Poster
WE725

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

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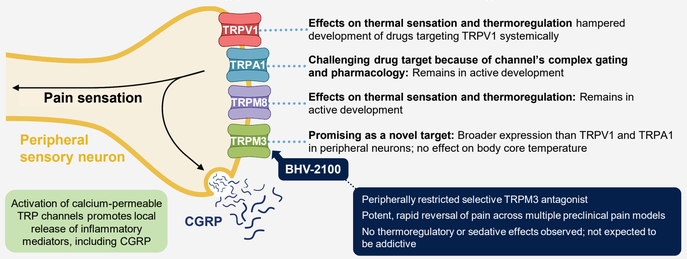
INTRODUCTION

- Transient receptor potential (TRP) melastatin-3 (TRPM3) is a novel target for the treatment of migraine and pain
- TRPM3 is a calcium-permeable, nonselective TRP channel expressed in somatosensory neurons, including nociceptors[1,2]
- Several lines of evidence (eg, preclinical and human genetic data) implicate TRPM3 in pain signaling[1,3-9]
  - 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 pain and heat sensitivity[8,9]
- TRPM3 expression and activity are markedly increased in sensory neurons innervating inflamed tissues[5]
- Selective activation of TRPM3 induces the release of calcitonin gene-related peptide in rodents[10]
- BHV-2100 is a first-in-class, oral, peripherally restricted TRPM3 antagonist (**Figure 1**) in development for pain and migraine that has demonstrated potent pain reversal in preclinical models

Figure 1. BHV-2100: A First-in-Class Orally Administered TRPM3 Antagonist in Development for Migraine and Pain With a Differentiated Profile vs Other TRP Channel Antagonists[11-13]

BHV-2100 is being developed with an improved profile compared with 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.

OBJECTIVES

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

METHODS

- This randomized, placebo-controlled, sequential single-ascending dose (SAD)/multiple-ascending dose (MAD) study enrolled healthy adult males and females aged 18-55 years
- SAD cohorts
  - Participants were 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 cohorts
  - 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
- A safety review committee reviewed the safety, tolerability, and PK data after completion of each dose level
- Samples were collected up to 120 hours post dosing. BHV-2100 was analyzed by a validated liquid chromatography/mass spectrometry assay and PK parameters were calculated by noncompartmental methods
- Safety evaluations throughout the study included adverse event (AE) monitoring, clinical laboratory tests, vital signs, electrocardiograms, physical examinations, and Columbia-Suicide Severity Rating Scale questionnaire
- This analysis summarizes initial safety and PK data that are currently available from the SAD and MAD cohorts

RESULTS

Study Population

- Thirty-nine participants were treated in the SAD cohorts, and 32 participants were treated in the MAD cohorts; 94% were male, 80% were White, 17% were Black, and 3% were Asian

Overall Summary of Safety Data Across All Cohorts

- There were no dose-limiting toxicities
- No serious AEs or severe treatment-emergent AEs (TEAEs) were reported
- Most AEs were mild and resolved spontaneously without treatment
- There were no AEs leading to discontinuation
- No clinically significant trends in vital signs (including body temperature), laboratory values, or electrocardiograms were observed

SAD Safety: Single Doses

- One moderate TEAE unrelated to study drug was reported (sapovirus gastroenteritis); all other TEAEs were mild
- TEAEs occurring in more than 1 participant across the pooled SAD cohorts are shown in **Table 1**

MAD Safety: Multiple Doses for 14 Days

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

Table 1. 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)
No TEAEs Occurred in > 1 Participant Across the MAD Cohorts (N = 32)		

MAD, multiple-ascending dose; SAD, single-ascending dose; TEAE, treatment-emergent adverse event.

PK Data: SAD

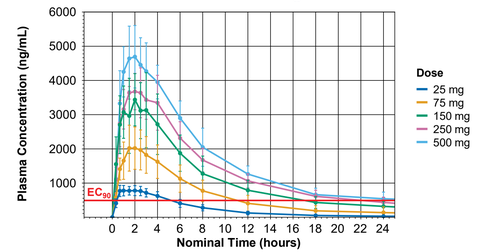
- Maximal drug concentrations (T_{max}) were achieved after approximately 1.5 to 2 hours, and the mean terminal elimination half-life ($T_{1/2}$) ranged between approximately 8 to 12 hours
- The PK of BHV-2100 was approximately dose proportional
- Plasma concentrations exceeded 90% maximal effective concentration (EC_{90}), the estimated effectiveness threshold based on a preclinical model, after 20 minutes and were sustained above EC_{90} for several hours at all dose levels (**Figure 2**)
- A high-fat meal delayed T_{max}, but concentrations exceeded EC_{90} by 20 minutes (**Figure 3A**)
- Famotidine did not significantly impact BHV-2100 exposures (**Figure 3B**)

