Poster
WE727

# BHV-2100, a First-in-Class TRPM3 Antagonist for the Treatment of Pain and Migraine

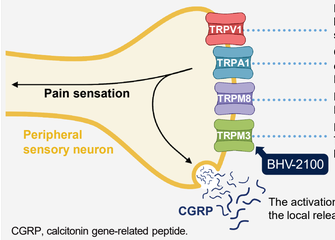
**Joris Vriens, PhD[1]; Jean-Christophe Vanherck, PhD[2]; Arnaud Marchand, PhD[2]; Sílvia Pinto, MSc[1,3]; Annelies Janssens, BSc[1,3]; Sara Kerselaers, MSc[1,3]; Melissa Benoit, BSc[1,3]; Bruce Car, DVM, PhD, DACVP[4]; Gene Dubowchik, PhD[4]; Reese Caldwell[4]; Volkan Granit, MD, MSc[4]; Lawrence Marcin, PhD[4]; David Pirman, PhD[4]; Patrick Chaltin, PhD[2,5]; Thomas Voets, PhD[1,3]**

[1]Laboratory of Ion Channel Research, KU Leuven, Leuven, Belgium; [2]CISTIM Leuven vzw, Leuven, Belgium; [3]VIB Center for Brain & Disease Research, Leuven, Belgium; [4]Biohaven, New Haven, CT, USA; [5]Centre for Drug Design and Discovery (CD3), KU Leuven, Leuven, Belgium

## INTRODUCTION

- Over the last 25 years, the identification and characterization of transient receptor potential (TRP) ion channels as receptors of painful stimuli in sensory neurons have led to a better understanding of the biology of nociception, fueling development of TRP channel–based next-generation analgesics that target pain at its origin[1-4]
- TRPV1, TRPA1, and TRPM8 have been the most extensively studied TRP channel targets for the development of novel analgesics, but this has not yet resulted in new analgesic drugs for human use[3]
- Clinical development of antagonists for TRPV1 and TRPM8 has been hampered by significant effects on thermosensation and thermoregulation. TRPA1 is a challenging drug target because of the channel's complex gating and pharmacology (**Figure 1**)[1,3,5]
- TRPM3 is a calcium-permeable, nonselective cation channel expressed in a large subset of somatosensory neurons, including nociceptors, both in rodents and in humans. Its activation by chemical ligands or noxious heat evokes pain[6-8]
- TRPM3 is functionally upregulated in animal models of inflammatory hyperalgesia and chemotherapy-induced neuropathic pain[9,10]

**Figure 1. TRPM3: A Novel Peripheral Target for Migraine and Pain[1,3,16]**




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

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

**Effects on thermal sensation and thermoregulation:** Remains in active development

**Promising as a novel target:** Broader expression than TRPV1 and TRPA1 in peripheral neurons; no effect on body core temperature

The activation of calcium-permeable TRP channels can promote the local release of inflammatory mediators, including CGRP[3]

CGRP, calcitonin gene-related peptide.

- TRPM3-deficient mice do not develop mechanical or thermal hypersensitivity in various pain models[8,11,12]
- Gain-of-function mutations in TRPM3 have been associated with altered pain sensation in humans. Further, machine learning studies identified single nucleotide polymorphisms in the *TRPM3* gene that are associated with a change in pain thresholds[13-15]
- BHV-2100 is a selective TRPM3 antagonist (**Figure 1**) in clinical development for pain and migraine; we present the key preclinical data supporting its advancement to the clinical stage

## OBJECTIVE

- To evaluate in vitro activity and in vivo efficacy and safety of BHV-2100, a first-in-class, orally administered, peripherally restricted, selective TRPM3 antagonist in clinical development for migraine and pain

## METHODS

### In Vitro Activity

**The in vitro activity of BHV-2100 against TRPM3 and its selectivity toward other relevant ion channels was evaluated using:**

- Whole-cell patch-clamp experiments
- Microfluorimetric calcium imaging in transfected HEK293 cells
- Rodent dorsal root ganglion neurons
- Human stem cell–derived sensory neurons

### Telemetric Assay

**Implantable sensors for longitudinal monitoring of biopotentials evaluated the effect of BHV-2100 in rats on:**

- Body core temperature
- Heart rate

### Pharmacokinetics and Toxicology

- IND-enabling ADME and toxicology studies were performed

### In Vivo Pain Models

**The analgesic potential of BHV-2100 was evaluated in a panel of novel and established rodent models, including:**

- **Acute pain:** BHV-2100 or vehicle administered 30 minutes prior to intraplantar injection of the TRPM3 agonist pregnenolone sulfate (PS) in the hind paw of mice and rats
- **Nerve injury:** partial sciatic nerve ligation model in rats. BHV-2100, pregabalin, or vehicle administered 14 days after unilateral sciatic nerve injury
- **Chemotherapy-induced neuropathic pain:** mouse acute oxaliplatin model. BHV-2100, tramadol, or vehicle administered 6 days after oxaliplatin treatment
- **Diabetic neuropathy:** streptozocin-induced diabetic neuropathy model in rats. BHV-2100, pregabalin, or vehicle administered 7 days after streptozocin treatment

ADME, absorption, distribution, metabolism, and excretion; HEK, human embryonic kidney; IND, Investigational New Drug application.

