BHV-8000, a Selective Brain-Penetrant TYK2/JAK1 Inhibitor in Development for Neuroinflammatory and Neurodegenerative Diseases, Demonstrates Efficacy in an Alpha-Synuclein Overexpressing Parkinson's Disease Mouse Model

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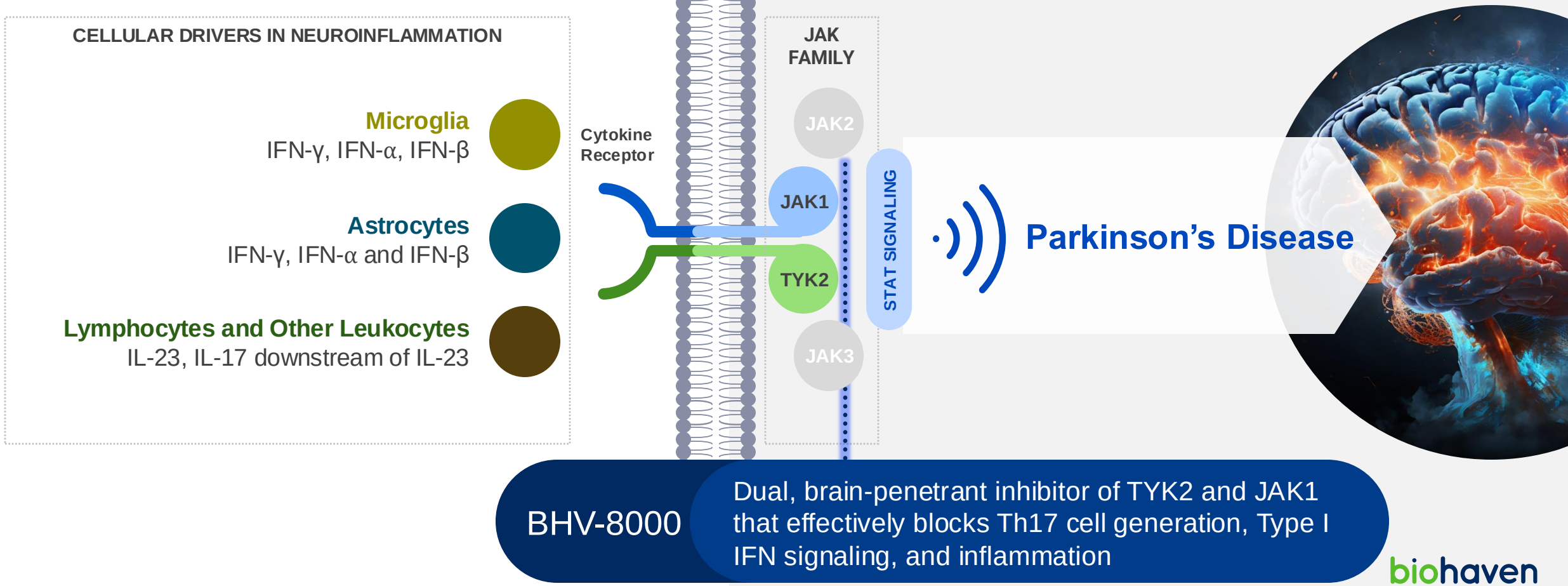
Lindsey Lee Lair, MD is an employee of and holds stock/stock options in Biohaven Pharmaceuticals.

BHV-8000: Compelling Rationale for Brain-Penetrant TYK2/JAK1 Inhibitor to Treat Neuroinflammatory and Neurodegenerative Disorders

Inflammation plays a key role in the pathogenesis of neurodegenerative diseases

Nonclinical, clinical, genetic, and epidemiological data show that interrupting chronic inflammation may slow disease progression



