biohaven®

DAYS MATTER™

BIOHAVEN R&D DAY

May 29, 2024

BHVN LISTED NYSE

WELCOME

Vlad Coric, M.D.
Chairman and Chief Executive Officer

biohaven®

BHVN
LISTED
NYSE

Forward-Looking Statement

This presentation includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements about Biohaven Ltd. (the “Company”) and our planned and ongoing trials for our BHV-2100, troriluzole, BHV-1300, BHV-1310, BHV-1510, taldefgrobep alfa, BHV-8000 and BHV-7000 development programs, the timing of and the availability of data from our clinical trials, the timing and our decisions to proceed with our planned regulatory filings, the timing of and our ability to obtain regulatory approvals for our product candidates, the clinical potential utility of our product candidates, alone and as compared to other existing potential treatment options, and the potential advancement of our early phase programs including BHV-1400, BHV-1500, BHV-1600. The use of certain words, including “continue”, “plan”, “will”, “believe”, “may”, “expect”, “anticipate” and similar expressions, is intended to identify forward-looking statements. Investors are cautioned that any forward-looking statements, including statements regarding the future development, timing and potential marketing approval and commercialization of our development candidates, are not guarantees of future performance or results and involve substantial risks and uncertainties. Actual results, developments and events may differ materially from those in the forward-looking statements as a result of various factors including: the expected timing, commencement and outcomes of Biohaven's planned and ongoing clinical trials; the timing of planned interactions and filings with the Food and Drug Administration; the timing and outcome of expected regulatory filings; complying with applicable U.S. regulatory requirements; the potential commercialization of Biohaven's product candidates; the potential for Biohaven’s product candidates to be first in class, best in class , best in clinic or best in category therapies; and the effectiveness and safety of Biohaven's product candidates. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this presentation. Additional important factors to be considered in connection with forward-looking statements are described in the Company’s filings with the Securities and Exchange Commission, including within the sections titled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations”. This presentation also contains market data and other information based on industry publications, reports by market research firms or published independent sources. Some market data and information is also based on the Company’s good faith estimates, which are derived from management’s knowledge of its industry and such independent sources referred to above.

biohaven

ION CHANNEL PLATFORM

New Treatments for Neurological & Neuropsychiatric Disorders and Pain

MoDE™ PLATFORM

New Modality with Transformational Potential for Immunological & Inflammatory Disorders

biohaven®

NEUROSCIENCE | IMMUNOLOGY | ONCOLOGY

MIGRAINE

Building on Our Legacy

MYOSTATIN

Innovative Approach for Improving Muscle Health & Disrupting the Public Health Crisis of Obesity

NEUROINFLAMMATION PLATFORM

Selectively Targeting the Immune System to Treat Neurodegenerative Diseases

ONCOLOGY

Building an Antibody Drug Conjugate Franchise

BIOHAVEN IS CREATING VALUE

Building a Sustainable and Balanced Pipeline

Rare and Common Disease Indications with High Unmet Need

Strategic Partnering Opportunities

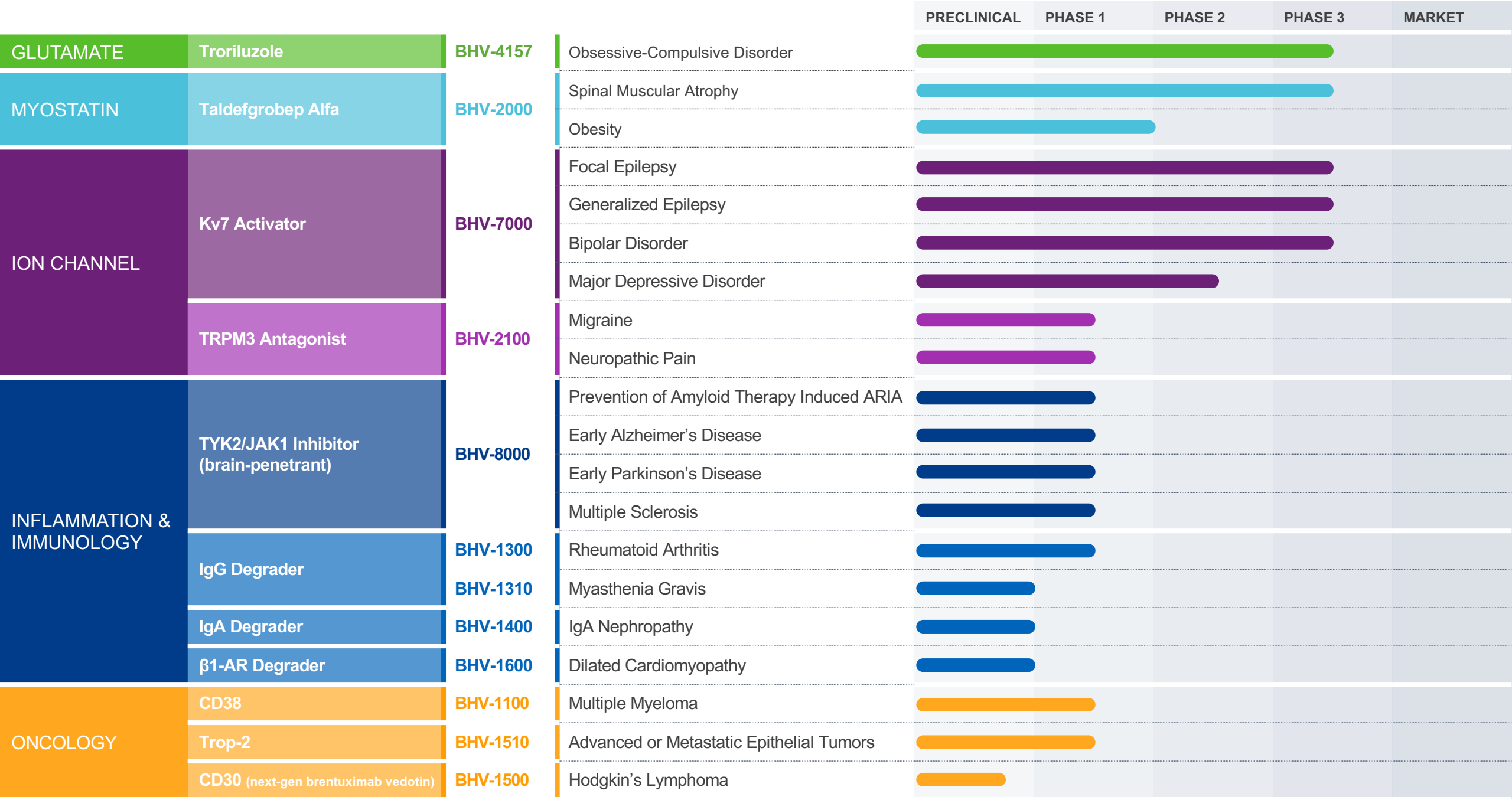
8 Pivotal Studies Ongoing

5+ Mid-Stage Studies Ongoing & Planned for 2024

3 MoDE™ Platform INDs Planned in 2024

10+ Innovative Preclinical Programs

biohaven®



ARIA, Amyloid-related imaging abnormalities.

biohaven

Michael Bozik, M.D.
President, Ion Channel Research and Development
biohaven®

Michael A. Rogawski, M.D., Ph.D.
Distinguished Professor, Neurology and Pharmacology
UCDAVIS

John Krystal, M.D.
McNeil Professor and Chair Department of Psychiatry
Yale SCHOOL OF MEDICINE

Steven Dworetzky, Ph.D.
Senior Vice President, Ion Channel Research & Development
biohaven®

Ion Channel Platform: Kv7 Activation

biohaven®

Michael Bozik, M.D.

President, Ion Channel
Research and Development

biohaven®

BHV-7000

biohaven®

BHV-7000
SELECTIVE
Kv7 ACTIVATOR

BREAKING
NEWS

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

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

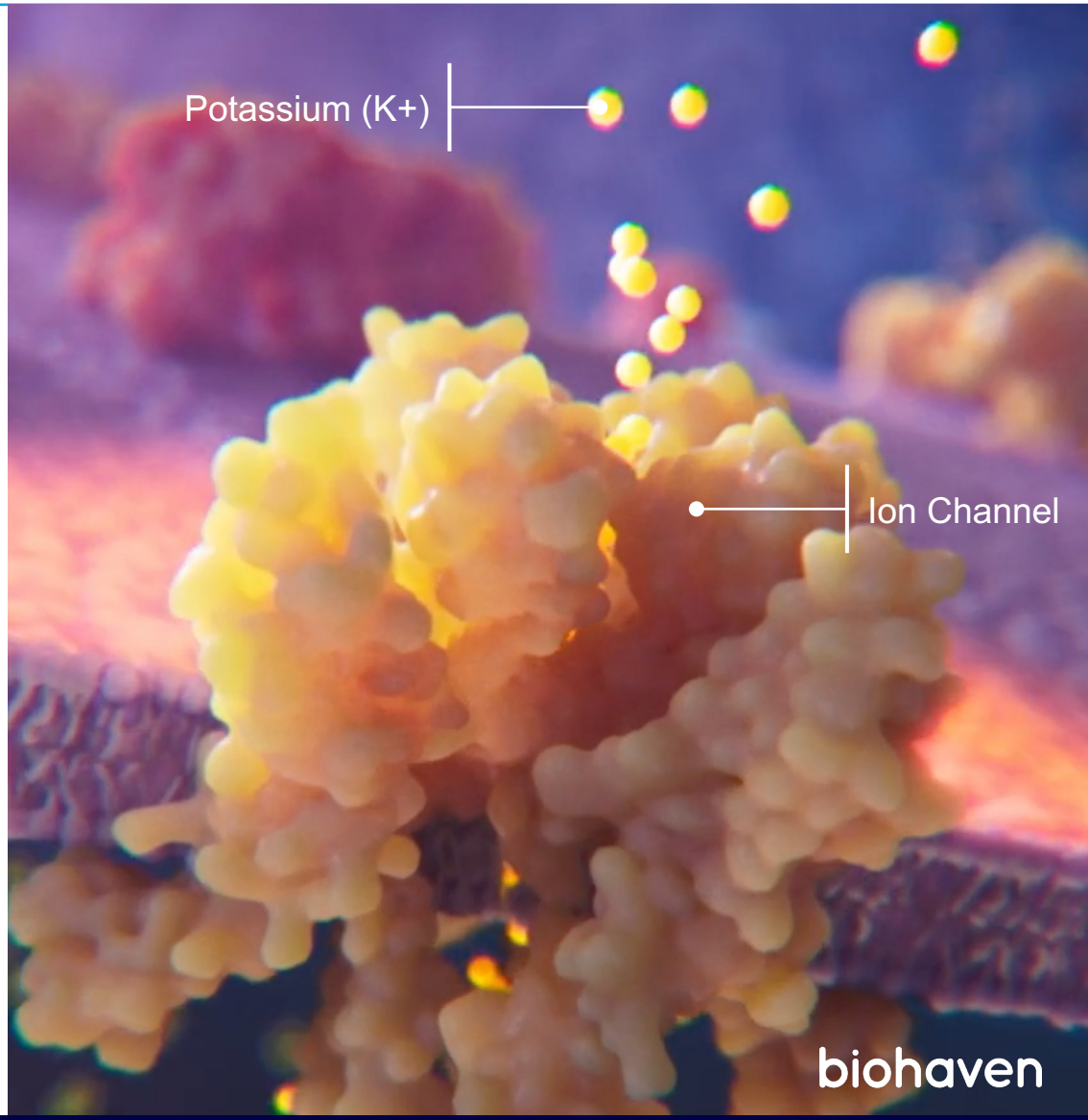
IEM, inherited erythromelalgia; **SN-iPSC**, human induced pluripotent stem cell derived sensory neurons; **GABA**, γ-aminobutyric acid.

biohaven

Kv7: A Transformational Target

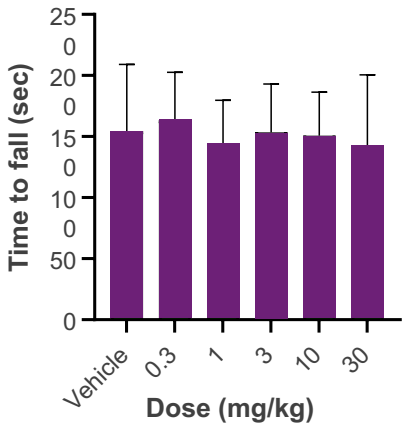
Kv7.2/7.3 voltage-gated potassium channels

- Key regulator of excitatory/inhibitory balance
- Broadly expressed in the CNS
- Molecular substrate of the M-Current
- Finely tunes resting membrane potential and depolarization threshold for action potential firing
- Selective Kv7 activators offer the potential to deliver a paradigm shift in the treatment of CNS disorders



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

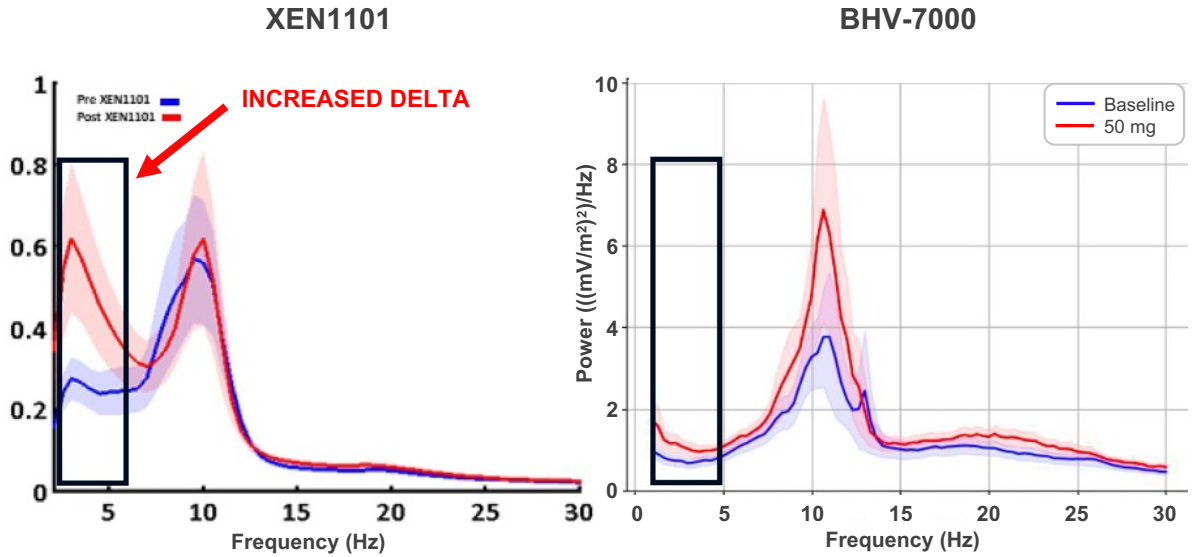
PRECLINICAL
No effects on motor performance on rotarod



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

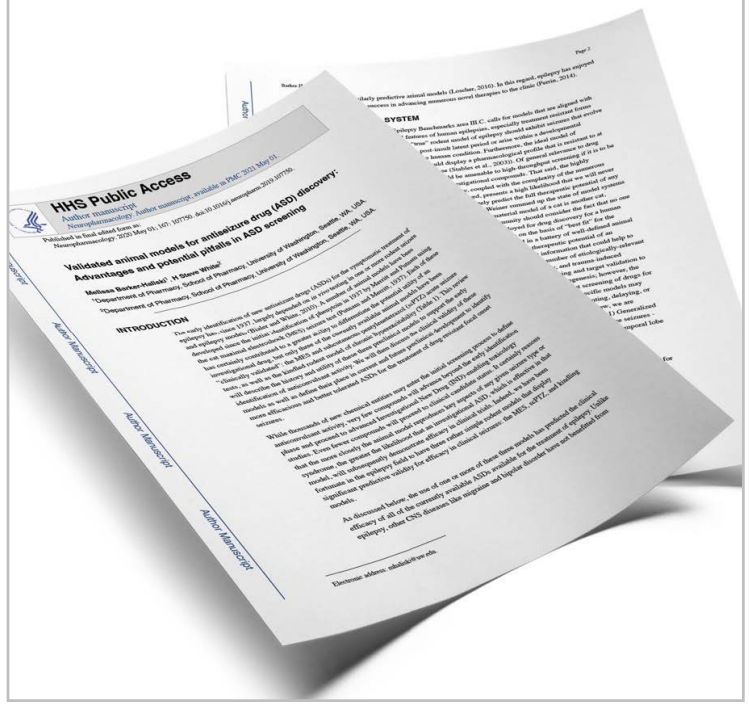
Pooled CNS AEs	BHV-7000 MAD Pooled N=29	XEN1101 MAD Pooled N=18
Somnolence	0%	39%
Headache	21%	39%
Balance disorder/ dizziness	10%	34%
Memory impairment	0%	28%
Sensory disturbance	0%	11%
Speech disorder	0%	33%

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



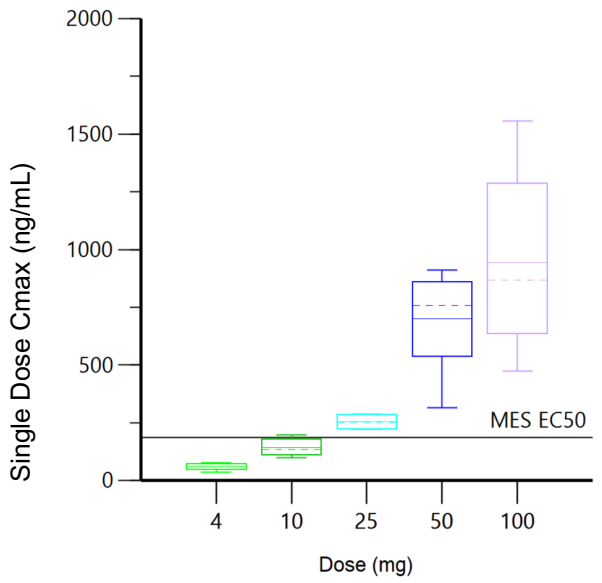
BHV-7000 Profile Allows for Optimizing Efficacy and Safety

MES Predicts Clinical Efficacy

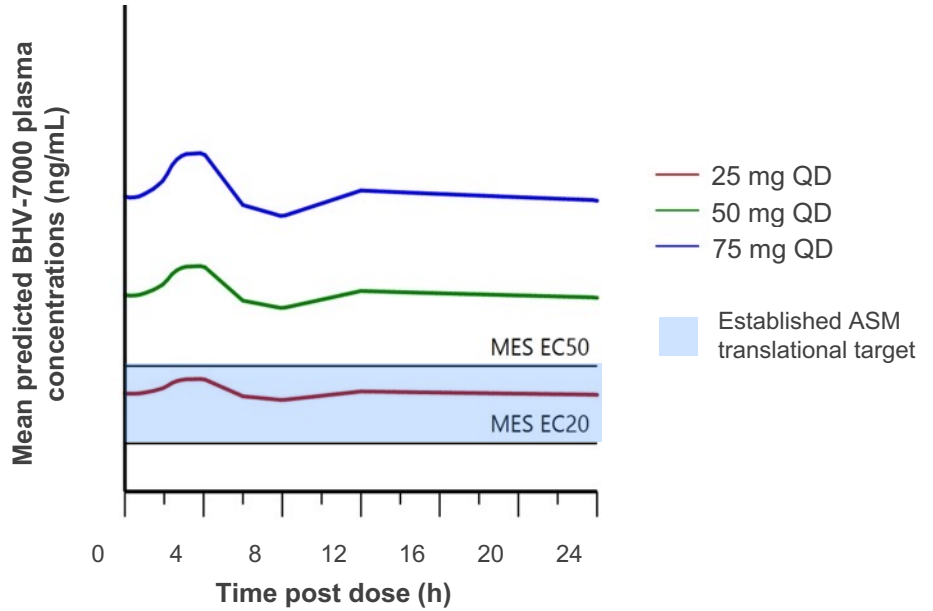


Loscher, 2016.

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.

BHV-7000: Five Phase 2/3 Clinical Trials Launched to Change the Treatment Paradigm in Epilepsy, Depression, and Bipolar Disorder

Epilepsy

- Global trials initiated in refractory focal epilepsy and idiopathic generalized epilepsy
- CNS target engagement without typical ASM side effects at predicted therapeutic doses underscores differentiated profile

Major Depressive Disorder

- Clinical trial in MDD initiated
- Proof-of-concept results with ezogabine and XEN1101 in MDD highlight Kv7.2/7.3 target potential

Bipolar Disorder

- Clinical trial in acute mania initiated
- ANK3 is a susceptibility gene for bipolar disorder and is required for Kv7.2/7.3 channel localization at the axon initial segment

biohaven

John Krystal, M.D.

McNeil Professor and Chair
Department of Psychiatry

Yale SCHOOL OF MEDICINE

Kv7 for the Treatment of Mood Disorders

biohaven®

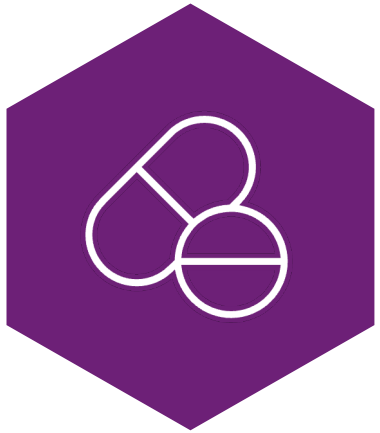
Current Treatment Options for MDD Are Limited By Low Efficacy and Side Effects

Disease Burden

- 21M adults + 5M adolescents in US[1]
- $326B economic burden[2]
- **70% fail to respond** to 1st line SSRIs[3]
- 33% remain refractory to 2nd & 3rd line[3]
- Treating **anhedonia** is key unmet need[4]

Differentiation opportunities

- Novel mechanism
- Addressing anhedonia
- Improved efficacy
- Better tolerability with fewer side effects



Significant opportunity for a new medication with a novel mechanism and differentiated tolerability and efficacy profile

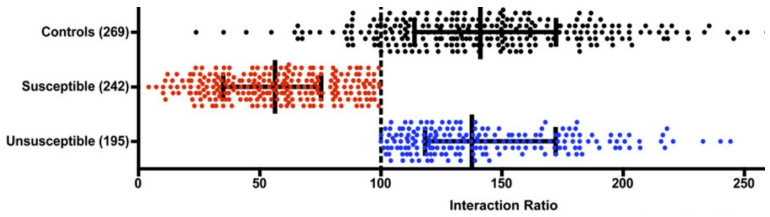
- **60%** are **medication nonadherent** most commonly due to **side effects**[5]
- SSRIs cause significant **sexual side effects and withdrawal**[6]
- Atypical antipsychotics carry risks of **extrapyramidal symptoms (tardive dyskinesia), metabolic dysfunction, weight gain, sedation, and cognitive slowing**[7]
- Esketamine **requires in-office dosing** and is only appropriate for treatment-resistant patients[8]
- All approved medications have **limited efficacy**[9]

1: https://www.nimh.nih.gov/health/statistics/major-depression. 2. Greenberg, et al. Pharmacoeconomics. 2021 Jun;39(6):653-665. 3: Al-Harbi KS. Patient Prefer Adherence. 2012;6:369-88. 4: Wong, et al. Journal of Affective Disorders, 356, 684-698. 5: Unni, et al. Journal of Affective Disorders, 344, 446-450. 6: Wong, et al. Nature Reviews Drug Discovery, 4(9), 764-774. 7: Nelson, et al. Neuropsychiatric Disease and Treatment, 4(5), 937–948. 8: Henter, et al. CNS Drugs, 35(5), 527. 9: Khan, et al. Psychopharmacology Bulletin, 51(3), 79-108.

Potassium Channels Provide a Biological Means of Resilience Against the Pathological Effects of Stress in Depression Models

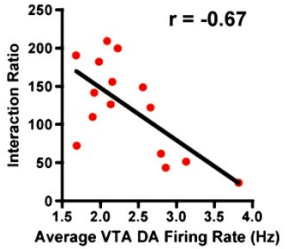
The role of potassium channels in mood disorders was discovered via a unique unbiased approach[1]

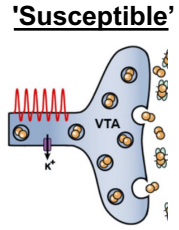
Of Mice Exposed to an Identical Stressor, 50% Are Resilient and Do Not Show a Depressed Phenotype

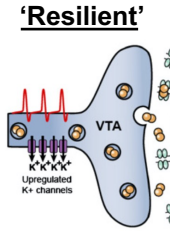


- Resilience is a latent trait and cannot be predicted by pre-stress interaction-ratio or open-field exploration testing (risk-seeking)
- Mice are homogenous (in-bred, same age, from a single vendor)

Mice Susceptible to the Effects of Stress Show a Depressed Phenotype and Greater VTA Hyperactivity Compared to Resilient Mice







- Susceptible, depressed mice → high VTA firing rate
- Resilient, non-depressed mice → low VTA firing rate
- Firing rates correlate with extent of depressed phenotype

Resilient Mice Correct Pathological VTA Hyperactivity by Actively Upregulating K+ Channels

Ventral Tegmental Area

Gene (Definition)	Susceptible	Unsusceptible
Gal (Galanin)	⇑	⇔
Gdnf (Glia derived neurotrophic factor)	⇔	⇑
Kcnf1 (Voltage gated K^+ channel F1)	⇔	⇑
Kcnh3 (Voltage gated K^+ channel H3)	⇔	⇑
Kcnk4 (K^+ channel K4 [TRAAK])	⇔	⇑
Kcnq3 (Voltage gated K^+ channel Q3)	⇔	⇑
Kif1b (Kinesin family member 1B)	⇔	⇓
Lcn2 (Lipocalin-2)	⇑	⇑

- Microarray analysis of the VTA reveal 'resilient' mice modify expression of a far larger number of genes than susceptible
- **The major expressional change in 'resilient' mice is upregulation of voltage-gated potassium channels**

In the chronic social defeat stress model, pathological hyperactivity is corrected both by:

- **Gene therapy**: viral overexpression of KCNQ3 (Kv7.3)[2]
- **Pharmacological approach**: systemic ezogabine[2]

VTA, ventral tegmental area.

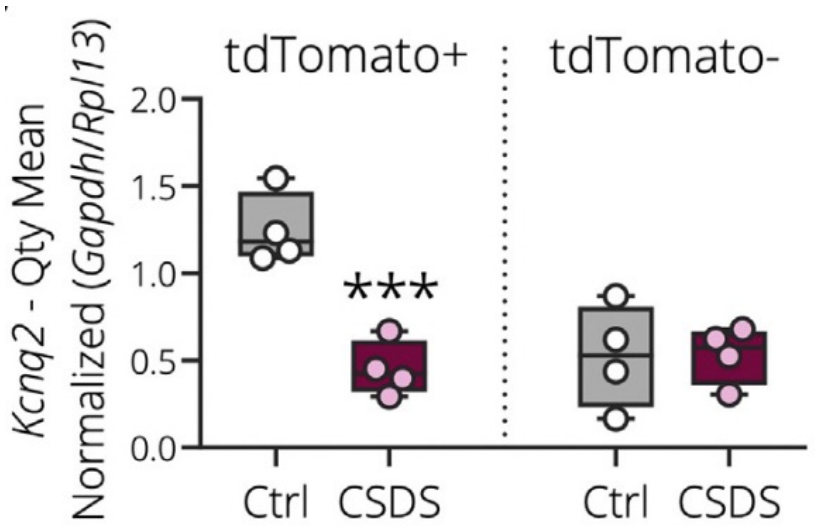
1. Krishnan V, et al. Cell. 2007 Oct 19;131(2):391-404. 2. Friedman AK, et al. Nat Commun. 2016 May 24;7:11671.

biohaven

Kv7.2 (KCNQ2) Is Downregulated by Stress in Ventral Hippocampal Glutamate Neurons and Upregulated by Ketamine but Not SSRI

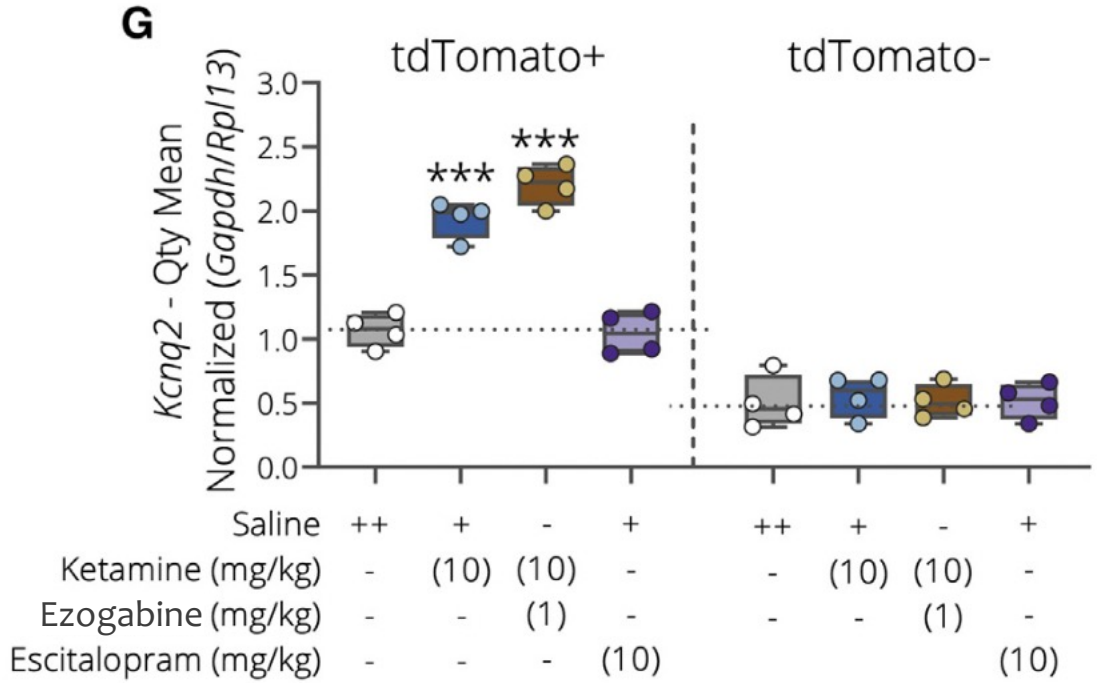
Synergy between Kv7 activator (Ezogabine) and Ketamine

Downregulated by Stress



- tdTomato-labeled conditional mice were studied
- tdTomato+ cells represent hippocampal glutamate neurons

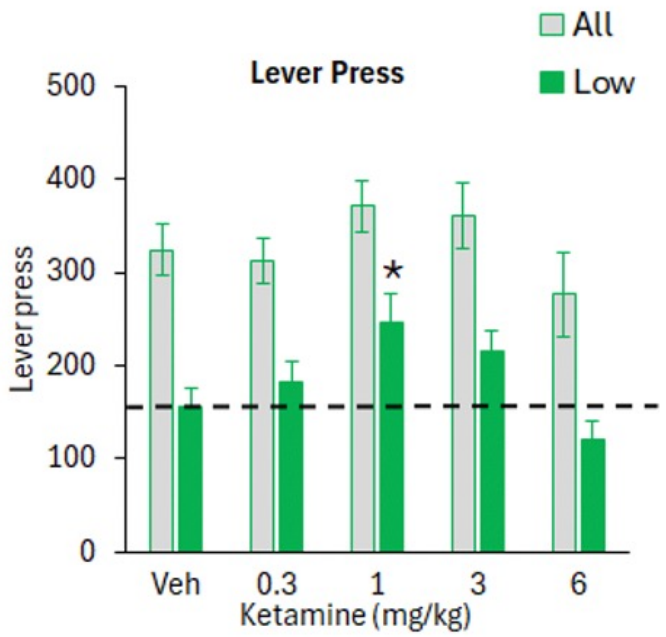
Upregulated by Ketamine and Ezogabine



CSDS, chronic social defeat stress; **tdTomato**, tandem dimer Tomato (fluorescent resin).
Lopez et al. Neuron 2022.

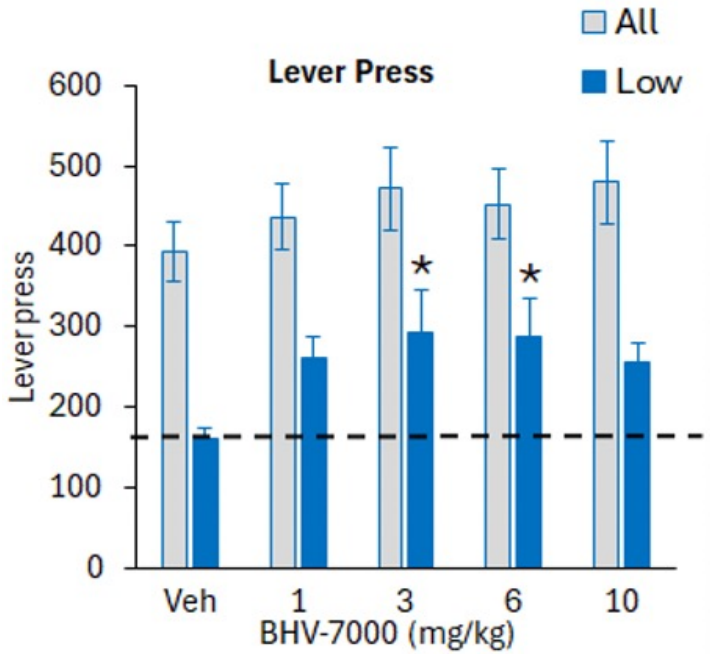
Potential Convergence of Therapeutic Effects of BHV-7000 and Ketamine

Ketamine Effects In 5-Choice Operant Model



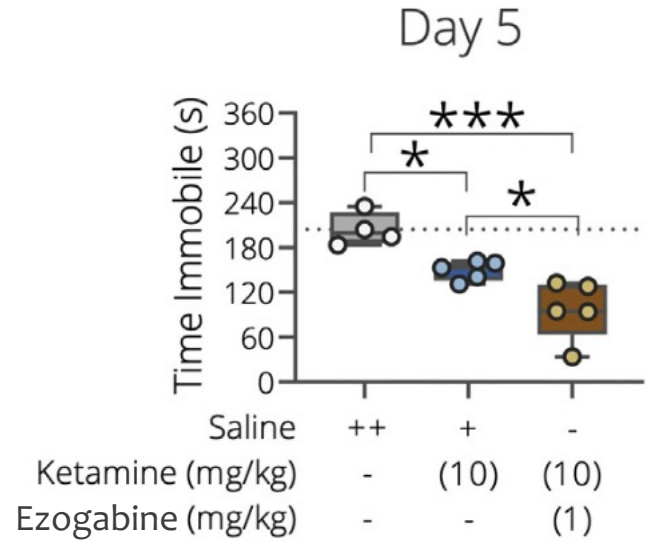
Higgins et al. Front Pharmacol. 2021 Feb 26; 12:640241.

Similar BHV-7000 Effects in 5-Choice Operant Model



Biohaven data on file.

Ezogabine Enhances Ketamine Efficacy in Forced Swim Test Model

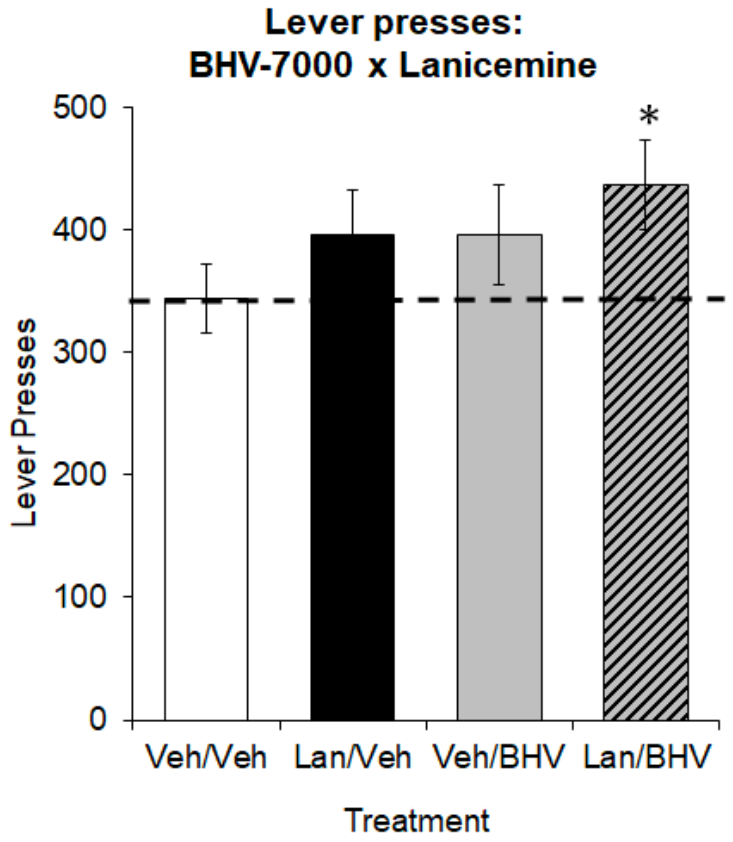


Lopez et al. Neuron. 2022 Jul 20;110(14):2283-2298.e9.

biohaven

BHV-7000 in Combination With NMDA Antagonist (Lanicemine/BHV-5500) Demonstrates Additive Effects

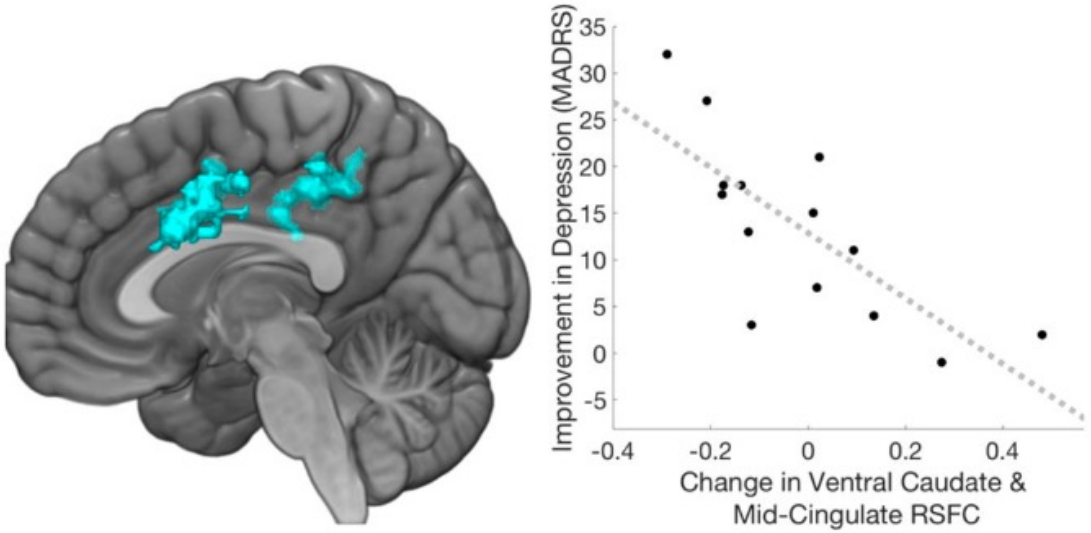
Progressive Ratio Operant Test:
BHV-7000 + Lanicemine (BHV-5500) in All Rats (N=40)



- The combination of BHV-7000 and Lanicemine (BHV-5500) results in a significant increase in lever presses relative to Vehicle controls
- The significant effect of BHV-7000 and Lanicemine (BHV-5500) combination was evident in the total cohort of all rats

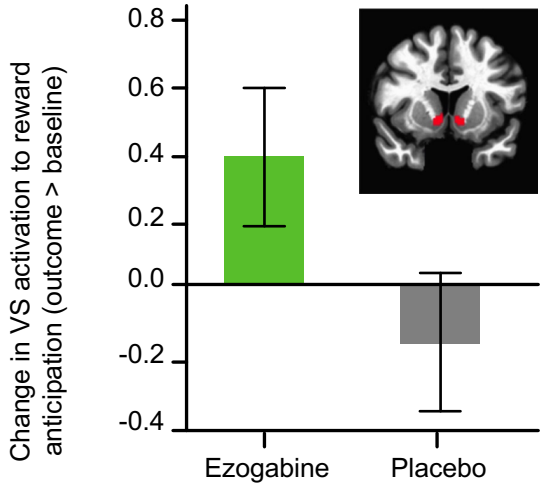
In Patients With MDD, Ezogabine Improves Depression and Anhedonia Symptoms With Concordant Changes in fMRI Measures

Open-label, Mechanistic Validation Study (N = 10)



- Clinically significant changes observed in MADRS (15pts in 4wk)
- Changes in depressive symptoms significantly associated with decreased functional connectivity in reward-related regions (vCa, MCC, PCC)
- Improvements also detected in reward-learning task

RCT With Functional Imaging and Clinical Endpoints



- Large, non-significant improvements in fMRI-based reward anticipation task seen in subjects randomized to ezogabine
- No serious AEs

Costi S et al, Am J Psychiatry. 2021 May 1;178(5):437-446.

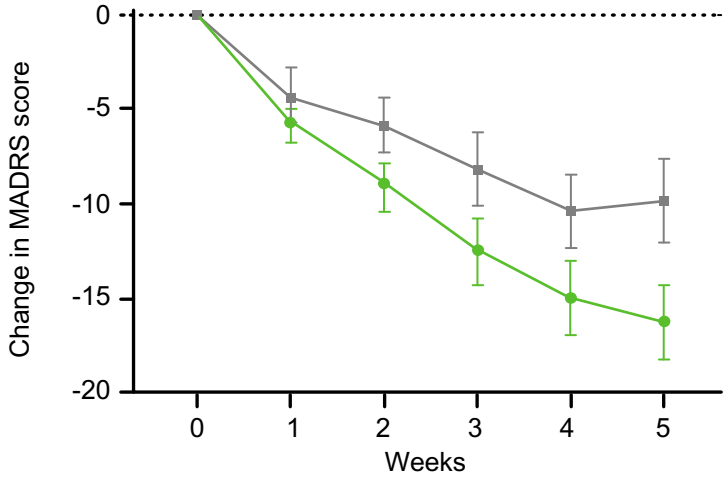
MDD, major depressive disorder; **MADRS**, Montgomery-Asberg depression rating scale; **vCA**, vertical Commissure anterior; **MCC**, midcingulate cortex; **PCC**, posterior cingulate cortex; **VS**, Ventral Striatum; **RCT**, randomized control trial.

biohaven

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

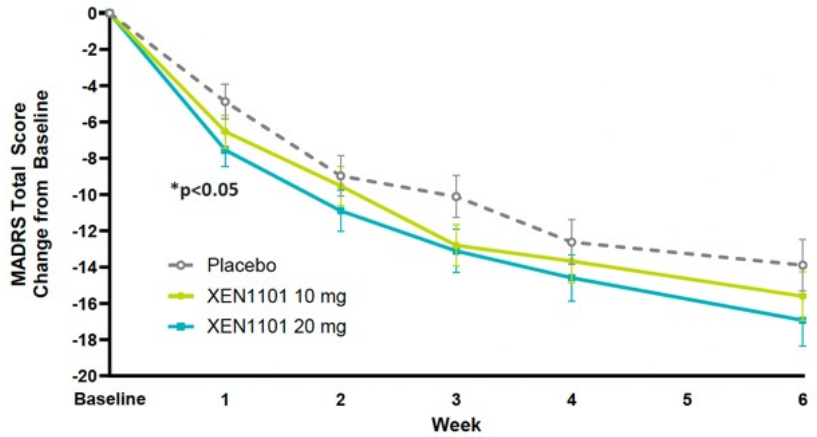
Ezogabine Demonstrated Robust Clinical Benefit (n=45)[1]



- 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**

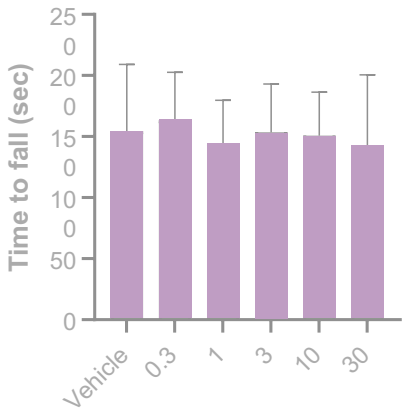
Xenon Pharmaceuticals Corporate update, November 27, 2023

KEY POINT

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

BHV-7000: Clinically Proven to Reduce CNS Side Effects at Therapeutic Doses

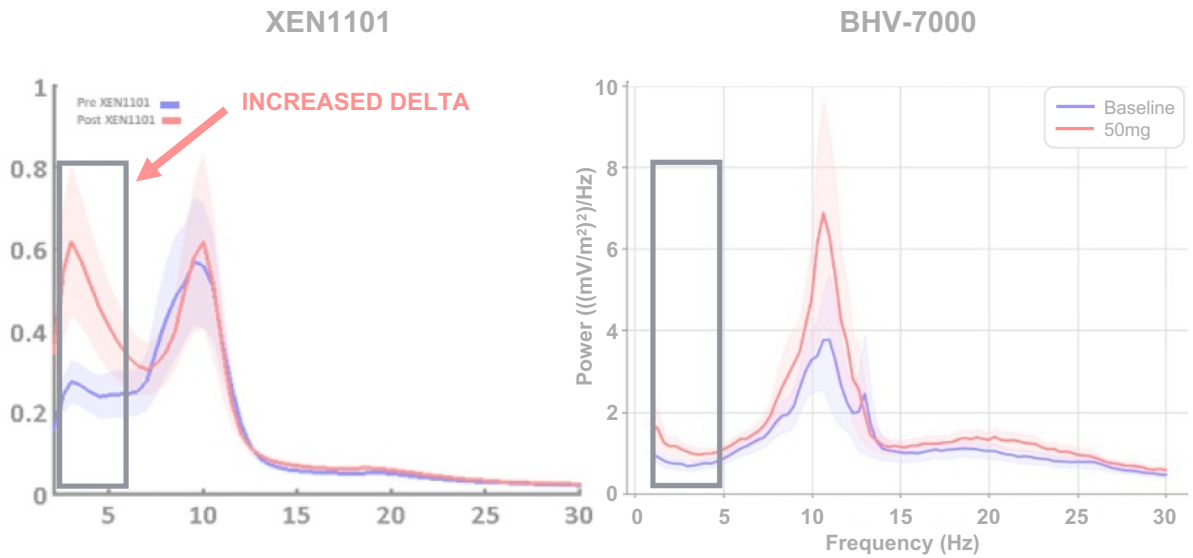
PRECLINICAL
No effects on motor performance on rotarod



PHASE 1
Not associated with CNS AEs typical of other ASMs in healthy volunteers

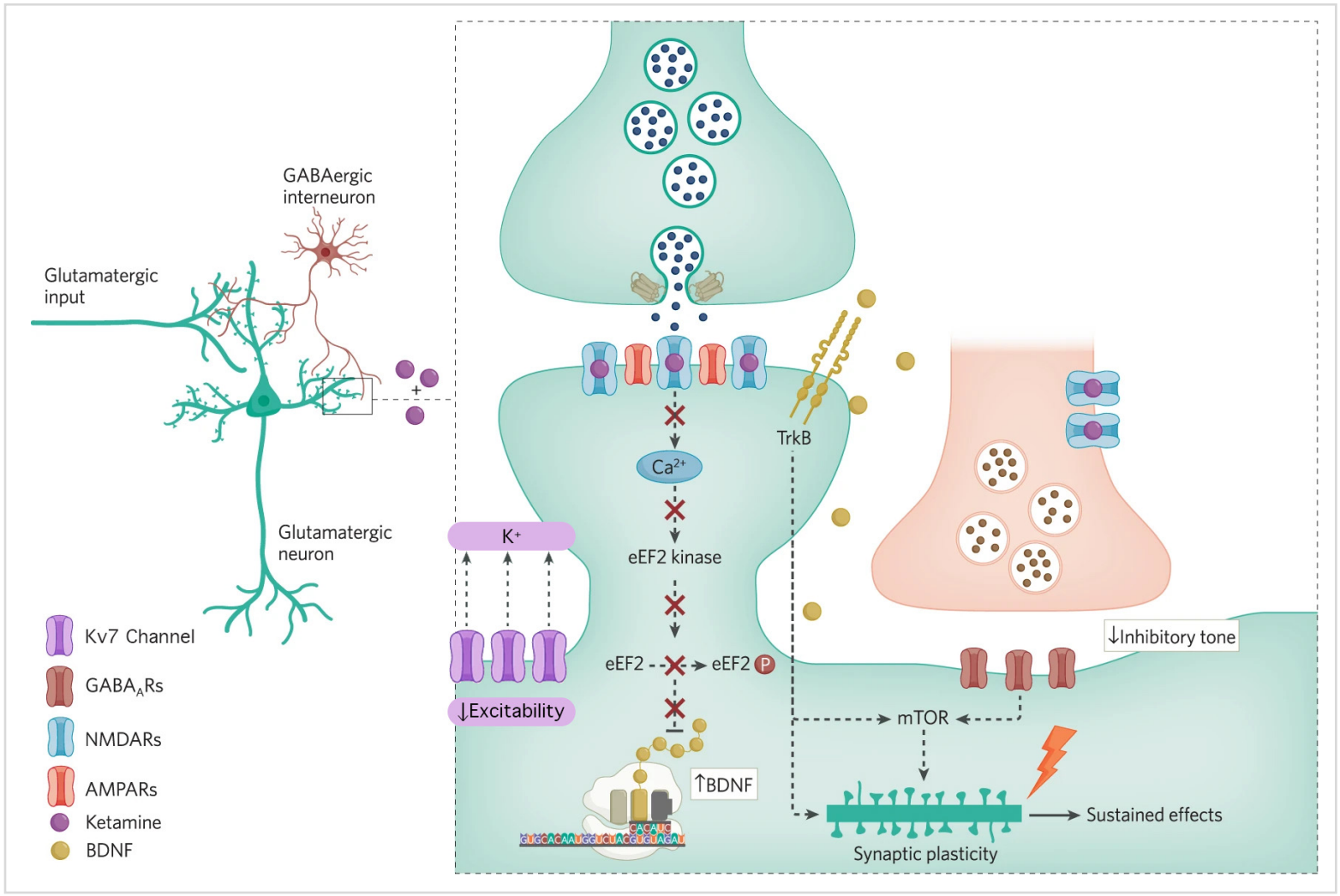
Pooled CNS AEs	BHV-7000 MAD Pooled N=29	XEN1101 MAD Pooled N=18
Somnolence	0%	39%
Headache	21%	39%
Balance disorder/ dizziness	10%	34%
Memory impairment	0%	28%
Sensory disturbance	0%	11%
Speech disorder	0%	33%

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



BHV-7000: Convergent Effects With Ketamine on Homeostatic Plasticity May Account for Synergistic Effects

- Stress and depression may cause homeostatic downregulation of glutamate synapses:
  - Excess glutamate release
  - Impairment in glutamate uptake
- Ketamine restores glutamate homeostasis via blockade of NMDA-R (GluN2B)
- Activation of Kv7 could restore E/I balance and restore synaptic homeostasis



Adapted from Krystal JH et al, Neuropsychopharmacology. 2024 Jan;49(1):41-50.

E/I, excitatory/inhibitory.

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

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

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

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

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

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

AE, adverse event.

biohaven

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

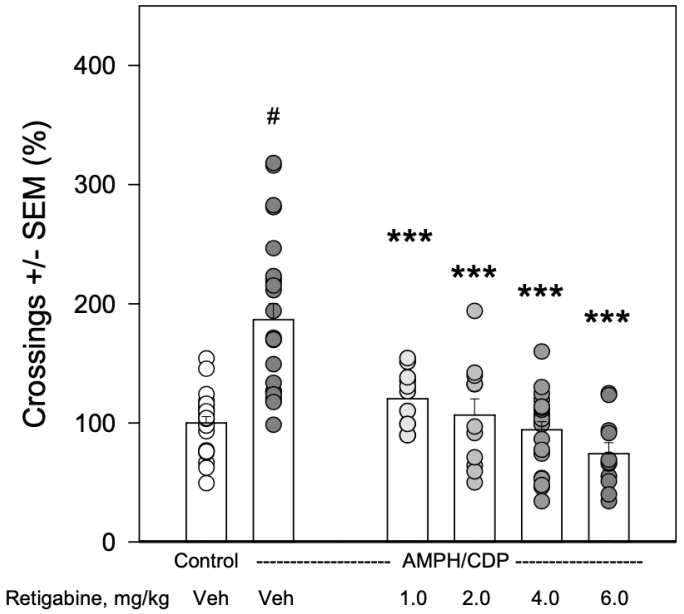
Kv7 activation demonstrates treatment benefits in preclinical models

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

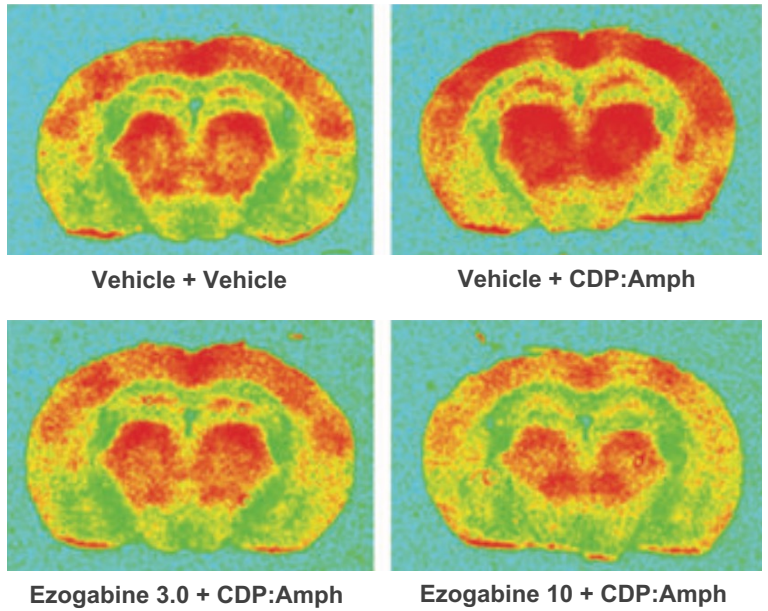
Ezogabine Reduces Hyperactive Locomotion



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

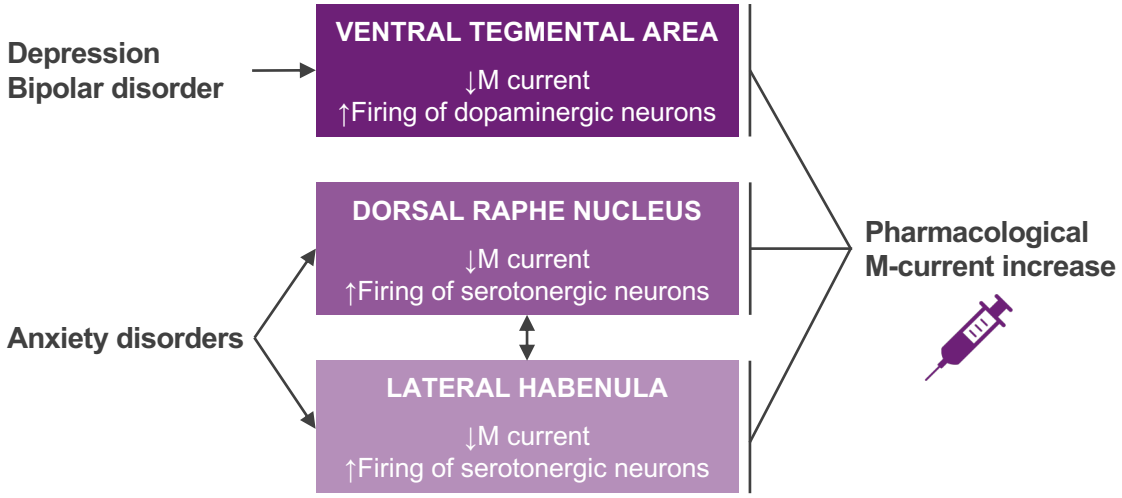
Kristensen LV et al , J Neurochem. 2012 May;121(3):373-82 .

biohaven

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

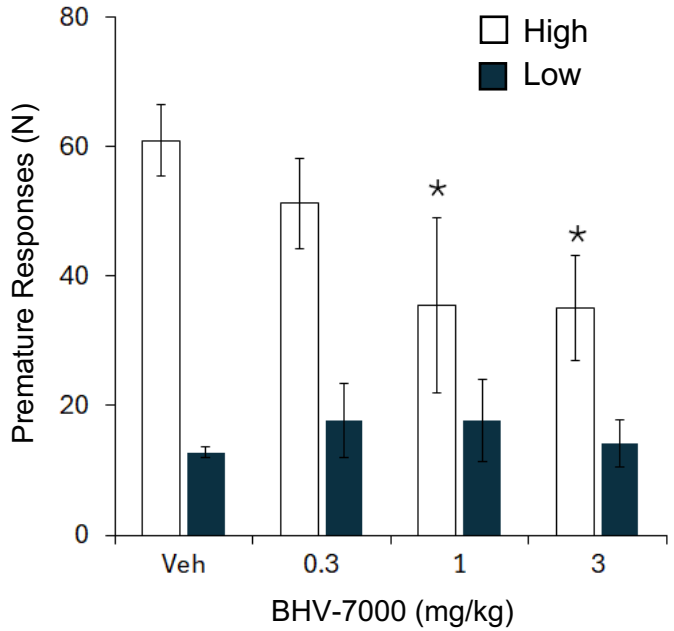
Operant Model Behavior and Stratification in 5-choice Serial Reaction Time Task

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)



biohaven

BHV-7000: Potential to Overcome Challenges With Existing Therapies

Potential for best-in-category tolerability and safety

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

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

●○○ Patient burden

SJS, Stevens-Johnson syndrome.

biohaven

Steven Dworetzky, Ph.D.
Senior Vice President,
Ion Channel Research & Development

biohaven®

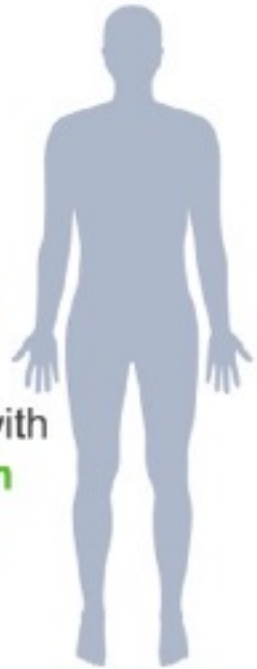
Additional Opportunities for Creating Value With Kv7

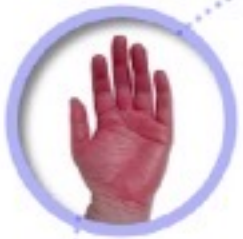
biohaven®

Leveraging Kv7 Channel Expertise to Create Transformational Treatments

Ion channel mutations

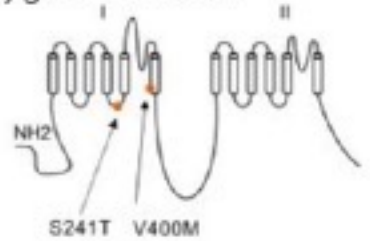
are aassociated with **epilepsies, pain and migraine**





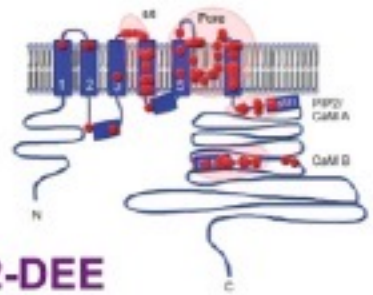
INHERITED ERYTHROMELALGIA

- Caused by Nav1.7 mutations
- Resilience mediated by KCNQ2 (Kv7.2) gain of function



Kv7.3

Kv7.2



KCNQ2-DEE

Caused by KCNQ2 (Kv7.2) mutations

OTHER PAIN DISORDERS

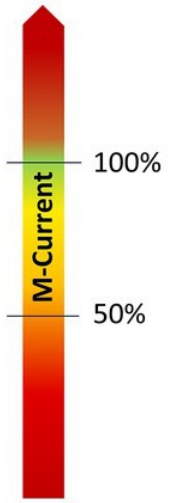
MIGRAINE

Mungoven et. al. Pain Res. 2021.

biohaven

BHV-7000 Restores Channel Function Across a Broad Set of Dominant Negative Kv7.2/KCNQ2 Mutations

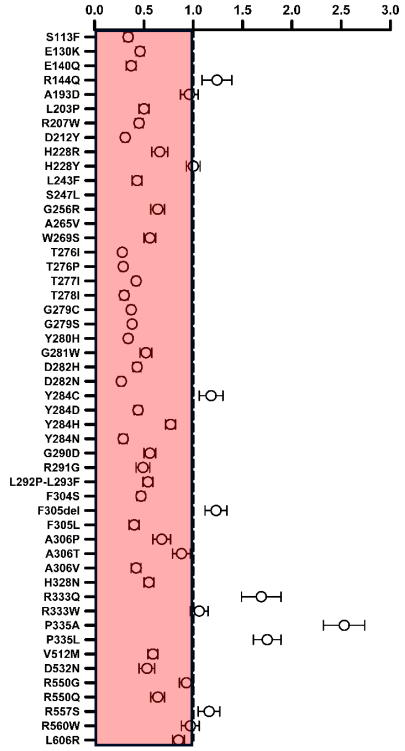
Link between Kv7 Current and Clinical Phenotype



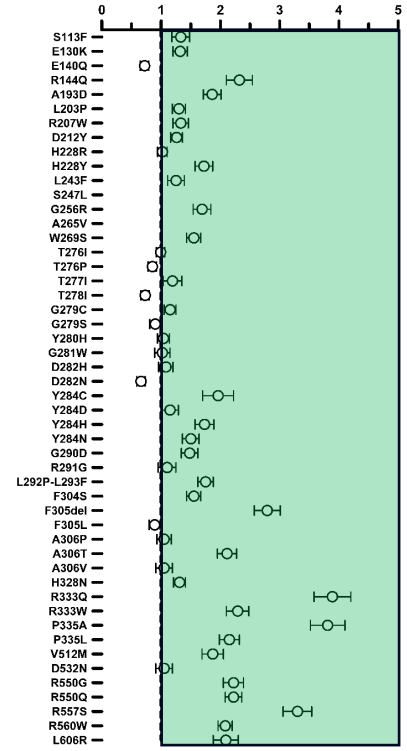
Mutation	Disorder	Clinical Phenotype
Gain of Function	KCNQ2-E	Developmental delay Infantile or childhood onset seizures Startle-like myoclonus
Loss of Function	KCNQ2-B	Neonatal seizures
Dominant Negative Loss of Function	KCNQ2-E	Developmental delay Neonatal seizures

Dirkx et. al. Front. Physiol, 27 October 2020 Volume 11

Current Density at -30 mV, Control (Fold WT Channel Control)



Current Density at -30 mV, +1 µM BHV-7000 (Fold WT Channel Control)



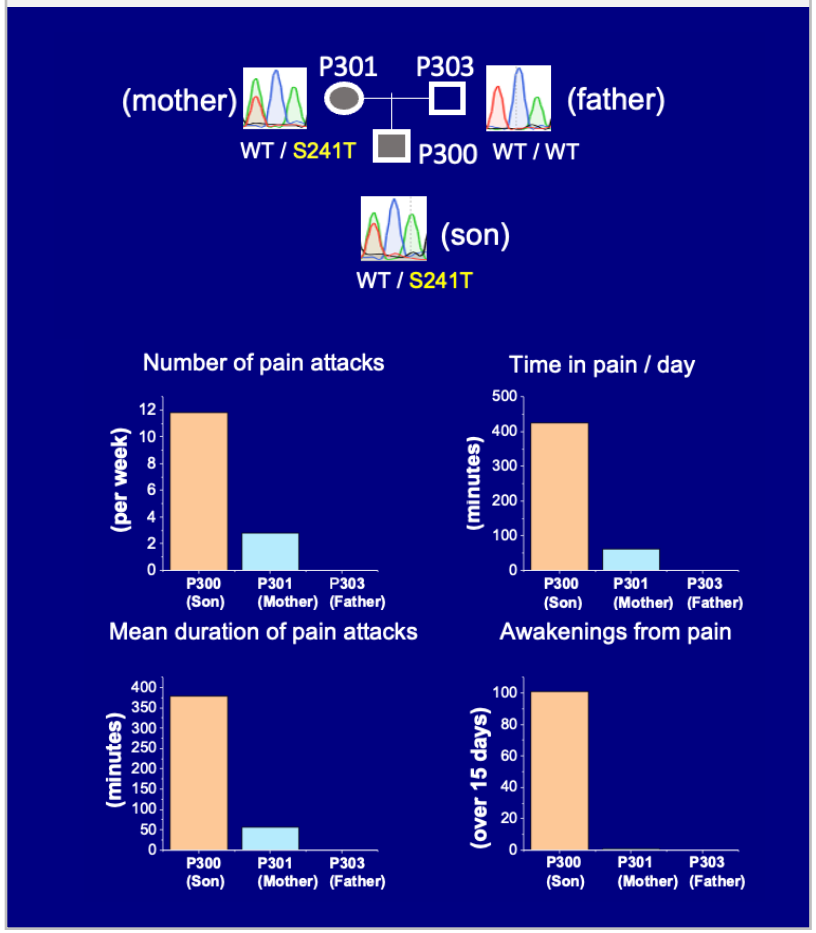
In collaboration with the George lab (Northwestern).

