Novel Bispecific Degrader BHV-1300 Achieves Rapid, Robust, Selective, and Transient IgG Reduction in Preclinical Models Including Nonhuman Primates

Anna Bunin[1], Seong Lee[1], Wes Kazmierski[1], Kathleen McGrath[1], Ann Marie Rossi[1], Simone Nicholson[1], Gene Dubowchik[1], Elizabeth Dierks[1], Neal Sharpe[1], David Pirman[1], Bruce Car[1], Irfan Qureshi[1], Vlad Coric[1], David Spiegel[2]

[1] *Biohaven Pharmaceuticals, Inc., New Haven, CT, USA*

[2] *Yale University, New Haven, CT, USA*

Anna Bunin, PhD is an employee of and holds stock/stock options in Biohaven Pharmaceuticals

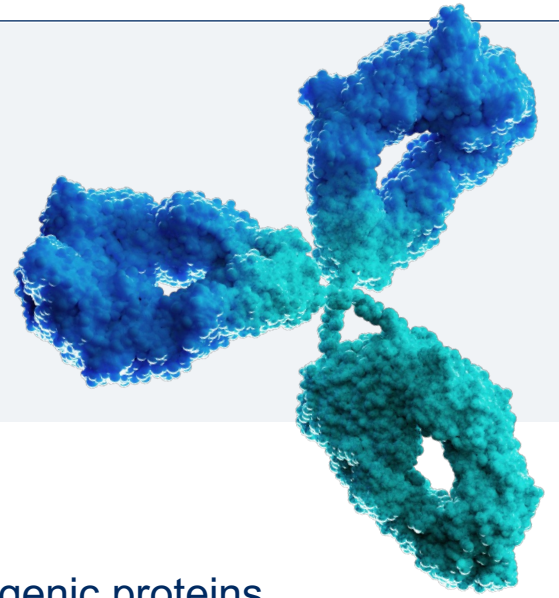
Targeted Extracellular Protein Degradation is a Next-Generation Approach for Treating Antibody Mediated Diseases

ANTIBODY MEDIATED NEUROLOGICAL DISEASES SUCH AS MYASTHENIA GRAVIS

Pathogenic autoantibodies (IgG) target specific components of the nervous system leading to disease onset and progression

EXTRACELLULAR PROTEIN DEGRADATION CAN LOWER PATHOGENIC ANTIBODIES

Potentially offers significant advantages over existing therapeutic approaches



MOLECULAR DEGRADER OF EXTRACELLULAR PROTEIN (MoDE™)

- Powerful new approach to treat antibody mediated diseases
- Harnesses the body's protein recycling machinery to degrade pathogenic proteins
- Several potential benefits compared to other IgG lowering therapies (FcRn inhibitors)

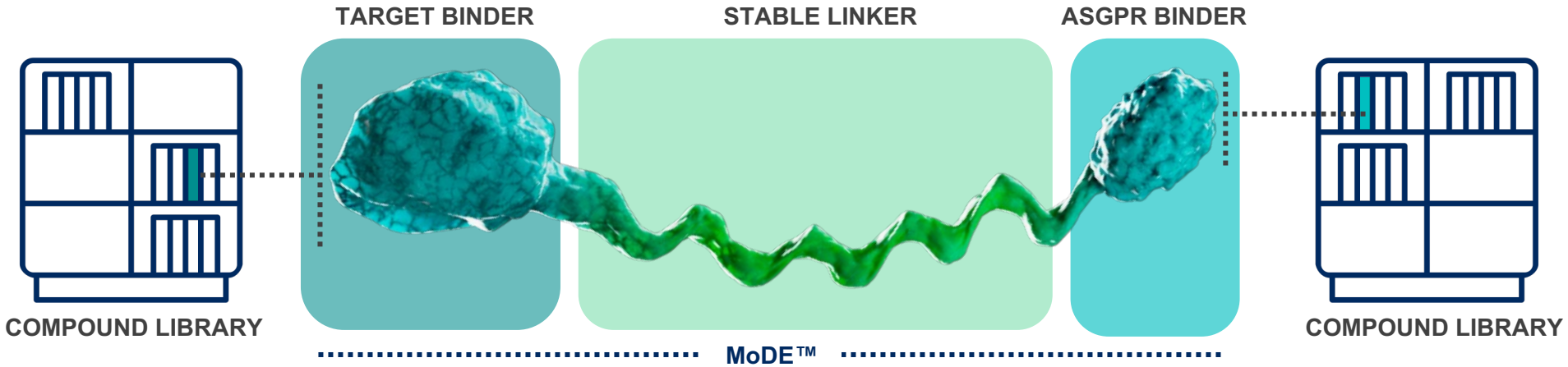
FIRST-IN-CLASS IgG LOWERING AGENT BHV-1300

- **Rapid onset of IgG lowering**
- **Depth of IgG lowering**
- **Lower risk of infection**
- **SC self-administration**
- **Co-administration with Fc-containing biologics**

SC, subcutaneous; **FcRn,** neonatal Fc receptor; **IgG**, immunoglobulin.

