
WELCOME
Vlad Coric, M.D.
Chairman and Chief Executive Officer
biohaven
BHVN
LISTED
NYSE

Forward-Looking Statement

This presentation includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements about Biohaven Ltd. (the “Company”) and our planned and ongoing trials for our BHV-2100, troriluzole, BHV-5500, BHV-1100, BHV-1200, taldefgrobep alfa, BHV-8000, BHV-7000 and BHV-7010 development programs, the timing of and the availability of data from our clinical trials, the timing and our decisions to proceed with our planned regulatory filings, the timing of and our ability to obtain regulatory approvals for our product candidates, the clinical potential utility of our product candidates, alone and as compared to other existing potential treatment options, and the potential advancement of our early phase programs including ARM™, MATE™, MODE™, TRPM3, TDP-43, UC1MT, TYK2/JAK1, and Kv7. The use of certain words, including “continue”, “plan”, “will”, “believe”, “may”, “expect”, “anticipate” and similar expressions, is intended to identify forward-looking statements. Investors are cautioned that any forward-looking statements, including statements regarding the future development, timing and potential marketing approval and commercialization of our development candidates, are not guarantees of future performance or results and involve substantial risks and uncertainties. Actual results, developments and events may differ materially from those in the forward-looking statements as a result of various factors including: the expected timing, commencement and outcomes of Biohaven's planned and ongoing clinical trials; the timing of planned interactions and filings with the Food and Drug Administration; the timing and outcome of expected regulatory filings; complying with applicable U.S. regulatory requirements; the potential commercialization of Biohaven's product candidates; the potential for Biohaven’s product candidates to be first in class or best in class therapies; and the effectiveness and safety of Biohaven's product candidates. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this presentation. Additional important factors to be considered in connection with forward-looking statements are described in the Company’s filings with the Securities and Exchange Commission, including within the sections titled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations”. This presentation also contains market data and other information based on industry publications, reports by market research firms or published independent sources. Some market data and information is also based on the Company’s good faith estimates, which are derived from management’s knowledge of its industry and such independent sources referred to above.

WHY DAYS MATTER

NEUROPSYCHIATRIC ILLNESS
LEADING CAUSE OF DISABILITY
WORLDWIDE

100 MILLION
PEOPLE IN THE US
SUFFER FROM
NEUROLOGICAL DISEASES

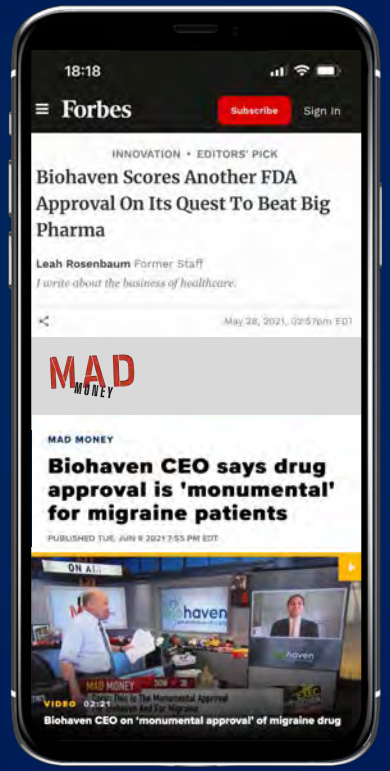
1 IN 5
US ADULTS
LIVE WITH A
NEUROPSYCHIATRIC ILLNESS

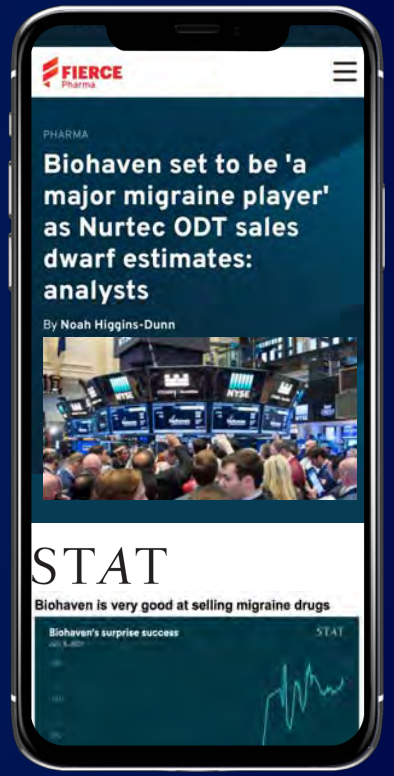
$1 TRILLION IN THE US
ANNUAL COSTS
RELATED TO NEUROLOGICAL AND NEUROPSYCHIATRIC DISORDERS

DEVASTATING BURDEN
WILL SIGNIFICANTLY WORSEN AS
POPULATION OF 65+ YEARS OF AGE
DOUBLES
BY 2050

LEGACY OF DRUG DEVELOPMENT AND VALUE CREATION

Pivotal Phase 3
Rimegepant ODT
trial results published





CLINICAL EXCELLENCE

REGULATORY ACHIEVEMENT

COMMERCIAL DOMINANCE

HIGH VALUE PLATFORMS

Pursuing novel paths of science to transform the treatment of neurological and neuropsychiatric diseases

INNOVATIVE PORTFOLIO

In-house scientific expertise to enable a broad therapeutic portfolio addressing patient needs with intention

PROVEN BUSINESS FORMULA

Formula for continued growth built upon past success of experienced team and a resilient focus on creating value for patients and shareholders

BIOHAVEN TODAY

DRIVING A ROBUST PIPELINE WITH

Biohaven's Discovery Research

5 Clinical Programs

8 Preclinical Programs

6 Novel Small Molecule Approaches

4 Novel Large Molecule Approaches

11+ Indications with High Unmet Medical Need

Comprehensive In-House Functional Expertise

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Through state-of-the-art drug discovery and passionate scientists
— LARRY

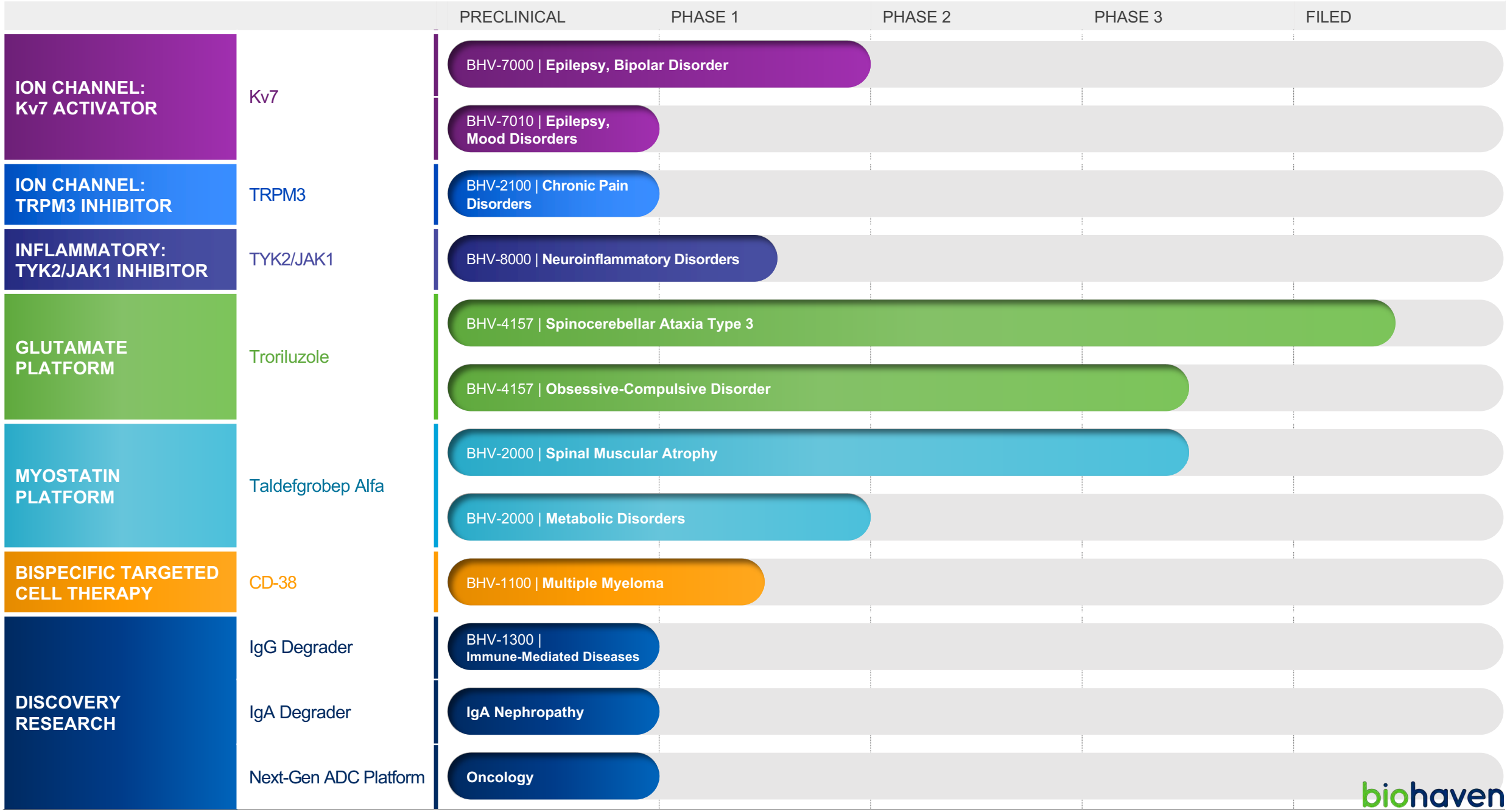
With a powerful R&D engine
— JAVIER

With a commitment to transforming patients' lives
— KATRINA

We never forget patients need us
— JEREMY

Because we are passionate about the work we do every day — FRANCINE

OUR EMPLOYEES KNOW WE WILL DO IT AGAIN


PRECLINICAL
PHASE 1
PHASE 2
PHASE 3
FILED
ION CHANNEL: Kv7 ACTIVATOR
Kv7
BHV-7000 | Epilepsy, Bipolar Disorder
BHV-7010 | Epilepsy, Mood Disorders
ION CHANNEL: TRPM3 INHIBITOR
TRPM3
BHV-2100 | Chronic Pain Disorders
INFLAMMATORY: TYK2/JAK1 INHIBITOR
TYK2/JAK1
BHV-8000 | Neuroinflammatory Disorders
GLUTAMATE PLATFORM
Troriluzole
BHV-4157 | Spinocerebellar Ataxia Type 3
BHV-4157 | Obsessive-Compulsive Disorder
MYOSTATIN PLATFORM
Taldefgrobep Alfa
BHV-2000 | Spinal Muscular Atrophy
BHV-2000 | Metabolic Disorders
BISPECIFIC TARGETED CELL THERAPY
CD-38
BHV-1100 | Multiple Myeloma
DISCOVERY RESEARCH
IgG Degrader
BHV-1300 | Immune-Mediated Diseases
IgA Degrader
IgA Nephropathy
Next-Gen ADC Platform
Oncology
biohaven

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Bispecific Platform

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Building a Franchise of Targeted Protein Degradation

DEGRADER PLATFORM Overview

A Pipeline of Therapies

Potential to support numerous clinical candidates across a wide range of indications by targeting pathogenic proteins and antibodies

First-in-Class Targeted Degradation MOA

Extracellular protein degradation provides unique advantages, such as an accelerated path from discovery to clinic

BHV-1300

First-in-human MOA for efficient removal of pathogenic IgG with proven mechanism for autoimmune disorders

Galactose Deficient IgA1 Degradation

Novel antibody-based degrader for treatment of IgA nephropathy

Disease-Specific, Autoantibody-Targeted Degraders

Selective removal of autoantibodies implicated in multiple immune driven degenerative disorders

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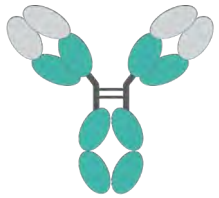
MoDE™ Degraders: Multiple Asset Opportunities and Efficient Timelines



IgG and IgA antibodies are the first targets for Biohaven's powerful degradation platform

Key Value Inflection Points

PROGRAM	2023	2024	2025	2026	2027
IgG *RA, autoimmune*	IND Filing (2H)				
IgA *IgA nephropathy*		IND Filing (1H)			
Undisclosed AutoAb #1			IND Filing		
Undisclosed AutoAb #2			IND Filing		
Discovery targets					

Realization of value inflection points will be project specific and aligned with cohesive portfolio strategy
AutoAb, autoantibody; **Ig**, immunoglobulin; **IND**, Investigational New Drug; **MoDE™**, molecular degrader of extracellular proteins; **RA**, rheumatoid arthritis

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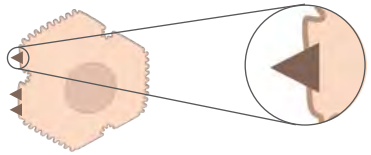
A First-in-Class Mechanism: Hepatic ASGPR Receptor Harnessed for Efficient and Safe Removal of Circulating Pathogenic Targets

Symbol Legend

Degradation Target

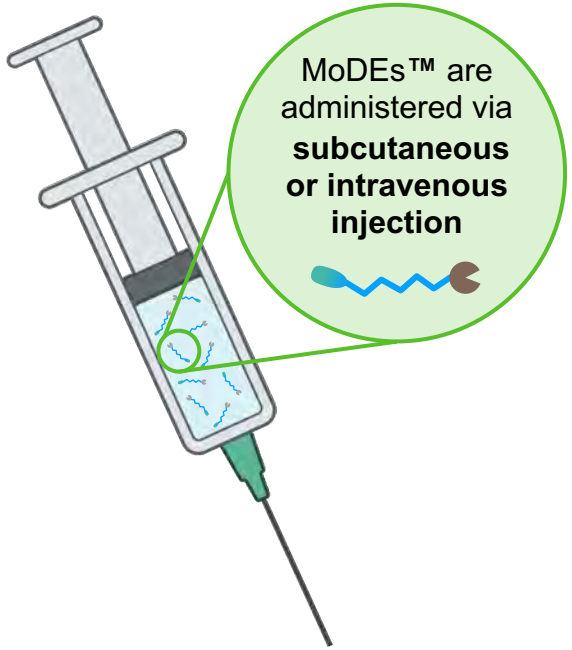
Bifunctional MoDE™ Degrader

Hepatocyte

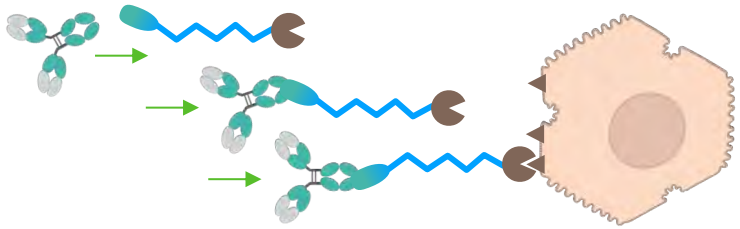


Asialoglycoprotein Receptor (ASGPR)*

1

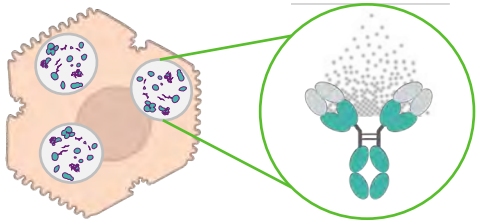


2



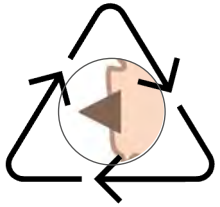
MoDE™ binds circulating target to ASGPR on hepatocyte

3



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

4



- ASGPR receptors rapidly recycled, with potentially differentiated kinetics over target, resulting in optimized safety and liver balance
- Dosing schedule dependent on resynthesis rate of target

*Stylistic representation

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

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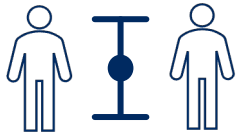
BHV-1300: A Potent Extracellular Pan-IgG Lowering Agent

Degrading and depleting pathogenic IgG in chronic and acute conditions may present multiple opportunities in neurological and non-neurological indications

INNOVATIVE MECHANISM OF ACTION

Protein **degradation** rather than inhibition



Low projected human **dose range**

Potential for **subcutaneous** dosing

BHV-1300

First drug candidate using **MoDE**™ technology

Studies in a NHP model show:

- **50%-75% IgG depletion** with a single dose
- **Safe** in doses up to 250 mg/kg
- More **rapid** IgG reduction vs efgartigimod

IND SUBMISSION

2H 2023

Ig, immunoglobulin; **IND**, Investigational New Drug; **MoDE™**, molecular degrader of extracellular proteins; **NHP**, non-human primate

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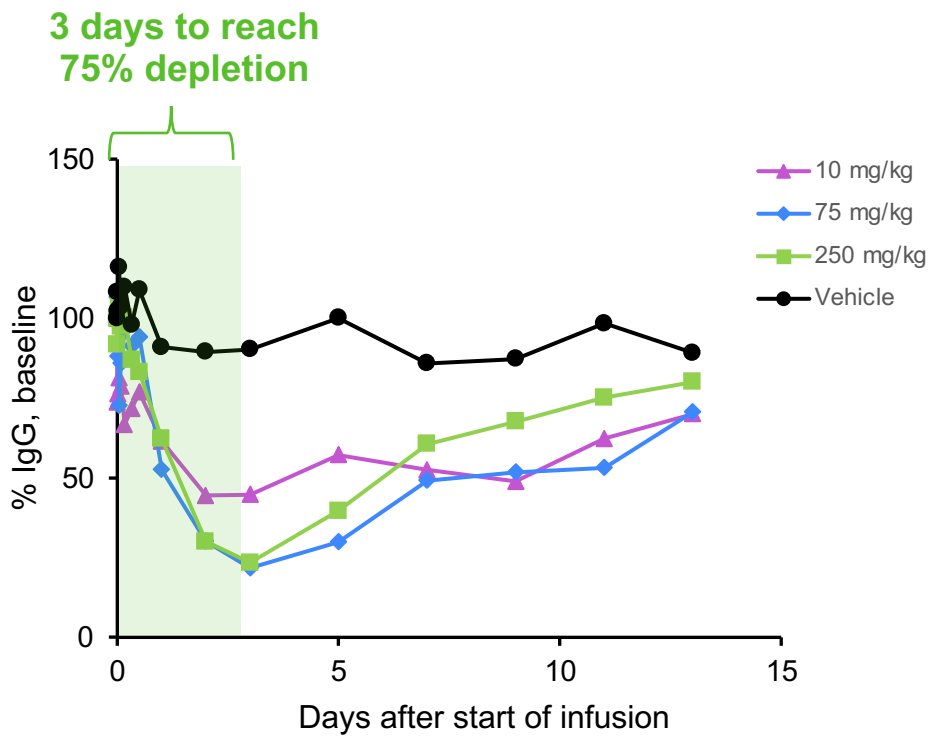
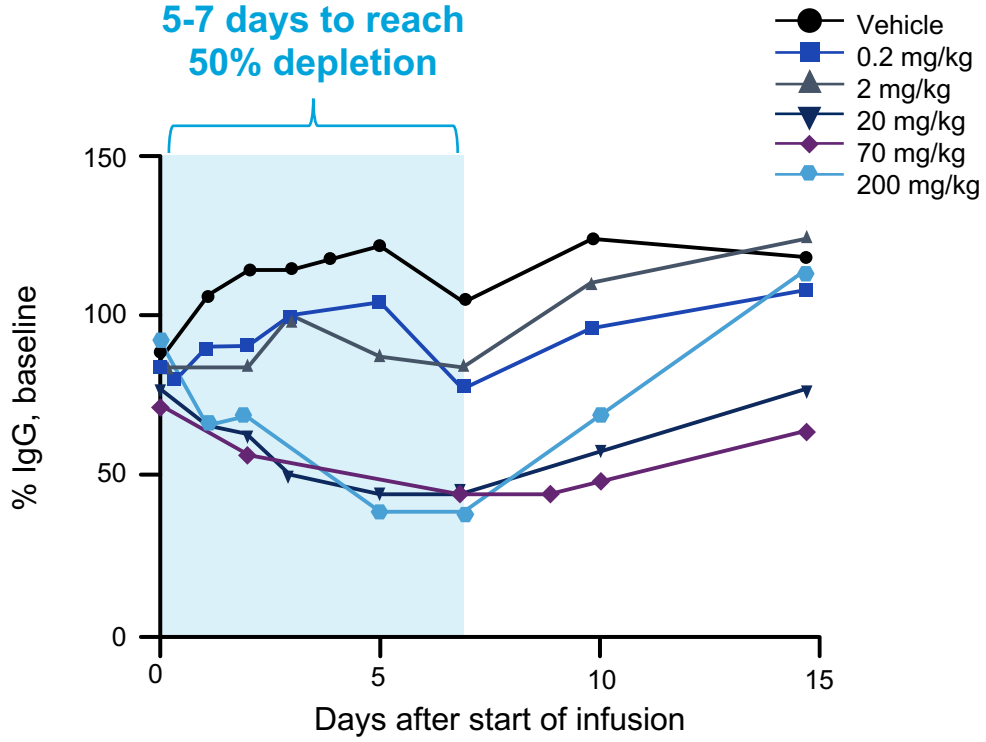
BHV-1300: Shows Potential for Superiority Over SOC (Efgartigimod)

BHV-1300 demonstrated faster depletion of IgG in a non-human primate (NHP) compared to efgartigimod

BHV-1300: NHP Pharmacodynamics



Efgartigimod: NHP Pharmacodynamics



The Journal of Clinical Investigation 2018:128(10):4372-4386. https://doi.org/10.1172/JC197911.
IgG, immunoglobulin G; **NHP**, non-human primate; **SOC**, standard of care

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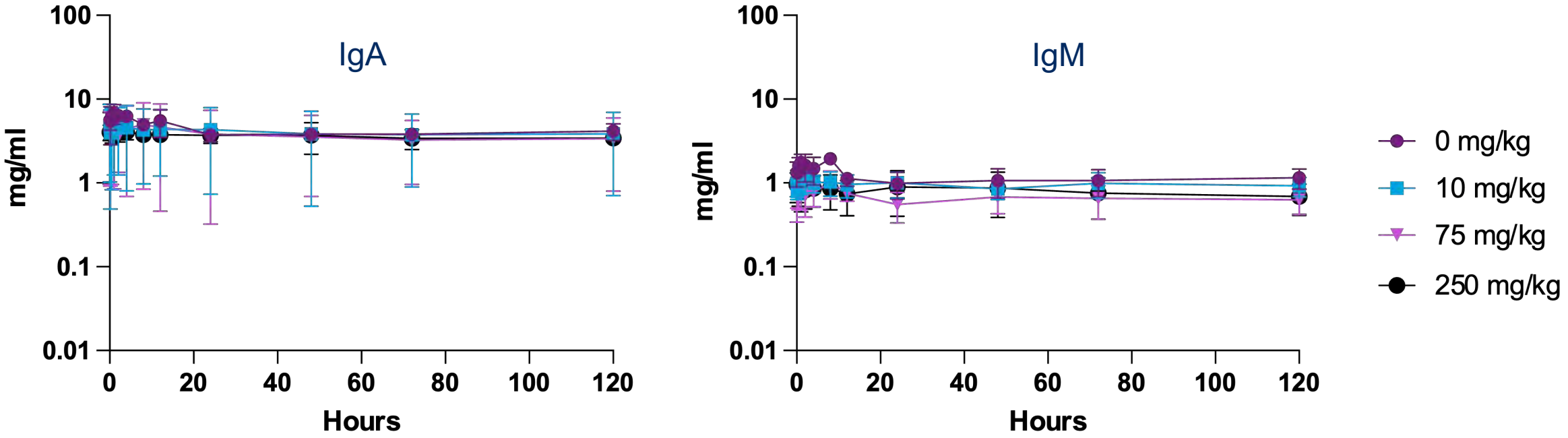
BHV-1300: IgG Specificity Leads to Improvements in Disease Targeting Without Unintended Consequences on Other Antibodies

IgA and IgM levels unaffected

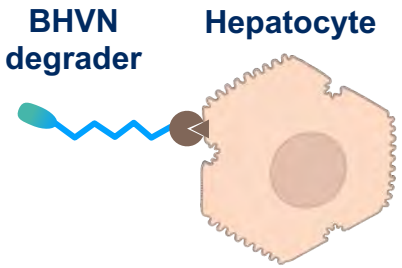
BHV-1300 Administered IV to NHP



- Preliminary BHVN data and literature are consistent with an absence of effects on serum albumin, LDL, HDL or triglycerides—limiting target-based toxicity as seen with FcRn

Ab, antibody; **FcRn,** neonatal Fc receptor; **HDL**, high-density lipoprotein; **Ig**, immunoglobulin; **IV,** intravenous; **LDL**, low density lipoprotein; **NHP**, non-human primate

BHV-1300: Specific and Rapid Pathogenic Target Removal



BHV-1300 can specifically remove target IgG from circulation **faster than FcRn inhibitory antibodies, antibody fragments, or immunosuppressants**

- Mechanism not expected to cause hypoalbuminemia or dyslipidemia
- Improved and optimizable potency for target removal
- Deeper target removal when required
- Improved pharmacodynamics with faster onset of action than FcRn inhibition
- Improved safety profile expected (fewer side effects, rapid drug elimination)

FcRn, neonatal Fc receptor**; Ig,** immunoglobulin; **MoDE™**, molecular degrader of extracellular proteins

BHV-1300: Has Potential to Add Significant Value Across Rare And Common Diseases With a Differentiated Profile from FcRn Class

BHV-1300 DIFFERENTIATED FROM COMPETITORS

in FcRn class such as efgartigimod and nipocalimab with a **unique MOA, faster onset, and predicted to have improved safety**

PHASE 2 STUDY

Start in 2024

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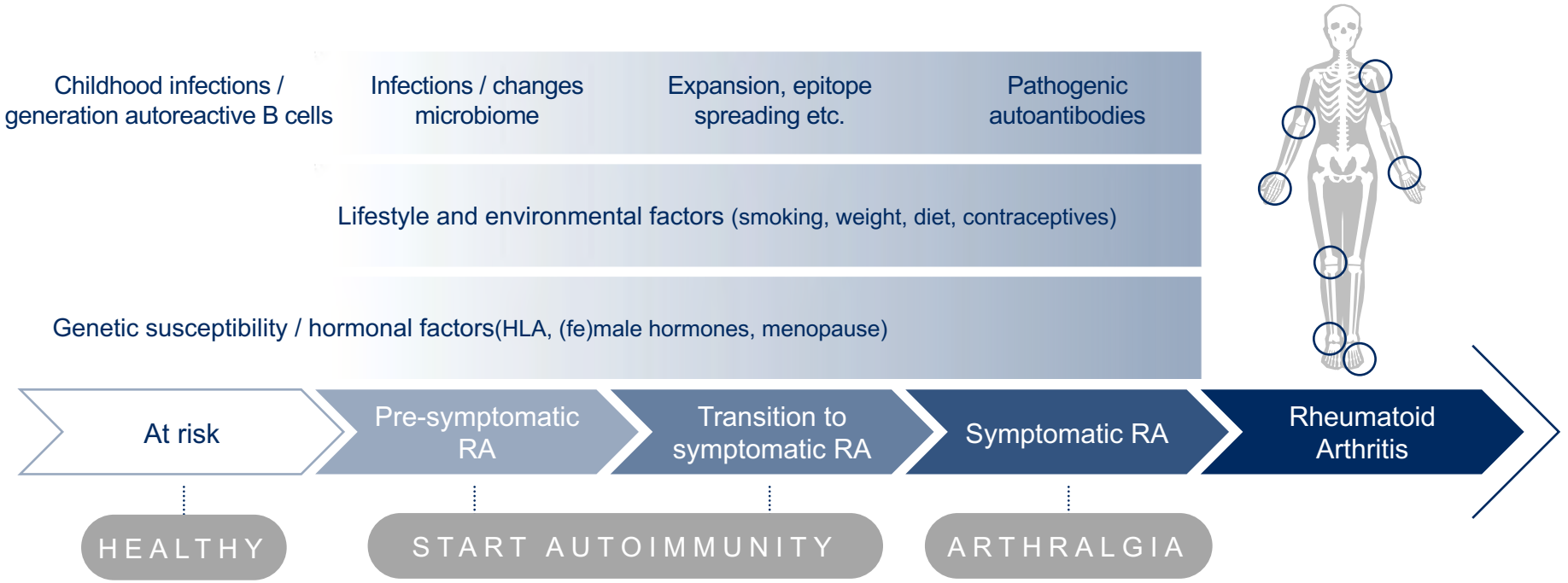
Rheumatoid Arthritis Is a Heterogenous Autoimmune Disorder Marked by Autoantibodies of Various Classes

Autoantibodies can start to accumulate 10 years prior to clinical arthritis[1]

THE ACR/EULAR DIAGNOSTIC CRITERIA INCLUDE[2]:

- 3+ joints involved
- Acute phase biomarkers of inflammation including elevated ESR and CRP
- Symptom duration
- Presence of RF and ACPA

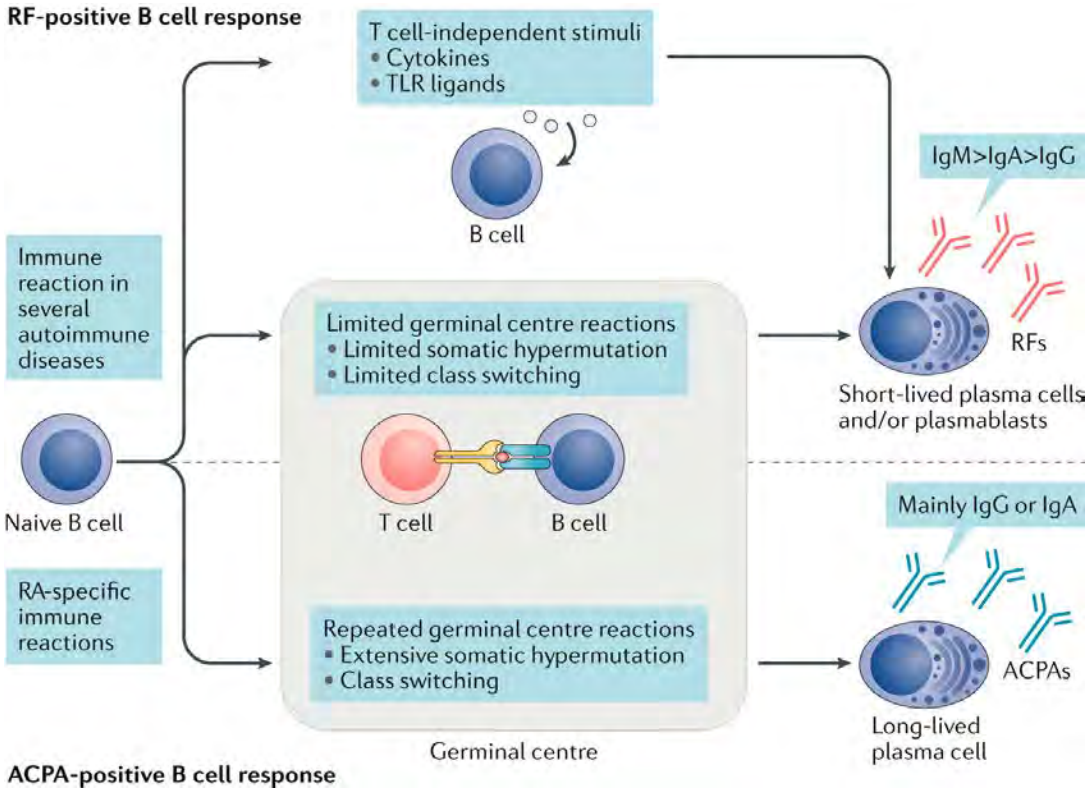
IgG+ ACPA in ~70% of RA population with increasing evidence they may be pathogenic in RA



Without effective and early intervention, inflammation and joint destruction lead to loss of physical function and extremely poor QoL
Additional health risks include elevated risk for cardiovascular disease, osteoporosis, and certain types of cancer (e.g., lymphoma)

1. Adapted from Van Delft and Huizinga, An overview of autoantibodies in rheumatoid arthritis; J *Autoimmun* 2020. 2. UpToDate accessed Jan 2023.

Exact Etiology of RA is Multifactorial With Environmental, Genetic, and T Cell Components, However Autoantibody Presence is a Main Feature



- **Rheumatoid Factor (RF)** antibodies are primarily IgM but form immune complexes with IgG
- **Anti-citrillunated protein antibodies (ACPAs)** including anti-cyclic citrullinated peptide-2 (anti-CCP2) are primarily IgG, but some IgA and IgM species exist
- All **immune complexes** can cause **damage** in joints, connective tissue in many organs, and bone
- **Comorbidities** from cardiovascular to malignancy need to be closely monitored
- In patients who are not in remission, **status every 4-12 weeks needed to tightly control severity** of flares and progression
- **An IgG degrader could remove a major component of these immune complexes without lowering B cell counts**

Figure adapted from Malmstrom and Gronwall, The parallel worlds of ACPA-positive and RF-positive B cells; *Nature Rev Rheum* 2018.

Bruce Car, Ph.D.

