Safety, Tolerability, and Pharmacokinetics of BHV-2100, a First-in-Class TRPM3 Antagonist for Pain and Migraine

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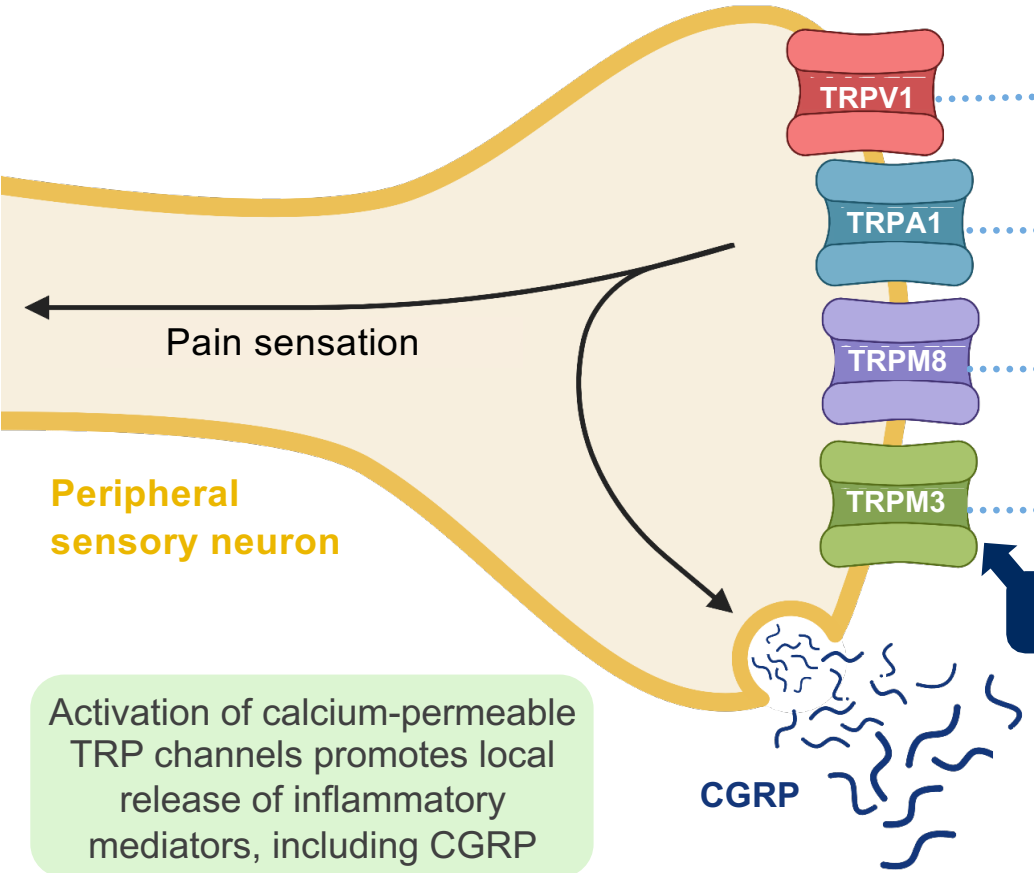
Volkan Granit, MD, MSc is employed by and holds stock / stock options in Biohaven