KEY POINT

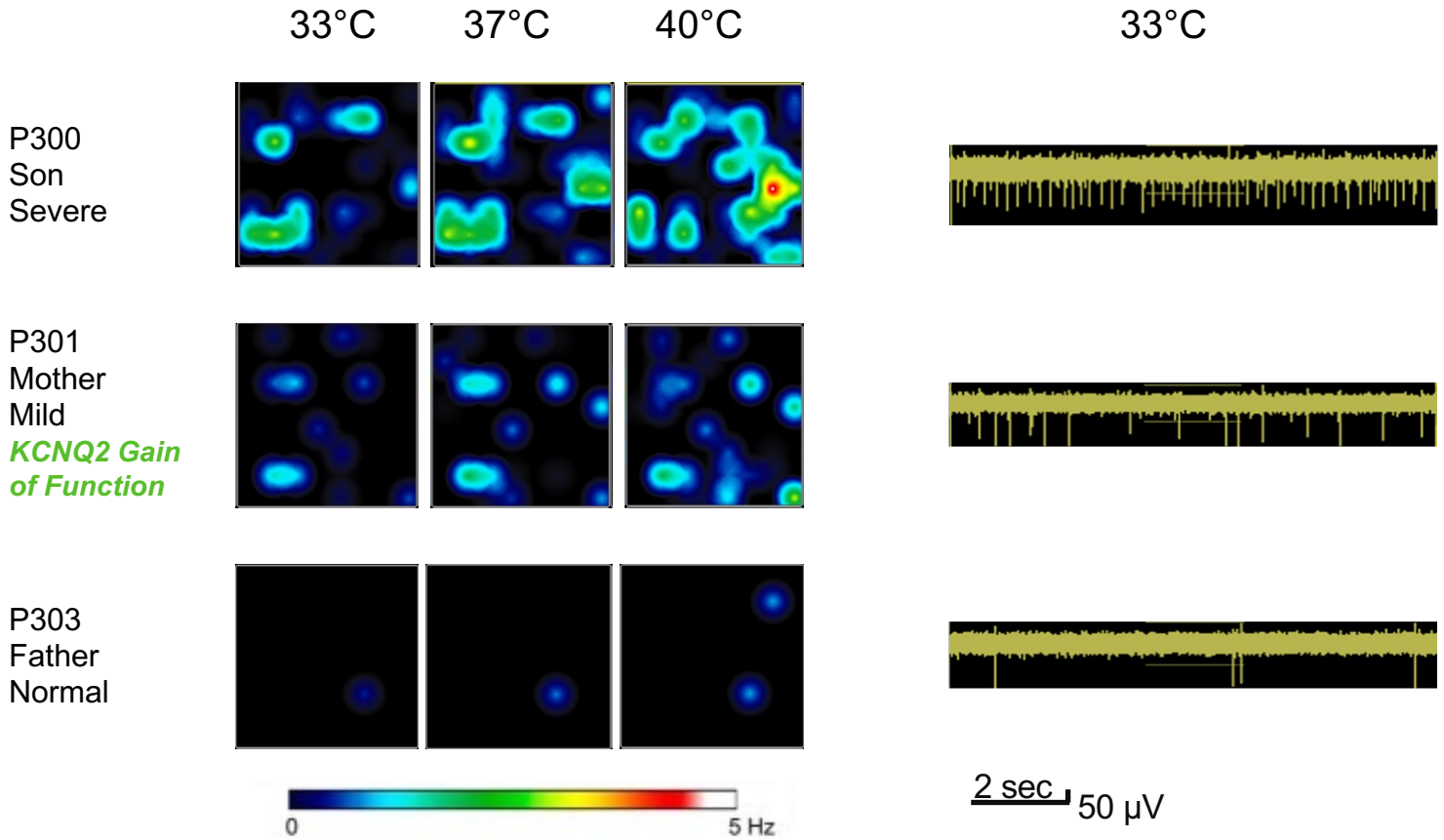
Ability to restore current to wild type levels in cells co-expressing disease-causing variant subunits suggests potential for BHV-7000 to modify disease phenotype in patients with KCNQ2-DEE

KCNQ2 (Kv7.2) Gain of Function Mutation Confers Pain Resilience in IEM Patient

Effects of NaV1.7-S241T Mutation



MEA Recordings of AP Firing of iPSC-SNs From P300, P301, and 303



Mis et al. J Neurosci. 2019 Jan 16;39(3):382-392.

IEM, inherited erythromelalgia; **SN-iPSC**, human induced pluripotent stem cell derived sensory neurons; **GOF**, γ-aminobutyric acid; **MEA,** multi-electrode-array; **AP,** action potential

biohaven

BHV-7000 Attenuates Action Potential Firing in IEM Patient-derived IPSCs

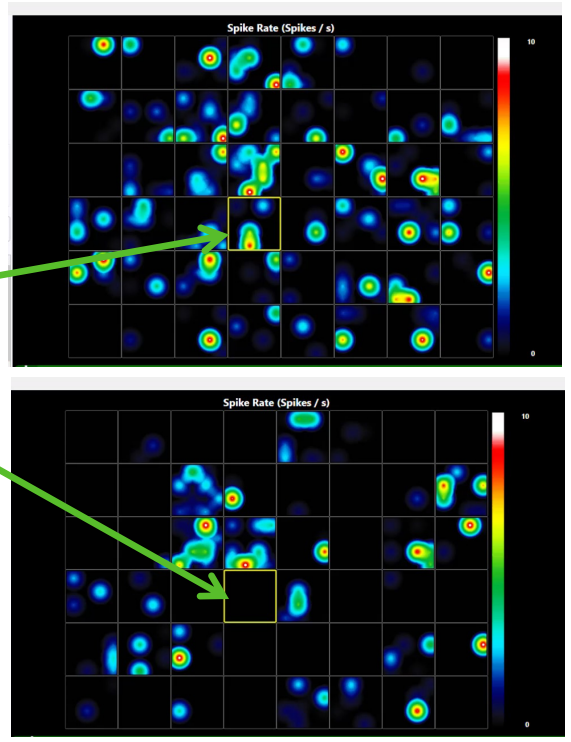
MEA Recordings of AP Firing of iPSC-SNs From P300

Spontaneous activity of cells before BHV-7000 addition

BHV-7000

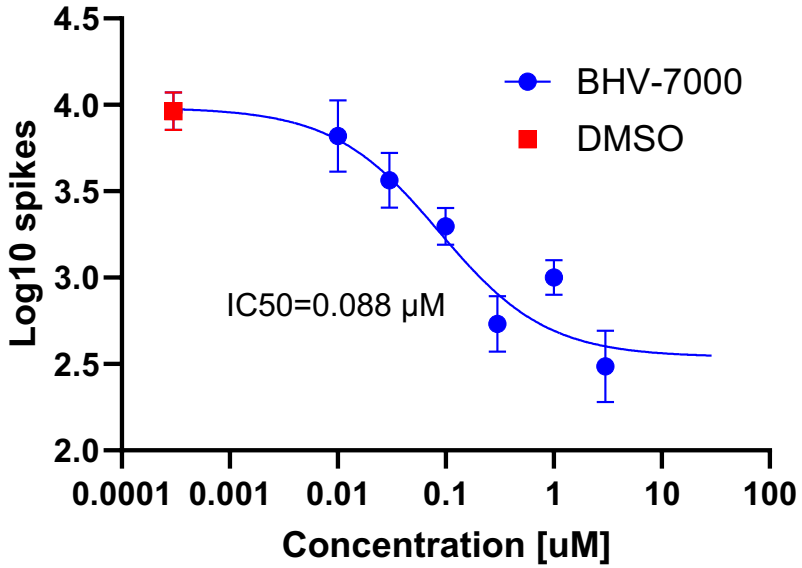
\+

Spontaneous activity of cells after BHV-7000 addition



In collaboration with the Waxman lab (Yale)

BHV-7000 Potency on AP Firing of iPSC-SNs From P300



In collaboration with the Waxman lab (Yale)

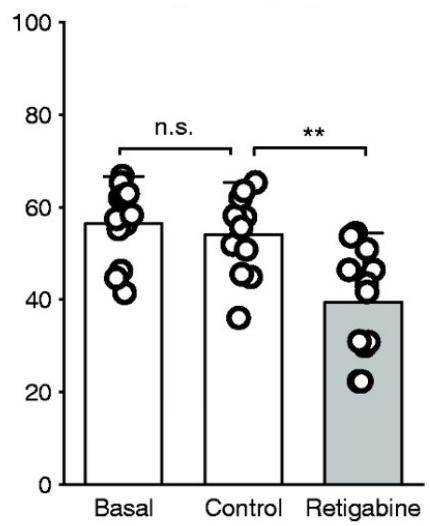
KEY POINT

Potential for BHV-7000 to modify disease phenotype in patients with IEM and other pain disorders

MEA, multi-electrode-array; **AP,** action potential **IPSC-SNs,** induced pluripotent stem cell derived sensory neurons.

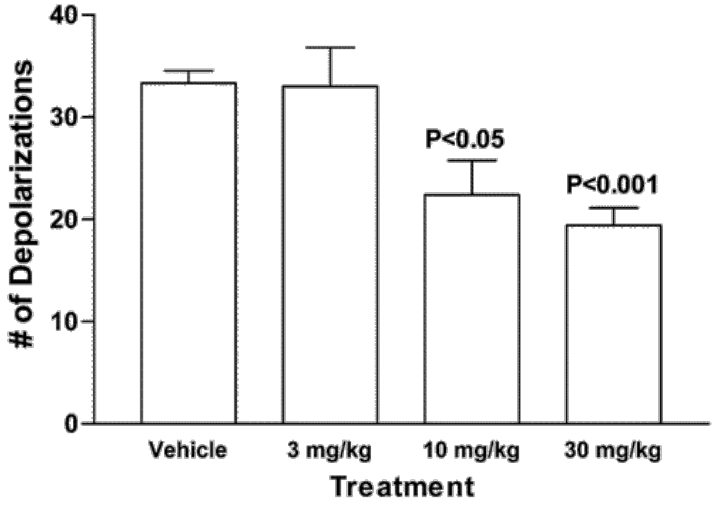
Kv7 Activation Is a Potential Strategy for Treating Migraine

Preclinical Data
Central and Peripheral Effects on Calcitonin Gene-Related Peptide Release



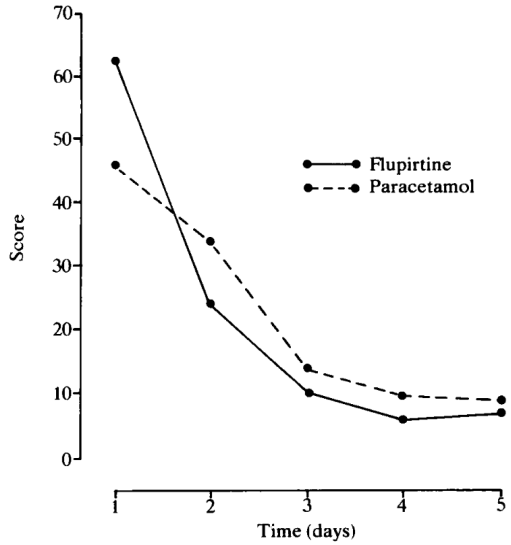
- Kv7 channel activator retigabine (ezogabine) significantly reduced basal and agonist-induced CGRP release in the trigeminovascular system in rats[1]
- Included both peripheral (dura mater and trigeminal ganglia) and central trigeminal components

Preclinical Data
Central Effects on Cortical Spreading Depression



- Kv7 activation decreases cortical spreading depression (CSD) in a dose dependent manner in rats[2]
- CSD is involved in the pathophysiology of classic migraine and suppressing CSD is a potential therapeutic approach

Clinical Data
Proof-of-concept with Nonselective Kv7 Activator Flupirtine



- Flupirtine lowered pain (VAS score) and disability in acute migraine patients in randomized double-blind trial[3]
- Flupirtine demonstrated convincing effect in primary headache in children in randomized double-blind trial[4]

VAS, visual analogue scale.

1. Citak A et al. 2022. *Cephalalgia*. Nov;42(13):1375-1386. 2. Wu YJ et al. J Med Chem. 2003, 46,3197-3200. 3. Million et al. 1984 Curr Med Res Opin. 1984;9(3):204-12; 4. Pothman and Lobish. 2000. Schmerz. Feb;14(1):1-4.

biohaven

Michael Bozik, M.D.

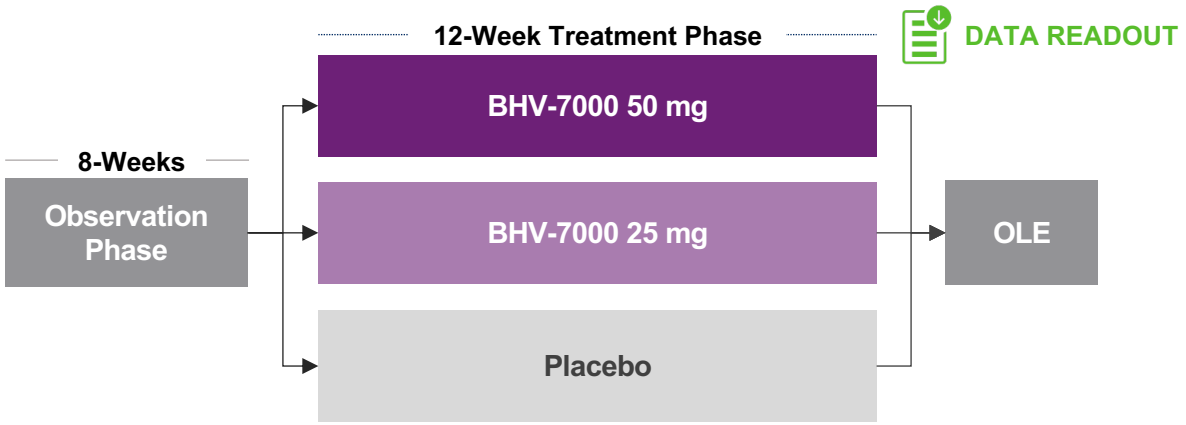
President, Ion Channel
Research and Development

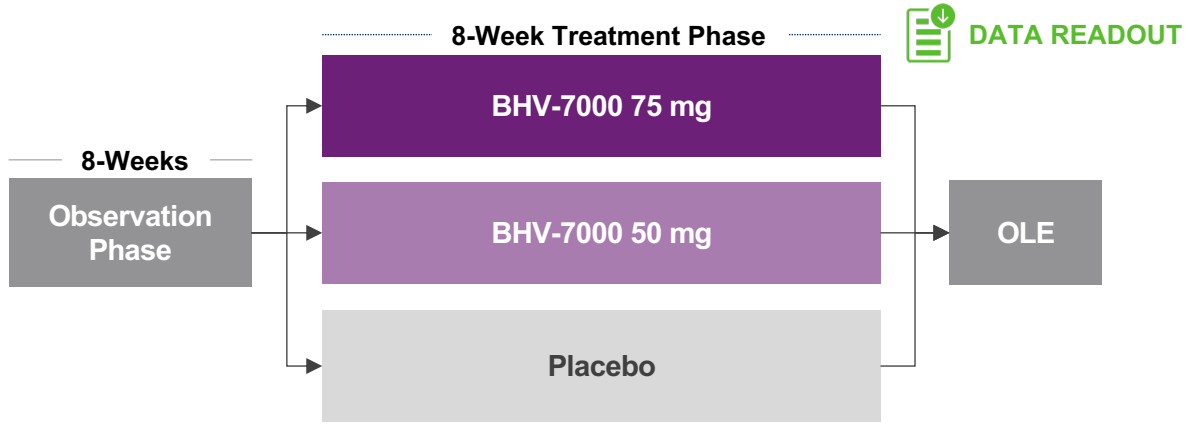
biohaven®

BHV-7000: 5 Phase 2/3 Trials Underway in Epilepsy and Mood Disorders

biohaven®

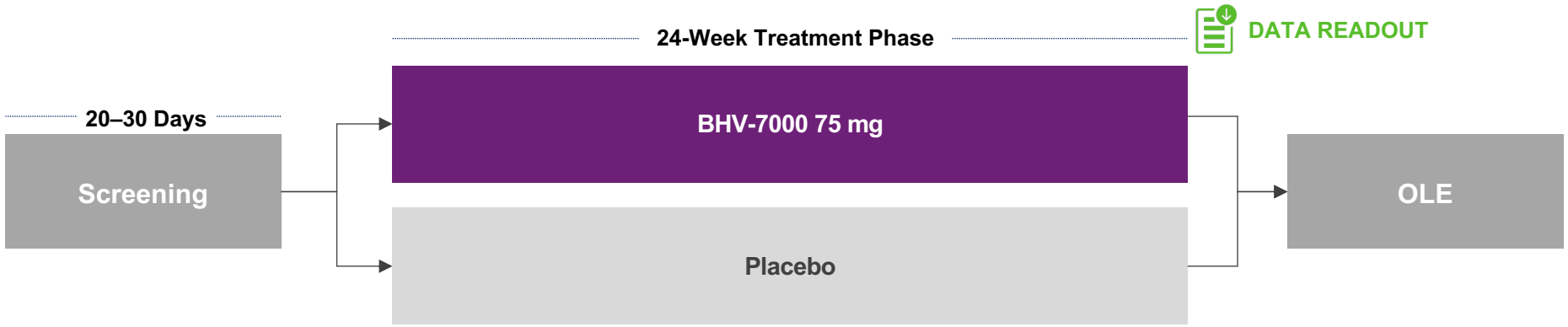
Two Phase 2/3 Studies in Focal Epilepsy Are Ongoing





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 (IGE) Is Ongoing

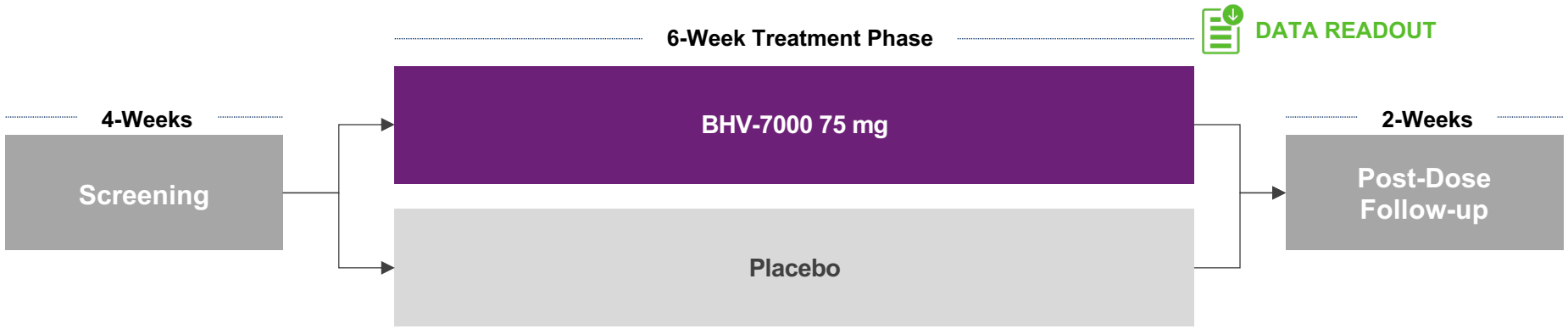


DESIGN	Randomized, double-blind, placebo-controlled trial
POPULATION	Subjects 18-75 years old with idiopathic generalized epilepsy with intractable generalized tonic-clonic seizures
SAMPLE SIZE	242 subjects (randomized 1:1)
TREATMENT	BHV-7000 75 mg vs. placebo
TREATMENT DURATION	Up to 24-week double-blind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

BREAKING NEWS

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

Phase 2 Study in Major Depressive Disorder Is Now 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

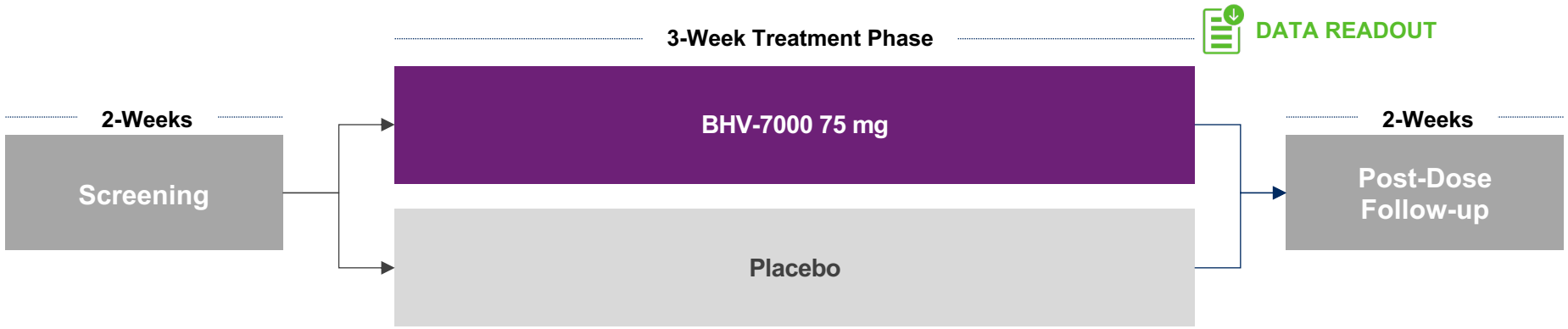
BREAKING NEWS

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.

biohaven

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



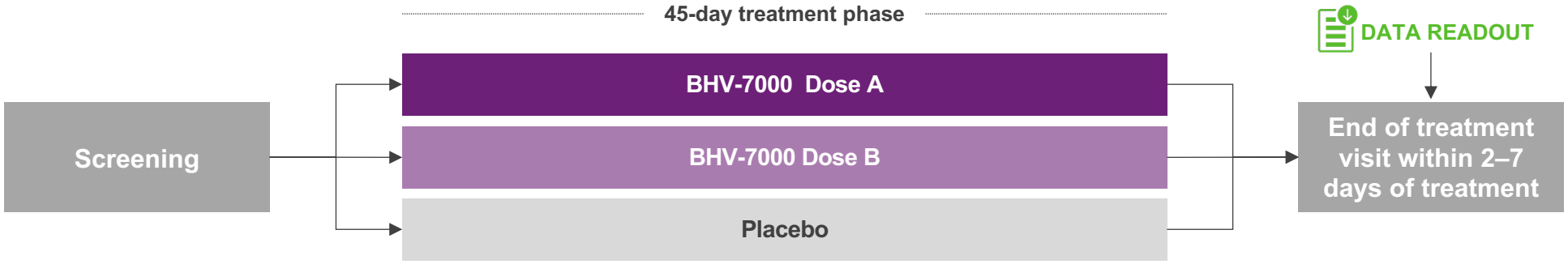
DESIGN	Randomized, double-blind, placebo-controlled trial
POPULATION	Subjects with Bipolar Disorder I with at least one prior mood episode who are currently experiencing a manic episode (YMRS ≥ 20)
SAMPLE SIZE	256 subjects (randomized 1:1)
TREATMENT	BHV-7000 vs. placebo
TREATMENT DURATION	3-weeks
ENDPOINTS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

BREAKING NEWS

Pivotal Phase 2/3 study initiated in 1H 2024

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

BHV-7000: Phase 2 Study in Acute Treatment of Migraine (in Planning)



DESIGN	Randomized, double-blind, placebo-controlled trial
POPULATION	Participants with at least 1-year history of migraine (with or without aura)
TREATMENT	BHV-7000 (dose-ranging) vs. placebo
TREATMENT DURATION	Single dose, up to 45 days to treat eligible migraine
ENDPOINTS	Pain relief, Freedom from most bothersome symptom

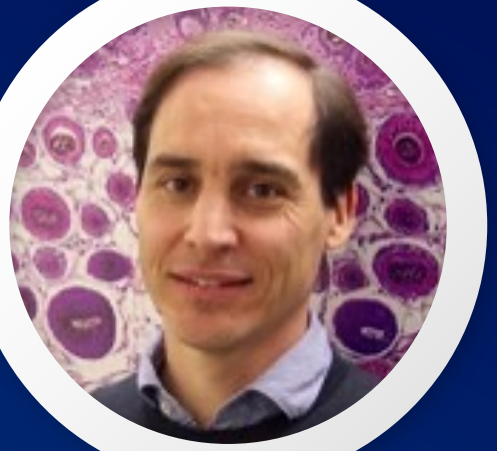
Preliminary study design

BHV-7000: Summary and Clinical Program Status

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

There is a missing piece in epilepsy and neuropsychiatry for better-tolerated, efficacious treatments

biohaven



Professor Thomas Voets

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

KU LEUVEN

Richard Lipton, M.D.

Professor & Vice Chair, Neurology
Director, Headache Center

Montefiore | EINSTEIN
Albert Einstein College of Medicine

Volkan Granit, M.D., MSc

Medical Director, Clinical Development

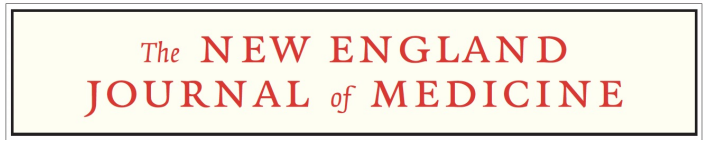
biohaven®

Ion Channel Platform: TRPM3 Antagonism

biohaven®

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

biohaven

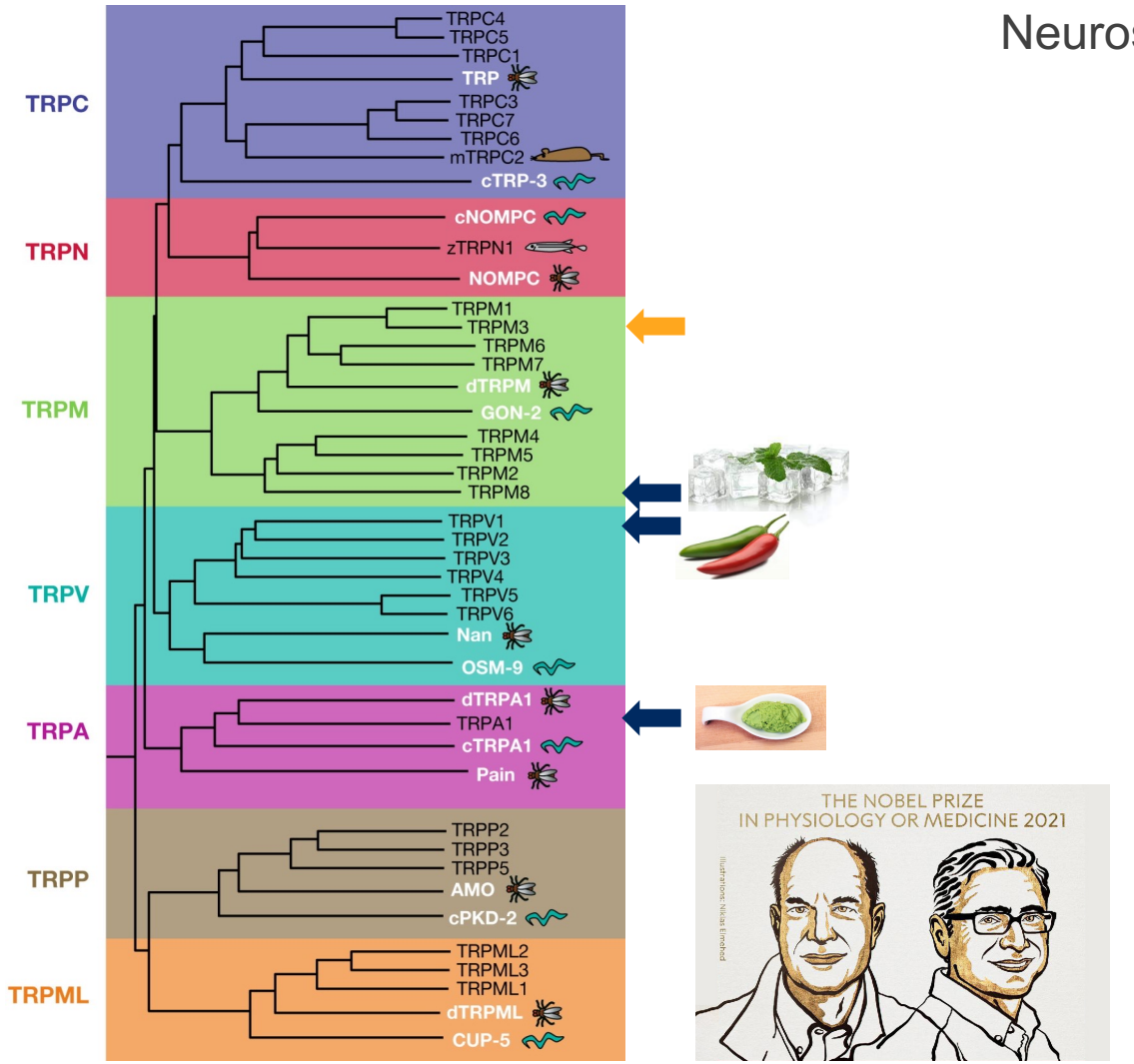
Professor Thomas Voets

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

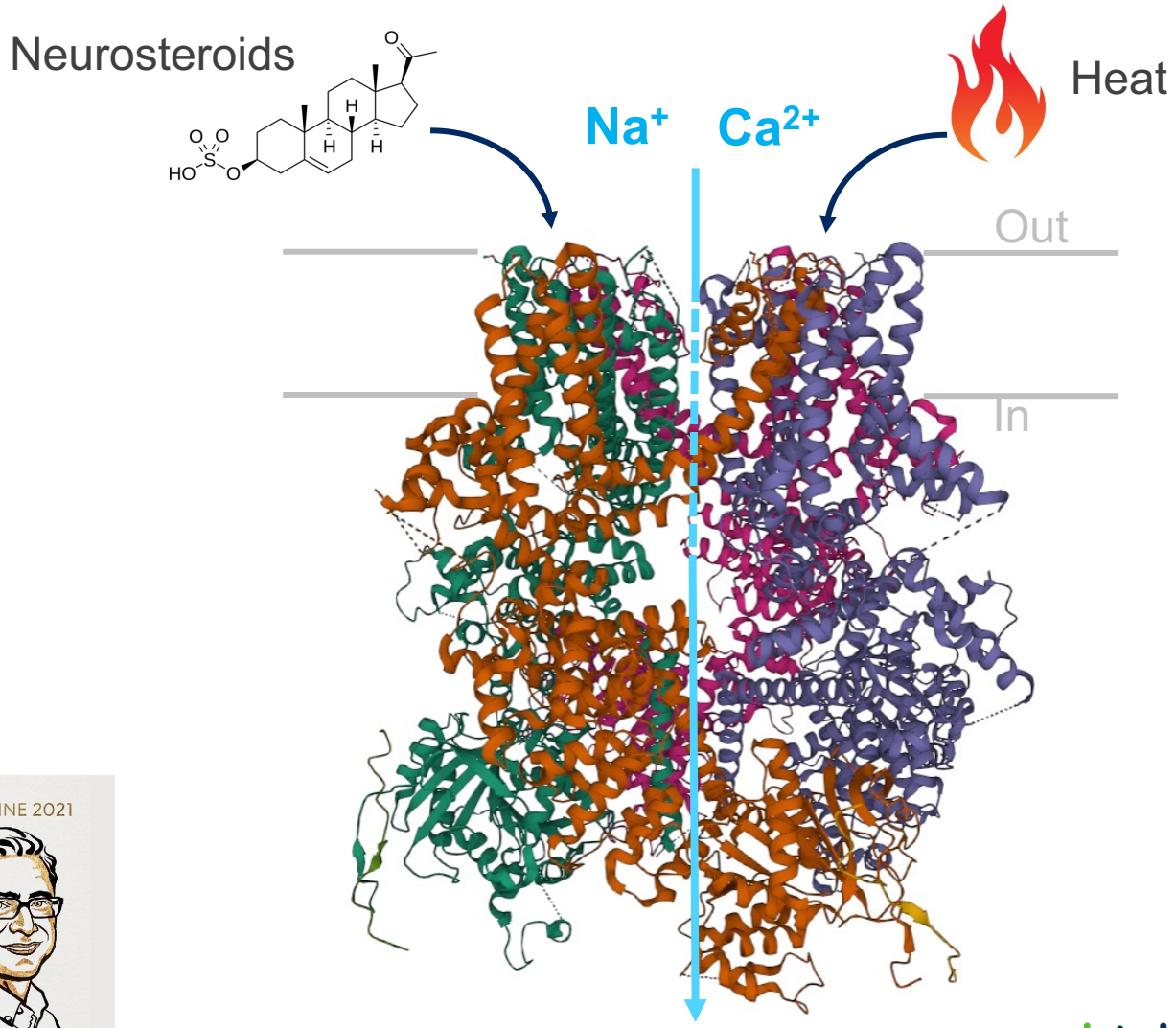
KU LEUVEN

TRPM3 Biology and BHV-2100 for the Treatment of Pain and Migraine

Introducing Transient Receptor Potential Melastatin 3 (TRPM3)



Modified from: Annual Review of Biochemistry Volume 76, 2007 Venkatachalam, pp 387-417

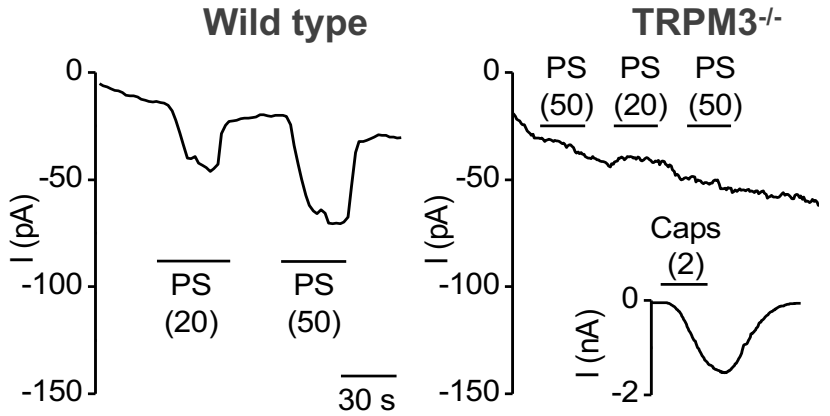


Based on Zhao C, MacKinnon R. Neuron. 2022

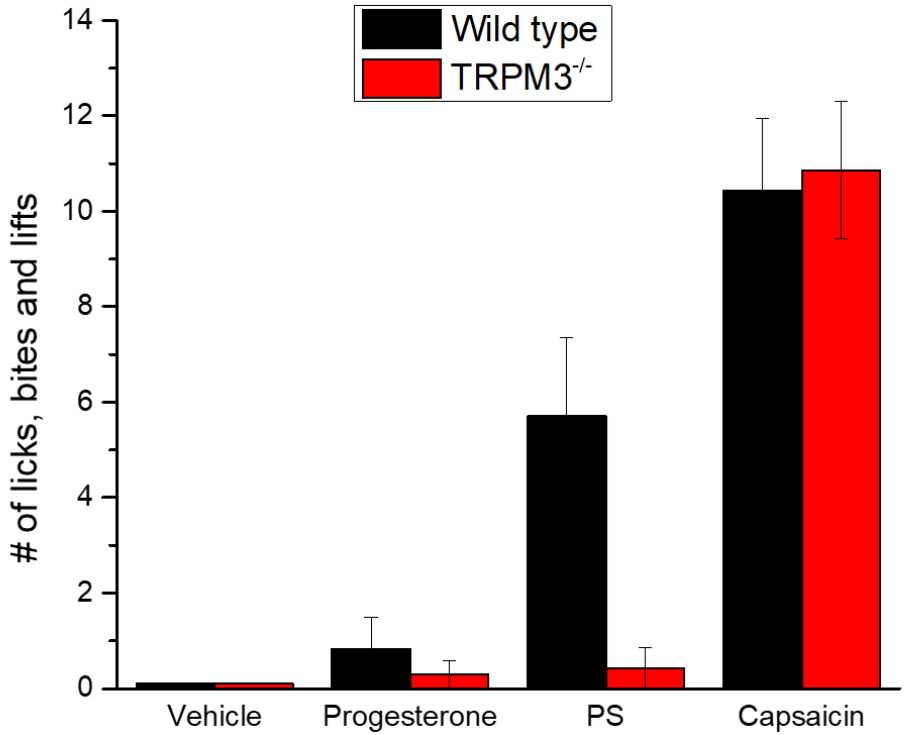
biohaven

Functional Expression of TRPM3 in Mouse Nociceptive DRG Neurons

TRPM3 Receptors Are Functionally Expressed in Mouse DRG



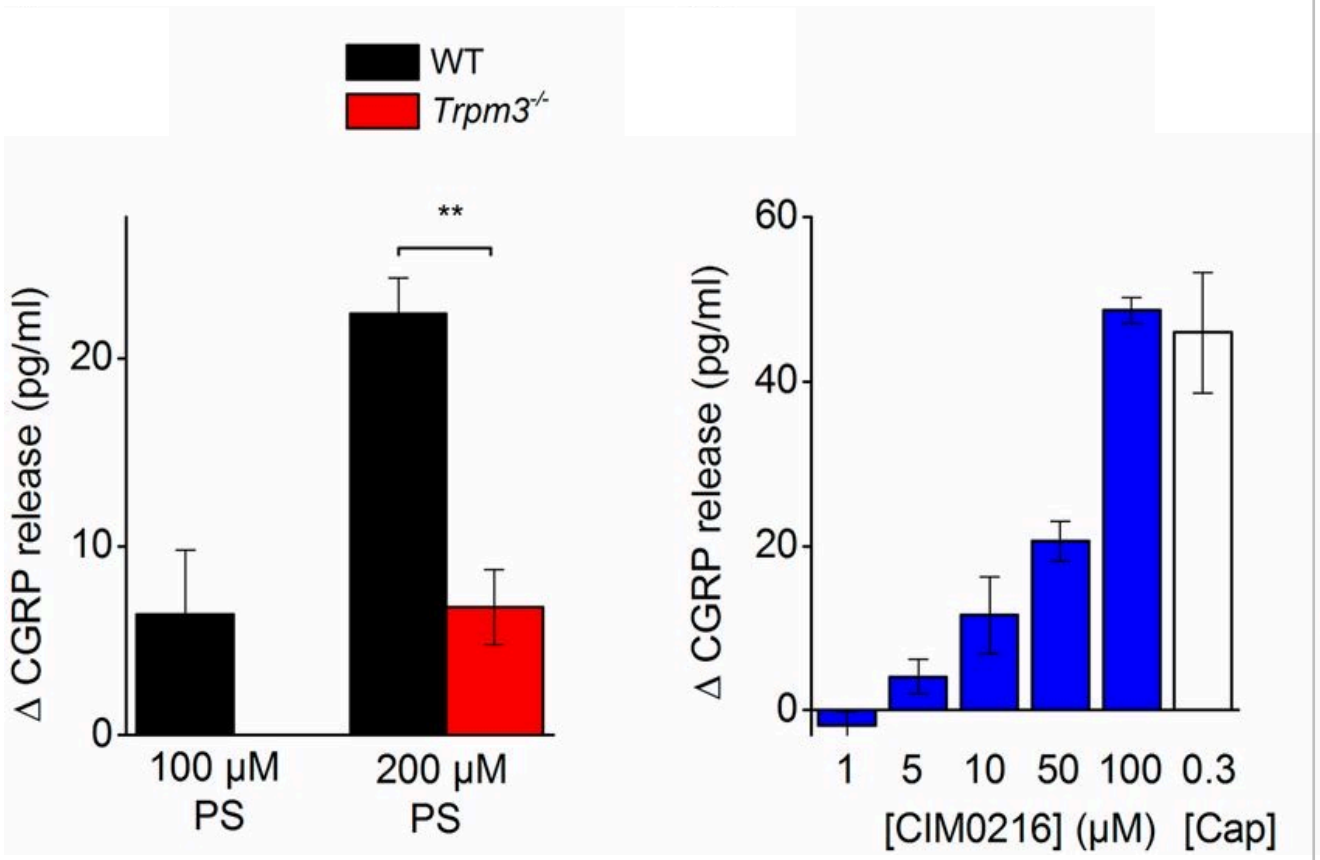
Activation of TRPM3 Induces Acute Ongoing Pain



PS, pregnenolone sulfate; **DRG**, dorsal root ganglion.
Vriens J, Nat Chem Biol. 2014 Mar;10(3):188-95.

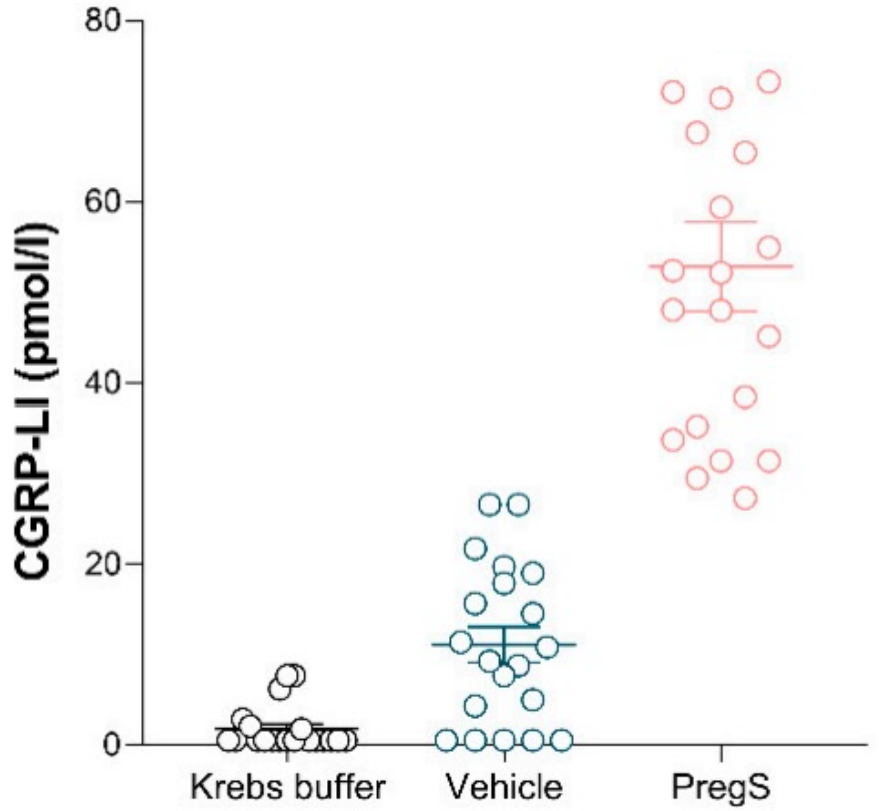
TRPM3 Activation Leads to CGRP Release in Mouse and Human Skin

TRPM3 Agonists Evoke CGRP Release in Mouse Skin



PS, pregnenolone sulfate; **CIM0216,** a potent synthetic ligand of TRPM3; **Cap,** capsaicin.
Held et al. PNAS, 2014.

Activation of TRPM3 Causes CGRP Release From Sensory Nerve Terminals Around Human Arteries

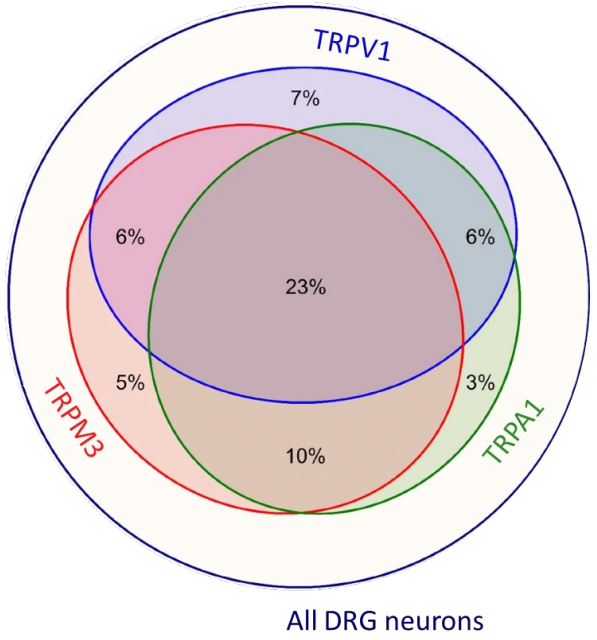


PregS, pregnenolone sulfate; **CGRP-LI**, CGRP-Like Immunoreactivity.
Rivera-Mancilla et al. Pharmaceuticals, 2024

biohaven

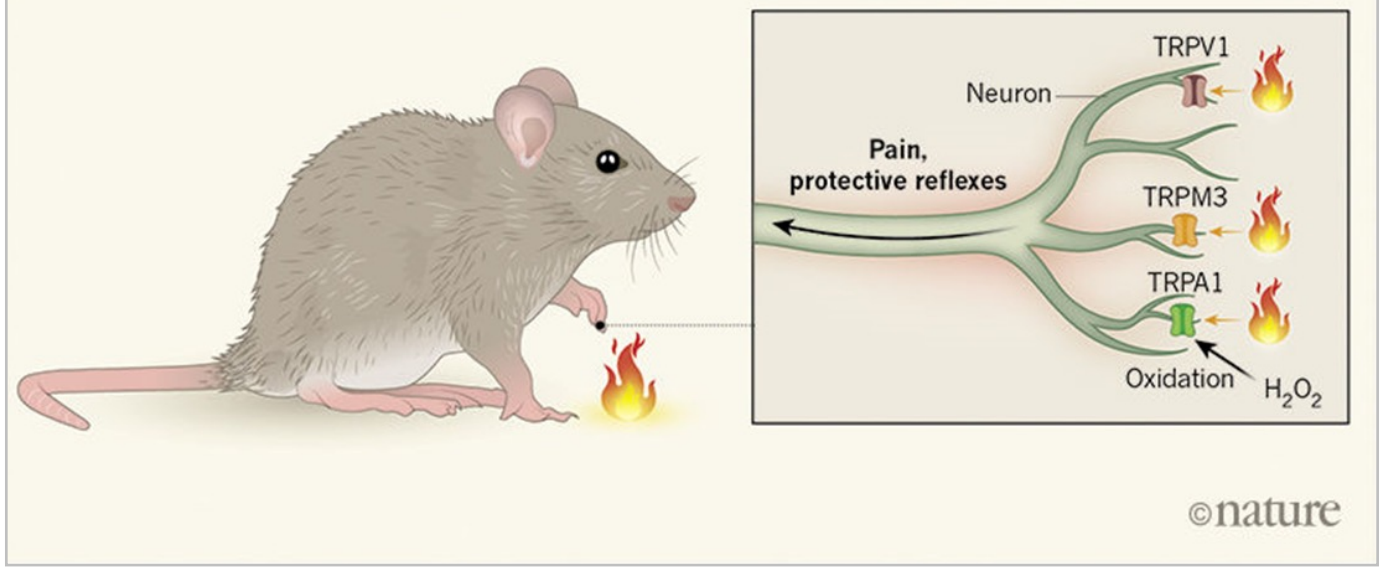
Redundant Role of TRPM3 in Acute Heat Sensing

Co-expression of TRPM3 With TRPV1 and TRPA1



Vandewauw I et al, Nature. 2018 Mar 29;555(7698):662-666.

Normal Heat Sensitivity Is Retained as Long as TRPV1 Is Functional



Wimalasena NK et al, Neuron. 2021 Oct 6;109(19):3075-3087.e2.

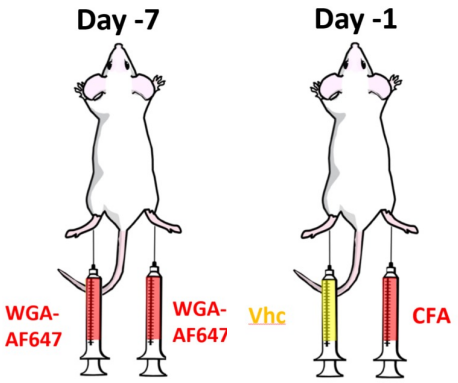
KEY POINT

Inhibition of TRPM3 has very little impact on thermosensation, as long as TRPV1 function is preserved

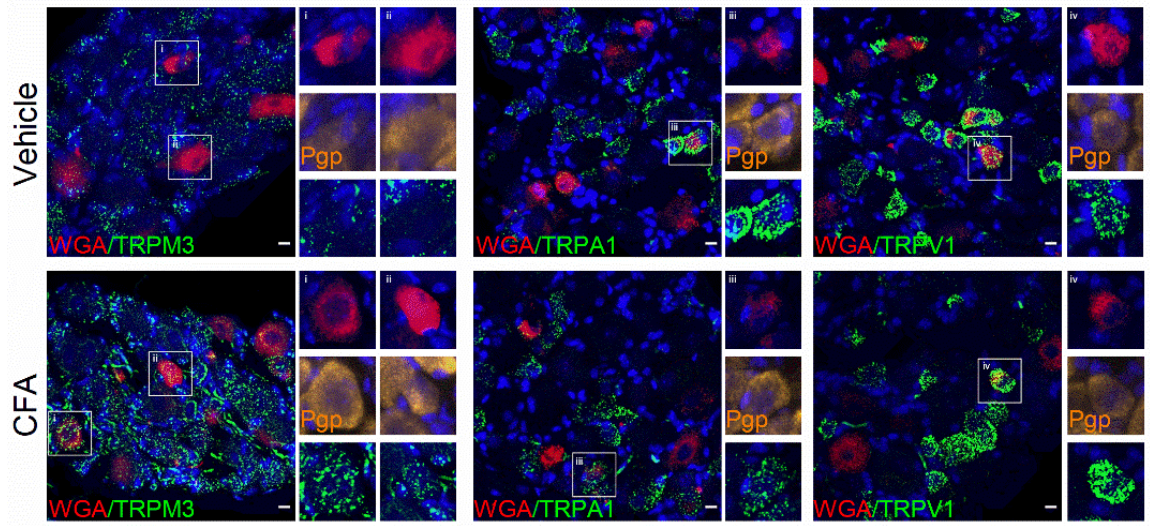
DRG, **d**orsal root ganglia.

biohaven

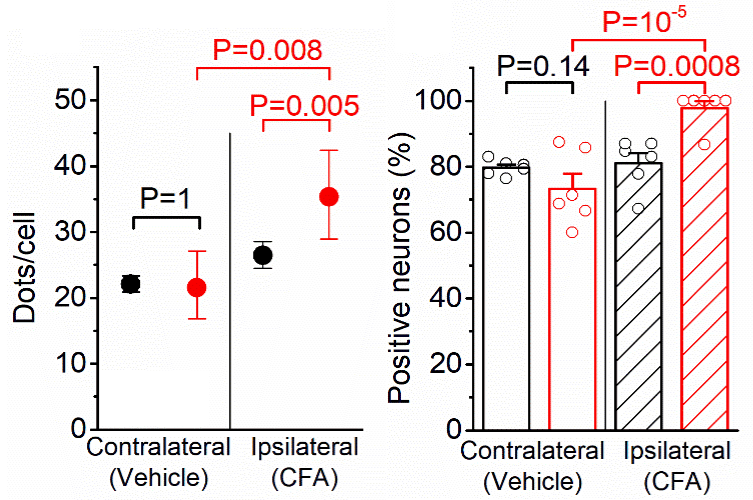
TRPM3 in DRG Neurons is Upregulated in Various Pathological Pain Models



RNAscope of L5 DRGs[1]



Increased TRPM3 RNA[1]



Increased functional TRPM3 expression in sensory neurons innervating injured tissue in several rodent models, including

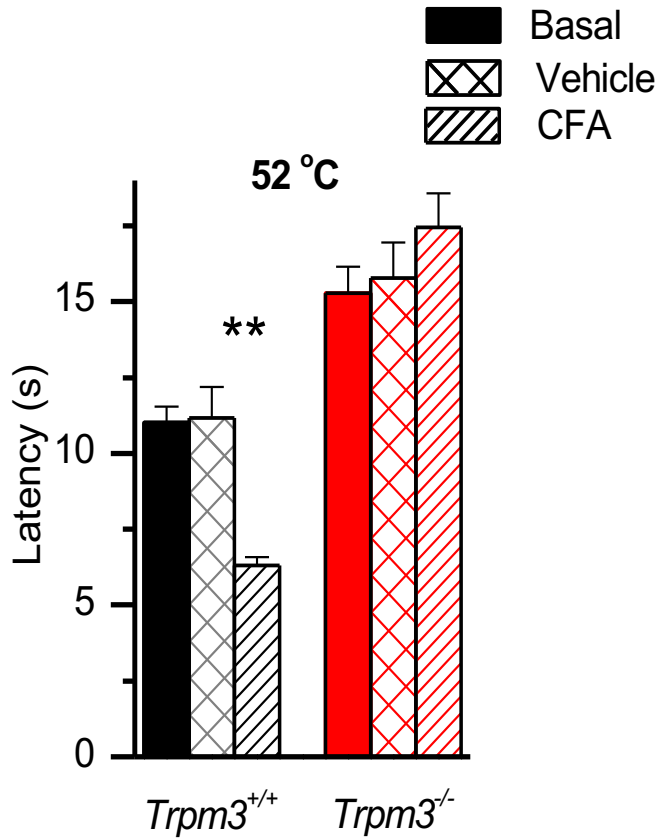
- Inflamed hind paw[1]
- Bladder cystitis[2,3]
- Chemotherapy-induced neuropathic pain[4]

WGA, wheat germ agglutinin (nerve labeling agent); **CFA**, Complete Freund's Adjuvant; **Vhc,** Vehicle; **DR,** Dorsal Root Ganglion.

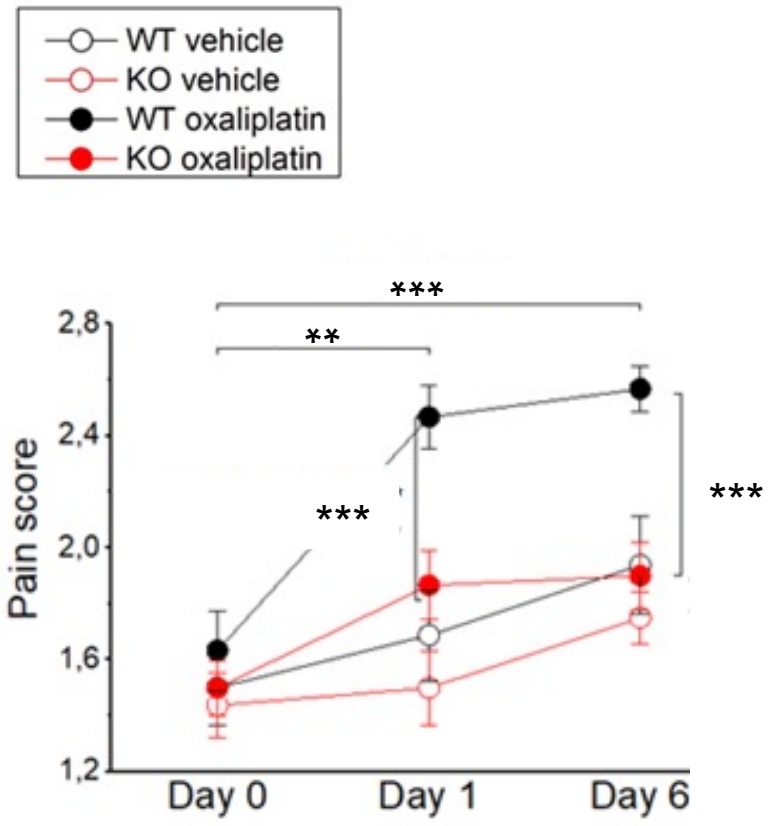
1. Mulier M, et al. Elife. 2020 Sep 3;9:e61103.; 2. Rescifina A. 2022. Int J Mol Sci. 2023 May 29;24(11):9442 3. Zhao M et al, Pain. 2022 Nov 1;163(11):2200-2212 ; 4. Aloi VD et al, Pain. 2023 Sep 1;164(9):2060-2069.

TRPM3-Deficient Mice Do Not Develop Hypersensitivity in Pathological Pain Models

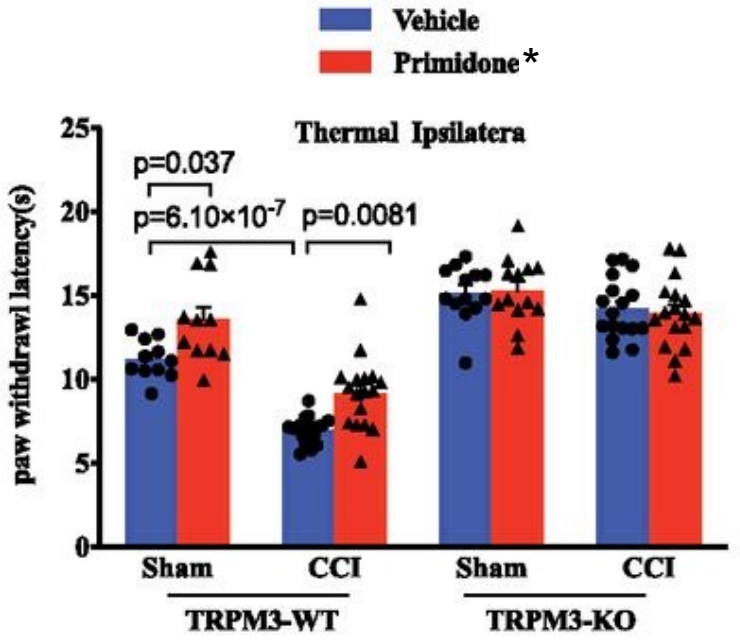
CFA Model[1]
(Inflammatory Pain — Heat Hyperalgesia)



Oxaliplatin Model[2]
(CIPN — Cold and Mechanical Allodynia)



Nerve Constriction Model[3]
(CCI – Heat Hypersensitivity and Ongoing Pain)



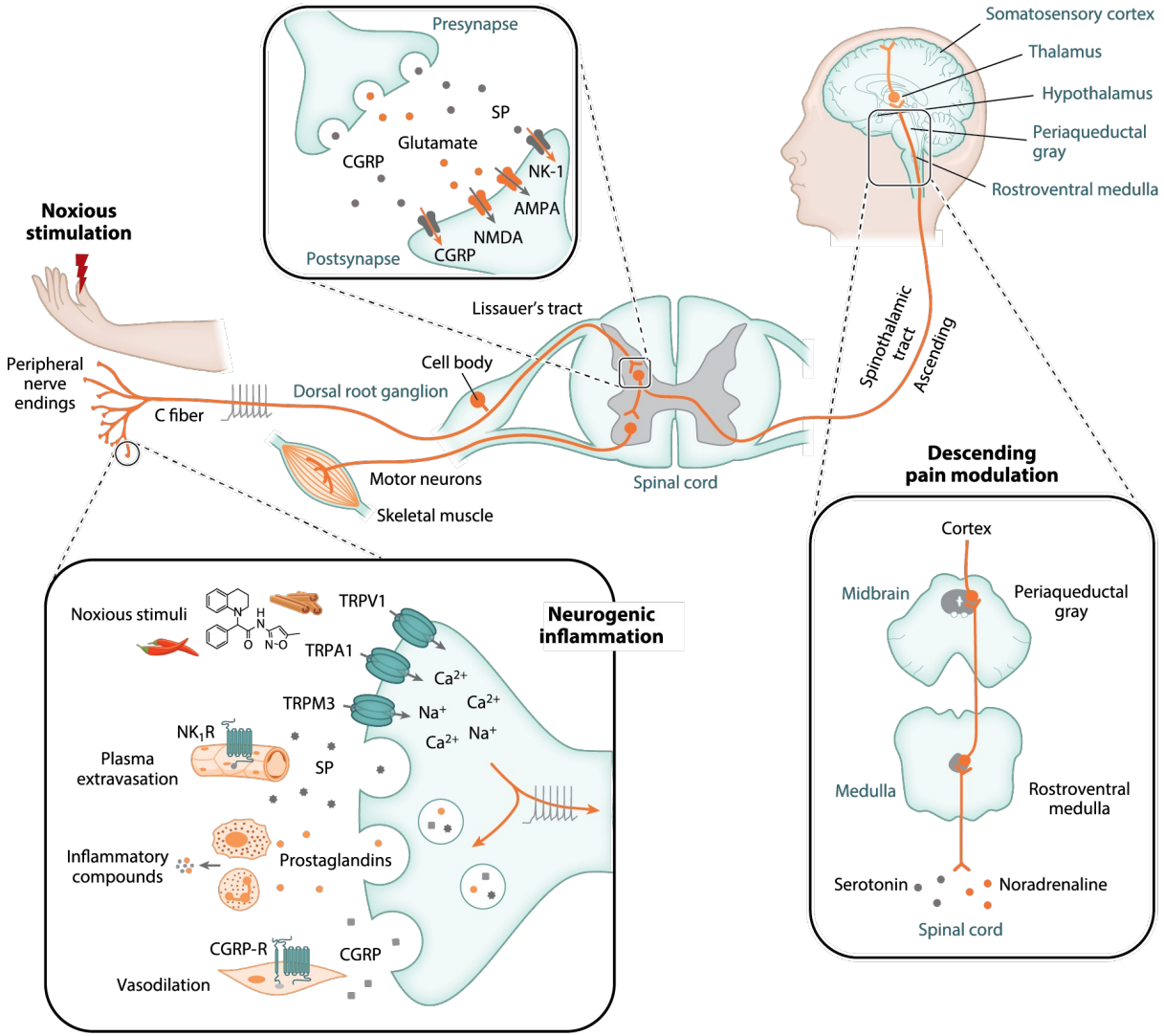
*Primidone in an inhibitor of TRPM3

CFA, Complete Freund's Adjuvant; **CIPN**, chemotherapy induced polyneuropathy; **CCI**, chronic constriction injury.

1. Vriens J, Nat Chem Biol. 2014 Mar;10(3):188-95; 2. Aloi VD et al, Pain. 2023 Sep 1;164(9):2060-2069 3. Su S et al, J Neurosci 2021; 41(11): 2457-74.

biohaven

TRPM3 Is a Key Player in Nociception and Neurogenic Inflammation



- Lack of TRPM3 protects against pathological pain and hypersensitivity in diverse rodent pain models
- TRPM3-deficient mice are healthy, fertile, and show no obvious abnormalities

TRPM3 antagonism is novel approach for treating pain

Adapted from Bamps D. et al, Annu Rev Pharmacol Toxicol. 2021 Jan 6;61:655-677.