Chief Scientific Officer

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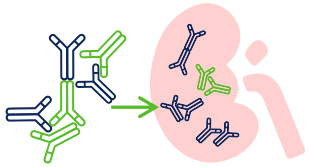
Galactose Deficient (Gd) IgA Degradation

Gd-IgA1 Degradation to Treat IgA Nephropathy (IgAN)

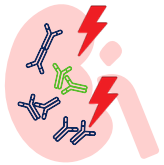
Pathophysiology of IgAN

1. Increased circulating levels of galactose-deficient IgA (Gd-IgA1)

2. Anti-IgA1 antibodies (IgA or IgG) are produced



3. Immune complexes form in the circulation and *in situ* in organs



4. Immune complexes in the mesangium of the kidney cause local immune activation and injury

Ab-based MoDE™

Biohaven is developing a rat-human Gd-IgA1–specific Ab-based degrader for the treatment of IgA nephropathy via selective removal of Gd-IgA1

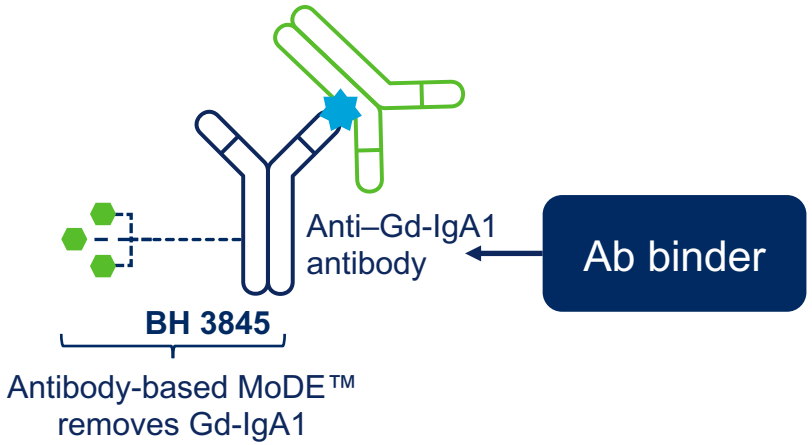
- Expected low subcutaneous dose
- Competitive target opportunity profile
- Avoids host-defense issues of competitive approaches

Ab, antibody; **Gd**, galactose deficient; **Ig**, immunoglobulin; **IgAN**, IgA nephropathy; **MoDE™**, molecular degrader of extracellular proteins

Preclinical Studies Show the Gd-IgA1–Specific MoDE™ Selectively Degrades the Gd-IgA1 Present in IgAN

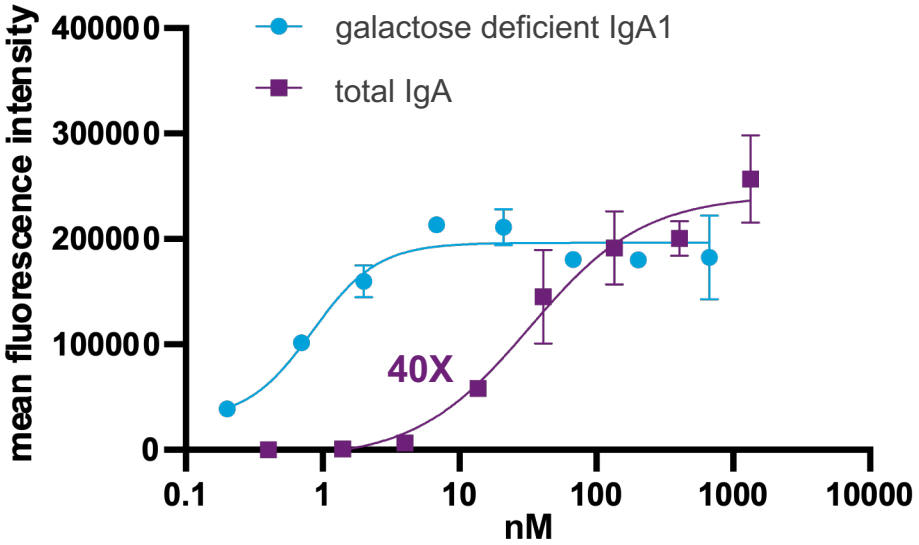
At low concentrations, this Gd-IgA1–specific MoDE™ selectively degrades Gd-IgA1 and spares total IgA, limiting the impact on the immune system

Gd-IgA1–Specific MoDE™



- Reduces only pathogenic Gd-IgA1
- Spares IgA, limiting immune impacts

Gd-IgA1–Specific MoDE™ Selectively Degrades Gd-IgA1



	EC_{50}
Galactose deficient IgA1	0.84
Total IgA	33

Ab, antibody; **EC_{50}**, half maximal effective concentration **Gd**, galactose-deficient; **Ig**, immunoglobulin; **IgAN**, IgA nephropathy; **MoDE™**, molecular degrader of extracellular proteins

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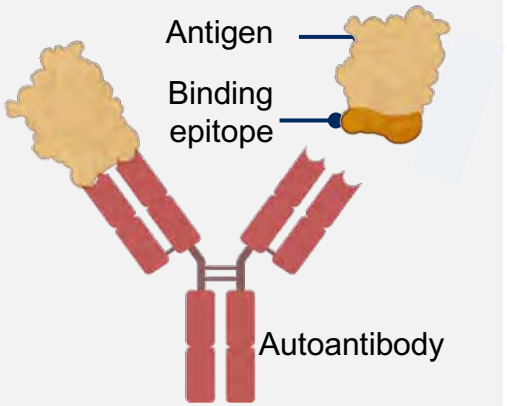
David Spiegel M.D., Ph.D.
Professor
Department of Chemistry

Yale SCHOOL OF MEDICINE

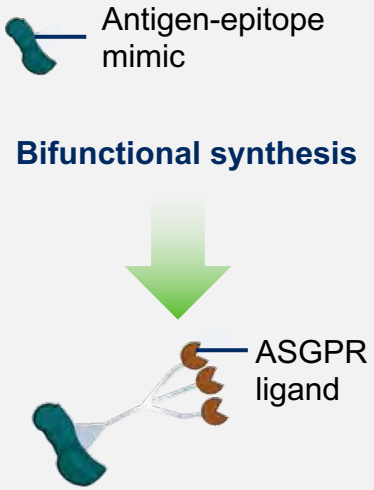
Autoantibody Specific Degradation

Selective Degradation of Autoantibodies as Next-Generation Degraders Preserving Immune Function

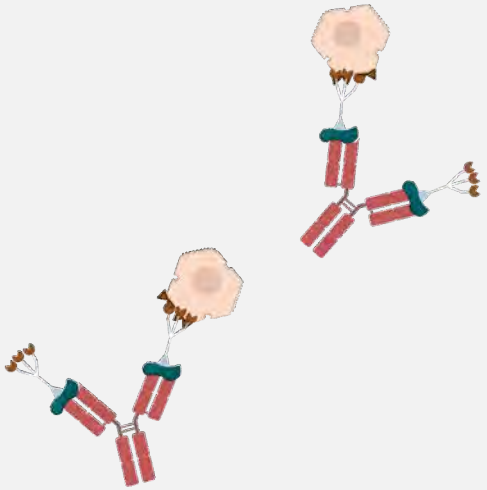
Pathogenic autoantibody



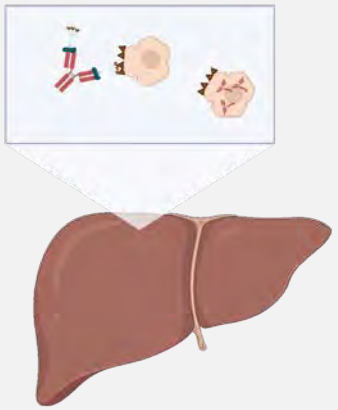
Convert antigenic epitope mimic to bifunctional degrader



Novel degraders serve as bait for autoantibody



Baited autoantibody taken up and degraded by hepatocytes



Selective removal of pathogenic and retention of nonpathogenic antibodies **preserves host defense**, providing a **personalized and immune-sparing approach** for immune-driven degenerative disorders

ASGPR, asialoglycoprotein receptor

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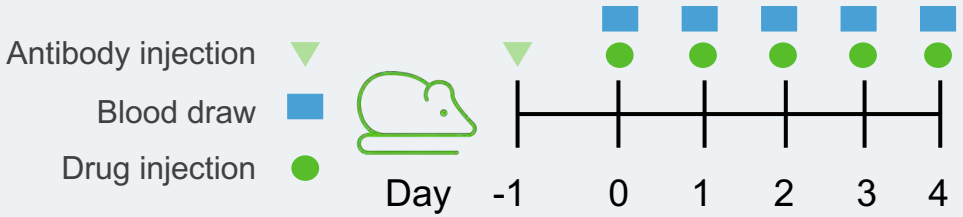
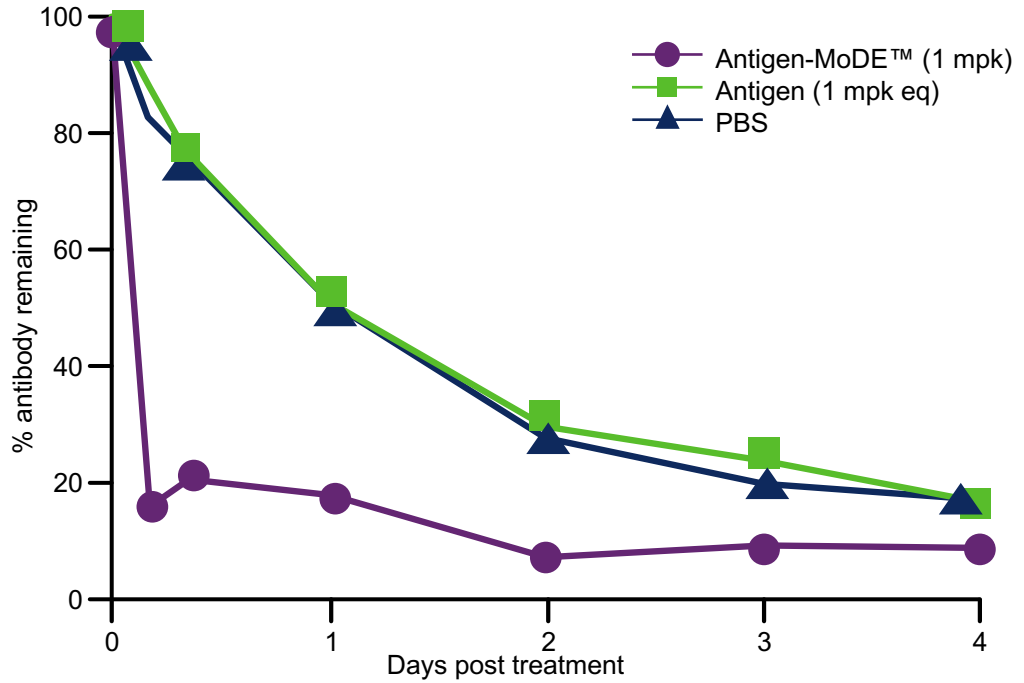
Leveraging Known AutoAb Epitope–MoDE™ Shows Rapid Reduction of Pathogenic AutoAb

Study Design



Greatly Reduced Half-life Compared to Controls	
Treatment	**Half-life (h)**
Antigen-MoDE™	**<2**
Antigen (Neg. Control)	27.5
PBS	29.7

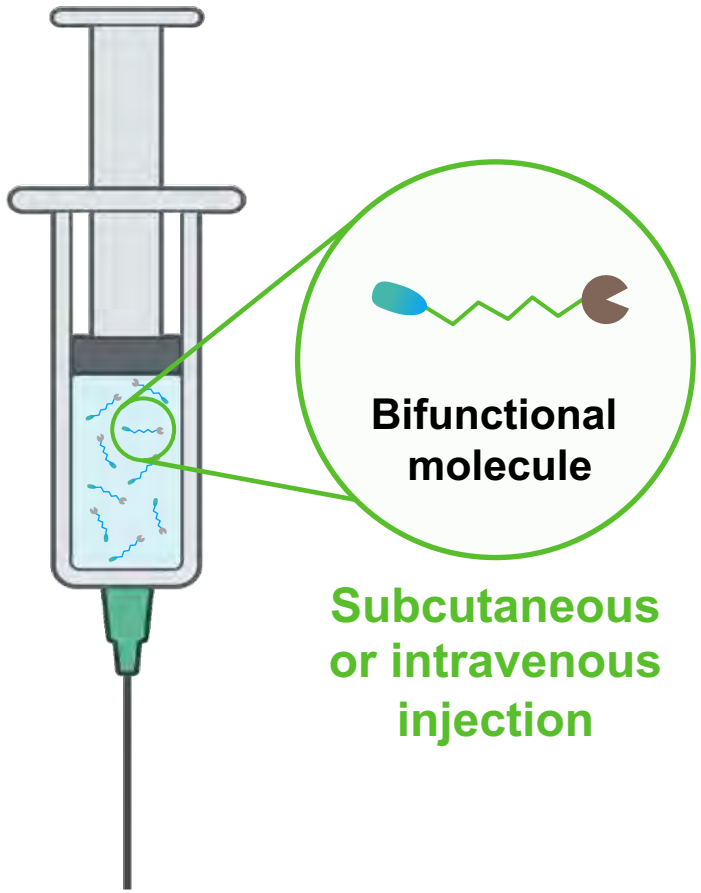
Nearly Complete AutoAb Degradation in 4 Hours



Rapid, potent depletion with antibody half-life reduced by at least 15-fold

AutoAb, autoantibody; **MoDE™**, molecular degrader of extracellular proteins; **PBS**, phosphate-buffered saline

Summary: Biohaven MoDE™ Extracellular Degraders Provide Optionality



- ✓ **Numerous extracellular** and circulating **targets** are involved in pathology and make excellent targets
- ✓ **IND 2H 2023 for lead program BHV-1300** which has “pipeline in a product” potential
  - BHV-1300 has optimized chemistry with differentiated mechanism of action compared to standard of care, as well as to other novel agents in development
- ✓ Additional programs in development exploring targeting specific **autoantibodies** and **Gd-IgA1**
- ✓ **Once a target is identified, approximately ~1 year to degrader candidate**
  - Extracellular degrader as fast as 1.5-3 years to IND versus 6-10 years for typical small molecule program

Select ligand for valid target, conjugate → **Dev, discovery tox combined, pharmacology in parallel**

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Gene Dubowchik, Ph.D.
SVP, Molecular Technologies

biohaven

Bruce Car, Ph.D.
Chief Scientific Officer

biohaven

Next-Generation ADC Platform

Biohaven's Next-Generation Site-Specific ADCs

CONJUGATION CHEMISTRY SUPERIOR TO INDUSTRY STANDARD
maleimide and lipophilic click chemistry

Attachment to two specific lysines provides stable and consistent **drug antibody ratio** (DAR)

- ✓ **ADAPTABLE** Complements and improves multiple existing ADC payload-linker technologies
- ✓ **STABLE** Improved ADC plasma stability with controlled DAR potentially improves therapeutic index
- ✓ **EFFECTIVE** Improved efficacy in mouse tumor model also suggests potential for increased therapeutic index
- ✓ **MULTIPURPOSE** Conjugates IgG1, 2 & 4 and manufacturable: Single step conjugation with predictable good yields, low aggregation
- ✓ **NOVEL IP** filed globally in key markets

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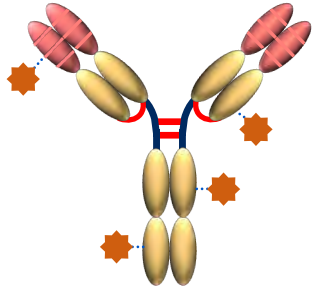
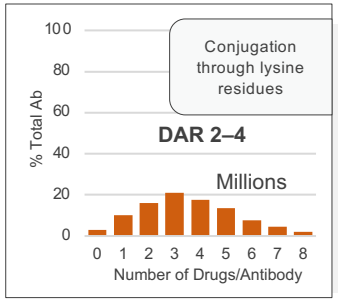
Challenges of Alternate ADC Protein Engineering and Chemistry

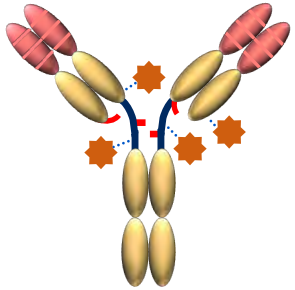
Kadcyla®

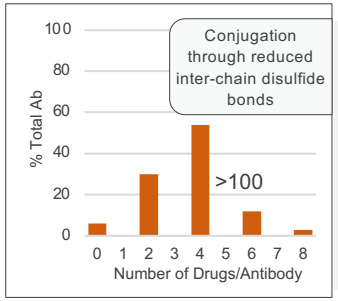




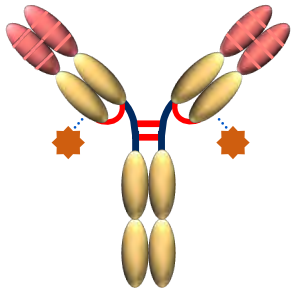
- High DAR species can cause CMC issues like aggregation, *in vivo* instability leading to toxicity
- Heterogeneity complicates CMC, may compromise efficacy

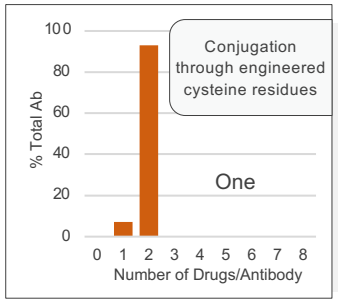
Adcetris®





- Drug linkage can reverse over time, “leaking” free payload





- Nearly all existing methods involve extensive antibody manipulation or engineering
- Potential impact on activity, clearance, immunogenicity, and COGs

DAR, drug antibody ratio

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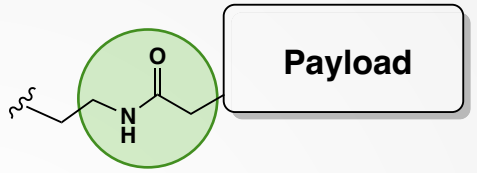
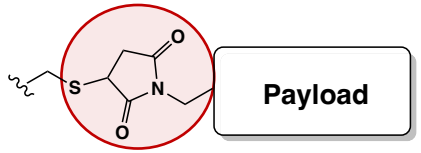
Potential “Best-in-class” Site-specific ADCs

Biohaven chemistry



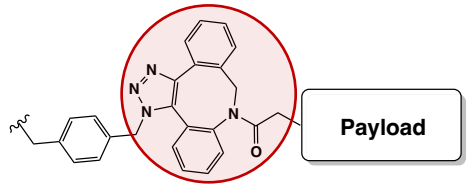
Stable, physicochemically benign amide linkage

Industry standard maleimide



Poorly stable linkage

Click chemistry to engineered antibody



Undesirably large, lipophilic linkage

IMPROVED LINKER STABILITY predicted to improve **therapeutic index**

- ✓ **Improved safety:** Reduced untargeted payload in systemic circulation driving toxicity
- ✓ **Improved efficacy:** Increased targeted payload reaches tumor, higher doses possible

USES NATIVE ANTIBODY

Likely improved CMC vs. current site-specific technologies

ADCs prepared based on Adcetris®

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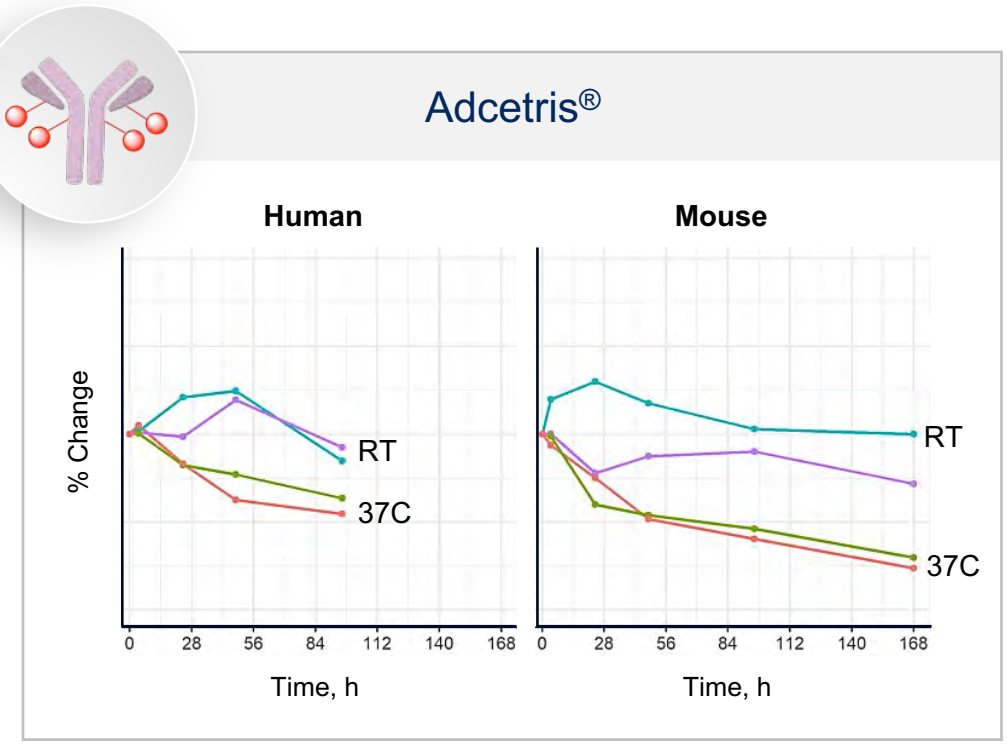
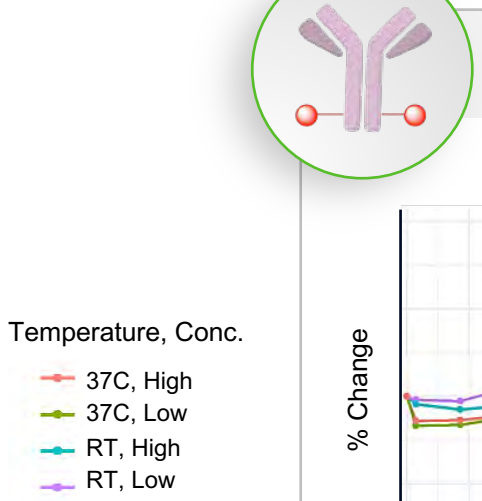
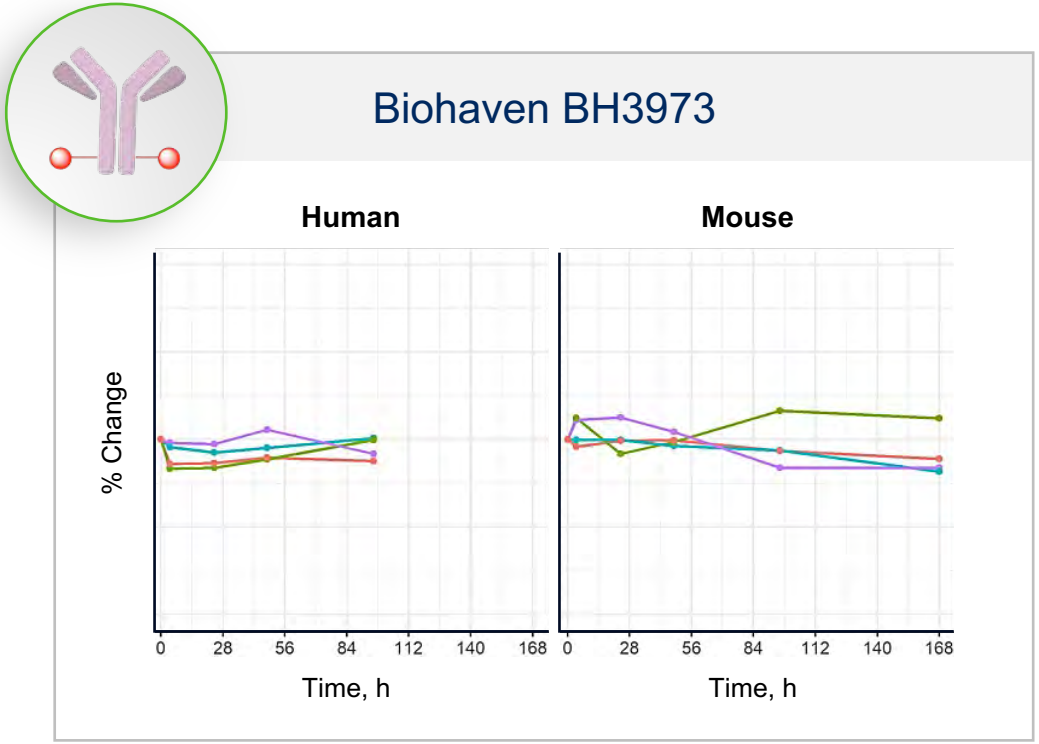
BH3973: Improved Plasma Stability Over Adcetris®

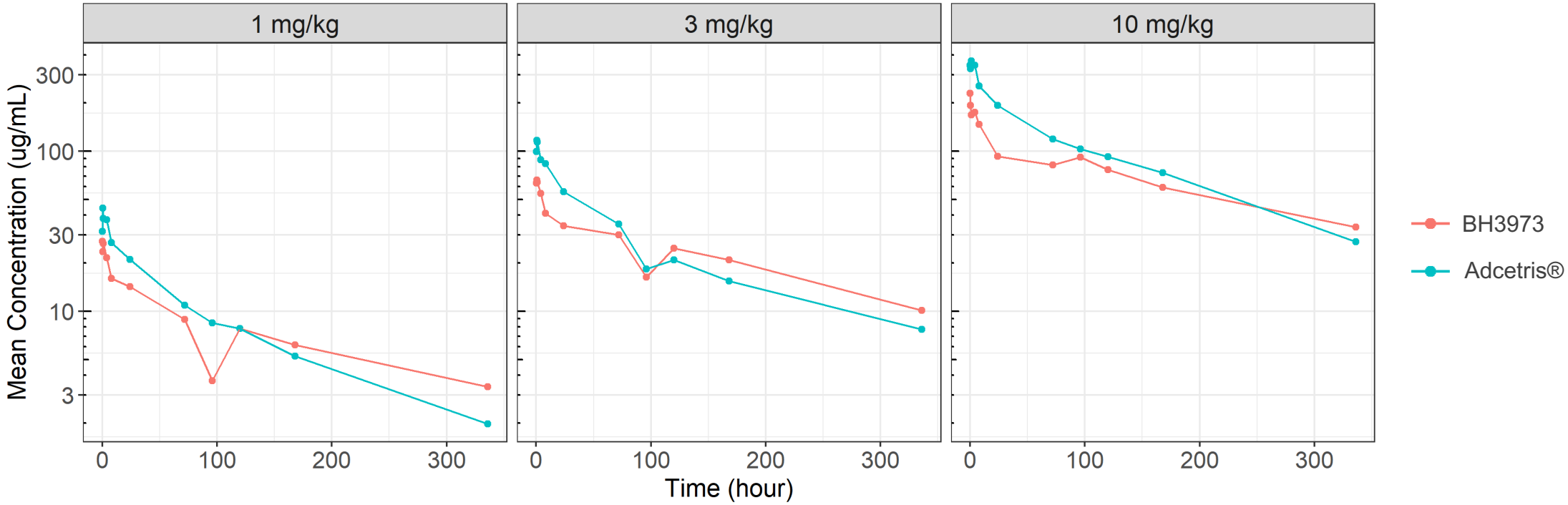






- ADC toxicity/tolerability directly relates to free payload
- Enhanced stability reduces free payload, and potentially allows for higher drug concentration at targeted tumor site for same tolerability

Adcetris® and BH3973 Demonstrate Comparable PK



- BH3973 half-life 7-8 days across all doses
- Adcetris® half-life 5-6 days across all doses

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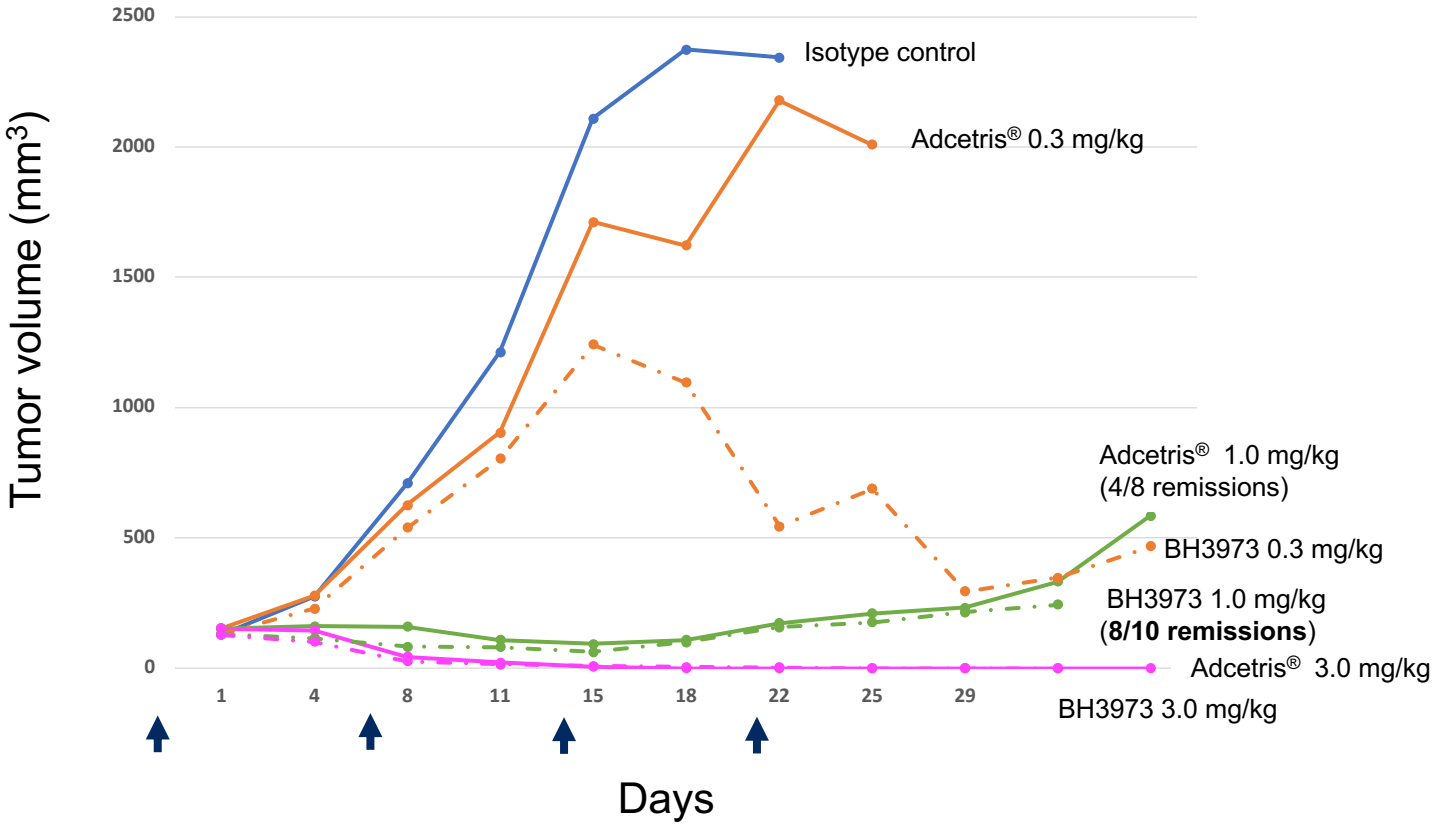
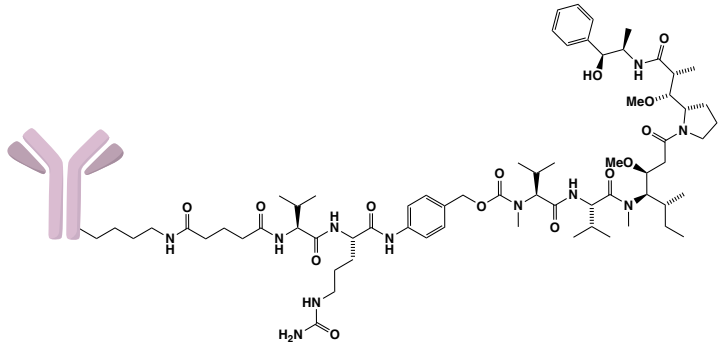
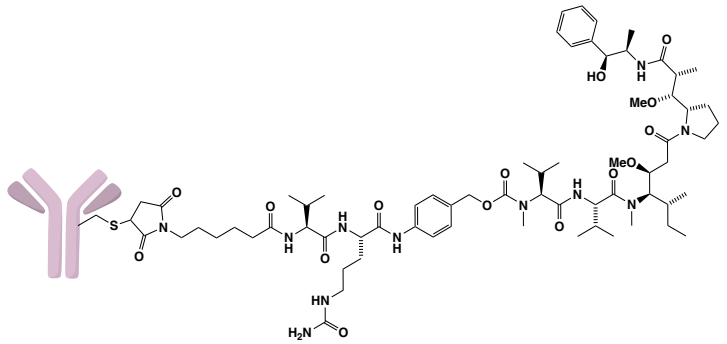
BH3973: Demonstrates Potential for Superior Efficacy to Adcetris®

SCID Mouse Karpas-299 Anaplastic Large Cell Lymphoma Model





BH3973 (DAR 2)



Adcetris® (DAR 3.8)

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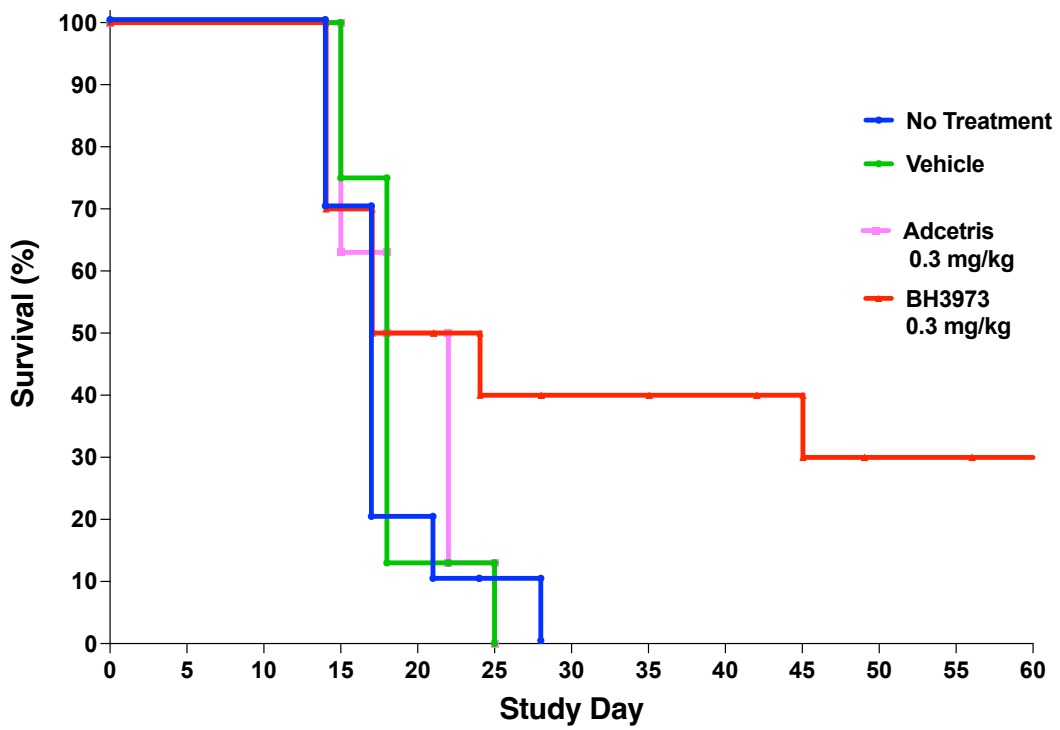
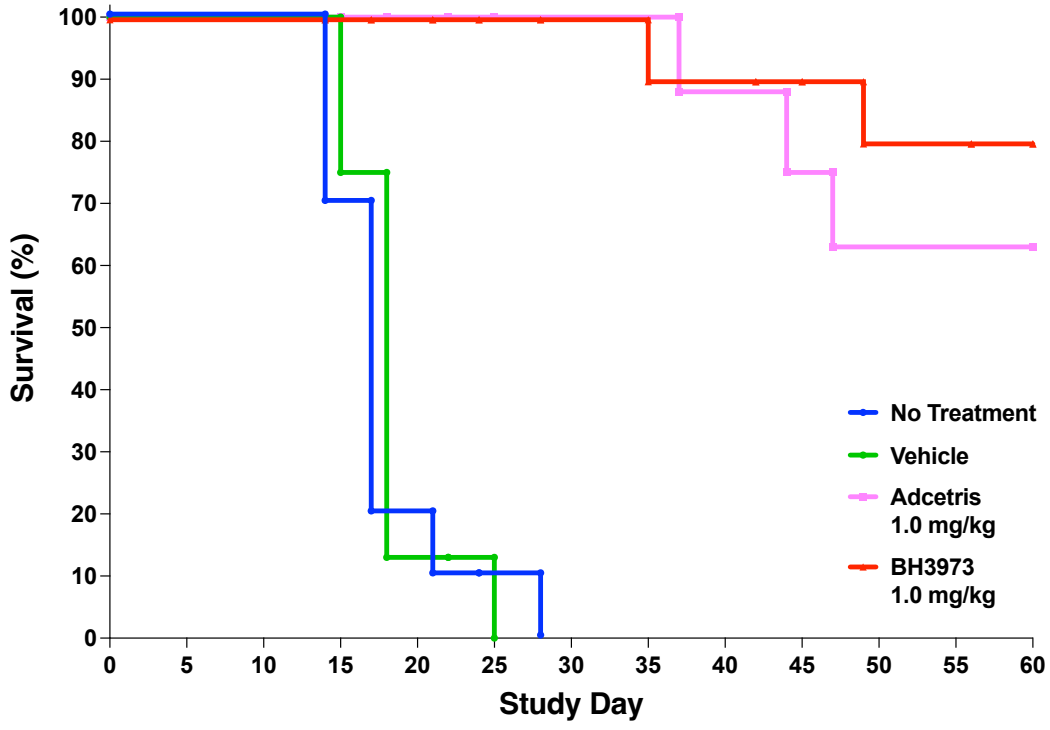
BH3973: Improves Survival in Preclinical Model Compared to Adcetris® With Half the Payload

Effect of Treatment on Survival
(Dose @ 0.3 mg/kg + Controls)



Effect of Treatment on Survival
(Dose @ 1.0 mg/kg + Controls)



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BH3973: Summary

BIOHAVEN'S ADC TECHNOLOGY IS AN IDEAL ADD-ON TO IN-HOUSE DEVELOPED UNIQUE ANTIBODIES, BISPECIFICS

Even competitor molecules

- ✓ Existing, highly effective ADC formats such as Adcetris® and optimized warheads may potentially be enhanced with improved safety, efficacy, manufacturability and patent life
- ✓ Differentiated *in vivo* efficacy and safety results of BH3973 compared to Adcetris®
- ✓ Broad patent coverage

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PANEL DISCUSSION

Bispecific Platform

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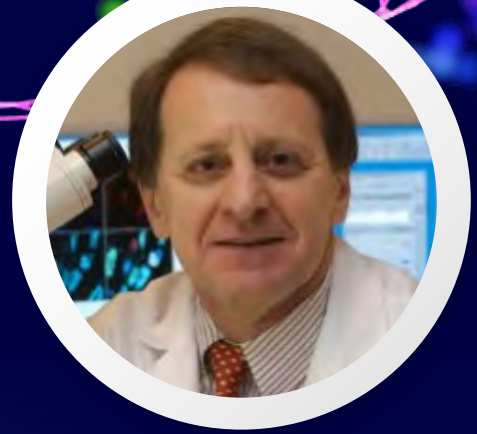
John Krystal, M.D.

