

A Novel Mechanism for the Treatment of Autoimmune Neurologic Diseases: Robust, Rapid, and Tunable Removal of IgG With the MoDE™ Degradar BHV-1300

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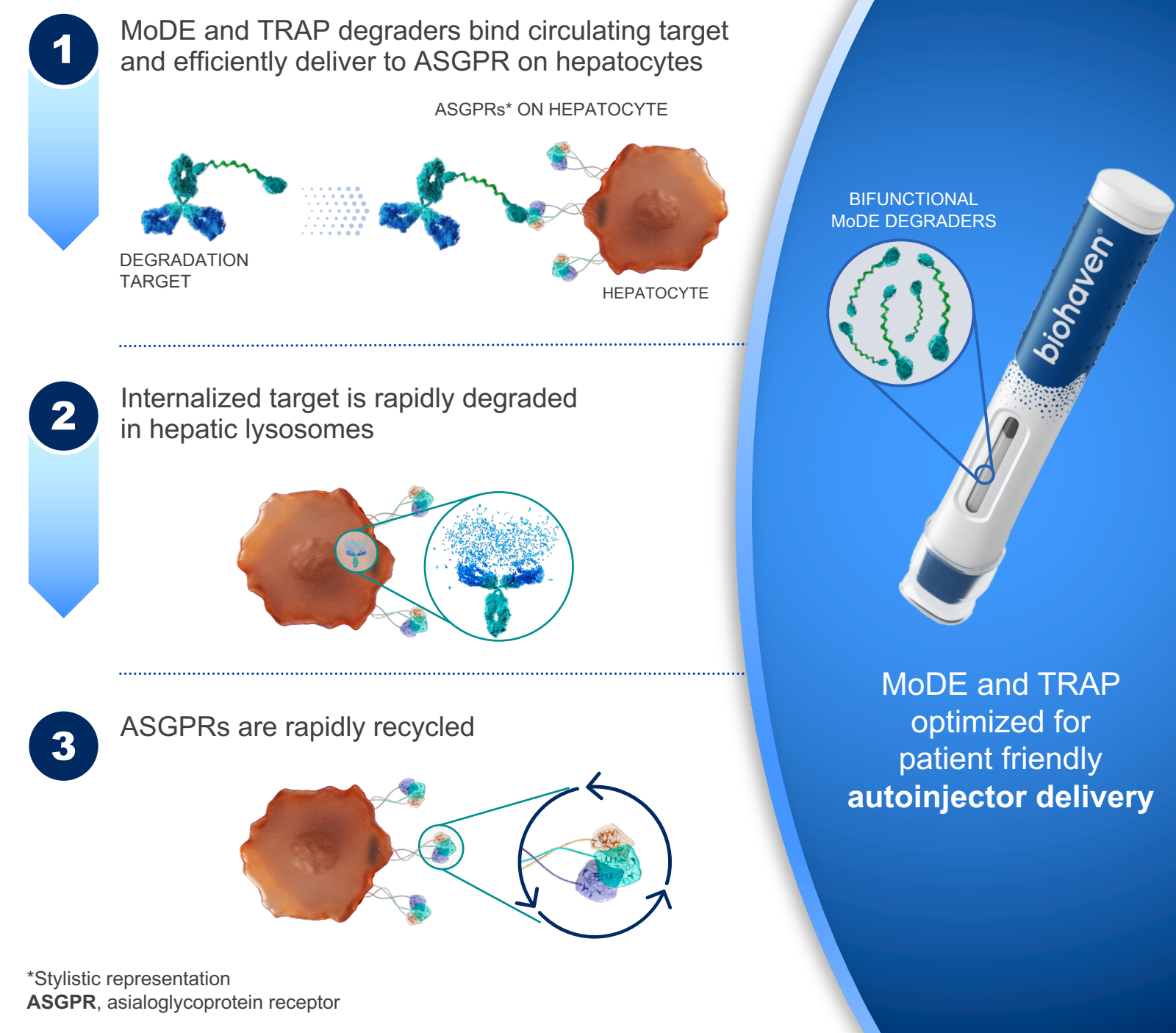
INTRODUCTION

- MoDE™ and TRAP™ degraders represent novel mechanisms for rapid and selective depletion of pathogenic extracellular proteins, such as IgG autoantibodies. Leveraging the liver's highly effective natural process for removal of senescent proteins, they direct proteins of interest to the hepatocyte lysosomes via the asialoglycoprotein receptor (ASGPR) for degradation.
- The degrader platform has the potential to treat various antibody-mediated neurological disorders, including myasthenia gravis, autoimmune encephalopathy and chronic inflammatory demyelinating polyneuropathy.
- BHV-1300 is a novel small-molecule bifunctional MoDE degrader rationally designed to remove IgG₁, IgG₂ and IgG₄ while preserving humoral immunity by sparing other immunoglobulin subclasses and isotypes, including IgG₃, IgM, IgA and IgE (see **Figure 1** for a visual overview of BHV-1300's mechanism of action).

