P4-002

Novel Bispecific Degrader BHV-1310 Eliminates Intravascular and Interstitial IgG in Multiple Organs and Anatomical Structures, Including the Neuromuscular Junction

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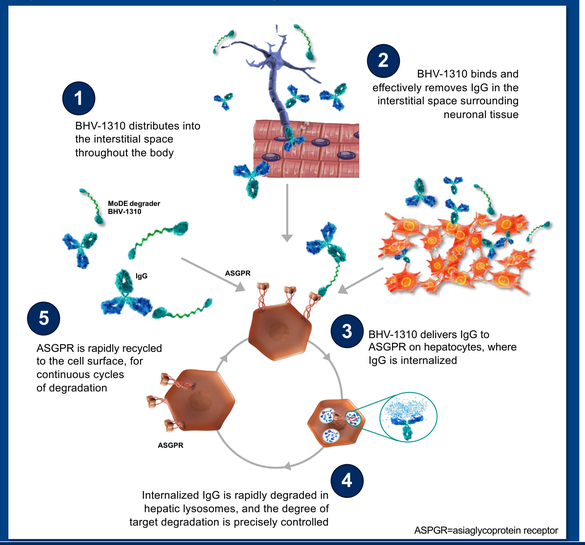
INTRODUCTION

- BHV-1310, a novel IgG degrader from the Molecular Degraders of Extracellular Proteins (MoDE™) drug platform, is being developed for the treatment of IgG-driven diseases
- BHV-1310 selectively targets and eliminates IgG in the circulation and in disease-relevant tissues
- As such, this new therapeutic modality offers a unique strategy to address antibody mediators of neurological disorders, such as myasthenia gravis, autoimmune encephalitis, chronic inflammatory demyelinating polyradiculoneuropathy, neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein antibody-associated disease & other antibody-mediated diseases

MoDE and BHV-1310

- The MoDE platform encompasses bifunctional molecules that bind to IgG and hepatic asialoglycoprotein receptors (ASGPRs), leading to internalization and endolysosomal degradation of IgG in the liver (**Figure 1**)
- Biohaven designed BHV-1310, a novel, selective, bifunctional extracellular protein degrader that specifically targets and reduces plasma IgG in a rapid, efficient, and selective manner
- Using a mouse model, we demonstrated that BHV-1310 mediates robust IgG clearance from the circulation and from the interstitial space surrounding peripheral and central nervous tissue
- These findings strongly support the use of BHV-1310 to treat neurological diseases driven by autoantibodies

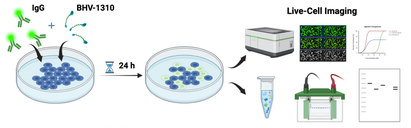
Figure 1. Extracellular MoDE™ degrader BHV-1310 mechanism of action



METHODS AND RESULTS

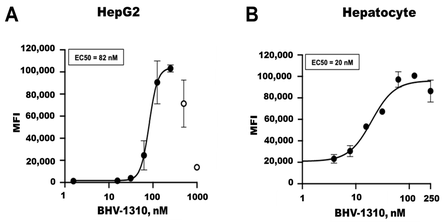
1. BHV-1310 Mediates In Vitro Internalization and Degradation of IgG

Figure 2. In vitro validation of BHV-1310 mechanism of action



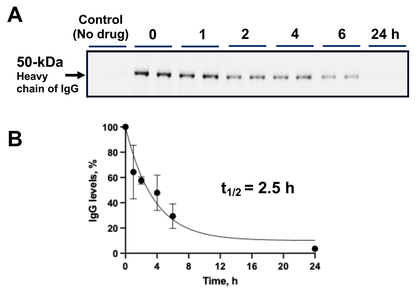
- ASGPR1-expressing cells were incubated with fluorescently labeled human IgG and BHV-1310 (**Figure 2**)
- Internalized IgG was measured by live-cell imaging (**Figure 3**)
- Cultures were also harvested for IgG degradation analysis by gel electrophoresis (**Figure 4**)

Figure 3. BHV-1310 promotes cellular uptake of IgG in HepG2 cells and primary human hepatocytes



HepG2 cells (A) or primary hepatocytes (B) were incubated for 24 hours with Alexa Fluor 488 (AF488)-labelled human IgG with a dose curve of BHV-1310. IgG uptake was monitored by live-cell imaging. EC50, half-maximal effective concentration; MFI, mean fluorescence intensity.

