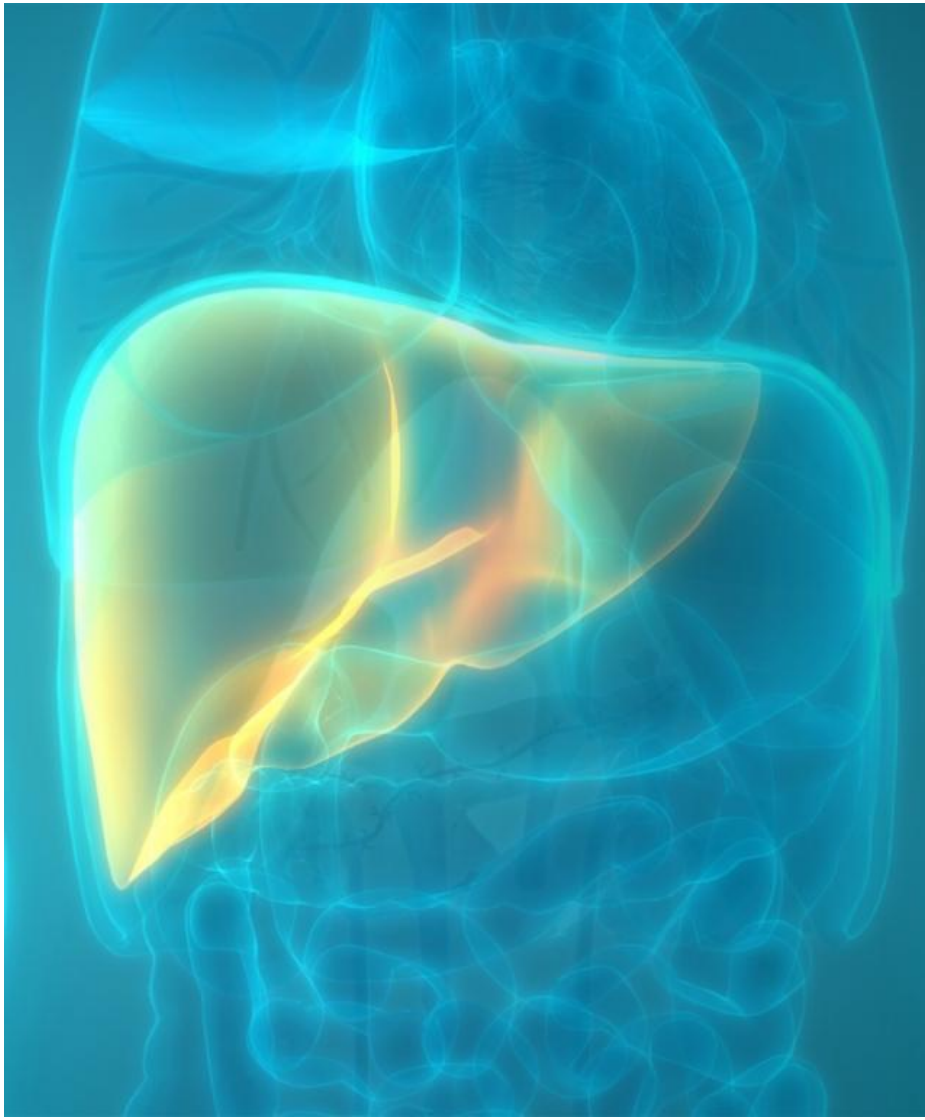


BIOHAVEN'S NEW APPROACH TO IMMUNE-MEDIATED DISEASES USING YALE SCIENCE FOR TARGETED EXTRACELLULAR PROTEIN DEGRADATION

David Spiegel, M.D., Ph.D.
Professor of Chemistry and Pharmacology, Yale University
Scientific Advisor, Biohaven


spiegel
SPIEGEL
RESEARCH
GROUP

2015

PROTEIN

AGING PROTEIN

IDEA!

