P9-010

BHV-8000, a selective brain-penetrant TYK2/JAK1 inhibitor for neuroinflammatory and neurodegenerative diseases, demonstrates favorable pharmacokinetics/pharmacodynamics and safety in phase 1 studies

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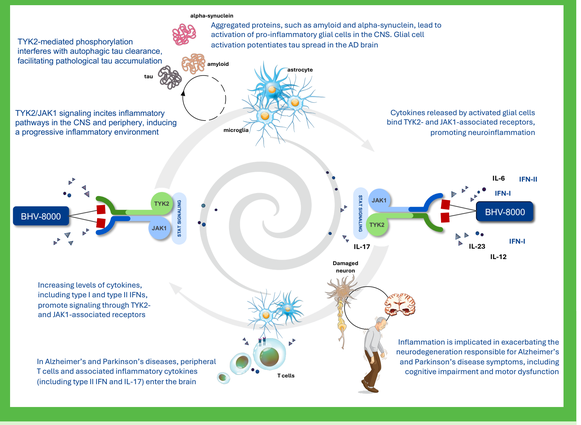
INTRODUCTION

- Central and peripheral inflammation drive the progression of Alzheimer's and Parkinson's diseases[1-3]
- The Janus kinase (JAK)—signal transducer and activator of transcription (STAT) signaling pathway, which is critical for regulating immune response, is highly dysregulated in Alzheimer's and Parkinson's diseases[2,4-7]
  - JAK1 signaling mediates interferon (IFN)-γ–associated microglial dysfunction and escalating inflammation in the central nervous system (CNS)[2,3,7]
  - Tyrosine kinase 2 (TYK2) signaling promotes activation of glial cells in the CNS, B and T cells in the periphery, and downstream production of interleukin (IL)-17A[8-12]
  - TYK2-mediated phosphorylation of tau interferes with the autophagic clearance of this protein, facilitating its pathological accumulation in the brain. Knockdown of TYK2 reduces pathogenic tau levels in a tauopathy mouse model[13]
- BHV-8000—a novel, highly selective inhibitor of TYK2/JAK1 that avoids the safety liabilities of JAK2/3 inhibition—is being developed as a disease-modifying therapy for Alzheimer's and Parkinson's diseases as well as other neurodegenerative conditions (**Figure 1**)

Figure 1. TYK2/JAK Signaling Drives Neuroinflammation in Alzheimer's and Parkinson's Diseases[1-3,5,7,9,13-21]



BHV-8000 is a brain-penetrant inhibitor of TYK2 and JAK1 that effectively blocks both glial activation in the CNS and T-cell infiltration from the periphery, which drive neuronal loss in neurodegenerative disorders like Alzheimer's and Parkinson's diseases

OBJECTIVES

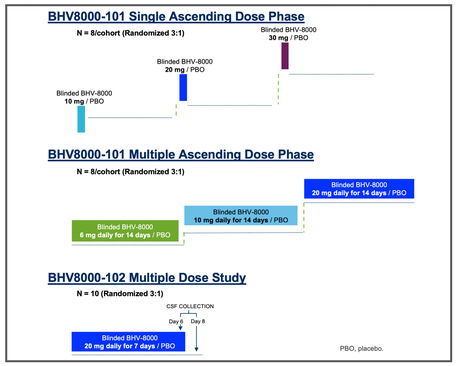
To use preliminary data from the study BHV8000-101 and repeat-dose data from the study BHV8000-102 to evaluate:

- Safety and tolerability *(BHV8000-101 and -102)*
- Plasma pharmacokinetics (PK) (*BHV8000-101 and -102)*
- Cerebrospinal fluid (CSF) PK *(BHV8000-102)*
- Pharmacodynamics (PD) of BHV-8000 *(BHV8000-101)*

METHODS

- BHV8000-101 and BHV8000-102 are each single-center, phase 1, double-blind, placebo-controlled studies conducted in healthy adult males and females aged 18-55 years (**Figure 2**)

Figure 2. BHV8000-101 and BHV8000-102 Study Design



Randomization and Dosing

- BHV8000-101 single ascending dose (SAD) phase: 8 participants randomized 3:1 to receive one dose of either BHV-8000 (10, 20, or 30 mg) or placebo
- BHV8000-101 multiple ascending dose (MAD) phase: 8 participants randomized 3:1 to receive either BHV-8000 (6, 10, or 20 mg) or placebo by mouth once daily × 14 days
- BHV8000-102: 10 participants randomized 3:1 to receive BHV-8000 (20 mg) or placebo by mouth once daily × 7 days

Pharmacokinetics and Pharmacodynamics

- In BHV8000-101, plasma PK samples were collected up to 72 hours post-dosing in the SAD and MAD phases. Inflammatory biomarkers were collected pre-dosing (Days 1 and 14) and 24 hours post-dosing (Day 15)
- In BHV8000-102, CSF PK samples were collected at 6 hours (Day 6) and 24 hours (Day 8) post-dosing
- All BHV-8000 PK data were analyzed with a validated liquid chromatography/mass spectrometry assay, and PK parameters were calculated using noncompartmental methods
- Evaluations of safety included adverse event (AE) monitoring, clinical laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations, and the Columbia Suicide Severity Rating Scale

RESULTS

Study Population

- A total of 43 participants were treated with BHV-8000
  - Eighteen (18) participants each in the SAD and MAD phases of BHV8000-101 and 7 participants in BHV8000-102
  - Mean age was 39 years; 88% male; 49% Black/African American and 47% White
- A total of 15 participants received matching placebo
  - Six (6) participants each in the SAD and MAD phases of BHV8000-101 and 3 participants in BHV8000-102
  - Mean age was 41 years; 93% male; 73% White and 27% Black/African American (**Table 1**)