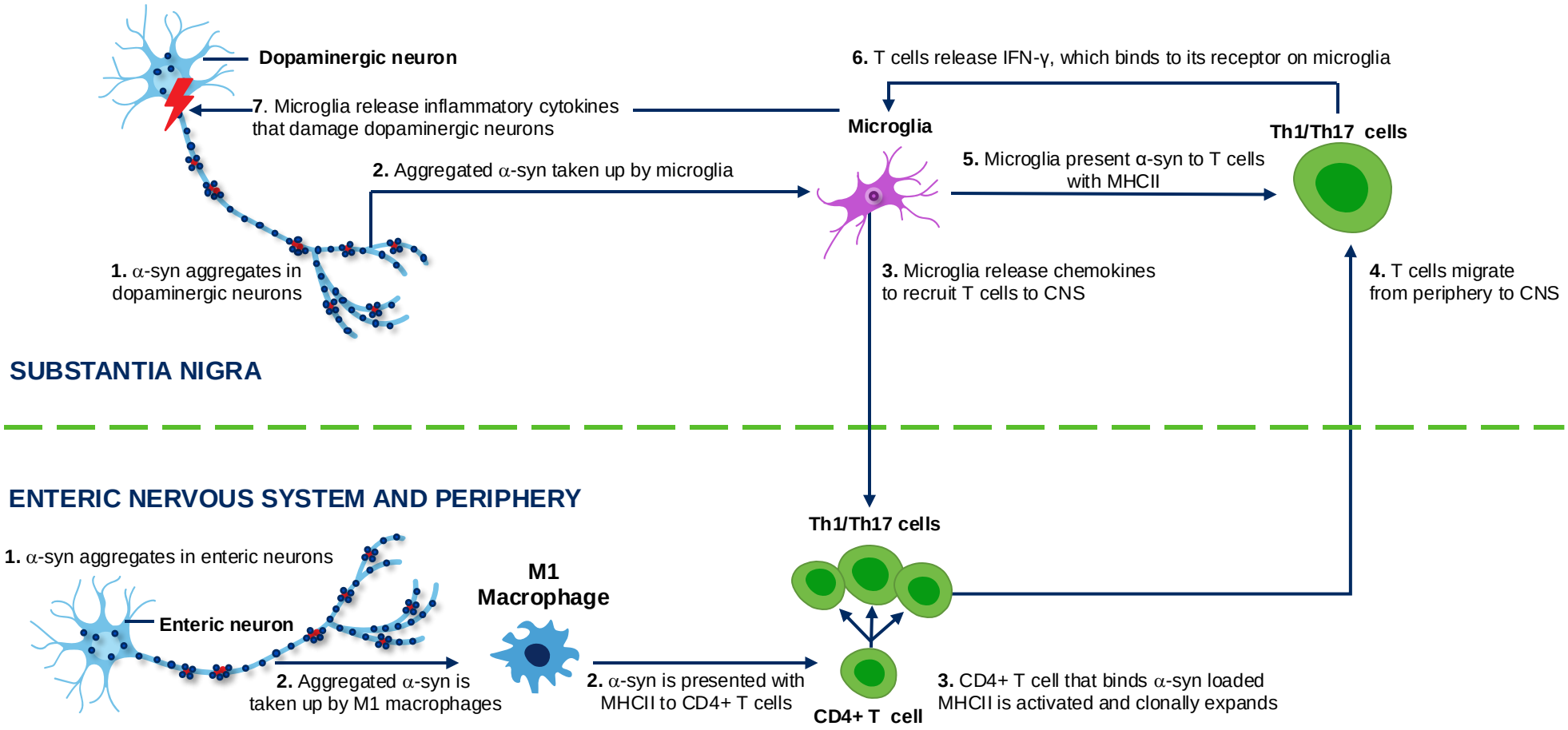
BHV-8000 Dual, brain-penetrant inhibitor of TYK2 and JAK1 that effectively blocks Th17 cell generation, Type I IFN signaling, and inflammation

biohaven

BHV-8000: Targets Both Axes of Neuroinflammation in Parkinson's Disease

TYK2/JAK1 INHIBITION OF PARKINSON'S NEUROINFLAMMATORY CASCADE

TYK2/JAK1 inhibitors reduce Th17 cell activation and expansion by inhibiting IL-23 signaling and reduce microglial activation by inhibiting IFN-γ signaling triggered by pathogenic α-synuclein aggregates[1,2]



α-syn, alpha-synuclein; **CD4**, cluster of differentiation 4; **CNS**, central nervous system; **IFN-γ**, interferon-gamma; **IL**, interleukin; **JAK**, Janus kinase; **M1**, classically activated; **MHC**, major histocompatibility complex; **Th**, T helper cell; **TYK**, tyrosine kinase

1. Allen Reish, Standaert. *J Parkinsons Dis*. 2015;5(1):1-19. 2. Fu et al. *J Neuroinflammation.* 2022;19(1):98.

Real-World Analytics of Large Healthcare Database Show Parkinson's Disease Risk Reduction With TNF/IL-17 Targeting Therapies

- Biohaven conducted analysis using Komodo Health database (over 320 million patients since 2012) examining treatment with anti-TNF or anti-IL17 and incidence of PD
- Millions of patients over 8+ years of dosing captured key epidemiologic confirmation of the neuroinflammatory hypothesis
- Results support rationale for the effectiveness of BHV-8000 in treating PD

