BHV-2100, a First-in-Class TRPM3 Antagonist for the Treatment of Neuropathic Pain

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BACKGROUND
- 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 root.
- 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 analgesics for human use.
- Clinical development of antagonists for TRPV1 and TRPM8 has been hampered by significant effects on thermoregulation and thermoregulation. TRPA1 is a challenging drug target because of the channel's complex gating and pharmacology (Figure 1).

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 for the treatment of neuropathic pain.
- BHV-2100 is a selective TRPM3 antagonist (Figure 1), and we present the key preclinical data supporting its advancement to the clinical stage.

RESULTS

In Vitro Findings
- BHV-2100 inhibited human, mouse, and rat TRPM3-mediated calcium responses in heterologous expression systems and sensory neurons, with high-magnitude inhibition (IC50) values below 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 (Figures 2A and B), allowing further testing of its efficacy in a panel of in vivo pain models.
- Tissue distribution data for 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 liability.

In Vivo Pain Models
- Orally administered BHV-2100 inhibited P5-induced pain in rodents with median effective dose (ED50) values between 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 thermolabile-induced neuropathic pain model and the diabetic neuropathy model, BHV-2100 showed significant dose-dependent efficacy in reversing cold-induced pain and mechanical hyperalgesia, respectively (Figure 4).

METHODS

In Vivo Activity
- The in vivo activity of BHV-2100 against TRPM3 and its selectivity to other relevant ion channels was evaluated using:
  - Whole-cell patch-clamp experiments
  - Microsaturimetric calcium imaging in transfected HEK293 cells

Toxicology 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
- ADME, Toxicology, PKS, and PKS 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 (P5) in the hind paw of mice and rats.
  - Neuronal injury: partial sciatic nerve ligation model in rats. BHV-2100, pregabalin, or vehicle administered 14 days after unilateral sciatic nerve injury.
  - Chemotherapeutic-induced neuropathic pain: mouse oxaliplatin model. BHV-2100, tramadol, or vehicle administered 6 days after oxaliplatin treatment.
  - Diabetic neuropathy: streptozotocin-induced diabetic neuropathy model in rats. BHV-2100, pregabalin, or vehicle administered 2 days after simplification treatment.

REFERENCES