## RESULTS

### In Vitro Findings

- BHV-2100 inhibited human, mouse, and rat TRPM3-mediated calcium responses in heterologous expression systems and sensory neurons, with half-maximal inhibitory concentration ($IC_{50}$) values between 1 and 10 nM (**Table 1**)
- BHV-2100 exhibited > 1000-fold selectivity to a large panel of other ion channels and receptors (**Table 1**)

### Pharmacokinetics and Toxicology

- BHV-2100 exhibited high oral bioavailability in mice and rats without noticeable side effects (**Table 2**) or impact on body core temperature regulation or heart rate (**Figure 2A** and **B**), allowing further testing of its efficacy in a panel of in vivo pain models
- Tissue distribution of BHV-2100 activity is highly restricted to the peripheral nervous system and therefore is less susceptible to potential adverse events such as sedation (**Figure 2C**) or abuse liability

### In Vivo Pain Models

- Orally administered BHV-2100 inhibited PS-induced pain in rodents with median effective dose ($ED_{50}$) values of 1.3 mg/kg and 2.5 mg/kg in mice and rats, respectively (**Figure 3A**)
- BHV-2100 also reduced pain in a dose-dependent manner following nerve injury in rats (**Figure 3B**) without the significant sedation effects seen with pregabalin when dosed at 30 mg/kg
- In both the chemotherapy-induced neuropathic pain model and the diabetic neuropathy model, BHV-2100 showed significant dose-dependent efficacy in reversing cold-induced pain and mechanical hypersensitivity, respectively (**Figure 4**)

**Table 1. In Vitro Findings**

| Parameter | Test | Value |
|---|---|---|
| **TRPM3 electrophysiology** | Patch clamp HEK293 cells | 8.8 nM $IC_{50}$ |
| **TRPM3 neuronal activity** | hES-derived sensory neurons | 3 nM $IC_{50}$ |
| **TRP selectivity** | TRPA1/TRPV1/TRPM8; TRPM7 | All > 10 µM $IC_{50}$ |
| **CV selectivity** | NaV1.5; NaV1.7; CaV1.2; hERG | All > 10 µM $IC_{50}$ |
| **General selectivity** | Eurofins | Clean in BioPrint™ |

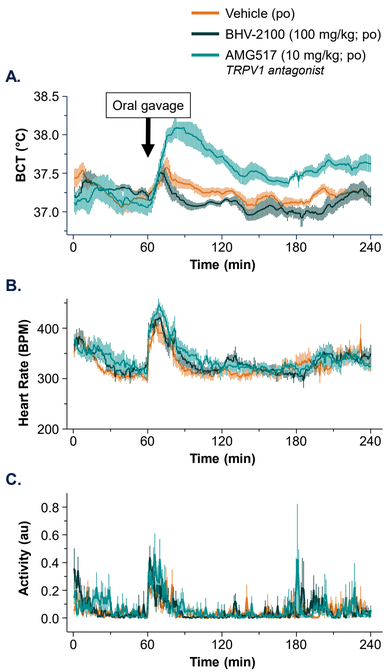
CV, conduction velocity; hERG, human ether-a-go-go-related gene; hES, human embryonic stem cell.

**Table 2. Pharmacokinetics and Toxicology Findings**

| Parameter | Test | Value |
|---|---|---|
| **ADME** | Clearance across species | Low/moderate |
| **ADME** | CYP450 | All isoforms > 10 µM |
| **ADME** | Bioavailability (mouse, rat, dog) | 55%-85% |
| **Toxicology** | IND-enabling toxicology studies | Wide safety margins, no genotoxicity |

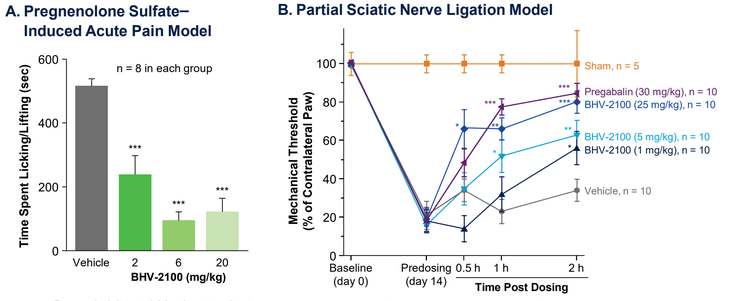
CYP450, cytochrome P450.

