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NYSE

Biohaven R&D Day

May 27, 2026

DAYS MATTER™

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 (including those for our taldefgrobep alfa, opakalim, BHV-2100, BHV-8000, BHV-8100, BHV-1300, BHV-1310, BHV-1400, BHV-1510, BHV-1530 and BHV-1600 development programs), the timing of and the availability of data from our clinical trials, the timing of 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 a s compared to other existing potential treatment options, and the potential advancement of our early phase programs, including BHV-1955, BHV-8200, BHV-2110, BHV-1490, BHV-1420, BHV-1440, BHV-6500 and BHV-1500. The use of certain words, including “continue”, “plan”, “will”, “believe”, “may”, “expect”, “anticipate” “potential first-in-class” 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, including those regarding the resubmission of our new drug application for troriluzole for SCA; the timing and outcome of expected regulatory filings; Biohaven’s compliance with applicable U.S. regulatory requirements; the potential commercialization of Biohaven's product candidates; and the effectiveness and safety of Biohaven's product candidates, including open label clinical data in ongoing studies. 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 are 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.

WELCOME

Vlad Coric, M.D.

Chairman and Chief Executive Officer

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INNOVATION

Novel, paradigm-shifting science

Potential paradigm shifting therapies from discovery to ongoing clinical trials

EXECUTION

>6 clinical-stage trials in 2026

Milestones on track

VALUE

Targeting unmet patient needs and addressable markets each with blockbuster potential

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DAYS MATTER™

BHV-1400
TRAP™ degrader
First Gd-IgA1 target
IgA nephropathy

First Gd-IgA1 degrader

BHV-1300
MoDE™ degrader
First IgG degrader
Graves' disease

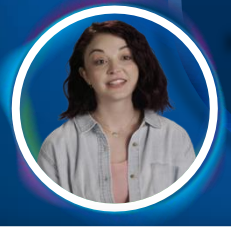
First IgG degrader

Novel brain-penetrant TYK2/JAK1

BHV-8000
First TYK2/JAK1 inhibitor
Brain-penetrant
Parkinson's disease

Ion Channels
BHV-7000
Opakalim
Selective Kv7 activator
Paradigm tolerability

Potential paradigm shifting Kv7 activator



Novel myostatin-activin

Obesity
BHV-2000
Taldefgrobep
Myostatin/activin
High-quality weight loss
Obesity

biohaven®
DAYS MATTER™

INNOVATION *in* ACTION

Next-Gen Discovery Targets
Degraders for diabetes, IgG4 diseases and emerging targets

Innovative next-gen molecules

BHV-1955
Potential first-in-clinic
Nasal oxytocin
Tinnitus targets

Oncology
BHV-1530
First FGFR3 ADC
Unique Topolx payload
Oncology

First FGFR3 ADC

First-in-clinic brain-penetrant PKM2

BHV-8100
PKM2 activator
Brain-penetrant
Neurodegenerative disease

Troriluzole
SCA
Continued advocacy
Days Matter™
SCA patients

Pursuing first therapy for SCA


BHV-1400
TRAP™ Degrader
First G1-IgA1 Target IgA
Nephropathy
BHV-1300
MoDE™ Degrader
First IgG Degrader
Graves' Disease
BHV-8000
First TYK2/JAK2 Inhibitor
Brain-Penetrant
Parkinson's Disease
Ion Channels
BHV-7000
Opaxalin
Selective Kv7 Activator
Paradigm Tolerability
Epilepsy
Obesity
Obesity
BHV-2000
Taldefgrobep
Myostatin/Activin
High-Quality
Weight Loss
Obesity
BHV-1400
First-in-Class
Nasal Oxytocin
Tinnitus
Targets
biohaven®
DAYS MATTER™
INNOVATION
in ACTION
Oncology
BHV-1530
First FGFR3 ADC
Unique Topoix Payload
Oncology
Next-Gen Discovery
Targets
Degraders for
Diabetes, IgG4 Diseases &
Emerging Targets
Troriluzole
SCA
Continued Advocacy
DaysMatter™
SCA Patients
BHV-0100
PKM2 Activator Brain-
Penetrant
Neurodegenerative
Disease

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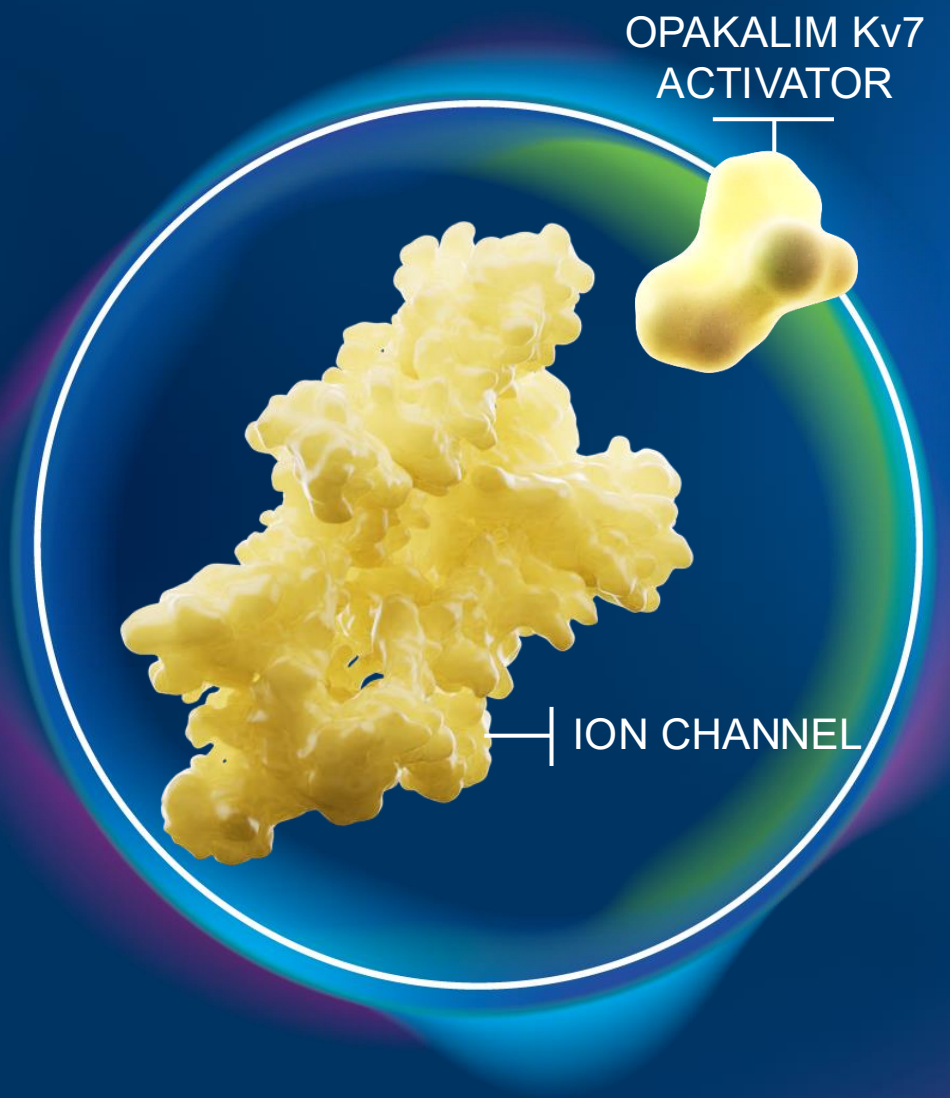
ION CHANNEL: OPAKALIM SELECTIVE Kv7 ACTIVATOR

Revolutionizing Epilepsy Treatment With a Modern Kv7 Activator



Matthias Koepp, MD, PhD

Professor of Neurology
University College London

UCL

Jason Lerner, MD

Medical Director

biohaven®

Steven Dworetzky, PhD

Senior Vice President,
Kv7, Strategy & Development

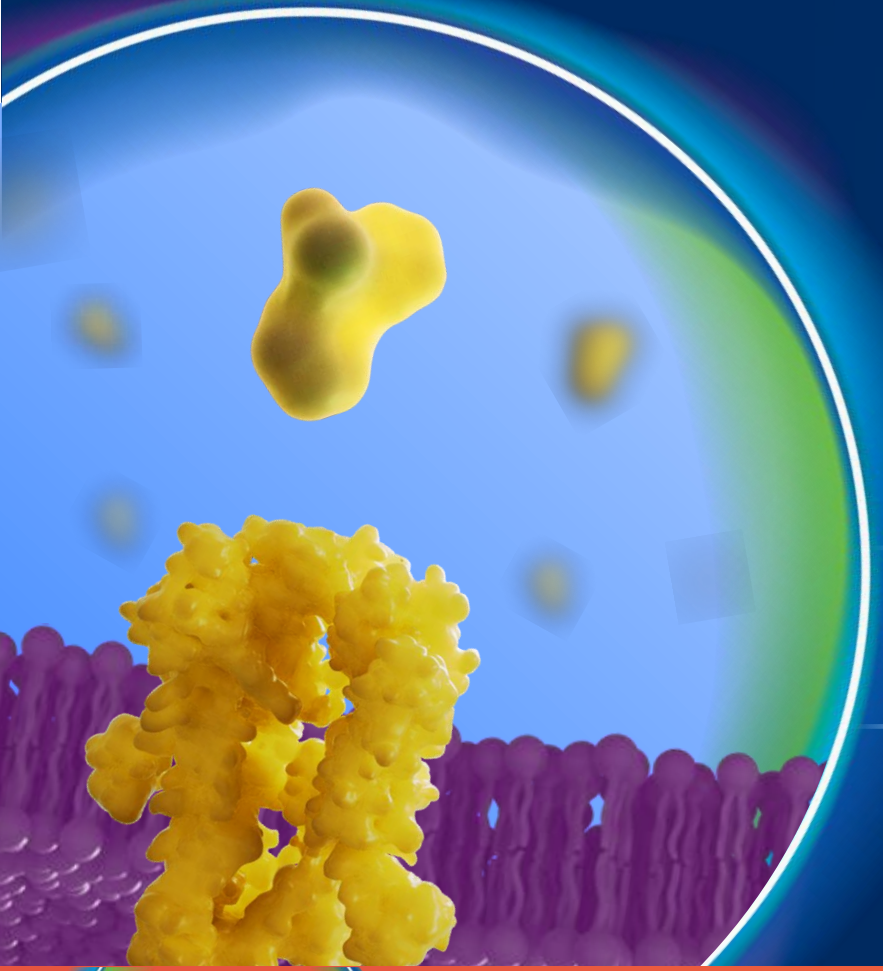
biohaven®

Ion Channel

biohaven®

An Epilepsy Treatment Designed With Patients and Physicians in Mind

Kv7



Opakalim offers potential for easy-to-use, once-daily treatment with no titration to control seizures without the burdensome side effects frequently reported with approved ASMs and those in development

Selectively activates Kv7.2/7.3 channels—a validated MOA for treating epilepsy—without impacting GABA receptors

Exhibits preliminary efficacy signals in focal epilepsy OLE, KCNQ2-DEE and now idiopathic generalized epilepsy

Demonstrates exceptional safety profile with low rates of CNS adverse events across all trials (1000+ subjects)

BREAKING NEWS

Recent clinical data updates reinforce efficacy and differentiated tolerability

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Idiopathic Generalized Epilepsy (IGE)

Matthias Koepp, MD, PhD

Professor of Neurology
University College London

UCL

Opakalim:
Selective Kv7 Activation for IGE

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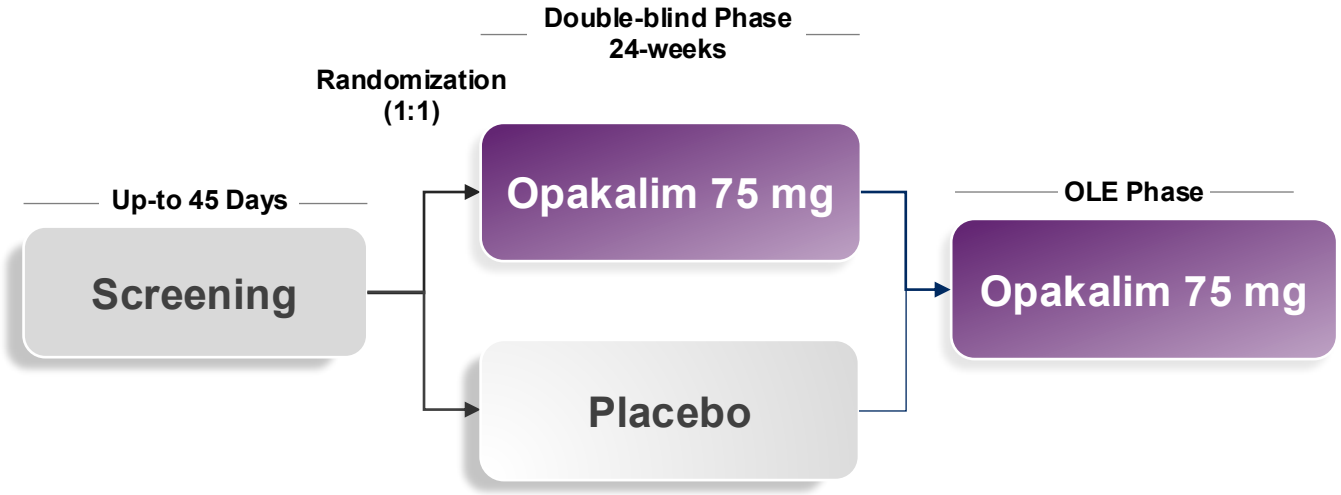
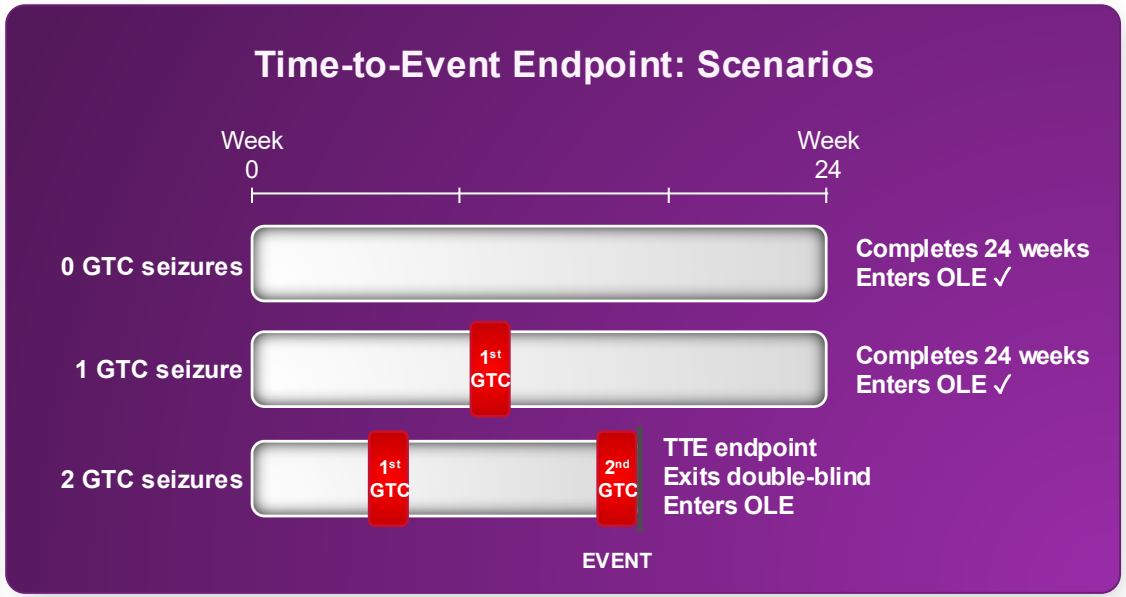
Idiopathic Generalized Epilepsy Time-to-Event Study Design

Kv7





KEY STUDY DETAILS

Study Design: Randomized, double-blind, placebo-controlled, event-driven trial

Endpoint: Primary - Time-to-event (Event = 2nd day with GTC seizure); **Secondary -** GTC seizure freedom

Population: Subjects 18-75 with IGE and intractable GTC seizures

Key Entry Criteria: 3 GTC seizures within the historic 16-week seizure assessment period

Study terminated early due to enrollment and strategic portfolio prioritization; GTC: generalized tonic-clonic; IGE: idiopathic generalized epilepsy; TTE: time-to-event

Demographics and Baseline Disease Characteristics

Kv7

	Opakalim 75 mg n=15	Placebo n=12*
Age (mean)	**37**	43
Sex (% female)	**73%**	83%
Region (% US)	**47%**	25%
BMI (mean)	**27**	28
Number of epilepsy treatments at screening		
1 to 2	**60%**	67%
3 to 4	**40%**	33%
Number of previous and current ASMs		
≤ 6	**11 (73%)**	10 (83%)
> 6	**4 (27%)**	2 (17%)
Age at IGE diagnosis (mean)	**14**	13
Years since IGE diagnosis (mean)	**23**	30

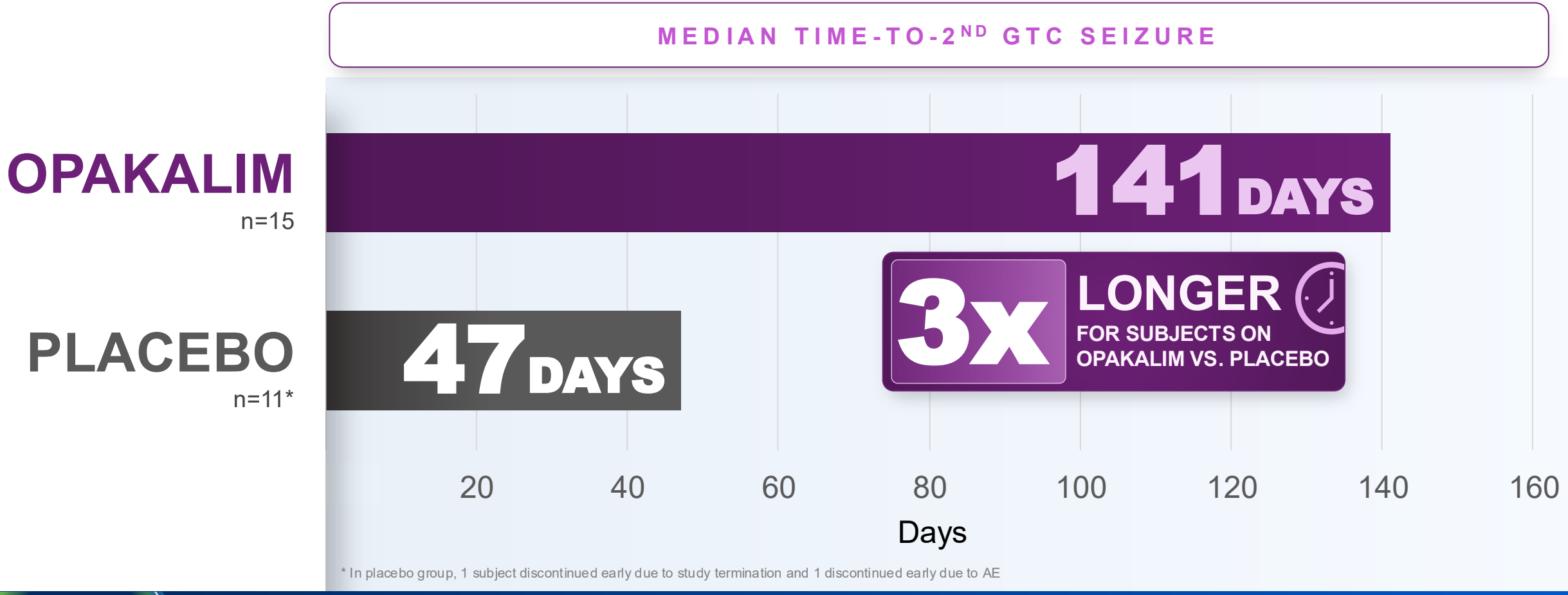
* In placebo group, 1 subject did not have post-dose efficacy data

KEY POINT

Highly treatment-resistant idiopathic generalized epilepsy population

Opakalim Prolongs Time-to-2nd GTC Seizure

Kv7



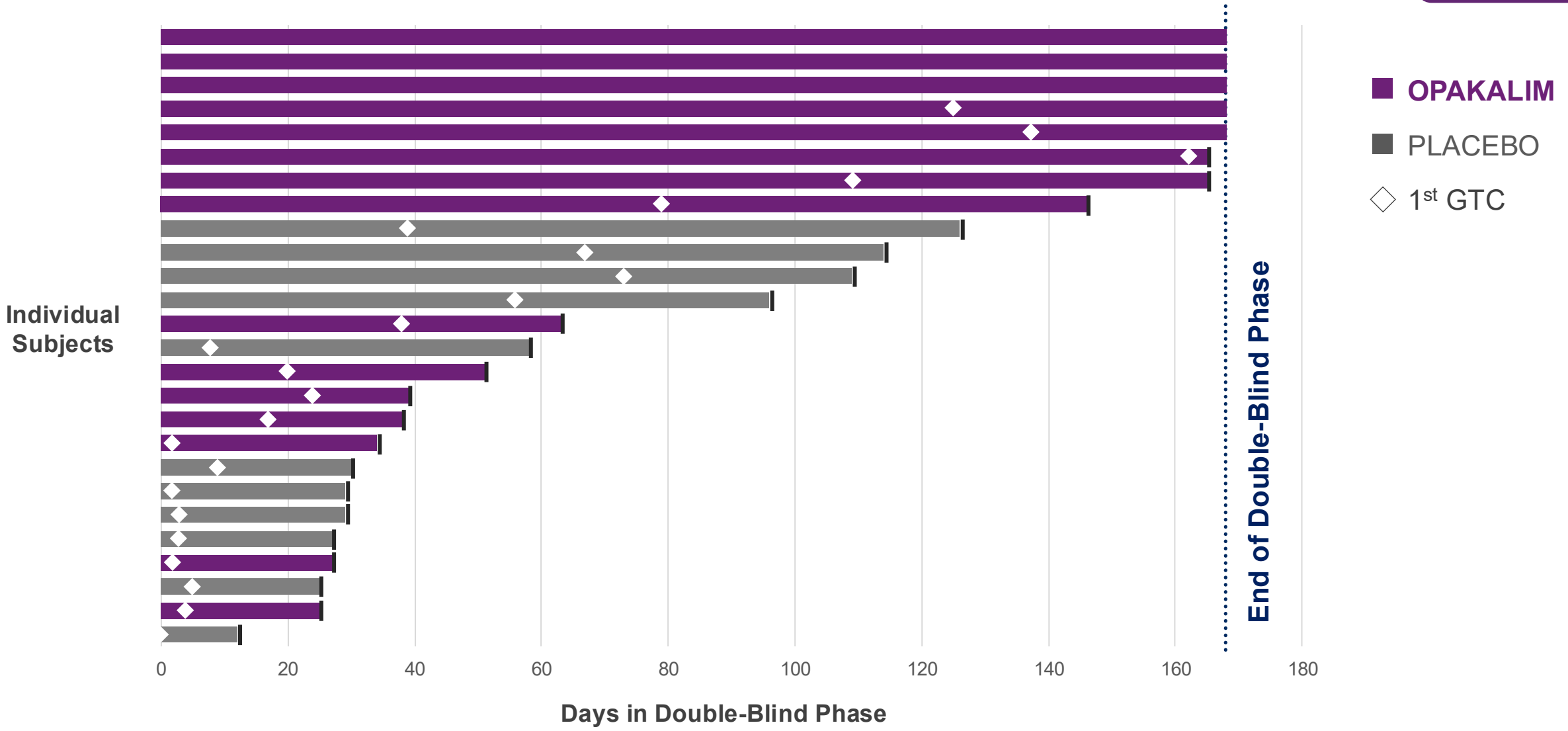
* In placebo group, 1 subject discontinued early due to study termination and 1 discontinued early due to AE

KEY POINT

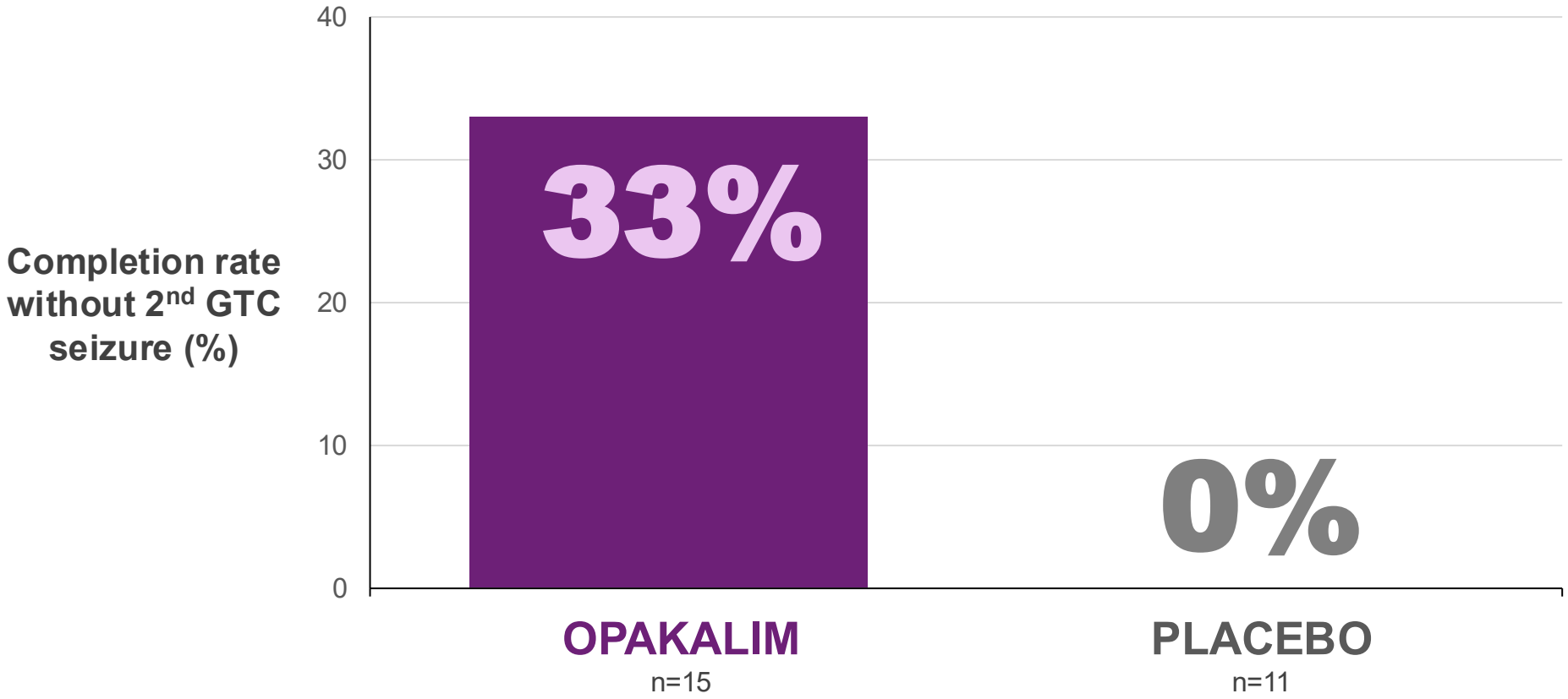
Efficacy signal observed in idiopathic generalized epilepsy population

Opakalim Prolongs Time-to-2nd GTC Seizure & Time in Double-Blind

Kv7

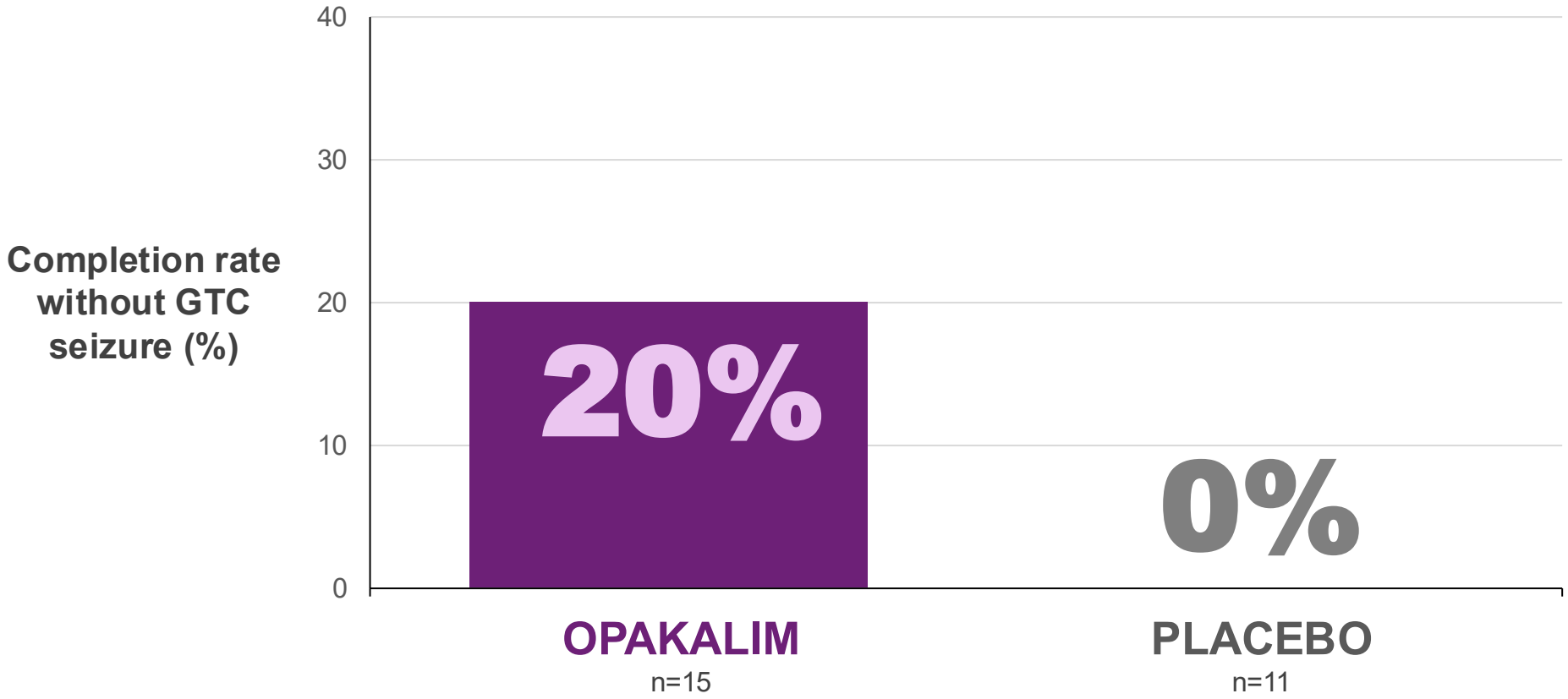


One-Third of Opakalim-Treated Subjects Completed Six-Month Double-Blind Phase Without 2nd GTC



* In placebo group, 1 subject discontinued early due to study termination and 1 discontinued early due to AE

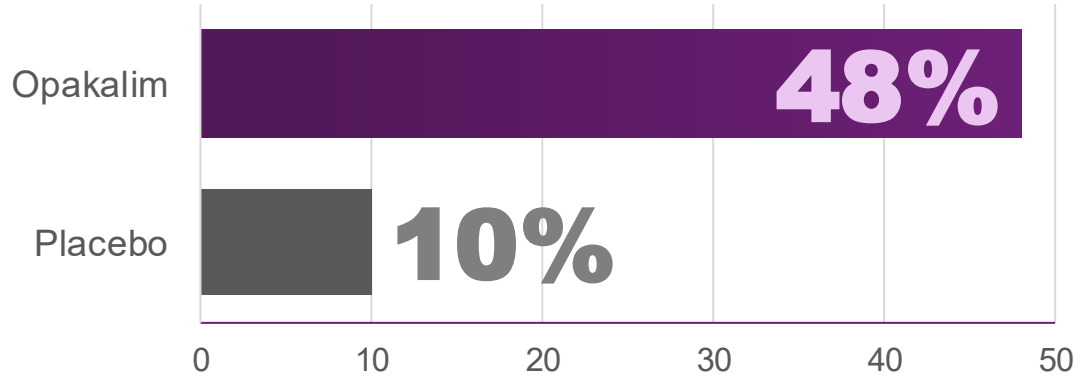
20% of Opakalim-Treated Subjects Completed Six-Month Double-Blind Phase Seizure Free



* In placebo group, 1 subject discontinued early due to study termination and 1 discontinued early due to AE

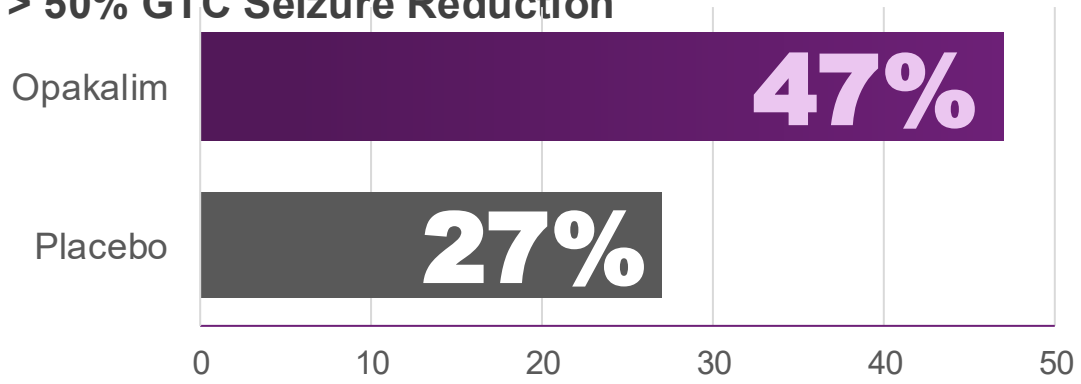
Opakalim-Treated Subjects Showed Improvements on Seizure and Patient Reported Outcomes

Median % Change in Days With GTC Seizures*

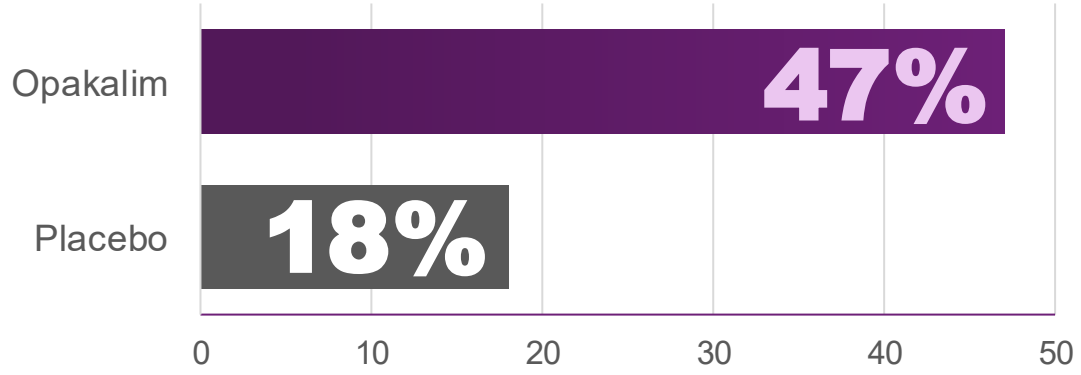


Responder Rate*

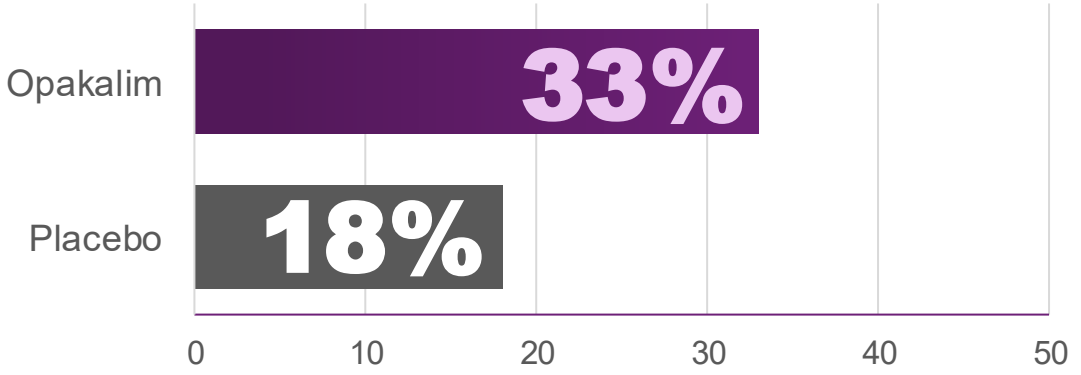
> 50% GTC Seizure Reduction



Patient Global Impression of Severity (PGI-C)**



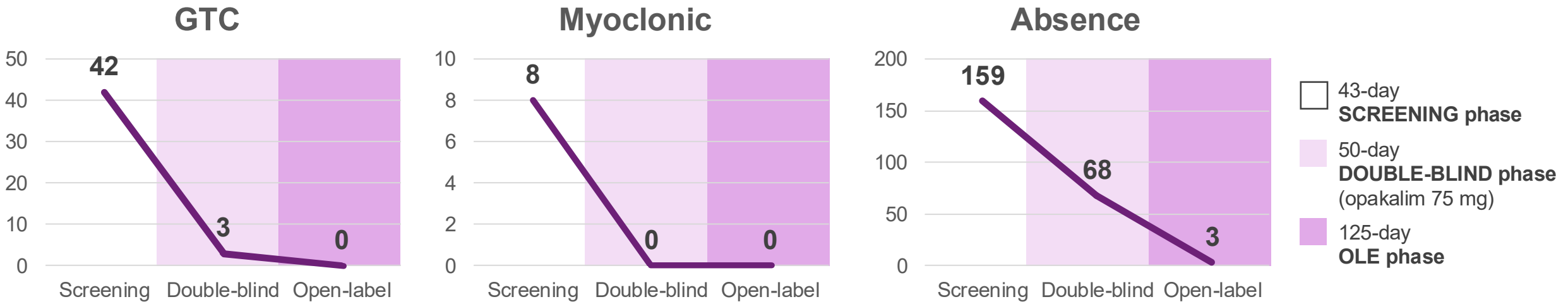
> 75% GTC Seizure Reduction



*28-day adjusted. **PGI-C – based on last assessment in double-blind phase

Promising Case of Broad-Spectrum Generalized Seizure Efficacy

Our patient has very difficult-to-treat IGE, since entering the opakalim trial she has experienced reduction in all seizure types.



In terms of tolerability, she continues to do very well, with no adverse events.

Opakalim IGE Double-Blind Phase topline data, 1H 2026

KEY POINT

- **50% of subjects with myoclonic seizures became myoclonic seizure free on opakalim**
- **33% of subjects with absence seizures became absence seizure free on opakalim**

Opakalim Exhibits Low Rates of Nervous System Adverse Events

Kv7

Preferred Term	Opakalim (n=15) n (%)	Placebo (n=12) n (%)
Generalized tonic-clonic seizure	1 (6.7)	0
Headache	1 (6.7)	2 (16.7)
Hypotonia	1 (6.7)	0
Paraesthesia	1 (6.7)	0
Presyncope	1 (6.7)	0
Coordination abnormal	0	1 (8.3)
Dysarthria	0	1 (8.3)
Dysgeusia	0	1 (8.3)

Opakalim IGE Double-Blind Phase topline data, 1H 2026

KEY POINT

No somnolence, dizziness, or fatigue

Jason Lerner, MD

Medical Director

biohaven®

Opakalim:
Selective Kv7 Activation for Epilepsy

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Promising Case Reports in Idiopathic Generalized Epilepsy

CASE STUDY #1 • IMPROVED QUALITY OF LIFE

Able to **travel**

Comfortable traveling from Louisiana to California to attend a wedding

33 F | Intractable GTC seizures | Almost daily seizures at baseline | Does not travel

RESPONSE TO OPAKALIM

Decreased GTC seizure frequency with **seizure-free periods lasting weeks** and no side effects

ABLE TO TRAVEL

Traveled to California with her husband, attended a wedding and returned to Louisiana without having a single seizure

CASE STUDY #2 • SEIZURE FREEDOM

425+ DAYS seizure free

Reduced risk of mortality and epilepsy-related comorbidities

60 F | Intractable GTC seizures since age 16 | Frequent seizures at baseline (7 GTC seizures in 30-day screening phase) | Pulmonary and CV comorbidities

RESPONSE TO OPAKALIM

Seizure free in double-blind phase and open-label phase for total of 425+ consecutive days

REDUCED RISK OF MORTALITY DUE TO SUDEP

SUDEP-3 Inventory score at baseline **was 3/4 and is now 0/4** on treatment with opakalim indicating reduced risk of SUDEP

Sudden **U**nexpected **D**eath in **EP**ilepsy

- Uncontrolled seizures are a major risk factor
- SUDEP-3 Inventory: validated tool to predict and quantify risk of SUDEP. For each point on the SUDEP-3, odds of SUDEP increase by 180%

Tarighati Rasekhi. Epilepsia. 2021.

Opakalim Demonstrates Antiseizure Efficacy With Favorable Tolerability in Idiopathic Generalized Epilepsy

SEIZURE FREEDOM

20%

on opakalim completed 24-week double-blind phase **seizure free**

COMPLETERS

33%

on opakalim completed 24-week double blind phase **without 2nd GTC seizure**

TOLERABILITY

Well-tolerated

No somnolence, dizziness, or fatigue

SAFETY

Potentially **reduced risk of mortality** due to **SUDEP**

TIME-TO-EVENT

On opakalim

3x

longer to 2nd GTC seizure

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KCNQ2-DEE

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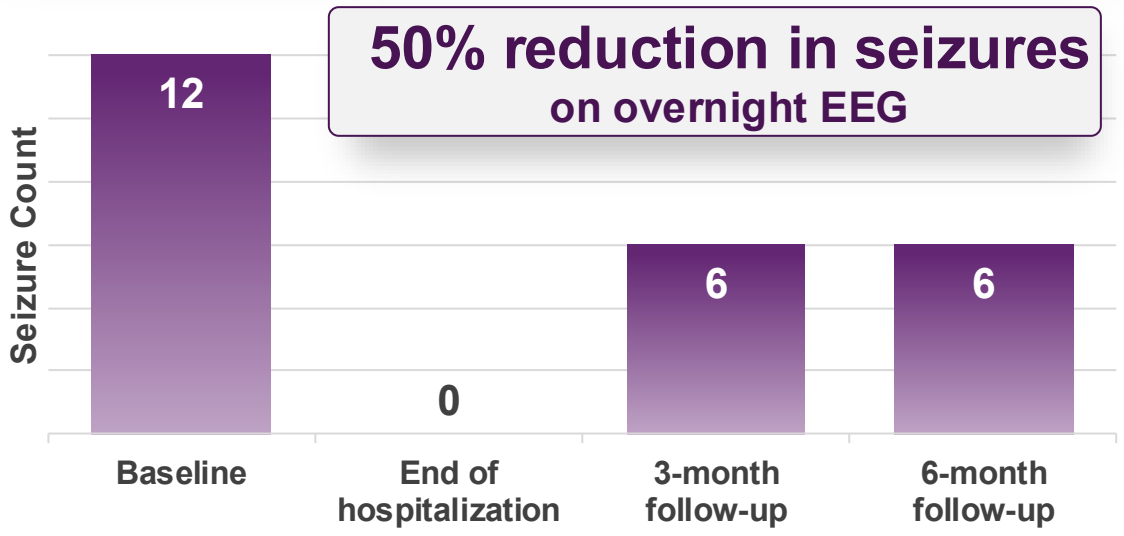
Efficacy Signal Demonstrated in KCNQ2-DEE

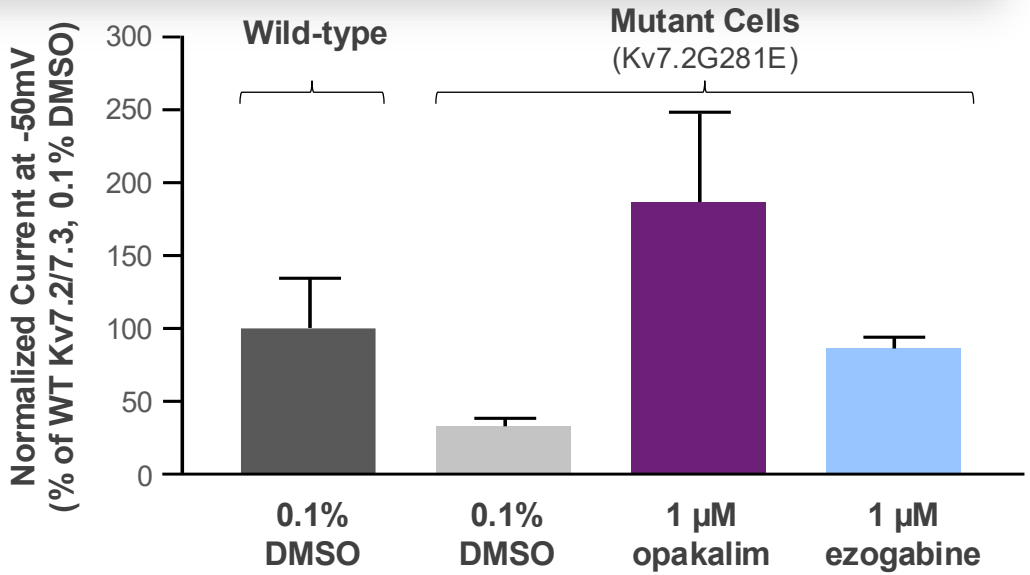
Kv7

9-year-old boy with

- **Refractory KCNQ2-DEE**
- **Kv7 activation-dependence**

- Heterozygous for Kv7.2 G281E mutation
- Daily tonic seizures at baseline despite 3 ASMs including 1st gen Kv7 activator
- Prior attempts to taper 1st gen Kv7 activator resulted in **status epilepticus, ICU admission and developmental regression**





Olson. AAN 2026. Poster #P10 11-002; Equivalent exposures to 75 mg dose in pivotal focal epilepsy studies

KEY POINT

Successfully transitioned from 1st gen Kv7 to opakalim and stable for 6+ months

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Focal Epilepsy

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High Retention and Rollover in Opakalim Focal Epilepsy Trials

Double-Blind Completion Rate **~95%**

Rollover Rate to OLE **~95%**

>200 subjects in OLE for >6 months

Opakalim ongoing focal epilepsy trials preliminary data 1H 2026

Efficacy Signal Observed in Focal Epilepsy Open-Label Data

Kv7

SEIZURE FREQUENCY
Pretreatment Baseline in OP

VS

SEIZURE FREQUENCY
On Treatment with Opakalim 75 mg in OLE

>54% OF PATIENTS SHOWED

50% RESPONSE RATE

OVER ANY CONSECUTIVE 6-MONTH PERIOD IN OLE (n>100)

* RISE 2 Part B: opakalim 75 mg

Opakalim ongoing focal epilepsy preliminary data 1H 2026 for open-label 6-month completers; French. Epilepsia Open. 2025; Indirect comparisons between compounds based on publicly available data.

