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Biohaven Reports First-in-Human Dosing of Oral PKM2 Modulator, BHV-8100, Targeting Metabolic Restoration and Immunomodulation

June 1, 2026

- *BHV-8100 is an orally administered, brain-penetrant PKM2 modulator; a novel therapeutic class addressing the bioenergetic and immunometabolic basis of systemic and central nervous system disorders*
- *First-in-human study initiated with dose escalation ongoing; preliminary data in healthy participants demonstrates favorable pharmacokinetics supporting convenient, once-daily dosing and well tolerated profile at projected therapeutic exposures*
- *Penetrates blood-brain barrier and reverses metabolic dysfunction with 3-fold improvement in glucose utilization in human, whole brain model (Bexorg BrainEx platform, physiologically reactivated brains from human donors); preferential metabolic rescue in Alzheimer's disease donor brains vs controls*
- *Exhibits robust beneficial effects across a spectrum of preclinical models of Alzheimer's, and multiple sclerosis: restores metabolic deficits, reduces inflammation and neurodegeneration, and enhances remyelination*
- *PKM2 modulation offers a potential new paradigm for treating large, underserved, and high-value indications in neurology, ophthalmology, and immunology*

NEW HAVEN, Conn., June 1, 2026 /PRNewswire/ -- Biohaven Ltd. (NYSE: BHVN) ("Biohaven"), a global clinical-stage biopharmaceutical company focused on the discovery, development, and commercialization of life-changing therapies for rare and common diseases, today announced the initiation of first-in-human (FIH) dosing for BHV-8100, its oral, brain-penetrant pyruvate kinase M2 isoform (PKM2) modulator.

Dr. Bruce Car, Chief Scientific Officer of Biohaven, stated, "BHV-8100 represents a potential fundamental breakthrough in a new class of medicines with potential therapeutic effects in both systemic and brain disorders that involve metabolic and immune dysfunction. PKM2 acts as a bridge between metabolism and immune function. By modulating PKM2, we are striving to correct the core energy deficit known to underpin a number of inflammatory and neurological disorders including atopic dermatitis, Alzheimer's disease, and retinitis pigmentosa. Achieving this important milestone to advance a convenient oral, once-daily and brain-penetrant PKM2 modulator reflects Biohaven's mission to deliver innovative and potentially transformative therapies in areas of profound unmet medical need."

BHV-8100 Mechanism of Action

PKM2 is the final, rate-limiting enzyme in glycolysis, converting phosphoenolpyruvate to pyruvate, and it serves as a master metabolic regulator in energy-intensive cells and tissues, including the brain, retina, and immune system. The accumulation of the less enzymatically active, dimeric form of PKM2 leads to bioenergetic deficits and drives disease pathogenesis. Conversion to its more active, tetrameric form by an allosteric PKM2 modulator, such as BHV-8100, can restore energy homeostasis and promote health.

The brain and retina are two of the most metabolically demanding tissues in the body with a significant reliance on glucose to produce cellular energy as adenosine triphosphate (ATP). When glucose uptake and ATP generation are deficient, as has been documented in multiple neurodegenerative and retinal diseases, including aging, Parkinson's disease, multiple sclerosis, age-related macular degeneration (AMD), and retinitis pigmentosa, neurodegeneration and immune activation result.

Compelling evidence from preclinical models employing BHV-8100 and the literature suggest a breadth of disease indications for which BHV-8100 could provide significant benefit. By pharmacologically increasing ATP generation from glycolysis and through fueling the tricarboxylic acid (TCA) cycle, as well as rebalancing glycolytic biosynthetic intermediates, neurons, photoreceptor cells and glial cells become resilient and are better able to sustain cell function, plasticity, and survival.

