LP026

BHV-8000, a Selective Brain-Penetrant TYK2/JAK1 Inhibitor in Development for Neuroinflammatory and Neurodegenerative Diseases, Demonstrates Favorable PK/PD and Safety Profile in Phase 1 Studies

Peter Ackerman[1], Nick Kozauer[1], Raj Bhardwaj[2], Bavani Shankar[1], Bharat Awsare[1], Randall Killingsworth[1], Eric Ashbrenner[1], Jo Ann Malatesta[2], Emily Thompson[1], Dustin Walters[1], Alyssa Cheng[1], Lindsey Lee Lair[1], Richard Bertz[1], Bruce Car[1], Irfan Qureshi[1], Vlad Coric[1]

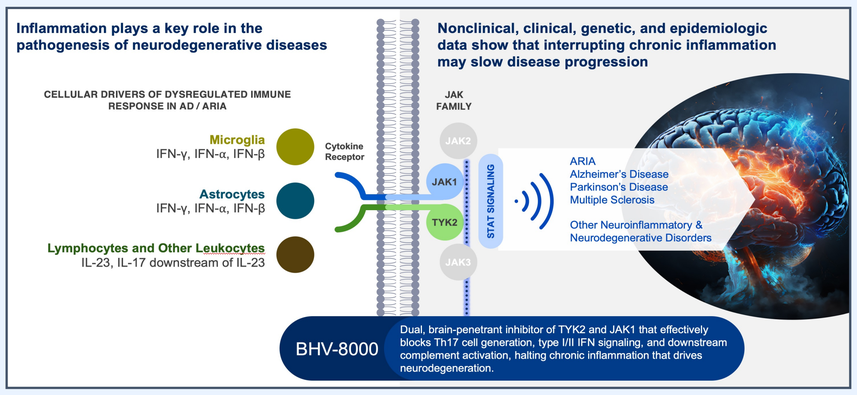
[1]Biohaven Pharmaceuticals, New Haven, CT, USA; [2]Certara, Radnor, PA, USA.

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

INTRODUCTION

- BHV-8000, a novel, oral, highly selective dual TYK2/JAK1 inhibitor designed to avoid JAK2/3 safety liabilities, is being developed as a disease-modifying therapy for Alzheimer's disease (AD) and as a preventive strategy against amyloid-related imaging abnormalities (ARIA)
- Central and peripheral inflammation both play important roles in the onset and progression of neurodegenerative diseases including AD[1]
- ARIA represent a mixed inflammatory response to amyloid deposits within the neurovasculature and pose a major barrier limiting the clinical utilization of anti-amyloid immunotherapies[2-5]
- The JAK-STAT signaling pathway is highly dysregulated in AD, contributing to the proliferation of pro-inflammatory cytokines and activated immune cells[6-8] (**Figure 1**)
  - JAK1 signaling (via type I interferons [IFNs], type II IFN, interleukin 6 [IL-6], and other cytokines) mediates microglial dysfunction and escalating inflammation within the central nervous system (CNS)[9,10]
  - TYK2 signaling (via type I IFNs, IL-12, IL-23, etc) plays an important role in the activation of glial cells in the CNS, activation of B and T cells in the periphery, and promoting downstream proliferation of IL-17A[11-13]

Figure 1. TYK2/JAK1 Inhibition and the Neuroinflammatory-Neurodegenerative Cycle



OBJECTIVES

- Evaluate safety and tolerability of single- and multiple-dose oral administration of BHV-8000 in healthy adults (BHV8000-101 and -102 studies)
- Evaluate the plasma pharmacokinetics (PK) of single and multiple doses of BHV-8000 (BHV8000-101)
- Evaluate the PK of BHV-8000 in cerebrospinal fluid (CSF) of healthy adults following administration of multiple doses of BHV-8000 (BHV8000-102)
- Evaluate the pharmacodynamics (PD) of BHV-8000 (BHV8000-101)

METHODS

- BHV8000-101 (TLL041-101) and BHV8000-102 are each single-center, phase 1, double-blind, placebo-controlled studies conducted in healthy adults (**Figure 2**)
- Both studies included healthy males and females aged 18-55 years with a BMI of 18-30 kg/m^2