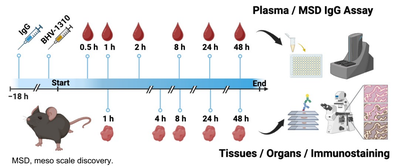
Figure 4. BHV-1310 mediates degradation of IgG in ASGPR-expressing HEK 293 cells



(A) Direct fluorescent signal from IgG-AF488 observed with denaturing gel electrophoresis. (B) Quantification of IgG-AF488 degradation with values normalized to time 0 h. Individual data points and error bars represent means and standard errors. The results show a BHV-1310 and time-dependent decrease in intercellular IgG-AF488 following endocytosis. A half-life of approximately 2.5 h was determined by fitting the data to a 1-phase decay model. $t_{1/2}$, half-life.

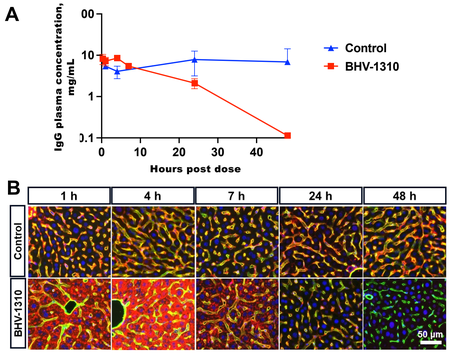
2. BHV-1310 Reduces Plasma IgG Level via Hepatic Absorption and Degradation in a Mouse Model

Figure 5. In vivo validation of BHV-1310 mechanism of action



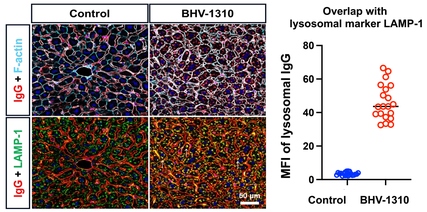
- Animals received human IgG followed by BHV-1310 treatment. Blood and tissues were collected at the indicated time points (**Figure 5**)
- IgG levels in plasma and tissues were measured using the MSD human IgG assay and immunostaining (**Figures 6-8**)

Figure 6. BHV-1310 redirects IgG to hepatocytes for degradation within hours of dosing in a mouse model



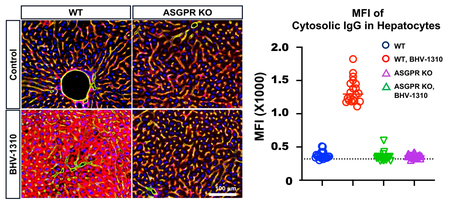
(A) Circulating plasma IgG levels in mice receiving BHV-1310 vs Control. (B) IgG uptake and reduction in the liver. 4H = BHV-1310 targets IgG from sinusoids to hepatocytes for degradation. Hepatic sinusoid (green); human IgG (red); nucleus (blue).

Figure 7. BHV-1310 induces hepatic endocytosis and lysosomal degradation of human IgG



F-actin, actin filaments; LAMP-1, lysosomal-associated membrane protein 1; co-localization of IgG and lysosomes (yellow). Cell membrane (cyan); human IgG (red); lysosome (green); nucleus (blue).

Figure 8. ASGPR is required for BHV-1310–mediated IgG endocytosis

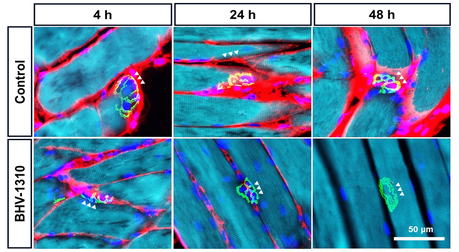


KO, knockout; WT, wild-type. Hepatic sinusoid (green); human IgG (red); nucleus (blue).