ASGPR asialoglycoprotein receptor

21 OCT 2015

23 NOV 2015

spiegel began experiments

16 SEP 2016

First MoDE experiments were effective

9 APR 2018

Yale filed U.S. patent

3 JAN 2019

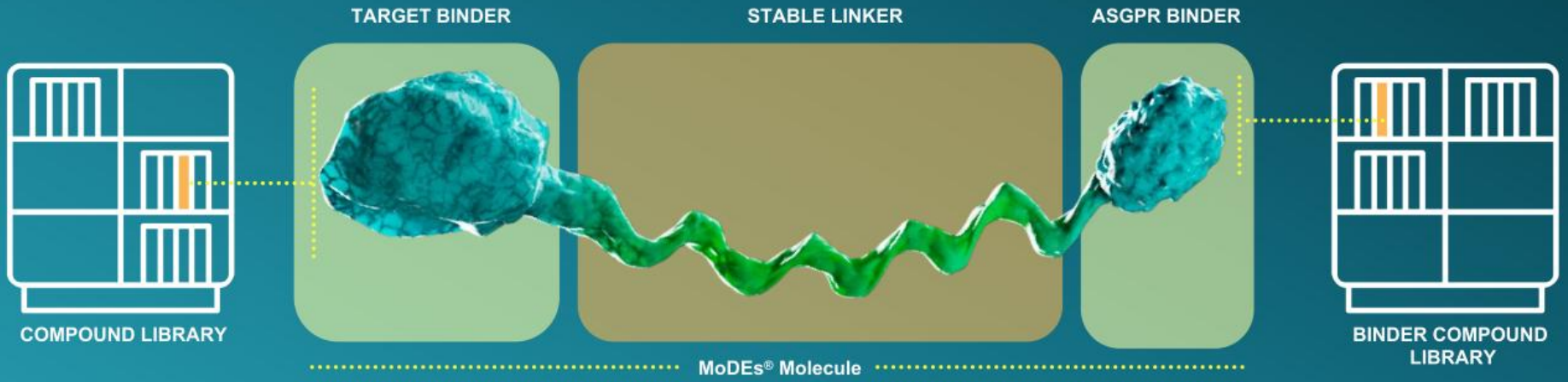
Yale filed U.S. patent

29 JUL 2020

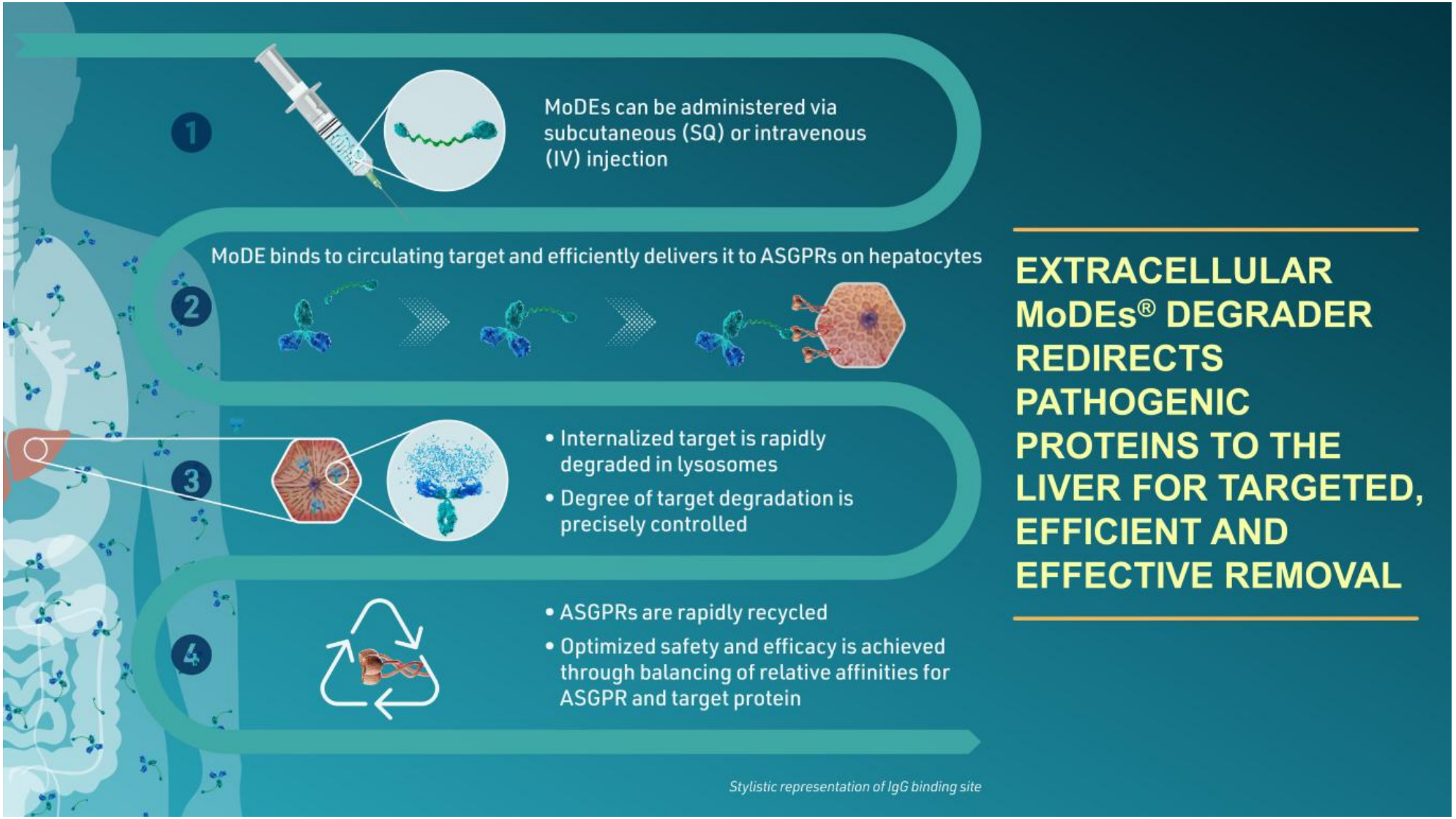
17 SEP 2021

MoDE™ PLATFORM

MOLECULAR DEGRADERS OF EXTRACELLULAR PROTEINS



TRANSFORMATIONAL DRUG PLATFORM

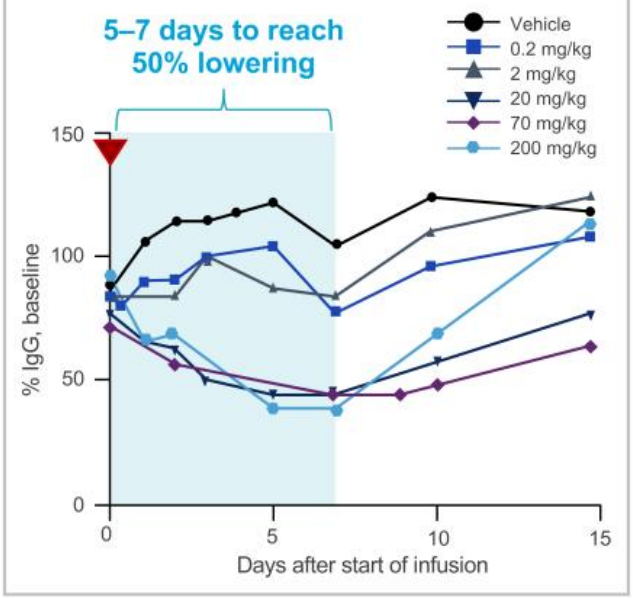

1
MoDEs can be administered via subcutaneous (SQ) or intravenous (IV) injection
MoDE binds to circulating target and efficiently delivers it to ASGPRs on hepatocytes
2
3
• Internalized target is rapidly degraded in lysosomes
• Degree of target degradation is precisely controlled
4
• ASGPRs are rapidly recycled
• Optimized safety and efficacy is achieved through balancing of relative affinities for ASGPR and target protein
Stylistic representation of IgG binding site
EXTRACELLULAR MoDEs® DEGRADER REDIRECTS PATHOGENIC PROTEINS TO THE LIVER FOR TARGETED, EFFICIENT AND EFFECTIVE REMOVAL