Pierre Magistretti, M.D., Ph.D., Ibn Sina Distinguished Professor at King Abdullah University of Science and Technology, an expert in the effects of neuronal metabolism in disease and discoverer of the astrocyte-neuron lactate shuttle which is critical in neuronal homeostasis, commented, "Neurodegenerative and retinal diseases with early and worsening metabolic hypofunction develop into profoundly disabling conditions. BHV-8100 has the potential to change that. BHV-8100 provides astrocytic lactate to neurons, correcting metabolic dysfunction, improving bioenergetics and offering real hope to the millions of patients to reverse the relentless decline in cognition and eyesight."

BHV-8100 is an oral, potent, selective, small-molecule PKM2 allosteric modulator designed for once-daily administration. By binding to and stabilizing the active tetrameric form of PKM2, BHV-8100 restores flux through the glycolytic pathway, producing three interconnected therapeutic effects:

- **Rescues metabolic deficits:** Increased PKM2 activity drives cytoplasmic ATP production, while further fueling mitochondrial TCA cycle ATP production thereby correcting inadequate ATP levels in neurons, glia and retinal cells. Adequate ATP enables cellular resilience based on restoring energetically expensive processes such as supporting am efficient unfolded protein response (UPR), antioxidant mechanisms, ion channel function, synaptic signaling, and axonal transport which all collectively deteriorate in neurodegeneration.
- **Reduces neuroinflammation:** PKM2 modulation to the tetramer form clears glycolytic intermediates, robustly suppressing pro-inflammatory cytokine production (including IL-1β, TNF-α) and shifting microglia/macrophages toward anti-inflammatory, neuroprotective phenotypes. Th17 lymphocyte specific inhibition is noted in the neuroinflammatory processes associated with allergic encephalomyelitis (EAE).
- **Rescues neurodegeneration:** By correcting the energetic and inflammatory drivers of neuronal and glial stress, BHV-8100 protects against synapse loss, axonal degeneration, myelin loss and cell death in preclinical disease models, including EAE and cuprizone-induce myelopathy.

BrainEx Human Translational Data: Compelling Preclinical Confirmation of Novel PKM2 Modulating Pharmacology, Pharmacokinetics, Target Engagement, and Human Biology

Biohaven's ongoing collaboration with Bexorg's BrainEx platform allows for early testing of brain penetrance, target engagement, target pharmacology and dose-response relationships in human brain prior to Phase 1 initiation. BrainEx uses ex-vivo, decedent human brains with specific disease diagnoses to generate uniquely powerful translational data prior to Phase 1 first-in-human dosing. Key findings from administration of BHV-8100 in BrainEx demonstrated:

- **Excellent blood-brain barrier penetration** confirmed in intact human brains. Target blood plasma and brain drug concentrations determined in other preclinical models were employed in the BrainEx platform, allowing precise determination of brain uptake of drug.
- **Dose- and brain concentration-pharmacology response relationships** confirmed in samples from input and output blood vasculature, brain tissue and cerebrospinal fluid, allowing optimal dose targeting
- **Up to 3 times improvement in cerebral glucose utilization and lactate production**, direct readouts of enhanced glycolytic flux, confirming expected PKM2 activation in intact human brain tissue (**see Figure 1**).   Maintenance of the enhanced glycolytic flux well after removing drug in the blood supply suggests a durable PKM2 tetramer state, further amplifying efficacy
- **Preferential metabolic rescue in Alzheimer's disease:** BHV-8100 demonstrated selectively greater glucose utilization improvements in donor brains from individuals diagnosed with Alzheimer's disease versus cognitively normal controls, suggesting that BHV-8100's activity occurs precisely where the metabolic deficit is most severe, a highly favorable mechanistic profile for disease modification.

Figure 1: BHV-8100 improves brain glucose utilization from brain of subjects in the BrainEx platform with a diagnosis of pooled causes of dementia and Alzheimer's disease.