BHV-2100 Is a Novel, Peripherally-Restricted TRPM3 Antagonist

In Vitro Findings

Parameter	Test	Value
TRPM3 electrophysiology	Patch clamp	8.8 nM IC_{50}
TRPM3 neuronal activity	hES-derived sensory neurons	3 nM IC_{50}
TRP selectivity	TRPA1/TRPV1/TRPM8; TRPM7	All > 10 μM IC_{50}
CV selectivity	NaV1.5; NaV1.7; CaV1.2; hERG	All > 10 μM IC_{50}
General selectivity	Eurofins	Clean in BioPrint™

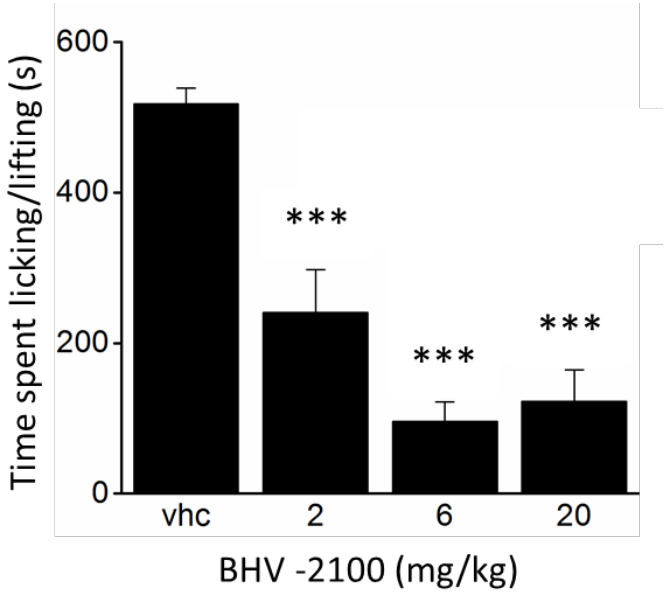
Pharmacokinetics and Toxicology Findings

Parameter	Test	Value
ADME	Clearance across species	Low/moderate
ADME	CYP450 inhibition	All isoforms > 10 μM
ADME	Oral bioavailability (mouse, rat, dog)	55–85%
Toxicology	IND-enabling toxicology studies	Wide safety margins, no genotoxicity

CV, conduction velocity; **hERG**, human ether-a-go-go-related gene; **hES**, human embryonic stem cells; **CYP450**, cytochrome P450.

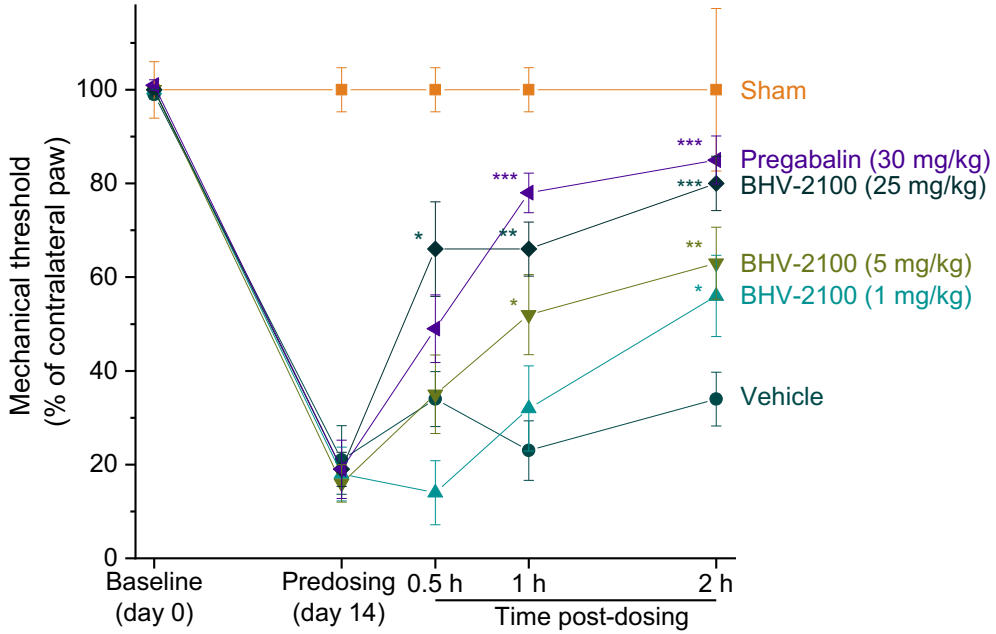
BHV-2100 Potently Reduces Pain Following Nerve Injury and Acute Chemogenic Pain

PS-Induced Acute Pain Model



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

Partial Sciatic Nerve Ligation Model



Drug administered 14 days after unilateral sciatic nerve injury in rats

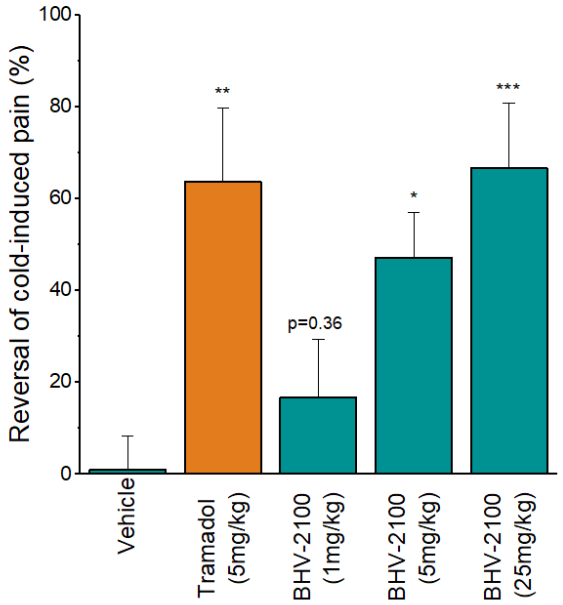
KEY POINT

Pain reduction without the sedation observed with high-dose pregabalin

PS, Pregnenolone Sulfate.
*** p<0.001, ** p<0.01 , * p<0.05

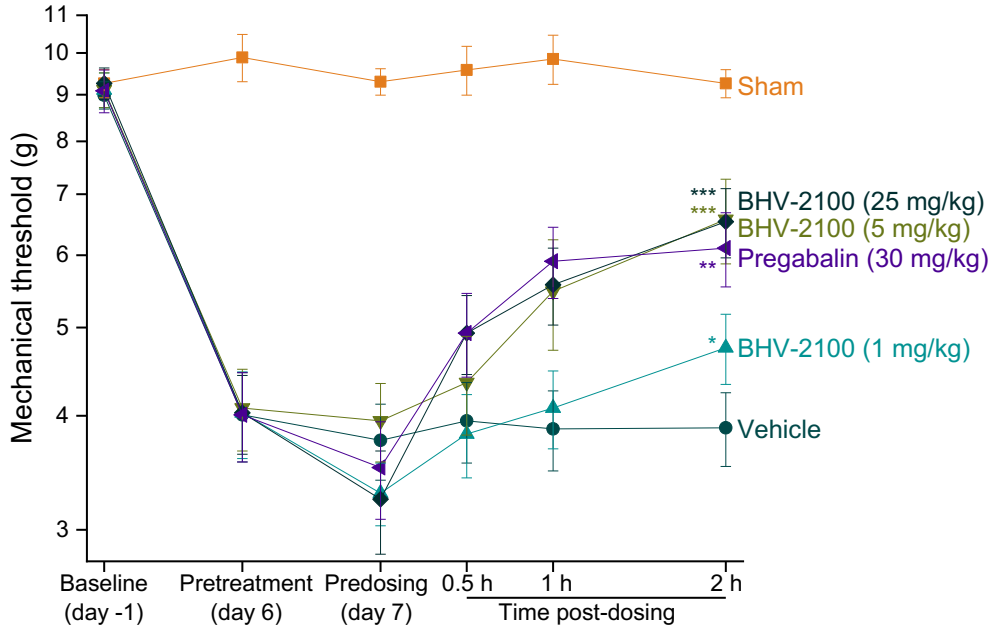
BHV-2100 Reverses Established Pain States in Peripheral Neuropathic Pain Models

Chemotherapy-Induced Neuropathic Pain Model



Drug administered 6 days after oxaliplatin treatment in mice

Diabetic Neuropathy Model



Drug administered 7 days after STZ treatment in rats

KEY POINT

Pain reduction without the sedation observed with high-dose pregabalin/tramadol

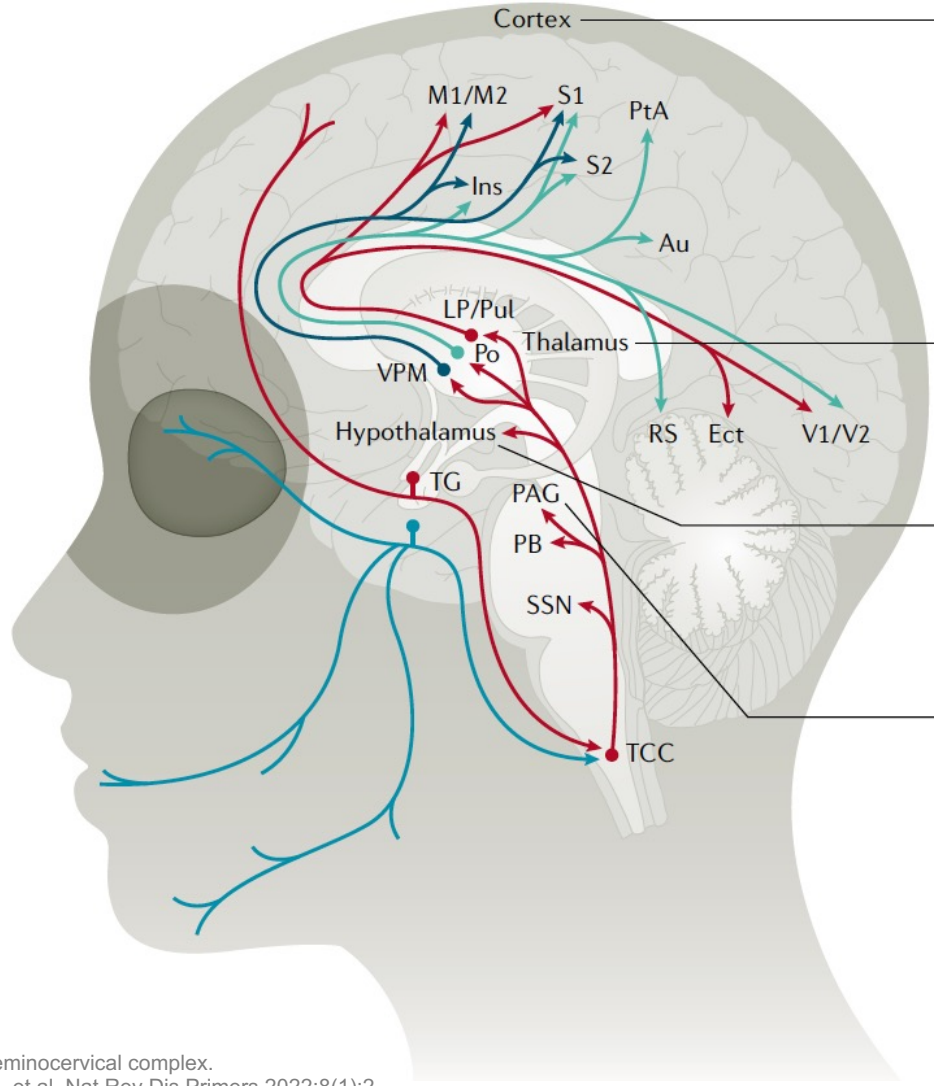
*** p<0.001, ** p<0.01 , * p<0.05

Compelling Rationale for TRPM3 Antagonism as a Treatment for Migraine

- **Strong mechanistic evidence supports the role of TRPM3 in neurogenic inflammation and sensitization of the trigeminovascular system, which underlie migraine pathogenesis[1]**
  - TRPM3 receptors sensitize and activate the nociceptors of the trigeminovascular system[2–4]
  - TRPM3 inhibition normalizes the sensitivity of nociceptors[3,4]
  - TRPM3 is a key driver of neurogenic inflammation in a CGRP-dependent and independent manner[5,6]
  - Inhibition of TRP receptors systemically or locally, decreases CGRP release, nociceptive neuron activity, and animal nocifensive behavior[7]
- **Human genetics validates role of TRPM3 in migraine and pain[8,9]**
  - TRPM3 gene variants are associated with migraine risk and pain sensitivity in humans
- **TRPM3 expression profile in the human trigeminovascular system indicates a functional role in migraine pathophysiology[10]**
  - TRPM3 is highly expressed in cells of the human trigeminal ganglia
  - TRPM3 is co-expressed with a network of other migraine-relevant genes in human trigeminal ganglia
- **Therapeutic effect of TRPM3 antagonism is supported by preliminary clinical data**
  - TRPM3 regulates the activity of other TRP channels (TRPV1 and TRPA1); and preliminary clinical data supports therapeutic benefit of inhibiting these TRP channels in migraine[5,11]

1. Ramachandran R. Semin Immunopathol 2018;40(3):301-314. 2. Vriens J et al, Neuron 2011;70(3):482-94. 3. Kelemen B et al, Biochemical pharmacology 2021;183:114310. 4. Krivoshein G et al, J Headache Pain 2022;23(1):. 5. Mulier, M., et al, Elife, 2020. 6. Bamps DAnnu Rev Pharmacol Toxicol. 2021 Jan 6;61:655-677. 7. Held, K., et al., Proc Natl Acad Sci U S A, 2015. 112(11): p. E1363-72.
8. Burglen L et al. Elife 2023. 9. Biohaven internal data. 10. Yang, L., et al., Neuron, 2022. 110(11): p. 1806-1821 e8. 11. Diamond, S., et al., Cephalalgia, 2000. 20(6): p. 597-602.

Migraine Pathophysiology: Anatomy of the Trigeminovascular Pathway



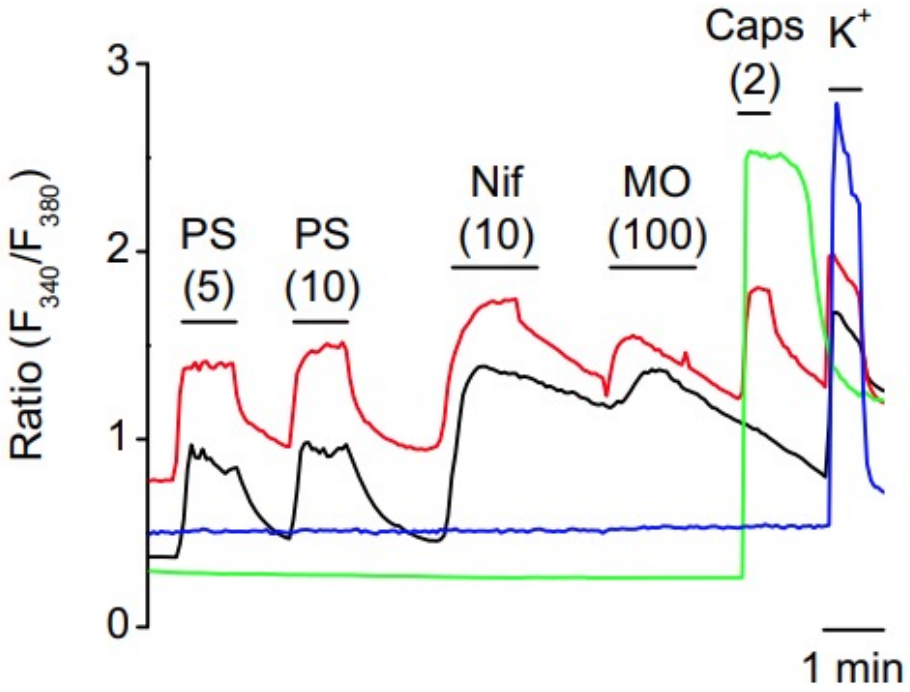
- Trigeminal Ganglion neurons extend to dura, pia, and large cerebral arteries
- The central projections of the TG neurons extend to the trigeminocervical complex
- TCC axons project to brainstem, hypothalamus, and thalamus leading to pain, as well as emotional, autonomic, behavioral changes in migraine

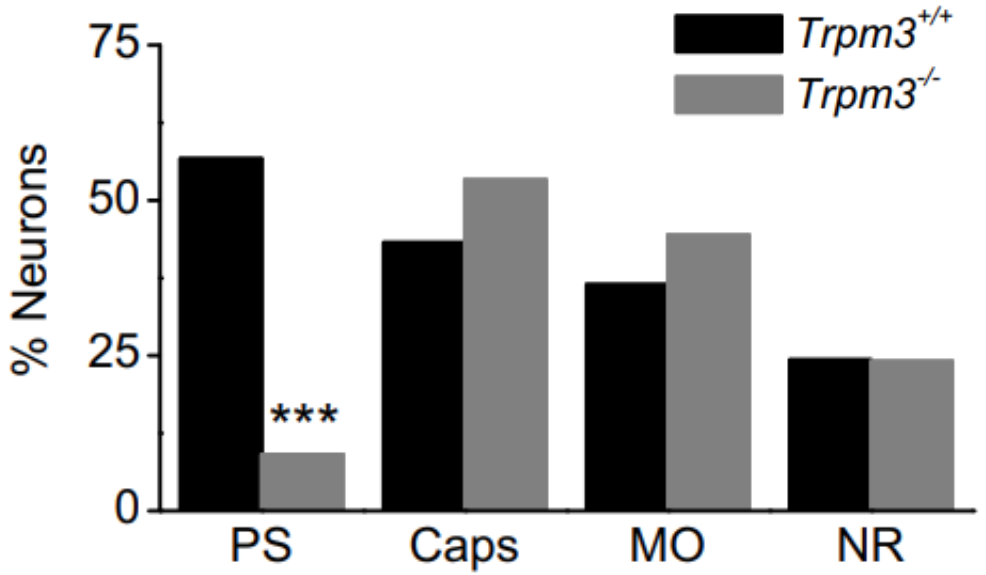
TCC, Trigeminocervical complex.
Ferrari MD, et al. Nat Rev Dis Primers 2022;8(1):2.

biohaven

TRPM3 Is Expressed and Active in Mouse Trigeminal Ganglion Neurons

TRPM3-Mediated Calcium Responses in the Majority of Mouse Trigeminal Ganglion Neurons

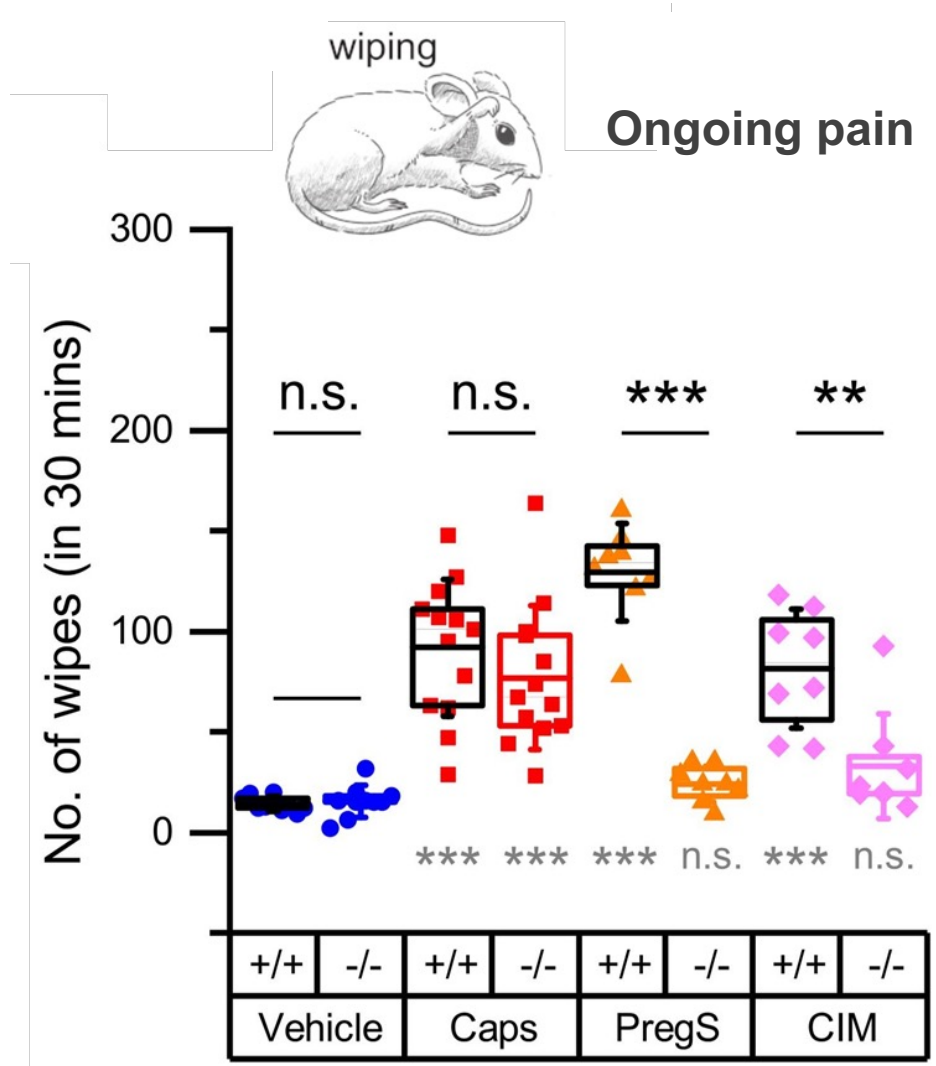




PS, pregnenolone sulfate; **Nif**, nifedipine; **Caps**, capsaicin; **MO**, mustard oil; **NR,** non-responsive to PS/Caps/MO.
Vriens J et al, Neuron. 2011 May 12;70(3):482-94.

TRPM3 Agonists Evoke Trigeminally-Mediated Pain in Mouse

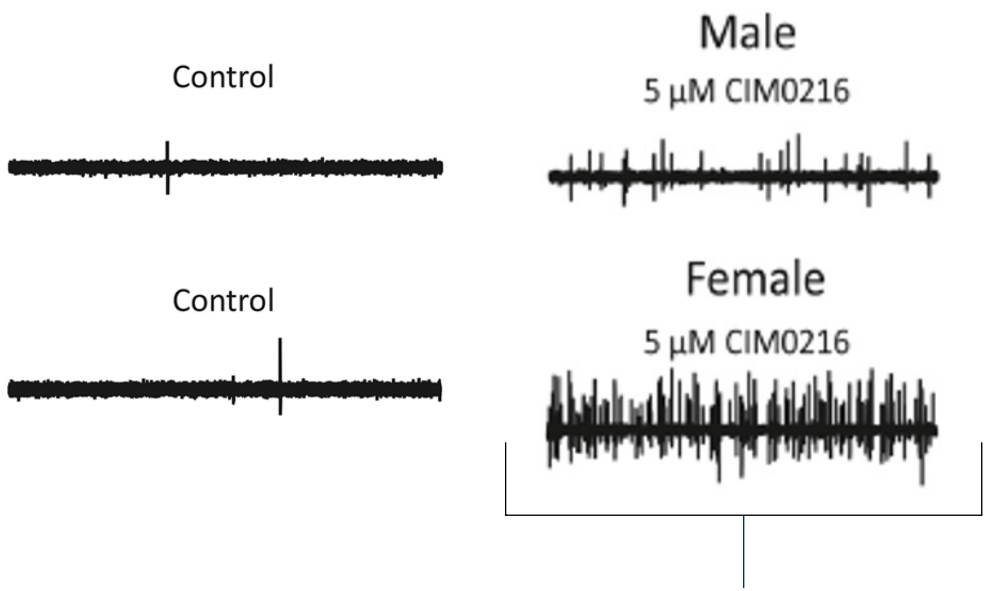
- Capsaicin (TRPV1 agonist), Pregnenolone sulfate (neurosteroid TRPM3 agonist) or CIM0216 (synthetic TRPM3 agonist) were injected into the cheek of wild-type and TRPM3$^{-/-}$ mice
- Capsaicin and TRPM3 agonists evoked ongoing pain lasting at least 30 minutes in wild type mice
- TRPM3 agonists did not evoke pain behavior in TRPM3$^{-/-}$ mice, demonstrating the TRPM3-specificity of the trigeminal pain



PregS, Pregnenolone Sulfate; **Caps,** Capsaicin; **CIM,** A Potent Synthetic Ligand of TRPM3. Kelemen B, et al. Biochem Pharmacol. 2021 Jan;183:114310.

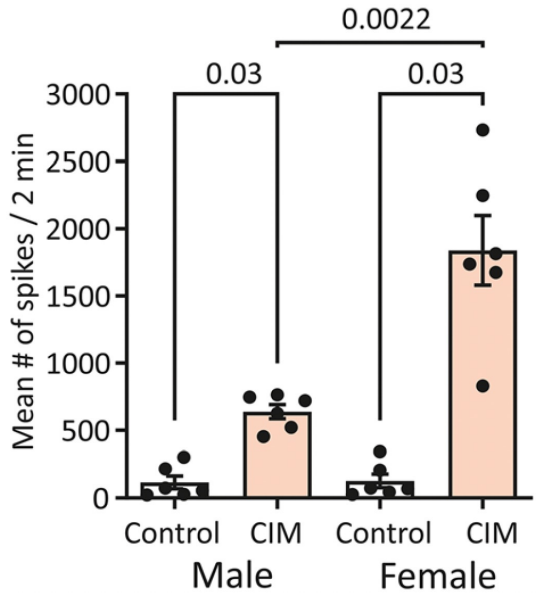
TRPM3 Receptors Are Functionally Active in Mouse Meningeal Afferents

Example Traces of Multi Unit Activity in TG Nerves of Male and Female Mice



Nociceptive spike activity in nerve terminals from meninges in hemiskull preparations dramatically increases in response to TRPM3 agonism

TRPM3 Functional Activity in Mouse Meninges



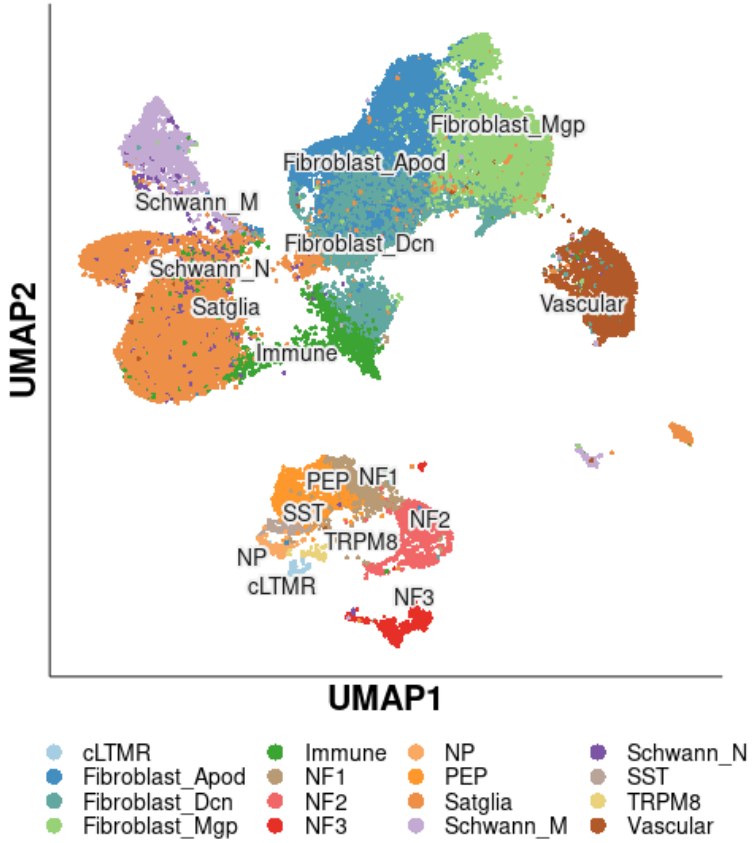
- TRPM3 receptors are functionally active in mouse meninges
- TRPM3 responsiveness in the meninges is even more pronounced in females

CIM0216, A Potent Synthetic Ligand of TRPM3; **TG,** Trigeminal Ganglion.
Krivoshein G, et al. J Headache Pain 2022;23(1):4.

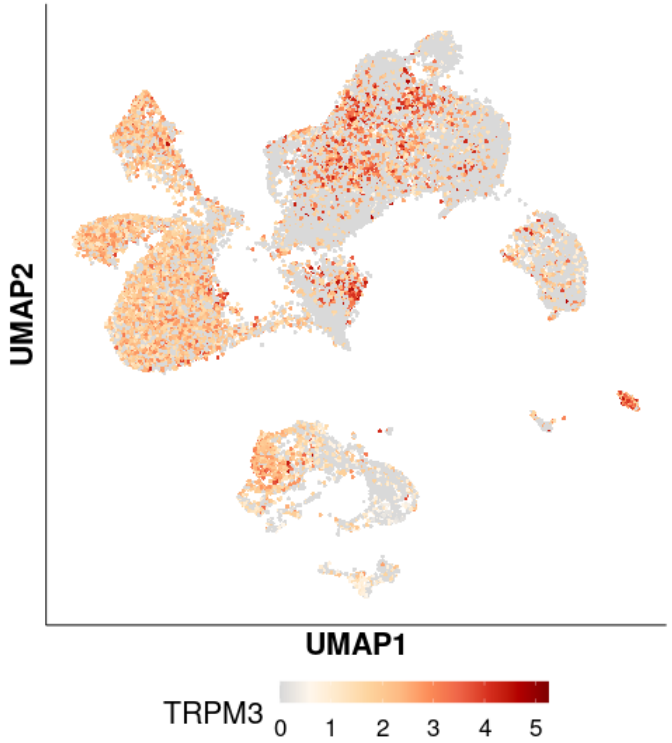
biohaven

TRPM3 Is Highly Expressed in Cells of the Human Trigeminal Ganglia

sn-RNA Sequencing Map Identifying TG Cell Types



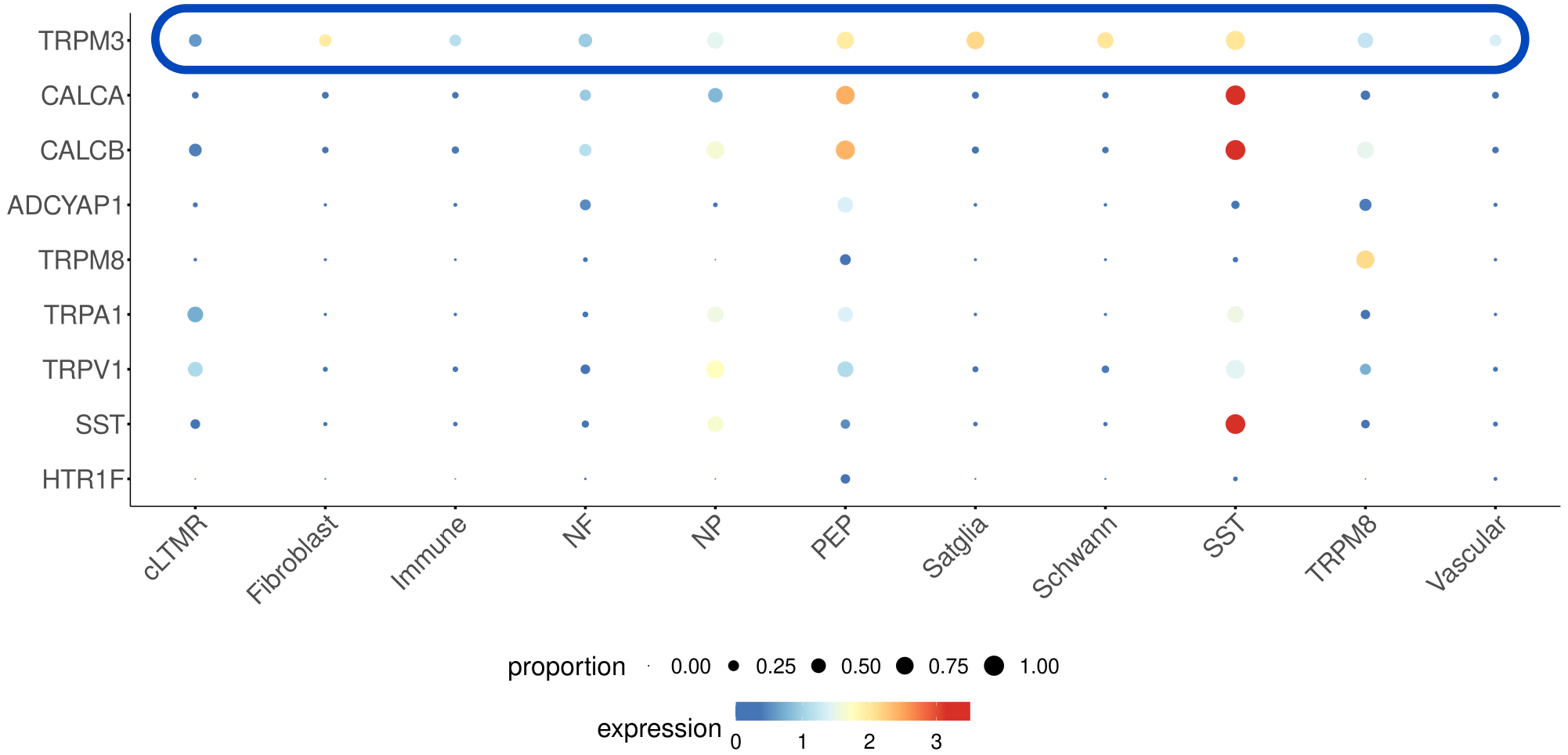
Heat Map of TRPM3 Expression in TG Cell Types



TG, trigeminal ganglion; **UMAP**, uniform manifold approximation and projection.
Derived from https://painseq.shinyapps.io/tg-painseq and Yang, L et al. Neuron 2022. 110(11): 1806-1821 e1808.

biohaven

TRPM3 Is Co-expressed with Other Migraine-Relevant Genes in Human Trigeminal Ganglia



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

biohaven

Richard Lipton, M.D.

Professor & Vice Chair, Neurology

Director, Headache Center

Montefiore | EINSTEIN
Albert Einstein College of Medicine

Unmet Need in Migraine and Potential Role of TRPM3 Antagonism

Overview

- The prevalence of migraine in the United States has remained stable over the past three decades[1]
- Migraine burden and disability remain high despite advances in treatment
- Need to make better use of existing and emerging treatments
- Persistent need for better treatments: TRPM3 is a promising target

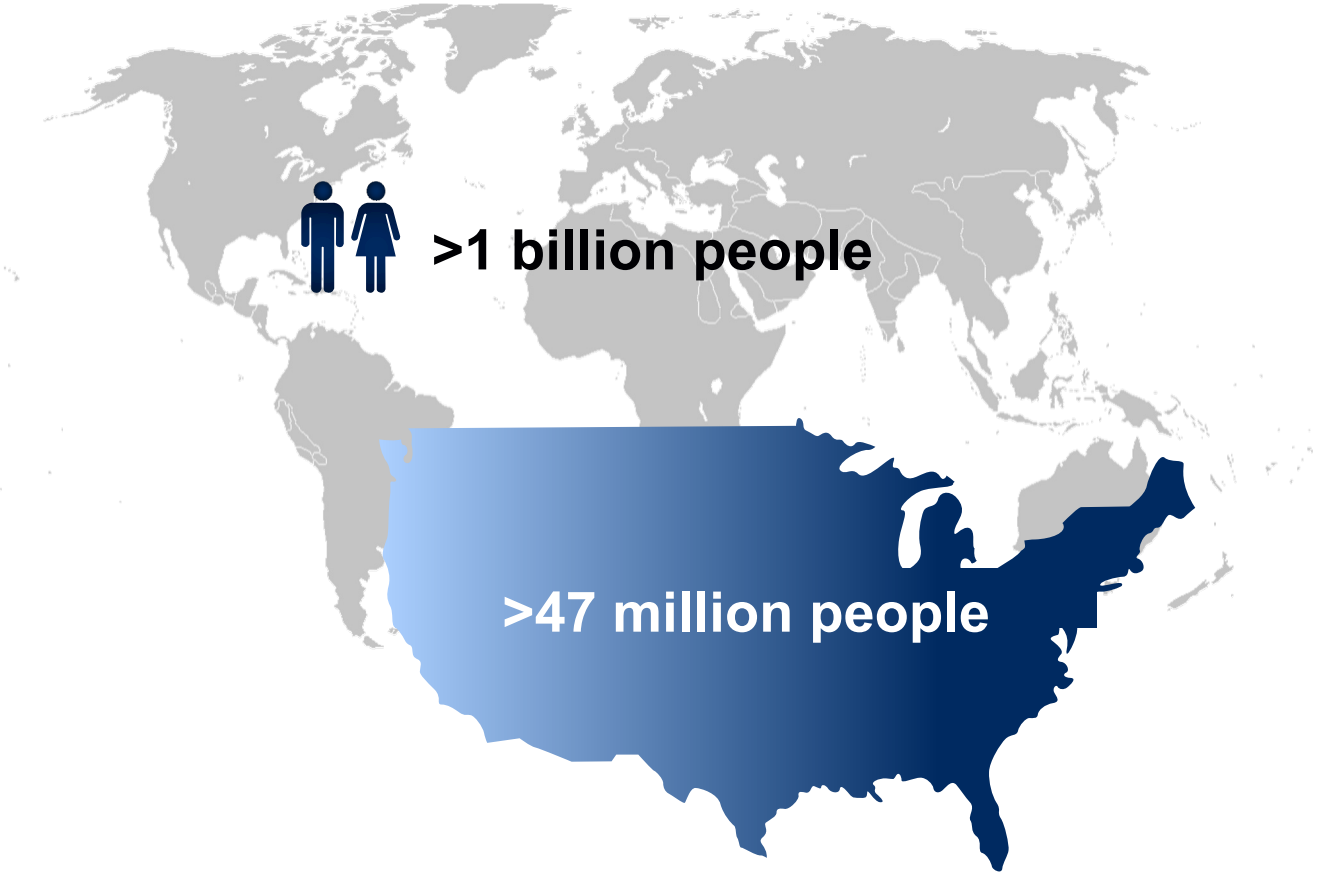
KEY POINT

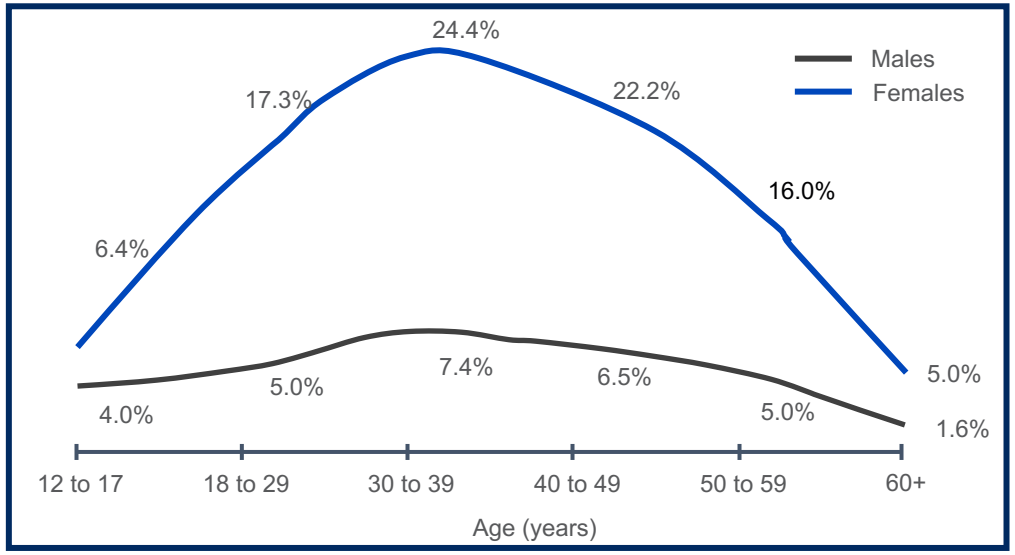
Further development of differentiated treatments with novel mechanisms of action is needed

1. Cohen F et al. Headache. 2024.

biohaven

Migraine is Highly Prevalent

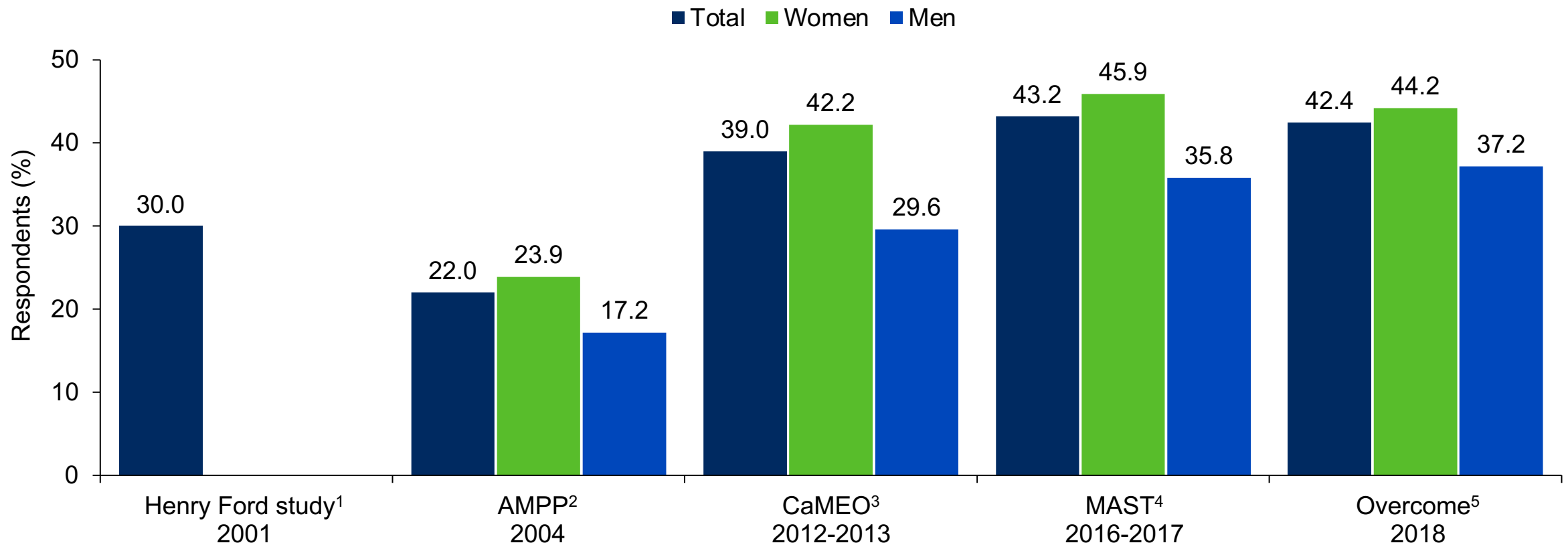




Of these, ~7% have chronic migraine

Lancet Neurol. 2018;17:954-976; Headache. 2016;56:1280-1289.

Migraine MIDAS Grade III-IV



CaMEO, MAST, and OVERCOME do not report prevalence data.

MIDAS, migraine disability assessment.

1. Neurology. 2004;63(8):1432-8; 2. Neurology. 2007;68(5):343-9; 3. Cephalalgia. 2019;39(2):296-305; 4. Headache. 2018;58(9):1408-1426; 5. Headache. 2022;62(2):122-140.

Significant Unmet Need Remains for Acute Treatment of Migraine

- **Goals of the acute treatment of patients with migraine (2021 AHS Consensus Position Statement)**[1]
  - Rapid and consistent freedom from pain and associated symptoms, especially the most bothersome symptom, without recurrence
  - Restored ability to function
  - Minimal need for repeat dosing or rescue medications
  - Optimal self-care and reduced subsequent use of resources (e.g., emergency room visits, diagnostic imaging, clinician and ambulatory infusion center visits)
  - Minimal or no adverse events
  - Cost considerations
  - Effective acute treatment can reduce the pain, associated symptoms, and disability associated with attacks. Suboptimal acute treatment is associated with higher migraine-related disability and risk of disease progression[1]

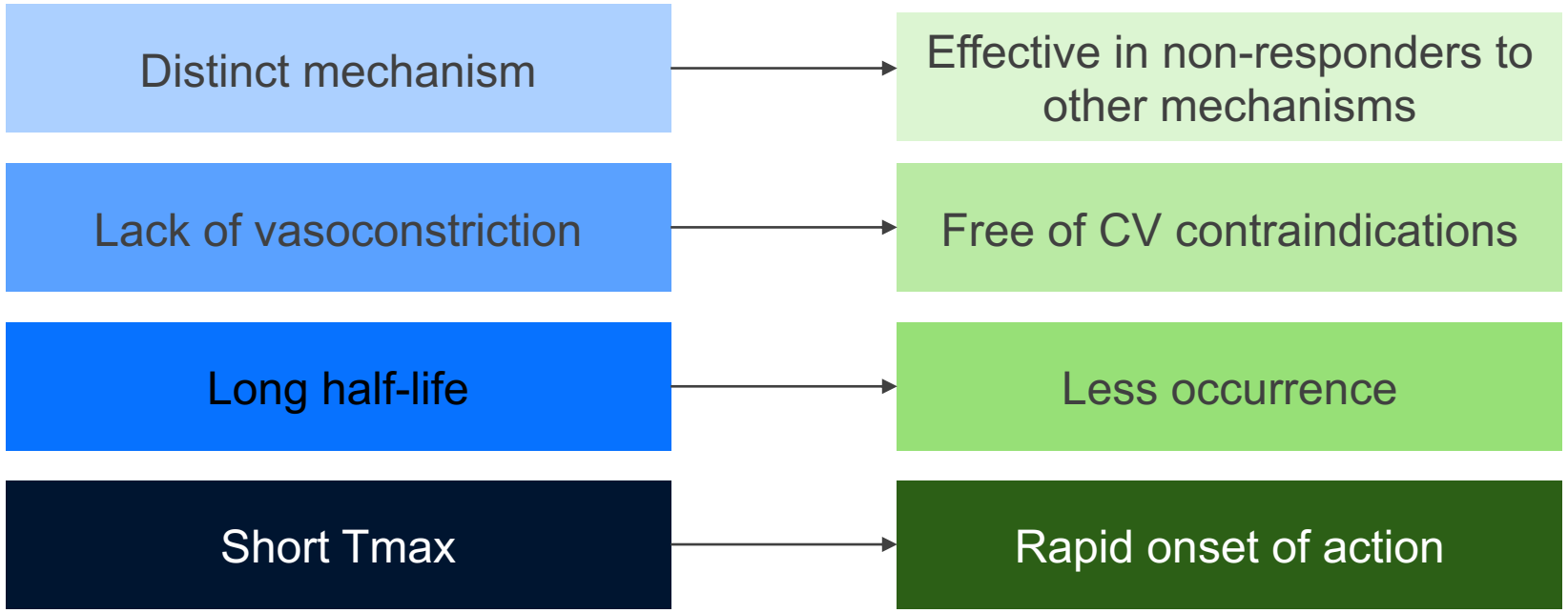
- **Current approach for acute treatment of migraine**[2]
  - There is no one-size-fits-all treatment
  - Multiple treatment trials are sometimes necessary to determine the optimal regimen
  - Switching within and between classes, using the maximum allowed dose, and using combination therapy may be needed

1. American Headache Society. Headache. 2021; 2. Burch R. Continuum. 2024

biohaven

TRPM3 Targeted Small Molecule Receptor Antagonist for Acute Treatment of Migraine

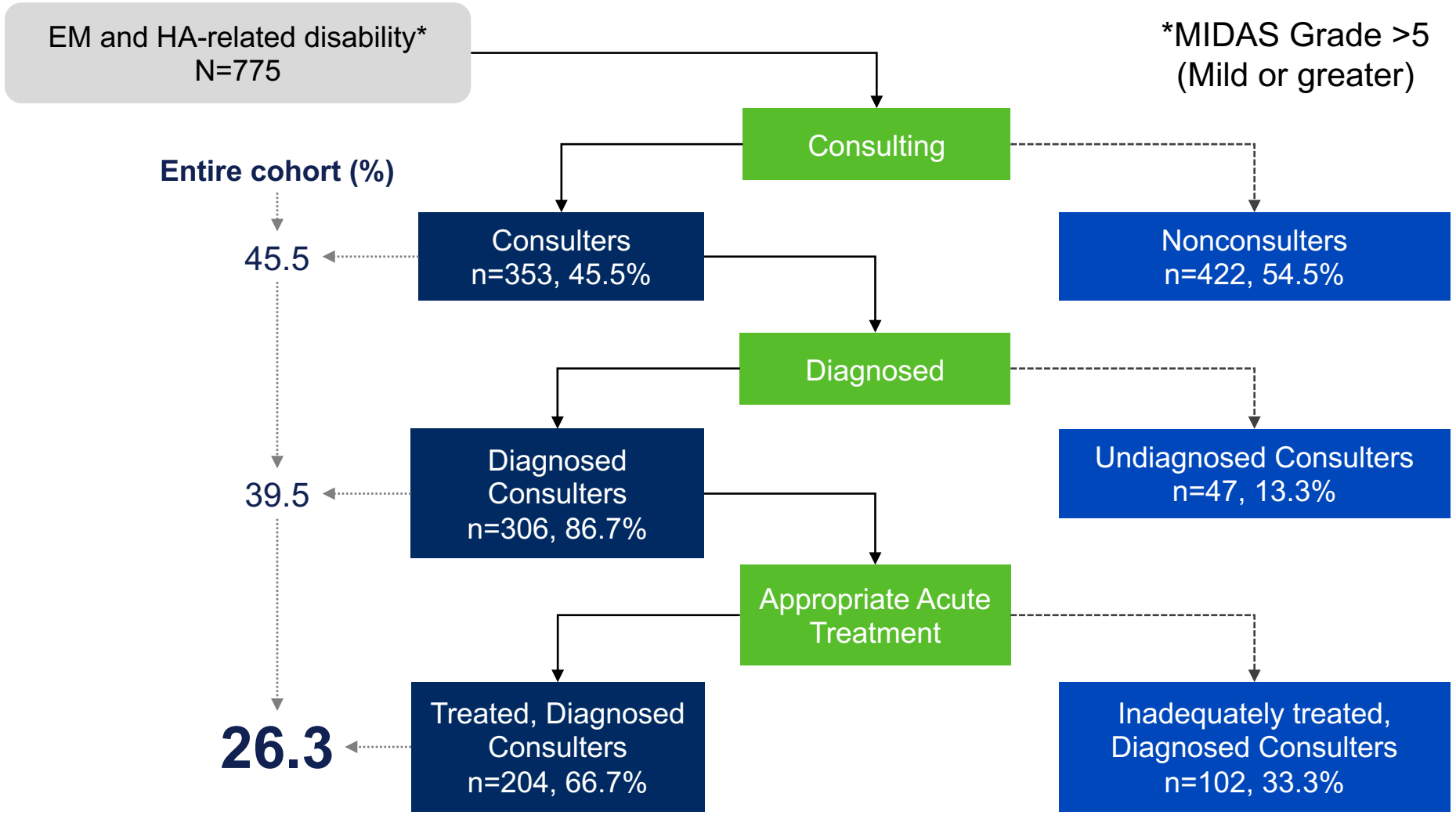
Mechanism-based treatment targeting



Opportunities for Novel Treatment Strategies

biohaven

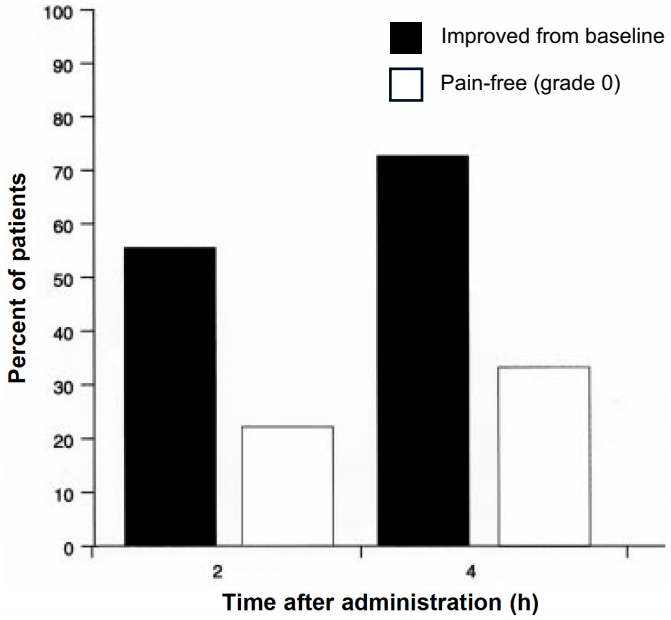
Assessing Barriers to Care in Episodic Migraine (CaMEO)



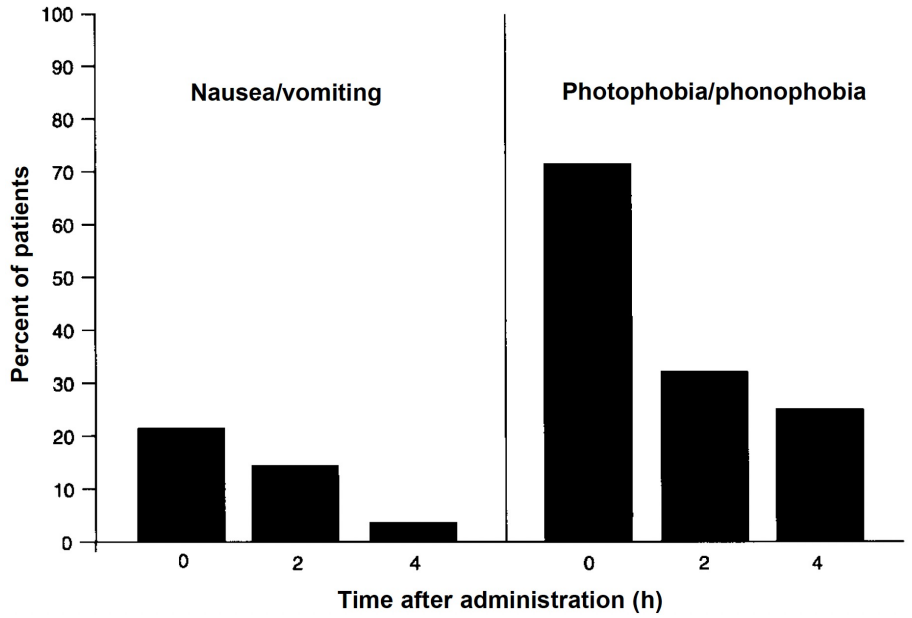
Headache. 2013;53:81–92.

Silencing TRP Channel + Nociceptors Is Efficacious in Migraine

Improvement in Headache Pain Severity



Reporting Nausea/Vomiting and Photophobia/Phonophobia



Civamide (TRPV1 Modulator)

- Intranasal civamide decreases release of inflammatory neurotransmitters by the trigeminal plexus to meninges and dural blood vessels

- **Clinical Trial**
- 34 patient double-blind trial of intranasal civamide
- 2h post dose:
  - 55.6% had decrease in pain
  - 22.2% were pain-free
- 4h post dose:
  - 72.7% had decrease in pain
  - 33% were pain-free

KEY POINT

TRPM3 is key TRP channel and modulates TRPV1 in sensory neurons innervating inflamed tissue

Diamond S, et al. Intranasal civamide for the acute treatment of migraine headache. Cephalalgia. 2000 Jul;20(6):597-602.

Summary

- The prevalence of migraine in the United States has remained stable over the past three decades[1]
- Migraine burden and disability remain high despite advances in treatment
- Need to make better use of existing and emerging treatments
- Persistent need for better treatments-TRPM3 is a promising target

KEY POINT

Further development of differentiated treatments with novel mechanisms of action is needed

1. Cohen F et al. Headache. 2024

biohaven

Volkan Granit, M.D., MSc

Medical Director, Clinical Development

biohaven®

BHV-2100 for the Treatment of Migraine and Pain

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 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 2nd leading cause of disability worldwide, 1st 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]

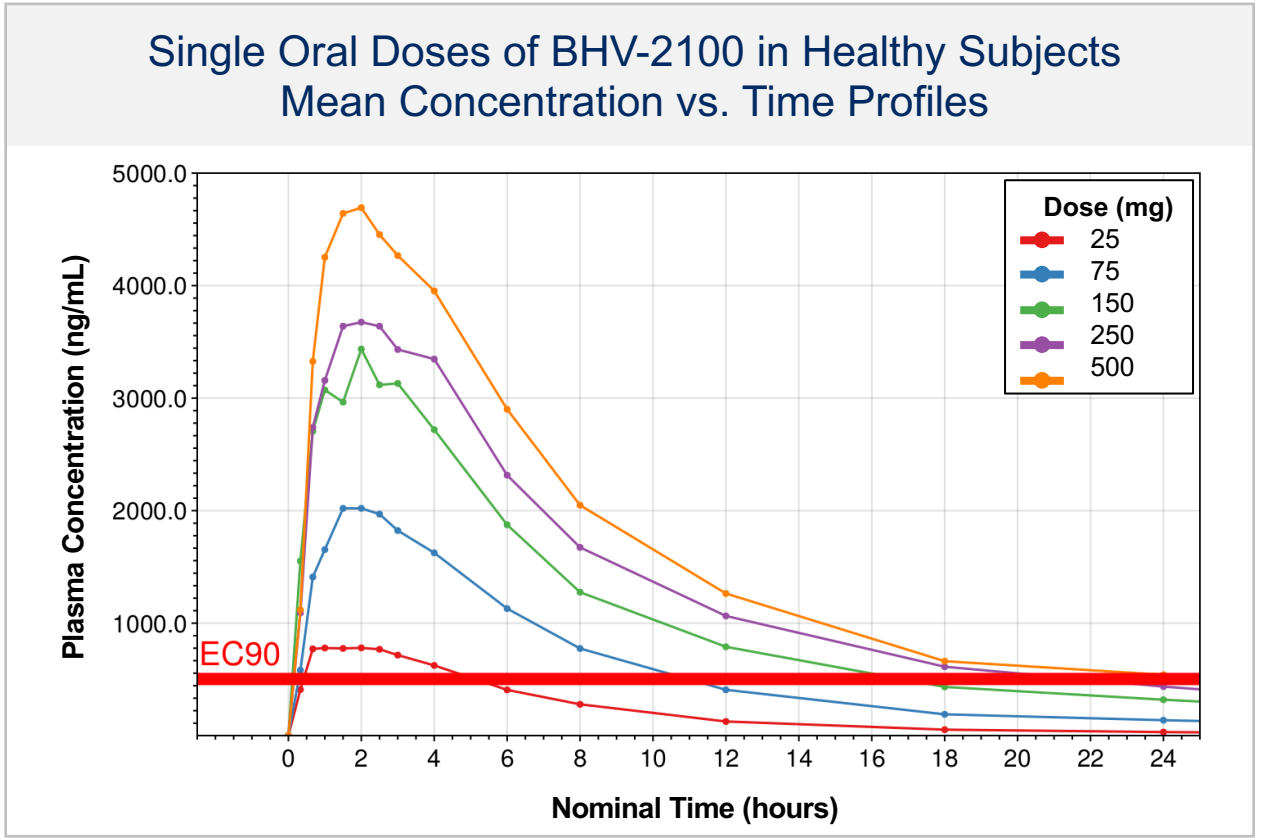
Upcoming Milestones

- Initiate Phase 2 trial for acute treatment of migraine in 2H 2024
- Initiate laser-evoked potential proof-of-concept trial for pain in 2H 2024

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.

biohaven

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



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.

biohaven

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

SAFETY AND TOLERABILITY

- No dose limiting toxicities
- No SAEs
- No severe TEAEs; 1 moderate TEAE not related to study drug; all other TEAEs mild
- No clinically significant trends in vital signs (including body temperature), laboratory values, or ECGs

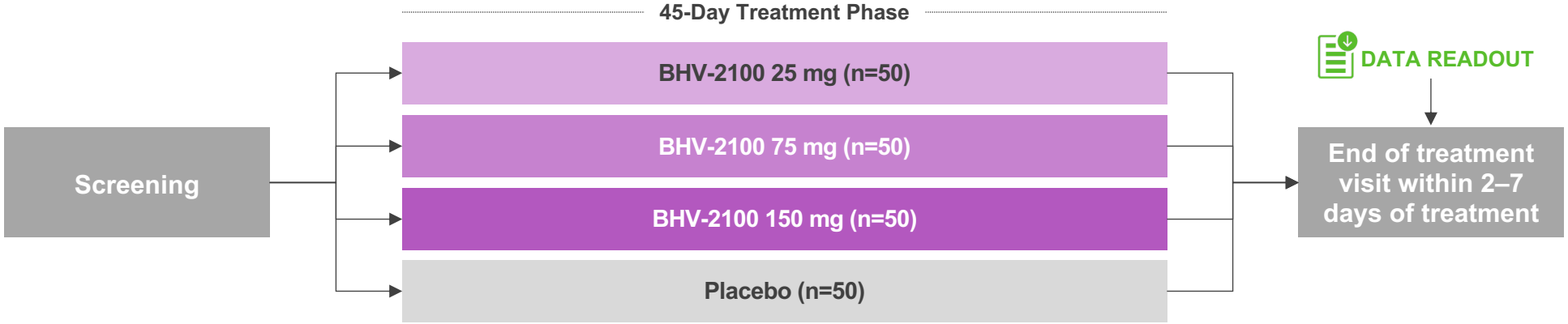
DOSING

- SAD single doses up to 500 mg completed
- MAD is completed

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

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

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	200 (randomized 1:1:1:1 across 3 doses and placebo)
TREATMENT	BHV-2100 (dose-ranging [25/75/150 mg]) vs. placebo
TREATMENT DURATION	Single dose, up to 45 days to treat eligible migraine
ENDPOINTS	Pain relief, Freedom from most bothersome symptom

KEY POINT

All doses exceed EC90 by 20 minutes and are well tolerated

Preliminary study design.

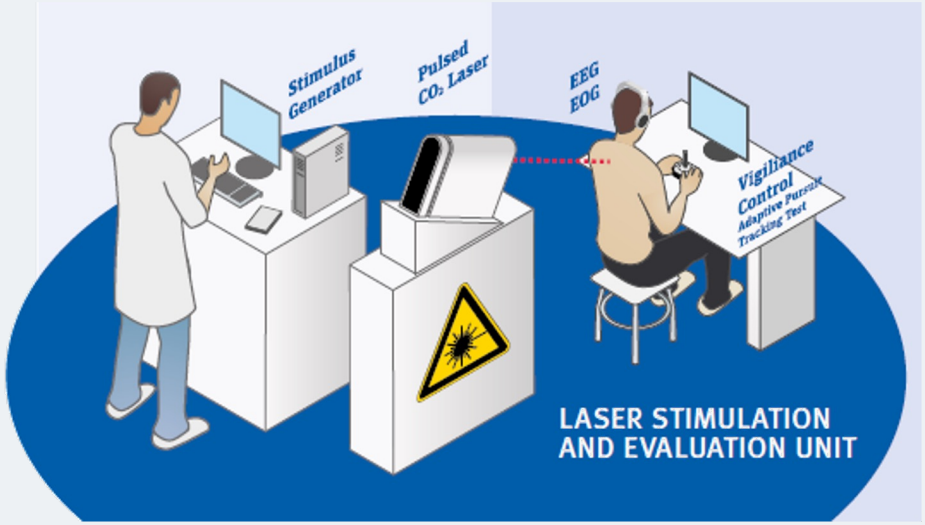
BHV-2100: Innovative Study to Generate Objective POC Data for Pain

Laser-Evoked Potential Experimental Pain Paradigm

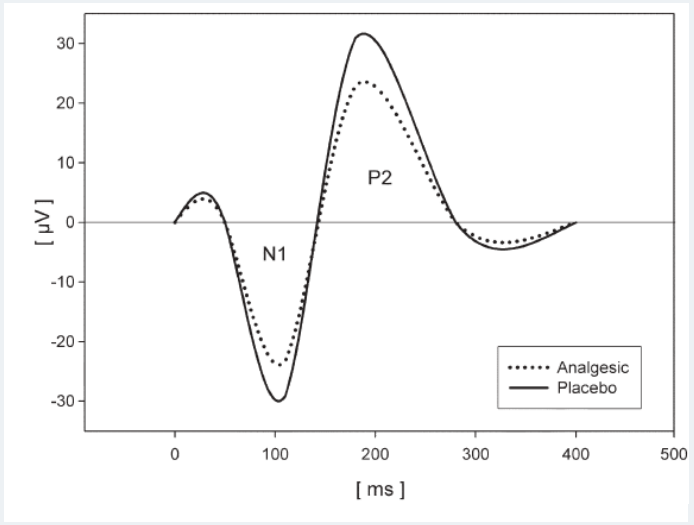
- Employs a reproducible pain stimulus (with negligible habituation)
- Allows reliable quantitative measurements of nociceptive processing
- Provides objective profile of anti-nociceptive effects including dose-response

Advantages

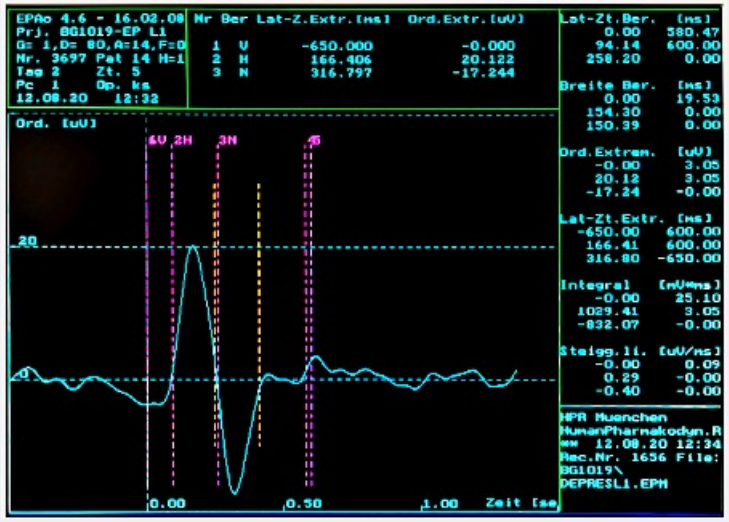
- Provides early prediction of efficacy
- Enables smaller, faster, less expensive Phase 3 programs for pain indications



https://hpr-cro.com/approach/.



