# DAYS MATTER™

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BHVN
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NYSE

November 2024

**Nikki, Living with Epilepsy**
AND HELPING RECRUIT IN
BIOHAVEN CLINICAL TRIALS

# Forward-Looking Statements

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 clinical trials, the timing of and the availability of data from those 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. 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 FDA; the timing and outcome of expected regulatory filings; complying with applicable U.S. regulatory requirements; the potential commercialization of Biohaven's product candidates; 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". The forward-looking statements are made as of the date of this presentation, and Biohaven does not undertake any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law. 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.

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GROUNDBREAKING LEGACY OF SUCCESS IN MIGRAINE

Nurtec® ODT (rimegepant)

Zavzpret™ (zavegepant)

# Biohaven's R&D team is focused on growing the next generation of innovative therapeutics

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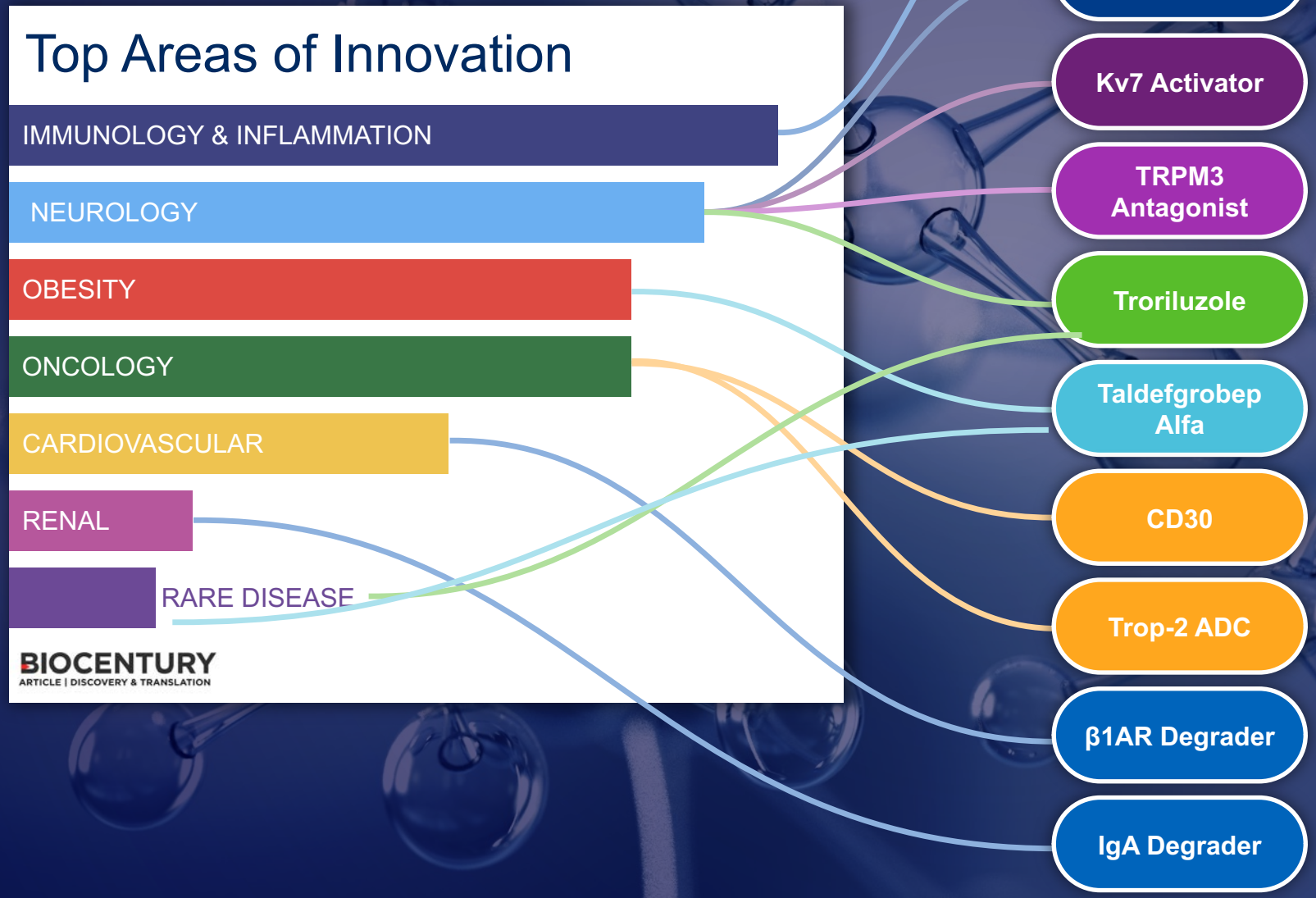
NEUROSCIENCE | IMMUNOLOGY | ONCOLOGY

# BIOHAVEN PORTFOLIO

## Positioned for Future Value Creation for Patients and Investors




1. Adapted from BioCentury survey: https://www.biocentury.com/article/650883/move-over-oncology-i-i-will-write-the-next-big-stories-in-innovation#

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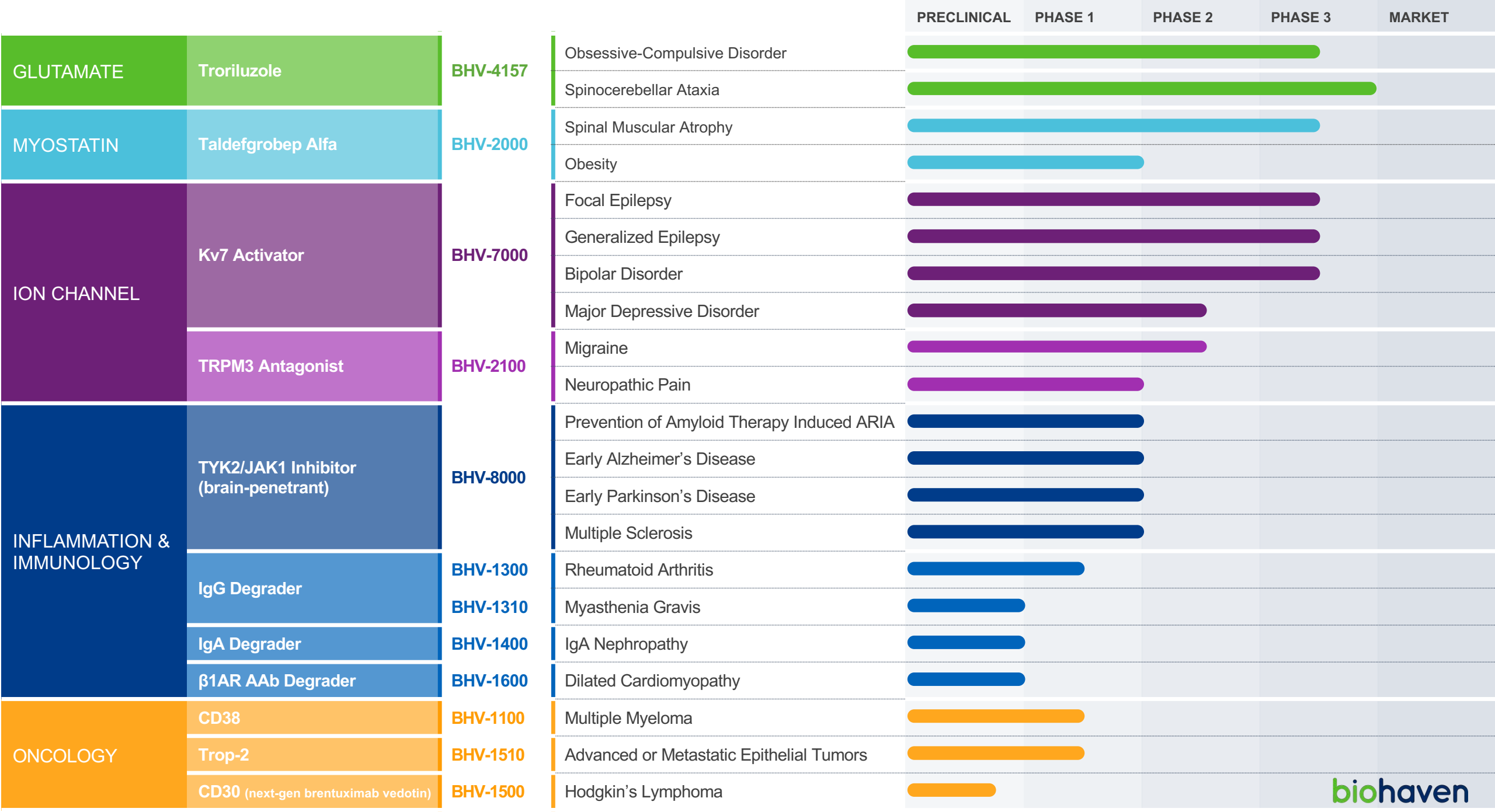
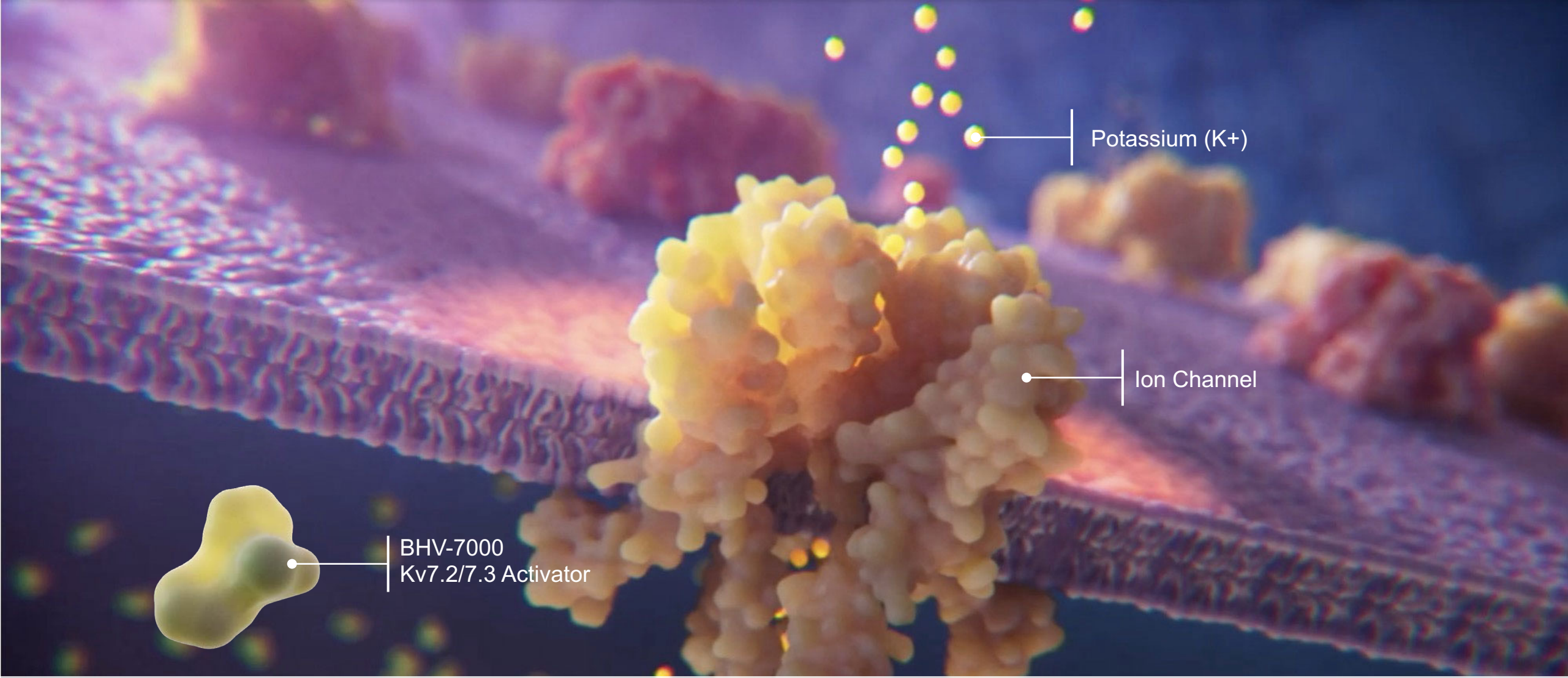



**ARIA**, Amyloid-related imaging abnormalities




# Ion Channels

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# BHV-7000
## SELECTIVE Kv7 ACTIVATOR

### Kv7 is Transformational Target in Neurology and Neuropsychiatry
- Selective Kv7 activation avoids unwanted CNS side effects
- Clinically validated in epilepsy, MDD and pain

### BHV-7000 is Potential Best-in-Clinic Selective Kv7 Activator with Blockbuster Potential
- Rationally designed to eliminate $GABA_A$ receptor activation
- No dose-limiting CNS side effects observed in Phase 1
- CNS target engagement at predicted therapeutic concentrations confirmed in Phase 1 EEG study

### BHV-7000 Also has Potential to Deliver Treatment in Rare Genetic Disorders and Broader Indications
- Efficacious in activation of channels across a broad set of KCNQ2-DEE mutations
- Attenuates hyperexcitability in SN-iPSC from IEM patients
- Opportunity to initiate POC clinical trials as gateway to broader indications

### Recruitment now underway in 5 late-stage trials with enrollment exceeding timeline expectations in MDD and bipolar disorder

**KEY POINT**

5 Phase 2/3 trials underway in epilepsy and mood disorders

**IEM**, inherited erythromelalgia; **SN-iPSC**, human induced pluripotent stem cell derived sensory neurons; **GABA**, γ-aminobutyric acid.

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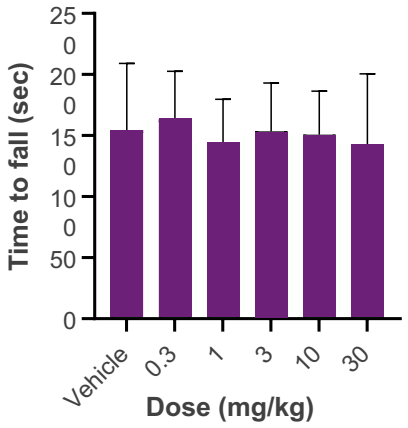
# Dialing Out $GABA_A$ Receptor Activation Clinically Proven to Reduce CNS Side Effects With Selective Kv7 Activator BHV-7000

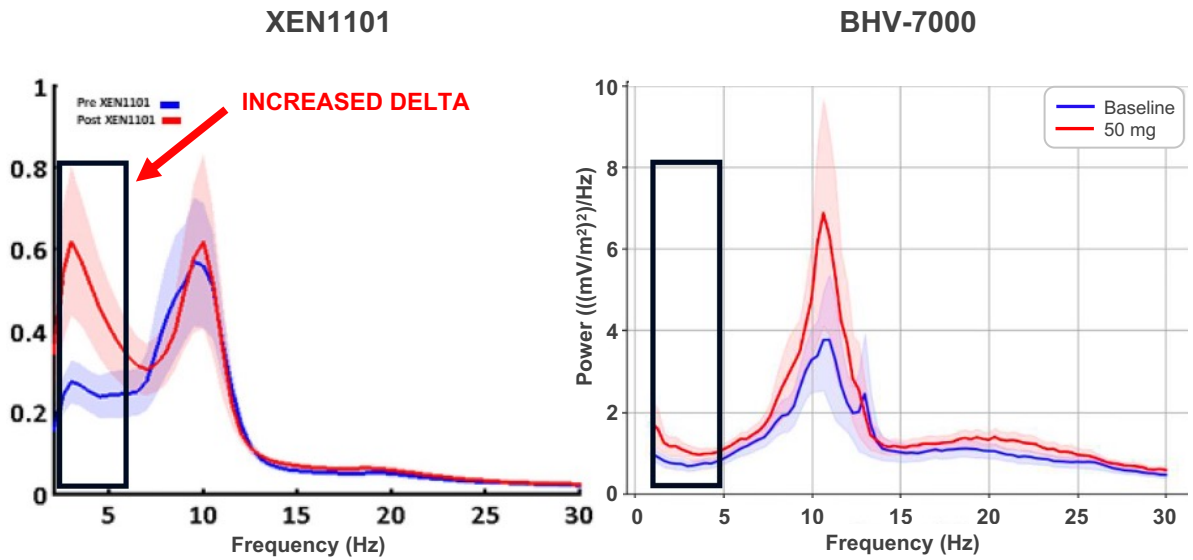
**PRECLINICAL**
No effects on motor performance on rotarod




**PHASE 1**
Not associated with CNS adverse events (AEs) typical of other ASMs in healthy volunteers

| Pooled CNS AEs | BHV-7000 MAD Pooled N=29 | XEN1101 MAD Pooled N=18 |
|---|---|---|
| Somnolence | 0% | 39% |
| Headache | 21% | 39% |
| Balance disorder/ dizziness | 10% | 34% |
| Memory impairment | 0% | 28% |
| Sensory disturbance | 0% | 11% |
| Speech disorder | 0% | 33% |

**EEG**
Significant impact on alpha spectral power confirms target engagement, minimal impact on delta-theta spectral power consistent with lack of somnolence in Phase 1

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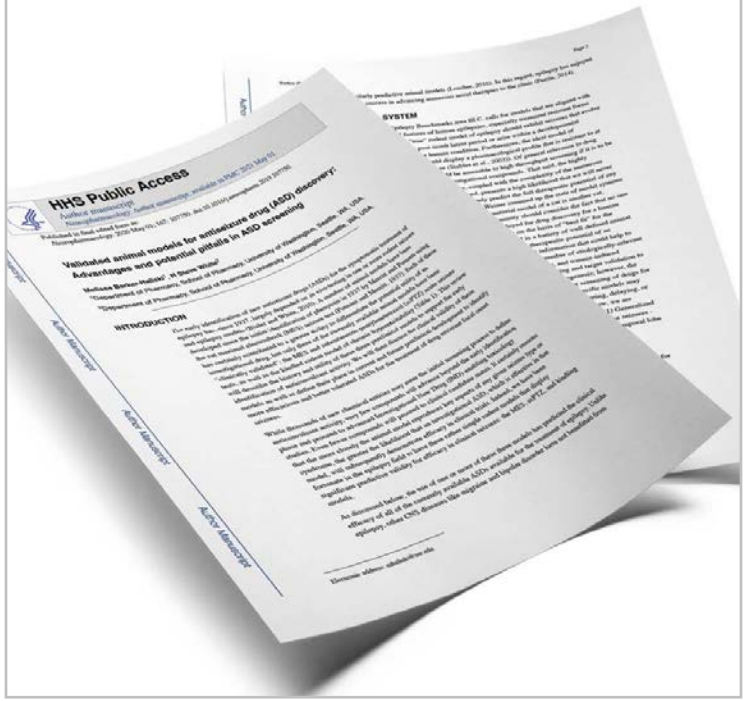
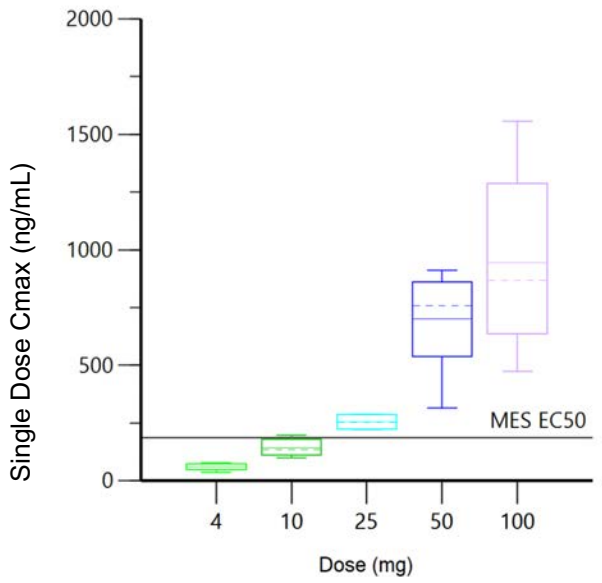
# BHV-7000 Profile Allows for Optimizing Efficacy and Safety

## MES Predicts Clinical Efficacy

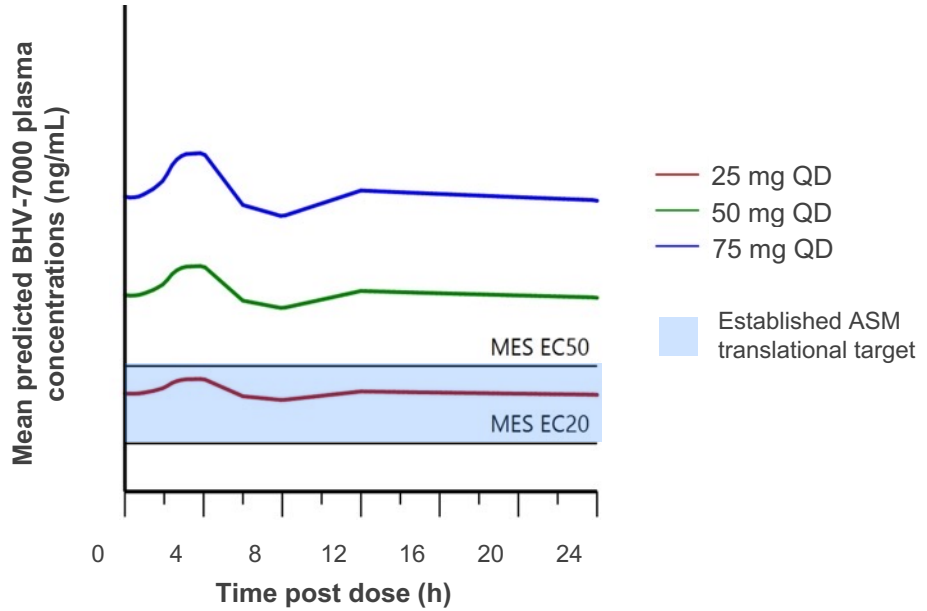



Loscher, 2016.

## Single Doses (up to 100 mg) of Spray-Dried Dispersion Suspension




## Phase 2/3 Clinical Trial Doses Provide Broad Coverage of Predicted Therapeutic Target Levels




**KEY POINT**

Concentrations greater than 5x therapeutic target levels predicted by MES model achieved in Phase 1 studies

*EC50 based on preclinical maximal electroshock seizure (MES) models.

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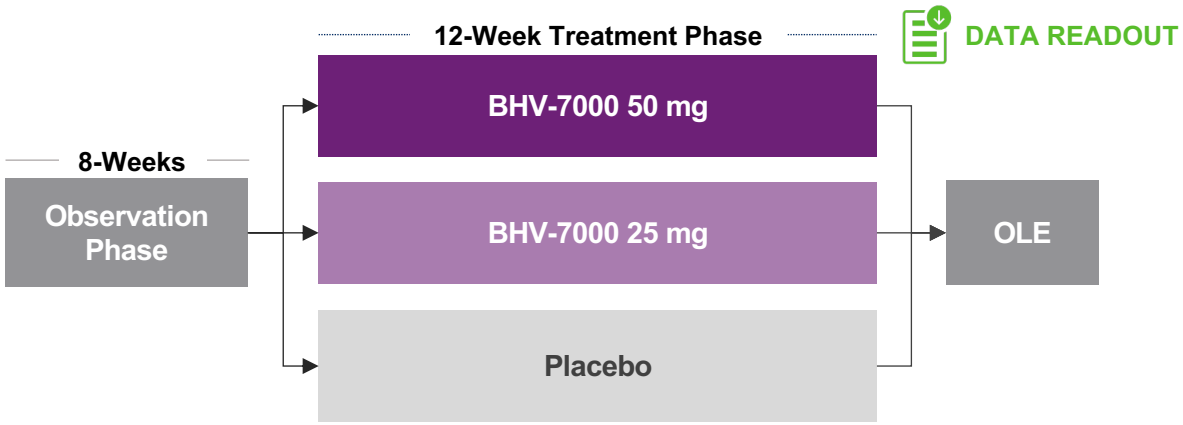
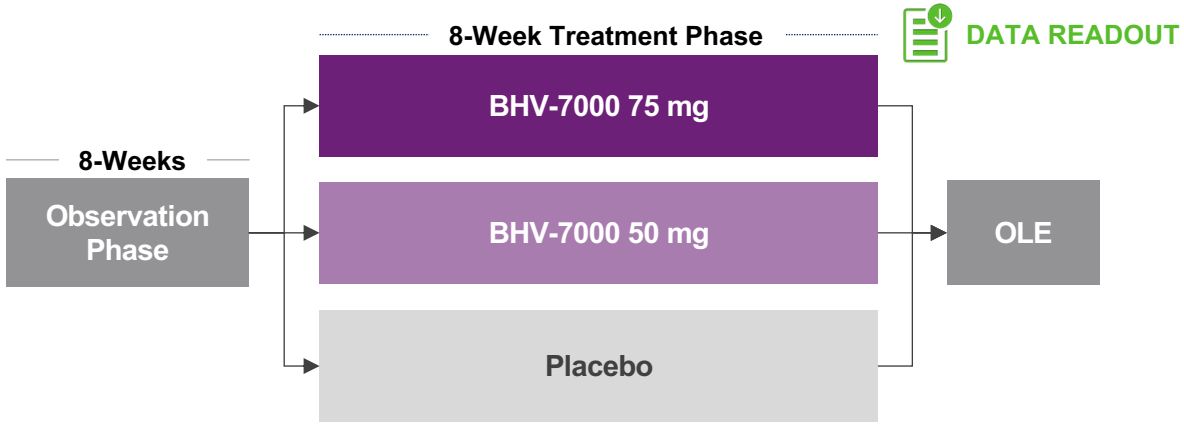
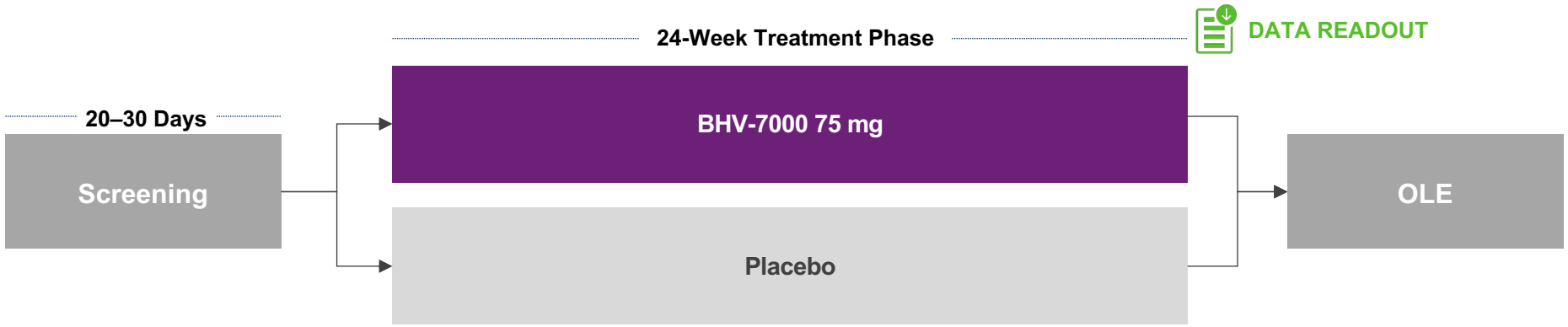
# Two Phase 2/3 Studies in Focal Epilepsy Are Ongoing




| | |
|---|---|
| **DESIGN** | Randomized, double-blind, placebo-controlled trials |
| **POPULATION** | Subjects 18-75 years of age with refractory focal epilepsy |
| **SAMPLE SIZE** | 390 subjects in each study (randomized 1:1:1) |
| **KEY ENTRY CRITERIA** | Average of ≥4 observable focal seizures per 28 days |
| **ENDPOINTS** | Change in seizure frequency, 50% responder rate, seizure freedom |

# Phase 2/3 Study in Idiopathic Generalized Epilepsy Is Ongoing




| | |
|---|---|
| **DESIGN** | Randomized, double-blind, placebo-controlled trial |
| **POPULATION** | Subjects 18-75 years old with idiopathic generalized epilepsy with intractable generalized tonic-clonic seizures |
| **SAMPLE SIZE** | 242 subjects (randomized 1:1) |
| **TREATMENT** | BHV-7000 75 mg vs. placebo |
| **TREATMENT DURATION** | Up to 24-week double-blind phase |
| **ENDPOINT** | Time to event (2nd day with generalize tonic-clonic seizure) |

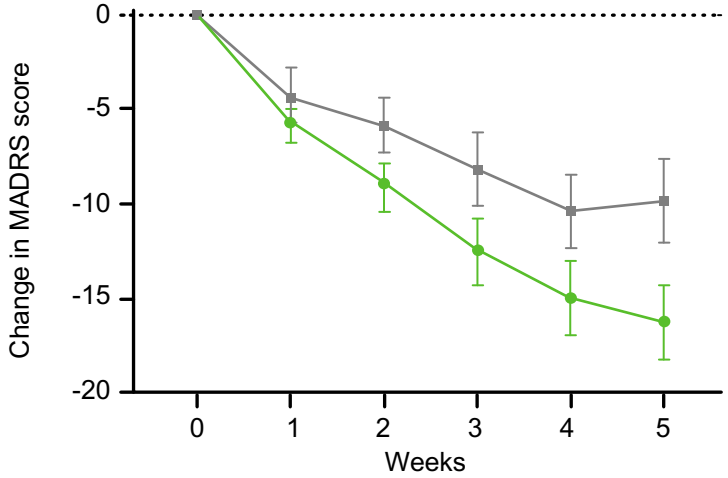
KEY POINT

Pivotal Phase 2/3 IGE study initiated in 1H 2024

# Kv7 Activation Validated in the Clinic for Major Depressive Disorder

**Randomized clinical trials in MDD with two nonselective Kv7 activators have demonstrated potential for rapid onset of clinically meaningful benefit in symptoms of depression and anhedonia**

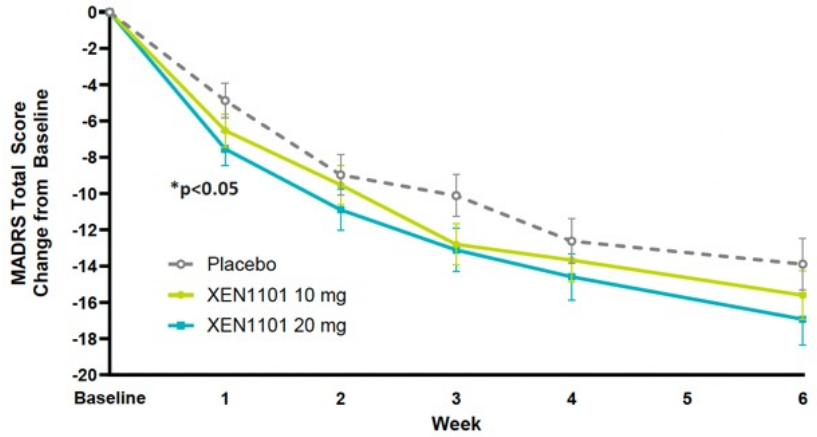
## Ezogabine Demonstrated Robust Clinical Benefit (n=45)[1]




- 7.9-point benefit vs. placebo on MADRS (p<0.001)
- 6.9-point benefit vs. placebo on SHAPS (p<0.001)
- **Dose-limiting side effects in 20% of study subjects**

Costi et al, Am J Psychiatry. 2021 May 01; 178(5): 437–446.

## XEN1101 Demonstrated Rapid Onset of Clinical Benefit With a Clear Dose Response (n=167)[2]




- 3-point benefit on MADRS (p=0.135) vs. placebo in 20 mg group, at week 1, 2.7-point benefit (p<0.05)
- 2.5-point benefit on SHAPS at week 6 (p<0.05) vs. placebo in 20 mg group
- **Efficacy not optimized likely due to dose limiting tolerability concerns**

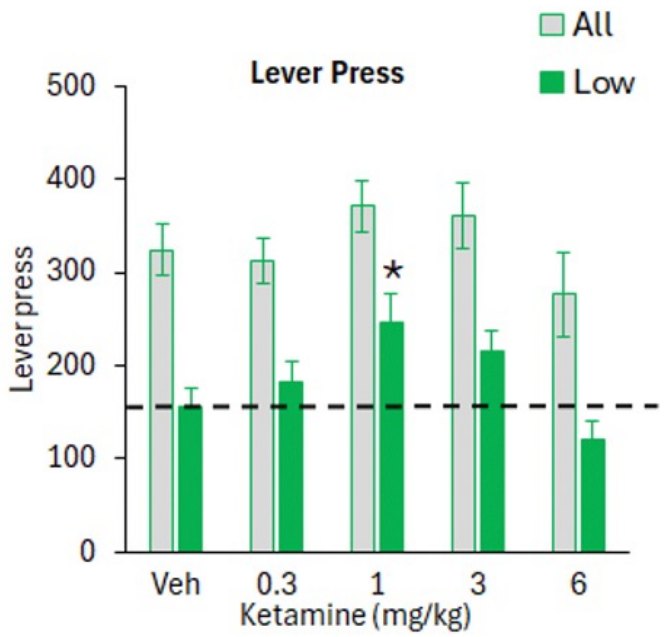
Xenon Pharmaceuticals Corporate update, November 27, 2023

**KEY POINT**

BHV-7000 has ideal profile for MDD due to **higher potential dose** and lower rates of CNS AEs vs. nonselective Kv7 activators

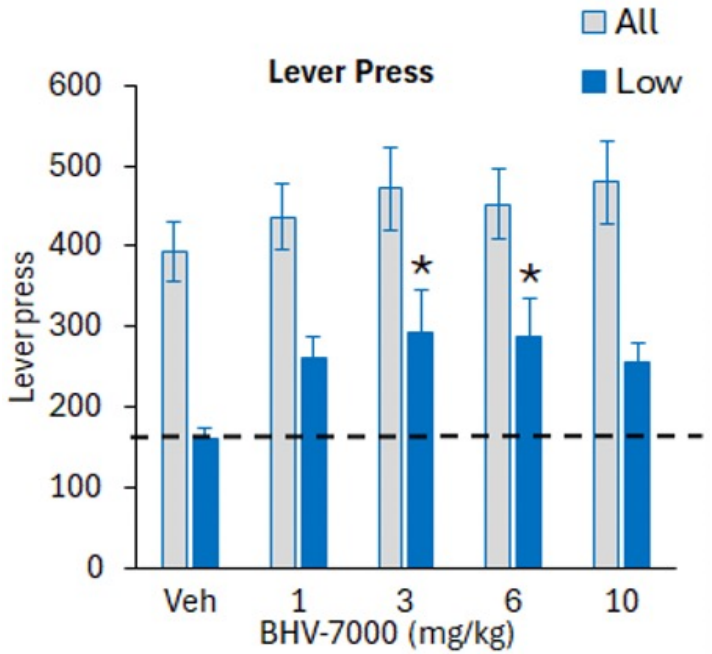
# Potential Convergence of Therapeutic Effects of BHV-7000 and Ketamine

## Ketamine Effects In 5-Choice Operant Model



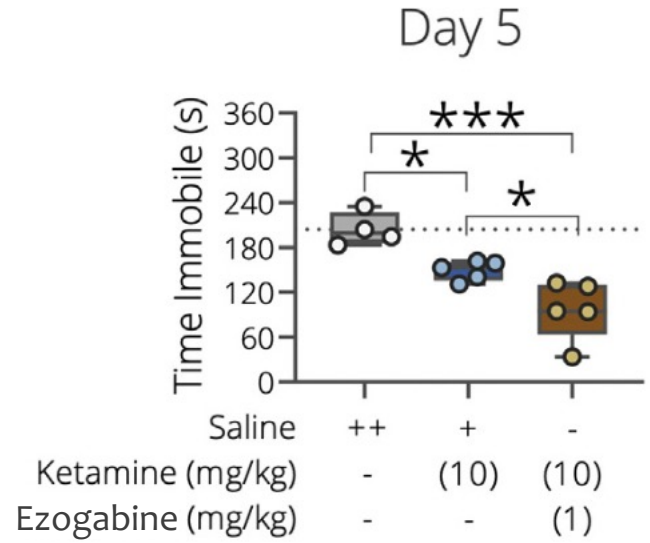

Higgins et al. Front Pharmacol. 2021 Feb 26; 12:640241.