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



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

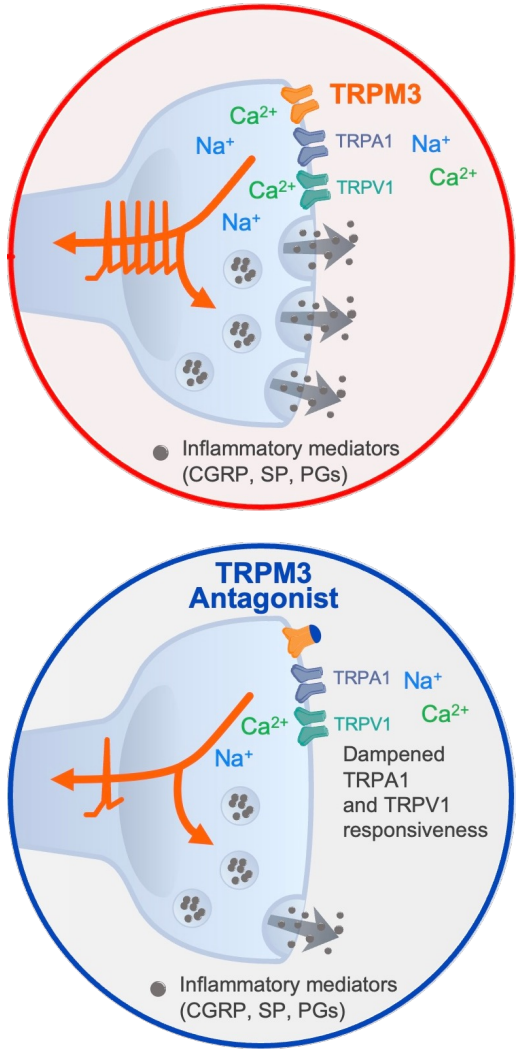
No thermoregulatory or sedative effects; not expected to be addictive

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.

Rationale for Targeting TRPM3 in the Treatment of Pain and Migraine

- TRPM3 is expressed in somatosensory neurons of the DRG and TG[1,2]
- Data implicating TRPM3 in pain signaling[1,3-8]
  - TRPM3 evokes pain when activated by noxious heat or select chemical ligands[1]
  - Mice deficient in TRPM3 do not develop pathological, mechanical, or thermal hypersensitivity[1,6,7]
  - TRPM3 genetic polymorphisms in humans are associated with migraine risk and altered thermal pain sensitivity [4, 8]
  - Inhibition of TRP receptors systemically or locally, decreases CGRP release, nociceptive neuron activity, and animal nocifensive behavior [9]
- TRPM3 expression and activity are markedly increased in sensory neurons innervating inflamed tissues[5]
- Inhibition of TRPM3 in nociceptors innervating inflamed tissues also dampens the responsiveness of the other key TRP channels (TRPV1 and TRPA1) on the same nociceptors [5]



1. Vriens J, et al. Neuron. 2011;70(3):482-494. 2. Vangeel L, et al. Br J Pharmacol. 2020;177(12):2683-2695. 3. Aloi VD, et al. Pain. 2023;164(9):2060-2069. 4. Lötsch J, et al. Int J Mol Sci. 2020;21(12):4367. 5. Mulier M, et al. Elife. 2020;9:e61103. 6. Alkhatib O, et al. J Neurosci. 2019;39(40):7840-7852. 7. Su S, et al. J Neurosci. 2021;41(11):2457-2474. 8. Biohaven Pharmaceuticals. Data on file. 9. Held K, et al. Proc Natl Acad Sci U S A. 2015;112(11):E1363-1372.