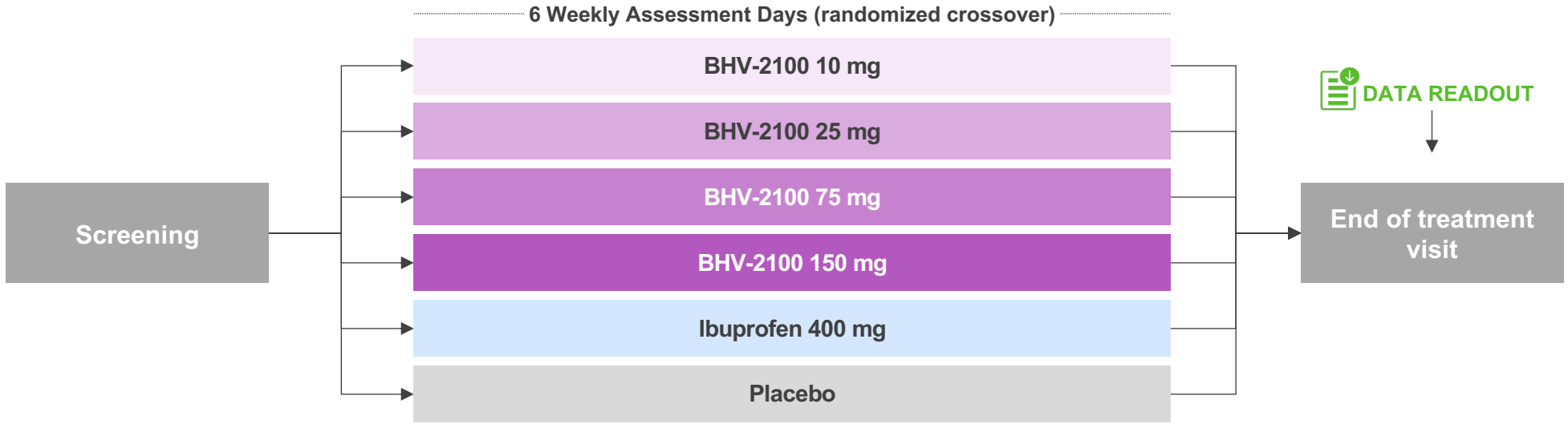
Schaffler, K., et al. British Journal of Clinical Pharmacology, 2017. 83(7): p. 1424-1435.



https://hpr-cro.com/approach/.

biohaven

BHV-2100: Laser-Evoked Potentials PoC Study in Pain



DESIGN	6-way crossover, randomized, double-blind, placebo- and active comparator-controlled trial
POPULATION	Healthy male volunteers
SAMPLE SIZE	24 participants
TREATMENT	BHV-2100 (4 dose levels), ibuprofen 400 mg (active control), placebo
PARADIGM	Assessment of antihyperalgesic and antinociceptive properties of BHV-2100 using Ultraviolet B-induced skin inflammation
ENDPOINTS	Laser-induced evoked potentials, subjective pain, heat pain threshold, erythema index, mechanical pain threshold, PK/PD, safety

KEY POINT

Enables smaller, faster, less expensive Phase 3 programs for pain indications

Preliminary study design.

Panel Discussion

MODERATOR

Tyler Van Buren

Equity Research Analyst

TD Cowen

PANELISTS

Michael Bozik, M.D.
President, Ion Channel Research and Development, Biohaven

Steven Dworetzky, Ph.D.
Senior Vice President, Kv7 Strategy and Development, Biohaven

Volkan Granit, M.D., MSc
Medical Director, Clinical Development, Biohaven

John H. Krystal, M.D.
Robert L. McNeil, Jr., Professor of Translational Research; Chair, Department of Psychiatry, Yale University School of Medicine
Chief of Psychiatry, Yale-New Haven Hospital

Richard B. Lipton, M.D.
Professor and Vice Chair of Neurology , Albert Einstein College of Medicine

Michael Rogawski, M.D., Ph.D.
Distinguished Professor of Neurology and Pharmacology, School of Medicine, University of California, Davis

Professor Thomas Voets
Laboratory of Ion Channel Research
VIB Center for Brain and Disease Research, KU Leuven, Department of Cellular and Molecular Medicine

BHVN
LISTED
NYSE

Irfan Qureshi, M.D.

Chief Medical Officer

biohaven®

Glutamate Platform

biohaven®

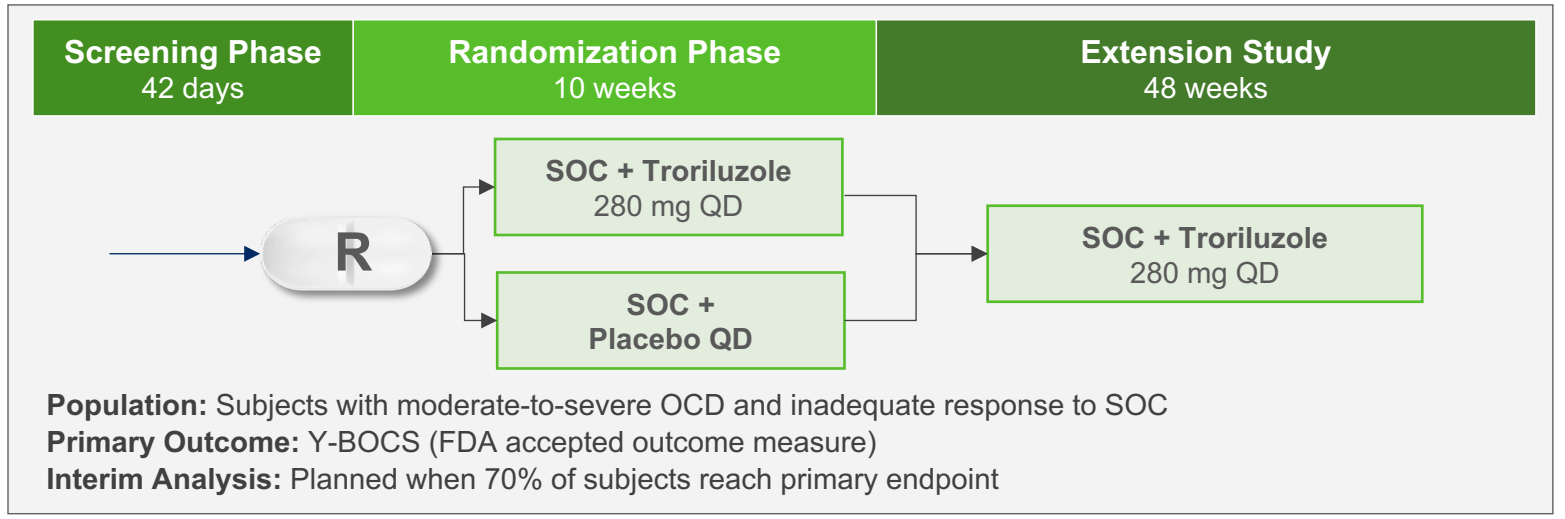
TRORILUZOLE
OCD

BREAKING NEWS

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

- **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.

biohaven

TRORILUZOLE
SCA

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

Efficacy and Safety of Troriluzole in SCA
The totality of efficacy and safety data from Studies BHV4157-206 and BHV4157-201 3-year open-label extension phase demonstrates therapeutic benefit and disease stabilization for troriluzole in SCA
- 2 randomized clinical studies in SCA were conducted over 7 years, representing the largest, multicenter, placebo-controlled dataset for SCA (n = 358)
- Confirmatory evidence of efficacy provided by data from the 3-year, long-term open-label extension phase of two studies (BHV4157-206 and BHV4157-201) using a Matching Adjusted Indirect Comparison to an external control group

Regulatory Status
- FDA: Constructive dialogue ongoing regarding SCA development program and potential future data analyses to address regulatory concerns
- EMA: Marketing Authorization Application is under review

biohaven

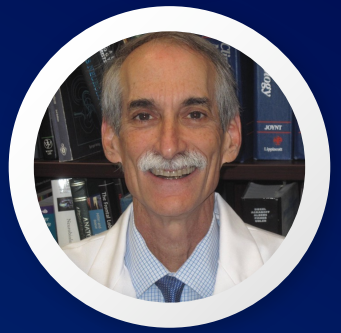
Nick Kozauer, M.D.
Senior Vice President, Clinical Development & Regulatory Strategy, Biohaven

Cynthia Lemere, Ph.D.
Professor of Neurology, Brigham & Women's Hospital, Harvard Medical School

Lindsey Lair, M.D., MBA, F.A.A.N.
Vice President, Clinical Development, Biohaven

Peter Ackerman, M.D.
Vice President, Clinical Development, Biohaven

Mark Albers, M.D., Ph.D.
Assistant Professor of Neurology, Massachusetts General Hospital, Harvard Medical School



Stephen Salloway, M.D., MS
Professor, Psychiatry and Human Behavior, Professor of Neurology, Alpert Medical School of Brown University
Associate Director, Brown Center for Alzheimer's Research

Neuroinflammation Platform

biohaven®

Nick Kozauer, M.D.

Senior Vice President, Clinical Development & Regulatory Strategy

biohaven®

BHV-8000

biohaven®

BHV-8000

TYK2/JAK1 INHIBITOR (brain-penetrant)

BREAKING NEWS

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

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 Preliminary Results from Ongoing Phase 1 Trial

- Completed dosing of 3 cohorts in both SAD and MAD
- Safe and well-tolerated to date
- Preliminary data indicative of target engagement

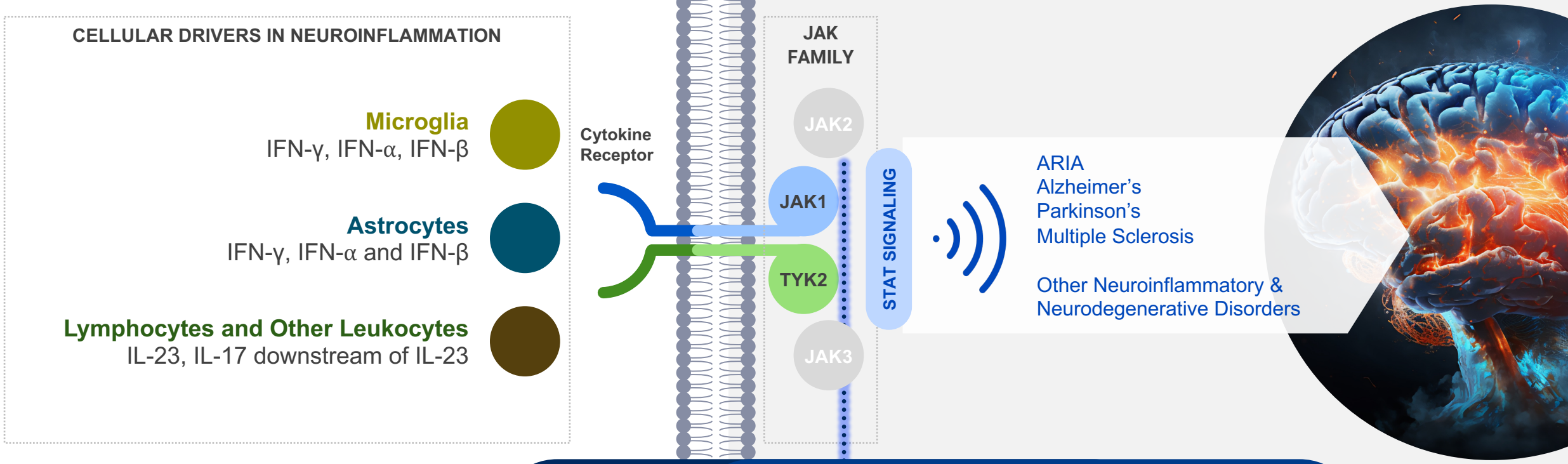
ARIA, Amyloid-related imaging abnormalities; **SAD**, single ascending dose; **MAD**, multiple ascending dose; **TYK**, tyrosine kinase; **JAK**, Janus kinase.

biohaven

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

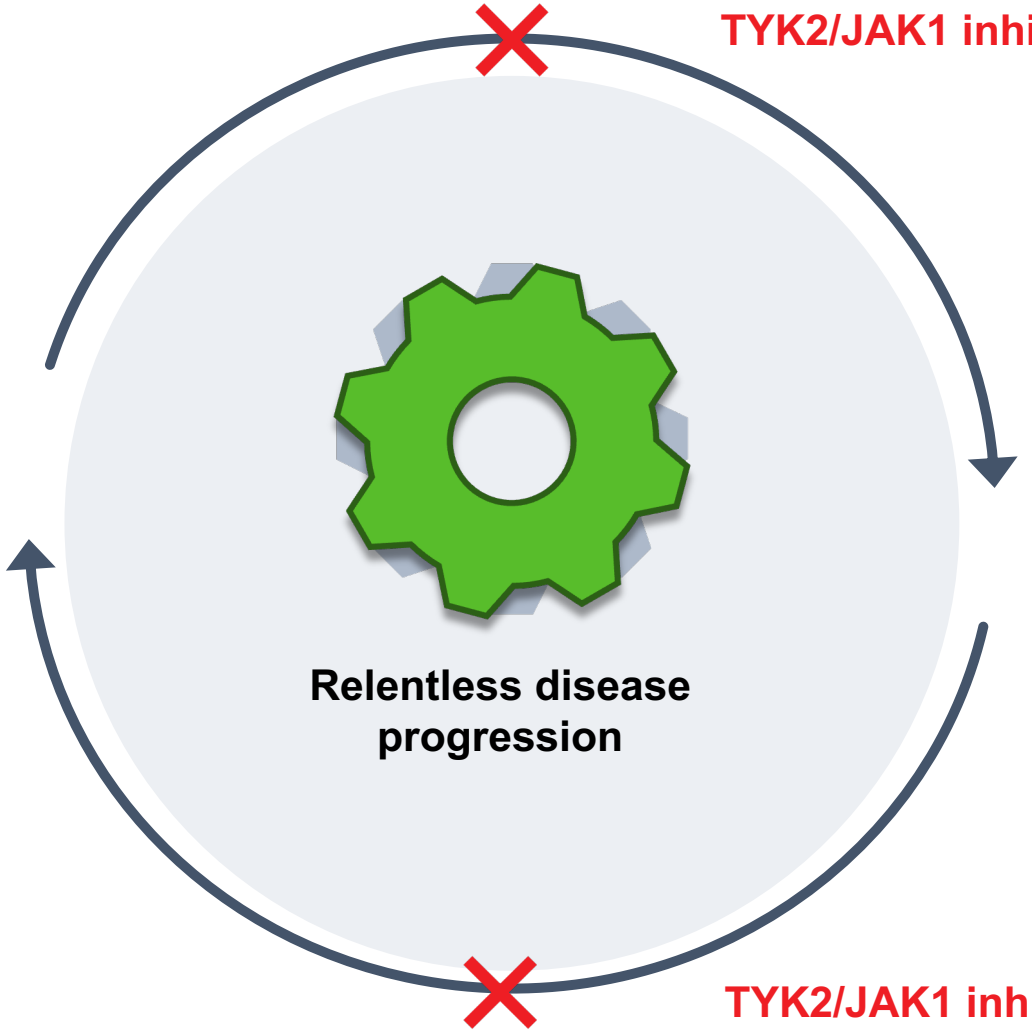


BHV-8000 Dual, brain-penetrant inhibitor of TYK2 and JAK1 that effectively blocks Th17 cell generation, Type I IFN signaling, and inflammation

biohaven

Central TYK2/JAK1 Modulation Breaks Inexorable Neuroinflammatory-Neurodegenerative Cycle

Genetic and environmental factors induce neuronal loss and CNS inflammation



Self-perpetuating inflammation drives further neurodegeneration and inflammation

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

Selectivity of BHV-8000 Predicts Improved Safety With Targeted Efficacy

Approved JAK Inhibitors — Significant Safety Risks Associated with JAK2 and/or JAK3 Inhibition						
		IC_{50} in nM				
Inhibitor	Status	JAK1 (autoimmune)	JAK2 (hematology)	JAK3 (leucocyte)	TYK2 (inflammation)	Safety
Tofacitinib[1]	Approved	15	77	55	489	Boxed Warning (MACE, malignancy, thrombosis, serious infections)
Baricitinib[1]	Approved	4	7	787	61	Boxed Warning
Upadacitinib[1]	Approved	47	120	2304	4690	Boxed Warning
Abrocitinib[1] (selective JAK1)	Approved	29	803	>15,000	1250	Boxed Warning* (*Development program suggests no increased clinical risk for these events)
Deucravacitinib[1] (selective TYK2)	Approved	>10,000	>10,000	>10,000	0.2	NO Boxed Warning

BHV-8000 Expected to Have a Favorable Safety Profile (avoids JAK2 and JAK3 inhibition)						
		IC_{50} in nM				
Inhibitor	Status	JAK1 (autoimmune)	JAK2 (hematology)	JAK3 (leucocyte)	TYK2 (inflammation)	Safety
BHV-8000	Phase 2 ready	4	118	>500	4	No expected risk of JAK2 and JAK3-related safety issues

IC_{50}, half maximal inhibitory concentration; **JAK**, Janus kinase; **MACE**, major adverse cardiac event; **TYK**, tyrosine kinase.

1. Wrobleski et al. *J Med Chem*. 2019;62(20):8973-8995.

biohaven

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:

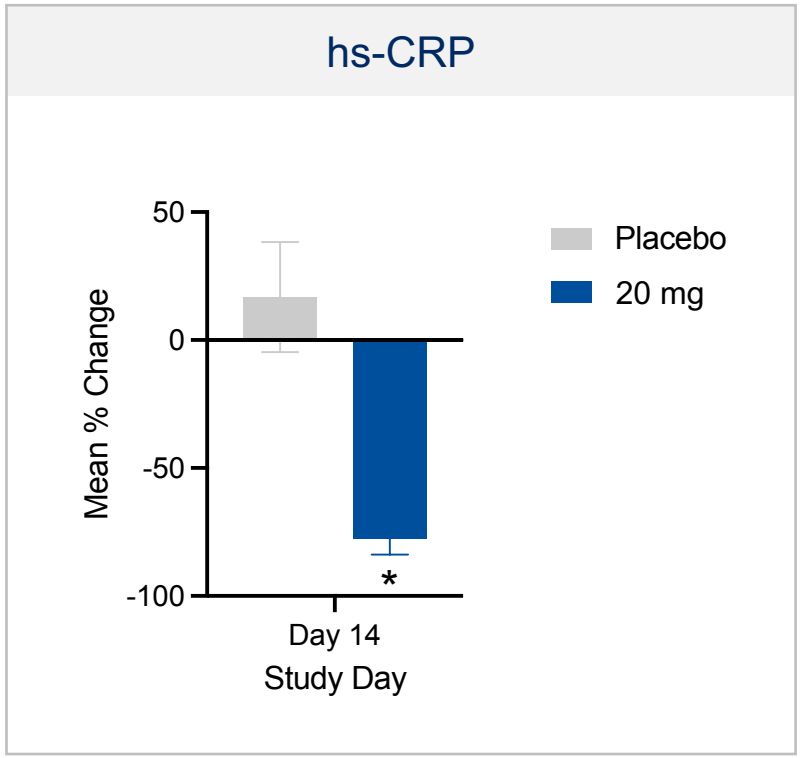
- hs-CRP and IFN-beta showed drug-related changes

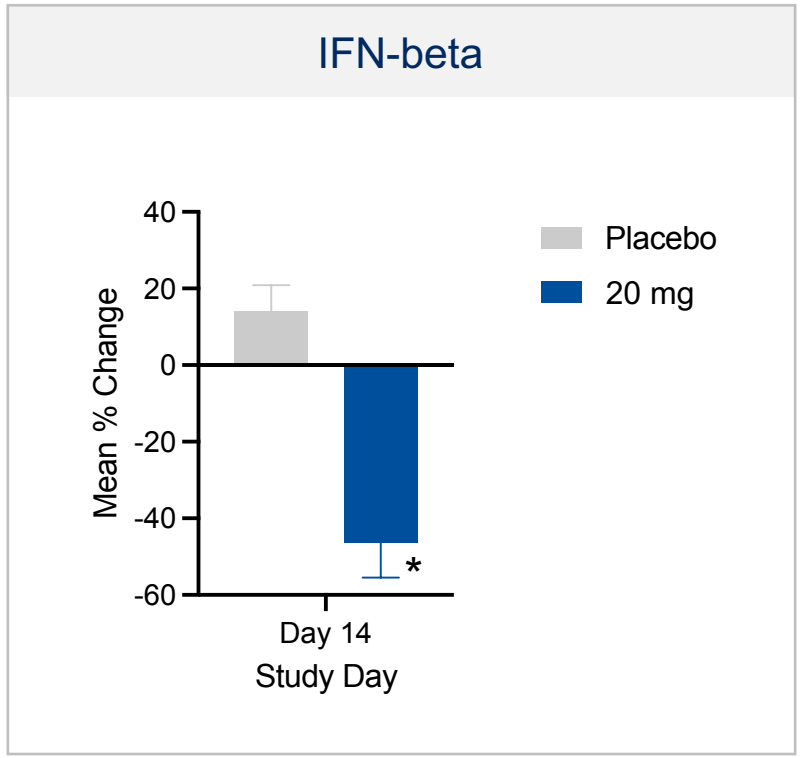
KEY POINT

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.

BHV-8000 Shows Evidence of Pharmacodynamic Effects





* p<0.05

KEY POINT

Pharmacodynamic data is indicative of target engagement in healthy subjects

Preliminary Phase 1 data. **hs-CRP**, high-sensitivity C-reactive protein; **IFN-beta**, Interferon beta.

Cynthia Lemere, Ph.D.

Professor of Neurology

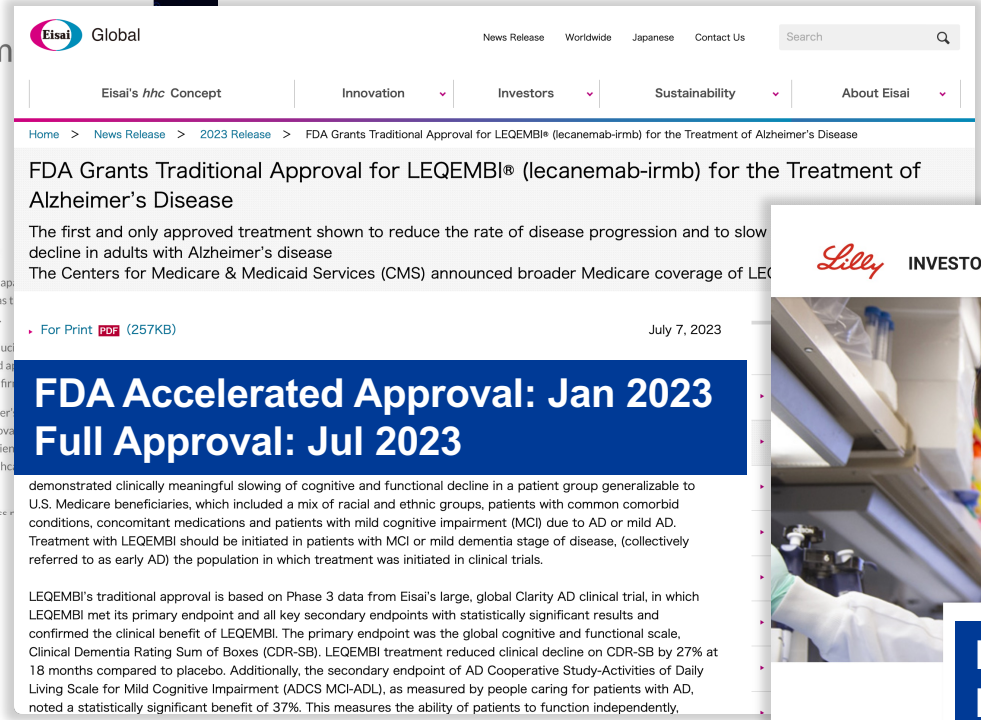
BRIGHAM AND WOMEN'S HOSPITAL

Vascular Side Effects of Anti-Amyloid Immunotherapy

HARVARD MEDICAL SCHOOL

BRIGHAM AND WOMEN'S HOSPITAL

Anti-Amyloid Immunotherapies: First DMTs for AD



DMT, disease modifying therapy.

What is ARIA?

- ARIA is a spectrum of MRI imaging abnormalities (i.e., vasogenic edema [ARIA-E] and microhemorrhage [ARIA-H])[1]
- ARIA can occur as part of the natural history of AD or with amyloid-modifying therapies[1]
- ARIA events typically occur early after initiation of anti-amyloid therapy[2]
- While most ARIA-E are asymptomatic and transient, these events can be severe and life-threatening

Fig 1: ARIA-E- Vasogenic Edema

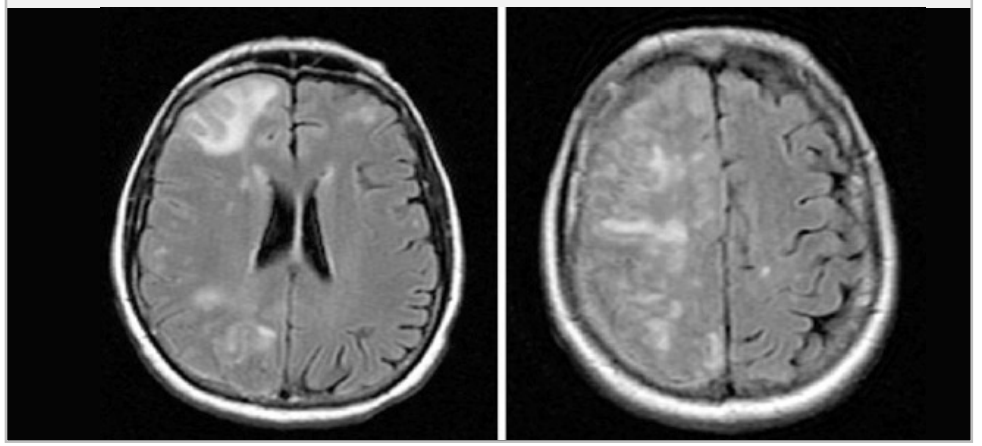
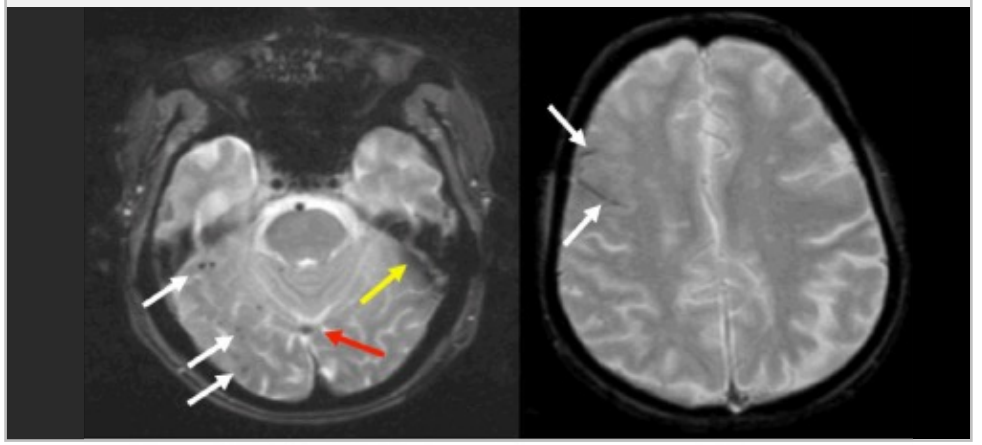


Fig 2: ARIA-H- Hemorrhage and Superficial Siderosis



1. Sperling RA., et al., Amyloid related imaging abnormalities (ARIA) in amyloid modifying therapeutic trials: recommendations from the Alzheimer's Association research roundtable workgroup. Alzheimers Dement. 2011;7(4):367-85. doi:10.1016/j.jalz.2011.05.02351. 2. Cummings et al, *J Prev Alz Dis.* 2023;3(10):362-77,

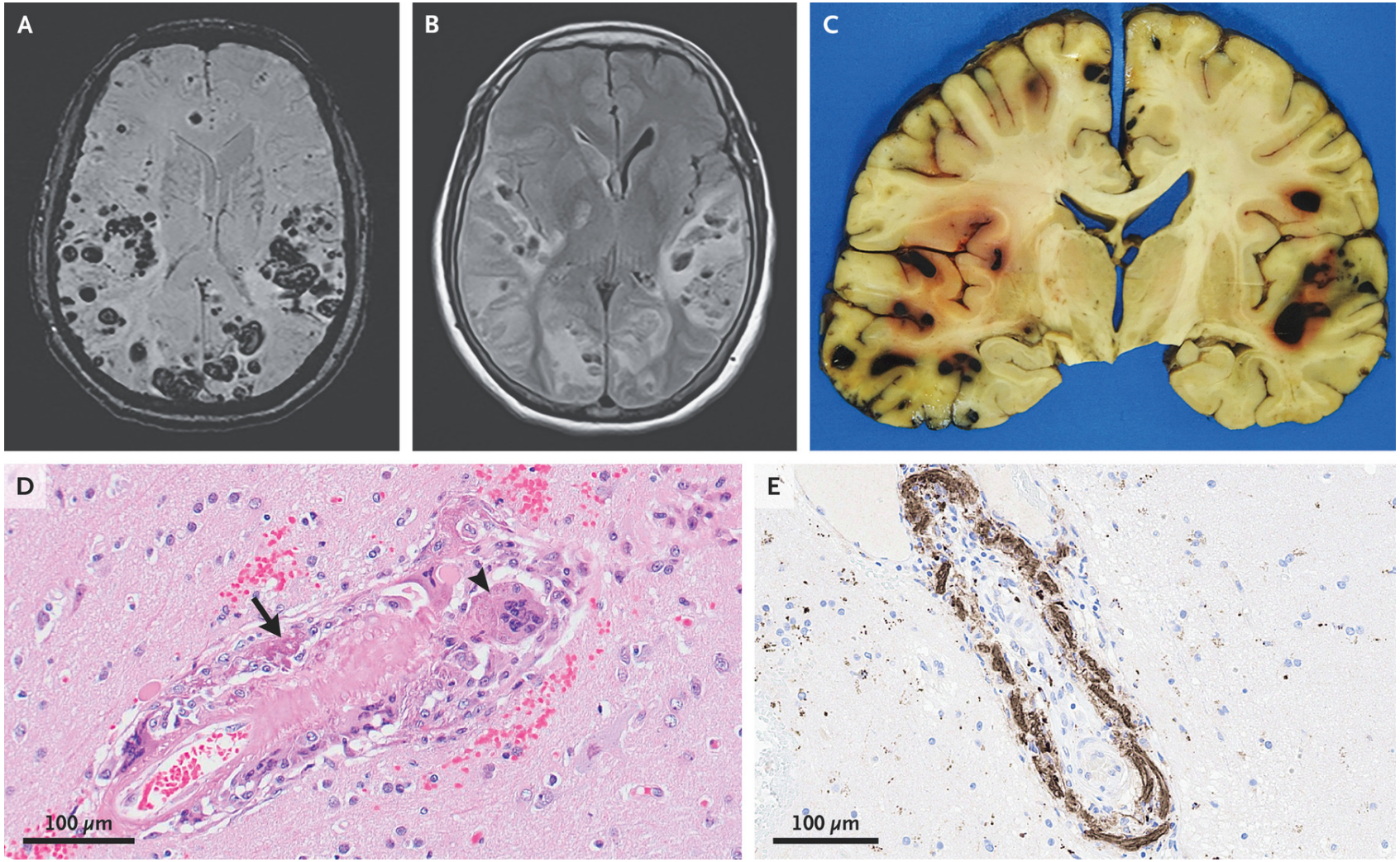
Incidence of ARIA-E with Anti-Amyloid Therapy

Anti-Amyloid mAb, (n)	Overall, % (n)	APOE4/4, % (n)	APOE4/-, % (n)	Non-carriers, % (n)
EMERGE & ENGAGE TRIALS[1]				
Aducanumab[2] (1,029)	35.2 (362)	43.0[3] (290/674)		20.3 (72/355)
Placebo (1,076)	2.7 (29)	2.2[3] (16/742)		3.9 (13/334)
CLARITY-AD[4]				
Lecanemab (898)	12.6 (113)	32.6 (46/141)	10.9 (52/479)	5.4 (15/278)
Placebo (897)	1.7 (15)	3.8 (5/133)	1.9 (9/478)	0.3 (1/286)
TRAILBLAZER-ALZ2[5]				
Donanemab (853)	24.0 (205)	40.6 (58/143)	22.8 (103/452)	15.7 (40/255)
Placebo (874)	18 (2.1)	3.4 (5/146)	1.9 (9/474)	0.8 (2/250

- APOE4 carriers at increased risk for ARIA and accelerated progression of AD[6,7]
- Risk of ARIA can complicate the benefit-risk assessment of anti-amyloid mAbs, the only approved disease-modifying treatment for AD[8]

1. Salloway S., et al., JAMA Neurol. 2022;79(1):13-21. doi:10.1001/jamaneurol.2021.4161. 2. Results represent ARIA rates with aducanumab 10 mg/kg. 3. Represents ARIA-E rates with aducanumab (10 mg/kg) in APOE4 carriers (both hetero- and homo-zygotes); 4. van Dyck CH., et al., Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948. 5. Sims JR., et al., Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512-27. doi:10.1001/jama.2023.13239. 6. Doran SJ., et al., Risk factors in developing amyloid related imaging abnormalities (ARIA) and clinical implications. Front Neurosci. 2024;18:1326784. doi: 10.3389/fnins.2024.1326784. 7. Hunsberger HC., The role of APOE4 in Alzheimer's disease: strategies for future therapeutic interventions. Neuronal Signal. 2019;3(2):NS201180203. doi: 10.1042/NS20180203. 8. Doran SJ., et al., Risk factors in developing amyloid related imaging abnormalities (ARIA) and clinical implications. Front Neurosci. 2024;18:1326784. doi: 10.3389/fnins.2024.1326784.

Lecanemab Case Report: Fatal ARIA



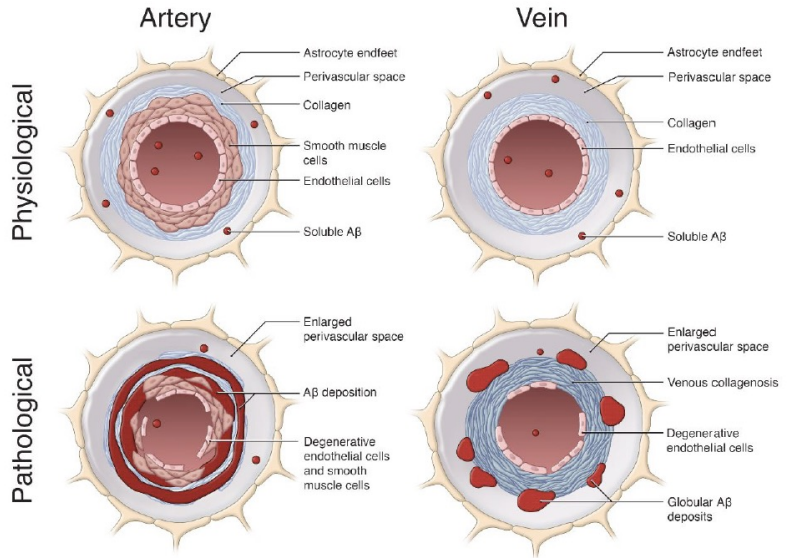
- 65 yo female
- early AD
- APOE4/4
- Pre-Tx no MCB or edema
- CLARITY Ph III
- Placebo
- OLE 3 doses Q2W
- 4 days later had stroke-like symptoms including aphasia, seizures
- Treated with tPA

Reish et al., New Engl J Med Feb 2023.

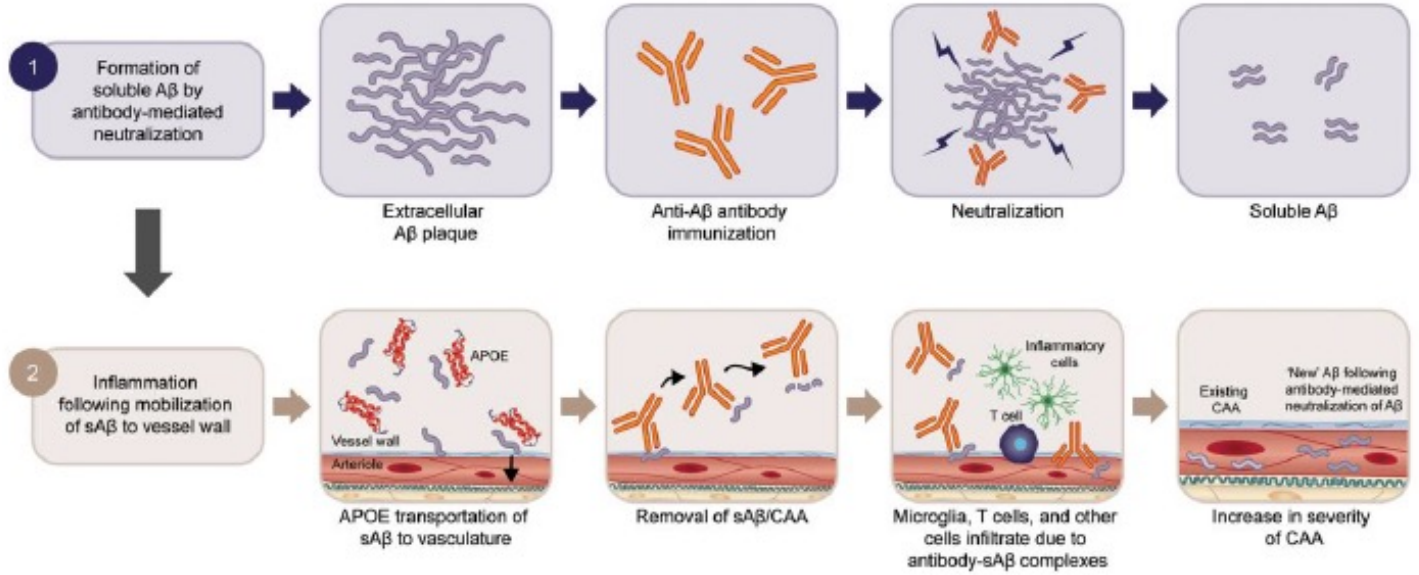
ARIA is a Mixed Inflammatory Response to Vascular Amyloid

- Anti-amyloid antibodies bind to amyloid deposits in cerebral blood vessels[1-3]
- Antibody-Aβ complexes accumulate in perivascular clearance pathways[1-3]
- A mixed inflammatory response ensues causing a loss of vascular integrity and leakage of proteinaceous fluid and blood[1-3]

Vascular Injury Caused by Aβ Deposits[3]



Pathophysiological Progression of ARIA[2]

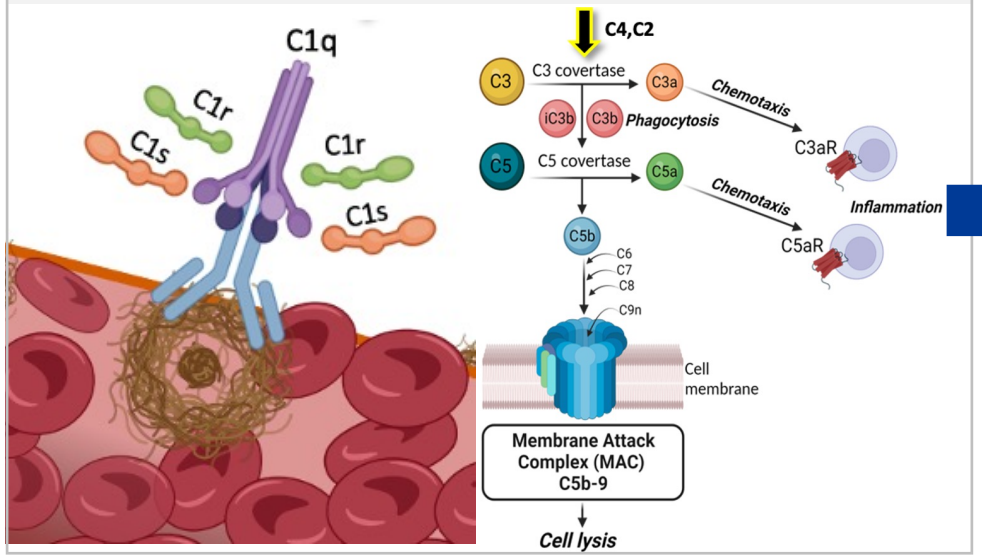


1. Alzforum, 2023 https://www.alzforum.org/news/conference-coverage/aria-inflammatory-reaction-vascular-amyloid. Accessed 20-MAY-2024. 2. Hampel et al, *Brain.* 2023 146;4414-24. 3. Morrone CD.,. Int J Mol Sci. 2020;21(6):1985. doi: 10.3390/ijms21061985.

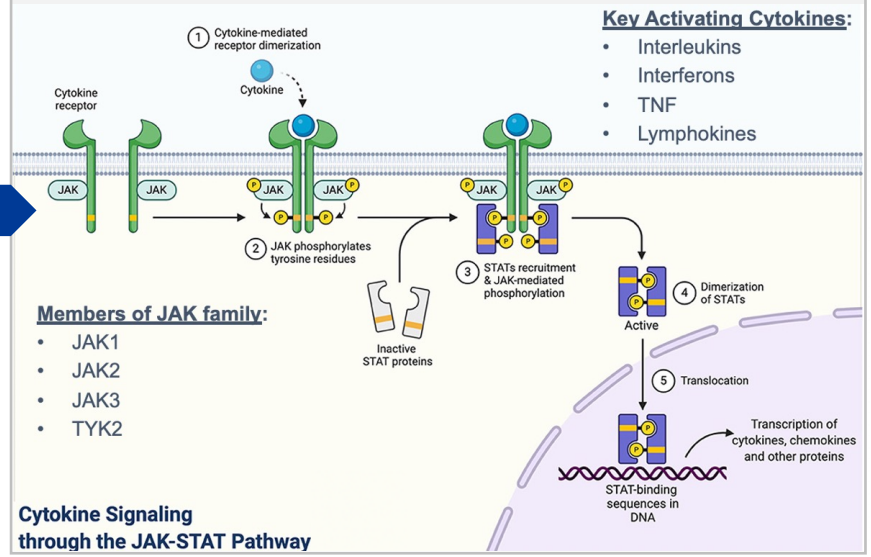
Potential Role of Complement Cascade and JAK-STAT Signaling

- ARIA-associated mixed inflammatory response[1]
  - Activation of classical complement cascade[2]
  - Overexpression of complement components C3a and C5a activate JAK/STAT3 pathway[3,4]
  - Activation of glial cells within the CNS[1]
  - Activation of local macrophages and peripheral T-cells and monocytes[1,5]
- Corticosteroids and other immunosuppressive drugs have been effective in treating ARIA[1,6]

Classical Complement Pathway[2]



JAK-STAT Signaling Pathway[7]



1. Hampel et al, Brain. 2023 146;4414-24. 2. Alzforum, 2023 https://www.alzforum.org/news/conference-coverage/aria-inflammatory-reaction-vascular-amyloid; 3. Yuan et al, J Exp Clin Cancer Res. 2020 V39;PMC6956509. 4. An X-Q., et al., Complement protein C5a enhances the beta-amyloid-induced neuro-inflammatory response in microglia in Alzheimer's disease. Med Sci. 2018;34:116-20. doi: 10.1051/medsci/201834f120. 5. Taylor X., et al., Amyloid-β (Aβ) immunotherapy induced microhemorrhages are associated with activated perivascular macrophages and peripheral monocyte recruitment in Alzheimer's disease mice. Mol Neurodegener. 2023;18(1):59. doi: 10.1186/s13024-023-00649-w. 6. Regenhardt et al, JAMA Neurol. 2020 Oct;77(10)1-10.

Perivascular Macrophages, Inflammation and ECM Remodeling

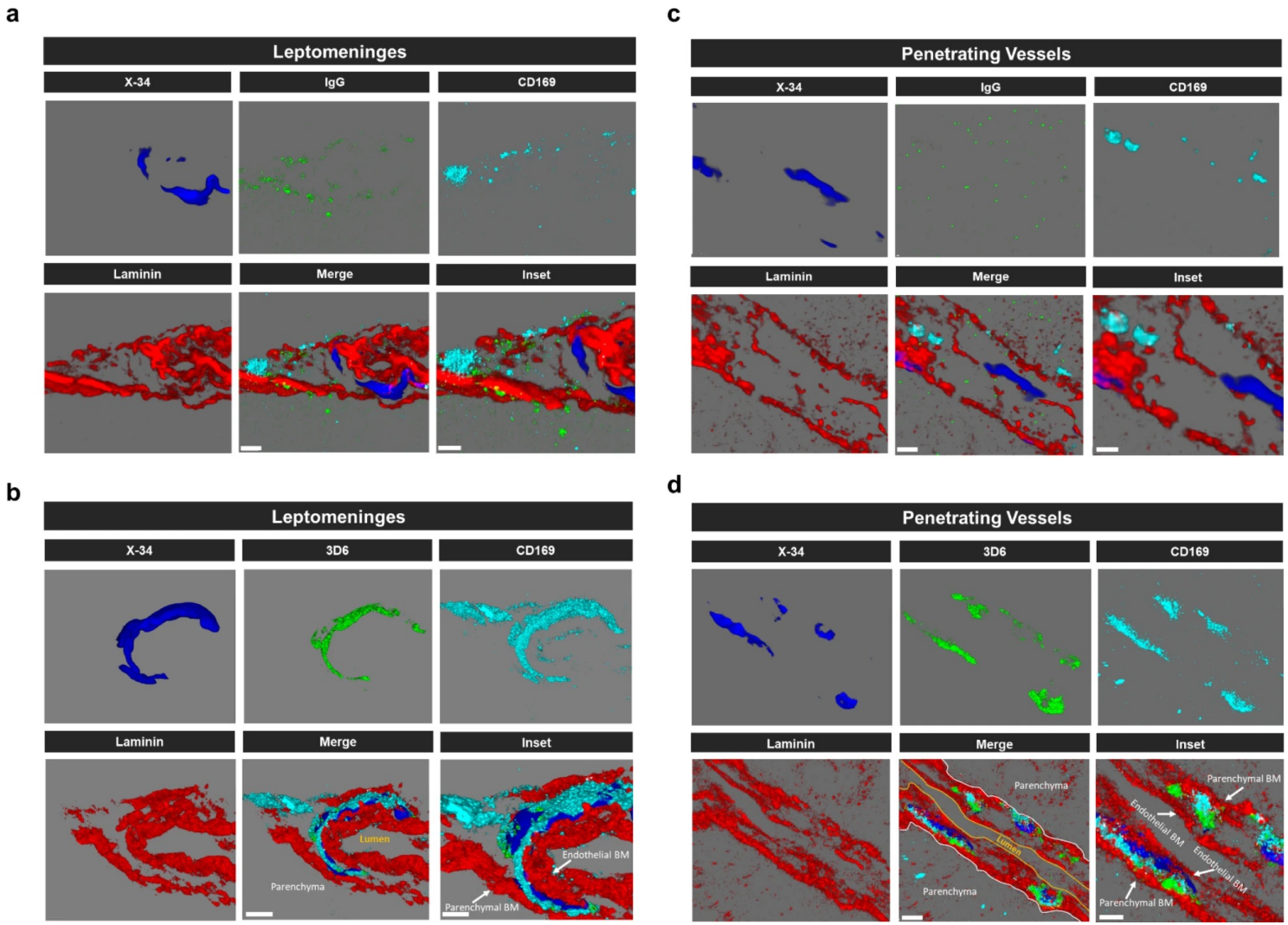
- 23–26 mo hTau APP KI mice
- Inj. s.c. weekly x 4 weeks
- Biotinylated 3D6 IgG2b 25 mg/kg
- 3D6 binds CAA
- Associated with CD169+ pvm and inflammatory monocytes
- Enhanced MMP9/TIMP1 ratio

Molecular Neurodegeneration

Research article | Open access |
Published: 30 August 2023

Amyloid-ß (Aß) immunotherapy induced microhemorrhages are associated with activated perivascular macrophages and peripheral monocyte recruitment in Alzheimer's disease mice

Taylor, X., Clark, I.M., Fitzgerald, G.J. *et al.* Amyloid-β (Aβ) immunotherapy induced microhemorrhages are associated with activated perivascular macrophages and peripheral monocyte recruitment in Alzheimer's disease mice. *Mol Neurodegeneration*18, 59 (2023). https://doi.org/10.1186/s13024-023-00649-w



Taylor et al. Molecular Neurodegeneration (2023)18:59. https://doi.org/10.1186/s13024-023-00649-w.

TYK2/JAK1 Inhibition Can Block Central and Peripheral Cellular Signaling Associated With ARIA Pathogenesis

Microglia

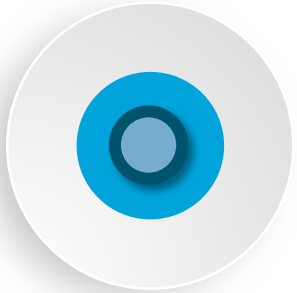
- **IFN-γ**
- **IFN-α and IFN-β**
- IL-β
- TNF downstream of IFN-γ
- IL-8
- GM-CSF, MCP-1

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

Astrocytes

- **IFN-γ**
- **IFN-α and IFN-β**
- IL-12
- TNF
- IL-8

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



Lymphocytes, other leukocytes

- **IL-23**
- **IL-17 downstream of IL-23**
- **IL-27**
- IL-2, IL-4

Strong evidence for Th17 lymphocyte involvement as a driver of neurodegeneration

Nick Kozauer, M.D.

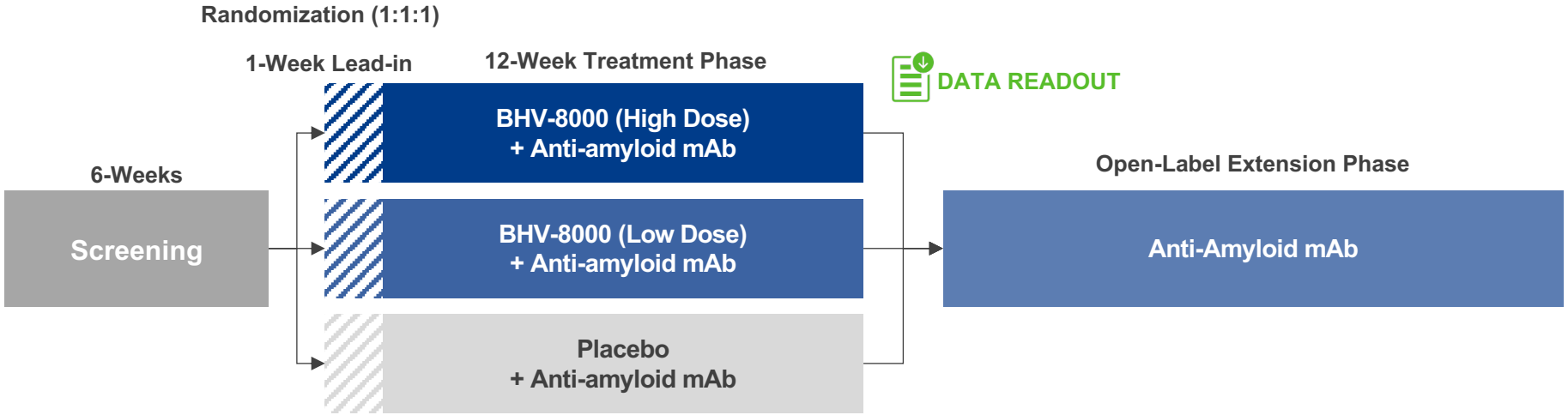
Senior Vice President, Clinical Development & Regulatory Strategy

biohaven®

BHV-8000 for the Prevention of ARIA and Treatment of Parkinson's Disease

biohaven®

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



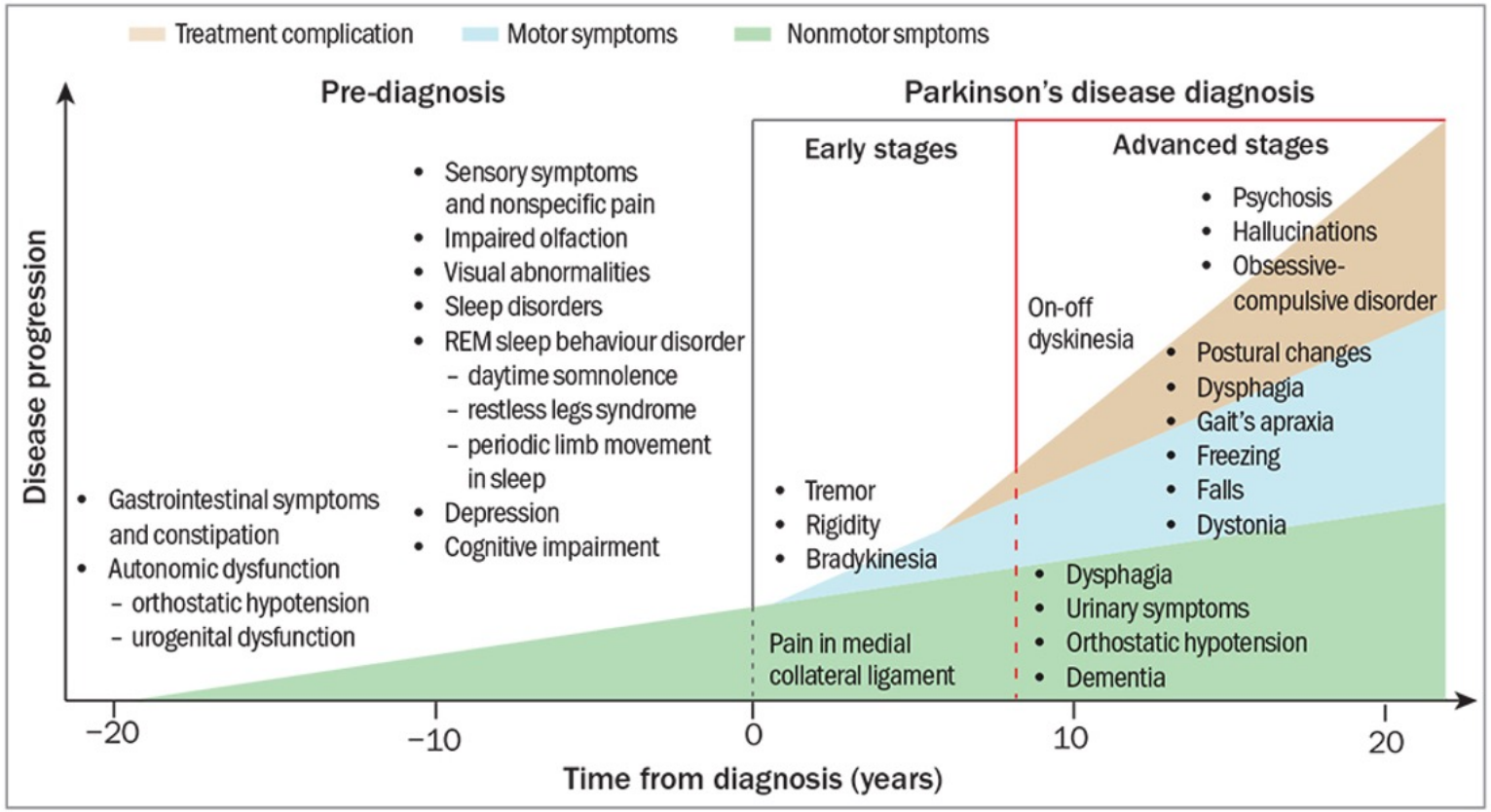
DESIGN	Randomized, double-blind, placebo-controlled trial
POPULATION	Male and female adults with early Alzheimer's disease who are APOE4 gene carriers
SAMPLE SIZE	450 participants (randomized 1:1:1 across 2 active and 1 placebo arm)
TREATMENT	BHV-8000 (high/low dose) vs. Placebo + anti-amyloid mAb
TREATMENT 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

BREAKING NEWS

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

Parkinson's Disease Has a High Unmet Need

- 1 million people living with PD in the US; 10 million people worldwide
- Second most common neurodegenerative disease in the US
- No approved disease-modifying treatments

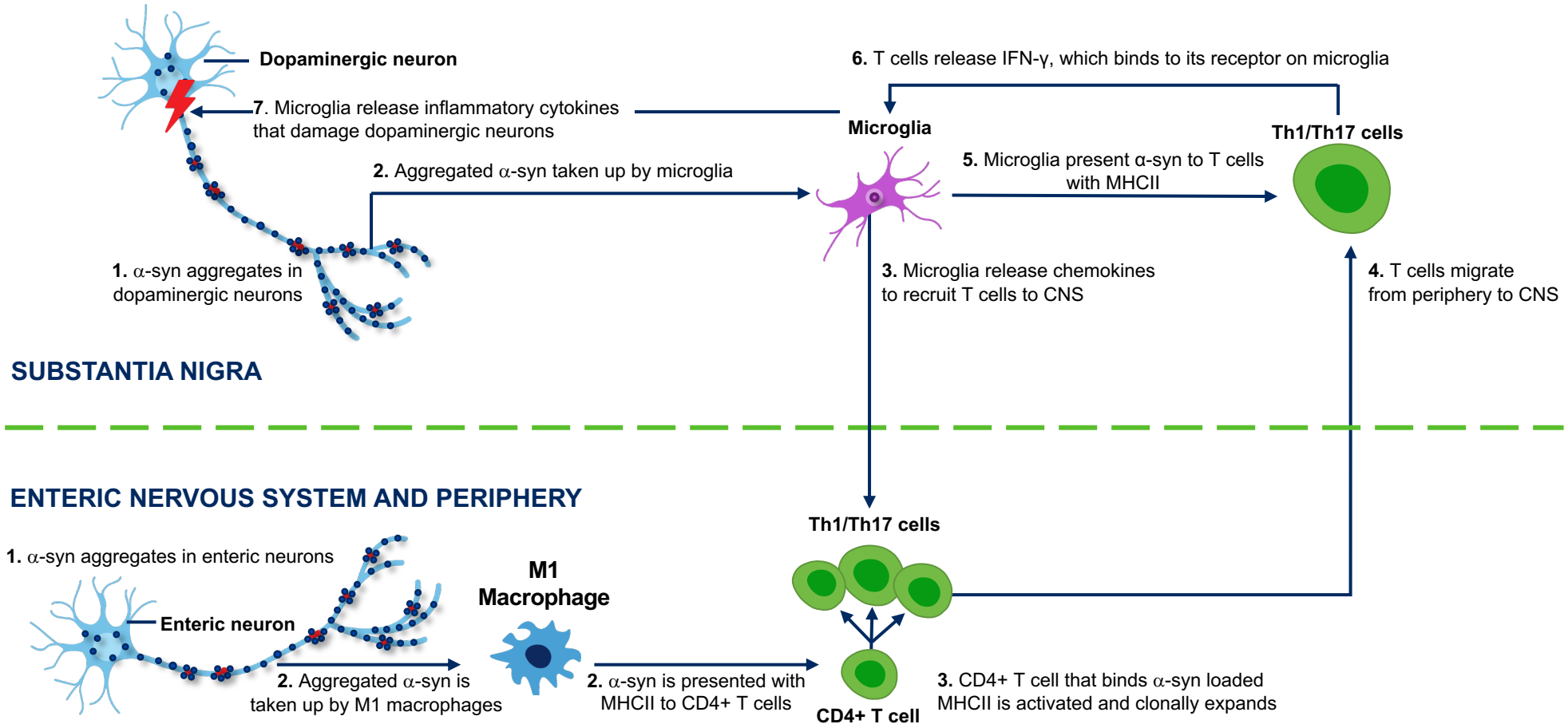


https://www.researchgate.net/figure/Chronology-of-clinical-symptoms-in-Parkinsons-disease-modified-from-Kalia-et-al-8_fig2_339186483.

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

TYK2/JAK1 INHIBITION OF PARKINSON'S NEUROINFLAMMATORY CASCADE

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



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

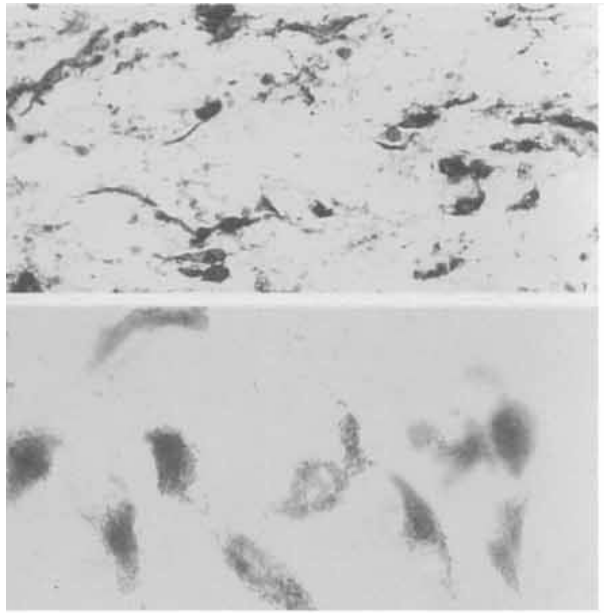
1. Allen Reish, Standaert. *J Parkinsons Dis.* 2015;5(1):1-19. 2. Fu et al. *J Neuroinflammation.* 2022;19(1):98.

biohaven

Clinical Data Supports Targeting Neuroinflammation in Parkinson's Disease

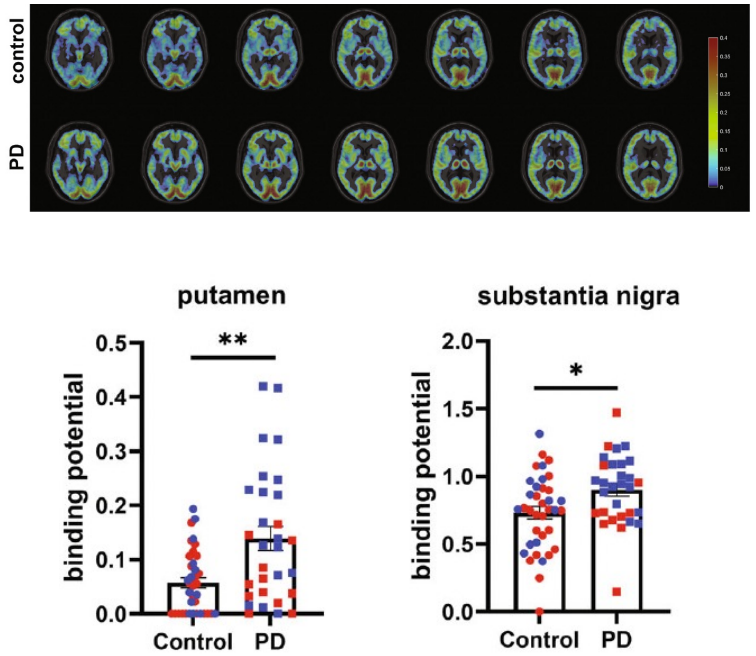
Post-Mortem Data[1]

PD patient brains express high levels of HLA-DR+ reactive microglia



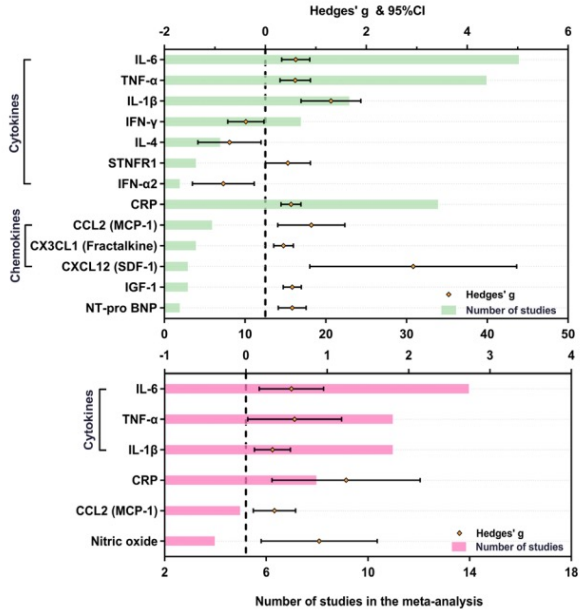
In Vivo Imaging[2]

^{18}F-DPA-714 TSPO imaging increased in early PD relative to healthy controls



In Vivo Cytokine Levels[3]

Elevated levels of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α, IFN-ɣ) found in the CSF and blood of PD patients



1. McGeer PL, et al. *Neurology*. 1988 Aug;38(8):1285-91. 2. Yacoubian TA, et al. *Mov Disord*. 2023 May;38(5):743-754. 3. Qu Y, et al. *NPJ Parkinsons Dis*. 2023 Feb 4;9(1):18.