## Similar BHV-7000 Effects in 5-Choice Operant Model



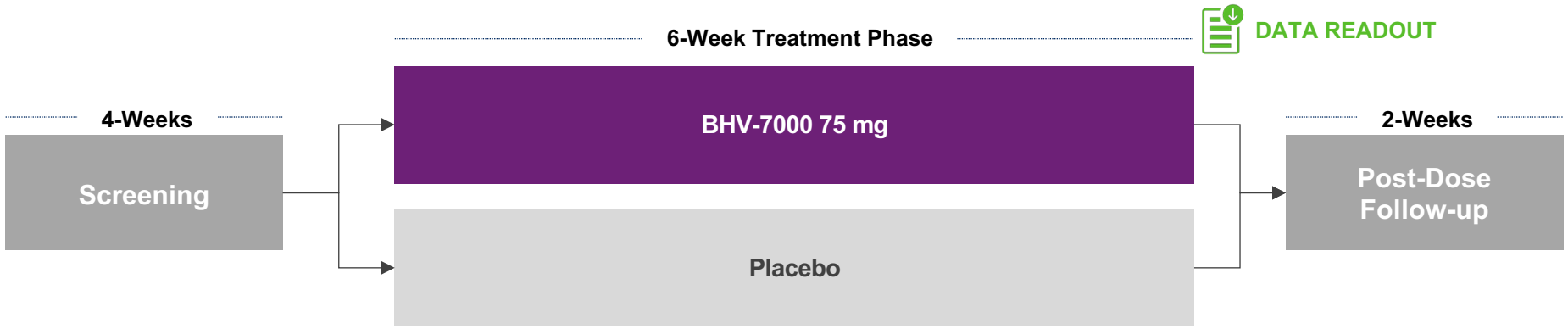

Biohaven data on file.

## Ezogabine Enhances Ketamine Efficacy in Forced Swim Test Model




Lopez et al. Neuron. 2022 Jul 20;110(14):2283-2298.e9.

# Phase 2 Study in Major Depressive Disorder Is Ongoing




| | |
|---|---|
| **DESIGN** | Randomized, double-blind, placebo-controlled trial |
| **POPULATION** | Subjects with Major Depressive Disorder (MDD) with at least one prior depressive episode who are currently experiencing a depressive episode with anhedonia (HAM-D ≥ 20, SHAPS ≥ 20) |
| **SAMPLE SIZE** | 300 subjects (randomized 1:1) |
| **TREATMENT** | BHV-7000 vs. placebo |
| **TREATMENT DURATION** | 6-weeks |
| **ENDPOINTS** | MADRS (primary), SHAPS, CGI-S, Q-LES-Q-SF |

KEY POINT

Pivotal Phase 2 study initiated in 1H 2024

**HAM-D**, Hamilton Depression Rating Scale; **SHAPS**, Snaith-Hamilton Pleasure Scale; **MADRS**, Montgomery–Åsberg Depression Rating Scale; **CGI-S**, clinical global iimpression, severity; **Q-LES-Q-SF**: Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form.

# Compelling Evidence for Targeting Kv7 in Bipolar Disorder

## Human Genetics

- Bipolar disorder risk is heritable
- Ankyrin G (ANK3) is highly associated bipolar disorder risk gene in GWAS[1,2]
  - Ankyrin G anchors Kv7.2/7.3 channels to neuronal cell membrane[3]
  - Most significant gene-gene interaction in bipolar disorder GWAS is between ANK3 and Kv7.2[4]
- Kv7.2 and Kv7.3 are also directly linked to bipolar disorder risk by several studies[4,5]

## Molecular Profiling of Bipolar Disorder Patient Tissues

- Evidence of significant transcriptional, epigenetic and proteomic changes in Kv7 channels in bipolar disorder
  - Bipolar disorder patient brain tissue demonstrates deregulation of Kv7 channels[6,7]
  - Kv7.3 gene DNA methylation patterns are altered, and expression is decreased, in bipolar disorder patients[7]

## Preclinical Models

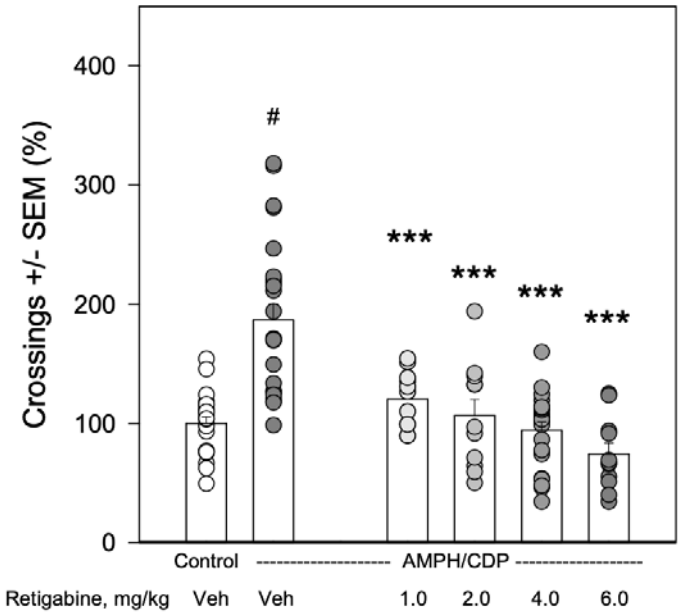
Kv7 activation demonstrates treatment benefits in preclinical models

1. Ferreira MA et al, Nat Genet. 2008 Sep;40(9):1056-8. 2. Psychiatric GWAS Consortium Bipolar Disorder Working Group. Nat. Genet. 2011. 3. Pan Z et al, J Neurosci. 2006 Mar 8;26(10):2599-613 . 4. Judy JT et al, Front Genet. 2013 May 17;4:87. 5. Koromina M et al, medRxiv [Preprint]. 2024 Feb 13:2024.02.12.24302716. 6. *Smolin et al. International Journal of Neuropsychopharmacology*, Volume 15, Issue 7, August 2012, Pages 869–882. 7. Kaminsky Z et al, Bipolar Disord. 2015 Mar;17(2):150-9.

# Ezogabine Improves Behavioral and Imaging Outcomes in Preclinical Mania Models

## Amphetamine-chlordiazepoxide (AMPH/CDP) rodent mania model

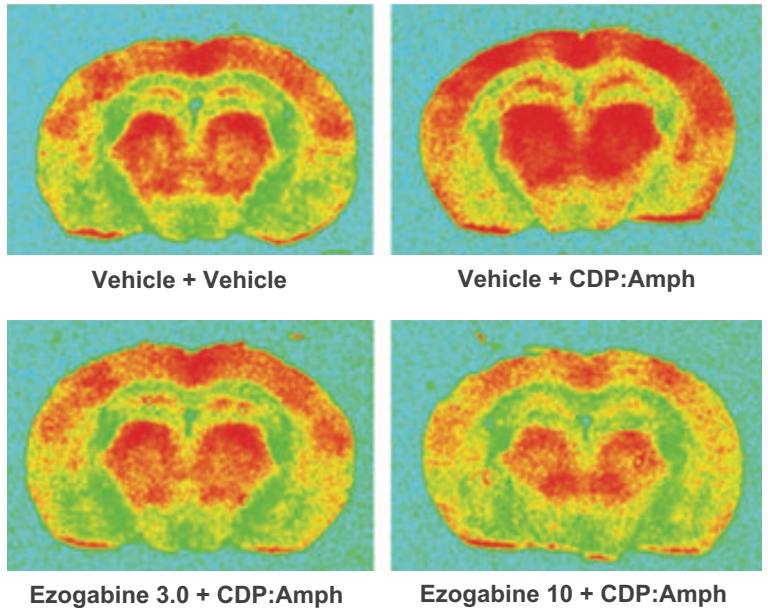
### Ezogabine Reduces Hyperactive Locomotion




Kv7.2/7.3 activation results in dose-dependent decreases in AMPH/CDP induced hyperlocomotion without affecting basal locomotor activity at these doses

Dencker D, et al Epilepsy Behav. 2008 Jan;12(1):49-53 .

### Ezogabine Reduces Brain Hypermetabolism




Kv7.2/7.3 activation results in dose-dependent decreases in brain hypermetabolism assessed via 2-deoxyglucose uptake

Kristensen LV et al , J Neurochem. 2012 May;121(3):373-82 .

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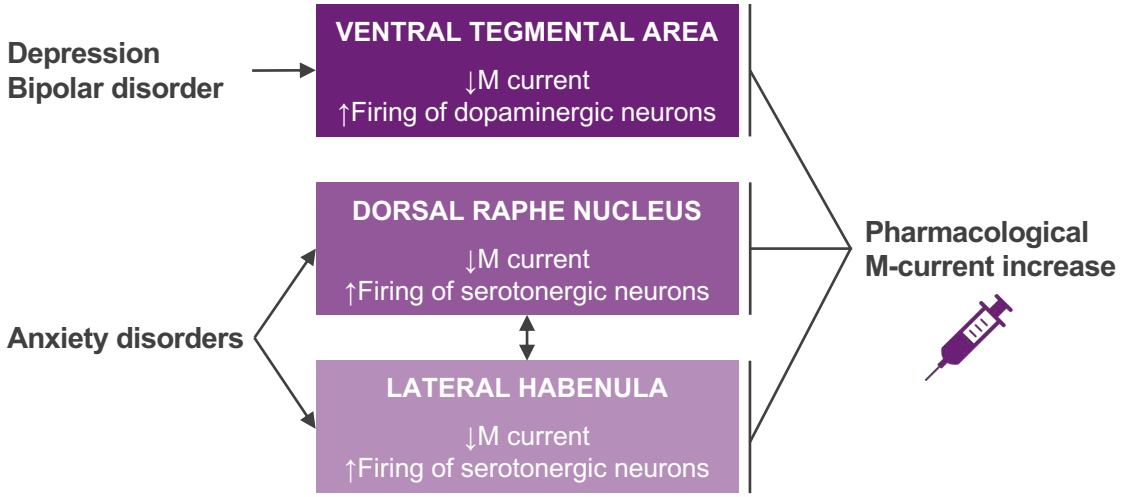
# BHV-7000 Demonstrates Positive Effects in Modulating Impulsive Behavior Consistent with M-current Activation

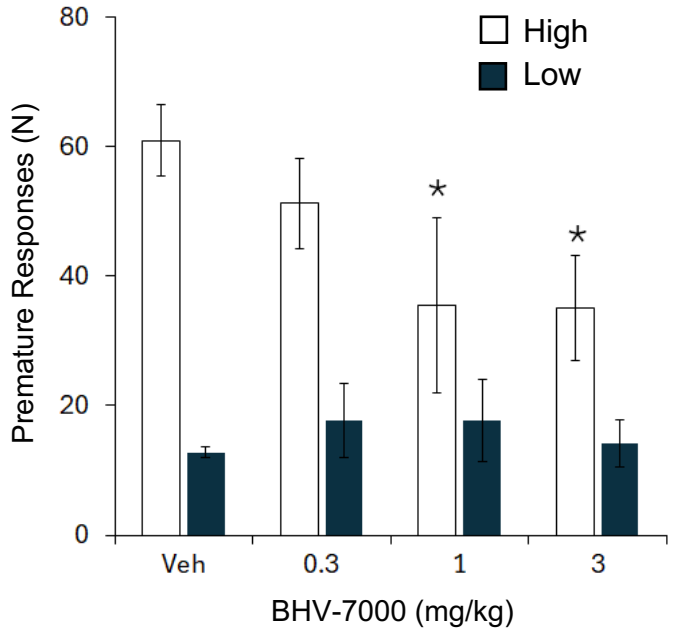
## Operant model behavior and stratification in 5-choice serial reaction time task

Scientific rationale:

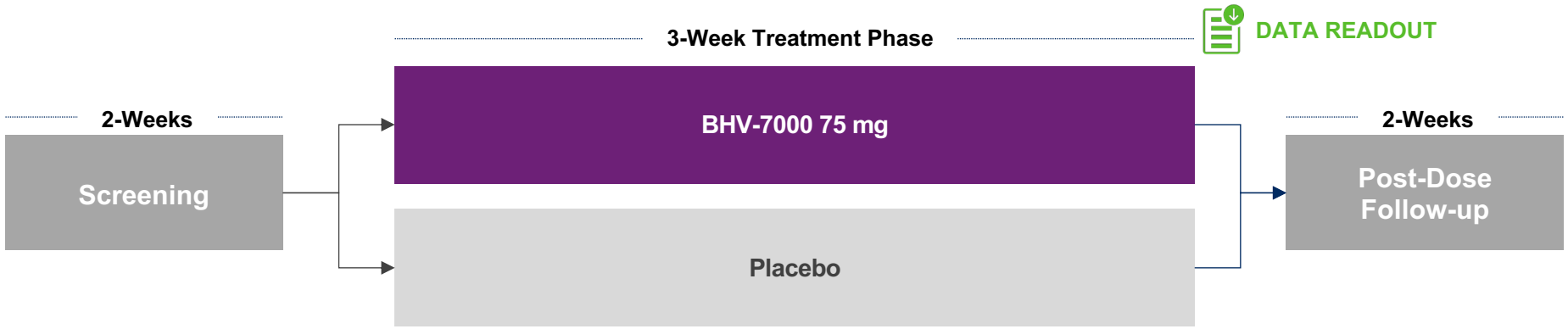



- BHV-7000 (1–3 mg/kg) shows evidence of reducing a measure of impulsiveness
- Effect seen in 2 task conditions: 5 and 10 sec inter trial intervals

Premature Responses
(High vs. Low Impulsive)



# Phase 2/3 Study in Bipolar Disorder (Acute Mania) Is Ongoing




| | |
|---|---|
| **DESIGN** | Randomized, double-blind, placebo-controlled trial |
| **POPULATION** | Subjects with Bipolar Disorder I with at least one prior mood episode who are currently experiencing a manic episode (YMRS ≥ 20) |
| **SAMPLE SIZE** | 256 subjects (randomized 1:1) |
| **TREATMENT** | BHV-7000 vs. placebo |
| **TREATMENT DURATION** | 3-weeks |
| **ENDPOINTS** | YMRS (primary), CGI-S |

KEY POINT

Pivotal Phase 2/3 study initiated in 1H 2024

**YMRS**, Young Mania Rating Scale; **CGI-S**, clinical global impression, severity.

# BHV-2100
## TRPM3 ANTAGONIST

### First-in-Clinic TRPM3 Antagonist — Novel Mechanism for the Treatment of Migraine and Pain

- BHV-2100 is an orally administered, peripherally-restricted and selective TRPM3 antagonist
- Preclinical data shows robust efficacy in pain models
- Highly differentiated from programs that target TRPV1 and TRPA1, avoids TRP family liabilities such as hyperthermia
- Phase 2 trial initiated for acute treatment of migraine in 2H 2024; POC trial initiated in neuropathic pain

### Phase 1 Study Data Supports Evaluation in Acute Migraine and Pain

BHV-2100 demonstrated excellent tolerability, safety, and favorable PK profile in ongoing Phase 1 trials

### Significant Unmet Need Remains for both Migraine and Pain

- Migraine is 2$^{nd}$ leading cause of disability worldwide, 1$^{st}$ among young women[1]
- 30–40% of patients do not respond to treatments that block CGRP or its receptor
- The CDC estimates the prevalence of chronic pain to be 20%[2]
- The global opioid crisis highlights the unmet needs in pain management[3]

1. Steiner TJ et al, J Headache Pain. 2020 Dec 2;21(1):137 2. Cohen SP, Vase L, Hooten WM. Lancet 2021;397(10289):2082-2097.
3. Volkow, N.D. and W.J. Koroshetz, Nat Rev Neurol, 2019. 15(5): p. 301-305.

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# Targeting the Unmet Medical Need in Pain and Migraine

## Biohaven's legacy of success

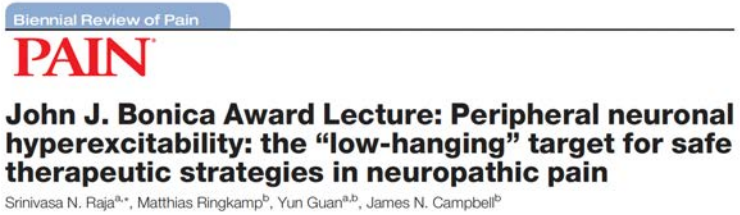

The NEW ENGLAND JOURNAL of MEDICINE

Rimegepant, an Oral Calcitonin Gene–Related Peptide Receptor Antagonist, for Migraine

Richard B. Lipton, M.D., Robert Croop, M.D., Elyse G. Stock, M.D., David A. Stock, Ph.D., Beth A. Morris, B.A., Marianne Frost, M.A., Gene M. Dubowchik, Ph.D., Charles M. Conway, Ph.D., Vladimir Coric, M.D., and Peter J. Goadsby, M.D., Ph.D.

**MIGRAINE**

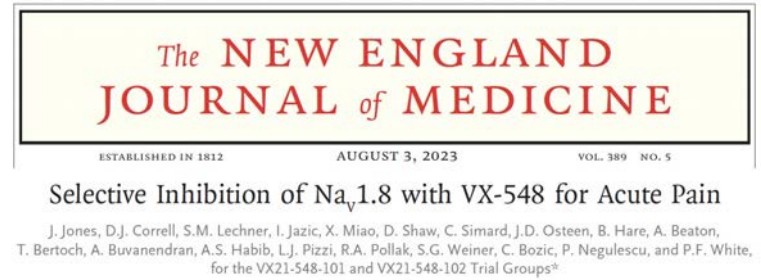
## Emerging role of novel mechanisms: ion channels in the periphery


Biennial Review of Pain

PAIN

**John J. Bonica Award Lecture: Peripheral neuronal hyperexcitability: the "low-hanging" target for safe therapeutic strategies in neuropathic pain**

Srinivasa N. Raja[a,*], Matthias Ringkamp[b], Yun Guan[a,b], James N. Campbell[b]


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 3, 2023 VOL. 389 NO. 5

Selective Inhibition of $Na_v1.8$ with VX-548 for Acute Pain

J. Jones, D.J. Correll, S.M. Lechner, I. Jazic, X. Miao, D. Shaw, C. Simard, J.D. Osteen, B. Hare, A. Beaton, T. Bertoch, A. Buvanendran, A.S. Habib, L.J. Pizzi, R.A. Pollak, S.G. Weiner, C. Bozic, P. Negulescu, and P.F. White, for the VX21-548-101 and VX21-548-102 Trial Groups*

**ACUTE PAIN & NEUROPATHIC PAIN**

KEY POINT

BHV-2100 is a selective, peripherally-restricted TRPM3 antagonist that is a potentially highly-effective, non-sedating, non-opioid treatment for pain and migraine

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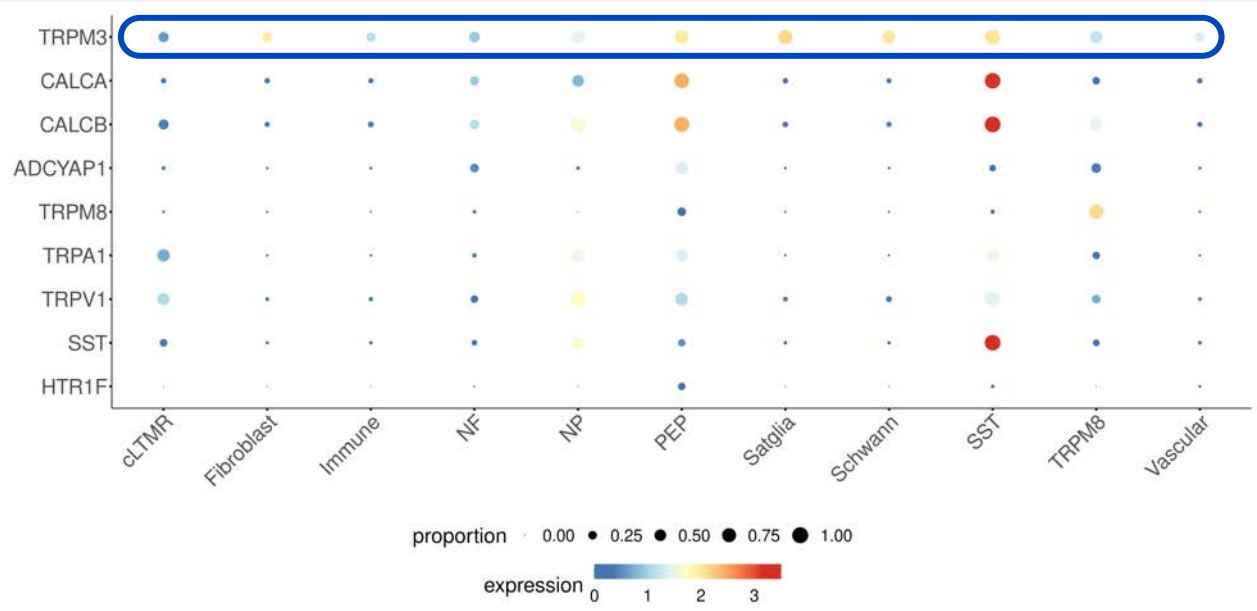
# Beyond CGRP — TRPM3 is Next-Generation Target for Migraine

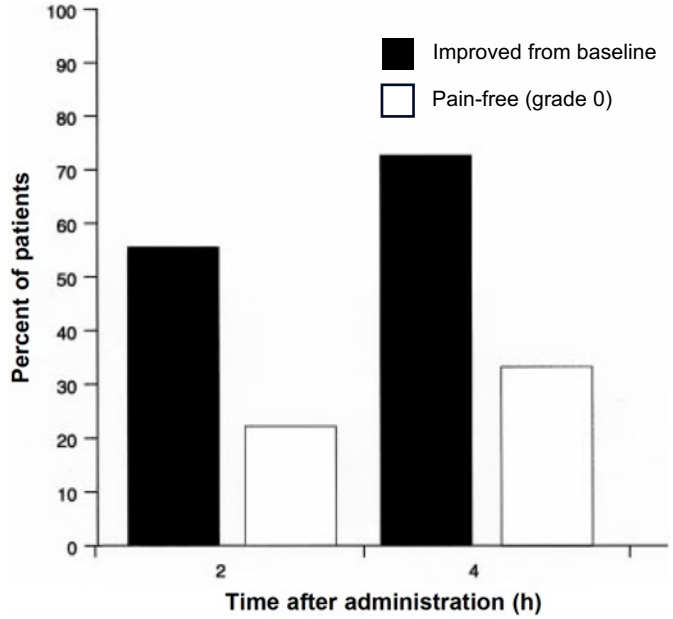
- Expressed in the trigeminovascular system, where it drives neurogenic inflammation and sensitization/activation of nociceptors[1]
- Gene mutations/variants are associated with migraine risk and pain sensitivity in humans[2]
- Regulates activity of other TRP channels (TRPV1 and TRPA1); and preliminary clinical data supports therapeutic benefit of inhibiting these TRP channels in migraine[3]

## TRPM3 is Co-Expressed in Human Trigeminal Ganglia Along with Other Migraine Genes




Derived from https://painseq.shinyapps.io/tg-painseq/ and Yang, L et al. Neuron 2022. 110(11): 1806-1821 e1808

## Civamide Reduces Pain Severity in Patients with Migraine

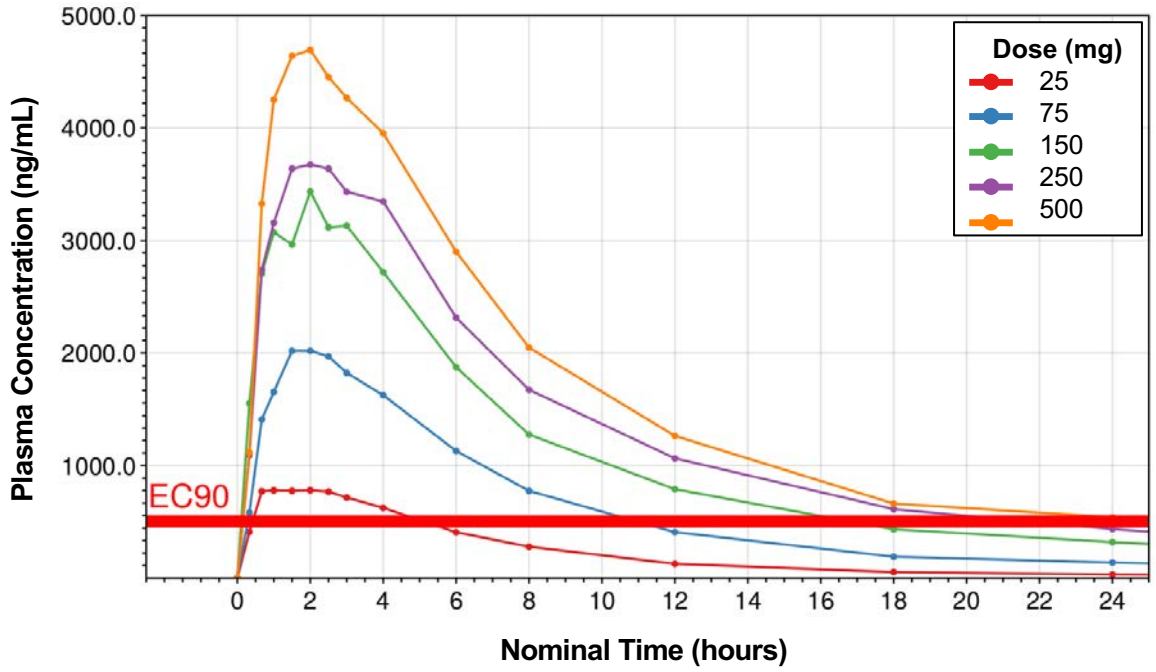



Diamond S, et al. Cephalalgia. 2000 Jul;20(6):597-602.

1, Vriens J et al, Neuron. 2011 May 12;70(3):482-94. 2, Burglen L, Van Hoeymissen E, Qebibo L, et al. Gain-of-function variants in the ion channel gene TRPM3 underlie a spectrum of neurodevelopmental disorders. Elife 2023;12. DOI: 10.7554/eLife.81032. 3, Mulier M, et al. Elife. 2020 Sep 3;9:e61103.

# BHV-2100: Ideal Pharmacokinetic Profile for Acute Treatment of Migraine

## Single Oral Doses of BHV-2100 in Healthy Subjects
## Mean Concentration vs. Time Profiles




**KEY POINT**

Plasma concentrations exceed EC90 by 20 min and are sustained above EC90 for several hours at all dose levels

EC90 represents the estimated plasma concentration threshold based on a preclinical model.

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# BHV-2100: Safe and Well-Tolerated in Healthy Subjects

## SAFETY AND TOLERABILITY

- No dose limiting toxicities in studies
- No SAEs
- No severe TEAEs; most TEAEs were mild
- No clinically significant trends in vital signs (including body temperature), laboratory values, or ECGs

## DOSING

- SAD: single doses up to 500 mg
- MAD: multiple doses up to 150 mg twice a day for 14 days

| SAD Cohorts (pooled) TEAEs in ≥ 2 subjects | Placebo (N=9) n (%) | BHV-2100 (N=30) n (%) |
|---|---|---|
| Dizziness | 0 (0) | 2 (6.7) |
| Fatigue | 0 (0) | 2 (6.7) |

| MAD Cohorts (pooled) TEAEs in ≥ 2 subjects | Placebo (N=8) n (%) | BHV-2100 (N=24) n (%) |
|---|---|---|
| | 0 (0) | 0 (0) |

KEY POINT

No TEAE occurred in > 1 participant across the MAD cohorts

**MAD**, multiple ascending dose; **SAD**, single ascending dose; **SAE,** serious adverse events; **TEAE,** treatment emergent adverse events.
Pooled preliminary data.

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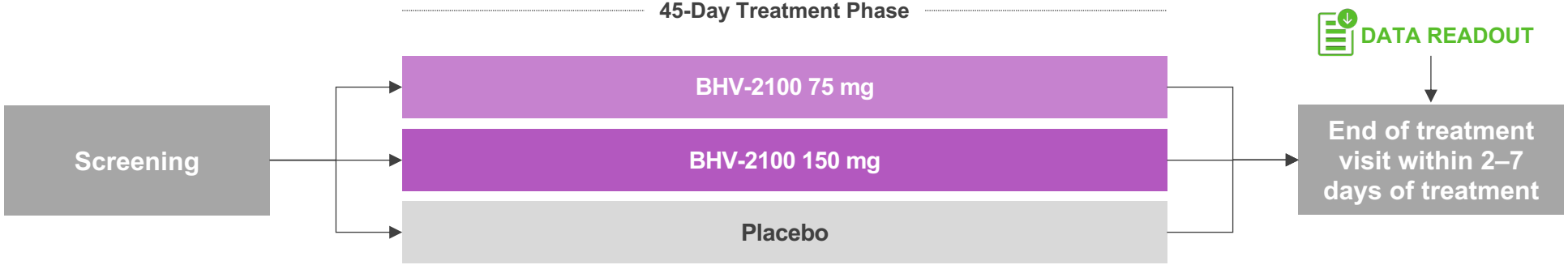
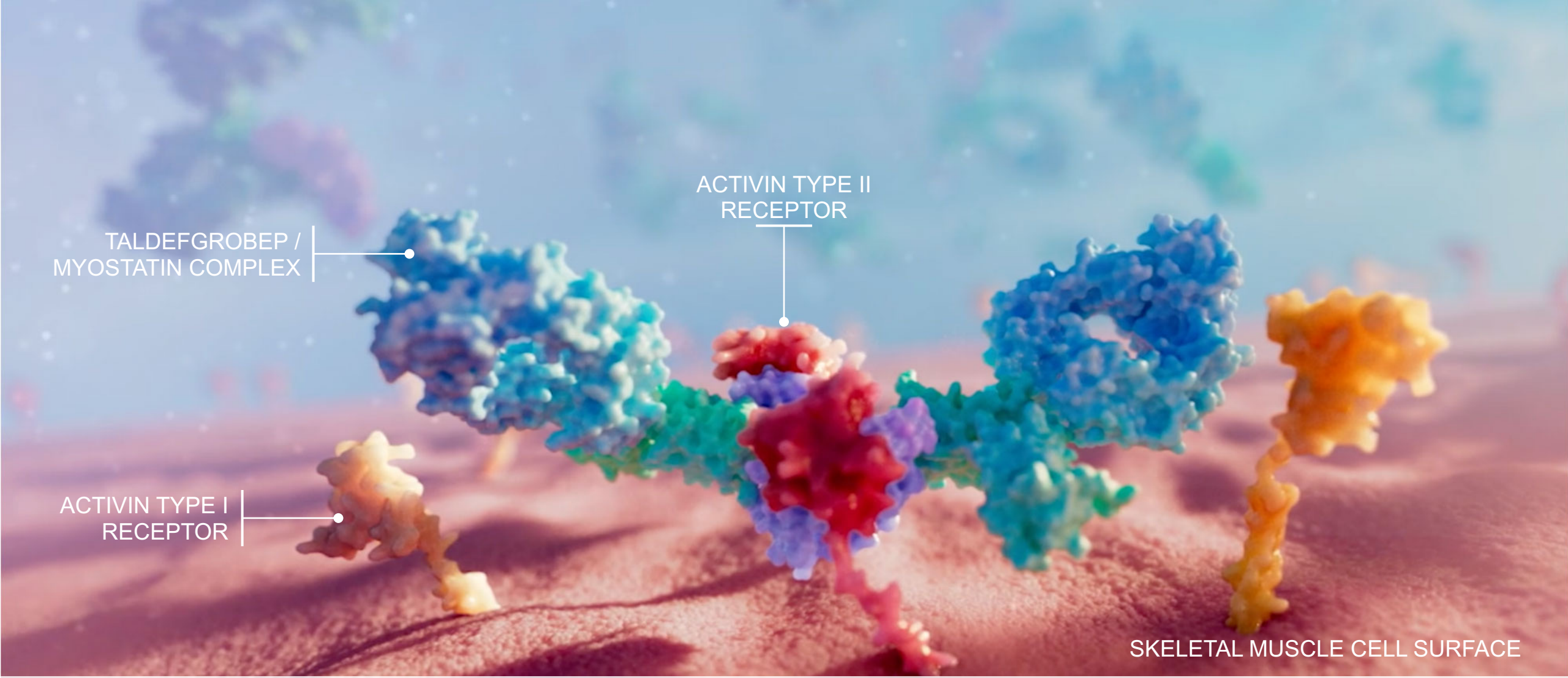
# BHV-2100: Phase 2 Study in Acute Treatment of Migraine




| | |
|---|---|
| **DESIGN** | Randomized, double-blind, placebo-controlled trial |
| **POPULATION** | Participants with at least 1 year history of migraine (with or without aura) |
| **SAMPLE SIZE** | 575 enrolled (1:1:1 across 2 doses and placebo) |
| **TREATMENT** | BHV-2100 (75/150 mg) vs. placebo |
| **TREATMENT DURATION** | Single dose, up to 45 days to treat eligible migraine |
| **ENDPOINTS** | Pain relief, Freedom from most bothersome symptom |

Preliminary study design.