3. BHV-1310 Promotes IgG Reduction Across Various Tissues

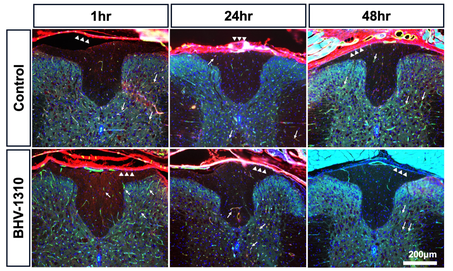
- IgG levels were measured, focusing on neuronal tissues, including areas within the neuromuscular junction, brain, spinal cord, and dorsal root ganglion (**Figures 9-12**)

Figure 9. IgG reduction in the neuromuscular junction with BHV-1310 treatment



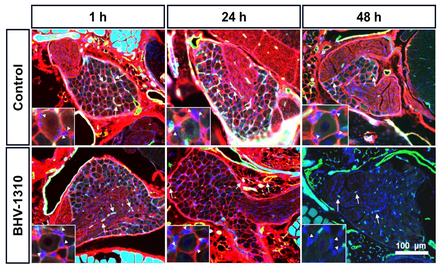
▲, NMJ, neuromuscular junction (green); Human IgG (red); muscle fiber (cyan); nucleus (blue).

Figure 10. IgG reduction in the dural meninges of the spinal cord with BHV-1310 treatment



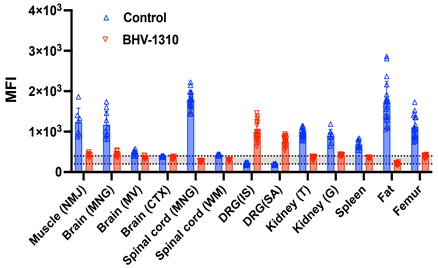
Numbers represent MFI in the selected areas. ▲, meninges; ↑, microvascular vessels. Blood vessel (green); human IgG (red); nucleus (blue); spinal cord grey matter (cyan).

Figure 11. IgG reduction in the dorsal root ganglion with BHV-1310 treatment



The inset images show IgG deposition at the periphery of dorsal root ganglion neurons. ↑, microvascular vessels; ▲, satellite cells. blood vessel (green); human IgG (red); muscle (cyan); nucleus (blue).

Figure 12. BHV-1310 mediates IgG reduction across various tissues



MFI = Mean Fluorescence Intensity quantifies IgG. Gray shaded area represents the range of background noise. NMJ, neuromuscular junction; MNG, meninges; MV, microvascular vessel; CTX, cortex; WM, white matter; DRG, dorsal root ganglion; IS, interstitial space; SA, satellite cell; T, tubule; G, glomerulus.

CONCLUSIONS

- BHV-1310 rapidly and effectively degrades IgG via the lysosomal pathway.
- Animal models demonstrate depletion from neurologic disease relevant tissues and anatomical structures.
- These findings underscore the therapeutic rationale for using BHV-1310 to treat neurological diseases mediated by autoantibodies.

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DISCLOSURES: SL, KM, AE, HY, WK, SDC, GD, DP, AB, VC, and BC are employed by and hold stock/stock options in Biohaven Pharmaceuticals. DS is a scientific advisor to Biohaven Pharmaceuticals.

Goebel A, Krock E, Gentry C, et al. J Clin Invest. 2021;131(13):e144201. doi:10.1172/JCI144201. Irani SR, Alexander S, Waters P, et al. Brain. 2010;133(9):2734-2748. doi:10.1093/brain/awq213. Liu Y, Wang W, Li J. Int J Neurosci. 2011;121(10):570-574. doi:10.3109/00207454.2011.596293. Phillips WD, Vincent A. F1000Res. 2016;5:F1000 Faculty Rev-1513. doi:10.12688/f1000research.8206.1. Pişkin ŞA, Korkmaz HY, Ulusoy CA, et al. Front Immunol. 2023;14:1268986. doi:10.3389/fimmu.2023.1268986. Querol L, Dalakas MC. Neurol Neuroimmunol Neuroinflamm. 2025;12(1):e200365. doi:10.1212/NXI.0000000000200365. van Sonderen A, Schreurs MW, Wirtz PW, Sillevis Smitt PA, Titulaer MJ. Autoimmun Rev. 2016;15(10):970-974. doi:10.1016/j.autrev.2016.07.018

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