First-in-Human Study Evaluating the Safety, Tolerability, and Pharmacokinetics of the First-in-Class TRPM3 Antagonist BHV-2100 in Development for Migraine and Pain

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Richard Bertz, PhD is employed by and holds stock / stock options in Biohaven

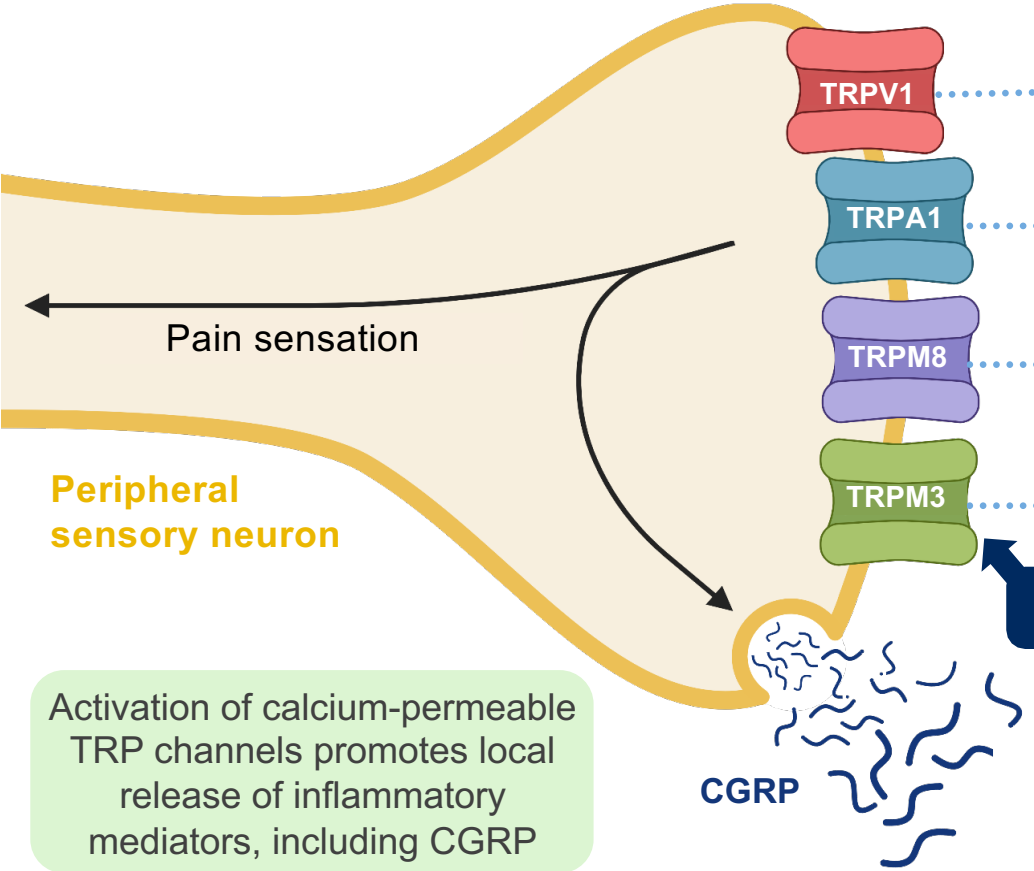
Rationale for TRPM3 Antagonism as a Treatment for Migraine

- **Strong mechanistic evidence supports the role of TRPM3 in neurogenic inflammation and sensitization of the trigeminovascular system, which underlie migraine pathogenesis[1]**
  - TRPM3 receptors sensitize and activate the nociceptors of the trigeminovascular system[2–4]
  - TRPM3 inhibition normalizes the sensitivity of nociceptors[3,4]
  - TRPM3 is a key driver of neurogenic inflammation in a CGRP-dependent and independent manner[5,6]
  - Inhibition of TRP receptors systemically or locally, decreases CGRP release, nociceptive neuron activity, and animal nocifensive behavior [7]
- **Human genetics validates role of TRPM3 in migraine and pain[8,9]**
  - TRPM3 gene variants are associated with migraine risk and pain sensitivity in humans
- **TRPM3 expression profile in the human trigeminovascular system indicates a functional role in migraine pathophysiology[10]**
  - TRPM3 is highly expressed in cells of the human trigeminal ganglia
  - TRPM3 is co-expressed with a network of other migraine-relevant genes in human trigeminal ganglia
- **Therapeutic effect of TRPM3 antagonism is supported by preliminary clinical data**
  - TRPM3 regulates the activity of other TRP channels (TRPV1 and TRPA1); and preliminary clinical data supports therapeutic benefit of inhibiting these TRP channels in migraine[5,11]