METHODS

- Single-ascending-dose (SAD) cohorts were administered BHV-1300 in doses of up to 2000 mg. Each SAD cohort included approximately 6 subjects treated with BHV-1300 and 2 with placebo.
- Four multiple-ascending-dose (MAD) cohorts were administered BHV-1300 up to 2000 mg for up to 4 weeks. Each MAD cohort included approximately 8 subjects treated with BHV-1300 and 2 with placebo.

Figure 1. Mechanism of Action of BHV-1300



RESULTS

Study Population

In the Phase 1 clinical development program, 93 healthy, adult, male or non-childbearing female participants received a dose of BHV-1300 (n=72) or placebo (n=21) (**Table 1**).

Table 1. Participant Demographics

Demographic Characteristic	BHV-1300 (n=72)	Placebo (n=21)
Age, y, mean (SD)	34.1 (8.28)	32.5 (8.61)
Sex, n (%)		
Female	3 (4.2)	3 (14.3)
Male	69 (95.8)	18 (85.7)
Race, n (%)		
American Indian	4 (5.6)	1 (4.8)
Asian	11 (15.3)	4 (19.0)
Black	4 (5.6)	3 (14.3)
Hawaiian	1 (1.4)	0 (0)
White	51 (70.8)	12 (57.1)
Multiple	1 (1.4)	0 (0)
Other	0 (0)	1 (4.8)
Weight, kg, mean (SD)	78.5 (8.9)	79.2 (10.1)
BMI, kg/m ² , mean (SD)	26.0 (2.5)	26.0 (2.7)

BMI, body mass index.