MoDE™ is a Novel Platform that Allows Lowering of Pathogenic Immunoglobulins and Antigen Specific Autoantibodies with Potential to Treat a Diverse Range of Diseases

A Transformational Drug Platform: Molecular Degraders of Extracellular Proteins (MoDE™)



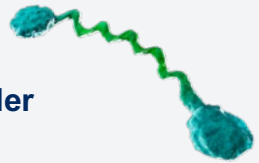
Opportunity to reduce protein of choice by varying target binders

MoDE™ Degraders Direct Pathogenic Extracellular Proteins to the Liver for Targeted, Effective Removal

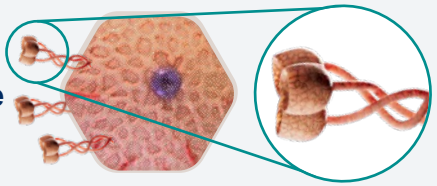
Legend

Degradation Target

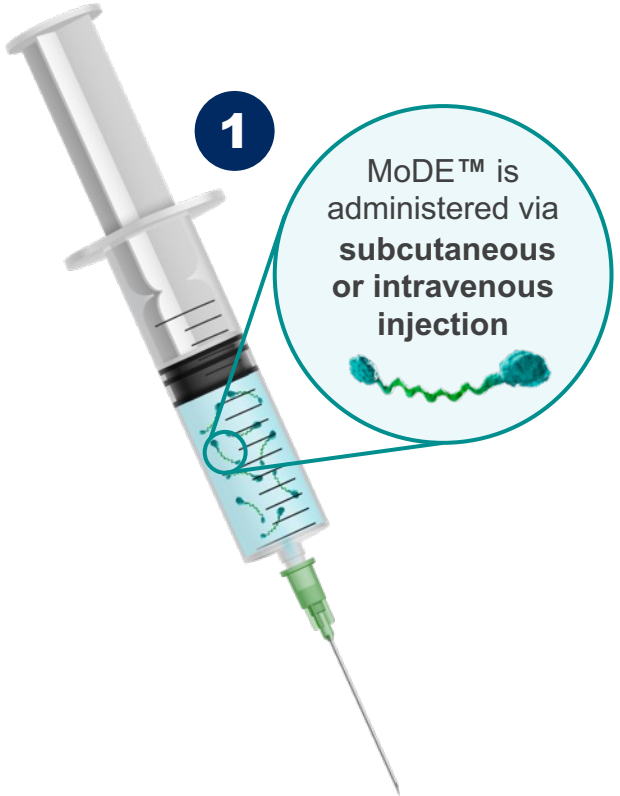
MoDE™ Degrader



Hepatocyte

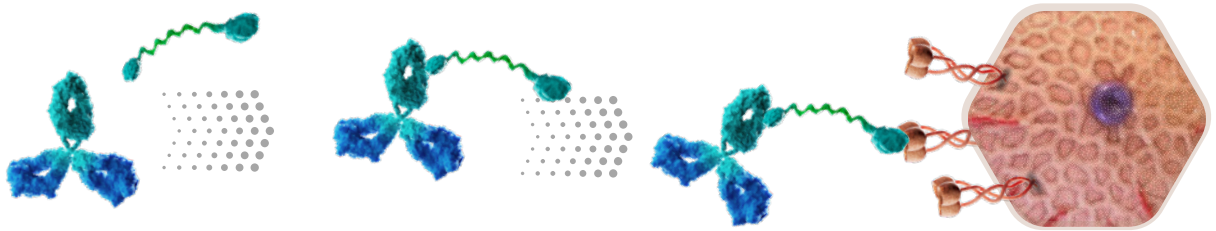


Asialoglycoprotein Receptor*

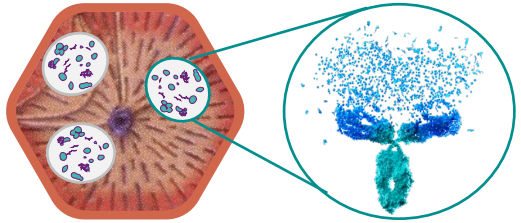


1 MoDE™ is administered via **subcutaneous or intravenous injection**

2 MoDE™ degrader binds to circulating target and efficiently delivers it to ASGPRs on hepatocytes

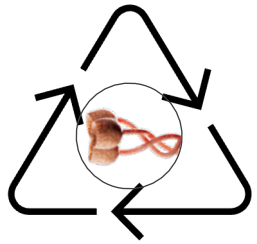


3



- Internalized target is rapidly degraded in hepatic lysosomes
- Degree of target degradation is precisely controlled