McNeil Professor and Chair
Department of Psychiatry

Yale
SCHOOL OF MEDICINE



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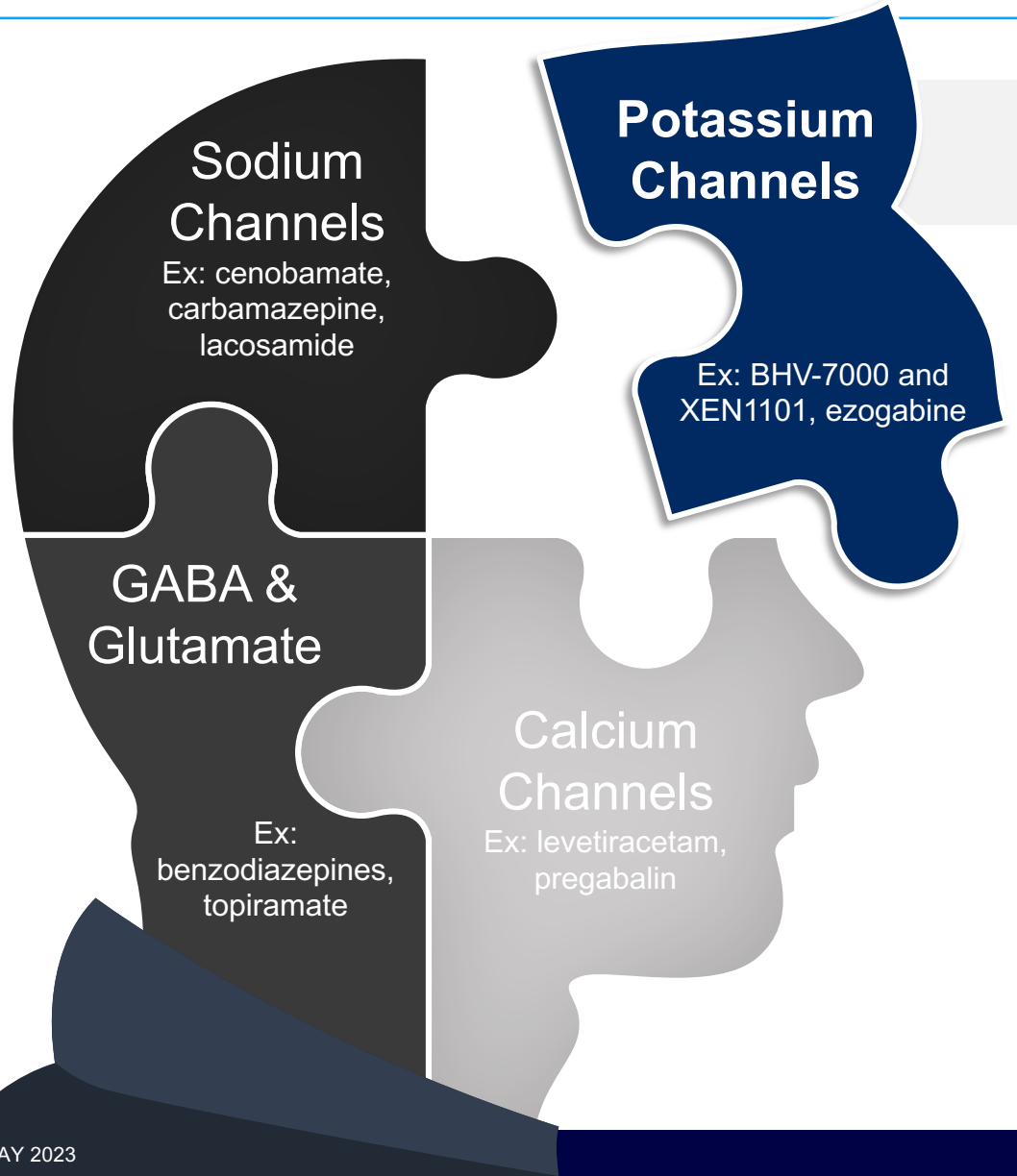
Kv7 Platform

Kv7 Potassium Channels Are a Critical Regulator of Cell Excitability



A key missing piece in epilepsy treatment

- Clinically validated mechanism of action for treating focal epilepsy
- Strong rationale for development in adjacent indications
- BHV-7000: First Kv7.2/7.3 modulator specifically designed to exclude GABA activation

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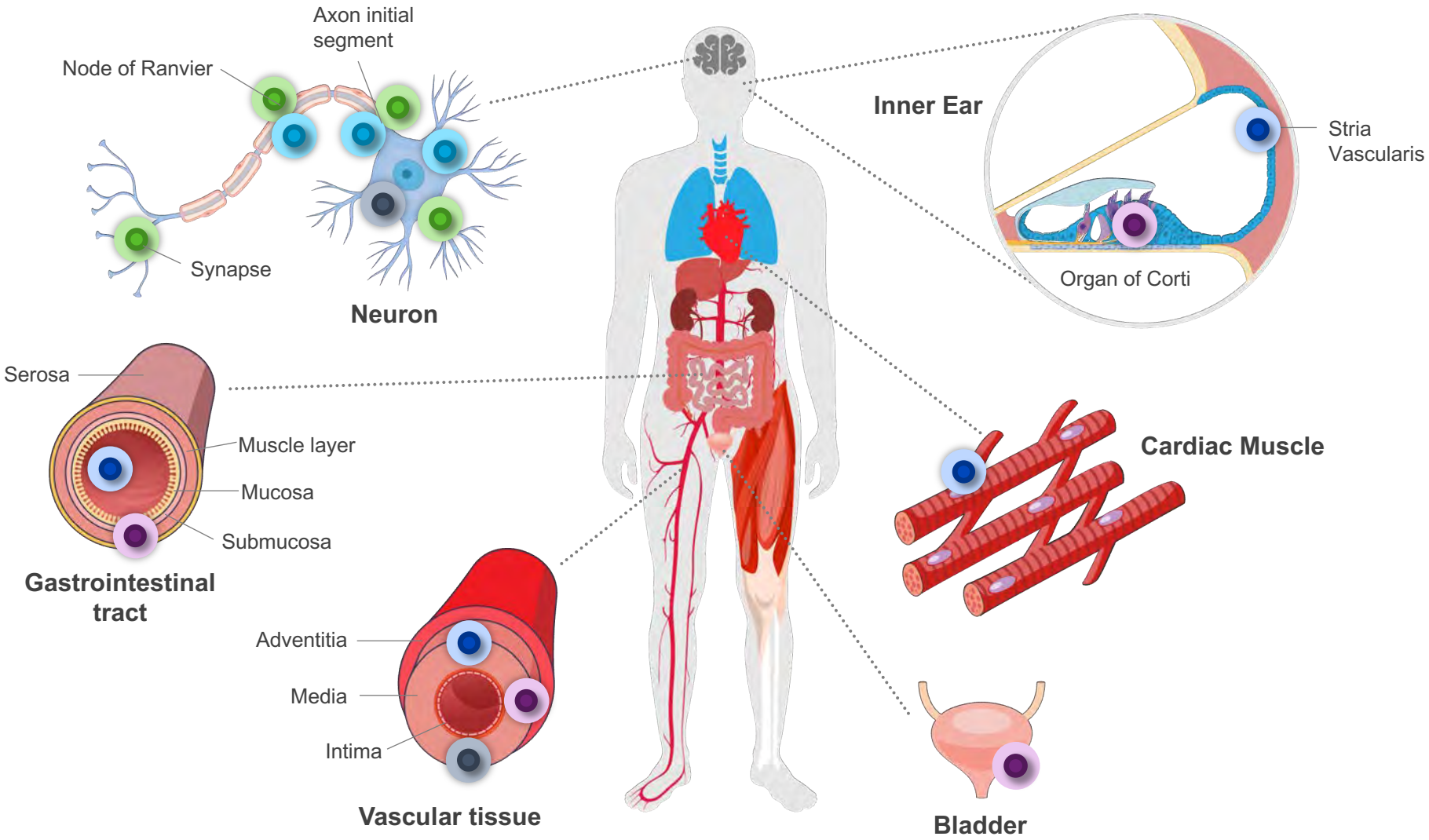
Kv7 Platform Is Broadly Applicable to Hyperexcitability Disorders Beyond Epilepsy



5 FAMILY SUBTYPES

Primary localizations:

- Kv7.1: cardiac
- Kv7.2: CNS **BHV-7000 activator**
- Kv7.3: CNS **BHV-7000 activator**
- Kv7.4: smooth muscle and inner ear
- Kv7.5: vascular tissue, neurons, skeletal muscle

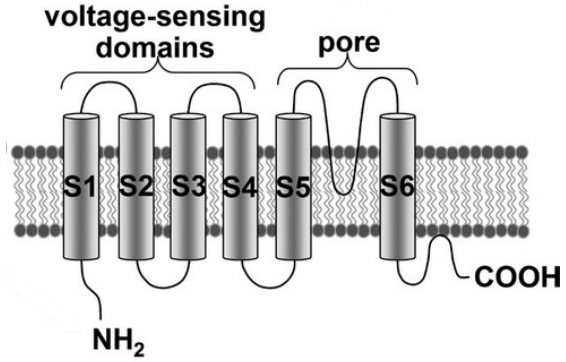
Source: Adapted from Soldovieri et al. *Physiology*. 2011;26(5):365-376.

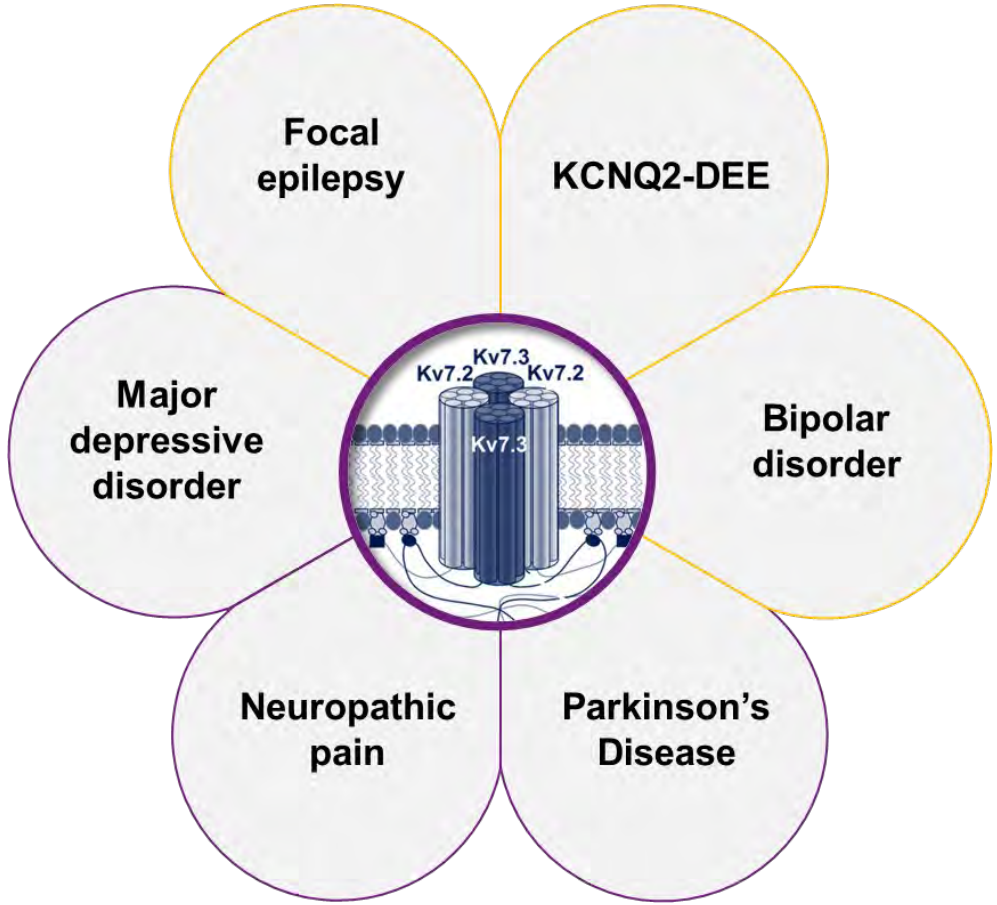
Kv7.2/7.3 Channels: The Molecular Substrates Underlying the M-current

american physiological society® PHYSIOLOGY

Driving With No Brakes: Molecular Pathophysiology of Kv7 Potassium Channels

PHYSIOLOGY 26: 365–376, 2011; doi:10.1152/physiol.00009.2011





- **1980s** Ezogabine synthesized and showed activity in seizure models
- **1990s** KCNQ 2, 3, and 5 genes first cloned by Steven Dworetzky
- **1995** Ezogabine shown to activate KCNQ2 and KCNQ3 currents and demonstrated efficacy in seizure models broadly
- **2013** Knopp Biosciences initiates Kv7 discovery platform
- **2022** Biohaven acquires Channel Biosciences (Knopp), Kv7 activator platform, and BHV-7000

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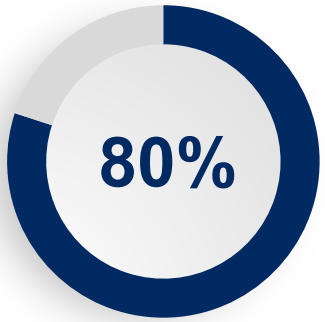
Significant Unmet Needs Remain for the 3.5 Million Patients Living with Epilepsy in the US

1/3 people are treatment refractory despite the availability of anti-seizure medications (ASMs), surgery, and diet modifications



After starting an ASM, **80% of patients will experience burdensome adverse events**, which can include:

- Somnolence
- Dizziness
- Cognitive dysfunction
- Mood disturbances

Devinsky et al. *Nat Rev Dis Primers.* 2018;4:18024; Kanner, Bicchi. *JAMA.* 2022;327(13):1269-1281.

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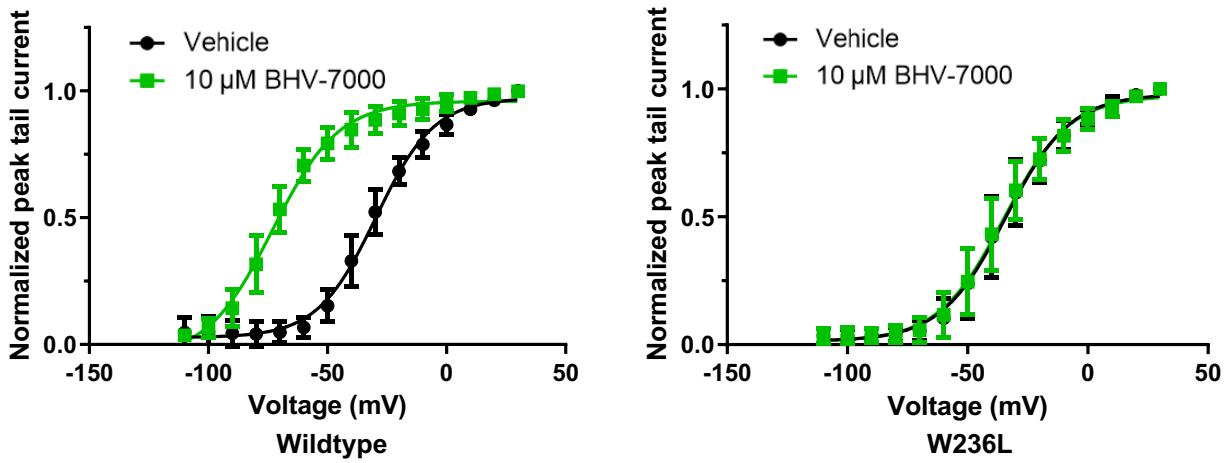
BHV-7000: Interacts at W236 Kv7 Site and Has Differential *In Vitro* and *In Vivo* Effects from Ezogabine and XEN1101

BHV-7000 Activation of KCNQ2 (Kv7.2) Requires W236



BHV-7000 More Potent *In Vivo* than Ezogabine and XEN1101

Compound	Brain *In vivo* EC_{50} (μM)	*In vitro* EC_{50} (μM)
BHV-7000	0.13	0.60
Ezogabine*	3.3	0.92
XEN1101*	0.42	0.042

*Presented virtually at AES2020, the American Epilepsy Society Annual Meeting, December 4-8, 2020.

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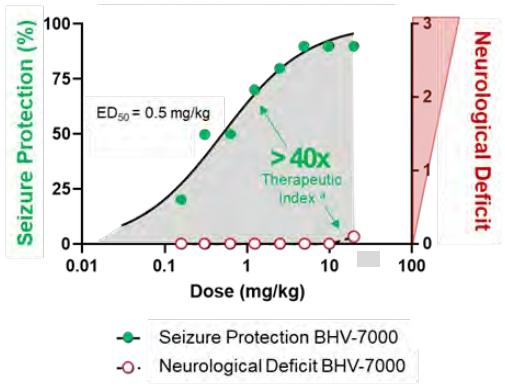
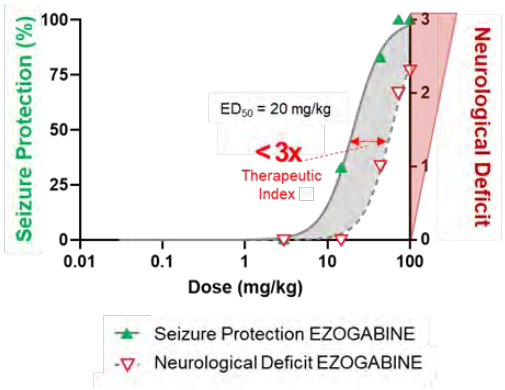
BHV-7000: First Kv7.2/7.3 Activator in Clinical Development Designed Specifically to Exclude $GABA_A$ Receptor Activation

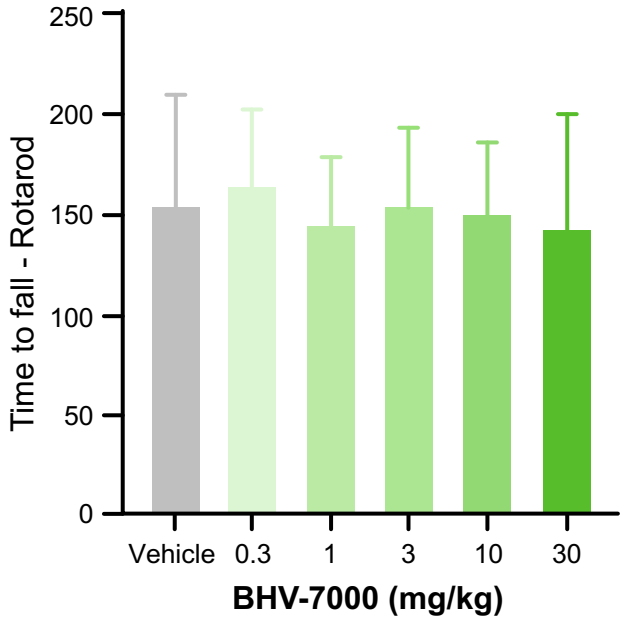
BHV-7000



Ezogabine

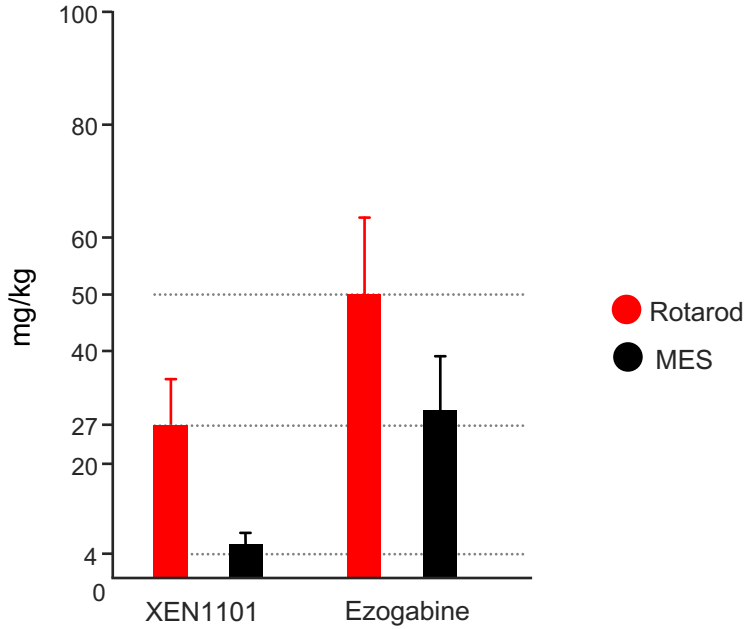


Rat Rotarod



No impact on motor function observed with BHV-7000 across effective dose range

*Mouse ED_{50} or TD_{50} (Mean 95% CI)



* Adapted from https://www.xenon-pharma.com/wp-content/uploads/2018/05/XEN1101_EILAT_15May2018_FINAL_YPG_web.pdf

Presented at 2023 American Society for Experimental Neurotherapeutics (ASENT) Annual Meeting March 13-15, 2023.
EC_{50}, half maximal effective concentration; **EZO**, ezogabine

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BHV-7000: First-in-Human SAD/MAD Phase 1 Study to Assess Safety, Tolerability and Pharmacokinetics

Objectives

PRIMARY

Evaluate safety and tolerability of single and multiple dose oral administration of BHV-7000 in healthy participants

SECONDARY

Evaluate the pharmacokinetics of single and multiple doses of BHV-7000

Evaluate the effect of a high-calorie/high-fat meal on the pharmacokinetics of BHV-7000

Population:

- Healthy adult males and females aged 18-55 years

Study Design:

- Single center, randomized, double-blind, placebo controlled, sequential SAD/MAD study
- Participants were randomized 3:1 (BHV-7000 to placebo) in each dose cohort
- Safety Review Committee assessment after each dose cohort prior to dose escalation

MAD, multiple ascending dose; **PK**, pharmacokinetics**; SAD**, single ascending dose

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BHV-7000: Well Tolerated Across Phase 1 SAD/MAD Cohorts

SAFETY AND TOLERABILITY

No SAEs

No severe TEAEs, 1 moderate TEAE, remaining TEAEs mild by severity

DOSING

SAD: single doses up to 100 mg

MAD: multiple doses up to 40 mg daily x15 days

Exposures exceeded EC_{50} in MES preclinical seizure model

MedDRA System Organ Class	Placebo (N=15) n (%)	BHV-7000 (N=46) n (%)
Nervous system disorders	1 (6.7)	7 (15.2)
Gastrointestinal disorders	1 (6.7)	6 (13.0)
Musculoskeletal disorders	0	5 (10.9)
Infections	0	2 (4.3)
Investigations	1 (6.7)	2 (4.3)
Respiratory disorders	0	2 (4.3)
Skin disorders	0	2 (4.3)
Eye disorders	0	1 (2.2)
General disorders	0	1 (2.2)
Procedural complications	1 (6.7)	1 (2.2)
Psychiatric disorders	0	1 (2.2)
Renal disorders	1 (6.7)	1 (2.2)

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BHV-7000: Phase 1 SAD/MAD CNS TEAEs by Dose and Cohort

Single Ascending Dose

CNS AEs[a]	Placebo N=10	4 mg N=6	10 mg N=6	25 mg (Fasted) N=6	25 mg (Fed) N=6	50 mg N=6	100 mg N=5	BHV-7000 Overall N=29
Headache	0	0	1 (16.7)	1 (16.7)	0	1 (16.7)	0	3 (10.3)
Dizziness	0	0	1 (16.7)	0	0	0	0	1 (3.4)
Myoclonus	0	0	0	1 (16.7)	0	0	0	1 (3.4)

[a]MedDRA® Preferred Term within the System Organ Class of "Nervous System Disorders"

Multiple Ascending Dose

CNS AEs[a]	Placebo N=5	10 mg N=5	25 mg N=6	40 mg N=6	BHV-7000 Overall N=17
Headache	1 (20.0)	0	0	3 (50.0)	3 (17.6)

[a]MedDRA® Preferred Term within the System Organ Class of "Nervous System Disorders"

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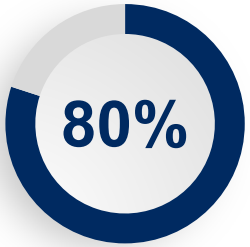
BHV-7000: Not Associated with CNS AEs Typical of Other ASMs

Challenges with Existing ASMs



80% of patients will experience an AE after starting an ASM[1]

$GABA_A$ pathway activated by other ASMs is associated with AEs such as somnolence and dizziness[2]

Several ASMs cause behavioral (irritability, anger, aggression) or psychiatric (depressive mood, anxiety, psychosis) AEs[3,4]

Pooled CNS AEs[a,5]	BHV-7000 MAD Pooled N=17	Xen1101 MAD Pooled N=18
Somnolence	0%	39%
Headache	18%	39%
Balance disorder	0%	17%
Dizziness	0%	17%
Memory impairment	0%	28%
Sensory disturbance	0%	11%
Speech disorder	0%	33%

[a]MedDRA® Preferred Term within the System Organ Class of "Nervous System Disorders"
Data presented is not the result of any head-to-head clinical trials and does not mean or suggest that BHV-7000 is clinically more safe and effective.[5]

Devinsky et al. *Nat Rev Dis Primers.* 2018;4:18024. 2. Abou-Khalil. *Continuum (Minneap Minn).* 2022;28(2):500-535. 3. Steinhoff et al. *Epilepsy Behav.* 2021;123:108270. 4. Chen et al. *Epilepsy Behav.* 2017;76:24-31. 5. 73rd Annual American Epilepsy Society Meeting 2019, Abstract #3.31. Poster presented November 25, 2019.

AE, adverse event; **ASM**, anti-seizure medication; **CNS**, central nervous system; **GABA**, gamma-aminobutyric acid; **MAD**, multiple ascending dose; **MedDRA**, Medical Dictionary for Regulatory Activities

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BHV-7000: Summary and Clinical Program Status

- Potent, selective activator of Kv7.2/Kv7.3 potassium channels, a clinically validated target to regulate the hyperexcitable state in epilepsy
- Structurally and pharmacologically distinct from other potassium channel activators
- Minimal $GABA_A$ receptor activation, potentially providing better tolerability
- Potent in the MES epilepsy model without adverse effects on neurobehavior
- Well-tolerated in Phase 1 SAD/MAD study without CNS adverse effects typical of anti-seizure medications

There is a missing piece in epilepsy treatment for better-tolerated, efficacious anti-seizure medications

Phase 1 SAD/MAD

Phase 1 EEG

Phase 2/3 Focal Epilepsy

CNS, central nervous system; **EEG**, electroencephalography; **GABA**, gamma-aminobutyric acid; **MAD**, multiple ascending dose; **MES**, maximal electroshock seizure; **SAD**, single ascending dose

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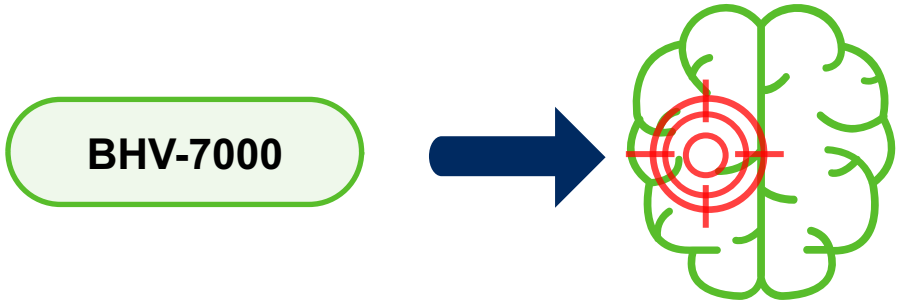
BHV-7000: Phase 1 Healthy Volunteer EEG Study to Demonstrate Pharmacodynamic Activity



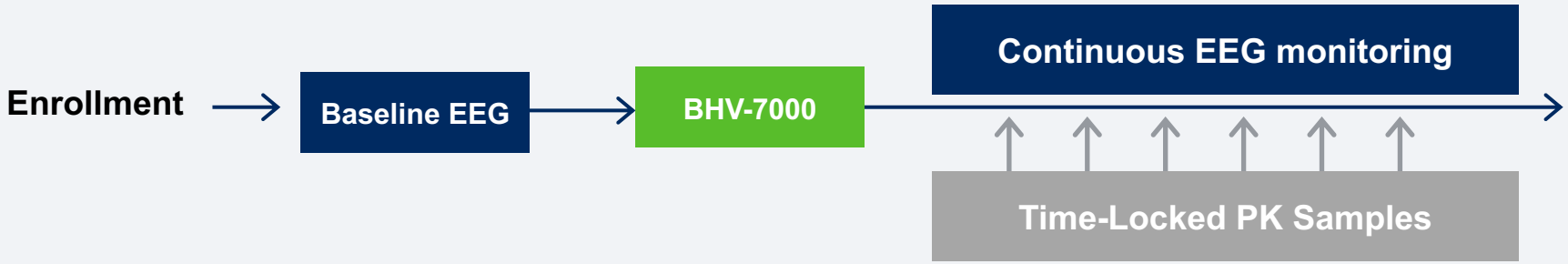
Study Objective:

- Demonstrate BHV-7000 target engagement in the cerebral cortex and refine dose selection for Phase 3

Study Measures:

- Continuous EEG monitoring & PK sampling
- Evaluation of changes in EEG spectral power post dose

Study Design



EEG, electroencephalography; **PK**, pharmacokinetics

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BHV-7000: Phase 3 Trials in Focal Epilepsy

Two multicenter, international, placebo-controlled, double-blind studies to evaluate the efficacy of BHV-7000 in adolescents and adults with refractory focal epilepsy

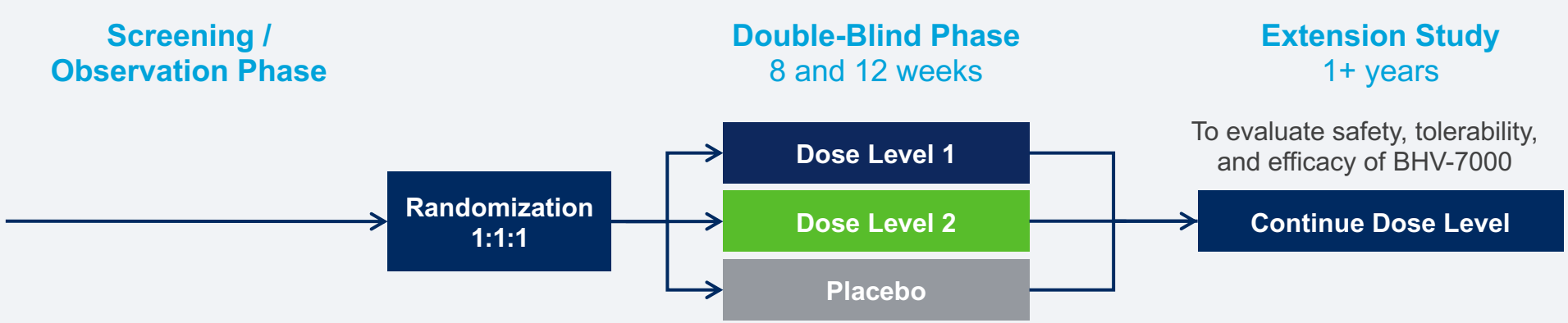
Key Inclusion Criteria:

- 12-75 years old
- Refractory focal epilepsy

Primary Endpoint: median percent change (US), ≥50% responder rate (EU)

Secondary Endpoint: QOLIE-31, Seizure Freedom

Study Design



QOLIE-31, Quality of Life in Epilepsy Inventory; Planned study design for Phase 3 trials

Kv7 PLATFORM
Summary

Proprietary Chemical Library of Novel Kv7 Activators

In-house synthesis with differentiated pharmacological profiles with potential for multiple indications

Kv7.2/7.3 Activation

Clinically validated mechanism of action in epilepsy

BHV-7000: Potential Best-in-Class with Differentiation

Preclinical data suggests wide therapeutic index in the clinic by dialing out GABA risk (*somnolence, sedation, dizziness*)

BHV-7000 Series

COM Patent Protection covered until 2039

Status Update

BHV-7000 Phase 1 SAD/MAD study completed

BHV-7000 Phase 1 EEG study initiation 1H 2023

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John Krystal, M.D.

