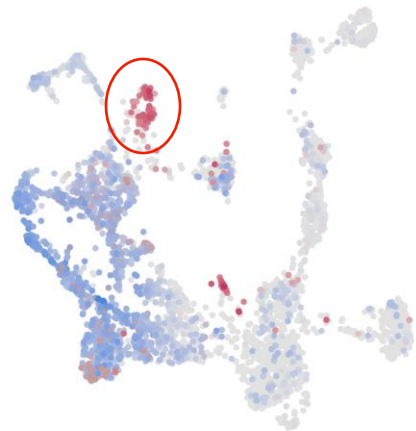
 Allele-specific expression observed in disease-relevant tissue (sensory neurons) suggesting therapeutic benefit with TRPM8 blockade⁹



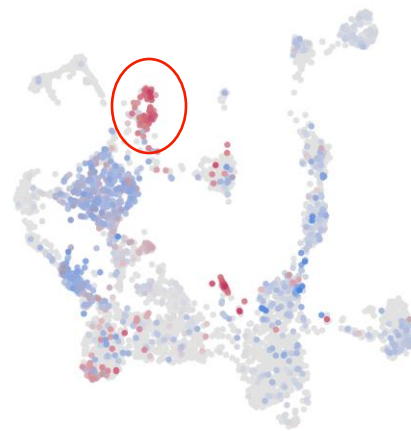
1. McKemy, D. et al., Nature, 2002;
2. Peier, A. et al. Cell, 2002;
3. Yarmolinsky, D. et al Neuron
4. Yang, L. et al., Neuron, 2022
5. Bhuiyan, S. et al., Sci. Advances, 2024
6. Wei, C. et al, Pain, 2022
7. Chasman, D. et al., Nat. Genetics, 2011;
8. Hautakangas, H. et al., Nat. Genetics, 2022.
9. Gavva, N. et al., Sci Rep 2019

TRPM8 Expression in Trigeminal Ganglia is Distinct From Other Migraine Targets

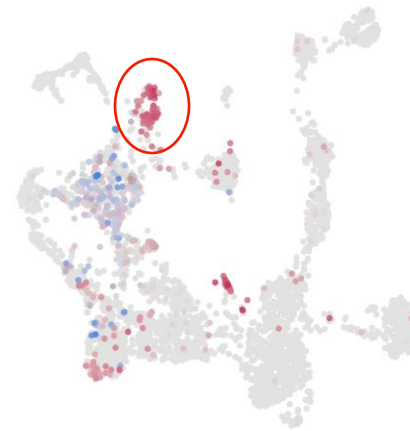
Expression of select migraine-relevant genes in human trigeminal ganglion (*TRPM8 in red*¹)



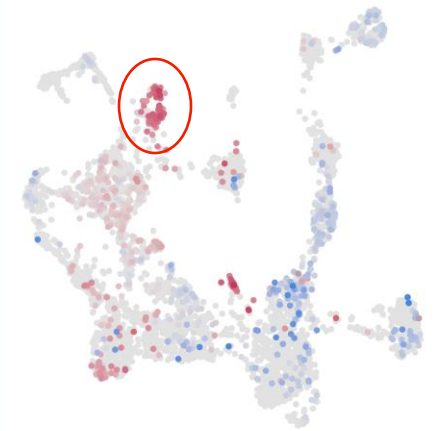
CALCA
(CGRP)



ADCYAP1
(PACAP)



HTR1F
(5HTR1F)