BHV-1300:
SHOWS POTENTIAL FOR SUPERIORITY OVER FcRn INHIBITORS

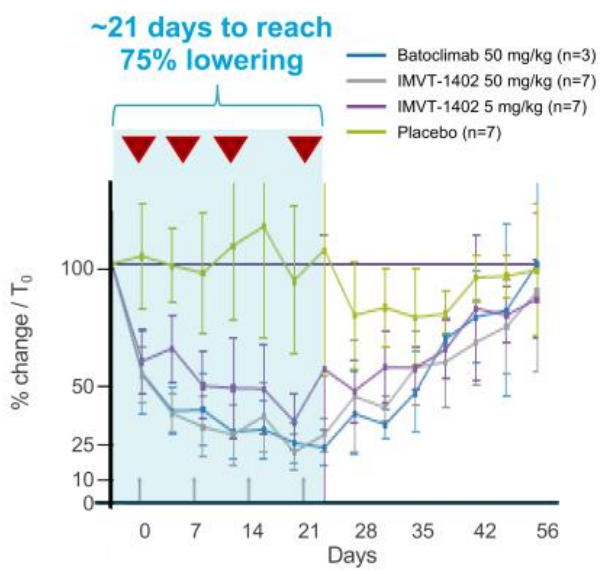
KEY | DATA

BHV-1300 demonstrated faster IgG lowering in non-human primates

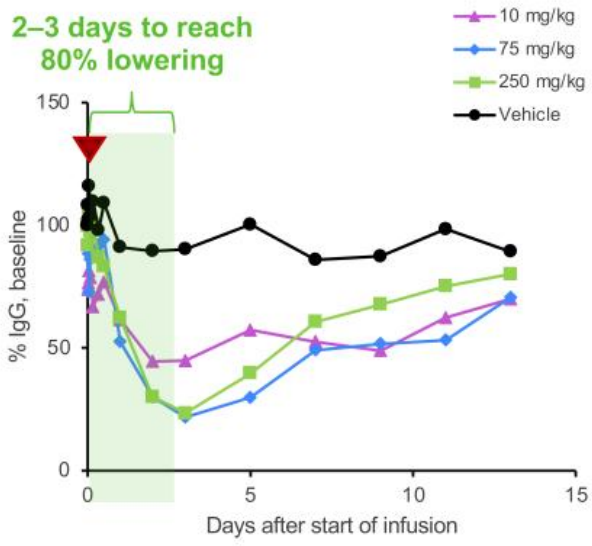
Efgartigimod NHP Pharmacodynamics



Immunovant NHP Pharmacodynamics



BHV-1300 NHP Pharmacodynamics



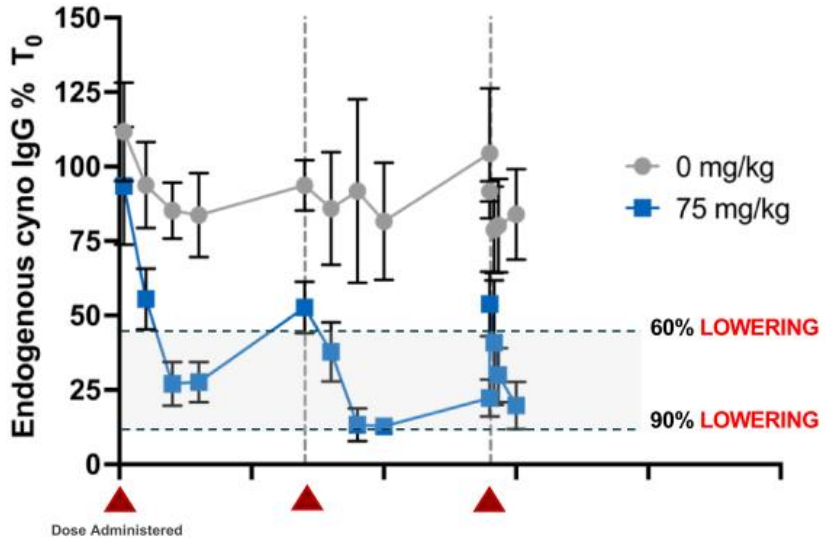
Dose Administered

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.

BHV-1300:
UNIQUE PROPERTIES MATCHED TO CHRONIC INDICATIONS

BHV-1300 Preclinical Pharmacodynamics (Multiple Dose)



KEY POINTS

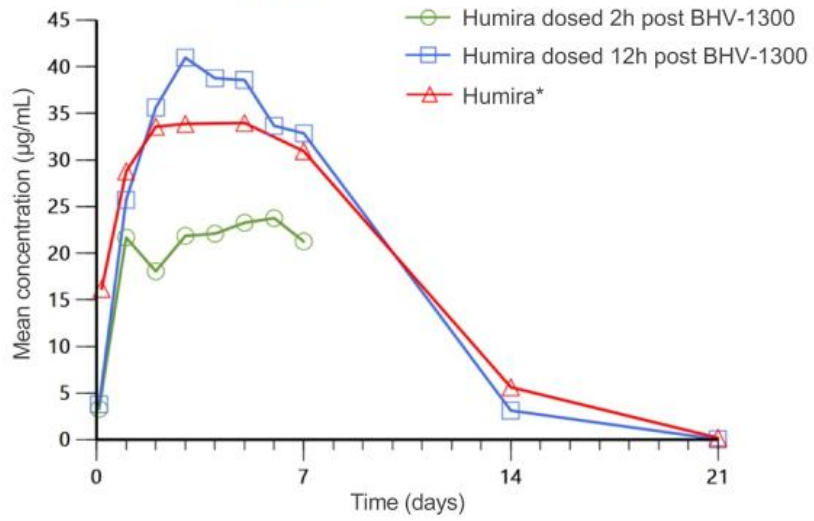
- **Depth of lowering reaches 90% after second dose**
- **Depth of lowering is tunable: easily adjusted by frequency of administration**
- **Adaptable to suit ideal target product profiles for different indications**