# Myostatin

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# TALDEFGROBEP ALFA

## MYOSTATIN INHIBITOR

### Differentiated Profile Balancing Both Efficacy and Safety

- Taldefgrobep alfa inactivates free myostatin (GDF-8), an inhibitor of muscle growth
- Pharmacology uniquely sustained by taldefgrobep alfa/myostatin complex
- Taldefgrobep alfa/myostatin complex inhibits skeletal muscle ActRII receptor signaling, and thus, enhances muscle mass

### Clinical Development Summary

- Broad range of doses (4 mg to 180 mg SC QW) explored for up to 120 weeks of repeat dosing, ~500 trial participants (male & female children, adolescents, and adults)
- No identified serious signature adverse events (AEs), low rates of serious AEs, and few AEs leading to discontinuation throughout the development program
- Does not have the pharmacologic AEs that are commonly reported with bimagrumab (including muscle spasms)

### Potential Paradigm Shift in the Treatment of Obesity

- Reduction in fat mass while increasing lean mass in healthy adults
- Sustained activity of the taldefgrobep alfa/myostatin complex is demonstrated by continued improvement in body composition beyond the dosing period

### Phase 3 Program in SMA

- Global Phase 3 study in broad population of SMA patients now fully enrolled
- Weekly SC taldefgrobep alfa on top of standard of care continues to be well tolerated
- Orphan designation granted in the US and EU, along with Fast Track designation by FDA
- Rare pediatric disease designation granted by FDA in 1H 2024 providing potential to receive priority review voucher (PRV) if approved

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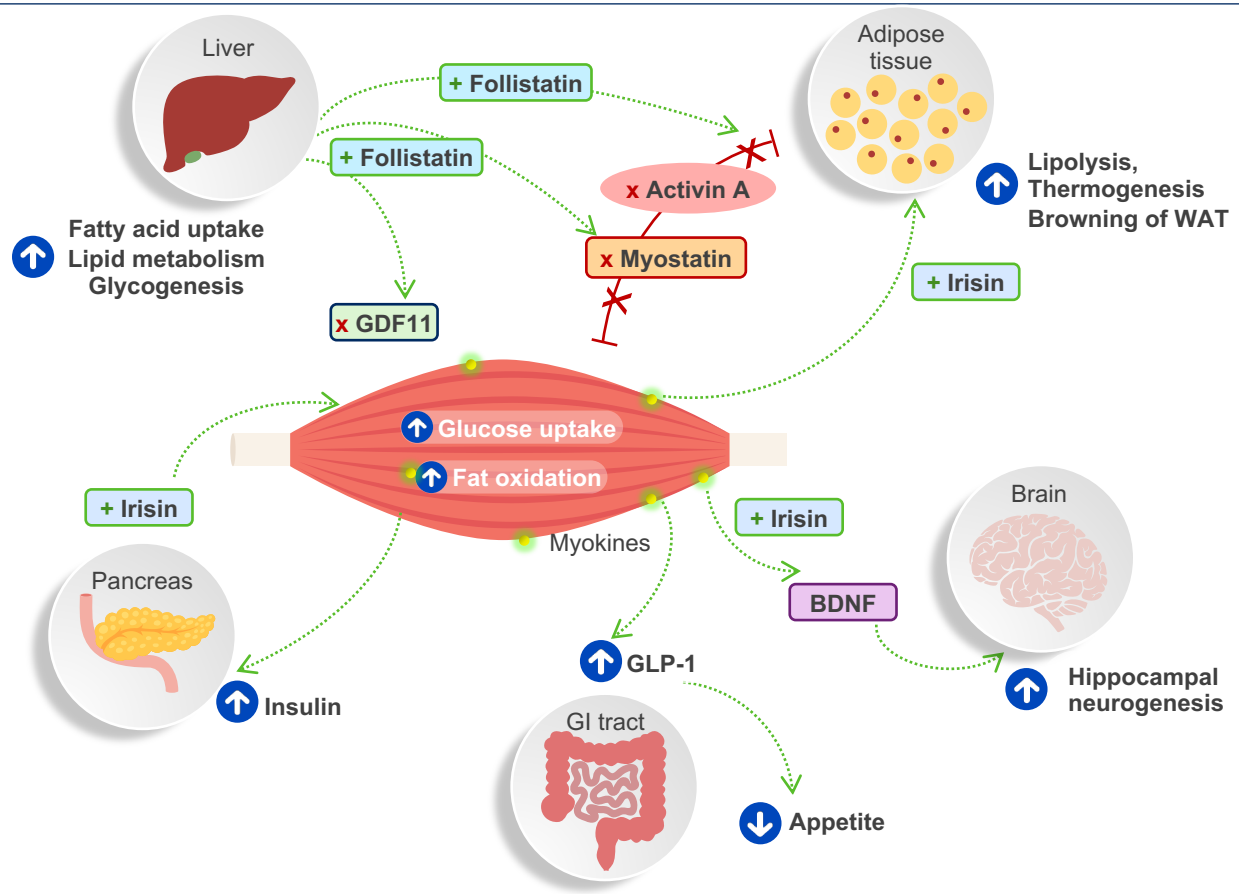
# Muscle and Fat Endocrine Crosstalk Enables Precise Pharmacologic Intervention in Muscle Loss and Obesity

**LOW MUSCLE MASS** is associated with age-related cognitive decline[2] and increase in all-cause mortality[3]

**HIGH MUSCLE MASS** is associated with improvements in overall health and wellness

**MYOKINES** are important in the regulation of fat metabolism, inflammation, appetite, glucose control, bone density, and basal metabolic rate[1]




**HIGH ADIPOSE MASS** increases TGF-β ligands, leads to insulin resistance, and is a multifactorial driver of the morbidity of obesity

**TALDEFGROBEP ALFA** targets TGF-β ligands that signal through Activin II receptors including myostatin, GDF-11, and Activin A.[3-4] Inhibition of 3 ligands and ActRIIB optimizes muscle growth.[5]

**KEY POINT**

Taldefgrobep alfa inhibits negative regulators of skeletal muscle and adipose tissue improving body composition and resulting in metabolic changes important to overall health and wellness

1. Illustration adapted from Severinsen et al. Endocr Rev. 2020 Aug 1;41(4):594–609. 2. Daghlas et al. BMJ Med. 2023;2(1):e000354. 3 Lee et al. Exp Biol Med. 2018;243:1275-85. 4. Chen et al. Life Metabolism, 2024.
5. Latres, E., Mastaitis, J., Fury, W. *et al. Nat Comm* 8, 15153 (2017). **MSTN,** myostatin; **GDF11,** growth differentiation factor 11; **BDNF,** brain-derived neurotrophic factor.

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# Taldefgrobep Alfa Has Differentiated Pharmacology that Balances Efficacy and Safety

## Apitegromab/GYM329
Scholar Rock/Roche

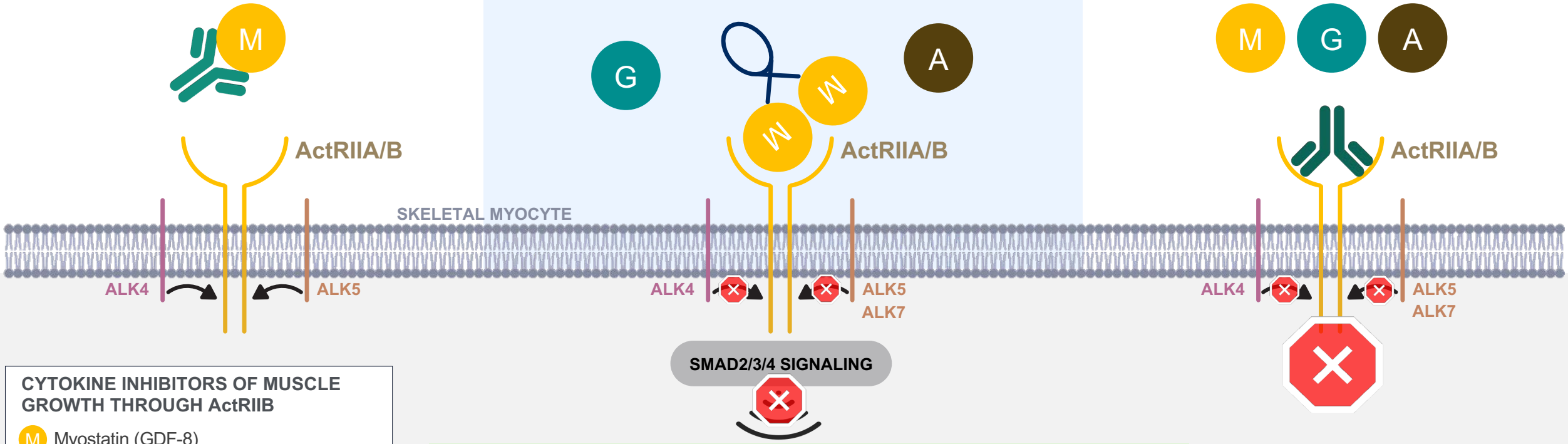
**TARGETS** pro- and latent myostatin

## Taldefgrobep alfa
Biohaven

**BLOCKS** active myostatin (GDF-8), GDF-11 and **INHIBITS** ActRIIA/B signaling to key ligands

## Bimagrumab
Versanis-Lilly

**BLOCKS** only ActRIIB signaling (all ligands) with very high affinity




**CYTOKINE INHIBITORS OF MUSCLE GROWTH THROUGH ActRIIB**

- M Myostatin (GDF-8)
- G Growth Differentiation Factor 11 (GDF-11)
- A Activin

**Inhibiting signal transduction in muscle leads to hypertrophy**

**Inhibition in adipocytes leads to lipolysis**

**Increased brown fat enhanced mitochondria activity and increased thermogenesis**

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# Taldefgrobep Alfa Offers a Highly Favorable and Differentiated Profile Within the "Myostatin Pharmacologic Class"

## Apitegromab/GYM329
Scholar Rock/Roche

### Pure Myostatin Agent
- Inhibits latent myostatin
- No direct ActRIIB receptor effects, so activity limited to PK of drug (limited PK/PD)
- Claims better safety due to selectivity
- Likely associated with decreased efficacy in muscle and adipose
- Requires IV infusion

## Taldefgrobep alfa
Biohaven

### Dual Myostatin Clearance and Activin Receptor Inhibition
- Binds active myostatin (pM), GDF-11 (pM) and Activin A (nM)
- Superior muscle growth to myostatin inhibition alone
- Accesses Activin A pharmacology
- Long lived T-alfa/myostatin complex reversibly binds ActRIIA/B inhibiting receptor signal transduction
- Low rates of AEs
- Favorable SC dosing

## Bimagrumab
Versanis-Lilly

### Activin Receptor Inhibitor
- Tight binding to and inhibition of ActRIIB receptors
- Superior muscle growth to myostatin inhibition alone
- Accesses Activin A pharmacology
- Long off-rate and tight binding results in **muscle spasms, fatigue, and diarrhea**
- Potent receptor inhibition results in lower FSH
- Requires IV infusion

**KEY POINT**

Taldefgrobep alfa potentially offers optimized efficacy, safety, and ease of use

**AE**, adverse event; **FSH**, follicle stimulating hormone; **SC**, subcutaneous; **IV**, intravenous; **PK**, pharmacokinetics; **PD**, pharmacodynamics.

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# Current Treatment Options for SMA Are Inadequate

## SMA is characterized by muscle atrophy and weakness

- SMA is a rare, inherited neuromuscular disease characterized by muscle atrophy and severe muscle weakness[1]
- Despite available treatments, SMA remains a progressive and debilitating condition[2–5]

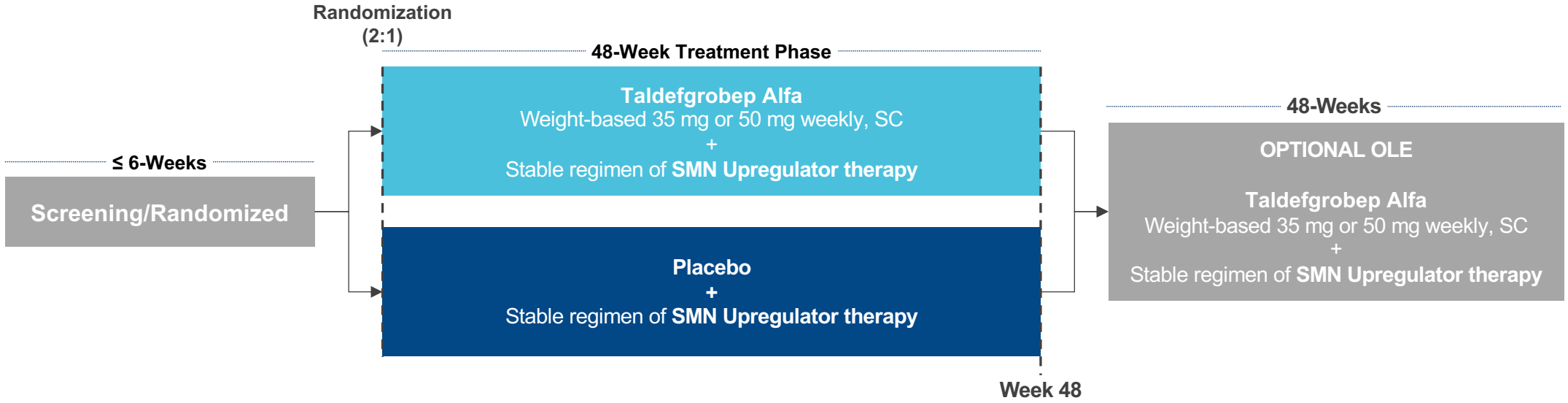
## Standard of care treatments target neurons, not muscle, and SMA patients still experience weakness and reduced functioning

- Available SMN (Survival Motor Neuron) upregulating treatments target motor neurons[2]
- Despite these treatments, SMA patients still experience significant muscle weakness, reduced levels of functioning, and impairment in quality-of-life[5-7]
- No treatment that specifically targets muscle in SMA is currently available

## Significant opportunity exists in SMA for novel treatments that target muscle to improve functioning and quality-of-life


1. Mercuri E et al Nat Rev Dis Primers. 2022 Aug 4;8(1):52 . 2. Day JW et al. BMC Pediatr. 2022;22(1):632. 3. Darras BT, et al. N Engl J Med. 2021;385(5):427-435. 4. Finkel RS, et al; ENDEAR Study Group. N Engl J Med. 2017;377(18):1723-1732 5. https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf 6. Darras BT, et al. N Engl J Med. 2021;385(5):427-435. 7. Finkel RS, et al; ENDEAR Study Group. N Engl J Med. 2017;377(18):1723-1732.

# RESILIENT Study Design Informed by Successful Prior SMA Studies




| | |
|---|---|
| **DESIGN** | Global, randomized, double-blind, placebo-controlled, Phase 3 trial |
| **POPULATION** | Ambulatory and non-ambulatory, male and female participants with 5q-autosomal recessive SMA, 4-21 years old |
| **SAMPLE SIZE** | Actual enrollment 269 participants (randomized 2:1) |
| **TREATMENT** | Adjunctive Taldefgrobep Alfa, weight-based 35 mg or 50 mg weekly, SC versus Placebo<br>+ Stable regimen of SMN Upregulator therapy (nusinersen, risdiplam, and/or history of treatment with onasemnogene abeparvovec-xioi) |
| **PRIMARY ENDPOINT** | Change in 32 item Motor Function Measure (MFM-32) total score from baseline to Week 48 |
| **KEY SECONDARY ENDPOINTS** | Revised Upper Limb Module (RULM), Revised Hammersmith Scale (RHS) |

KEY POINT

Topline results are anticipated in 2H 2024

# RESILIENT: Broad Population Selected Based on Unmet Need and Potential for Benefit on Validated Clinical Endpoints

| | Broad Ages | Broad Functional Capabilities | Broad SMA Types | Broad Background Therapy |
|---|---|---|---|---|
| Biohaven RESILIENT[1] | ✓ 4–21yo | ✓ Ambulatory and non-ambulatory | ✓ No restriction on SMA type | ✓ Stable regimen of nusinersen, risdiplam, and/or onasemnogene |
| Scholar Rock SAPPHIRE[2] | X 2–12yo primary population | X Non-ambulatory | X SMA Type 2 or 3 No Type 1 | X Nusinersen or risdiplam No history of onasemnogene No SMN upregulator combination therapy |
| Roche MANATEE[3] | ✓ 2–25yo | X Ambulatory (part 2) | X Not specified | X Risdiplam (+/- history of onasemnogene) No use of current nusinersen |

**60% of SMA patients have SMA Type 1**[4,5]

KEY POINT

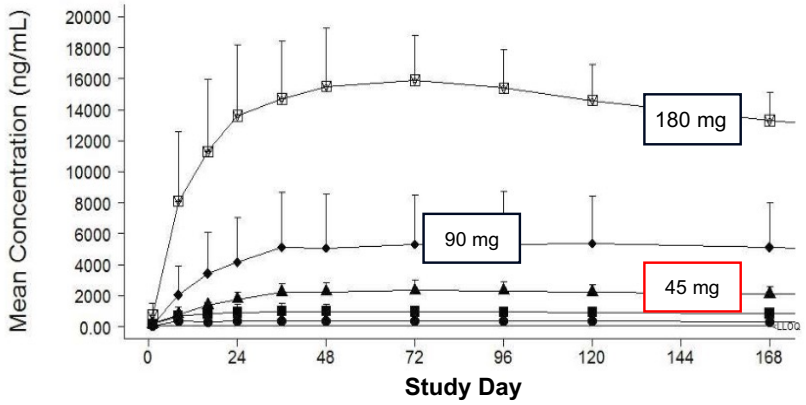
**RESILIENT** population overlaps Scholar Rock and Roche populations but is uniquely suited to demonstrate benefit on MFM-32 primary endpoint

1.ClinicalTrials.gov: NCT05337553 2. ClinicalTrials.gov: NCT05156320. 3. ClinicalTrials.gov: NCT05115110. 4. Lally C, et al. Orphanet J Rare Dis. 2017 Nov 28;12(1):175.5. Verhaart I, et al, Orphanet J Rare Dis. 2017 Jul 4;12(1):124.

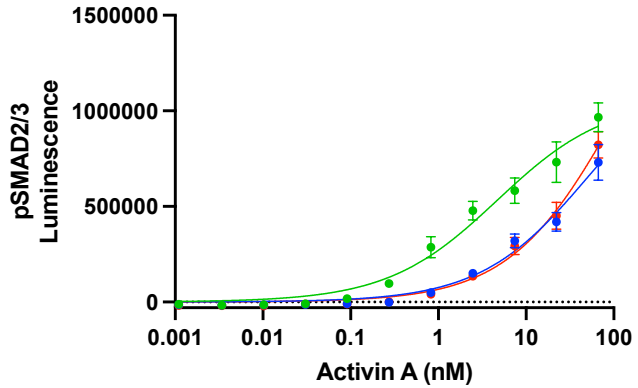
# Taldefgrobep Alfa Complexes Extend Favorable Effects

- Myostatin and GDF-11 exhibit low pM binding affinity to T-alfa and low nM to Activin A
- After a single 45 mg dose, T-alfa/myostatin complex is ~20nM in plasma, in excess over ligands
- T-alfa/myostatin complex interaction with ActRIIB receptor effectively competes with Activin A and GDF8/11
- Inhibition of SMAD2/3 signaling directly impacts muscle and adipose tissues

## Stable T-alfa-ligand complexes in human plasma remain elevated




## Stable T-alfa-ligand complexes inhibit Activin A mediated signal transduction through ActRIIA/B




| Ligand | $EC_{50}$ (nM) |
|---|---|
| Activin A only | 4.687 |
| GDF-8 complex | 50.58 |
| GDF-11 complex | 100.4 |

## KEY POINTS

- T-alfa complexes have longer serum half lives than T-alfa, extending T-alfa PK, PD, and breadth of pharmacology
- T-alfa complexes inhibit signal transduction at ActRIIB, improving both muscle growth and fat metabolism

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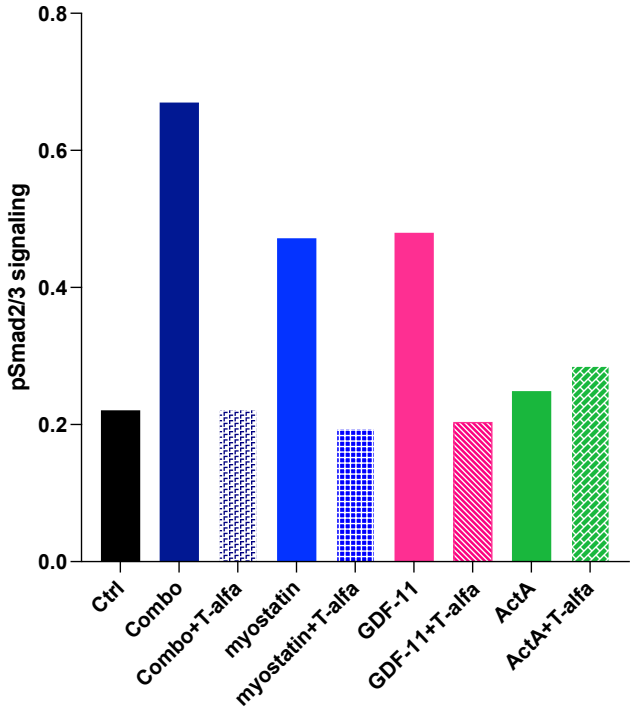
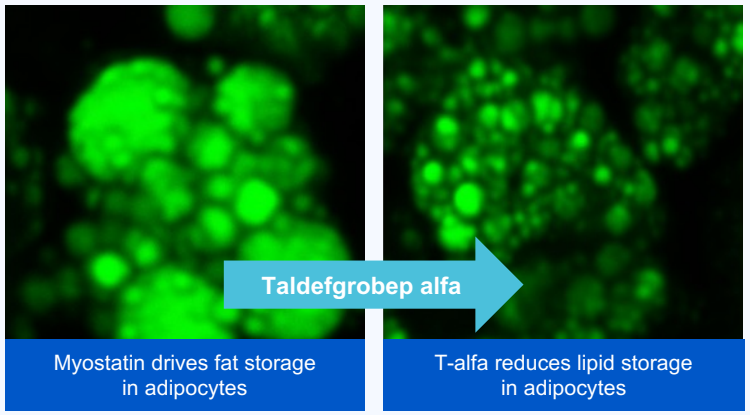
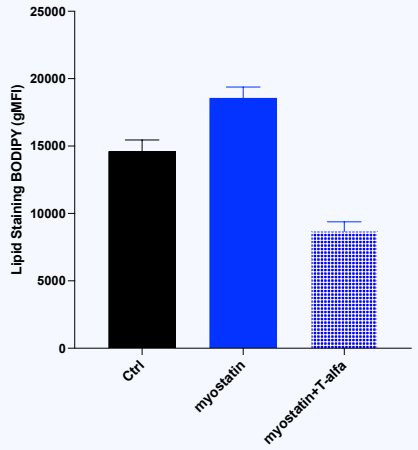
# Taldefgrobep Alfa Reduces Adipocyte Lipids and Increases Mitochondrial Content

## T-alfa Decreases pSmad2/3 Signaling, Directly Regulating Lipid Storage in Adipocytes

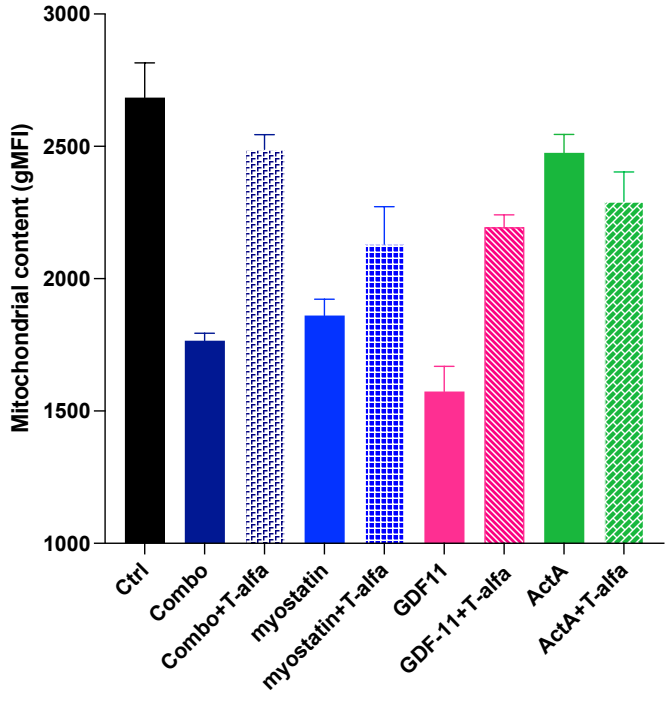



*combo—myostatin, GDF-11, activin




## T-alfa Increases Mitochondrial Content in Adipocytes



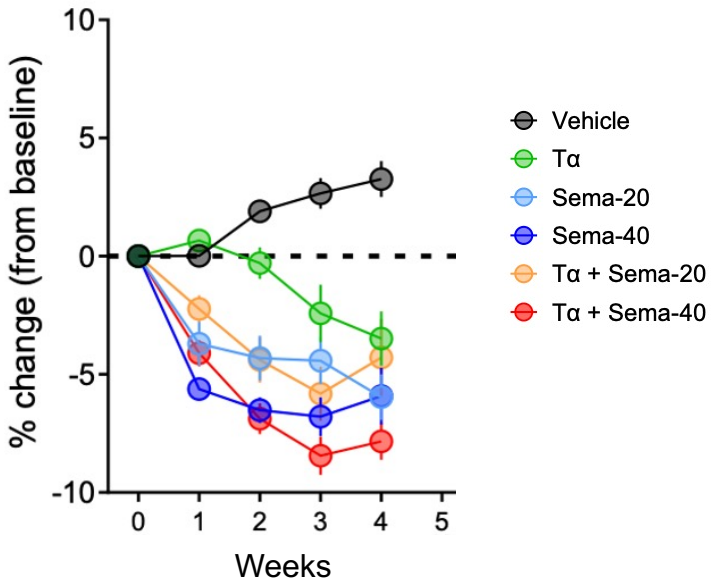

*combo—myostatin, GDF-11, activin

**KEY POINT**

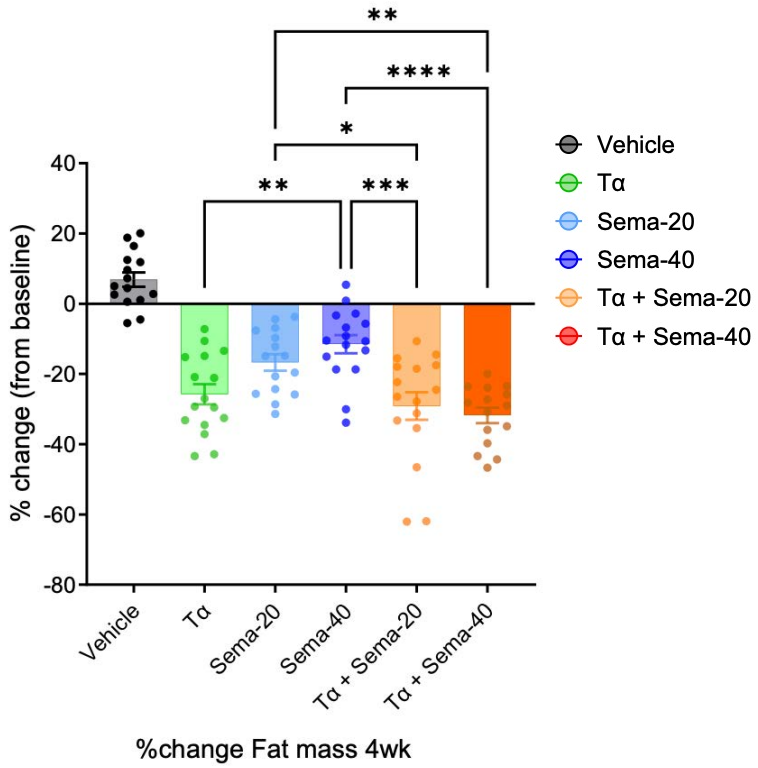
Taldefgrobep alfa directly reduces adipose tissue storage of fat

# Taldefgrobep Alfa Shows Greater Effect in Combination With Semaglutide than Semaglutide Alone in DIO Mice

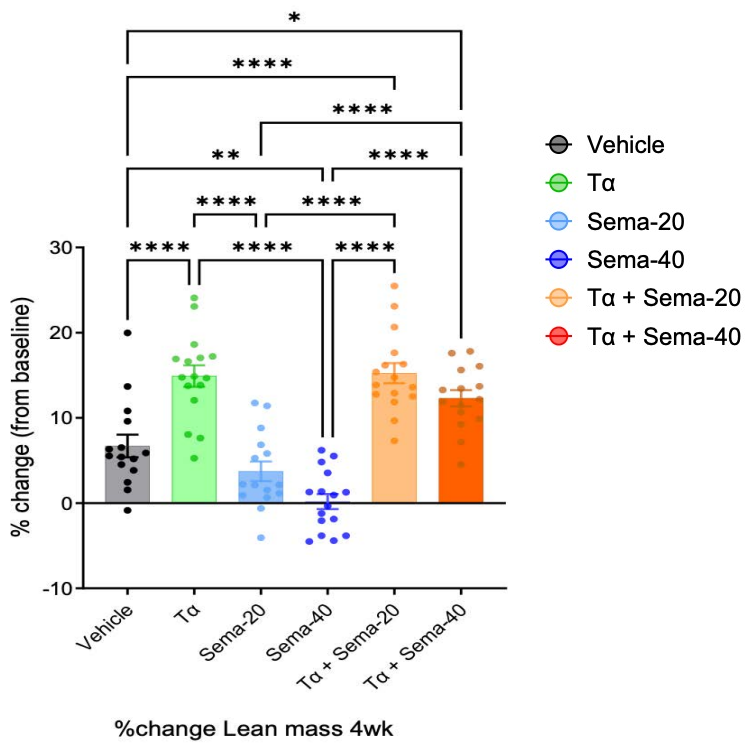
## T-alfa Shows Weight Loss, and Combination with Semaglutide Shows **Higher Reduction in Body Weight** Than Semaglutide Alone




## T-alfa and Combination Show **Greater Reduction in Fat Mass** Than Semaglutide Alone




## T-alfa and Combination Show **Greater Increases in Lean Mass** Than Semaglutide Alone




**Tα**, taldefgrobep alfa; **DIO**, diet induced obesity.
* <= 0.05, ** <= 0.01, *** < 0.001 and **** <0.0001.

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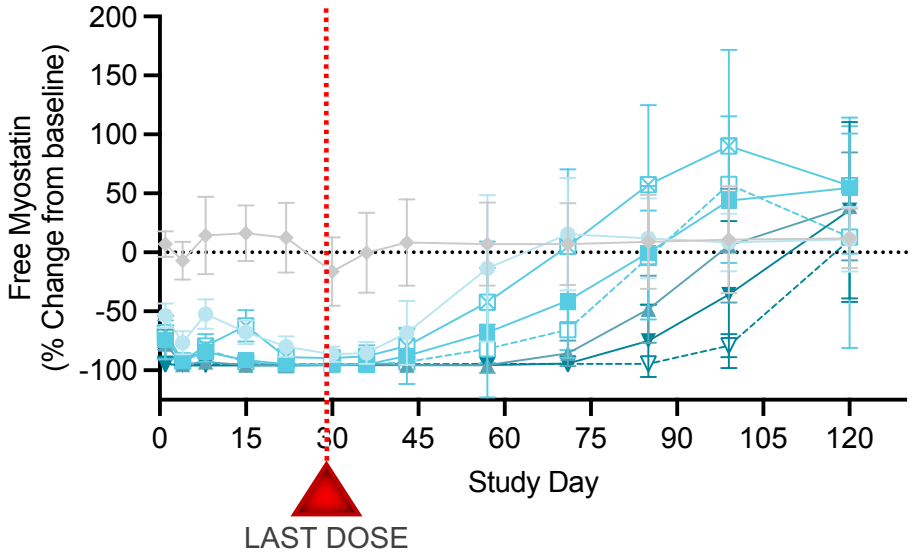
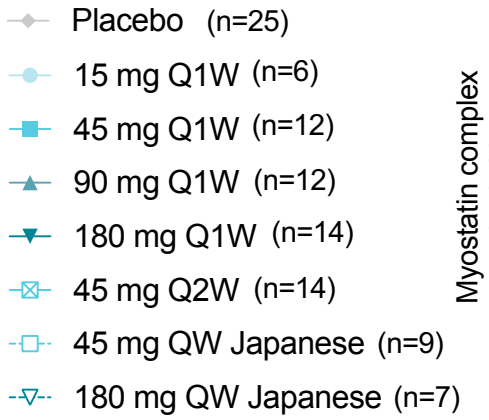
# Taldefgrobep Alfa Effectively Suppresses Free Myostatin in Healthy Adults and Has Prolonged Pharmacodynamic Effects

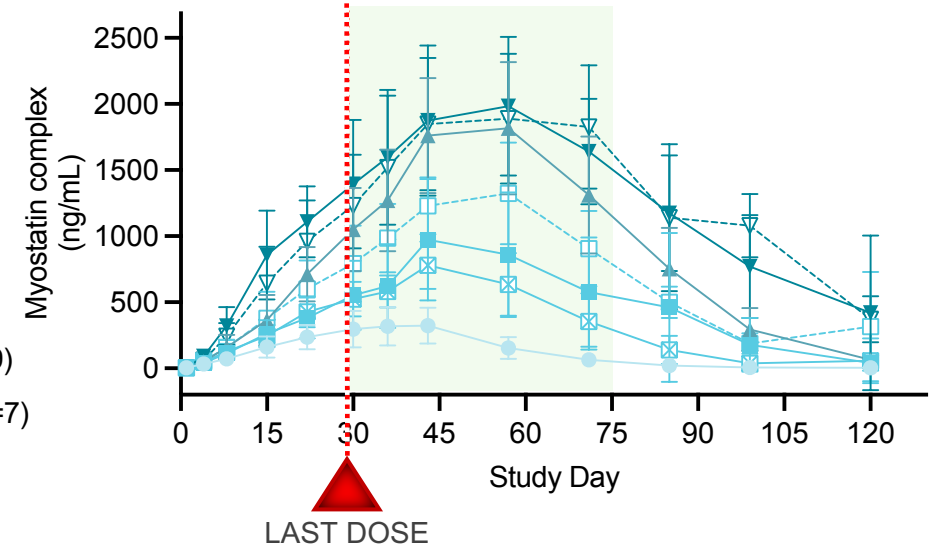
## Taldefgrobep alfa activity is sustained by circulating taldefgrobep alfa-myostatin complex

### Free Myostatin Levels




### Drug-Myostatin Complex Sustains Activity




**KEY POINTS**

- Robust lowering of free myostatin after administration of taldefgrobep alfa 45 mg Q1W
- Taldefgrobep-myostatin complex continues to exert activity for weeks after dosing stops

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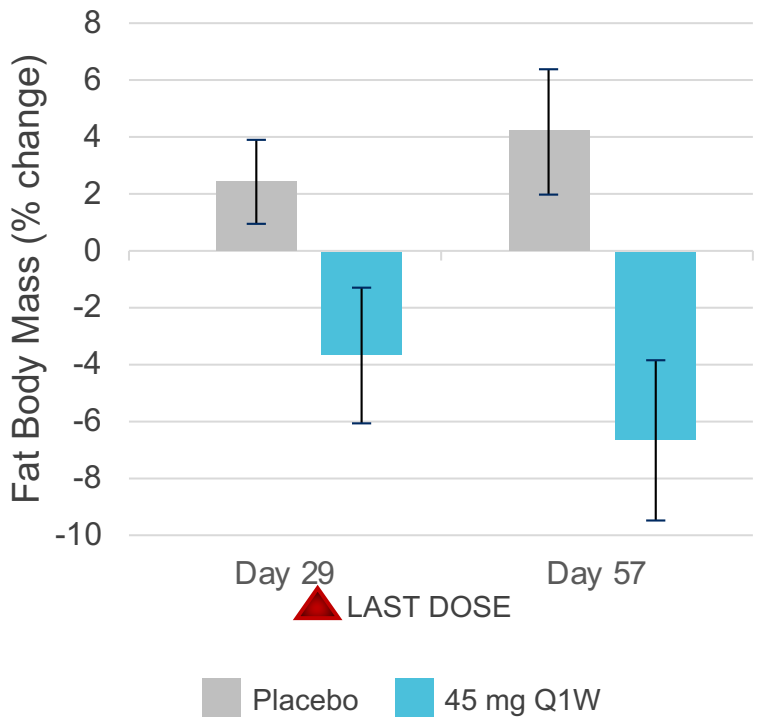
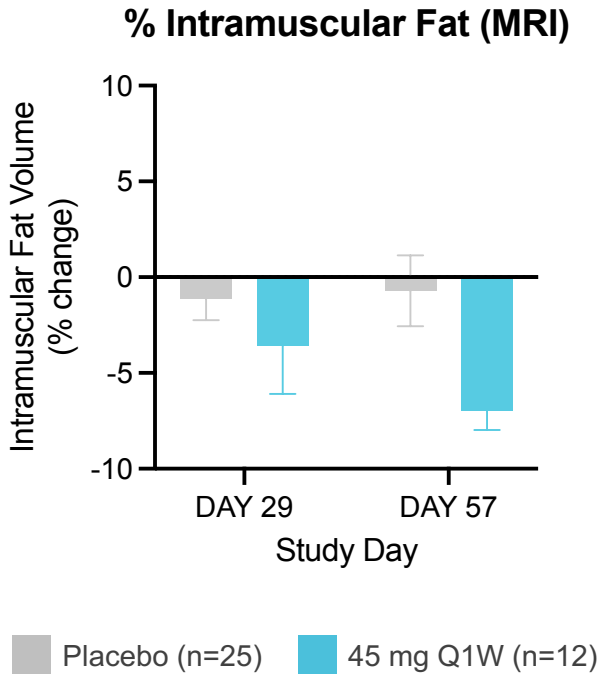
# Taldefgrobep Alfa Improves Body Composition in Non-Obese Adults

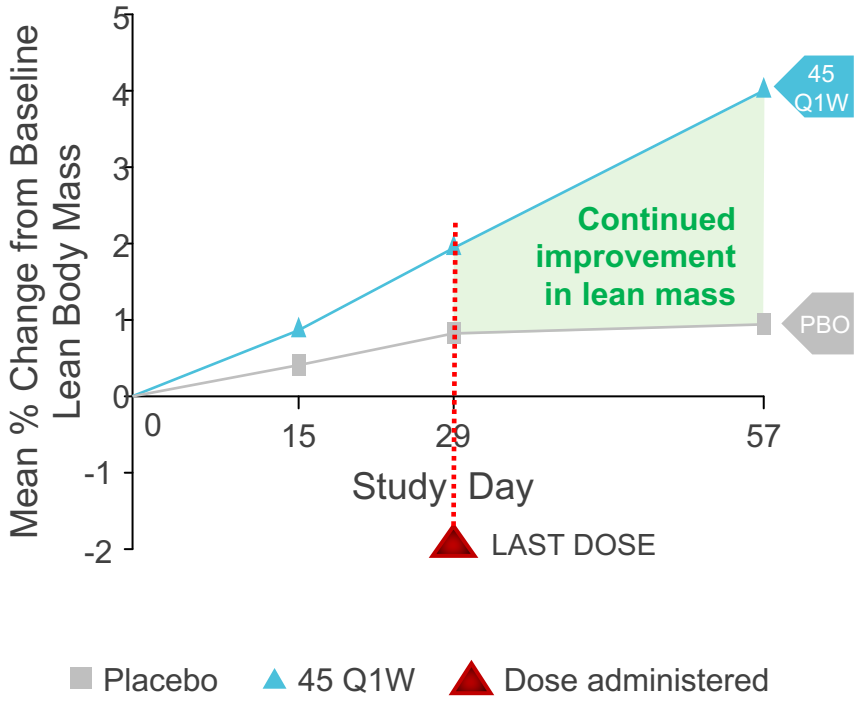
## Taldefgrobep Alfa Continued to Decrease **Total Fat Mass** Beyond the Dosing Period




## Effect of Taldefgrobep Alfa on **Intramuscular Fat** After 1 Month of Dosing — Healthy Adults




## Taldefgrobep Alfa Demonstrates Continued Improvement in **Lean Mass** in Healthy Adults at 30 Days Post-dosing




Muntoni F. et al, Neurol Ther. 2024 Feb;13(1):183-219.