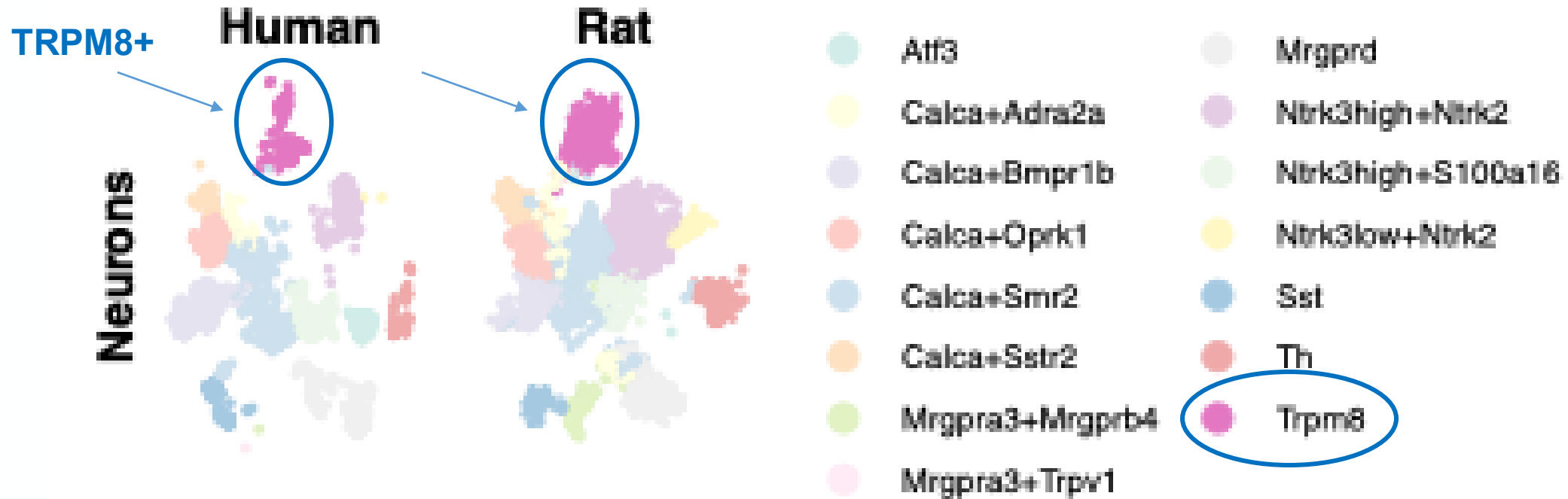


HTR1D
(5HTR1D)

- *TRPM8* expression defines a population of trigeminal ganglia neurons that has little overlap with CGRP, PACAP, and serotonin receptors
- This suggests that *TRPM8* is a mechanistically distinct target
- Therefore, we hypothesized that *TRPM8* blockers might work synergistically with other migraine therapeutics including gepants and triptans

TRPM8 Expression in Trigeminal Ganglia is Conserved from Rodent to Human

Supports use of the rat to understand TRPM8 function in migraine

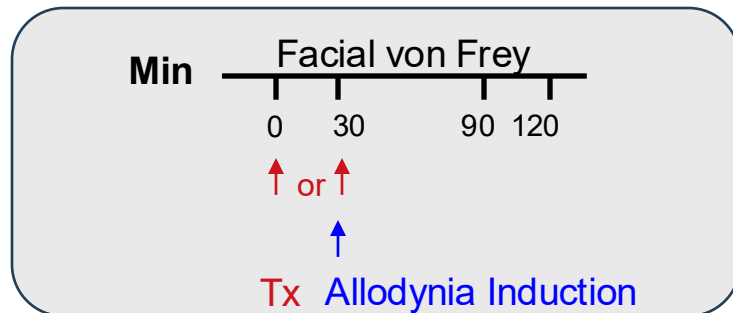


- Single cell sequencing of rat trigeminal ganglia performed to compare with human *TRPM8* expression^{1, 2}
- Expression observed only in neurons (not satellite glial cells) and defines a unique cluster of neurons