4

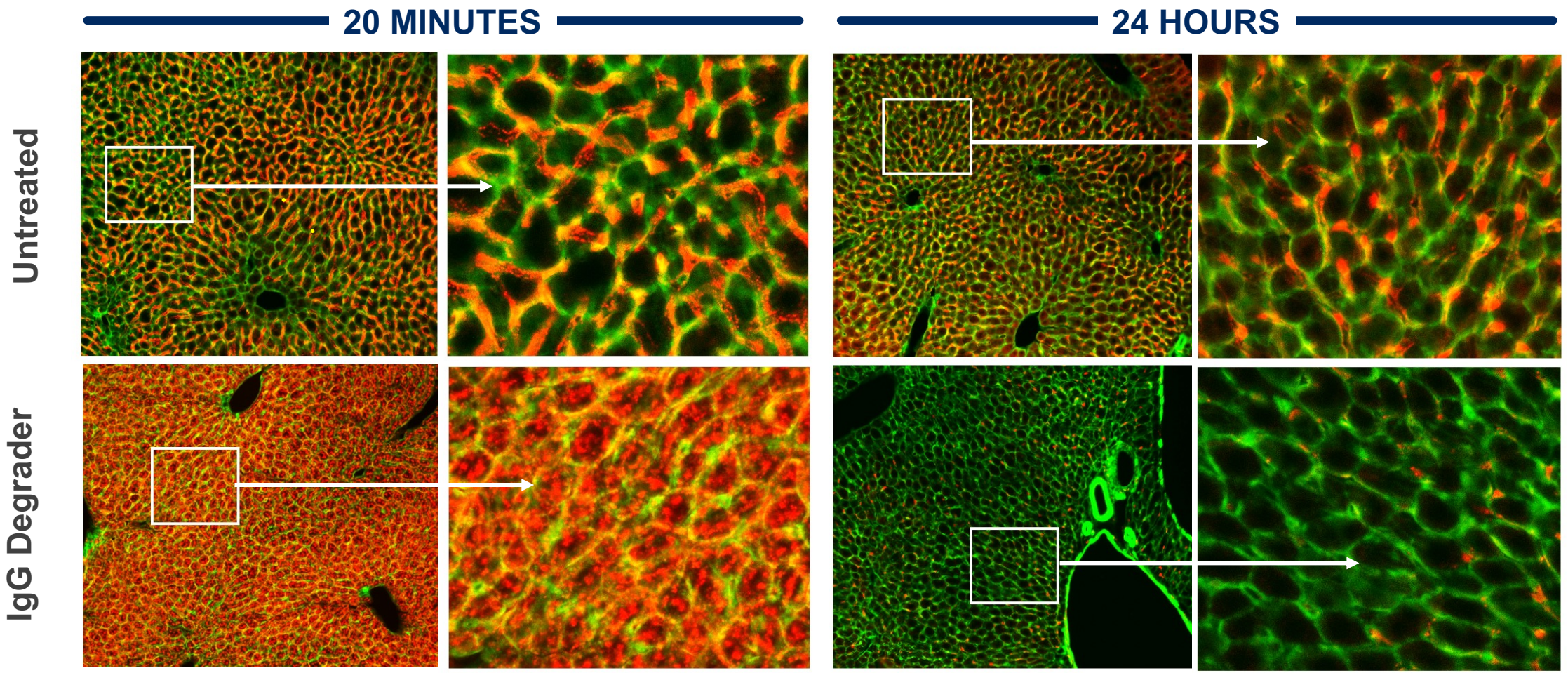


- ASGPRs are rapidly recycled
- Optimized safety and efficacy is achieved through balancing of relative affinities for ASGPR and target protein

*Stylistic representation

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

MoDE™ IgG Degrader Causes Rapid and Efficient IgG Lowering via Uptake into Hepatocytes