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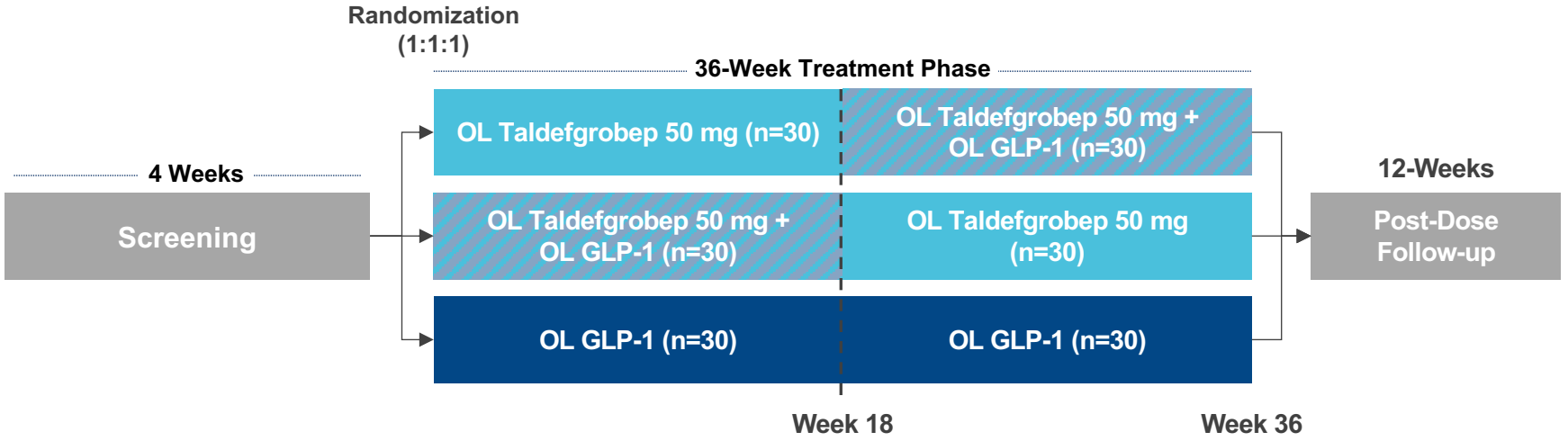
# Phase 2 Study to Evaluate Taldefgrobep Alfa +/- GLP-1 in the Treatment of Overweight and Obesity

- Impact of monotherapy on changes in body composition, total body weight, and metabolic parameters
- Ability of taldefgrobep alfa to augment fat mass loss when used as adjunct to GLP-1 agonist
- Potential for taldefgrobep alfa to prevent against GLP-1-induced lean muscle loss
- Influence of taldefgrobep alfa on weight regain following discontinuation of GLP-1 agonist




| | |
|---|---|
| **DESIGN** | Randomized, open label (OL), active comparator Phase 2 trial |
| **POPULATION** | Male and female adults with overweight or obesity |
| **SAMPLE SIZE** | 90 treated participants, randomized 1:1:1 across treatment groups |
| **TREATMENT** | Taldefgrobep alfa (50 mg Q1W) and GLP-1 |
| **TREATMENT DURATION** | 36-week treatment period, 12-week post-dose follow-up |
| **ENDPOINTS** | Changes in body composition, metabolic parameters, and total body weight over time, including post-dose follow-up period, PK/PD. |

Preliminary clinical trial design

# TRORILUZOLE
## Glutamate Modulator

### Spinocerebellar Ataxia
- Ultra-rare, genetically-defined, progressive and fatal neurodegenerative disease
- No currently approved treatments

### Troriluzole in SCA
- Troriluzole 200 mg QD dosed orally in patients with SCA **met the study's primary endpoint** on the change from baseline on the f-SARA at 3 years in all study population genotypes
- Achieved statistically significant superiority on a total of 9 consecutive, prespecified primary and secondary endpoints
- NDA planned in 2H 2024

### New Real-World Evidence Protocol
- Biohaven designed a new protocol, BHV4157-206-RWE (NCT06529146), in dialogue with FDA to assess the effectiveness of troriluzole in SCA after 3 years of treatment as measured by change from baseline in the f-SARA
- 3-year primary endpoint compared to an external control using the US SCA Natural History cohort (CRC-SCA)
- Leverages FDA Guidance on real-world evidence (RWE) of effectiveness using real-world data

**KEY POINTS**

- NDA submission planned 2H 2024
- European MAA documents updated to potentially include **all SCA** *(previously SCA3 only)* following clarification meeting with CHMP

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**Troriluzole 200 mg QD dosed orally in patients with SCA**

# MET THE STUDY'S PRIMARY ENDPOINT

**on the change from baseline on the f-SARA at 3 years in all study population genotypes**

## Sustained and clinically meaningful treatment benefit out to 3 years across analyses utilizing 2 large independent natural history external controls

- Troriluzole achieved statistically significant superiority on a total of **9 consecutive, prespecified primary and secondary endpoints**
- SCA patients treated with troriluzole showed a **50–70% slowing of disease progression**, representing 1.5–2.2 years delay in disease progression over the 3-year study period

**Large safety database demonstrates troriluzole is well tolerated in SCA**

## New Drug Application submission planned in 4Q 2024

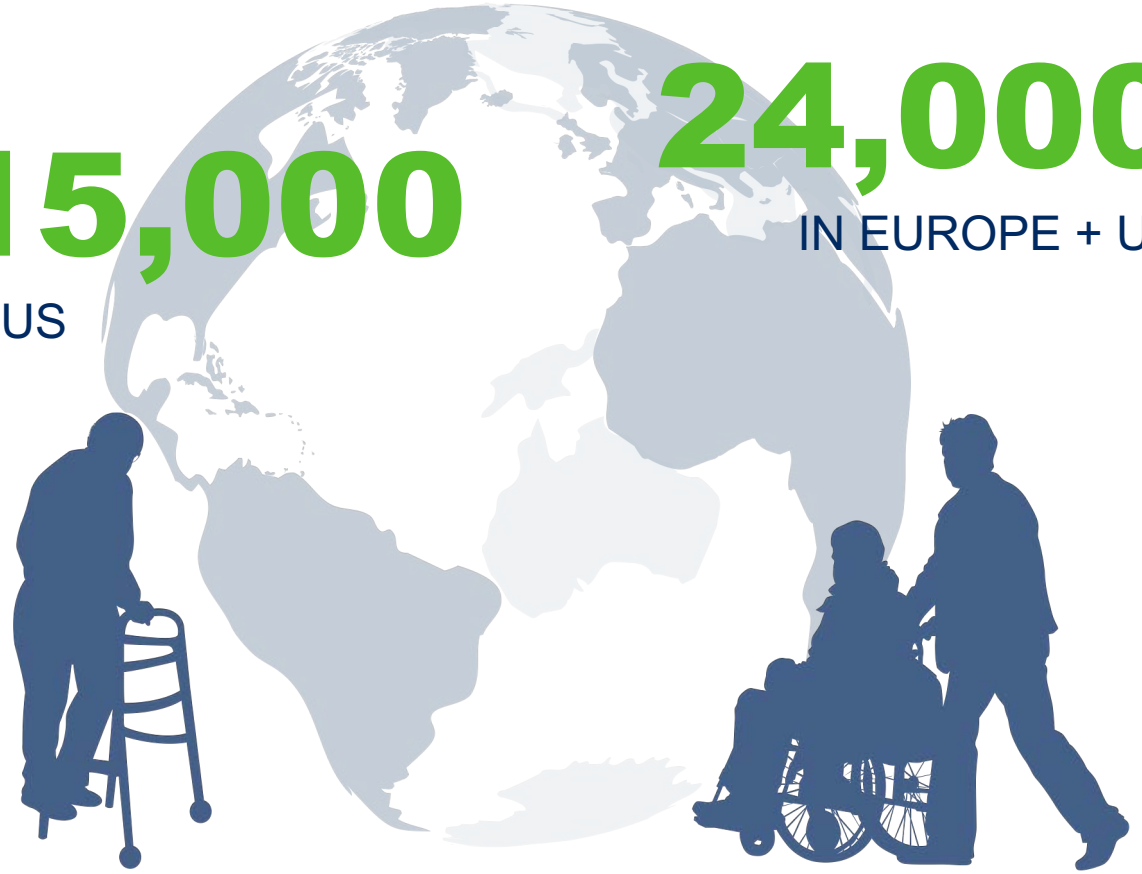
# SCA: Rare Progressively Debilitating and Fatal Neurodegenerative Disorder with No Approved Treatment

- Autosomal dominant, progressive, neurodegenerative disease with multiple genotypes[1–3]
- Onset in early adulthood with symptoms leading to severe disability and premature death[3]
- High unmet need and no approved therapies[1,2]

## SCA Prevalence[4]

**15,000**
IN US

**24,000**
IN EUROPE + UK



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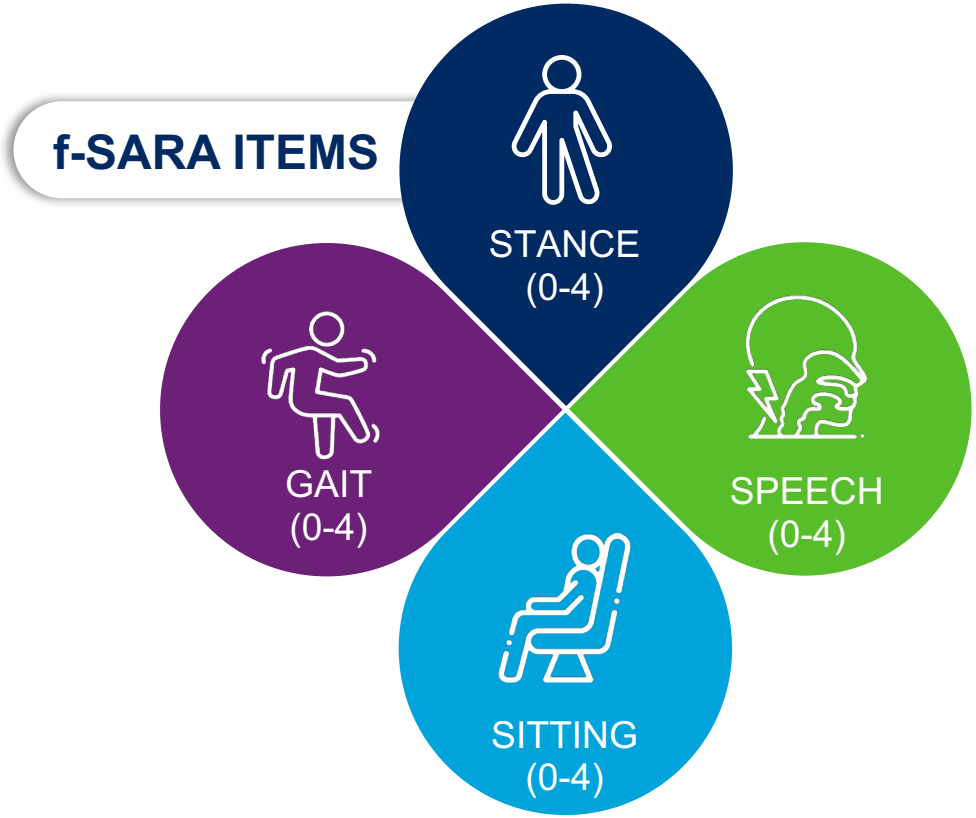
# f-SARA: Neurologist-Assessed Scale that Tracks SCA Disease Progression

- Measures 4 core functional items that are clinically meaningful and reflect hallmark symptoms of SCA[5]
- Individual items rated 0–4 with total score range 0–16
- Generally increases (worsens) 0.5 points annually
- Developed with FDA input
- Psychometric and qualitative validation performed according to FDA guidance[5,6]




KEY POINT

**f-SARA is an approvable endpoint in SCA**

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# Troriluzole: Novel Rationally-Designed Therapy for SCA


**Strong IP Protection**

- Issued NCE Composition of Matter patent expiration anticipated 2041 with extensions

## Potential Therapeutic Effects of Troriluzole

**Glutamate dysregulation linked to SCA**

- Increases intracellular calcium causing excitotoxicity
- Disrupts Purkinje neuron physiology and cerebellar network function
- Leads to neuronal cell death and progressive spinocerebellar degeneration

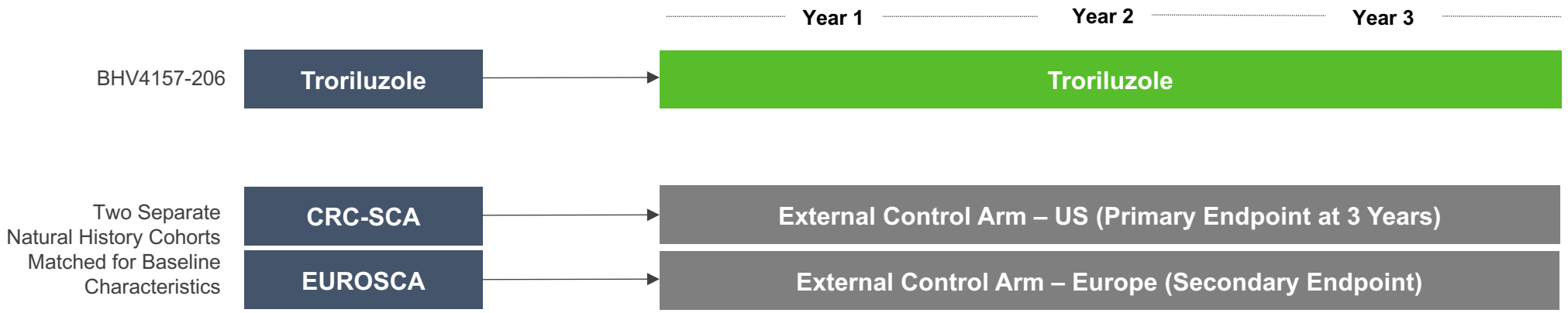
**Troriluzole restores glutamate homeostasis**

- Increases glial glutamate uptake and blocks presynaptic release of glutamate[7,8]
- Promotes healthy cerebellar Purkinje neuron functioning[1]
- Reduces excitotoxicity, neuronal damage and cell death

## Regulatory Designations for SCA Development

Fast Track in US & Orphan in US/Europe

# Study BHV4157-206-RWE (NCT06529146): Prespecified Propensity Score Matching with External Control Arm




| | |
|---|---|
| **DESIGN** | Propensity Score Matching (up to 3 untreated external control subjects matched to each troriluzole-treated subject) |
| **PRIMARY ENDPOINT** | **Total f-SARA Scale**<br>Change from baseline at 3 years in troriluzole-treated subjects vs untreated subjects from US Natural History control (CRC-SCA) |
| **SECONDARY ENDPOINTS INCLUDE** | • f-SARA change from baseline at 1 and 2 years vs US Natural History external control (CRC-SCA)<br>• f-SARA change from baseline at 1, 2, and 3 years vs EU Natural History external control (EUROSCA)<br>• f-SARA change from baseline at 1, 2, and 3 years vs pooled US & EU Natural History external control (CRC-SCA & EUROSCA) |

# Demographic and Baseline Characteristics

| | BHV4157-206 | CRC-SCA | EUROSCA |
|---|---|---|---|
| n | 105 | 446 | 358 |
| Age (years), n | 105 | 434 | 358 |
| mean (SD) | 47.6 (13.1) | 51.6 (13.8) | 47.3 (12.7) |
| median (range) | 49.0 (18, 73) | 52.0 (0, 89) | 47 (18, 84) |
| Sex, n | 105 | 446 | 358 |
| Male (%) | 47 (45) | 200 (45) | 171 (48) |
| Female (%) | 58 (55) | 246 (55) | 187 (52) |
| Age at symptom onset (years) | | | |
| mean (SD) | 37.7 (12.4) | 41.2 (13.9) | 36.7 (11.8) |
| median (range) | 38 (10, 71) | 41 (0, 76) | 37 (7, 76) |
| Genotype (%) | | | |
| SCA1 | 15 (14) | 66 (15) | 102 (29) |
| SCA2 | 31 (30) | 94 (21) | 141 (39) |
| SCA3 | 41 (39) | 153 (34) | 115 (32) |
| SCA6 | 6 (6) | 95 (21) | 0 |
| SCA7 | 5 (5) | 5 (1) | 0 |
| SCA8 | 3 (3) | 19 (4) | 0 |
| SCA10 | 3 (3) | 6 (1) | 0 |
| Multiple | 1 (1) | 3 (1) | 0 |
| f-SARA | | | |
| mean (SD) | 4.95 (1.6) | 3.97 (3.5) | 5.03 (4.1) |
| median (range) | 4.00 (2,10) | 3.00 (0,16) | 4.00 (0,16) |

Full Analysis Set

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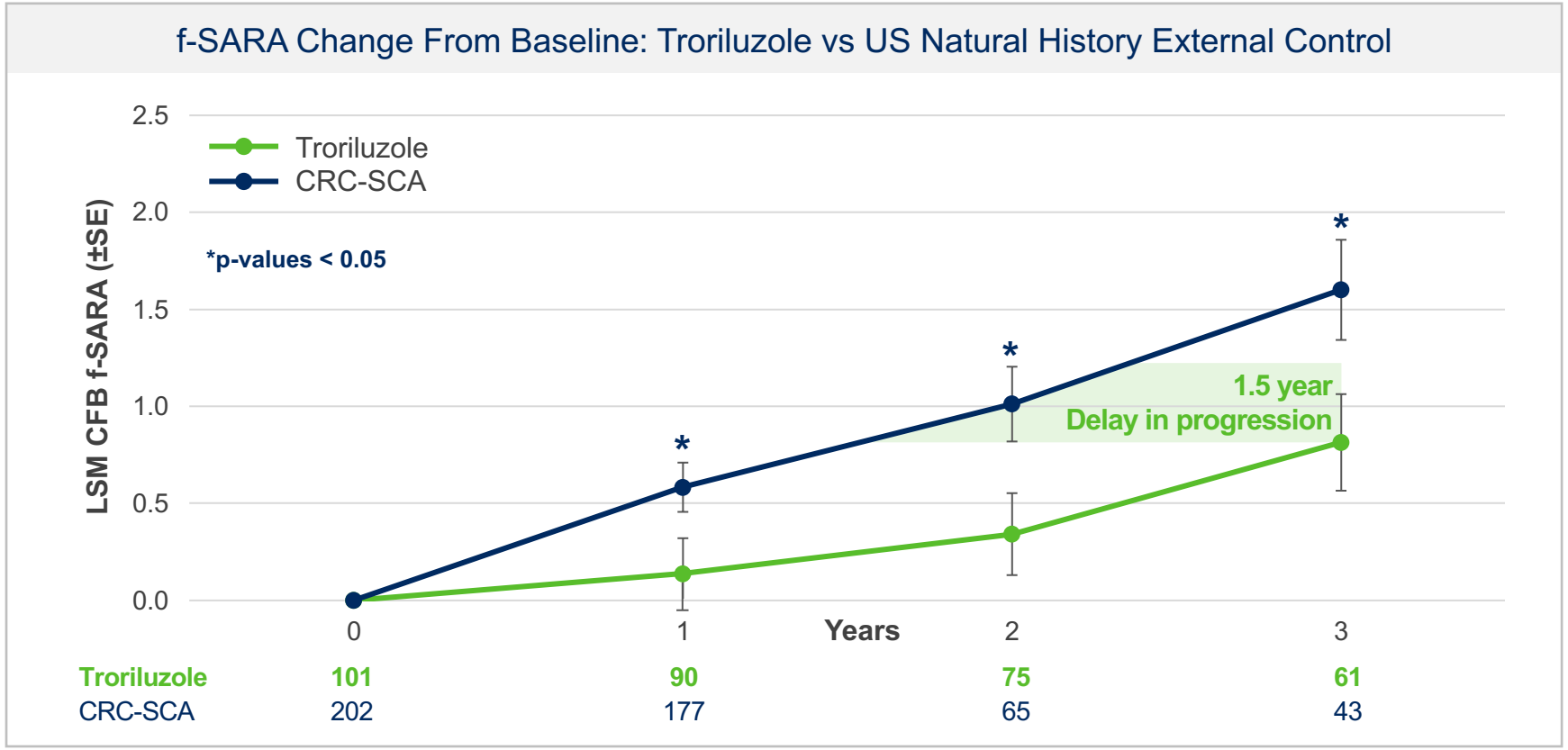
# Positive Prespecified Primary and Secondary Endpoints: Troriluzole vs US Natural History External Control




KEY POINT

**Troriluzole reduced SCA disease progression by ~50%**

**CRC-SCA**, Clinical Research Consortium for SCA; **EUROSCA,** European registry of SCA; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **LSM,** least squares mean; **PSM**, Propensity Score Matching; **CFB**, Change from baseline

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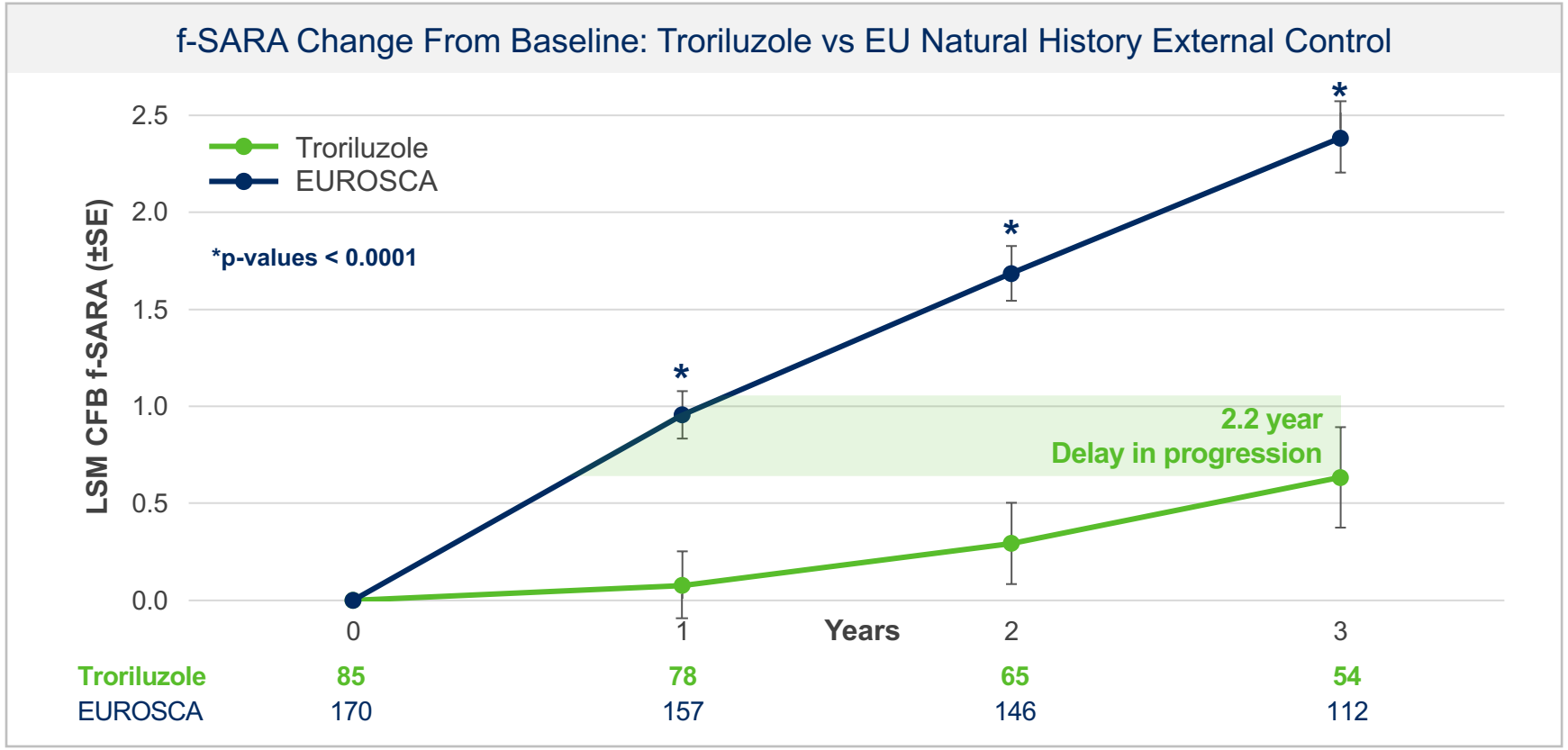
# Positive Prespecified Secondary Endpoints: Troriluzole vs Independent EU Natural History External Control




KEY POINT

**Troriluzole reduced SCA disease progression by ~70%**

**CRC-SCA**, Clinical Research Consortium for SCA; **EUROSCA,** European registry of SCA; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **LSM,** least squares mean; **PSM**, Propensity Score Matching; **CFB**, Change from baseline

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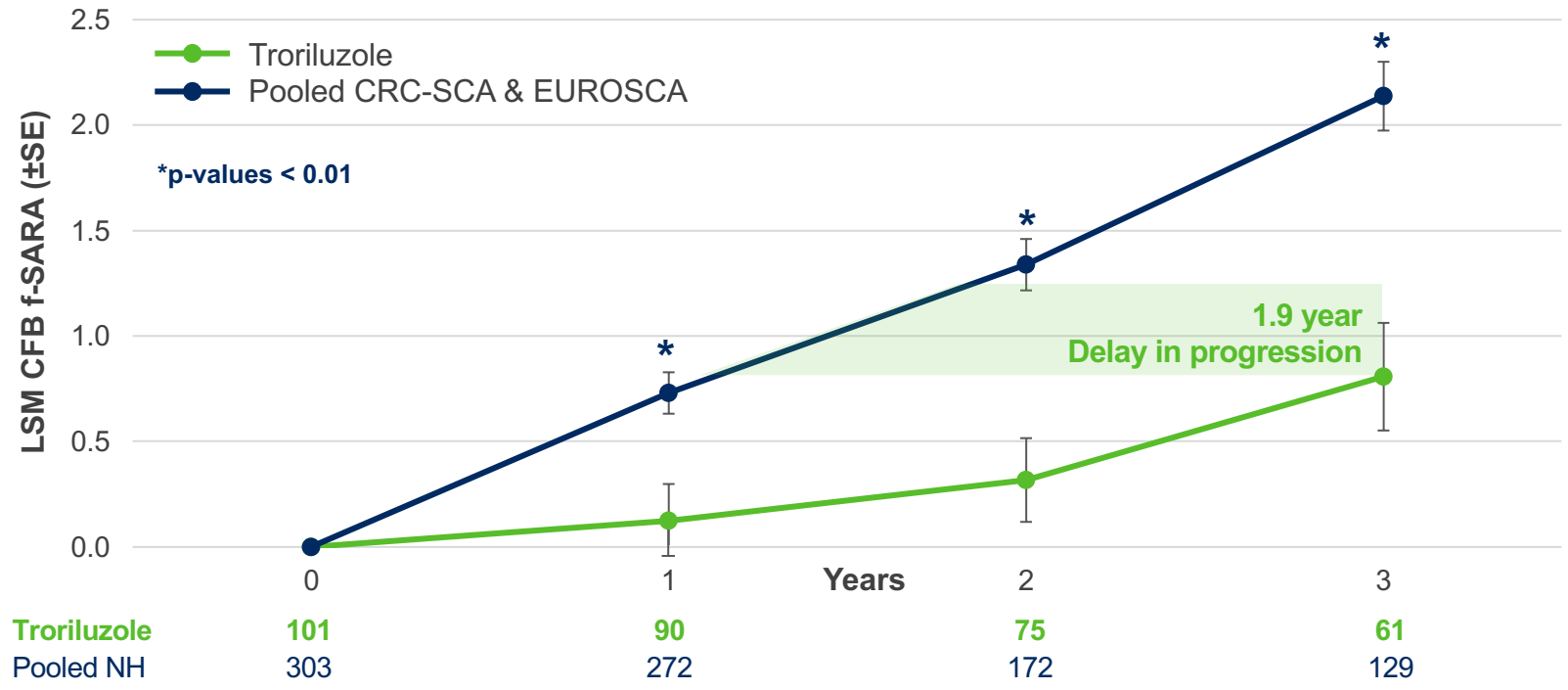
# Positive Prespecified Secondary Endpoints: Troriluzole vs Pooled US and EU Natural History External Control

f-SARA Change From Baseline: Troriluzole vs Pooled US and EU Natural History External Control




KEY POINT

**Troriluzole reduced SCA disease progression by ~60%**

**CRC-SCA**, Clinical Research Consortium for SCA; **EUROSCA,** European registry of SCA; **f-SARA**, Functional Scale for the Assessment and Rating of Ataxia; **LSM,** least squares mean; **PSM**, Propensity Score Matching; **CFB**, Change from baseline

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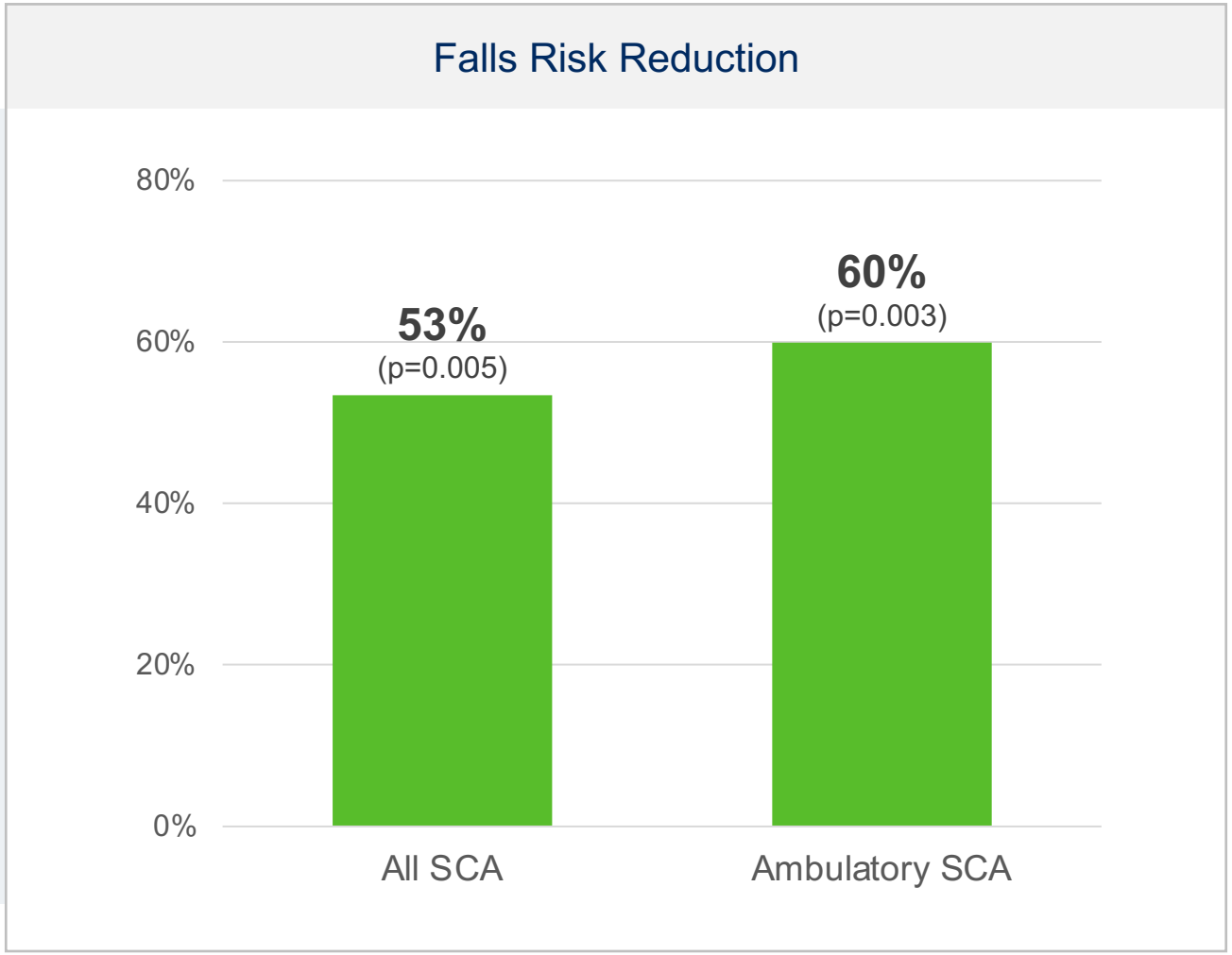
# Troriluzole Substantially Reduced Fall Risk in Double-Blind Phase