KEY POINT

50% RR for opakalim (54%) comparable to azetukalner (56%)

Exceptional Tolerability Observed in Focal Epilepsy Open-Label Data

Kv7

Preferred Term	Opakalim 50 mg	Opakalim 75 mg	Opakalim Pooled
Headache	4.5%	6.4%	5.7%
Nasopharyngitis	4.5%	6.4%	5.7%
Seizure	5.3%	3.7%	4.3%
Dizziness	3.0%	5.0%	4.3%
Fatigue	3.0%	4.1%	3.7%
Fall	2.3%	4.6%	3.7%
Upper Respiratory Tract Infection	3.0%	4.1%	3.7%
Back Pain	3.8%	3.2%	3.4%
Insomnia	5.3%	2.3%	3.4%
Nausea	3.8%	2.8%	3.1%
Diarrhea	6.0%	1.4%	3.1%

Adverse events reported in ≥3% of pooled participants, opakalim ongoing focal epilepsy open-label preliminary data 1H 2026

KEY POINT

Low incidence, majority mild and spontaneously resolved

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The Opportunity for Opakalim in Focal Epilepsy

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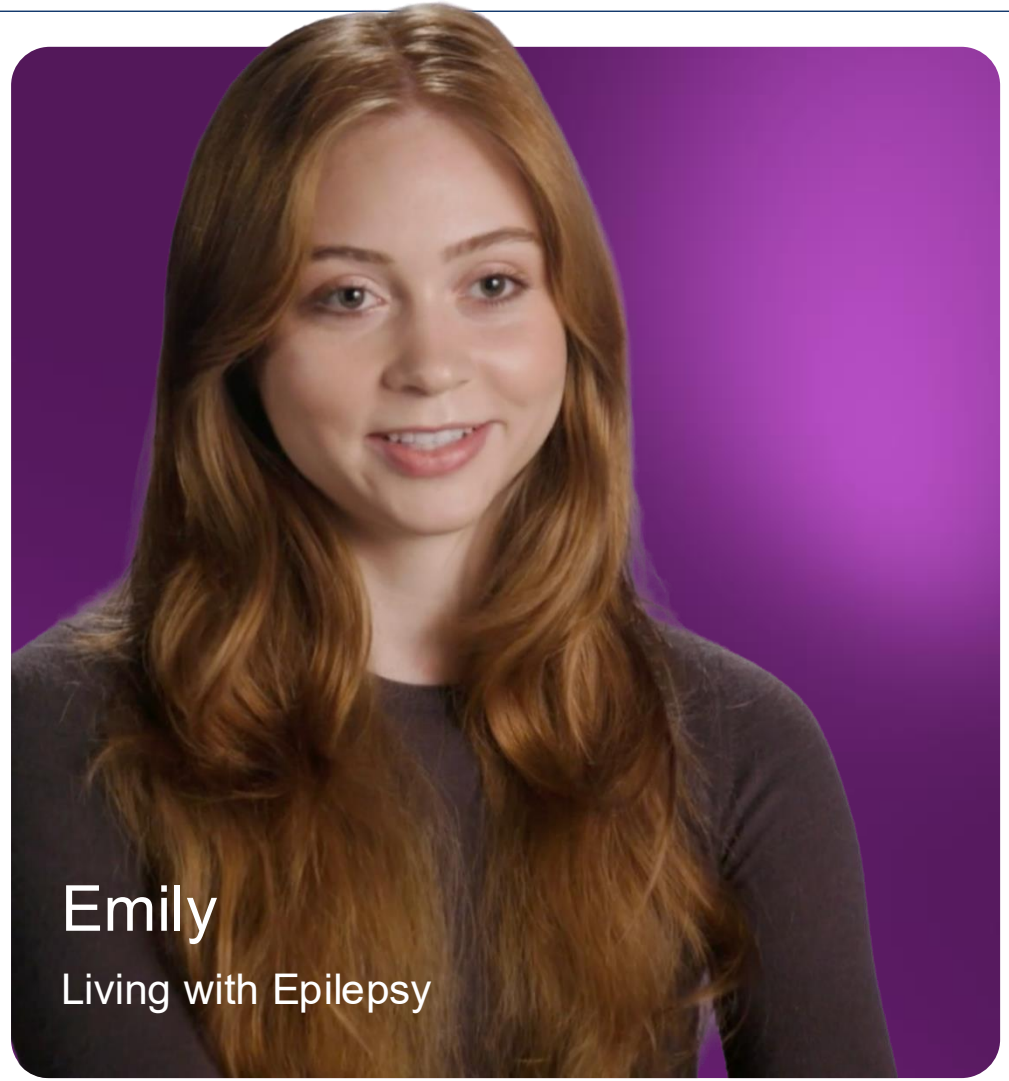
High Unmet Need Remains for Novel, Well-tolerated and Effective Antiseizure Medicines

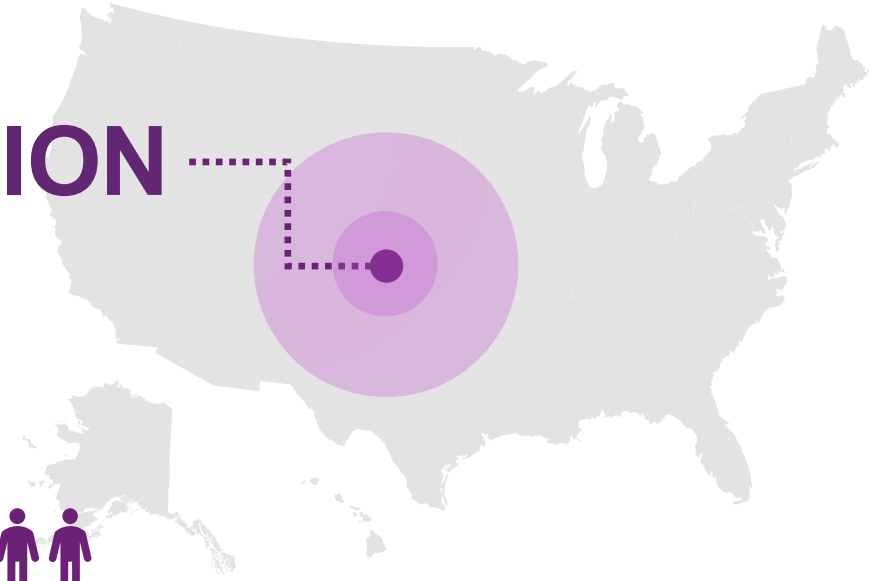
Kv7



PREVALENCE[1]

3.5 MILLION

people with epilepsy (PWE) in the US



REFRACTORY[2]

UP TO 40%

of PWE continue to have seizures despite treatment

HEALTHCARE SPENDING[3]

$24.5 BILLION

annual spending in the US (direct costs)

1. www.cdc.gov/mmwr/volumes/66/wr/mm6631a1.htm. **2.** French. Epilepsia. 2007. **3.** www.cdc.gov/epilepsy/data-research/facts-stats/index.html#:~:text=Health%20care%20spending

High Unmet Need Remains for Novel, Well-tolerated and Effective Antiseizure Medicines

Kv7

ADVERSE EVENTS[1]

80%
of PWE report AEs after starting an ASM

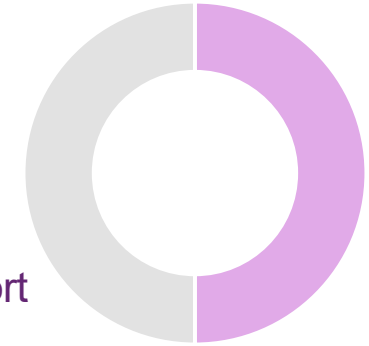
ADHERENCE[2]

UP TO 60%
of PWE report non-adherence to ASMs

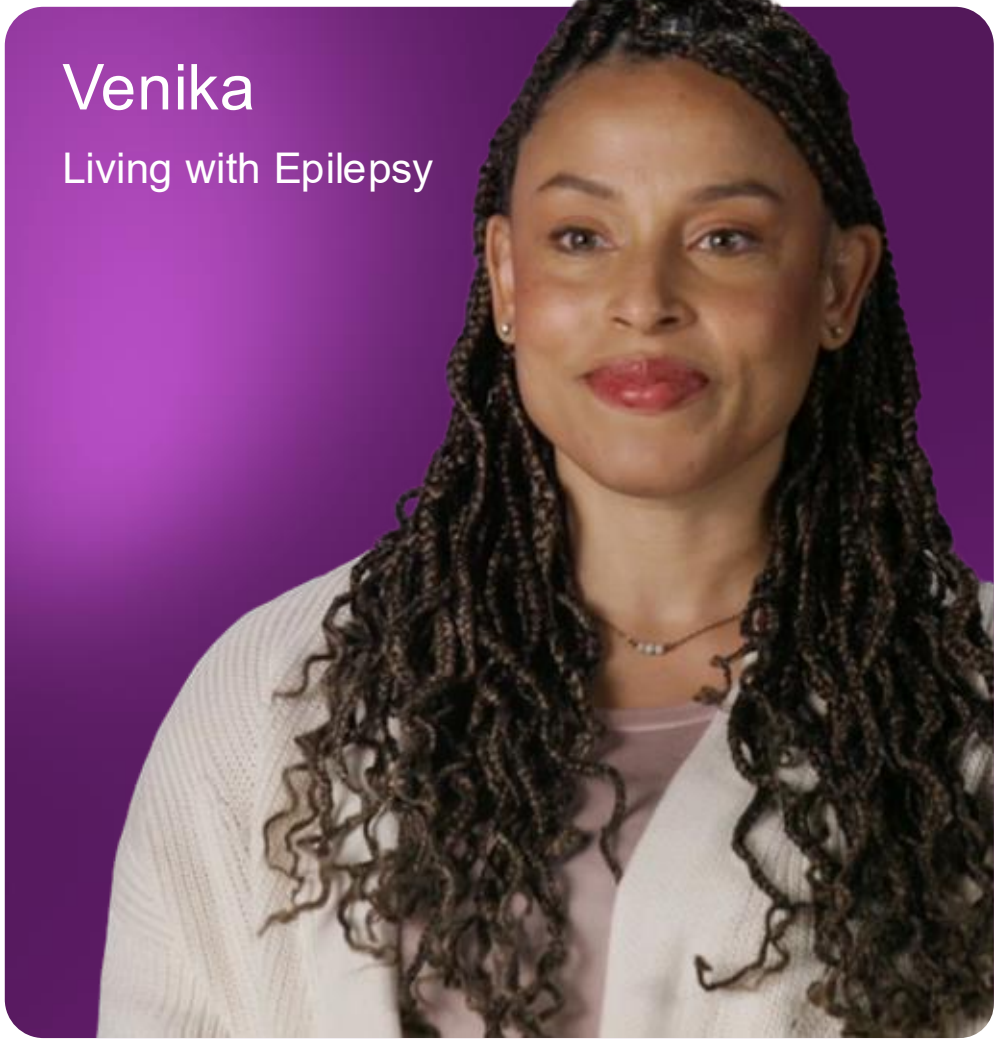
COMORBIDITIES[3]

50%
of PWE report at least 1 comorbidity

QUALITY OF LIFE[4]



50%
of PWE report lower QoL



1. Baker. Epilepsia. 1997. **2.** Donahue. Neurol Clin Pract. 2025. **3.** Bosak. Epilepsy & Behavior. 2025. **4.** Strzelczyk. Epilepsy & Behavior. 2023.

Similar Populations in Opakalim and Azetukalner Focal Epilepsy Trials

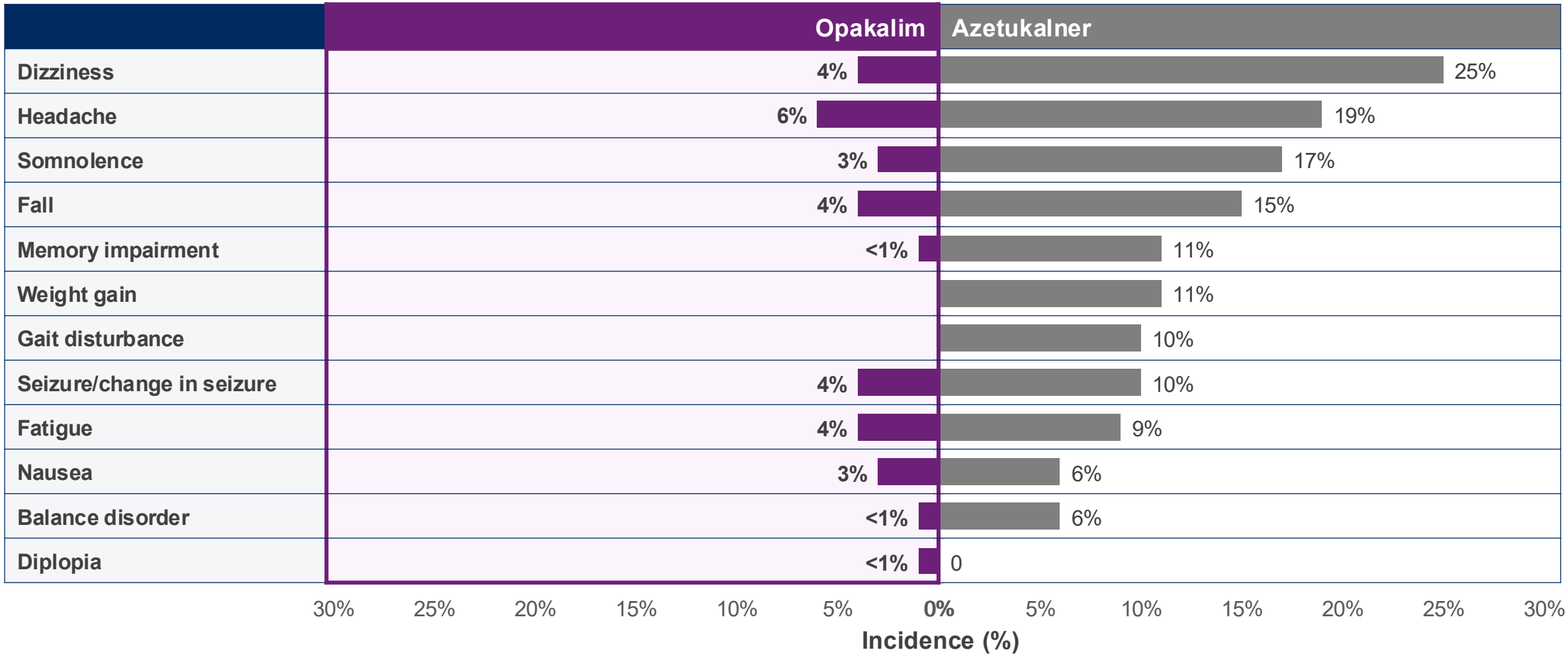
Kv7

	Opakalim	Azetukalner
n	**328**	374
Age (mean)	**39**	40
Sex	**50.4% F**	50.8% F
BMI (mean)	**25.97**	26.8
Baseline Seizure Frequency (median)	**13.00**	12.75
# of concomitant ASMs		
1	**11.4%**	10.2%
2	**36.5%**	38.5%
3	**50.7%**	51.3%
# of ASMs tried and discontinued (median)	**4**	5

Opakalim (all doses) ongoing focal epilepsy open-label preliminary data 1H 2026; Azetukalner (all doses) data from Phase 3 X-TOLE 2 Study: Topline Results, March 9, 2026, xenonpharma.com

Opakalim Demonstrates Favorable Tolerability vs. Azetukalner in Focal Epilepsy Open-Label Trials

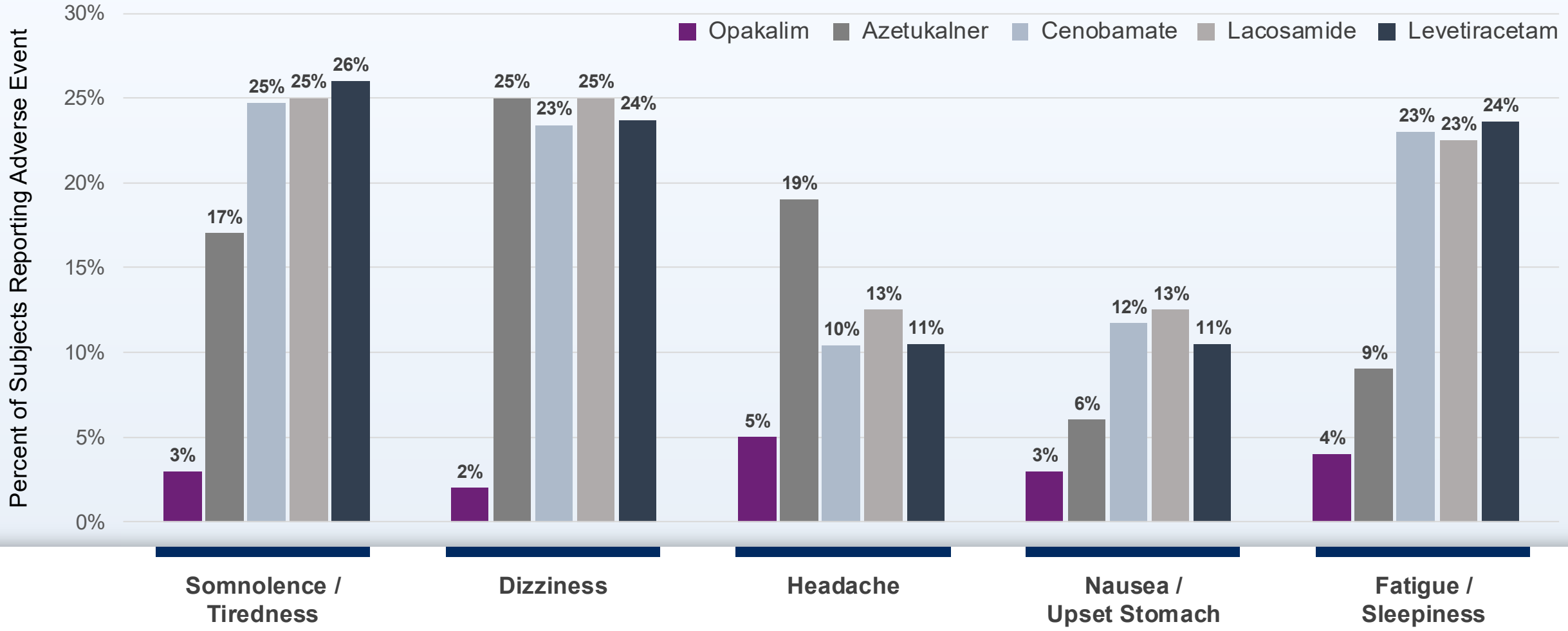
Kv7



Opakalim ongoing focal epilepsy open-label preliminary data 1H 2026; percentages rounded to the nearest whole percent; Azetukalner focal epilepsy data from Open Label Study – French. AES 2025. Poster #3.356.

Opakalim Demonstrates Favorable Tolerability vs. Approved and Investigational ASMs

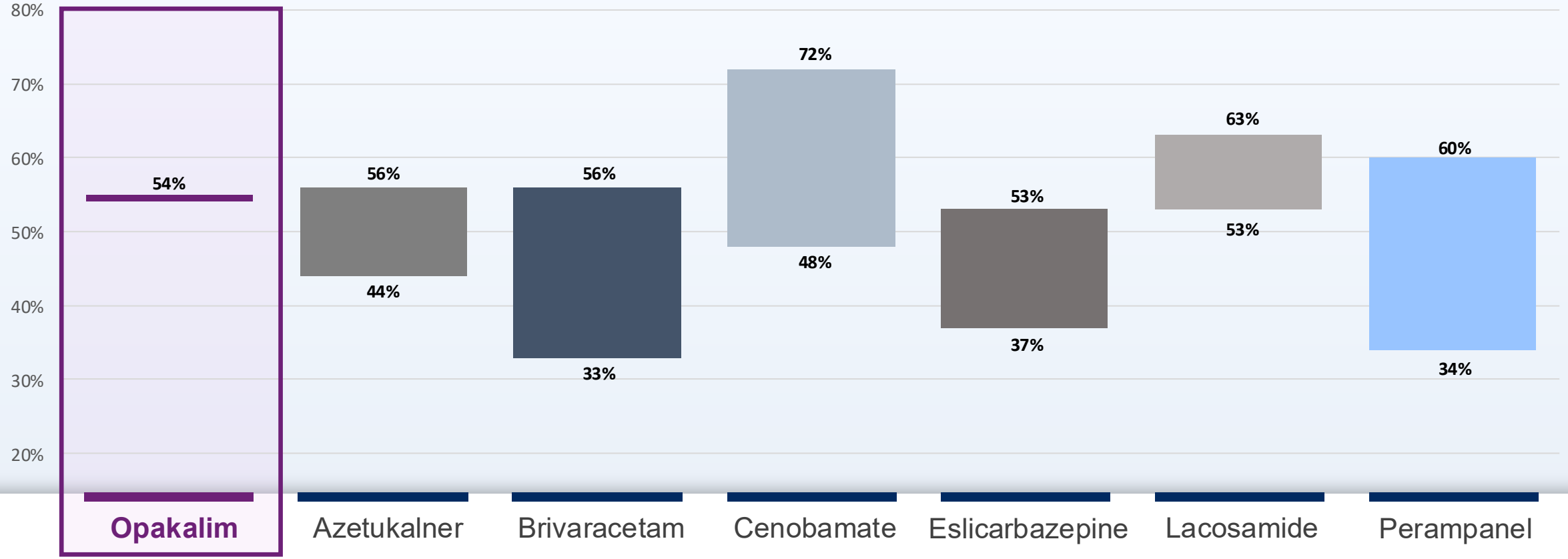
Kv7



Opakalim ongoing focal epilepsy open-label preliminary data 1H 2026; Azetukalner data from Open Label Study – French. AES 2025. Poster #3.356; Cenobamate, lacosamide and levetiracetam data from Winter. CNS Drugs. 2024.

50% Responder Rate in OLE Trials of Several Approved and Investigational ASMs

Kv7



Opakalim ongoing focal epilepsy open-label preliminary data 1H 2026; Hufnagel. Epilepsy Res. 2013; Halász. Epilepsia. 2010; Strzelczyk. Epilepsia. 2021; Ben-Menachem. Epilepsy Res. 2021; O'Brien. Epilepsia. 2020; Klein. Neurology. 2022; Strzelczyk. Expert Rev Clin Pharmacol. 2015; Husain. Epilepsia. 2012; French, J. Epilepsia Open. 2025; Rektor. Epilepsia. 2020.

KEY POINT

Opakalim OLE preliminary efficacy outcomes fall within reported range of responder rates for other ASMs in OLE trials

Opakalim Is Easy-to-Use With a Projected Favorable Tolerability Compared to Approved ASMs

Kv7

		No titration	Favorable CNS tolerability	Low neuropsychiatric AEs	Low metabolic / electrolyte AEs	Low SJS or DRESS risk
L1	Lamotrigine	✗✗	✓	✓	✓	✗✗
	Levetiracetam	✓	✓	✗	✓	~
	Oxcarbazepine	✗	✗	✓	✗	✗
L2	Lacosamide	✗	✓	✓	✓	✓
	Eslicarbazepine	✗	✗	✓	✗	~
	Brivaracetam	~	✗	✗	✓	✓
L3	Zonisamide	✗	✗	✗	✗	✓
	Cenobamate	✗✗	✗	✓	✓	✗✗
	Topiramate	✗	✗	✗	✗	✓
	Opakalim (Kv7)	✓	✓	✓	✓	✓

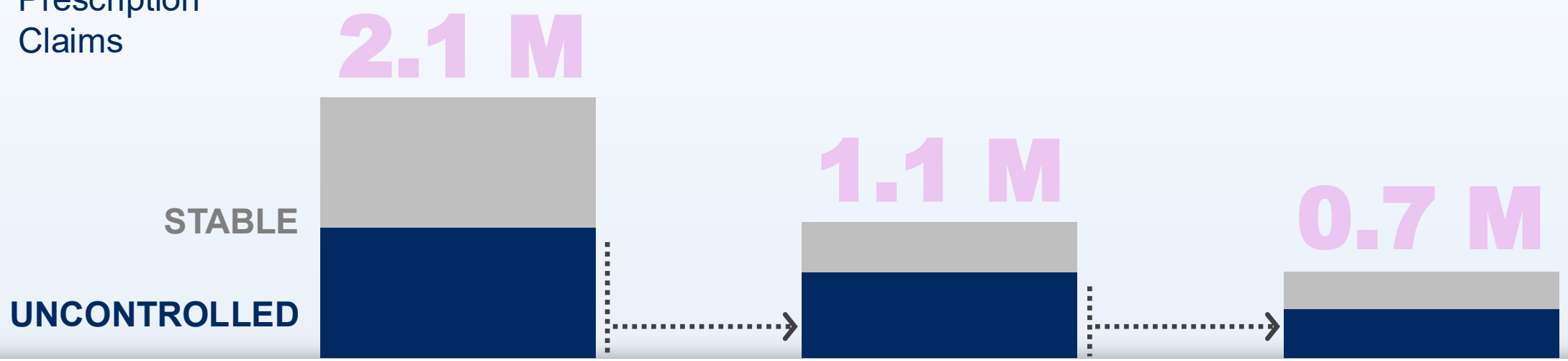
✓ Favorable ~ Variable ✗ Unfavorable ✗✗ Very Unfavorable

AE, Adverse Event. **SJS,** Stevens-Johnson Syndrome. **DRESS,** Drug Reaction with Eosinophilia and Systemic Symptoms

Opakalim Offers Potential To Address Unmet Needs in Epilepsy with Attractive Attributes for Epileptologists and General Neurologists

Kv7

Prescription Claims



	FIRST LINE	SECOND LINE	THIRD LINE +
POLYTHERAPY	Levetiracetam Lamotrigine Oxcarbazepine	Lacosamide Eslicarbazepine Brivaracetam	Zonisamide Topiramate Cenobamate

OPAKALIM

NOVEL MOA | EASY-TO-USE | EFFICACIOUS | GOOD TOLERABILITY

Forian claims data; diagnosis codes G400, G401, G402; prescribed ASM medications; dataset timeframe January 1, 2016 to June 30, 2022. US KOL Market Research 2026.

Key Opinion Leader Perspective

Kv7

If Opakalim tolerability seen in early studies is maintained, that would be a huge differentiator in clinical practice. That was the case with Keppra – it seemed to be as effective but so much better tolerated than other alternatives.

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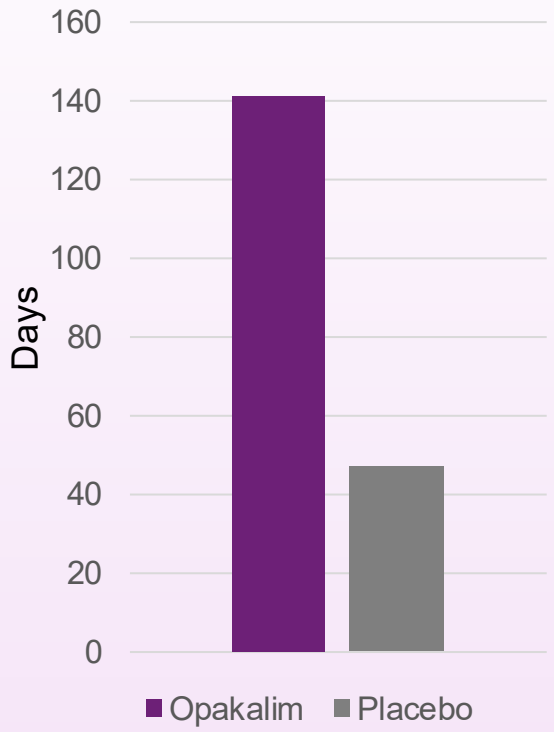
Epilepsy Summary

DAYS MATTER™

Opakalim Continues To Demonstrate Encouraging Results in Epilepsy

Kv7

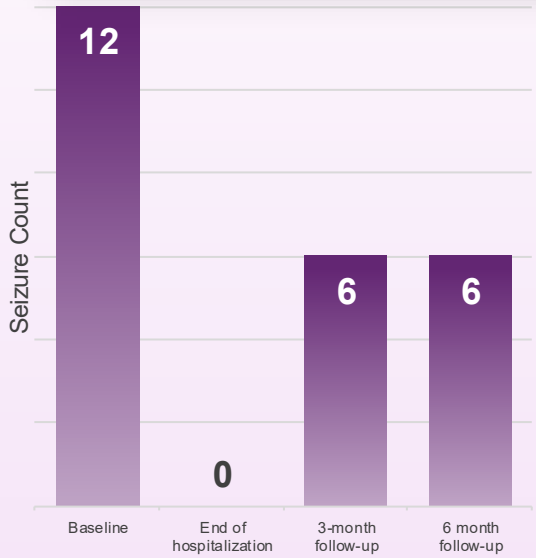


54% of subjects showed 50% Responder Rate

OVER ANY CONSECUTIVE 6-MONTHS (n>100)

Adverse Event	Opakalim
Headache	5.7%
Nasopharyngitis	5.7%
Seizure	4.3%
Dizziness	4.3%
Fatigue	3.7%
Fall	3.7%
Upper Respiratory Tract Infection	3.7%
Back Pain	3.4%
Insomnia	3.4%
Nausea	3.1%
Diarrhea	3.1%

50% reduction in seizures



IGE RCT

Promising efficacy and safety data in IGE with generalized tonic-clonic seizures

FOCAL EPILEPSY OLE

Efficacy signal observed in focal epilepsy OLE falls within reported range of 50% responder rates for other ASMs in OLE trials

OPAKALIM 75 MG

Continues to be exceptionally well-tolerated in focal epilepsy OLE

PATIENT WITH KCNQ2-DEE

Transitioned from 1st gen Kv7 to opakalim with clinical stability & ongoing seizure control for 6+ months

Steven Dworetzky, PhD
Senior Vice President,
Kv7, Strategy & Development

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Opakalim:
Selective Kv7 Activation for Pain and Tinnitus

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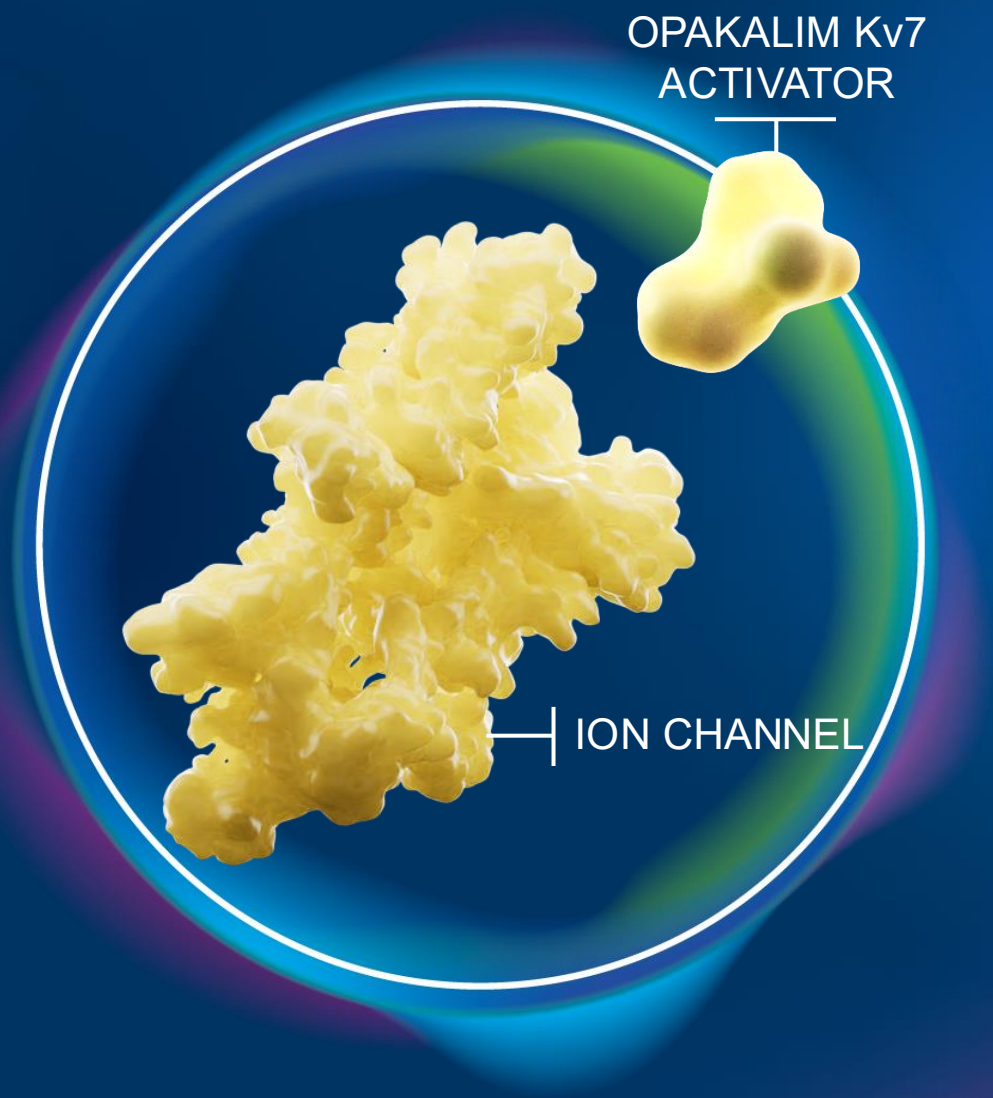
Kv7 Activation for the Treatment of Pain

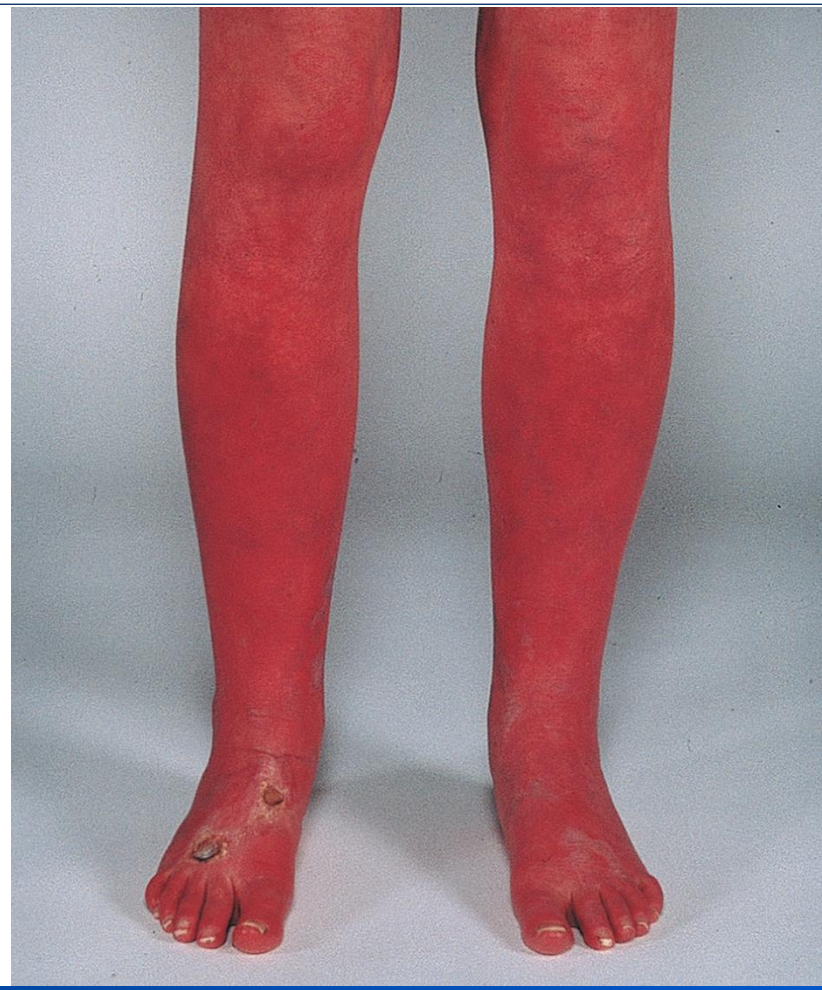


Inherited Erythromelalgia: Disease Model To Study Opakalim for the Treatment of Neuropathic Pain

INHERITED DISEASE: Caused by gain of function mutations in NaV1.7 channels[1] resulting in hyperexcitability of sensory neurons. Characterized by severe chronic neuropathic pain, episodic pain attacks, skin erythema and sleep disturbances.[1]

GENETIC RESILIENCE MECHANISM: Some individuals with IEM are resilient to pain compared to family members carrying the same mutation. Due to a second GoF mutation in the Kv7.2 or Kv7.3 genes, dampening neuronal hyperexcitability.[2]

THERAPEUTIC HYPOTHESIS: Increased excitability of sensory neurons is key to pathological pain. Kv7.2/7.3 channels control sensory dorsal root ganglion intrinsic excitability. **Opakalim targets neuronal excitability centrally and peripherally.**



1. McDonnell. Brain. 2016. **2.** Yuan. Brain Commun. 2021. **3.** Davis. Arch Dermatol. 2000 (image); IEM inherited erythromelalgia; GoF gain of function.

KEY POINT

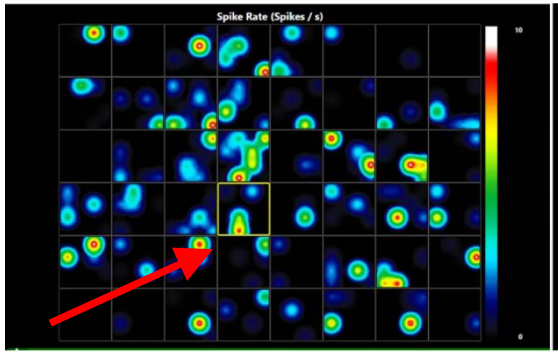
Human genetics validates Kv7 activation as a "protective" mechanism in IEM and provides rationale for Kv7 activation as a treatment for pain

Opakalim Treatment of iPSC-Derived Sensory Neurons From IEM Patients

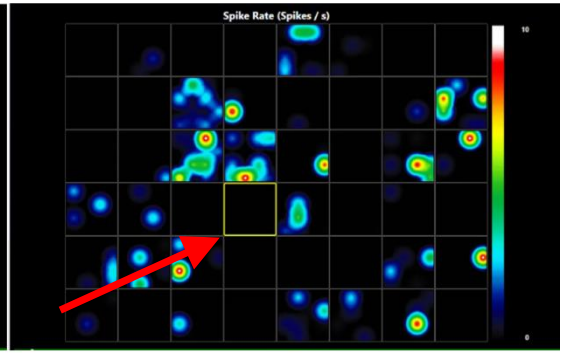
- Data visualized as color heatmap corresponding to number of spikes detected for each electrode during the preceding second
- Evaluating spontaneous neuronal firing
- The well indicated by a red arrow was exposed to opakalim 1 µM

Microelectrode Array: Real-time Visualization of Neuronal Activity on a 48-Well Plate

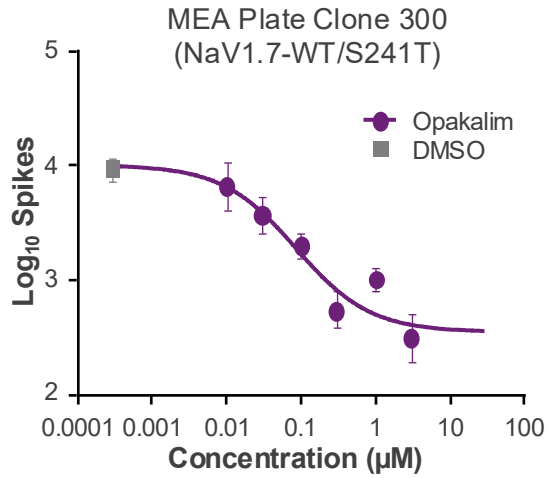
Activity Prior to Treatment

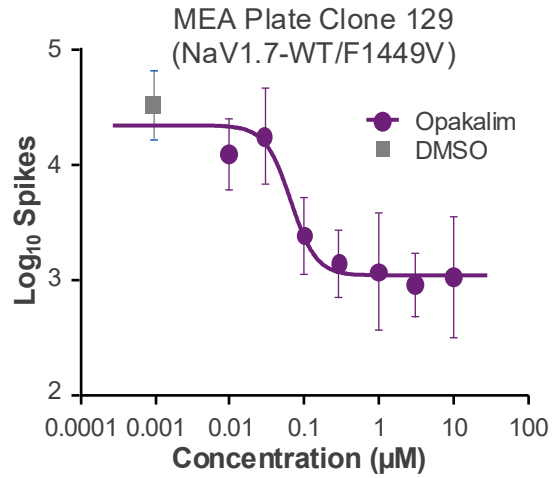


Activity With Opakalim Treatment



Microelectrode Array: Spike Counts Over 10-Minutes With Varying Concentrations of Opakalim Vehicle: 0.1% DMSO



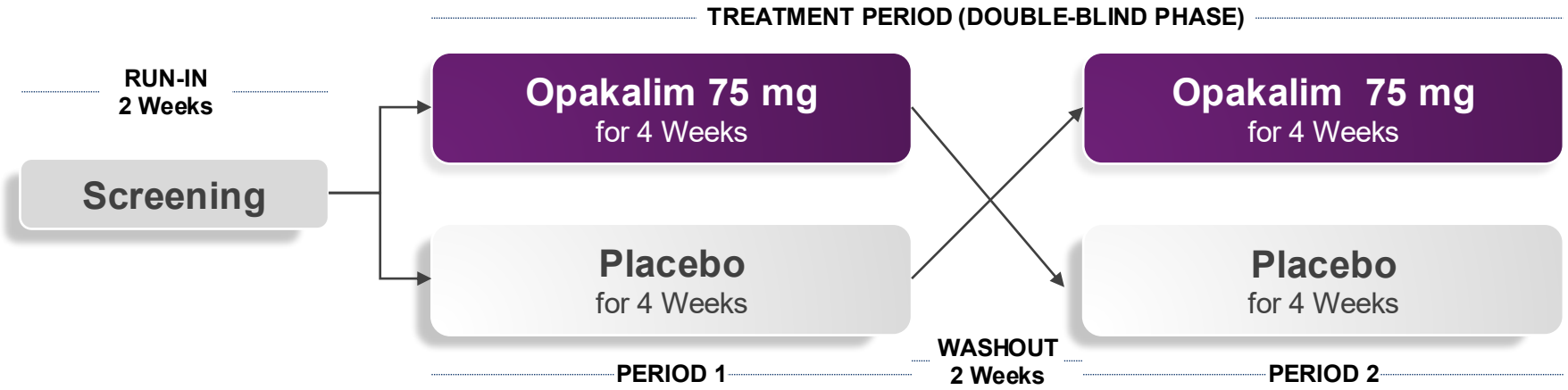


IASP 2024. Amsterdam, Netherlands 2024.