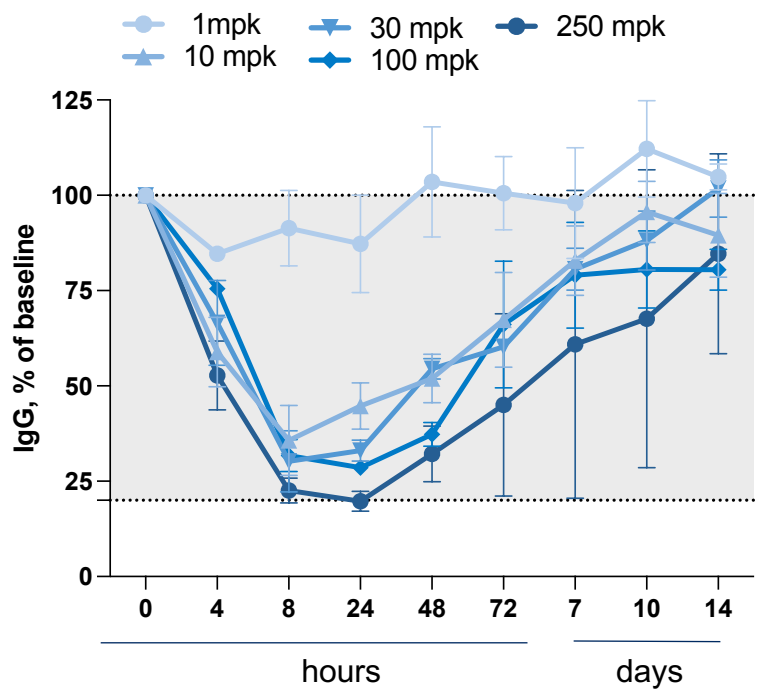


in nude mice

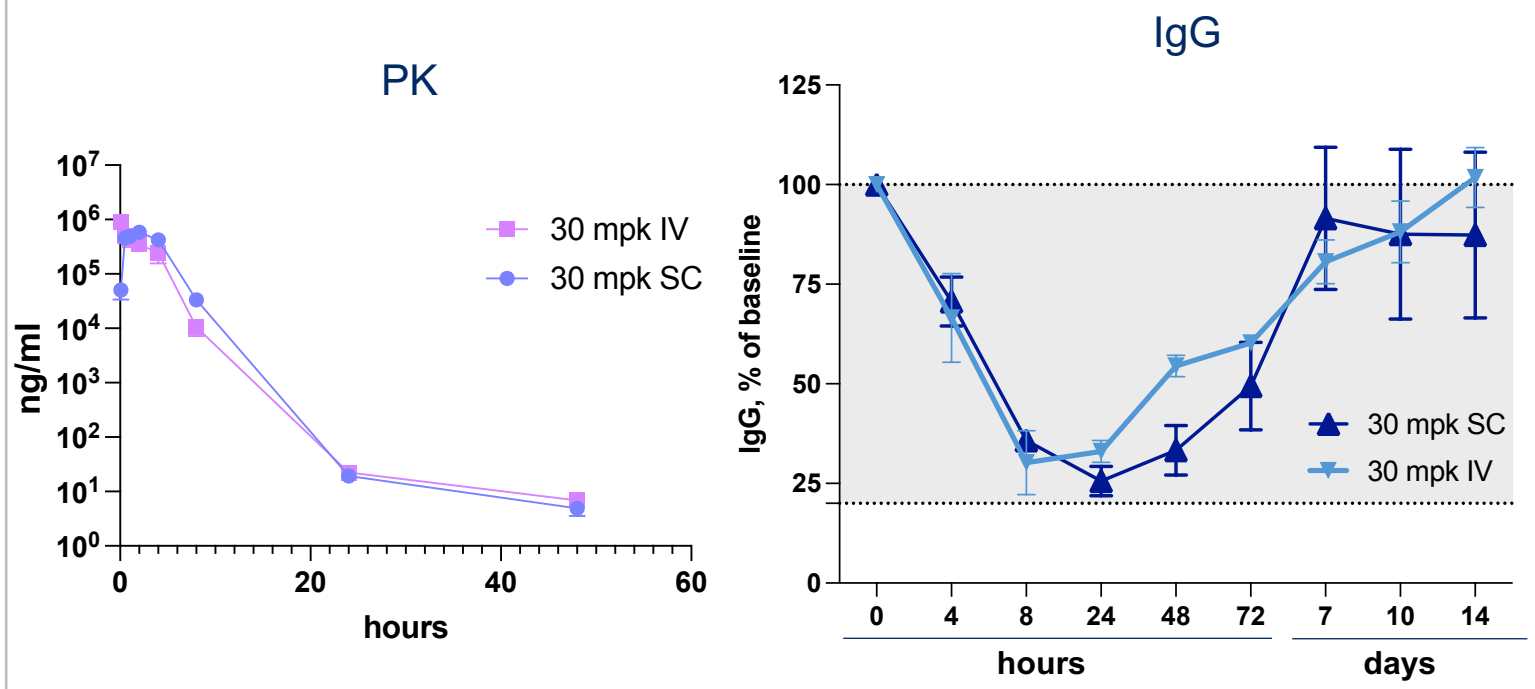
Red: Intravenous immunoglobulin (IVIg)
Green: Membrane Marker