1. Ramachandran R. Semin Immunopathol 2018;40(3):301-314. 2. Vriens J et al, Neuron 2011;70(3):482-94. 3. Kelemen B et al, Biochemical pharmacology 2021;183:114310. 4. Krivoshein G et al, J Headache Pain 2022;23(1):. 5. Mulier, M., et al, Elife, 2020. 6. Bamps DAnnu Rev Pharmacol Toxicol. 2021 Jan 6;61:655-677. 7. Held, K., et al., Proc Natl Acad Sci U S A, 2015. 112(11): p. E1363-72. 8. Burglen L et al. Elife 2023. 9. Biohaven internal data. 10. Derived from https://painseq.shinyapps.io/tg-painseq and Yang, L et al. Neuron 2022. 110(11): 1806-1821 e1808.11. Diamond, S., et al., Cephalalgia, 2000. 20(6): p. 597-602.

BHV-2100: A First-in-Class Orally Administered TRPM3 Antagonist in Clinical Development for Migraine and Pain

BHV-2100 is being developed with an improved profile compared to existing pain medications and other TRP antagonists



Effects on thermal sensation and thermoregulation hampered clinical development of drugs targeting TRPV1 systemically

Challenging drug target because of channel's complex gating and pharmacology
Remains in active drug development

Effects on thermal sensation and thermoregulation
Remains in active drug development

Promising as a novel target: broader expression than TRPV1 and TRPA1 in peripheral neurons; unlikely to affect body temperature homeostasis

Activation of calcium-permeable TRP channels promotes local release of inflammatory mediators, including CGRP

BHV-2100

- Peripherally restricted selective TRPM3 antagonist
- Potent, rapid reversal of pain across multiple preclinical pain models
- No thermoregulatory or sedative effects; not expected to be addictive

CGRP, calcitonin gene-related peptide

Koivisto AP, et al. *Nat Rev Drug Discov*. 2022;21(1):41-59. Bamps D, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:655-677. Vriens J, et al. Presented at NeuPSIG 2023. Lisbon, Portugal. Poster SA127

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BHV-2100 Phase 1 First-in-Human SAD/MAD Study

Objectives

Evaluate safety and tolerability of single and multiple dose oral administration of BHV-2100

Evaluate the PK of single and multiple doses of BHV-2100

Evaluate the effect of a high-calorie/high-fat meal on the PK of BHV-2100

Evaluate the effect of an acid-reducing agent (famotidine) on the PK of BHV-2100

Population:

- Healthy adult males and females aged 18-55 years

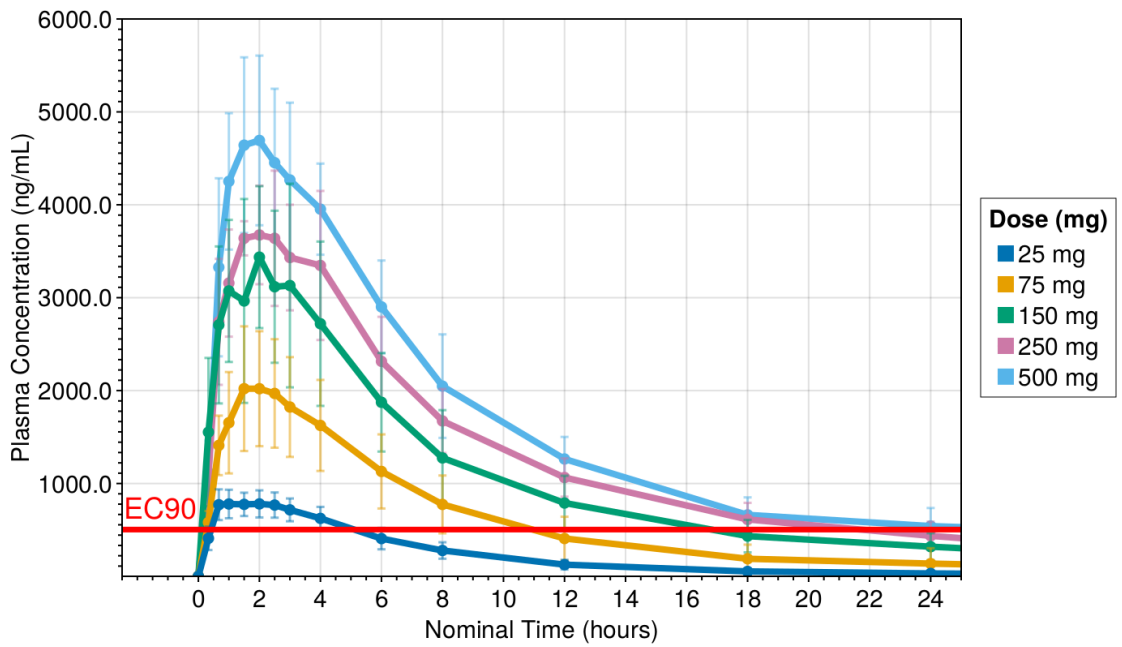
Study Design:

