BHV-2100, A First-In-Class TRPM3 Antagonist for the Treatment of Pain

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

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

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TRPM3: A Promising New Target for Treating Pain

- Novel approaches to the treatment of pain are needed to address inadequate efficacy, tolerability, and addiction potential of existing therapies

- Certain members of the TRP superfamily of cation channels act as molecular sensors of painful stimuli[1]
  - Among TRP channels, TRPV1, TRPA1, and TRPM8 most studied as new analgesic drugs[2]

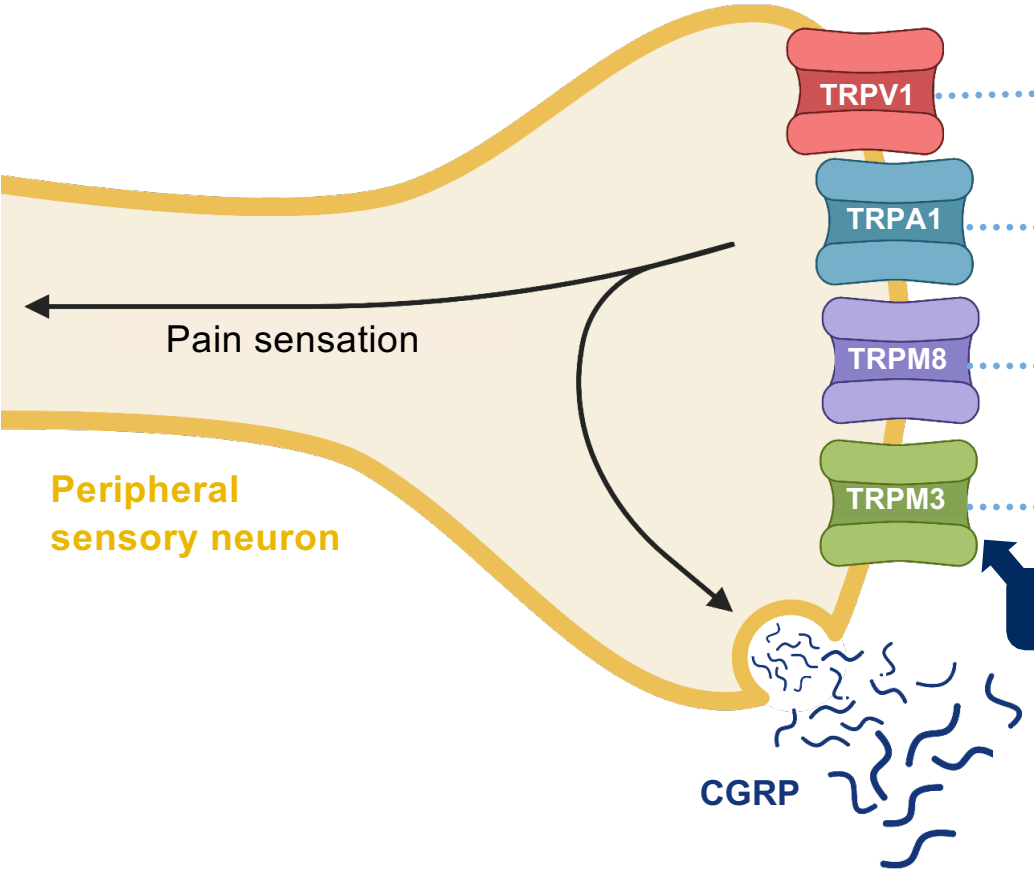
- TRPM3 is a calcium-permeable, nonselective TRP channel expressed in somatosensory neurons, including nociceptors of rodents and humans[3,4]
  - When activated by noxious heat or chemical ligands TRPM3 evokes pain[5]
  - Preclinical models and human genetics implicate a key role of TRPM3 in pain signaling[6-8]
  - TRPM3 genetic polymorphisms are associated with migraine and cluster headache[9]
  - TRPM3-deficient mice do not develop pathological mechanical or thermal hypersensitivity[5,10,11]
  - TRPM3 is functional in trigeminal nerve fibers innervating mouse meninges, and TRPM3 agonism evokes trigeminally induced pain[5,12,13]

TRP, transient receptor potential; **TRPM3**, transient receptor potential melastatin 3