A Single Dose of BHV-1300 Demonstrates Rapid and Deep IgG Lowering that is Equivalent via IV and SC Routes, Allowing for Convenient SC Administration

Single Dose IgG Lowering



Single Dose Plasma PK & IgG Lowering Following IV and SC Administration



in rabbits

KEY POINTS

- **Dose-dependent, rapid and deep IgG lowering with maximal response observed within 8 hours**
- **Similar PK and IgG lowering following IV and SC administration (100% bioavailable)**
- **Supports convenient SC self-administration**

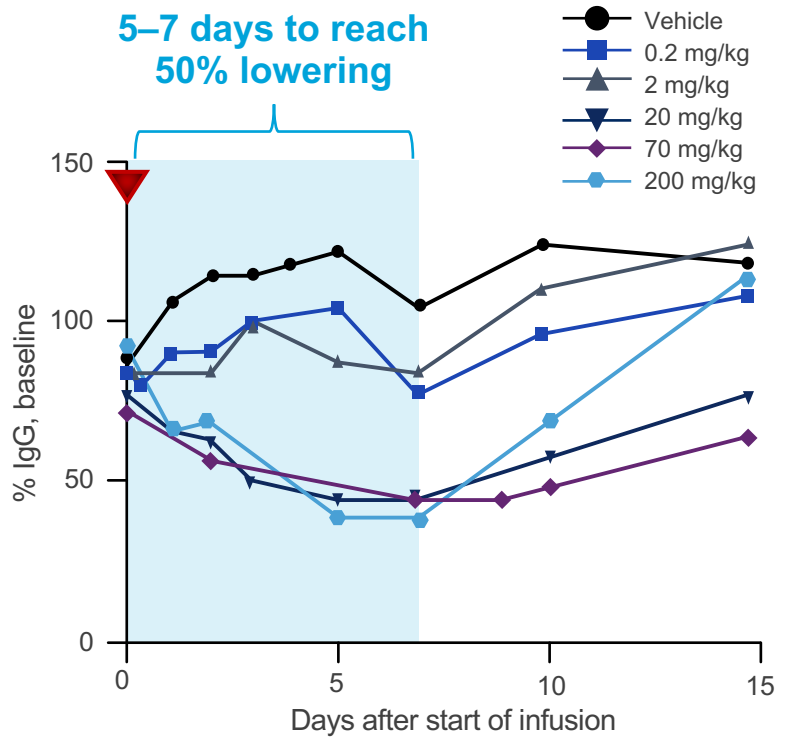
IgG, immunoglobulin. **PK**, pharmacokinetics; **IgG**, immunoglobulin **IV,** intravenous; **SC,** subcutaneous.

BHV-1300 Demonstrates Potential for Superior Clinical Efficacy Compared to FcRn Inhibitors