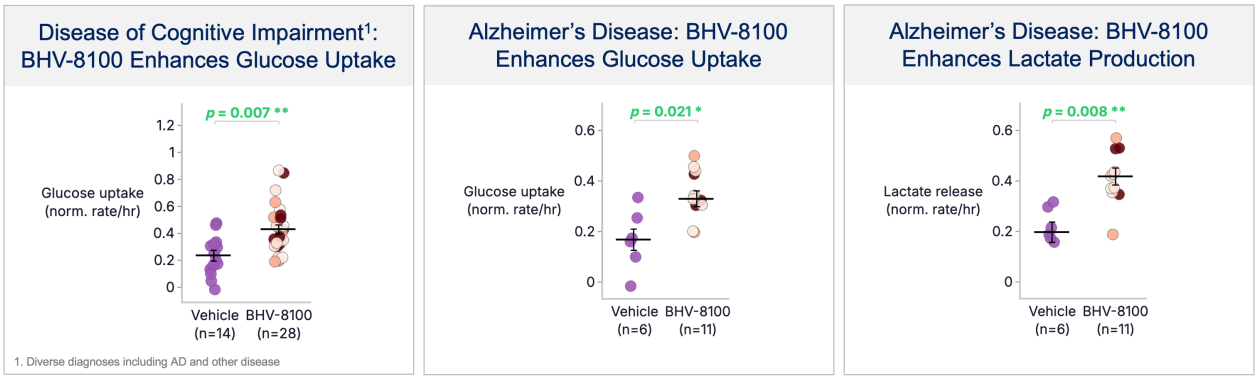
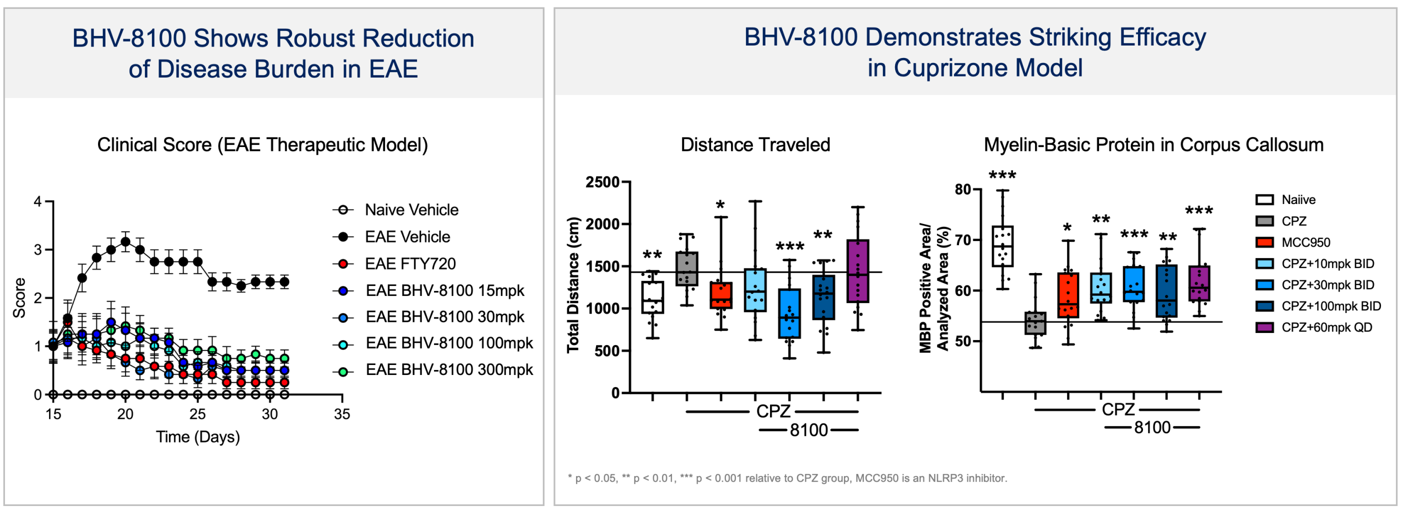


Figure 2: BHV-8100 demonstrates comparable effects to fingolimod, a highly effective T cell inhibitor in MS, in an EAE rodent model, and comparable-to-superior efficacy to NLRP3 inhibition, a promising new treatment for brain inflammation with documented effects on remyelination, in the cuprizone rodent model of demyelination.