1. Rosenbaum T, et al. *Nat Rev Neurosci*. 2022;23(10):596-610. 2. Bamps D, et al. *Annu Rev Pharmacol Toxicol*. 2021;61:655-677. 3. Vandewauw I, et al. *Nature*. 2018;555(7698):662-666. 4. Vangeel L, et al. *Br J Pharmacol*. 2020;177(12):2683-2695. 5. Vriens J, et al. *Neuron*. 2011;70(3):482-494. 6. Aloi VD, et al. *Pain*. 2023;164(9):2060-2069. 7. Mulier M, et al. *Elife*. 2020;9:e61103. 8. Lötsch J, et al. *Int J Mol Sci*. 2020;21(12):4367. 9. GSK patent, UK biobank associations. 10. Alkhatib O, et al. *J Neurosci*. 2019;39(40):7840-7852. 11. Su S, et al. *J Neurosci.* 2021;41(11):2457-2474. 12. Kelemen B, et al. Biochem Pharmacol. 2021 Jan;183:114310. 13. Krivoshein G, et al. J Headache Pain 2022;23(1):4.

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

BHV-2100 is being developed with an improved target product 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

The activation of calcium-permeable TRP channels promotes the local release of inflammatory mediators, including CGRP

TRPM3 channel inhibitors are expected to be nonaddictive

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.

Discovery and Early Development of BHV-2100

Objective 1	Methods (*In Vitro*)
• Demonstrate the **antagonist activity** of BHV-2100 against TRPM3 • Demonstrate that BHV-2100 activity **is specific against TRPM3**	• Whole-cell patch-clamp experiments • Microfluorimetric calcium imaging in transfected HEK293 cells
Objective 2	**Methods (*In Vivo*)**
Ensure BHV-2100 does **NOT** carry target-based liabilities: • Body core temperature • Heart rate • Motor activity	• Implantable sensors for longitudinal monitoring of biopotentials in rats • Toxicologic evaluation with multiple detailed endpoints
Objective 3	**Methods (*In Vivo*)**
• Demonstrate that BHV-2100 is safe and tolerable in multiple animal species to enable first-in-human studies • Demonstrate the analgesic efficacy of BHV-2100	• IND-enabling ADME and toxicology studies were performed • Novel and established rodent models for acute pain, nerve injury, chemotherapy-induced neuropathic pain, and diabetic neuropathy

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

In Vitro Findings, Pharmacokinetics and Toxicology

In Vitro Findings

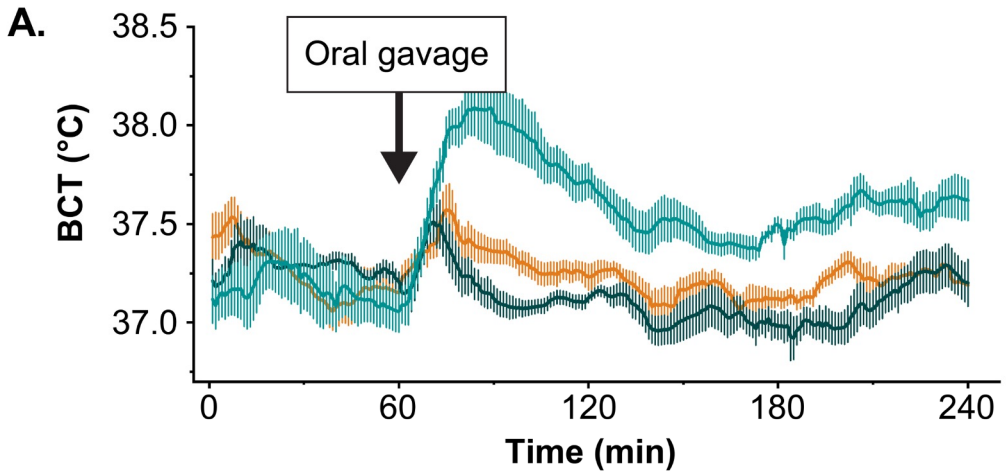
Parameter	Test	Value
TRPM3 electrophysiology	Patch clamp	8.8 nM IC_{50}
TRPM3 neuronal activity	hES-derived sensory neurons	3 nM IC_{50}
TRP selectivity	TRPA1/TRPV1/TRPM8; TRPM7	All > 10 µM IC_{50}
CV selectivity	NaV1.5; NaV1.7; CaV1.2; hERG	All > 10 µM IC_{50}
General selectivity	Eurofins	Clean in BioPrint™