- Phase 1, randomized, placebo controlled, sequential SAD/MAD study
- SAD – Complete
  - Participants randomized 3:1 to a single oral dose of BHV-2100 (25, 75, 150, 250, or 500 mg) or placebo under fasting conditions
  - 150 mg was also administered with food (high-fat meal) and with famotidine
- MAD – Dosing Complete, Data Pending
- A Safety Review Committee reviewed the safety, tolerability, and PK data after completion of each dose level
- Samples collected up to 120 hours, analyzed for BHV-2100 by validated LC/MS assay, PK by noncompartmental methods

LC/MS, liquid chromatography/mass spectrometry; MAD, multiple ascending dose; PK, Pharmacokinetics; SAD, single ascending dose

BHV-2100 Demonstrates Rapid Absorption and Sustained Concentrations

Mean Concentration vs. Time Profiles of Single Oral Doses of BHV-2100



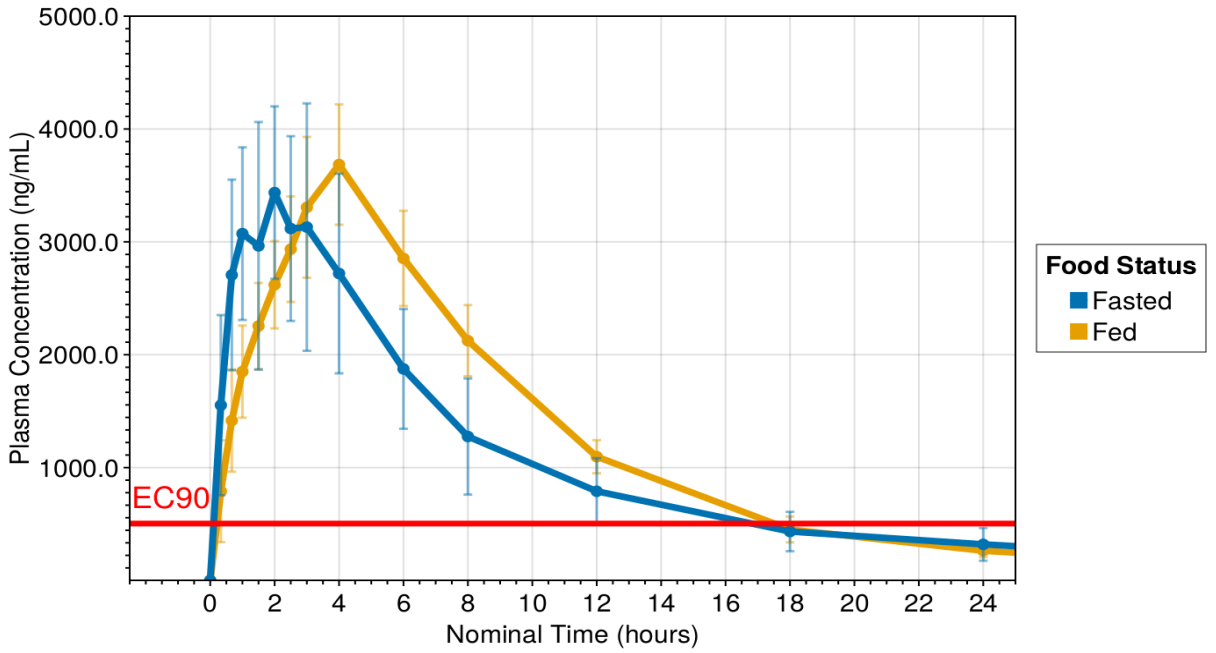
- T_{max} 1.5 to 2 hours
- $T_{1/2}$ ranges from 8 to 12 hours
- The PK of BHV-2100 was approximately dose-proportional at doses up to 150 mg
- At the lowest dose of 25 mg, plasma concentrations achieved EC90 by 30 minutes
- At 150 mg, plasma concentrations achieved 4x EC90 by 20 minutes and 7x EC90 by T_{max}

Plasma concentrations exceed EC90 after 20 minutes and are sustained above EC90 for several hours at all dose levels

EC90 represents the estimated plasma concentration threshold based on a preclinical model; Error bars represent the standard deviation from the arithmetic mean; N=6 for each dose group