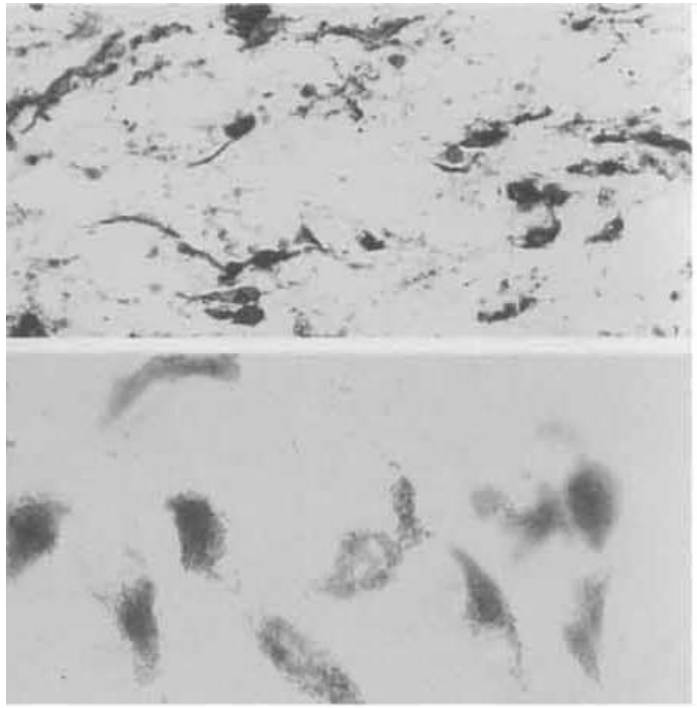
Treatment	PD Events	Person-years	Rate (per 100 person-years)	Adjusted IRR (95% CI)	P-value
Anti-TNF or Anti-IL-17 exposure	2,957	393,114	**0.66**	0.77 (0.74 – 0.80)	<0.0001
No Treatment	50,562	5,328,307	0.95		
Anti-TNF exposure	2,471	371,867	**0.66**	0.64 (0.52 – 0.80)	<0.0001
No Treatment	50,562	5,328,307	0.95		
Anti-IL-17 exposure	81	15,598	**0.52**	0.77 (0.78 – 0.81)	<0.0001
No Treatment	50,562	5,328,307	0.95		

IRR, incidence rate ratio; **TNF**, tumor necrosis factor.

BHV-8000: Clinical Data Supports Targeting Neuroinflammation in Parkinson's Disease

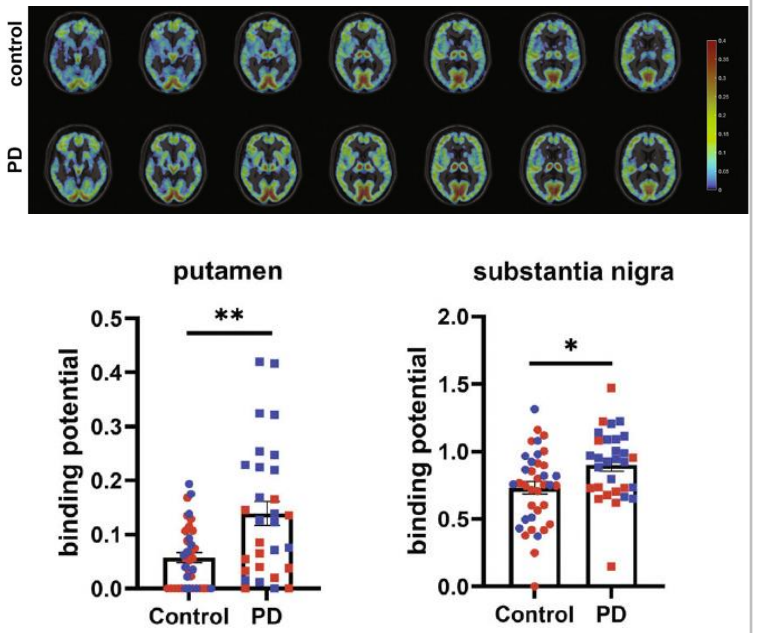
Post-Mortem Data[1]

PD patient brains express high levels of HLA-DR+ reactive microglia



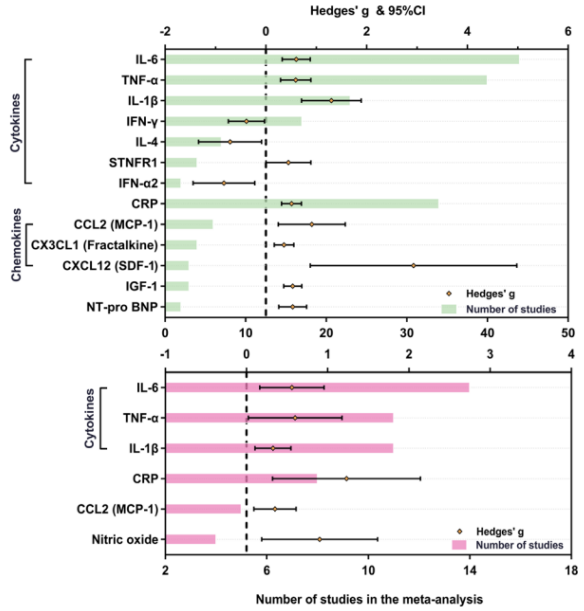
In Vivo Imaging[2]