KEY POINT

Opakalim reduces neuronal spike activity with sub-micromolar IC50s in a "pain in a dish model"

Pilot Translational Trial of Opakalim in Inherited Erythromelalgia



KEY STUDY DETAILS

Study Design: Randomized, double-blind, placebo-controlled, 2-way crossover design

Population: Participants with IEM, with NaV 1.7 GoF mutations w/o concomitant Kv7 mutations

Sample size: 5 Participants

Endpoints: Area under the curve of pain; frequency, intensity, and duration of pain attacks

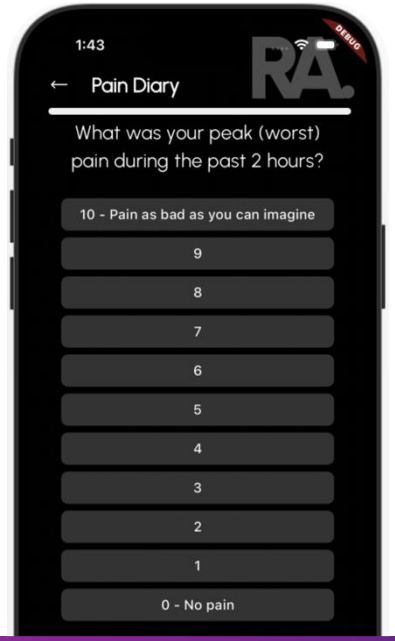
BREAKING NEWS

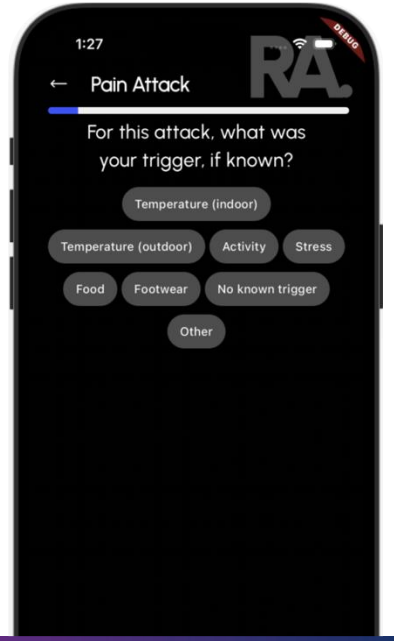
- **Trial initiated in 1Q 2026**
- **Subjects enrolled in the trial were iPSC donors for the in vitro experiments**

Leveraging Innovative Technologies To Monitor IEM Symptoms

Research Ally Phone App

Systematically profiling fluctuating **PAIN** throughout the day





Ōura ring

Monitoring effects of improved pain management on **SLEEP**

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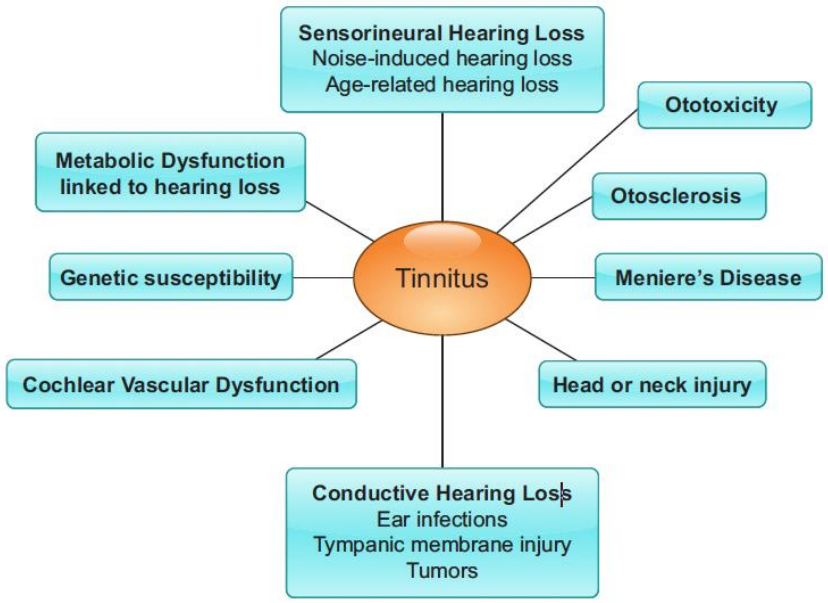
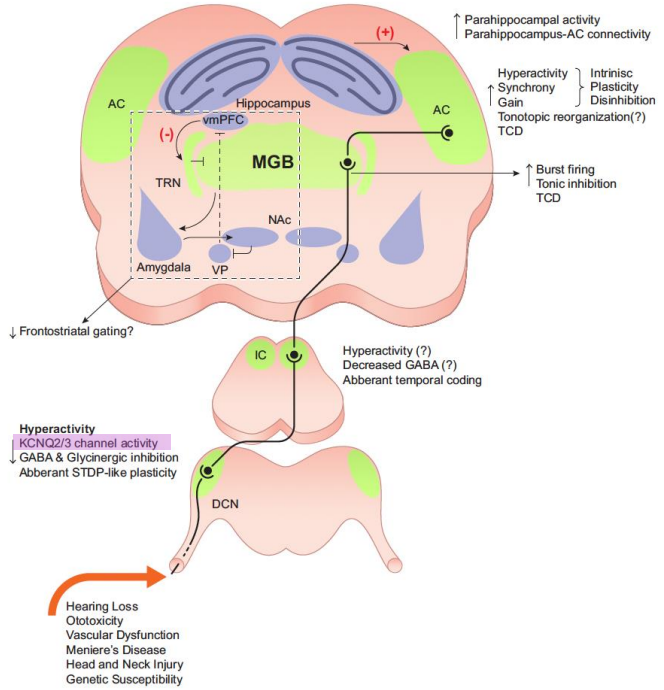
Kv7 Activation for the Treatment of Tinnitus

Rationale for Kv7 Activation in the Treatment of Tinnitus

Causes of Tinnitus



Changes in Auditory Circuitry Involve Kv7 Channel Activity



- Tinnitus affects **~50 million** Americans
- Driven in part by hyperexcitability in the auditory cortex
- Preclinical models of tinnitus show reduced Kv7.2/7.3 currents

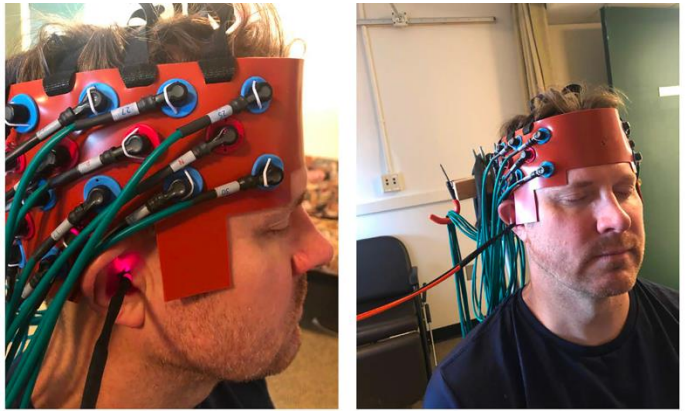
Henton and Tzounopoulou. Physiol Rev. 2021.

KEY POINT

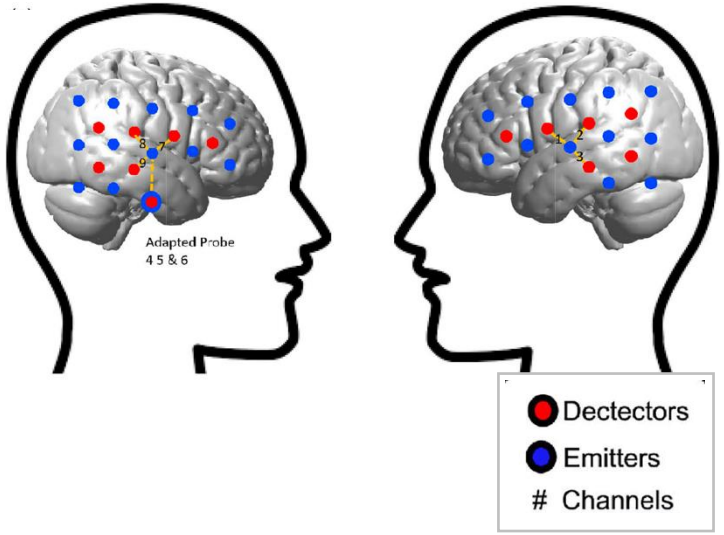
Kv7 activation reduces hyperexcitability and improves behavioral phenotypes in models of tinnitus

Investigator Sponsored Trial Planned To Test Opakalim for the Treatment of Tinnitus Using Functional Near-Infrared Spectroscopy (fNIRS)

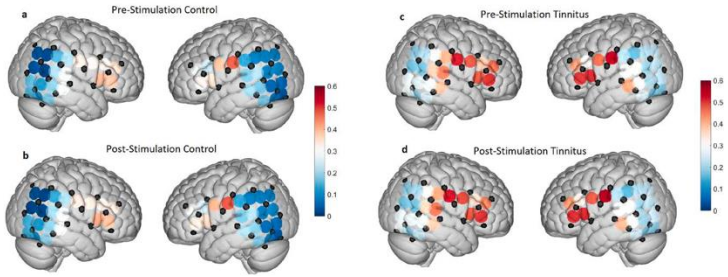
Basura Laboratory at UPitt



Channel Configuration for the Probes



Increased RSFC in the Tinnitus Brain



RSFC, Resting-state functional connectivity. San Juan. Neuroreport. 2021.

KEY POINT

fNIRS uses near-infrared light to measure hemoglobin & hemodynamic changes in brain regions – a validated proxy for neural activity ideal for tinnitus research

Panel

MODERATOR

Tessa Romero

Equity Analyst

J.P.Morgan

PANELISTS

Aline Herlopian, MD

Neurologist and Associate Professor of Neurology
Yale School of Medicine

Matthias Koepp, MD, PhD

Professor of Neurology
University College London

Jason Lerner, MD

Medical Director
Biohaven

Steven Dworetzky, PhD

Senior Vice President, Kv7, Strategy & Development
Biohaven

BHVN LISTED NYSE

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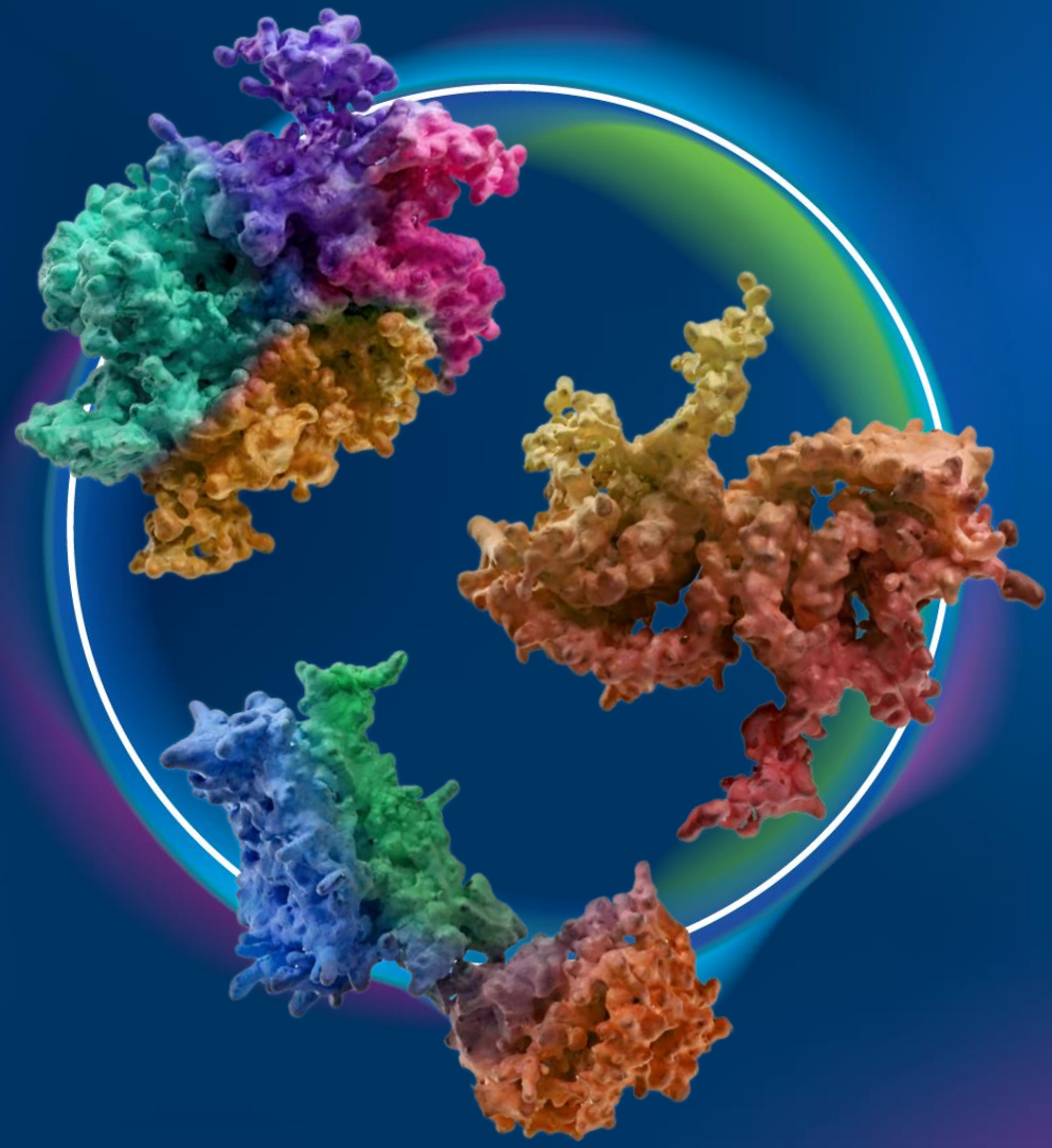
NEXT-GENERATION CNS SMALL MOLECULES

BHV-8100: Neurodegenerative and Retinal Diseases
BHV-1955: Tinnitus
BHV-8200: Parkinson's Disease
BHV-2120: Epilepsy, Pain



Pierre Magistretti, MD, PhD
Ibn Sina Distinguished Professor

KAUST

Lawrence C. Newman, MD, FAHS, FAAN
Director, Brain Health
Atria Health and Research Institute

atria Health and Research Institute

Bruce D. Car, DVM, PhD, DACVP
Chief Scientific Officer

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Bharat Awsare, MD
Executive Medical Director

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Next-Gen Neuroscience Small Molecules

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Pierre Magistretti, MD, PhD
Ibn Sina Distinguished Professor

KAUST

BHV-8100: PKM2 Activator for Neurodegenerative and Retinal Diseases

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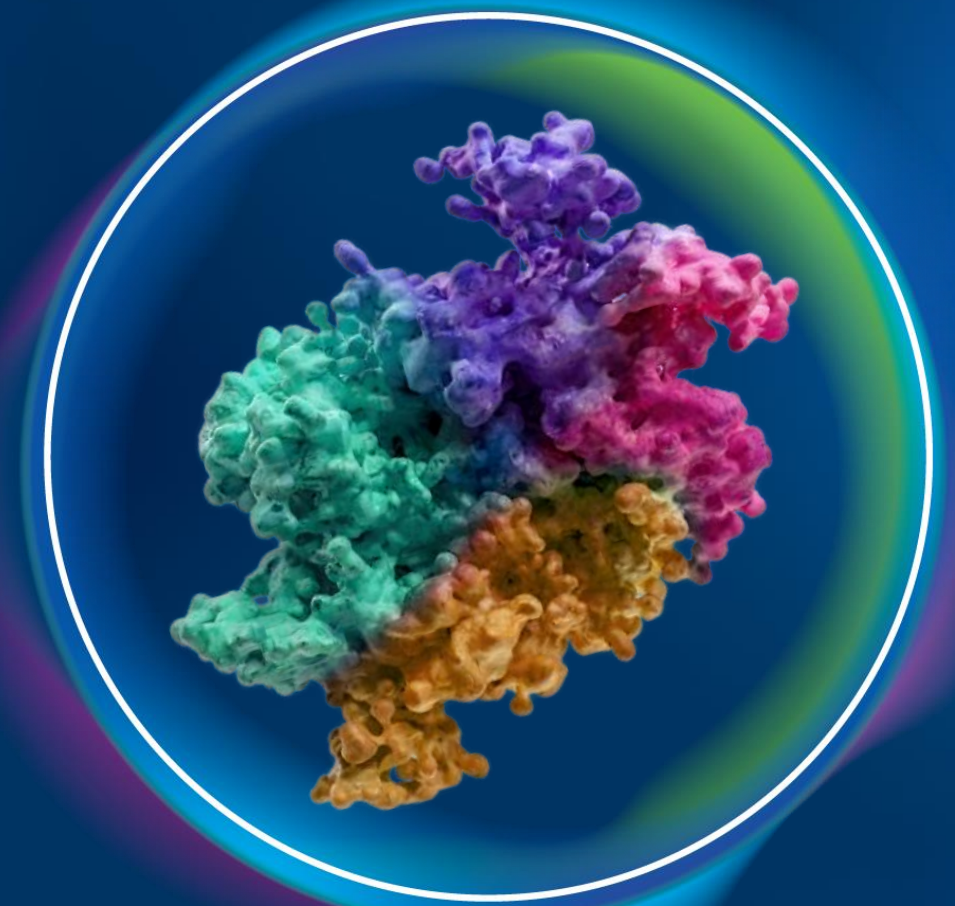
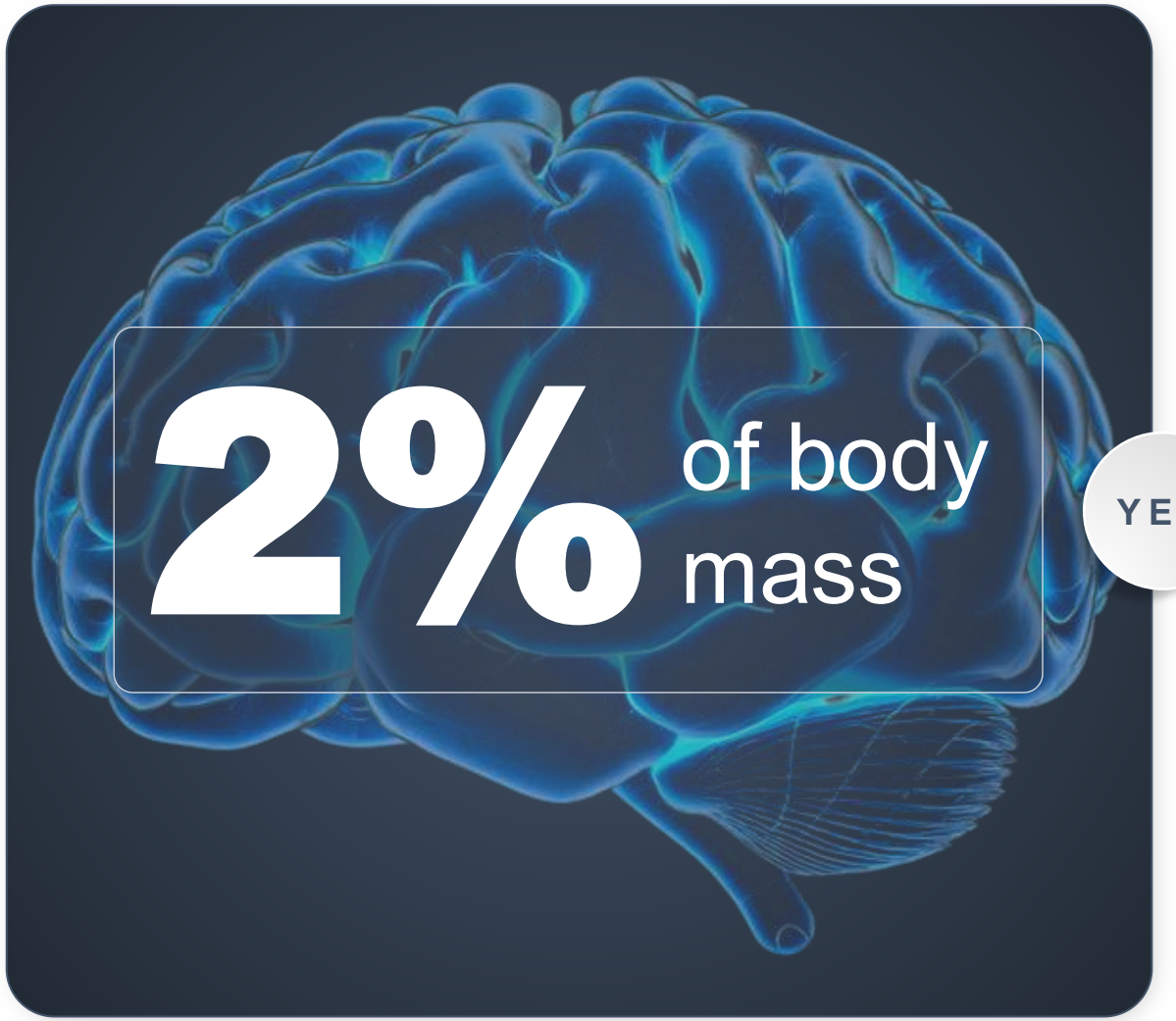
Disease Associated With Brain Metabolism and Aging



The Brain Has Considerable Energetic Requirements



YET

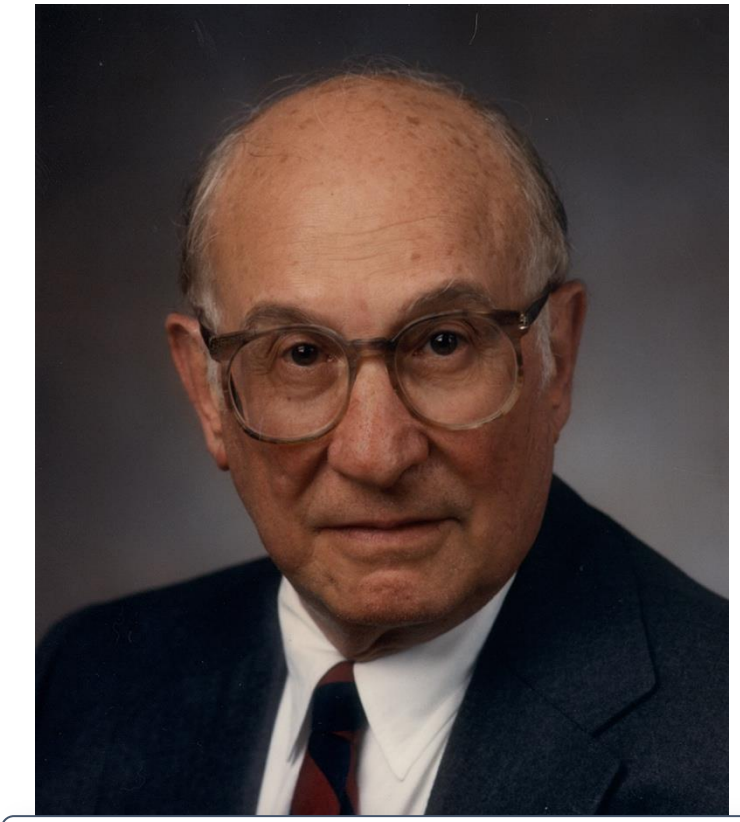
15% of **cardiac output**

25% of whole-body **glucose utilization**

20% of **oxygen consumption**

Energetics of Functional Activation in Neural Tissues

DISCOVERY

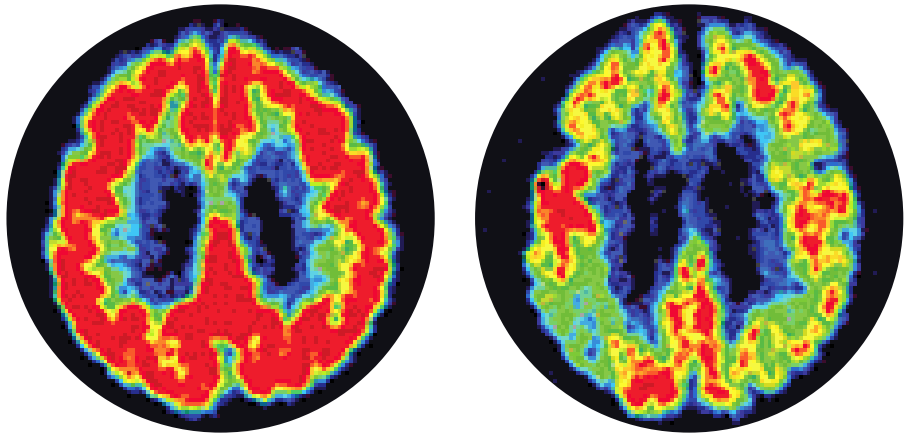


Louis Sokoloff

FDG-PET showing areas of cerebral glucose metabolism[1]

Healthy brain

Mild to moderate Alzheimer's disease brain



Normal cerebral glucose metabolism

Diminished cerebral glucose metabolism

Source: Neurochemical Research, Vol. 24, No. 2, 1999, pp. 321-329

1. Small. Proc Nati Acad Sci USA. 2000. Copyright 2013 National Academy of Sciences, U.S.A

Techniques for Functional Brain Imaging

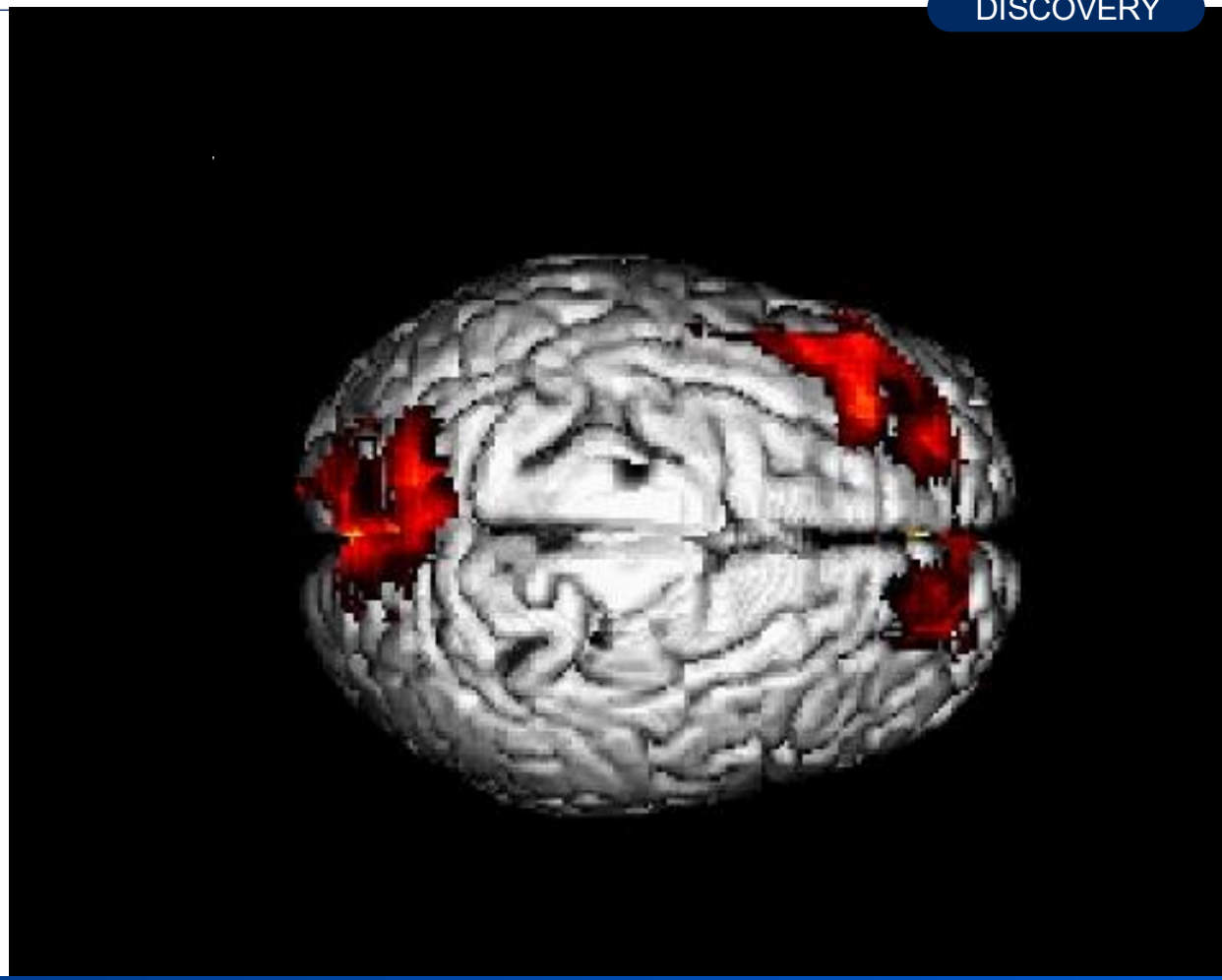
DISCOVERY

Positron Emission Tomography (PET):

- ^{18}F-deoxyglucose
- $^{15}O_2$
- $H_2{}^{15}O_2$

Functional MRI (fMRI):

- Change in the ratio of oxy-/deoxy hemoglobin



KEY POINT

They detect signals related to energy consumption

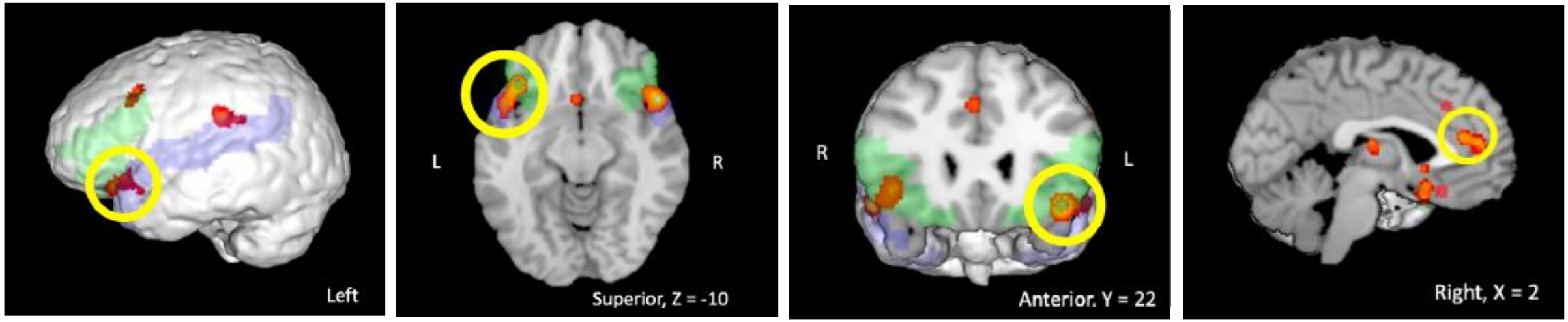
Brain Aging and Energy Metabolism

DISCOVERY

- Aging leads to **reduction in brain glucose utilization**, i.e., **brain hypometabolism**, as revealed by reduced FDG-PET signal[1]

- Clinical studies showed positive correlation between brain **glucose metabolism** measured with FDG-PET and **cognitive performances**[2, 3]

Meta-Analysis Showing Frontal and Temporal Glucose Hypometabolic Clusters in Aging Individuals (21 Clinical Studies, Total 911 Participants)[1]

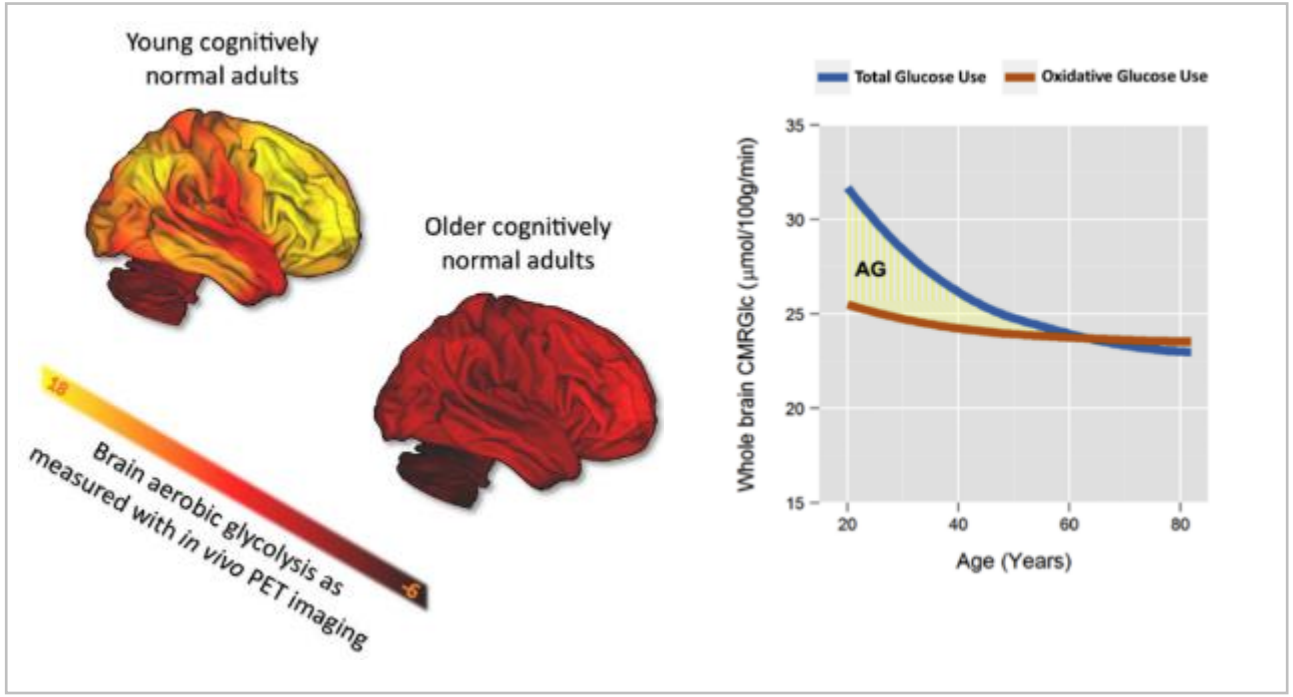


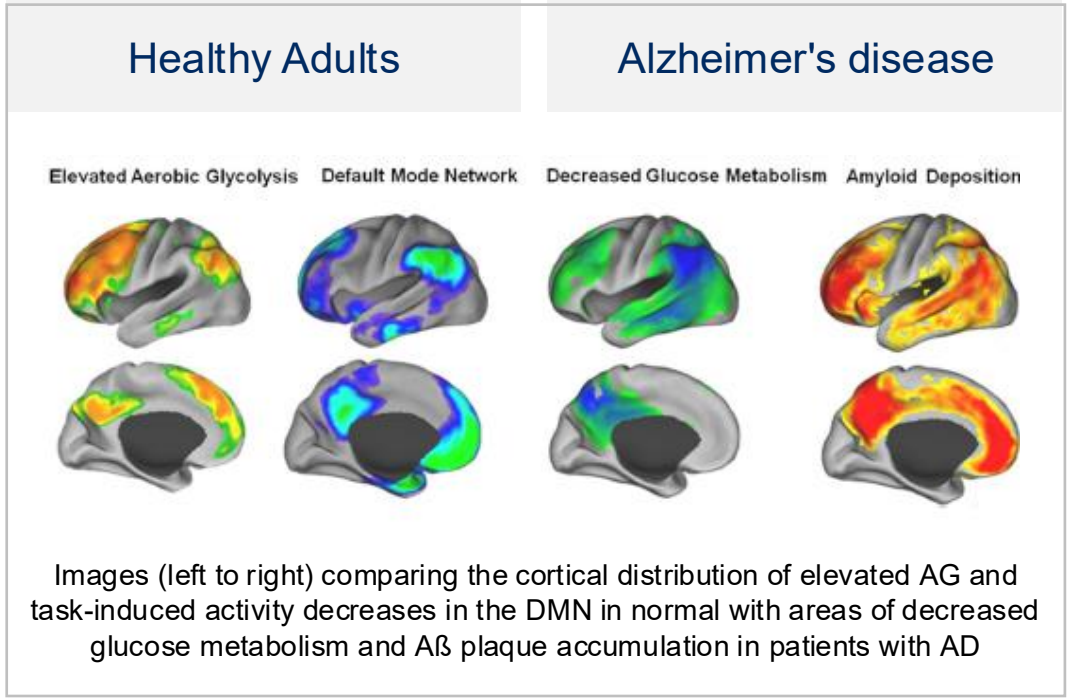
1. Deery. Human Brain Mapp, 2023. **2.** Matthews. Alzheimer's Dement. 2021. **3.** Matthews. Brain. 2021.

Aerobic Glycolysis Is Reduced in the Aging Brain

DISCOVERY

- **Aerobic glycolysis**, the metabolic process of glucose primarily promoted by astrocytes in the brain, is reduced in the aging brain[1]
- Reduction of aerobic glycolysis is pronounced in frontal and temporal regions[2]

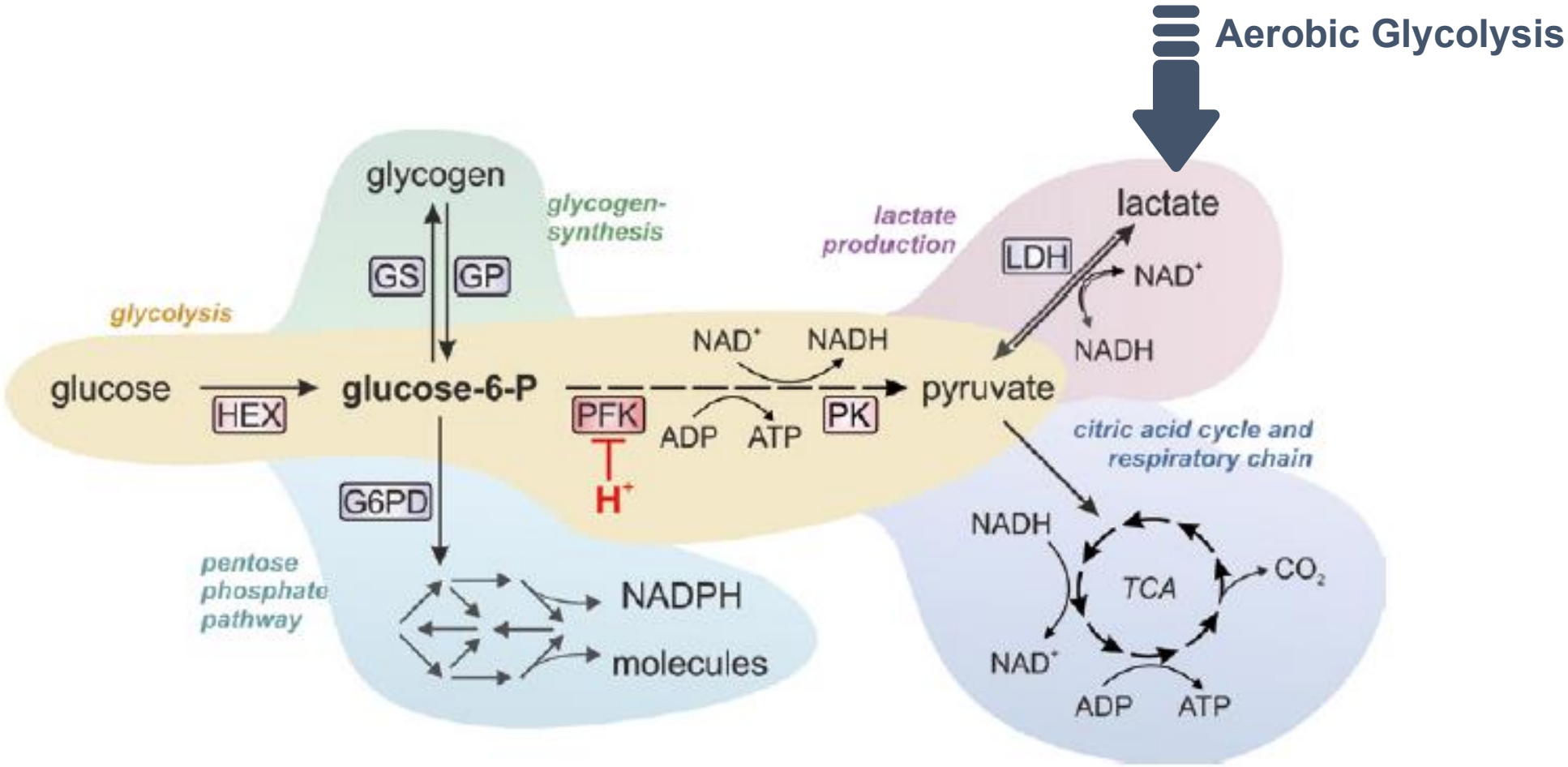




Images (left to right) comparing the cortical distribution of elevated AG and task-induced activity decreases in the DMN in normal with areas of decreased glucose metabolism and Aß plaque accumulation in patients with AD

1. Goyal. Cell Metab. 2017. **2.** Vlassenko. Clin Transl Imaging. 2015.

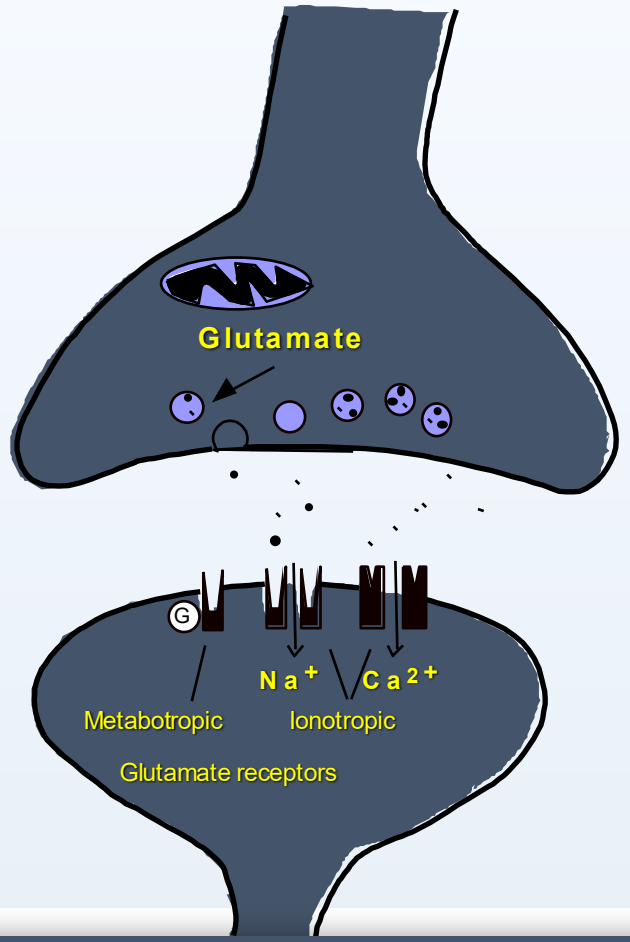
Metabolic Pathways of Glucose



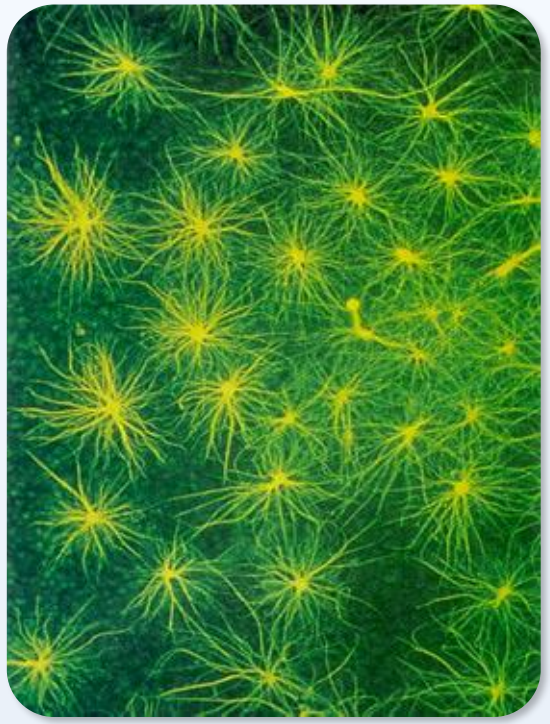
Source: Dietmer. 2017.

Which Are the Cellular and Molecular Mechanisms Underlying the Coupling of Synaptic Activity With Metabolic Responses?