McNeil Professor and Chair
Department of Psychiatry

Yale SCHOOL OF MEDICINE

BHV-7000 in Bipolar Disorder

Bipolar Disorder Affects 11 Million Adults in the US and Requires Lifelong Treatment

While bipolar disorder is characterized by mania, most of the time spent sick is with **depression**, yet there are **few effective options** for bipolar depression and maintenance treatment[1-4]

Approximately 50% of patients with bipolar disorder are **medication nonadherent,** with discontinuations most commonly due to **poor tolerability**[4,5]

In the last 20 years, no new mood stabilizer has been approved for the treatment of bipolar disorder, with the only new agents being antipsychotics[6]

- Lamotrigine is the last novel mood stabilizer approved in bipolar disorder; utility is primarily in maintenance with limited efficacy in acute depressive episodes
- Serious AEs observed with use of current mood stabilizers include thyroid and renal function issues, liver toxicity, thrombocytopenia, rash, and Stevens-Johnson syndrome[3,9]
- Atypical antipsychotics carry risks of metabolic dysfunction, weight gain, and cognitive slowing
- Adherence issues related to AEs lead to ineffective treatment and risk of relapse[5,7,8]

1. Tondo et al *Curr Neuropharmacol*. 2017;15(3):353-358. 2. Miller et al. *J Affect Disord*. 2014;169(Suppl 1):S3-11. 3. Carvalho et al. *N Engl J Med*. 2020;383(1):58-66. 4. McIntyre, Calabrese. *Curr Med Res Opin*. 2019;35(11):1993-2005. 5. Jawad et al. *Ther Adv Psychopharmacol*. 2018;8(12):349-363. 6. Rhee et al. *Am J Psychiatry*. 2020;177(8):706-715. 7. Fung et al. *J Affect Disord*. 2019;257:17-22. 8. Marzani, Neff. *Am Fam Physician*. 2021;103(4):227-239. 9. Bobo. *Mayo Clin Proc*. 2017;92(10):1532-1551.

AE, adverse event; **BD**, bipolar disorder

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Compelling Evidence for Kv7 Activation in Bipolar Disorder Treatment

Overlapping molecular, cellular mechanism in bipolar disorder

- ✓ ANK-3 is a highly implicated gene in bipolar disorder; ANK-3 codes for a protein that anchors Kv7 channels to the cell membrane[1]
- ✓ Kv7.2/7.3 channels are among the most dysregulated proteins in bipolar brain tissue[2]
- ✓ Bipolar patients exhibit several relevant epigenetic changes linked to Kv7[3]

Preclinical evidence for manic and depressive poles

- ✓ Mice who upregulate Kv7 are resilient to stress-induced depressive effects[4]
- ✓ Kv7 activators reverse and prevent pathologic hyperactivity in depression and mania models[5,6]
- ✓ Kv7 mutations cause transdiagnostic mood disturbances including hyperactivity, insomnia, anxiety, and cognitive dysfunction[1]

1. Judy et al. *Front Genet.* 2013;4:87. 2. Kristensen et al. *J Neurochem.* 2012;3:373-382. 3. Kaminsky et al. *Bipolar Disord*. 2015;2:150-159. 4. Friedman et al. *Nat Commun.* 2016;24(7):11671. 5. Dencker et al. *Behav Brain Res.* 2010;1:78-83. 6. Redrobe et al. *Behav Brain Res.* 2009;198(2):481-485.

ANK-3, ankyrin 3

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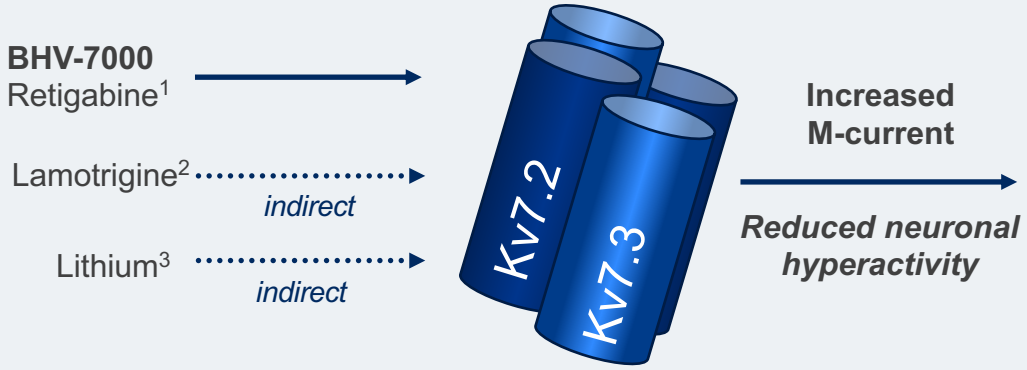
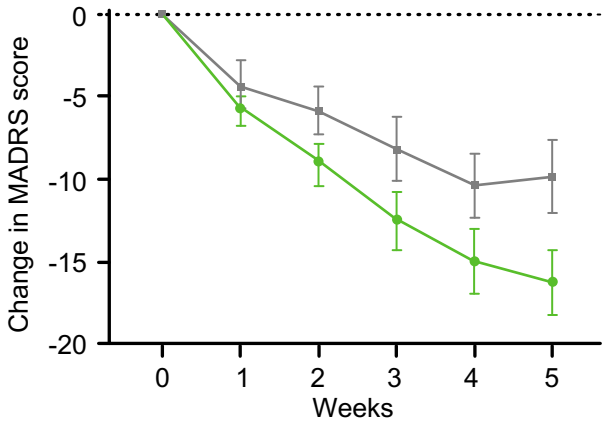
BHV-7000: Demonstrates Potential for Clinical Translation of Kv7 Activation in Bipolar Disorder

BHV-7000 shares mechanistic overlap with cornerstone bipolar treatments

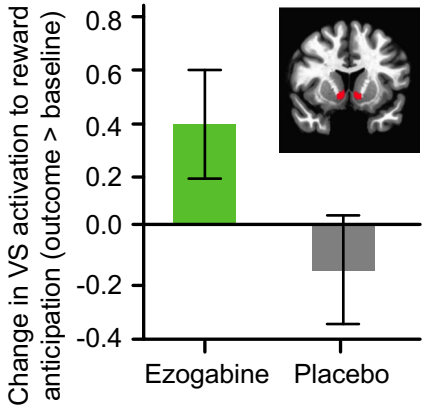


Robust Preliminary Acute Efficacy in MDD Likely To Translate to Bipolar Disorder

Retigabine vs placebo; MDD measured via MADRS and fMRI[4,5]



~7 decrease vs placebo with retigabine in depression improvement



fMRI study: Retigabine effects mediated by the limbic system

Medications such as antipsychotics and lithium have established efficacy in unipolar and bipolar depression

1. Friedman et al. *Nat Commun*. 2016; 24;7:11671. 2. Friedman et al. *Science*. 2014;344(6181):313-319. 3. Kristensen et al. *J Neurochem*. 2012;3:373-382. 4. Amann et al. *J Clin Psychopharmacol*. 2006;26(5):534-536. 5. Costi et al. *Am J Psychiatry*. 2021;178(5):437-446.

fMRI, functional magnetic resonance imaging; **GSK3B**, Glycogen Synthase Kinase 3 Beta; **MADRS**, Montgomery-Åsberg Depression Rating Scale; **MDD**, major depressive disorder

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BHV-7000: Potential to Overcome Challenges With Existing Therapies

Potential for best-in-category tolerability and safety

- Low burden to patients and providers, enabling safer, easier long-term treatment
- No expected long-term metabolic side effects, no “switching” risk, no titration, and no drug monitoring

	Lithium	Valproate	SSRI	Antipsychotics	Lamotrigine
Metabolic AEs	○○○	○○○	○○○	●●○	○○○
Hepatic AEs	○○○	●●○	○○○	○○○	○○○
Renal AEs	●●●	○○○	○○○	○○○	○○○
Rash / SJS	○○○	○○○	○○○	○○○	●●○
Sexual SE	○○○	○○○	●●○	○○○	○○○
Sedation / Cognitive AE	●●○	●○○	○○○	●●○	○○○
Drug monitoring	●●○	●●○	○○○	○○○	○○○
Switching risk	○○○	○○○	●●○	●○○	○○○
Titration	●○○	●○○	○○○	○○○	●●●

●○○ Patient Burden

SJS, Stevens-Johnson Syndrome

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BHV-7000: Potentially Addresses Key Unmet Needs in Bipolar Disorder by Reducing Stress-Related Hyperactivity While Enhancing Resilience

Current therapies for bipolar depression show minimal efficacy and widely prescribed antidepressants carry "switching" risk

✓ The novel mechanism of BHV-7000 has **potential for robust antidepressant effects** without "switching" risk

Patients change or discontinue medication after ~2 months; >50% of patients discontinue at 6 months due to intolerance[1]

✓ BHV-7000 **offers favorable safety and tolerability** over current mood stabilizers and antipsychotics

Current 1st line mood stabilizers require titration or frequent laboratory monitoring, burdening both prescribers and patients[3]

✓ BHV-7000: **no titration or safety laboratory monitoring** anticipated, an advantage over current mood stabilizers

1. Jawad et al. *Ther Adv Psychopharmacol.* 2018;8(12):349-363. 2. Vieta et al. *Nat Rev Dis Primers.* 2018;4:18008. 3. Yatham et al. *Bipolar Disord.* 2018;20(2):97-170.

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Bridget Flaherty Professor
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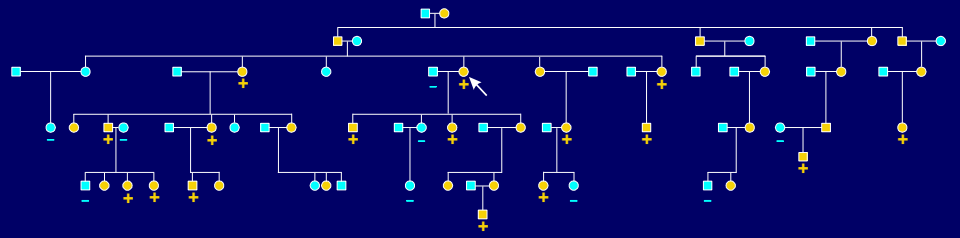
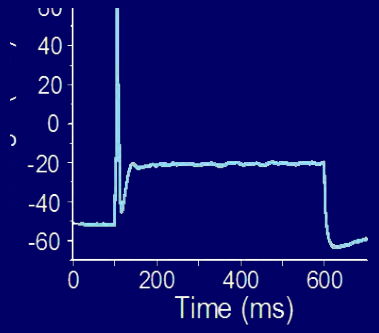
Kv7.2/3 and Modulation of Pain

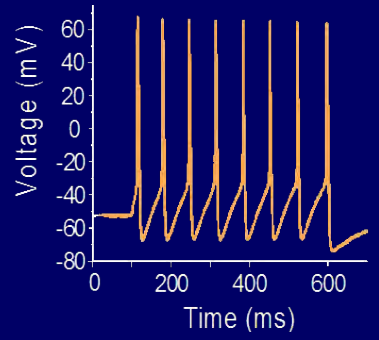


Our worldwide search identifies IEM (Nav1.7 GOF) as a human genetic model of Neuropathic Pain

- Rare genetic disorders are "experiments of nature" that can:
- Define molecular mechanisms in humans
- Identify therapeutic targets that are relevant to common disorders

EXAMPLE: the Statin medications



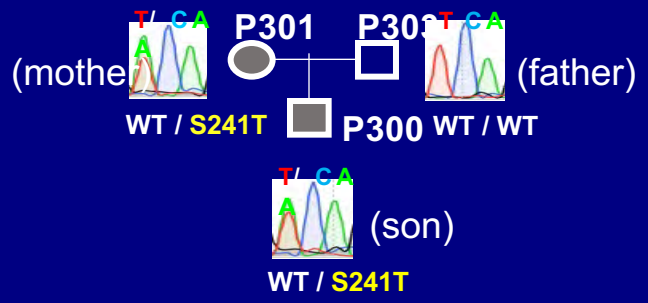


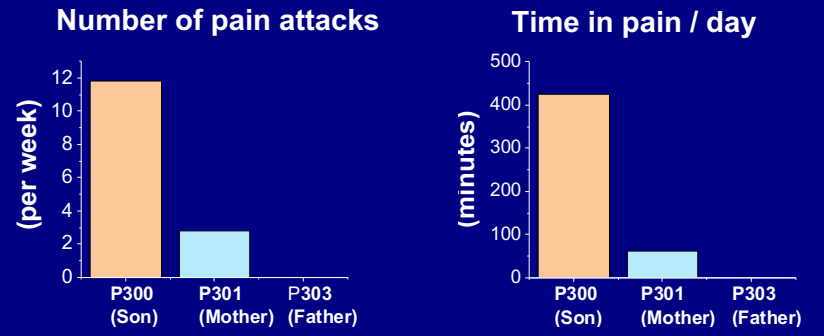
Dib-Hajj et al, 2005; Waxman, 2018

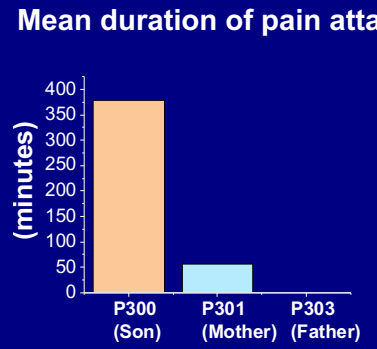
Can we pinpoint pain resilience genes?

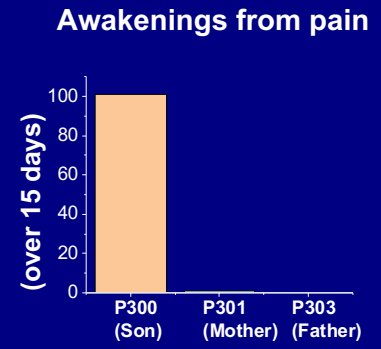
Mother / son both with IEM due to same Nav1.7 GOF mutation

What is protecting the mother from pain?









Malgorzata Mis

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Talia Adi

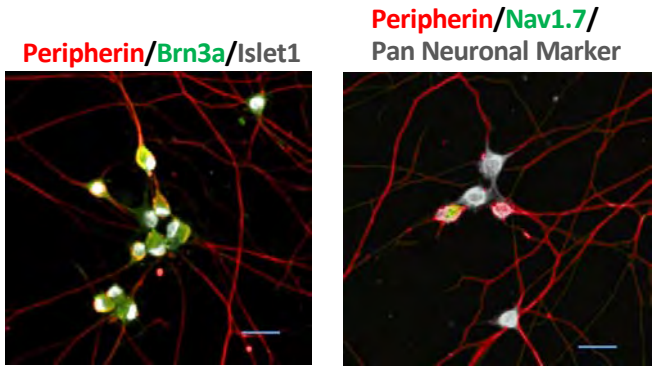
Rolando Garcia-Milian

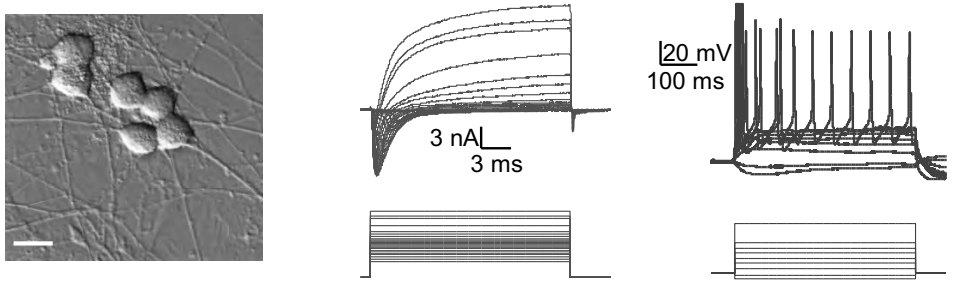
Betsy Schulman

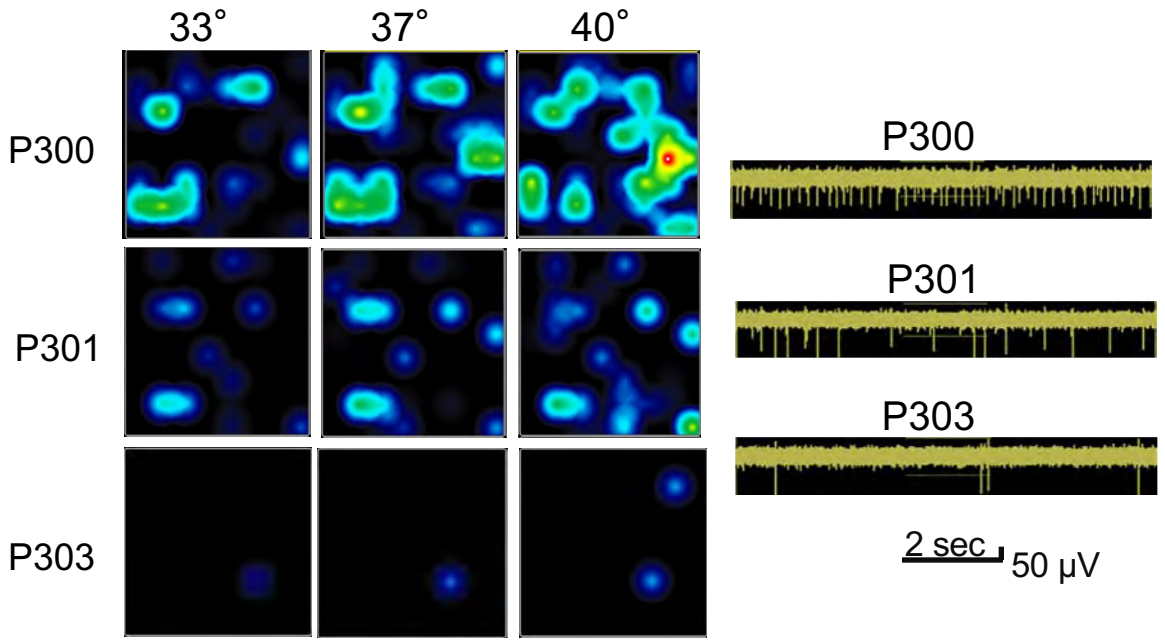
Sulayman Dib-Hajj

Stephen Waxman

Pain-in-a-Dish: Differences in excitability between iPSC-SNs from different subjects with the same S241T mutation parallel different pain profiles

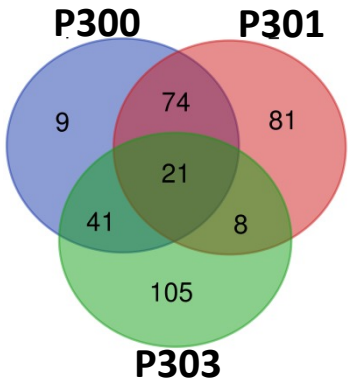




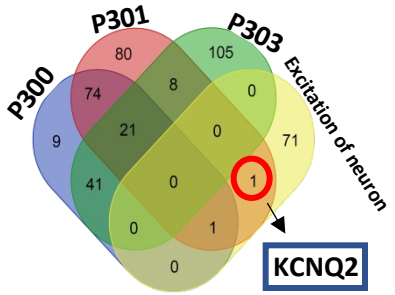


Mis et al, 2019

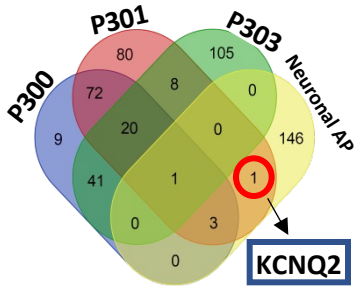
Whole exome sequencing reveals a variant in KCNQ2 gene as a potential modulator of neuronal excitability in iPSC-SNs from Pain-Resilient subject

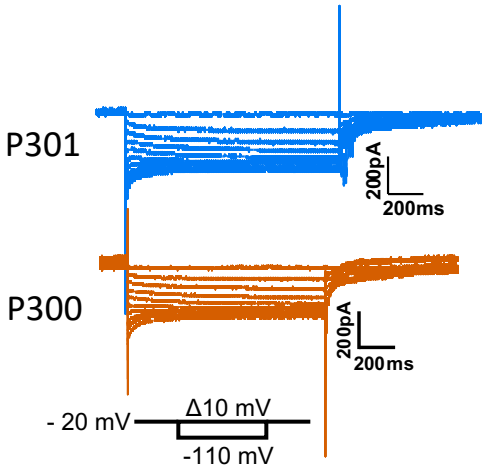


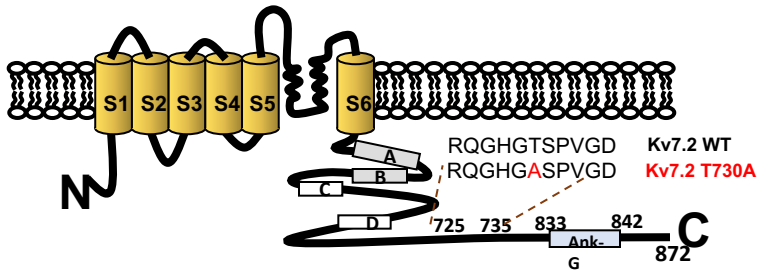
‘Excitation of Neuron’

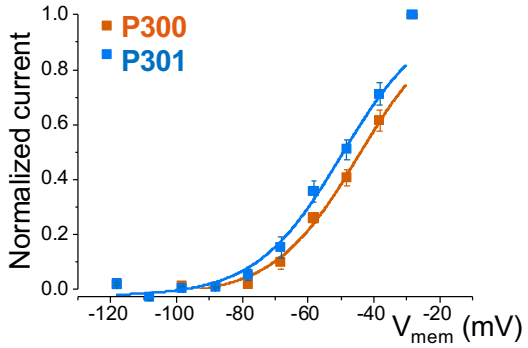


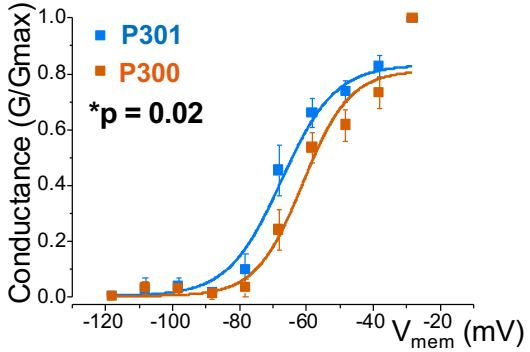
‘Neuronal Action Potential’





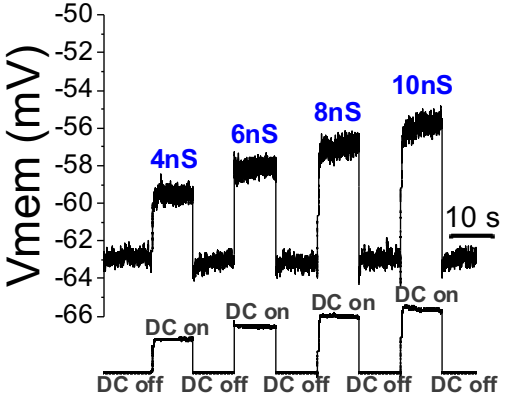


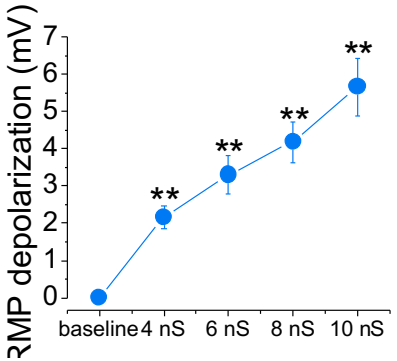


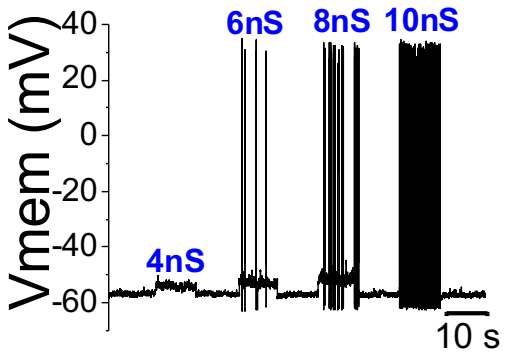


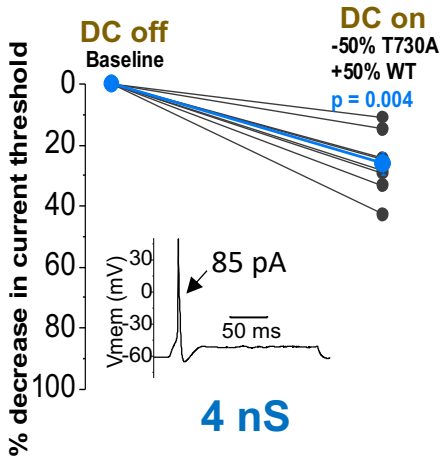
Mis et al, 2019

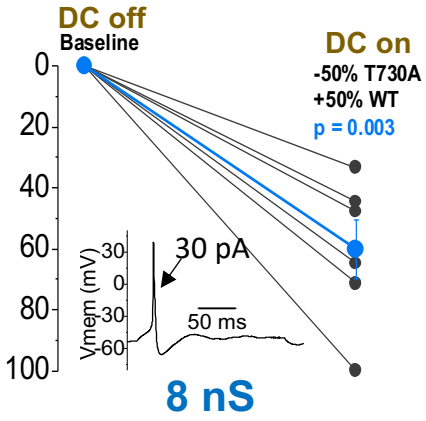
Dynamic-clamp: Kv7.2-T730A I_M reduces the excitability of iPSC-SNs, thereby contributing to Pain Resilience

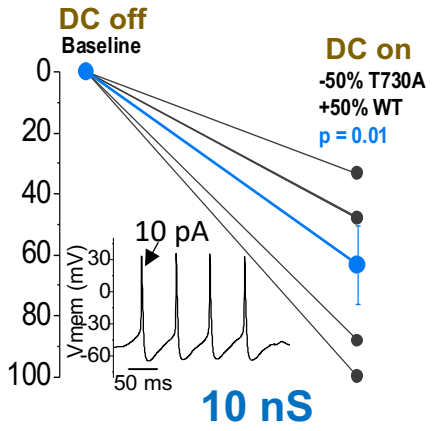






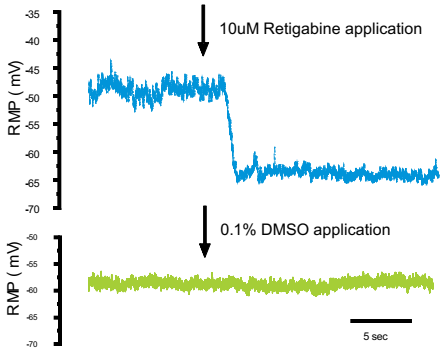


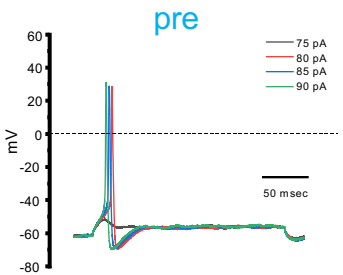


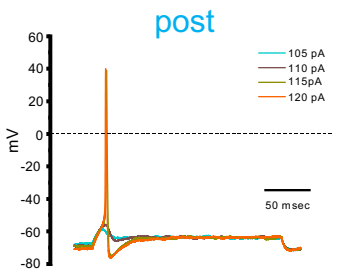


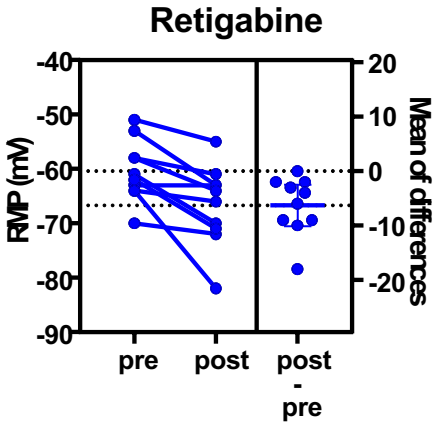
Mis et al, 2019

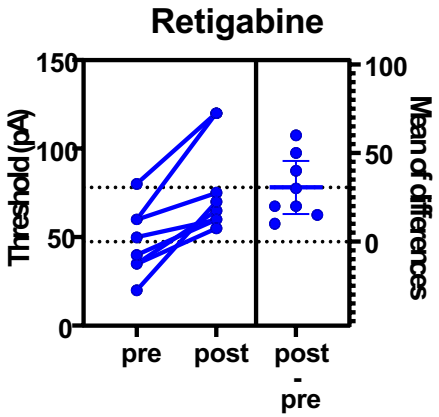
Kv7 activator hyperpolarizes RMP and reduces excitability in human IEM iPSC-SNs

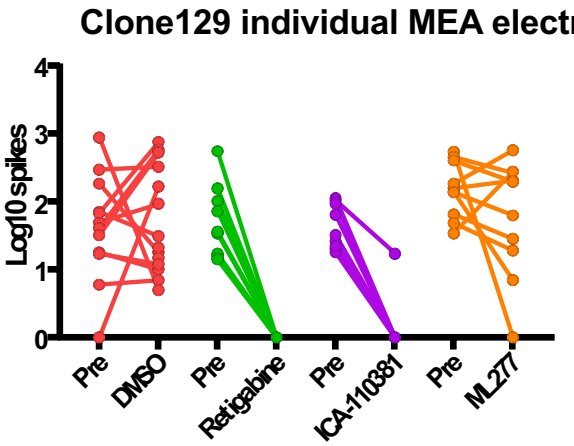












Estacion et al, 2023

Professor Thomas Voets

Laboratory of Ion Channel Research
VIB Center for Brain and Disease Research

KU LEUVEN

BHV-2100: TRPM3 Antagonism

TRPM3 (BHV-2100)
Overview

Novel Peripheral Target for Neuropathic Pain
Differentiated from existing programs targeting TRPV1 and TRPA1

First-in-Class & Best-in-Class Potential
BHV-2100 is the only TRPM3 antagonist in clinical development

Pain Reversal with Reduced Liabilities Compared to SOC
BHV-2100 preclinical data shows reversal of pain in various models, without sedative effects

Selective, Potent, and Peripherally-Restricted
- Selectivity within TRP family avoids potential class liabilities such as hyperthermia and provides a non-opioid option for the >50% of neuropathic pain patients who still have breakthrough pain
- High potency, selectivity, optimal ADME and toxicology characteristics

Status Update
IND submission planned for 2H 2023

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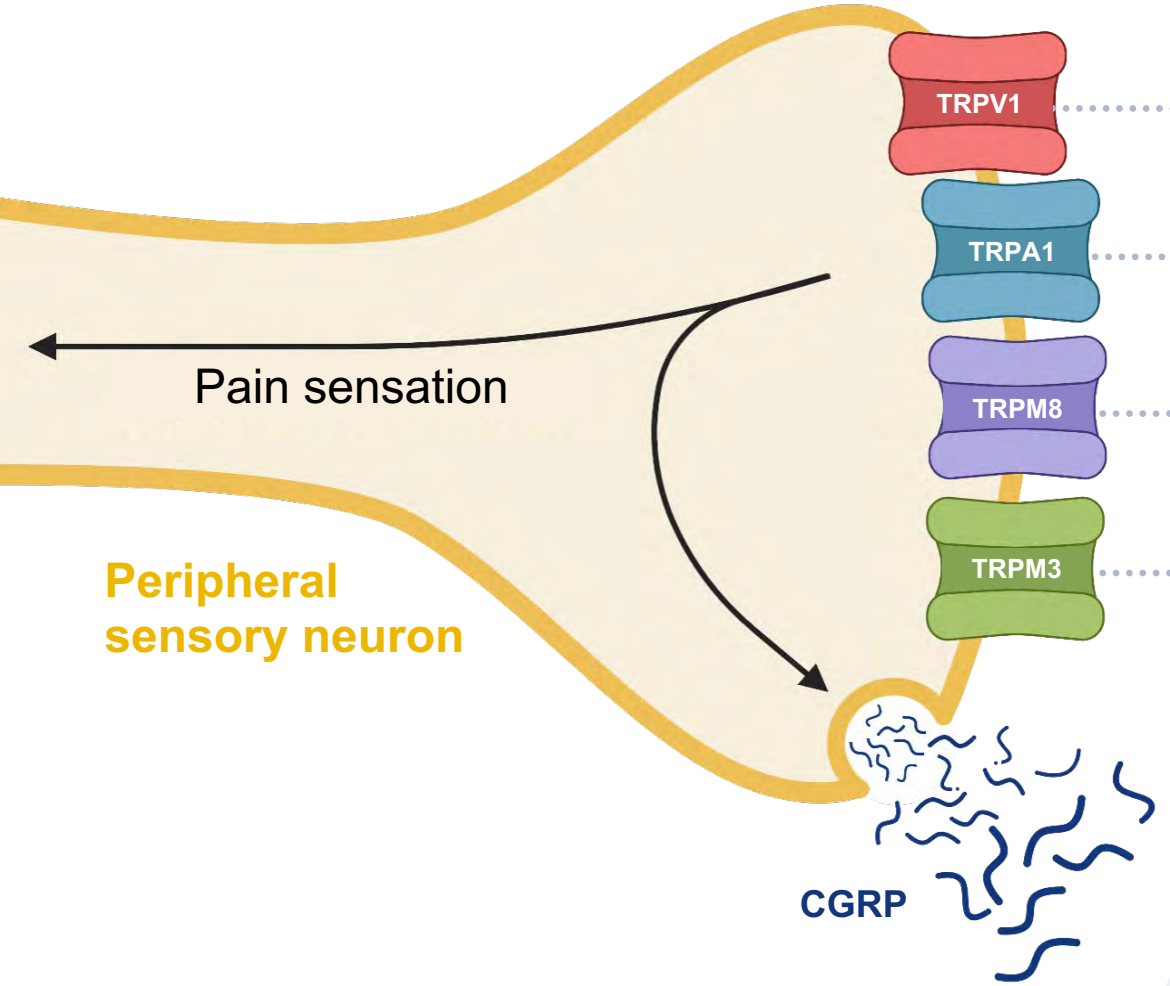
TRPM3: A Novel Peripheral Target for Neuropathic Pain



X

Oral class terminated for hyperthermia
No new molecules in this class despite promising

?

Multiple TRPA1 programs terminated

?