^{18}F-DPA-714 TSPO imaging increased in early PD relative to healthy controls



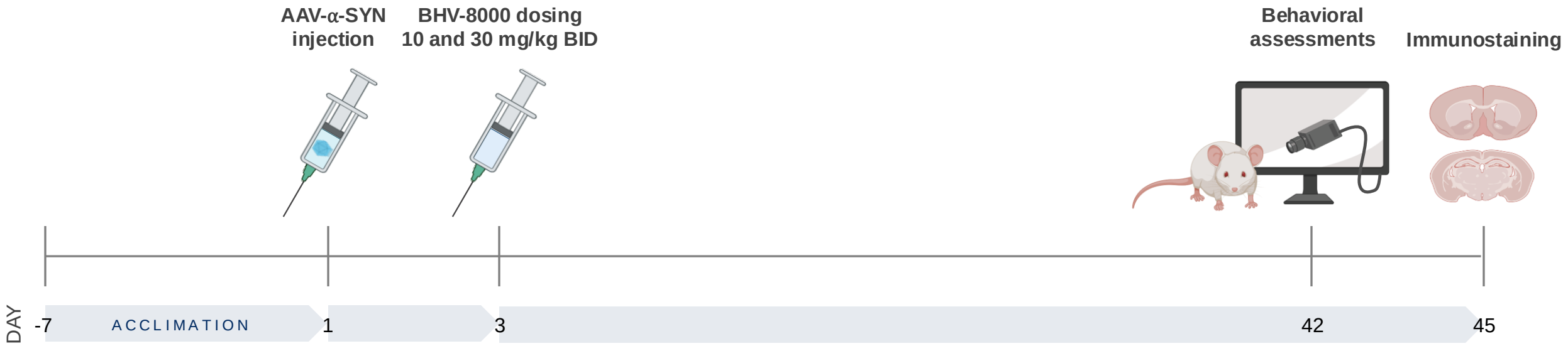
In Vivo Cytokine Levels[3]

Elevated levels of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α, IFN-ɣ) found in the CSF and blood of PD patients



1. McGeer PL, et al. *Neurology*. 1988 Aug;38(8):1285-91. 2. Yacoubian TA, et al. *Mov Disord*. 2023 May;38(5):743-754. 3. Qu Y, et al. *NPJ Parkinson's Dis*. 2023 Feb 4;9(1):18.

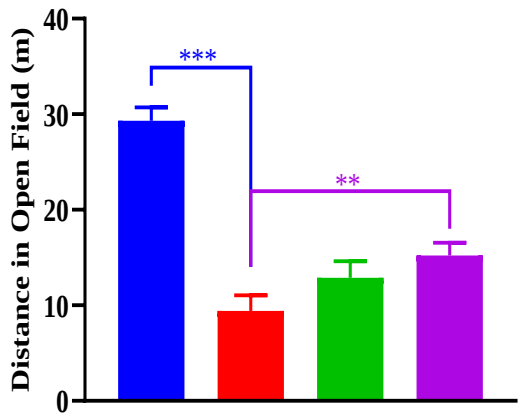
BHV-8000: AAV-α-synuclein Mouse Model of Parkinson's Disease

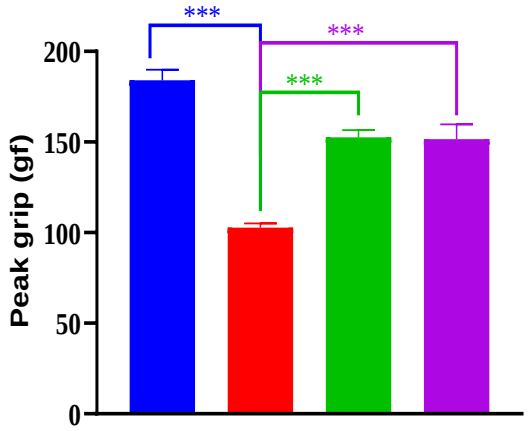


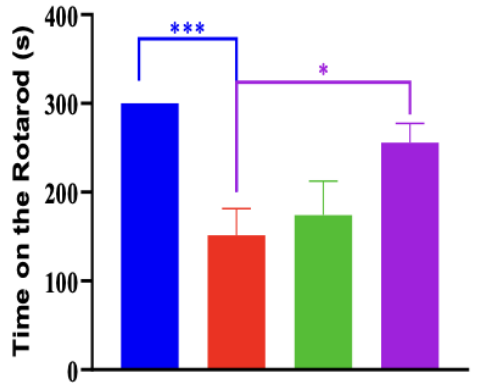
BHV-8000: Efficacious in AAV-α-synuclein Mouse Model of Parkinson's Disease