First-in-Human Dosing Initiated in Ongoing Phase 1 Study

Biohaven initiated a Phase 1 FIH study of BHV-8100 in healthy participants to characterize the safety, tolerability and pharmacokinetics of BHV-8100. Preliminary pharmacokinetic (PK) and safety data from the ongoing study:

- Confirmed PK profile is consistent with oral, once-daily dosing
- Achieved projected therapeutic exposures
- Demonstrated well tolerated profile at projected therapeutic exposures, with most AEs being mild and spontaneously resolving

Bharat Awsare, M.D., Executive Medical Director, Clinical Development at Biohaven stated, "The initiation of first-in-human dosing for BHV-8100, a brain-penetrant PKM2 modulator, ushers in a potential new paradigm for a broad range of systemic as well as neurodegenerative, neuroinflammatory, retinal, and age-related diseases. Through our pioneering discovery engine, we are advancing an innovative drug candidate into the clinic that targets the fundamental metabolic impairments underpinning these diseases in ways that simply have not been possible before."

Brain Penetration Allows for Extending Beyond Systemic Disorders: Potential in Aging, Neurodegenerative Disorders and Eye Disorders

The prevalence and economic burden of neurodegenerative and neuroinflammatory diseases are enormous. Alzheimer's disease alone affects over 6.5 million Americans, with global prevalence exceeding 55 million. Annual costs of treating patients with Alzheimer's disease exceed $300 billion in the United States. Parkinson's disease affects approximately 1 million Americans, and multiple sclerosis affects nearly 1 million U.S. adults. Retinal disease represents a compelling aspect of the BHV-8100 opportunity including Age-Related Macular Degeneration, Diabetic Retinopathy, Inherited Retinal Dystrophies and others. The global retinal disease market is projected to exceed $15 billion annually by 2030, with oral, disease-modifying therapies representing the single most sought-after unmet need in the field. Biohaven believes BHV-8100 could address this gap across multiple retinal indications.

About Biohaven

Biohaven is a biopharmaceutical company focused on the discovery, development, and commercialization of life-changing treatments in key therapeutic areas, including immunology, neuroscience, and oncology. Biohaven is advancing its innovative portfolio of therapeutics, leveraging its proven drug development experience and multiple proprietary drug development platforms. Biohaven's extensive clinical and preclinical programs include Kv7 ion channel modulation for epilepsy; MoDE™ and TRAP™ extracellular protein degradation for immunological diseases; myostatin inhibition for neuromuscular and metabolic diseases, including obesity; and PKM2 activation for neurodegenerative and retinal diseases. For more information, visit www.biohavenpharma.com.

Forward-Looking Statements

This news release includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. The use of certain words, including "continue," "plan," "will," "believe," "may," "expect," "potential," "potentially," and similar expressions, is intended to identify forward-looking statements. Investors are cautioned that any forward-looking statements, including statements regarding the future development, timing, potential marketing approval and commercialization of development candidates, are not guarantees of future performance or results and involve substantial risks and uncertainties. Actual results, developments, and events may differ materially from those in the forward-looking statements as a result of various factors, including: the expected timing, commencement, and outcomes of Biohaven's planned and ongoing clinical trials; the timing of planned interactions and filings with the FDA; the timing and outcome of expected regulatory filings; complying with applicable U.S. regulatory requirements; the potential commercialization of Biohaven's product candidates; and the effectiveness and safety of Biohaven's product candidates. Additional important factors to be considered in connection with forward-looking statements are described in Biohaven's filings with the Securities and Exchange Commission, including within the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations." The forward-looking statements are made as of the date of this news release, and Biohaven does not undertake any obligation to update any forward-looking statements, whether as a result of new information, future events, or otherwise, except as required by law.

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