DISCOVERY



COUPLING

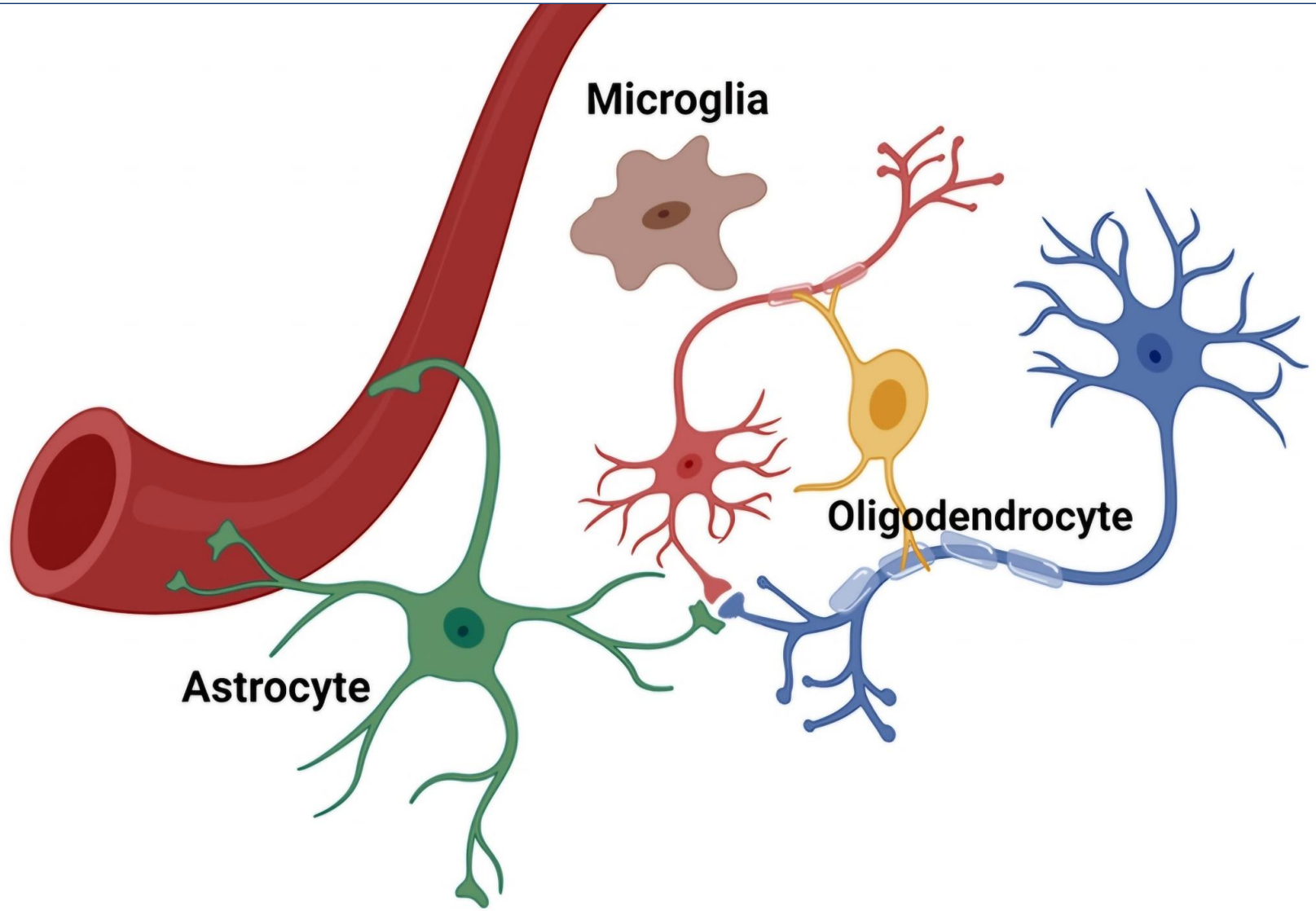


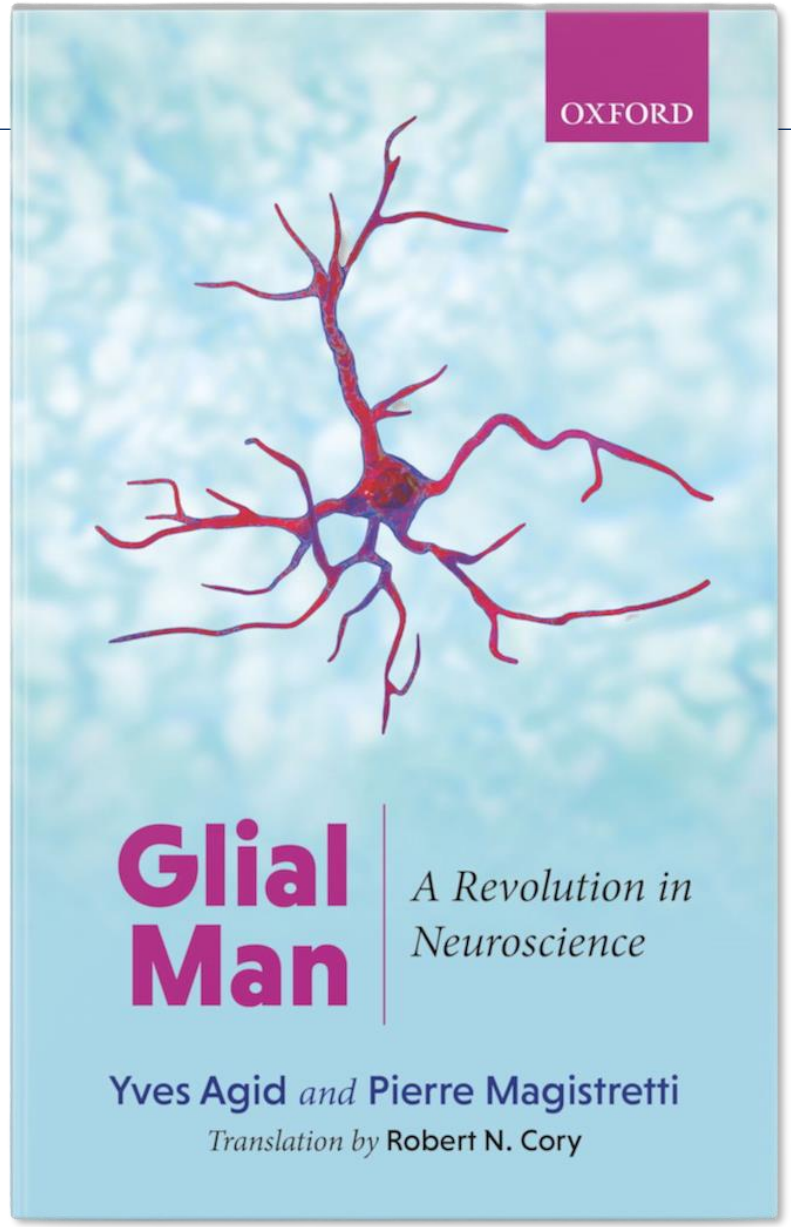
ASTROCYTES

Neuronal Activity ⟷ **Metabolic Responses** ⇒

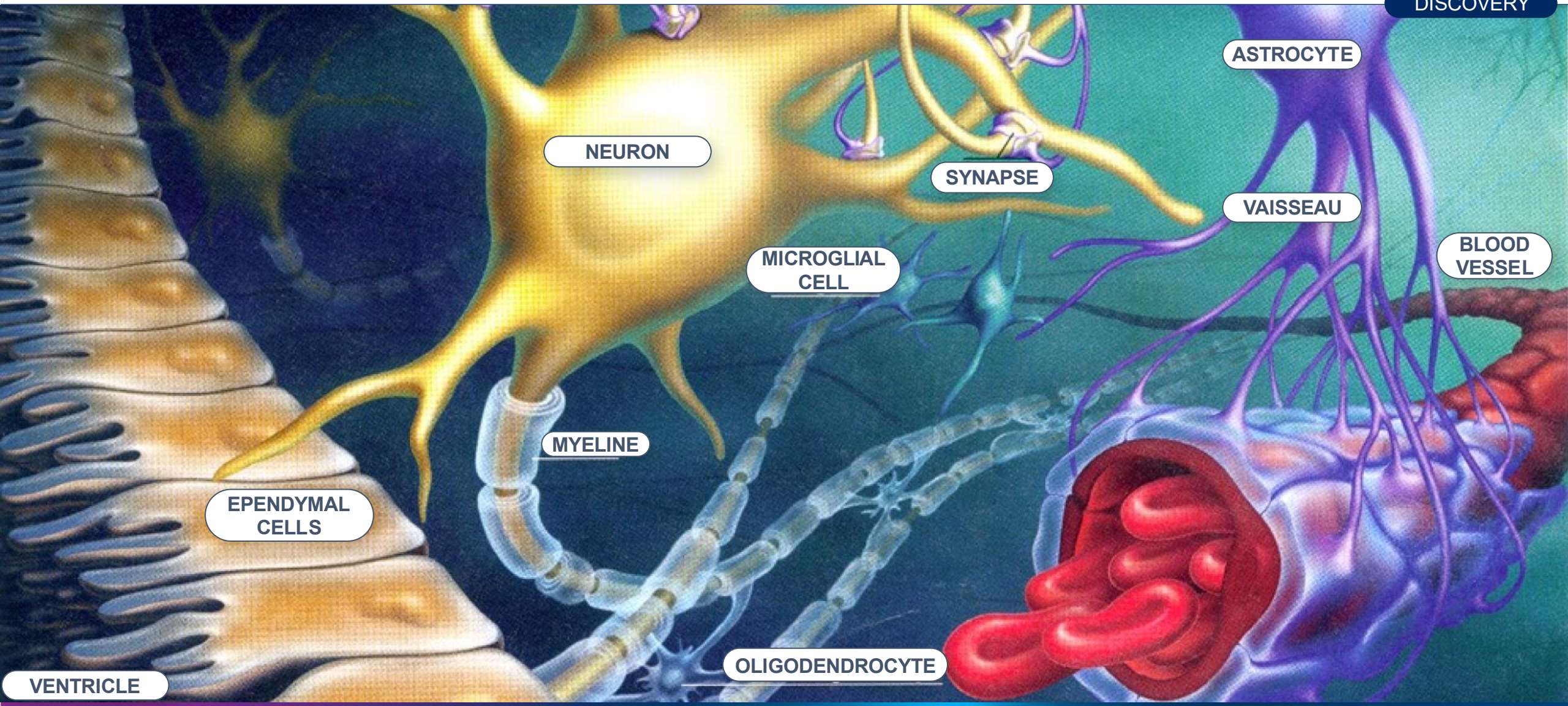
- Functional Imaging
- Synaptic function

Glia: “Glue”


Microglia
Oligodendrocyte
Astrocyte

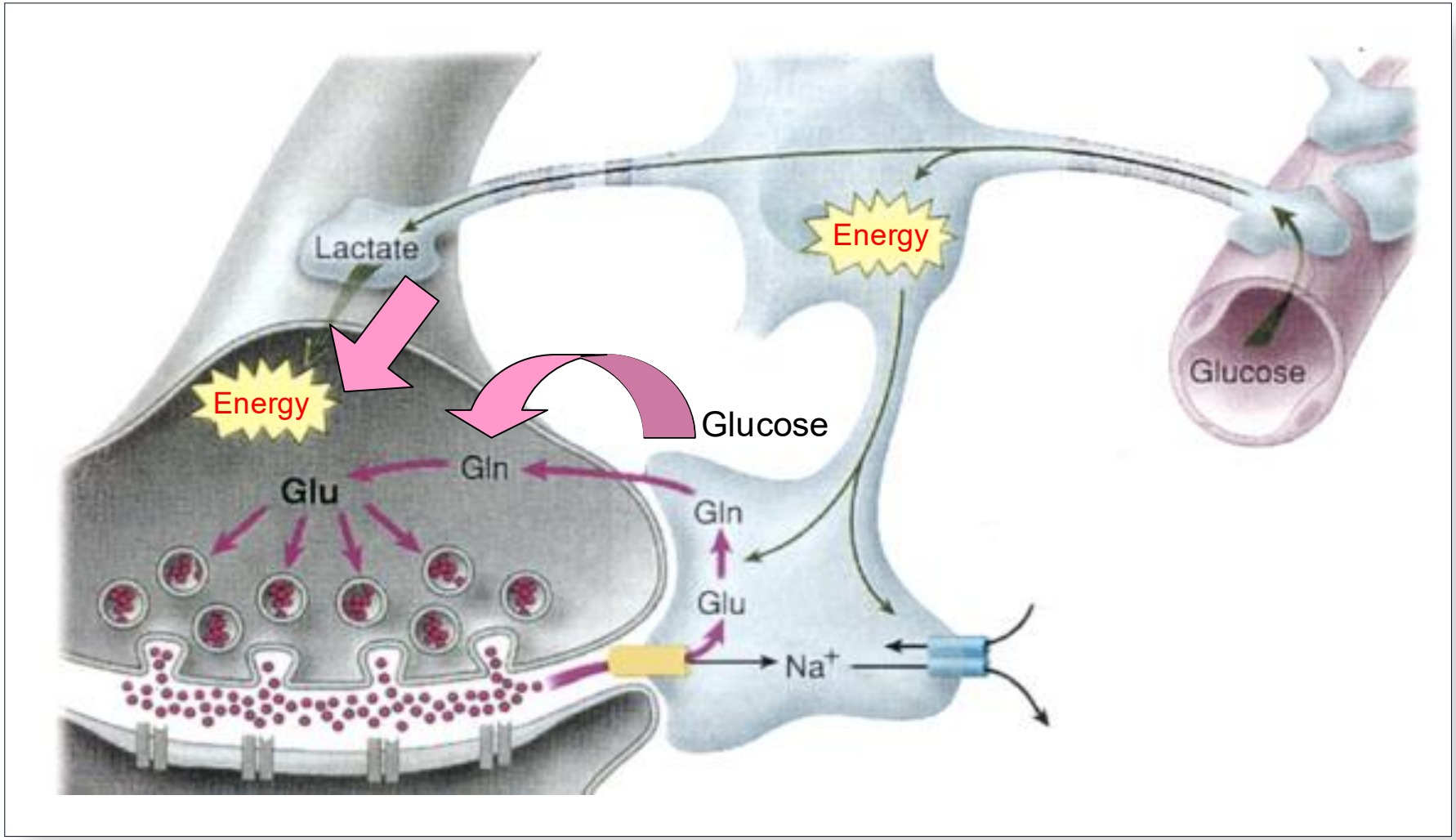

OXFORD
Glial Man
A Revolution in Neuroscience
Yves Agid and Pierre Magistretti
Translation by Robert N. Cory

Neuron – Astrocyte Relationship



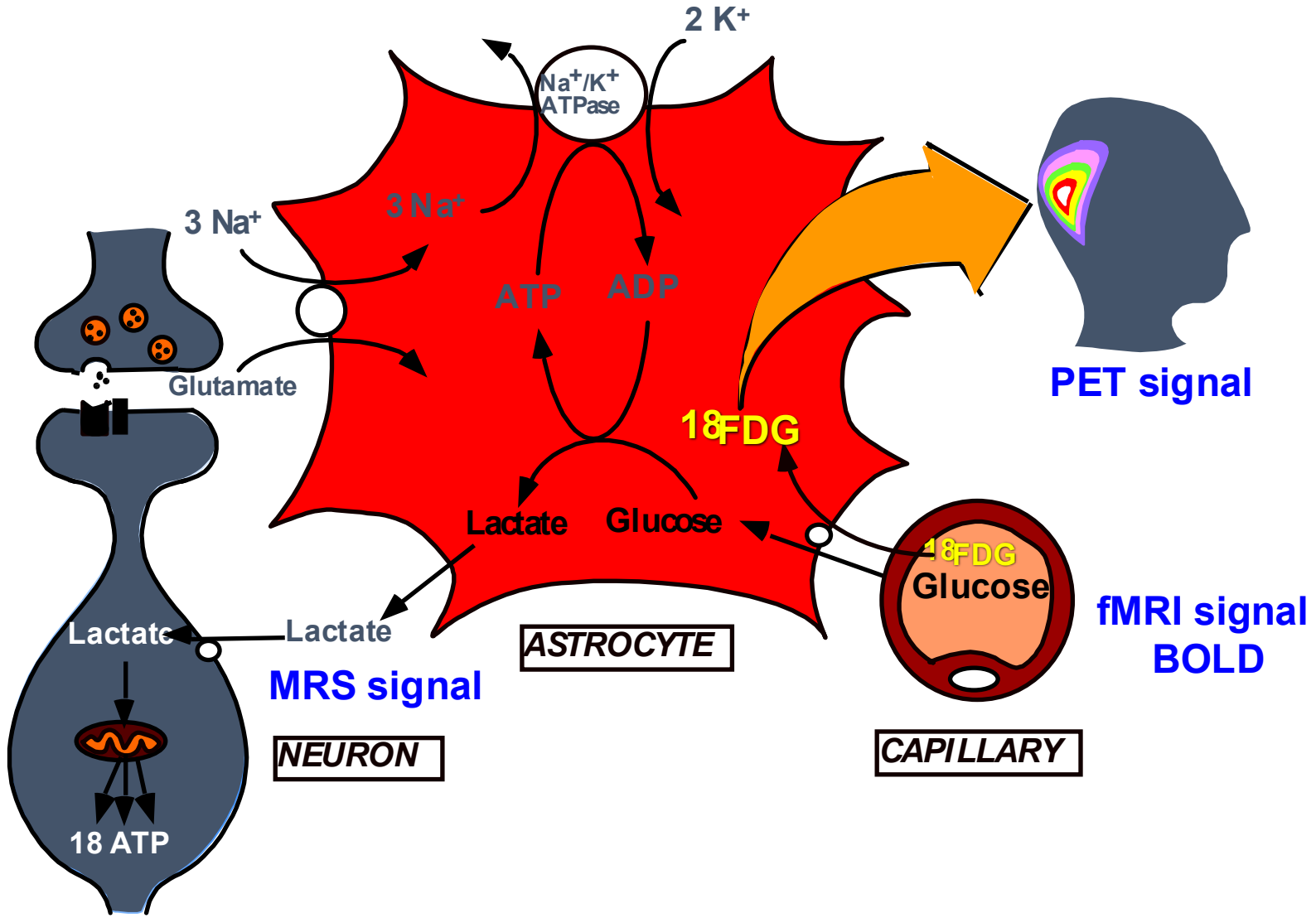
The Astrocyte-Neuron Lactate Shuttle (ANLS)

DISCOVERY



Modified from Magistretti. Science. 1999.

Role of Astrocytes in Brain Imaging Signals



Targeting Brain Hypometabolism

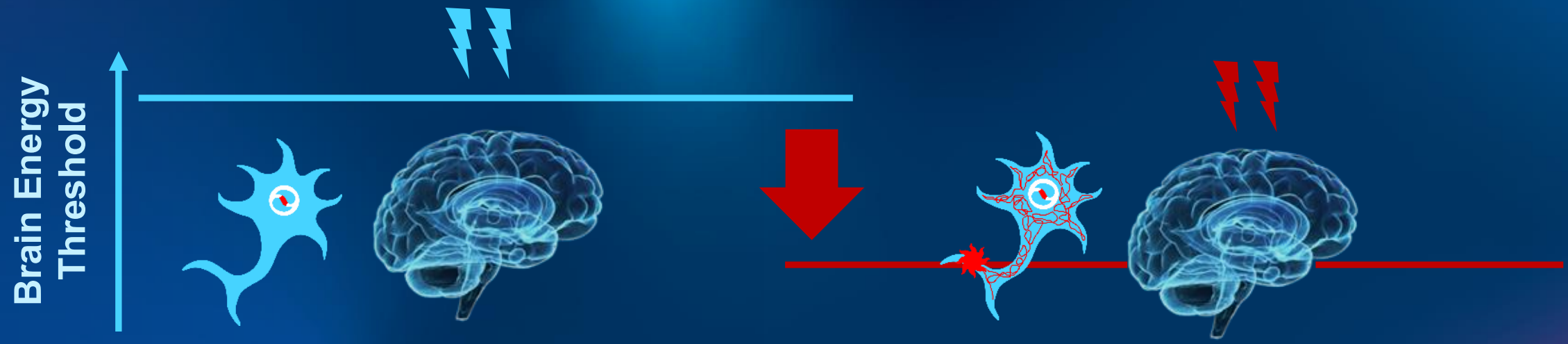
Maintaining Brain Energy Metabolism Is Key to Brain Health

Normal Brain Energy Metabolism
=
Healthy brain

Neurons are protected and resilient to insults such as oxidative stress and inflammation

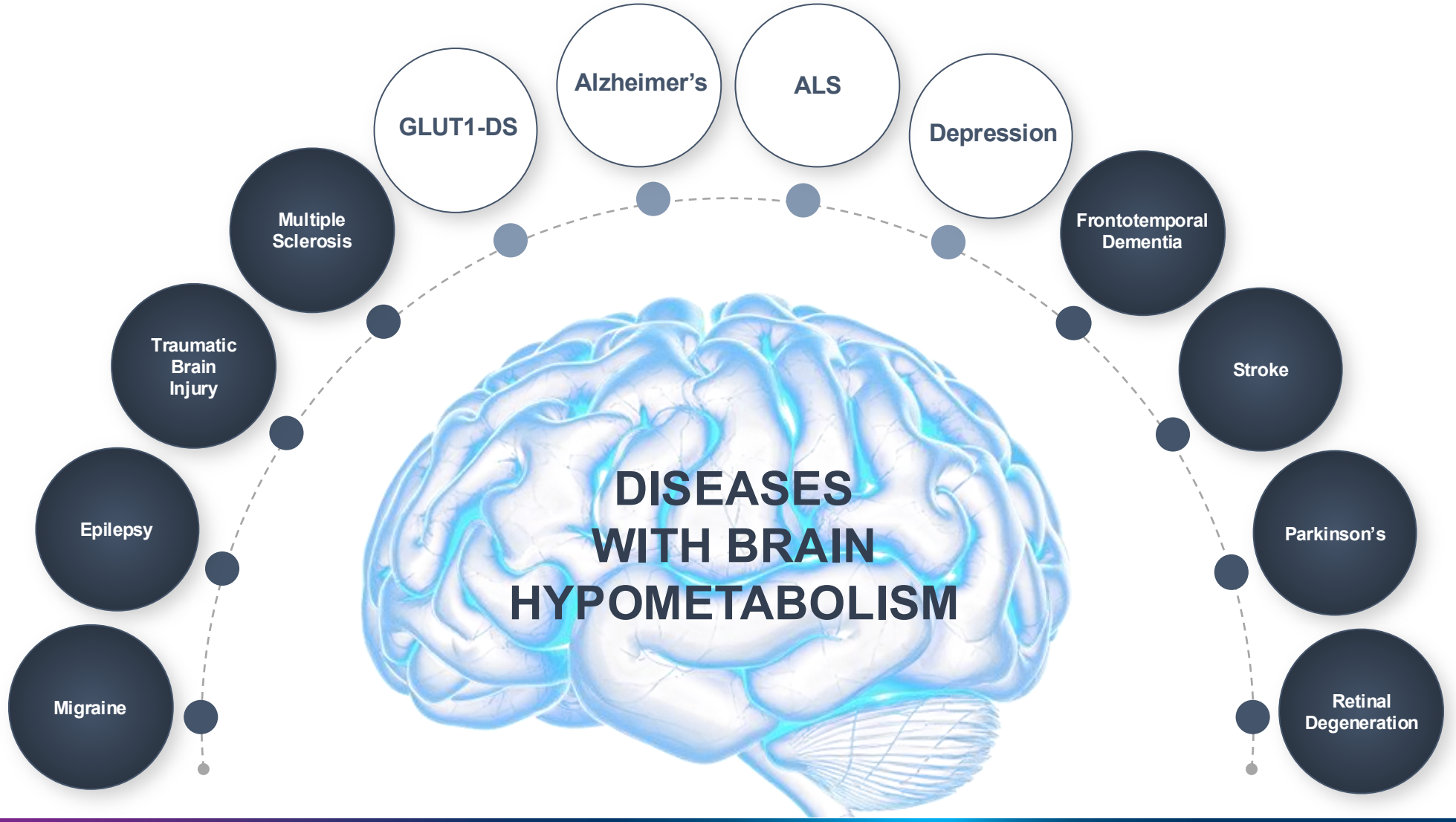
Brain Hypometabolism
=
Pathological Brain

Neurons are vulnerable to insults, leading to disease, aging and cognitive impairment



Targeting Brain Hypometabolism as a Therapeutic Approach

DISCOVERY



Targeting Hypometabolism as a Therapeutic Approach

DISCOVERY

- Astrocytes are the main providers of energy to neurons
- Targeting astrocytic metabolism is a viable therapeutic approach for maintaining cognitive function
- **BHV-8100 provides the first optimized, brain-penetrant clinical candidate and has entered Phase I in 2Q 2026**

Bruce D. Car, DVM, PhD, DACVP
Chief Scientific Officer

biohaven®

Bharat Awsare, MD
Executive Medical Director

biohaven®

BHV-8100: Preclinical and Clinic

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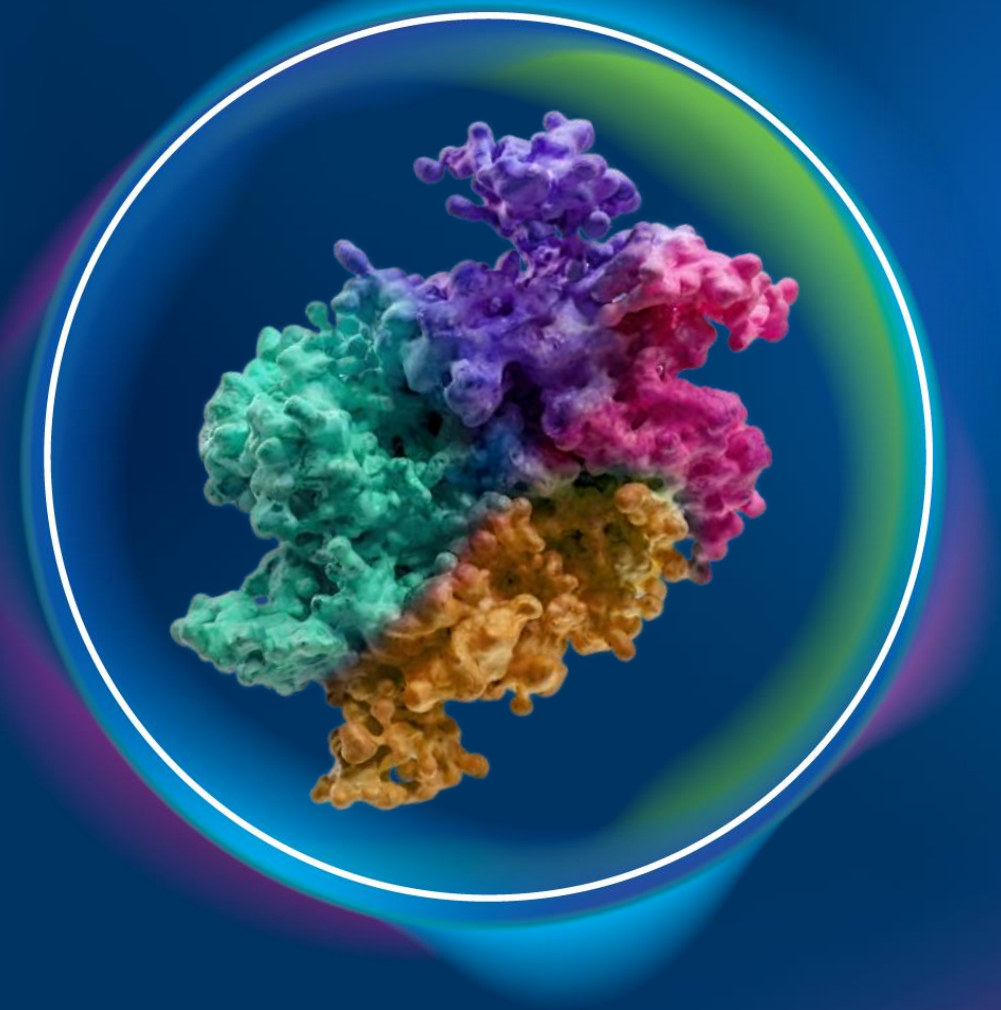
BHV-8100

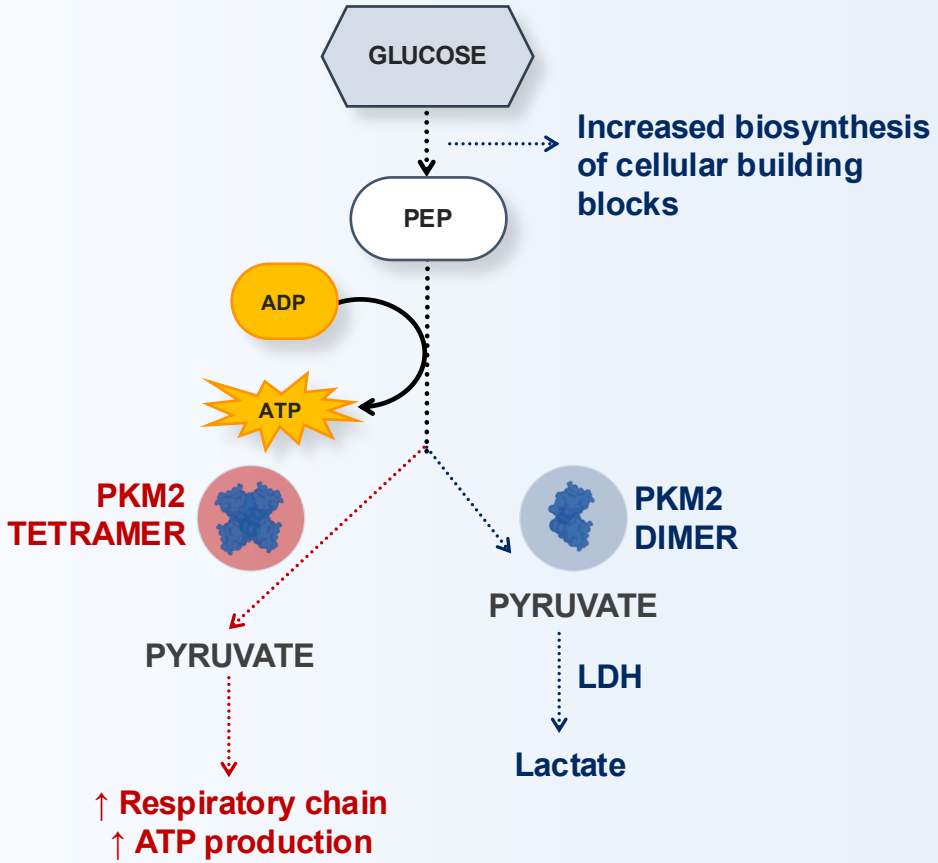
Pyruvate Kinase M2 Activator (PKM2)

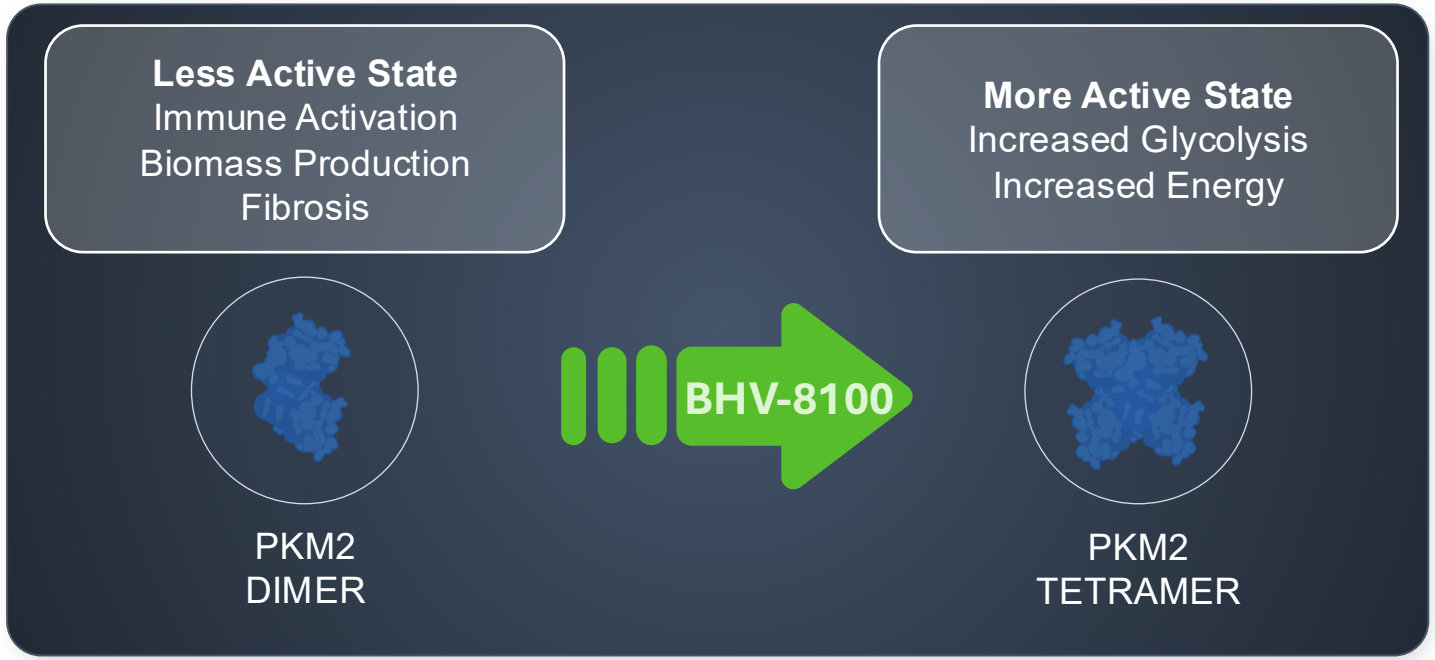
Corrects brain hypometabolism



Activation of Pyruvate Kinase Increases Glucose Consumption and ATP Production While Reducing Deleterious Metabolism

DISCOVERY



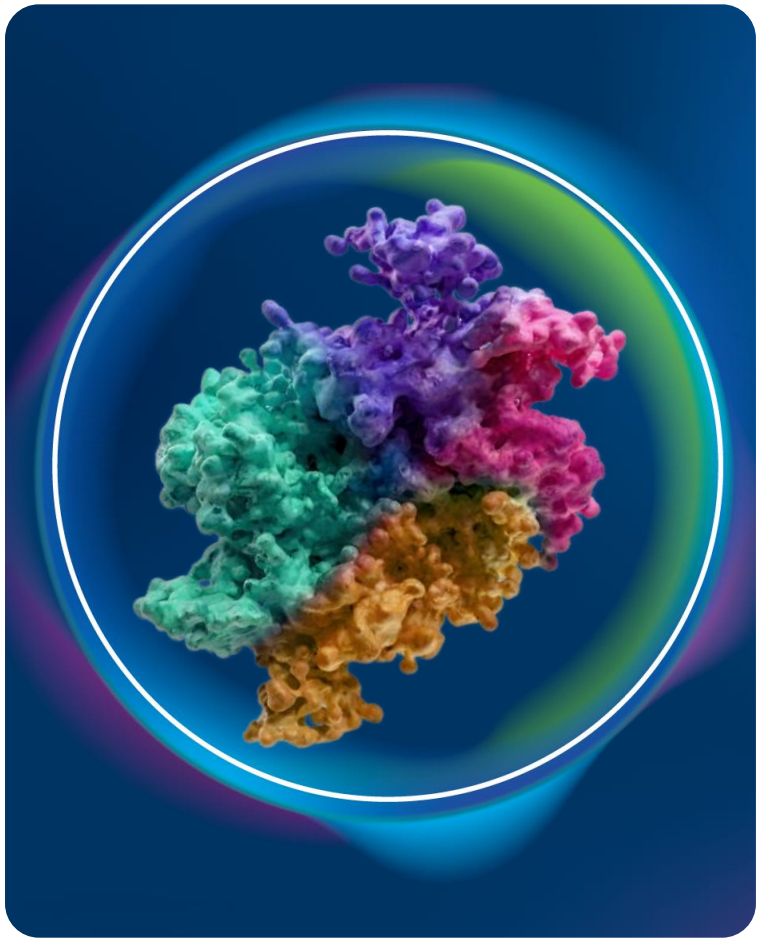


- BHV-8100 stabilizes enzymatically active tetramer state
- Increased energy in CNS
- Decreased neuroinflammation, angiogenesis and fibrosis
- Reduced deleterious metabolic intermediates

Source: Cancer Letters. 2015.

BHV-8100: First Brain-Penetrant PKM2 Activator

DISCOVERY



Oral small molecule medicine with multiple potential indications

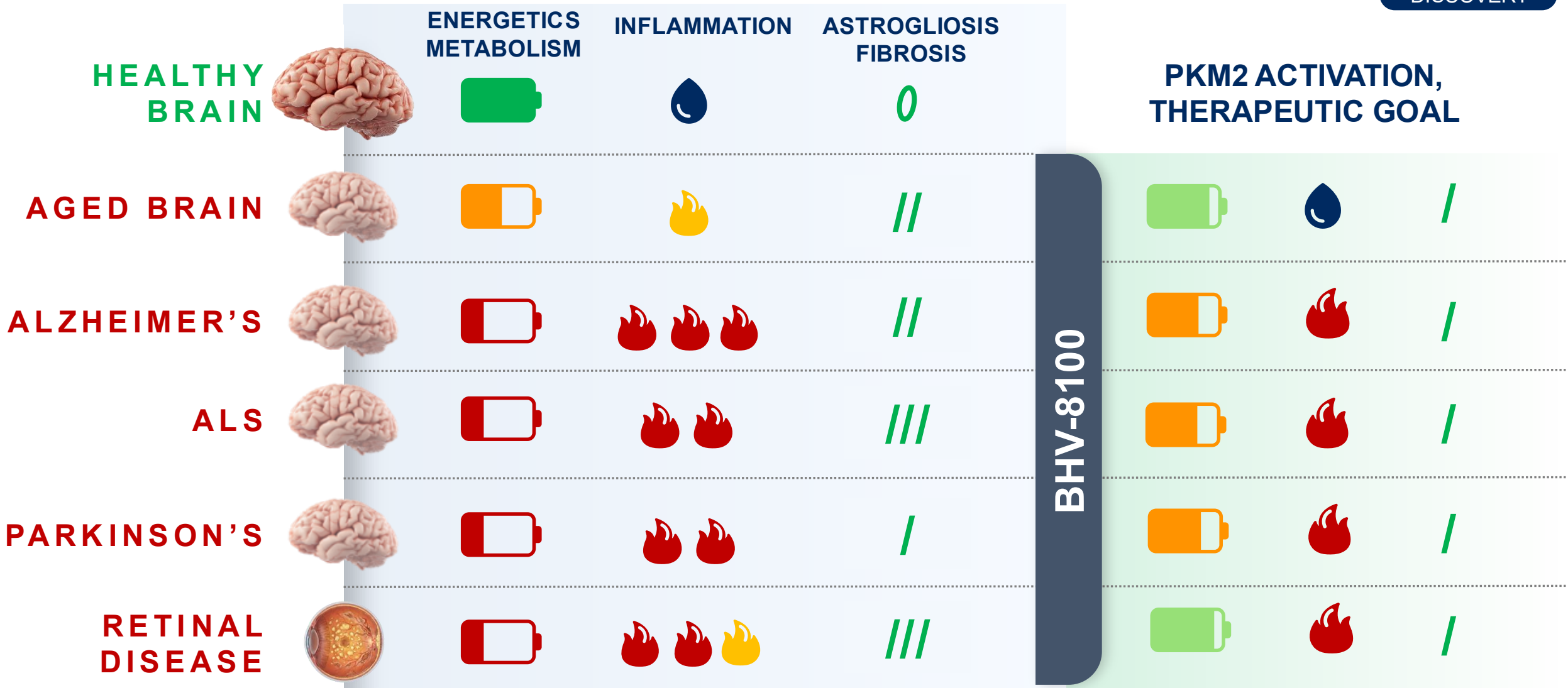
- Neurodegeneration
- Retinal degeneration and inflammation
- Neuroinflammation
- Age-related changes: Central/Peripheral
- Brain ischemia

KEY POINT

First-in-human dosing at pharmacologically relevant doses initiated 2Q 2026

Stimulation of Brain Energetics, Reprogramming Metabolism and Reduced Inflammation Is the Future of CNS Disease Treatment

DISCOVERY



1. Yang. Cells. 2025. 2. Klemmensen. Neurotherapeutics. 2024. 3. Wadan. Naunyn Schmiedebergs Arch Pharmacol. 2025.

Central/Peripheral PKM2 Activation: A Perfect Constellation of Anti-Aging Properties

DISCOVERY

PKM2 ACTIVATION

+1 Reversal of neurodegeneration through improved energetics and reduced toxic intermediates

+2 **Deprives fibroblasts of glycine for collagen and reduces inflammation[1]**

+3 Reversal of astrocytic scarring promotes normal pathway conductivity

+4 Central anti-inflammatory properties without immunosuppression

+5 Enhanced lactate provisioning through astroglial-neuronal lactate shuttle restores normal energetics

AGING

-1 Glycolytic pathway anabolic intermediates contribute to multiple neurodegenerative processes[2]

-2 CNS astrocytosis incrementally creates CNS dysfunction[3]

-3 Central inflammation increases and inversely correlates with longevity[4]

-4 **Peripheral inflammation and fibrosis drive aging**

-5 Neuronal glucose uptake declines with age due to GLUT3 receptor loss[5]

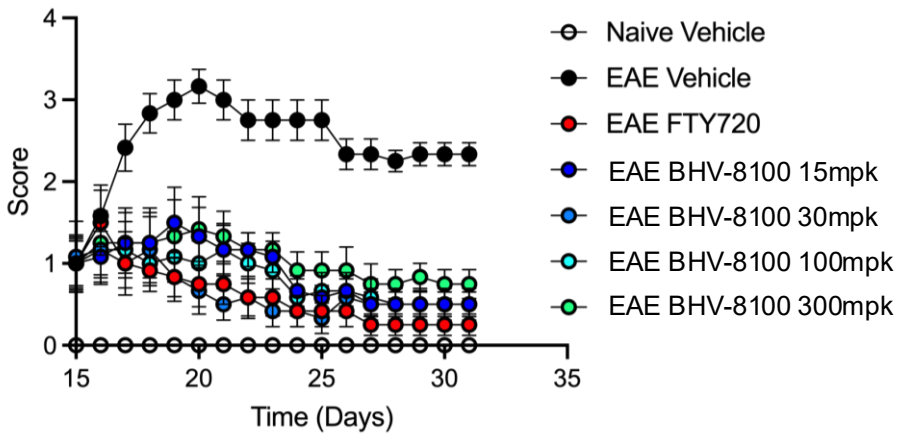
1. Selman. Aging Res Rev. 2021. **2.** Zhang. Mol Neurobiol. 2024. **3.** Cohen. Aging Cell. 2019. **4.** Sparkman. Neuroimmunomodulation. 2008, **5.** Oka. Science. 2021.

BHV-8100: Experimental Mitigation of Neuroinflammation and Restoration of Energetic Deficiency

DISCOVERY

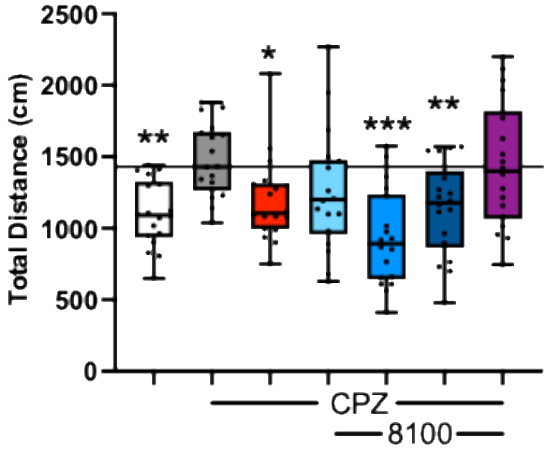
BHV-8100 Shows Robust Reduction of Disease Burden in EAE

Clinical Score (EAE Therapeutic Model)

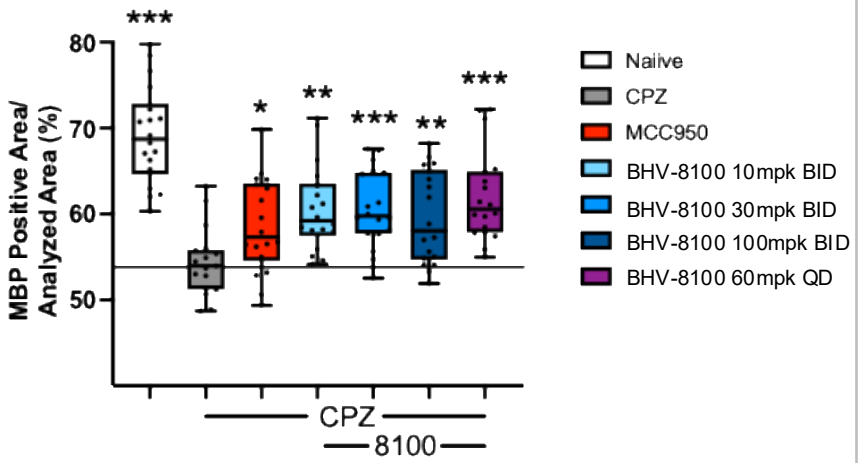


BHV-8100 Demonstrates Striking Efficacy in Cuprizone Model

Distance Traveled



Myelin-Basic Protein in Corpus Callosum



* p < 0.05, ** p < 0.01, *** p < 0.001 relative to CPZ group, MCC950 is a n NLRP3 inhibitor.

KEY POINT

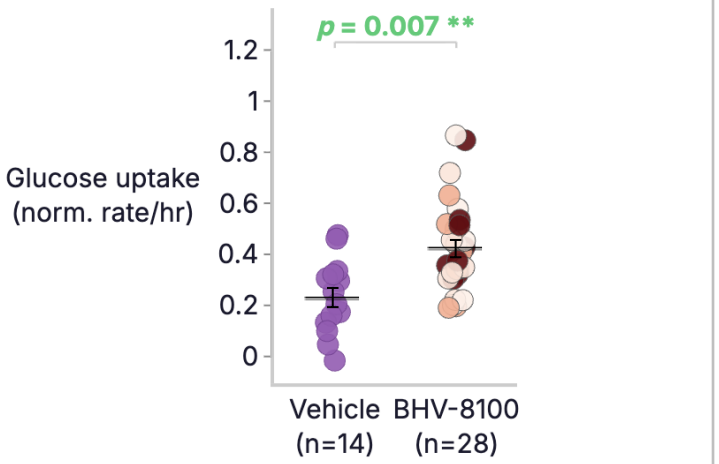
BHV-8100 demonstrates anti-inflammatory efficacy and a strong ability to promote oligodendroglial function in models of EAE

BHV-8100 Demonstrates Sustained Efficacy in Human Brains With Documented Alzheimer's Disease and All-cause Dementia

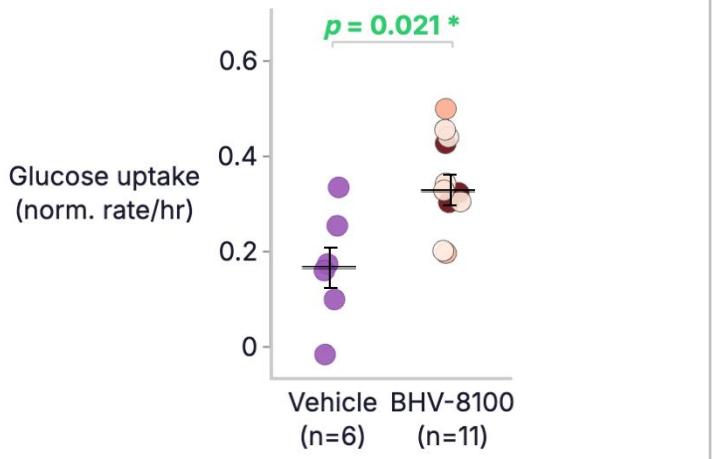
DISCOVERY

Reperfused human brains (Brainex™) allow precise study of brain penetrance, pharmacology, pharmacokinetics, pharmacodynamics and biomarkers in brains with documented diseases

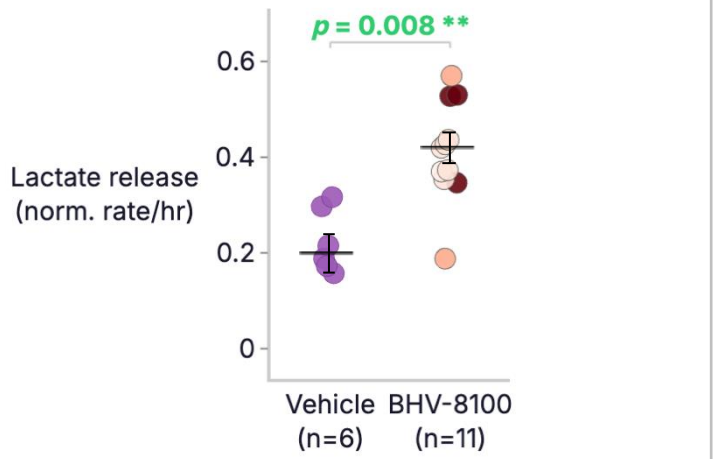
Disease of Cognitive Impairment[1]: BHV-8100 Enhances Glucose Uptake



Alzheimer's Disease: BHV-8100 Enhances Glucose Uptake



Alzheimer's Disease: BHV-8100 Enhances Lactate Production



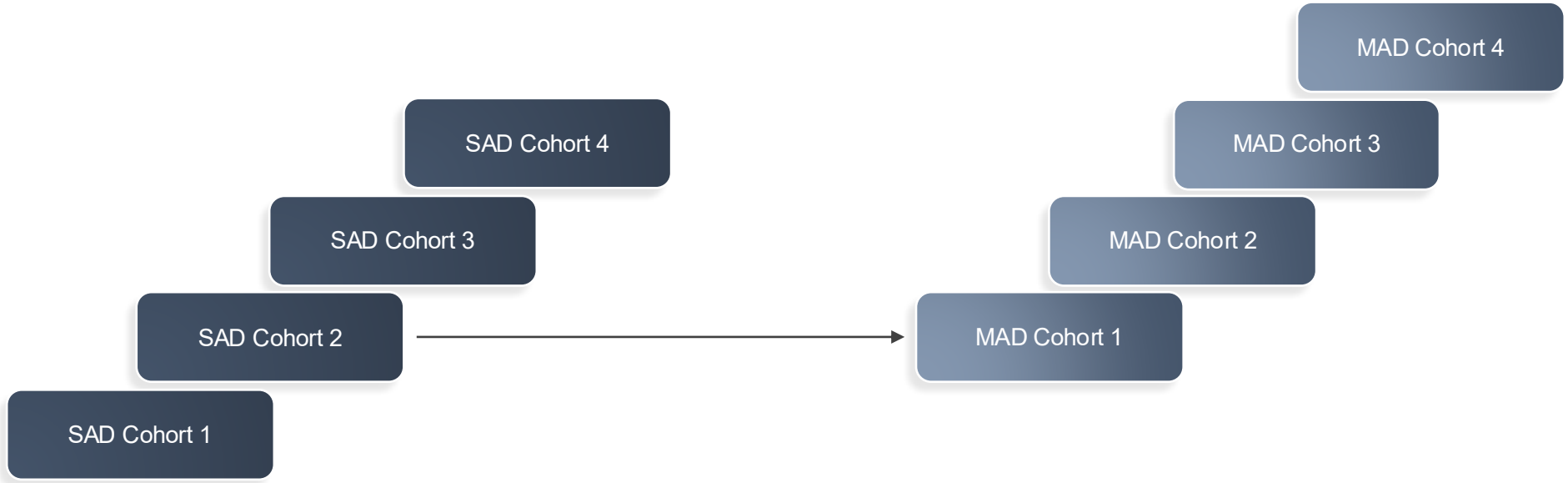
1. Diverse diagnoses including AD and other disease

KEY POINT

Precise determinations of brain penetrance and dose-response pharmacology confirm efficacy and guide human dosage

Open Label, Placebo-Controlled FIH SAD/MAD Study To Evaluate Safety, Tolerability and PK of BHV-8100 in Healthy Adults

DISCOVERY



KEY STUDY DETAILS

Population: Male and non-childbearing female healthy adults

Treatment: BHV-8100 in escalating single and multiple doses vs. matching placebo (6:2 ratio at each cohort)

Key Objectives: PRIMARY: Safety and tolerability; SECONDARY: PK in plasma. CSF concentration (MAD Cohorts only)

*Representative schema

BREAKING NEWS

BHV-8100 achieves clinical milestone with first human dose in SAD/MAD study 2Q 2026

Early FIH Data of BHV-8100 in SAD Shows Safety and Tolerability in Healthy Participants

DISCOVERY

- No SAEs or severe AEs
- Most AEs were mild and resolved spontaneously
- No clinically significant changes in ECG
- No clinically significant trends in safety labs including LFTs

Preliminary data from ongoing study as of 22-May-2026.