Improved Behavioral Assessments

	Increased Movement Distance in an Open Field by:	Increased Grip Strength by:	Increased Time on Rotarod by:
10 mg/kg	36.8%	48.5%	14.8%
30 mg/kg	61.4%	47.5%	64.4%

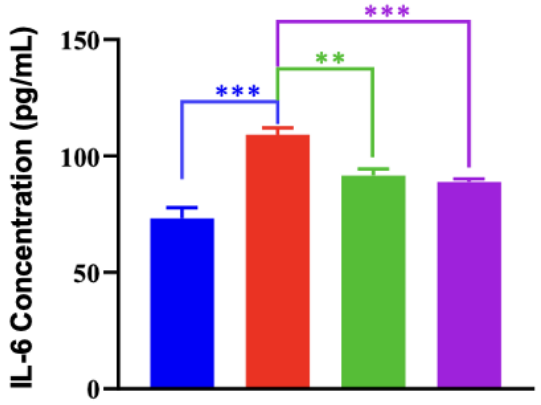






Alleviated Inflammatory Response

Significantly Decreased IL-6 Level in Str and SN Tissues of Mice



Note: IL-6 levels are elevated in PD patients

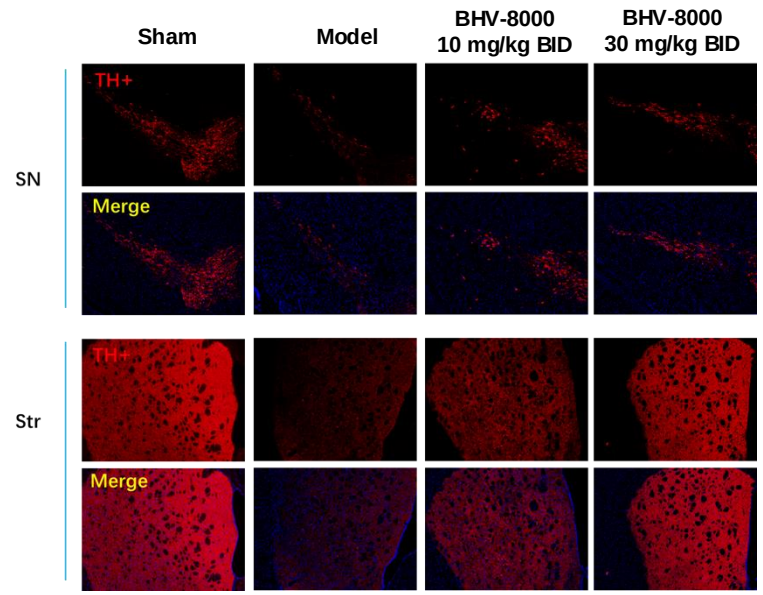
Sham | Model | BHV-8000 (10 mg/kg) | BHV-8000 (30 mg/kg) *p<0.05, **p<0.01, ***p<0.001, Note:Mean ± SEM

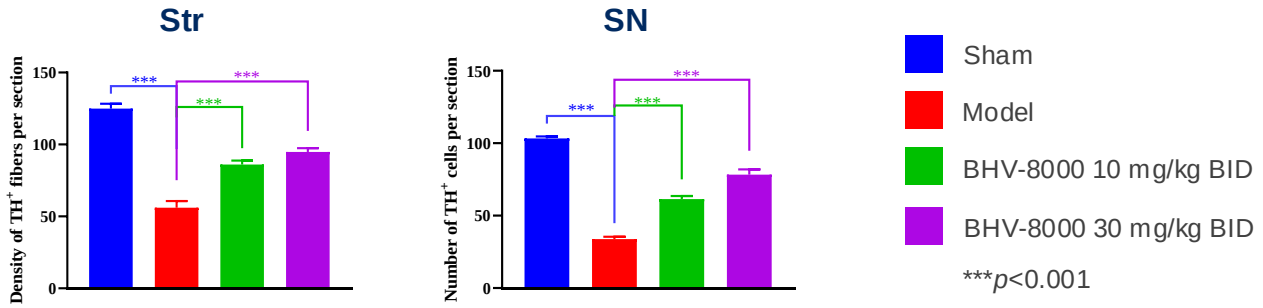
KEY POINTS

BHV-8000 improved PD-related motor behavior and alleviated inflammatory response in the brain in the α-syn overexpressing mouse model