1. Bhuiyan, S. et al., Sci. Advances, 2024; 2. Yang, L., et al., Neuron, 2022

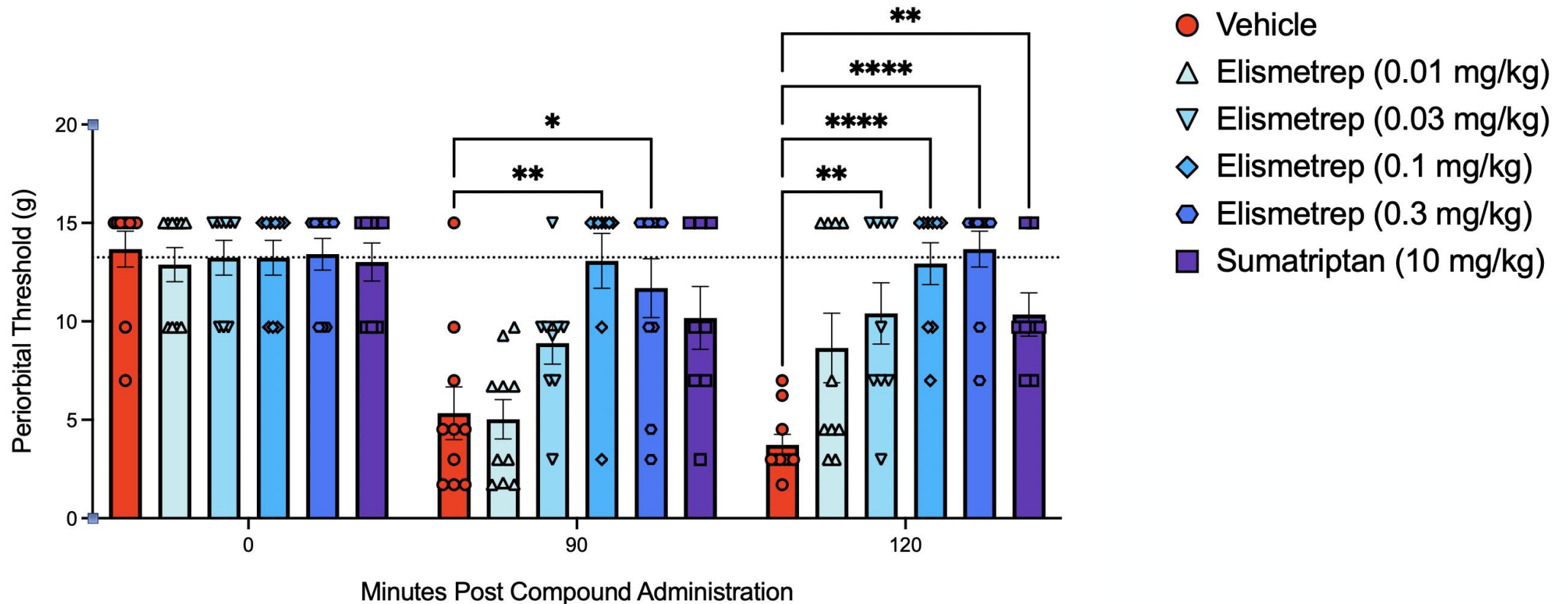
Methods to Understand TRPM8 Blockade in Migraine

- Elismetrep: an oral, potent, highly selective TRPM8 migraine-associated channel blocker (MACB)
 - Potent TRPM8 channel blocker ($IC_{50} = 0.61$, 95% Confidence Interval 0.41 to 0.90 nM)
 - No or minimal activity at other TRP channels (hTRPA1, hTRPC6, hTRPM2 and hTRPV1)
 - No off-target activity in screen of 81 receptors, ion channels, transporters, and enzymes
- In vivo assay:
 - Male Sprague Dawley rats age 8 - 9 weeks, $n = 8 - 10$
 - Periorbital allodynia measured by von Frey filaments
 - Allodynia induced by systemic (IP) delivery of isosorbide dinitrate (ISDN), CGRP, or PACAP
 - Elismetrep, olcegepant, and sumatriptan dosed orally



Elismetrep Blocks Periorbital Allodynia Induced by ISDN

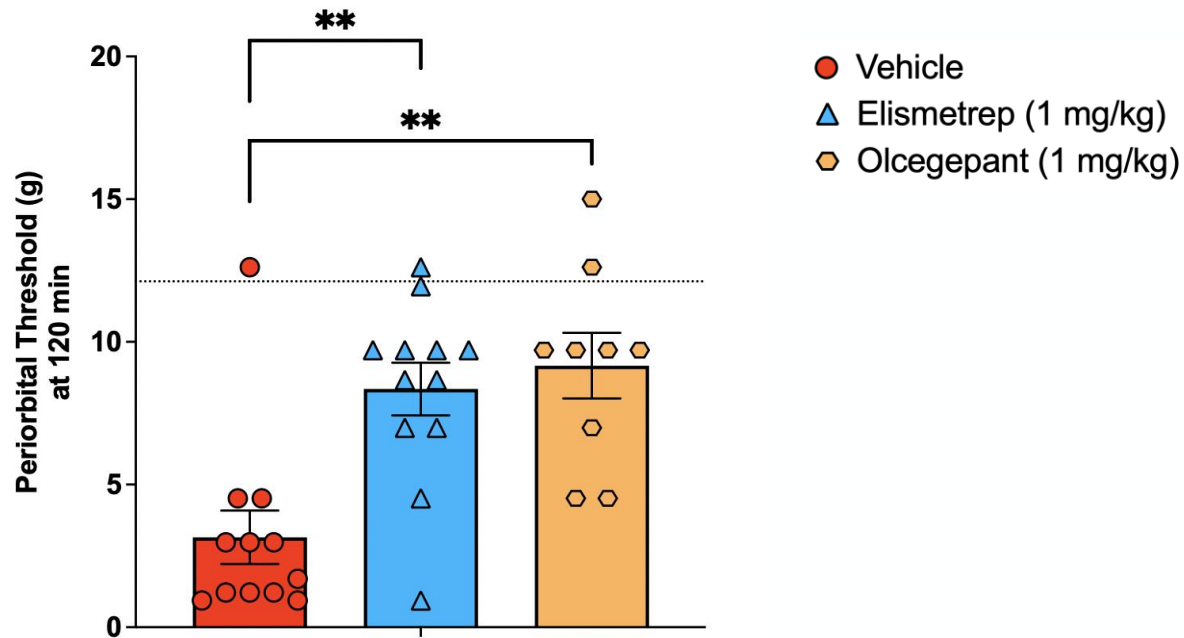
ISDN-Induced Periorbital Allodynia in Rat



