CONCLUSIONS

1. BHV-1400 is a novel, antibody-based, bifunctional conjugate designed to selectively bind and deplete pathogenic circulating Gd-IgA1 and Gd-IgA1-IgG immune complexes via ASGPR-mediated hepatocyte internalization.

2. BHV-1400 has demonstrated compelling preclinical evidence for rapid and robust degradation of deglycosylated IgA and related protein aggregates in cellular and rodent experiments.

3. BHV-1400 recognizes pathogenic Gd-IgA1 in human IgAN and kidney disease patient plasma samples.

4. BHV-1400 holds therapeutic potential as a transformative, non-immunosuppressive, disease-modifying treatment for patients with IgAN.

OBJECTIVE

To show biospray target engagement data, protein of interest cellular internalization, data and rodent pharmacokinetic (PK) and pharmacodynamic (PD) data related to the degradation of exogenous deglycosylated IgA (dg-IgA) by the preclinical development candidate BHV-1400

METHODS AND RESULTS

1) BHV-1400 Demonstrates Ability to Simultaneously Engage ASGPR and Protein of Interest (POI):

- dg-IgA is a semi-synthetic Gd-IgA1 surrogate prepared from pooled human serum IgA in 3 enzymatic steps.

- BHV-1400 demonstrated strong affinity for dg-IgA (KD = 4 nM) and the carbohydrate recognition domain of ASGPR (KD=148-291) (KD = 9 nM).

- Evidence for the formation of a viable ternary complex with high-efficiency was provided by a proximity-based time-resolved fluorescence resonance energy transfer assay.

2) Detection of Gd-IgA1 Levels in Human Plasma Samples:

- Gd-IgA1 antibody concentrations in patient plasma samples were measured using Macso Scale Discovery with immobilized BHV-1400 and SULFO-TAG anti-IgA antibody.

- Gd-IgA1 median levels in samples from patients with kidney disease and IgAN were 4-6-fold higher than median levels in healthy volunteers.

- Results were consistent with the literature reports using XM55 diagnostic and confirm that BHV-1400 recognizes significant levels of circulating human Gd-IgA1 and corresponding immune complexes.

3) In Vitro Cellular Internalization of dg-IgA with BHV-1400:

- Dose-dependent, selective endocytosis of dg-IgA was observed with BHV-1400 in human embryonic kidney (HEK) cells transfected with human ASGPR1 (hASGPR).

- Low-nanomolar half-maximal effective concentration and robust mean fluorescence were observed at 12 hours for internalization of dg-IgA conjugated to Alexa Fluor 594.

- BHV-1400 internalized POI for tyrosine degradation and spared normal IgA.

4) dg-IgA Aggregates by Size Exclusion Chromatography:

- dg-IgA conjugated to Alexa Fluor 594 was separated into 3 fractions corresponding to tetrameric, dimeric, and monomeric forms.

- All 3 forms of dg-IgA were advanced into the cellular internalization assay.

5) Cellular Internalization of Surrogates Gd-IgA1 Antibody Complexes:

- BHV-1400 demonstrated efficient internalization of dimeric and tetrameric dg-IgA complexes in HEK (hASGPR) cells at 12 hours.

- BHV-1400 can internalize and degrade large IgA antibody complexes.

6) BHV-1400 Achieves Robust Degradation of Exogenous dg-IgA in Mice:

- BHV-1400 demonstrated ASGPR-dependent clearance in wild-type (wt) mice vs ASGPR1 knockout (ko) mice after intravenous (iv) administration. Results were consistent with BHV-1400 mechanism of action.

- BHV-1400 depleted exogenous dg-IgA in wt mice to 58% area under the curve of control at 21 h (drug target) ratio after sequential iv administration.

- Parent control antibody, BHV5305, had no effect on degradation of exogenous IgA in wt mice, as anticipated.

- BHV-1400 rapidly and robustly degraded dg-IgA1 administered to mice.

Molecular Degradators of Extracellular Proteins (MoDe) 

- The MoDe platform discovers and develops bifunctional molecules that degrade extracellular protein targets, such as Gd-IgA1, via the asialoglycoprotein receptor (ASGPR)-mediated endosomal/lysosomal pathway.

- Biohaven engineered a novel anti-human Gd-IgA1 chimera antibody (BH5305) with human constant regions, using a human Ig2 Fc with reduced effector function.

- The ASGPR-binding bifunctional conjugate BHV-1400 was assembled from BH5305 in 1 step, using proprietary Fc-cleavable MATE(TM) technology.

- Linker and ASGPR binder were attached via a stable amine connection.

- BHV-1400 was isolated with good yield and excellent homogeneity (linker-to-antibody ratio = 2)

- Site-specific conjugation of dual lys248 residues was confirmed by peptide mapping.

Figure 1. Pathogenesis of IgAN

Hit 1. Increased levels of circulatory Gd-IgA1

Hit 2. Production of IgG autoantibodies to Gd-IgA1

Hit 3. Formation of Gd-IgA1-IgG immune complexes

Hit 4. Immune complex deposition in mesangium, causing renal injury

Hit 5. Cellular interaction of Surrogate Gd-IgA1 Antibody Complexes

- BHV-1400 demonstrated efficient internalization of dimeric and tetrameric IgA-1 complexes in HEK (hASGPR) cells at 12 hours.

- BHV-1400 can internalize and degrade large IgA antibody complexes.