BHV-1300:
PHARMACODYNAMIC DATA SUPPORTS ABILITY TO CO-ADMINISTER WITH mAbs REPRESENTING A POTENTIAL ADVANCEMENT TO FcRn INHIBITORS

Frequently Administered Fc-containing Biologics

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

Humira 3 mg/kg SC, After a 30 mg/kg SC Dose of BHV-1300 to NHP



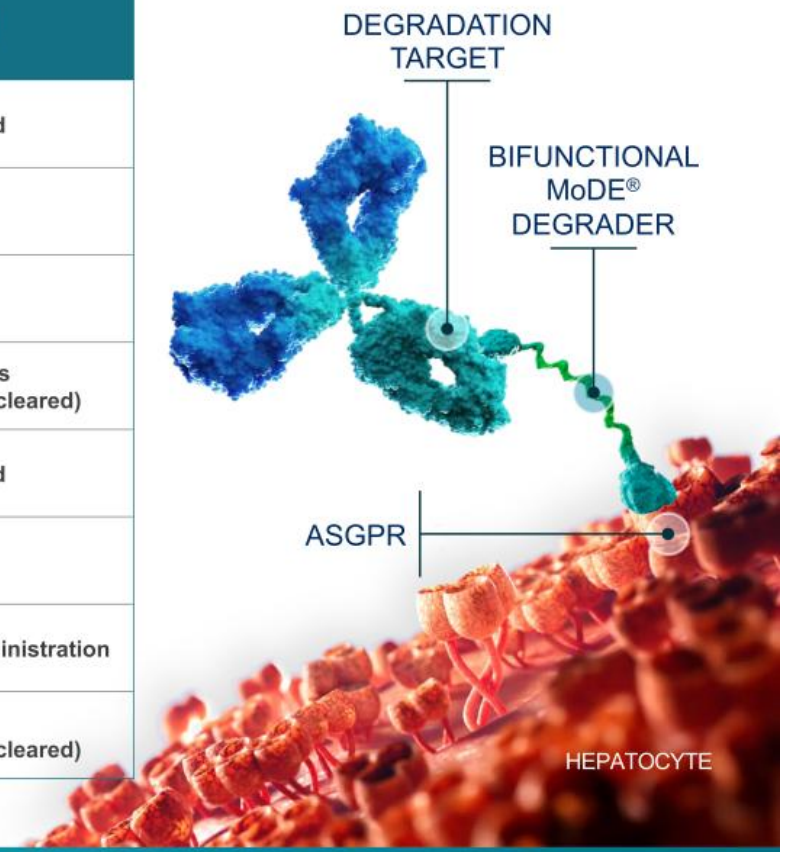
KEY POINTS

- **First NHP data to show that BHV-1300 does not alter PK of Humira® when dosed 12 hours earlier**
- **Allows for same-day dosing with biologics**
- **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.

IgG LOWERING WITH BHV-1300 OFFERS SIGNIFICANT POTENTIAL BENEFITS OVER FcRn INHIBITORS

	FcRn Inhibitors	BHV-1300 MoDE™
No Impact on AEs of Interest	Hypoalbuminemia, dyslipidemia, headache	**None expected**
No Impact on Host Defense (IgG_3)	Lowers IgG_3	**IgG_3-sparing**
Accelerated Time to Peak Effect (IgG lowering)	5–22 days	**24-48 hours**
Advantageous drug exposure window	Continuous	**Only ~ 24 hours (BHV-1300 is rapidly cleared)**
Immunogenicity	Emerging issue	**None expected**
Ability to dose on demand for disease flares or deeper IgG Lowering	Mechanistically impossible	**Allowed**
Convenient & Preferred Dosing	SC/IV infusion by health professional	**Anticipated SC self-administration**
Ability to administer with Fc-containing biologics	Precluded per label/MOA	**Allowed (BHV-1300 is rapidly cleared)**