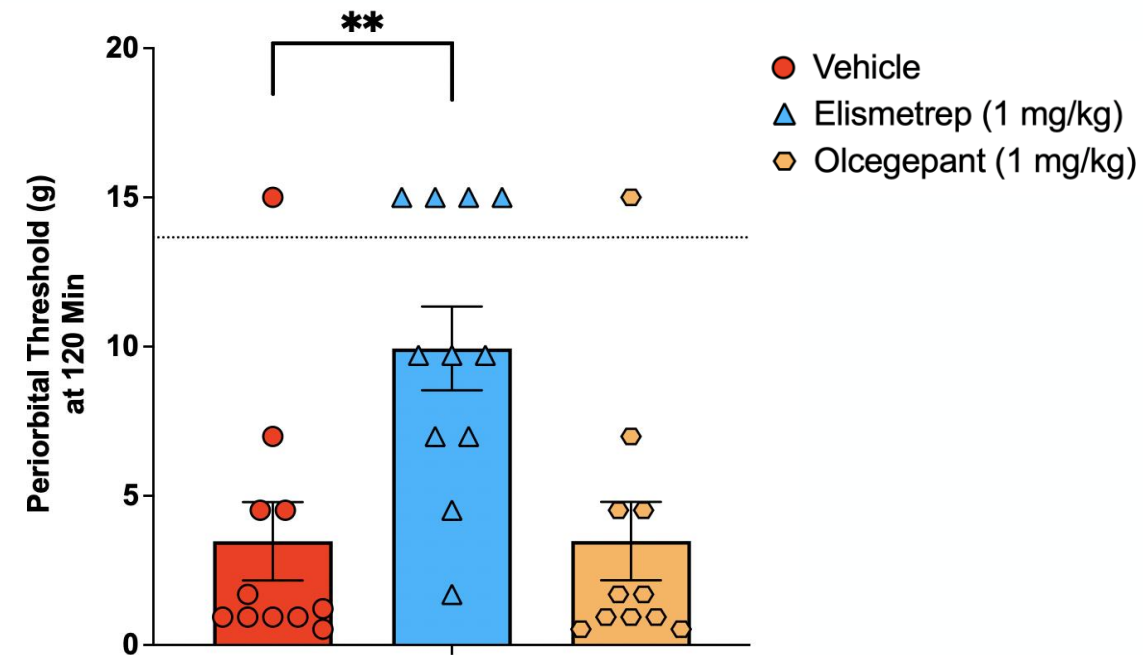
- ISDN dosed 30 minutes after compound
- Dunnet's Multiple Comparison Test * = 0.05, ** = 0.01, **** = 0.001

Elismetrep Blocks Periorbital Allodynia Induced by Multiple Migraine Challenge Agents