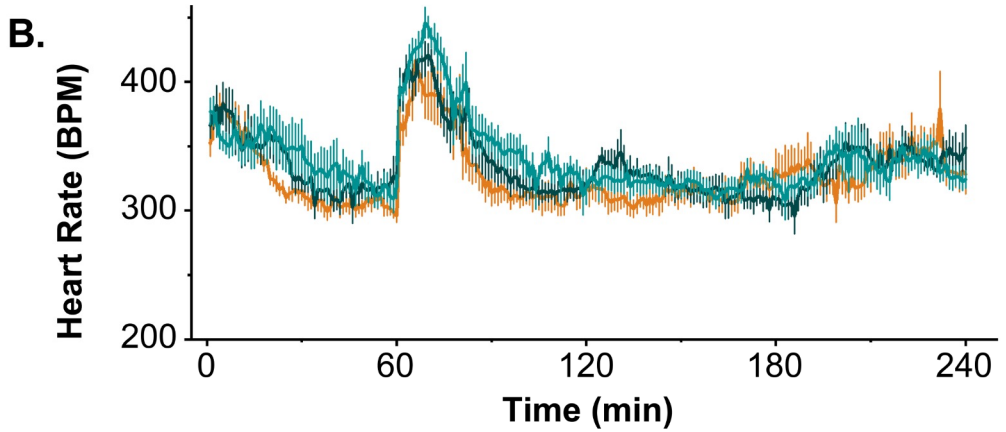
Pharmacokinetics and Toxicology Findings

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

CV, conduction velocity; **hERG**, human ether-a-go-go-related gene; **hES**, human embryonic stem cell; **CYP450**, cytochrome P450.

BHV-2100 Demonstrates No Significant Impact on Body Core Temperature, Heart Rate, or Activity



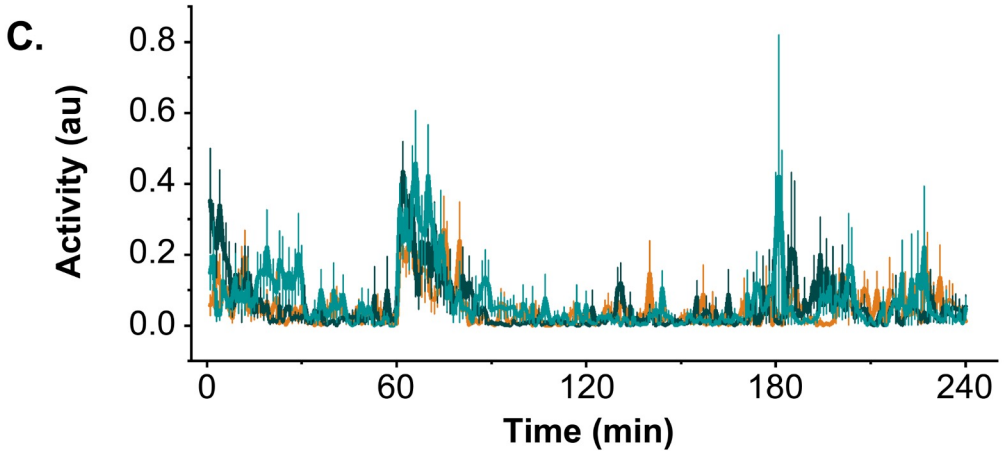


Vehicle (po)

BHV-2100 (100 mg/kg; po)

AMG517 (10 mg/kg; po)