PK Data: MAD

- At steady-state, $T_{1/2}$ ranged from 8 to 10 hours (**Figure 4**)
- With once-daily dosing, minimal accumulation was observed
- 75 mg QD dosing provides plasma concentrations > 50% EC_{50} over a 24-hour period
- 150 mg BID dosing provides > EC_{90} over a 24-hour period

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

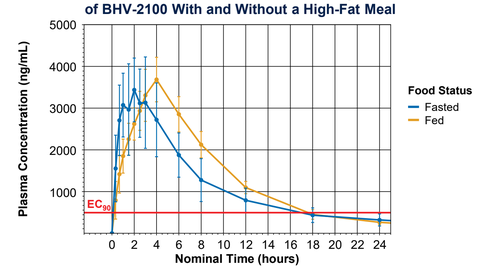
Mean Concentration vs Time Profiles of Single Oral Doses of BHV-2100



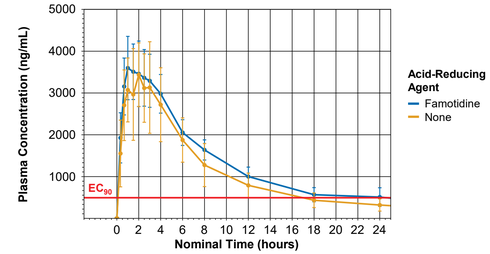
EC_{90} represents the estimated plasma concentration threshold based on a preclinical model. Error bars represent the standard deviation from the arithmetic mean. n = 6 for each dose group.
EC_{90}, 90% maximal effective concentration.

Figure 3. BHV-2100 PK Is Not Significantly Impacted by Food or Acid-Reducing Agent

A. Mean Concentration vs Time Profiles of Single Oral Doses of BHV-2100 With and Without a High-Fat Meal



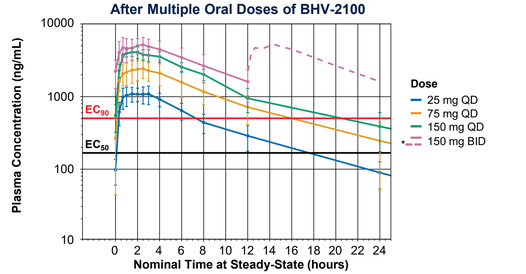
B. Mean Concentration vs Time Profile of Single Oral Doses of BHV-2100 With and Without Famotidine



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; PK, pharmacokinetics.

Figure 4. 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



	Dosing Schedule (at Steady-State)			
	25 mg QD	75 mg QD	150 mg QD	150 mg BID
Time above EC_{50}	17 hours	24 hours	24 hours	24 hours
Time above EC_{90}	7 hours	16 hours	21 hours	24 hours

*Dashed line represents the theoretical concentration-time profile of a second dose on a BID schedule (determined by superposition of steady-state data).
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.

CONCLUSIONS

- BHV-2100 is a first-in-class, orally administered, selective antagonist of TRPM3, a novel target for the treatment of migraine and pain
- Single doses demonstrated rapid absorption and sustained concentrations above predicted efficacious levels at all doses tested after 20 minutes, an ideal PK profile for the treatment of migraine and pain
- Daily dosing achieved plasma concentrations predicted to have sustained analgesic effects
- Excellent safety and tolerability, without thermoregulatory AEs observed with other TRP antagonists or sedation associated with standard-of-care pain medications
- These findings provide a compelling rationale for the advancement of BHV-2100 into clinical trials for migraine and pain as a novel, peripherally acting, nonopioid treatment

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REFERENCES: 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.** Kumar J, et al. Inhibitors of TRPM3 and their uses. US Patent US-20240173290-A1. May 30, 2024. **9.** Biohaven Pharmaceuticals. Data on file. **10.** Held K, et al. *Proc Natl Acad Sci U S A*. 2015;112(11):E1363-1372. **11.** Koivisto AP, et al. *Nat Rev Drug Discov*. 2022;21(1):41-59. **12.** Bamps D, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:655-677. **13.** Vriens J, et al. Presented at NeuPSIG 2023; 7-9 Sep 2023; Lisbon, Portugal. Poster SA127.

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DISCLOSURES: VG, **RB**, **EA**, **MD**, **CJ**, **BE**, **IQ**, and **VC** are employed by and hold stock/stock options in Biohaven Pharmaceuticals. **AL** and **PM** are paid consultants for Biohaven Pharmaceuticals. **JV** and **TV** have nothing to disclose.

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