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

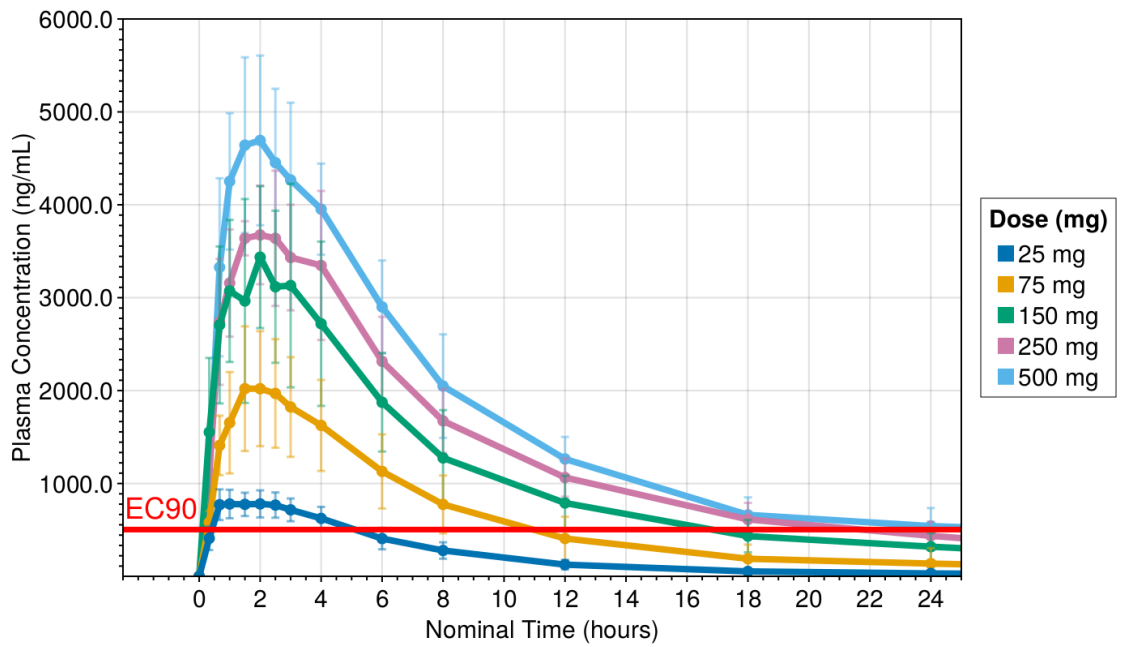
STUDY DESIGN

- Phase 1, randomized, placebo controlled, sequential SAD/MAD study
- SAD:
  - 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) or with famotidine
- MAD:
  - Participants were randomized 3:1 to BHV-2100 (25 mg once daily [QD], 75 mg QD, 150 mg QD, or 150 mg twice daily [BID]) or placebo and treated for 14 days

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
- $T_{1/2}$ ranged 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}

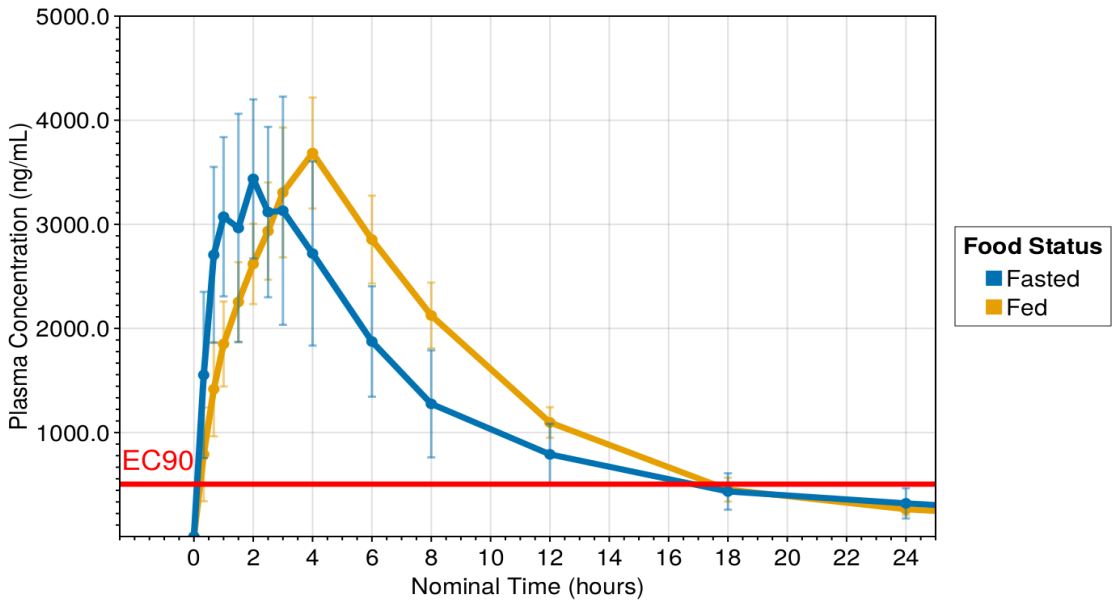
EC90 represents the estimated plasma concentration threshold based on a preclinical model; Error bars represent the standard deviation from the arithmetic mean; N=6 for each dose group