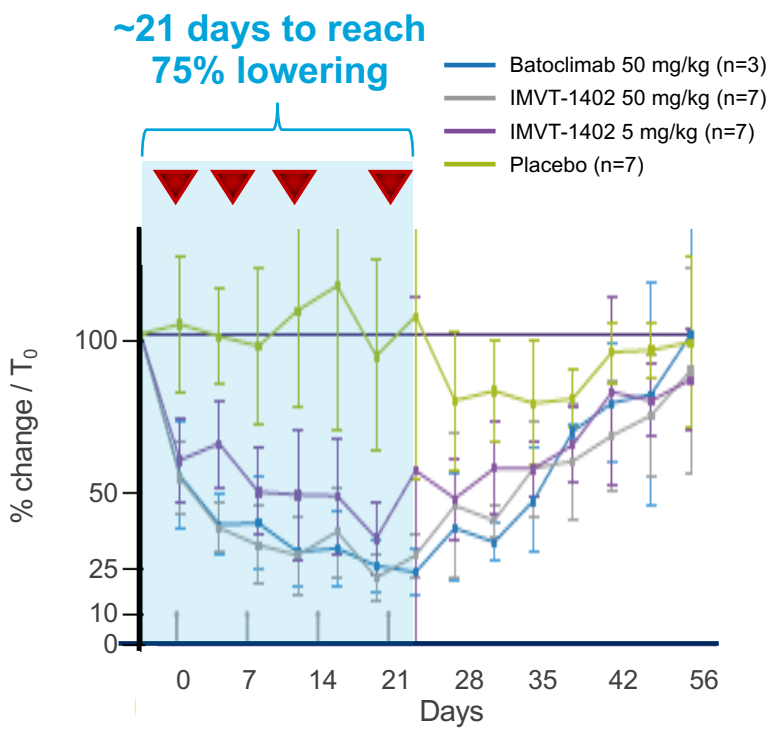
KEY | DATA

BHV-1300 achieves more rapid and deeper IgG lowering than FcRn inhibitors

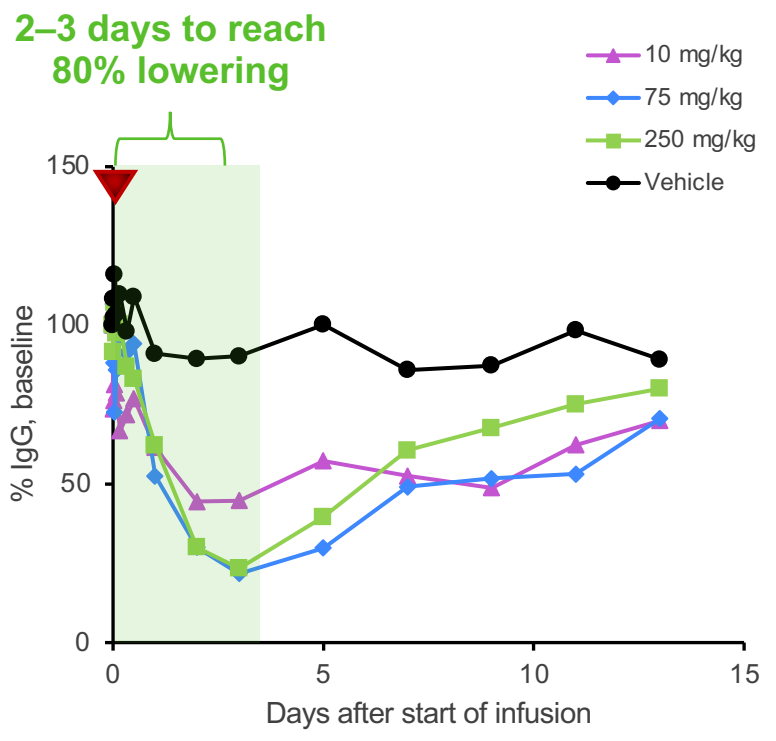
Efgartigimod NHP Pharmacodynamics



Immunovant NHP Pharmacodynamics



BHV-1300 NHP Pharmacodynamics



Dose Administered

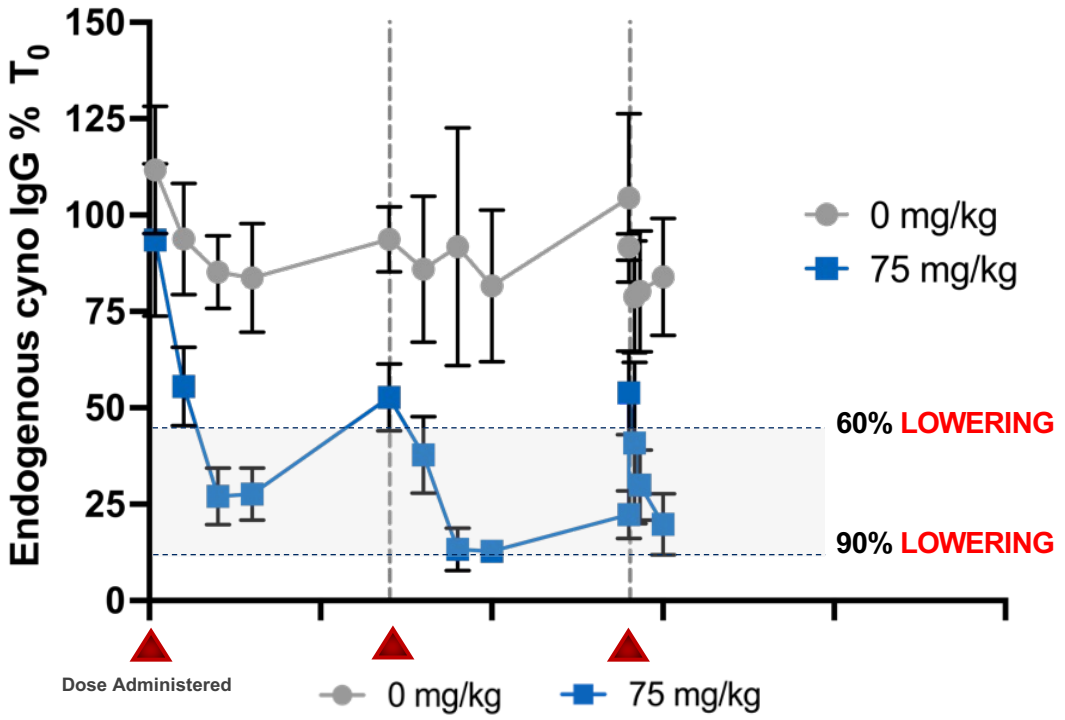
Ulrichts P et al, J Clin Invest. 2018 Oct 1;128(10):4372-4386. doi: 10.1172/JCI97911. Epub 2018 Jul 24. PMID: 30040076; PMCID: PMC6159959.

Excerpted from Immunovant Corporate Presentation, August 2023.

NHP, non-human primate.