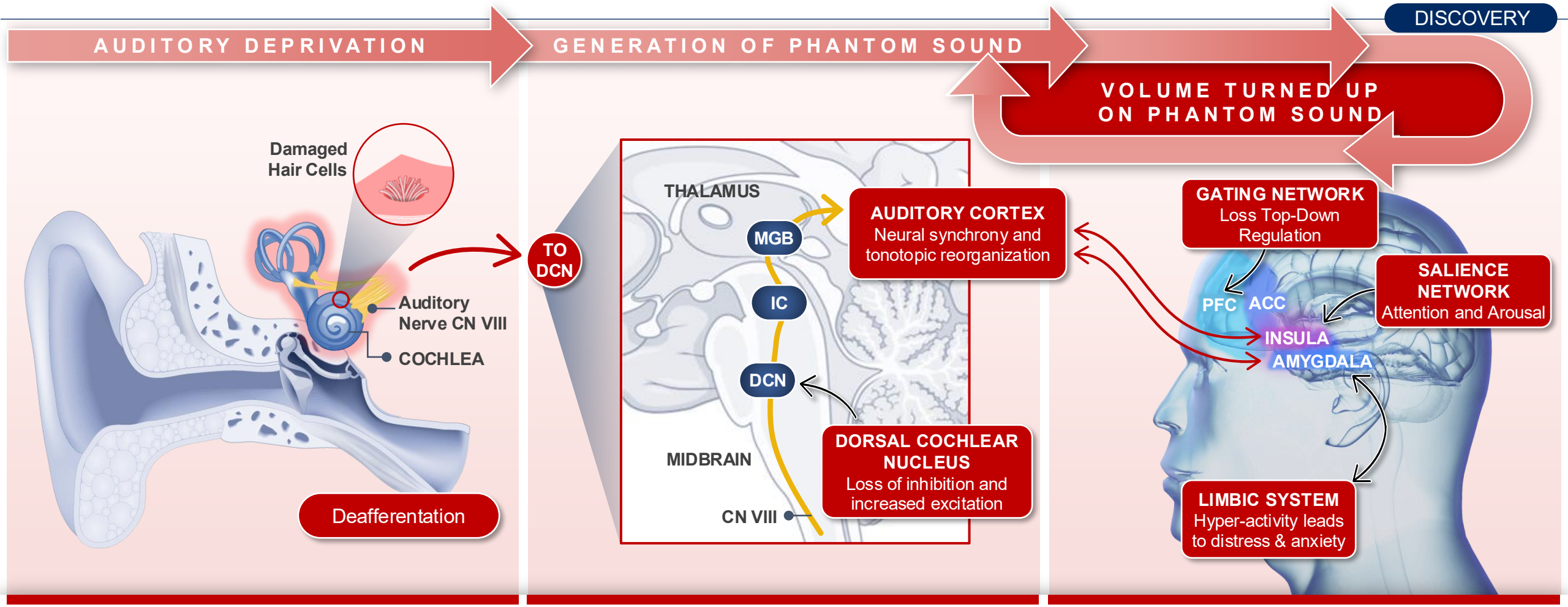
Lawrence C. Newman, MD, FAHS, FAAN
Director, Brain Health
Atria Health and Research Institute

atria Health and Research Institute

BHV-1955: Tinnitus

biohaven®

Tinnitus Is a Sound Volume Control Problem in the Brain



Peripheral Pathway
Peripheral Damage

Central Auditory Pathway
Central Gain and Plasticity

Non-Auditory Pathways
Attention and Distress

Tinnitus: There Is No FDA-Approved, Mechanism-Based Pharmacologic Therapy Despite High Prevalence

DISCOVERY

Large Patient Population

- **2 million chronic tinnitus patients** have severe, debilitating disease that requires treatment
- **120 million worldwide**
- **Risk factors:** hearing loss, presbycusis, exposure to loud noises, medications, head and neck injuries, infections

Debilitating Symptoms

- **Phantom noise that can not be ignored**
- **Severe tinnitus has debilitating consequences**: anxiety, difficulty concentrating, sleep impairment, social isolation, cognitive impairment, depression and increased risk of suicide

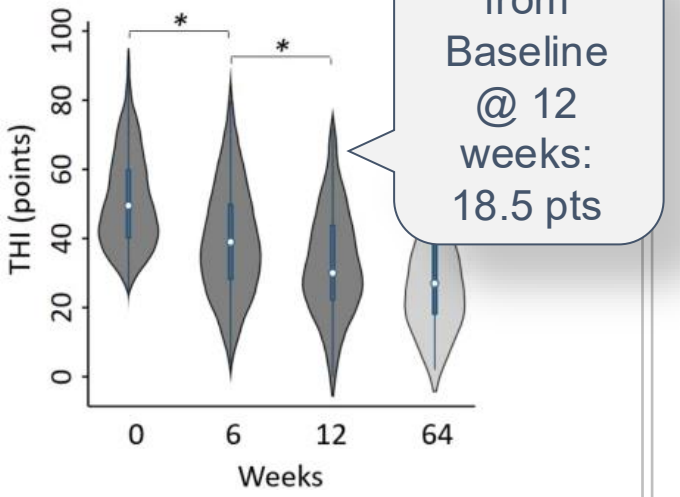
Limited Treatment Options

- **Hearing aides and sound therapy:** exposure to sound to mask phantom sound or reverse neural changes
- **Behavioral Therapy:** improve well being and quality of life
- **Medications:** There are no FDA-approved medications specifically for tinnitus

Clinical Evidence: Oxytocin Receptor Agonism Reduces Tinnitus Severity

DISCOVERY

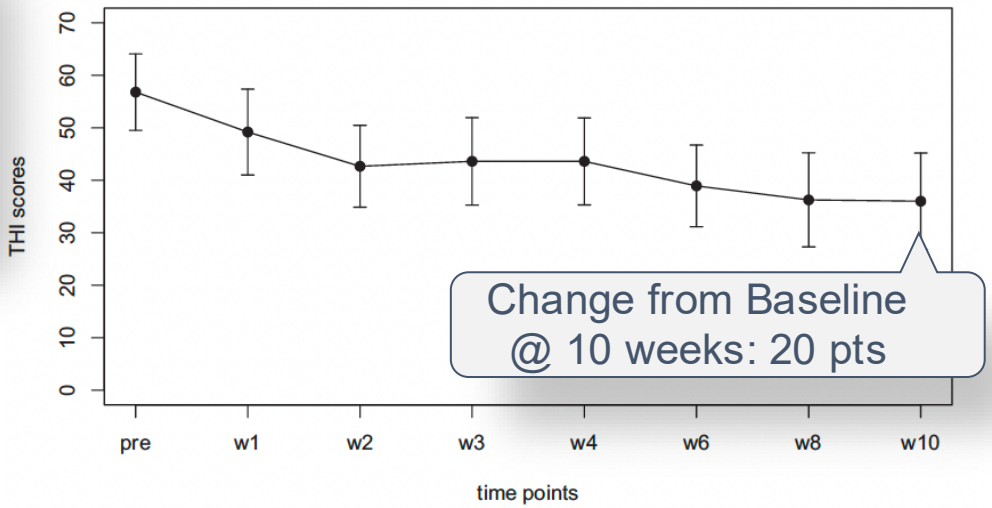
Lenire Device[1]



Change from Baseline @ 12 weeks: 18.5 pts

Bimodal stimulation
Only FDA-approved treatment for tinnitus

Low-Dose Oxytocin[2]



Change from Baseline @ 10 weeks: 20 pts

8 IU Oxytocin delivered intranasally BID led to similar reductions in the Tinnitus Handicap Index (THI)

High-Dose Oxytocin[3]

CASE STUDIES

	Patient 1	Patient 2
Dose	45 IU	45 IU
Frequency	QID	BID
THI Baseline	96	75
THI after treatment	16	18

Dosing started at 8 IU BID
Increased until tinnitus relief persisted until next dose

1. https://www.nature.com/articles/s41598-022-13875-x. **2.** https://pmc.ncbi.nlm.nih.gov/articles/PMC5613090/. **3.** NCT04210310 Clinical Research Protocol.

KEY POINT

Increasing dose and frequency of oxytocin extends duration of tinnitus symptom improvement

Patient Testimonials

DISCOVERY

BAROTRAUMA

My noise was so bad, that for two years I thought I lived on the deck of an aircraft carrier and constantly ideated because of it. I went to 14 ENTs and acupuncturists and cranial sacrals all over the country and nothing worked. Then one day ***Dr. Newman gave me a nose spray, and the sound went to whisper or disappeared on most days, and my life returned to normal.***

IED EXPLOSION IN IRAQ

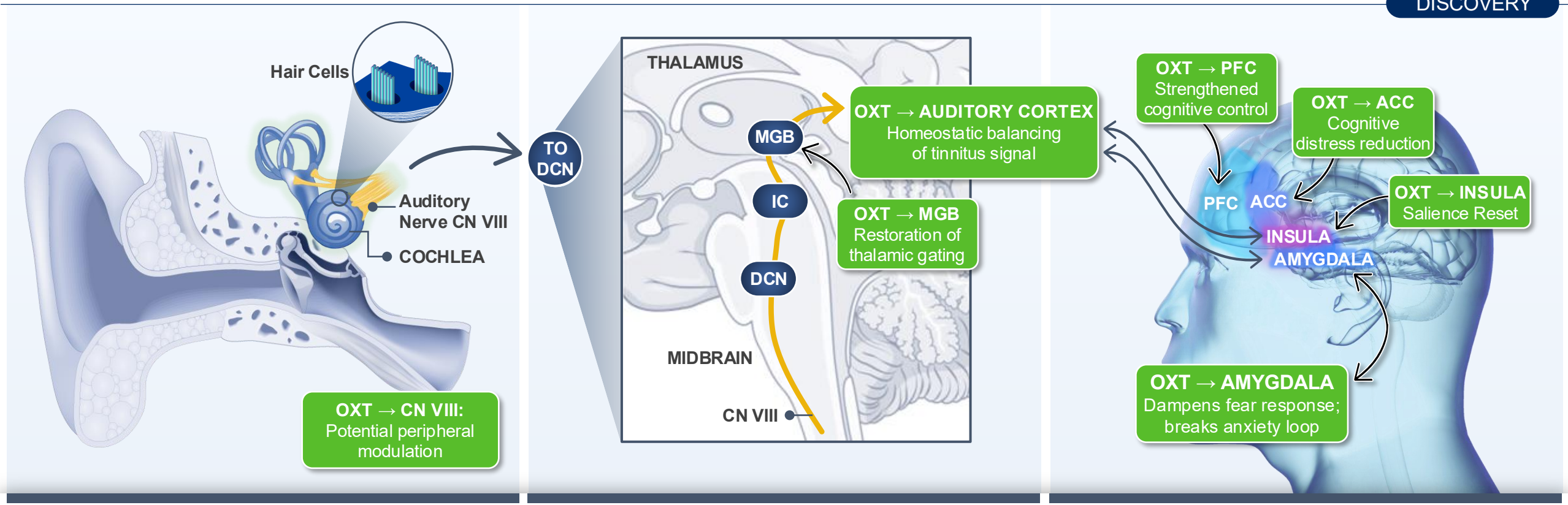
It did help. The spray reduced the high pitch frequency of the tinnitus *and although it did not resolve it completely it made it less obvious to me.*

Ménière's Disease

Despite being a physician and consulting several specialists, my tinnitus remained disabling. After intranasal oxytocin, it no longer does. ***My tinnitus improved rapidly and substantially. The benefit has been sustained, and I have experienced no adverse events.***

Oxytocin Tunes Neuronal Response to Phantom Noise

DISCOVERY



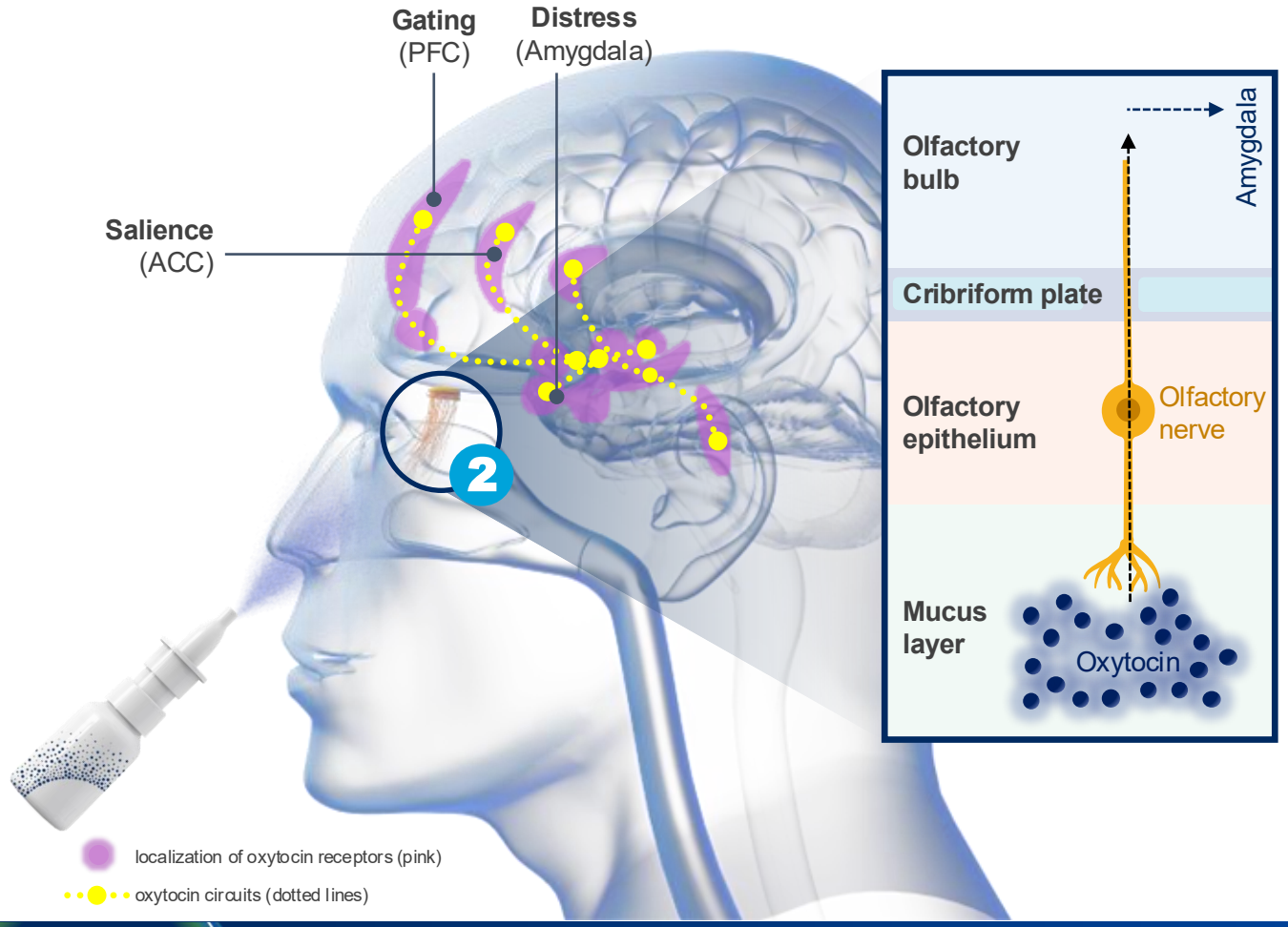
Peripheral Pathway | **Central Auditory Pathway** | **Non-Auditory Pathways**

KEY POINT

Oxytocin calms hyperactive pathways in the brain to turn down the volume on the phantom sound

Reformulation Strategy To Deliver High-Dose Oxytocin

DISCOVERY



1. Achieve room temperature stability to eliminate need for refrigeration
2. Ensure efficient deposition to the olfactory epithelium to bypass the blood brain barrier
3. Reduce mucosal clearance and nasal leakage
4. Reduce dosing frequency

KEY POINT

BHV-1955 is formulated to deliver oxytocin to brain regions impacted by tinnitus

BHV-1955: Improved Exposure in Non-Human Primates Over Clinically Used Formulation

DISCOVERY

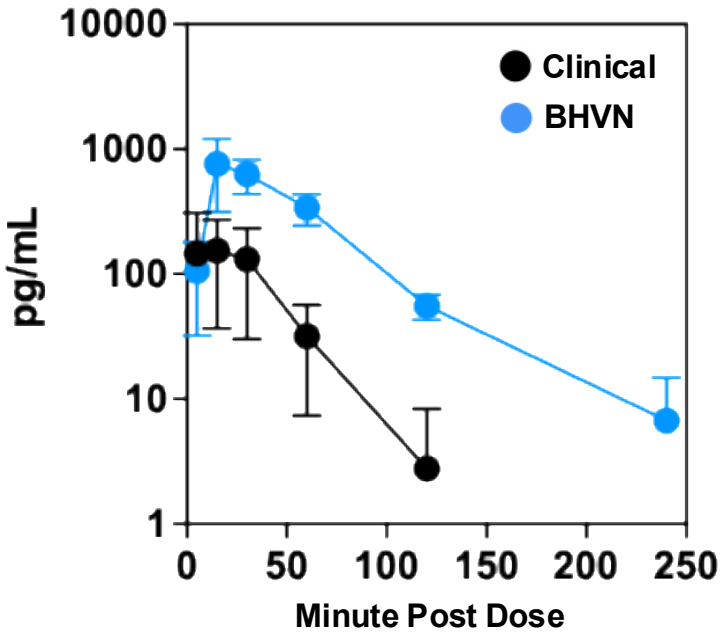
STUDY DESIGN

Test Articles and Formulations:

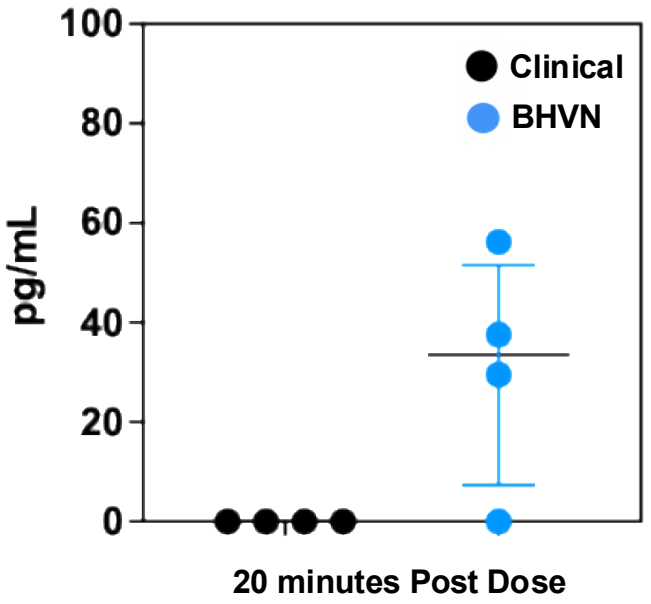
- **Clinical Formulation:** Formulated with mucolox
- **BHVN Formulation**

Dosing: Single dose IN, 48 IU
Subjects: n=4 non-naïve male cynomolgus macaques (7-8 kg)
Blood collection: Up to 4 hours
CSF collection: 20 minutes post dose

Plasma



CSF

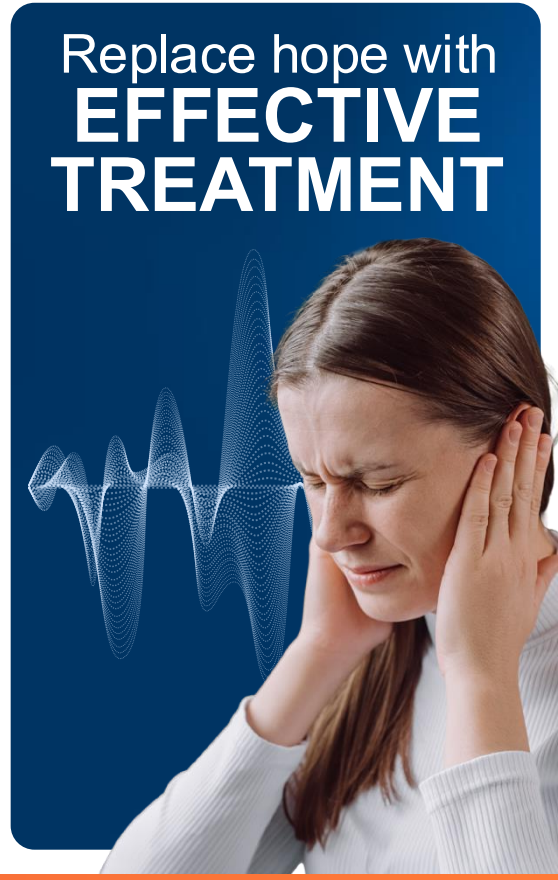


Formulation	Plasma C_{max} (pg/mL)	Plasma AUC_{last} (min*pg/mL)	Plasma T_{max} (min)	Plasma T_{last} (min)	CSF Concentration @ 20 min (pg/mL)
Clinical Formulation	191	12400	33.8	150	0; Detected in 0/4 animals
BHVN Formulation	**798**	**39700**	**18.8**	**180**	**41.1; Detected in 3/4 animals**

BHV-1955: Poised To Transform Tinnitus

DISCOVERY

MIGRAINE PRE-CGRP (BEFORE 2018) A proven blueprint	THE PARALLEL IS CLEAR		TINNITUS TODAY The Same Landscape-The Same Opportunity
• **~1 billion** people globally • **~39 million** in the US • **~4 million** in the US have chronic migraine	**Massive Unmet Need**		• **749 million** people worldwide have tinnitus • **25-40 million** people in the US experience tinnitus • **2 million** have severe, debilitating disease in the US
• **31%** reluctant to seek help • **~40%** eligible for prevention, only **17%** using it	**Low Treatment-Seeking**		• **~20%** of tinnitus sufferers seek medical help • **~34%** of all tinnitus sufferers plan to seek help
Repurposed drugs included anticonvulsants, beta-blockers, antidepressants, blood pressure drugs	**Disease-Specific Therapies Lacking**	**No FDA-Approved Therapies**	• No approved drug (pharmacotherapy) for tinnitus • Lenire® Device: FDA-authorized neurostimulation
"Believed a doctor could not do anything more"	**Patients Become Resigned to Suffering**		Patients are frequently told ”there are no medicines"
Nearly half stopped or modified prevention within 6 months due to poor tolerability or lack of efficacy	**High Discontinuation and Dissatisfaction**	**Limited Support and Access**	Only **~50%** who discuss tinnitus with a physician receive any **treatment recommendation**
CGRP approvals (2018) changes migraineurs lives	**Breakthrough Changed Everything**	**Breakthrough Can Change Everything**	**An effective therapy transforming millions of lives!**



BREAKING NEWS

The tinnitus landscape today mirrors the migraine landscape before CGRP – same scale, same gaps, same opportunity for a breakthrough

Bruce D. Car, DVM, PhD, DACVP
Chief Scientific Officer

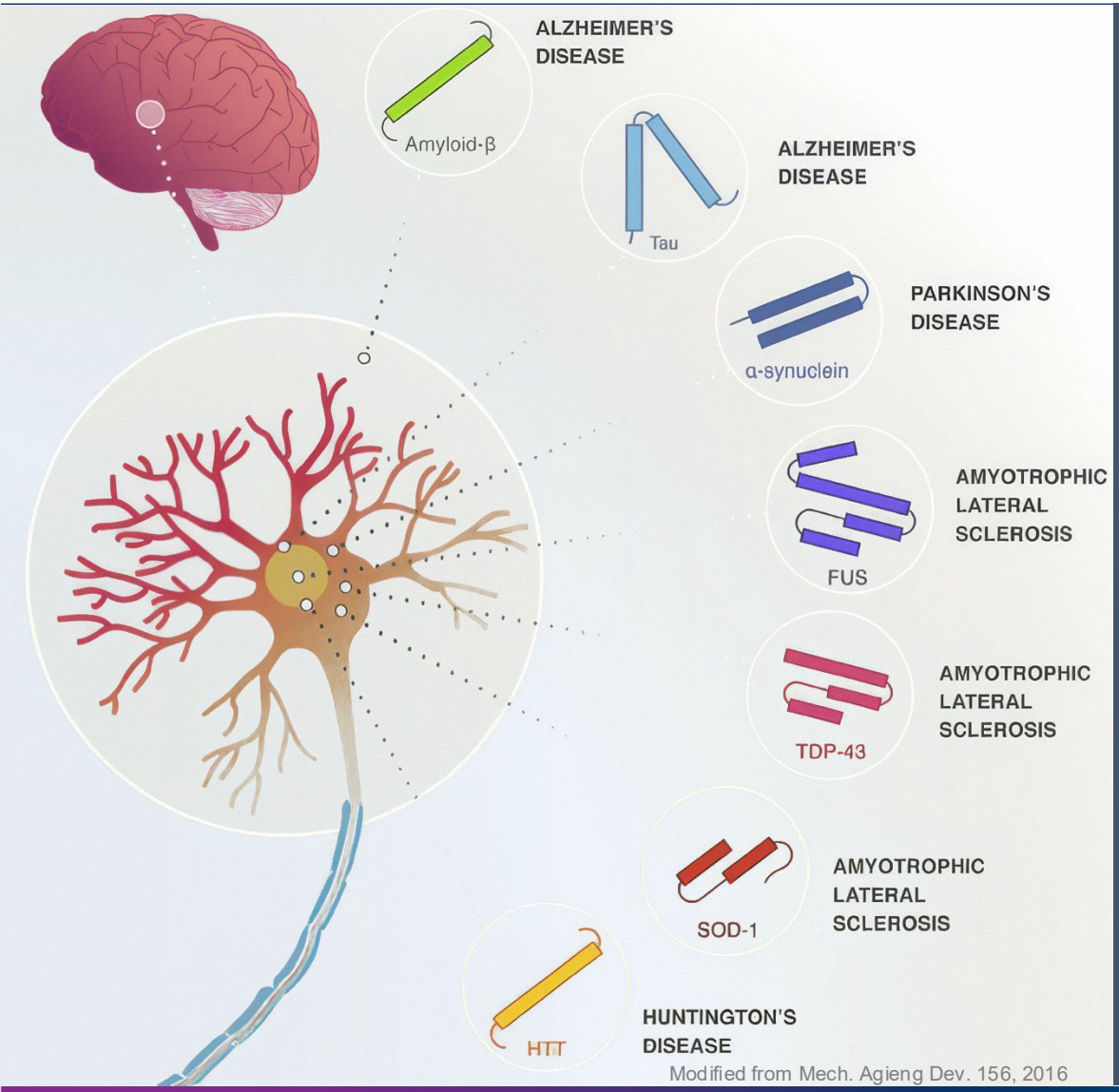
biohaven®

BHV-8200: Oral Doxycycline Prodrug Parkinson's Disease

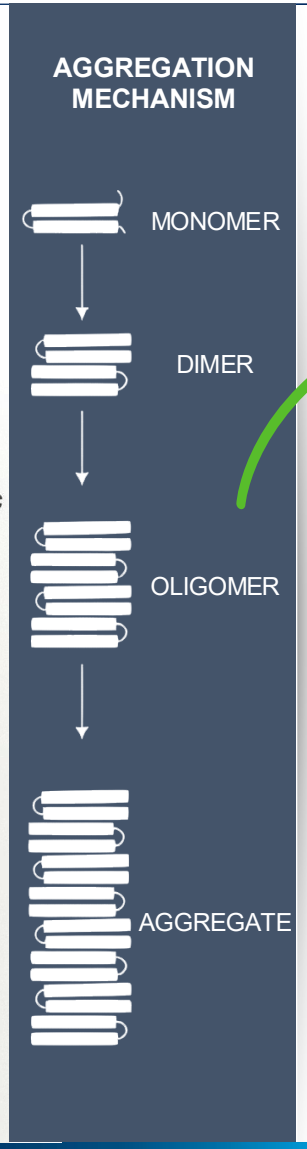
biohaven®

Doxycycline Reduces Protein Aggregates in Neurodegenerative Diseases

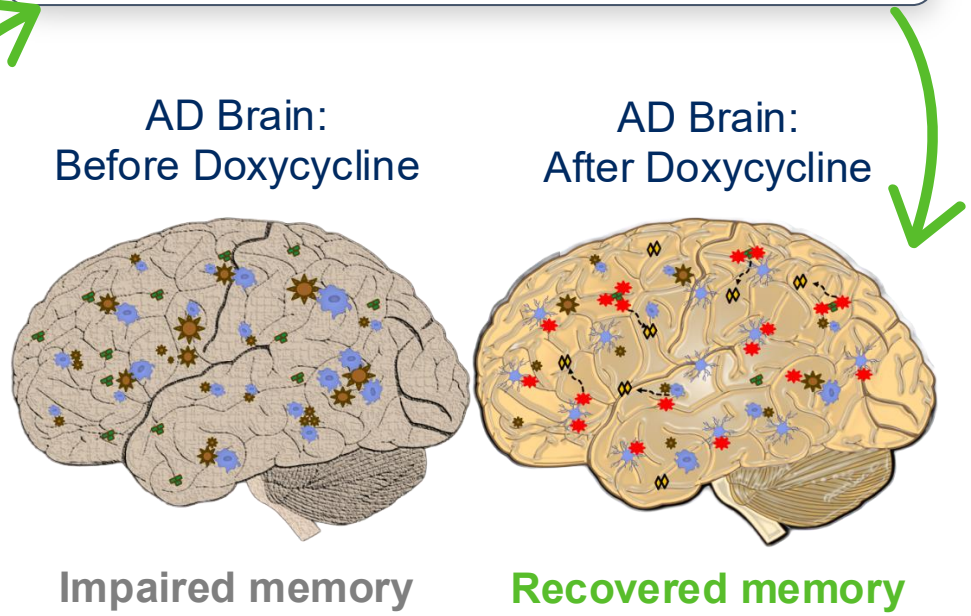
DISCOVERY



Modified from Mech. Agieng Dev. 156, 2016



Doxycycline shown to reduce and reduce protein aggregates



Modified from Front. Pharmacol. July 2019

Refining the Favorable Pharmacology of Doxycycline for Parkinson's Disease Treatment With BHV-8200

DISCOVERY

Abundant evidence exists for doxycycline mitigating Parkinson's disease progression[1,2,3]

- Alpha synuclein aggregation and Lewy body-driven pathology → Doxycycline prevents aggregation and disaggregates complexes at relevant concentrations
- Neuroinflammation driven by Th17 hypersensitivity → Mitigated Th17-driven neuroinflammation
- Dopaminergic neurodegeneration secondary to neuroinflammation and toxic aggregates → Reduced dopaminergic neurodegeneration secondary to toxic aggregates

However, doxycycline has undesirable properties, addressed by BHV-8200

	BHV-8200
Co-administration with food	Eliminates gastric irritation
Intestinal antibacterial dysbiosis	Eliminates antimicrobial activity in the GI
BID dosing required	Exposure suitable for QD administration

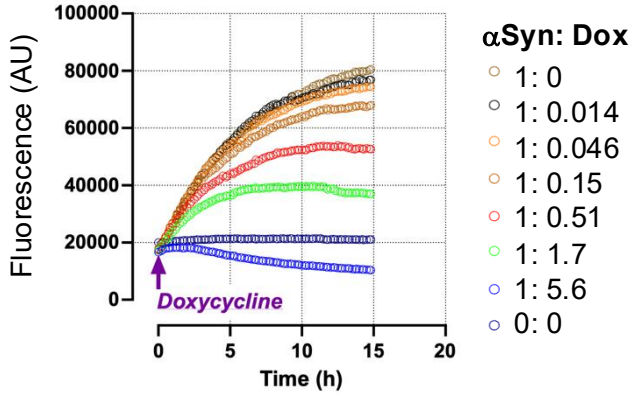
1. La Vitola. Parkinsonism Relat. Disord. 2023. **2.** Dominguez-Meijide. Neurobiol. Dis. 2021. **3.** Gonzalez-Lizarraga. Sci. Rep. 2017.

Doxycycline Prodrug Optimized for the Treatment of Parkinson's Disease

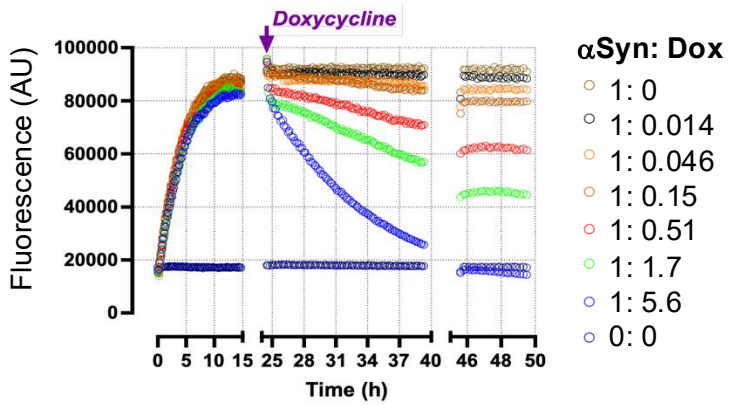
DISCOVERY

- Broad application through inhibition of aggregation:
  - α-synuclein
  - TDP43
  - Amyloid
  - Tau
- BHV-8200 purposefully synthesized to
  - Allow QD delivery
  - Sustain plasma and brain concentrations
  - Removes local (intestinal) anti-bacterial activity
  - Permits 505(b)(2) pathway for registration
- Active agent released by BHV-8200 shown to:
  - Inhibit α-synuclein aggregation
  - Drives disaggregation of preformed aggregates
  - Confirms optimal deliverable
  - Prodrugs show sustained systemic delivery

Inhibition of α-synuclein Aggregation



Disaggregation of Preformed of α-synuclein Aggregates

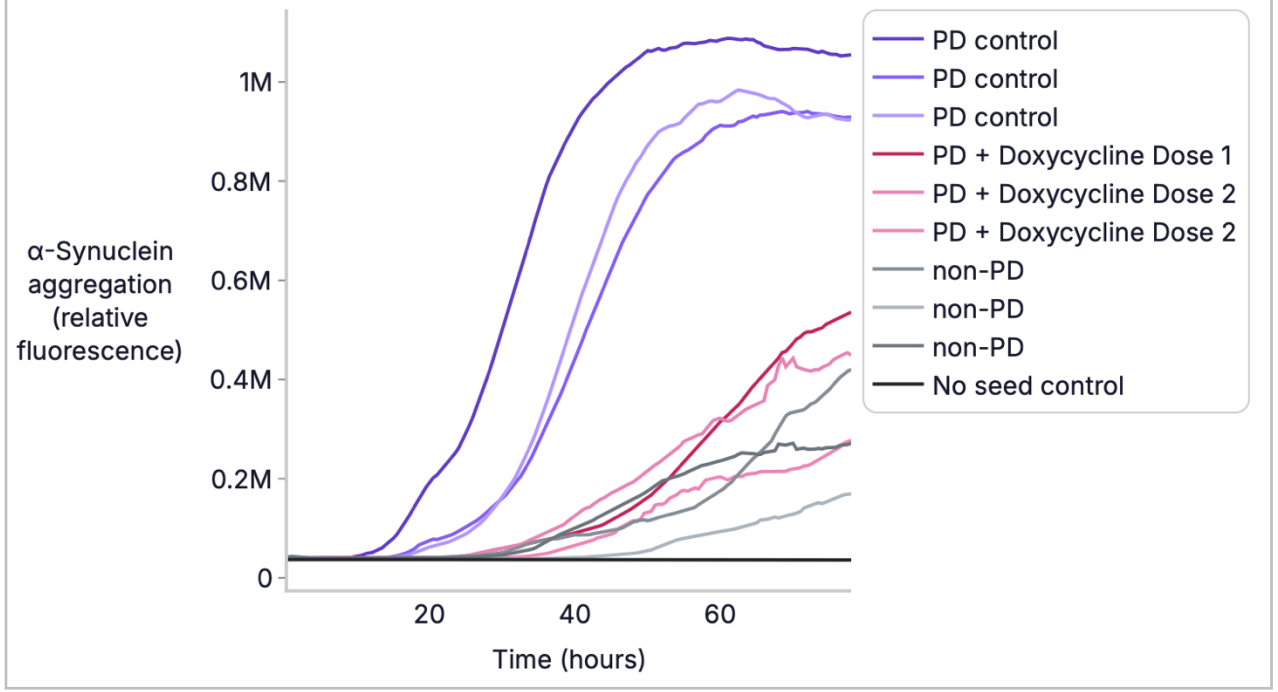


1. La Vitola. Parkinsonism Relat. Disord. 2023. **2.** Dominguez-Meijide. Neurobiol. Dis. 2021. **3.** Gonzalez-Lizarraga. Sci. Rep. 2017.

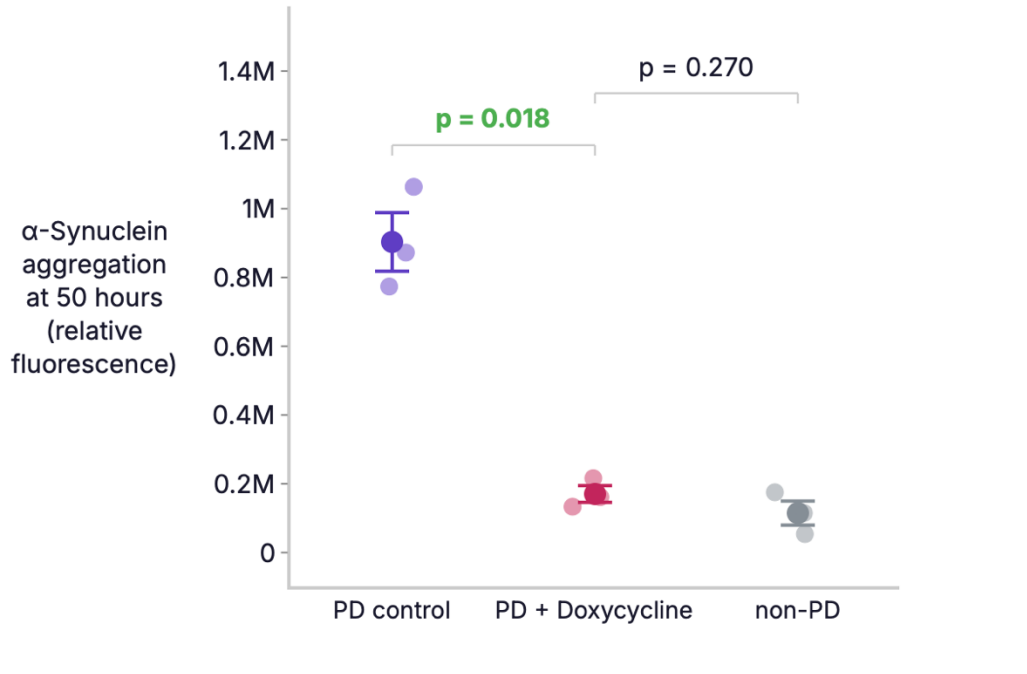
Bexorg BrainEx™: Doxycycline Delivered to Human Brains Reduces α-Synuclein Aggregation to Non-Parkinsonian Levels

DISCOVERY

α-Synuclein Aggregation Strongly Inhibited by BHV-8200



Statistically Significant Reduction in α-Synuclein Aggregation to Levels of Non-PD Brains



KEY POINT

Unexpected potency in human brains precisely confirms safe plasma and brain concentrations for correction of α-synuclein-driven pathology

Bruce D. Car, DVM, PhD, DACVP
Chief Scientific Officer

biohaven®

TRPM3 CNS Penetrant

biohaven®

BHV-2120: CNS Penetrant Molecule for Multiple Indications

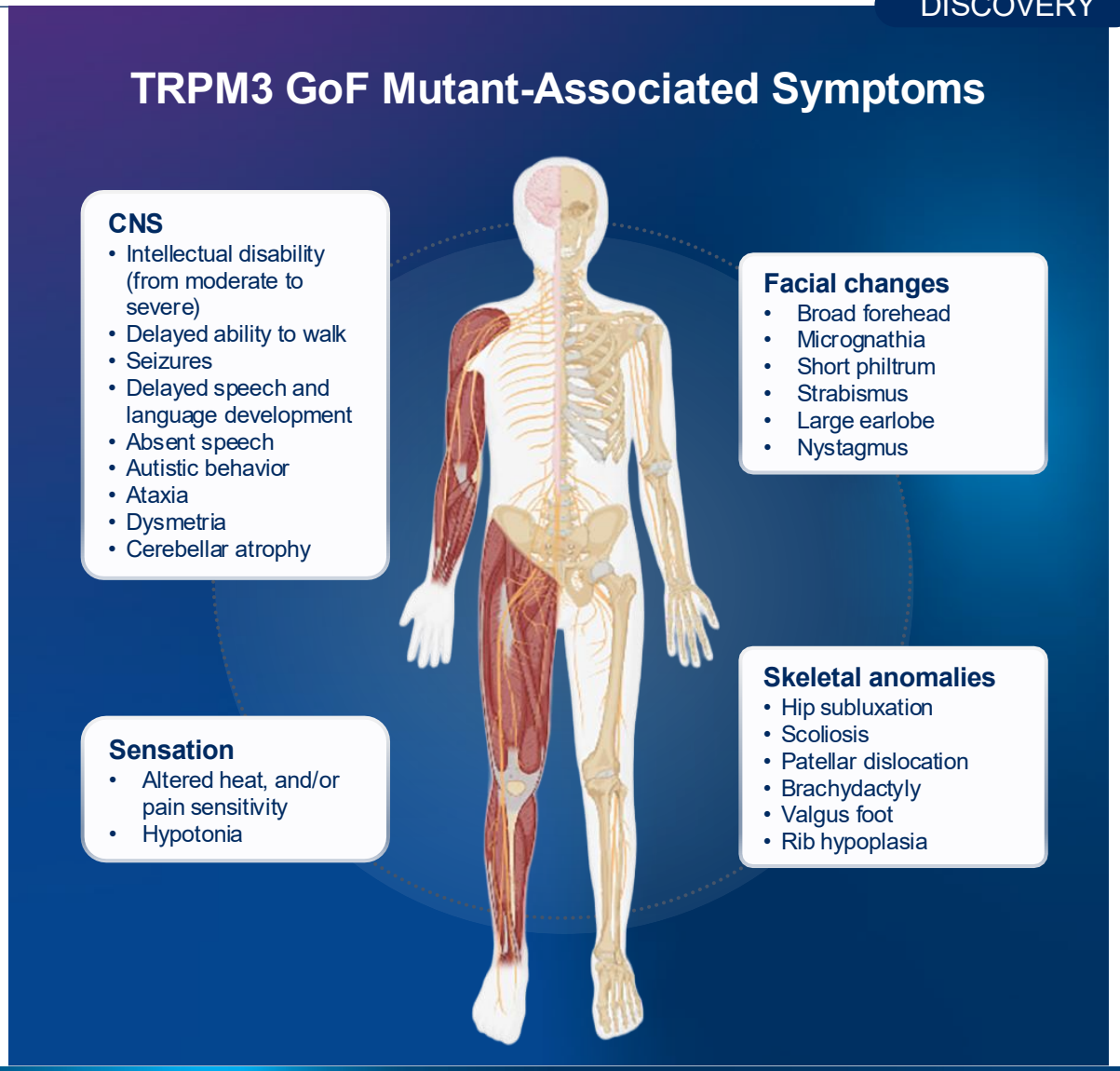
DISCOVERY

Central TRPM3

- Gain-of-function (GoF) variants in TRPM3 cause developmental and epileptic encephalopathies
- TRPM3 activation causes seizures in mice
- TRPM3 inhibition causes potent antiseizure efficacy in a preclinical model
- Brain-penetrant TRPM3 antagonists have the potential to treat a range of seizure, pain and neuropsychiatric disorders

BHV-2120

- BHV-2120 inhibition causes potent and long-lasting antiseizure efficacy rat maximal electroshock (MES)
- BHV-2120 is a development candidate demonstrating a wide therapeutic index preclinically
- Evaluating in additional seizure and neuropsychiatric models

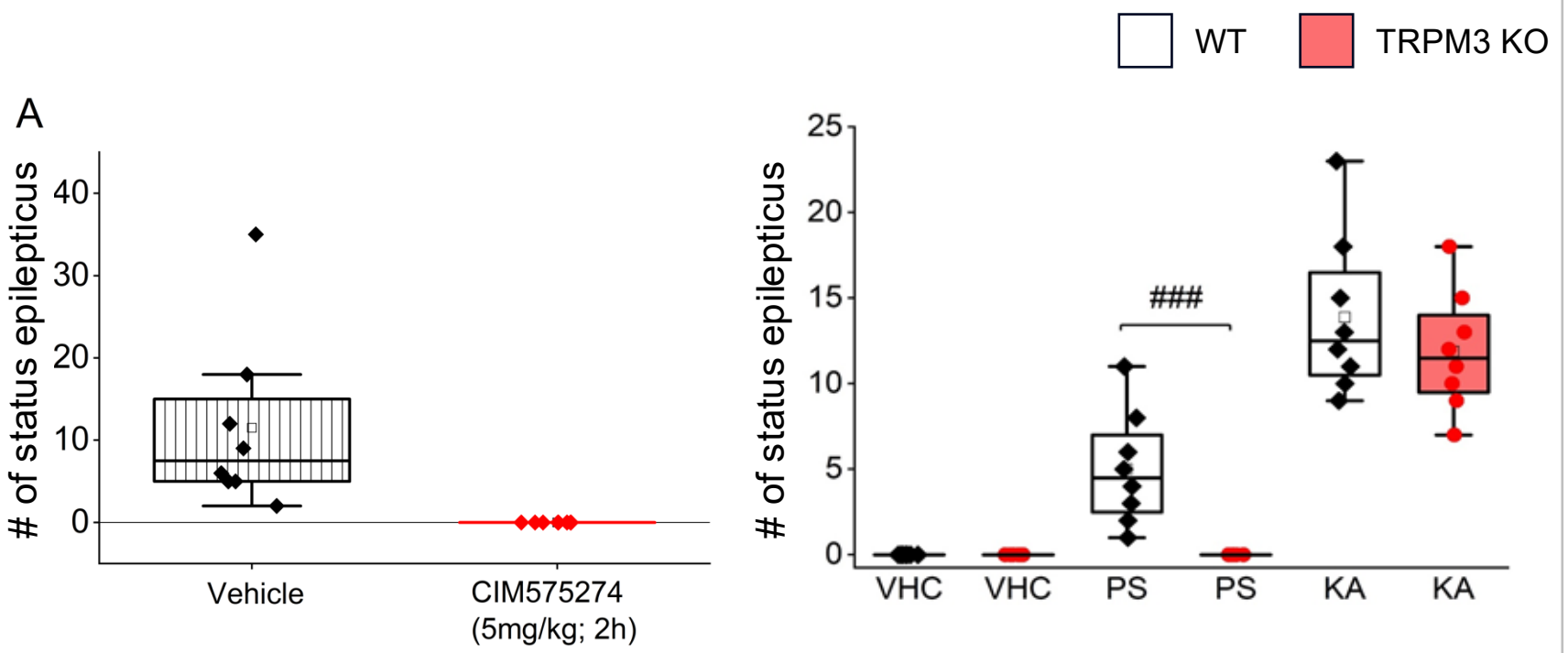


Source: Roelens. Biochim Biophys Acta Mol Cell Res. 2024.

