POSTER
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BHV-2100, a First-in-Class TRPM3 Antagonist in Development for the Treatment of Migraine

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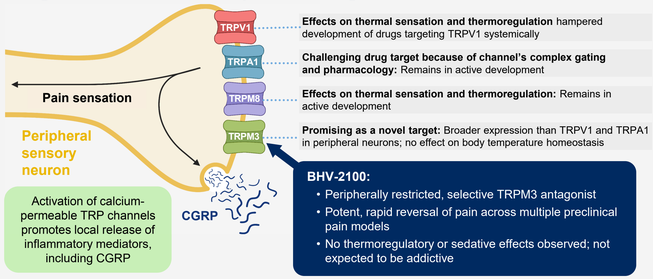
INTRODUCTION

- Despite advances in treatment, many people with migraine experience inadequate relief of pain and associated symptoms or face tolerability and safety issues with existing medications[1-3]
- Transient receptor potential (TRP) melastatin-3 (TRPM3) is a novel target for the treatment of migraine and pain
- TRPM3 is a calcium- and sodium-permeable, nonselective TRP channel expressed in sensory neurons of the trigeminal ganglion and dorsal root ganglion involved in neuroinflammatory pain signal transmission[4,5]
- Preclinical, mechanistic, genetic, and early clinical evidence support studying TRPM3 antagonism as a treatment for migraine (**Table 1**)
- BHV-2100 is a potential first-in-class, oral, peripherally restricted TRPM3 antagonist (**Figure 1**) in clinical development for migraine and pain[6,7]
- BHV-2100 has demonstrated potent pain reversal in preclinical models and excellent safety, tolerability, and pharmacokinetic properties in phase 1 clinical studies[6,7] (**Table 2**; **Figure 2**)

Figure 1. BHV-2100: A Potential First-in-Class, Orally Administered TRPM3 Antagonist in Clinical Development for Migraine and Pain[7-9]



BHV-2100 Has a Favorable Profile vs Existing Pain Medications and Other TRP Antagonists

CGRP, calcitonin gene-related peptide; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin-1; TRPM3, transient receptor potential melastatin-3; TRPM8, transient receptor potential melastatin-8; TRPV1, transient receptor potential vanilloid-1.

Table 1. TRPM3 Antagonism Is a Novel Mechanism for the Treatment of Migraine[4,10-19]

Mechanistic and preclinical evidence support the role of TRPM3 in neurogenic inflammation and sensitization of the trigeminovascular system	• TRPM3 receptors sensitize and activate the nociceptors of the trigeminovascular system • TRPM3 inhibition normalizes the sensitivity of nociceptors • TRPM3 is a key driver of neurogenic inflammation in a CGRP-dependent and -independent manner • Inhibition of TRP receptors, systemically or locally, decreases CGRP release, nociceptive neuron activity, and animal nocifensive behavior
Human genetic evidence supports the role of TRPM3 in migraine	• 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 • TRPM3 gene variants are associated with migraine risk and pain sensitivity in humans
TRPM3 antagonism in migraine is supported by early clinical data	• TRPM3 regulates other TRP channels such as TRPV1; civamide, a TRPV1 modulator, alleviated migraine pain in a small proof-of-concept clinical trial • BHV-2100 has favorable safety and tolerability with a PK profile suitable for acute treatment of migraine

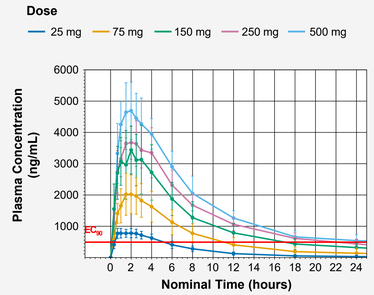
CGRP, calcitonin gene-related peptide; PK, pharmacokinetic; TRP, transient receptor potential; TRPM3, transient receptor potential melastatin-3; TRPV1, transient receptor potential vanilloid-1.

Table 2. BHV-2100 Was Safe and Well Tolerated in Healthy Adults[7]

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 (%)**
Any TEAE	0	0

SAD participants were randomized 3:1 to a single oral dose of BHV-2100 (25, 75, 150, 250, or 500 mg) or placebo. MAD participants were randomized 3:1 to BHV-2100 (25 mg QD, 75 mg QD, 150 mg QD, or 150 mg twice daily) or placebo and treated for 14 days.
MAD, multiple-ascending dose; QD, once daily; SAD, single-ascending dose; TEAE, treatment-emergent adverse event.

Figure 2. BHV-2100 Demonstrates Rapid Absorption and Sustained Concentrations With Single Doses[7]



EC_{90} 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.
EC_{90}: 90% maximal effective concentration.

OBJECTIVE

- To describe the rationale and design of a pivotal phase 2 clinical study of BHV-2100 for acute treatment of migraine

METHODS

- This is a pivotal phase 2 randomized, double-blind, placebo-controlled trial (NCT06603623)
- Key eligibility criteria and endpoints are shown in **Table 3** and **Figure 3**
- Approximately 625 participants across 60 sites in the United States will be randomized
- Participants are randomized 1:1:1 to a single oral dose of BHV-2100 150 mg, BHV-2100 75 mg, or placebo to treat a single migraine attack of moderate/severe pain intensity (**Figure 3**)
- The coprimary endpoints are tested hierarchically by dose