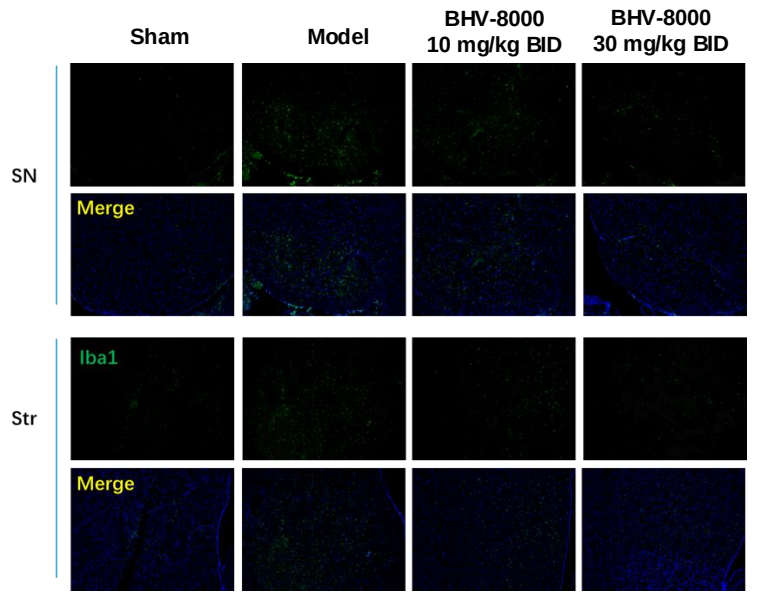
BHV-8000: Mitigated Microglia Activation and Rescued Neuronal Death in AAV-α-synuclein Mouse Model of Parkinson's Disease

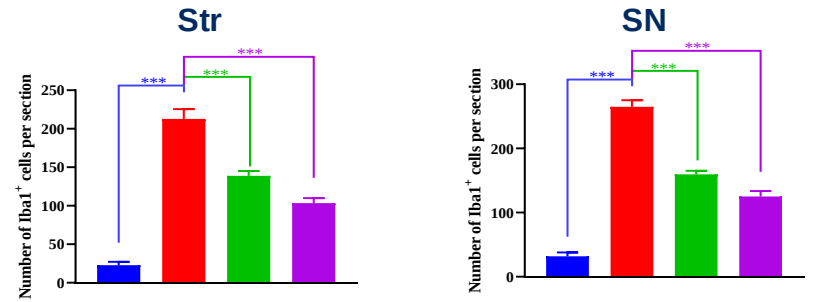
Reversed Neuron Death Indicated by Increased Counts of TH+ Neurons in SN





Mitigated Microglia Activation Represented by Reduced Numbers of 1ba1+ Microglia





BHV-8000: Brain-Penetrant TYK2/JAK1 Inhibitor Demonstrates Promising Phase 1 Profile

Study Completed: 3 SAD cohorts and 3 MAD cohorts

- SAD dose cohorts (10, 20 and 30 mg); MAD dose cohorts (6, 10 and 20 mg)
- 8 healthy participants per cohort (6 active: 2 placebo)

Safe and well-tolerated

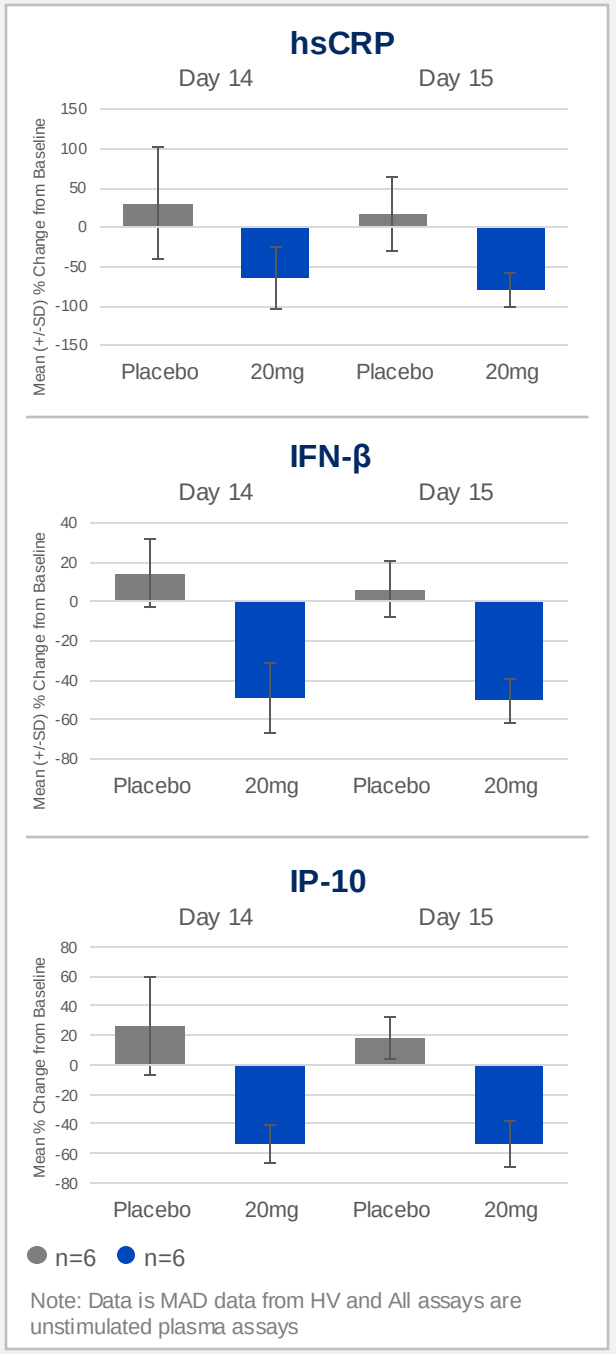
- No SAEs or severe AEs; only mild AEs observed that resolved spontaneously
- No adverse laboratory trends related to study drug