CGRP-Induced Periorbital Allodynia in Rat



PACAP-Induced Periorbital Allodynia in Rat

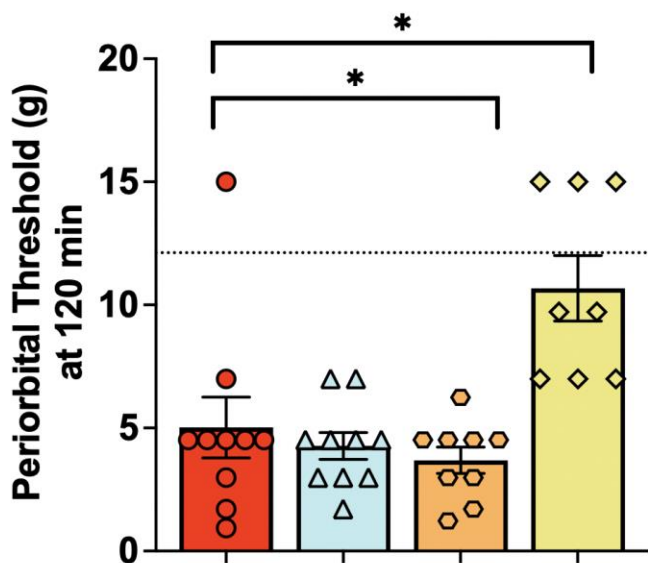


- Lack of efficacy for olcegepant in PACAP-induced allodynia consistent with published data in human challenge studies showing that CGRP mAB does not block PACAP-induced migraine¹
- Dotted line = Average baseline periorbital threshold
- CGRP (1 mg/kg, IP) or PACAP (1 mg/kg, IP) dosed 30 minutes after compound

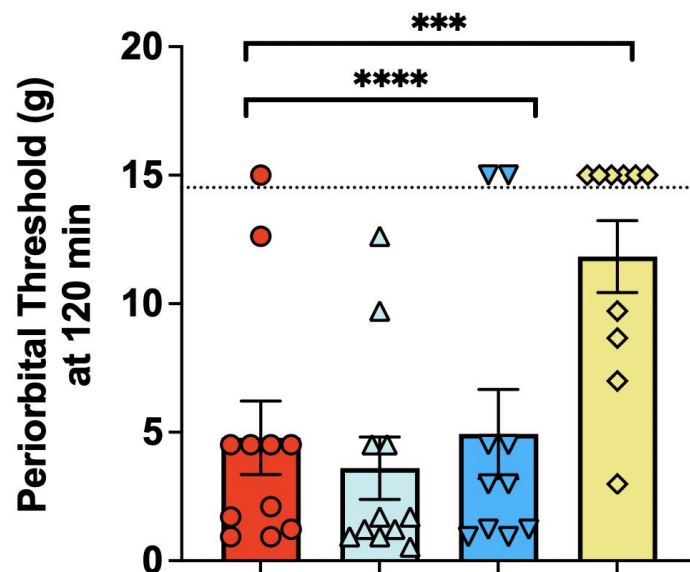
Elismetrep Combines with Olcegepant and Sumatriptan

Olcegepant and Sumatriptan Do NOT Combine to Block Allodynia

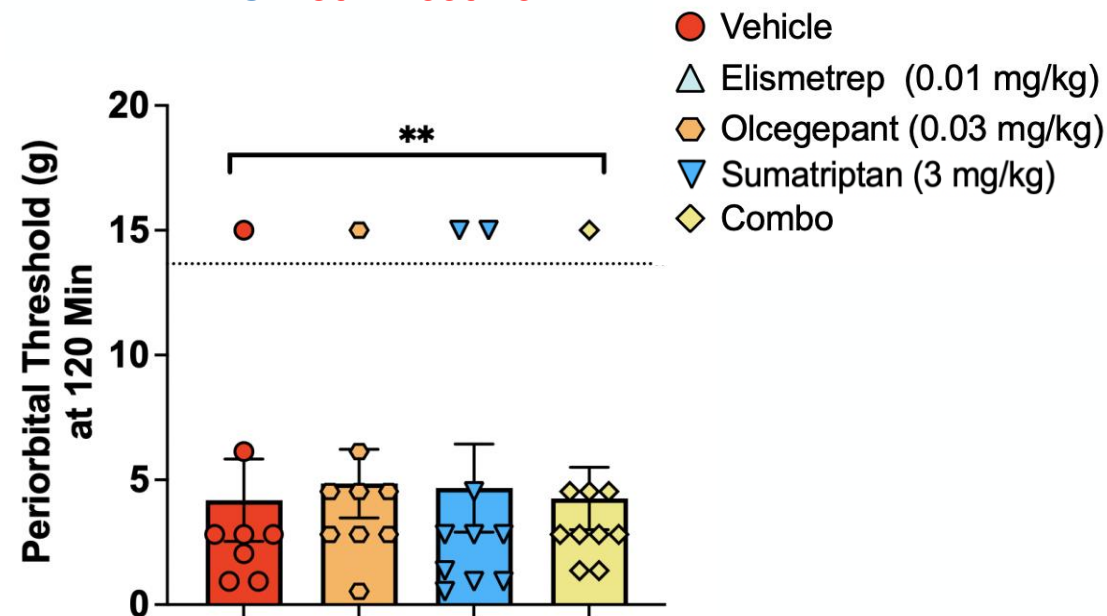
Combination of
Elismetrep + Olcegepant
Is Effective