## Burden of Falls in SCA[9–10]

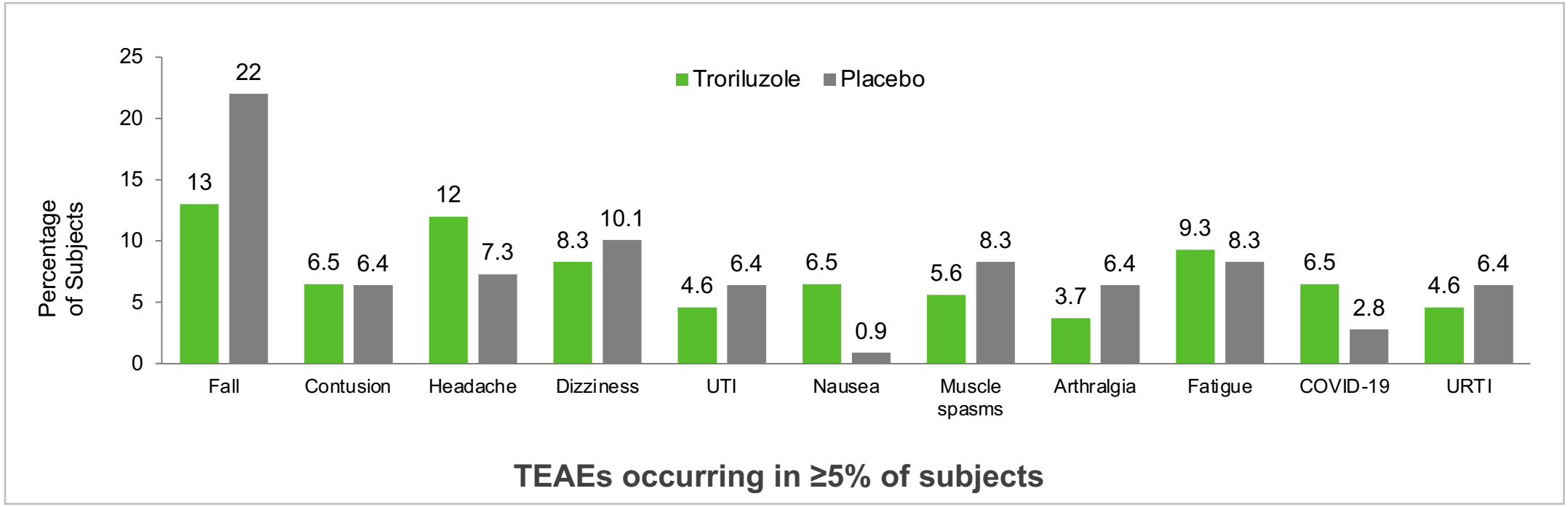
- Most SCA patients (74–84%) report falling in the preceding 12 months
- Falling is associated with a high rate of injury (74%)
- Frequent fallers report more fall-related injuries
- Fall frequency decreases when patients become wheelchair dependent or immobile




* Study BHV4157-206 double-blind phase results; Falls were captured in Study BHV4157-206 as adverse events if reported as “worsening falls” or if the fall resulted in an injury. For the analysis, a generalized linear model was fit using a Poisson family model with a log link function.
** Ambulatory SCA is defined as All SCA subjects who could ambulate without constant assistance (scoring 1 or 2 on the gait item of the f-SARA) at baseline

# Troriluzole was Well-Tolerated in Clinical Trials

| | Troriluzole N=108 | Placebo N=109 |
|---|---|---|
| Serious TEAE | **6 (5.6)** | 8 (7.3) |
| Severe TEAE | **3 (2.8)** | 8 (7.3) |
| TEAE Leading to Discontinuation | **5 (4.6)** | 5 (4.6) |




Study BHV4157-206 double-blind phase results; falls were captured as adverse events if reported as “worsening falls” or if the fall resulted in an injury.

# BHV4157-206-RWE: Study Designed In Discussion with FDA

| FDA Feedback | BHV4157-206-RWE Protocol |
|---|---|
| **Follow Industry Guidance for RWE*** ▶ | ✓ Regulatory precedent for NDA approval based on RWE |
| **Submit Protocol and Analysis Plan for FDA review prior to database lock** ▶ | ✓ Prespecified endpoints and analysis plan based on FDA input |
| **Use US SCA Natural History cohort as external control for primary analysis** ▶ | ✓ Minimizes potential for bias: Biohaven trial & US SCA Natural History study conducted by same sites/investigators, evaluating similar scales, over similar time period, with same population, on same standard of care treatment |
| **Use Propensity Score Matching (PSM) methodology** ▶ | ✓ Minimizes potential for bias by balancing baseline characteristics between treatment group and external control; Used in other NDAs leveraging RWE** |
| **Match populations based on trinucleotide repeat length** ▶ | ✓ Minimizes potential for bias by matching treatment group and external control based on an additional genetic factor associated with disease burden |
| **Match populations on year 1 progression rates by genotype** ▶ | ✓ Minimizes potential for bias by addressing non-linear patterns of disease progression and inherent heterogeneity of SCA genotypes |

*Guidance for Industry Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision Making for Drug and Biological Products (https://www.fda.gov/media/171667/download
**Lynch DR, et. al. Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data. Ann Clin Transl Neurol. 2024 Jan;11(1):4-16. doi: 10.1002/acn3.51897. Epub 2023 Sep 10. PMID: 37691319; PMCID: PMC10791025.

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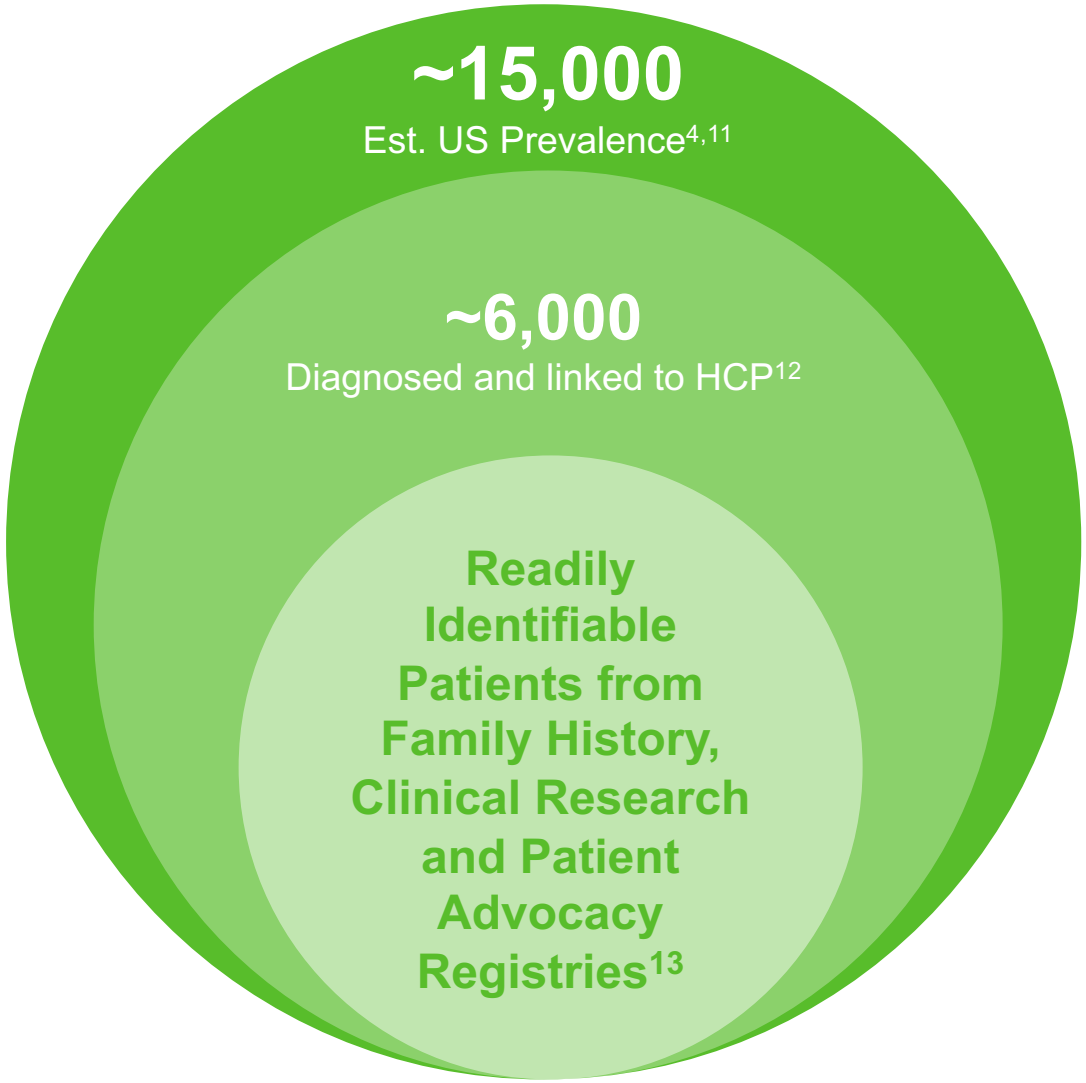
# SCA Represents a Significant Commercial Opportunity




- ~6,000 diagnosed US patients
- No currently approved SCA treatments
- Availability of genetic testing and advent of approved treatment will facilitate diagnosis
- Engaged, connected SCA patient community
- Strong patient advocacy support
- KOLs, HCPs and key centers treating SCA have been identified

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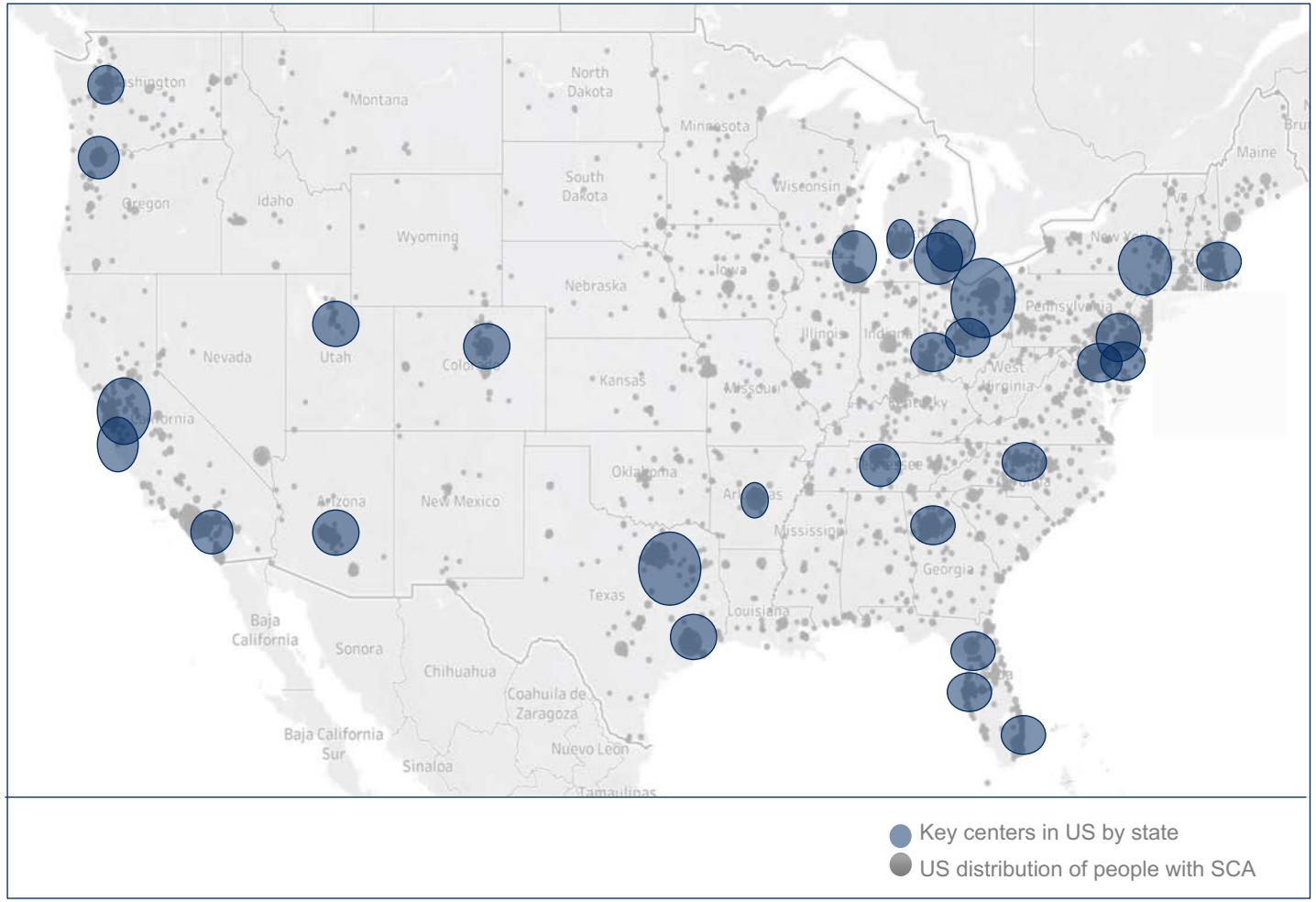
# Significant Commercial Opportunity: SCA Centralized Treatment Allows for Targeted and Efficient Commercialization Plan

## SCA treatment at key centers

121 KOLs, 22 NAF Ataxia Centers of Excellence and 73 additional Movement Disorder and Ataxia Centers have been identified and manage many patients with SCA[11,13]

## Experienced, efficient commercial team

Commercial team of ~50 staff will drive a focused and rapid troriluzole launch

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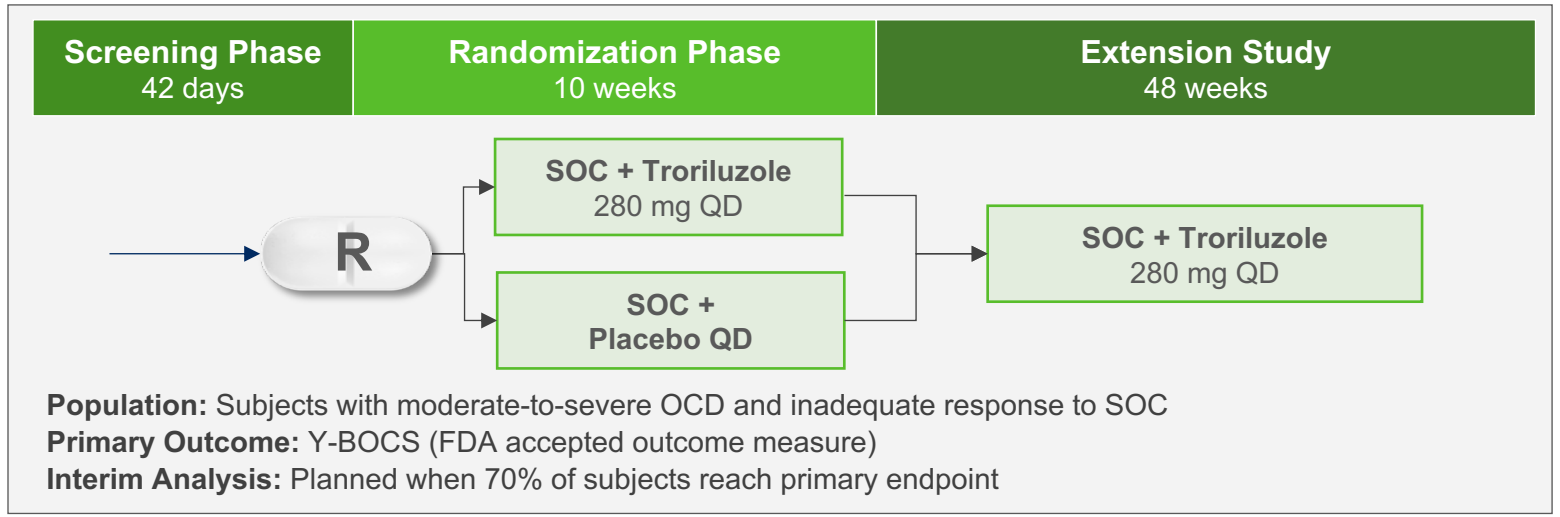
# TRORILUZOLE
## OCD

### 3M+ OCD Patients in US with High Unmet Medical Need
- 40–60% do not respond to first line treatment
- 10–40% are treatment refractory potentially requiring ablative neurosurgery or deep brain stimulation
- First novel mechanism in OCD in over 20 years and a potential breakthrough

### Phase 2 Troriluzole Trial in OCD Demonstrated Efficacy Signal
- Consistent numerical benefits vs. placebo on Y-BOCS (primary endpoint) at all timepoints (weeks 4 to 12); $p < 0.05$ at week 8 and $p = 0.22$ at week 12

### Global Phase 3 Program (2 Identical Studies) Currently Ongoing
Design informed by Phase 2 study




**Population:** Subjects with moderate-to-severe OCD and inadequate response to SOC
**Primary Outcome:** Y-BOCS (FDA accepted outcome measure)
**Interim Analysis:** Planned when 70% of subjects reach primary endpoint

### KEY POINTS
- Top-line data from first Phase 3 OCD trial expected in 1H 2025
- Interim analysis for second Phase 3 OCD trial by independent Data Monitoring Committee anticipated in 2H 2024

**OCD**, obsessive-compulsive disorder; **R**, randomization; **SOC**, standard of care; **Y-BOCS**, Yale-Brown Obsessive-Compulsive Scale.

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# BHV-4157 Troriluzole Treated OCD Patients: Strong Signal Observed in Phase 2 POC Supports Advancement to Phase 3

## STUDY BHV-4157-202

Patients with moderate-to-severe OCD (Y-BOCS score ≥ 19) and inadequate response to standard of care

## SAMPLE SIZE

226 subjects

## RANDOMIZATION

1:1

## DOSE

Troriluzole 200 mg QD vs Placebo QD (in patients on standard of care)

## PRIMARY OUTCOME

Y-BOCS, precedented outcome measure accepted by FDA

**Table 1: Troriluzole Effect on OCD in Phase 2/3 Trial[1]**

| Y-BOCS Total Change from Baseline | Week 4 (N=115[a], 111[b]) | Week 8 (N=108[a], 96[b]) | Week 12 (N=102[a], 99[b]) |
|---|---|---|---|
| **a.** Placebo[a] | -2.9 | -3.6 | -4.9 |
| **b. Troriluzole[b]** | **-3.4** | **-5.1*** | **-5.9** |
| p-value | 0.451 | 0.041 | 0.220 |

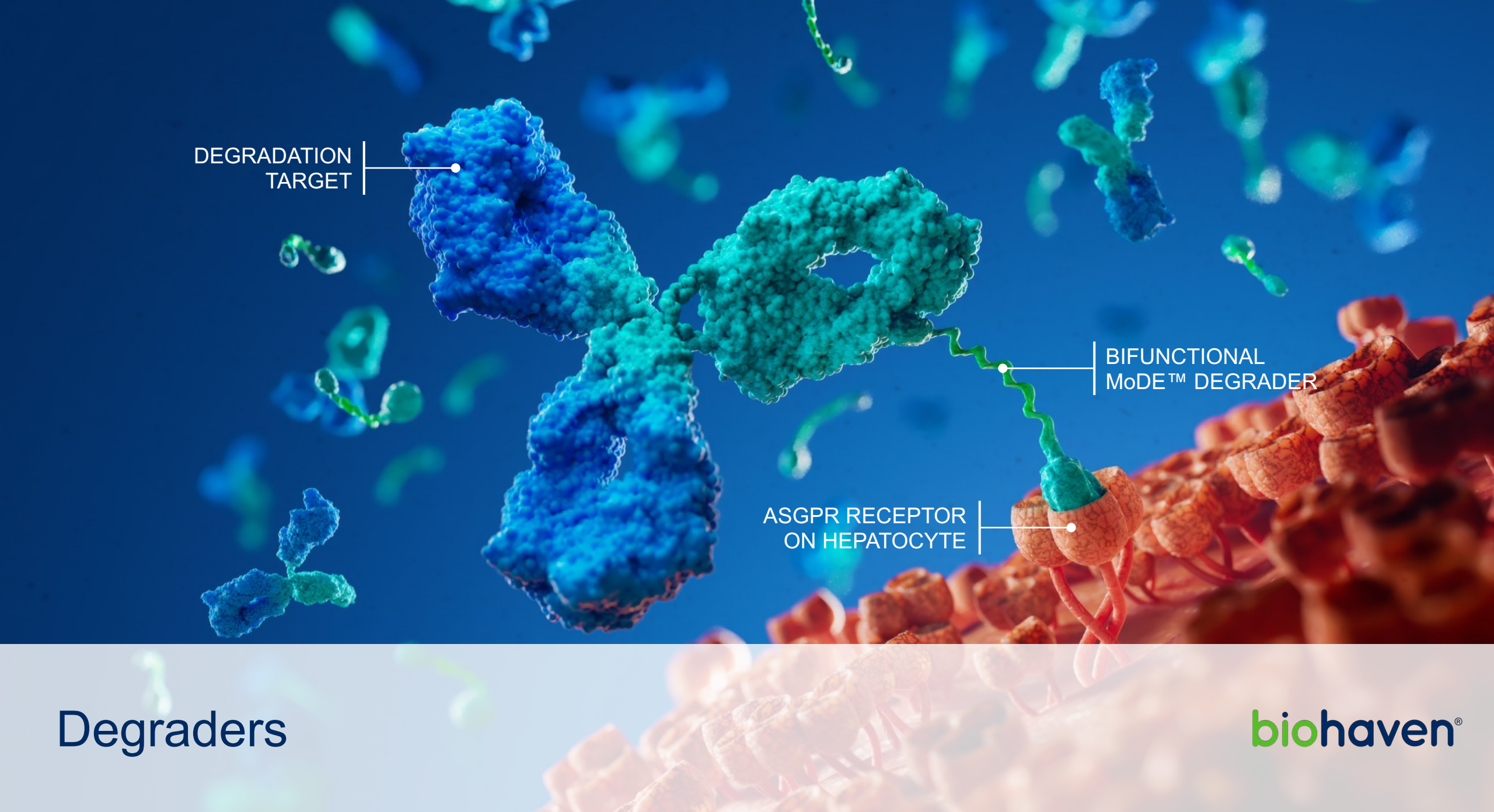
1. BHV-4157-202 Final Unblinded Analysis YBOCS Total Change from Baseline by Week LSMeans from MMRM Model MITT Data Set

**Table 2: Troriluzole Effect on Patients with Severe OCD[1]**

| Y-BOCS Total Change from Baseline | Week 4 (N=47[c], 49[d]) | Week 8 (N=45[c], 42[d]) | Week 12 (N=43[c], 44[d]) |
|---|---|---|---|
| **a.** Placebo[c] | -3.5 | -3.1 | -4.6 |
| **b. Troriluzole[d]** | **-4.1** | **-6.0*** | **-7.0** |
| p-value | 0.584 | 0.035 | 0.084 |

1. Patients at baseline with median Y-BOCS total scores > 26 (severe OCD symptoms).
* $p < 0.05$ versus placebo

**Y-BOCS**, Yale-Brown Obsessive Compulsive Scale (FDA accepted outcome measure)




# Degraders

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# PAN IgG DEGRADERS

## Pan-IgG Lowering Agents

Lowering pathogenic IgG presents multiple disease opportunities

## Innovative Mechanism of Action

- Protein degradation rather than inhibition
- Low projected human dose range
- Small molecule allows for small-volume subcutaneous dosing

## Faster and Deeper Depletion with Ease of Administration

- NHP studies showed 80% IgG depletion with a single dose of BHV-1300; increasing to ~90% after multiple doses
- More rapid IgG reduction vs. competitors
- Allows for co-administration with biologics
- Patient self-administered subcutaneous autoinjector in production given initial Phase 1 exposure and pharmacodynamic data

## Potential in Multiple Diseases

- Common diseases — RA, lupus erythematosus, lupus nephritis
- Rare diseases — Generalized myasthenia gravis, transplant, oncology, etc.

**KEY POINTS**

- BHV-1300: Dose-dependent and rapid IgG reductions within hours after administration in the ongoing Phase 1 study
- Provides early clinical validation of the degrader platform

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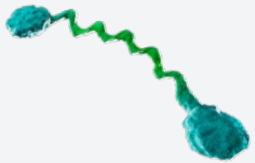
# A Novel Mechanism: Hepatic ASGPR Receptor Harnessed for Efficient and Safe Removal of Circulating Pathogenic Targets

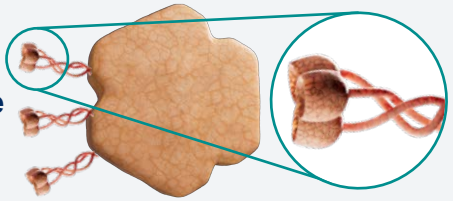
**Legend**

**Degradation Target**

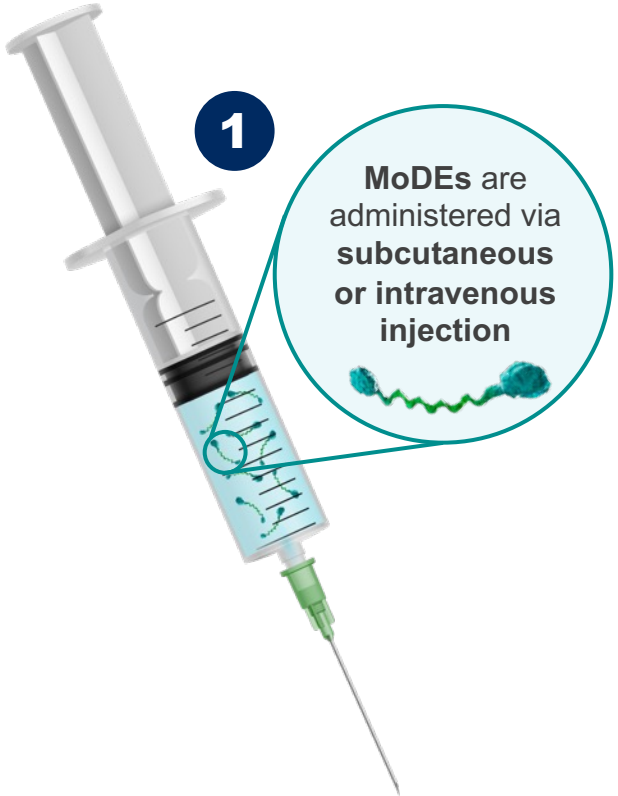
**Bifunctional MoDEs®**



**Hepatocyte**



**Asialoglycoprotein receptor***

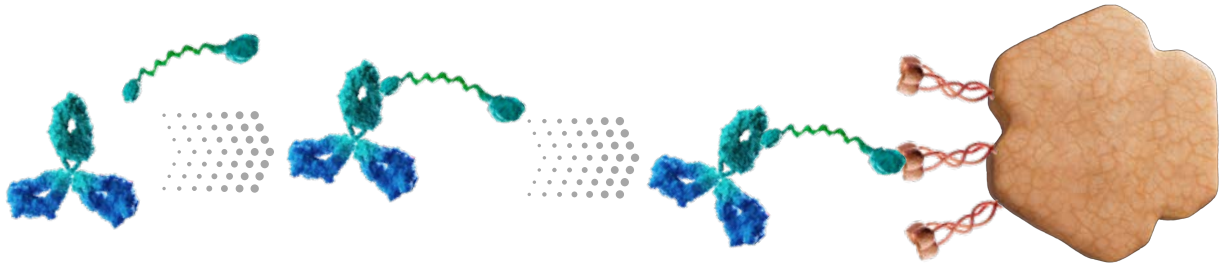


**1**

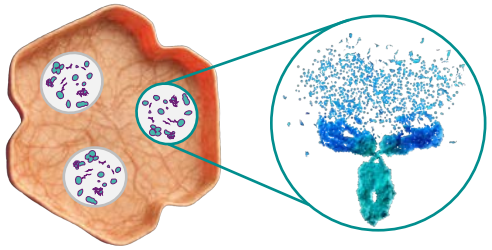
**MoDEs** are administered via **subcutaneous or intravenous injection**

**2**

**MoDEs** bind circulating target and efficiently delivers it to ASGPRs on hepatocytes

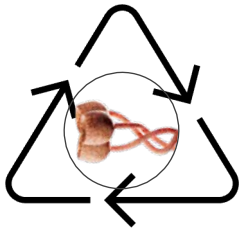


**3**



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

**4**



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

*Stylistic representation

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

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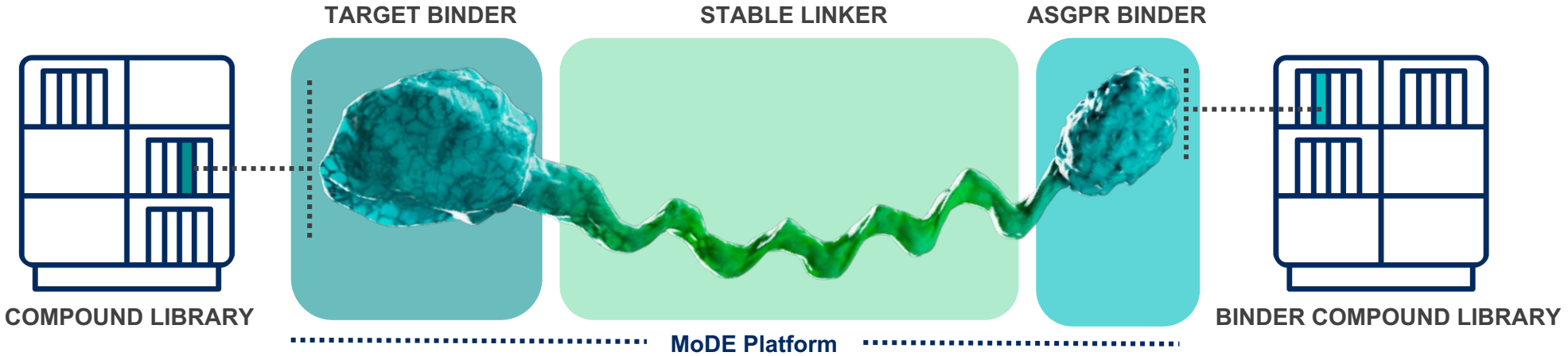
# A Transformational MoDE Drug Platform: Molecular Degraders of Extracellular Proteins (MoDE™)

## Precisely balanced components selected for optimal efficacy, safety, and product profile




- Efficiently removes immune targets causing disease
- Fast onset and potential for > 90% deep reduction in target
- Selective targeting of proteins avoids immunosuppression
- Ability to adjunctively dose Fc biologics
- Accelerate IND timelines (12–18 mo)

**KEY POINT**

Biohaven's MoDE platform is rapidly generating drug candidates for multiple diseases

**IND**, Investigational New Drug Application.

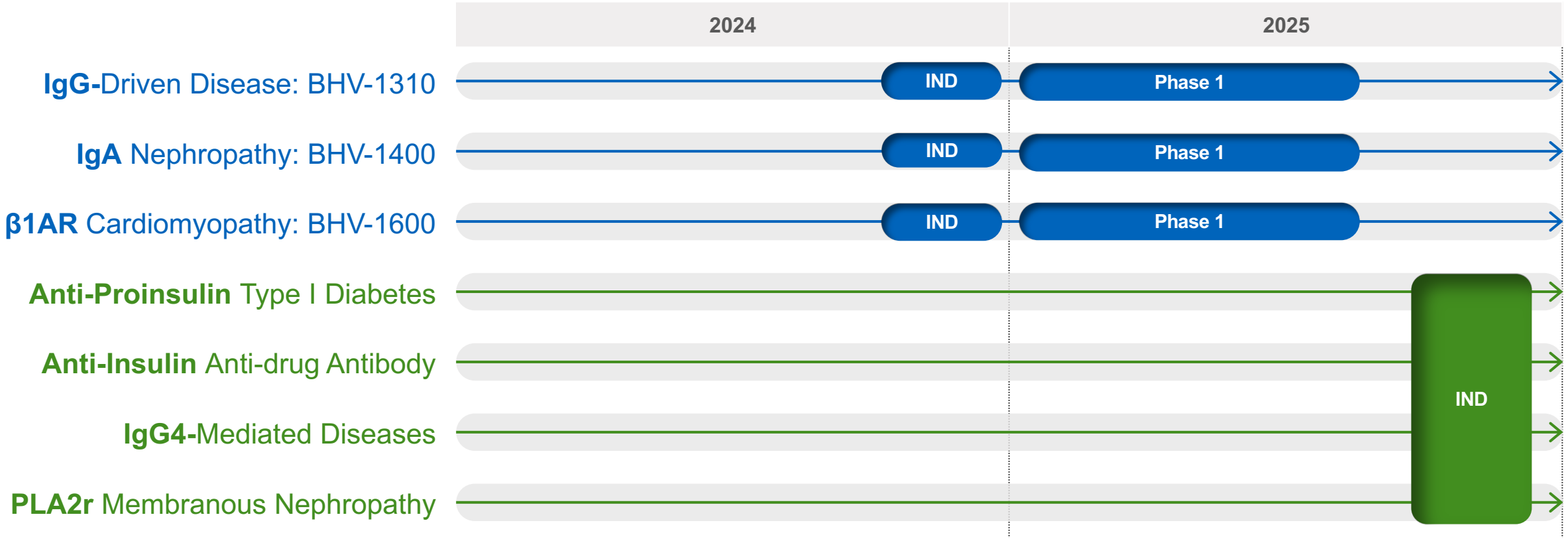
# Positive Differentiation Predicted for Bispecific Degraders Over Competition

## Antibody lowering therapeutic modalities

| Drug Modality | Discovery cycle time | Speed of onset | Depth of Ig-lowering | Administer with SoC | Immuno-suppression |
|---|---|---|---|---|---|
| **IgG Degraders** | ●●●● | ●●●○ | ●●●○ | ●●●○ | ●○○○ |
| **Autoantibody-specific degraders** | ●●●● | ●●●○ | ●●●○ | ●●●○ | ○○○○ |
| FcRN-inhibitor | ●●○○ | ●○○○ | ●●○○ | ●○○○ | ●●○○ |
| Imlifidase | ●●○○ | ●●●● | ●●●● | ●●●○ | ●●●● |
| BLyS/APRIL-i | ●○○○ | ●○○○ | ●●○○ | ●●●○ | ●●●○ |

Scoring of properties represent qualitative projections, based on MOA and available data.