Evidence of target engagement

Hs-CRP, IFN-β and IP-10 showed drug-related changes in plasma

Robust brain penetration

Approximately 50% CNS penetration in humans

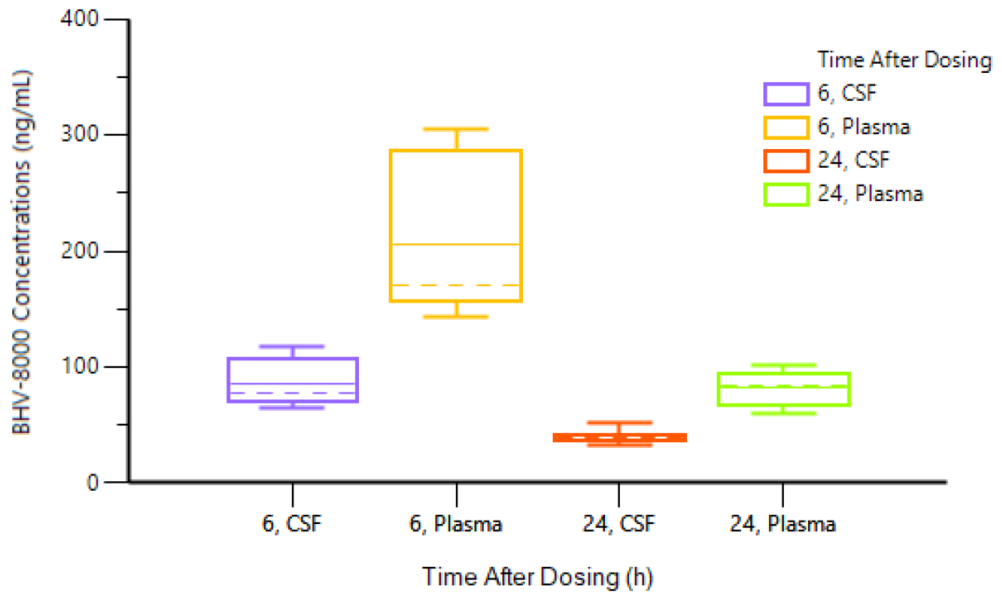


KEY POINT

Pharmacodynamic data shows target engagement in healthy subjects

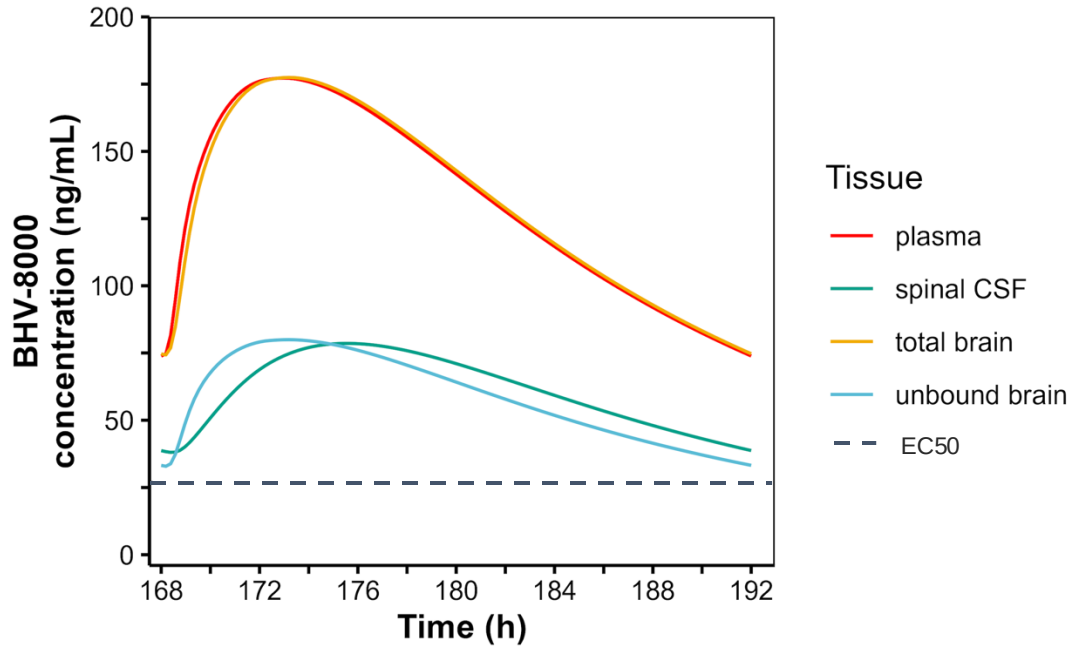
BHV-8000: Demonstrates Robust CNS Penetration in Phase 1