Conflicting data for pro- and anti-nociceptive role; remains in active drug development

Promising as a novel target: broader expression than TRPV1 and TRPA1 in peripheral neurons; unlikely to affect body temperature homeostasis

2021: Nobel Prize in Physiology or Medicine awarded to David Julius and Ardem Patapoutian for their discovery of the cellular sensors of temperature and pressure

See Koivisto et al. *Nat Rev Drug Discov*. 2022;21(1):41-59 for background on TRP channel drug development.

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Growing Evidence Implicates TRPM3 in Nociception and Pain

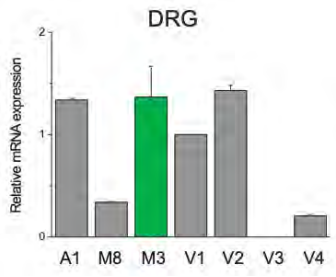
Majority of TRPM3 data emerged in past few years

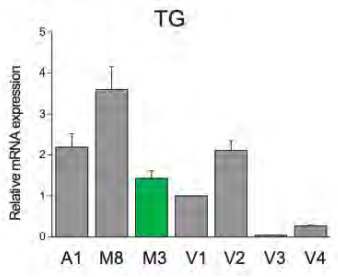
Knockouts Are Resistant To Injury-Induced Pain States

- TRPM3 knockout mice do not develop mechanical or thermal hypersensitivity in:
  - Nerve injury assay
  - Chemotherapy-induced neuropathic pain assay
  - Osteoarthritis model
  - Inflammatory pain assay (CFA)
- TRPM3 knockout mice have normal body temperature and minor changes in heat sensitivity[1,2]

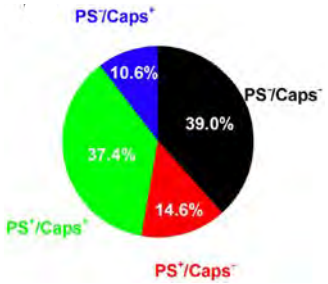
Highly Expressed in DRG/TG

- TRPM3 is highly expressed in human dorsal root ganglion and trigeminal ganglia[1,3,4]



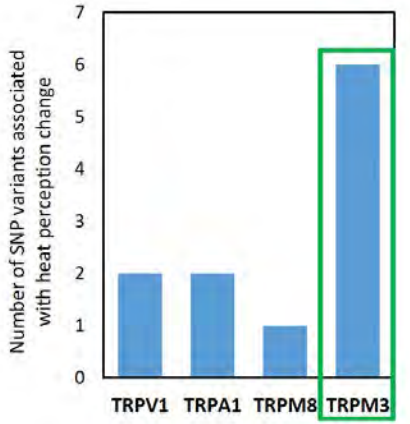


50% of human DRG respond to TRPM3 agonist (pregnenolone sulfate, PS+)



Human Genetic Validation

- Gain-of-function mutations associated with altered pain and heat sensation[5,6,3]
- Several SNPs associated with increased pain after UVB[3]



1. Vriens et al, 2011; 2. Vandewauw et al, 2018; 3. Lotsch et al 2020; 4. Vangeel et al 2020; 5 de Sainte Agathe et al, 2020; 6. Dyment et al, 2020; 6. Van Hoeymissen et al 2020; 7. Burglen et al. eLife, 2023

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BHV-2100: High Potency, Selectivity, and Optimal ADME and Toxicology Characteristics Predict High Likelihood of Clinical Success

Parameter	Test	Value
TRPM3 electrophysiology	Patch clamp	8.8 nM IC50
TRPM3 neuronal activity	hES derived sensory neurons	3 nM IC50
TRP selectivity	TRPA1/TRPV1/TRPM8	All >10 μM IC50
CV selectivity	NaV1.5; NaV1.7; CaV1.2; hERG	All >10 μM IC50
General selectivity	Eurofins	Clean in BioPrint™
ADME	Clearance across species	Low/moderate
ADME	Cyp P450	>10 μM all isoforms
ADME	Bioavailability (mouse, rat, dog)	55-85%
Toxicology	IND enabling toxicology studies	Strong safety margins, no genotoxicity

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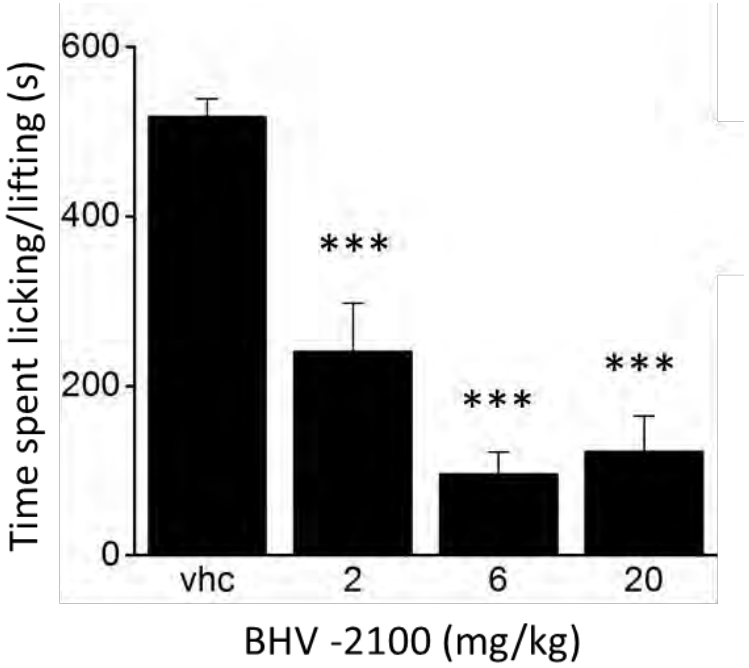
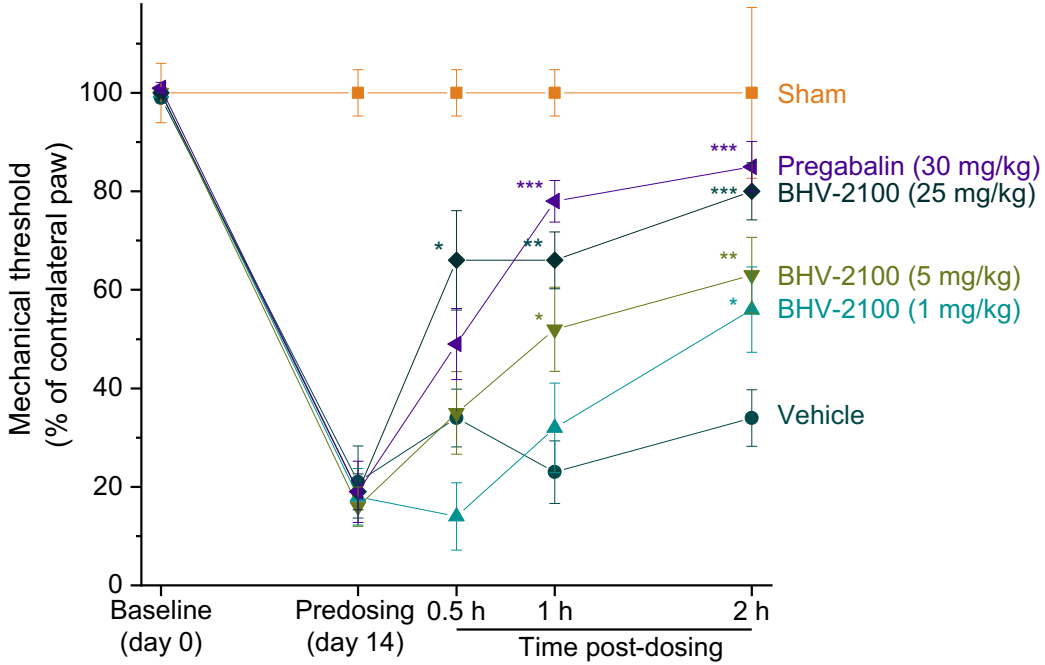
BHV-2100: Potently Reduces Acute Chemogenic Pain and Pain Following Nerve Injury

PS-Induced Acute Pain Model



Drug administered 30 minutes prior to TRPM3 agonist injection in a hind paw of rats

Partial Sciatic Nerve Ligation Model



Drug administered 14 days after unilateral sciatic nerve injury in rats

Encouraging evidence of pain reduction without the sedation observed with high-dose pregabalin

*** p<0.001, ** p<0.01 , * p<0.05

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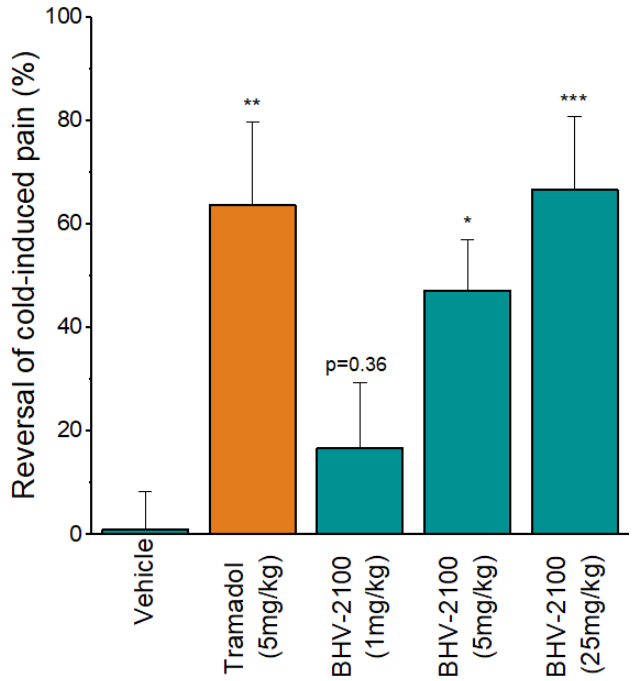
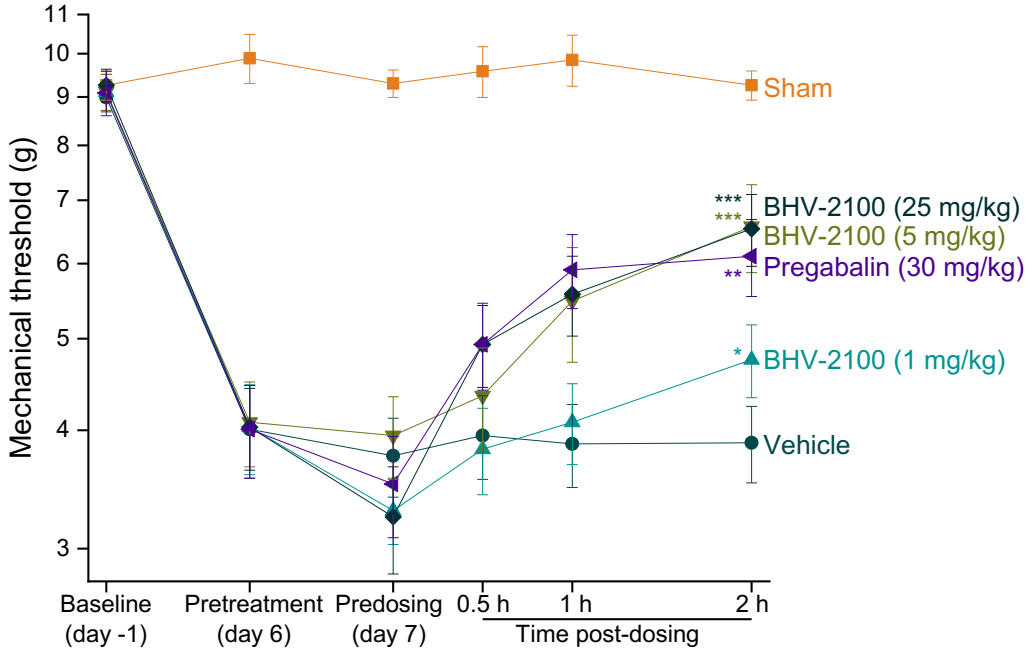
BHV-2100: Reverses Established Pain States in Peripheral Neuropathic Pain Models

Chemotherapy-Induced Neuropathic Pain Model



Drug administered 6 days after oxaliplatin treatment in mice

Diabetic Neuropathy Model



Drug administered 7 days after STZ treatment in rats

Encouraging evidence of pain reduction without the sedation observed with high-dose pregabalin/tramadol

*** p<0.001, ** p<0.01 , * p<0.05

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BHV-2100: A Versatile Agent for Treatment of Multiple Pain Conditions

Unmet Need in Neuropathic Pain Disorders

>50% of patients with common neuropathic pain disorders (e.g., diabetic peripheral neuropathy) are **inadequately controlled even with 2+ medications** to attempt to control pain

Selective and Potent

Selective and potent inhibition of TRPM3 provides a **novel, non-opioid approach** to neuropathic pain treatment

Selectivity within TRP family, **avoids** potential class liabilities such as **hyperthermia**

Preclinical Data

Preclinical data shows potent **reversal of pain** in multiple translatable animal models

Molecular Characteristics

Molecular characteristics predict **convenient, safe** molecule with optimal target product profile for a **daily oral medicine**

Investigational New Drug filing planned for 2H 2023

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PANEL DISCUSSION

Disruptive Potential of Kv7 and TRPM3 Ion Channel Modulation in Epilepsy, Mood Disorders, Pain, and Beyond

MODERATOR

Tessa Romero

Equity Research Analyst

J.P.Morgan

PANELISTS

Michael Bozik, M.D.

President, Ion Channel Research and Development

Steven Dworetzky, Ph.D.

SVP, Kv7 Strategy and Development

John Krystal, M.D.

McNeil Professor and Chair

Department of Psychiatry, Yale

Michael Rogawski, M.D., Ph.D.

Distinguished Professor

Department of Neurology and Pharmacology, UC Davis

Professor Thomas Voets

Laboratory of Ion Channel Research

VIB Center for Brain and Disease Research, KU Leuven

Stephen Waxman, M.D., Ph.D.

Bridget Flaherty Professor

Department of Neurology, Yale

BHVN LISTED NYSE

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DAYS MATTER

BIOHAVEN R&D DAY

Se-Jin Lee, M.D., Ph.D.
Professor

Lindsey Lair, M.D., MBA, F.A.A.N.
VP, Clinical Development
biohaven

Peter Ackerman, M.D.
VP, Clinical Development
biohaven

Myostatin Inhibition Platform Update

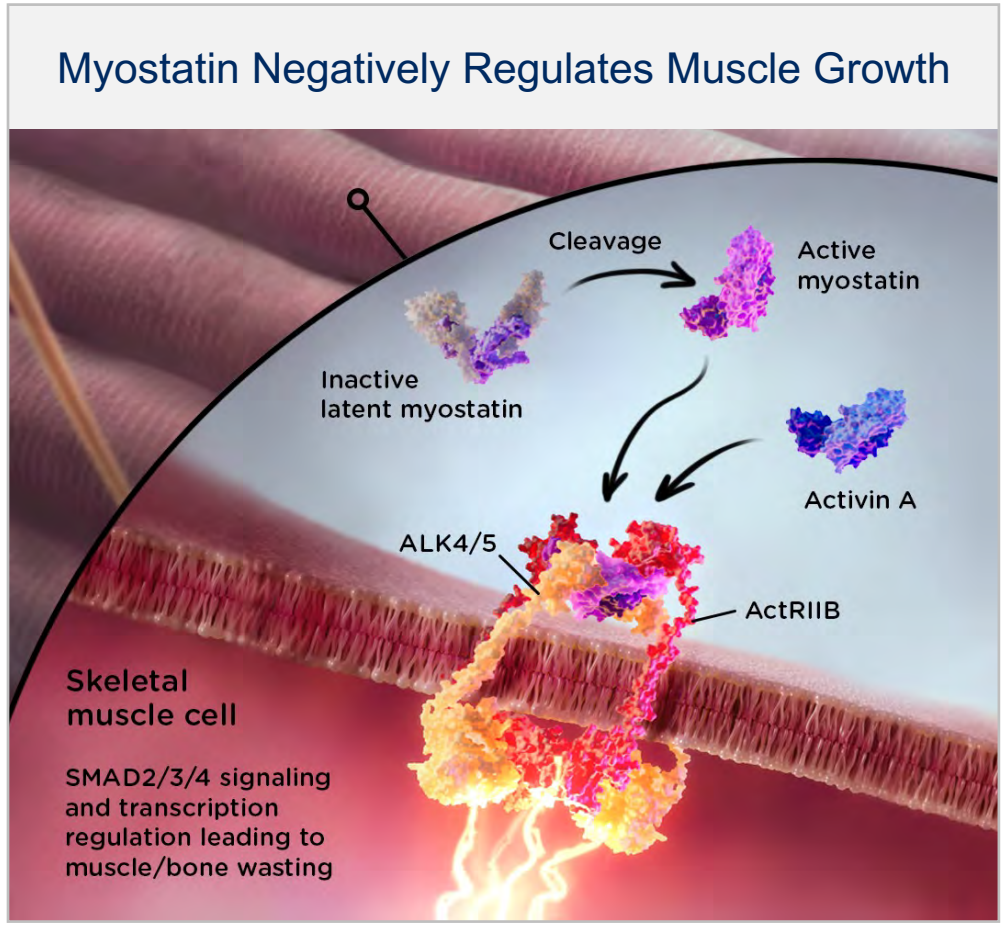
Se-Jin Lee, M.D., Ph.D.

Professor

Taldefgrobep Alfa: Novel Myostatin Inhibitor

Myostatin and Activin A are Potent Muscle Regulators

Myostatin (GDF-8) is naturally expressed by skeletal muscle and actively inhibits skeletal muscle growth

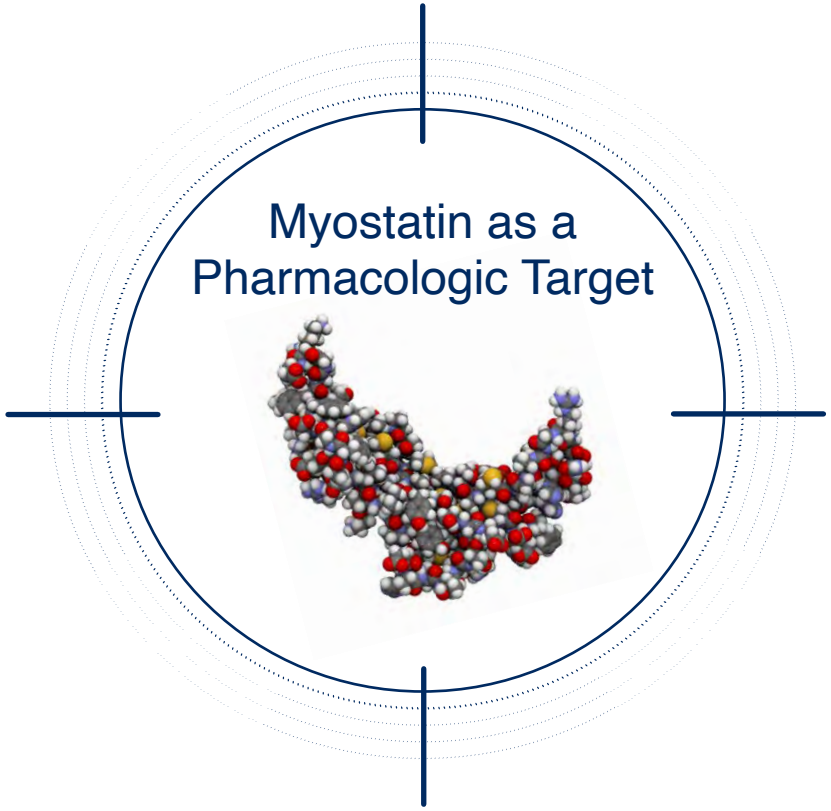


Blocking Myostatin and Activin A Leads to Muscle Hypertrophy

- Myostatin is a secreted protein belonging to the TGF-ß superfamily of signaling molecules
- Myostatin signals by binding initially to the activin type 2 receptors, ActRIIA and ActRIIB, which then engages the activin type 1 receptors, ALK4 and ALK5
- Genetic and pharmacological studies in multiple species, including humans, have shown that myostatin normally acts to block skeletal muscle growth
- The function of myostatin in muscle is partially redundant with that of the related protein activin A

Inhibiting Myostatin Signaling Demonstrates Important Physical and Metabolic Change

- Increased lean mass
- Improved insulin sensitivity
- Increased basal metabolic rate
- Improved bone mineral density



- Reduction in total body fat mass
- Reduction in visceral fat
- Reduction in intramuscular fat
- Reduction in intrahepatic fat

Current Therapeutic Approaches

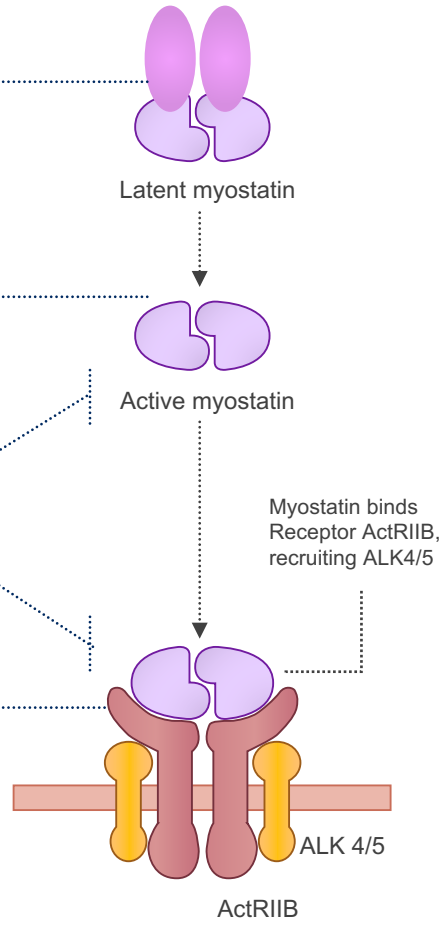
Anti-Myostatin Therapeutic Targets

Anti-propeptide myostatin
- GYM329 (Chugai/Roche)
- apitegromab (Scholar Rock)

Mature myostatin antibodies
- domagrozumab (Pfizer)
- REGN1033 (Regeneron)
- landogrozumab (Eli Lilly)

Mature and receptor blocking
taldefgrobep alfa (Biohaven)

Anti receptor antibody
- bimagrumab (Versanis)



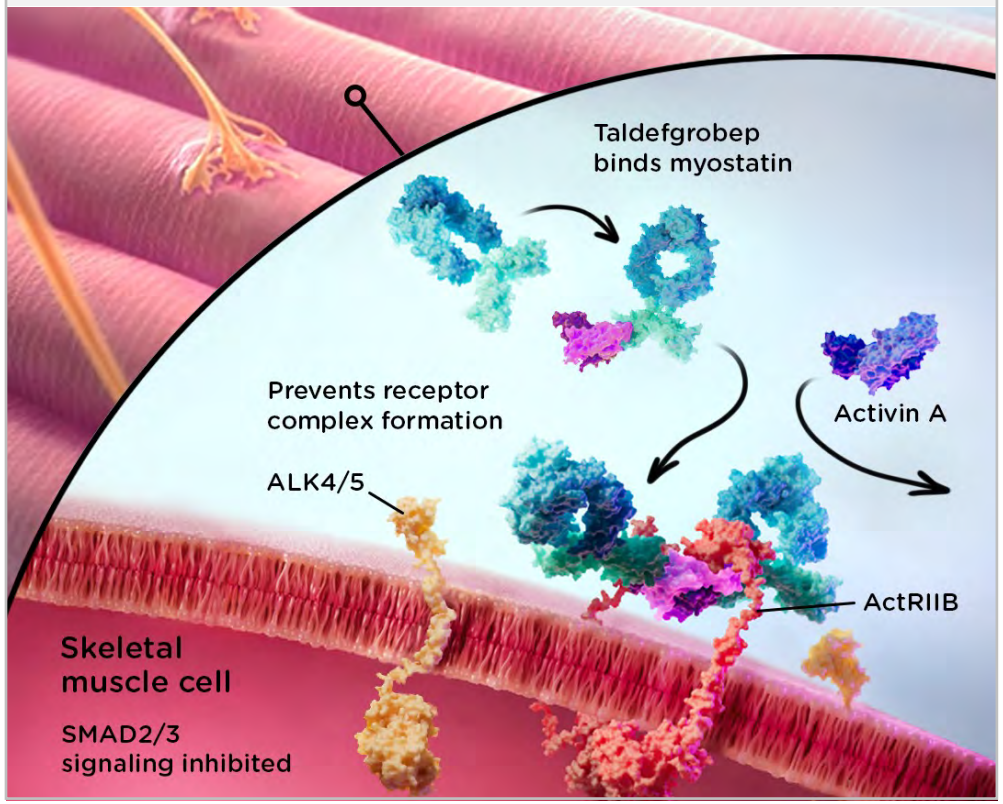
Advantages of a Differentiated MOA

- Nearly all anti-myostatin trials showed increases in muscle and lean body mass
  - Effects were in range of 3-5% with agents specific for MSTN/GDF-11
  - Effects were in range of 5-9% with agents capable of targeting MSTN/GDF-11 and other ligands (activin A)
- Most of the trials failed to show evidence of functional benefits:
  - Muscular dystrophy
  - Sporadic inclusion body myositis
  - Cachexia (Cancer, COPD, end-stage renal disease)
  - Exception:
    - Two trials in aged patients (sarcopenia, falls)
    - SMA (Scholar Rock)
- Nearly all of these trials showed reduction in body fat and/or improvements in glucose metabolism

Taldefgrobep Alfa: Differentiated Mechanism of Action

Only agent that reduces free myostatin and blocks receptor signaling

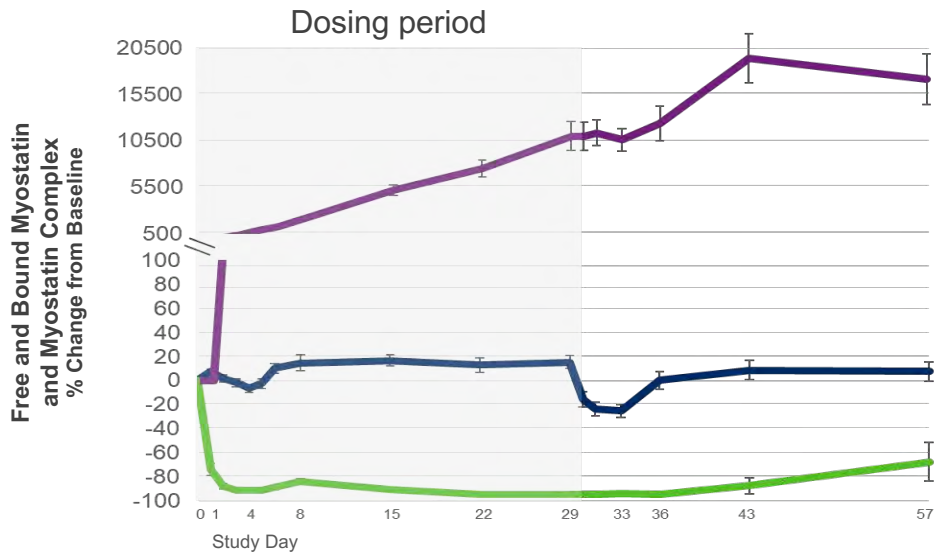
Taldefgrobep Binds to Myostatin To Inhibit Signaling



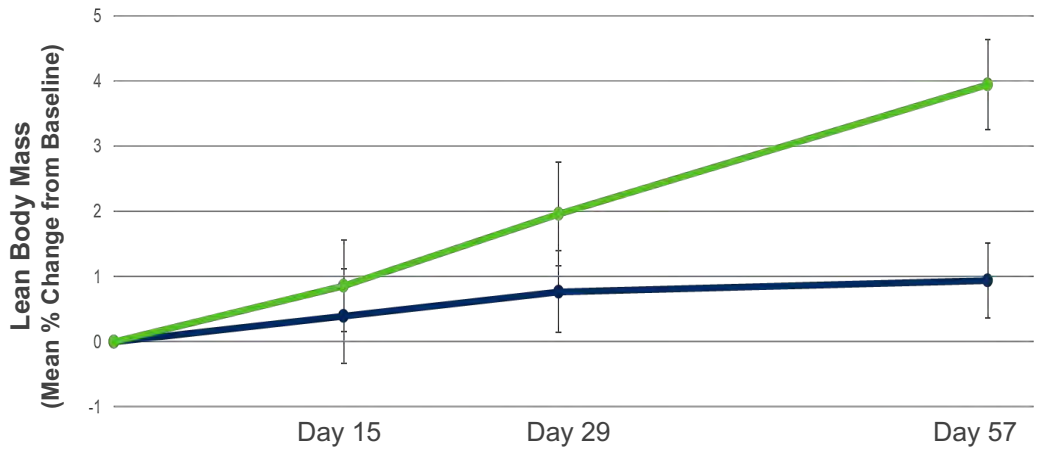
- Taldefgrobep is a fusion protein designed to have optimal affinity for myostatin and not other members of TGF-ß pathway
- Non-clinical studies show that taldefgrobep binds to myostatin at activin Type 1 receptor (ALK4/5) binding site and can inhibit signaling
- The complex taldefgrobep forms with myostatin inhibits both myostatin and activin A signaling in tissue where myostatin is active
- Potential for less off-target blockage of activin Type 2 receptor in non-muscular tissue

Taldefgrobep Alfa: Activity Confirmed in Human Studies

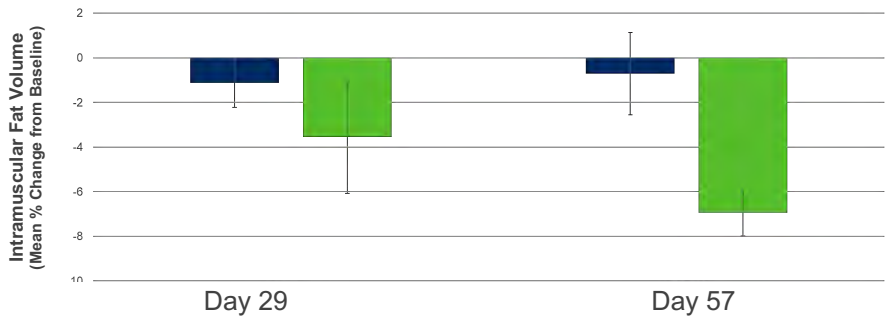
Myostatin Free and Drug Bound Levels



Increased Lean Body Mass



Decrease in Intramuscular Fat



- Healthy volunteers showed dose dependent increases in exposure and lowering of free myostatin when administered subcutaneously on a weekly basis for 4 weeks
- Accumulation of the taldefgrobep/myostatin complex drives competitive inhibition of free myostatin and activin A binding
- Participants demonstrated an increase in lean skeletal tissue (MRI) and increase in lean body mass along with a reduction of intramuscular fat volume (DXA)

Myostatin: Strong Scientific Rationale in Spinal Muscular Atrophy

COMBINATION THERAPY STUDIES OF SMN UPREGULATION IN SMA DISEASE MOUSE MODEL DEMONSTRATED:

- ✓ Improved life span and strength, along with improved muscle function
- ✓ Increased nerve branching, size of post-synaptic area, innervated neuromuscular junctions, enlarged sensory neurons in DRG

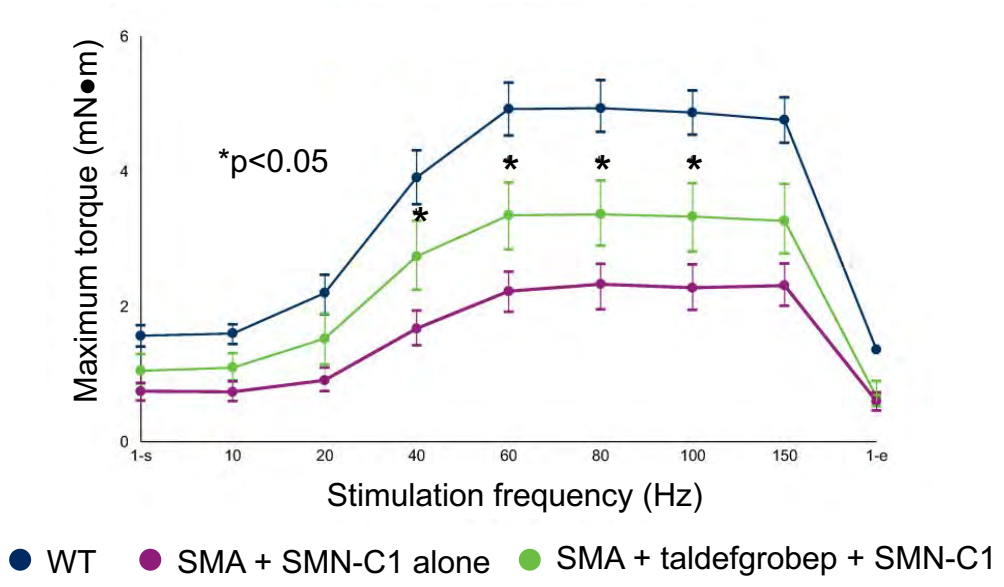
- SMA is a neurodegenerative disease; patients retain intact muscle as a target for improvements of function
- Disease modifying therapies approved and widely accessible and effective in SMA patients
- Disease area has well established validated clinical endpoints with proven regulatory path for approval

SMN, survival motor neuron; **DRG,** Dorsal root ganglia

Taldefgrobep in Combination with SMN Upregulation Demonstrated Improvements in SMA Disease Mouse Model

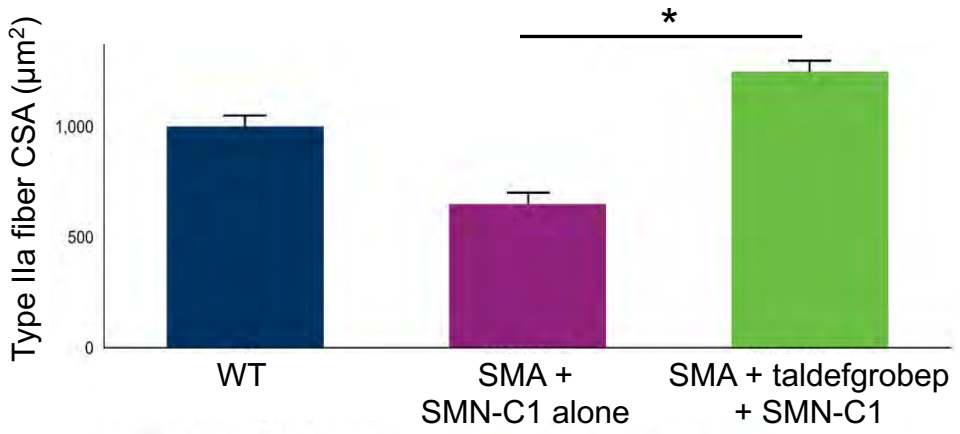
- SMNΔ7 mice were used as a model for SMA
- Taldefgrobep was given in combination with SMN-C1, an SMN upregulator, in 2 different preclinical studies

Taldefgrobep Increased Muscle Function (Torque)



The combination of taldefgrobep and high-dose SMN-C1 improved plantar flexor muscle function over SMN-C1 treatment alone in SMA mice (postnatal day 52)

Taldefgrobep Increased the Cross-Sectional Area of Muscle Fibers



*p<0.05 for taldefgrobep-treated SMA mice vs SMA mice treated with SMN-C1 alone.