# MoDEs: Multiple Asset Opportunities and Potential Timelines




**KEY POINTS**

- Three MoDEs on schedule for IND this year
- Four new targets announced and rapidly progressing

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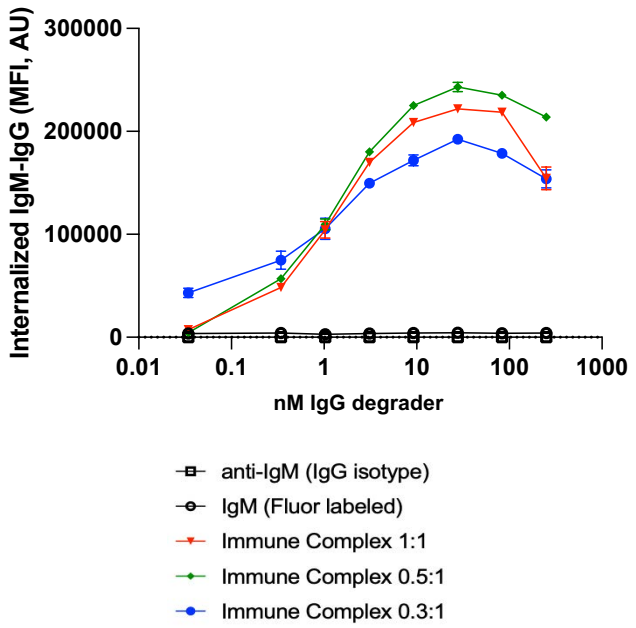
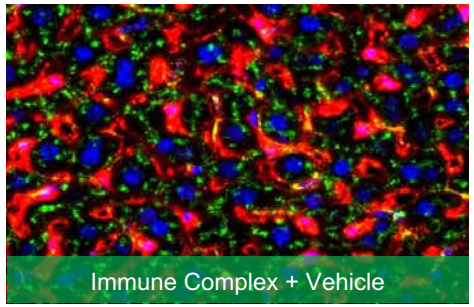
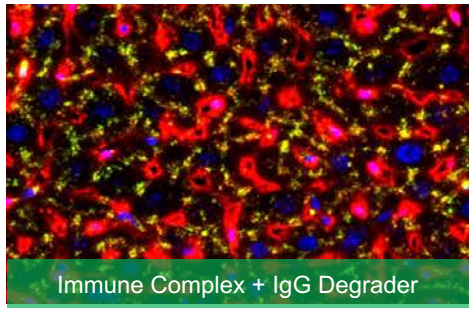
# IgG Degraders Remove Disease Relevant Immune Complexes (IC)

## *In Vitro* Lowering of IgM/IgG ICs



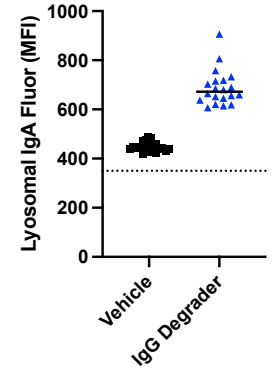

## Dg-IgA1/IgG ICs Colocalize with Lysosome (LAMP1) via BHV-1310

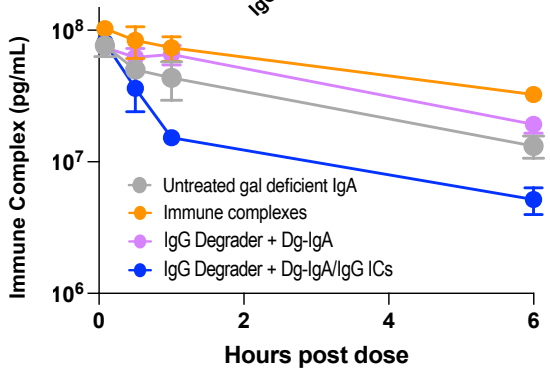



Staining: DAPI / IgA1 / LAMP-1
Combined (IgA1/LAMP-1)

## *In Vivo* ICs are Efficiency Removed in Mice



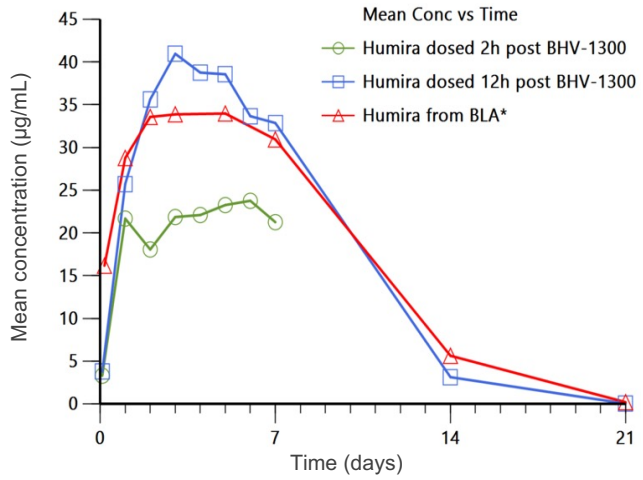

**KEY POINT**

First evidence of degraders directly removing IgM/IgG, IgG/IgG, Dg-IgA/IgG complexes *in vivo*

**Dg-IgA1,** Surrogate for natural form of galactose-deficient IgA1 (Gd-IgA).

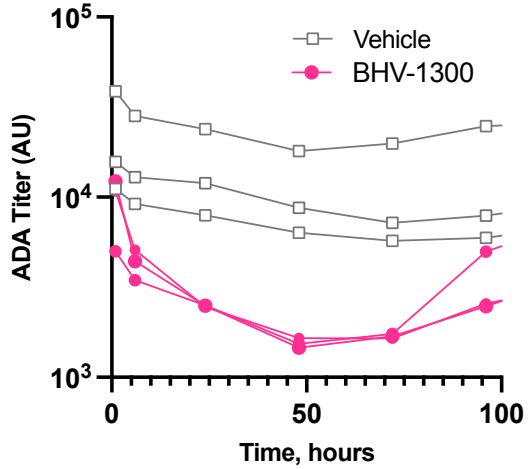
# IgG Degradation Improves Efficacy of Biologics Through Removal of ADAs

## BHV-1300 Compatible With Biologic Therapeutics When Dosed >12h Prior



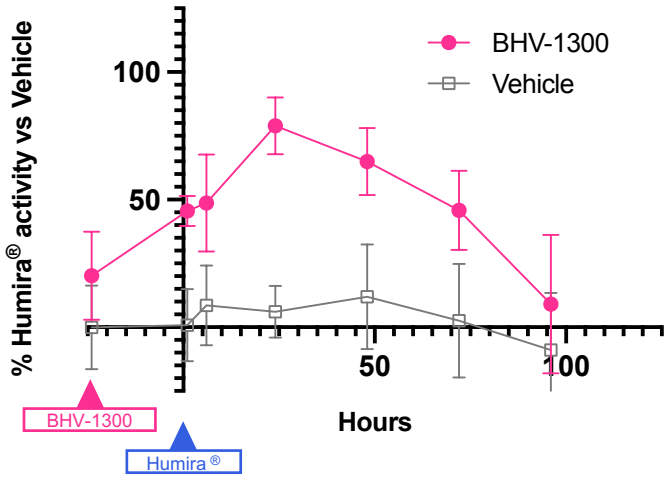

BHV-1300 dosed at 30 mg/kg SC followed by Humira® dosed at 3 mg/kg SC in NHPs

## BHV-1300 Effectively Removes ADAs in NHPs




ADAs[1] induced by administration of Humira® are reduced with a single dose of BHV-1300

## BHV-1300 Restores Effects of Biologics Through Removal of ADAs (TNFα Neutralization Assay)




Humira® activity measured by TNFα levels BHV-1300 dosed 24h prior to Humira®

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

**KEY POINT**

BHV-1300 can be co-administered with biologics, removing anti-drug antibodies and restoring efficacy[1]

**ADA,** Antidrug Antibody; **NHP,** Non-human Primates

1. Ann Rheum Dis. 2014 Dec;73(12):2178-82.

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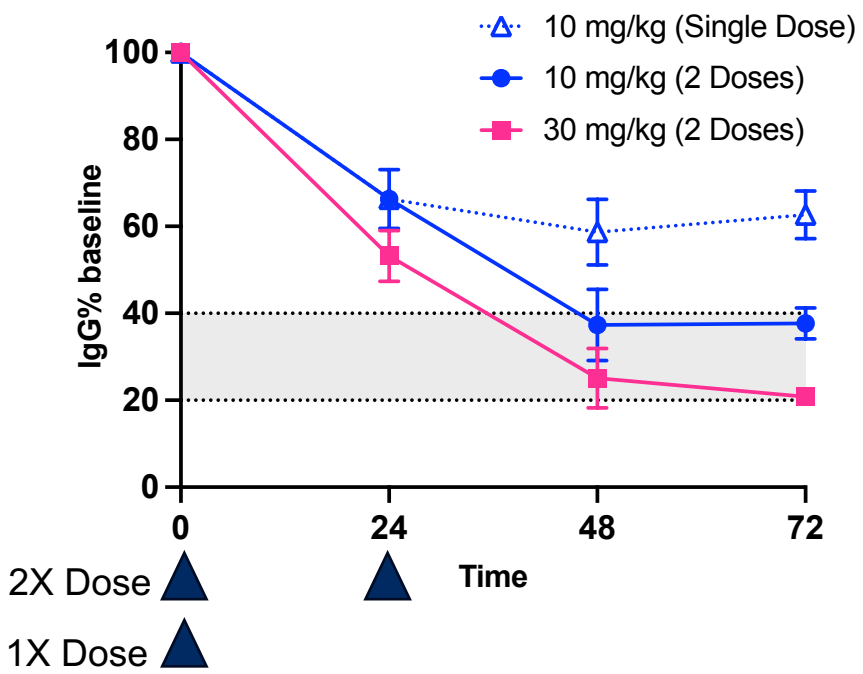
# Consecutive Doses of MoDE Doubles IgG Lowering in NHPs

IgG Lowering to Efficacious Levels (60-80%)
Is Achieved With Consecutive Daily Doses in 2 Days




KEY POINT

Unique pharmacology provides flexibility in dosing regimens

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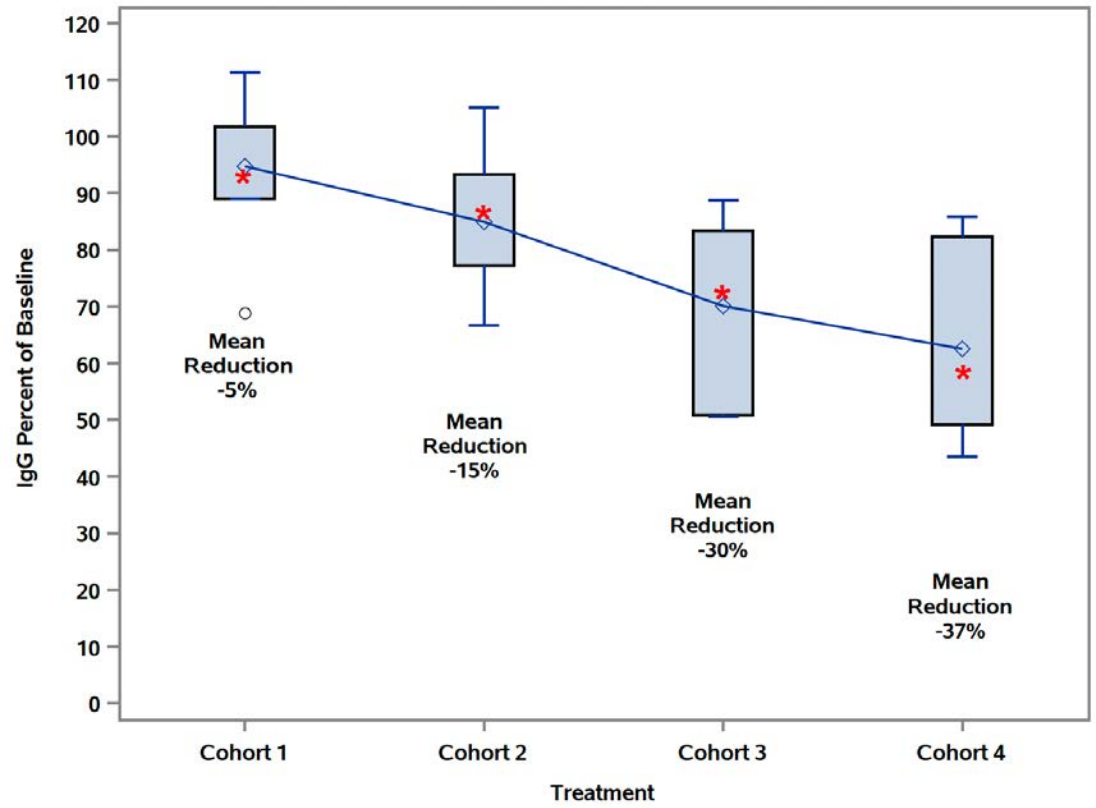
# Single Doses of BHV-1300 Reduce IgG in Dose-Dependent Manner in Ongoing SAD Study in Healthy Subjects

## BHV-1300 Maximum IgG Percent of Baseline Within 96 Hours



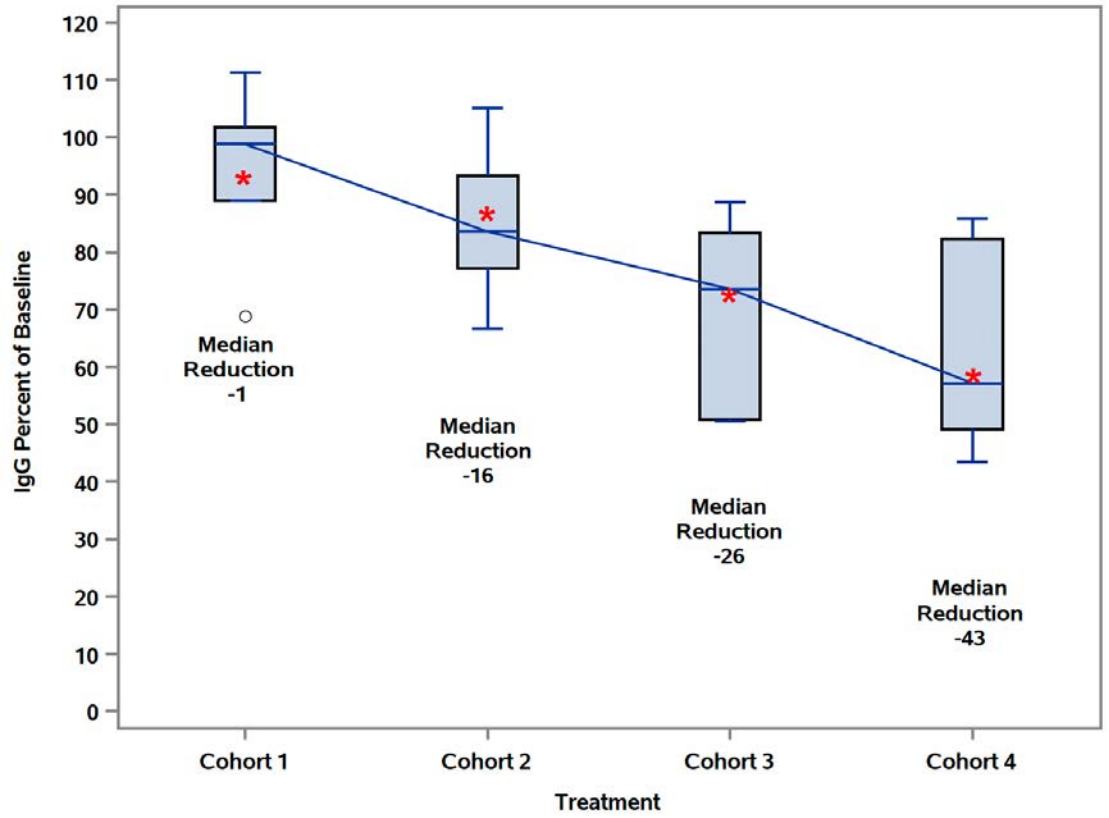

★ Predicted based on modeling

- Dose-dependent sustained lowering through follow-up period
- Based on modeling, anticipate achieving 70-80% IgG reduction when Phase 1 complete

Preliminary data from ongoing Phase 1 Study (as of May 28, 2024).

# Median IgG Lowering Within 96 Hours

## BHV-1300 Maximum IgG Percent of Baseline Within 96 Hours




★ Predicted based on modeling

- Fixed or non-weight based dosing for all cohorts
- Data shown represents median values across dose cohorts

Preliminary data from ongoing Phase 1 Study (as of May 28, 2024).

# BHV-1300 Is Selective for IgG

- No meaningful reduction of IgM, IgA, or IgE
- No meaningful impact on albumin
- No meaningful impact on low-density lipoprotein cholesterol

Preliminary data from ongoing Phase 1 Study (as of May 28, 2024).

# BHV-1300 Is Safe and Well-Tolerated in Healthy Subjects

SC formulation of BHV-1300 used in Phase 1 study delivered exposures higher than the intravenous formulation, enabling the profile of a convenient patient administered auto-injector to attain targeted reduction of IgG.

- No SAEs or severe AEs
- Most AEs were mild, not related, and resolved spontaneously
- No clinically significant ECG changes
- No clinically significant drug-related lab changes
- No hepatotoxicity or clinically significant changes in LFTs

Preliminary data from ongoing Phase 1 Study (as of May 28, 2024).

# BHV-1300 Rapidly, Selectively and Safely Lowers IgG in a Dose-Dependent Manner in Healthy Subjects

**EFFICACY**

- Dose-dependent and rapid onset of IgG lowering within hours
- Dose-dependent sustained lowering through follow-up period
- Based on modeling, anticipate achieving 70-80% IgG reduction in Phase 1 utilizing doses compatible with subcutaneous administration

**SELECTIVITY**

- No meaningful reduction of other immunoglobulins
- No meaningful impact on albumin and low-density lipoprotein cholesterol

**SAFETY**

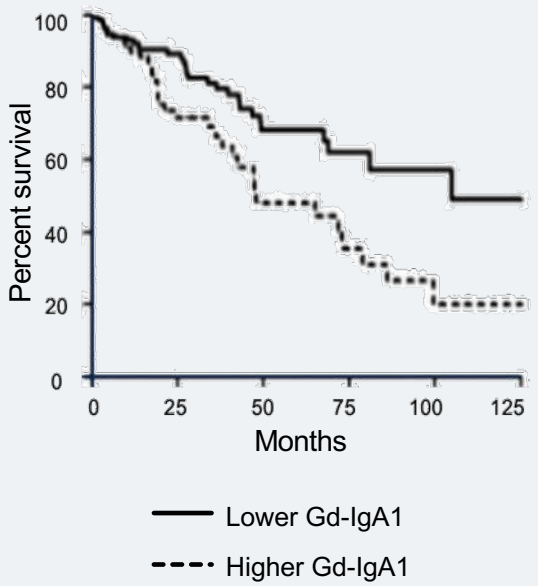
- Safe and well-tolerated
- No infusion reactions
- No hepatoxicity or clinically significant changes in LFTs

Preliminary data from ongoing Phase 1 Study (as of May 28, 2024).

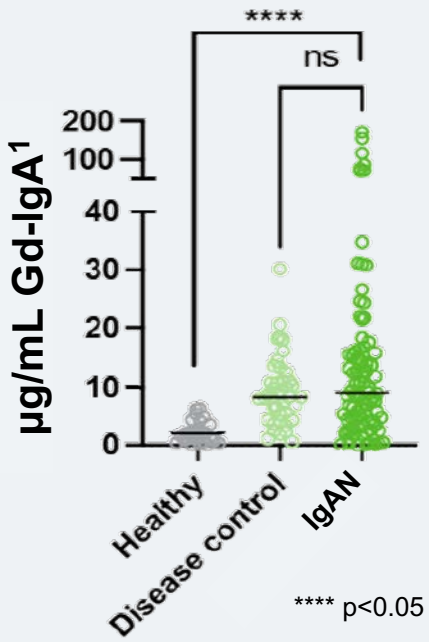
# BHV-1400 Degradation of Gd-IgA1 and Gd-IgA1 Immune Complexes (IC) for Treatment of IgA Nephropathy (IgAN)

**IgAN is a progressive kidney disease characterized by the chronic deposition of IC in the kidney following generation of autoantibodies to galactose-deficient IgA1**

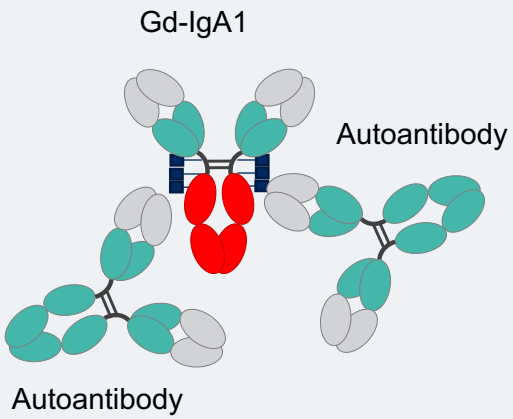
## Progression-free survival of IgAN patients stratified by serum Gd-IgA1 levels[1]



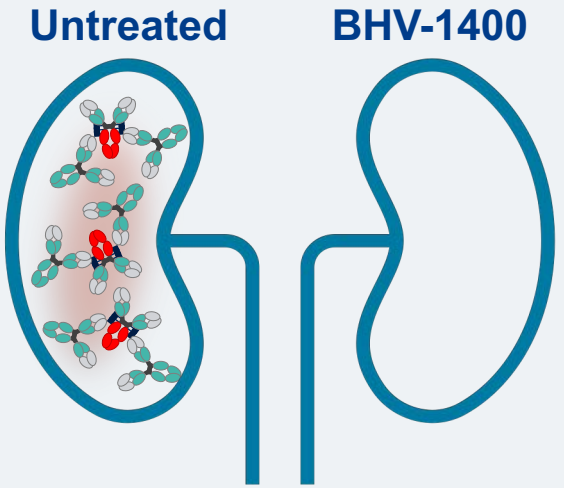

## Serum Gd-IgA1 levels across control and patient populations




## Autoantibodies to Gd-IgA1 and ICs are key drivers of pathology

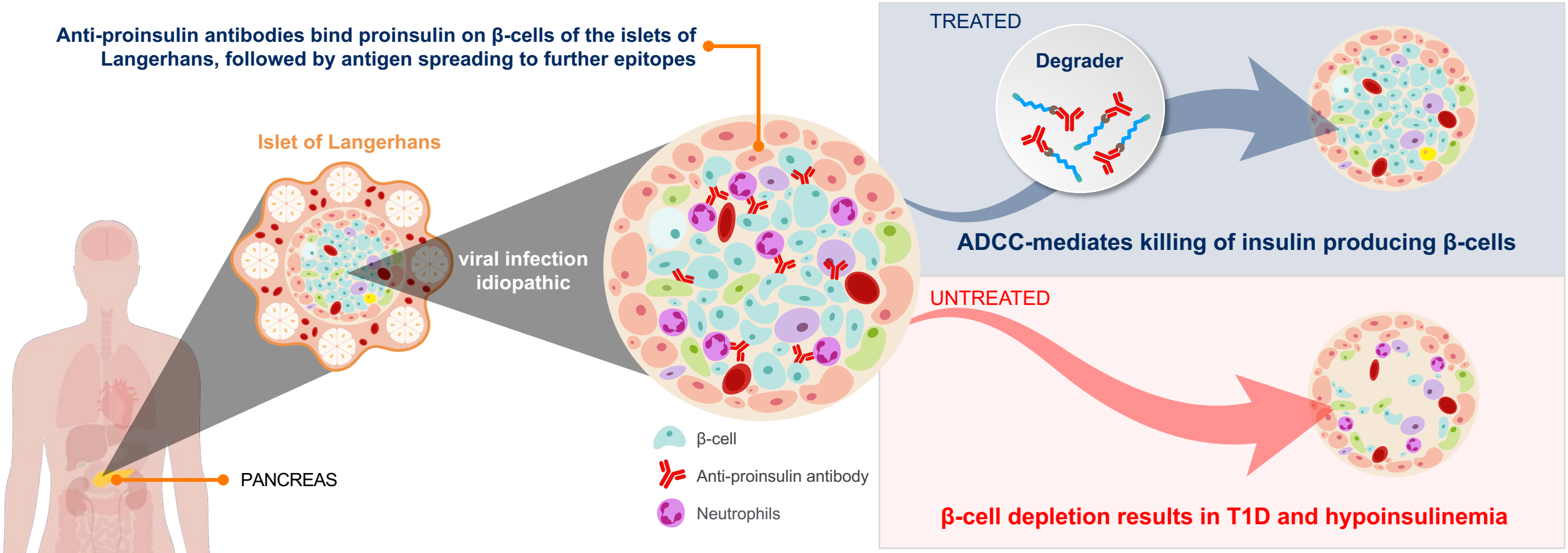



## ICs deposit in the kidney leading to inflammation and progressive loss of function




1. Kim JS, Hwang HS, Lee SH, Kim YG, Moon JY, Kong JY, Jeong KH. Clinical Relevance of Serum Galactose Deficient IgA1 in Patients with IgA Nephropathy. J Clin Med. 2020 Nov 4;9(11):3549. doi: 10.3390/jcm9113549. PMID: 33158064; PMCID: PMC7694202.

# Removal of Proinsulin Autoantibodies Halts Progression of Nascent Type 1 Diabetes (T1D)




KEY POINT

**THERAPEUTIC HYPOTHESIS** Lowering of antibodies early in course of disease may prevent loss of β-cells and stop cascading events which lead to Type 1 Diabetes

**ADCC**, Antibody dependent cellular toxicity.

# Degraders Bind to Insulin and Proinsulin Autoantibodies, Resulting in Uptake, Hepatic Degradation and Correction of Glucose Homeostasis

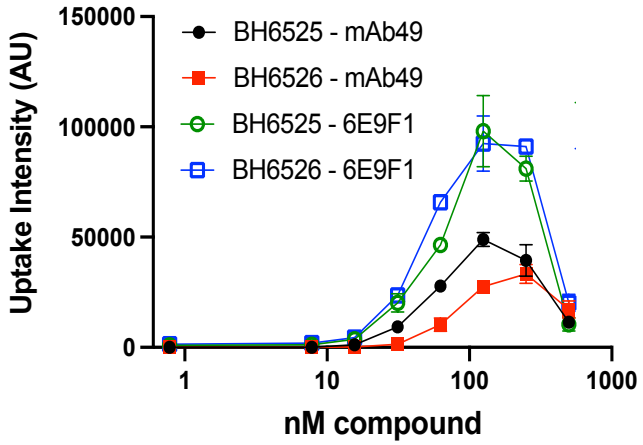
## Biochemistry Selectivity (Insulin Autoantibody)

EC50 (nM)

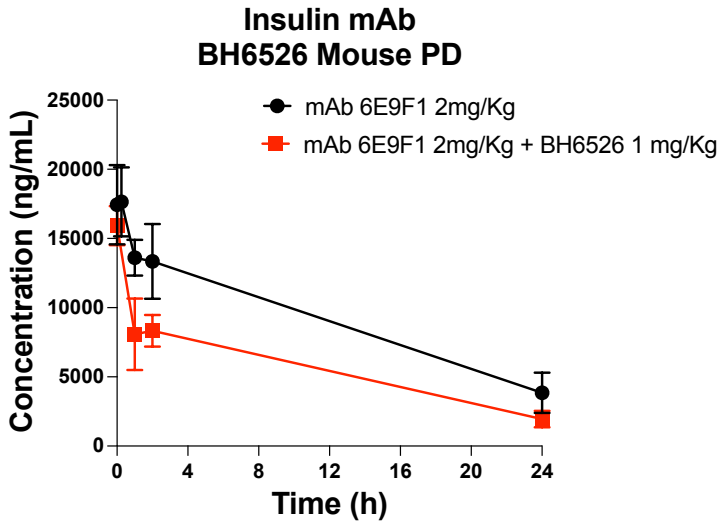
| | BH6525 | BH6526 |
|---|---|---|
| **mAb49** | 39.68 | 67.21 |
| **6E9F1** | 39.13 | 37.61 |

mAb49: Human anti-Insulin antibody
6E9F1: Mouse anti-Insulin antibody

## Cellular Autoantibody Uptake




## *In Vivo* Autoantibody Reduction




- Anti-insulin and anti-proinsulin autoantibody MoDEs form ternary complexes, show *in vitro* uptake and drive *in vivo* clearance without binding insulin receptors or IGF1R
- Robust and selective lowering of these autoantibodies shown in mouse PK/PD experiments
- Evaluation underway in efficacy studies and preliminary toxicology

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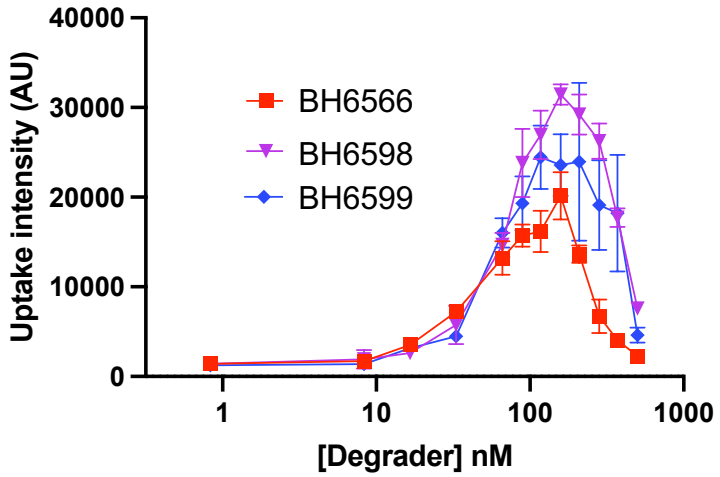
# Specific Degraders Designed to Efficiently Remove Only IgG4

## IgG4-Specific Degraders Bind Only Human IgG4 with 100X Selectivity

**Binding Affinity**

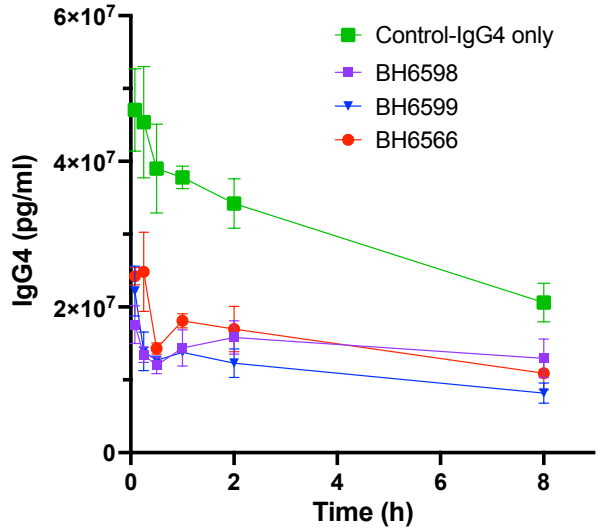
| | Native hIgG1 | Native hIgG2 | Native hIgG3 | Native hIgG4 |
|---|---|---|---|---|
| BH6566 | >1000 | >1000 | >1000 | 36 |
| BH6598 | >1000 | >1000 | >1000 | 33 |
| BH6599 | >1000 | >1000 | >1000 | 43 |

## Cellular IgG4 Uptake




## *In Vivo* IgG4 Reduction

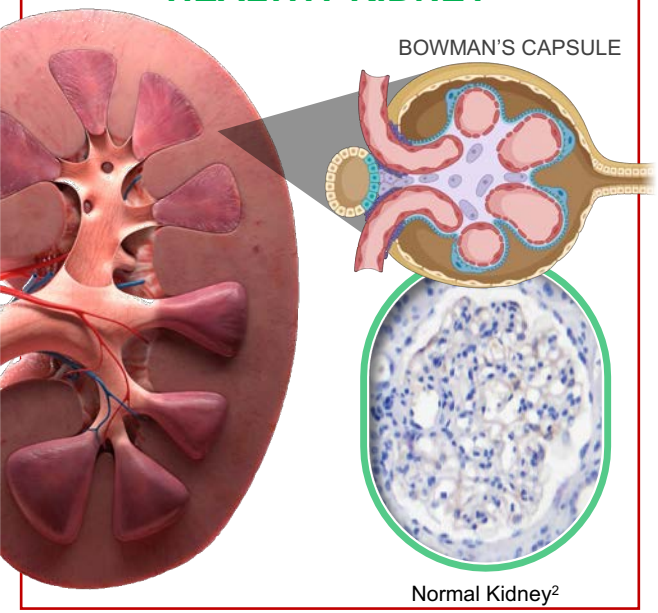
(single dose, 1 concentration POC)




- IgG4 selective degraders identified
- Robust and selective lowering of IgG4 in mouse PK/PD experiment
- Evaluation underway in disease relevant efficacy studies and preliminary toxicology

# Selective Targeting of Anti-Phospholipase A2 Receptor (PLA2r) Antibodies for Idiopathic Membranous Nephropathy (IMN)

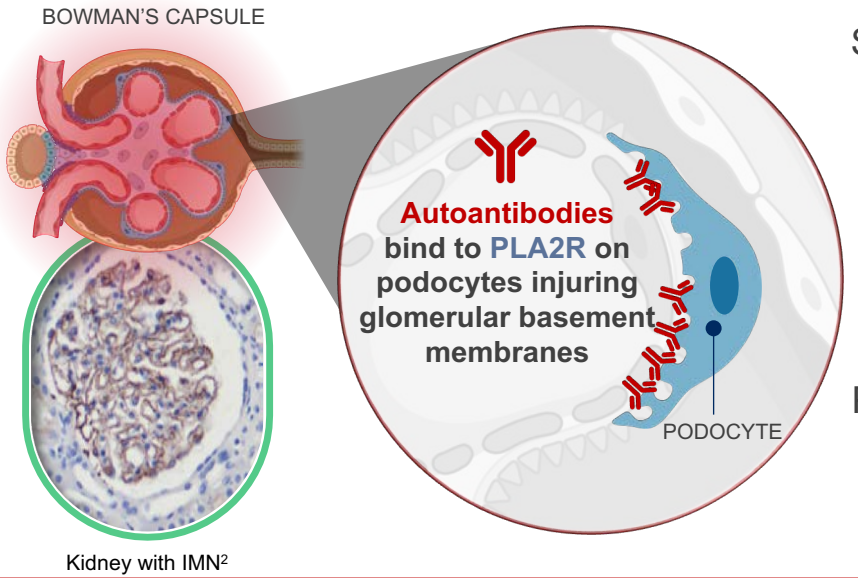
## HEALTHY KIDNEY




## NEPHROTIC KIDNEY

70–80% of IMN patients have high anti-PLA2r levels[1]

Anti-PLA2r autoantibodies levels are strongly associated with disease severity in IMN




Subepithelial immune complex deposits

▼

Podocyte injury, thickening of basement membrane

▼

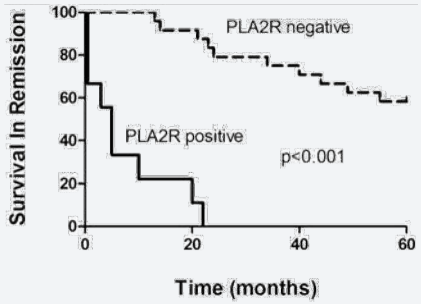
Proteinuria and hyperlipidemia

▼

**Kidney failure**

## Currently no specific therapies to treat IMN[2]

- Rituximab or cyclophosphamide + glucocorticoids are first-line therapies but have serious side effects
- Combination of plasmapheresis with SoC shows more favorable outcomes[3,4]




**Patients rendered anti-PLA2r negative by immunosuppression have greater disease remission**

1. Beck, L.H.; Bonegio, R.G.B.; Lambeau, G.; Beck, D.M.; Powell, D.W.; Cummins, T.D.; Klein, J.B.; Salant, D.J. M-Type Phospholipase A 2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy. *N. Engl. J. Med.* 2009, *361*, 11–21. 2. Adapted from *Kidney International* (2012) 82, 797–804 3. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int (2021) 100(4, Supplement):S1–276. doi: 10.1016/j.kint.2021.05.021. 4. Bennani HN, et al.,*J. Pers. Med.* 2024, *14*(3), 249. 5. Lu H et al. Medicine(Baltimore) 2019 May; 98(18): e15303.