BHV8000-101 Single Ascending Dose (SAD) Phase

- Eight (8) participants were randomized 3:1 to a single oral dose of BHV-8000 (10, 20, or 30 mg) or placebo (PBO)

BHV8000-101 Multiple Ascending Dose (MAD) Phase

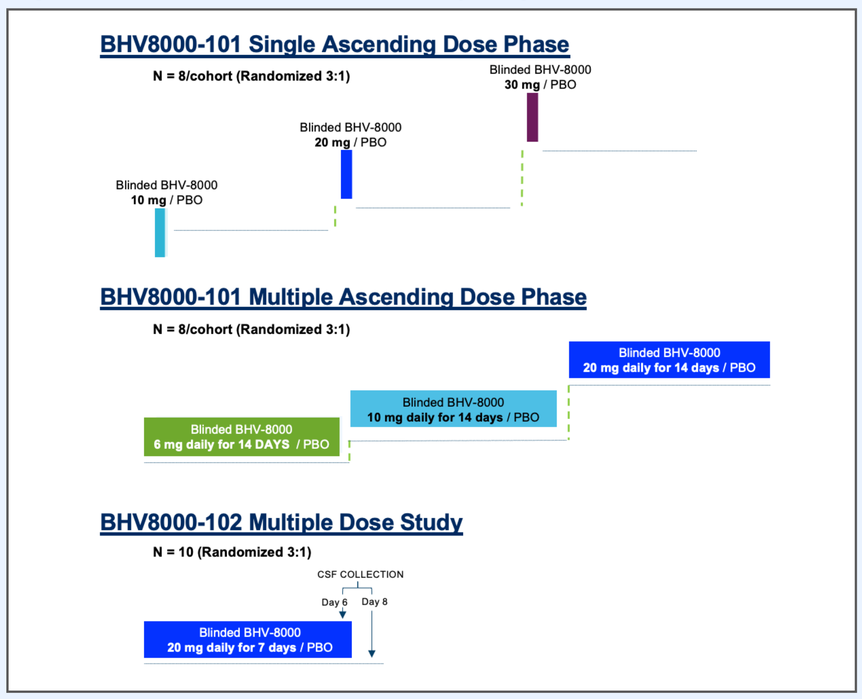
- Eight (8) participants were randomized 3:1 to once-daily doses of BHV-8000 (6, 10, or 20 mg) or PBO for 14 days

BHV8000-102, Part 3 Multiple Dose Phase

- Ten (10) participants were randomized 3:1 to once-daily doses of BHV-8000 20 mg or PBO for 7 days

- In BHV8000-101, plasma PK samples were collected up to 72 hours post dosing in the SAD and MAD phases. PD (inflammatory) biomarkers were collected pre-dose (Day 1 and Day 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 were analyzed by a validated liquid chromatography/mass spectrometry assay, and PK parameters were calculated by noncompartmental methods
- Safety evaluations throughout the studies included adverse event (AE) monitoring, clinical laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations, and a Columbia-Suicide Severity Rating Scale questionnaire
- The current analysis summarizes initial safety, PK, and PD data available from the BHV8000-101 and -102 studies

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



RESULTS

Study Population

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

Table 1. BHV8000-101 and -102 Participant Demographic Characteristics

	BHV-8000 (n = 43*)	Placebo (n = 15*)
Age, y, mean (SD)	39.2 (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)

*In BHV8000-101, one (1) individual was randomized to BHV-8000 as part of the SAD phase and later rescreened and rerandomized to PBO as part of the MAD phase.

Safety

Overall Summary of Safety Data Across All Cohorts

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

Single-Dose Safety

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

Multiple-Dose Safety (up to 14 days)

- Two (2) participants (1 each on BHV-8000 and PBO) discontinued early due to AEs, both in BHV8000-102
  - BHV-8000: moderate headache plus mild chills and palpitations; all symptoms resolved on the day of onset
  - PBO: mild triglycerides increased
- In BHV8000-101, there was dose-associated lowering of the platelet count, consistent with known JAK1 class effects. All platelet decreases were limited to CTCAE Grade 1. There were no meaningful reductions in platelet count in BHV8000-102
- There were no adverse trends across other laboratory parameters (including cholesterol), vital signs, or ECGs