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.

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)

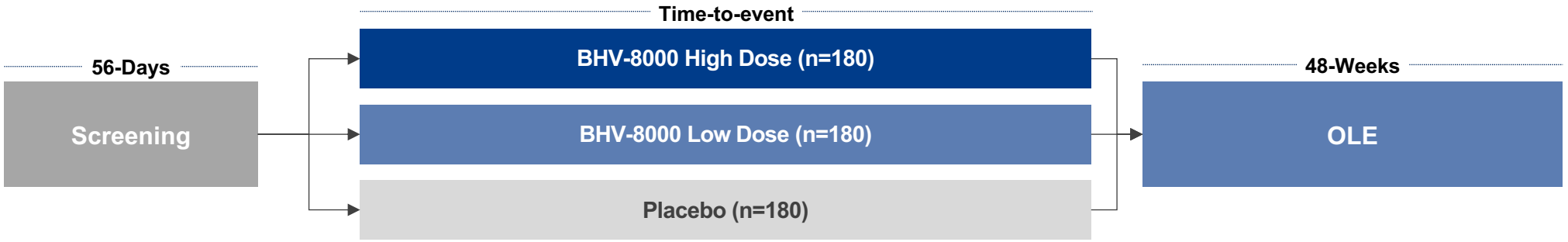
Provides a meaningful efficacy endpoint with a smaller sample size

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



BREAKING NEWS

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.

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

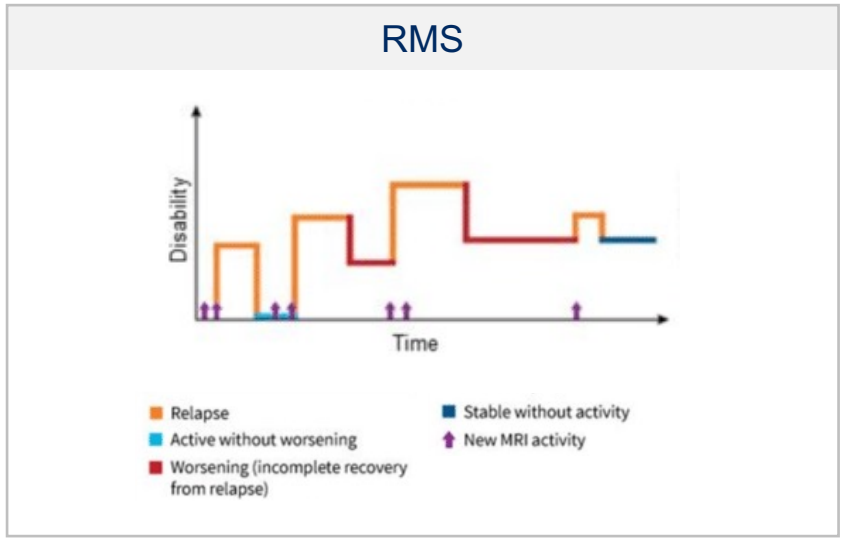
VP, Clinical Development

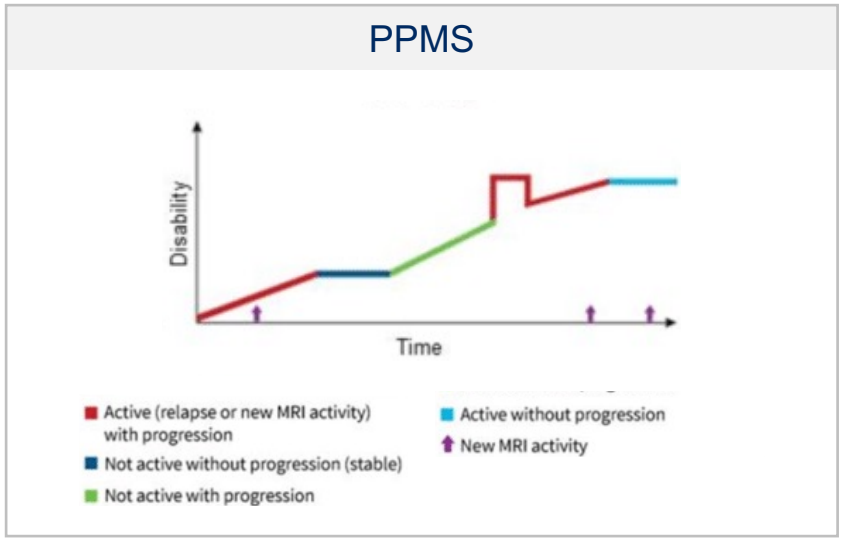
biohaven

BHV-8000 for the Treatment of Multiple Sclerosis

biohaven®

Multiple Sclerosis





Relapsing multiple sclerosis (RMS)[1-3]

Symptoms may improve and be followed by periods of remission

Progressive multiple sclerosis (PMS)[1-3]

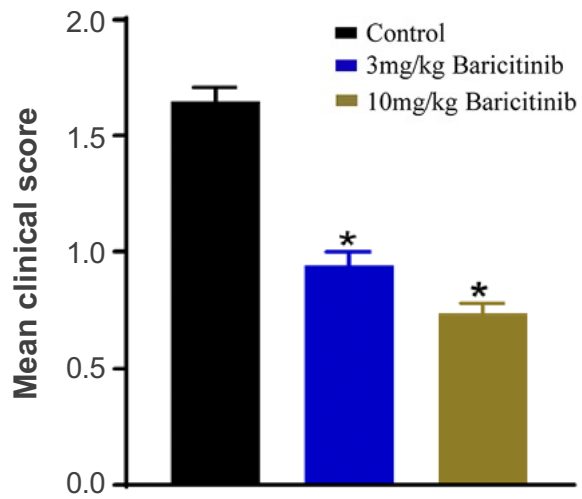
- Continued and progressive disability without remission, independent of relapses
- Greater impairment in function and quality of life leading to higher economic burden[4]
- 15% have Primary Progressive MS (PPMS) — disability accumulates from beginning, no early relapses/remissions[5]

1. Lublin FD, et al. Neurology. 2014 Jul 15;83(3):278-86. 2. Relapsing-Remitting Multiple Sclerosis (RRMS). National Multiple Sclerosis Society. (2024). https://www.nationalmssociety.org/understanding-ms/what-is-ms/types-of-ms/relapse-remitting-ms 3. Primary Progressive Multiple Sclerosis (PPMS). National Multiple Sclerosis Society. (2024). https://www.nationalmssociety.org/understanding-ms/what-is-ms/types-of-ms/primary-progressive-ms 4. Watson C, et al. Neurol Ther. 2023 Dec;12(6):1961-1979. 5. Filippi M. et al. Nat Rev Dis Primers. 2018 Nov 8;4(1):43.

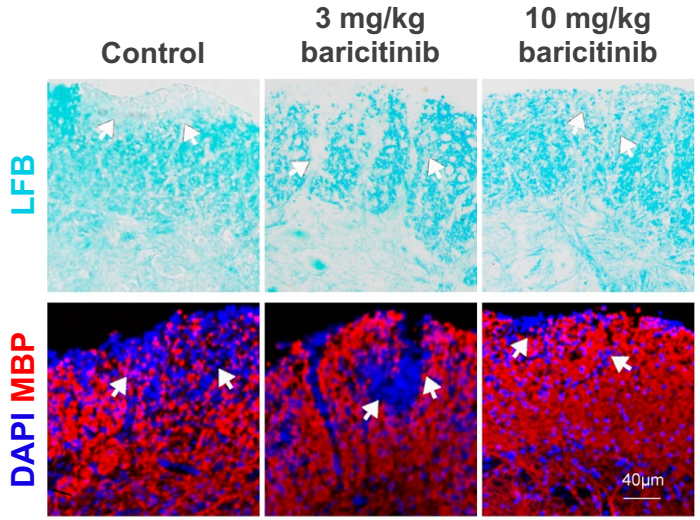
TYK2/JAK1 Inhibition Is a Potential Treatment for Multiple Sclerosis

- **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]

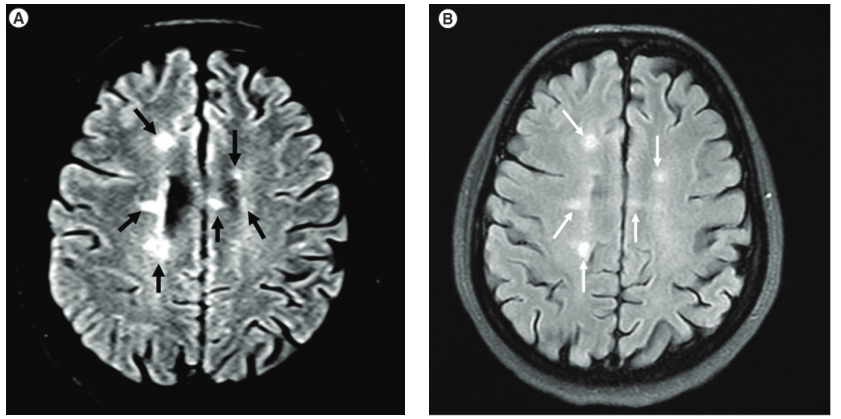


Baricitinib (JAK1/2 Inhibitor) Reduces Pathological Tissue Injuries In EAE Mice[2]



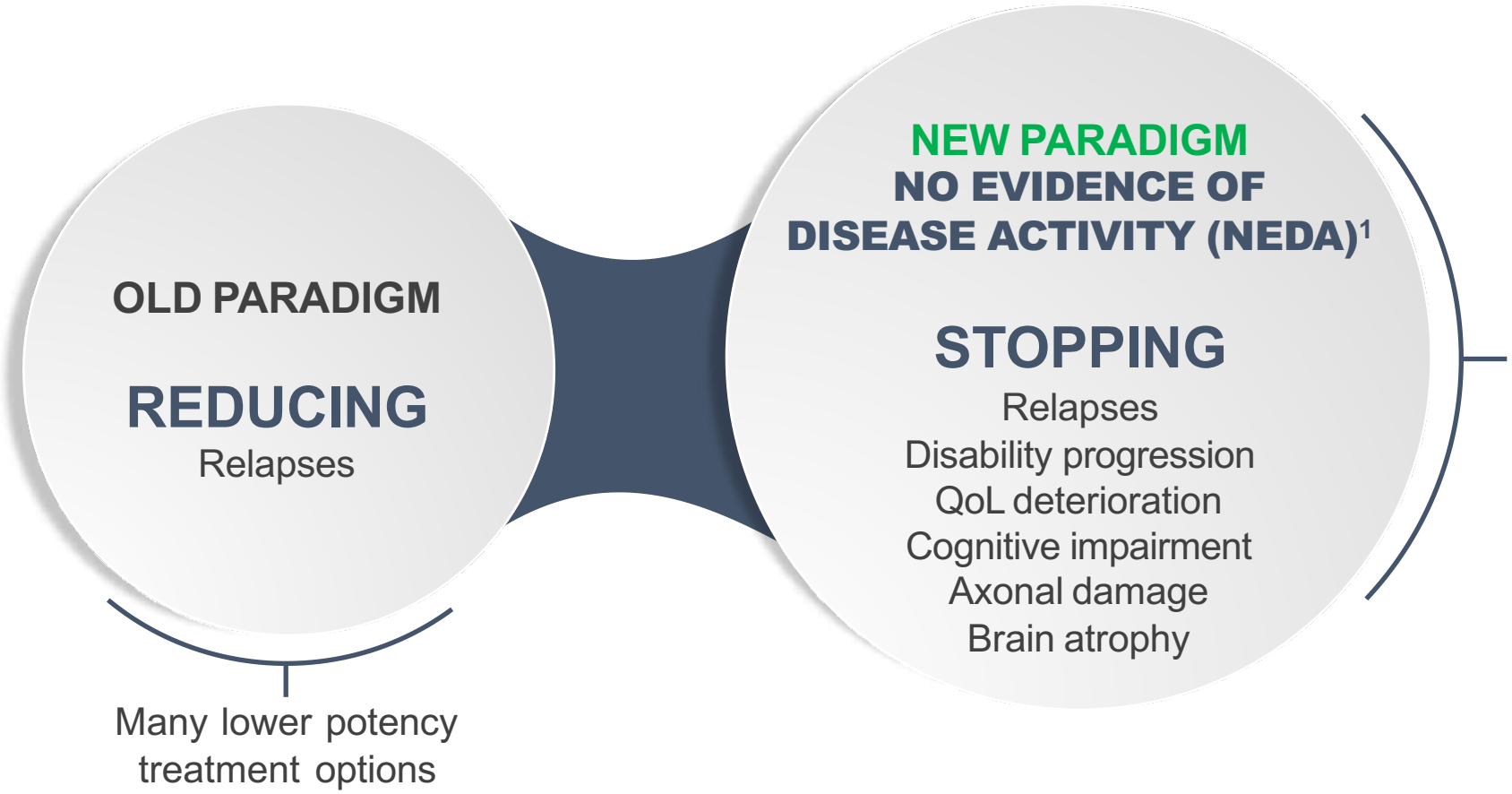
Secukinumab (IL-17A) Demonstrates an Effect in Relapsing Remitting MS[3]

Lesions regressed in MS patients 5 months of secukinumab treatment



1. Ban et al, European Journal of Human Genetics (2009) 17, 1309 – 1313; 2. Dang C et al, Front. Immunol. 12:650708; 3. Eksin MA et al, Immunotherapy. 2022 Apr;14(6):401-408
JAK/STAT, Janus kinase/signal transducers and activators of transcription.

Evolving Treatment Paradigm for Multiple Sclerosis: Early Treatment With Potent Therapy



Brain-penetrant TYK2/JAK1 inhibition with BHV-8000 targets pathophysiology of MS

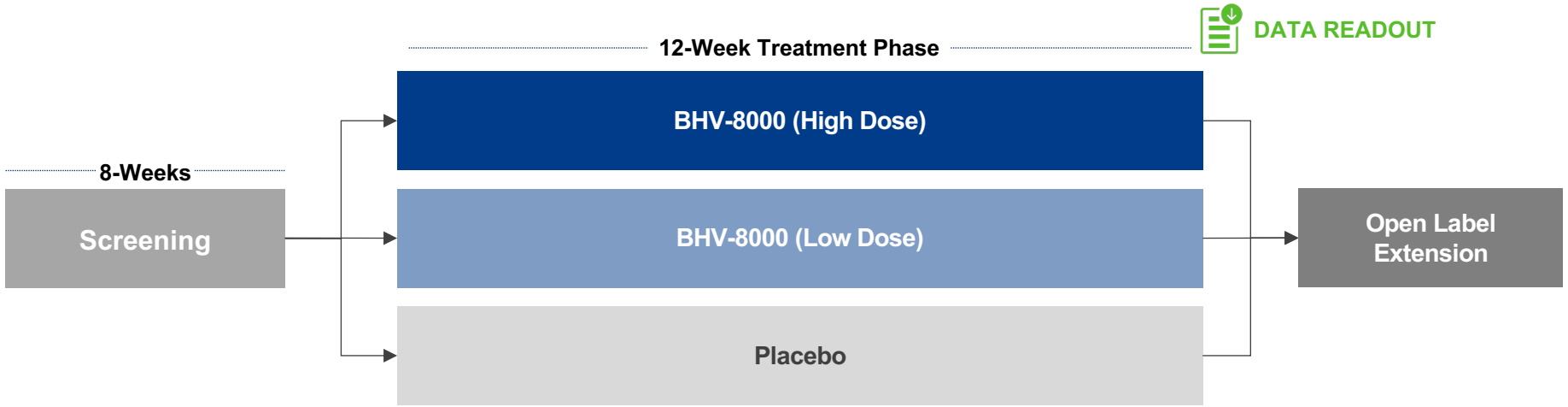
- **Modulation of pathogenic microglial cells:** which drive cognitive & physical disability[2-4]
- **Inhibition of Th1 and Th17 lymphocytes:** which drive neuroinflammation[5-7]

KEY POINT

Brain-penetrant TYK2/JAK1 inhibition with BHV-8000 offers a novel therapeutic approach for both relapsing and progressive forms of MS

1. Newsome et al. Neurol Ther. 2023 Dec;12(6):1909-1935; 2. Correale, Mult Scler Relat Disord, 56:103264, 2021; 3. Geladaris, Int. J.Mol. Sci. 22,3461, 2021; 4. Barros et al. Mult Scler Relat Disord. 2021 Jan;47:102622; 5. Arellano, Front Immunol, 8:753, 2017; 6. Shi et al, Front Immunol, 13:932152, 2022; 7. Dos Passos. Mediators Inflamm, 2016:5314541.

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

Panel Discussion

MODERATOR

Charles Duncan, Ph.D.

Equity Research Analyst

CANTOR

PANELISTS

Peter Ackerman, M.D.
Vice President, Clinical Development, Biohaven

Mark Albers, M.D., Ph.D.
Assistant Professor of Neurology, Massachusetts General Hospital, Harvard Medical School

Nick Kozauer, M.D.
Senior Vice President, Clinical, Development & Regulatory Strategy, Biohaven

Lindsey Lair, M.D., MBA, F.A.A.N.
Vice President, Clinical Development, Biohaven

Cynthia Lemere, Ph.D.
Professor of Neurology, Brigham & Women's Hospital, Harvard Medical School

Stephen Salloway, M.D., MS
Professor, Psychiatry and Human Behavior, Professor of Neurology, Alpert Medical School of Brown University
Associate Director, Brown Center for Alzheimer's Research

BHVN LISTED NYSE

Brian Lestini, M.D., Ph.D.
President, Oncology

biohaven®

Nushmia Khokhar, M.D.
CMO, Oncology

biohaven®

Gene Dubowchik, Ph.D.
SVP, Molecular Technologies

biohaven®

Oncology

biohaven®

Brian Lestini, M.D., Ph.D.
President, Oncology

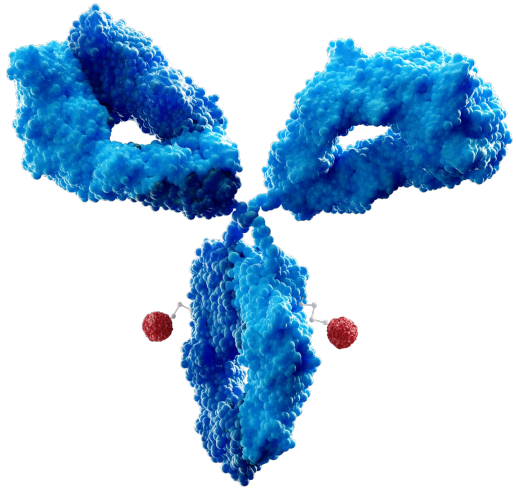
biohaven®

Oncology

biohaven®

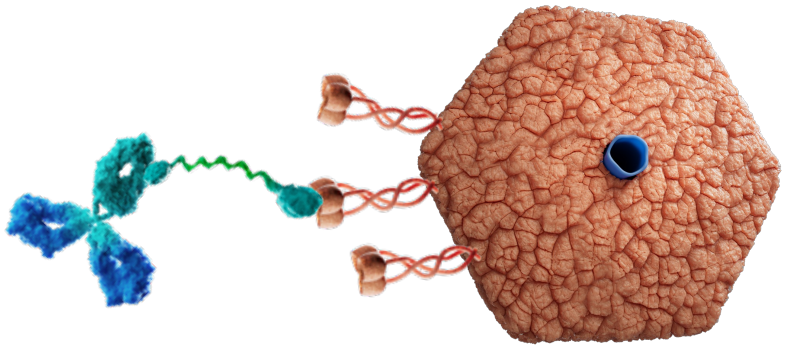
An Oncology Strategy that Leverages Our Core Strengths to Drive Value

Antibody Drug Conjugates



- Robust and flexible Biohaven platform approaches to optimize across ADC parameters
- Capable of generating a diverse and sustainable portfolio of highly differentiated ADCs
- Multiple programs positioned to enter clinic
  - Lead programs: novel Trop-2 (BHV-1510) and CD30 (BHV-1500) targeted ADCs

Targeted Protein Degradation



- Novel MOA with increasing importance in oncology and hematology
- Innovative Biohaven platform provides multiple opportunities for differentiated programs

Trop-2, trophoblast cell surface antigen-2.

biohaven

Biohaven ADC Portfolio Is Positioned to Deliver Differentiated Profiles and Address Unmet Needs in Oncology

Broad platform applicability

Multiple programs entering clinic

Future innovation to drive sustainable and differentiated pipeline

- Prior generation ADCs are limited by **narrow therapeutic margins**
  - High rates of dose limiting toxicities impact efficacy
- Portfolio of **11 BHVN ADCs** demonstrated superior stability and *in vitro* / *in vivo* differentiation

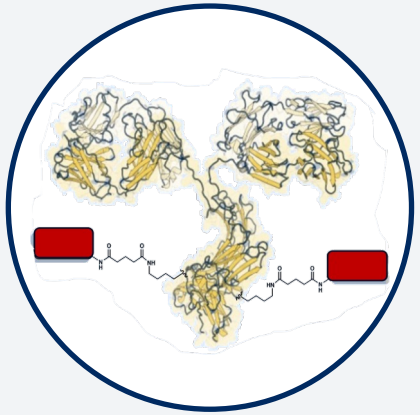
- BHV-1510 **currently in Phase 1**
  - Trop-2 ADC with superior preclinical efficacy, safety, and anti-PD-1 synergy
  - Monotherapy and anti-PD-1 combinations
- BHV-1500 **IND anticipated early 2025**
  - Differentiated CD30 ADC

- Optimized **tumor targeting** and **payload delivery**
- Optimized **tumor eradication**
  - Next-generation and non-cytotoxic payloads
  - Synergy with other MOAs including immuno-oncology

biohaven

Complimentary Approaches Position Biohaven With Multiple Routes to Achieve a Superior Safety and Efficacy Profile

MATE™ Platform Programs



Single step chemistry

Native mAbs

DAR2 or DAR4 capability

Site-specific conjugation

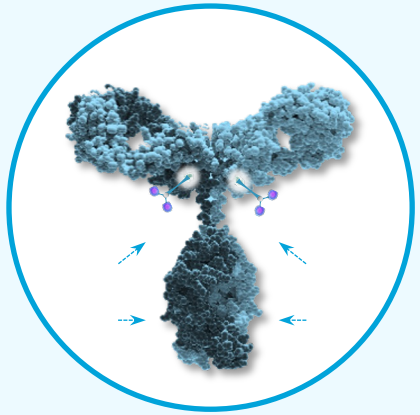
Irreversible, highly stable

Homogenous DARs

Payload flexibility

Potential for synergy with checkpoint inhibitors

BHV-1510 (Trop-2 ADC)



Choice of linkage sites

Natural amino acid residues

DAR2, DAR4 or DAR8 capability

KEY POINTS

- Broader therapeutic margin to increase time on treatment and improve efficacy
- Allows for fast-to-market strategies and IO combinations

DAR, drug antibody ratio; **IO,** immune-oncology.

biohaven

Nushmia Khokhar, M.D.
CMO, Oncology

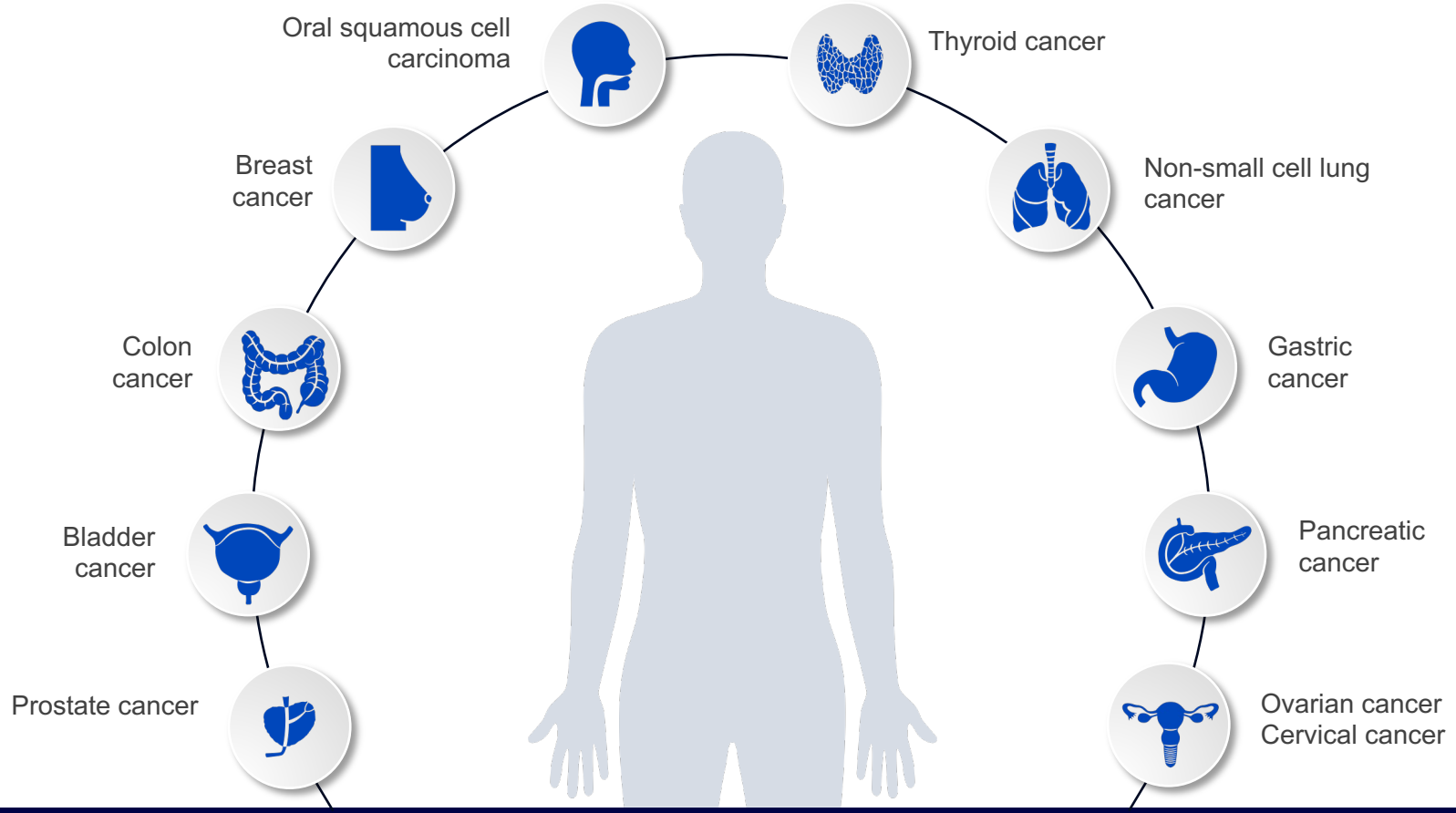
biohaven®

BHV-1510: Novel Clinical-Stage Trop-2 ADC

biohaven®

Trop-2 Is a Highly Attractive Target in Oncology

Trop-2 is a validated target expressed on a majority of epithelial tumors, including several with unmet need. Limited competition with only 1 drug approved



- Trop-2 ADCs have shown clinical benefit but with limitations set by a narrow therapeutic index
- Dose limiting toxicities can be related to unstable linker payload chemistry
- This leaves significant areas of unmet need and development opportunities for a superior Trop-2 ADC

biohaven

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

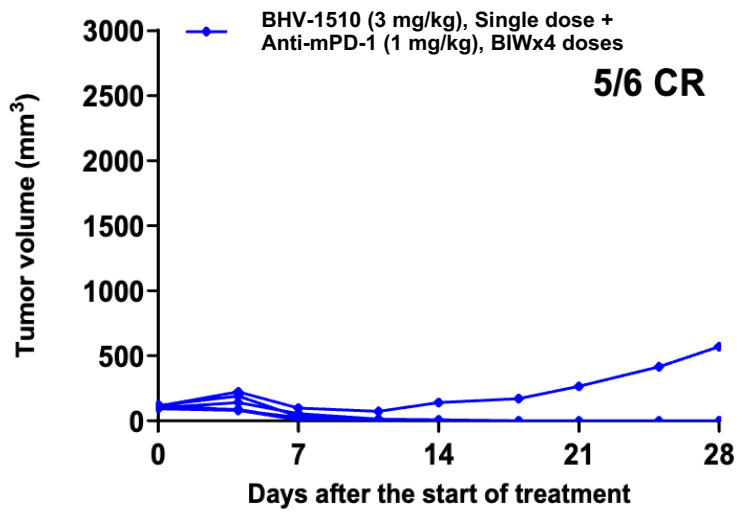
BREAKING NEWS

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

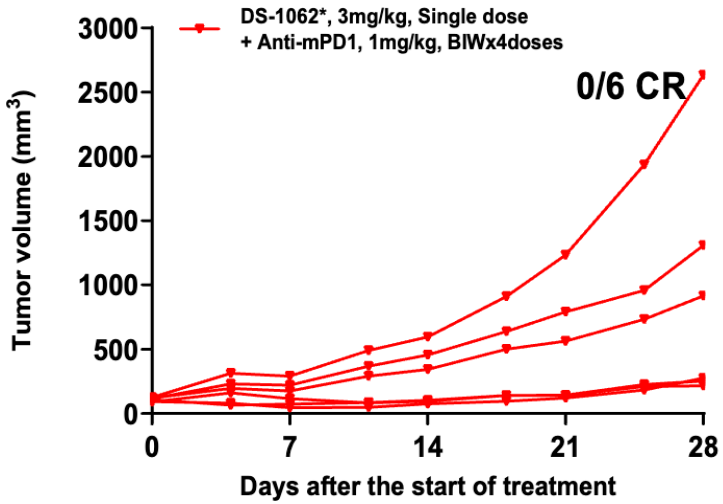
biohaven

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

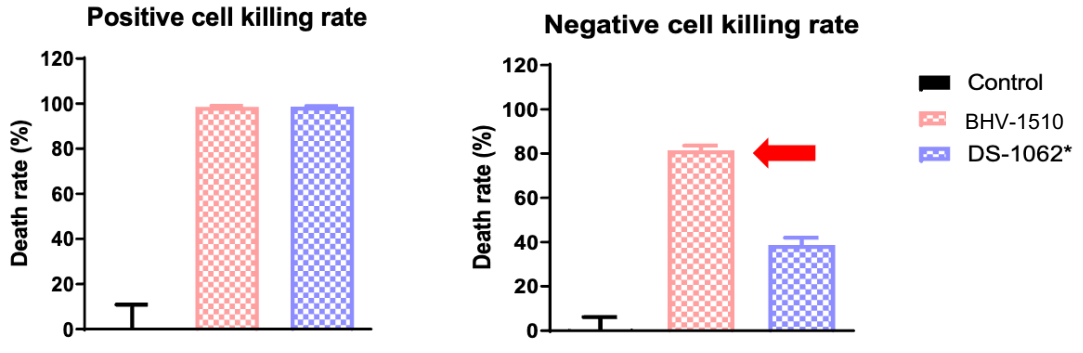
- Preclinical profile of BHV-1510 positions it for superiority in ADC therapy with anti-PD-1
- Landscape open for Trop-2 combinations with safer more efficacious ADC

AACR 2023 annual meeting, abstract #1549.

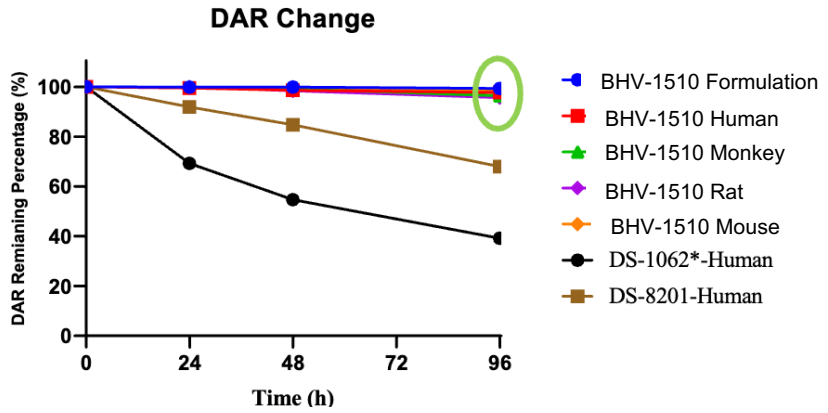
biohaven

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

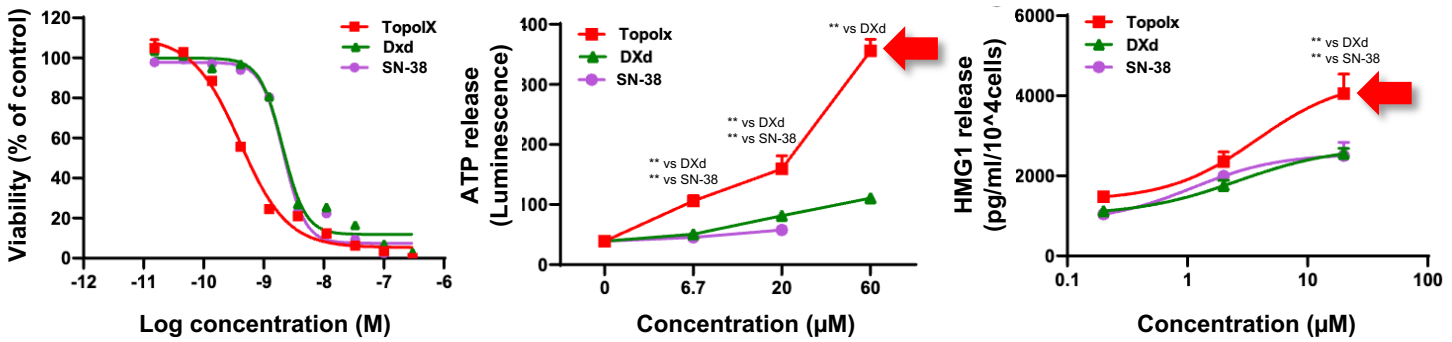
Superior Bystander Activity vs. DS-1062



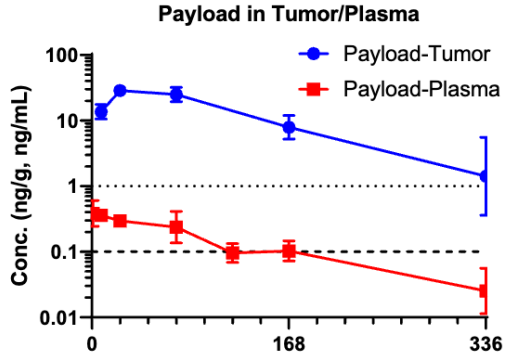
Highly Stable Linker vs. DS-1062



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



High Payload Delivery to Tumor



TopoIx Is a Proprietary Topoisomerase 1 Payload that Has a Superior Preclinical Profile Compared to DXd and SN-38

	Payload			Corresponding ADC		
	In vitro cytotoxicity	ICD*	Transported by ABCG2	*In vitro* cytotoxicity	*In vitro* bystander killing	*In vivo* efficacy
TopoIx	+++	++	-	+++	+++	+++
DXd	++	+	+	++	++	++
SN-38	++	+	n/a	++	n/a	+
Exatecan	+++	n/a	+	++	+++	n/a

*Immunogenic cell death.

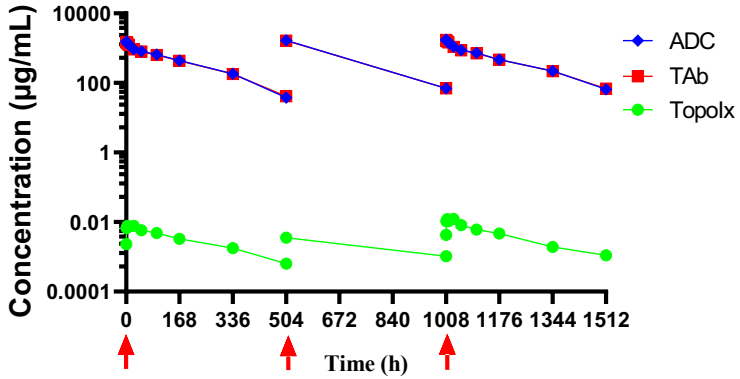
biohaven

Nonclinical Safety and PK Showed High Stability and Wide Therapeutic Margin

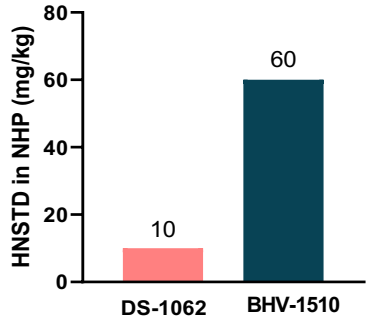
	BHV-1510	DS-1062[1]	SKB264/MK2870[2]
HNSTD	≥ 60 mg/kg (NOAEL)	10 mg/kg	50 mg/kg
Hematology/ chemistry	**No**	No	Heme tox
Major organs	**No gross/ histopathological findings in major organs including lungs** Skin and mild cornea findings	Severe pulmonary toxicity at ≥ 30 mg/kg Intestines, lung, cornea, skin, thymus, liver	Intestines, bone marrow, skin, vagina, thymus Moribund/death 75 mg/kg

- BHV-1510 shows excellent ADC stability and extremely low payload shedding in the systemic circulation
- Nonclinical safety data supports robust Phase 1 starting dose and efficient dose escalation design

Toxicokinetic Profile of BHV-1510 at 60 mg/kg



HNSTD compared to DS-1062



HNSTD, highest nonseverely toxic dose

1. Okajima D et al, Mol Cancer Ther. 2021 Dec;20(12):2329-2340. 2. Front. Oncol., 22 December 2022, Sec. Cancer Molecular Targets and Therapeutics, Volume 12 - 2022.

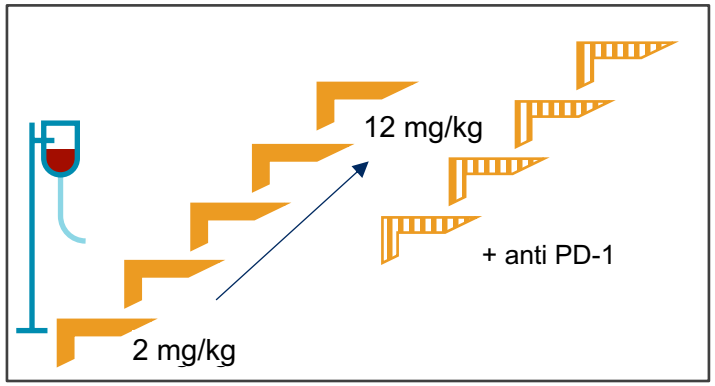
Phase 1/2 Study in Advanced Epithelial Tumors

Key eligibility

Select advanced refractory epithelial tumors

Tumor tissue available for testing (Trop-2 expression level not required for study entry)

Phase 1: Dose escalation



Phase 1/2: Cohort expansion(s)

Select 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.

Gene Dubowchik, Ph.D.
SVP, Molecular Technologies

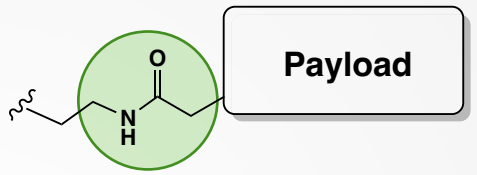
biohaven®

Biohaven's Differentiated ADC Technologies

biohaven®

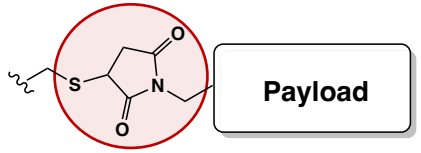
Multimodal Antibody Therapy Enhancers (MATE™): Biohaven's Next-Generation Site-Specific ADC Technology

Biohaven chemistry



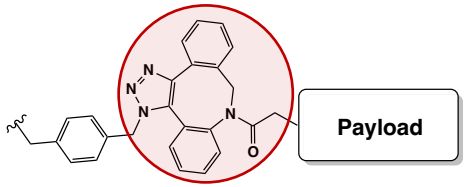
Stable, physicochemically benign amide linkage

Industry standard maleimide



Poorly stable linkage

Click chemistry to engineered antibody



Undesirably large, lipophilic linkage

IMPROVED CONJUGATION TECHNOLOGY

Efficient conjugation of single heavy chain lysine provides stable and precise DAR

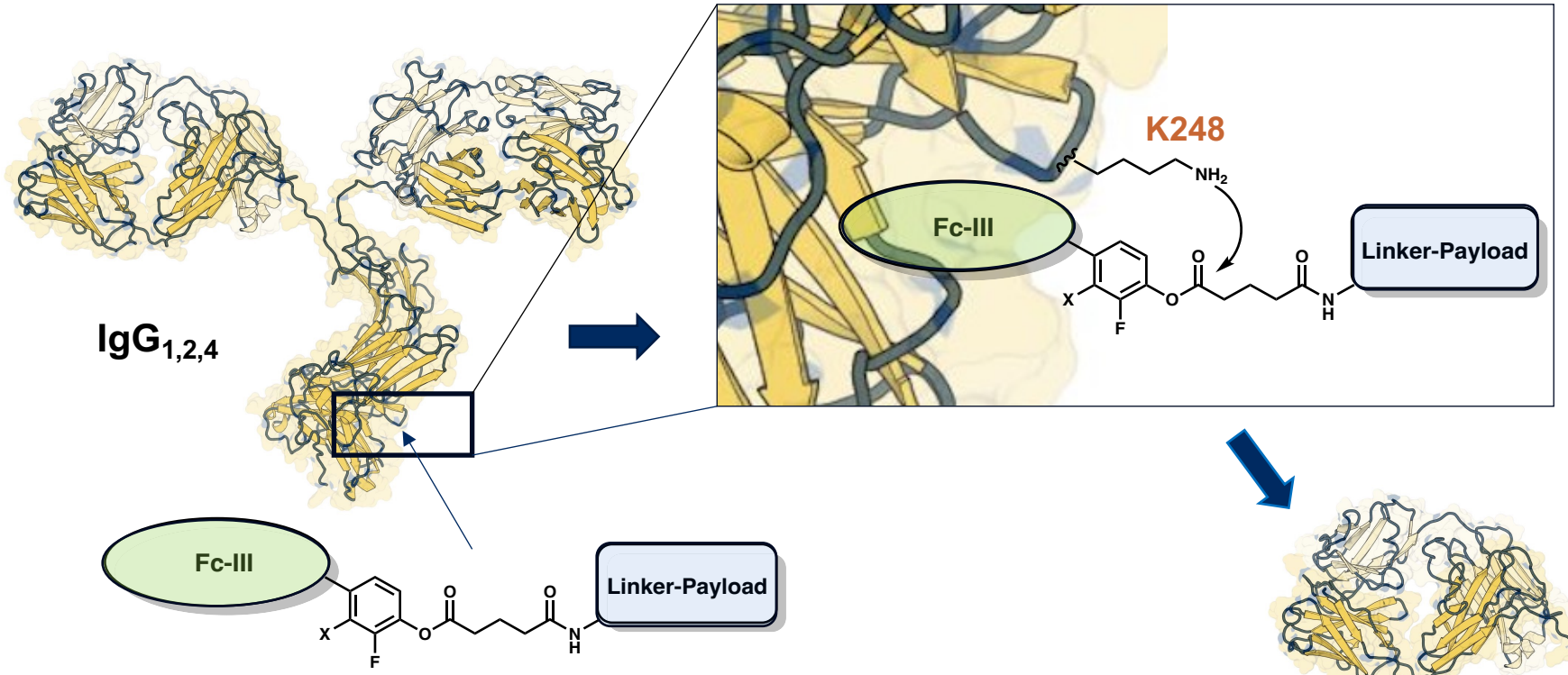
- ✓ **Improved safety:** Reduced untargeted payload in systemic circulation driving toxicity
- ✓ **Improved efficacy:** Increased targeted payload reaches tumor, higher doses possible
- ✓ **IP filed globally for conjugation technology footprint compositions** — applies to many antibodies / NMEs: 2042 patent expiration

USES NATIVE ANTIBODY

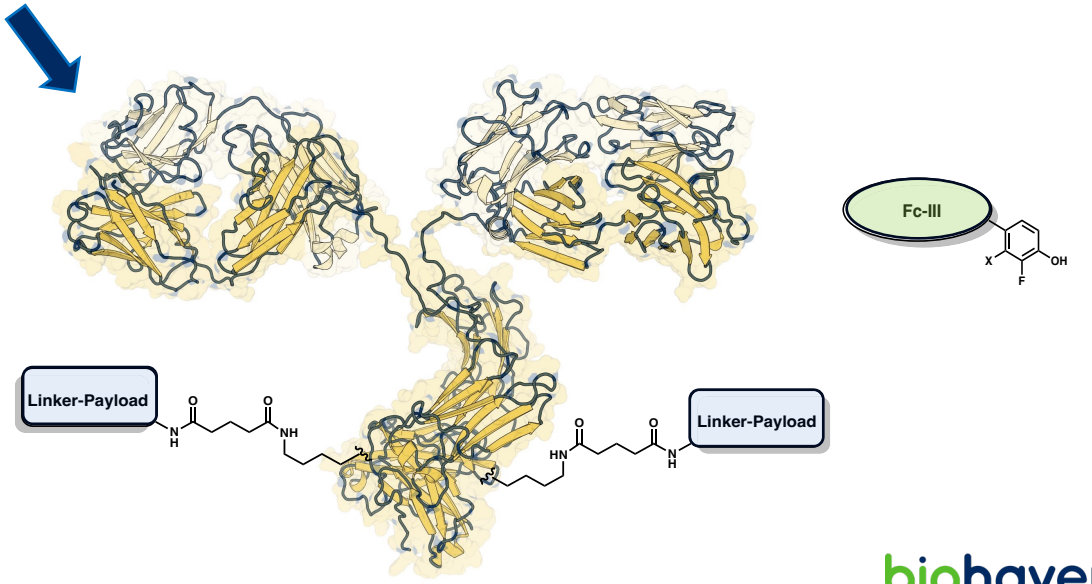
Improved CMC vs. current site-specific technologies

NME, new molecular entity.

One-Step Preparation: Site-Specific ADCs Using Native IgGs



Chemically modified Fc-III cyclic peptide binds site-specifically, allowing lysine (K248) to form stable amide bond with payload-linker



Chemistry has been scaled to prepare 1.1 kg of GLP conjugate (> 90% yield) and a diverse set of 12 ADCs

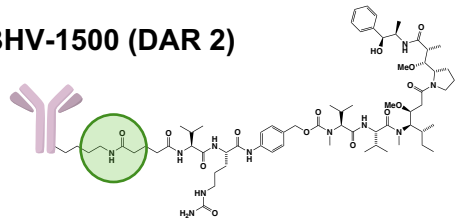
(Global IP filings on "fingerprint" of conjugation technology and individual composition of matter IP for specific ADC molecules)

biohaven

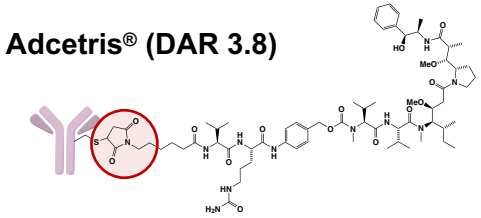
BHV-1500 Is a Differentiated CD30 ADC

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

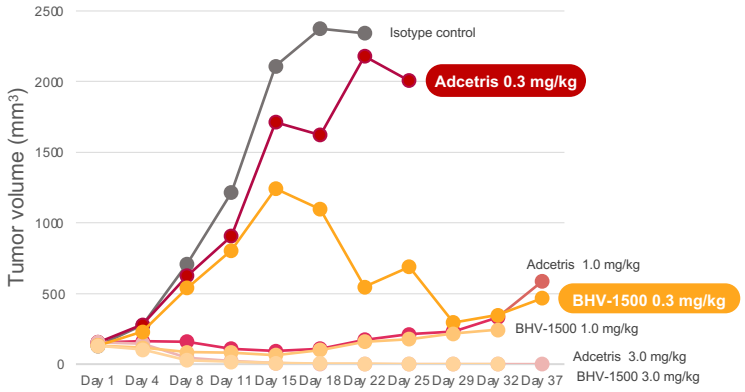
BHV-1500 (DAR 2)



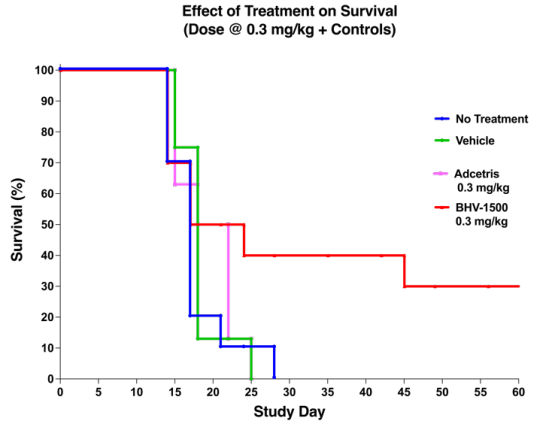
Adcetris® (DAR 3.8)



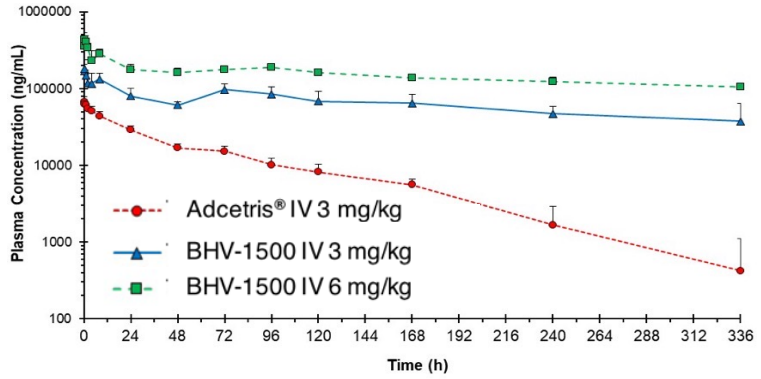
BHV-1500 Demonstrates Superior Efficacy to Adcetris® in a Mouse Xenograft Model



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.

biohaven

Validation of Biohaven's ADC MATE™ Technology

- 11 unique oncology targets selected from marketed compounds/lead Phase 3s for industry leading ADCs, demonstrating platform capabilities across a diverse range of payloads, targets, and tolerability
- Biohaven's ADC technology applied to each of these 11 and evaluated for key attributes translatable to improvements in clinical efficacy and safety

Attribute	Outcome
5 different payloads* in 11 ADCs	**Successful conjugation of each payload**
Cross-species plasma stability assessment	**Substantial stability improvements in 7/7 evaluated**
Cell target cytotoxicity	**Comparable in 7/8 evaluable culture systems**

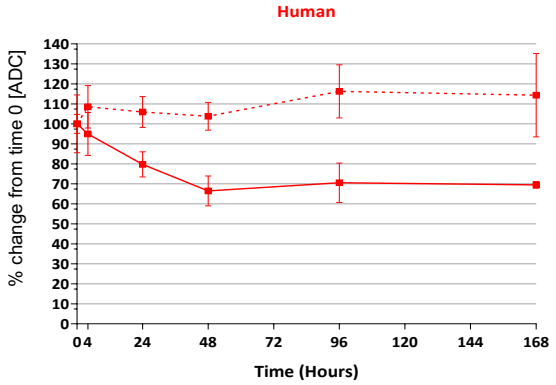
*MMAE, Eribulin, DM1, DXd, PBD dimer.

biohaven

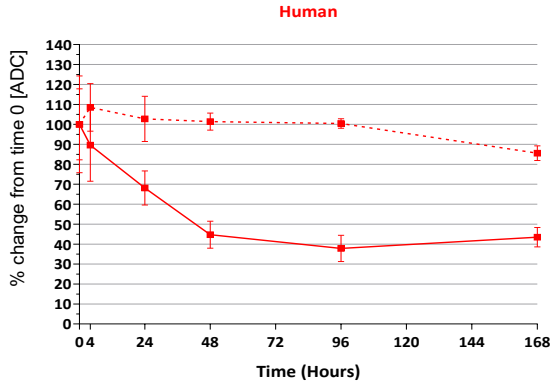
MATE™ Conjugation Platform Consistently Improved Plasma Stability

Biohaven ADC — Clinical Comparator

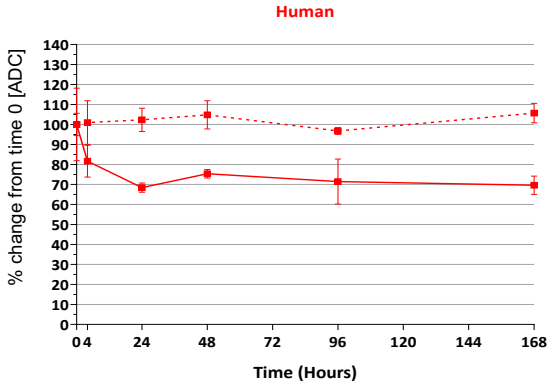
Total ADC @ 37˚
Target A vs. BH-3974



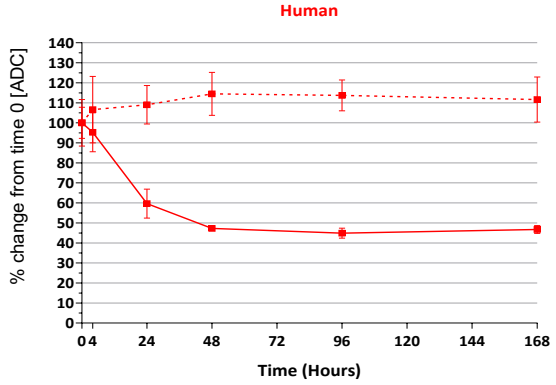
Total ADC @ 37˚
Target B vs. BH-3946016



Total ADC @ 37˚
Target C vs. BH-6015



Total ADC @ 37˚
Target D vs. BH-6028

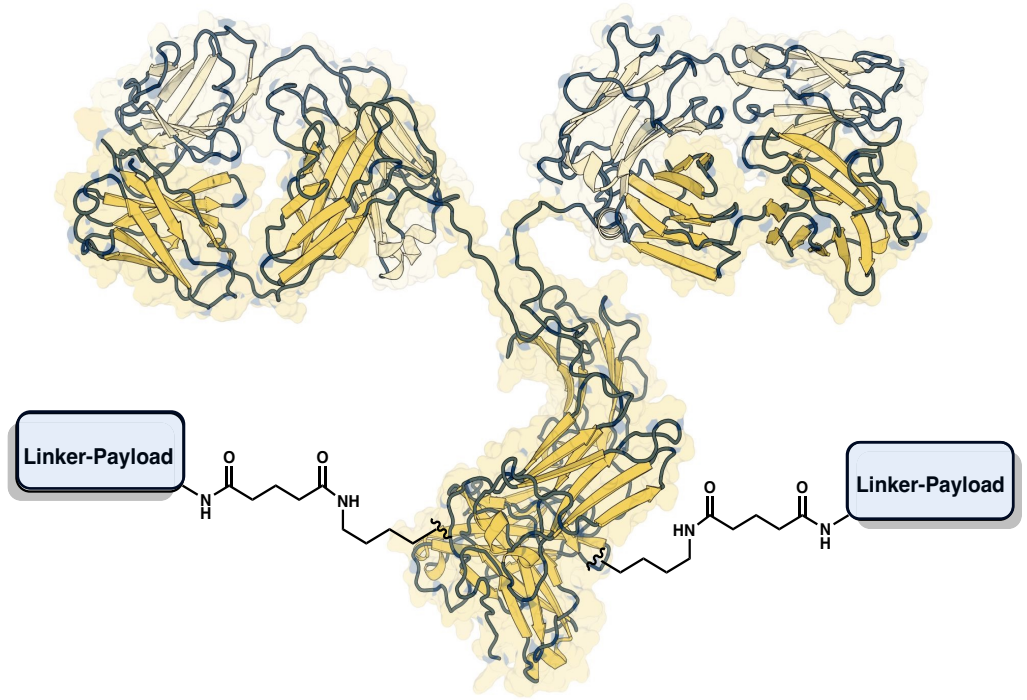


- Highly stable conjugation observed *in vitro* across multiple ADCs
- Able to generate a wide portfolio of stable constructs using native mAbs
- Potential to broaden therapeutic margin, increase time on treatment and improve efficacy

biohaven

Biohaven Is Positioned for Growth in Oncology and ADCs

- Builds on Biohaven's proven track record **of innovation and execution** in bringing transformative medicines to patients
- **Industry-leading expertise** and experience in oncology development, chemistry, discovery, and CMC
- ADC platform technology that provides **flexibility to optimize competitive profiles** and address unmet need
- **Sustainable portfolio** of differentiated ADC programs, with multiple programs entering clinic
- **Phase 1 initiated** for lead program BHV-1510 (Trop-2 ADC)



biohaven


Q&A
biohaven®

Bruce Car, DVM, Ph.D.
Chief Scientific Officer
biohaven®

Frank Greenway, M.D.
Medical Director and Professor
pb Pennington Biomedical Research Center Louisiana State University

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

Barry Byrne, M.D., Ph.D.
Professor and Director of UF Health Advanced Therapeutics
UF UNIVERSITY of FLORIDA

Myostatin for Muscle Health and Metabolic Disorders

biohaven®

Bruce Car, DVM, Ph.D.
Chief Scientific Officer, Biohaven

Frank Greenway, M.D.
Medical Director and Professor, Pennington Biomedical Research Center

Peter Ackerman, M.D.
Vice President, Clinical Development, Biohaven

Barry Byrne, M.D., Ph.D.
Professor and Director of UF Health Advanced Therapeutics, University of Florida

Lindsey Lair, M.D., MBA, F.A.A.N.
Vice President, Clinical Development, Biohaven

biohaven®

Bruce Car, DVM, Ph.D.