Unique Pharmacology of BHV-1300 Allows for Optimization of IgG Lowering Specifically Tailored to Treat Both Acute and Chronic Disease Indications

IgG Lowering in NHP after Multiple Dose Administration of BHV-1300



NHP, non-human primate.

KEY POINTS

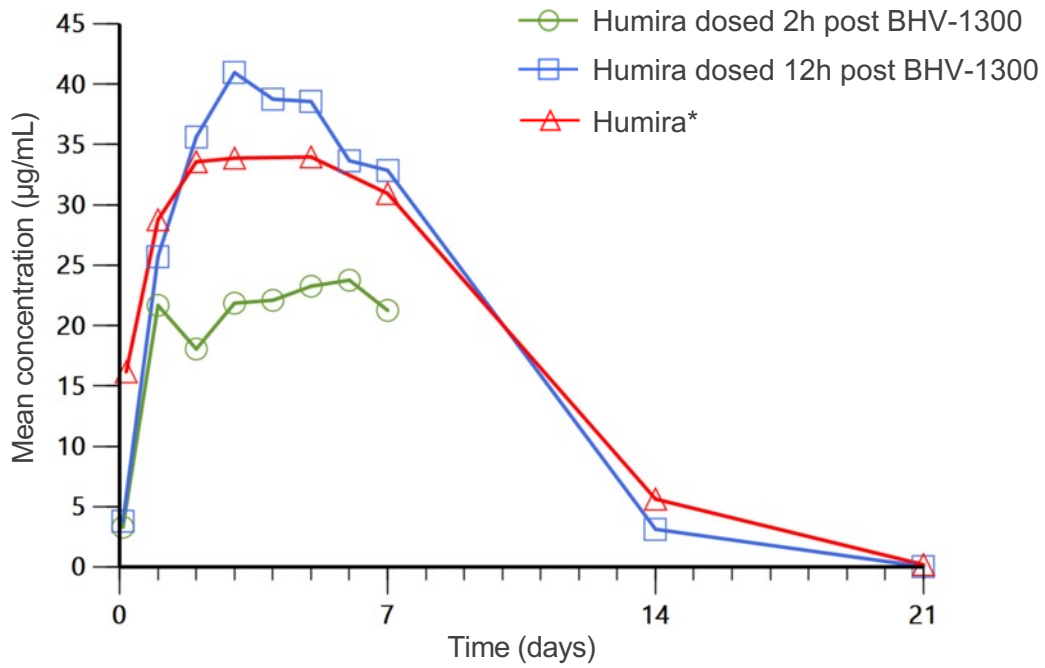
- **Depth of lowering reaches 90% after second dose**
- **Depth of lowering is tunable; easily adjusted by frequency of administration**
- **Adaptable to suit ideal target IgG lowering for different indications**

BHV-1300 can be Co-administered with Fc-containing Biologics Offering Potential for Combination Therapy, in Contrast to FcRn Inhibitors