KEY POINT

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

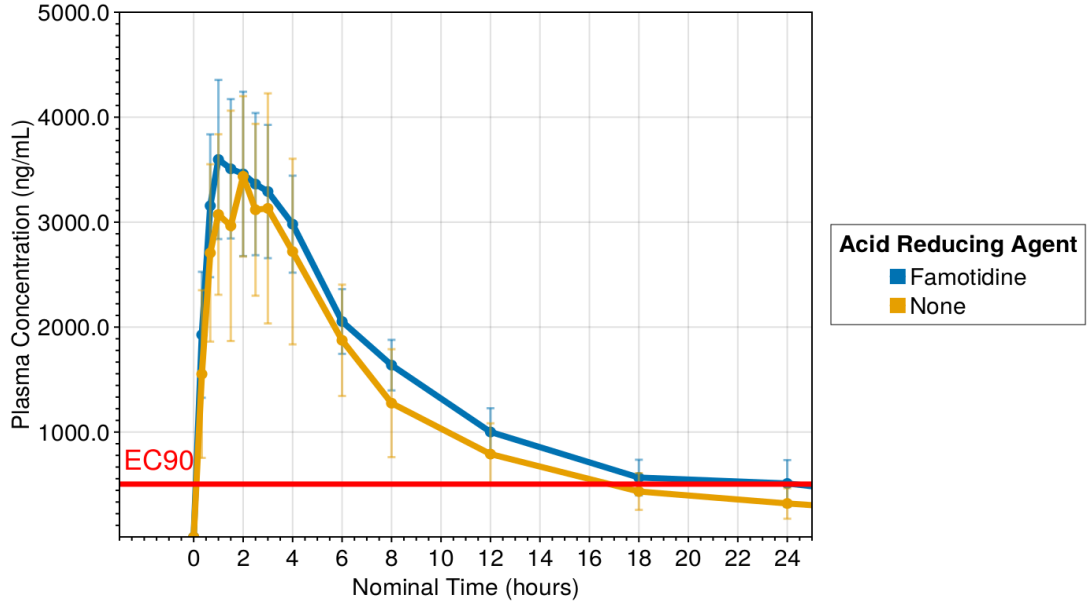
BHV-2100 PK Not Significantly Impacted by Food or Acid-Reducing Agent