Chief Scientific Officer

biohaven®

Taldefgrobep Alfa: Mechanism of Action

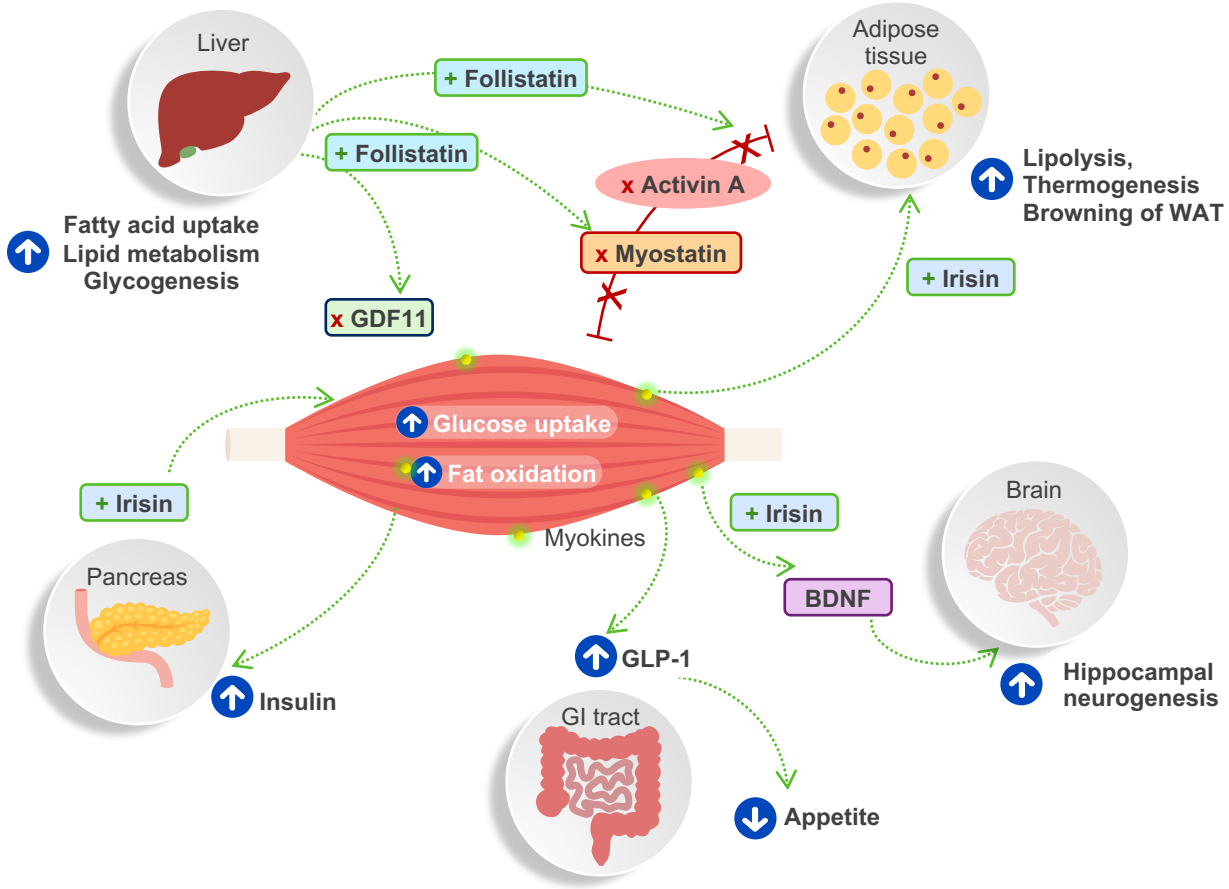
biohaven®

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

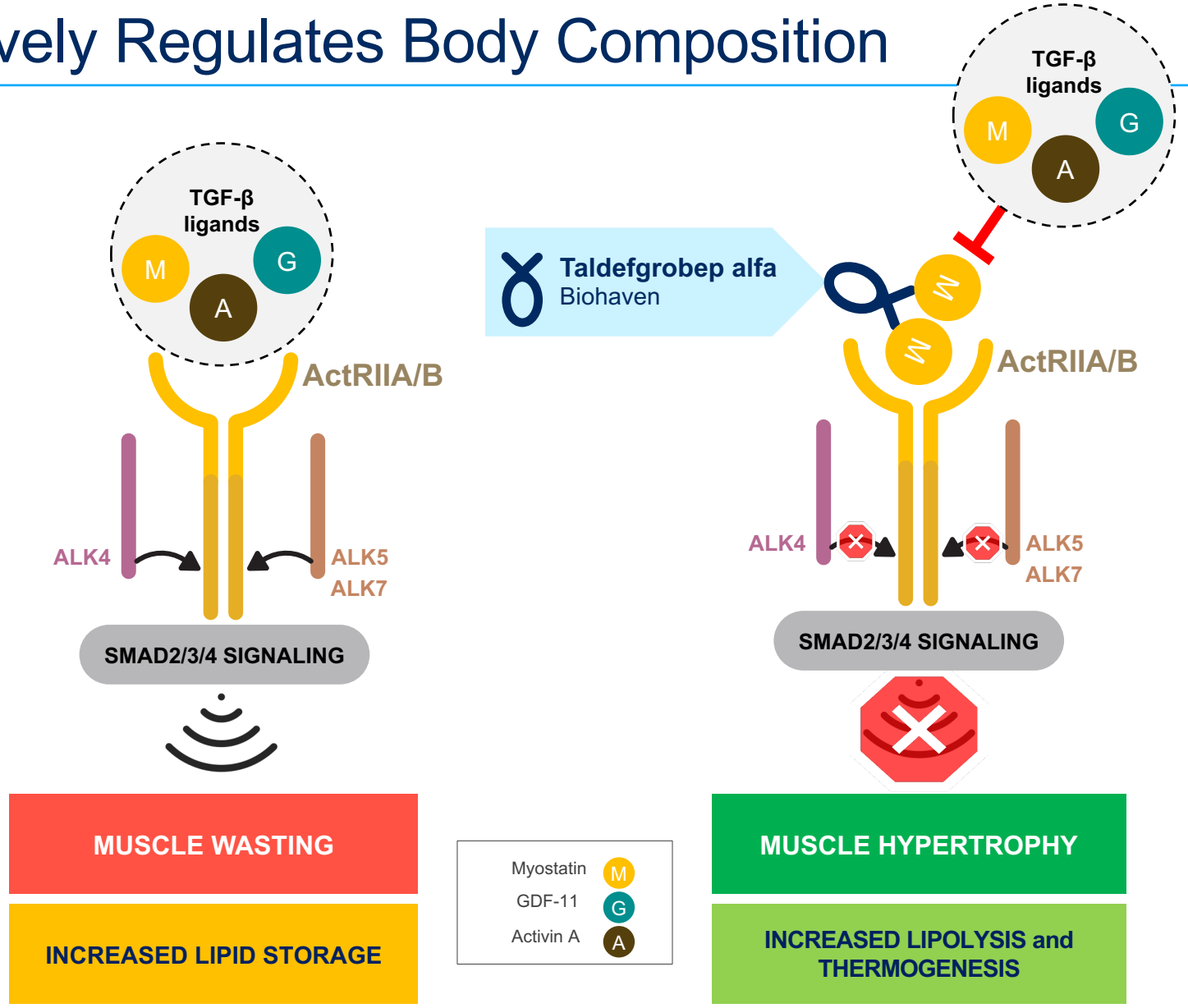
Taldefgrobep alfa inhibits negative regulators of skeletal muscle and adipose tissue improving body composition and resulting in metabolic changes important to overall health and wellness

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.

biohaven

Taldefgrobep Alfa (T-alfa) Positively Regulates Body Composition

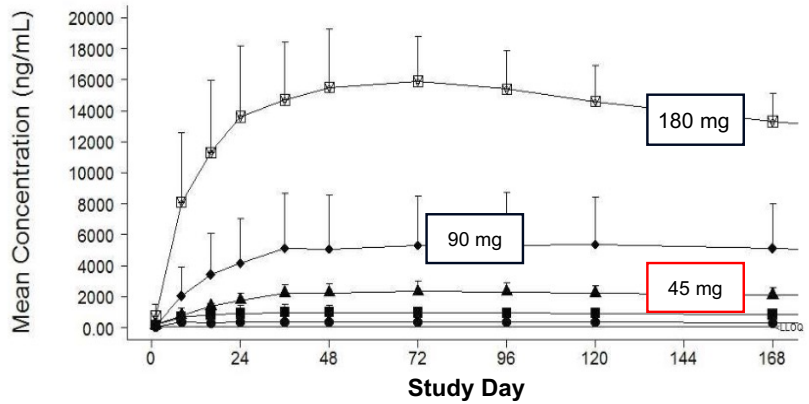
- Multiple TGF-β family ligands regulate muscle and adipose via the ActRIIB receptor
  - Myostatin (GDF-8)
  - GDF-11
  - Activin A
- Myostatin and Activin A expression are increased in obesity, driving reduced muscle and increased adipose mass
- Therapeutic benefit obtained through inhibition of TGF-β family ligand activity results in muscle gain and adipose loss



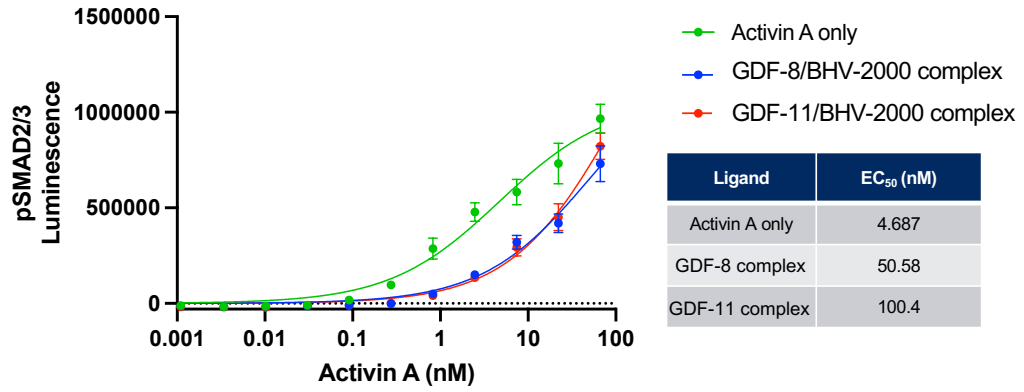
Taldefgrobep Alfa Complexes Extend Favorable Effects

- 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



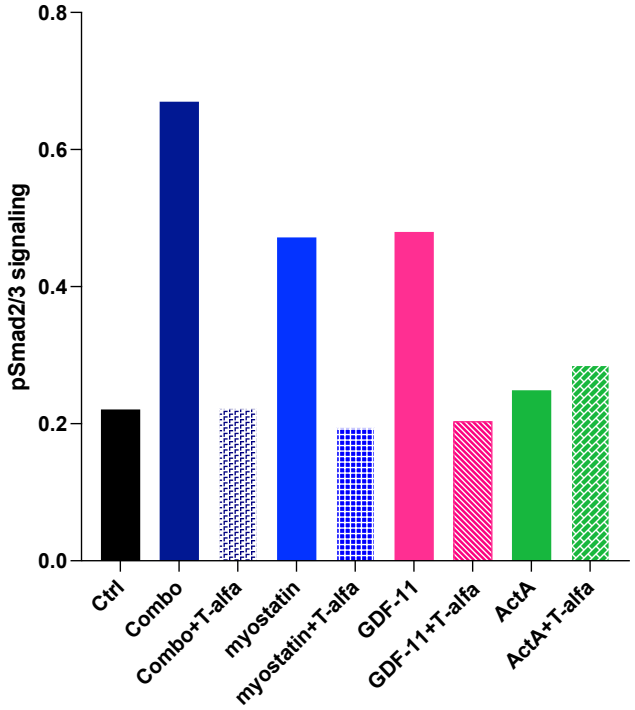
Ligand	EC_{50} (nM)
Activin A only	4.687
GDF-8 complex	50.58
GDF-11 complex	100.4

KEY POINTS

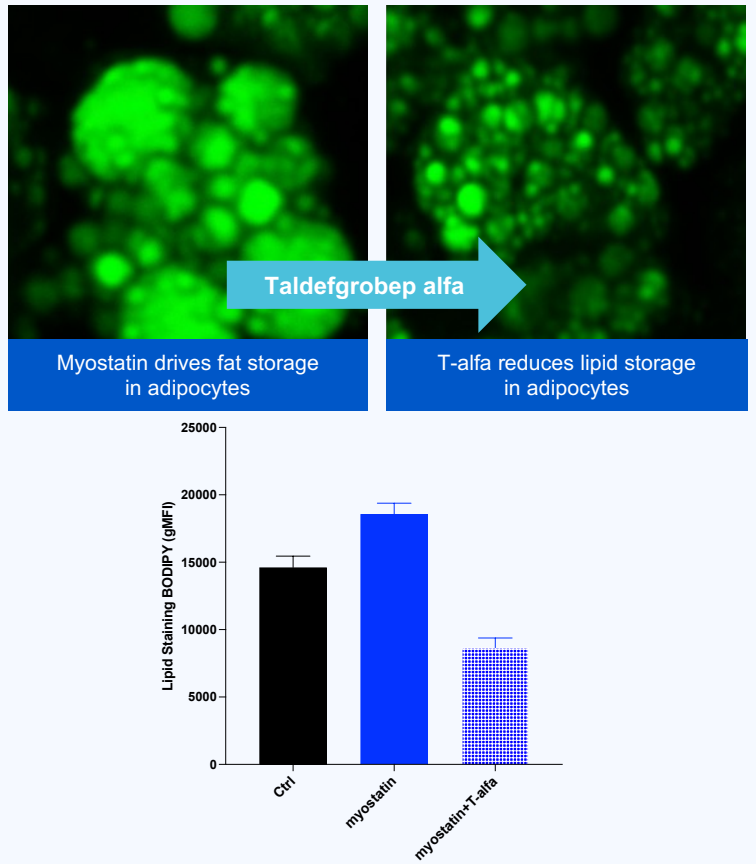
- T-alfa complexes have longer serum half lives than T-alfa, extending T-alfa PK, PD, and breadth of pharmacology
- T-alfa complexes inhibit signal transduction at ActRIIB, improving both muscle growth and fat metabolism

Taldefgrobep Alfa Reduces Adipocyte Lipids and Increases Mitochondrial Content

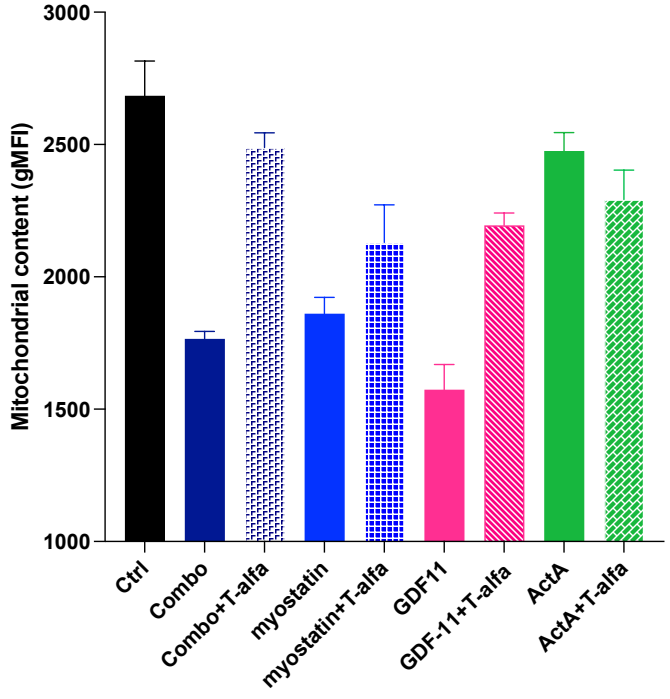
T-alfa Decreases pSmad2/3 Signaling, Directly Regulating Lipid Storage in Adipocytes



*combo—myostatin, GDF-11, activin



T-alfa Increases Mitochondrial Content in Adipocytes



*combo—myostatin, GDF-11, activin

BREAKING NEWS

Taldefgrobep alfa directly reduces adipose tissue storage of fat

Taldefgrobep Alfa Has Differentiated Pharmacology that Balances Efficacy and Safety

Apitegromab/GYM329
Scholar Rock/Roche

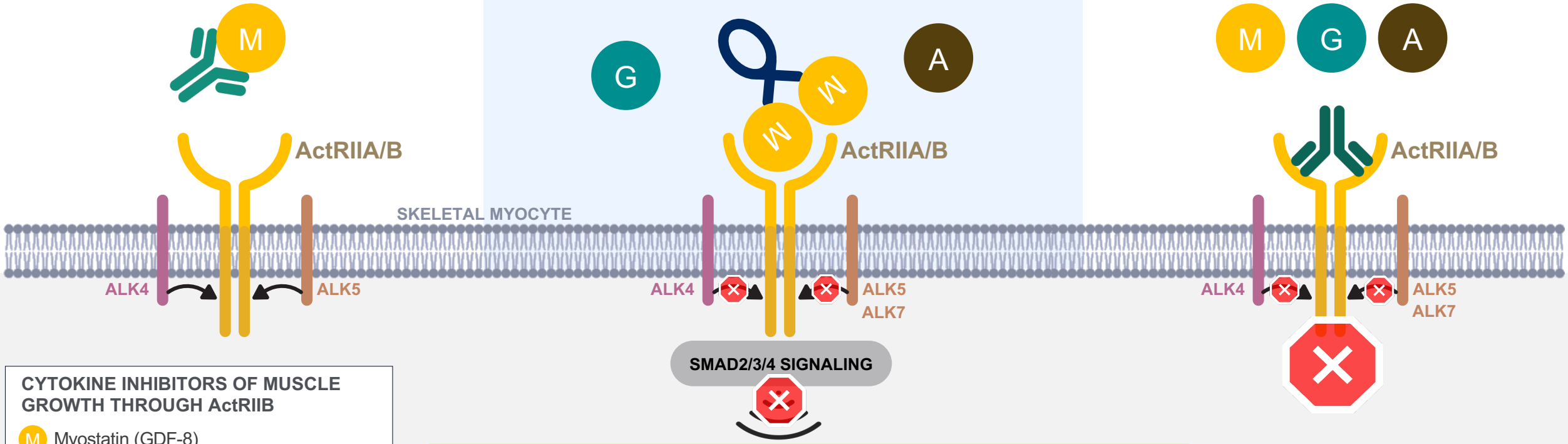
TARGETS pro- and latent myostatin

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

biohaven

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.

biohaven

Frank Greenway, M.D.

Medical Director and Professor

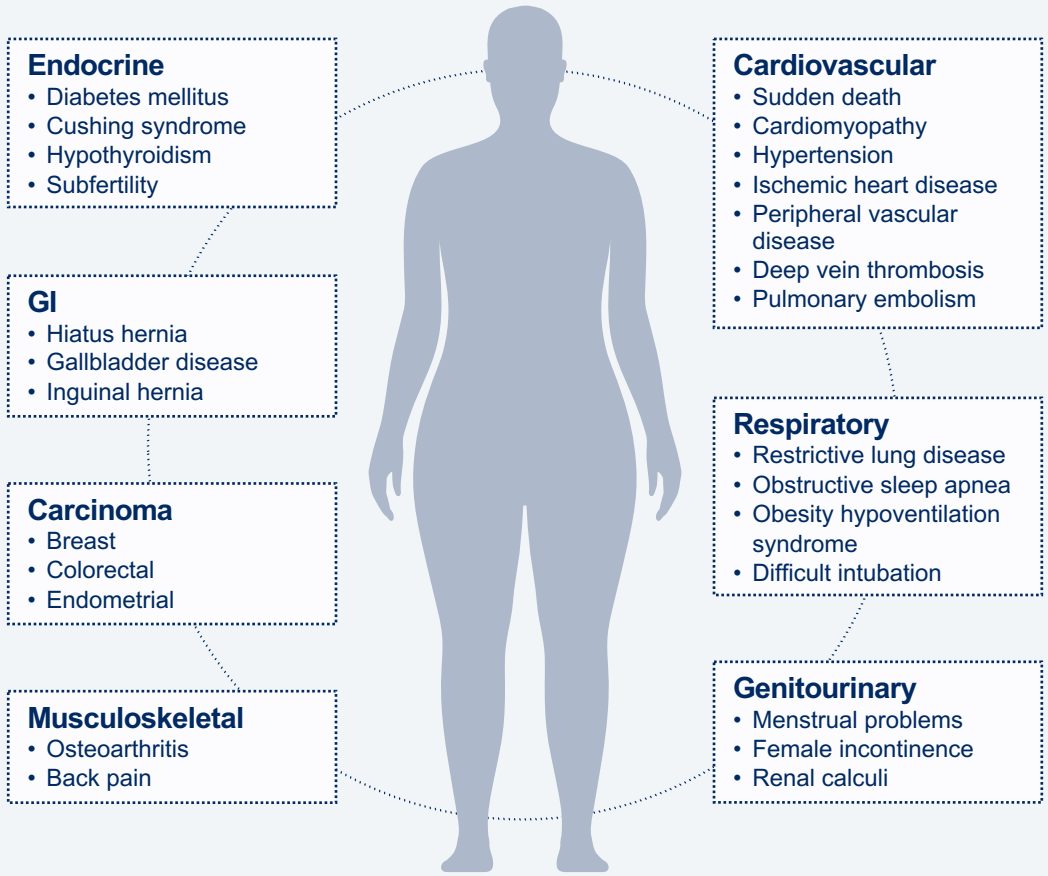
Pennington Biomedical Research Center
Louisiana State University

Obesity: Current Landscape, Challenges and Opportunities

Obesity Is a Global Public Health Crisis

- Obesity is a disease of excess and/or abnormal adipose tissue, not excess mass
  - Cardiometabolic risk correlates with adiposity
- By 2030, 1 billion people worldwide will be living with obesity, including 50% of American adults[1]
  - Obesity and its comorbidities including type 2 diabetes, CV disease, and cancer cost the US healthcare system $175 billion annually[2]
  - In the US, obesity accounts for nearly 20% of all deaths in adults ages 40–85[3]
- Optimized treatment of obesity is a critical unmet medical need

Complications of Obesity[4]

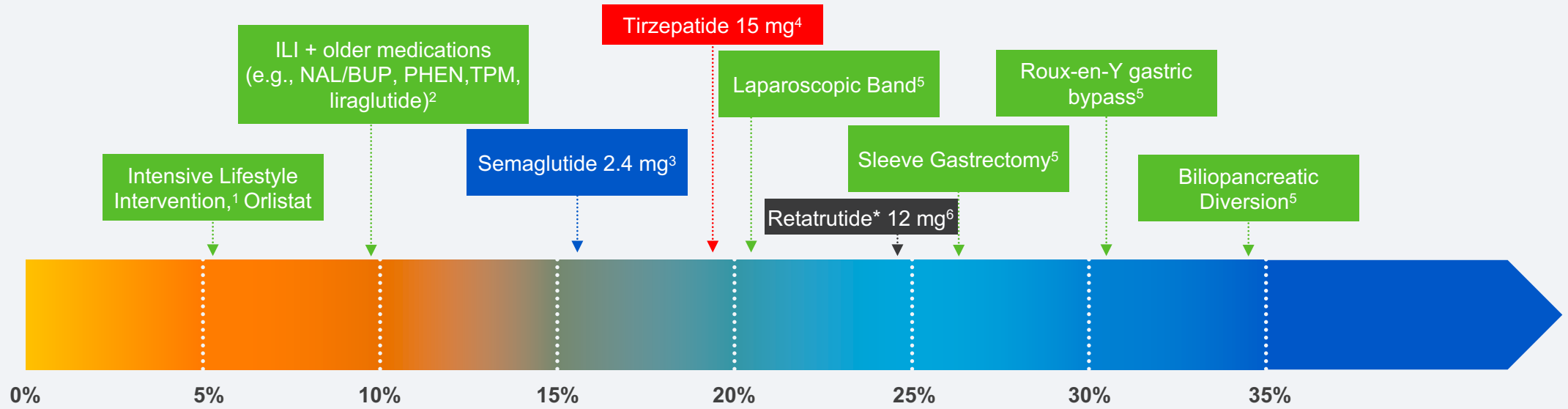


1 . https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022; Accessed 17-NOV-2022. 2. CDC. Adult obesity facts. https://www.cdc.gov/media/releases/2023/p0922-adult-obesity.html#. Accessed May 2024. 3. Goldman D. 2020. https://healthpolicy.usc.edu/article/obesity-second-to-smoking-as-the-most-preventable-cause-of-us-deaths-needs-new-approaches/#:~:text=Obesity%20is%20second%20only%20to,address%20this%20public%20health%20emergency. Accessed 15-MAY-2024. 4. Primeau V et al, Int J Obes (Lond). 2011 Jul;35(7):971-81.

New Medications Are Transforming the Treatment of Obesity

- Highly potent AOMs and combination therapies (based on gut hormones) are achieving reductions in total body weight previously only possible with bariatric surgery but are limited by heterogeneity, tolerability, and other factors
- Future treatment options with novel mechanisms, including those with synergistic or complimentary actions, will help clinicians optimize personalized regimens based on preference, comorbidities, and treatment response

Total body weight reduction by most common intervention



AOM, anti-obesity medications; **NAL**, Naltrexone; **BUP**, Buproprione; **PHEN**, Phentermine; **TPM**, Topiramate.

1. Look AHEAD Research Group. Obesity. 2014;22(1):5-13. 2. Yanovski SZ., et al., JAMA. 2014;311(1):74-86. 3. Wilding JPH., et al., N Engl J Med. 2021;384(11): 989-1002. 4. Jastreboff AM., et al., N Engl J Med. 2022;387(3):205-16. 5. Sylivris A., et al., Obes Rev. 2022;23(7):e13442. 6. Jastreboff AM., et al., N Engl J Med. 2023;389(6):514-26.

biohaven

GLP-1 Agonists Have Been Associated With Excess Lean Mass Loss

- Up to 40% of total body weight loss realized with GLP-1 agonists is due to lean mass loss[1,2]
- With aging, there is an involuntary loss of muscle mass (~3–8% per decade) after age 30[3,4]
- There are important benefits of retained muscle mass beyond power including improved glucose tolerance, increased bone density, and cognitive function[5]
- In a meta-analysis of 16 studies, low muscle mass index is a major risk factor for all-cause mortality (RR 1.57; 95% CI 1.25–1.96; p <0.001) (Figure 1)[6]
  - In people living with obesity, low muscle volume and low muscle quality (e.g., intramuscular fat) is associated with increased risk for early all-cause mortality, even when controlling for strength and comorbid disease[7]

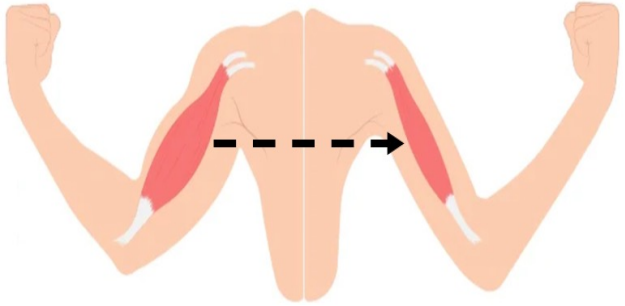
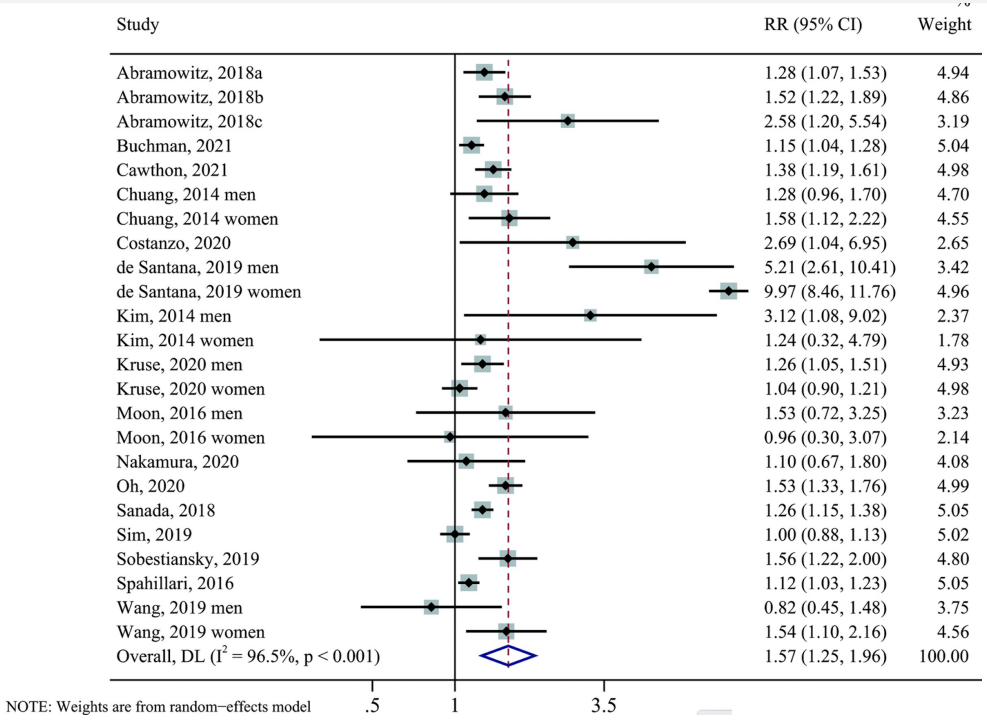


Figure 1

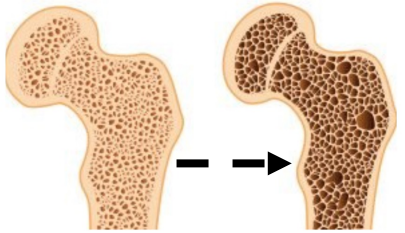


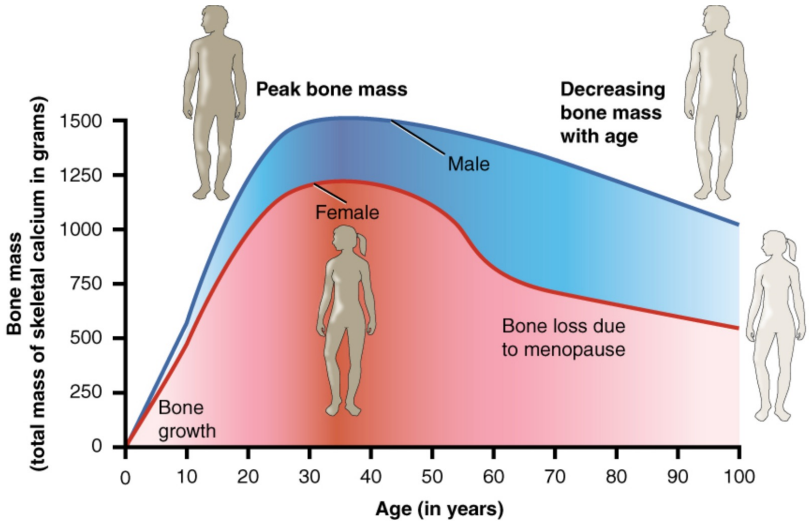
RR, risk ratio/relative risk; **CI**, confidence interval.

1. Wilding JPH et al, *N Engl J Med*. 2021;384(11):989-1002. 2. McCrimmon RJ et al, *Diabetologia*. 2020;63(3):473-485. 3. WebMD. Sarcopenia with aging. NOV 2022. https://www.webmd.com/healthy-aging/sarcopenia-with-aging. Accessed 15-MAY-2024. 4. Volpi E., et al., Curr Opin Clin Nutr Metab Care. 2004;7(4):405-10. 5. Severinsen MCK., et al., Endocr Rev. 2020;41(4):594-609. 6. Wang Y., et al., PLoS One. 2023;18(6):e0286745. 7. Medical Press. https://medicalxpress.com/news/2024-05-poor-muscle-health-common-people.html. Accessed 17-MAY-2024.

GLP-1 Agonists Have Been Associated With Accelerated Bone Loss

- Chronic use of GLP-1 agonists has been associated with reduced bone mass in the spine and hips, and decreased tibial cortical thickness relative to placebo[2]
- Muscle loss and bone loss often occur together[3]
  - Stress exerted by skeletal muscle can promote growth and development of bone
  - Bone loss and muscle loss occur naturally with aging
  - Bone loss is accelerated in individuals who develop sarcopenia
- In a CV outcomes trial, fractures of the hip and pelvis were 4–5x more common on Wegovy vs. PBO in females and participants ≥75 years old.[4]
- Complications of low bone density (osteoporosis) is expensive and a major cause of morbidity and mortality[5]
- Myostatin is a known promoter of osteoclast differentiation and inhibitor of osteoblast differentiation contributing to bone loss[6,7]
  - Inhibition of myostatin can accelerate bone regeneration[8]
  - Activin A signaling can adversely affect osteoblast gene expression and reduce bone mineralization[9,10]





1. Wikimedia Commons. 2. Hansen MS, et al., eClinicalMedicine. 2024;72:102624. 3. Laskou F et al, Climacteric. 2022;25:88–95. 4. Wegovy USPI. Accessed 15-MAY-2024. 5. Office of Surgeon General. Bone health and osteoporosis: a report of the surgeon general. Reports of the Surgeon General. 2004. 6. Dankbar B., et al., Nat Med. 2015;21(9):1085-90. 7. Qin Y., et al., J Biol Chem. 2017;292(26):11021-33. 8. Wallner C., et al., Sci Rep. 2017;7(10:9878. 9. Alves RDAM., et al., Mol Cell Proteomics. 2013;12(10):2890-900. 10. Baroncelli M., et al., J Cell Physiol. 2020;235(5):4865-77. doi: 10.1002/jcp.29365.

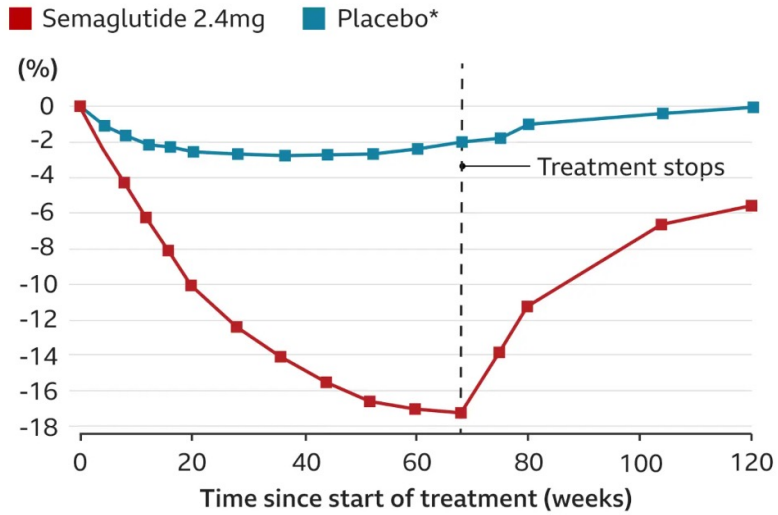
Discontinuation of GLP-1 Agonists Is Associated With Rapid Weight Regain, Often in the Form of Visceral Fat

- Approximately two-thirds of Americans stop GLP-1 therapy within 1 year of initiation[1]
  - GI-related side effects are the most common reasons for discontinuation[2]
- Approximately two-thirds of lost body weight returns within one year of stopping GLP-1 therapy [3]
  - After stopping GLP-1 therapy, weight returns in the form of central obesity and visceral adiposity[1]

Most common GI-related Reasons for Discontinuation of GLP-1 Therapy[2]

Reason	Rate
Made me feel sick	64.4%
Made me throw up	45.4%
Caused diarrhea/gas/bloating	26.3%

Weight Rebound Following Discontinuation of Wegovy[3]



1. Scientific American. What happens when you quit Ozempic. APR 2024. https://www.scientificamerican.com/article/you-quit-ozempic-or-wegovy-what-happens-next/#:~:text=About%20two%2Dthirds%20of%20those,according%20to%20an%20industry%20analysis. Accessed 15-MAY-2024. 2. Sikirica MV. Et al., Diabetes Metab Syndr Obes. 2017;10:403-12. 3. Wilding, et. al., Diabetes Obes Metab. 2022; 24(8):1553-64. doi: 10.1111/dom.14725.

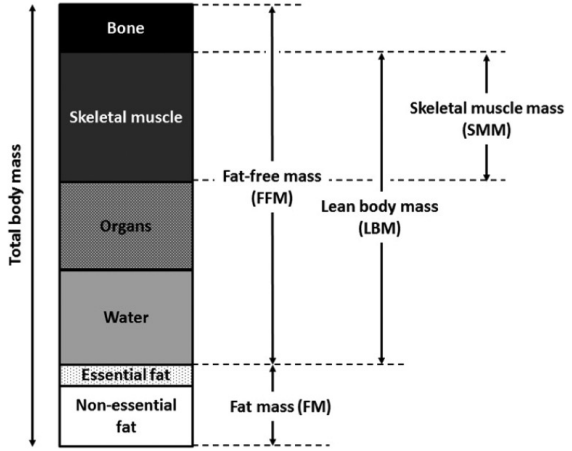
BMI and Total Body Weight Are Insufficient for Determining Obesity-Related Health Risk or Treatment Response

- Obesity is a disease of excess and abnormal adipose tissue, not excess mass
- In 2023, the AMA adopted a policy discouraging the use of BMI alone in the diagnosis of obesity[1]
  - BMI is not a measure of body fat
- Incorporating more sensitive measures of body composition including anthropometric measures of central obesity, imaging, and bioimpedance can provide important information about an individual's risk for cardiometabolic disease[2,3]
  - DEXA is not sufficient for determining changes in skeletal muscle mass

Limitations of Current Monitoring Techniques for Obesity[4]

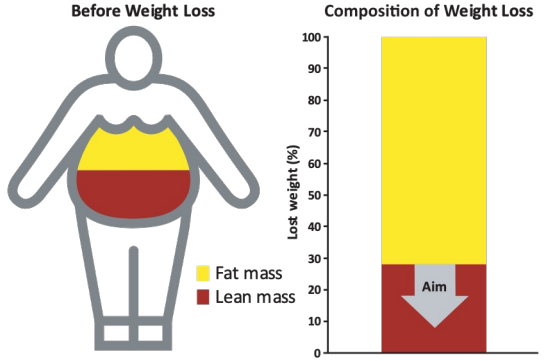
- Current practices to measure weight loss outcomes focus on **weight/BMI which has limited value**
- BMI is a **poor surrogate for body fat, body composition, fat distribution (visceral fat), and risk stratification** as it cannot distinguish lean muscle mass from adipose tissue
- It is more important than ever to know **where weight loss is coming from** so you don't leave someone worse off than when they started!
- **Losing too much lean mass has serious health consequences** (sarcopenia, frailty, psychological/emotional and neurological effects, and weight gain)

Limitations of DEXA Scans in Determining Body Composition Changes



Change in TBW is a Combination of FM + LM

GOAL: Loss of excess abnormal fat mass and preservation of lean mass



Christoffersen BØ, et al. Obesity (Silver Spring). 2022 Apr;30(4):841-857.

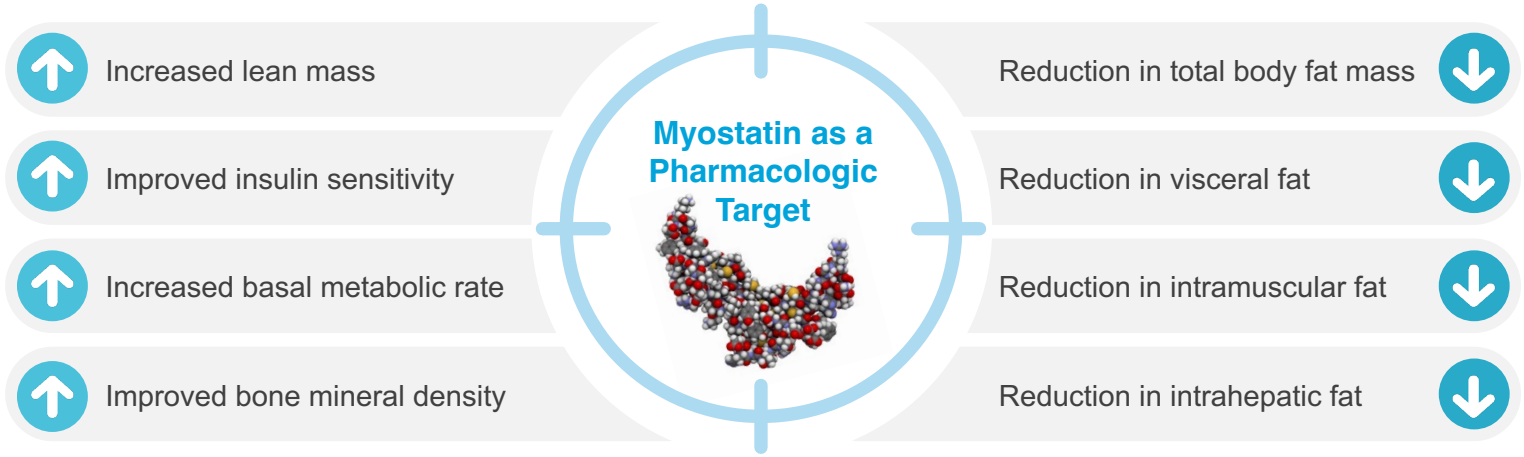
BMI, body mass index.

1. AMA. AMA adopts new policy clarifying role of BMI as a measure in medicine. 14-JUN-2023. https://www.ama-assn.org/press-center/press-releases/ama-adopts-new-policy-clarifying-role-bmi-measure-medicine#:~:text=Under%20the%20newly%20adopted%20policy,circumference%20and%20genetic/metabolic%20factors. Accessed 16-MAY-2024. 2. Browning LM et al, Nutr Res Rev 2010;23(2):247-69. 3. Roriz AP et al, Nutr clín diet hosp 2016;36(2):168-79. 4. Willoughby D. et. al., Nutrients. 2018;10(12):1876.

There Is Still More that can be Done to Improve the Quality of Care for People Living with Obesity

- Nonclinical and clinical data demonstrate blocking myostatin and other key TGF-beta ligands, including activin A, can produce metabolic and body composition changes highly relevant to people with overweight and obesity[1,2,3]
- Improvements in body composition are optimized by those agents that can target both myostatin and activin A signaling[4]
- May potentially be used alone or in combination with gut hormone-based treatments in the future

Anti-myostatin-Induced Physical and Metabolic Changes Important to People living with Obesity



Comparative Efficacy Outcomes in Adults Living with Overweight and Obesity

Drug	Dosing	Δ Total body weight	Δ Total fat mass	Δ Lean body mass	Δ A1C
Bimagrumab n=37	IV Q4W	-6.5%	**-20.5%**	**+3.6%**	-0.76%
Semaglutide 2.4 mg n=1,306	SC QW	-14.9%	-19.3%	-9.7%	-1.6%

Heymsfield SB, et. al. JAMA. 2021;384(11):989-1002; Wilding JPH, et. al. STEP 1 Body Composition. J Endocr Soc. 2021;5(1):A16-17; Wegovy USPI (STEP2); **NA**, not available; **PO**, oral; **QW**, once weekly; **Q4W**, once monthly..

1. Heymsfield SB, et al. JAMA Netw Open 2021;4(1):e2033457. 2. Ackerman P, et al. Presented at ObesityWeek 2023. Oct 14-17, 2023; Dallas, TX. Poster 211. 3. Jan J., et al., Nutrients. 2021;13(5):1508. 4. Latres, E. et al, *Nat Comm* 8, 15153 (2017).

Conclusions

- Obesity is a disease of excess and abnormal adipose tissue, not excess mass

- GLP-1-associated AOMs have demonstrated the ability to reduce total body weight at levels commensurate with bariatric surgery
  - However, these agents have been associated with liabilities that can possibly compromise long-term health including excess loss of lean mass, loss of bone density, and rapid weight regain with dosing interruption

- Newer therapies that can help address the limitations of the current standard of care are needed
  - Agents that can effectively reduce body fat and improve metabolic health, while mitigating against muscle loss would be ideal

- We need better methodologies in the clinic for accurately measuring the quality of weight loss and body composition change

biohaven

Peter Ackerman, M.D.

VP, Clinical Development

biohaven®

Taldefgrobep Alfa for the Treatment of Obesity

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 ActRIIB 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

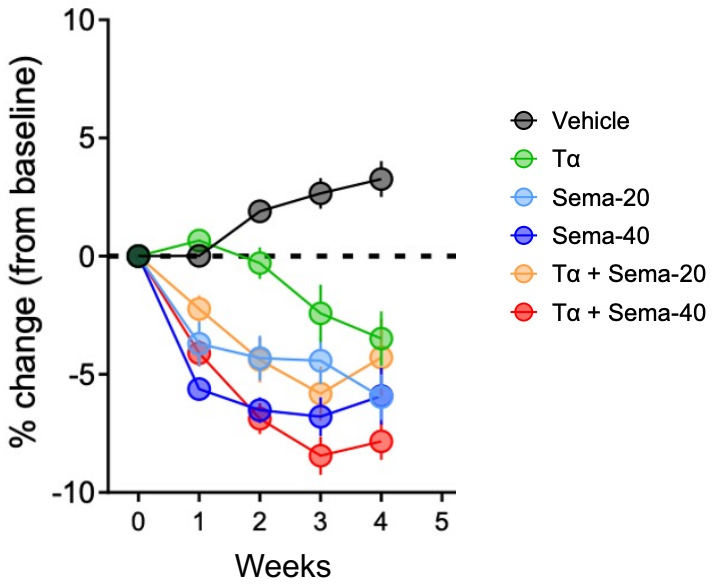
Phase 3 Program in SMA

- 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

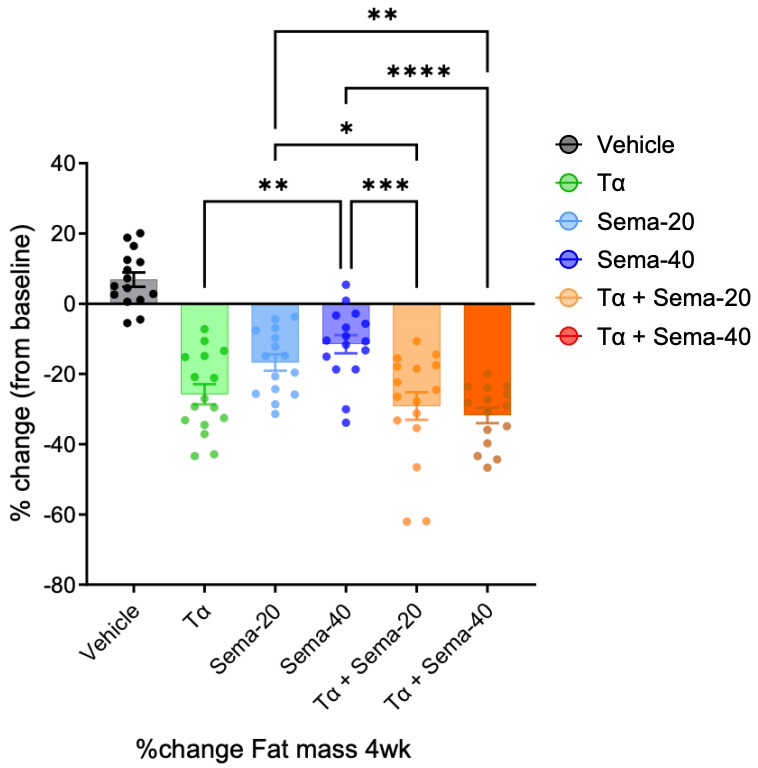
biohaven

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

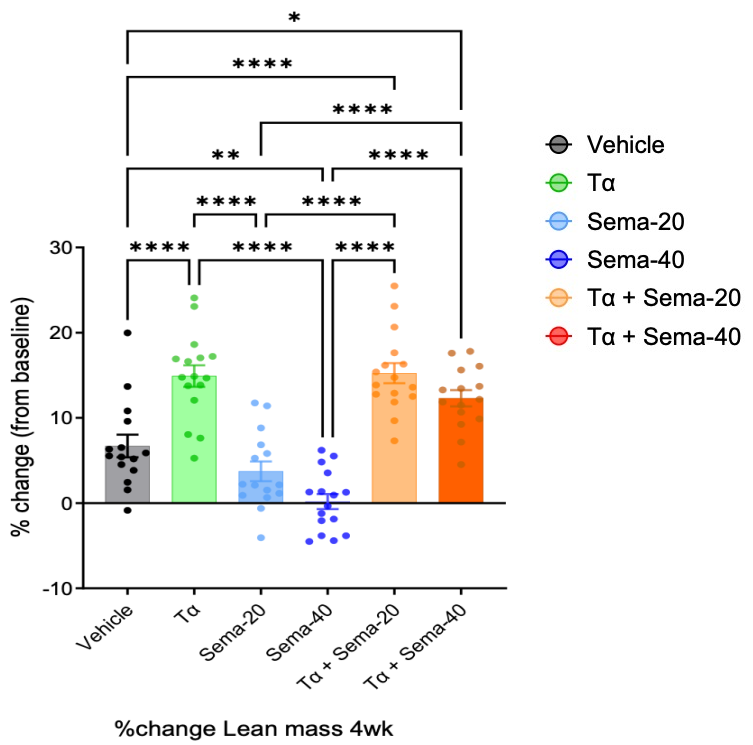
T-alfa Shows Weight Loss, and Combination with Semaglutide shows **Higher Reduction in Body Weight** than Semaglutide Alone



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



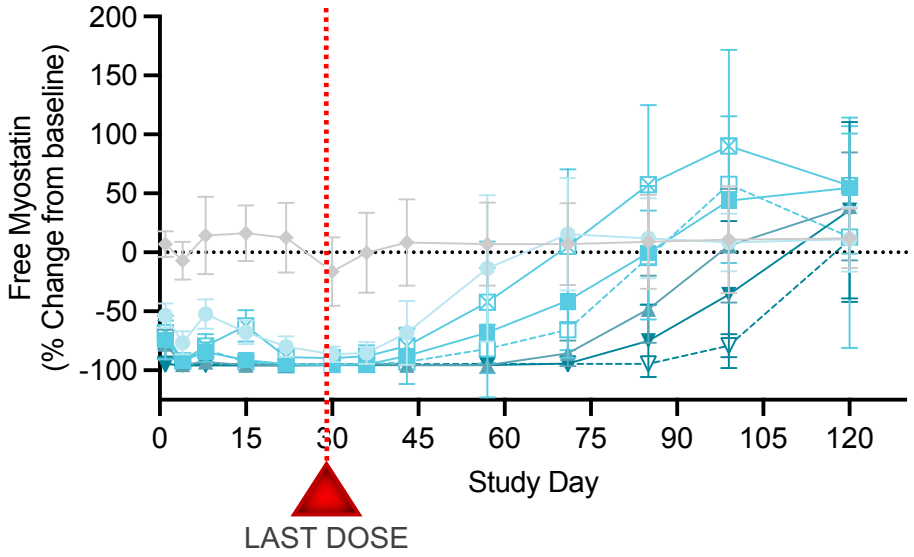
Tα, taldefgrobep alfa; **DIO**, diet induced obesity.
* <= 0.05, ** <= 0.01, *** < 0.001 and **** <0.0001.

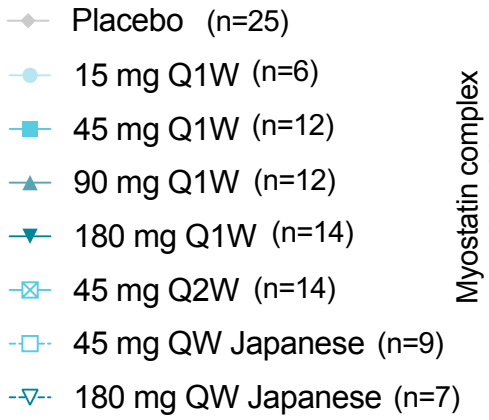
biohaven

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

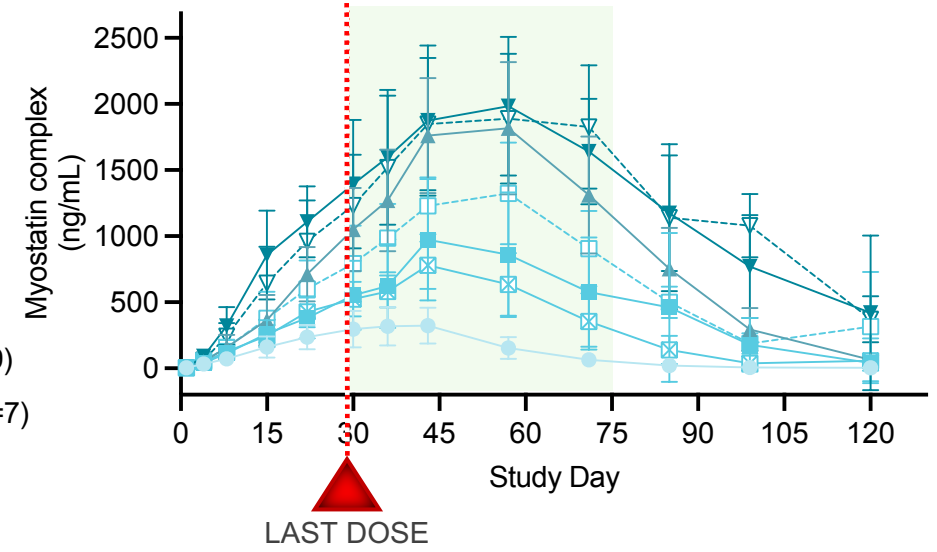
Taldefgrobep alfa activity is sustained by circulating taldefgrobep alfa-myostatin complex

Free Myostatin Levels





Drug-Myostatin Complex Sustains Activity



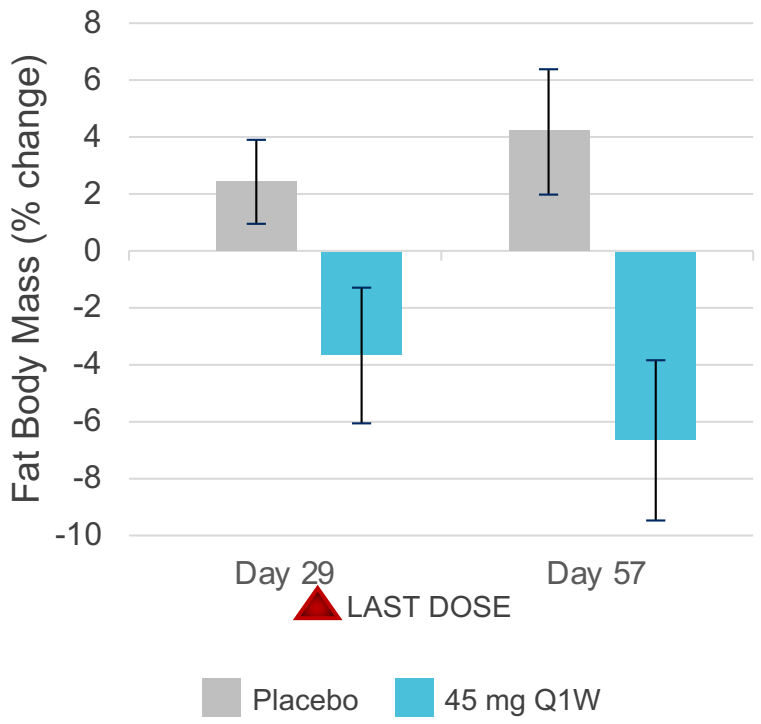
KEY POINTS

- 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

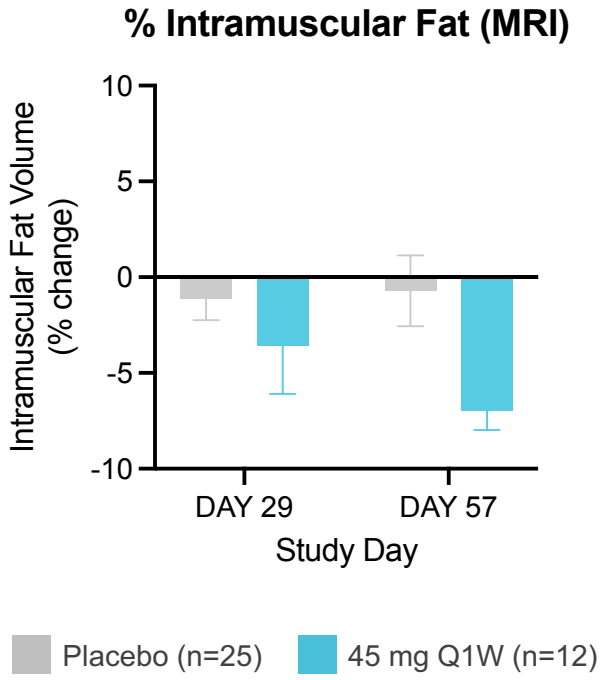
biohaven

Taldefgrobep Alfa Improves Body Composition in Non-Obese Adults

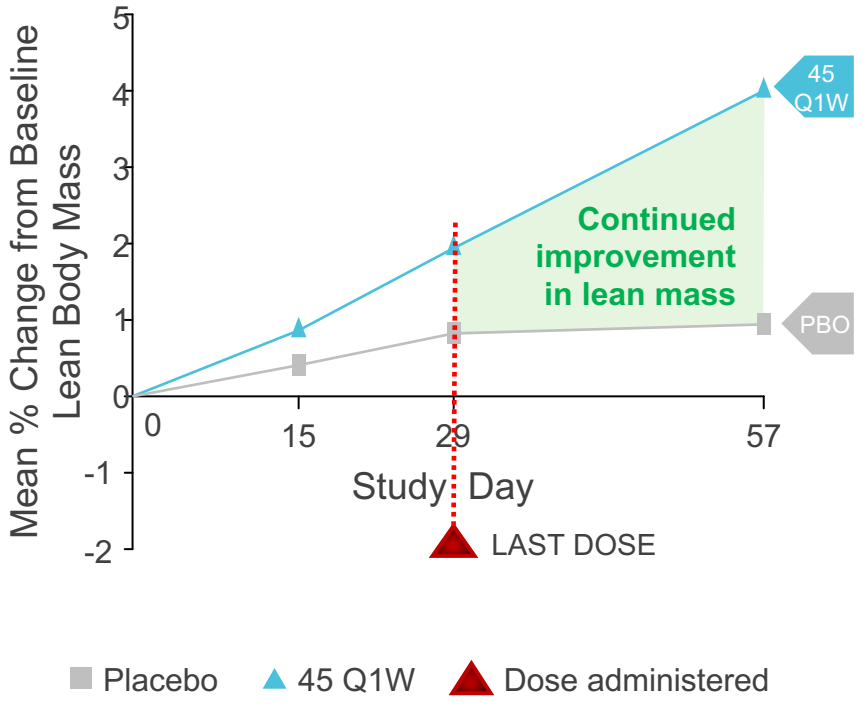
Taldefgrobep Alfa Continued to Decrease **Total Fat Mass** Beyond the Dosing Period



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.

biohaven

Taldefgrobep Alfa Has a Favorable Tolerability Profile Compared to Bimagrumab

Muscle- / GI-Related AEs	Taldefgrobep Alfa MAD Pooled[1] N=72	Bimagrumab 30 mg/kg[2] Single Dose Study N=10	Bimagrumab 10 mg/kg[3] Q4W Multi-dose Study N=37
Muscle spasm	4%	30%	41%
Musculoskeletal stiffness	0	30%	NA
Myalgia	1%	30%	NA
Muscle weakness	0	10%	NA
Diarrhea	1%	10%	41%
Nausea	0	NA	11%
Lipase level increased	0	0	11%

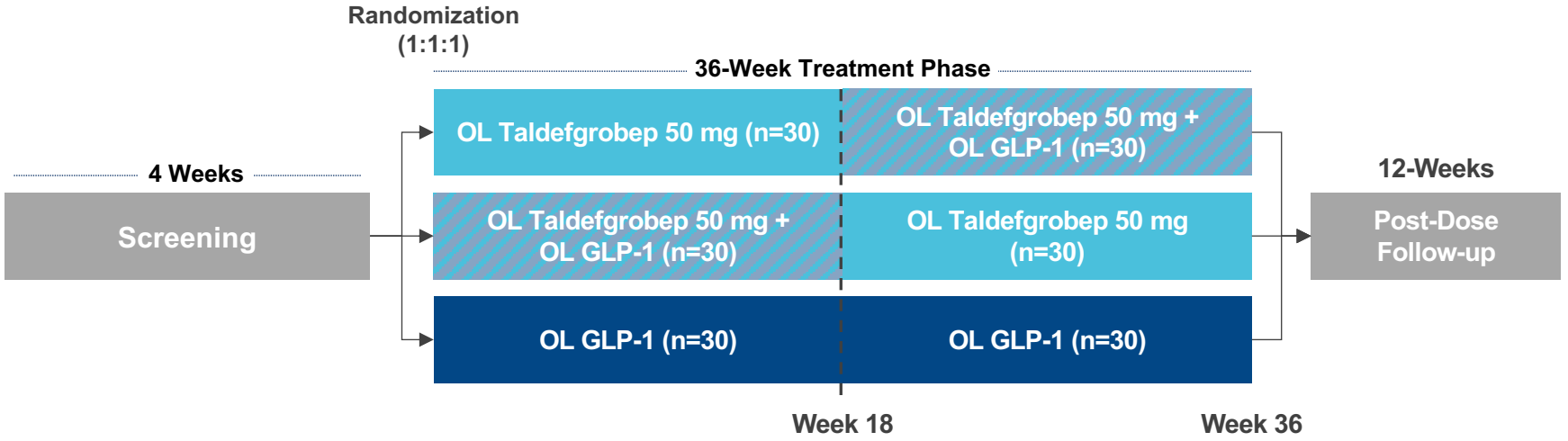
KEY POINT

Taldefgrobep alfa avoids GI- and muscle-related adverse events commonly reported in bimagrumab clinical trials

1. Study CN001001 conducted in healthy adults receiving taldefgrobep (15-180mg QW x 1 month). 2. Garito et al, Diabetes Obes Metab. 2018;20:94–102. 3. Heymsfield et al JAMA Network Open. 2021;4(1):e2033457.

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.

biohaven

Barry Byrne, M.D., Ph.D.

Professor and Director of UF Health
Advanced Therapeutics

UF UNIVERSITY of FLORIDA

Taldefgrobep Alfa for the Treatment of Spinal Muscular Atrophy

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

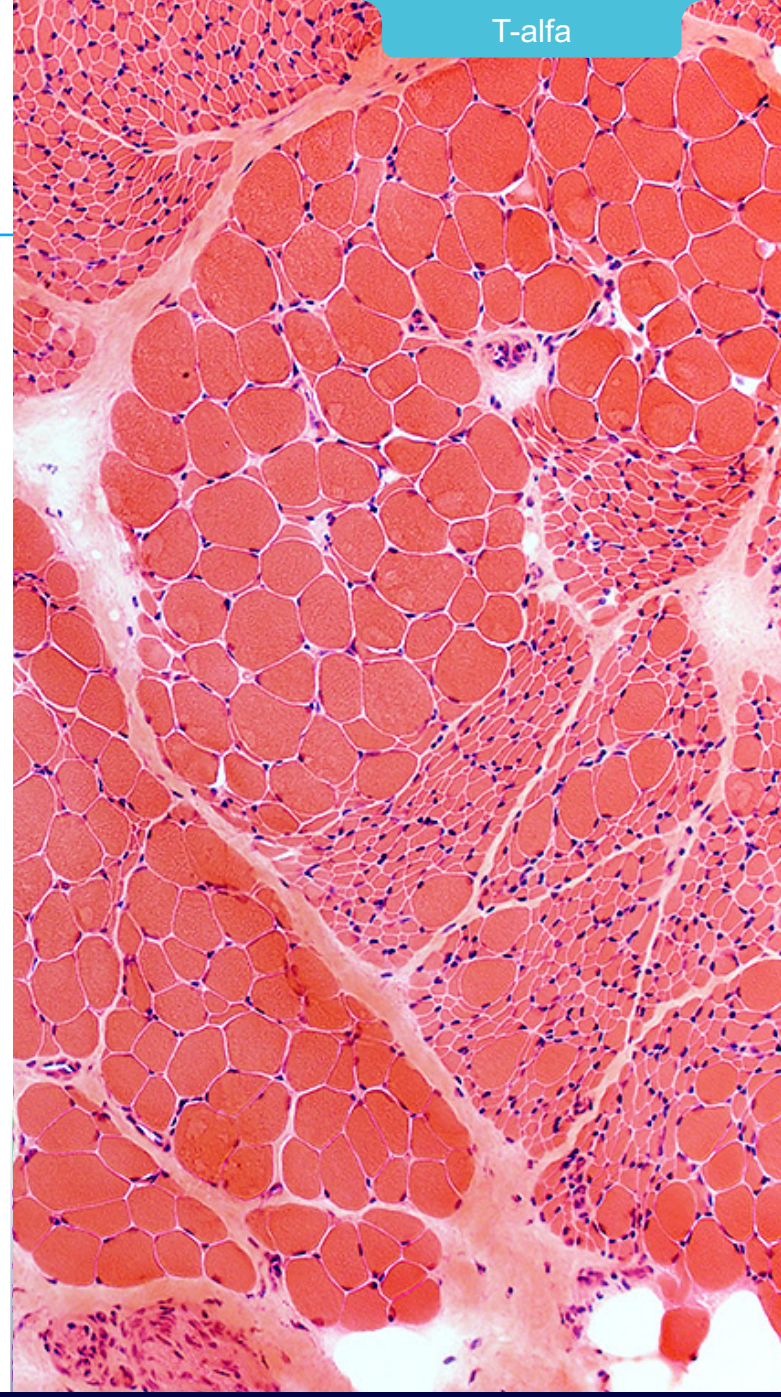
1. Mercuri E et al Nat Rev Dis Primers. 2022 Aug 4;8(1):52 . 2. Day JW et al. BMC Pediatr. 2022;22(1):632. 3. Darras BT, et al. N Engl J Med. 2021;385(5):427-435. 4. Finkel RS, et al; ENDEAR Study Group. N Engl J Med. 2017;377(18):1723-1732 5. https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf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

Taldefgrobep Alfa Directly Targets Muscle and Has Potential to Improve Function in SMA

Taldefgrobep alfa builds muscle and has potential to improve functioning and quality-of-life across a broad SMA population

- Taldefgrobep alfa has demonstrated ability to increase muscle mass in humans[1]
- SMA patients have intact muscle (unlike muscular dystrophy) that can potentially be enhanced by taldefgrobep alfa[2]
- Treatment with taldefgrobep alfa in combination with SMN upregulators has shown benefit in preclinical studies in SMA models[3]

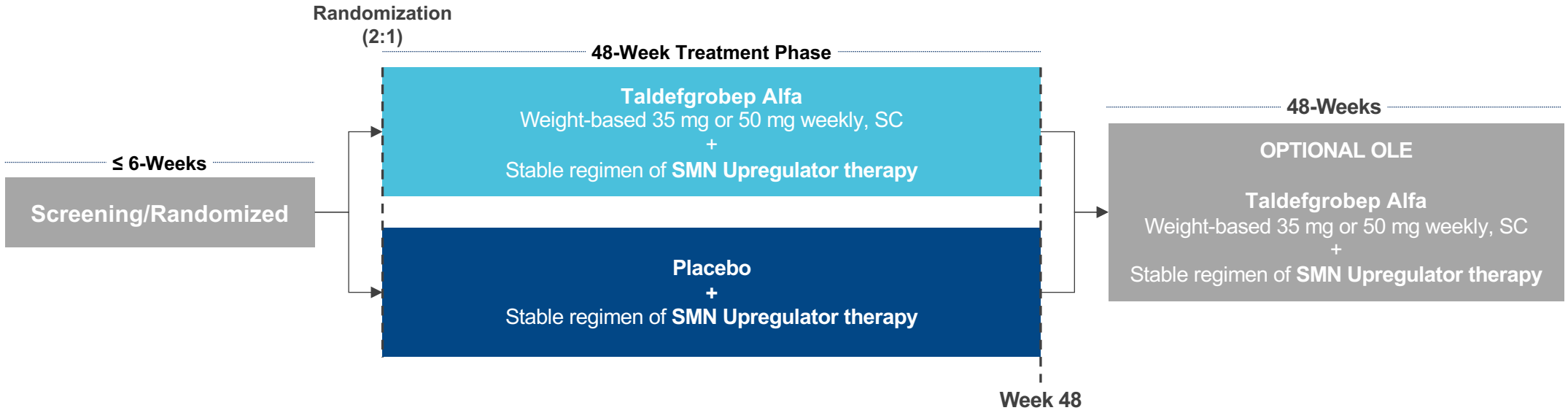
RESILIENT is an ongoing global Phase 3 trial evaluating the efficacy and safety of adjunctive taldefgrobep alfa in combination with SOC SMN upregulating treatments in SMA



SOC, Standard of care.

1. Biohaven data on file. 2. Neuromuscular Disease Center, Washington University, St. Louis. (2019, August 28). Spinal muscular atrophy (5q). https://neuromuscular.wustl.edu/pathol/sma.htm#xd_co_f=YzA2ODcyYjItMGI4Yi00NTEwLThjYjYtZTliMGQ2ODE0NTI3~. 3. Bechtold C, et al. June 20-24, 2023, EPNS, Prague, Czech Republic.

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 + Stable regimen of SMN Upregulator therapy (nusinersen, risdiplam, and/or history of treatment with onasemnogene abeparvovec-xioi)
TREATMENT DURATION	48-week treatment period, optional 48-week open-label extension (OLE)
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)

biohaven

RESILIENT Study Population

Selected based on unmet need and potential for benefit on validated clinical endpoints

Broad SMA population with high unmet need, inclusive of the following:

- Age
- Ambulatory status
- SMA Type
- Background therapy with nusinersen, risdiplam, and/or history of onasemnogene abeparvovec

Reflects evolution of SMA landscape with use of SMN upregulating therapies, widespread newborn screening, early treatment, and a focus on functional status rather than SMA Type[1–5]

Clinical benefit will be assessed on well established endpoints that are validated across a broad SMA population (MFM-32, RULM, and RHS)

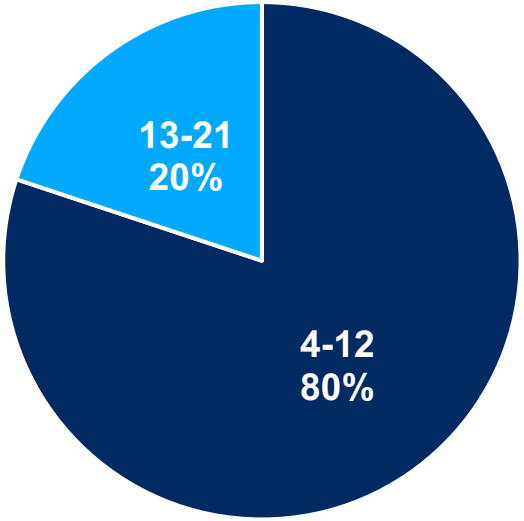
MFM-32, 32-item motor function measure; **RULM**, revised upper limb module; **RHS**, revised hammersmith scale.