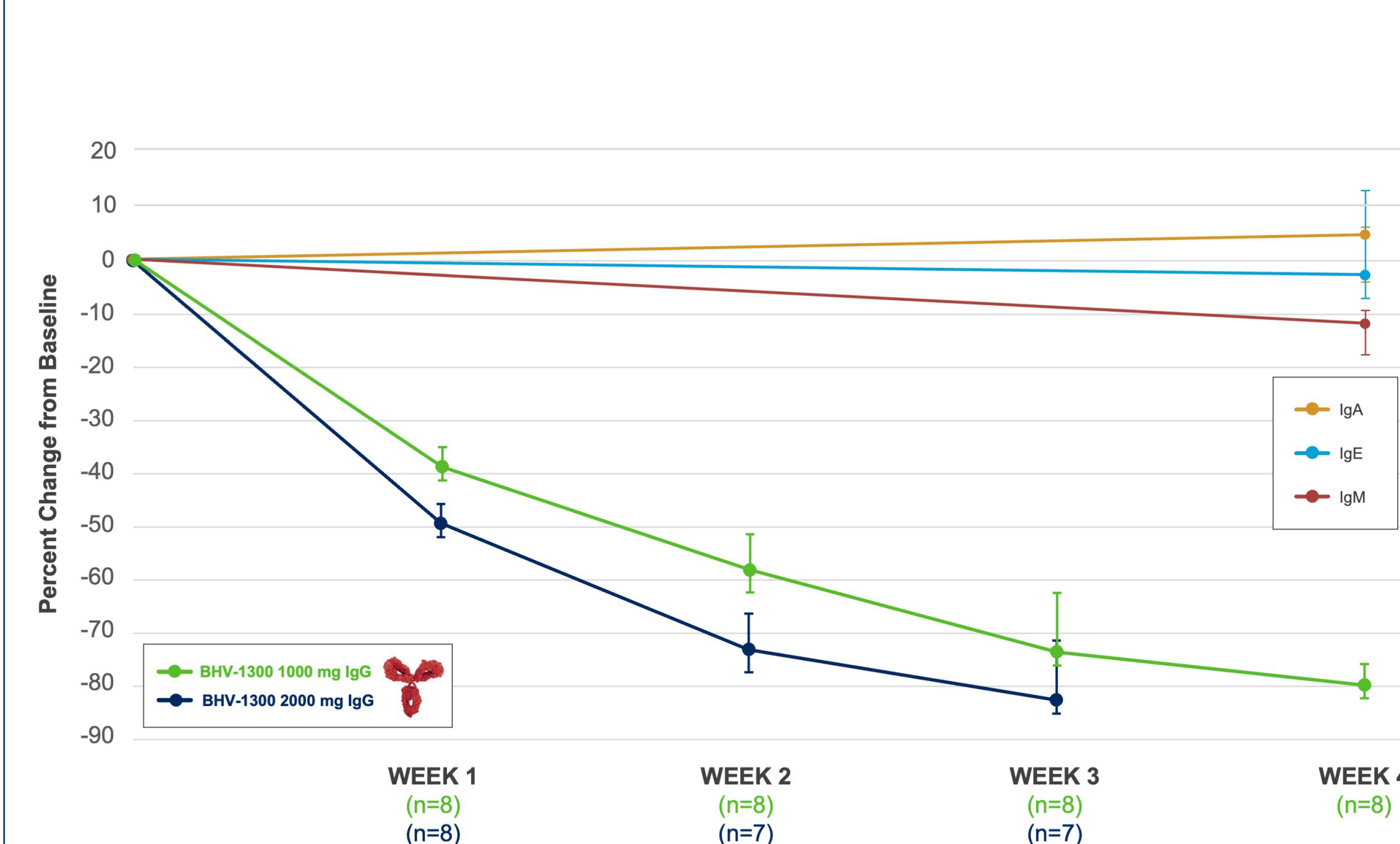
Pharmacodynamics

- Twenty-four subjects received BHV-1300 as single IV doses (50–500 mg), 19 subjects received BHV-1300 as single subcutaneous (SC) doses (500–2000 mg) and 29 subjects received multiple SC doses of BHV-1300.
- Weekly administration of 1000 mg SC resulted in a decrease in total IgG with a median maximal reduction of 80% from baseline (**Figure 2**).
- Weekly administration of 2000 mg SC also resulted in a decrease in total IgG with a median maximal reduction of 83% from baseline within 18 days of dosing (**Figure 2**).
- Total reduction in IgG was due to specific lowering of IgG₁, IgG₂ and IgG₄ while preserving the benefits of IgG₃ as well as IgM, IgA and IgE.

CONCLUSIONS

- BHV-1300 is a novel small-molecule that rapidly and precisely degrades IgG₁, IgG₂ and IgG₄ while preserving the beneficial effects of IgG₃, IgM, IgA and IgE, a property that has implications in the long-term treatment of chronic neurologic diseases.
- Robust, rapid and selective lowering of IgG was observed with BHV-1300, highlighting the potential benefit as a treatment in acute and chronic antibody-mediated neurologic diseases.
- BHV-1300 Phase 1 data demonstrate that SC administration of BHV-1300 achieves median maximal reductions of 83% in total IgG within 18 days of dosing.
- The unique mechanism of action of BHV-1300 causes a sustained PD effect with rapid elimination between doses resulting in an advantageous PK/PD profile that potentially offers deeper, rapid and more targeted lowering of disease-causing proteins with less opportunity for off-target effects.
- BHV-1300 was safe and well tolerated, with no clinically meaningful increases in AST, ALT, or bilirubin, reductions in albumin, or increases in cholesterol.
- With rapid and robust removal of IgG and a well-tolerated profile, BHV-1300 offers a novel therapeutic approach to the treatment of broad-ranging IgG-mediated neurologic disease.