Combination of
Elismetrep + Sumatriptan
Is Effective



Combination of
Sumatriptan + Olcegepant
is Not Effective



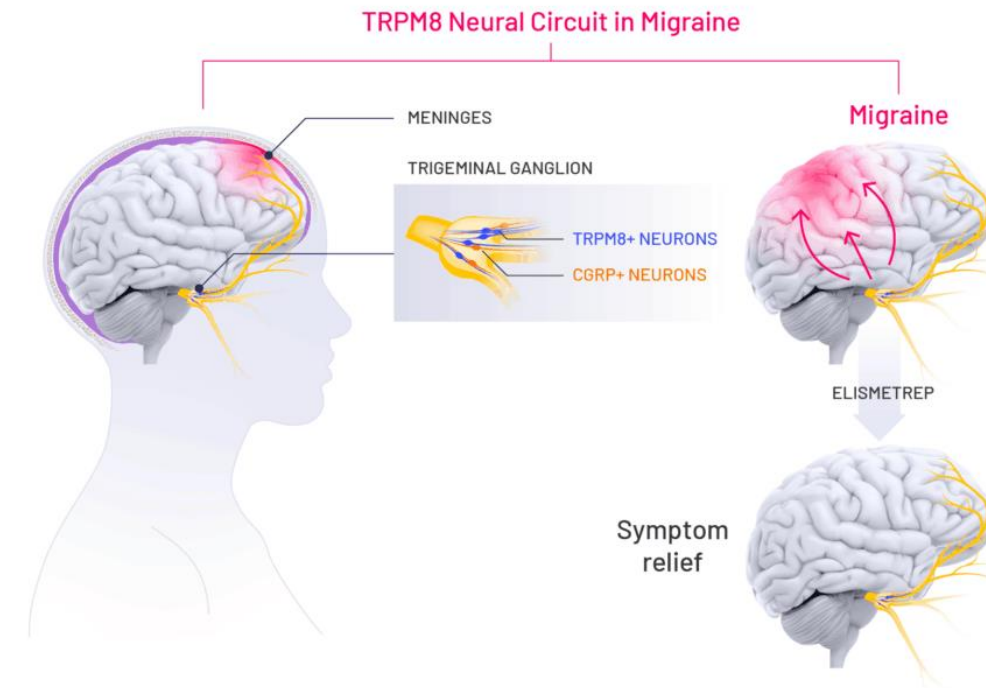
- Vehicle
- △ Elismetrep (0.01 mg/kg)
- Olcegepant (0.03 mg/kg)
- ▽ Sumatriptan (3 mg/kg)
- ◇ Combo

- Sub efficacious doses tested alone or in combination in ISDN-induced allodynia model
- Dose response studies of elismetrep, olcegepant, and sumatriptan informed selection of just sub-efficacious doses
- Lack of efficacy for sumatriptan + olcegepant consistent with published data¹
- Dotted line = Average baseline periorbital threshold

1. Ernsten, C. et al, *Cephalalgia* 2020

TRPM8 Channel Blockade Represents a New, Mechanistically Distinct Approach for the Treatment of Migraine

- TRPM8 blockade prevents periorbital allodynia in response to a variety of known migraine triggers in rats – suggesting potential for addressing heterogeneity in migraine
- Elismetrep works in combination with olcegepant and sumatriptan
 - Olcegepant and sumatriptan are not effective in combination; Sumatriptan is thought to block CGRP release – targeting the same pathway as the gepants
 - Suggests TRPM8 channel blockade works by a different mechanism



Phase 3 registration trials for elismetrep expected to initiate in mid-2026