Central TRPM3 Inhibition Prevents Pregnenolone Sulfate-Evoked Status Epilepticus

DISCOVERY

TRPM3 Activator Evoked Seizures

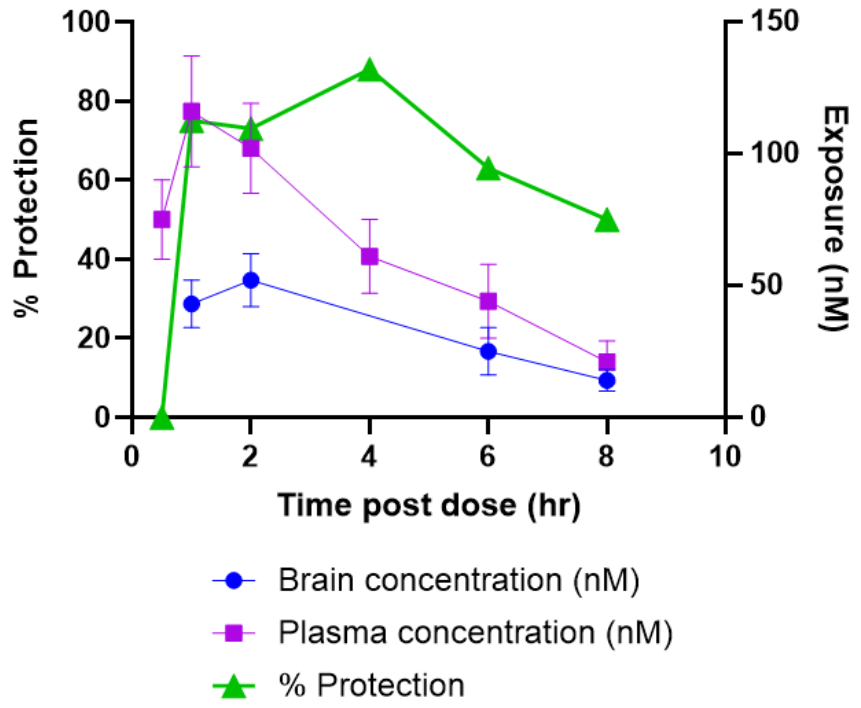


- Orally administered BHV-2120 completely blocks (PS)-evoked seizures
- PS evokes status epilepticus in wild-type (WT) mice but not TRPM3 knockout (KO) mice
- TRPM3 underlies PS ability to induce seizures

BHV-2120: Blocks Maximal Electroshock MES-Evoked Seizures

DISCOVERY

Time Course for Seizure Protection (0.1 mg/kg, oral dose)



- Rat MES is a highly translatable seizure model
- BHV-2120 is highly potent and effective at blocking MES-evoked seizures
- BHV-2120 effects are long-lasting with substantial efficacy remaining after brain concentration has diminished

Panel

MODERATOR

Brian Skorney

Equity Analyst

BAIRD

PANELISTS

Pierre Magistretti, MD, PhD
Ibn Sina Distinguished Professor
KAUST

Lawrence C. Newman, MD, FAHS, FAAN
Director, Brain Health
Atria Health and Research Institute

Bharat Awsare, MD
Executive Medical Director
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Bruce D. Car, DVM, PhD, DACVP
Chief Scientific Officer
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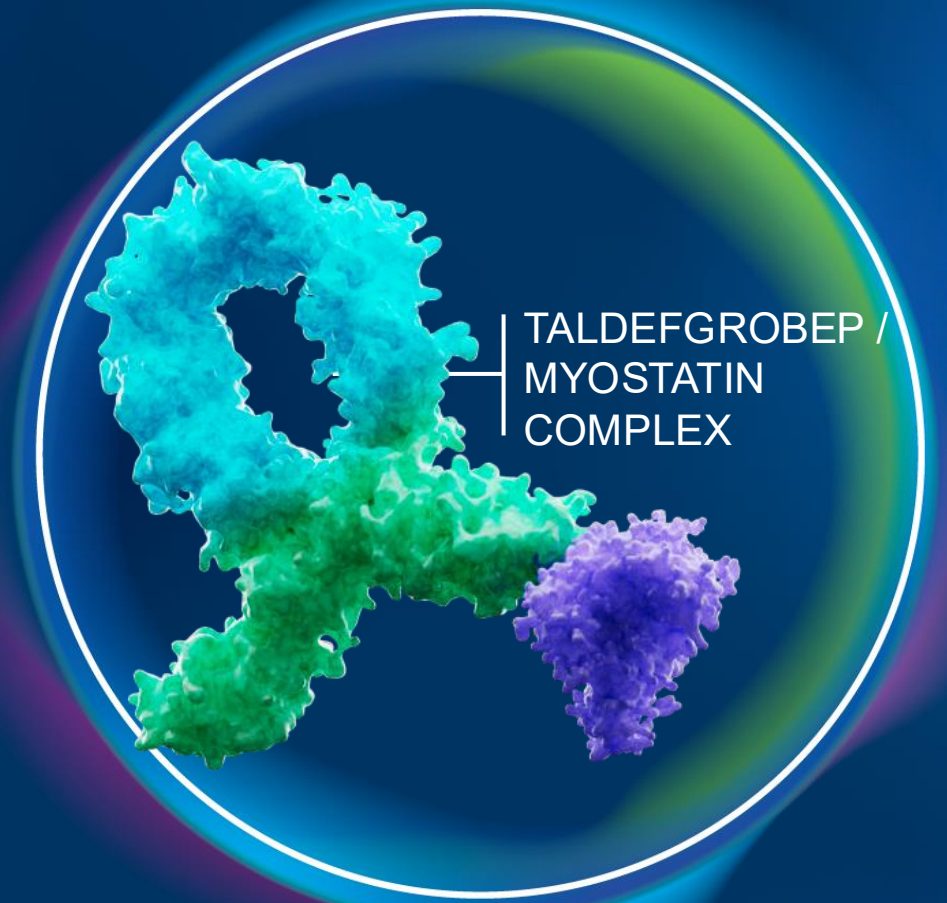
MYOSTATIN ACTIVIN INHIBITOR:
TALDEFGROBEP ALFA

Targeting High-Quality Weight Loss



Donna H. Ryan, MD

Professor Emerita
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Timothy R. Smith, MD, RPh

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Peter Ackerman, MD

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Taldefgrobep Alfa for Obesity

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Body Composition Concerns With Weight Loss Medications

biohaven®

Donna H. Ryan, MD	
Scientific advisor	AbbVie, Altimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Biohaven, Calibrate, Carmot/Roche/Genentech, CinRx, Currax, eMed, Epitomee, Fractyl, i2o, ICON, Kailera, Lilly, Nestle, Novo Nordisk, Pfizer, Protagonist, Regeneron, Regor, Rhythm, Souffle Source Bio, Structure Therapeutics, Tenvie, Wondr Health, WW, Zealand
Speaker's bureau	Novo Nordisk, Lilly
Stock options	Epitomee, Calibrate, Roman
DSMB	IQVIA setmelanotide (2); Lilly (1); CinRx (1)

State-of-the-Art in Obesity Medicine

TALDEFGROBEP

- Growing enthusiasm for robust weight loss achieved with GLP-1, GLP-1/GIP RA medications
  - More patients being treated and achieving **more weight loss, thus lean loss is a growing concern**
- Treatment includes broader patient profiles
  - More older individuals, more patients with chronic disease, many in lower BMI range = **more potential for excessive lean mass loss**
- Emerging new targets with new potential for disease modification (Glucagon, Amylin, Amylin/Calcitonin RAs)
  - Body composition effects are **always** a focus for new agents
- Growing guideline-driven movement for better diagnosis **beyond BMI**, and movement to **treat-to-target anthropometrics**

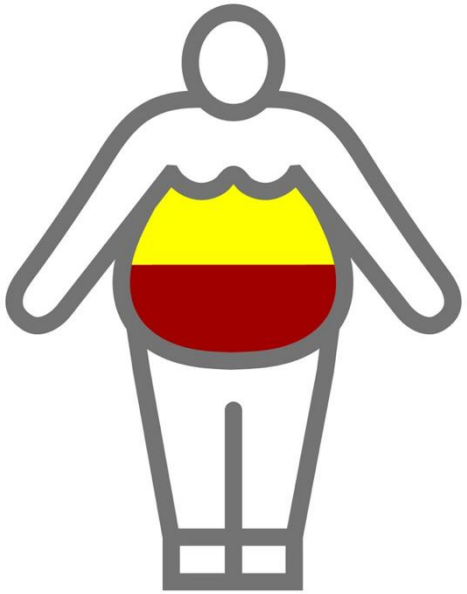
THE RESULT:

Growing concern for body composition optimization with pharmacotherapies

The Major Component of Lean Mass Loss Is Muscle

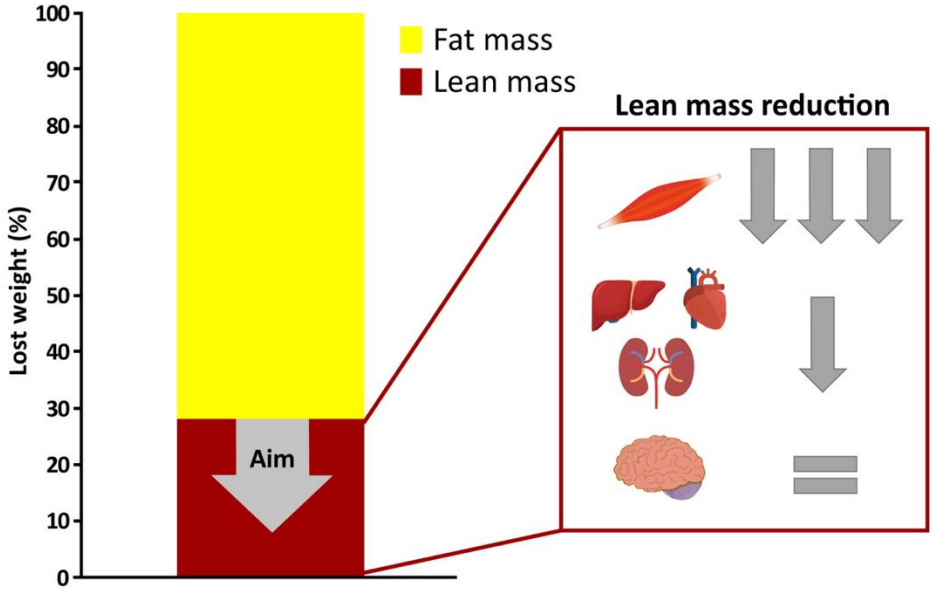
TALDEFGROBEP

Before Weight Loss[1]



Total body fat percentage can vary in adults with obesity (25-50+%). This percentage increases with age.

Composition of Weight Loss[1]



15-40% of weight loss due to sustained energy restriction comes from lean mass.

1. Christoffersen BØ. Obesity (Silver Spring). 2022. **2.** Mocciaro. BMJ Nutr Prev Health. 2025.

KEY POINT

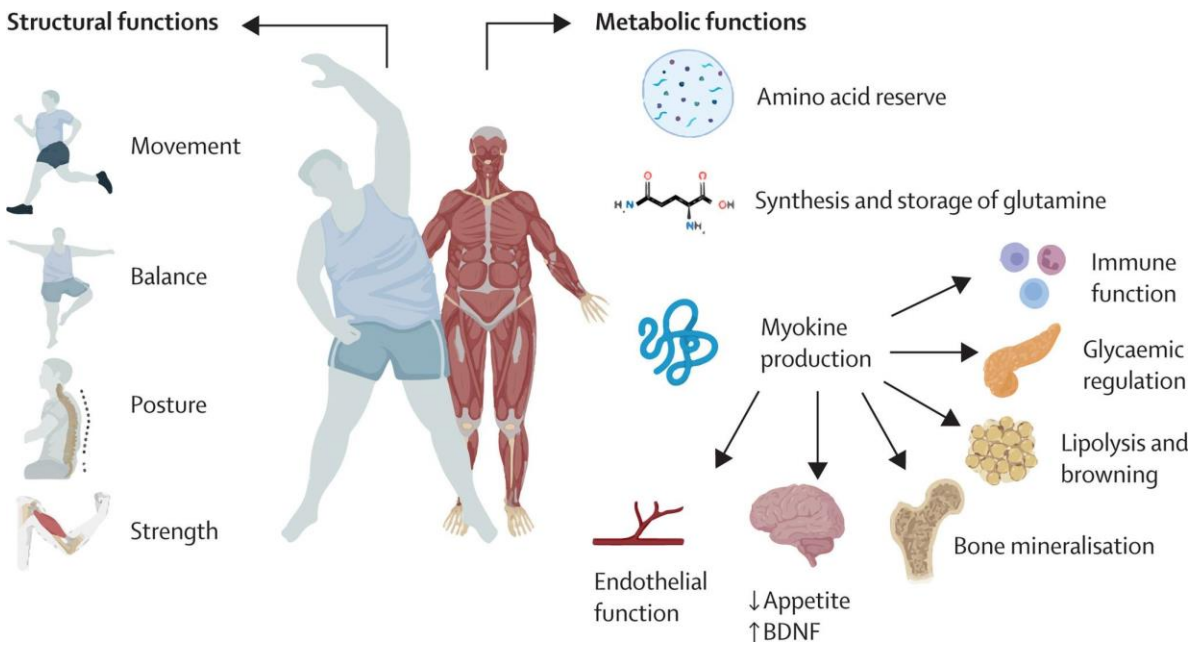
Up to 40% of total body weight loss with GLP-1-based therapies is due to reductions in healthy lean mass[2]

Lean Muscle Mass Is Critical Determinant of Metabolic Health, Physical Function and Healthy Aging

TALDEFGROBEP

- Muscle mass is important to glucose tolerance, bone density and cognitive function[1-3]
- After 30, adults experience accelerating age-related decline in muscle mass and strength[4]
- Low muscle volume is associated with increased risk for morbidity and mortality, independent of body weight and physical function[5-8]

Benefits of Lean Muscle Mass



1. Merz. Compr Physiol. 2021. **2.** Han. J Orthop Surg Res. 2023. **3.** Tessier. JAMA Netw Open. 2022. **4.** Wilkinson. Ageing Res Rev. 2018. **5.** Linge. J Cachexia Sarcopenia Muscle. 2021. **6.** Wang. PLoS One. 2023. **7.** Valenzuela. BMC Musculoskelet Disord. 2020. **8.** Medical Press. https://medicalxpress.com/news/2024-05-poor-muscle-health-common-people.html. Accessed 17-MAY-2026.

KEY POINT

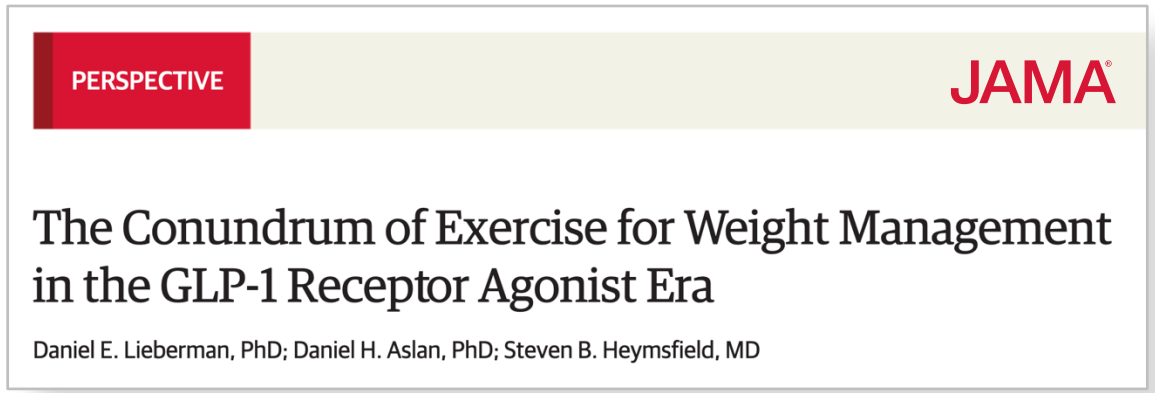
Excessive lean muscle loss can have significant long-term implications, especially in those at risk for sarcopenia

Lifestyle and Novel Pharmacotherapies for Weight Loss Have Not Been Effective in Preserving Muscle Mass

TALDEFGROBEP

LIFESTYLE

"The problem with exercise is effectiveness, not efficacy"[1]


PERSPECTIVE

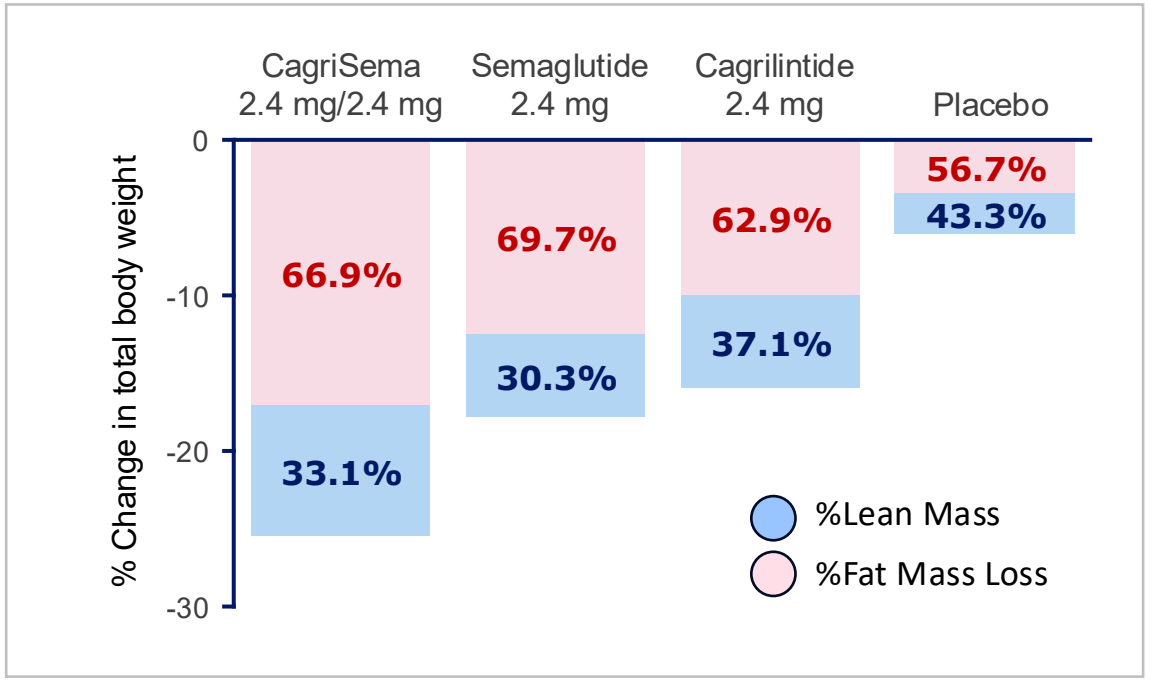
JAMA

The Conundrum of Exercise for Weight Management in the GLP-1 Receptor Agonist Era

Daniel E. Lieberman, PhD; Daniel H. Aslan, PhD; Steven B. Heymsfield, MD

NEW TARGETS

Amylin Calcitonin Dual Agonist Cagrilintide[2]



1. Lieberman. JAMA, May 2026. 2. Ravussin. 33rd European Congress on Obesity. 2026.

KEY POINT

Amylin agonists like cagrilintide have not been effective in sparing lean muscle mass

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

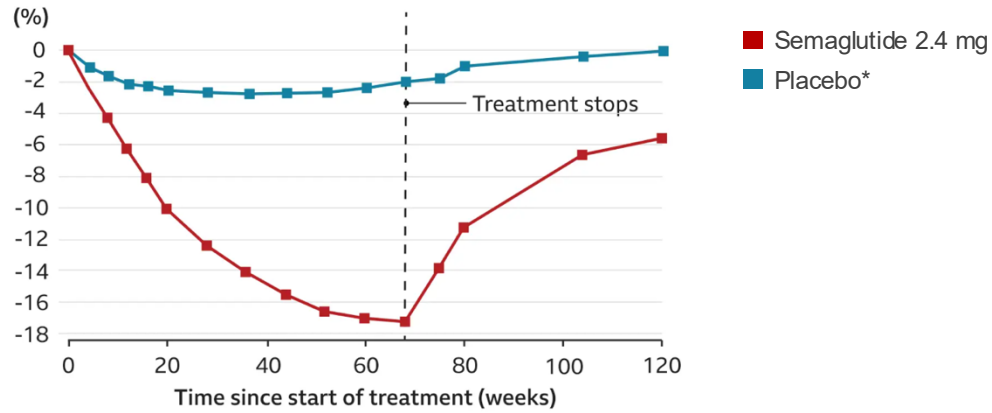
TALDEFGROBEP

- Approximately two-thirds of Americans stop GLP-1 therapy within one 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. Young. Scientific American. 2024. **2.** Sikirica. Diabetes Metab Syndr Obes. 2017.
3. Wilding. Diabetes Obes Metab. 2022. **4.** Pownall. Obesity. 2015.

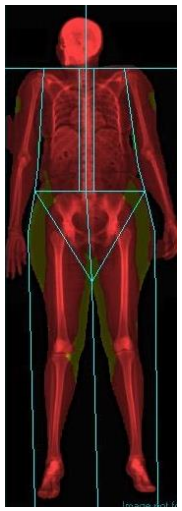
KEY POINT

Weight is regained primarily as fat
In Look AHEAD, a study of >5,000 persons with diabetes, weight regain was 100% fat[4]

State-of-the-Art, In-Clinic Assessment Tools: DEXA, BIA and 3-D DA To Be Validated by REAL Body Study

TALDEFGROBEP

	DEXA	BIA	3-D DA
PROS	Accurate bone mass, fat mass, lean mass and regional composition	Accurate extracellular water, intracellular water, total body water	Fat mass, fat free mass circumferences
CONS	Does not measure skeletal muscle, circumferences	Hydration affects accuracy; does not measure bone mineral content, circumferences	Does not measure skeletal muscle, bone mineral content



- Fat mass
- Lean soft tissue
- Bone mineral content

- Total body water
- Fat free mass
- Fat mass
- Body cell mass
- Skeletal muscle mass

- Fat mass
- Fat free mass

McMath. Obesity Reviews 2026

KEY POINT

Emerging body composition technologies are reshaping how obesity is diagnosed and how treatment success is defined

Inhibition of Myostatin + Activin Improves Body Composition Change

TALDEFGROBEP

EMBRAZE Study (Apitegromab + Tirzepatide) — Change in Baseline Body Composition at Week 24[1]

Body Compartment % (SE)	Apitegromab (10 mg/kg) + Tirzepatide n=43	Placebo + Tirzepatide n=44	Difference, Apitegromab vs. Placebo
%Change in TBW	-12.3	-13.4	-1.1
%TBW Loss due to LM	14.6 (3.19)	30.2 (2.89)	-15.6 (3.23)
%TBW Loss due to FM	85.3 (3.22)	69.5 (2.93)	15.8 (3.27)

COURAGE Study (Trevogrumab + Semaglutide +/- Garetosmab) — Change in Baseline Body Composition at Week 26[2]

Body Compartment % (SE)	Semaglutide n=151	Low-dose Combo n=149	Higher-dose Combo n=152	Triplet n=147
%Change in TBW	-10.6 (0.5)	-9.9 (0.5)	-11.1 (0.5)	-13.4*** (0.6)
%LM	-6.5 (0.5)	-3.3 (0.5)	-3.8 (0.5)	-2.0 (0.6)
%FM	-15.7	-17.3 (0.9)	-19.1 (0.9)	-27.1 (1.1)

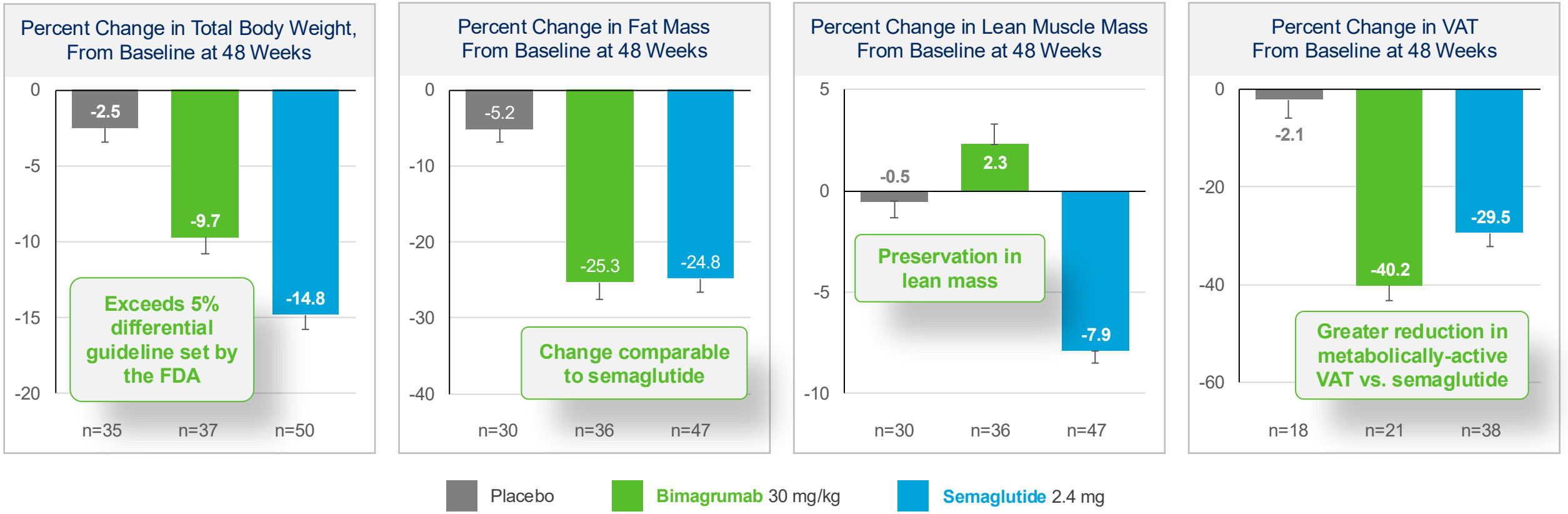
1. https://investors.scholarrock.com/news-releases/news-release-details/scholar-rock-reports-positive-phase-2-embraze-trial-results. **2.** https://investor.regeneron.com/news-releases/news-release-details/results-phase-2-courage-trial-demonstrating-potential-improve.
Low-dose combo – Trevogrumab 200 mg + semaglutide 2.4 mg; Higher-dose combo – Trevogrumab 400 mg + semaglutide 2.4 mg; Triplet – Trevogrumab 400 mg + garetosmab 10 mg/kg + semaglutide 2.4 mg.
***p<0.001; **SE**, standard error; **TBW**, total body weight; **LM**, lean mass; **FM**, fat mass

KEY POINT

Blocking myostatin alone yields negligible loss of fat mass and total body weight
Inhibition of myostatin plus activins drives favorable body composition change in obesity

Bimagrumab Provides Reason To "**Believe**" With Compelling Efficacy but Limited by Safety/Tolerability

TALDEFGROBEP



Heymsfield. Nature Medicine. 2026..

KEY POINT

Bimagrumab demonstrated the ability to achieve regulatory targets of TBW loss with comparable total fat loss to GLP-1

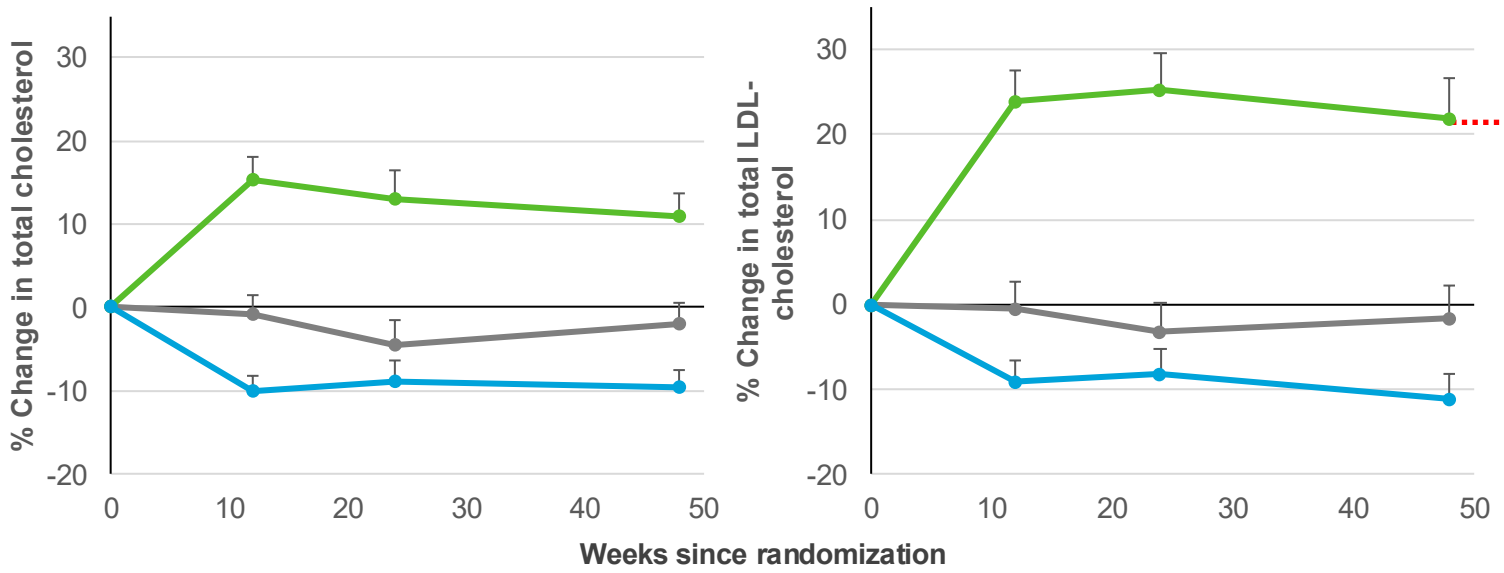
Bimagrumab Provides Reason To "**Believe**" With Compelling Efficacy but Limited by Safety/Tolerability

TALDEFGROBEP

	Placebo	Bimagrumab (30 mg IV)	Semaglutide (2.4 mg SC)
Muscle Spasms	5.5%	**73.7%**	8.9%
Diarrhea	5.5%	**49.1%**	35.7%
Acne	3.6%	**43.9%**	8.9%

Poor tolerability due to irreversible ActRIIB binding

Percent Change in Cholesterol From Baseline at 48 Weeks



Elevation in lipids secondary to high peak exposures following IV administration

Bimagrumab 30 mg/kg
Semaglutide 2.4 mg
Placebo

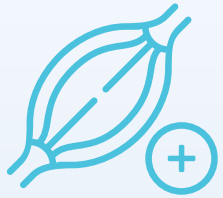
Heymsfield. Nature Medicine. 2026.

The Focus on Lean Loss With GLP-1 Therapies Is Not Going Away

TALDEFGROBEP

Anthropometric targets (e.g., WHtR) are a guidelines-driven reality

GLP-1-associated frailty is a growing concern, especially in vulnerable populations



Preserving muscle mass is important for overall health, beyond physical function

Myostatin-activin pathway inhibitors have demonstrated early promise in people living with overweight and obesity

Peter Ackerman, MD

Senior Vice President,
Clinical Development

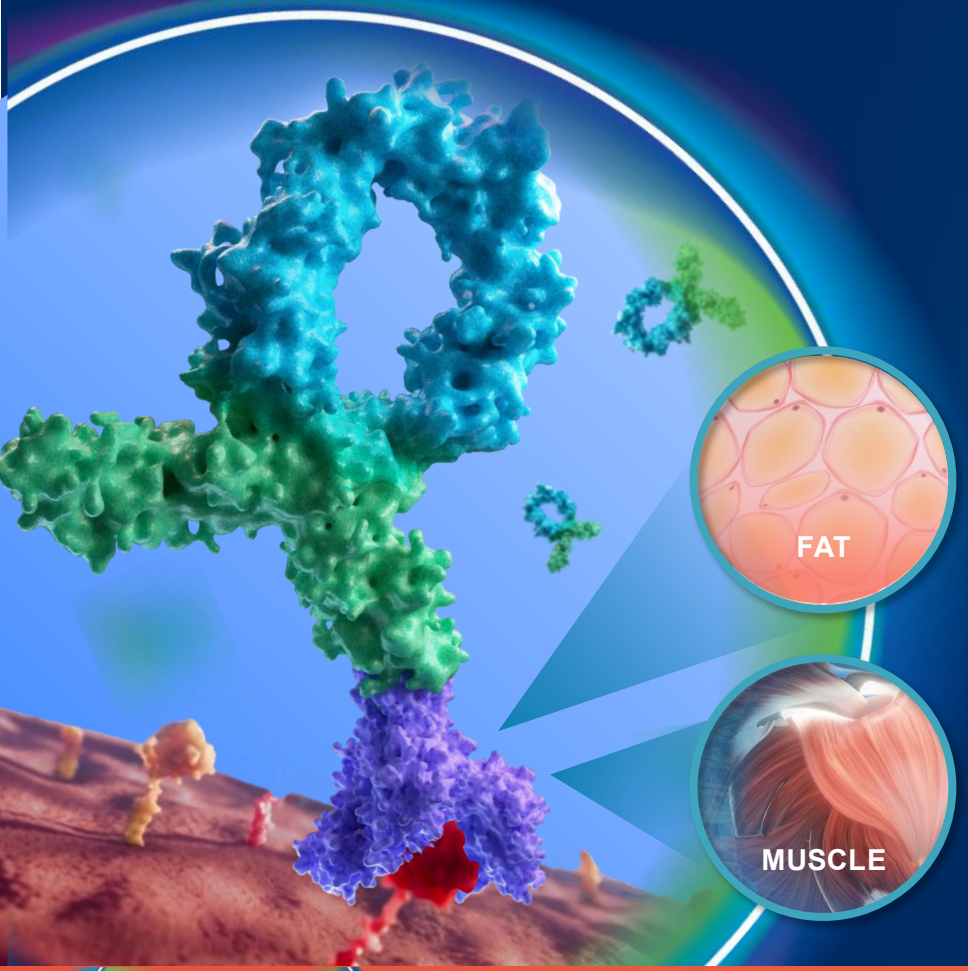
biohaven®

Taldefgrobep Alfa: Myostatin-Activin Pathway Inhibitor Targeting High-Quality Weight Loss

biohaven®

Targeting High-Quality Weight Loss With Myostatin-Activin Inhibition

TALDEFGROBEP



Taldefgrobep directly targets fat and muscle while avoiding intolerable adverse effects

Novel myostatin-activin MOA for healthy weight loss
Inhibits ActRII signaling in muscle and adipose tissue

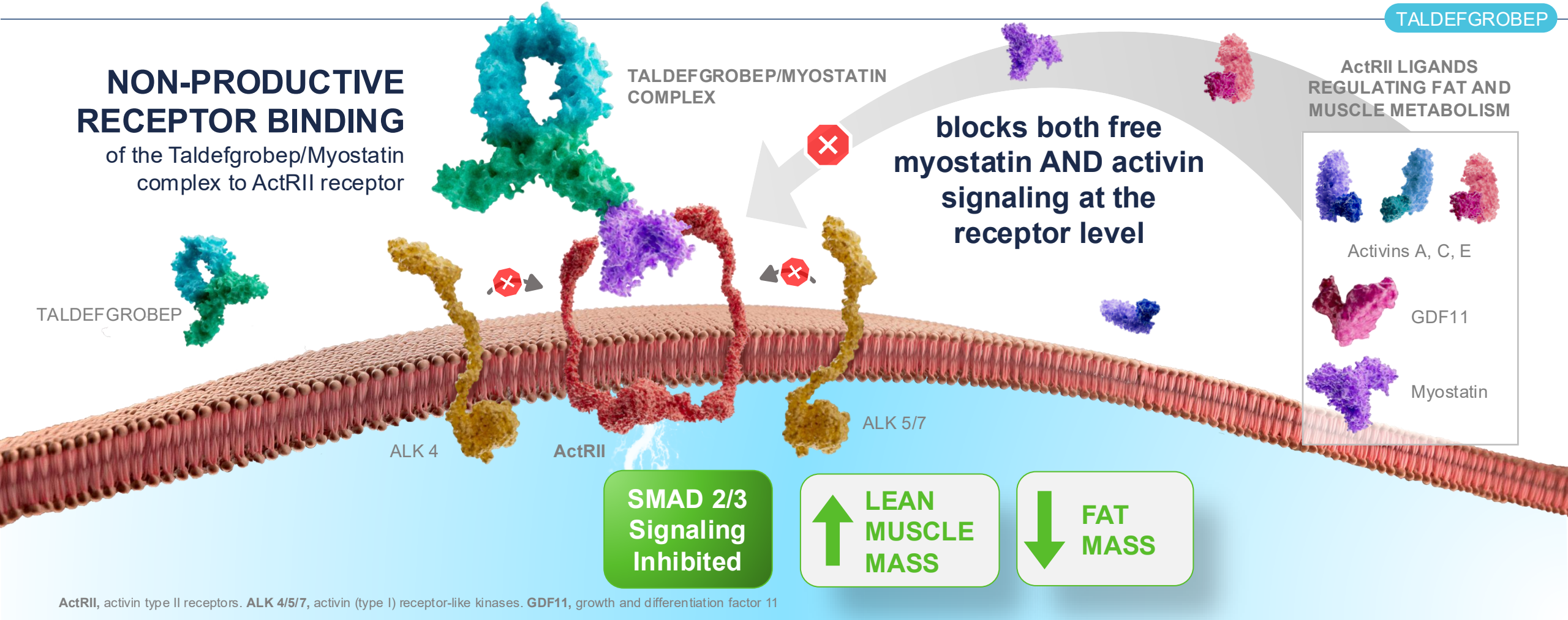
Favorable safety profile established in >700 treated to date
Low rates of muscle- and GI-related AEs

Convenient dosing
Administration by subcutaneous autoinjector

BREAKING NEWS

Phase 2 proof-of-concept study topline expected 2H 2026

Taldefgrobep Is a Novel Competitive Inhibitor of ActRII Signaling



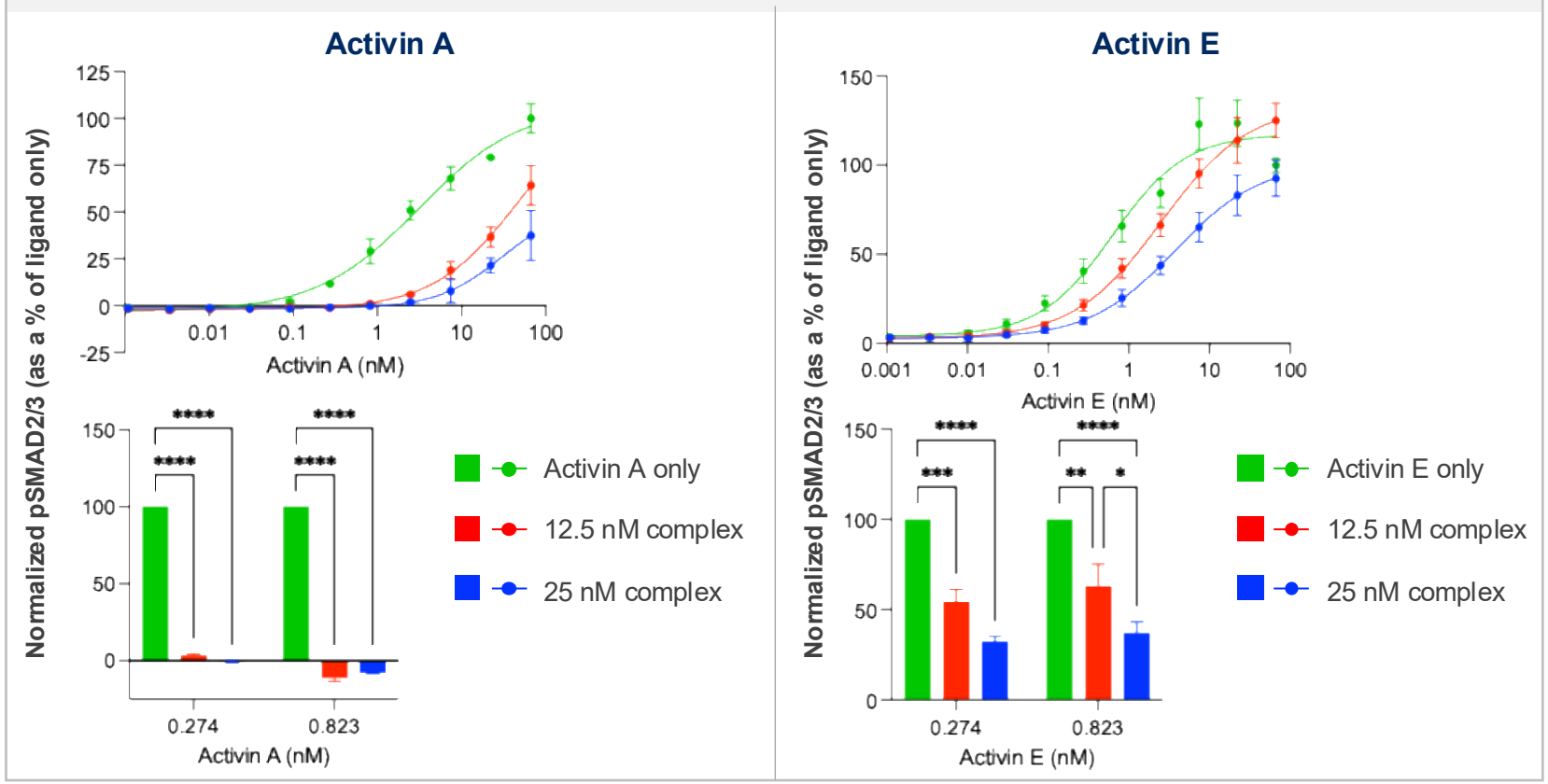
ActRII, activin type II receptors. **ALK 4/5/7,** activin (type I) receptor-like kinases. **GDF11,** growth and differentiation factor 11