TRPV1 antagonist



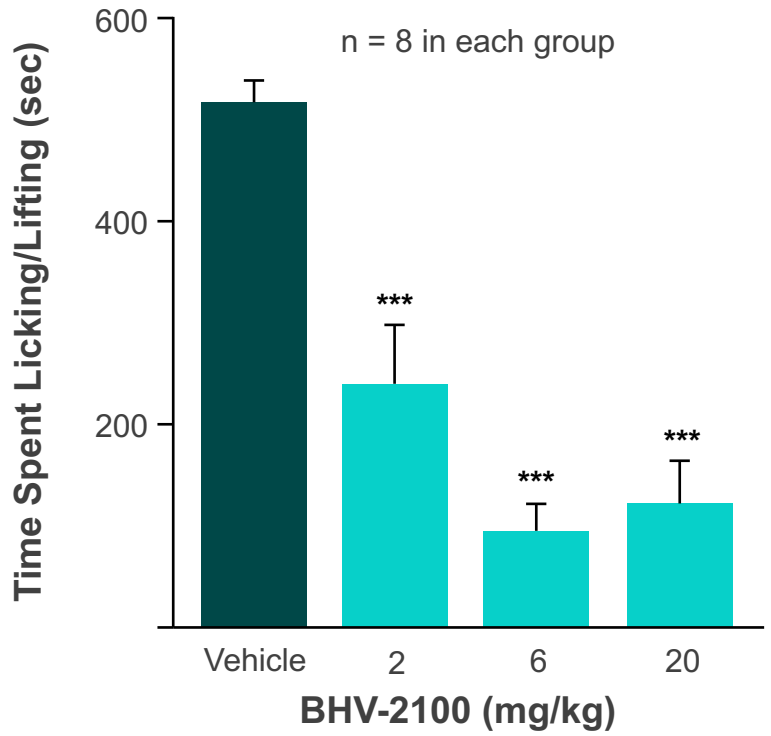
Target-related liabilities of other TRP family inhibitors are not expected with TRPM3 inhibition

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.[1]

BCT, body core temperature; **BPM**, beats per minute; **po**, by mouth. 1. Bamps D, et al. *Annu Rev Pharmacol Toxicol.* 2021;61:655-677.

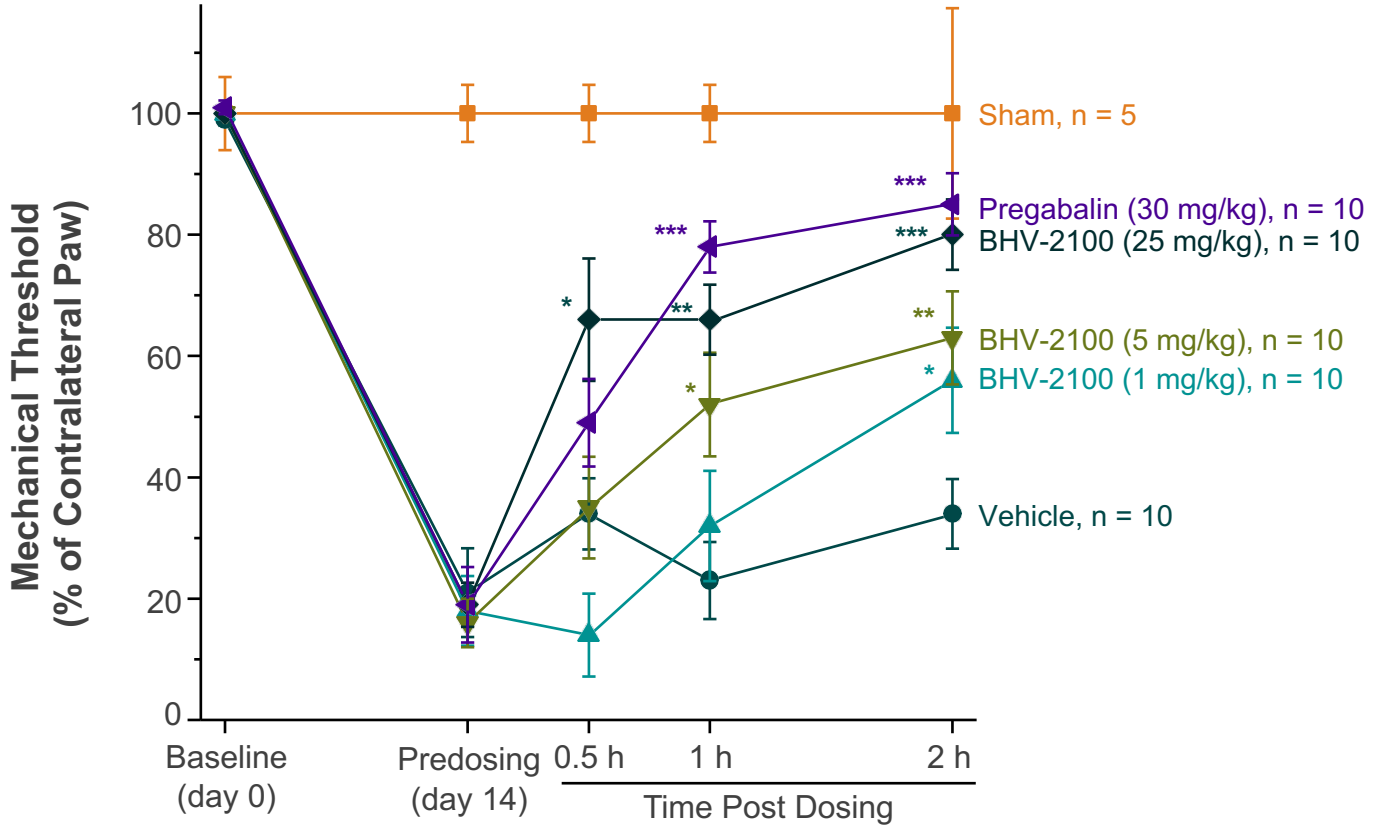
BHV-2100 Reduces Acute Chemogenic Pain and Pain Following Nerve Injury