The combination of taldefgrobep and low-dose SMN-C1 increased the mean type IIa muscle fiber cross-sectional area in SMA mice (postnatal day 48)

Bechtold C, et al. Poster 161. MDA Clinical and Scientific Conference, 2023.

Taldefgrobep Alfa: A Differentiated Myostatin Inhibitor

MYOSTATIN IS A VIABLE TARGET OF THE TGF-β PATHWAY TO INFLUENCE NEUROMUSCULAR AND METABOLIC DISEASES

Area challenged by numerous failed translational clinical studies

Taldefgrobep Has a Differentiated MOA From Other Myostatin Inhibitors

- ✓ Taldefgrobep is a biologic capable of binding and neutralizing myostatin activity
- ✓ The taldefgrobep-myostatin complex can also act as a receptor antagonist
- ✓ By blocking receptors, taldefgrobep antagonizes both myostatin and activin A signaling
- ✓ Activity of myostatin/activin A signaling inhibition is specific to tissue where myostatin is normally active

Targeting myostatin and activin A signaling is an attractive target for neurodegenerative and metabolic diseases

Lindsey Lair, M.D., MBA, F.A.A.N.

VP, Clinical Development

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Spinal Muscular Atrophy (SMA)

Myostatin Platform TALDEFGROBEP ALFA BHV-2000

Non-Clinical

- Well characterized in over 20 animal studies for safety and models of disease
- Includes juvenile animals permitting the safety down to 2 years of age

Clinical

- In prior studies, 359 participants received taldefgrobep: 179 healthy participants and 180 participants with Duchenne Muscular Dystrophy 5-12 years old
- Administration by subcutaneous injections in the arm, thigh, and abdomen
- Demonstrated dose-dependent suppression of free serum myostatin
- MRI and DXA data was consistent with a positive beneficial effect on muscle health
- Generally safe and well-tolerated

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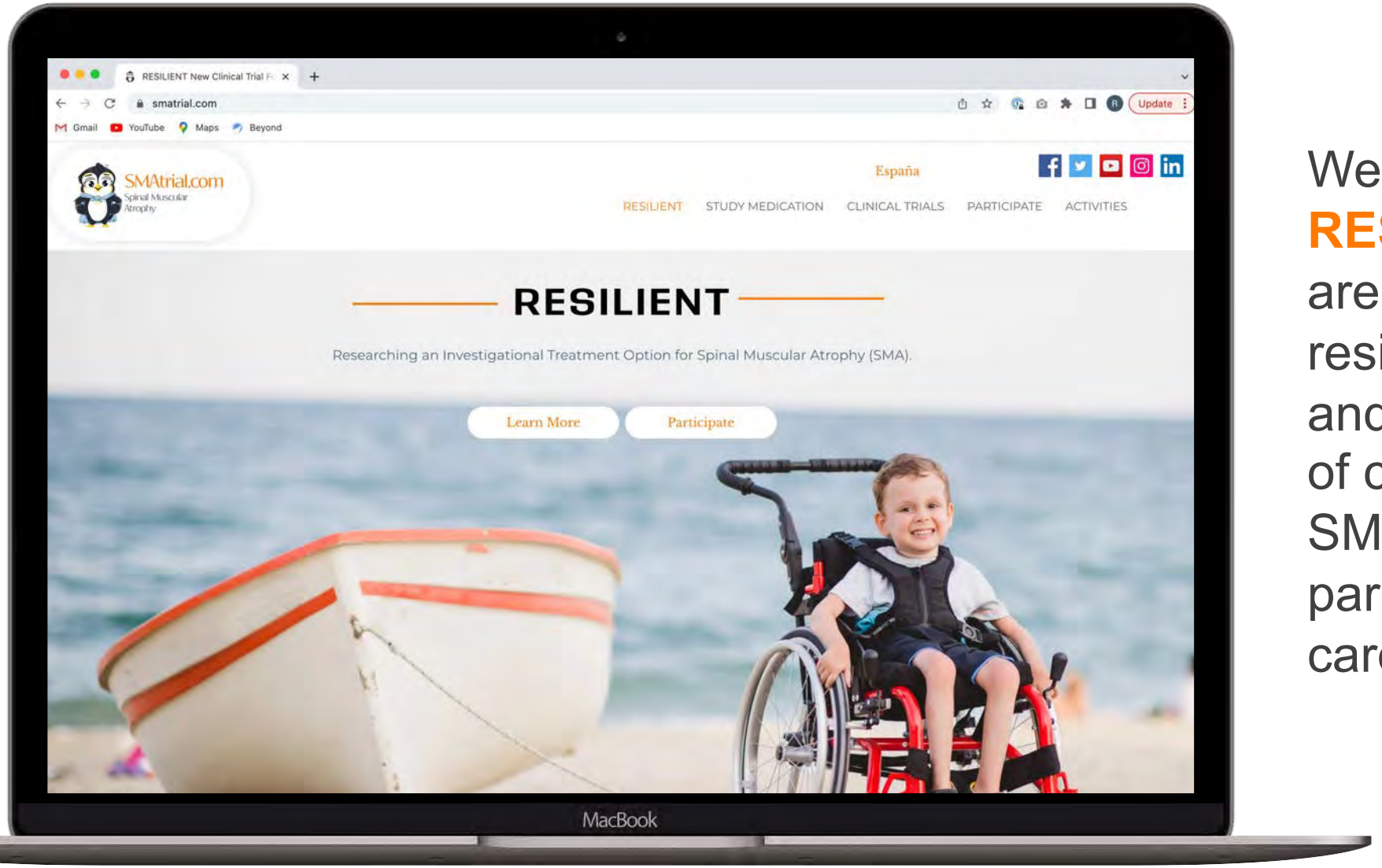
Taldefgrobep Alfa is Well Positioned for Development in SMA

- Taldefgrobep is a novel myostatin antagonist that is being developed as a therapeutic to increase muscle mass and strength
- Taldefgrobep was well characterized in numerous pre-clinical and clinical studies to support development
- SMA is an inherited neuromuscular disease characterized by muscle atrophy
  - Primary symptom is severe muscle weakness
  - Medications recently approved for treatment of SMA target the Survival Motor Neuron 1 (SMN1) gene and SMN2 transcript and may help to preserve motor neurons
  - However, SMA remains a progressive and debilitating condition

No treatment that specifically targets muscle weakness is currently available

The high unmet need for treatments for SMA, together with the available preclinical and clinical data with taldefgrobep, provide a compelling and favorable overall benefit-risk assessment for the development of taldefgrobep as a treatment for SMA

Introducing RESILIENT



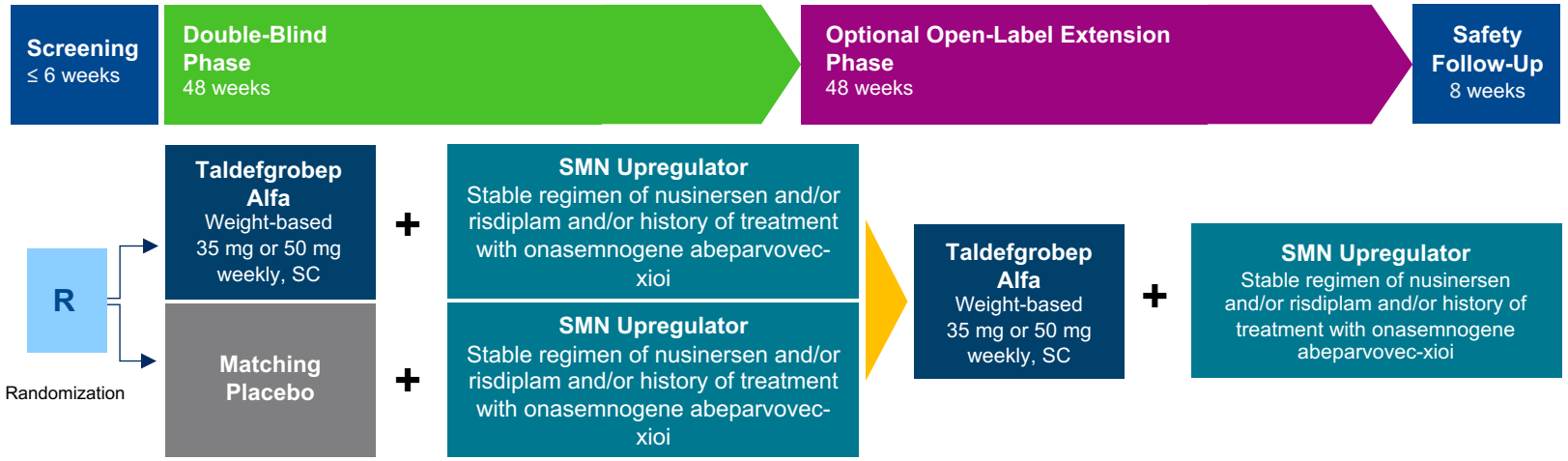
We named the study **RESILIENT** because we are in absolute awe of the resilience, perseverance, and never-give-up attitude of children and adults with SMA, as well as their parents, guardians, and caregivers.

Phase 3 **RESILIENT** Study Overview

RESILIENT Phase 3 Study Design

48-Week, Double-Blind, Placebo-Controlled Study in Pediatric and Adult Participants With Spinal Muscular Atrophy

- Estimated enrollment: 180 participants
- 2:1 randomization: taldefgrobep alfa vs placebo



PRIMARY OBJECTIVE

Change in the 32 item Motor Function Measure (MFM-32) total score between Baseline and Week 48

RESILIENT is a randomized, placebo-controlled trial testing the effectiveness and safety of taldefgrobep as an adjunctive treatment

Taldefgrobep, or a placebo, will be given while the participant is:

- Already taking a stable dose of **nusinersen and/or**
- Already taking a stable dose of **risdiplam and/or**
- Have a history of **onasemnogene abeparvovec-xioi**

RESILIENT Study Population

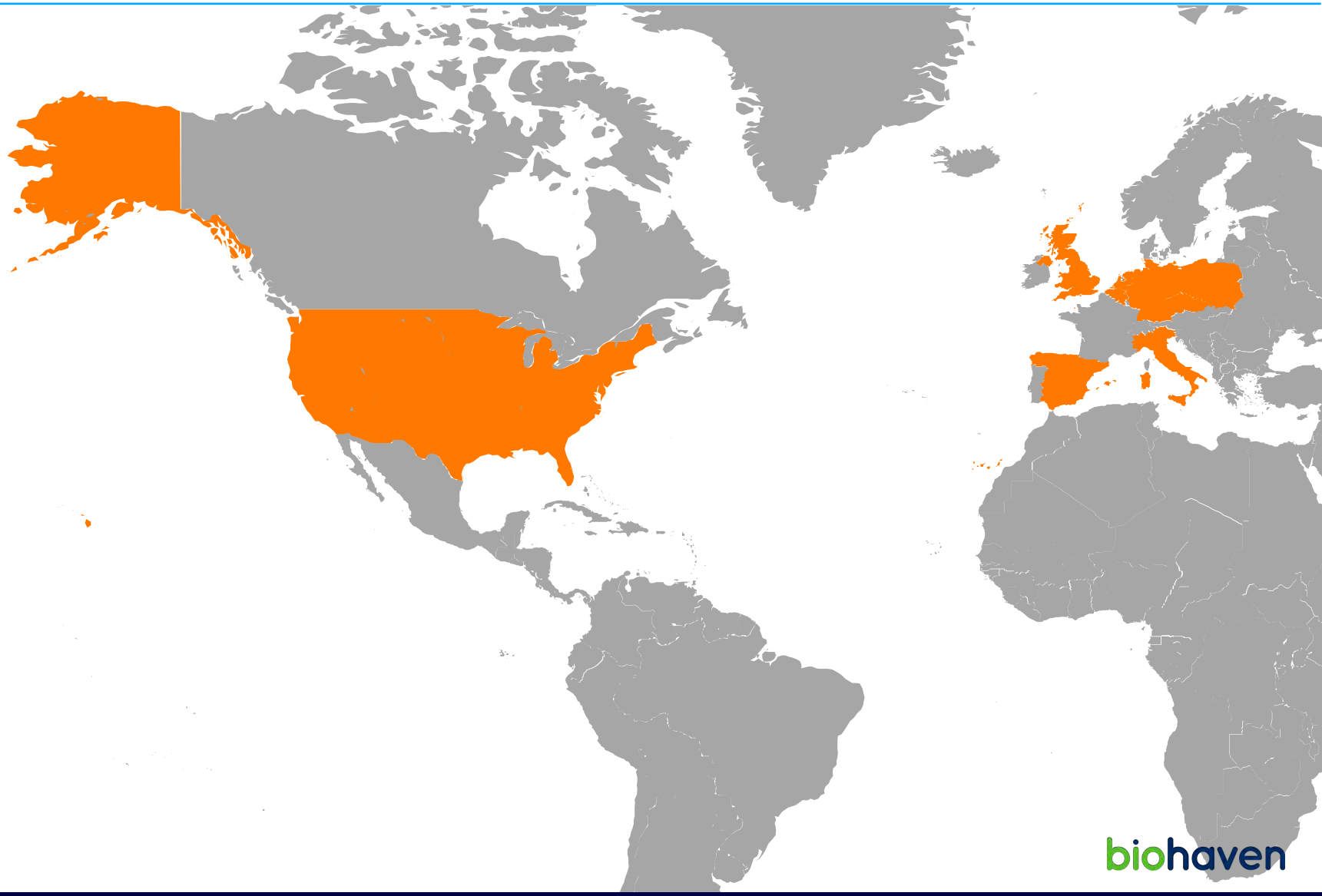
- We include a broad population given high unmet need across SMA population, and changing treatment paradigms
- Field has evolved with disease modifying therapies and widespread newborn screening, early treatment, and potentially combinations of therapies
- Shift to focus more on functional status rather than SMA Type; treated patients are achieving milestones they would not have otherwise
- Approximately 180 participants with SMA are expected to enter the treatment phase

RESILIENT is not restricted nor limited to patients based on ambulatory status, background therapy, or classification of SMA

RESILIENT Anticipated Completion of Enrollment 2H 2023

STUDY IS RECRUITING PARTICIPANTS FROM

- Belgium
- Czech Republic
- Germany
- Italy
- Netherlands
- Poland
- Spain
- UK
- United States



Peter Ackerman, M.D.

VP, Clinical Development

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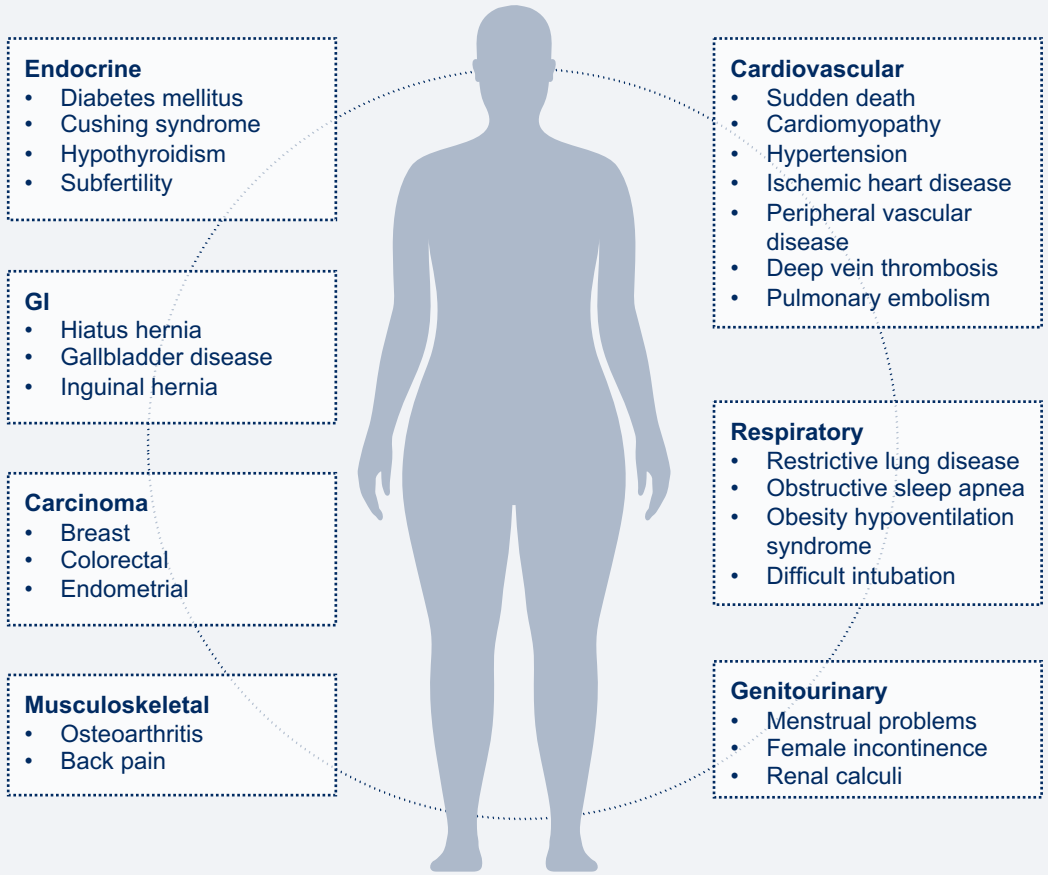
Treatment of Adults Living with Overweight and Obesity

Obesity is a Public Health Crisis

- Obesity is a DISEASE of excess and/or abnormal adipose tissue
  - Cardio-metabolic risk is closely correlated with visceral adiposity
- By 2030, it is estimated that 1 billion people worldwide will be living with obesity, including ~50% of American adults[1]
  - Obesity and related comorbid disease costs the US healthcare system ~175 billion USD annually[2]
  - A small proportion of eligible individuals are currently being treated with anti-obesity medications (AOMs)[3]
- Treatment of obesity is an area of critical unmet medical need

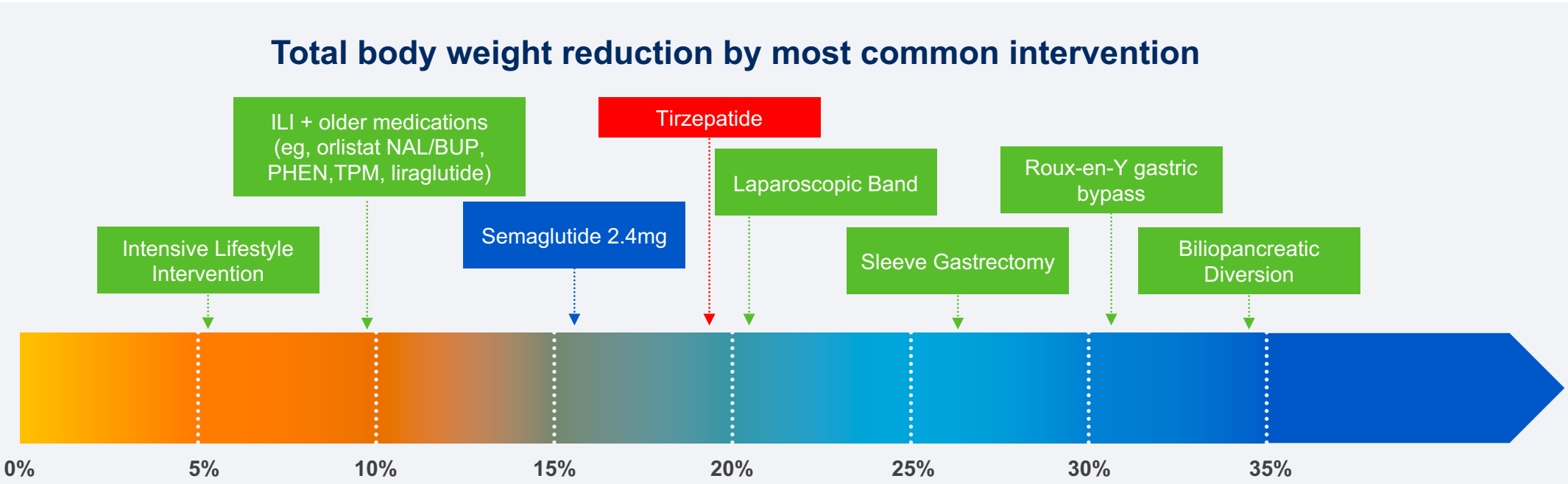
Complications of Obesity[4]



1, The World Obesity Federation. World Obesity Atlas 2022. https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022; Accessed 17-NOV-2022. 2, CDC. Adult obesity facts. https://www.gov/obesity/data/adult.html; Accessed 13-NOV-2022. 3. Saxon DR, et. al., Antiobesity medication use in 2.2 million adults across eight large health care organizations: 2009-2015. dPrimeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, Sladek R, Rabasa-Lhoret R. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond). 2011 Jul;35(7):971-81. doi: 10.1038/ijo.2010.216. Epub 2010 Oct 26. PMID: 20975726.

Entering a New Era of Hope and Opportunity for Adults Living with Obesity

- This is a time of rapid change and renewed excitement in the weight management space
- Highly potent anti-obesity medications (AOMs) and combination therapies are approaching efficacy outcomes comparable to bariatric surgery
- Competition in the weight loss space is intensifying but opportunities for disruption exist



Comparative Efficacy Outcomes in Adults Living with Overweight and Obesity

Drug	Dosing	Δ Total Body Weight	Δ Total Fat Mass	Δ Lean Body Mass	Δ A1C
Phentermine/ topiramate n=1,469	PO once daily	-7.8% to -9.8%	NA	NA	-0.4%
Naltrexone/ bupropion n=1,161	1-2 PO twice daily	-5.4%	-11.7%	NA	-0.6%
Bimagrumab n=37	IV Q4W	-6.5%	**-20.5%**	**+3.6%**	-0.76%
Semaglutide 2.4 n=1,306	SC QW	-14.9%	-19.3%	-9.7%	-1.6%
Tirzepatide n=1,896	SC QW	-20.9%	-33.9%	-10.9%	-2.3%
Sleeve Gastrectomy n=85	NA	-26.4%	-40.3%	-16.5% to -19.5%	-2.67%

- In the clinic, anti-myostatin therapies have repeatedly demonstrated the ability to increase lean mass, reduce fat mass, and improve glucose metabolism across diverse patient populations
- Improvements in body composition are optimized by those agents that can target both myostatin and activin A signaling

Qsymia USPI; Greenway FL, et. al. COR-I. Lancet. 2010(9741):595-605; Contrave USPI (32/650mg); Heymsfield SB, et. al. JAMA. 2021; Wilding JPH, et. al. STEP1. NEJM 2021;384(11):989-1002; Wilding JPH, et. al. STEP 1 Body Composition. J Endocr Soc. 2021;5(1):A16-17; Wegovy USPI (STEP2); Jastreboff AM, et. al. SURMOUNT1. NEJM. 2022;387(3):205-16; Mounjaro USPI (15mg); Sylivris A. et. al. Obes Rev. 2022;23(7):e13422; Maimoun L. et. al. Surg Obes Relat Dis. 2019;15(11):1965-73; Zhang H-W, et. al. Gastric Bypass in Chinese w/ DM and obesity. Ann Transl Med. 2020;8(6):372-82; The Phase 2 bimagrumab study was conducted in adults living with obesity and Type-2 DM, while the Phase 3 phentermine/topiramate, naltrexone/bupropion, semaglutide, and tirzepatide studies were conducted in adults with overweight or obesity but no history of T2DM (unless otherwise specified). The time to analysis varies by asset, phentermine/topiramate (1 year), naltrexone/bupropion (56 weeks), bimagrumab (48 weeks), semaglutide (68 weeks), tirzepatide (72 weeks), sleeve gastrectomy (1 year). Notably, change in HbA1c data have been standardized (all representative of change seen in adults with overweight/obesity plus T2DM). In the tirzepatide (15mg) and semaglutide (1mg) studies, conducted in non-diabetic adults with overweight/obesity, the mean change in HbA1c was -0.52 and -0.52%, respectively; Represents cumulative mean change in fat mass across all tirzepatide dose levels. Abati E, Manini A, Comi GP, et. al. Inhibition of myostatin and related signaling pathways for the treatment of muscle atrophy in motor neuron diseases. Cell Mol Life Sci. 2022;79(7):374; Lee S-J. Targeting the myostatin signaling pathway to treat muscle loss and metabolic dysfunction. J Clin Invest. 2021;131(9):e148372

AM, morning; **BP**, blood pressure; **HDL**, high-density lipoprotein; **LDL**, low-density lipoprotein; **NA**, not available; **PO**, oral; **QW**, once weekly; **TC**, total cholesterol; **TG**, total glucose.

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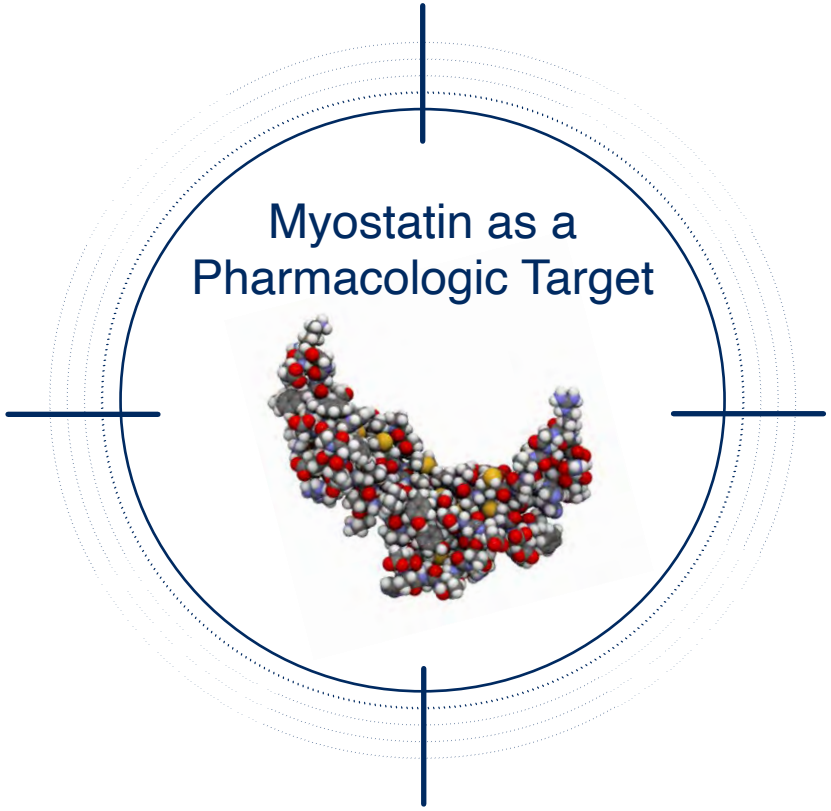
Inhibiting Myostatin Signaling Demonstrates Important Physical and Metabolic Change

- Increased lean mass
- Improved insulin sensitivity
- Increased basal metabolic rate
- Improved bone mineral density



- Reduction in total body fat mass
- Reduction in visceral fat
- Reduction in intramuscular fat
- Reduction in intrahepatic fat

- Clinically, taldefgrobep has been generally safe and well-tolerated with low rates of GI and musculoskeletal complaints
- In healthy adults, taldefgrobep generated significant improvements in body composition relative to placebo

Advancing Taldefgrobep in Obesity

NOVEL MECHANISM TARGETING BODY COMPOSITION

Potential for combination with GLP-1 class

- Leveraging available pre-clinical and early clinical data allows for significant acceleration of development timelines
- Interaction with FDA planned
- Proof-of-concept trial in adults living with overweight and obesity

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Myostatin Platform TALDEFGROBEP ALFA BHV-2000

Novel Mechanism of Blocking Myostatin and Activin A Signaling

- Human data showing potent reduction in free myostatin and accumulation of myostatin-taldefgrobep complex
- Short duration clinical studies demonstrated improvement in lean body mass and loss of adipose tissue

Advanced Development Program

- Large preclinical and clinical safety package licensed from BMS
- Existing database includes pediatric and adult clinical data
- Generally safe and well tolerated in multiple clinical studies

Spinal Muscular Atrophy (SMA)

- Single Pivotal Study launched in mid-2022
- Orphan and Fast-Track Designation Obtained in the US
- Global Study with Enrollment Targeted for Completion in 2023

Development Opportunities

- Attractive opportunity for metabolic disorders including obesity
- Additional neuromuscular, bone, and metabolic indications being evaluated

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PANEL DISCUSSION

Myostatin Platform Discussion Panel

MODERATOR

Charles Duncan

Equity Research Analyst

CANTOR Fitzgerald

PANELISTS

Peter Ackerman, M.D.
VP, Clinical Development

Lindsey Lair, M.D., MBA, F.A.A.N.
VP, Clinical Development

Se-Jin Lee, M.D., Ph.D.
Professor

Donna H. Ryan, M.D.
Professor Emerita,
Pennington Biomedical Research Center

BHVN LISTED NYSE

Bruce Car, Ph.D.

Chief Scientific Officer

biohaven

TYK2/JAK1 Platform

TYK2/JAK1 (BHV-8000)

Overview

First-in-Class Oral Brain-Penetrant TYK2/JAK1 Inhibitor

BHV-8000 is a uniquely potent, TYK2/JAK1 selective, brain penetrant inhibitor

Breaks the Cycle of Neuroinflammation

Reduces inflammatory impacts of microglia, astrocytes, and infiltrating T-lymphocytes

Potential in Multiple Neuroinflammatory Disorders

Strong evidence supports efficacy in Parkinson's disease, Alzheimer's disease, Multiple Sclerosis and other neuroinflammatory diseases

Favorable PK/PD and Selectivity Profile

Avoids class risks associated with JAK2/3 inhibition

First-in-Human Phase 1 Clinical Trial Initiated

First participants dosed May 2023

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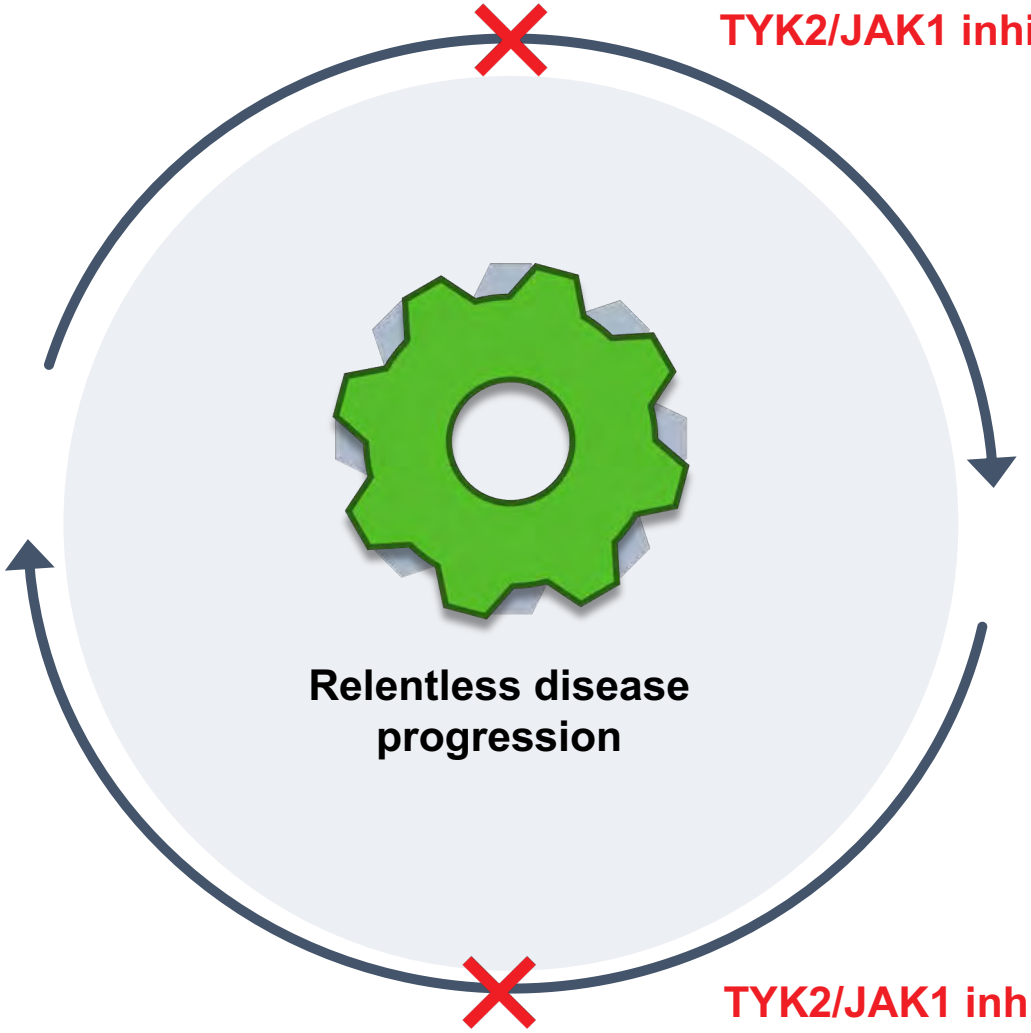
Central TYK2/JAK1 Modulation Breaks Inexorable Neuroinflammatory-Neurodegenerative Cycle



Genetic and environmental factors induce neuronal loss and CNS inflammation

Self-perpetuating inflammation drives further neurodegeneration and inflammation

CNS, central nervous system; **JAK**, Janus kinase; **TYK**, tyrosine kinase

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Selectivity of BHV-8000 Predicts Improved Safety With Targeted Efficacy

Pan-JAK inhibitors have side effects and black box warning from the FDA/EMA

Inhibitor	Status	IC_{50} in nM				Safety
		JAK1 (autoimmune)	JAK2 (hematology)	JAK3 (leucocyte)	TYK2 (inflammation)	
Tofacitinib[1]	Approved	**15**	**77**	**55**	489	MACE & cancer risk ↑ Black box warning
Baricitinib[1]	Approved	**4**	**7**	787	61	Black box warning, no MACE
Upadacitinib[1]	Approved	**47**	**120**	2304	4690	Black box warning, no MACE
Brepocitinib[1]	Phase 2	**17**	77	6494	23	OCT2 inhibitor (renal tox),[2] JAK2

Selective TYK2 and JAK1 inhibitors do not carry side effects or black box warning from the FDA/EMA

Inhibitor	Status	IC_{50} in nM				Safety
		JAK1 (autoimmune)	JAK2 (hematology)	JAK3 (leucocyte)	TYK2 (inflammation)	
Abrocitinib[1] (selective JAK1)	Approved	**29**	803	>15,000	1250	No MACE or cancer risk ↑
Deucravacitinib[1] (selective TYK2)	Approved	>10,000	>10,000	>10,000	**0.2**	No black box warning
BHV-8000	Phase 1	**4**	118	>500	**4**	**No off-target effects; No safety issue to date**