KEY POINT

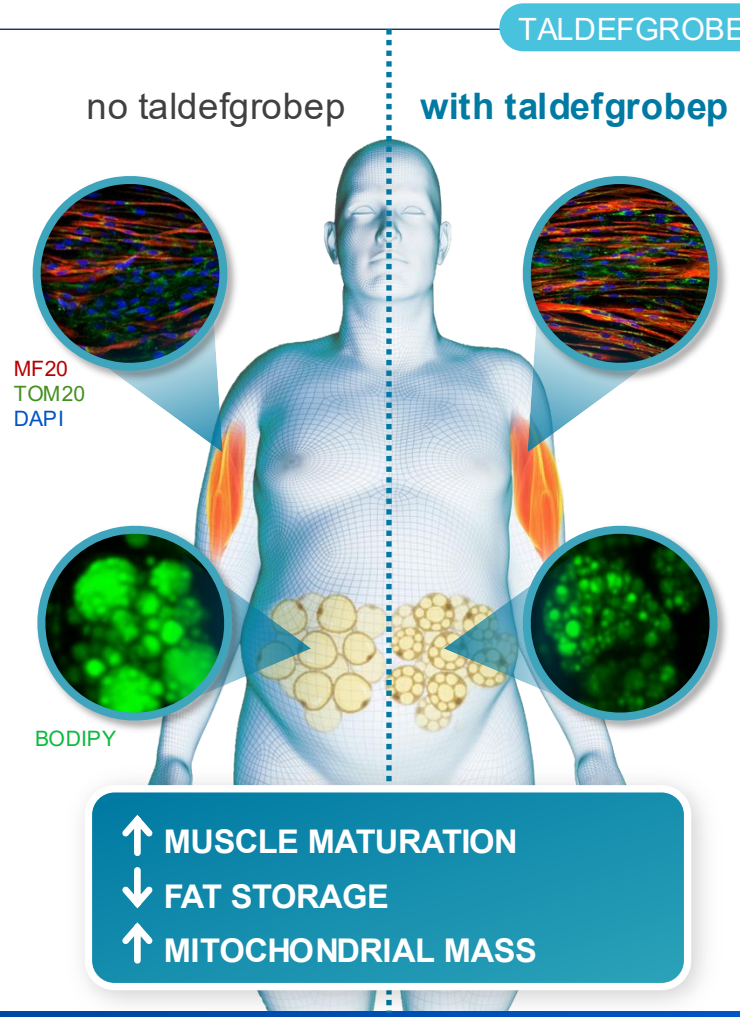
Taldefgrobep binds ligands and competitively inhibits receptor activation in tissues where myostatin and multiple activins (e.g., A, C, E) are active

Taldefgrobep/Myostatin Complex Competes With Activin Signaling To Improve Muscle Differentiation and Fat Storage

T/M Complex Inhibits Activin-Induced Signaling Through ActRII



*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001



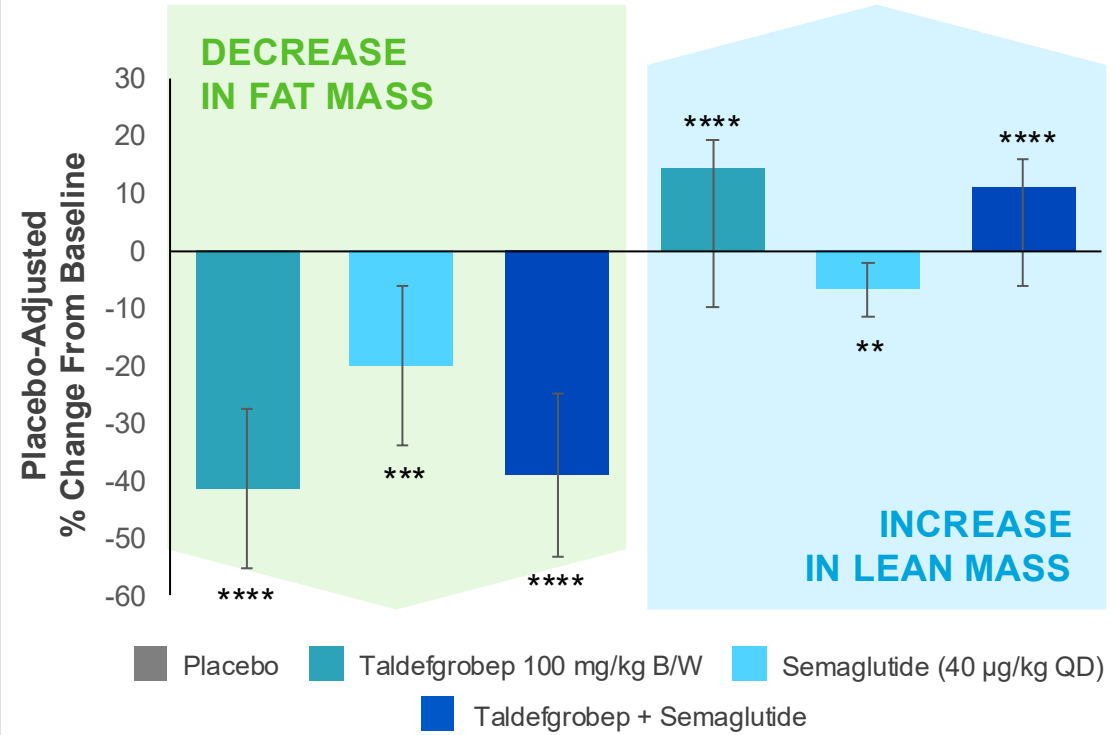
KEY POINT

The T/M complex, at clinically relevant exposures, inhibits activin A- and activin E-induced ActRII signaling

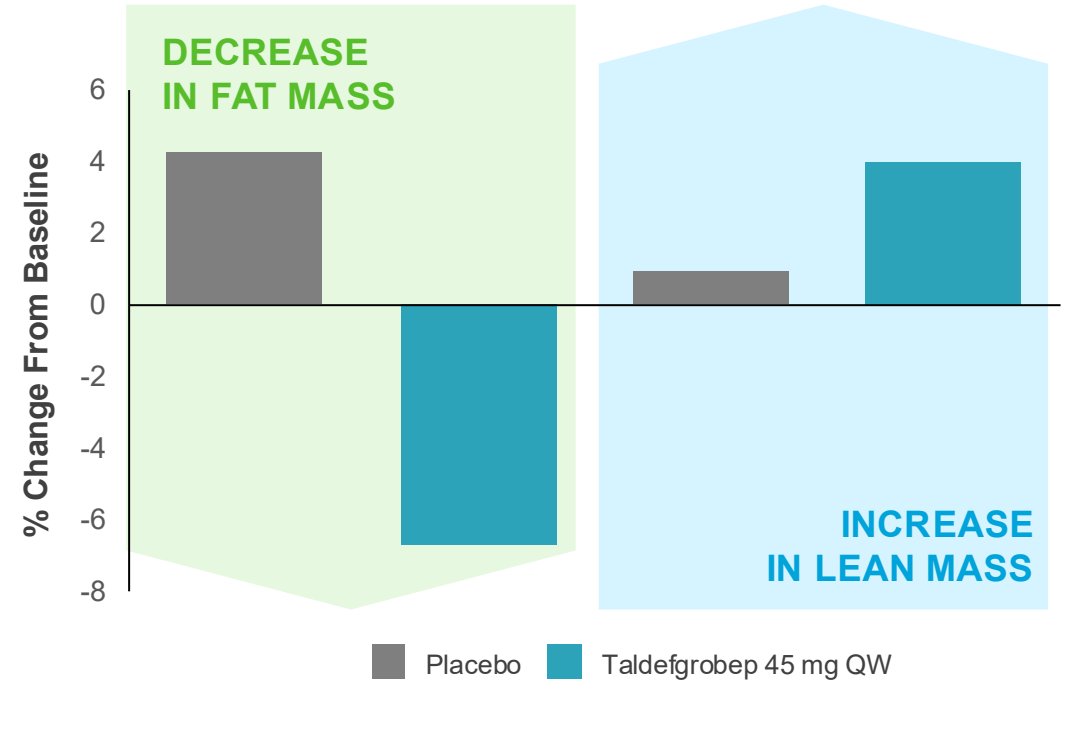
Taldefgrobep Improves Body Composition in Obese Mouse Model and Non-Obese Adults

TALDEFGROBEP

In Obese Mouse Model, Taldefgrobep Demonstrated Significant Reductions in Fat Mass While Increasing Lean Mass



In Healthy Adults, after One Month of Dosing[1], Taldefgrobep Demonstrated Meaningful Reductions in Fat Mass and Increases in Lean Mass



n=15 for vehicle; n=16 for all other groups. Error bars represent 95.00% CI of diff. Significance evaluated using Tukey's multiple comparisons test. **P < 0.01; ***P < 0.001; ****P < 0.0001; **QD,** once daily; taldefgrobep alfa. Bechtold. ObesityWeek 2024. Poster 350. **1.** CN001001 CSR, Day 57 data. **2.** Heymsfield. JAMA Network Open. 2021. **3.** Garito. Diabetes Obes Metab. 2018.

KEY POINT

In non-obese adults, taldefgrobep-induced changes in body composition are comparable to bimagrumab[2,3]

Taldefgrobep Has an Established, Favorable Safety Profile

Safety database includes **more than 700** treated trial participants

Assessed across a **wide dose range** (4 mg to 180 mg SC QW) and **broad demography**

Data from repeat dosing up to **192 consecutive weeks**

- **LOW RATES** of SAEs and AEs leading to discontinuation
- **LOW RATES** of GI- and muscle-related AEs commonly reported with other myostatin-activin pathway inhibitors
- **No identified serious signature clinical safety events**

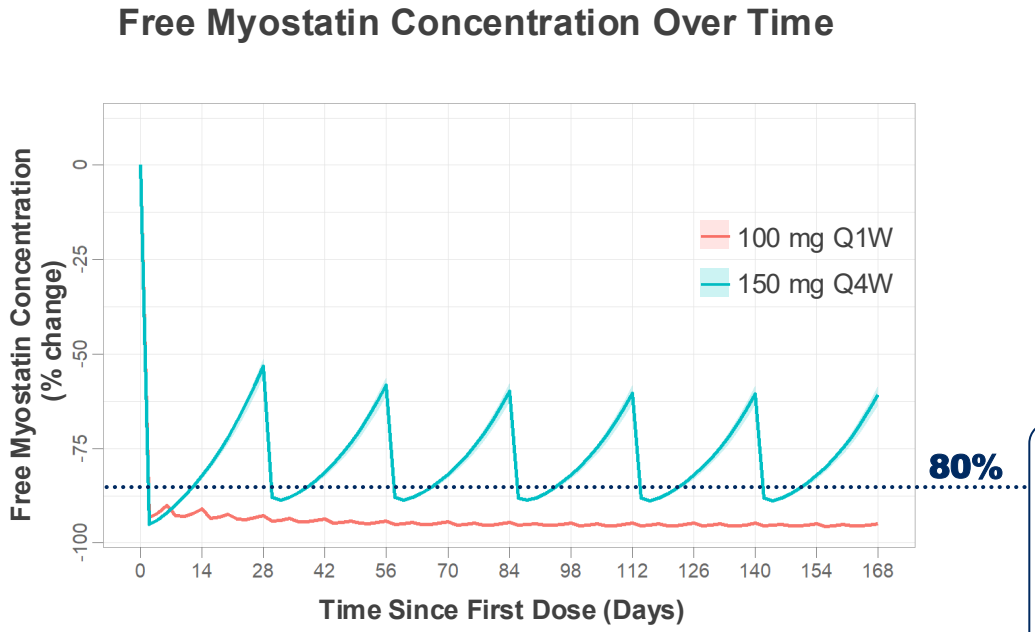
KEY POINT

Safety profile well-suited for indication in chronic weight management

Taldefgrobep PK/PD Modeling Supports Convenient SQ Dosing in Adults With Obesity

TALDEFGROBEP

Pharmacodynamics of Taldefgrobep Weekly and Monthly Dosing



MODELING FOR DOSE SELECTION:

- Population PK/PD model using target-mediated drug disposition (TMDD) was developed to simulate taldefgrobep pharmacokinetics, free myostatin suppression and taldefgropeb/myostatin (T/M) complex concentrations in an obese population
- The model incorporated body weight effects on clearance, volume of distribution and relative bioavailability
- Using demographics from NHANES, simulations were conducted in 500 virtual adults with a BMI of 30-40 kg/m^2

MODELING PREDICTS:

- Taldefgrobep 100 mg Q1W and 150 mg Q4W should suppress free myostatin >80%
- T/M complex concentrations should exceed the established IC_{50} associated with ActRII signaling at both dose levels

KEY POINT

Taldefgrobep 100 mg Q1W and 150 mg Q4W are predicted to suppress free myostatin and yield T/M complex concentrations that competitively inhibit ActRII signaling

Timothy R. Smith, MD, RPh
Senior Medical Director
StudyMetrix Research

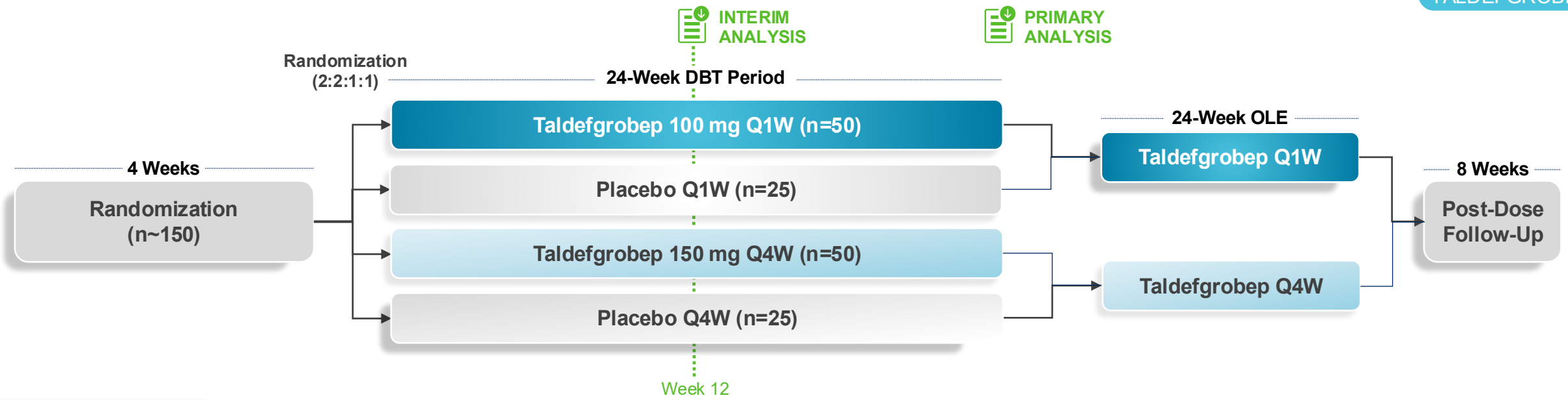
StudyMetrix Research

Ongoing Phase 2 Proof-of-Concept Study in Obesity

biohaven®

Ongoing Phase 2 Monotherapy Dose-Ranging (Q1W + Q4W) Study

TALDEFGROBEP



KEY STUDY DETAILS

Study Design: Phase 2, randomized, double-blind, placebo-controlled dose-ranging study

Population: Male and female adults (18 to 65 years-old) with overweight or obesity

Blinded Interim Analysis (when 30% complete Week 12)**:** Taldefgrobep PK/PD (free myostatin and T/M complex concentrations) and plasma lipids by treatment assignment

Endpoints: % change in total body weight, fat mass and lean mass at Week 24. Whole-body MRI in subset

KEY POINT

PK/PD interim analysis completed
Topline primary analysis expected 2H 2026

Baseline Demography by Q1W vs. Q4W, Taldefgrobep + Placebo

TALDEFGROBEP

Parameter	Q1W (n=79)	Q4W (n=78)
Age, years, mean (SD)	46.6 (11.59)	48.1 (10.93)
Sex, female, n (%)	53 (67.1)	53 (67.9)
Race, n (%)		
White	59 (74.7)	57 (73.1)
Black	13 (16.5)	15 (19.2)
Asian	2 (2.5)	2 (2.6)
Other	5 (6.3)	4 (5.1)
Ethnicity, Hispanic/Latino, n (%)	24 (30.4)	25 (32.1)
TBW, kg, mean (SD)	99.2 (14.01)	101.1 (14.17)
WHtR, mean (SD)	0.7 (0.05)	0.7 (0.06)
BMI, kg/m^2, mean (SD)	35.3 (3.32)	35.5 (3.49)
BMI ≥35 kg/m^2, n (%)	40 (50.6)	41 (52.6)
HbA1c, %, mean (SD)	5.5 (0.34)	5.5 (0.32)

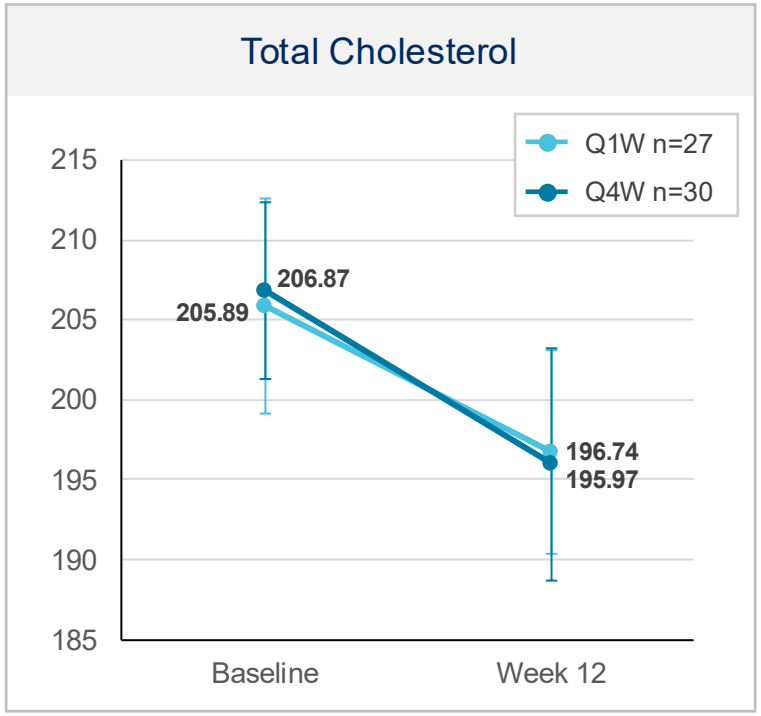
TBW, Total Body Weight; **Kg,** kilograms; **WHtR,** Waist-to-Height Ratio; **BMI,** Body Mass Index; **M²,** meters squared; **HbA1c,** Hemoglobin A1c; **SD,** Standard deviation

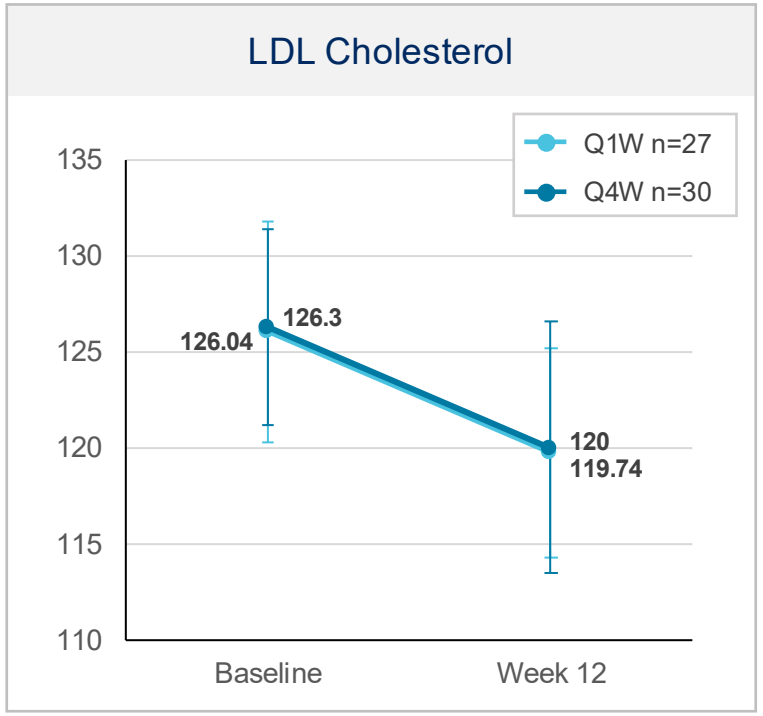
KEY POINT

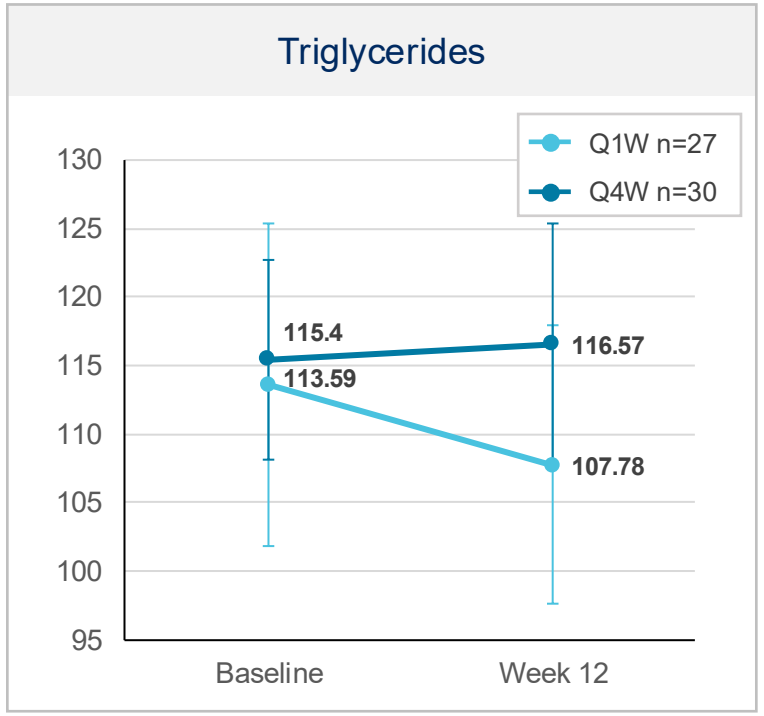
Baseline characteristics evenly distributed across the treatment groups and consistent with standard obesity trial population

Blinded Interim Data by Q1W vs. Q4W, Taldefgrobep + Placebo
No Adverse Effects on LIPIDS at Week 12

TALDEFGROBEP







- No treatment-emergent G2-4 elevations in total cholesterol or triglyceride values
- 1 participant with emergent G3 LDL elevation; had G2 elevation at Baseline

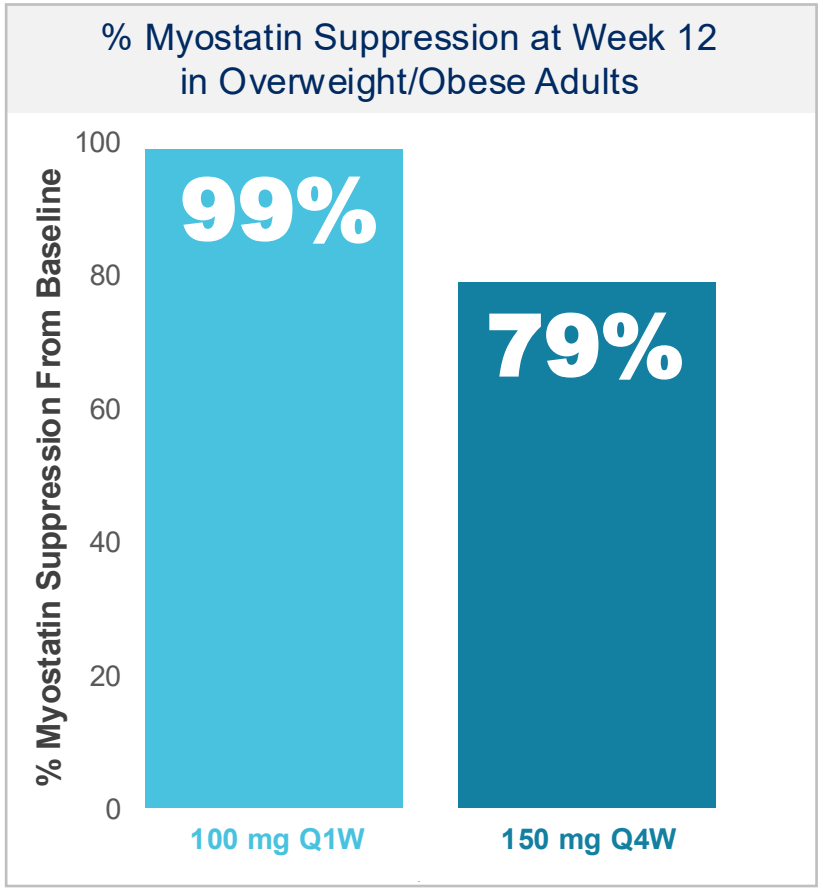
Error bars represent Standard Error

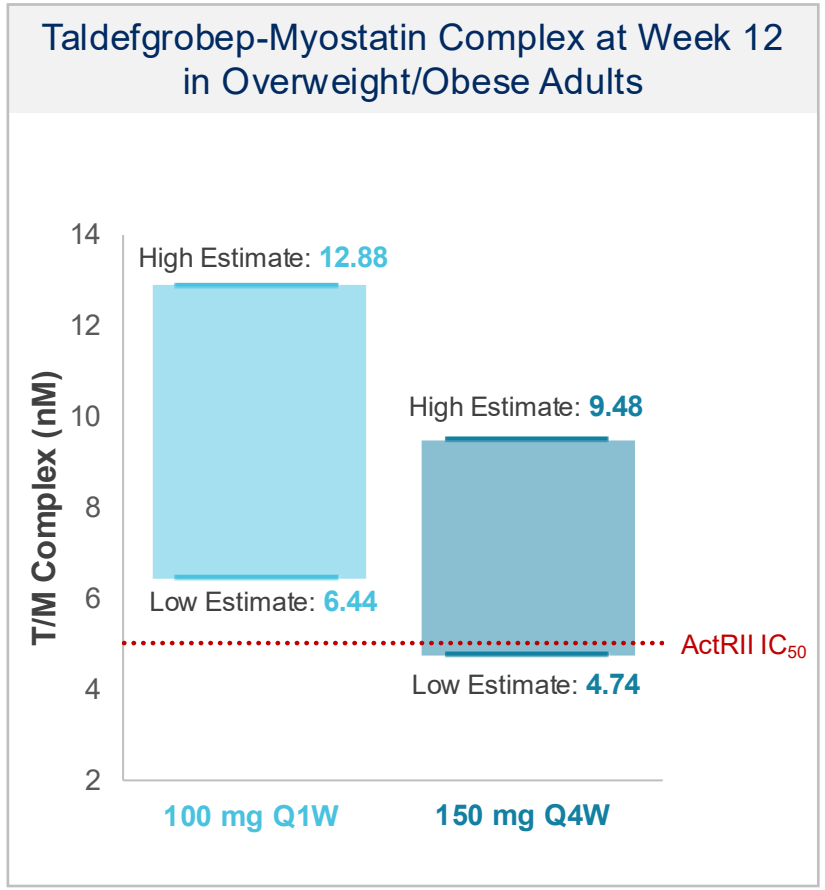
KEY POINT

No identified adverse trends in lipid parameters demonstrating differentiated safety from other myostatin-activin pathway inhibitors

Interim Phase 2 PK/PD Data Supports Weekly and Monthly Dosing in Obesity

TALDEFGROBEP





AT WEEK 12:

- Observed mean taldefgrobep concentrations are consistent with model-predicted
- Robust suppression of free myostatin throughout Q1W and Q4W dosing intervals
- T/M complex concentrations comparable between dosing regimens and at/above target ActRII IC_{50}

KEY POINT

Interim data suggest monthly dosing can achieve robust myostatin suppression and formation of T/M complex levels at/above targeted ActRII IC_{50} levels

Peter Ackerman, MD

Senior Vice President,
Clinical Development

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Taldefgrobep for Obesity – Potential for Differentiated Benefit Across a Broad Patient Population

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Taldefgrobep Offers a Novel Approach To Address the Needs for People Living With Obesity

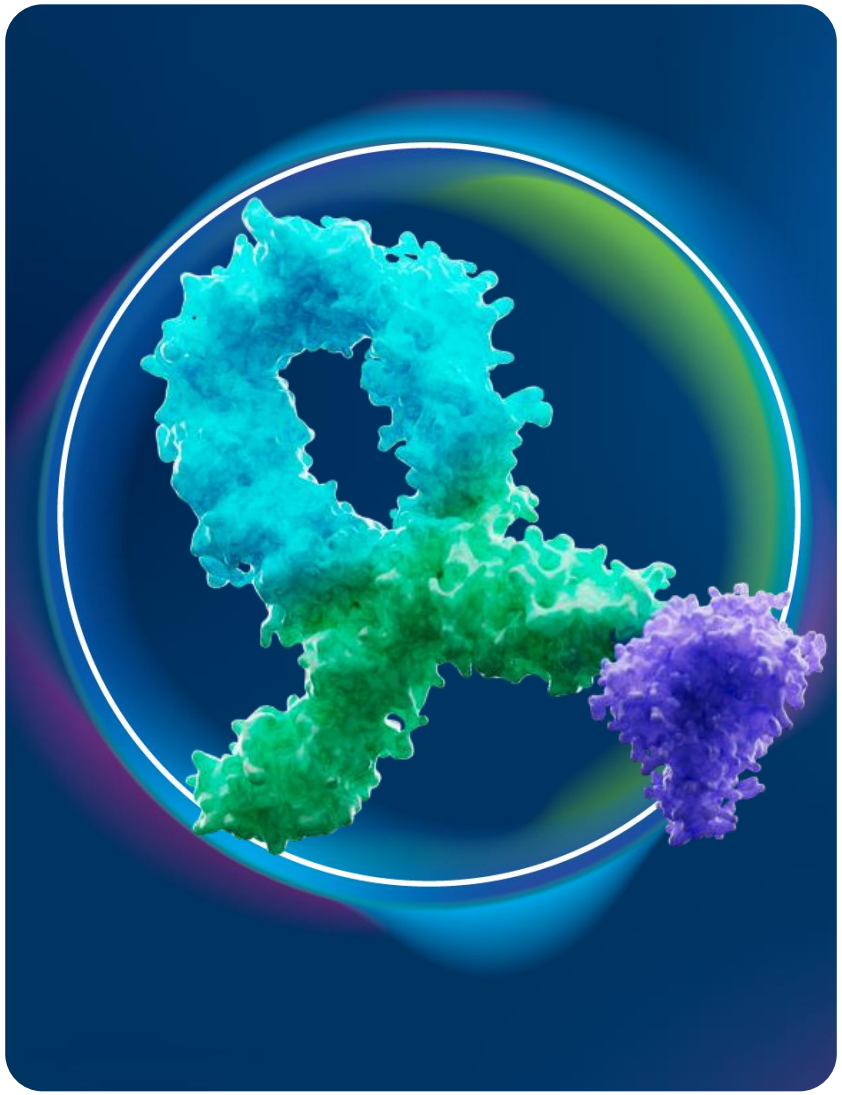
TALDEFGROBEP

Total body weight loss meeting current regulatory standards

Benefit as monotherapy and in combination with GLP-1 therapies

Convenient subcutaneous autoinjector with potential for monthly dosing

Favorable safety and tolerability



Fat mass loss comparable to GLP-1 therapies

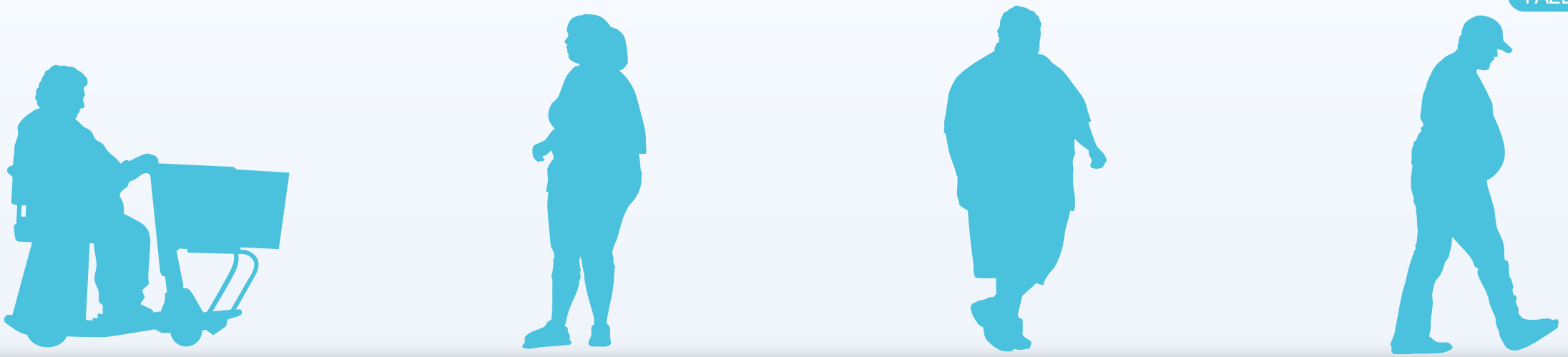
Visceral adipose tissue loss favorable to GLP-1 therapies

Increase in lean muscle mass highly differentiated from GLP-1 therapies

Increase in bone density favorable to GLP-1 therapy

Taldefgrobep Can Benefit a Broad Spectrum of People Living With Obesity

TALDEFGROBEP



6.6M-10M
Older patients at risk of sarcopenia

5-8M
People intolerant or refractory to GLP-1

5-7M
People living with BMI ≥40

5-10M
People unable to tolerate high dose GLP-1

MONOTHERAPY

GLP-1 ADJUNCT

Source: BHVN Market Research and Analytics Data on file

KEY POINT

Meaningful reductions in fat mass, preservation of lean muscle mass, once-monthly dosing and high tolerability drive market potential

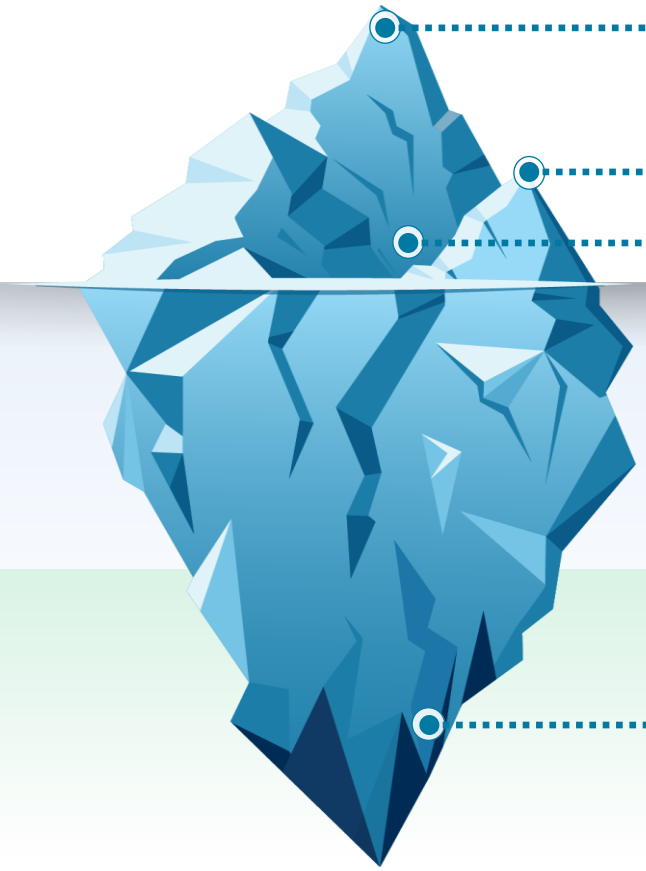
A Shift Toward Body Composition Targets Expands the Market Opportunity for Taldefgrobep

TALDEFGROBEP

Obesity

Overweight

Enhanced Body Composition



EXTREME OBESITY GLP-1 REFRACTORY

GLP-1 ADJUNCT

GLP-1 INTOLERANT

HEALTHY WEIGHT AND BODY COMPOSITION MANAGEMENT

KEY POINT

Obesity may be the category's tip of the iceberg

Panel

MODERATOR

Amy Li

Equity Analyst

Jefferies

PANELISTS

Donna H. Ryan, MD
Professor Emerita
Pennington Biomedical Research Center

Timothy R. Smith, MD, RPh
Senior Medical Director
StudyMetrix Research

Peter Ackerman, MD
Senior Vice President, Clinical Development
Biohaven

BHVN
LISTED
NYSE

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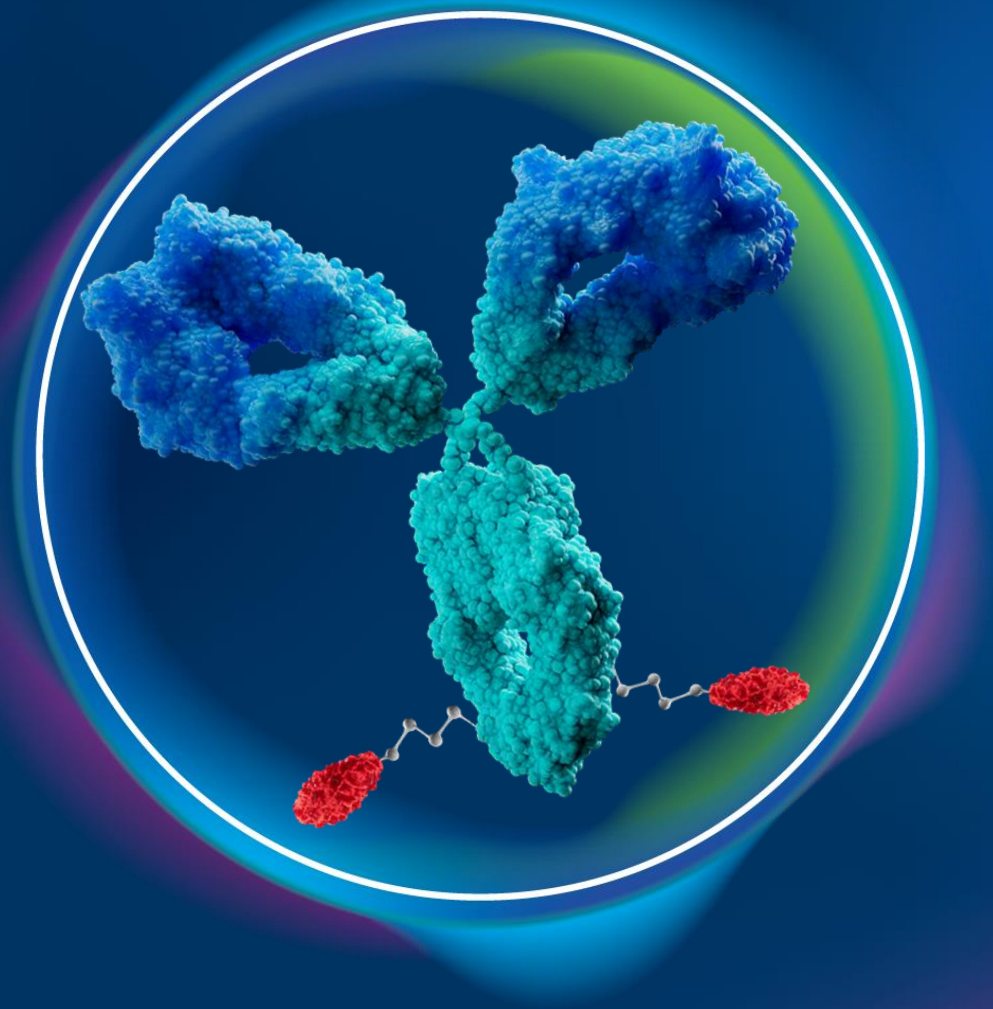
ONCOLOGY

Modular Next-Generation ADC Technologies: Optimizing for Clinical Performance



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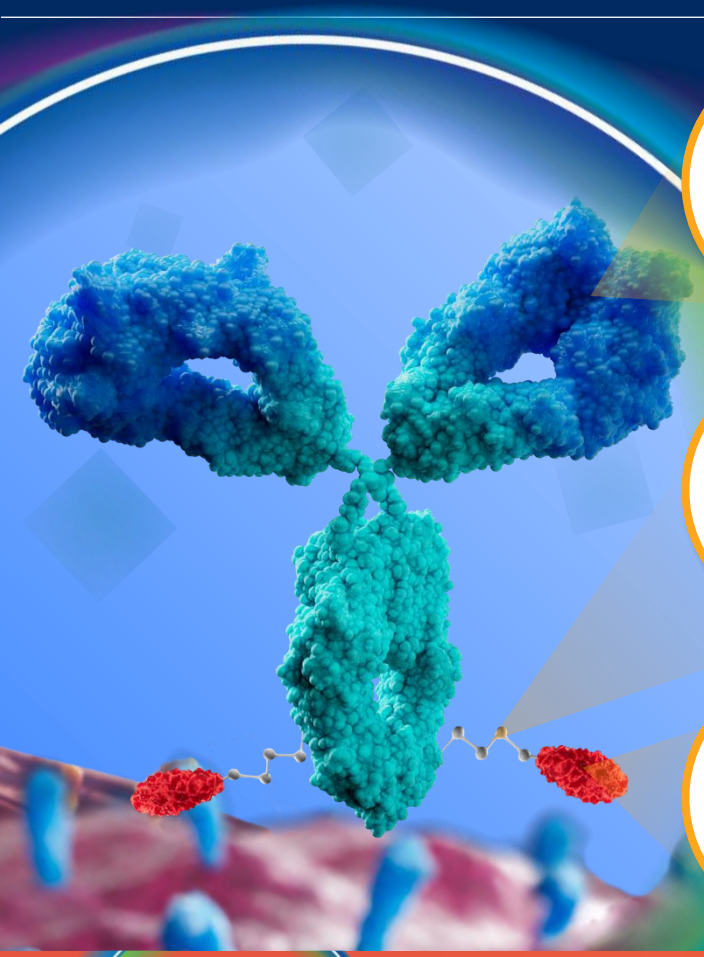
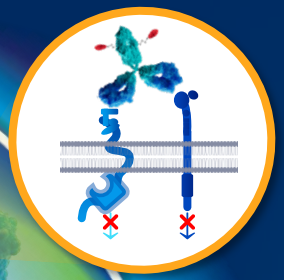
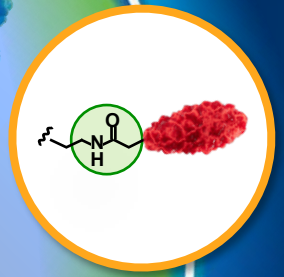
Innovative Biohaven Technologies Enabling Differentiated Next-Generation ADCs

ONCOLOGY

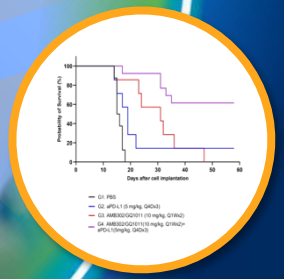




OPTIMIZED MONO AND BISPECIFIC MABS



NEXT-GEN MODULAR ADC CONJUGATION TECHNOLOGIES



PROPRIETARY TOPOIX AND MULTI-CLASS PAYLOADS

Clinical Proof-of-Principle Establishing the Power and Flexibility of the Platform to Optimize Across Broad Range of ADC Designs and Combination Strategies Including CPI

First clinical demonstration (BHV-1510 Trop2)
Highly stable, differentiated PK and safety, compelling activity with CPI combination

First-in-class potential FGFR3 ADC (BHV-1530)
Novel mAb, potential to address both FGFR3 alterations and overexpression

Platform tech enables multi-class payload loading
Clinically differentiated TopoIx payload, foundational for CPI and other potentially synergistic MOA combinations

BREAKING NEWS

- **BHV-1510:** Robust enrollment in endometrial + cemiplimab combination expansion cohort
- **BHV-1530:** First activity observed, including pretreated FGFR3-altered urothelial cancer patient
- **Discovery:** Preclinical data supporting next-wave bispecific mAb, multi-payload formats