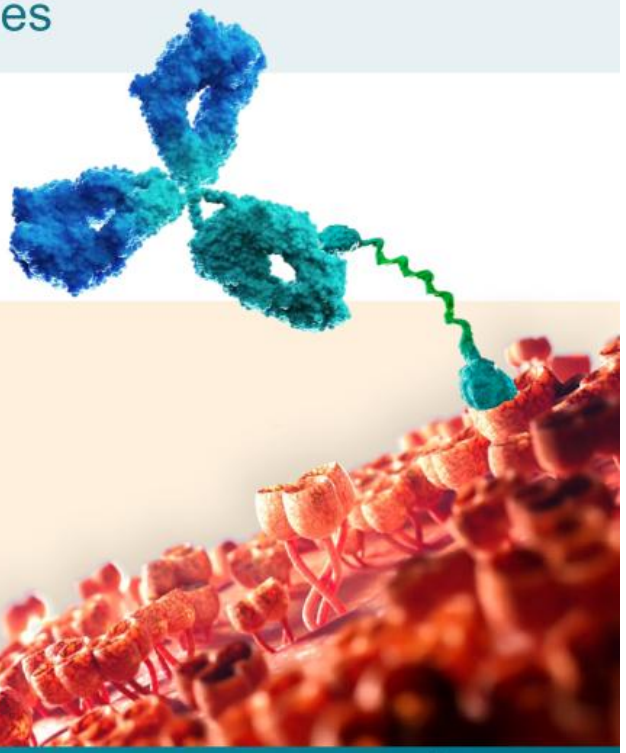
FcRn, neonatal Fc receptor; **IgG**, immunoglobulin; **IV**, intravenous; **SC**, subcutaneous.

MoDE™ SUMMARY

A FIRST-IN-CLASS PLATFORM TO ADDRESS UNMET NEED IN ANTIBODY-MEDIATED DISEASES

Selective extracellular protein degradation provides many predicted and potential advantages

- **Rapid onset of IgG lowering**
- **Depth of IgG lowering**
- **Lower risk of infection**
- **Ability to co-administer with 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 MOA for efficient removal of pathogenic IgG species in multiple immune-mediated disorders

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

Biohaven's Study BHV1300-101:

PRELIMINARY FIRST-IN-HUMAN SINGLE ASCENDING DOSE (SAD) STUDY UPDATE

STATUS: 16 Subjects Completed Two Dosing Cohorts to Date

- Sentinel dosing paradigm: 1 sentinel subject treated with BHV-1300 in each cohort prior to dosing other subjects
- Given novel MOA, robust data collection with standard Safety Review Committee meeting to review at least two weeks of follow-up data for each cohort before next dose group; review includes cumulative safety, PK and pharmacodynamic data
- All cohorts have proceeded as initially planned without any cohort expansion or interruption

SAFETY: BHV-1300 Has Been Safe and Well-Tolerated to Date

- No SAEs
- No moderate or severe AEs; only mild AEs observed, judged not related to BHV-1300 with most resolving spontaneously
- No clinically significant laboratory abnormalities (including LFTs, albumin) or ECG changes

IGG LOWERING: Preliminary Data Consistent With Modeling Based on Nonclinical Experience

- Dose- and time-dependent IgG lowering observed even in initial low dose cohorts
- Reductions were greater for IgG1, IgG2 and IgG4 subclasses compared to IgG3**; BHV-1300 was designed to spare IgG3

KEY POINTS

- **First-in-human dosing of BHV-1300 well tolerated with no clinically significant laboratory abnormalities to date**
- **Preliminary dose- and time-dependent IgG lowering observed; with IgG1, IgG2 and IgG4 lowering > IgG3**
- **Further updates planned at the Company's R&D Day on May 29, 2024**

* Preliminary data from Study 1300-101 is from an ongoing study and subject to change (database not yet cleaned or locked) **IgG1-4 analyzed at Mayo Clinic Laboratories, Rochester MN

THANK YOU!

spiegel

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THE SPIEGEL RESEARCH GROUP

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KEEP UP TO DATE ON BIOHAVEN'S
DEGRADER PROGRAMS