1. Dangouloff T et al, Current Perspectives. Ther Clin Risk Manag. 2019 Oct 2;15:1153-1161. 2. Sumner CJ et al Nat Med. 2022 Jul;28(7):1348-1349. 3. https://www.curesma.org/newborn-screening-for-sma. 4. https://www.sma-europe.eu/newborn-screening-in-sma 5. https://www.curesma.org/wp-content/uploads/2023/06/9062023_State-of-SMA_vWeb.pdf

RESILIENT Enrolled Target SMA Population

Baseline characteristics of randomized participants

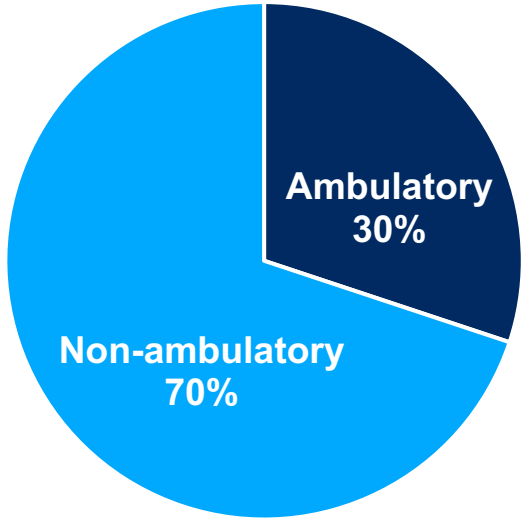
Age (Years)



Majority of SMA patients are adolescents and adults[1]

RESILIENT includes ages 4–21
SAPPHIRE includes only ages 2–12 in primary population[6]
MANATEE includes ages 2-25 in part 2[7]

Ambulatory Status



Ambulatory status varies based on SMA type and age at treatment onset[2-5]

RESILIENT includes ambulatory and non-ambulatory
SAPPHIRE includes only non-ambulatory[6]
MANATEE includes only ambulatory in part 2[7]

1. Cure SMA. (2023, June 18). *State of SMA 2022 report*. https://www.curesma.org/wp-content/uploads/2023/06/9062023_State-of-SMA_vWeb.pdf 2. Staunton Het al, J Neuromuscul Dis. 2023;10(6):1093-1109. 3. Farrar MA et al, J Pediatr. 2013 Jan;162(1):155-9. 4. Dangouloff T et al, Current Perspectives. Ther Clin Risk Manag. 2019. 5. Sumner CJ et al Nat Med. 2022 Jul;28(7):1348-1349. 6. ClinicalTrials.gov: NCT05156320. 7. ClinicalTrials.gov: NCT05115110.

MFM32 Is Ideal Endpoint for the Broad RESILIENT Population

DISEASE SEVERITY

AMBULATORY → NON-AMBULATORY

MFM32 (2–60 years)
Motor Function Measure-32
Designed for evaluation of neuromuscular diseases, including SMA, in ambulant and non-ambulant patients covering a full severity spectrum and variety of motor functions; well-validated in SMA including magnitude of clinically meaningful change; absence of floor and ceiling effects; primary endpoint in a successful registrational trial in SMA[1–8]

Does not have floor or ceiling effects

HFMSE (>2 years)
Hammersmith Functional Motor Scale Expanded
SMA specific; useful for assessment of gross motor skills in stronger sitters and walkers; subject to floor and ceiling effects; lacks measurement stability across SMA phenotypes; failed to identify a difference in a successful registrational trial in SMA which utilized MFM32 as primary endpoint[8-10]

Modified to address floor and ceiling effects

RHS (>2 years)
Revised Hammersmith Scale
SMA specific; designed to assess a broad range of physical abilities from weak Type 2 through strong Type 3, and to improve upon HFMSE limitations; published psychometric evidence is incomplete (no data yet published on magnitude of clinically meaningful change)[9,11]

Subject to floor effects

1. Bérard C et al, Neuromuscul Disord. 2005 Jul;15(7):463-70. 2. Trundell D et al, PLoS ONE 15(9): e0238786. 3. Trundell, D. et al, Neurol Ther 9, 575–584 (2020) 4. Wijngaarde et al, Neurology 95 (14) e1988-e1998 5. Wu et al, American Journal of Physical Medicine & Rehabilitation 101(6): p 590-608, June 2022. 6. Chabanon A et al, PLoS One. 2018 Jul 26;13(7): e0201004. 7. Duong T, et al, Front Neurol. 2022 Jan 17;12:770423. 8. Mercuri et al, The Lancet Neurology, Volume 21, Issue 1, P42-52, January 2022.. 9. Ramsey D et al, PLoS One. 2017 Feb 21;12(2): e0172346. 10. Cano et al, Muscle Nerve. 2014 March; 49(3): 422–430. 11. Stimpson G et al, J Clin Med. 2023 Feb 28;12(5):1920

biohaven

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.

RESILIENT: Designed to Address the High Unmet Need in SMA

RESILIENT

- Fully enrolled with most patients continuing on drug post 48-weeks
- Targeted the ideal population most likely to respond to potential taldefgrobep benefit
- Endpoints selected to match the study population
- Designed to fill the high unmet need across the SMA population

OPPORTUNITY FOR TALDEFGROBEP ALFA

- No approved treatments specifically target muscle in SMA patients
- SMA patients still experience significant weakness, reduced levels of functioning, and significant quality of life impairment
- **Taldefgrobep alfa builds muscle and has potential to improve function and quality of life in SMA patients**

KEY POINT

Top-line results are anticipated in 2H 2024

biohaven

Panel Discussion

MODERATOR

Christopher Raymond

Sr. Research Analyst

PIPER | SANDLER

PANELISTS

Peter Ackerman, M.D.
Vice President, Clinical Development, Biohaven

Barry Byrne, M.D., Ph.D.
Professor and Director of UF Health Advanced Therapeutics, University of Florida

Bruce Car, DVM, Ph.D.
Chief Scientific Officer, Biohaven

Frank Greenway, M.D.
Medical Director and Professor, Pennington Biomedical Research Center

Lindsey Lair, M.D., MBA, F.A.A.N.
Vice President, Clinical Development, Biohaven

BHVN LISTED NYSE

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

Bruce Car, DVM, Ph.D.
Chief Scientific Officer, Biohaven

Bharat Awsare, M.D.
Senior Medical Director, Biohaven

James F. Howard, Jr., M.D.
Professor of Neurology & Medicine, University of North Carolina, School of Medicine

Dennis Moledina, M.D., Ph.D.
Assistant Professor of Medicine-Nephrology, Yale University School of Medicine

MoDE™ Degrader Platform

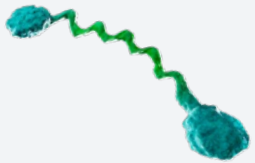
biohaven®

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

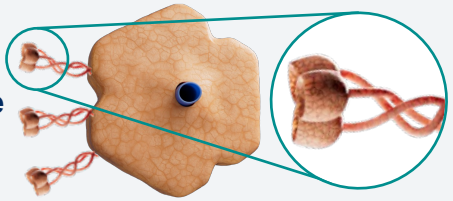
Legend

Degradation Target

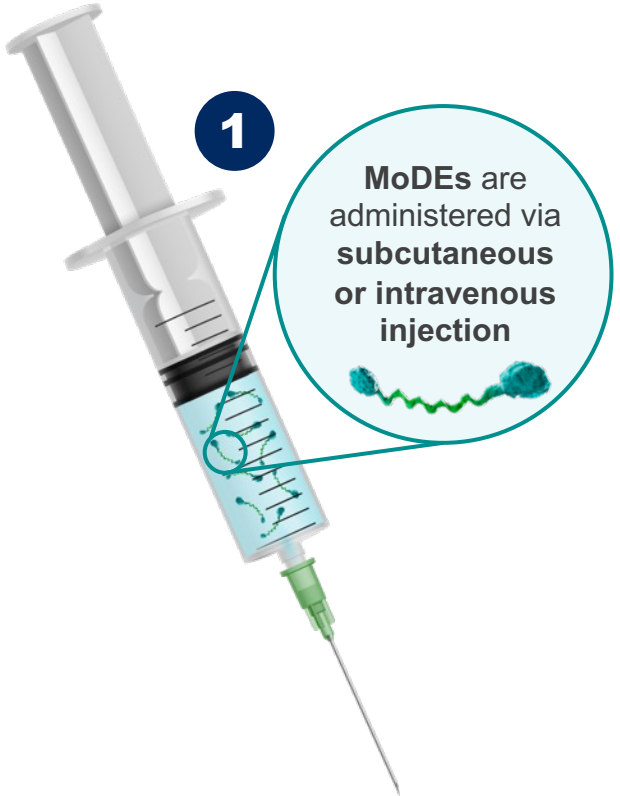
Bifunctional MoDEs®



Hepatocyte

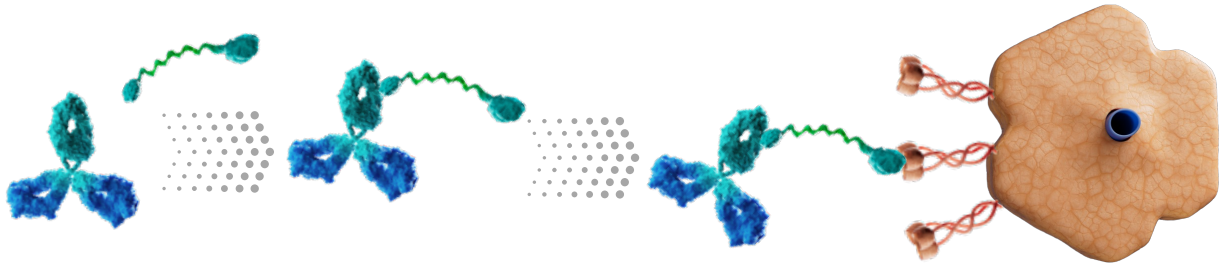


Asialoglycoprotein receptor*

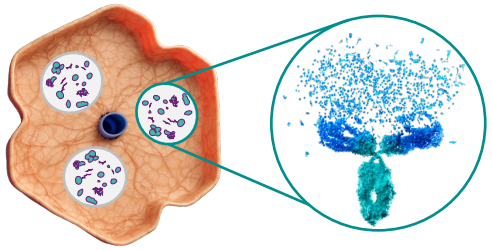


2

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

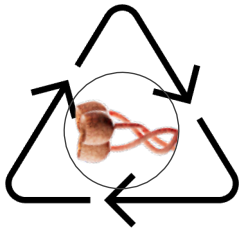


3



- 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

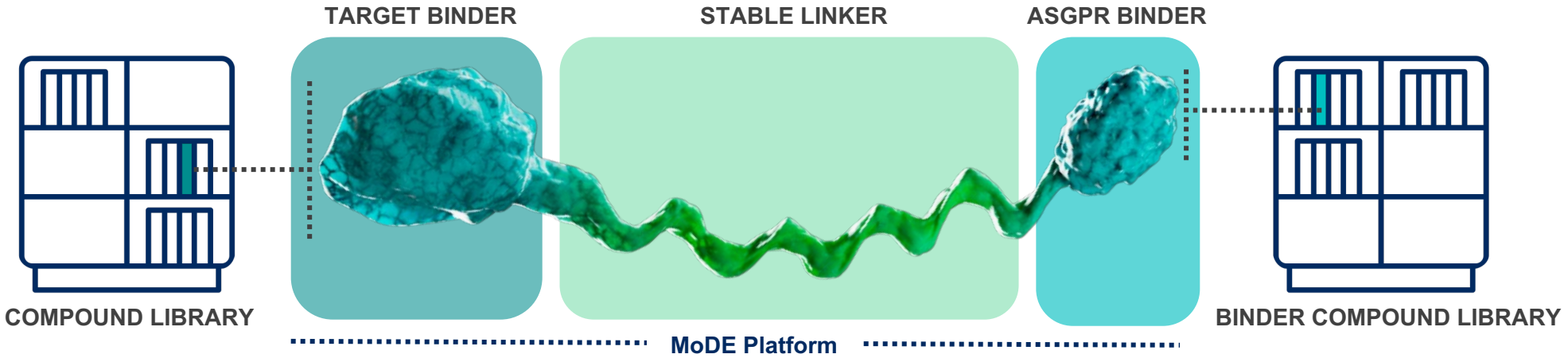
*Stylistic representation

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

biohaven

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.

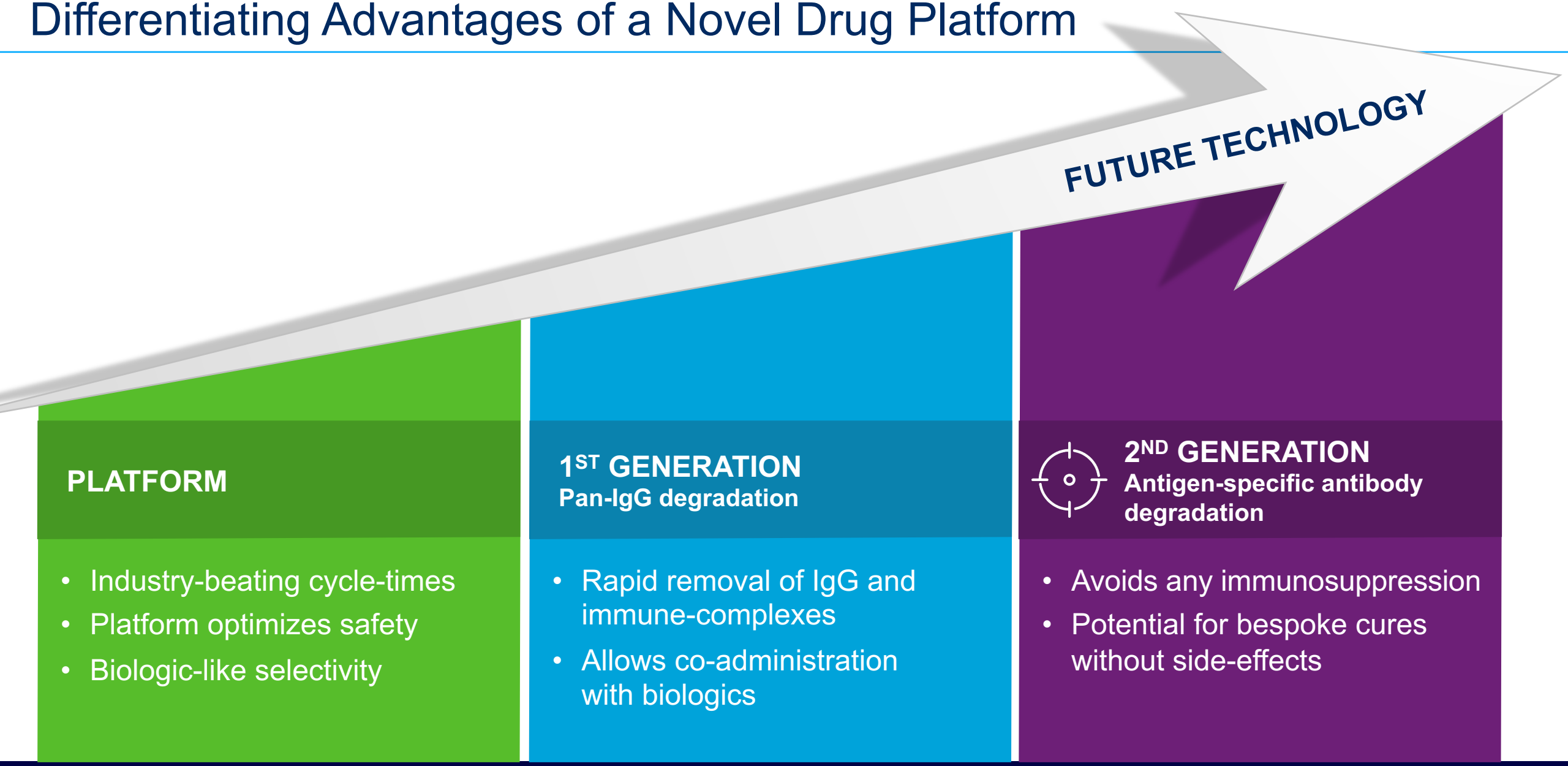
Positive Differentiation Predicted for Bispecific Degraders Over Competition

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.

MoDE Platform:
Differentiating Advantages of a Novel Drug Platform



Future Technology Wins for the MoDE™ Platform

In parallel to drug candidate advancement, the Biohaven and Yale Spiegel teams are innovating with academic and commercial partners to sustain competitive leadership for future generations of extracellular MoDEs degraders

biohaven

Bruce Car, DVM, Ph.D.
Chief Scientific Officer

DEGRADERS

biohaven®

Bispecific MoDE™ Degrader Programs

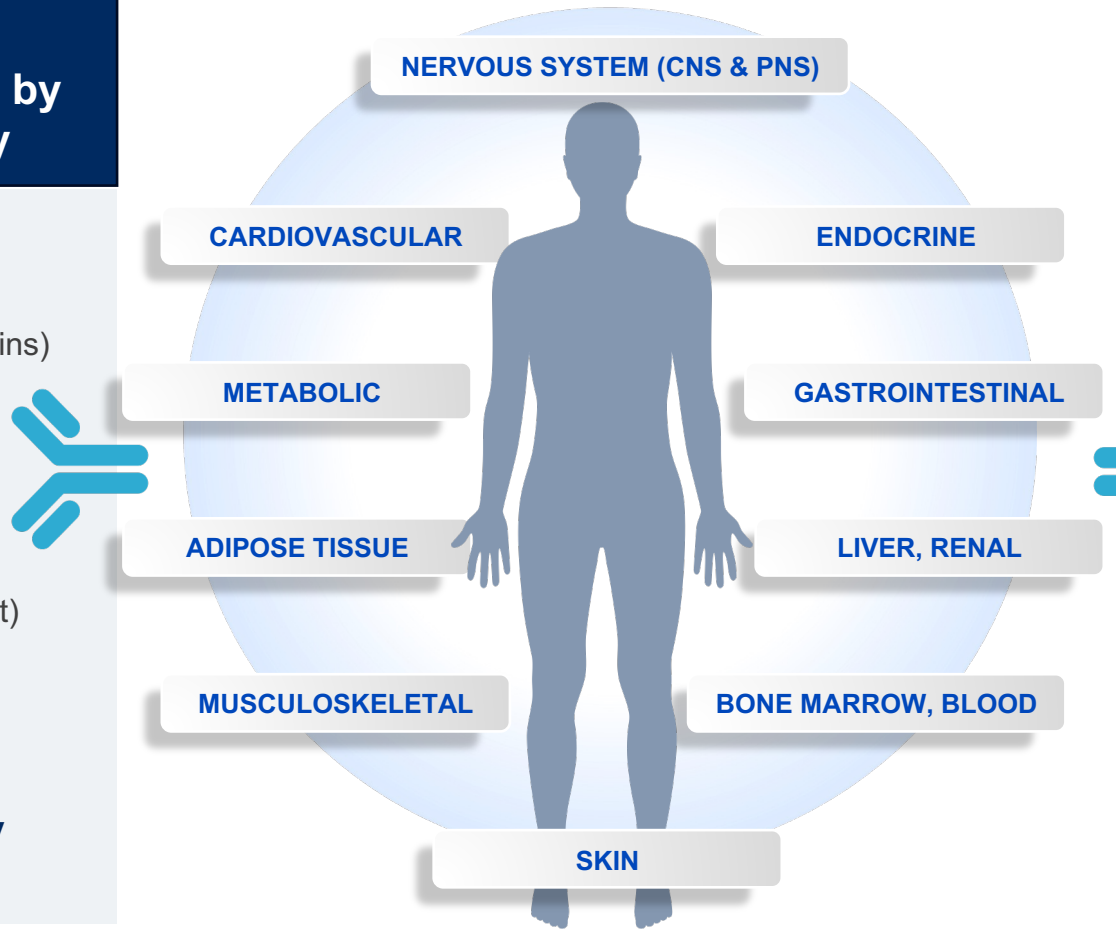
biohaven®

MoDEs Address Multiple Diseases Recently Ascribed to Autoantibodies

Idiopathic diseases increasingly de-orphaned by autoantibody discovery

Year	Disease (antigen)
2004	Neuromyelitis optica (AQP4)
2008	Autism (multiple discrete proteins)
2010	Encephalitis (LGI1)
2014	IgLON5 Disease (IgLON)
2022	Encephalitis (GABA)
2023	Fibromyalgia (DRG protein)
2023	Lipodystrophy (PLIN1)
2023	Long Covid (αIFN-I)
2024	Aging (unknown adipose target)

Autoantibody titers directly correlate with disease severity



Newly defined targets rapidly turned into MoDEs

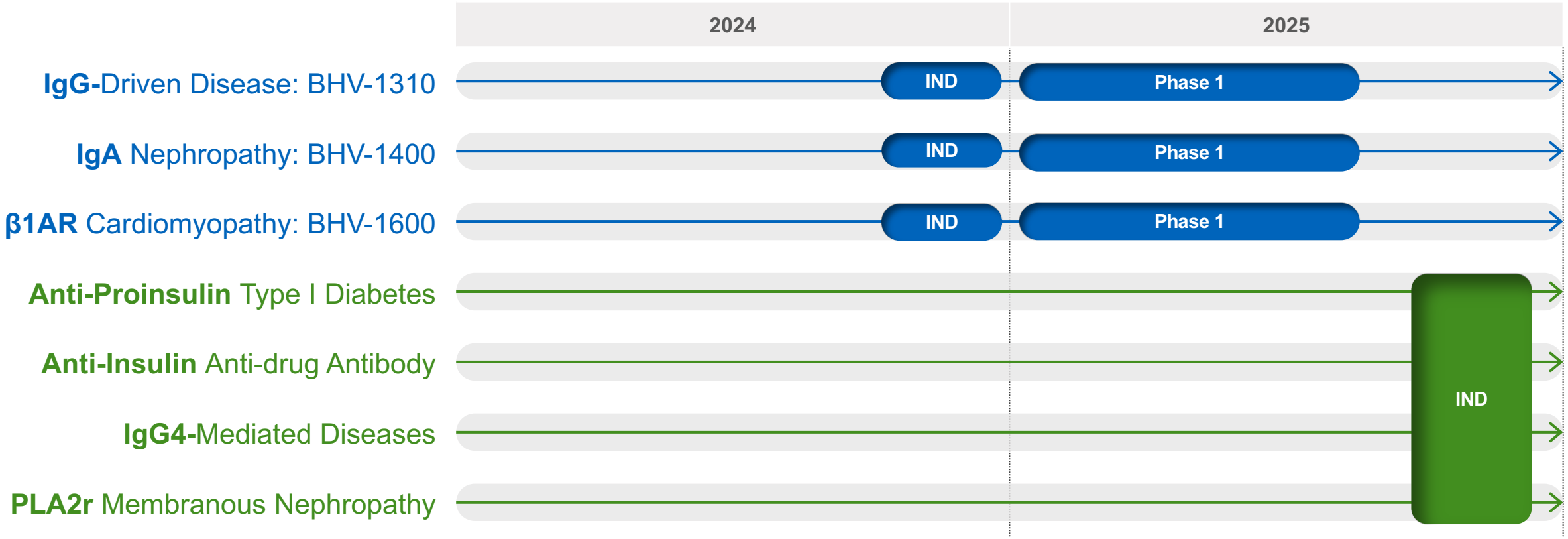
- Disease diagnostic
- PD biomarker
- Efficacy biomarker

Autoantibody measurements enable facile trial endpoints for POC and registration

Glover K. et al, Front. Immunol. 12:744396. doi: 10.3389/fimmu.2021.74439.

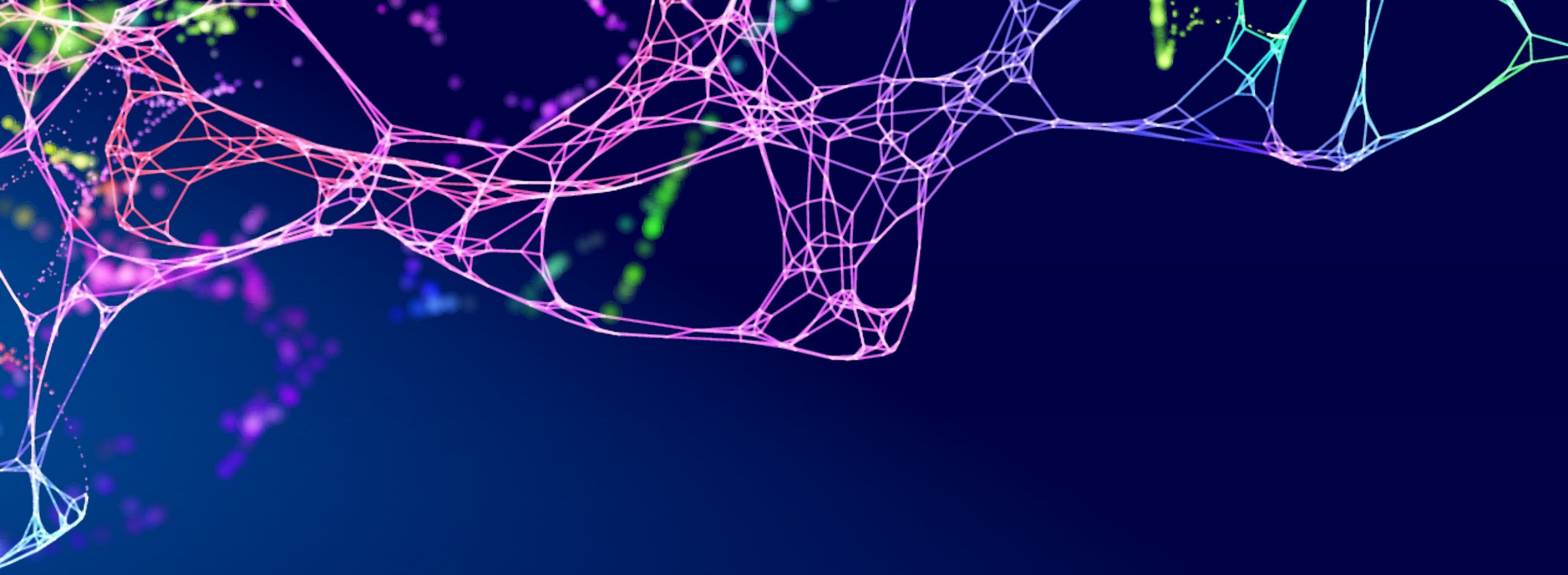
biohaven

MoDEs: Multiple Asset Opportunities and Potential Timelines



BREAKING NEWS

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



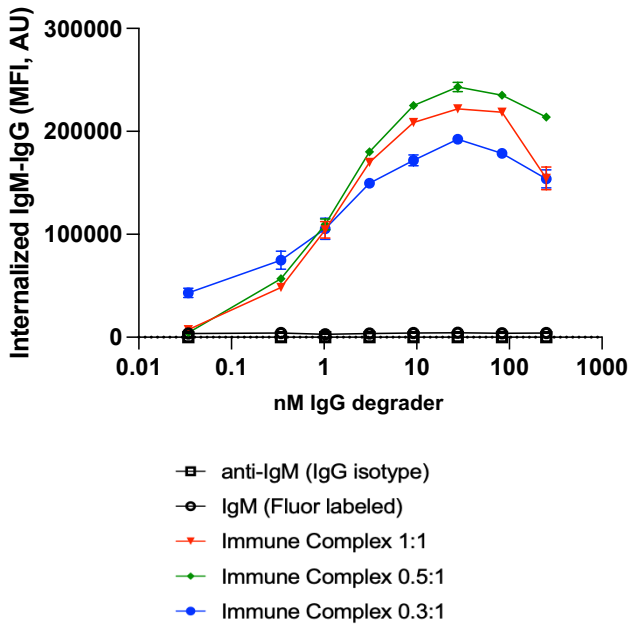
DEGRADERS

IgG Degraders – Uniquely Differentiated

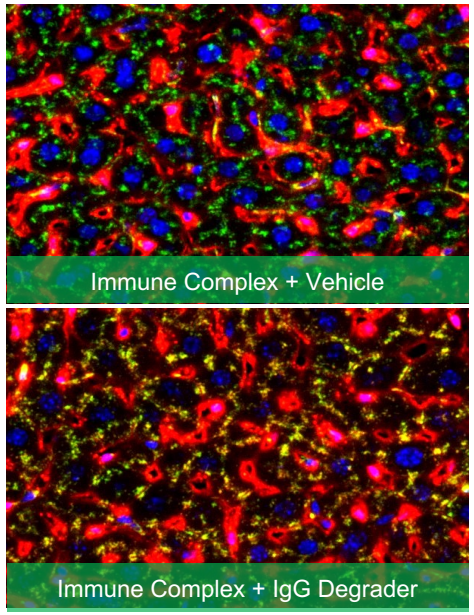
biohaven®

IgG Degraders Remove Disease Relevant Immune Complexes (IC)

In Vitro Lowering of IgM/IgG ICs

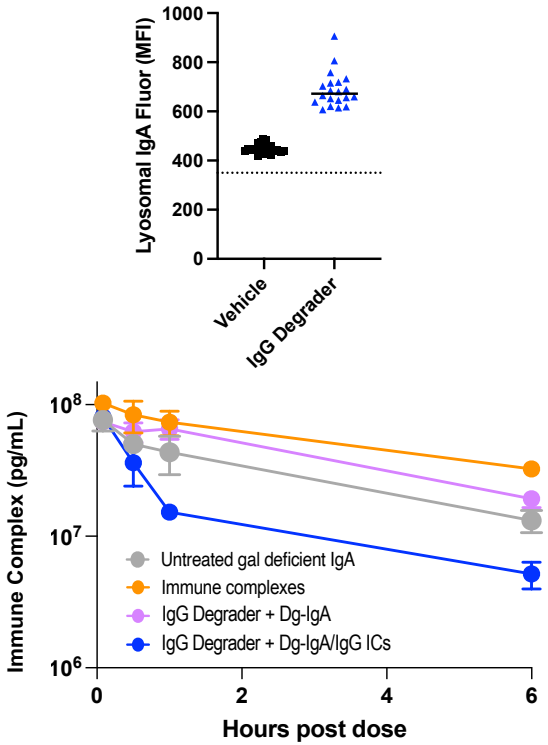


Dg-IgA1/IgG ICs Colocalize with Lysosome (LAMP1) via BHV-1310



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

In Vivo ICs are Efficiency Removed in Mice

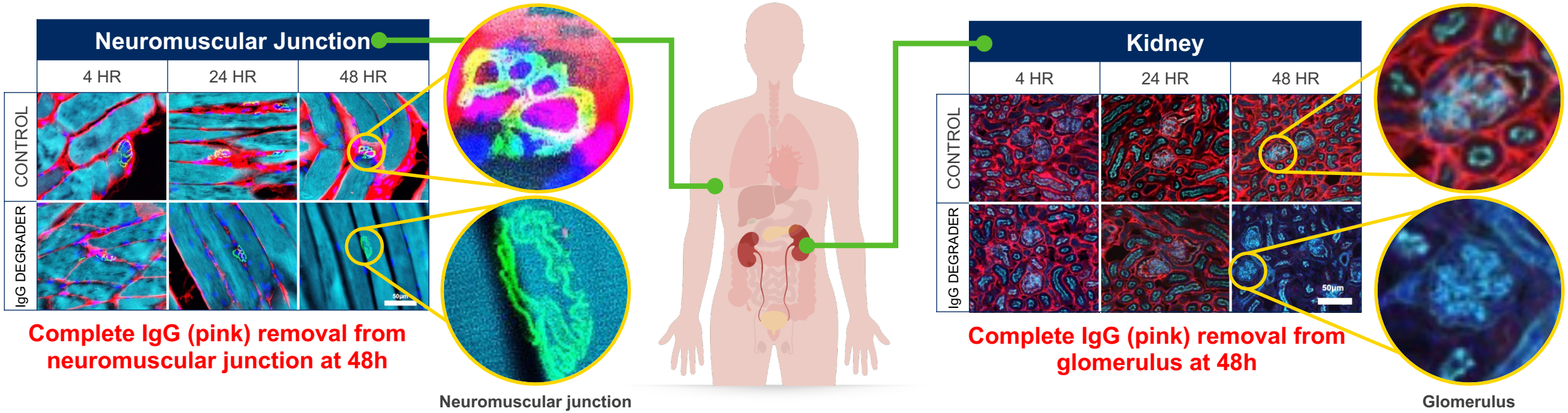


BREAKING NEWS

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 Degrader Shows Rapid and Complete Lowering of Interstitial IgG



- Disease-causing autoantibodies exert pathogenic effects directly within tissue and organs
- Plasma titers correlate with severity of multiple diseases, as surrogates for IgG at the interstitial site of action[1]
- Intravascular IgG and immune complex reduction is rapidly followed by depletion of IgG in tissues

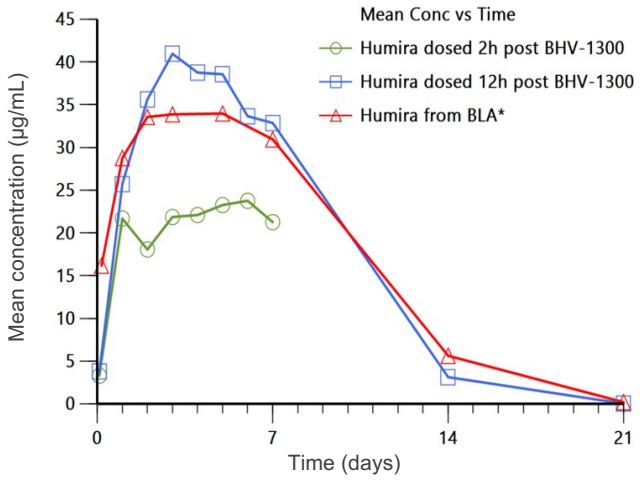
KEY POINT

Efficient removal of autoantibodies from tissues is a significant differentiator for MoDEs

1. Kim JS et al , J Clin Med. 2020 Nov 4;9(11):3549.

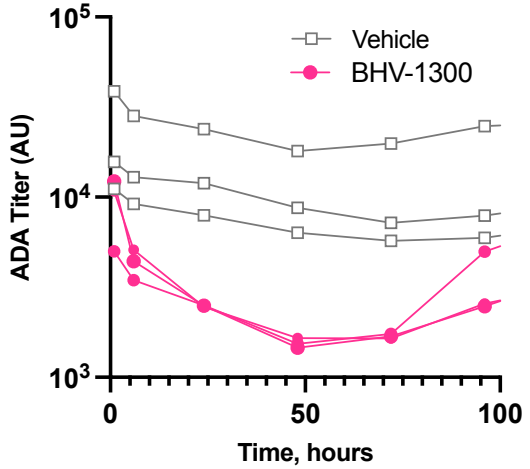
IgG Degradation Improves Efficacy of Biologics Through Removal of ADAs

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



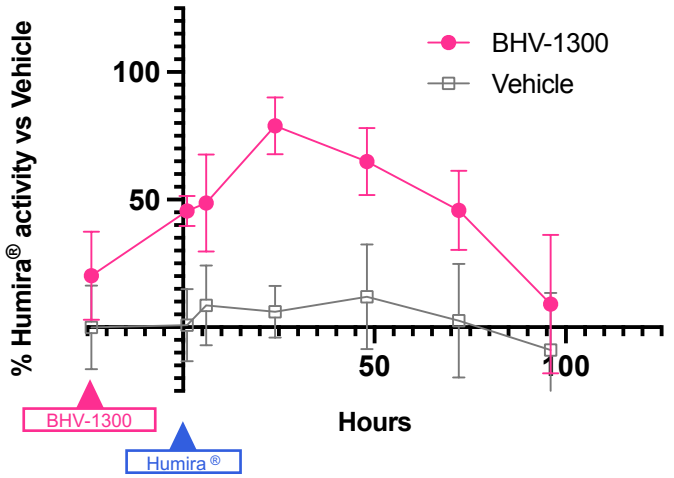
BHV-1300 dosed at 30 mg/kg SC followed by Humira® dosed at 3 mg/kg SC in NHPs

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

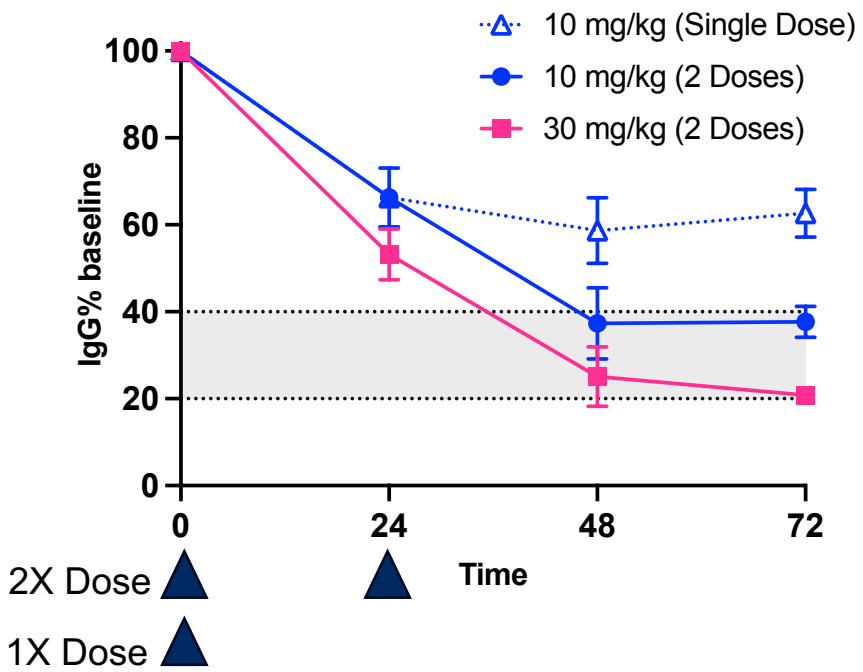
BHV-1300 can be co-administered with biologics, removing anti-drug antibodies and restoring efficacy[1]

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

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

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

BHV-1300: Preliminary Results from Ongoing First-in-Human Single Ascending Dose Study in Healthy Subjects

biohaven®

PAN IgG DEGRADERS

BREAKING NEWS

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

- NHP studies showed 80% IgG depletion with a single dose of BHV-1300; increasing to ~90% after multiple doses
- Safe in doses up to 500 mg/kg in nonclinical studies
- More rapid IgG reduction vs. competitors
- Allows for co-administration with biologics

Potential in Multiple Diseases

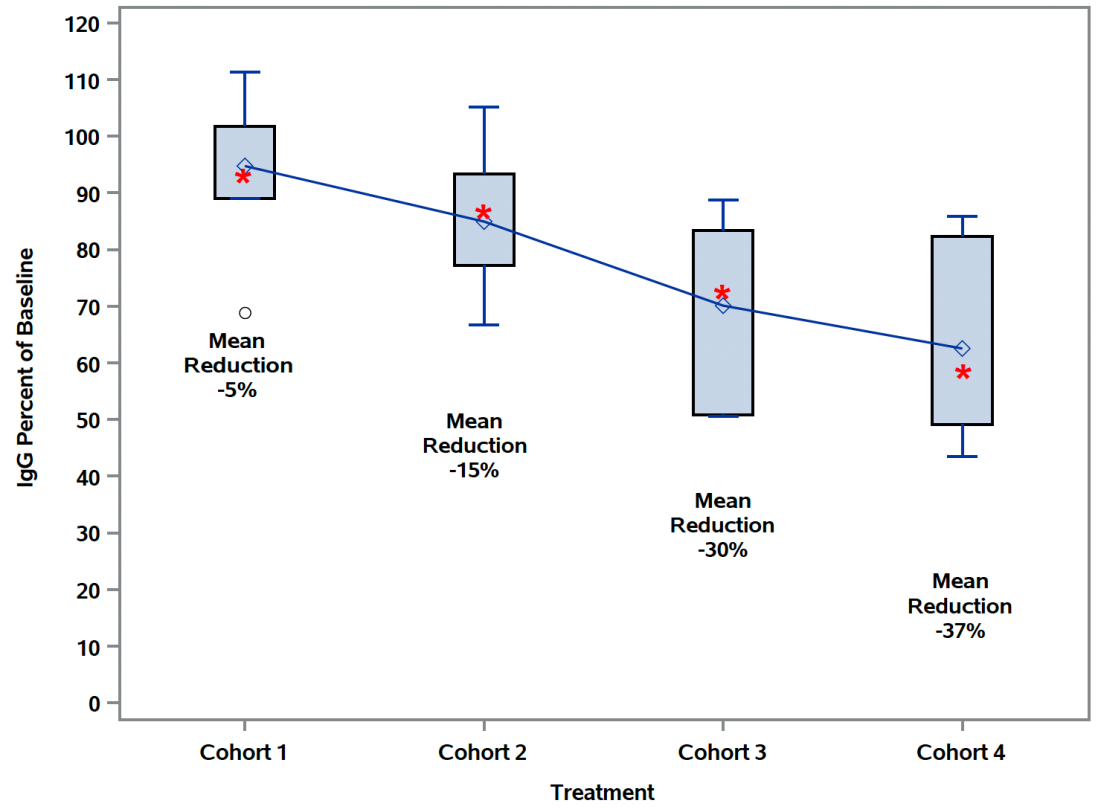
- Common diseases — RA, lupus erythematosus, lupus nephritis
- Rare diseases — Generalized myasthenia gravis, transplant, oncology, etc.

- **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**

biohaven

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



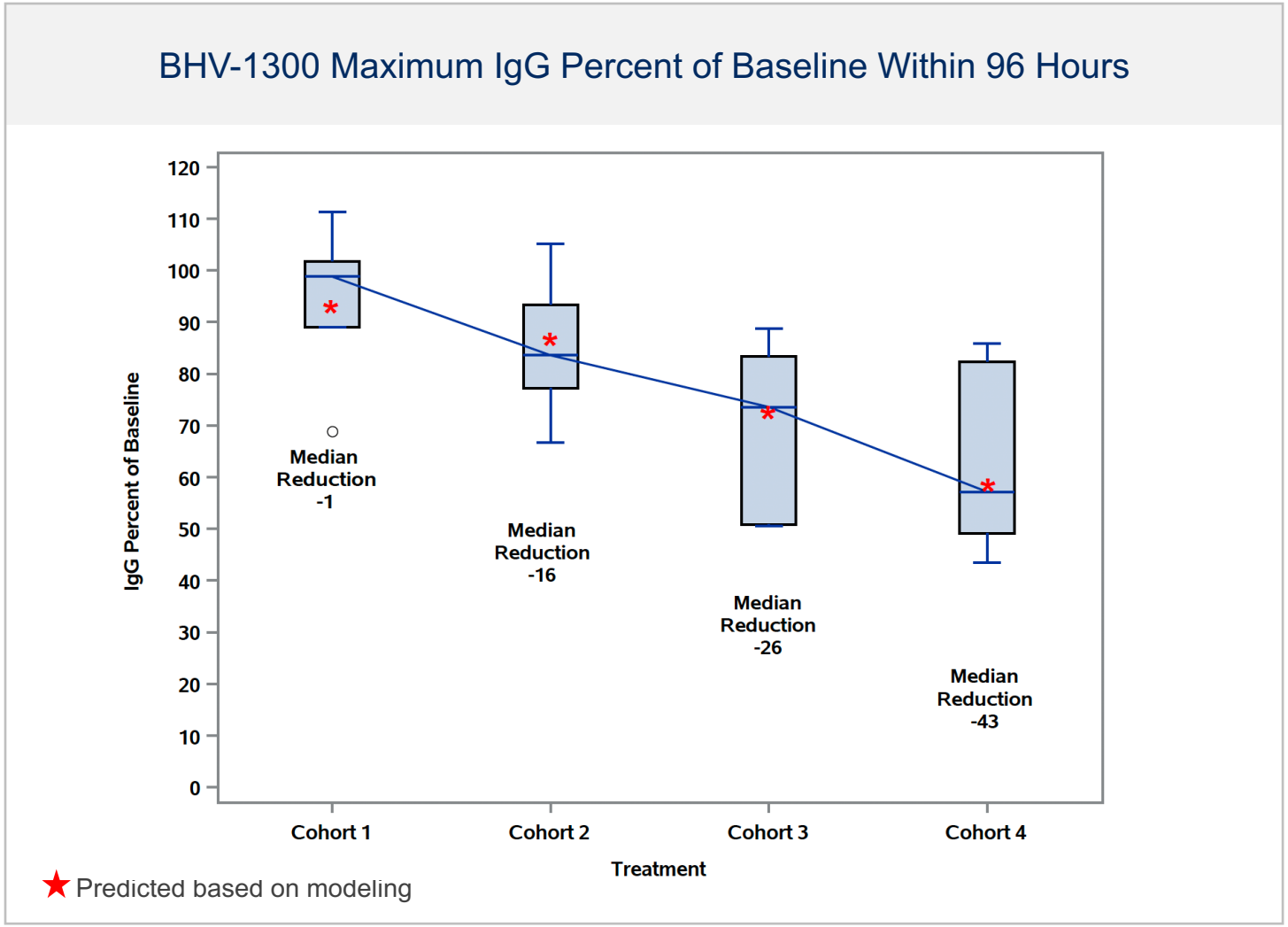
★ Predicted based on modeling

- 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).

biohaven

Median IgG Lowering within 96 hours



- 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).

biohaven

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

- 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).

biohaven

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

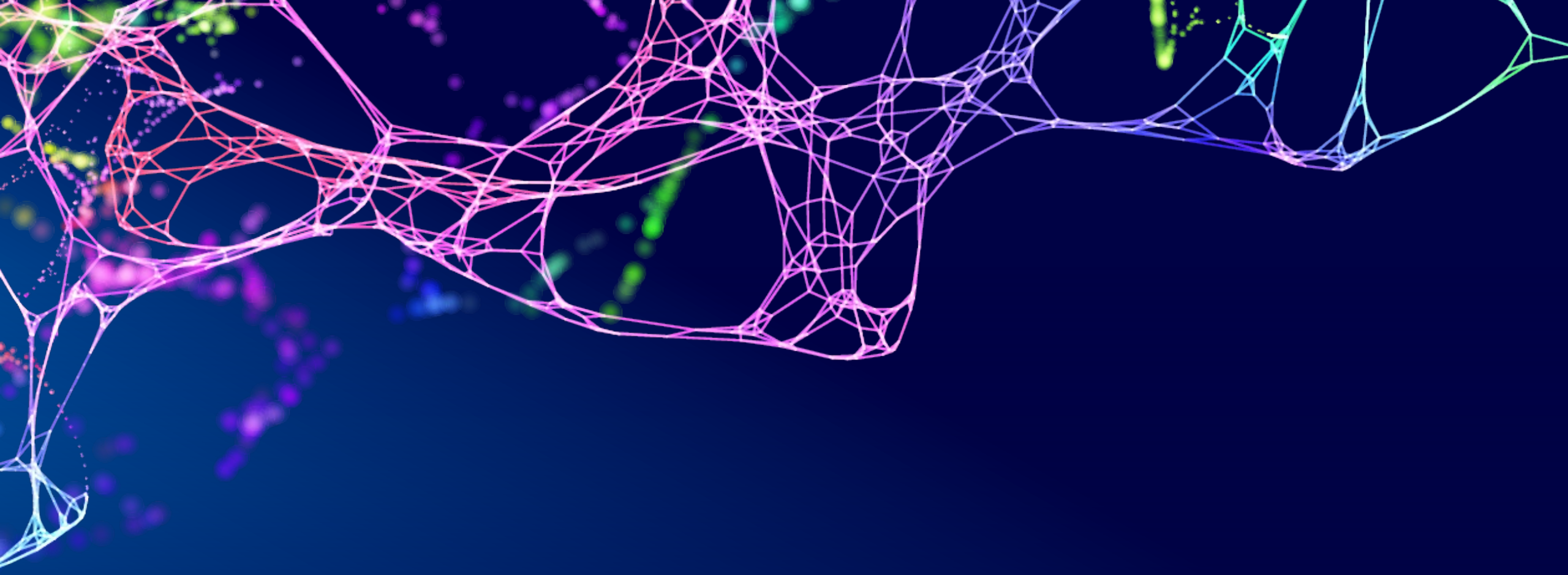
- No meaningful reduction of other immunoglobulins
- No meaningful impact on albumin and low-density lipoprotein cholesterol

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).

biohaven



DEGRADERS

BHV-1600: Next-Generation Selective MoDE Targeting β1AR Autoantibodies

biohaven®

BHV-1600

Specific Targeting of anti-β1AR Autoantibodies

Specifically degrading selected autoantibodies against the beta-1 adrenergic receptor (β1AR) presents novel therapeutic opportunity

Innovative Mechanism of Action

- Protein degradation rather than inhibition
- Small molecule degrader approach specifically removes anti-β1AR
- Low projected human dose range
- Small molecule allows for small-volume subcutaneous dosing
- Specific removal of pathogenic antibody to low levels, preserving host-defense

Status

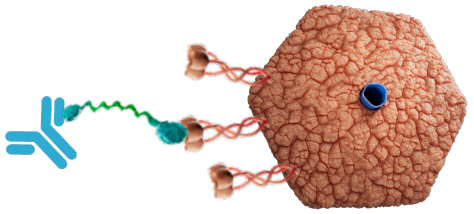
IND to be filed in 2H 2024

biohaven

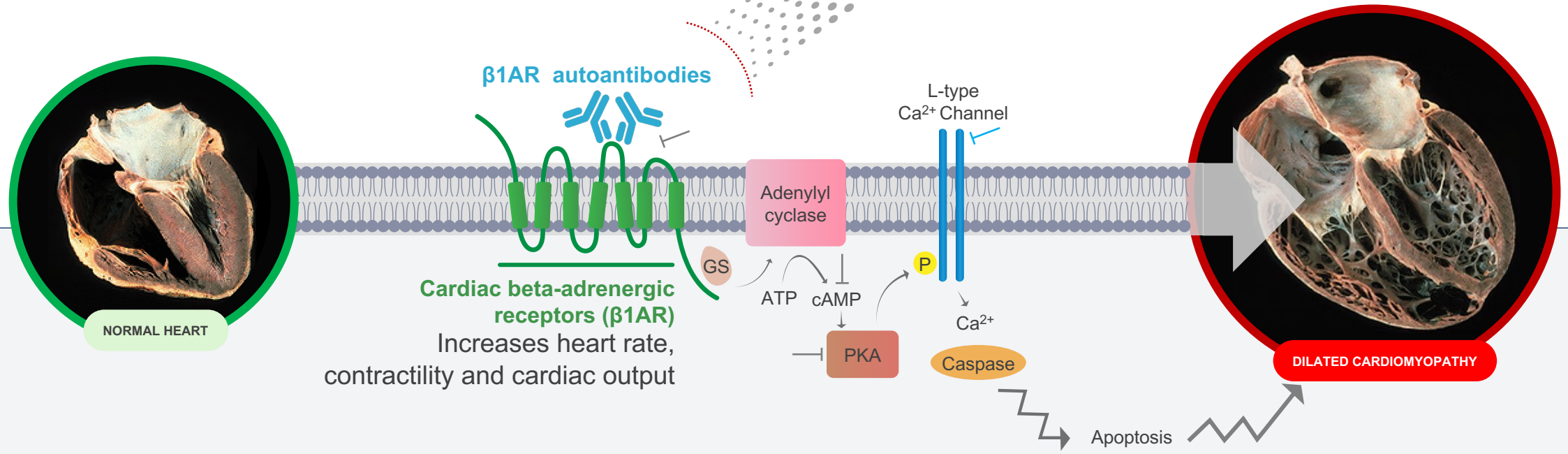
Selective Targeting of β1AR Autoantibodies for Cardiomyopathy

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:

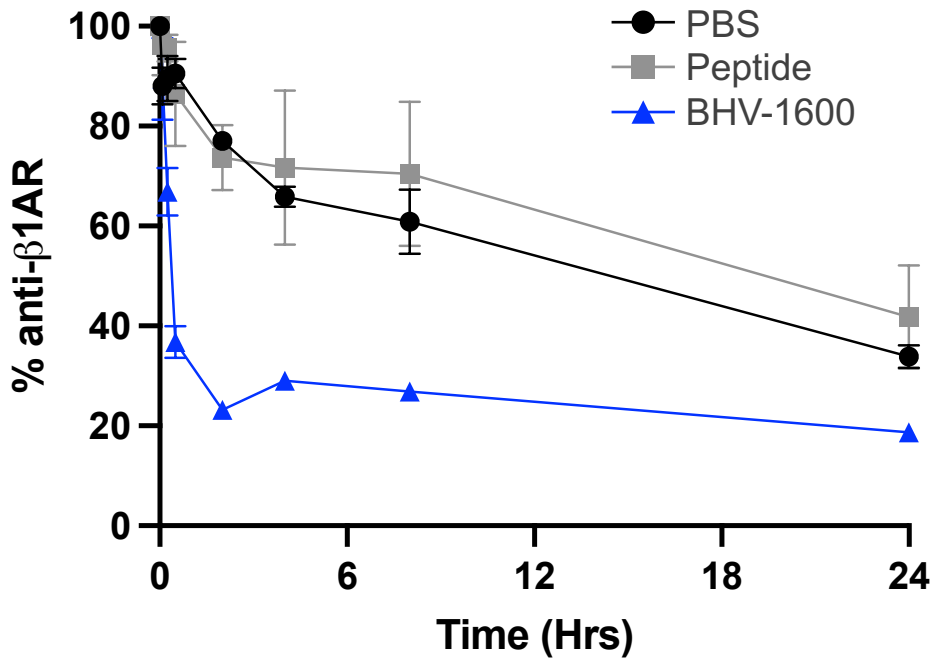
- **BETA BLOCKERS:** Ineffective treatment limited to supportive treatment, diuresis, etc.
- **REMOVAL OF ANTIBODIES:** Plasmapheresis[1,2] demonstrates POC but requires hospitalization

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.

biohaven

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

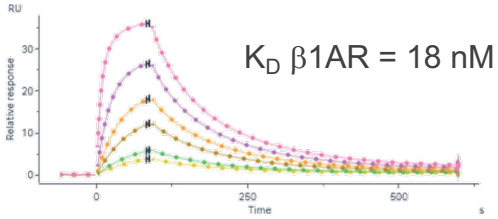
Marked Degradation of Anti-β1AR Antibody in Mice



- 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

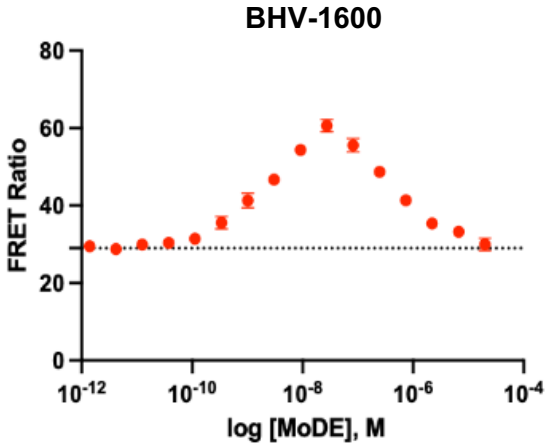
High affinity for monoclonal mouse anti-β1AR antibody and ASGPR protein construct by SPR



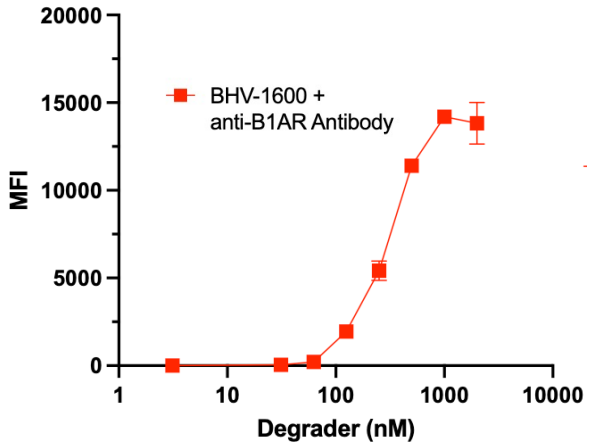
K_D β1AR = 18 nM

Ternary Complex Formation Followed by Cell Uptake

Formation of ternary complex confirmed in TR-FRET assay



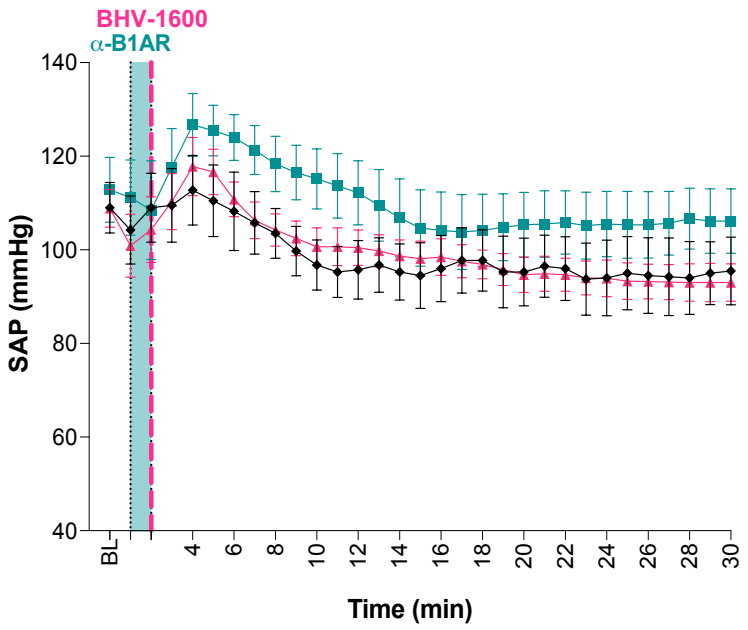
Cellular internalization of anti-β1AR Ab demonstrated in HEK293 (hASGPR) cells



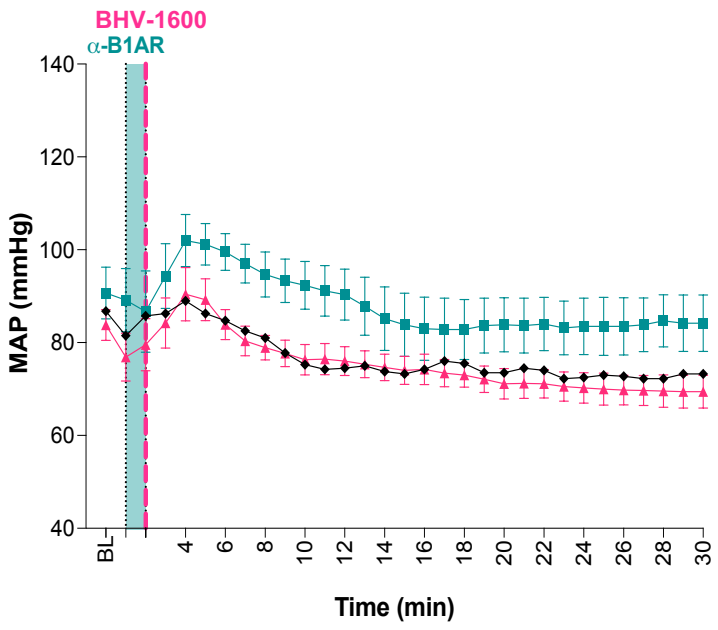
SPR, Surface Plasmon Reference; MFI, Mean Fluorescence Intensity; **TR-FRET,** Time Resolved - Förster´s Resonance Energy Transfer.

BHV-1600 Reverses β1AR Autoantibody-Induced Cardiovascular Changes in Rats

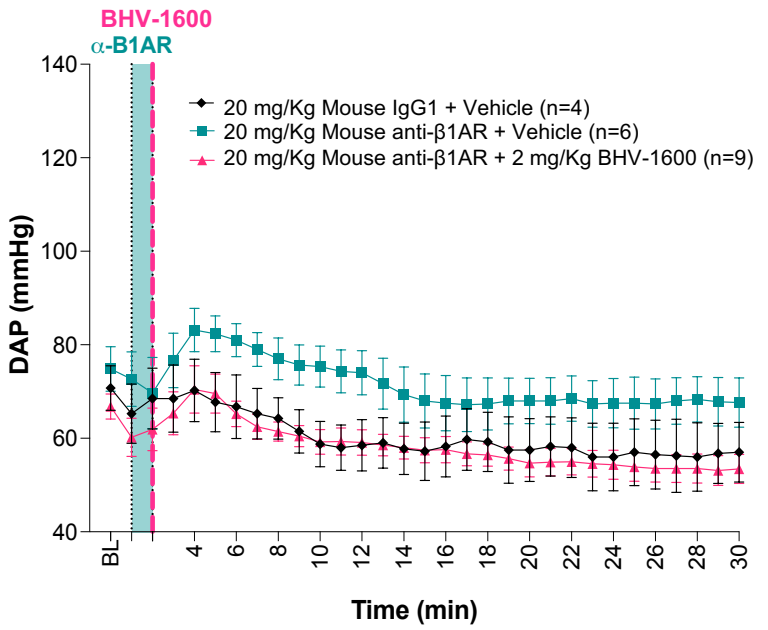
BHV-1600: Systolic Arterial Pressure



BHV-1600: Mean Arterial Pressure (MAP)



BHV-1600: Diastolic Arterial Pressure



Statistically significant reversal of autoantibody-induced blood pressure changes is paralleled by numerical correction of heart rate alterations, indicating normalization of myocardial β1-adrenergic receptor function

BREAKING NEWS

BHV-1600 reverses β1AR autoantibody-driven changes in cardiac function

SAP, Systolic arterial pressure; **MAP,** mean arterial pressure; **DAP,** Diastolic arterial pressure.

Potential for Accelerated Development of BHV-1600

SAD study in healthy volunteers
IND 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 β-1AR Ab levels[4]
- Lowering of β-1AR autoantibody levels by immunoadsorption leads to rapid clinically meaningful improvements in DCM[5]

Registrational program

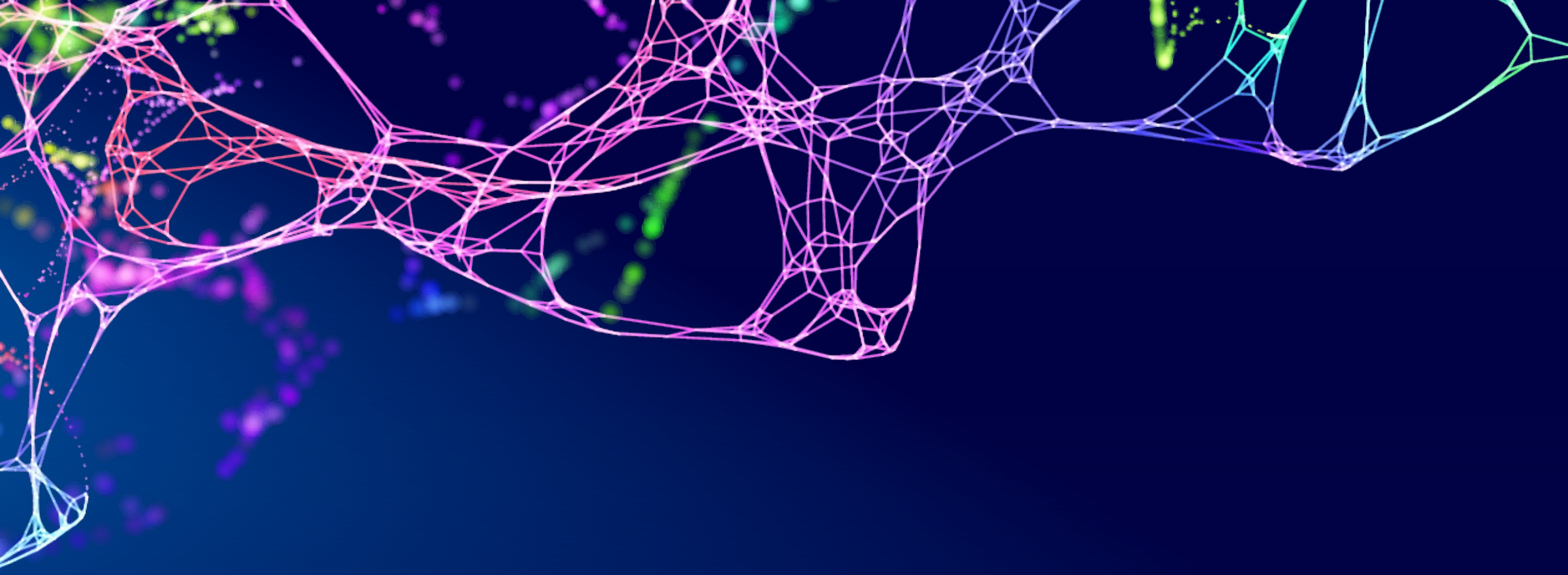
ENDPOINTS
- β-1AR autoantibodies
- NT-proBNP
- TTE parameters (e.g., LVEF)
- 6 Minute Walk Test
- Hospitalizations
- Overall survival
- Composite outcome endpoint

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.