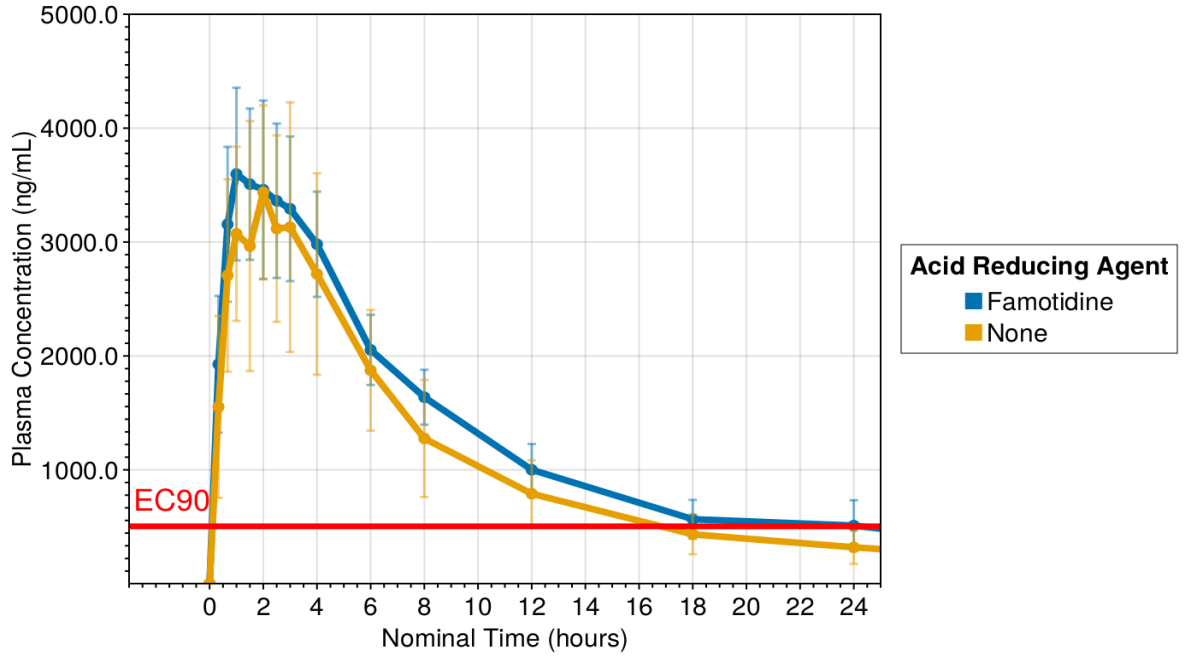
BHV-2100 PK Not Significantly Impacted by Food or Acid-Reducing Agent

Mean Concentration vs. Time Profiles of Single Oral Doses of 150 mg BHV-2100 With and Without Food



High-fat meal delayed T_{max} but concentrations >EC90 by 20 minutes

Mean Concentration vs. Time Profile of Single Oral Doses of 150 mg BHV-2100 With and Without Famotidine



Famotidine did not significantly impact BHV-2100 exposures

Results suggest dosing with food or an acid-reducing agent will not have a clinically significant impact on BHV-2100 PK/efficacy at doses up to 150 mg

EC90 represents the estimated plasma concentration threshold based on a preclinical model; Error bars represent the standard deviation from the arithmetic mean; N=6 for each dose group

BHV-2100: Safe and Well-Tolerated to Date in Healthy Adults

SAFETY AND TOLERABILITY

- No dose limiting toxicities
- No SAEs
- No severe TEAEs; 1 moderate TEAE not related to study drug; all other TEAEs mild
- No clinically significant trends in vital signs (including body temperature), laboratory values, or ECGs

DOSING

- SAD single doses up to 500 mg completed
- MAD dosing completed; data pending

SAD Cohorts (pooled) TEAE's in ≥ 2 subjects	Placebo (N=9) n (%)	BHV-2100 (N=30) n (%)
Dizziness	0	2 (6.7)
Fatigue	0	2 (6.7)

Pooled preliminary data; MAD, multiple ascending dose; SAD, single ascending dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event

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BHV-2100: A Clinical-Stage TRPM3 Antagonist for Migraine and Pain

- TRPM3 represents a novel target for the treatment of migraine and pain
- BHV-2100 is a first-in-class, orally administered, peripherally-restricted and selective TRPM3 antagonist
- BHV-2100 demonstrated rapid absorption and sustained concentrations above predicted efficacious levels at all doses tested after 20 min, supporting an ideal PK profile for treatment of migraine
- BHV-2100 demonstrated excellent safety and tolerability, without thermoregulatory AEs observed with other TRP antagonists, sedation, or gastrointestinal AEs associated with standard-of-care pain medications
- A Phase 2 clinical trial of BHV-2100 for acute treatment of migraine is planned to begin in 2024, evaluating efficacy and safety of of 25 mg, 75 mg, and 150 mg doses vs placebo

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Thank you!