Pharmacokinetics

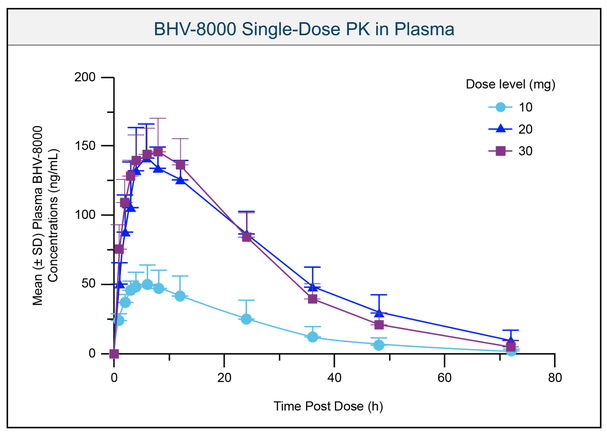
Overall Summary of PK Data

- The geometric mean half-life for BHV-8000 ranged from 11-14 hours
- The median Tmax ranged from 5-6 hours
- Low to moderate PK variability was observed
- Apparent oral clearance was approximately 9 L/h

Single-Dose Plasma PK

- Dose-proportional increases in Cmax and area under the curve (AUC) occurred at doses of 10 mg and 30 mg.
- 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



Multiple-Dose Plasma PK

- The accumulation ratio at steady state for AUC and Cmax was ~1.7-fold across the MAD cohorts (**Figure 4**), (**Table 2**)

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

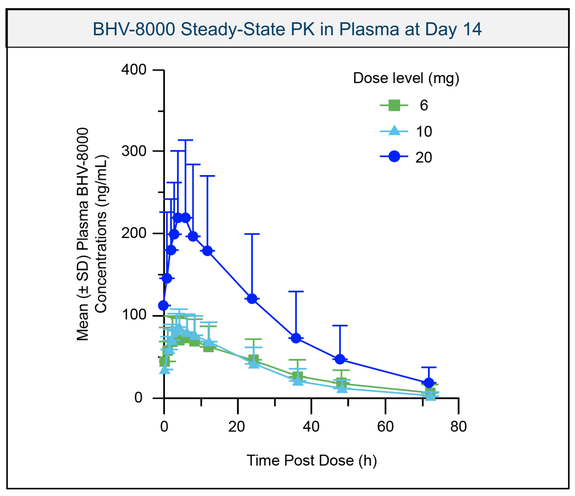


Table 2. BHV-8000 Steady-State Plasma Cmax and AUC

Dose (mg)	Cmax ng/mL (CV %)	AUC0-tau ng*h/mL (CV%)
6	72.8 (38.1%)	1391.7 (42.4%)
10	85.7 (28.0%)	1490.3 (37.2%)
20	210.3 (39.4%)	3693.7 (50.7%)

Multiple-Dose CSF PK

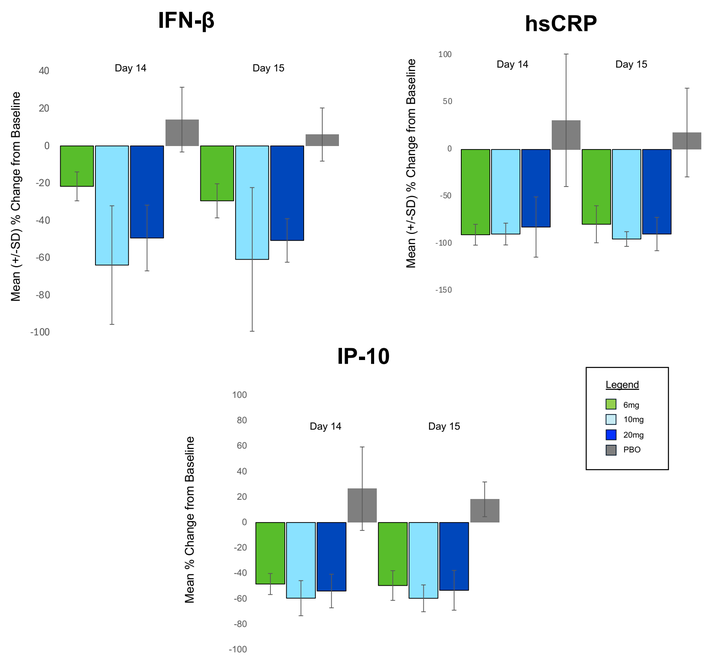
- Mean exposures in the CSF remained above the target IC50 through 24 hours post dose