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

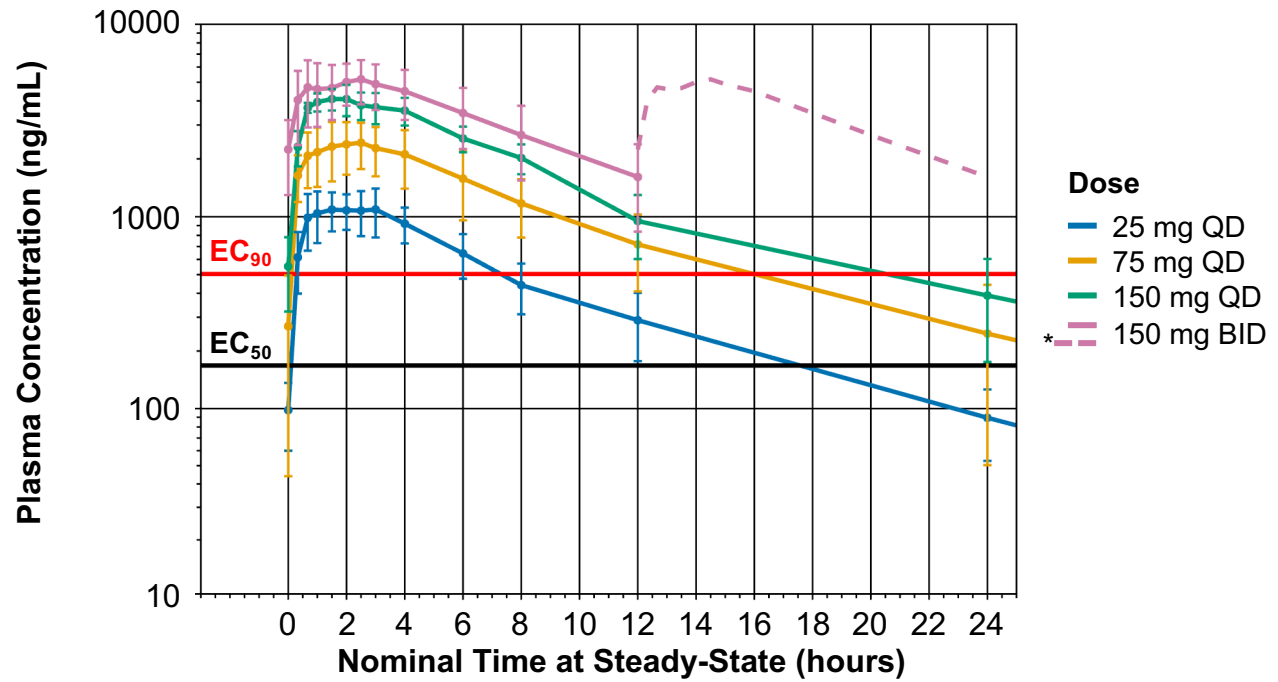
EC90 represents the estimated plasma concentration threshold based on a preclinical model; Error bars represent the standard deviation from the arithmetic mean; N=6 for each dose group

KEY POINT

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

BHV-2100 Demonstrates Sustained Concentrations Above Predicted Efficacious Levels With Multiple Doses

Mean Concentration vs Time Profiles at Steady-State After Multiple Oral Doses of BHV-2100



*Dashed line represents the theoretical concentration-time profile of a second dose on a BID schedule

EC_{50} and EC_{90} represent 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 (n = 5 for 150 mg QD at steady-state).

BID, twice daily; **EC_{50}**, 50% maximal effective concentration; **EC_{90}**, 90% maximal effective concentration; **QD**, once daily

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

Overall Safety Across All SAD/MAD Cohorts:

- No dose limiting toxicities
- No SAEs, no severe TEAEs
- No TEAEs leading to discontinuation
- No clinically significant trends in vital signs (including body temperature), laboratory values, or ECGs

SAD Safety: Single Doses

One moderate TEAE not related to study drug; all other TEAEs were mild

MAD Safety: Multiple Doses for 14 Days

- No TEAE occurred in more than 1 participant
- One moderate TEAE unrelated to study drug; all other TEAEs were mild
- No TEAEs reported at the highest dose 150 mg BID

Adverse Events Observed in More Than 1 Participant

SAD Cohorts (Pooled) TEAEs in > 1 Participant	Placebo (N = 9) n (%)	BHV-2100 (N = 30) n (%)
Dizziness	0	2 (6.7)
Fatigue	0	2 (6.7)
MAD Cohorts (Pooled) TEAEs in > 1 Participant	**Placebo (N = 8) n (%)**	**BHV-2100 (N = 24) n (%)**
	0 (0)	0 (0)

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

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

- TRPM3 represents a novel target for the treatment of pain and migraine
- 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 acute and chronic treatment of pain and migraine
- BHV-2100 demonstrated excellent safety and tolerability, without thermoregulatory AEs observed with other TRP antagonists or sedation associated with standard-of-care pain medications
- A preliminary human proof-of-concept study suggests BHV-2100 has antihyperalgesic effects in the setting of inflammation
- A Phase 2 clinical trial of BHV-2100 for acute treatment of migraine is ongoing and additional pain studies are being planned

Thank you!