1. Wrobleski et al. *J Med Chem*. 2019;62(20):8973-8995. 2. Banfield et al. *J Clin Pharm*. 2018;58:434.

EMA, European Medicines Agency; **FDA**, US Food and Drug Administration; **IC_{50}**, half maximal inhibitory concentration; **JAK**, Janus kinase; **MACE**, major adverse cardiac event; **OCT2**, organic cation transporter-2, **TYK**, tyrosine kinase

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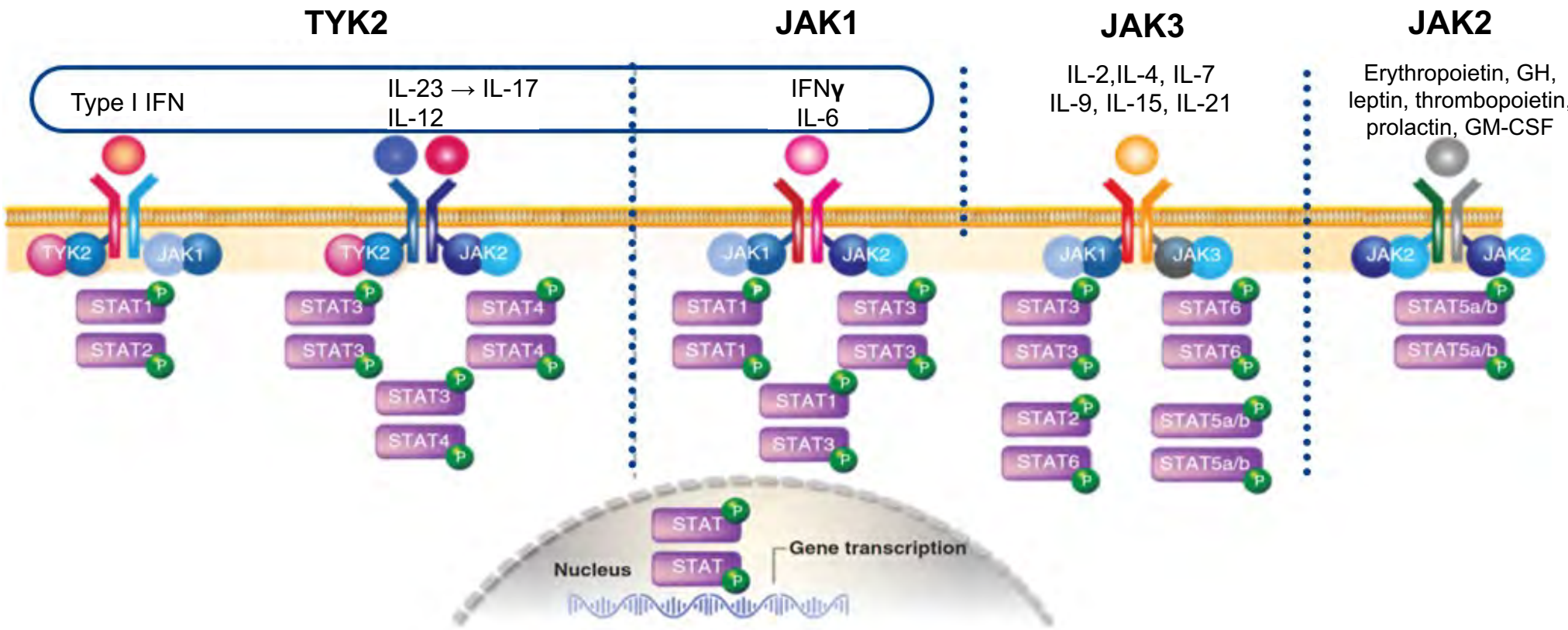
BHV-8000: TYK2/JAK1 in Neuroinflammatory Disease

- Dual inhibition of TYK2 and JAK1 can effectively block Th17 cell generation, Type I IFN signaling, and inflammation
- JAK inhibitors are more efficacious anti-inflammatory agents than anti-TNFs



Adapted from Gonciarz et al. *Immunotherapy* 2021;13(13):1135-1150.
GH, growth hormone; **GM-CSF**, granulocyte macrophage colony stimulating factor; **IFN**, interferon; **IL**, interleukin; **JAK**, Janus kinase; **STAT**, signal transducer and activator of transcription proteins; **Th**, T helper cell; **TNF**, tumor necrosis factor; **TYK**, tyrosine kinase

Cellular Drivers in Neuroinflammation: Predominant TYK2/JAK1 Effects

Microglia

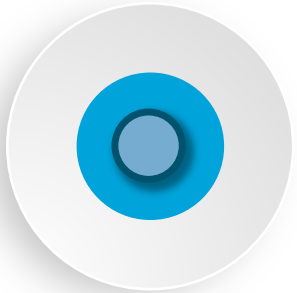
- **IFN-γ**
- IL-β
- TNF downstream of IFN-γ
- IL-8
- GM-CSF, MCP-1

Microglia are the resident macrophages of the CNS, playing an important role in neuroinflammation, repair and maintenance

Astrocytes

- **IFN-γ**
- **IL-12**
- TNF
- IL-8

Abnormal astrocytic activity may exacerbate inflammatory reactions and contribute to tissue damage



Lymphocytes, other leukocytes

- **IL-23**
- **IL-17 downstream of IL-23**
- IL-2, IL-4

Strong evidence for Th17 lymphocyte involvement as a driver of neurodegeneration

These cells are key players that drive immune dysfunction in neurodegeneration

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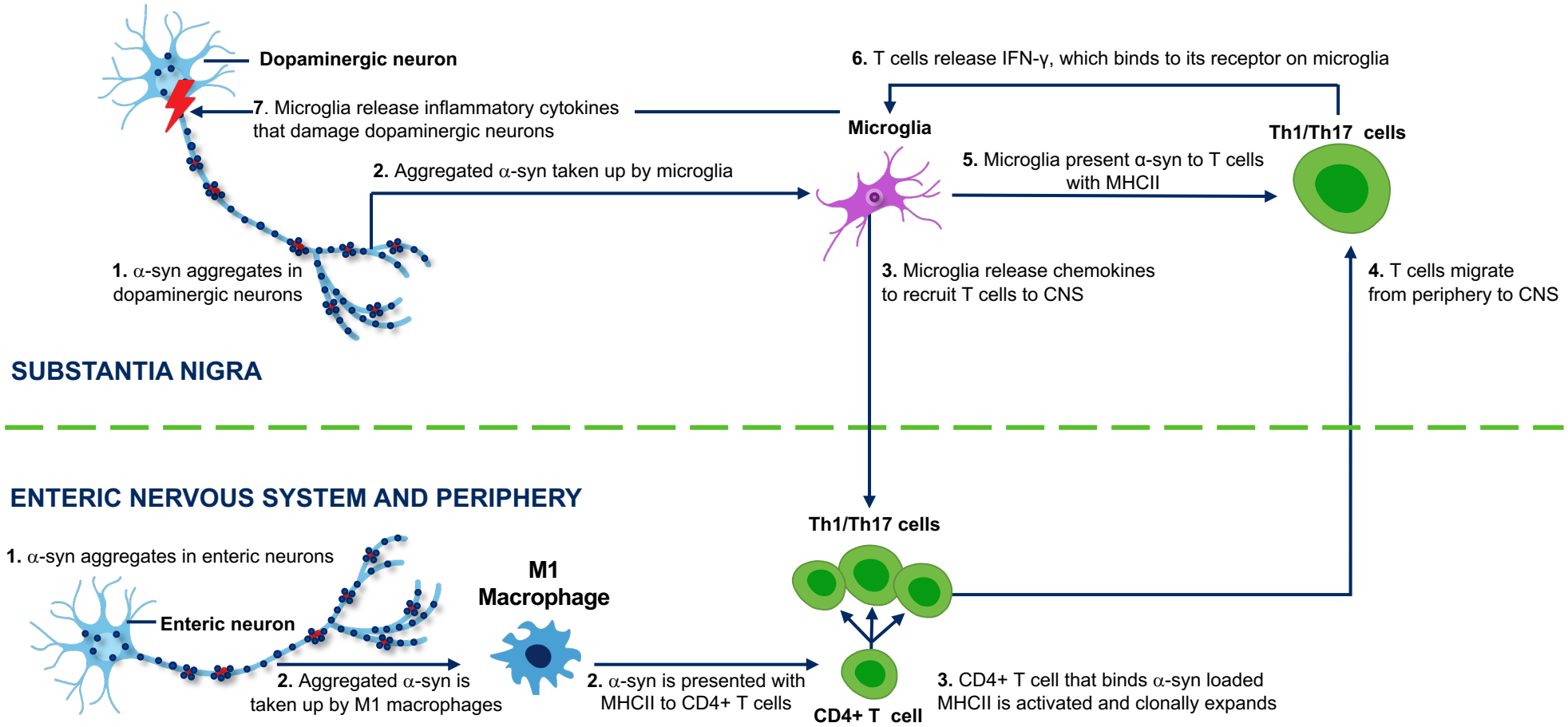
BHV-8000: Targets Both Axes of Neuroinflammation in Parkinson's Disease

TYK2/JAK2 INHIBITION OF PARKINSON'S NEUROINFLAMMATORY CASCADE

TYK2/JAK1 inhibitors reduce Th17 cell activation and expansion by inhibiting IL-23 signaling and reduce microglial activation by inhibiting IFN-γ signaling triggered by pathogenic α-synuclein aggregates[1,2]



1. Allen Reish, Standaert. *J Parkinsons Dis.* 2015;5(1):1-19. 2. Fu et al. *J Neuroinflammation.* 2022;19(1):98.

α-syn, alpha-synuclein; **CD4**, cluster of differentiation 4; **CNS**, central nervous system; **IFN-γ**, interferon-gamma; **IL**, interleukin; **JAK**, Janus kinase; **M1**, classically activated; **MHC**, major histocompatibility complex; **Th**, T helper cell; **TYK**, tyrosine kinase

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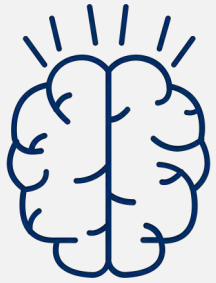
TYK2/JAK1 Inhibition Reduces Several Key Cytokines Driving Alzheimer's Disease (AD) Pathology

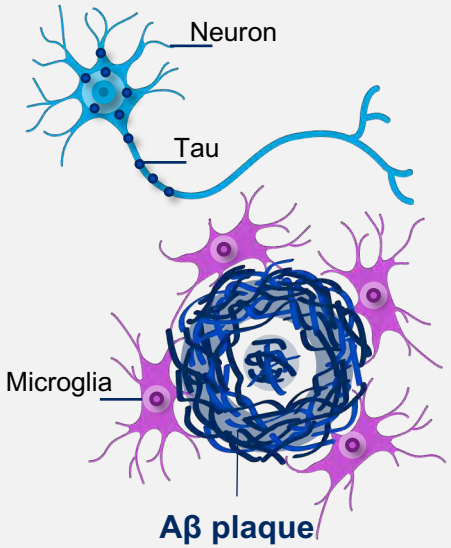
Neuroinflammation is a key event in AD pathogenesis, suggesting that a combination of anti-amyloid β (Aβ)/tau and anti-inflammation therapies is necessary[1,2]

Neuroinflammation

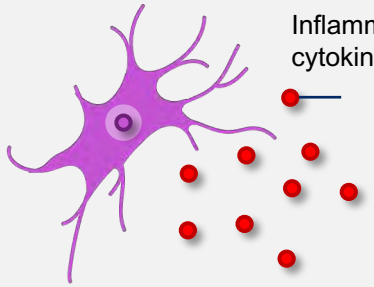


- Cytokines and chemokines affect tau phosphorylation and amyloid β (Aβ) deposition

Aβ plaque deposition + tau accumulation

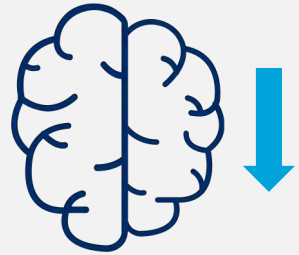


Microglia activation and release of cytokines



- Cytokines released include IL-1b, IL-6, TNF-α, and IFN- γ
- Aβ deposition also induces expression TYK2 and JAK1
- TYK2 is the most prominent gene altered by Aβ[3]

Synapse removal + cognitive decline



- Concomitant presence of Aβ, tau, and microglial activation abnormalities dramatically increases odds of cognitive symptoms[2]

Adapted from Neher. *Immunity.* 2022;55(5):821-823.

1. Domingues et al. *Curr Alzheimer Res.* 2017;14(8):870-882. 2. Pascoal et al. *Nat Med.* 2021;27(9):1592-1599. 3. Nevado-l et al. *Cells.* 2019;8:825.

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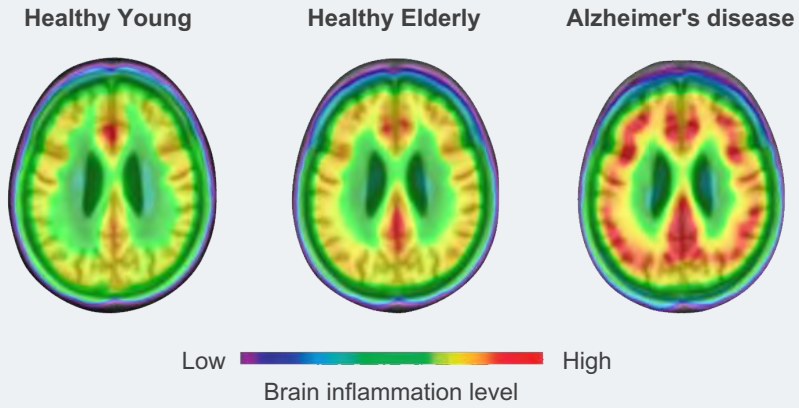
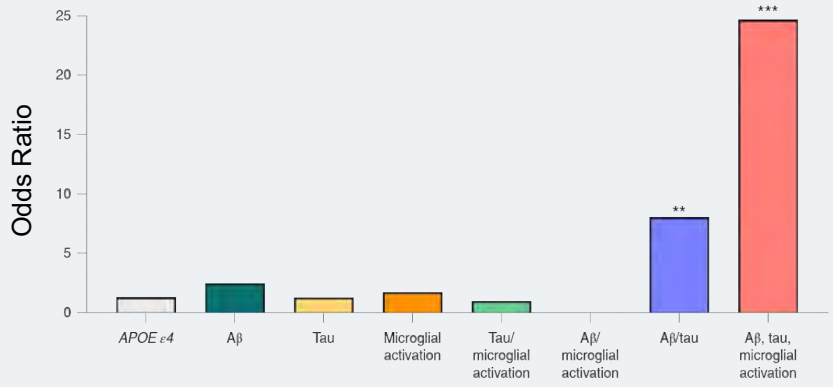
Microglial Activation and Tau Propagation Lead to a Cycle of Neurodegeneration and Neuroinflammation in AD

PET scan of 130 subjects shows that AD pts have much higher brain inflammation than healthy or elderly



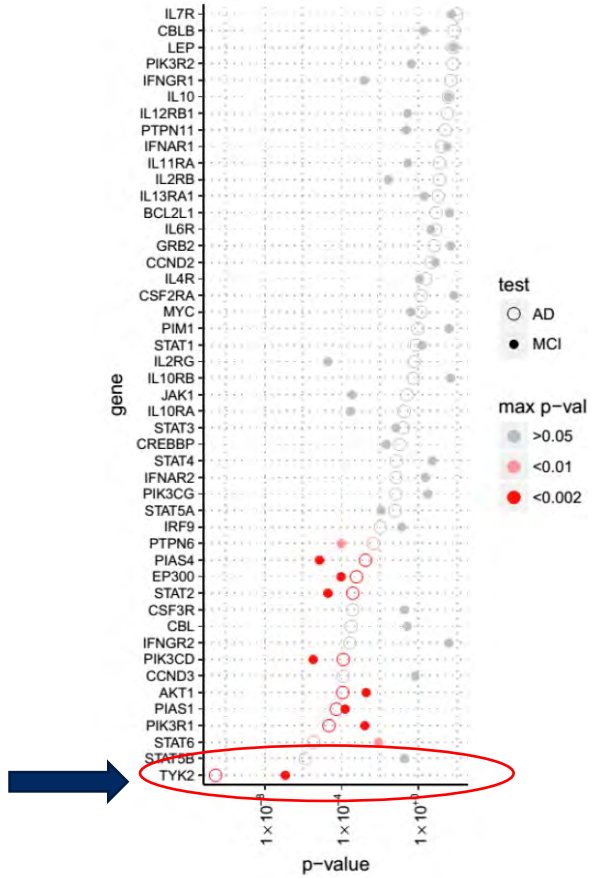
Pascoal et al. *Nat Med*. **2021**, 27(9):1592-1599.

Co-occurrence of Aβ, tau and microglial activation abnormalities was the strongest predictor of cognitive impairment in the AD population.



Pascoal et al. *Nat Med*. **2021**, 27(9):1592-1599.

TYK2 Is the Most Prominent Blood Leukocyte Gene in AD Patients



Nevado-Holgado et al. *Cells*. **2019**, 8, 425-442.

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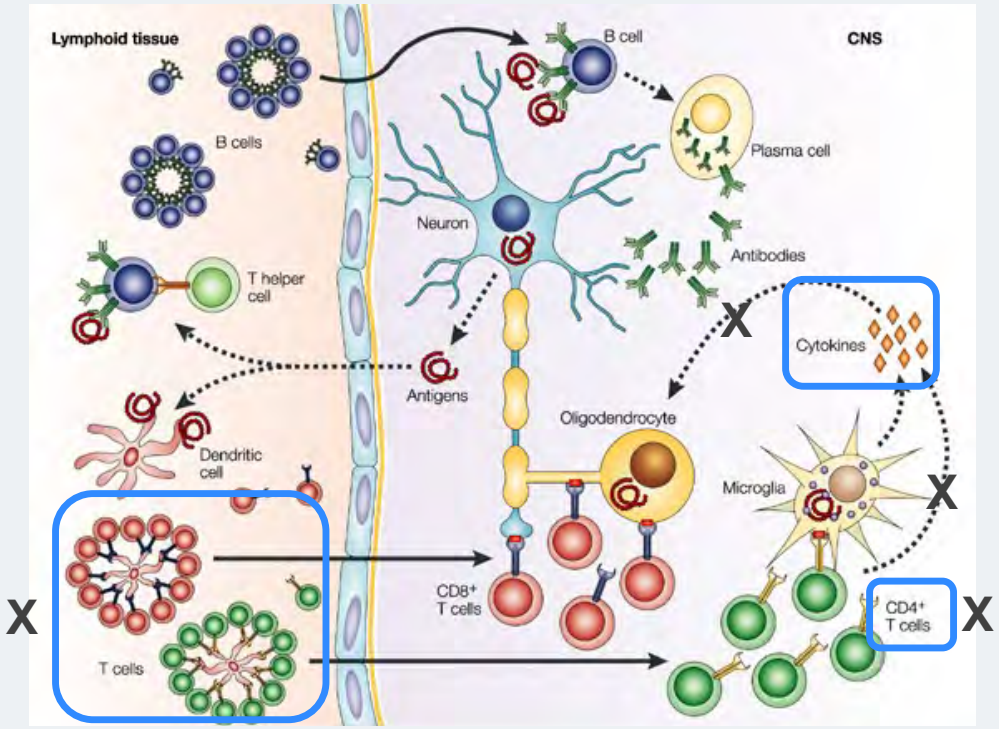
TYK2/JAK1 Inflammatory Pathways in Multiple Sclerosis



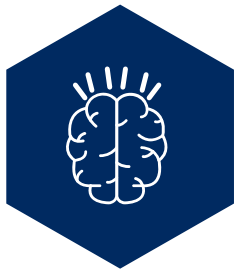
- Multiple sclerosis is an inflammatory disease in which humoral immune and cell-mediated immune responses target CNS antigens
- IL-17A-defective mice are highly resistant to induction of EAE
- PKM2 activators mediate potent inhibitory effects in EAE model due to Th17 cell effects
- In a meta-analyses of literature, TNF-α, IL-15, IL-12, IL-23/IL-17, and IFNγ were elevated in or predictors of MS patients vs. controls
- Secukinemab (IL-17A) demonstrates an effect in relapsing remitting MS
- Brain penetrant TYK2/JAK1 kinase inhibitors reduce **Th17 cells (IL-17 and IL-23)** and target IL-12 signal transduction
  - BHV-8000 is ideally suited to reducing **neuroinflammation** in MS

McGinley et al, Immunity 52:342-356, Palle et al, *Med Sci*, 5:23, 2017; Bai et al, *Frontiers in Neuroscience*, 10.3389, Oct 4, 2019, Havrdova, *Multiple Sclerosis Journal*, 18_509, 2012; Figure from *Nat Rev Neurosci.* 2002 Apr;3(4):291-301. doi: 10.1038/nrn784.

BHV-8000: Summary

Selectivity is a differentiator

- Selective inhibition of TYK2/JAK1 provides potential for best-in-class immunomodulation in neuroinflammatory disorders
- Selectivity for TYK2/JAK1 mitigates non-selective JAK class liabilities, largely related to JAK2 and JAK3 inhibition, and offers potential to improve benefit-risk for the highly selective BHV-8000 dual kinase inhibitor



Potential in multiple neuroinflammatory disorders

- Complements other approaches directly addressing neurodegeneration such as amyloid, α-synuclein, tau, and mitochondrial targeting therapies
- Strong evidence supports potential efficacy in Parkinson's disease, Alzheimer's disease, and further neuroinflammatory diseases

Clinical trials underway and anticipated in 2024

- Phase 1 initiated in May 2023
- Phase 2 in Parkinson's disease anticipated to begin in 2024
- Partner (Highlightll Pharmaceuticals) anticipates initiating a study in Alzheimer's disease in China in 2024

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PANEL DISCUSSION

Exploring the Potential of TYK2/JAK1 Inhibition in Neuroinflammation

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Glutamate Platform

Glutamate Platform
TRORILUZOLE
SCA

US NDA Submitted
2Q 2023

MAA Submission planned
for 2023

SCA

Ultra-rare, genetically-defined, progressive neurodegenerative disease associated with chronic disability, frequent falls, loss of ambulation, speech and swallowing impairment, and premature death

Regulatory Designations

- Orphan Drug Designations in both US and EU
- Fast Track Designation in US

Efficacy and Safety of Troriluzole in SCA3

- The totality of efficacy and safety data from Study BHV4157-206 and BHV4157-201 3-year open label extension phase demonstrates therapeutic benefit and disease stabilization for troriluzole in SCA3
  - 2 randomized clinical studies in SCA were conducted over 6 years, representing the largest, multicenter, placebo-controlled dataset for SCA (N = 358)
  - Consistent treatment benefits observed in patients with SCA3 in Study BHV4157-206 across multiple outcome measures including the change from baseline f-SARA at Week 48, CGI-I total score at Week 48, and a robust reduction in fall risk over the study period
  - Confirmatory evidence of efficacy provided by data from the 3-year, long-term open-label extension phase of two studies (BHV4157-206 and BHV4157-201) using a Matching Adjusted Indirect Comparison (MAIC) to an external control group

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Spinocerebellar Ataxias (SCAs)

Ultra-rare, progressively debilitating neurodegenerative disorders for which no approved treatment options are available[1-3]

Progressive, degenerative, genetic disease with multiple clinical subtypes[1-3]

~50 GENOTYPES with distinct clinical phenotypes and pathophysiology[10]

Patients with SCA types 1-3 & 7 report severe disease and early onset

DOMINANTLY INHERITED and cause cerebellar degeneration[1,2,4]

SCA3 diagnosed in up to 6,000 North America, 4,600 EU/Japan*[5-8]

AVERAGE ONSET ~40 years old[3] (SCA3)

RELENTLESS PROGRESSION OF SCA RESULTS IN **frequent falls, wheelchair dependence, speech and swallowing difficulty**

OFTEN LEADS TO **disability and premature death** [1,3]

NO DISEASE-MODIFYING TREATMENTS[1,2,9]

HIGH UNMET NEED[1,2]

1. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. *Nat Rev Dis Primers.* 2019;5(1):24. 2. Yap KH, Azmin S, Che Hamzah J, Ahmad N, van de Warrenburg B, Mohamed Ibrahim N. Pharmacological and non-pharmacological management of spinocerebellar ataxia: a systematic review. *J Neurol.* 2022;269(5):2315-2337. 3. Diallo A, Jacobi H, Tezenas du Montcel S, Klockgether T. Natural history of most common spinocerebellar ataxia: a systematic review and meta-analysis. *J Neurol.* 2021;268(8):2749-2756. 4. Matilla-Dueñas A, Ashizawa T, Brice A, et al. Consensus paper: pathological mechanisms underlying neurodegeneration in spinocerebellar ataxias. *Cerebellum*. 2014;13(2):269-302. 5. Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology*. 2014;42(3):174-83. 6. Ashizawa T, Figueroa KP, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. *Orphanet J Rare Dis*. 2013 Nov 13;8:177. 7. U.S. and World Population Clock. United States Census Bureau. Accessed September 17, 2022. https://www.census.gov/popclock 8. EUROSTAT. Accessed May 22, 2023 https://ec.europa.eu/eurostat/ 9. Brooker SM, Edamakanti CR, Akasha SM, Kuo SH, Opal P. Spinocerebellar ataxia clinical trials: opportunities and challenges. *Ann Clin Transl Neurol.* 2021;8(7):1543-1556. 10. Müller U. Spinocerebellar ataxias (SCAs) caused by common mutations. *Neurogenetics*. 2021 Oct;22(4):235-250. * EU refers to EU4, UK and select other countries

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Falls Directly Due to Gait Abnormalities Occur Commonly in SCA

CONSEQUENCES OF FALLING	MOST PATIENTS REPORTED	
Injuries in 75% of patients	Fear of falling	Trying to prevent falls
Fractures in ~20% of patients	Restriction of activities	Troubled by near-falls

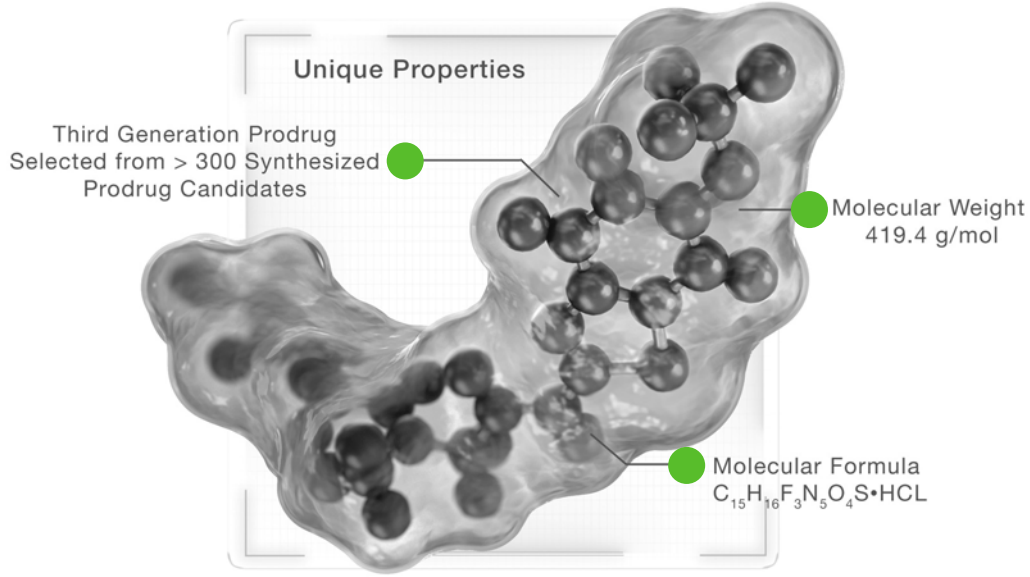
EUROSCA is a cross-European registry of SCA patients

- **More SCA3 patients experienced falls** vs other SCA genotypes*
- Frequent fallers reported more injurious falls and less balance confidence
  - They also used a walking aid or walking support more often than non-frequent fallers
- Frequent fallers were less often able to go outdoors alone
- Over 60% of patients fear falling, limiting quality of life

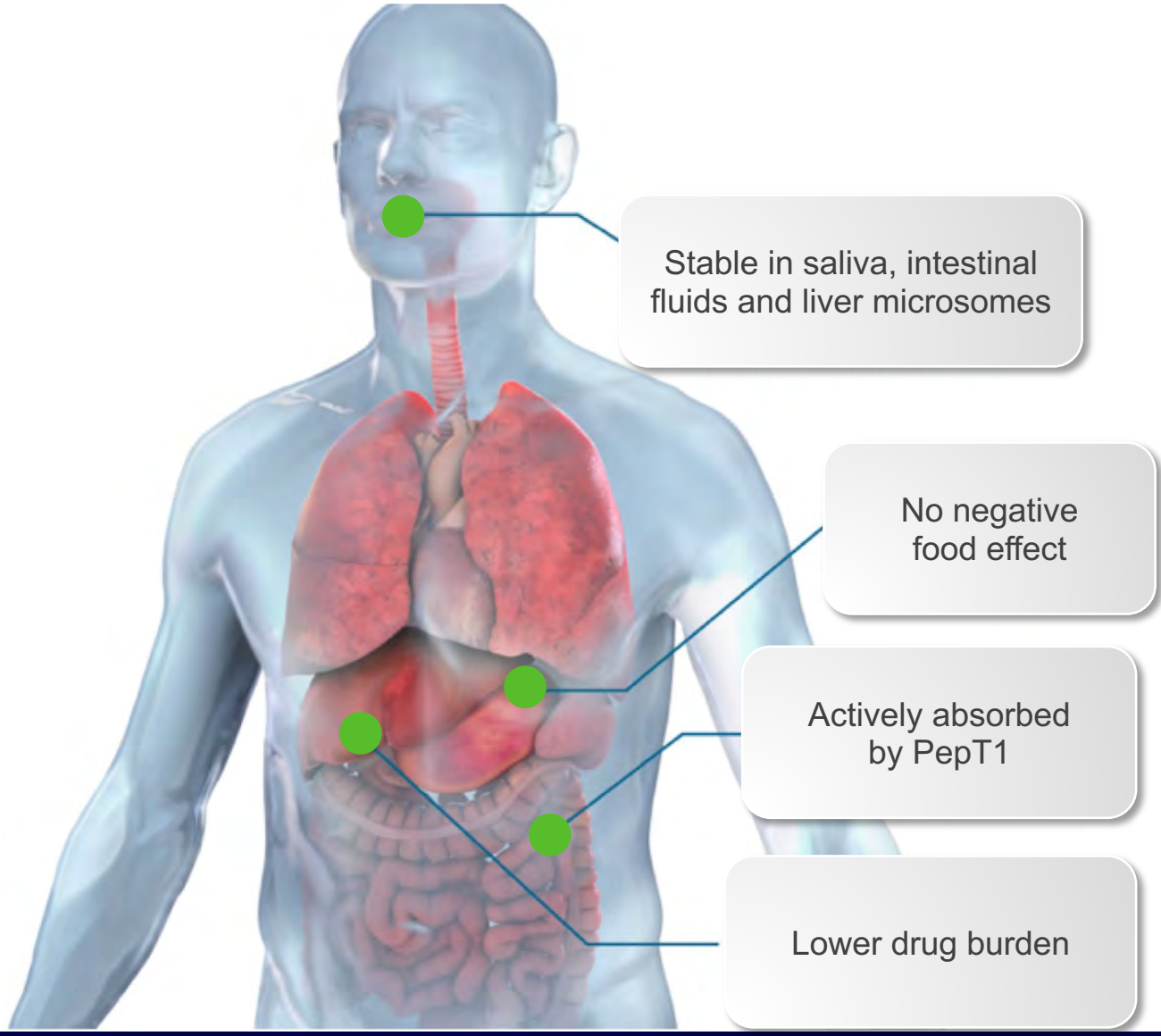
*Data based on univariate regression analysis or descriptive statistics.
Fonteyn et al. *Cerebellum.* 2010;9(2):232-239.

Troriluzole: Rational Drug Discovery to Optimize Therapy

Troriluzole



- ✓ **Improved absorption**
- ✓ **Enhanced bioavailability**
- ✓ **Reduced drug burden**
- ✓ **Reduced first pass metabolism**
- ✓ **Favorable safety profile**
- ✓ **Once-daily dosing**



PepT1, peptide transporter 1

BHV4157-206: Design of Troriluzole in SCA Phase 3 Study

48-week, double-blind, placebo-controlled study in adult participants with spinocerebellar ataxia

Population

- 18-75 years of age
- Diagnosis of SCA confirmed by genetic testing (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10)
- Ambulatory
- Stratified by SCA genotype

Primary outcome: Modified SARA scale (f-SARA)

FDA-aligned outcome measure

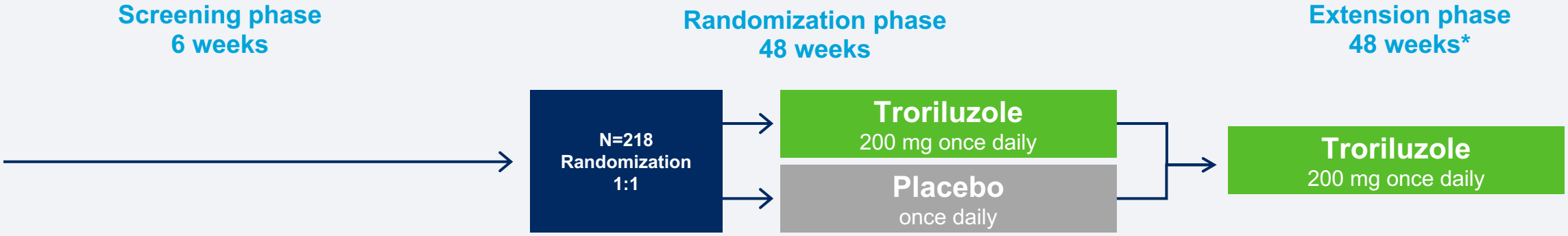
Secondary outcomes

- Safety as measured by frequency of TEAEs
- PIFAS
- FARS-ADL
- FARS-FUNC

Exploratory outcomes

- CGI-I
- PGI-C
- Neuro-QOL Lower Extremity Scale
- Neuro-QOL Upper Extremity Scale
- Neuro-QOL Fatigue Scale

Phase 3 Study Design



*Extension phase amended to follow-up to 192 weeks

CGI-I, Clinical Global Impression-Global Improvement Scale; **FARS-ADL**, Activities of Daily Living Scale from the Friedreich Ataxia Rating Scale; **FARS-FUNC**, Functional Staging for Ataxia Scale from the Friedreich Ataxia Rating Scale; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **Neuro-QOL**, Neurology Quality of Life; **PGI-C**, Patient Global Impression Change Scale; **PIFAS**, Patient Impression of Function and Activities of Daily Living Scale; **SARA**, Scale for the Assessment and Rating of Ataxia; **SCA**, spinocerebellar ataxia; **TEAE**, treatment-emergent adverse event.