Pregnenolone Sulfate (TRPM3 Agonist) — Induced Acute Pain Model



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

Partial Sciatic Nerve Ligation Model

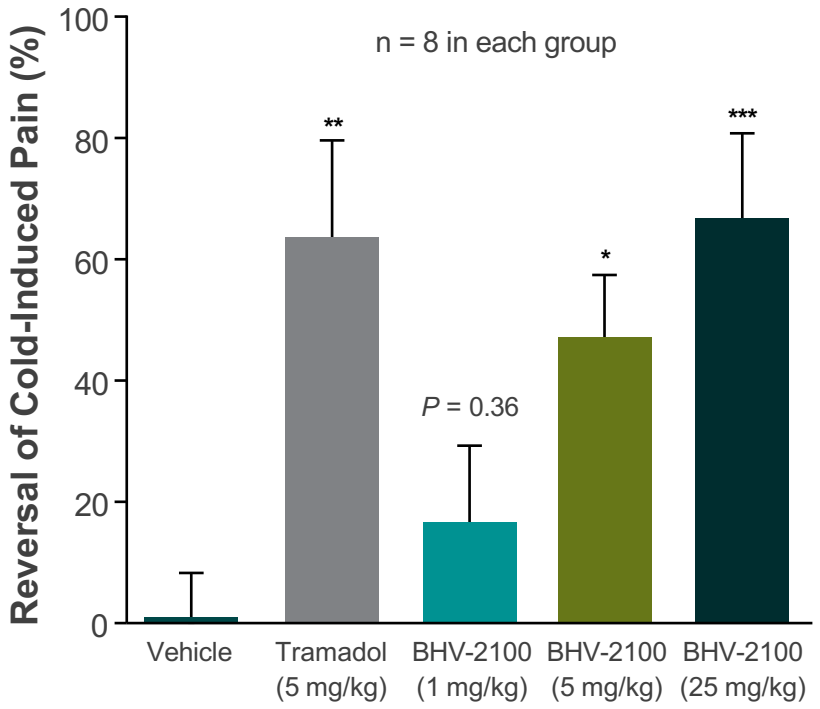


Drug administered 14 days after unilateral sciatic nerve injury in rats

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

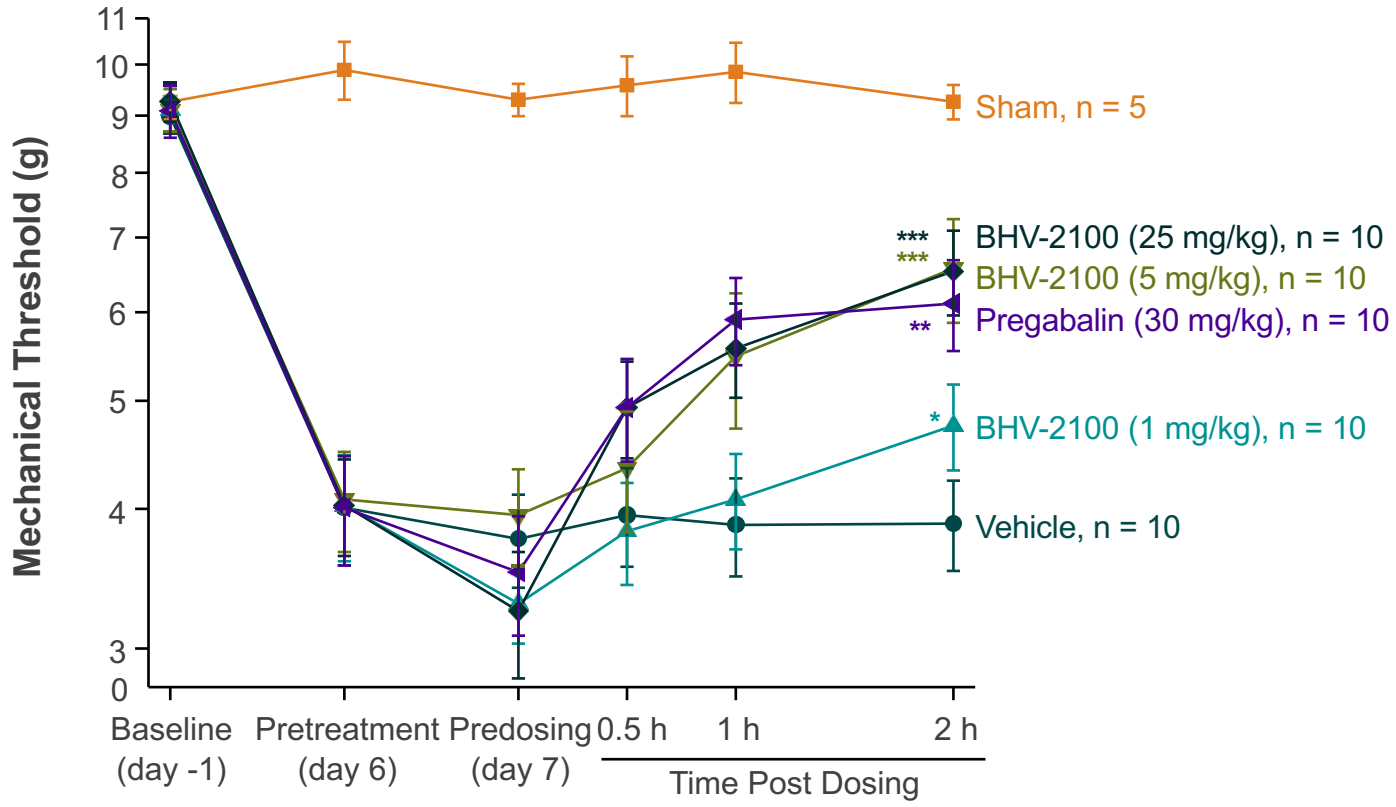
BHV-2100 Reverses Established Pain States in Peripheral Neuropathic Pain Models

Chemotherapy-Induced Neuropathic Pain Model



Drug administered 6 days after oxaliplatin treatment in mice

Diabetic Neuropathy Model



Drug administered 7 days after STZ treatment in rats

*P < 0.05. **P < 0.01. ***P < 0.001. **STZ**, streptozoticin.

BHV-2100: A First-in-Class, Clinical Stage TRPM3 Antagonist for Pain

- TRPM3 represents a safe and druggable target as a novel nonopioid, non-addictive treatment of pain
- BHV-2100 is a first-in-class, orally administered, peripherally-restricted and selective TRPM3 antagonist
- Potent, rapid reversal of pain with BHV-2100 was demonstrated across multiple preclinical pain models
- BHV-2100 does not cause thermoregulatory side effects observed with other TRP antagonists, sedation, or gastrointestinal side effects associated with standard-of-care pain medications
- BHV-2100 demonstrated excellent tolerability, safety, and favorable PK properties in ongoing Phase 1 trials
- Clinical trials of BHV-2100 in migraine and pain are planned to begin in 2024

Thank you!