Pharmacodynamics

Multiple-Dose Serum PD Biomarkers

- Reductions from baseline interferon-gamma inducible protein 10 kDa (IP-10), high-sensitivity C-reactive protein (hsCRP), and interferon-beta (IFN-ß) were numerically greater for each BHV-8000 cohort vs placebo (**Figure 5**)
- Inflammatory biomarker levels were reduced by treatment with BHV-8000, albeit in healthy adults without baseline elevations

Figure 5. BHV-8000 Effectively Reduces Inflammatory Biomarker Levels



CONCLUSIONS

- ❖ BHV-8000 is a novel, oral, highly selective, brain-penetrant TYK2/JAK1 inhibitor with a favorable PK profile and promising PD effects at clinically relevant doses that are well tolerated in healthy adults
- ❖ BHV-8000 PK and PD demonstrate differentiated potential to address inflammation in the periphery and within the CNS, which drive Alzheimer's disease progression
- ❖ BHV-8000 modulates innate and adaptive immune response and complement signaling and has the potential to mitigate the risk of ARIA upon initiation of anti-amyloid therapy, the only approved disease-modifying treatment for Alzheimer's disease

DISCLOSURES: PA, NK, BS, BA, RK, EA, LLL, RBe, BC, IQ, and VC are employees of and have stock in Biohaven; AC, DW, and ET completed an internship at Biohaven; RBh and JAM are consultants to Biohaven.

Presented at the *17th Clinical Trials on Alzheimer's Disease Conference*
October 29–November 1, 2024 | Madrid, Spain

References: 1. Chen X, Holtzman DM. *Immunity.* 2022;55(12):2236-2254. doi:10.1016/j.immuni.2022.10.0163 **2.** Hampel H, Elhage A, Cho M, Apostolova LG, Nicoll JAR, *Brain*. 2023;146(11):4414-4424. doi:10.1093/brain/awad188 **3.** Taylor X, Clark IM, Fitzgerald GJ, et al. *Mol Neurodegener.* 2023;18(1):59. doi:10.1186/s13024-023-00649-w **4.** Yuan K, Ye J, Liu Z, et al. *J Exp Clin Cancer Res*. 2020;39(1):9. doi:10.1186/s13046-019-1514-3 **5.** An XQ, Xi W, Gu CY, Huang X. *Med Sci (Paris).* 2018;34 Focus issue F1:116-120. doi:10.1051/medsci/201834f120 **6.** Rodriguez S, Hug C, Todorov P, et al. *Nat Commun*. 2021;12(1):1033. doi:10.1038/s41467-021-21330-0 **7.** Nevado-Holgado AJ, Ribe E, Thei L, et al. *Cells.* 2019;8(5):425. doi:10.3390/cells8050425 **8.** Rusek M, Smith J, El-Khatib K, et al. *Int J Mol Sci.* 2023:24(1):864. doi: 10.3390/ijms2401086 **9.** Roy ER, Wang B, Wan Y-W, et al. *J Clin Invest*. 2020;130(4):1912-30. doi: 1172/JCI133737 **10.** Yan Z, Gibson SA, Buckley JA, et al. *Clin Immunol*. 2018;189:4-13. doi: 10.1016/j.clim.2016.09.014 **11.** Brigas HC, Ribeiro M, Coelho JE, et al. *Cell Rep.* 2021;36(9):109574. doi: 10.1016/j.celrep.2021.109574 **12.** Wan J, Fu AK, Ip FC, et al. *J Neurosci.* 2010;30(20):6873-6881. doi:10.1523/JNEUROSCI.0519-10.2010 **13.** König LE, Rodriguez S, Hug C, et al. Preprint. *bioRxiv*. 2024;2024.06.04.595773. doi:10.1101/2024.06.04.595773.

biohaven