Table 3. Inclusion and Exclusion Criteria

Key Inclusion Criteria

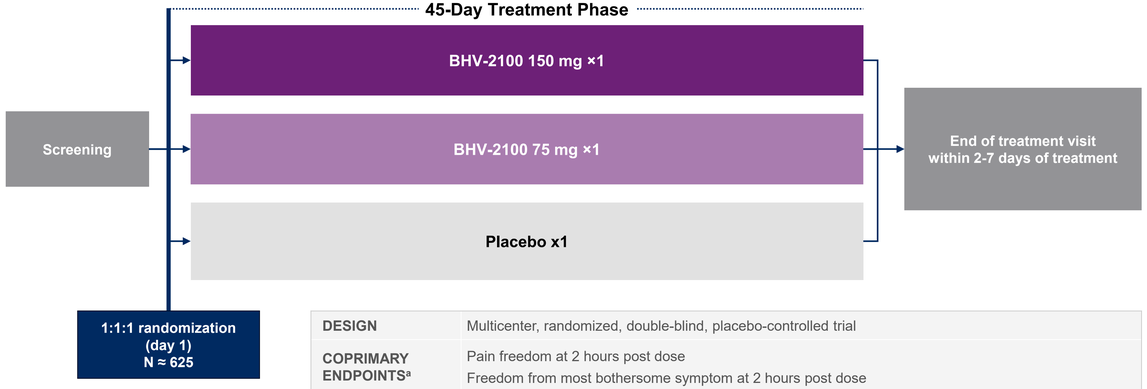
- Aged 18-64 years
- ≥ 1 year history of migraine (with or without aura), including
  - 2-8 migraine headache attacks of moderate or severe intensity in each of the 3 months prior to the screening visit and during the screening period
  - < 15 days with headaches (migraine or nonmigraine) per month in each of the 3 months prior to the screening visit and during the screening period
- Participants on a stable dose of prophylactic migraine medication for ≥ 3 months prior to the screening visit are permitted to remain on therapy

Key Exclusion Criteria

- History of basilar migraine or hemiplegic migraine
- Participants who have taken medication for acute treatment of headache (including triptans, ergotamine, opioids, acetaminophen, NSAIDs, or combination analgesics) on ≥ 10 days in any of the 3 months prior to the screening visit
- Participants who have used a neuromodulation device for migraine treatment over the preceding 3 months before screening
- Evidence of uncontrolled, unstable, or recently diagnosed cardiovascular disease
- Current diagnosis of major depression, other pain syndromes, psychiatric conditions, dementia, or other neurological disorders that, in the investigator's opinion, might interfere with study assessments

NSAID, nonsteroidal anti-inflammatory drug.

Figure 3. Ongoing Phase 2 Proof-of-Concept Study of BHV-2100 in Acute Treatment of Migraine



DESIGN	Multicenter, randomized, double-blind, placebo-controlled trial
COPRIMARY ENDPOINTS[a]	Pain freedom at 2 hours post dose Freedom from most bothersome symptom at 2 hours post dose
KEY SECONDARY ENDPOINTS	Pain relief, return to normal function, and freedom from phonophobia, photophobia, and nausea at 2 hours; sustained pain freedom and sustained pain relief 2 through 24 and 48 hours; pain relapse from 2 to 48 hours; use of rescue medication within 24 hours; pharmacokinetics; safety/tolerability

[a]Coprimary endpoints are tested hierarchically by dose.

CONCLUSIONS

- TRPM3 represents a novel target for the treatment of migraine and pain
- Several lines of evidence support TRPM3 antagonism as a potential new approach in the treatment of migraine
- BHV-2100 is a first-in-class, orally administered, peripherally restricted, and selective TRPM3 antagonist with favorable pharmacokinetics and excellent safety and tolerability
- BHV-2100 is being studied in a phase 2 proof-of-concept clinical trial for acute treatment of migraine with the potential to address the needs of millions of patients who continue to seek better migraine relief

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REFERENCES: 1. Ailani J, et al. *Headache*. 2021;61(7):1021-1039. **2.** Lipton, RB et al. *Headache*. 2013;53(8):1300-1311. **3.** Malik SN, et al. *Headache*. 2006;46(5):773-780. **4.** Vriens J, et al. *Neuron*. 2011;70(3):482-494. **5.** Vangeel L, et al. *Br J Pharmacol*. 2020;177(12):2683-2695. **6.** Vriens J, et al. Presented at: IASP 2024; Aug 5-9, 2024; Amsterdam, Netherlands. Poster WE727. **7.** Granit V, et al. Presented at: IASP 2024; Aug 5-9, 2024; Amsterdam, Netherlands. Poster WE725. **8.** Koivisto AP, et al. *Nat Rev Drug Discov*. 2022;21(1):41-59. **9.** Bamps D, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:655-677. **10.** Krivoshein G, et al. *J Headache Pain*. 2022;23(1):4. **11.** Kelemen B, et al. *Biochem Pharmacol*. 2021;183:114310. **12.** Held K, et al. *Proc Natl Acad Sci USA*. 2015;112(11):E1363-1372. **13.** Kumar J, et al. *Inhibitors of TRPM3 and Their Uses*. Patent WO2022152715A1. 2022. Accessed Mar 11, 2025. https://patents.google.com/patent/WO2022152715A1. **14.** Sollis E, et al. *Nucleic Acids Res*. 2023;51(D1):D977-D985. **15.** Diamond S, et al. *Cephalalgia*. 2000;20(6):597-602. **16.** Granit V, et al. *Headache*. 2024;64(2024):707-708. Abstract LB-IOR-01. **17.** Burglen L, et al. *Elife*. 2023;12:e81032. **18.** Yang L, et al. *Neuron*. 2022;110(11):1806-1821.e8. **19.** Mulier M, et al. *Elife*. 2020;9:e61103.

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