Table 1. BHV8000-101 and -102 Participant Demographics

	BHV-8000 (n = 43)	Placebo (n = 15)
Age, y, mean (SD)	39.3 (9.1)	41.1 (10.7)
Sex, n (%)		
Female	5 (11.6)	1 (6.7)
Male	38 (88.4)	14 (93.3)
Race, n (%)		
White	20 (46.5)	11 (73.3)
Black or African American	21 (48.8)	4 (26.7)
American Indian or Alaskan Native	1 (2.3)	-
Other	1 (2.3)	-
Ethnicity, n (%)		
Hispanic / Latino	23 (53.5)	9 (60.0)

Safety

Overall Summary of Safety

- Comparable rates of AEs were observed between participants receiving BHV-8000 (9/43, 21%) and placebo (3/15, 20%)
- All AEs were mild in intensity, except 1 moderate event (headache)
- Three (3) treatment-emergent AEs (TEAEs) were observed in more than 1 participant receiving BHV-8000: headache (n = 4), constipation (n = 2), and increased LDL cholesterol (n = 2)
- There were no serious AEs

Single-Dose Safety

- Two (2) participants experienced a TEAE, 1 each receiving BHV-8000 (headache) and placebo (diarrhea)

Multiple-Dose Safety

- Consistent with known JAK1 class effects, mild and asymptomatic dose-associated lowering of platelet count was observed at Day 14 in BHV8000-101. All platelet decreases were limited to CTCAE grade 1. There were no meaningful reductions in platelet count in BHV8000-102
- Overall, no adverse trends were observed across other laboratory parameters (including hematology), vital signs, or ECG findings

Pharmacokinetics

Overall Summary of PK

- Median Tmax ranged from 4 to 6 hours
- The geometric mean half-life for BHV-8000 ranged from 11 to 14 hours
- Low to moderate PK variability was observed

Single-Dose Plasma PK

- Increasing the dose of BHV-8000 resulted in a general trend of increased drug exposure
- BHV-8000 demonstrated sustained concentrations over time, supporting once-daily dosing (**Figure 3**)

Figure 3. BHV-8000 Single-Dose PK Support Once-Daily Oral Dosing

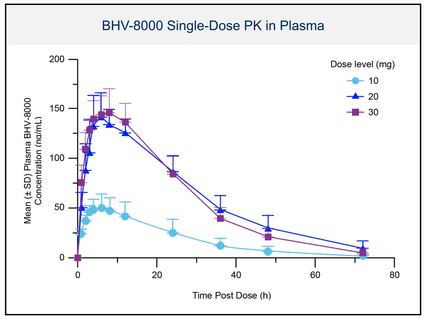
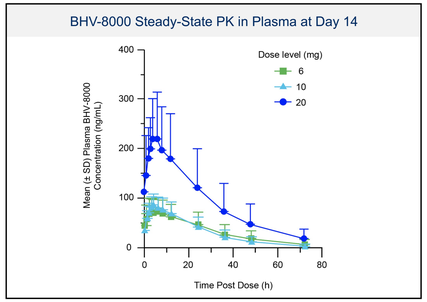


Figure 4. BHV-8000 Steady-State PK Support Once-Daily Oral Dosing



Multiple-Dose Plasma and CSF PK

- The accumulation ratio at steady state for AUC and Cmax was ~1.8-fold across the MAD cohorts (**Figure 4** and **Table 2**)
- Mean exposures in the CSF remained above the target half-maximal inhibitory concentration through 24 hours post-dose in the MAD study arm

Table 2. BHV-8000 Mean Steady-State Plasma Cmax and AUC

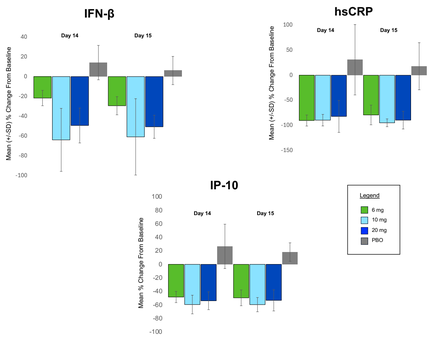
Dose (mg)	Cmax ng/mL	AUC0-tau ng*h/mL
6	72.8	1,391.7
10	85.7	1,490.3
20	210.3	3,693.7

Pharmacodynamics

Serum PD Biomarkers

- There were greater reductions from baseline in IFN-γ–inducible protein 10 kDa (IP-10), high-sensitivity C-reactive protein (hsCRP), and IFN-ß in each BHV-8000 cohort vs placebo (**Figure 5**)

Figure 5. BHV-8000 Effectively Reduces Inflammatory Biomarker Levels



CONCLUSIONS

- BHV-8000 is a first-in-class TYK2/JAK1-selective inhibitor with the potential to interrupt peripheral and central hyperactive immune responses that drive progression of neurodegenerative disorders, including Alzheimer's and Parkinson's diseases
- In the clinic, BHV-8000 has generally been safe and well tolerated, with rates of AEs comparable to placebo, no serious AEs, and no dose-limiting changes in laboratory parameters, vital signs, or ECG findings
- BHV-8000 CSF PK data show effective brain penetration and support once-daily oral dosing
- Recruitment for a global phase 2/3 study in individuals with early Parkinson's disease is starting in the second quarter of 2025

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DISCLOSURES: LLL, PA, BS, BA, RK, EA, JP, RBe, BC, IQ and VC are employees of and have stock in Biohaven; RBh and JAM are consultants to Biohaven.

Data previously presented at CTAD24 and ADPD25.

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