Figure 2. BHV-1300 Lowers Total IgG Without Effect on IgA, IgE or IgM

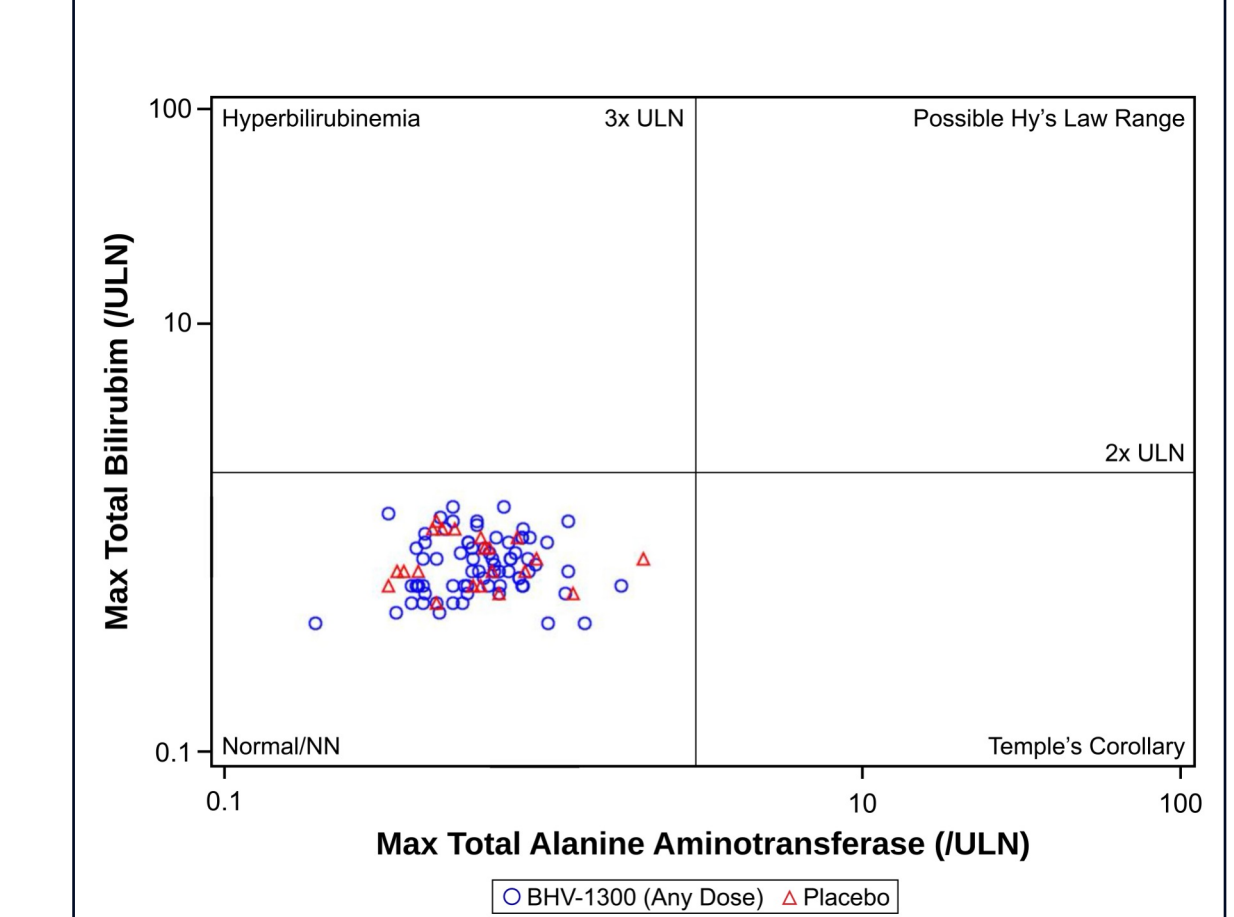


The figure presents preliminary data. Baseline IgG values are the average of the values on Day -1 and Day 1 pre-dose. Solid dots represent the median of the maximal % change from baseline in the week and bars represent the 25th and 75th percentiles. The IgA, IgE and IgM were measured at baseline and Study Day 25 only. Target IgG lowering was achieved after 4 weekly doses in the 1000 mg cohort and with 3 weekly doses in the 2000 mg cohort. Week 4 immunoglobulin data are presented for the 1000 mg cohort.

Safety

- BHV-1300 is rapidly eliminated and does not accumulate after weekly dosing, with more than 90% of the molecule being cleared within the first 4 days.
- BHV-1300 was well tolerated, with most adverse events (AEs) being mild (grade 1).
- No serious AEs, severe AEs or deaths were reported.
- There were no clinically meaningful increases in AST, ALT or bilirubin (**Figure 3**, eDISH plot).
- There were no clinically meaningful reductions in albumin and no clinically meaningful increases in cholesterol over the dosing period.
- There was no evidence of renal, hepatic or cardiac toxicity.

Figure 3. eDISH Plot of Maximum Total Bilirubin Versus Maximum Alanine Aminotransferase*



*Preliminary data