**Figure 2. BHV-2100 Did Not Demonstrate a Significant Impact on BCT, Heart Rate, or Activity**




Time course of the changes in BCT, activity, and heart rate in rats (n = 8) during 1 hour prior and 3 hours post oral dosing of vehicle, BHV-2100 (100 mg/kg), or AMG517 (10 mg/kg). The parameter activity is expressed in arbitrary units (au), corresponding to the number of automatically detected activity counts per second. AMG517 is a TRPV1 antagonist, causing hyperthermia.[3]
BCT, body core temperature; BPM, beats per minute; po, by mouth.

**Figure 3. BHV-2100 Potently Reduces Acute Chemogenic Pain and Pain Following Nerve Injury**

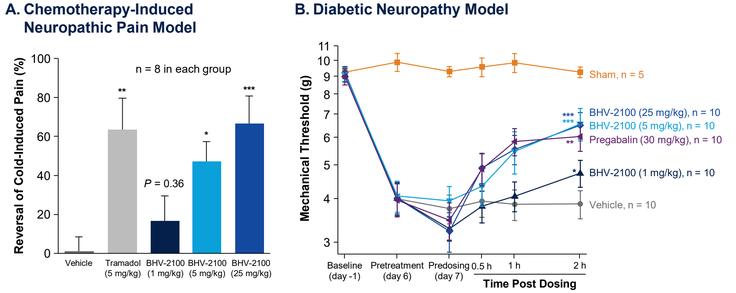



*Drug administered 30 minutes prior to TRPM3 agonist injection in a hind paw of rats*

*Drug administered 14 days after unilateral sciatic nerve injury in rats*

*$P$ < 0.05. **$P$ < 0.01. ***$P$ < 0.001.

**Figure 4. BHV-2100 Reverses Established Pain States in Peripheral Neuropathic Pain Models**




*Drug administered 6 days after oxaliplatin treatment in mice*

*Drug administered 7 days after STZ treatment in rats*

*$P$ < 0.05. **$P$ < 0.01. ***$P$ < 0.001.
STZ, streptozotocin.

## CONCLUSIONS

- BHV-2100 is a first-in-class, orally administered, highly potent, and selective TRPM3 antagonist
- Preclinical data show potent reversal of pain with reduced potential for thermoregulatory side effects or sedation
- The findings support the hypothesis that TRPM3 represents a safe and druggable target as a novel nonopioid treatment of pain
- These data support the advancement of BHV-2100 into clinical trials
- Poster WE725 presented by V Granit et al describes safety, tolerability, and pharmacokinetic data from the first-in-human phase 1 study of BHV-2100

**Presented at the International Association for the Study of Pain (IASP) 2024 World Congress on Pain | 5-9 August 2024 | Amsterdam, Netherlands**

**REFERENCES: 1.** Koivisto AP, et al. *Nat Rev Drug Discov.* 2022;21(1):41-59. **2.** Mickle AD, et al. *Pharmaceuticals.* 2016;9(4):72. **3.** Bamps D, et al. *Annu Rev Pharmacol Toxicol.* 2021;61:655-677. **4.** Patapoutian A, et al. *Nat Rev Drug Discov.* 2009;8(1):55-68. **5.** Fernández-Carvajal A, et al. *Expert Opin Investig Drugs.* 2020;29(11):1209-1222. **6.** Vandewauw I, et al. *Nature.* 2018;555(7698):662-666. **7.** Vangeel L, et al. *Br J Pharmacol.* 2020;177(12):2683-2695. **8.** Vriens J, et al. *Neuron.* 2011;70(3):482-494. **9.** Aloi VD, et al. *Pain.* 2023;164(9):2060-2069. **10.** Mulier M, et al. *Elife.* 2020;9:e61103. **11.** Alkhatib O, et al. *J Neurosci.* 2019;39(40):7840-7852. **12.** Su S, et al. *J Neurosci.* 2021;41(11):2457-2474. **13.** Zhao S, et al. *Elife.* 2020;9:e55634. **14.** Lötsch J, et al. *Int J Mol Sci.* 2020;21(12):4367. **15.** Dyment DA, et al. *Eur J Hum Genet.* 2019;27(10):1611-1618. **16.** Vriens J, et al. Presented at NeuPSIG 2023; 7-9 Sept 2023; Lisbon, Portugal. Poster SA127.

**ACKNOWLEDGMENTS:** The authors would like to Sara Sloan and Shannon Davis of Apollo Medical Communications, part of Helios Global Group, for layout of the poster. The authors from Leuven would also like to thank Grünenthal for their contribution.

**DISCLOSURES: BC, GD, VG, LM,** and **DP** are employed by and hold stock/stock options in Biohaven; **RC** is a former employee of Biohaven. **JV, JCV, AM, SP, AJ, SK, MB, PC,** and **TV** have nothing to disclose.

To download a copy of this poster, scan QR code.