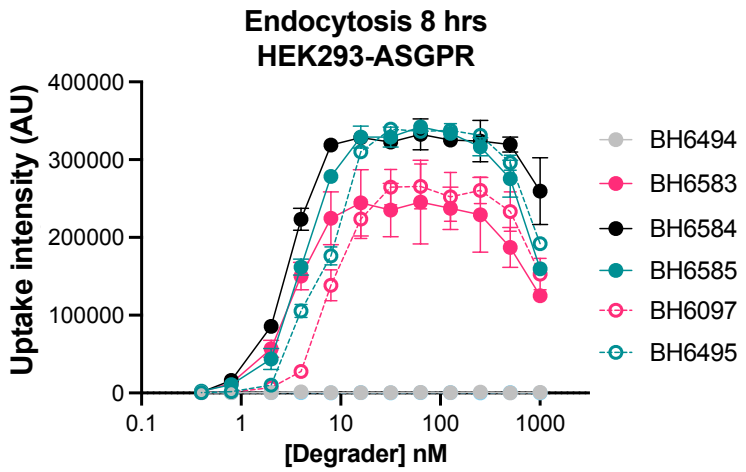
# PLA2r Antigen-Specific MoDEs Rapidly Remove Pathogenic Autoantibodies

## Biochemical Selectivity

**Binding Affinity (nM)**

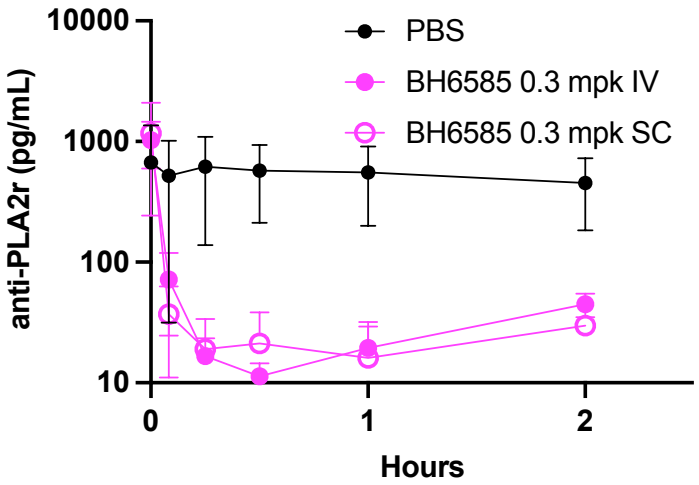
| | Anti-PLA2r |
|---|---|
| **BH6494** | 0.3 |
| **BH6583** | 10 ± 3 |
| **BH6584** | 3 ± 0.3 |
| **BH6585** | 7 ± 1 |
| **BH6097** | 23 ± 1 |
| **BH6495** | 7 |

## Cellular Autoantibody Uptake




*BH6494 lacks ASGPR binder

## *In Vivo* Autoantibody Reduction




KEY POINT

Deep reductions in anti-PLA2r autoantibodies will prevent further glomerular injury

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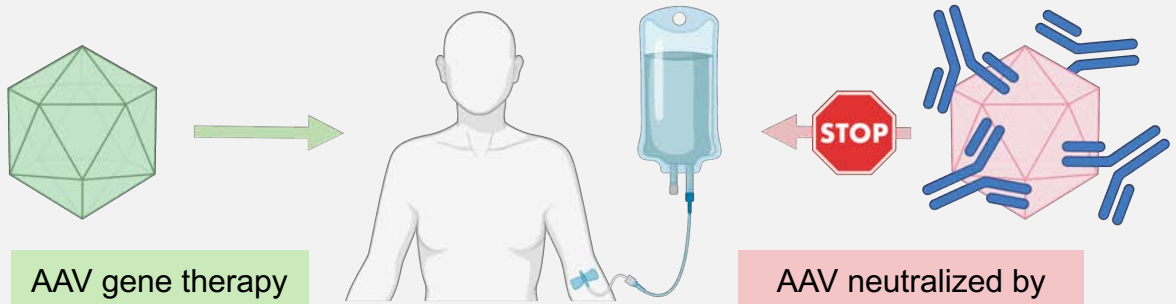
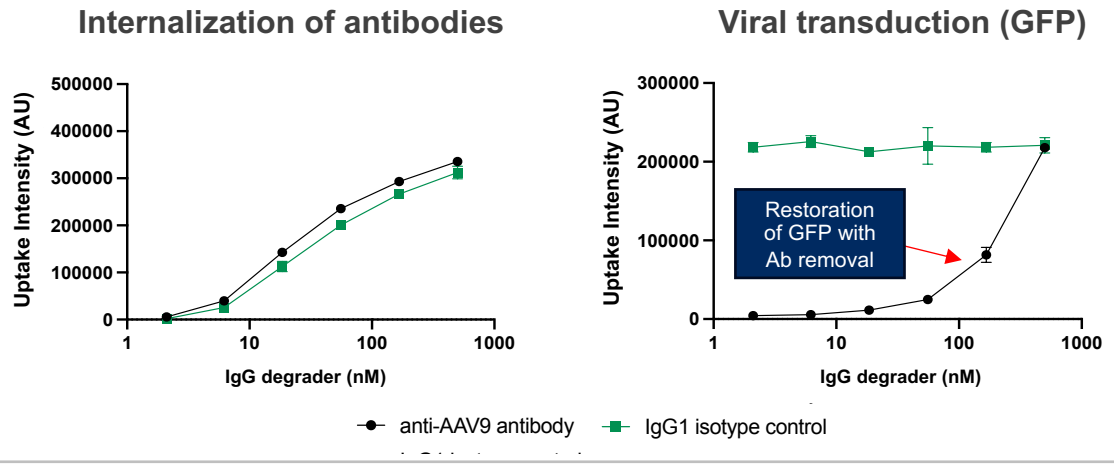
# Removal of Neutralizing Antibodies to Capsids to Optimize Gene Therapy Uptake and Allow Repeat Administration



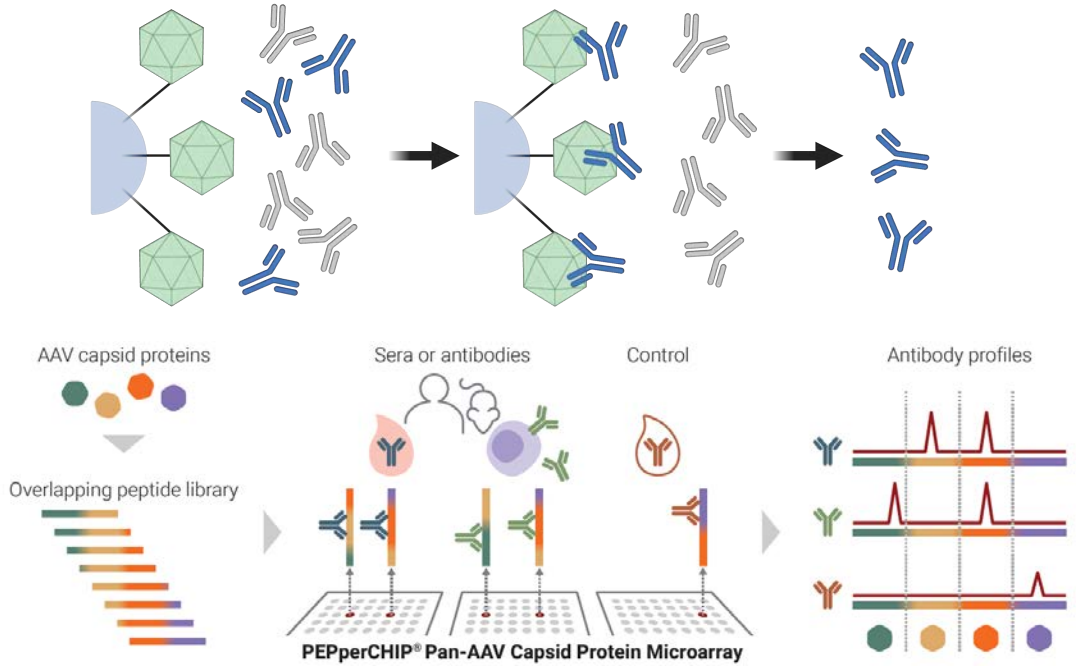

**Preexisting anti-AAV antibodies limit the use of AAV-based gene therapy**

## POC Using GFP Viral Transduction




## Discovery of Dominant Epitopes for Anti-AAV Antibodies

Enrich anti-AAV antibodies (blue) with immobilized capsids identify binders using array of display techniques

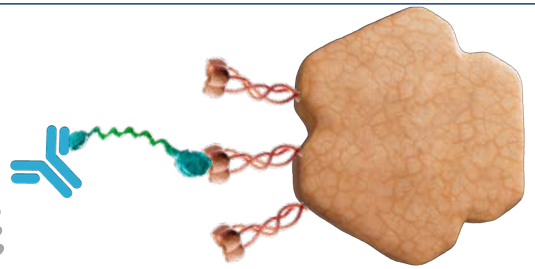



Peptide binders which bind comprehensive antibody populations can be quickly converted to MoDEs

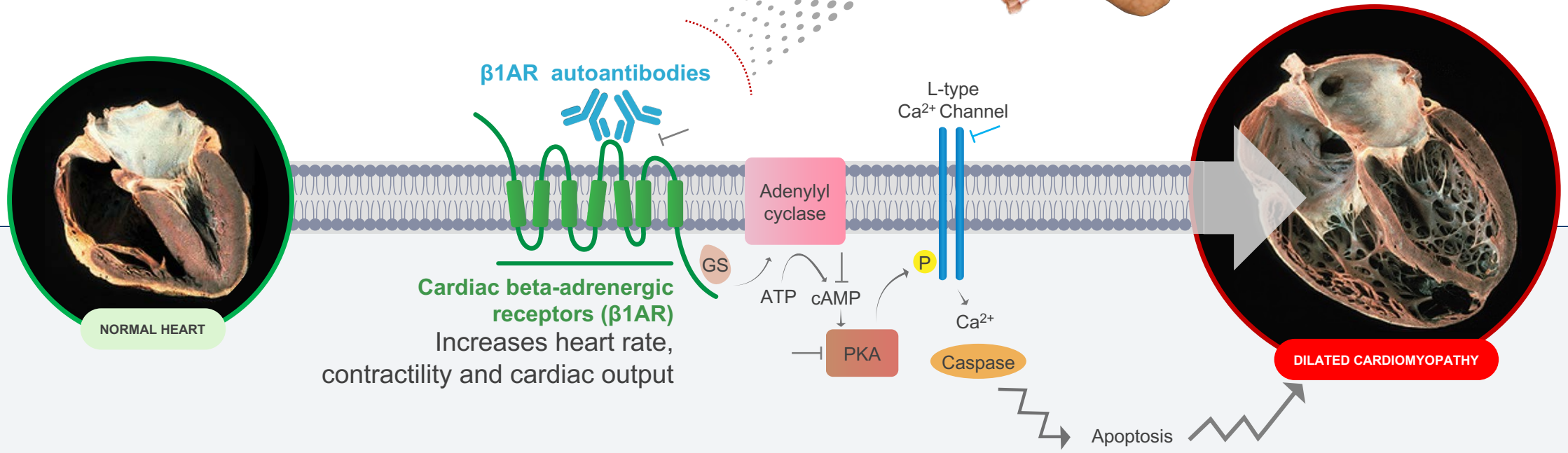
# Selective Targeting of β1AR Autoantibodies for Cardiomyopathy

## β1AR autoantibodies

Agonistic autoantibodies to β1AR increase basal heart rate
Sustained β1AR agonism ▶ dilated cardiomyopathy ▶ heart failure



**BHV-1600 targeted hepatic degradation of autoantibodies**




**Cardiac beta-adrenergic receptors (β1AR)**
Increases heart rate, contractility and cardiac output

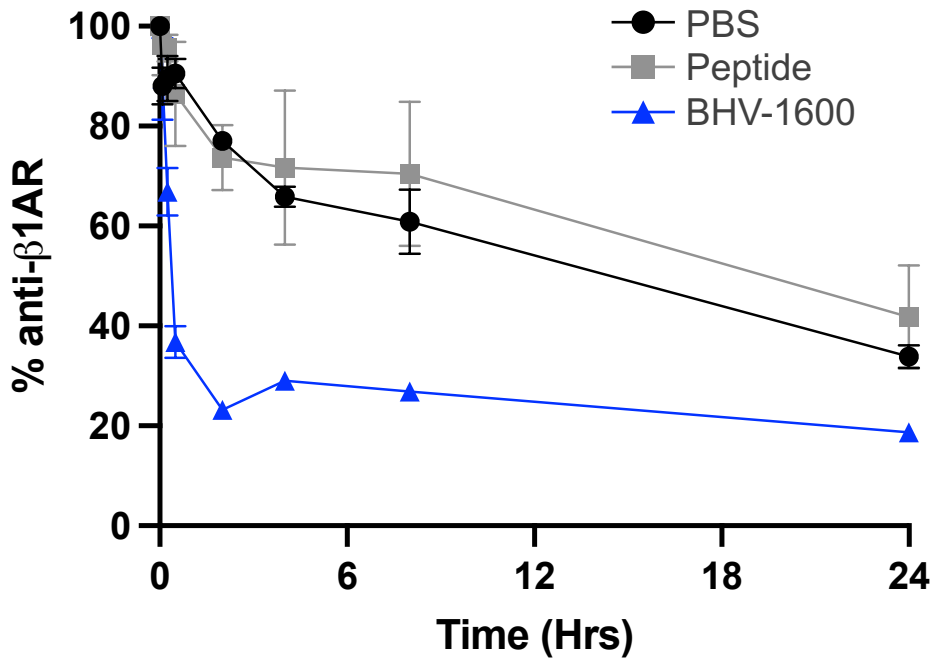
**CURRENT TREATMENT FOR β1AR AUTOANTIBODY-DRIVEN CARDIAC DISEASE:**

- **BETA BLOCKERS:** Ineffective treatment limited to supportive treatment, diuresis, etc.
- **REMOVAL OF ANTIBODIES:** Plasmapheresis[1,2] demonstrates POC but requires hospitalization

1. *Eur J Heart Fail.* 2013; 15(7): 724–729. 2. *Nat. Rev. Nephrol.* 2014; 10(3): 125-125. Illustration adapted from European Journal of Heart Failure (2013) 15, 724–729. Heart image adapted from https://thoracickey.com/clinical-presentation-and-therapy-of-cardiomyopathies.

# BHV-1600: *In Vitro* and *In Vivo* Properties Ideal for Degrading β1AR Abs

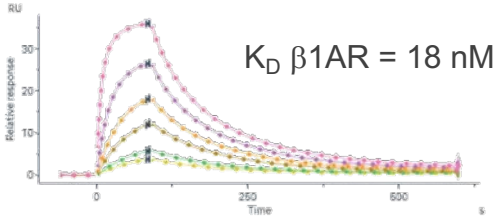
## Marked Degradation of Anti-β1AR Antibody in Mice




- Rapid ASGPR-mediated hepatic clearance in mouse and rat
- Stoichiometric degradation of exogenously administered anti-β1AR Ab in mice compared to controls

## High Affinity to the Target

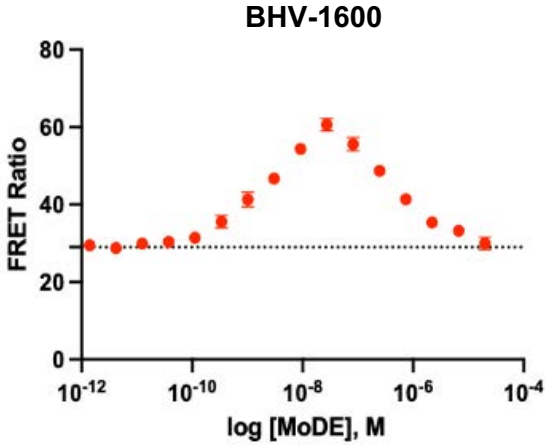
High affinity for monoclonal mouse anti-β1AR antibody and ASGPR protein construct by SPR



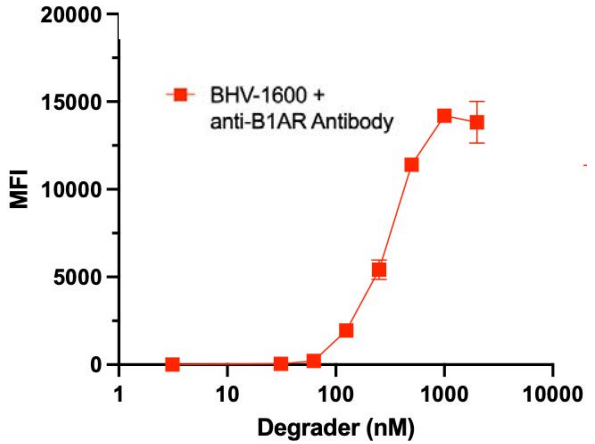

$K_D$ β1AR = 18 nM

## Ternary Complex Formation Followed by Cell Uptake

Formation of ternary complex confirmed in TR-FRET assay




Cellular internalization of anti-β1AR Ab demonstrated in HEK293 (hASGPR) cells




**SPR,** Surface Plasmon Reference; MFI, Mean Fluorescence Intensity; **TR-FRET,** Time Resolved - Förster´s Resonance Energy Transfer.

# Potential for Accelerated Development of BHV-1600

**SAD study in healthy volunteers**
2H 2024

**ENDPOINTS**
- Safety
- Pharmacokinetics

## Dilated Cardiomyopathy (DCM)

- DCM that progresses to heart failure has a 5-year mortality rate of 50%[3]
- Up to 75% of idiopathic DCM patients have elevated β1AR Ab levels[4]
- Lowering of β1AR autoantibody levels by immunoadsorption leads to rapid clinically meaningful improvements in DCM[5]

## Registrational program

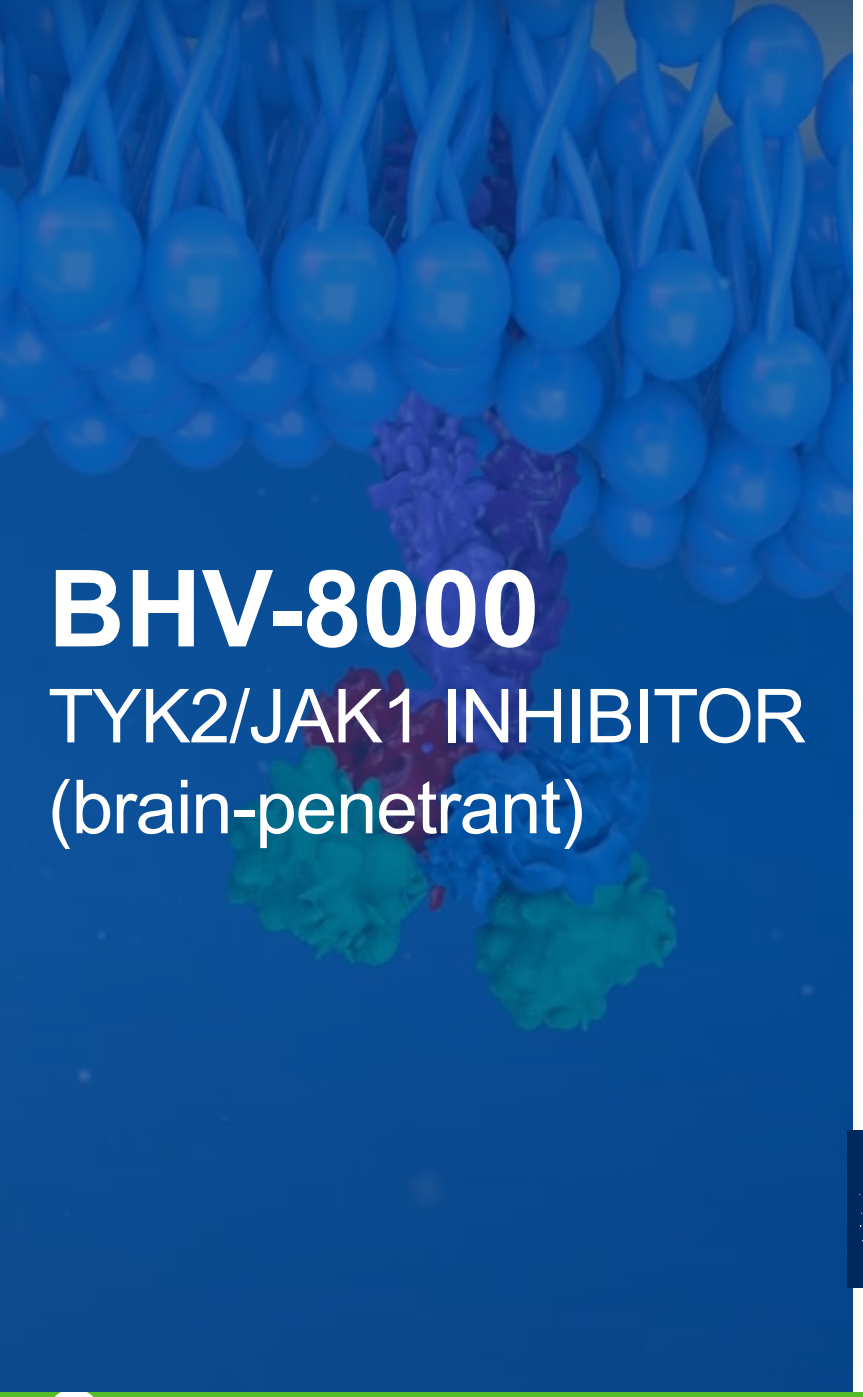
**ENDPOINTS**
- β1AR autoantibodies
- NT-proBNP
- TTE parameters (e.g., LVEF)
- 6 Minute Walk Test
- Hospitalizations
- Overall survival
- Composite outcome endpoint

**KEY POINT**

Autoantibody-specific degrader platform enables rapid clinical proof-of-concept

**IND**, Investigational New Drug Application; **TTE**, transthoracic echocardiogram; **LVEF**, Left ventricular ejection fraction; **NT-proBNP**, N-terminal pro-B-type natriuretic peptide.

1. Arany, NEJM. 2020. 2. Dungen et al., Circulation: Heart Failure. 2020. 3. Juilliere et al., International Journal of Cardiology. 1988. 4. Dandel et al., Immunobiology. 2012. 5. Patel et al., European Journal of Heart Failure. 2013.



# BHV-8000

## TYK2/JAK1 INHIBITOR (brain-penetrant)

### First-in-Clinic, Oral, Selective, Brain-Penetrant TYK2/JAK1 Inhibitor

- Uniquely potent, TYK2/JAK1 selective, brain-penetrant inhibitor
- Selectivity profile avoids class risks associated with JAK2/3 inhibition

### Breaks the Cycle of Neuroinflammation

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

### Potential to Treat Multiple Neuroinflammatory Disorders

Evidence supports efficacy in prevention of amyloid therapy induced ARIA, Alzheimer's disease, Parkinson's disease, multiple sclerosis and other disorders

### Encouraging Results from Completed Phase 1 SAD/MAD Cohorts

- Safe and well-tolerated to date
- Preliminary data indicative of target engagement
- Confirmed CNS penetration, target exposures achieved in CSF of healthy subjects

**KEY POINT**

FDA meetings successfully completed with favorable feedback enabling registrational programs for Parkinson's disease and Prevention of ARIA

**ARIA**, Amyloid-related imaging abnormalities; **SAD**, single ascending dose; **MAD**, multiple ascending dose; **TYK**, tyrosine kinase; **JAK**, Janus kinase.

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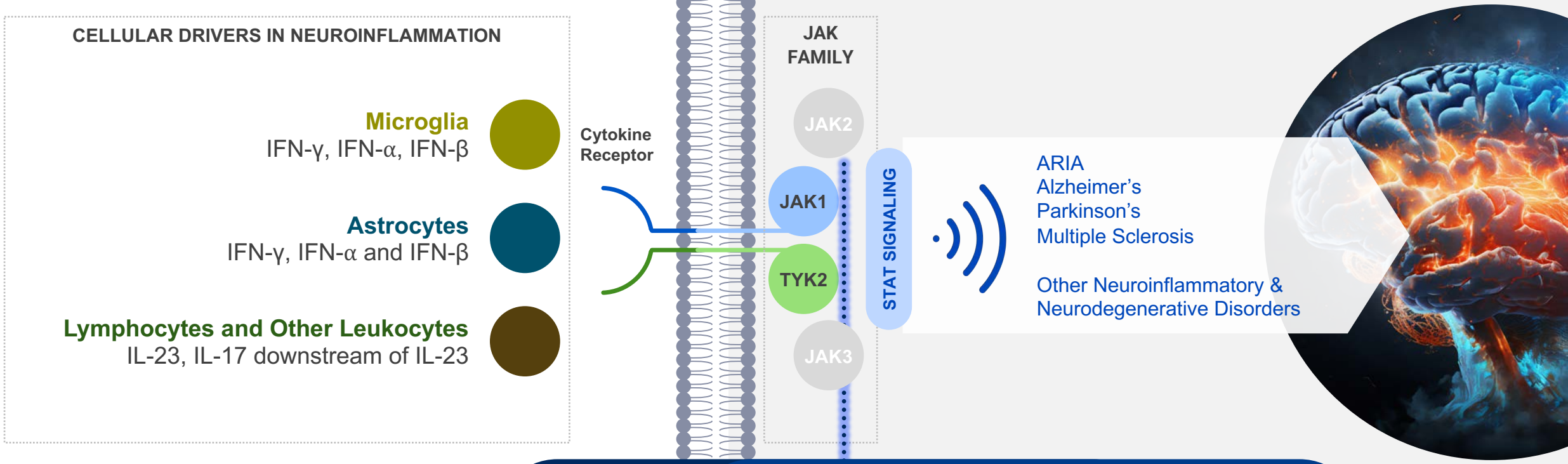
# BHV-8000 Is a Brain-Penetrant TYK2/JAK1 Inhibitor With Potential to Treat Neuroinflammatory & Neurodegenerative Disorders

**Inflammation plays a key role in the pathogenesis of neurodegenerative diseases**

**Nonclinical, clinical, genetic, and epidemiological data show that interrupting chronic inflammation may slow disease progression**




**BHV-8000** Dual, brain-penetrant inhibitor of TYK2 and JAK1 that effectively blocks Th17 cell generation, Type I IFN signaling, and inflammation

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# BHV-8000 Demonstrates a Promising Phase 1 Profile

## STUDY STATUS: Completed dosing in 3 SAD cohorts and 3 MAD cohorts

- SAD dose cohorts (10, 20 and 30 mg); MAD dose cohorts (6, 10 and 20 mg)
- 8 healthy subjects per cohort (6 active: 2 placebo)

## SAFETY PROFILE: Safe and well-tolerated to date

- No SAEs or severe AEs; only mild AEs observed that resolved spontaneously
- No clinically significant ECG or vital sign abnormalities
- No adverse laboratory trends related to study drug

## PHARMACODYNAMIC EFFECTS:

- hs-CRP, IP-10, and IFN-beta showed drug-related changes

KEY POINT

BHV-8000 is safe and well-tolerated at doses showing evidence of target engagement

Preliminary Phase 1 data. **AE**, adverse event; **hs-CRP**, high-sensitivity C-reactive protein; **IFN-beta**, Interferon beta; **MAD**, multiple ascending dose; **SAD**, single ascending dose; **SAE**, serious adverse event.

# Real-World Analytics of Large Healthcare Database Show Parkinson's Disease Risk Reduction With TNF/IL-17 Targeting Therapies


- Biohaven conducted analysis using Komodo Health database (over 320 million patients since 2012) examining treatment with anti-TNF or anti-IL17 and incidence of PD
- Millions of patients over 8+ years of dosing captured key epidemiologic confirmation of the neuroinflammatory hypothesis
- Results support rationale for the effectiveness of BHV-8000 in treating PD

| Treatment | PD Events | Person-years | Rate (per 100 person-years) | Adjusted IRR (95% CI) | P-value |
|---|---|---|---|---|---|
| Anti-TNF or Anti-IL-17 exposure | 2,957 | 393,114 | **0.66** | 0.77 (0.74 – 0.80) | <0.0001 |
| No Treatment | 50,562 | 5,328,307 | 0.95 | | |
| Anti-TNF exposure | 2,471 | 371,867 | **0.66** | 0.64 (0.52 – 0.80) | <0.0001 |
| No Treatment | 50,562 | 5,328,307 | 0.95 | | |
| Anti-IL-17 exposure | 81 | 15,598 | **0.52** | 0.77 (0.78 – 0.81) | <0.0001 |
| No Treatment | 50,562 | 5,328,307 | 0.95 | | |

**IRR**, incidence rate ratio; **TNF**, tumor necrosis factor.

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# BHV-8000: Unique Phase 2/3 Study Design for Parkinson's Disease

## Novel Primary Efficacy Endpoint

**Time-to-event (≥ 2-point worsening on MDS-UPDRS-Part II)**

- Addresses FDA requirement for a functional endpoint in PD trials
  - MDS-UPDRS-Part II recommended, but declines very slowly in early PD
- 300 fewer patients per trial versus a mean change on MDS-UPDRS-Part II
- Based on comprehensive analyses of PPMI and placebo-arm clinical trial data (C-Path)

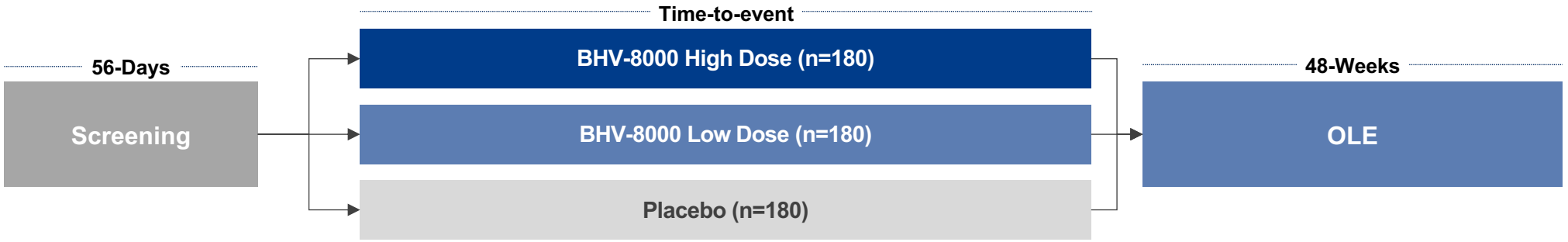
**Provides a meaningful efficacy endpoint with a smaller sample size**

## Novel Composite Endpoint

**Parkinson's Disease Composite Score (PARCOMS)**

- Based on established methodology (i.e., Alzheimer's Disease Composite Score [ADCOMS])
- Leverages PPMI and placebo-arm clinical trial data (C-Path)
- Comprises the most responsive items from common endpoints in early PD trials

**Provides a highly-sensitive supportive secondary efficacy endpoint**

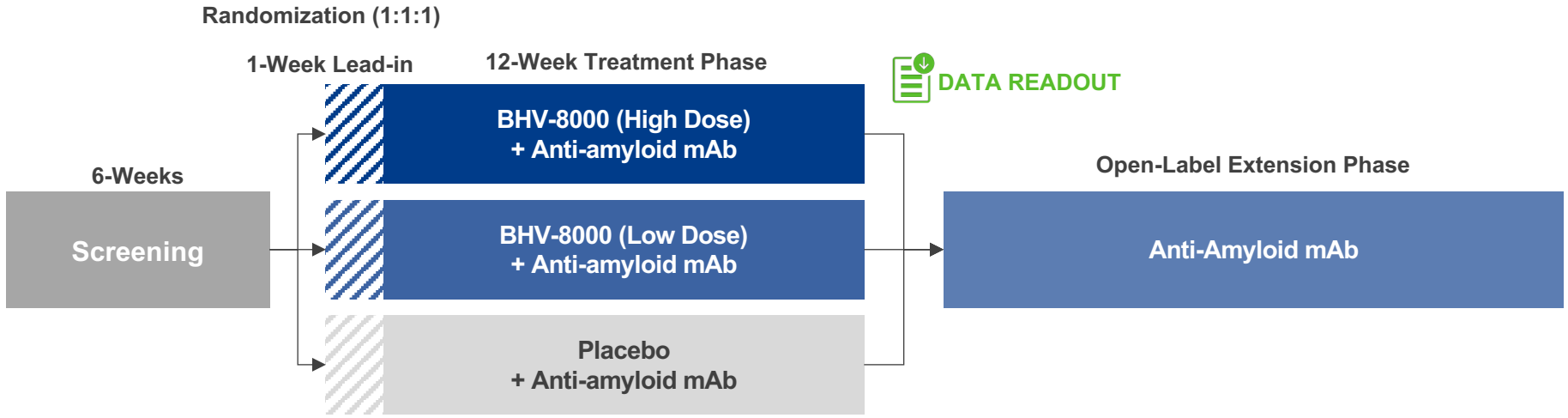



KEY POINT

Positive FDA feedback on novel time-to-event primary efficacy endpoint allows for a more efficient registrational study

Preliminary clinical trial design; **PPMI**, Parkinson's Progression Markers Initiative; **MDS-UPDRS**, Movement Disorder Society – Unified Parkinson's Disease Rating Scale.