DEGRADERS

BHV-1400 for IgAN

biohaven®

BHV-1400

Specific Targeting of Galactose-Deficient IgA1 (Gd-IgA1)

Targeting only pathogenic antibodies presents a novel therapeutic opportunity

Unique MOA for IgAN

- Protein degradation rather than IgA/IgM/IgG synthesis inhibition
- Antibody-based degrader specifically removes Gd-IgA1 and immune-complexes containing Gd-IgA1
- Depletes Gd-IgA1 to very low levels, while preserving host-defense

Favorable product profile

- Low projected human dose range
- Rapid onset of activity
- Well defined patient population with unmet clinical need

Status

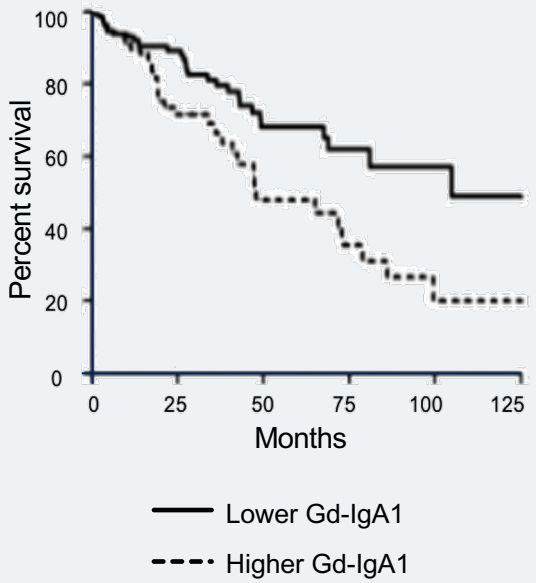
IND to be filed in 2H 2024

biohaven

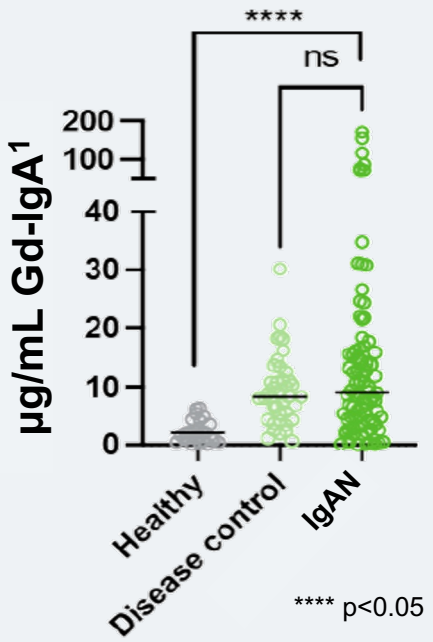
BHV-1400 Degradation of Gd-IgA1 and Gd-IgA1 Immune Complexes (IC) for Treatment of IgA Nephropathy (IgAN)

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

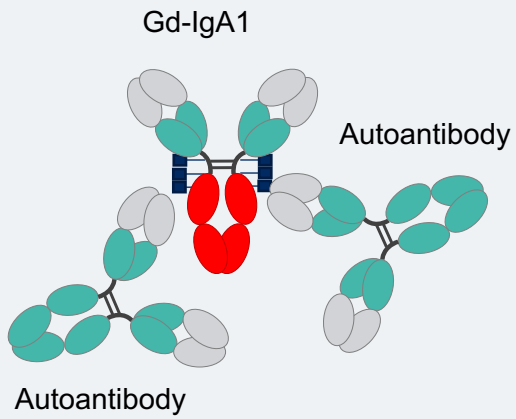
Progression-free survival of IgAN patients stratified by serum Gd-IgA1 levels[1]



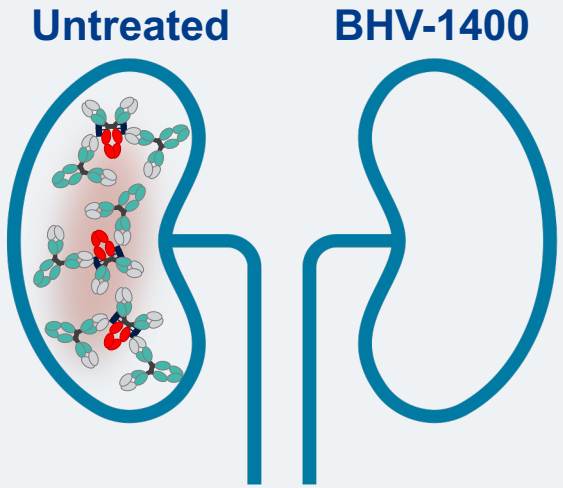
Serum Gd-IgA1 levels across control and patient populations



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

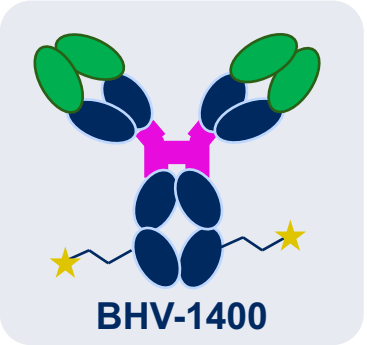


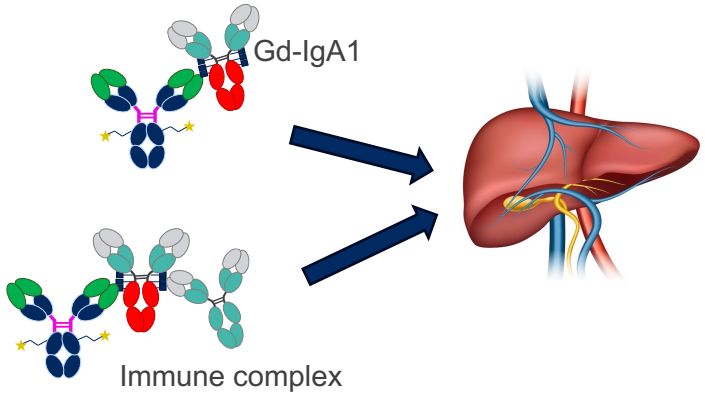
ICs deposit in the kidney leading to inflammation and progressive loss of function



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.

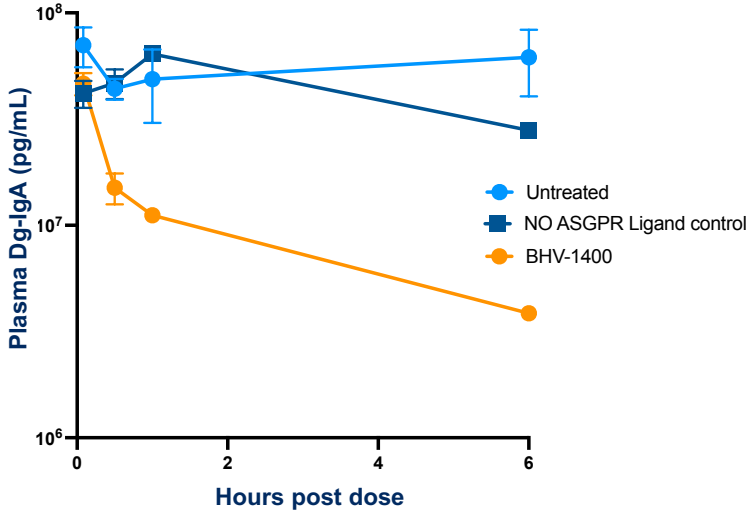
BHV-1400 Directs Dg-IgA1 and Associated Immune Complexes to the Liver for Degradation



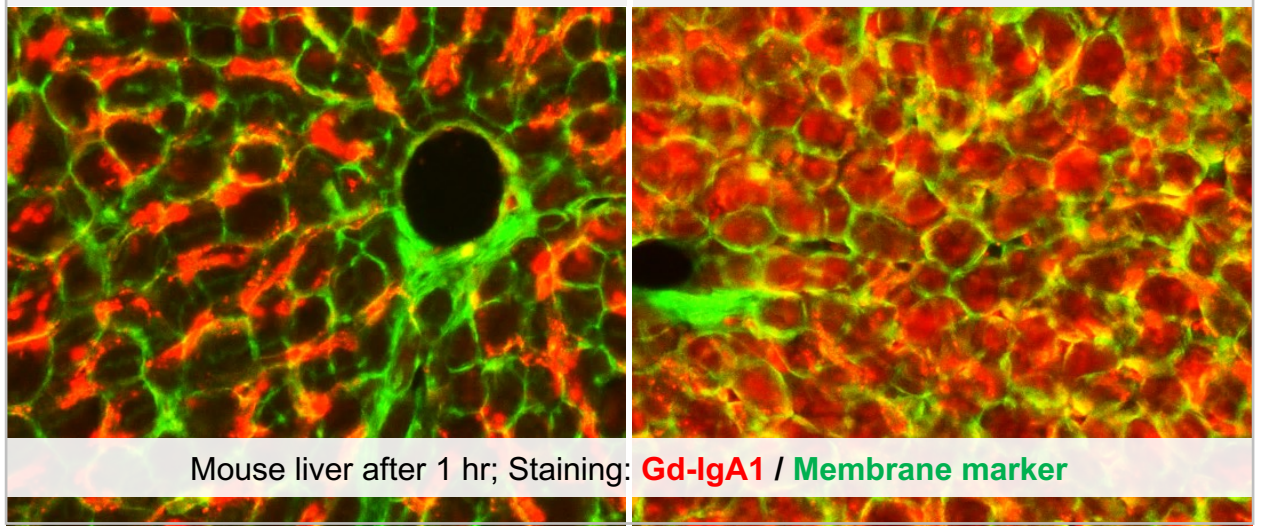


- BHV-1400 spares normal IgA1, IgA2, IgG, and IgM
- Rapid degradation of Dg-IgA1 and immune complexes prevents their deposition in glomeruli

BHV-1400 Specifically Removes Dg-IgA1 From Circulation Through Liver



Dg-IgA1 in hepatic vascular sinusoids	Dg-IgA1 internalized by BHV-1400 into hepatocytes for degradation
Dg-IgA1 + Unconjugated Ab	**Dg-IgA1** + BHV-1400

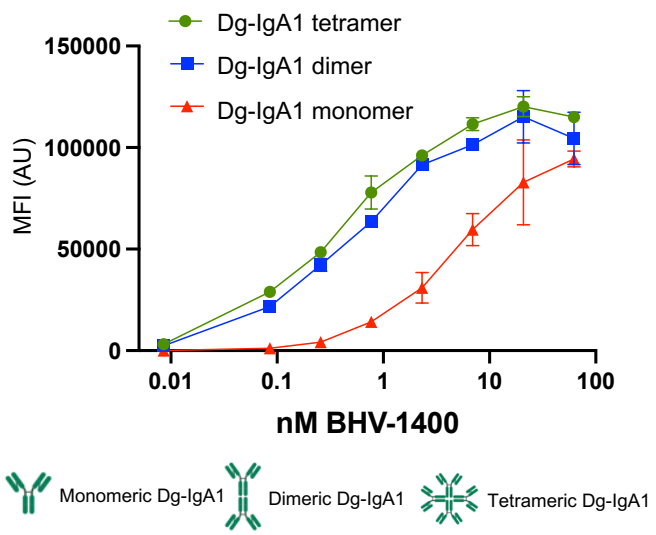


Mouse liver after 1 hr; Staining: **Gd-IgA1** / **Membrane marker**

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

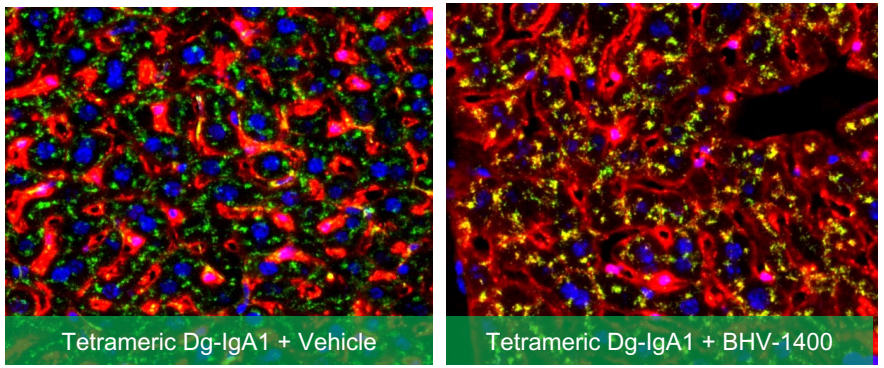
BHV-1400 Drives the Internalization of Multiple Species of Dg-IgA1 ICs

ASGPR Facilitates the Uptake and Degradation of Large ICs *In Vitro*



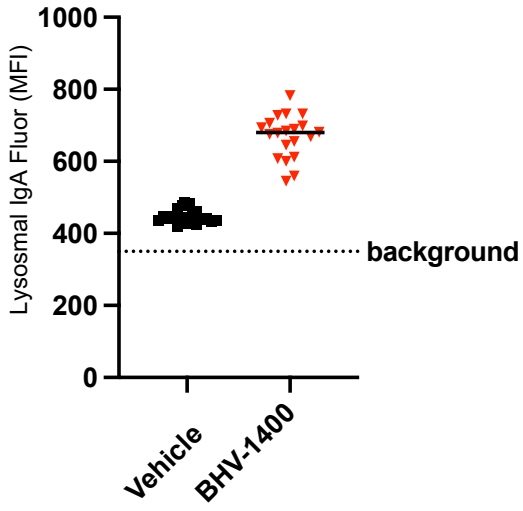
BHV-1400 Binds and Degrades Large ICs in Mouse Efficacy Study

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



ICs colocalize with lysosomes (LAMP-1) for subsequent degradation as soon as 1h after treatment with BHV-1400; ICs administered via IV

Immune Complex Internalization Quantified



MFI, Mean fluorescence intensity measured within lysosomes, taken from immunofluorescent measurements in middle panel

KEY POINT

BHV-1400 targets and degrades multiple species of pathogenic immune complexes in IGAN

biohaven

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

Specific Targeting of Gd-IgA1 for Degradation by BHV-1400 Offers Precision Approach for Treating IgA Nephropathy

POTENTIAL FOR
Superior Efficacy

- Targeting of upstream pathology
- Rapid Gd-IgA1 reduction within hours
- Near complete Gd-IgA1 elimination possible
- More rapid and greater UPCR reduction
- Higher remission rates
- Stabilization and improvement in eGFR
- Allows for acute or rescue treatment

POTENTIAL
Safety Advantages

- No immunosuppression
- No impact on mucosal immunity
- No impact on vaccine responses

IND
2H 2024

→

SAD Study in Healthy Subjects

- Safety
- Pharmacokinetics
- Early evidence of Gd-IgA1 lowering

→

MAD Study in IgAN provides POC

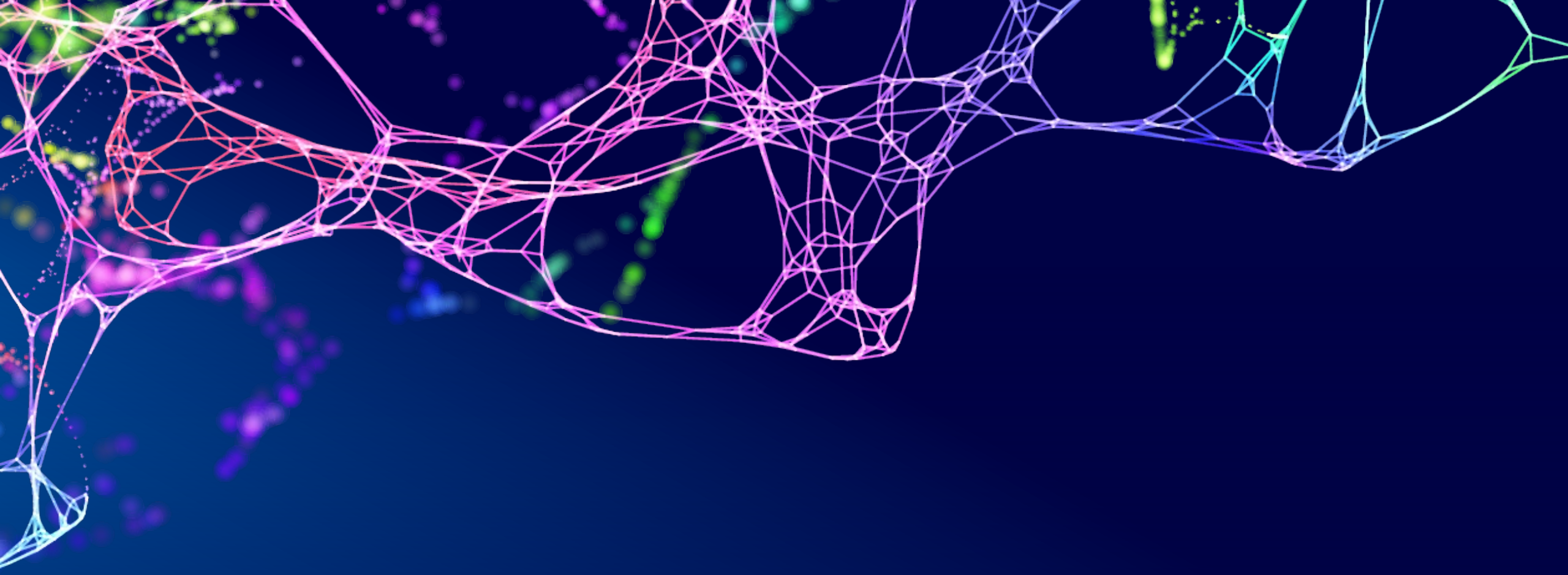
- Gd-IgA1
- Immune complex
- Renal response
- eGFR
- Proteinuria (UPCR) to serve as basis for **ACCELERATED APPROVAL**

→

Confirmation Study in IgAN

- Renal response
- eGFR
- Proteinuria (UPCR)

eGFR, Estimated glomular filtration rate; **UPCR,** Protein-to-creatine ratio.



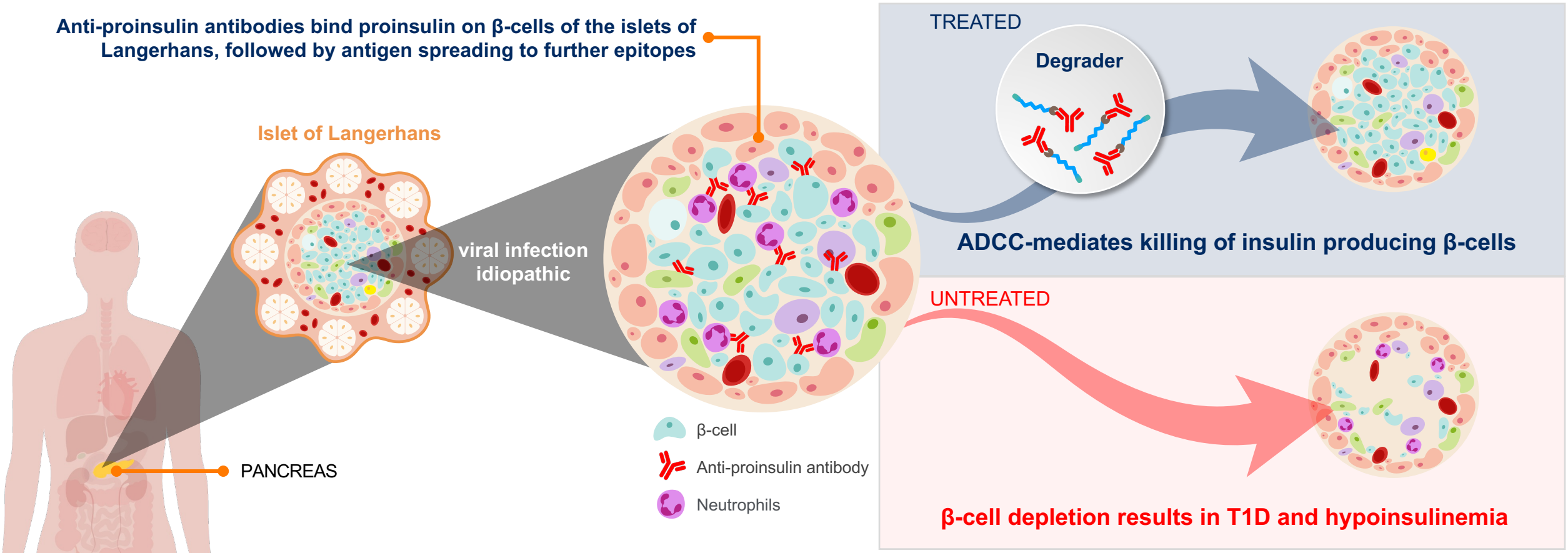
DEGRADERS

Anti-insulin and Anti-proinsulin Targeted Autoantibody-Degradation

biohaven®

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

Anti-proinsulin antibodies bind proinsulin on β-cells of the islets of Langerhans, followed by antigen spreading to further epitopes



KEY POINT

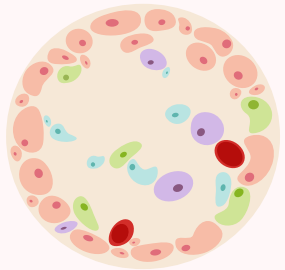
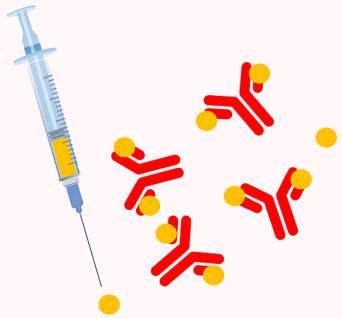
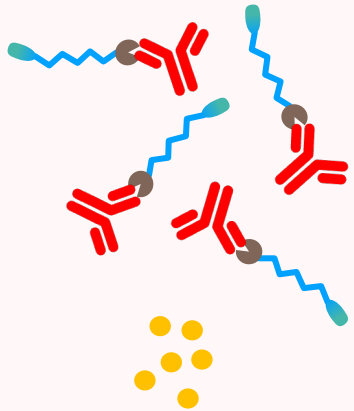
THERAPEUTIC HYPOTHESIS Lowering of antibodies early in course of disease may prevent loss of β-cells and stop cascading events which lead to Type 1 Diabetes

ADCC, Antibody dependent cellular toxicity.

Removal of Anti-Insulin Autoantibodies Restores Optimal Insulin Sensitivity in Type 1 Diabetic Patients

Anti-insulin antibodies reduce insulin effectiveness

High titers of insulin autoantibodies can be lethal[1]

β-cells depleted, insulin production stops	Autoantibodies render insulin ineffective[1]	Degrader targets autoAb for removal	Glucose homeostasis restored
			

KEY POINT

Lowering of neutralizing antibodies to insulin will restore glucose homeostasis

1. Pavithran et al, Clin Diabetes. 2016 Jul; 34(3): 164–167

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

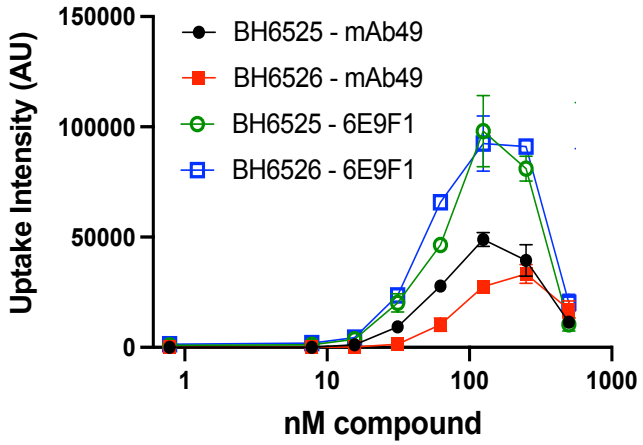
Biochemistry Selectivity (Insulin Autoantibody)

EC50 (nM)

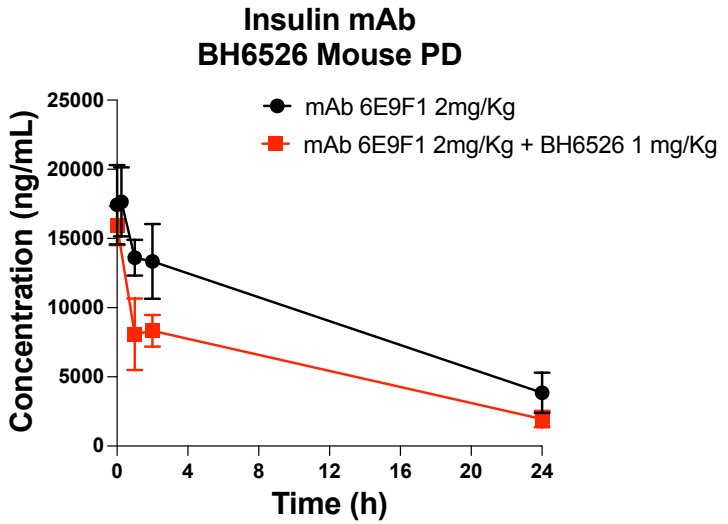
	BH6525	BH6526
mAb49	39.68	67.21
6E9F1	39.13	37.61

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

Cellular Autoantibody Uptake



In Vivo Autoantibody Reduction

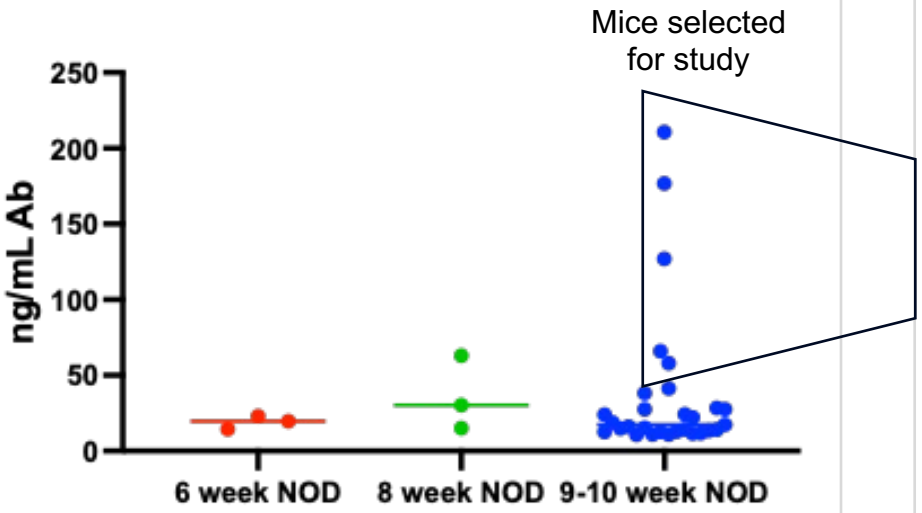


- Anti-insulin and anti-proinsulin autoantibody MoDEs form ternary complexes, show *in vitro* uptake and drive *in vivo* clearance without binding insulin receptors or IGF1R
- Robust and selective lowering of these autoantibodies shown in mouse PK/PD experiments
- Evaluation underway in efficacy studies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

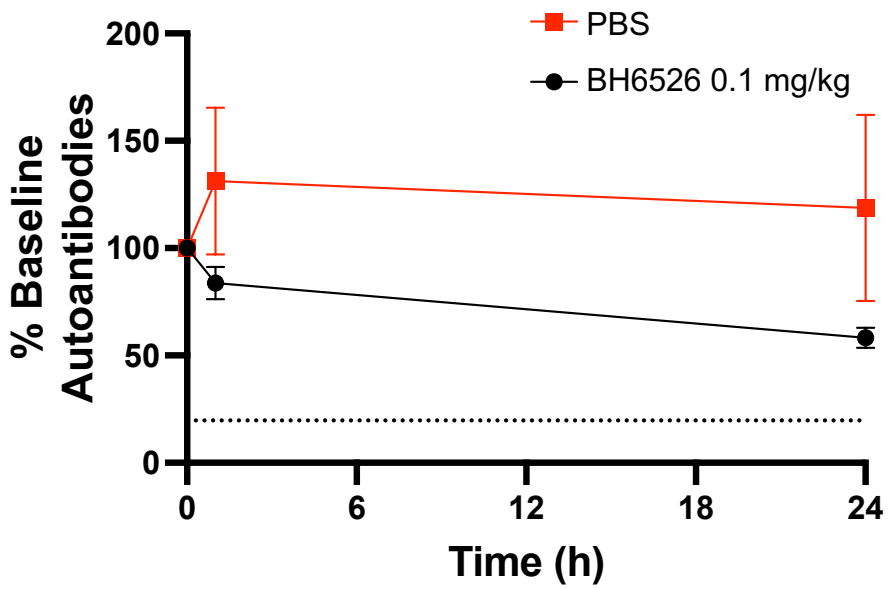
biohaven

MoDE Depletes Naturally Occurring Insulin Autoantibodies in Non-Obese Diabetic (NOD) Mice

Insulin Autoantibodies in NOD Mice



NOD Mouse Insulin Autoantibody Titers



KEY POINT

Lowering of neutralizing antibodies in NOD mice suggests potential for restoration of glucose homeostasis in T1D patients

biohaven

A Potential Disease Modifying Therapy for Type 1 Diabetes Mellitus (T1DM)

SAD study in adults with T1DM
IND 2H 2025

ENDPOINTS
- Safety
- Pharmacokinetics
- Pharmacodynamics (i.e., autoantibody levels)

Stage 2 T1DM

- 100% of children and adolescents with T1DM have elevated anti-proinsulin and anti-insulin autoantibodies, which drive disease onset and progression (i.e., insulitis and β-cell loss)[1]
- Early treatment in presymptomatic patients (Stage 2) may preserve pancreatic function and help maintain insulin levels and glucose homeostasis, potentially serving as basis for **SINGLE STUDY APPROVAL**
- Precedented development pathway and differentiation opportunity based on teplizumab

POC study

ENDPOINTS
- Anti-proinsulin, anti-insulin, and other autoantibody levels
- Stimulated C-peptide levels
- Exogenous insulin requirements
- Glycemic control
- Time to development of Stage 3 T1DM

T1DM

- Type I diabetes (T1DM) usually progresses to complete insulin dependence
- Lowering of autoantibody levels offers potential for disease modifying therapy
- Potential for **ACCELERATED APPROVAL**[2]

Registrational program

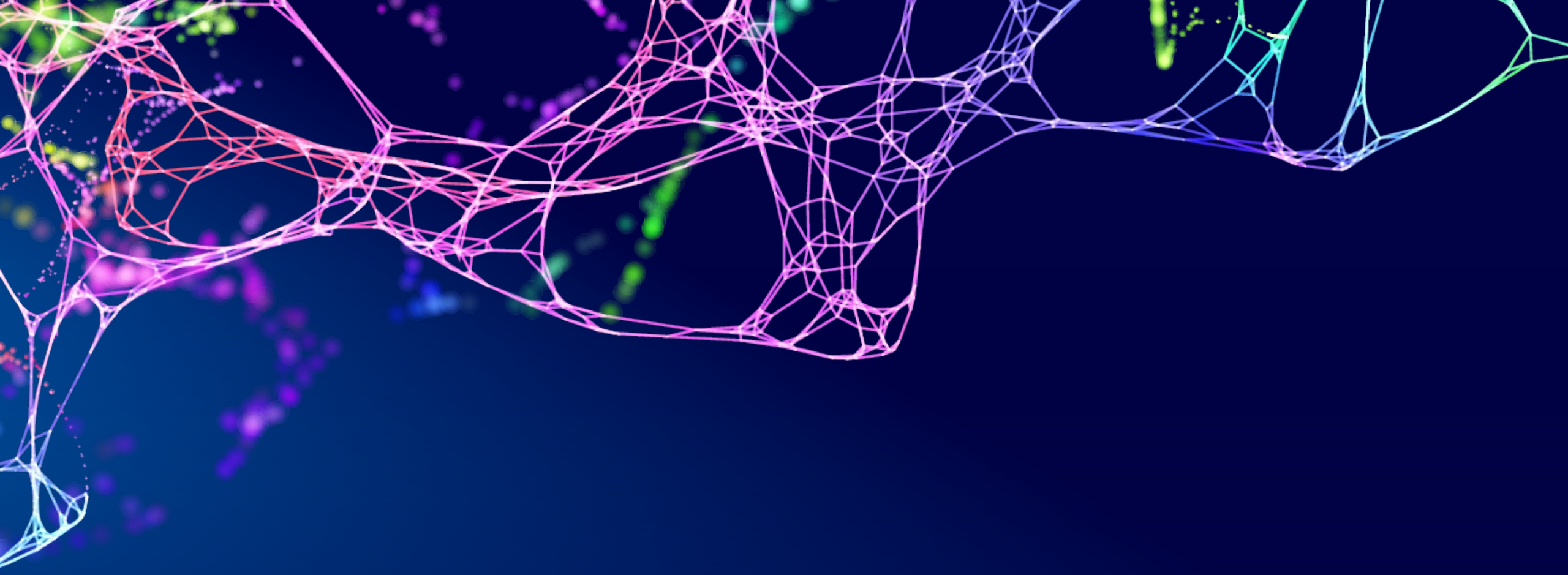
ENDPOINTS
- Anti-proinsulin, anti-insulin, and other autoantibody levels
- Stimulated C-peptide levels
- Exogenous insulin requirements
- Glycemic control
- Hypoglycemic episodes
- End organ complications
- Short term acute events (i.e., ketoacidosis and hyperosmolar hyperglycemic coma)

KEY POINT

Anti-proinsulin and anti-insulin autoantibody-specific degraders offer potential to delay or prevent disease progression in T1DM

biohaven

1. Taplin. Autoimmunity. 2008. 2. Latres et al. Diabetes. 2024.



DEGRADERS

IgG4 Specific Degrader for the Treatment of Multiple IgG4-Mediated Diseases

biohaven®

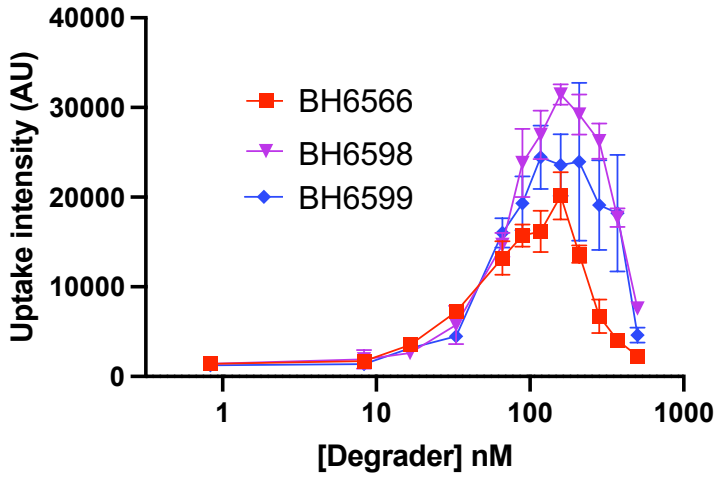
Specific Degraders Designed to Efficiently Remove Only IgG4

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

Binding Affinity

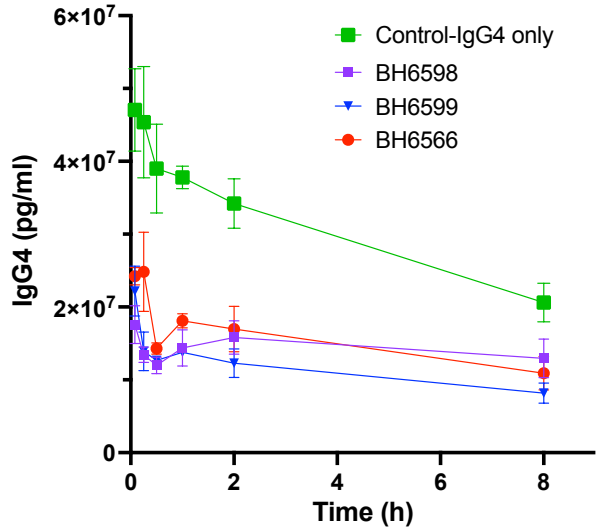
	Native hIgG1	Native hIgG2	Native hIgG3	Native hIgG4
BH6566	>1000	>1000	>1000	36
BH6598	>1000	>1000	>1000	33
BH6599	>1000	>1000	>1000	43

Cellular IgG4 Uptake



In Vivo IgG4 Reduction

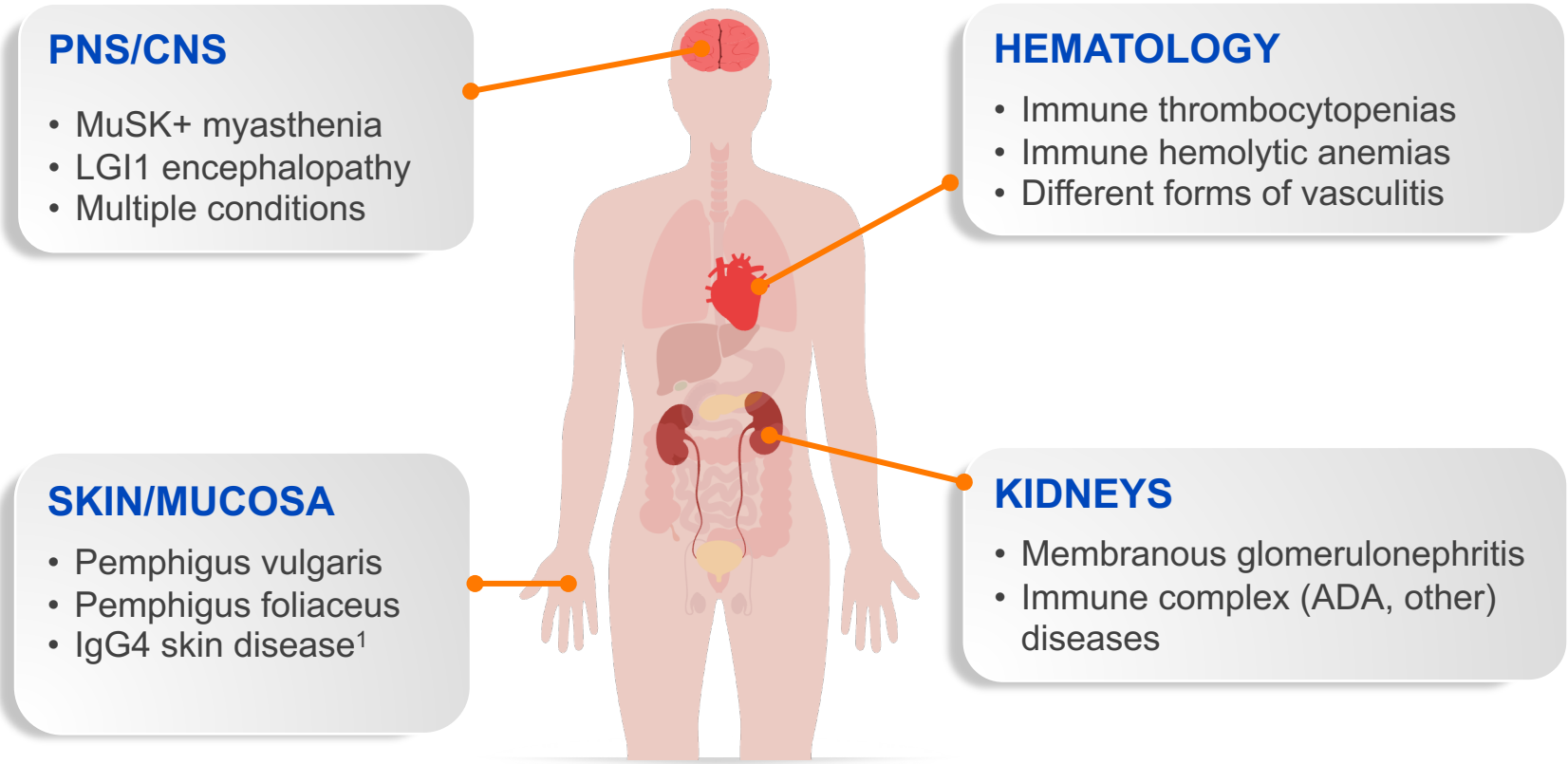
(single dose, 1 concentration POC)



- 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

biohaven

Multiple IgG4-Driven Diseases Provide Large Opportunity



- Pathology for multiple diseases associated with the direct inhibitory effects of IgG4 on a targeted antigen
- IgG4 is the most common antidrug antibody (ADA) subclass, limiting the efficacy of many biologics

Figure adapted from Koneczny et al, Front. Immunol., January 2021, Volume 11, Article 605214
1. Sato et al, Mod Pathol 26:523, 2012

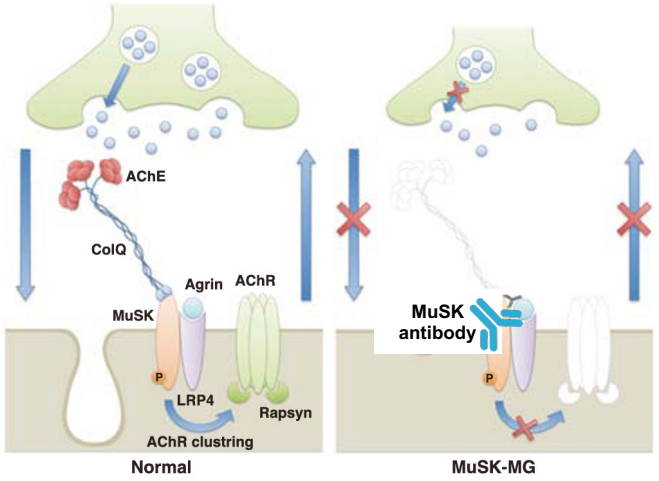
LGI1, Leucine-rich glioma-inactivated 1.

biohaven

Diverse IgG4-Mediated Disease Indications Potentially Treated by MoDEs

MuSK Positive Myasthenia Gravis (MG)

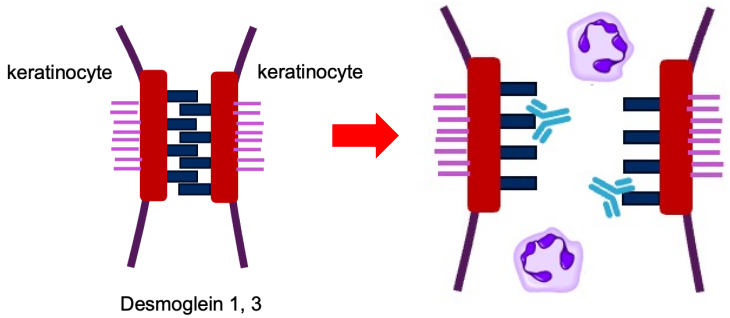
- MuSK is key organizer of neuromuscular junctions
- IgG4-bound MuSK disrupts Lrp4-MuSK thereby reducing AChR clustering and neuromuscular junction function



Mori S et al, Am J Pathol. 2012 Feb;180(2):798-810.

Pemphigus Vulgaris

- IgG4 autoantibodies disrupt tight junctions causing keratinocyte dissociation and inflammation
- Loss of cell-cell adhesion in skin and mucous membranes-leads to blistering

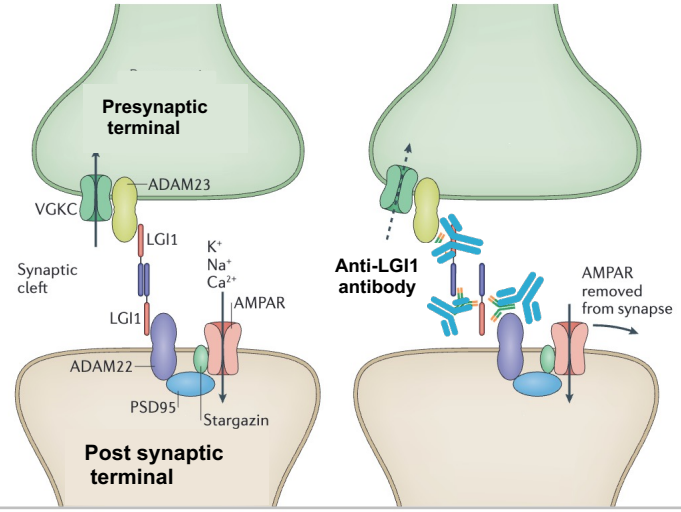


Loss of tight junctions, cell death, neutrophil infiltration, cutaneous blistering

Koneczny I.. *Autoimmun Rev*. 2020;19(10):102646.

Anti-LGI1 Encephalitis

- LGI1 IgG4 autoantibodies disrupt LGI1 binding to ADAM22
- Reduced synaptic transmission and plasticity
- Leads to seizures and neurocognitive effects

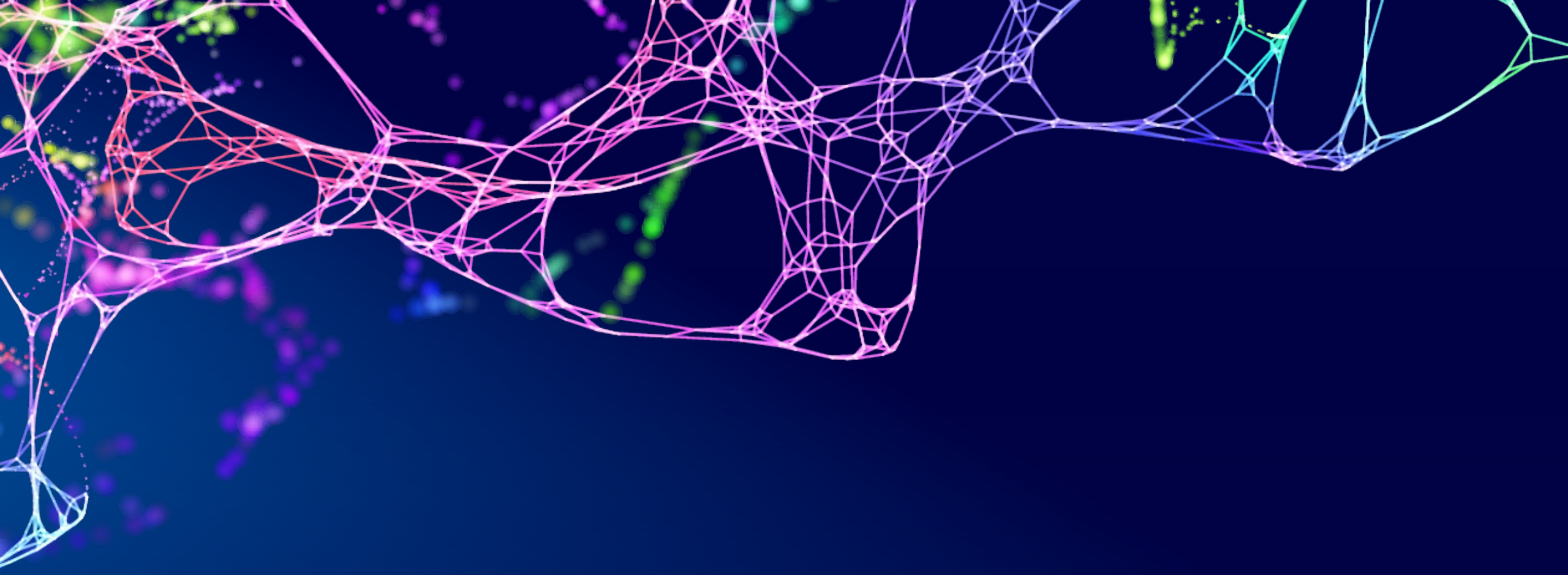


van Sonderen et al, Nat Rev Neurol 13, 290–301 (2017).

KEY POINT

IgG4 specific degraders reverse functional deficits or pathology induced by IgG4 binding in multiple diseases

LGI1, Leucine-rich glioma-inactivated; **MuSK**, Muscle-specific tyrosine kinase; **AChR**, acetylcholine receptor; **ADAM,** a disintegrin and metalloproteinase.



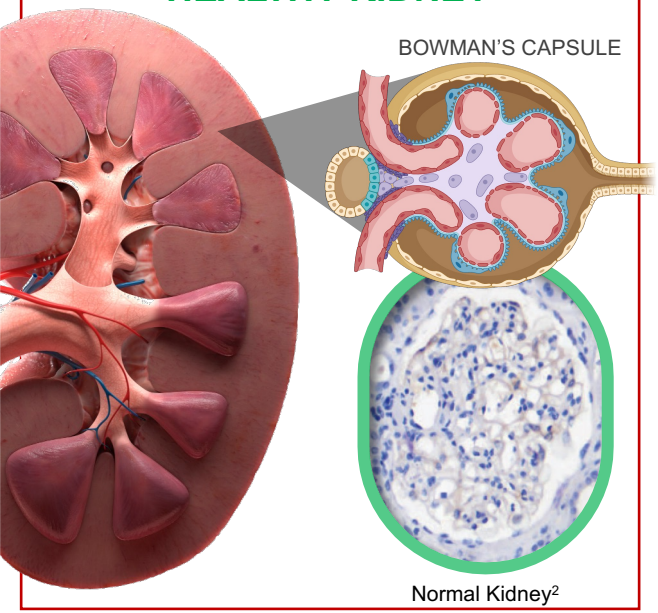
DEGRADERS

Removal of PLA2r Autoantibodies in Idiopathic Membranous Nephropathy

biohaven®

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

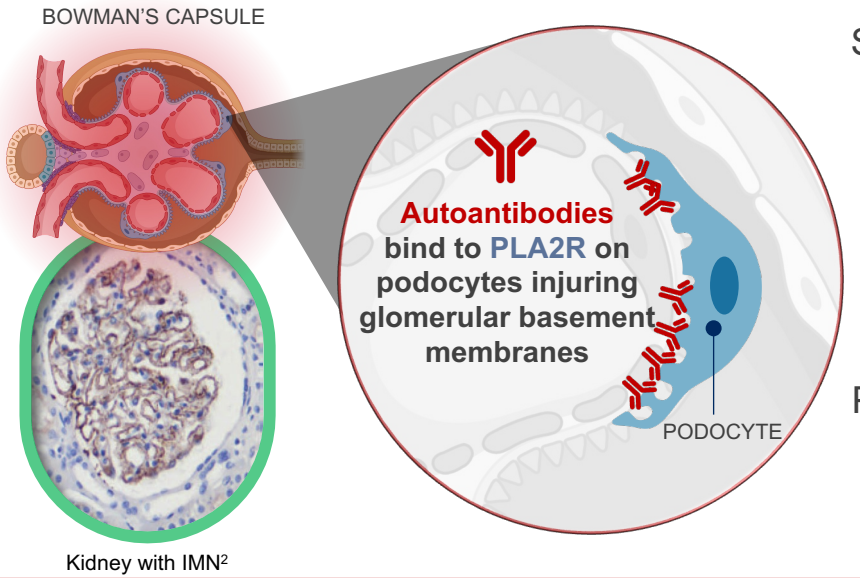
HEALTHY KIDNEY



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

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

NEPHROTIC KIDNEY



Subepithelial immune complex deposits

▼

Podocyte injury, thickening of basement membrane

▼

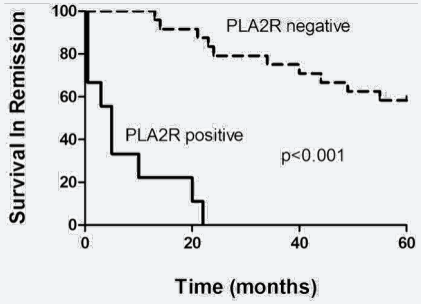
Proteinuria and hyperlipidemia

▼

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.

biohaven

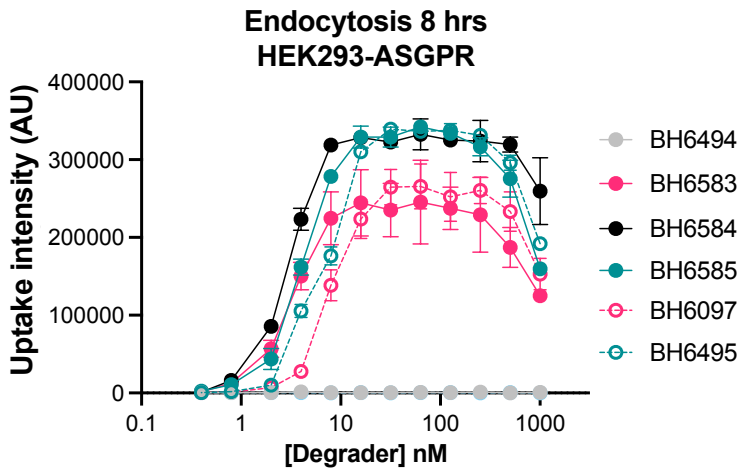
PLA2r Antigen-Specific MoDEs Rapidly Remove Pathogenic Autoantibodies

Biochemical Selectivity

Binding Affinity (nM)

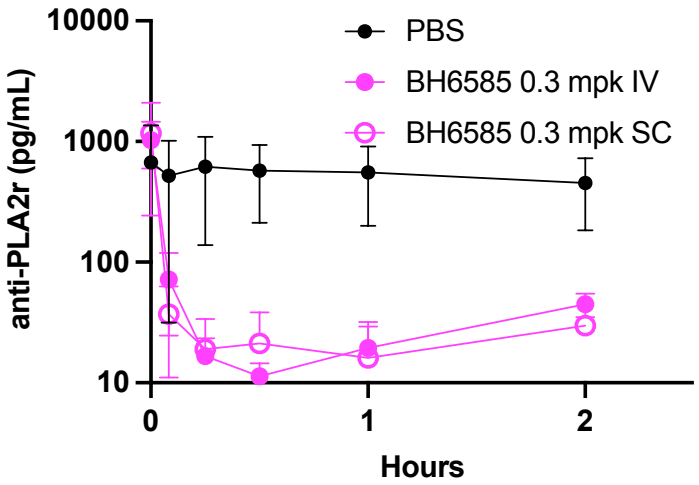
	Anti-PLA2r
BH6494	0.3
BH6583	10 ± 3
BH6584	3 ± 0.3
BH6585	7 ± 1
BH6097	23 ± 1
BH6495	7

Cellular Autoantibody Uptake



*BH6494 lacks ASGPR binder

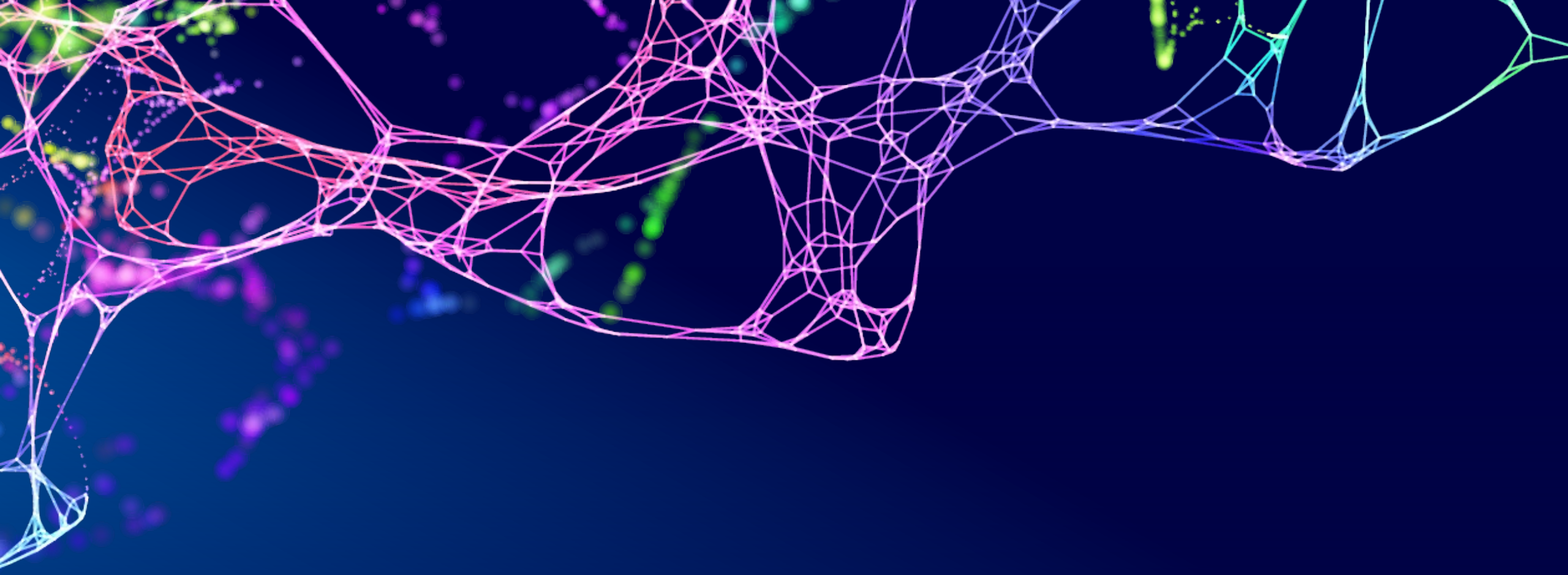
In Vivo Autoantibody Reduction



KEY POINT

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

biohaven

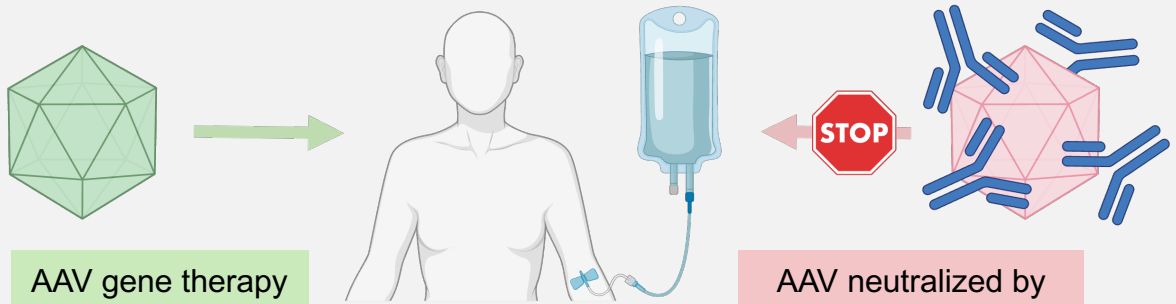


DEGRADERS

AAV9 Targeted Degradation

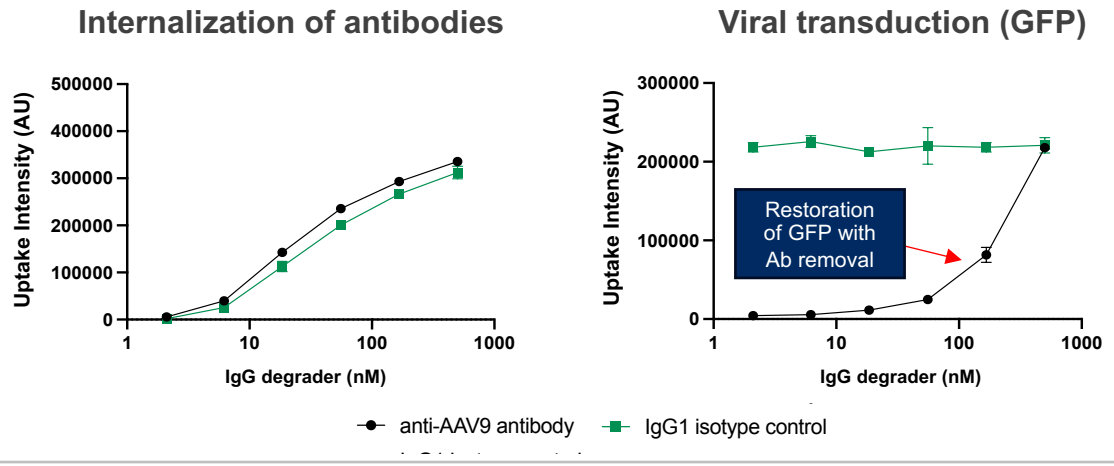
biohaven®

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



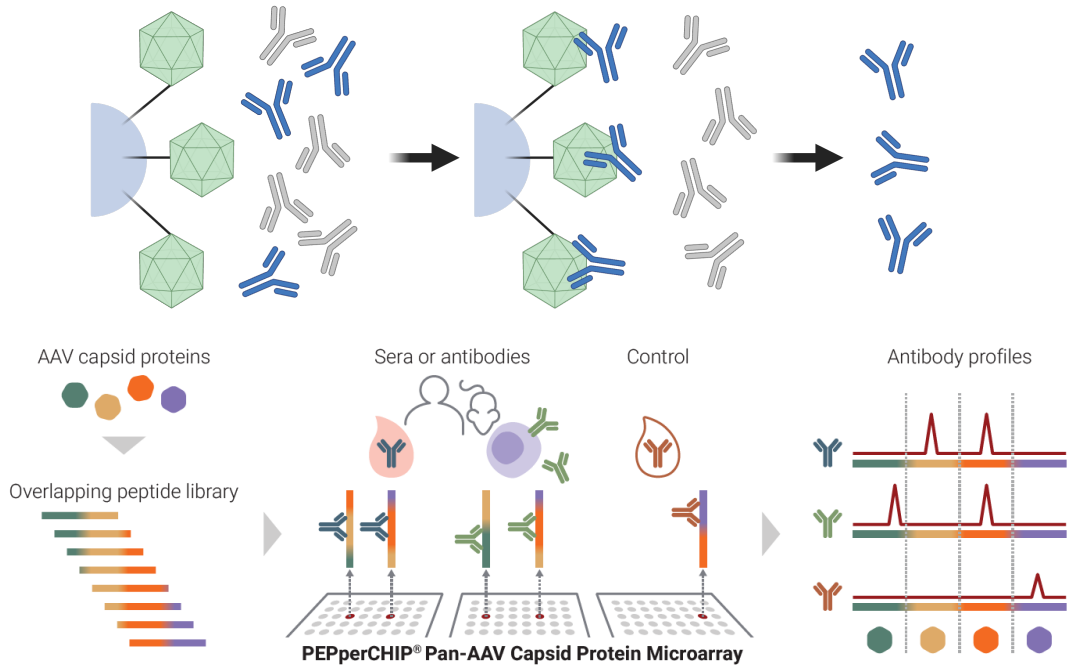
Preexisting anti-AAV antibodies limit the use of AAV-based gene therapy

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

Biohaven is at the forefront of a new immune targeting modality with significant potential for diseases caused by autoantibodies

biohaven®

TRANSFORMATIVE IMMUNOTHERAPIES

NOVEL AND TRANSFORMATIONAL
MoDE™ PLATFORM

- Target Pan IgG
- BHV-1300
- BHV-1310

NextGen Antigen Specific Targets

- BHV-1400 gd-IgA
- BHV-1600 beta-1AR
- Numerous other Autoantibodies

- TARGETING TRANSPLANT REJECTION
- PATHOGENIC PROTEINS
- COMBINATION THERAPIES
- REMOVAL OF ADAs
- DISCOVERY OF NEW AUTOANTIBODY DISEASES TO TARGET

Panel Discussion

MODERATOR

Tessa Romero

Equity Research Analyst

J.P.Morgan

PANELISTS

Bharat Awsare, M.D.
Senior Medical Director, Biohaven

Bruce Car, DVM, Ph.D.
Chief Scientific Officer, Biohaven

James F. Howard, Jr., M.D.
Professor of Neurology & Medicine, University of North Carolina, School of Medicine

Dennis Moledina, M.D., Ph.D.
Assistant Professor of Medicine-Nephrology, Yale University School of Medicine

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

BHVN LISTED NYSE