Frequently Administered Fc-containing Biologics

- Adalimumab (Humira)
- Ravulizumab
- Eculizumab
- Inebilizumab
- Ocrelizumab
- Ofatumumab
- Rituximab
- Satralizumab
- Tocilizumab

Humira 3 mg/kg SC Administered Following Dosing of BHV-1300 30 mg/kg SC in NHP



KEY POINTS

- **No change in PK of Humira® when administered 12 hours following BHV-1300**
- **Supports same-day dosing of BHV-1300 with Fc-containing biologics (mAbs)**
- **FcRn inhibitors reduce effectiveness of Fc-containing biologics and should not be used together**

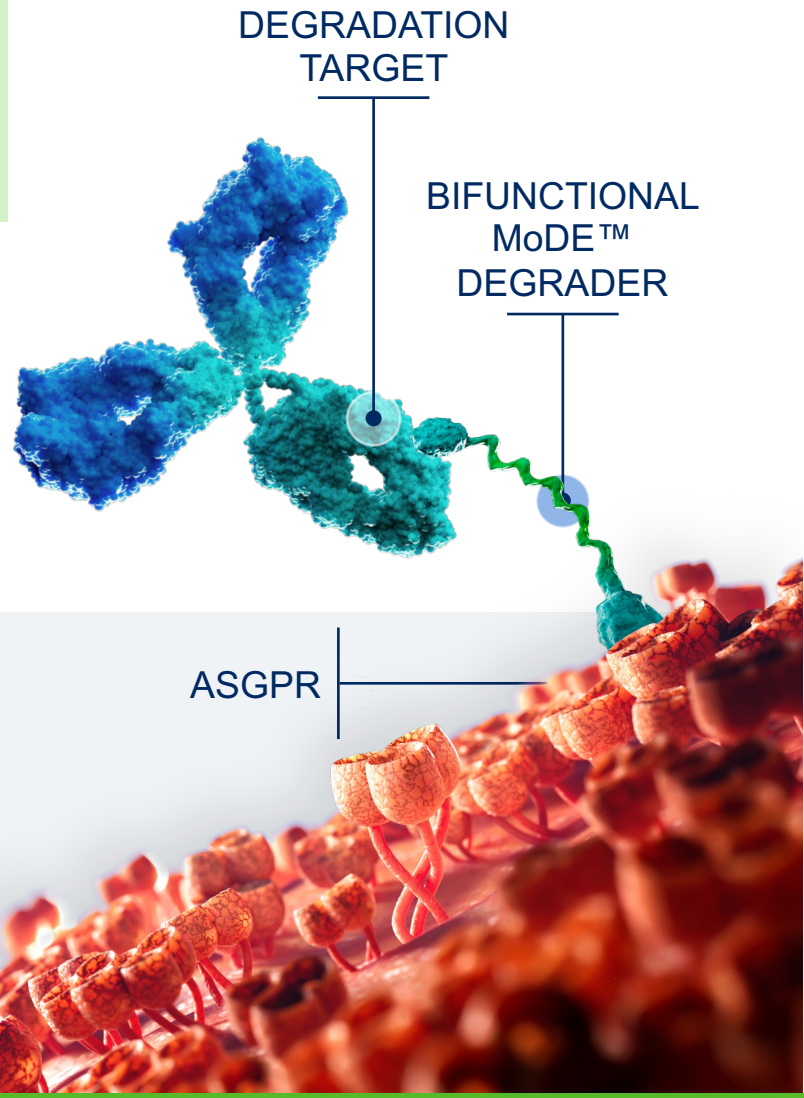
* Adapted from BLA 761154, IND 116471, Study no. r-fkb327-01

mAbs, monoclonal antibodies; **NHP**, non-human primate.

Targeted Extracellular Protein Degradation is a Next-Generation Approach for Treating Antibody Mediated Diseases

MoDE™ degraders offer many potential advantages

- **Rapid onset of IgG lowering**
- **Depth of IgG lowering**
- **Lower risk of infection**
- **SC self-administration**
- **Co-administration with Fc-containing biologics**



MoDE™: AN INNOVATIVE PLATFORM FOR A PIPELINE OF THERAPEUTICS

Potential to develop numerous clinical drug candidates for targeted degradation of pathogenic antibodies and other extracellular proteins to treat a broad range of diseases

NOVEL IgG LOWERING DRUG CANDIDATES: BHV-1300 & BHV-1310

Exemplify a first-in-human approach for efficient removal of pathogenic IgG species in multiple antibody mediated disorders

FcRn, neonatal Fc receptor; **IgG**, immunoglobulin.