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New Primary Endpoint Was Utilized in Phase 3 Trial: **f-SARA**
Novel FDA-Aligned Outcome Measure Developed by Biohaven

SARA

Scale for the Assessment and Rating of Ataxia
8-item scale with total score of 0 to 40 (most severe)

Modified based on FDA input and patient data to enhance scale reliability

f-SARA

Functional Scale for the Assessment and Rating of Ataxia
4-item scale with total score of 0 to 16 (most severe)

FDA-aligned and focused on function (but less sensitive than original scale)

f-SARA

Any change in the f-SARA score is highly clinically meaningful

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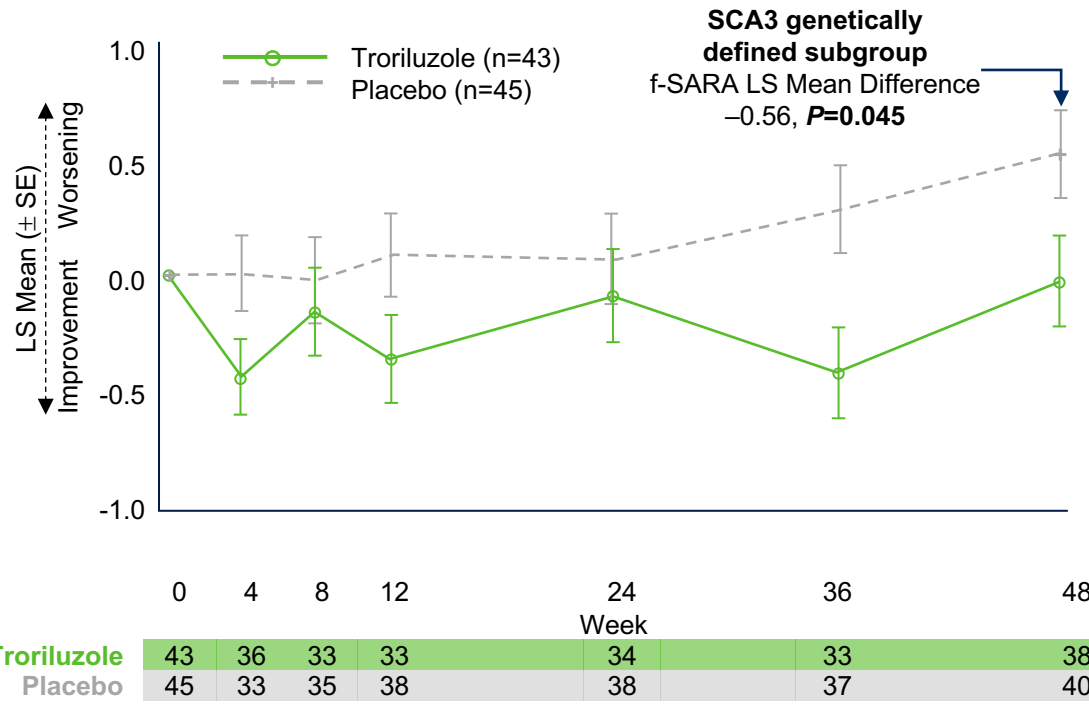
BHV4157-206: Treatment Benefit of Troriluzole Observed vs Placebo in SCA3 Randomization Stratum

Phase 3 Study in SCA Top-line Results

Primary Outcome (All SCAs)

	Troriluzole (N=106)	Placebo (N=107)	Difference TRO – PBO
Baseline f-SARA, All SCAs Mean Score	4.9	4.9	
Week 48 f-SARA, All SCAs Mean Score	5.0	5.1	
Week 48 change from baseline Least Squares Mean (SE)	0.20 (0.19)	0.27 (0.18)	-0.06 (0.20) (*P*-value 0.75)

Genotype Analysis Shows Treatment Benefit in SCA3 (41% of Participants)



SCA3 genotype demonstrates treatment benefit in the f-SARA, as well as across key secondary and exploratory endpoints, including a clinically relevant risk reduction in falls in the troriluzole arm

Results for the SCA3 group are based on a model with no covariates with fixed effects for treatment, visit, and visit-by-treatment interaction; p-values are descriptive.

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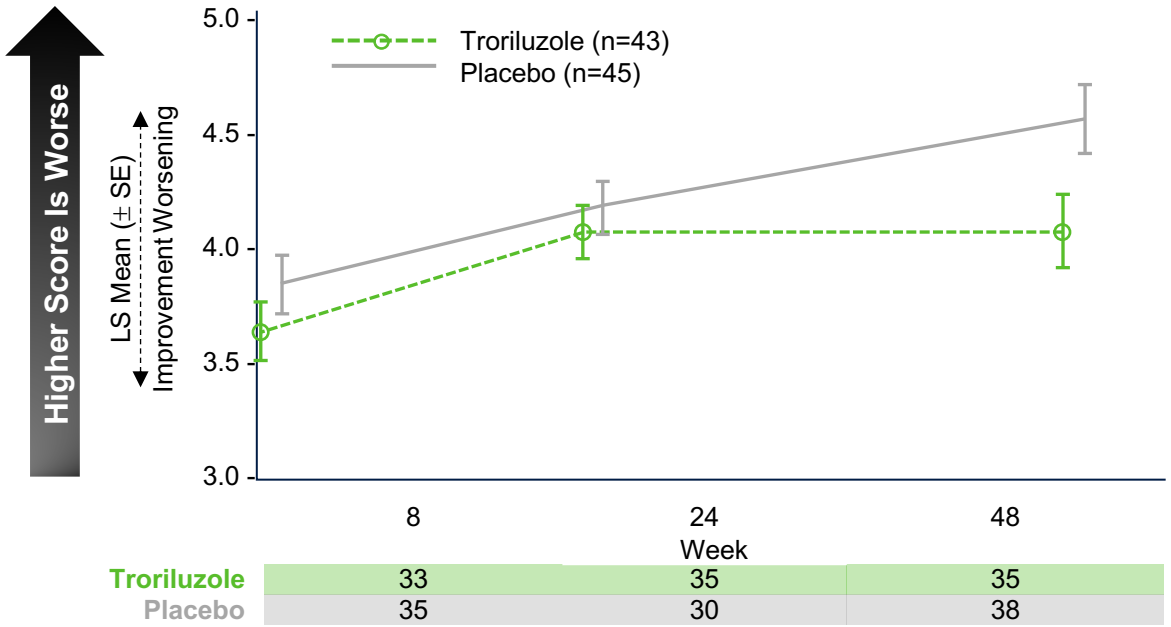
BHV4157-206: Treatment Benefit of Troriluzole Observed vs Placebo in SCA3 Participants on Clinical Global Impression of Improvement (CGI-I)

CGI-I requires the clinician to assess how much the patient's illness has improved or worsened relative to the baseline visit

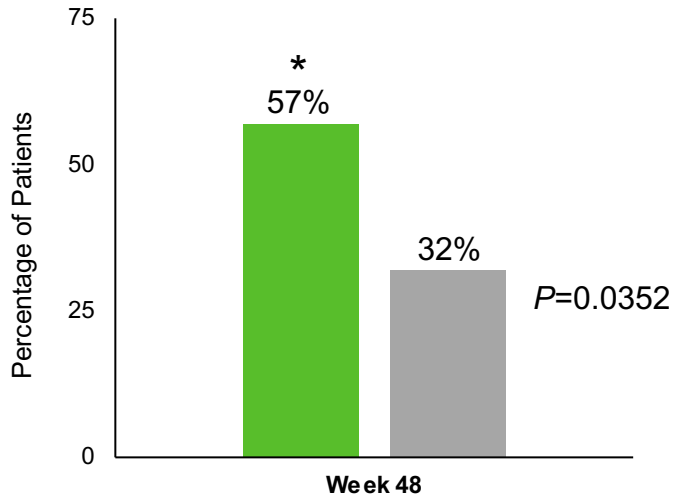
CGI-I Analysis



Troriluzole	33	35	35
Placebo	35	30	38

Improvement for **troriluzole** relative to placebo was observed at Week 48 (treatment difference -0.54; 95%CI=±1.02; *P*=0.0297)

CGI-I Categorical Responder Analysis



A higher percentage of patients treated with **troriluzole** were stable or improved on the CGI-I categorical responder analysis at Week 48

Results for the SCA3 group are based on a model with no covariates with fixed effects for treatment, visit, and visit-by-treatment interaction; p-values are descriptive.
CGI 1-4: No change or improved from baseline; CGI 5-7: Worse relative to baseline

BHV4157-206: Consistent Treatment Benefit of Troriluzole Observed vs Placebo in SCA3 Participants Across Multiple Prespecified Outcome Measures

Fall risk: Incidence Rate Ratio base on number of fall events

*Genotype analysis was post hoc as the All SCA study population (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA 10) was the mITT population for the primary analysis. PGI-C, QOL-UE, and QOL-LE scales reversed on x-axis. Results for the SCA3 group are generally based on a model with no covariates with fixed effects for treatment, visit, and visit-by-treatment interaction; p-values are descriptive.

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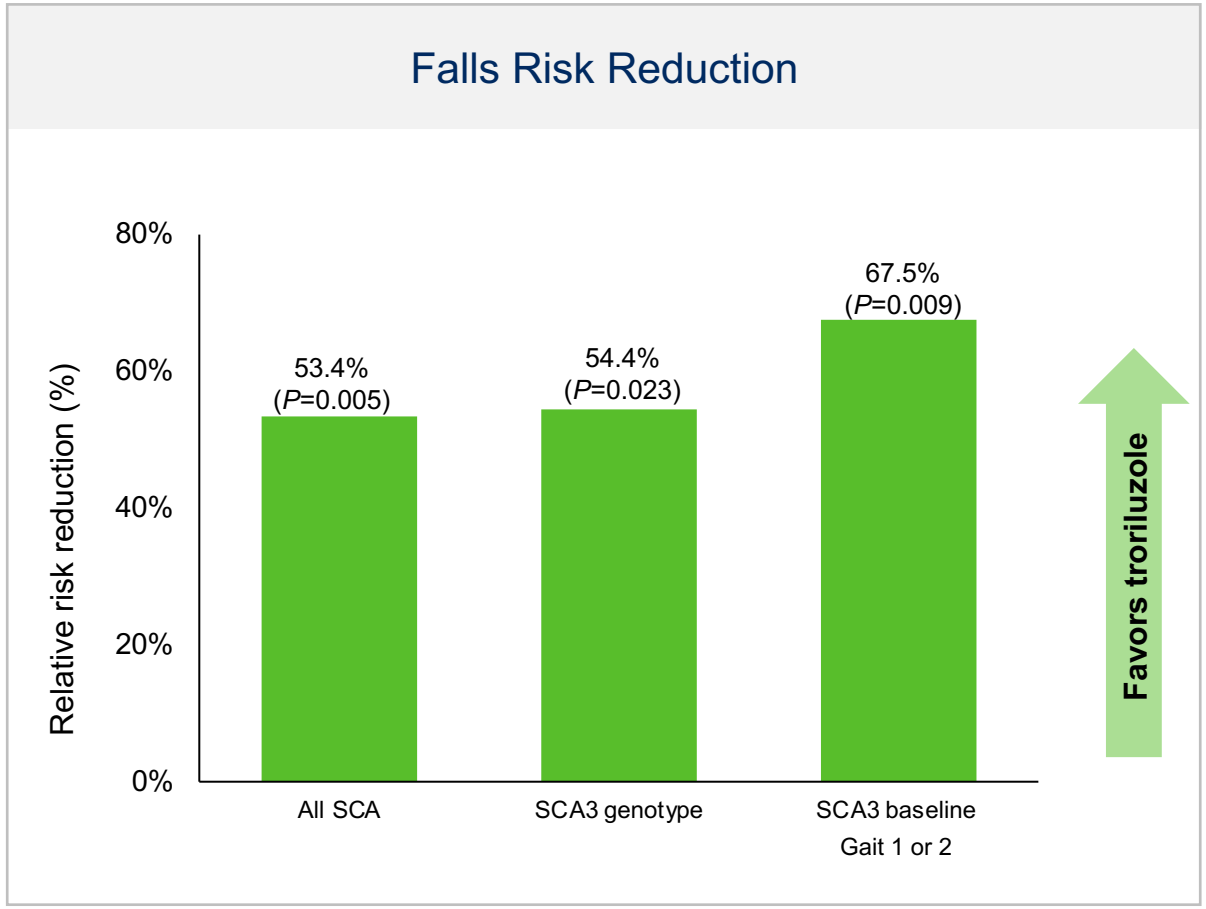
BHV4157-206: Troriluzole-Treated Participants Showed a Substantial Risk Reduction in Falls in SCA3, as well as All SCA Study Population

Treatment with troriluzole for 48 weeks reduced the risk of fall events by 53% in subjects in the overall (All SCA) population, by 54% in participants in the SCA3 population, and by 68% in participants with SCA3 who were ambulatory (i.e., baseline Gait 1 or 2).

"The importance of morbidity related to falls in this patient population cannot be overstated." – Jeremy Schmahmann, MD

Professor of Neurology at Harvard Medical School and Founding Director of the Ataxia Center at Massachusetts General Hospital

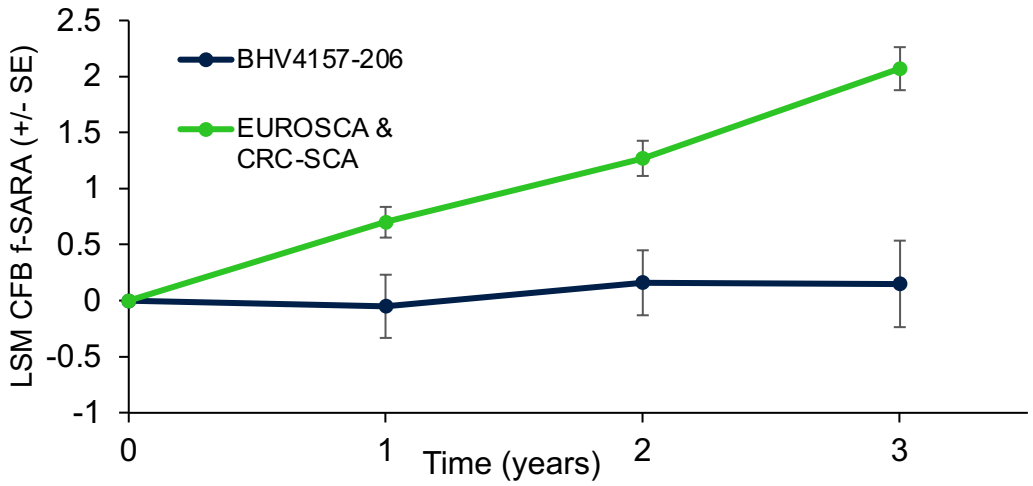


Falls were captured as adverse events if reported as "worsening falls" or if the fall resulted in an injury.
For the events analysis, a generalized linear model was fit using a Poisson family model with a log link function.

BHV4157-206: Matching Adjusted Indirect Comparison (MAIC)-Troriluzole Demonstrated Benefit in SCA3, as Well as All SCA, Over 3 Years

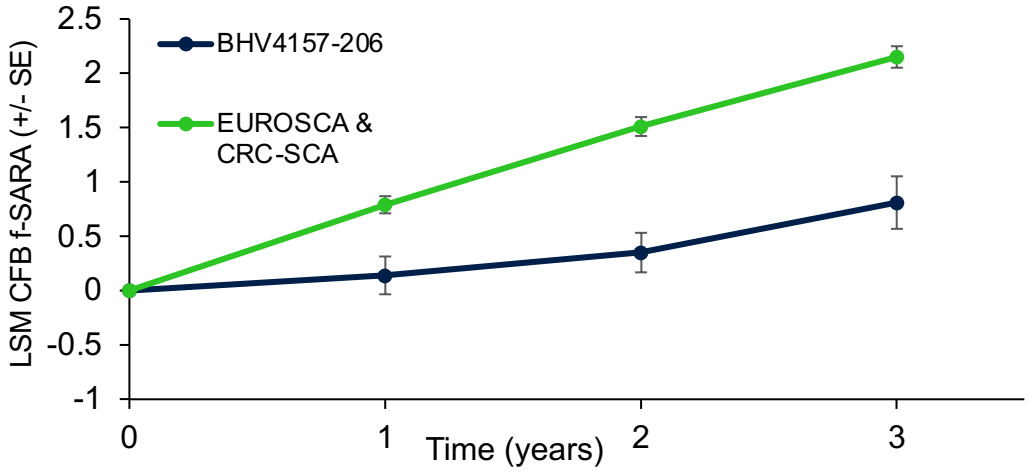
- At years 1, 2, and 3, change from baseline in f-SARA scores was significantly better among troriluzole patients vs the matched external control
- Validation metrics from f-SARA confirm that these changes are clinically relevant and meaningful to patients

SCA3 Only



EUROSCA & CRC-SCA	205	193	121	76
BHV4157-206	38	38	34	14

All SCA



EUROSCA & CRC-SCA	611	568	384	273
BHV4157-206	96	94	79	35

Combined CRC-SCA and EUROSCA data – *P* values < 0.018

LSM, least squares mean; **CFB,** change from baseline; **EUROSCA,** cross-European registry of SCA patients; **CRC-SCA**, Clinical Research Consortium for Spinocerebellar Ataxias

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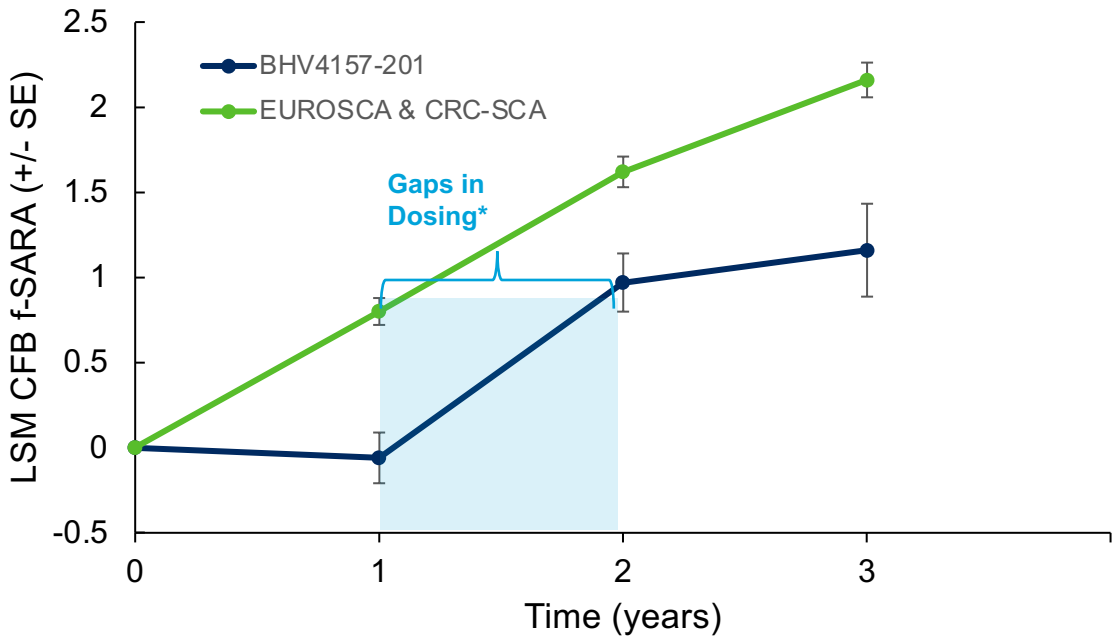
BHV4157-201: Matching Adjusted Indirect Comparison (MAIC)- Troriluzole Demonstrated Benefit in All SCA vs Natural History Cohorts

Progression During Treatment Gap and Stabilization Post-Gap (All SCA)



EUROSCA & CRC-SCA	**611**	**568**	**384**	**273**
BHV4157-201	**103**	**102**	**65**	**20**

*Gaps in troriluzole dosing occurred after year 1, and ranged from 2 weeks to >1 year

At year 1, change from baseline in f-SARA scores was significantly reduced among troriluzole-treated patients vs the matched natural history referent (EUROSCA & CRC-SCA), with progression observed during troriluzole treatment gap and stabilization post-treatment gap

Combined CRC-SCA and EUROSCA data – P values ≤0.0007

LSM, least squares mean; **CFB,** change from baseline; **EUROSCA,** cross-European registry of SCA patients; **CRC-SCA**, Clinical Research Consortium for Spinocerebellar Ataxias

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John Tilton

Chief Commercial Officer,
Rare Disease

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Preparing to Serve People Living with SCA3

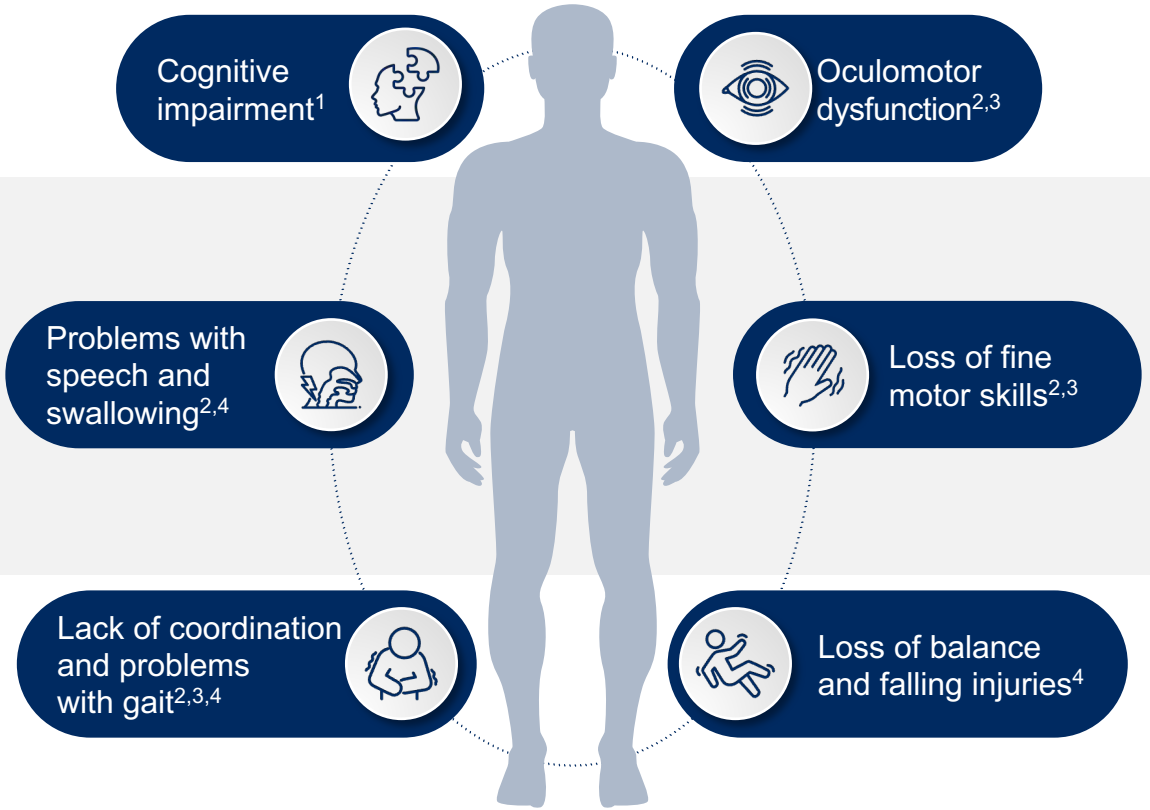
SCAs Are Characterized by Relentlessly Progressive Cerebellar Degeneration and Premature Death With No Approved Treatment

If approved, troriluzole will be the first and only approved treatment for people living with SCA3

SCA genotypes differ in:

- Range of symptoms[5]
- Disease severity and progression[5]

In SCA3, the 10-year survival rate is 73%[6]

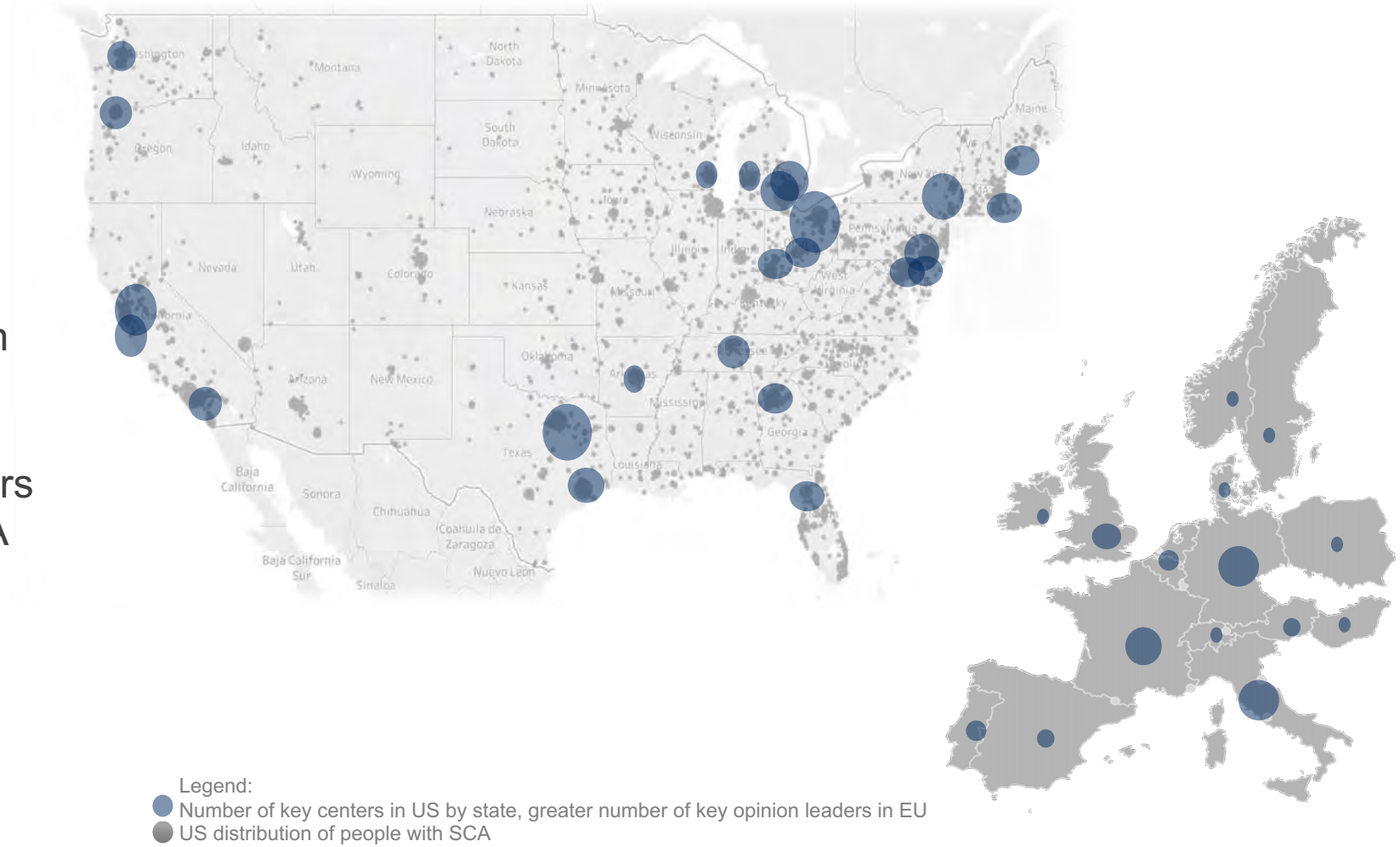


Patients may present with symptoms several years before the diagnosis of SCA[3]

1. Moriarty A, Cook A, Hunt H, Adams ME, Cipolotti L, Giunti P. A longitudinal investigation into cognition and disease progression in spinocerebellar ataxia types 1, 2, 3, 6, and 7. *Orphanet J Rare Dis.* 2016;11(1):82. 2. What is Ataxia? National Ataxia Foundation. Accessed September 17, 2022. www.ataxia.org/what-is-ataxia/#whatIsAtaxia 3. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. *Nat Rev Dis Primers.* 2019;5(1):24. 4. Machado-Joseph Disease and the Spinocerebellar Ataxias Fact Sheet. National Institute of Neurological Disorders and Stroke. Updated June 7, 2021. Accessed September 17, 2022. www.ninds.nih.gov/machado-joseph-disease-and-spinocerebellar-ataxias-fact-sheet 5. Brooker SM, Edamakanti CR, Akasha SM, Kuo SH, Opal P. Spinocerebellar ataxia clinical trials: opportunities *and challenges. Ann Clin Transl Neurol. 2021;8(7):1543-1556. 6. Diallo A, Jacobi H, Cook A,et al. Survival in patients with spinocerebellar ataxia types 1, 2, 3, and 6 (EUROSCA): a longitudinal cohort study. Lancet Neurol. 2018;17(4):327-334.*

Centralized Treatment for People Living With SCA Allows for a Targeted and Efficient Rare Disease Commercialization Plans in US and Europe

- SCA3 diagnosed in up to 6,000 North America, 4,600 EU/Japan[1-4]
- Despite geographical distribution of people with SCA, key ataxia/movement disorder centers led by key opinion leaders manage many patients with SCA
- Focused Rare Disease Commercial staff of ~50 in US and ~40 in Europe will drive successful launches



1. Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology*. 2014;42(3):174-83. 2. Ashizawa T, Figueroa KP, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. *Orphanet J Rare Dis*. 2013 Nov 13;8:177. 8. U.S. and World Population Clock. United States Census Bureau. Accessed September 17, 2022. https://www.census.gov/popclock 9. EUROSTAT. Accessed May 22, 2023 https://ec.europa.eu/eurostat/

Biohaven Continues to Closely Collaborate With the Ataxia Organizations and Will be Ready to Serve Patients Across the Globe

- Collaborations with leading SCA researchers
- Partnerships with advocacy organizations
- Scientific membership in research groups
- Key contribution to the ongoing development of a quality natural history study in SCA

Biohaven Pharmaceuticals Inaugural Partner Of National Ataxia Foundation's Drug Development Collaborative

National Ataxia Foundation

ARCA GLOBAL

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

CPTA
CRITICAL PATH TO THERAPEUTICS FOR THE ATAXIAS

MGH 1811

ATAXIA
Ataxia UK

HOUSTON Methodist
CONTINUING CARE HOSPITAL

ATAXIA GLOBAL INITIATIVE

SCA Global

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SCA3 Summary

Pivotal Phase 3 Completed

Troriluzole demonstrates significant treatment benefit in SCA3 across multiple efficacy and safety endpoints

Safety Database

Large safety database shows safe and well tolerated for up to 6 years

Regulatory

- Orphan Designations in both US and EU
- Fast Track Designation in US
- US NDA Submitted 2Q 2023
- MAA Submission planned for 2023

Market Opportunity and Commercial Readiness

- Ultra-rare, genetically-defined, progressive neurodegenerative disease
- No currently approved treatments
- Partnership with KOLs, centers of excellence and patient advocacy
- Extensive rare disease commercialization experience
- Preparing to serve people living with SCA3 in US/EU upon approvals

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PANEL DISCUSSION

Glutamate Platform

MODERATOR

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Equity Research Analyst

CANTOR Fitzgerald

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Associate Professor

Department of Neurology, Johns Hopkins

John Tilton

Chief Commercial Officer, Rare Disease

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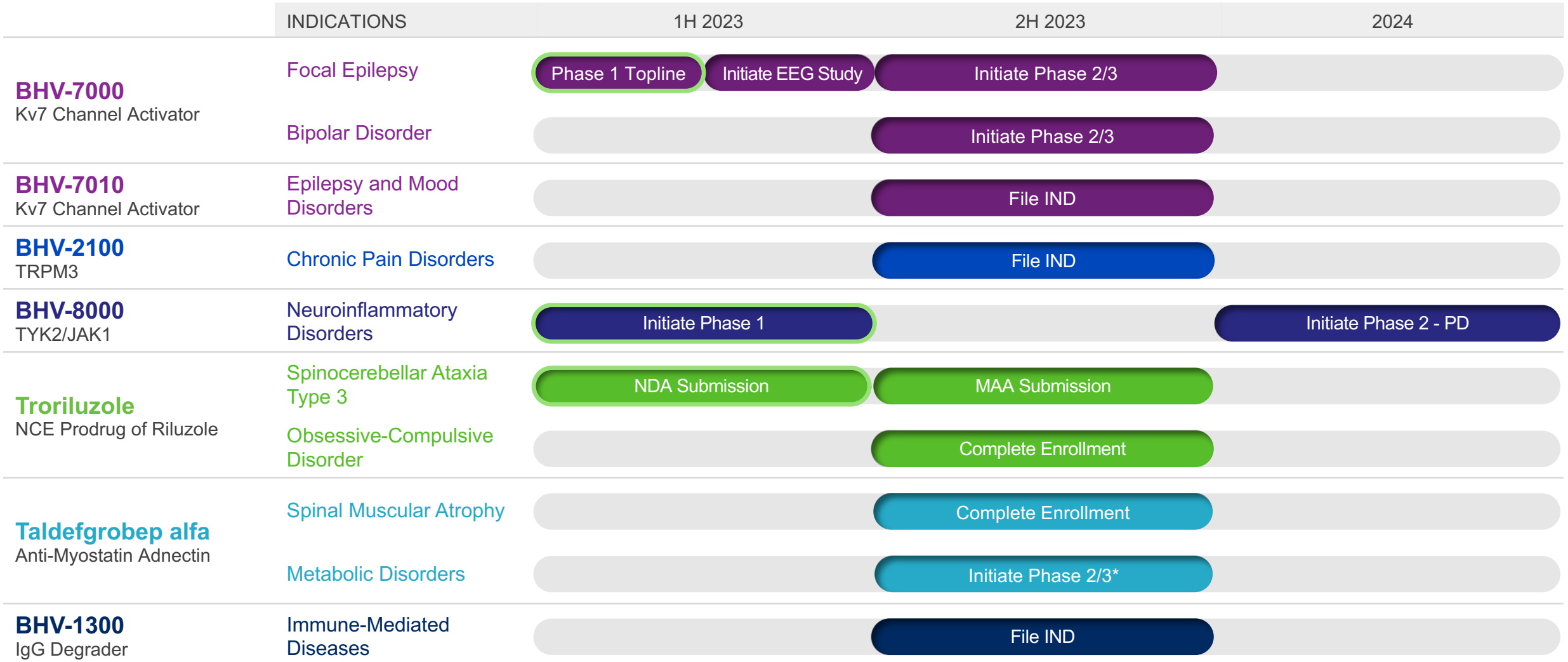
Anticipated Near-Term Milestones

Milestone achieved



* Planning in progress
PD, Parkinson's disease

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THANK YOU!

BHVN
LISTED
NYSE