# BHV-8000: Phase 2/3 Prevention of ARIA Study Design




| | |
|---|---|
| **DESIGN** | Randomized, double-blind, placebo-controlled trial |
| **POPULATION** | Male and female adults with early Alzheimer's disease who are APOE4 gene carriers |
| **SAMPLE SIZE** | 450 participants (randomized 1:1:1 across 2 active and 1 placebo arm) |
| **TREATMENT** | BHV-8000 (high/low dose) vs. Placebo + anti-amyloid mAb |
| **TREATMENT DURATION** | 1-week lead-in with BHV-8000 or Placebo; 12-week treatment period with BHV-8000 + anti-amyloid mAb; OLE with anti-amyloid mAb only |
| **ENDPOINTS** | Incidence of ARIA-E at Week 13; PK/PD; change in inflammatory and AD biomarkers |

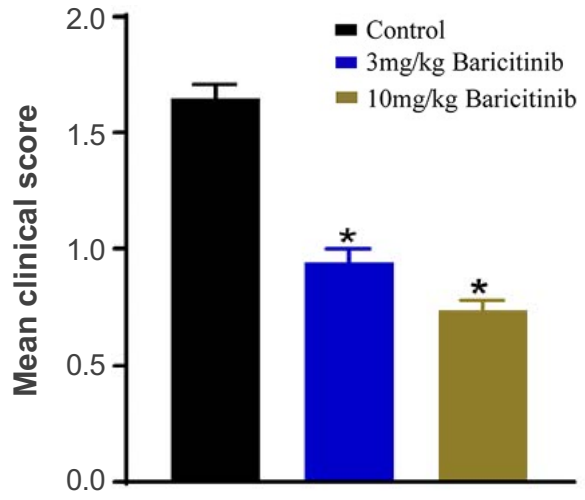
**KEY POINT**

Positive FDA feedback on novel Prevention of ARIA indication, and on study design and clinical development plan

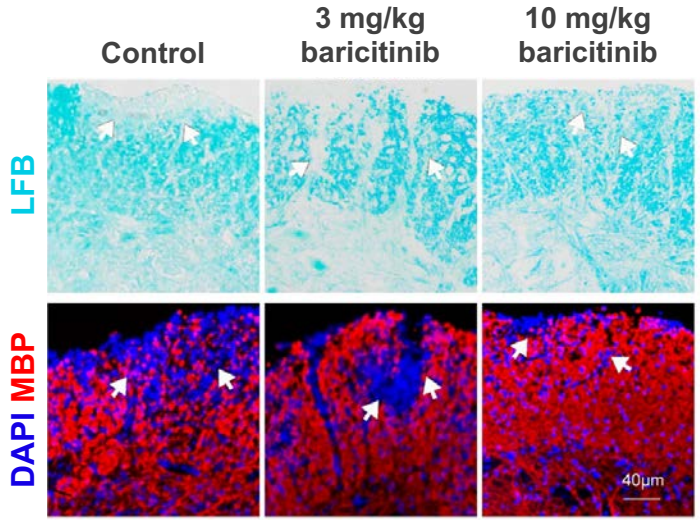
# TYK2/JAK1 Inhibition Is a Potential Treatment for Multiple Sclerosis

- **Genetic evidence:** Recent study found a protective genetic variation in the TYK2 gene that decreased signaling capacity in response to IL-12 and IL-23, reducing the function of TYK2, resulting in reduction in risk for developing MS[1]
- **Nonclinical data:** Suggests JAK/STAT pathway regulates differentiation and function of Th1 and Th17 cells which are essential for development of experimental autoimmune encephalomyelitis (EAE)[2]
- **Clinical data:** Supports the presence of abnormal immune activation in MS patients[3]

## Baricitinib (JAK1/2 Inhibitor) Improved Mean Clinical Scores in Mice With EAE[2]

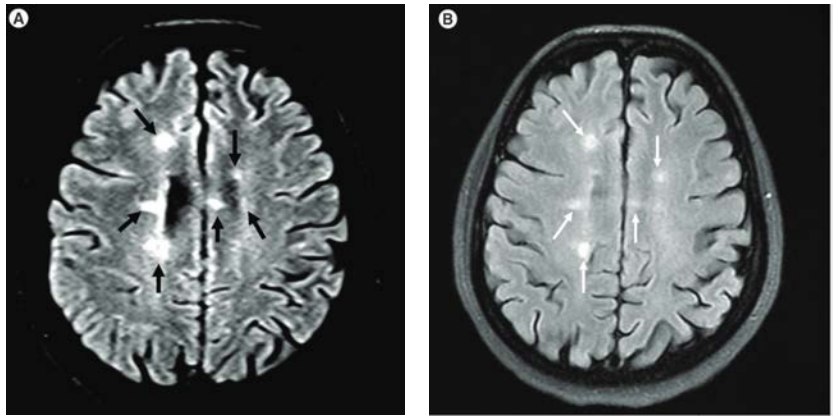



## Baricitinib (JAK1/2 Inhibitor) Reduces Pathological Tissue Injuries In EAE Mice[2]

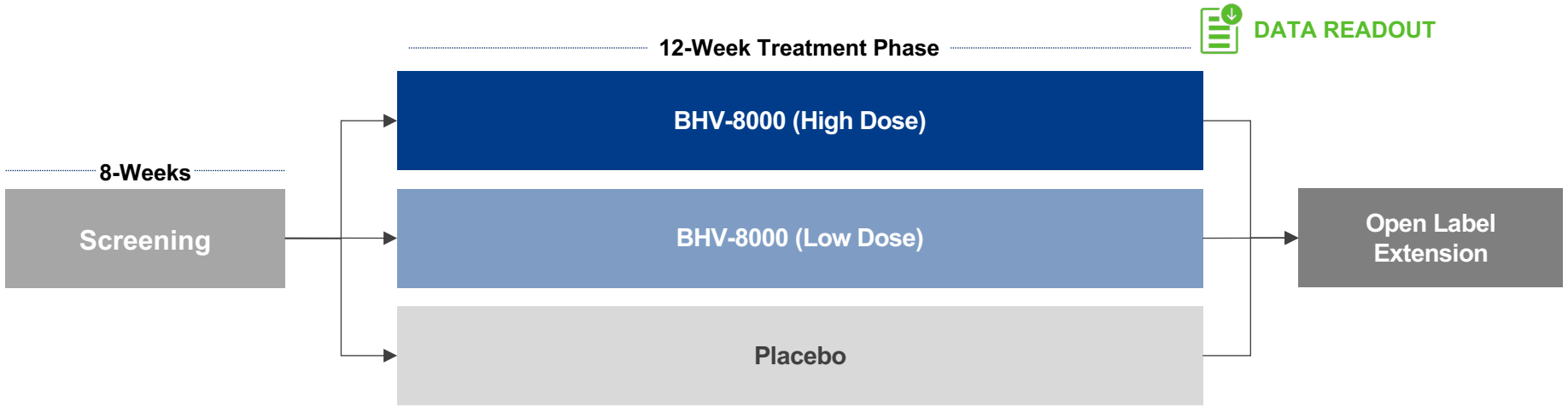



## Secukinumab (IL-17A) Demonstrates an Effect in Relapsing Remitting MS[3]

**Lesions regressed in MS patients 5 months of secukinumab treatment**

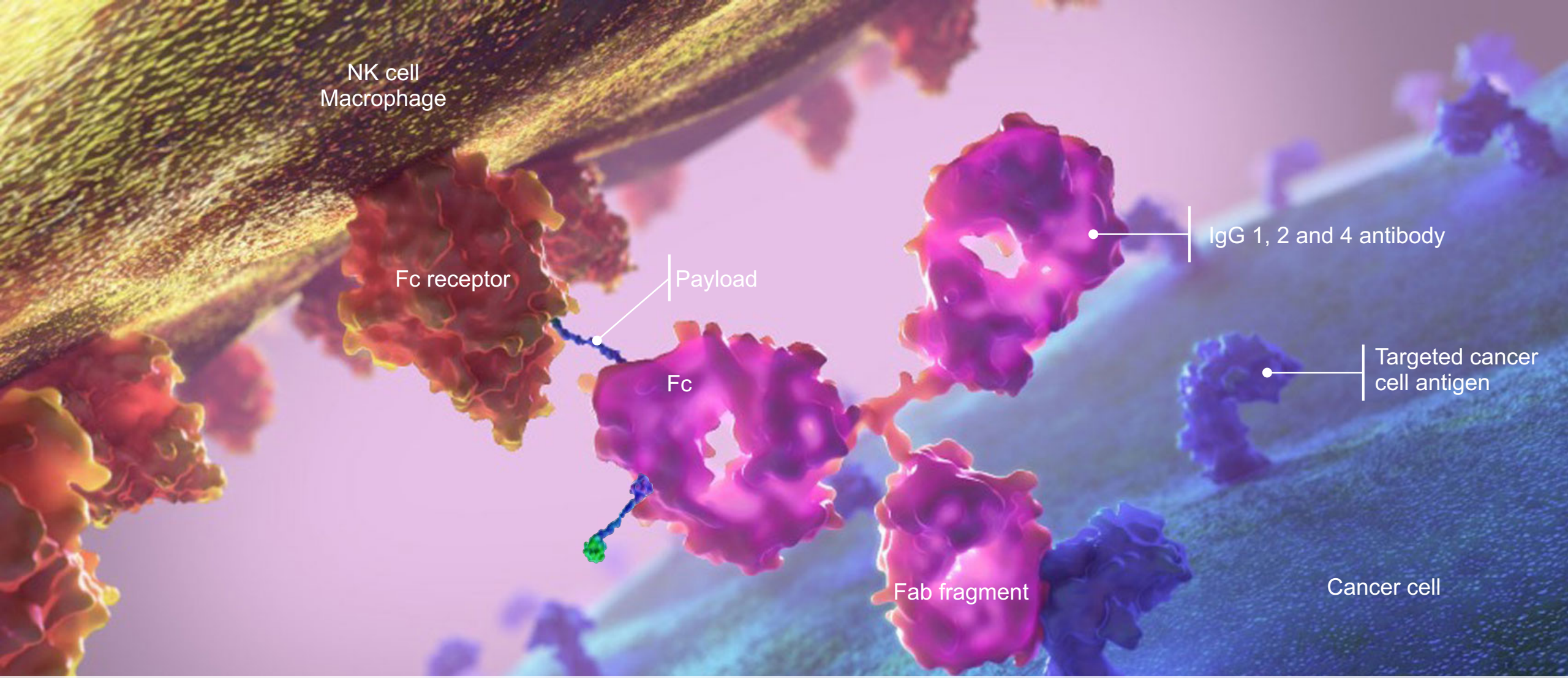


# BHV-8000: Phase 2 Imaging POC Study in Relapsing Multiple Sclerosis




| | |
|---|---|
| **DESIGN** | Randomized, double-blind, placebo-controlled Phase 2 imaging proof-of-concept study |
| **POPULATION** | Adults with relapsing multiple sclerosis (RMS) |
| **SAMPLE SIZE** | 140 participants (randomized 2:2:1) |
| **TREATMENT** | BHV-8000 low dose or high dose versus placebo |
| **TREATMENT DURATION** | 12-week double-blind phase followed by open label study |
| **ENDPOINTS** | Cumulative number of new gadolinium (Gd)-enhancing T1 lesions, total number of Gd-enhancing T1 lesions, number of new or enlarging T2 lesions, change in phase rim lesions, PK/PD |

Preliminary clinical trial design




# Oncology

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# BHV-1510

## BHV-1510 Is a Novel, Highly Differentiated Next-gen Trop-2 ADC

- Ideally positioned for fast-to-market strategy
- Partner of choice with anti-PD-1 combinations

## Fully Optimized Next-generation ADC

- Novel and highly stable linker-payload (DAR4)
- Enzymatic, site-specific conjugation

## Synergistic Efficacy With Anti-PD-1 *In Vivo*

- Novel TopoIx payload induces immunogenic cell death
- Superior to Datopotamab Deruxtecan (DS-1062) plus anti-PD-1

## Differentiated Preclinical Safety Profile

- Datopotamab Deruxtecan (DS-1062): interstitial lung disease (ILD), stomatitis
- Sacituzumab Tirumotecan (MK2870/SKB264): hematological toxicities
- TRODELVY®: neutropenia, diarrhea

**KEY POINTS**

- First patient dosed with monotherapy in Phase 1/2 study
- Clinical Supply Agreement with Regeneron for combination with Libtayo®

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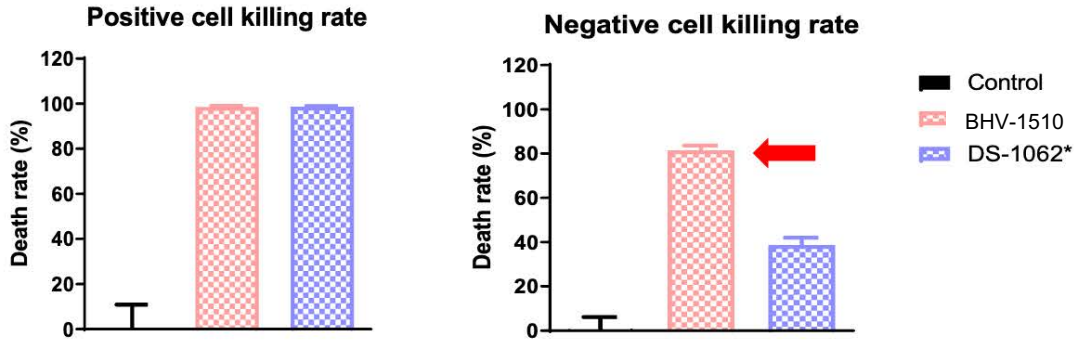
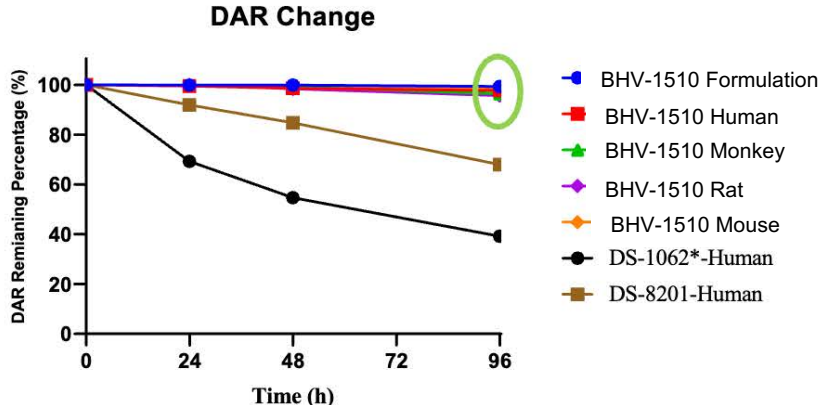
# BHV-1510 Improves Bystander Killing and Immunogenic Cell Death vs. DS-1062

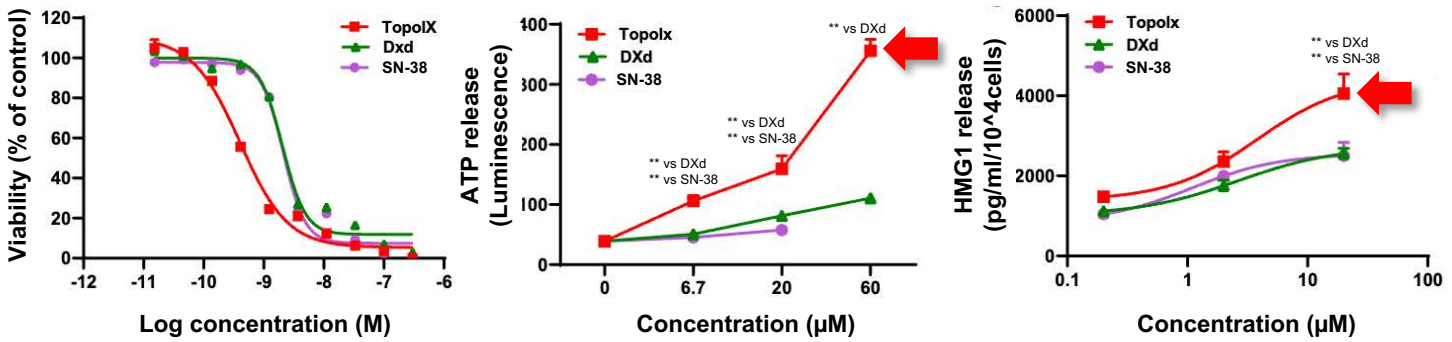
## Superior Bystander Activity vs. DS-1062



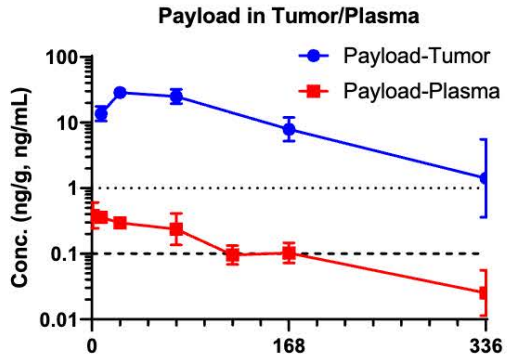

## Highly Stable Linker vs. DS-1062




## Superior Immunogenic Cell Death with Topolx Compared to Other Payloads (DXd and SN-38)

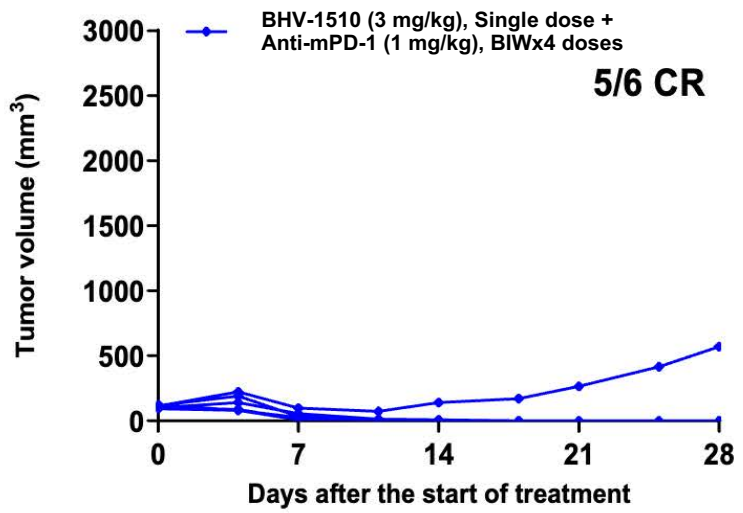



## High Payload Delivery to Tumor

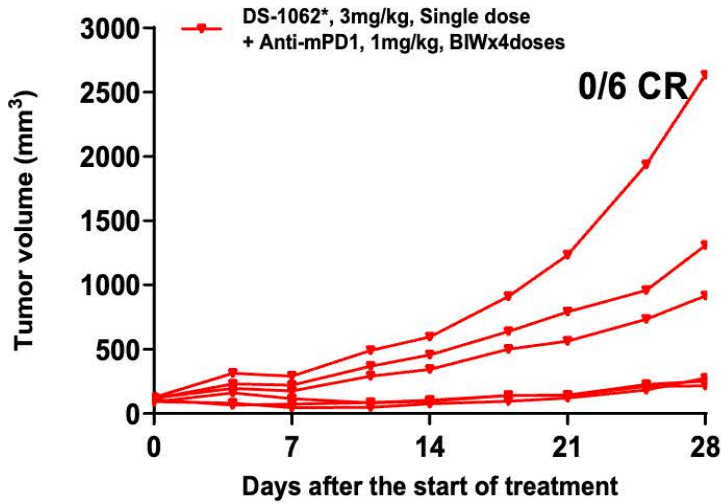


# BHV-1510 + Anti-PD-1 Combination Shows Compelling Synergy in Syngeneic Models and Is Superior to DS-1062

BHV-1510 + Anti-PD-1




DS-1062 + Anti-PD-1

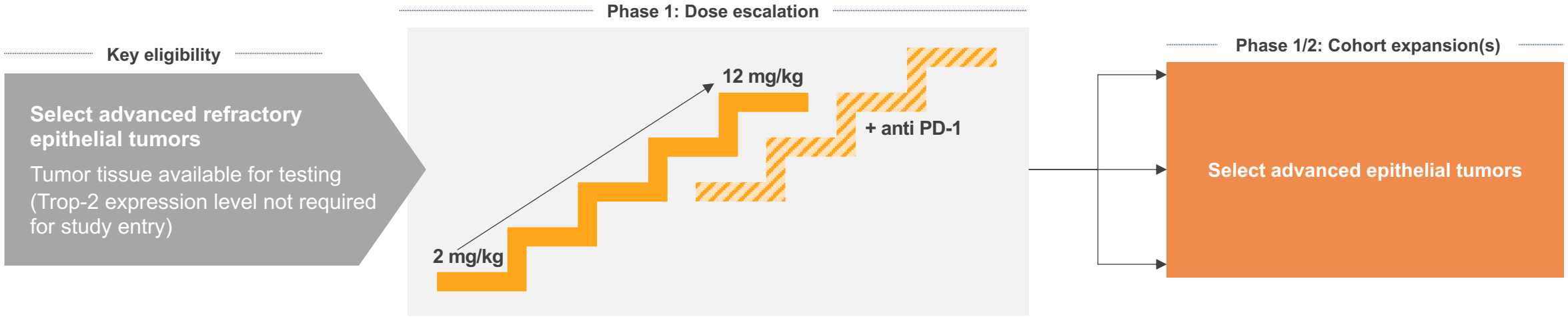



KEY POINTS

- Preclinical profile of BHV-1510 positions it for superiority in ADC therapy with anti-PD-1
- Landscape open for Trop-2 combinations with safer more efficacious ADC

AACR 2023 annual meeting, abstract #1549.

# Phase 1/2 Study in Advanced Epithelial Tumors




| | |
|---|---|
| **DESIGN** | Open label, dose escalation (Ph1) and dose expansion (Ph2) |
| **POPULATION** | Advanced epithelial tumors having failed SOC therapy |
| **SAMPLE SIZE** | 170 patients |
| **TREATMENT** | BHV-1510 |
| **TREATMENT DURATION** | Until disease progression or toxicity |
| **KEY ENDPOINTS** | Safety and tolerability, ORR, PFS, PK and ADA |

**KEY POINTS**

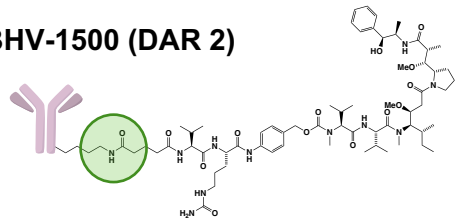
- Phase 1 monotherapy dose escalation initiated
- Early monotherapy safety data and initiation of PD-1 combo anticipated as early as 2H 2024

**ORR,** Overall Response Rate; **PFS,** Progression Free Survival; **ADA,** Antidrug Antibody.

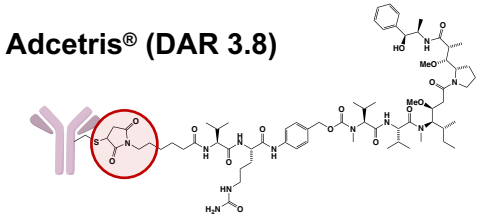
# BHV-1500 Is a Differentiated CD30 ADC

- Validated target
- Superior *in vivo* efficacy head-to-head vs. Adcetris® at ***50% lower*** DAR
- Highly stable and site-specific conjugation

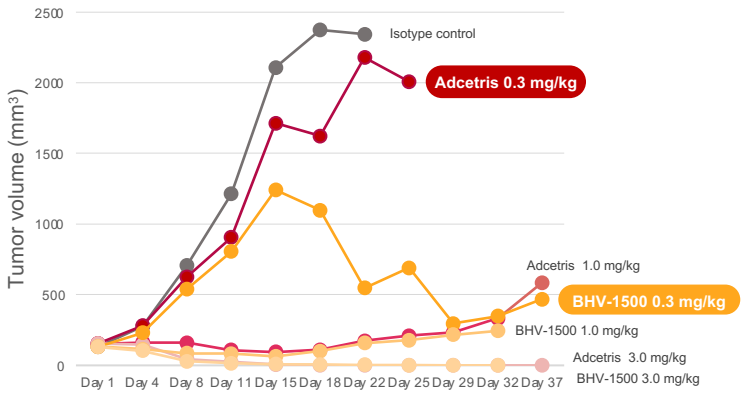
**BHV-1500 (DAR 2)**



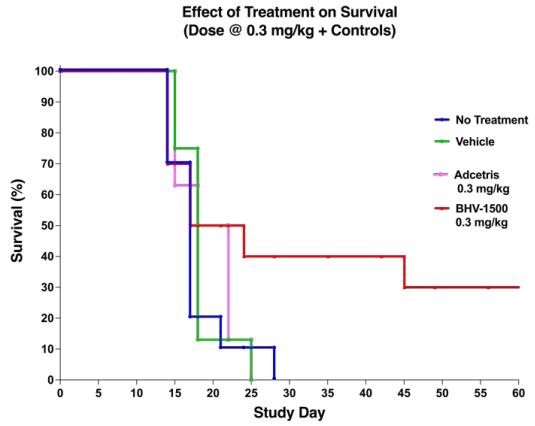
**Adcetris® (DAR 3.8)**



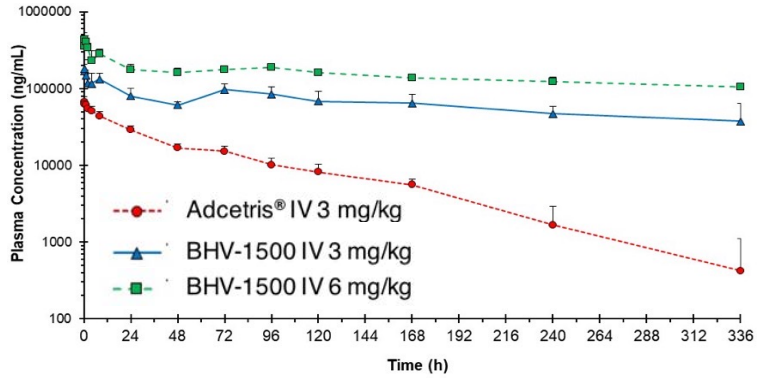
## BHV-1500 Demonstrates Superior Efficacy to Adcetris® in a Mouse Xenograft Model




## BHV-1500 Improved Survival in Mouse Compared to Adcetris®




## Total ADC Stability *in vivo* in Cynomolgous Monkey




**KEY POINT**

IND anticipated in early 2025

BHV-1500 is a CD30 (next-gen brentuximab vedotin) ADC.

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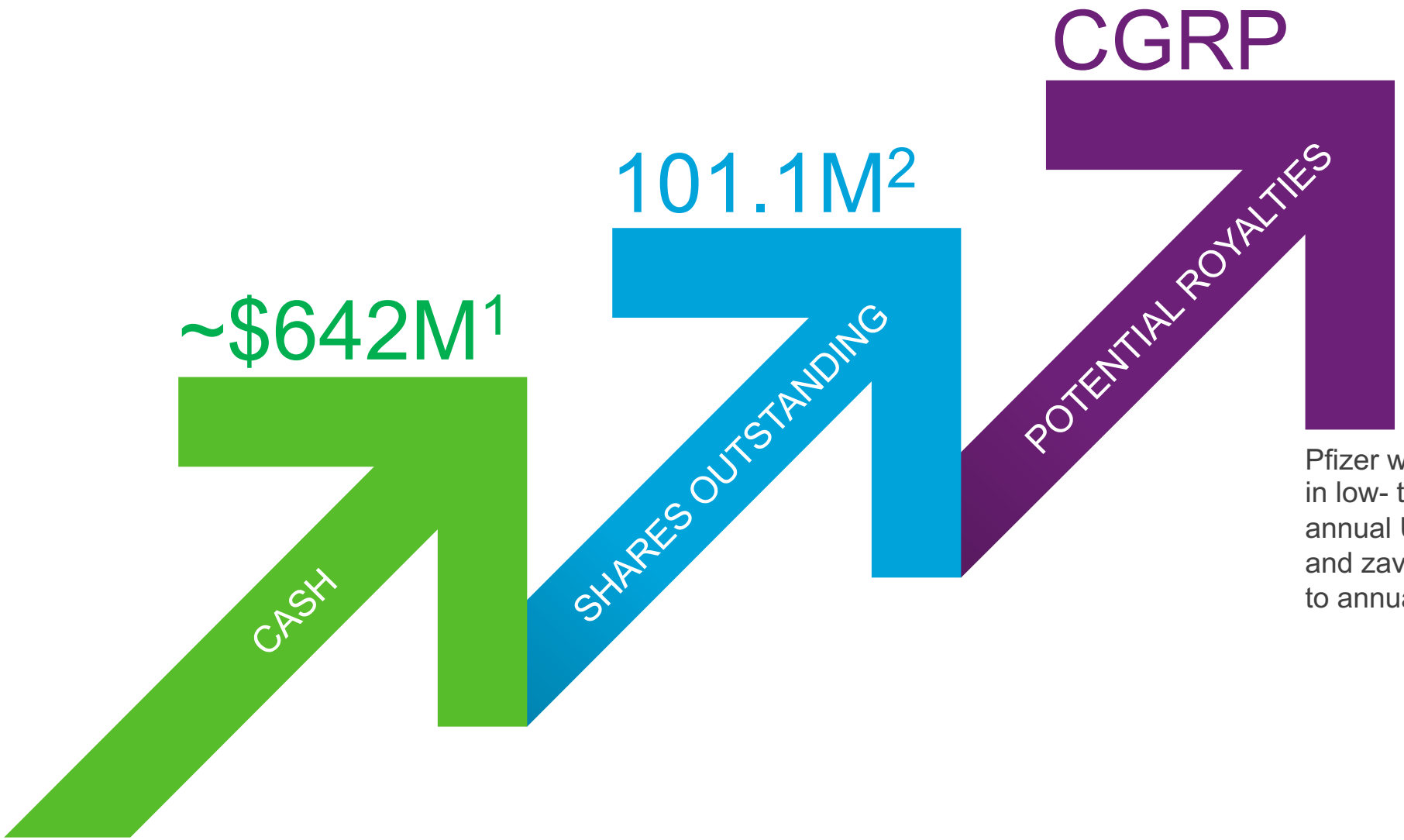
# Capitalization Updates




Pfizer will make royalty payments in low- to mid-teens% in respect of annual US net sales of rimegepant and zavegepant >$5.25B, subject to annual cap ($400M/year)[3]

1. As of October 2, 2024; includes proceeds raised from underwritten public offering 2. As of November 8, 2024; excludes outstanding options. 3. Cap reached if aggregate annual U.S. net sales of rimegepant and zavegepant amount to $8.15B. Royalty payments would be in respect of years ended on or before 12/31/40.

# Top Areas of Innovation

- IMMUNOLOGY & INFLAMMATION
- NEUROLOGY
- OBESITY
- ONCOLOGY
- CARDIOVASCULAR
- RENAL
- RARE DISEASE

BIOCENTURY SURVEY[1]

| | PATIENTS[2] INDICATION | |
|---|---|---|
| IgG Degrader | **80–130K** RHEUMATOID ARTHRITIS | **100K** MYASTHENIA GRAVIS |
| TYK2/JAK1 Inhibitor | **3.5M** ARIA PREVENTION[2] | **0.5M** EARLY PARKINSON'S DISEASE |
| | **3.5M** EARLY ALZHEIMER'S DISEASE[3] | **950K** MULTIPLE SCLEROSIS |
| Kv7 Activator | **2M** FOCAL EPILEPSY | **7M** BIPOLAR DISORDER |
| | **1.2M** GENERALIZED EPILEPSY | **21M** MAJOR DEPRESSIVE DISORDER |
| TRPM3 Antagonist | **40M** MIGRAINE | **10M** PAIN |
| Troriluzole | **15K** SPINOCEREBELLAR ATAXIA | **3.2M** OBSESSIVE-COMPULSIVE DISORDER |
| Taldefgrobep Alfa | **10K** SPINAL MUSCULAR ATROPHY | **10M** OBESITY |
| CD30 | **173K** HODGKIN'S LYMPHOMA | |
| Trop-2 | **660K** EPITHELIAL TUMORS | |
| β1AR Degrader | **388K** DILATED CARDIOMYOPATHY | |
| IgA Degrader | **100-150k** IgA NEPHROPATHY | |

## Biohaven's pipeline working to help millions of patients

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1. Adapted from BioCentury survey: https://www.biocentury.com/article/650883/move-over-oncology-i-i-will-write-the-next-big-stories-in-innovation#.
2. Patient numbers are US prevalence from Biohaven market research;
3. With amyloid therapy; 4. Disease modifying

Milestone achieved

# Upcoming Milestones: Potential for Multiple Value Inflection Points

| | | 1H 2024 | 2H 2024 |
|---|---|---|---|
| Troriluzole \| BHV-4157 | Obsessive-Compulsive Disorder<br>*2 ongoing trials* | Phase 3 Interim Analysis | Phase 3 Interim Analysis |
| | Spinocerebellar Ataxia | | Topline Results – RWE protocol |
| | | | NDA Submission |
| Taldefgrobep Alfa \| BHV-2000 | Spinal Muscular Atrophy | | Phase 3 Topline |
| | Obesity | | Initiate Phase 2 |
| Kv7 Activator \| BHV-7000 | Focal Epilepsy | Initiate Phase 2/3 | |
| | Generalized Epilepsy | Initiate Phase 2/3 | |
| | Bipolar Disorder | Initiate Phase 2/3 | |
| | Major Depressive Disorder | Initiate Phase 2 | |
| TRPM3 Antagonist \| BHV-2100 | Migraine | | Initiate Phase 2 |
| | Neuropathic Pain | | Initiate POC |
| TYK2/JAK1 \| BHV-8000 (brain-penetrant) | Neurodegenerative Disorders | | Initiate Phase 2 |
| IgG Degrader \| BHV-1300 | Rheumatoid Arthritis | Phase 1 IgG Interim Data | SAD & MAD data update |
| IgG Degrader \| BHV-1310 | Myasthenia Gravis | | Initiate Phase 1 |
| IgA Degrader \| BHV-1400 | IgA Nephropathy | | Initiate Phase 1 |
| β1-AR AAB Degrader \| BHV-1600 | Dilated Cardiomyopathy | | Initiate Phase 1 |
| Trop2 \| BHV-1510 | Advanced or Metastatic Epithelial Tumors | Initiate Phase 1 | |

**AAB**, Autoantibody

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OUR COMMITMENT

# Building Value for Patients and Shareholders