POSTER
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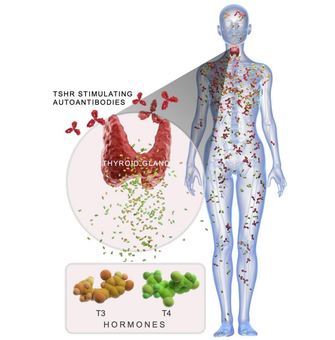
Targeting the Autoimmune Etiology of Graves' Disease: BHV-1300, a Small Molecule Degrader, Demonstrates Deep and Rapid Reductions of IgG in Humans

Bharat Awsare[1], Tova Gardin[1,2], Richard Bertz[1], Randall Killingsworth[1], Eric Ashbrenner[1], Camille Schrier[1], Bruce Car[1], David Spiegel[2] | [1]Biohaven Pharmaceuticals, Inc., New Haven, CT, USA; [2]Yale University, New Haven, CT, USA

1. INTRODUCTION

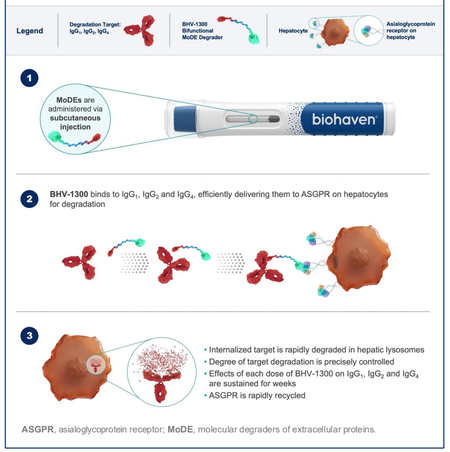
- Graves' disease is an autoimmune disease affecting 1–2% of the global population and is caused by the production of IgG1 autoantibodies that activate the thyroid-stimulating hormone receptor (TSHR), resulting in overproduction of thyroid hormones and hyperproliferation of thyrocytes.
- These autoantibodies also contribute to other associated conditions, including thyroid eye disease, Graves' embryopathy, and Graves' dermopathy (**Figure 1**).[1,2]
- Conventional treatments such as antithyroid drugs, radiation and surgery do not address the underlying autoimmune etiology of Graves' disease and can be limited by adverse effects (e.g., permanent hypothyroidism, agranulocytosis, hepatotoxicity, and teratogenesis). There has been a growing interest in developing agents that specifically modulate the autoimmune process underlying Graves' disease.[4,5]

Figure 1. TSHR antibodies cause Graves' disease and associated conditions: thyroid eye disease, Graves' embryopathy and Graves' dermopathy



- Biohaven's Molecular Degraders of Extracellular Protein (MoDE) platform offers a novel mechanism for the rapid and selective depletion of pathogenic proteins, such as IgG autoantibodies, by targeting these proteins for degradation in hepatic lysosomes via the asialoglycoprotein receptor (ASGPR).[6]
- BHV-1300 is a novel small molecule bifunctional MoDE degrader rationally designed to remove IgG_1, IgG_2 and IgG_4 while preserving humoral immunity by sparing other immunoglobulin subclasses and isotypes, including IgG_3, IgM, IgA and IgE[7] (see **Figure 2** for a visual overview of BHV-1300's mechanism of action).

Figure 2. Mechanism of action of BHV-1300



ASGPR, asialoglycoprotein receptor; **MoDE**, molecular degraders of extracellular proteins.

2. 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.
- Multiple-ascending-dose (MAD) cohorts were administered BHV-1300 up to 2000 mg (4 cohorts) for up to 4 weeks. Each MAD cohort included approximately 8 subjects treated with BHV-1300 and 2 with placebo.

3. 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

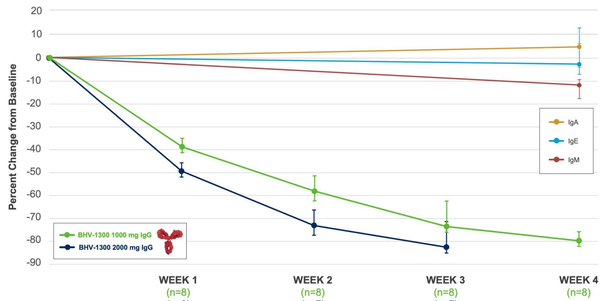
Demographic Characteristic	BHV-1300 (n = 72)	Placebo (n = 21)
Age, y, mean (SD)	34.1 (8.28)	32.5 (8.61)
Sex, n (%)		
Female	3 (4.2)	3 (14.3)
Male	69 (95.8)	18 (85.7)
Race, n (%)		
American Indian	4 (5.6)	1 (4.8)
Asian	11 (15.3)	4 (19.0)
Black	4 (5.6)	3 (14.3)
Hawaiian	1 (1.4)	0 (0)
White	51 (70.8)	12 (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/m², mean (SD)	26.0 (2.5)	26.0 (2.7)

BMI, body mass index

Pharmacodynamics

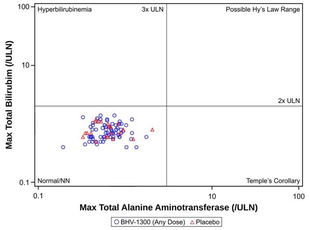
- Twenty-four subjects received BHV-1300 as single IV doses (50–500 mg), 18 subjects received BHV-1300 as single subcutaneous (SC) doses (500–2000 mg) and 30 subjects received multiple SC doses of BHV-1300.
- Weekly administration of 1000 mg SC resulted in a decrease in total IgG with a median maximal reduction of 80% from baseline (**Figure 3**).
- 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 3**).
- Total reduction in IgG was due to specific lowering of IgG_1, IgG_2 and IgG_4 while preserving the benefits of IgG_3 as well as IgM, IgA and IgE.

Figure 3. 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 doses in the 1000 mg cohort and with 3 doses in the 2000 mg cohort. Week 4 immunoglobulin data are presented for the 1000 mg cohort.

Figure 4. eDISH plot of maximum total bilirubin versus maximum alanine aminotransferase*.



*Preliminary data

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 4**, 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.

4. CONCLUSIONS

- BHV-1300 is a novel small molecule that rapidly and precisely degrades IgG_1, IgG_2 and IgG_4 to target the autoimmune driver of Graves' disease (TSHR autoantibodies) while preserving the beneficial effects of IgG_3, IgM, IgA and IgE.
- 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.
- Phase 1 data support the advancement of BHV-1300 into patients with Graves' disease.

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DISCLOSURES: BA, TG, RB, RK, EA, CS, BC and DS are employed by and hold stock/stock options in Biohaven Pharmaceuticals. DS is a scientific advisor to Biohaven Pharmaceuticals and holds stock in Biohaven Pharmaceuticals.

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