CSF and Plasma Concentrations (20 mg QD)



Healthy subjects

Brain PK Sustained Above EC50 for 24 Hours at 20 mg QD



Modelling data

CSF, Cerebro Spinal Fluid

KEY POINT

Expected to have sustained brain exposures above EC50 (target engagement)

BHV-8000: Phase 2/3 Study in Early Parkinson's Disease

Novel Primary Efficacy Endpoint

Time-to-event (≥ 2-point worsening on MDS-UPDRS-Part II)

- Addresses FDA requirement for a functional endpoint in PD trials
  - MDS-UPDRS-Part II recommended, but declines very slowly in early PD
- 300 fewer patients per trial versus a mean change on MDS-UPDRS-Part II
- Based on comprehensive analyses of PPMI and placebo-arm clinical trial data (C-Path)

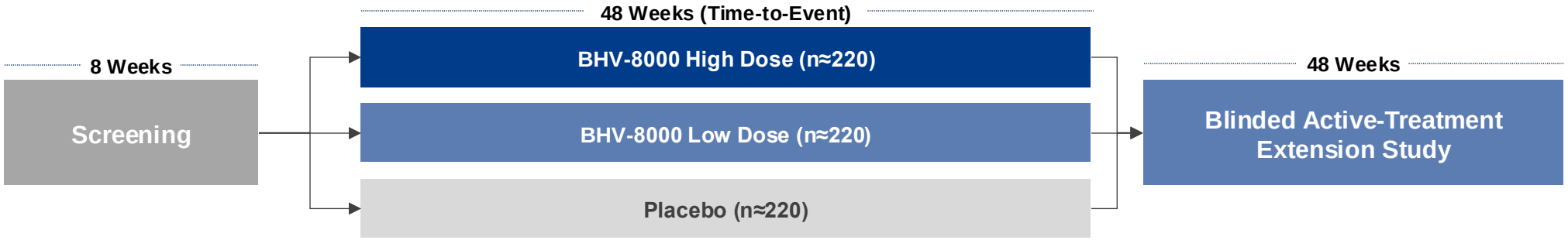
Provides a meaningful efficacy endpoint with a smaller sample size

Novel Composite Endpoint

Parkinson's Disease Composite Score (PARCOMS)

- Based on established methodology (i.e., Alzheimer's Disease Composite Score [ADCOMS])
- Leverages PPMI and placebo-arm clinical trial data (C-Path)
- Comprises the most responsive items from common endpoints in early PD trials

Provides a highly-sensitive supportive secondary efficacy endpoint



Preliminary clinical trial design; **PPMI**, Parkinson's Progression Markers Initiative; **MDS-UPDRS**, Movement Disorder Society – Unified Parkinson's Disease Rating Scale.

KEY POINT

Positive FDA feedback on novel time-to-event primary efficacy endpoint allows for a more efficient registrational study

First-in-Clinic, Oral, Selective, Brain-Penetrant TYK2/JAK1 Inhibitor

- Selectivity profile avoids class risks associated with JAK2/3 inhibition

Potential to Treat Multiple Neuroinflammatory & Neurodegenerative Disorders

- Supported by a broad range of clinical, translational, and epidemiological evidence
- Indications include early Parkinson's disease, anti-amyloid therapy-induced ARIA, early Alzheimer's disease, and multiple sclerosis

Efficacious α-Syn overexpressing PD mouse model

- Reduced PD-related motor behavior
- Decreased neuroinflammation
- Reversed neuron cell death

Phase 1 Trials are Completed

- Safe and well-tolerated
- Evidence of target engagement
- Robust brain penetration

BHV-8000

TYK2/JAK1 INHIBITOR (brain-penetrant)

PD, Parkinson's disease; **ARIA**, Amyloid-related imaging abnormalities; **TYK**, tyrosine kinase; **JAK**, Janus kinase.

KEY POINT

Pivotal study in early Parkinson's disease planned to initiate in 1H 2025