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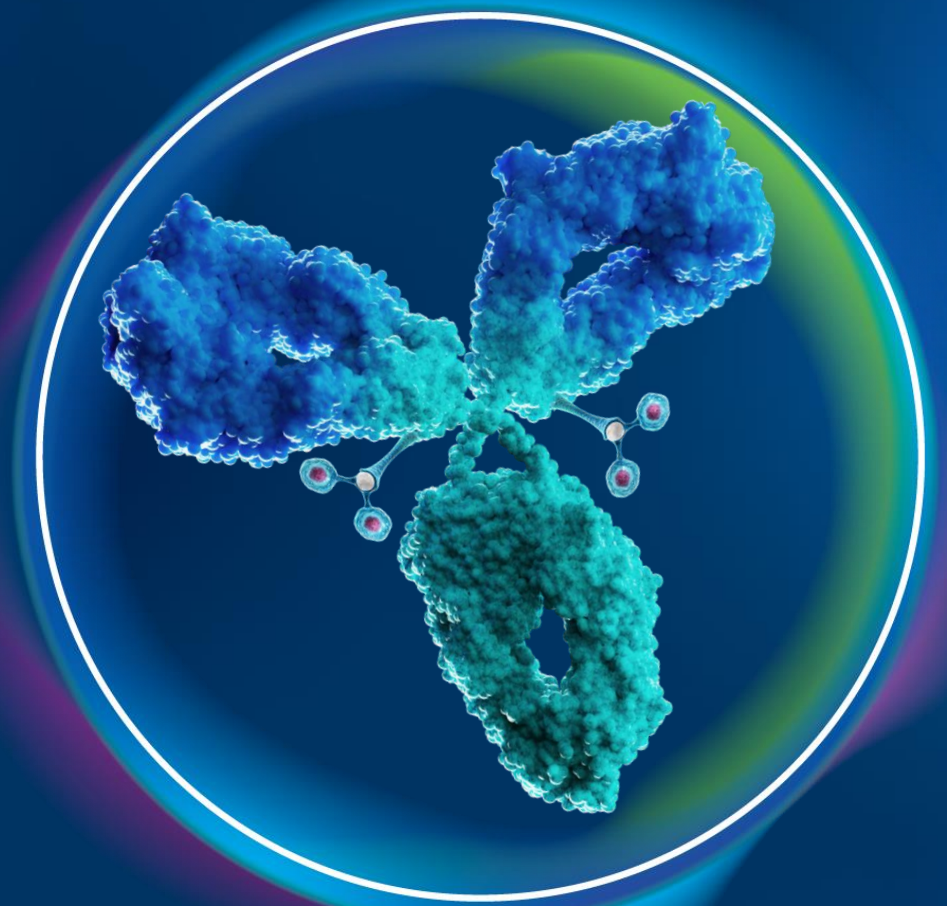
BHV-1510

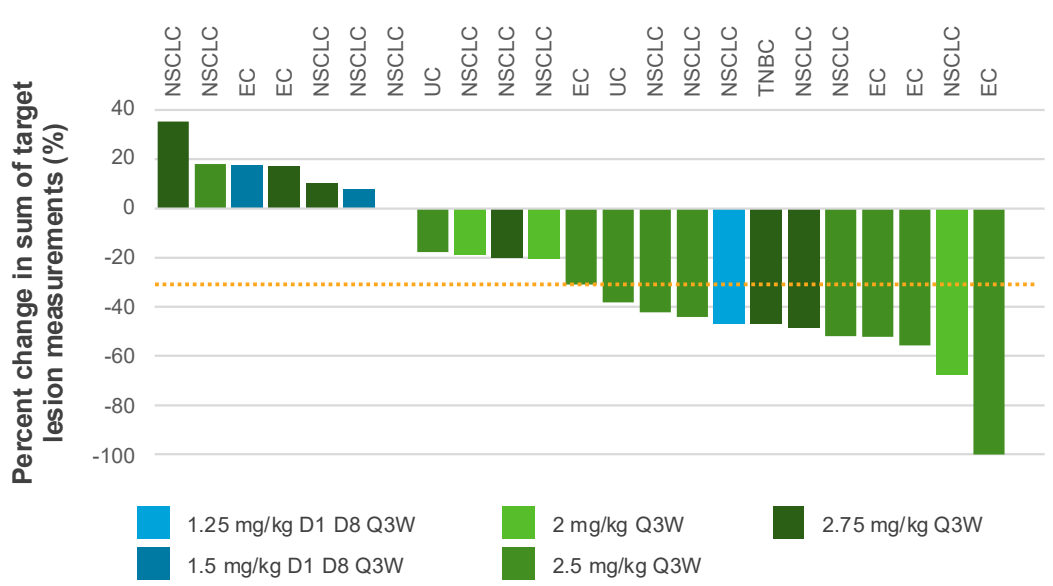
Trop2 ADC



BHV-1510 + Cemiplimab Leads to Rapid, Deep and Durable Responses in Heavily Pretreated Patients, Majority With Prior Anti-PD(L)1

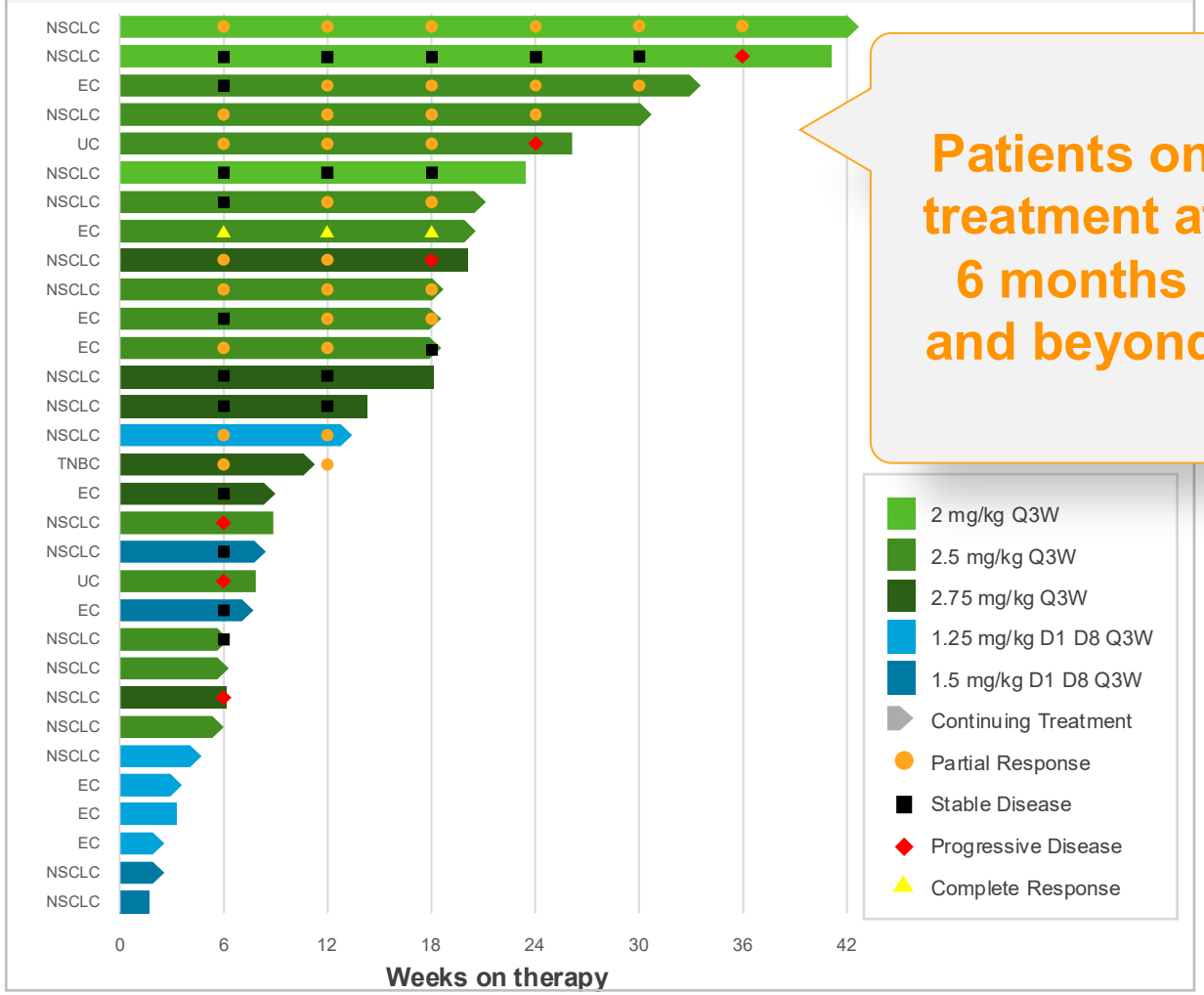
ONCOLOGY

BHV-1510 + Cemiplimab*: Percent Change in Target Lesions



Majority (87.1%) had prior anti-PD(L)1 exposure

BHV-1510 + Cemiplimab: Treatment Duration



Patients on treatment at 6 months and beyond

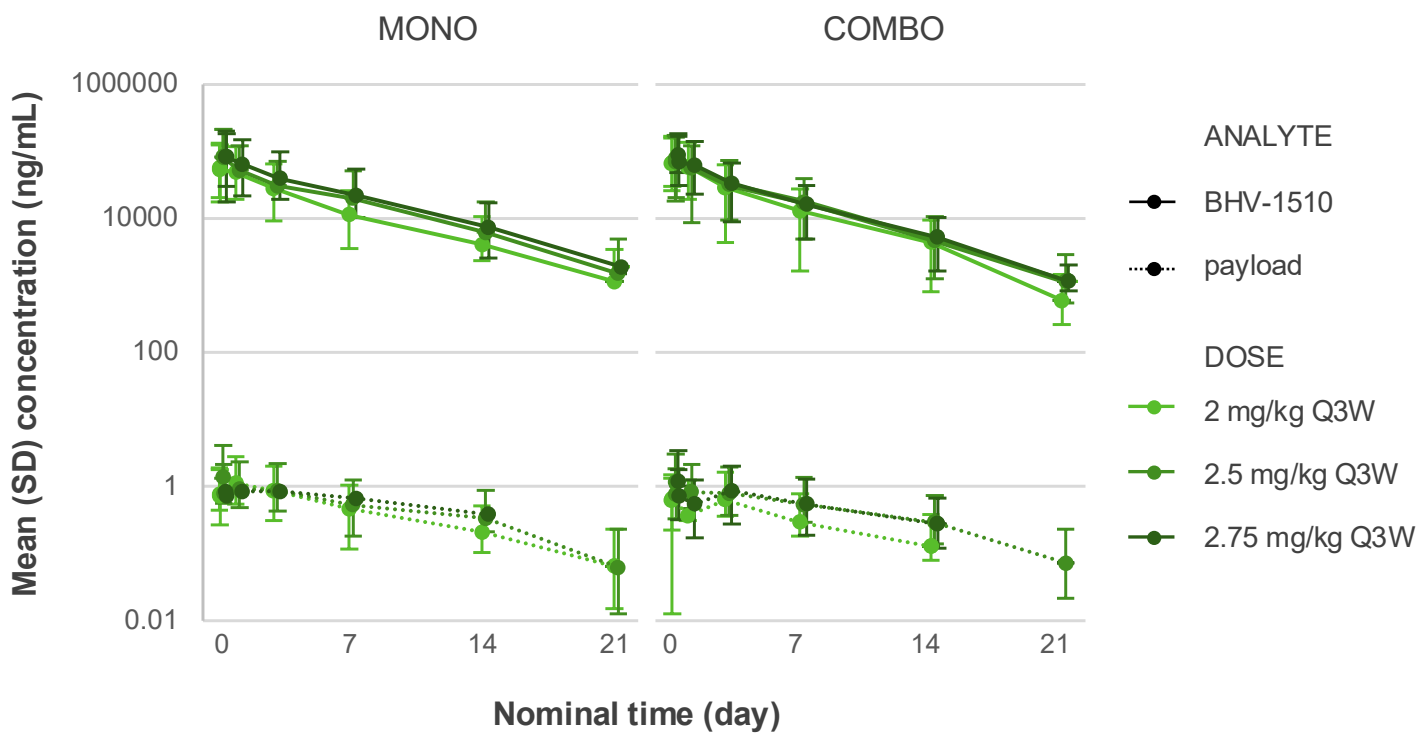
*Cemiplimab (anti-PD1) provided through a supply agreement with Regeneron; dose of cemiplimab 350 mg Q3W

Source: Micaily. ESMO Immuno-Oncology Congress 2025. Poster 252P.

BHV-1510 Demonstrates a Favorable PK Profile With Highly Stable ADC

ONCOLOGY

BHV-1510 (ADC) and Payload Concentration-Time Plots for Cycle 1 (with or without Cemiplimab)



Source: Micaily. ESMO Immuno-Oncology Congress 2025. Poster 252P.

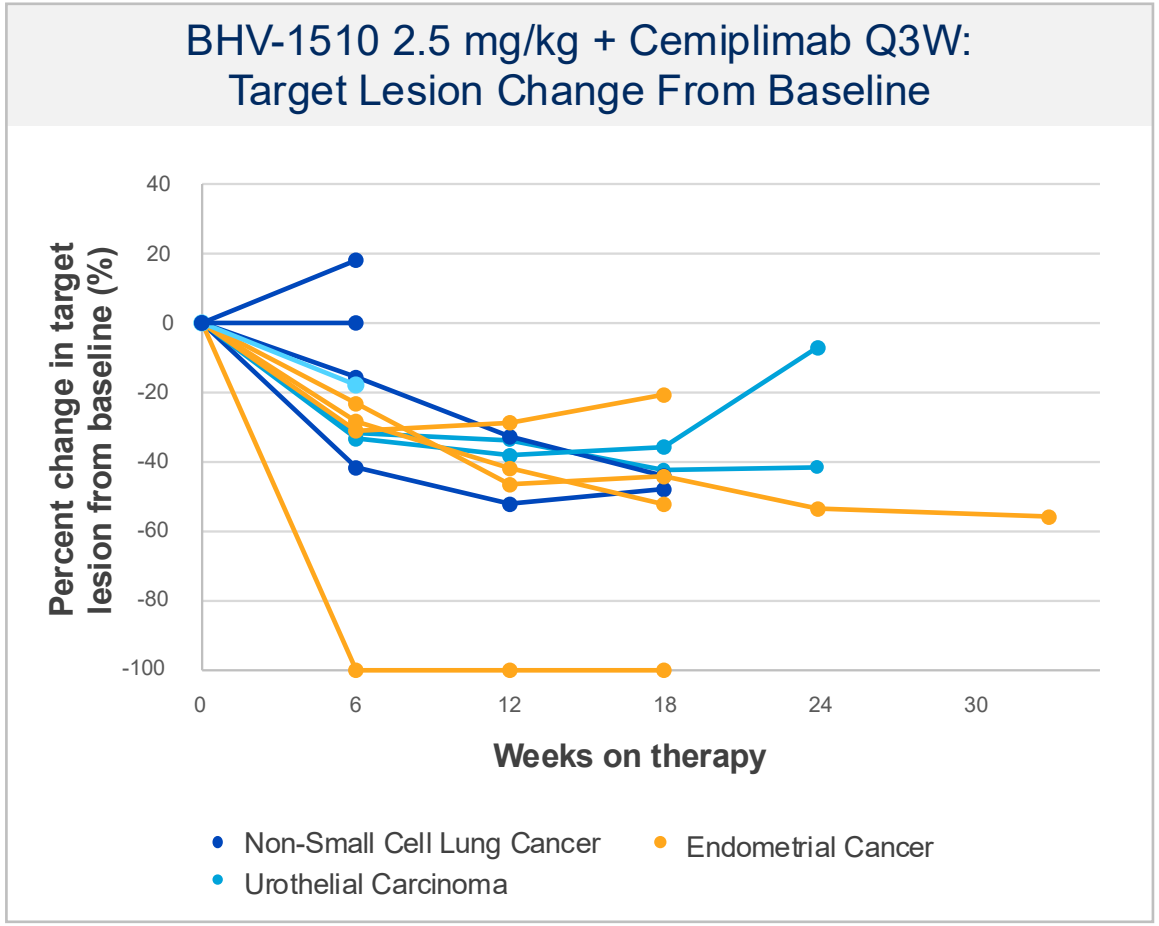
KEY POINT

The unconjugated payload concentration was low with a payload-to-ADC molar ratio <1%, indicating that ADC was highly stable in the circulation

Encouraging Early Clinical Activity and High Response Rates of BHV-1510 + Cemiplimab Enable First Tumor-Specific Expansions

ONCOLOGY

- **Dose escalation complete:** Compelling efficacy in difficult-to-treat patients
  - Responses in heavily pretreated patients, including with brain metastases; majority with prior anti-PD(L)1 exposure
- **Rapid onset of benefit:** Tumor shrinkage / PRs at 1st scan
- **Differentiated safety profile:** Low rates of hematological toxicities and diarrhea; no ILD observed*
- **Favorable PK profile:** Highly Stable ADC



* By independent adjudication

Source: Micaily. ESMO Immuno-Oncology Congress 2025. Poster 252P.

KEY POINTS

- **Early data suggests synergy with anti-PD-1 and potential to move into earlier lines**
- **Endometrial cancer expansion cohort with combination enrolling robustly - data to inform pivotal path**

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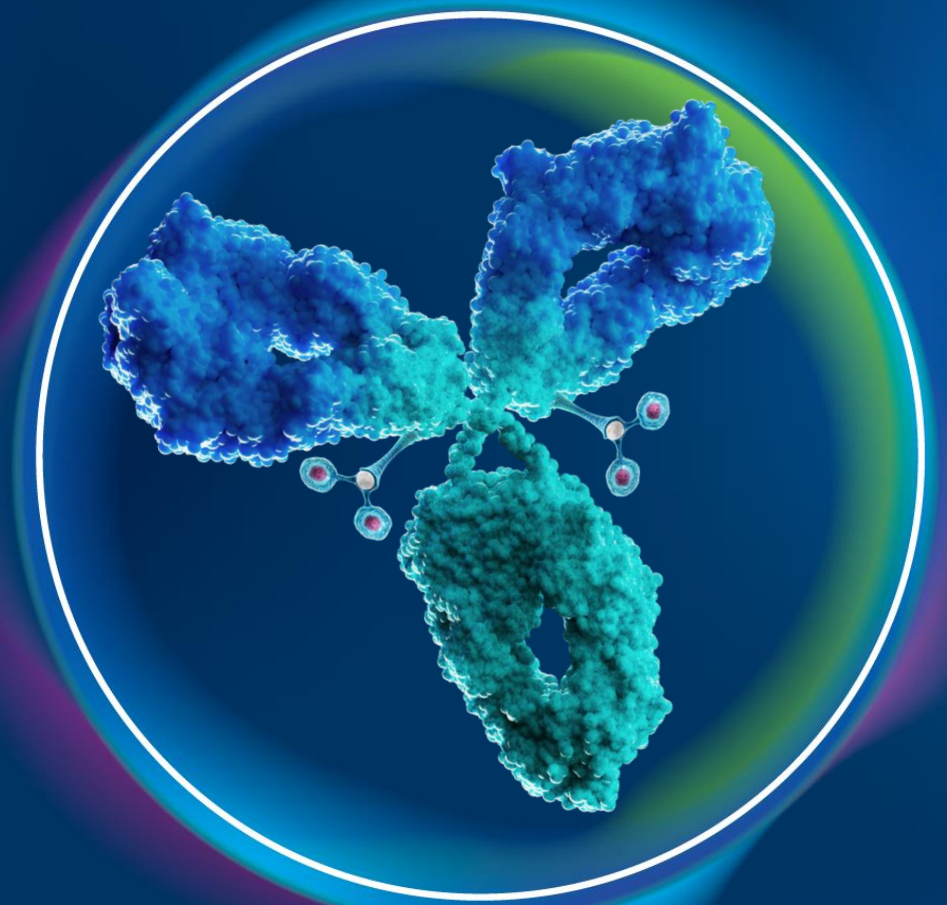
BHV-1530

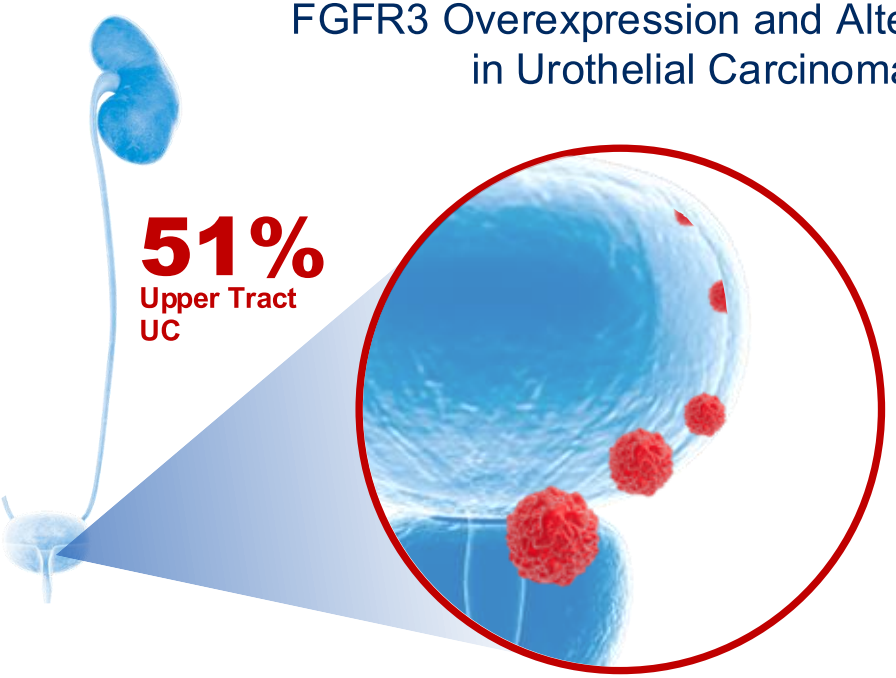
FGFR3 ADC



BHV-1530: Favorable Early Clinical Profile
No FGFR-Class Toxicities and Early Signs of Antitumor Activity

ONCOLOGY

FGFR3 Overexpression and Alteration (%)
in Urothelial Carcinoma



51%
Upper Tract UC

70–80%
Non-muscle-invasive BC

40–60%
Muscle-invasive BC

~50%
Metastatic UC

FGFR3

~50% of HNSCC

~ 40% of NSCLC

4% to ~8% alterations in other cancers

As of April 2026. Data from ongoing study

Compelling preclinical efficacy across FGFR3-altered and FGFR3-overexpressing tumor models:
Demonstrated as monotherapy and in combination with CPI

Clinical progress: First patient dosed April 2025: initial cohorts successfully completed:

- No dose limiting toxicities
- No treatment related SAEs
- TRAEs predominantly mild (Grade 1–2)
- No hyperphosphatemia, nail disorders, central serous retinopathy

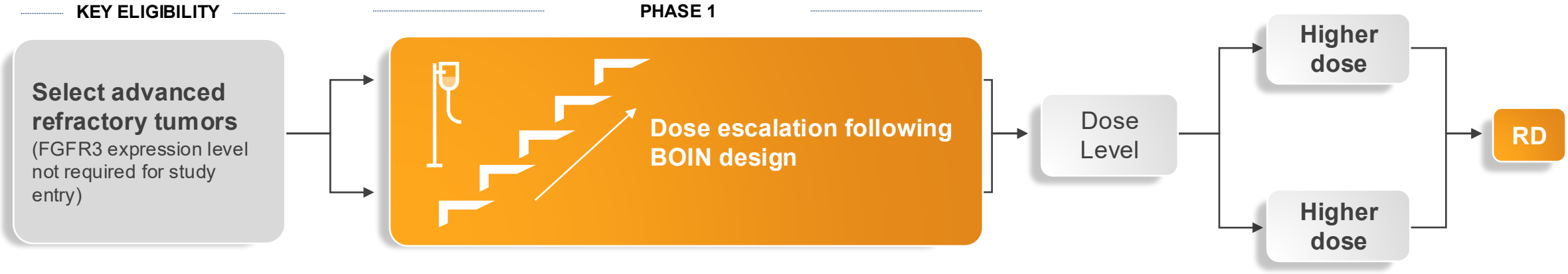
Early signs of activity: Early tumor reduction in patients with FGFR3 alterations and wild-type overexpression, as dosing in the predicted efficacious range

KEY POINT

Early tumor reductions in FGFR3-altered and WT overexpressing patients, including urothelial cancer
Dose escalation continuing with no DLTs to date

BHV-1530: Phase 1 Study in Advanced Tumors

ONCOLOGY



KEY STUDY DETAILS

Study Design: Open label, dose escalation (Ph1)
Population: Advanced UC, HNSCC, NSCLC having failed SOC therapy
Treatment Duration: Until disease progression or toxicity
Endpoints: Safety and tolerability, ORR, PFS, PK and ADA

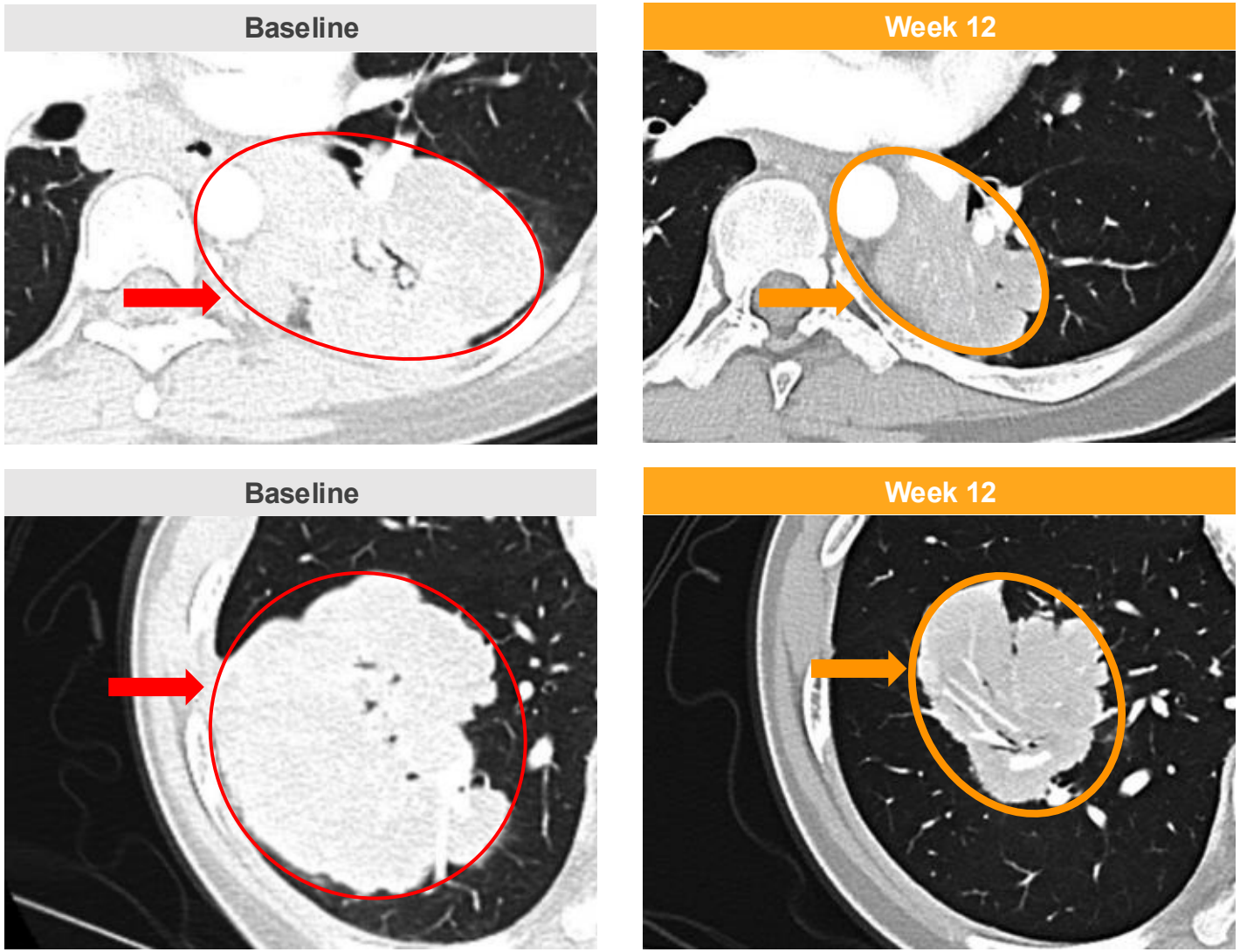
ORR, Overall Response Rate; **PFS,** Progression Free Survival; **ADA,** Antidrug Antibody; **BOIN**, Bayesian Optimal Interval; **RD**, Recommended Dose.

KEY POINT

Early tumor reduction in patients as dosing in the predicted efficacious range

Case Narrative: Metastatic Urothelial Cancer

- 28 y/o female with urothelial cancer with a FGFR3::TACC3 fusion, with metastasis to lungs and thoracic lymph node
- 4 prior lines of therapy including
  - Padcev and Keytruda and 2 FGFR targeting small molecules-Balversa and LOXO-435
- Tolerating treatment with mild nausea and no FGFR related toxicity



BHV-1530: Potential First FGFR3 ADC — Broader Reach, No Class Toxicities, Clear Development Path

BHV-1530 ADC vs. Small-Molecule FGFR3 Inhibitor

	Small Molecule Inhibitor	BHV-1530
Target Population	FGFR3-altered only ~limited addressable population	**Altered AND overexpressing — full FGFR3+ population**
Class Toxicities	Hyperphosphatemia nail disorders, retinopathy	**None observed — no FGFR inhibitor-class toxicities**
Mechanism	Kinase inhibition resistance develops readily	**ADC: targeted delivery of cytotoxic payload**
CPI Combination	Limited — overlapping toxicity concerns	**Engineered for CPI synergy** **TopoIx → ICD →**

DEVELOPMENT ROADMAP

PH1 DOSE ESCALATION
NOW • ACTIVE
- No DLTs; no FGFR-class toxicities
- Early tumor reduction in altered + WT overexpressing

DOSE OPTIMIZATION+POC
- Identify recommended Ph2 dose
- UC expansion POC
- Confirm activity across FGFR3 subtypes

COMBO EXPANSION
- Expansion cohort in UC with CPI combo
- Pivotal design conversations begin

1L mUC - PIVOTAL PATH
- 1L mUC combination with CPI
- Monotherapy in 2L+-selected pts

Summary: BHV-1510 and BHV-1530 Program Milestones and Next Steps

ONCOLOGY

BHV-1510

Trop2 ADC | Solid Tumors (NSCLC • Endometrial Ca • Urothelial Ca)

PRECLINICAL
COMPLETE

Superior cytotoxicity and immunogenic cell death vs. benchmark Topo-I ADCs; strong *in vivo* anti-PD-1 synergy; favorable PK, stability and safety profile

PHASE 1 DOSE ESCALATION
COMPLETE

Mono and PD-1 combo activity across solid tumors; differentiated safety — no ILD, low hematologic toxicity and diarrhea; <1% free payload in circulation

INITIAL PROOF-OF-CONCEPT CLINICAL DATA (ESMO IO 2025)
COMPLETE

BHV-1510 + Cemiplimab: rapid, deep, durable responses in heavily pretreated patients; most had prior anti-PD(L)1 exposure

PHASE 2 EXPANSION — ENDOMETRIAL CANCER
ACTIVE

Expansion cohort with anti-PD-1 combination enrolling; early efficacy readouts to inform pivotal path in endometrial cancer

BHV-1530

FGFR3 ADC – Potential First Urothelial Carcinoma ADC targeting • FGFR3-Driven Tumors

PRECLINICAL
COMPLETE

Robust antitumor activity in FGFR3-altered and overexpressing models - expanding addressable biology vs. small molecules; CPI combination synergy; superior efficacy vs. erdafitinib and EV

PHASE 1 DOSE ESCALATION — UC AND FGFR3-DRIVEN TUMORS
ACTIVE

Ongoing — no DLTs observed; no FGFR inhibitor-class toxicities; high systemic stability; early clinical activity as dosing in predicted efficacious range

NEAR-TERM: POC AND EXPANSION DATA
UPCOMING

Multiple near-term value drivers from dose-escalation readouts; proof-of-concept data expected to trigger expansion cohorts in UC and beyond

STRATEGIC PATH: 1L mUC + BROAD EXPANSION
UPCOMING

Clear path into 1L metastatic UC and earlier disease settings; mono and combination potential; expansion to NSCLC, HNSCC and other FGFR3-high tumors

Source: Biohaven data on file; Micaily. ESMO Immuno-Oncology Congress 2025. Poster 252P. **ADC**, antibody–drug conjugate; **ICD**, immunogenic cell death; **EV**, enfortumab vedotin; **mUC**, metastatic urothelial carcinoma.

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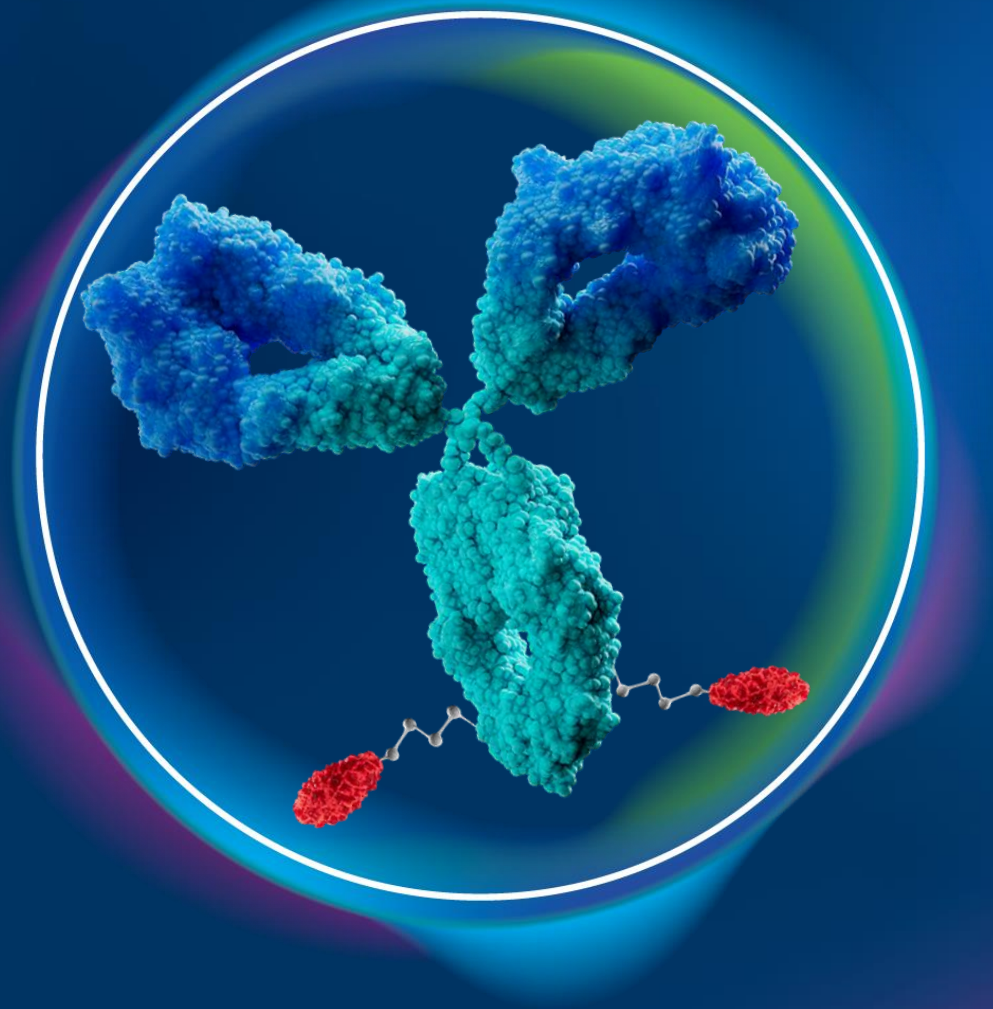
ADC DISCOVERY PLATFORM

Biohaven Technologies Enabling Next Wave of Differentiated ADCs



David Pirman, PhD

SVP and Head of Drug Discovery

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Next-Generation ADCs

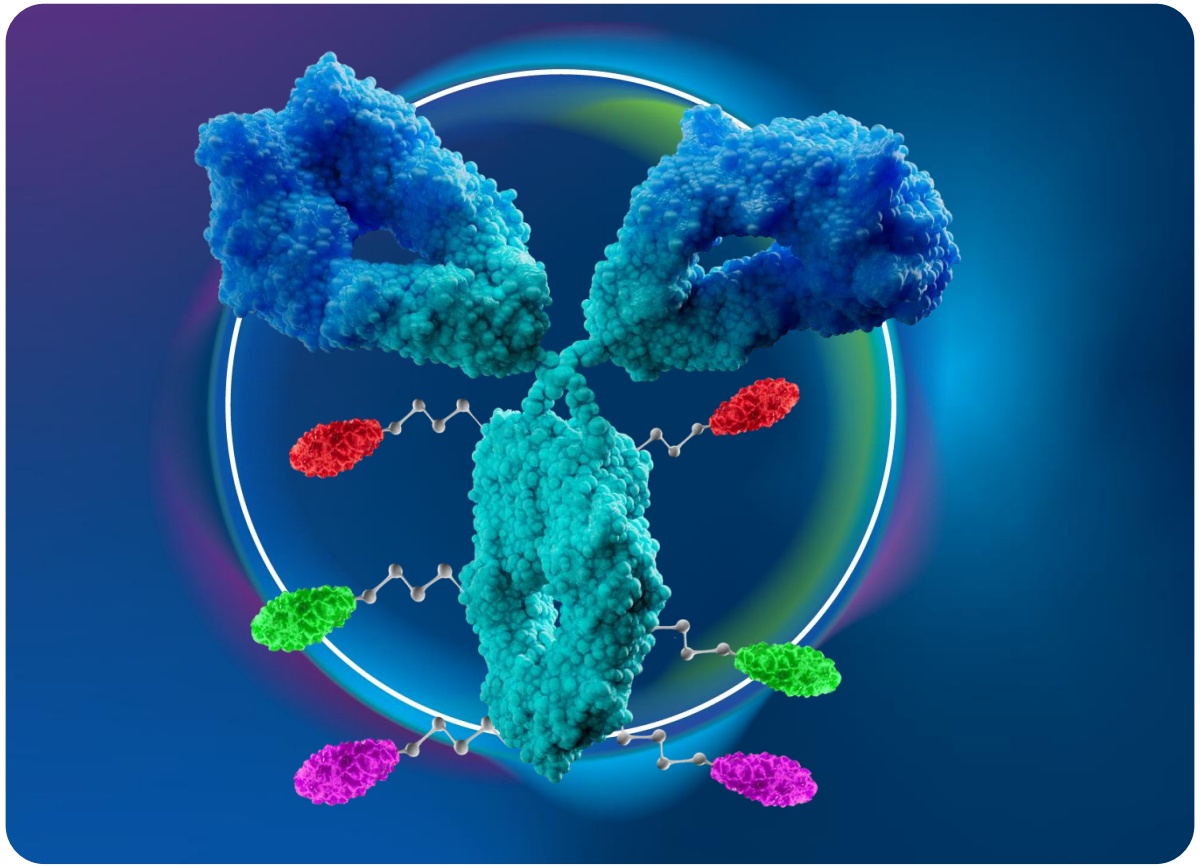
biohaven®

Leveraging Unique Modular Technologies To Overcome Key Clinical Limitations of Current-Generation ADCs

ONCOLOGY

Novel **mono- and bi-specific mAbs** against validated and emerging targets

Affinity tuned mAbs to improve tumor penetrance and limit off-target toxicities



Synergistic **multi-payload** optionality with **diverse MOA** to overcome resistance from conventional ADC

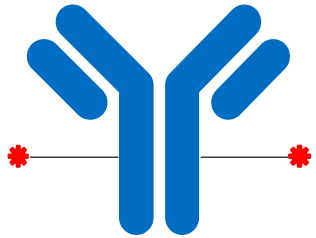
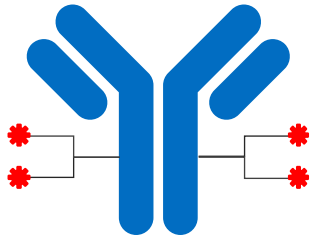
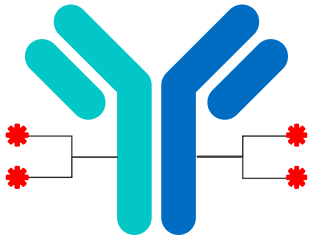
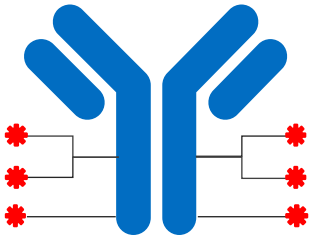
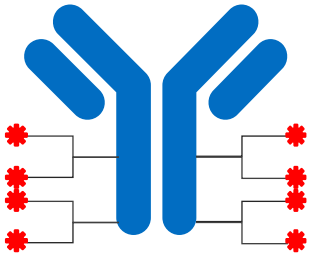
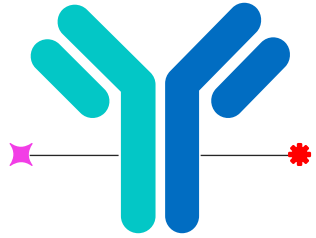
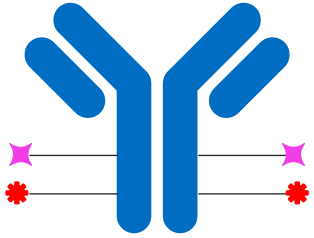
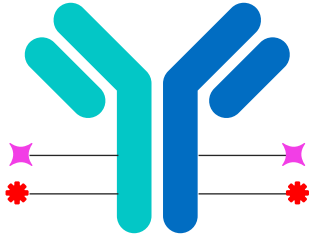
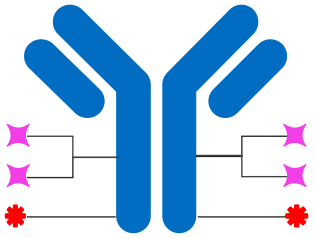
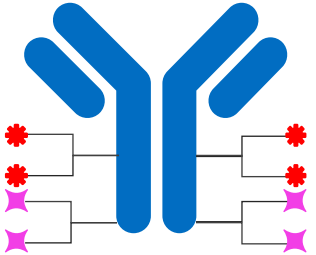
Multiple **site-specific stable conjugation** technologies to optimize precise linker-payload stoichiometries

OBJECTIVES

Enhance efficacy and therapeutic index through rational combinations that address tumor heterogeneity, improved immune activation and mechanisms of payload resistance

Complimentary Conjugation Technologies Enable ADCs With Precise DAR Ratios of Multiple Payloads Across Most Antibody Designs

ONCOLOGY

	DAR=2	DAR=4		DAR=6	DAR=8
Single Payload					
Dual Payload	 *Bispecific only				

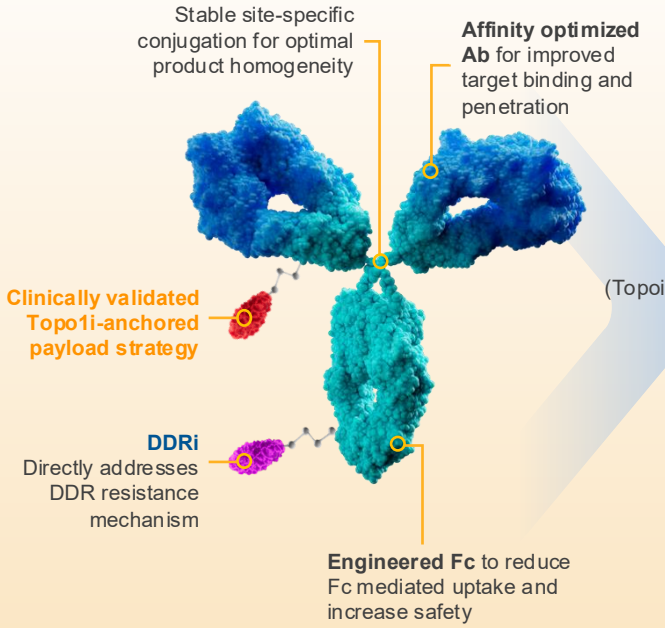
KEY POINTS

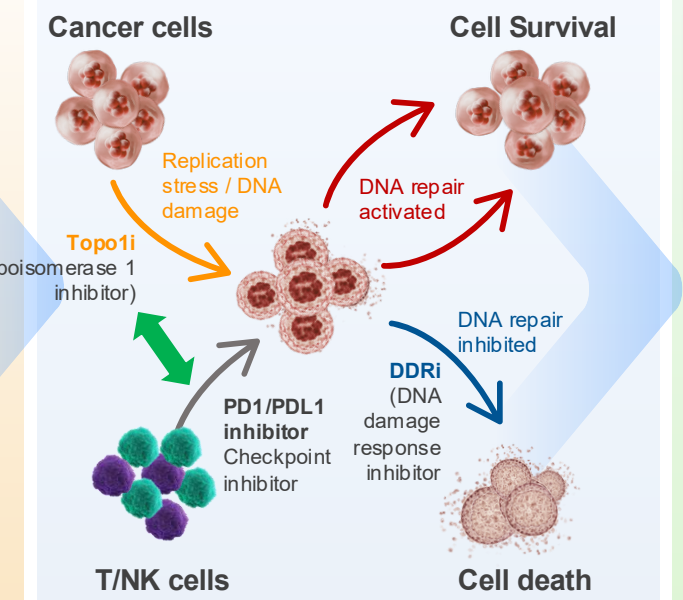
- **Leverage serial conjugations to generate a diversity of stable, site-specific multi-payload combinations**
- **Applicable to mono- and bispecific mAbs and other Fc-fused antigen targeting modalities**

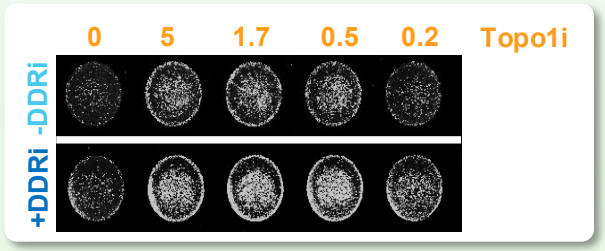
Multi-Payload Combinations Provide Potential To Synergize Through Overlapping Mechanisms of Cell Killing and Enhancing Antitumor Immunity

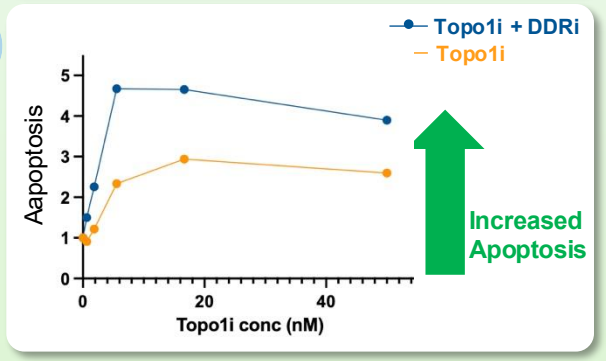
ONCOLOGY

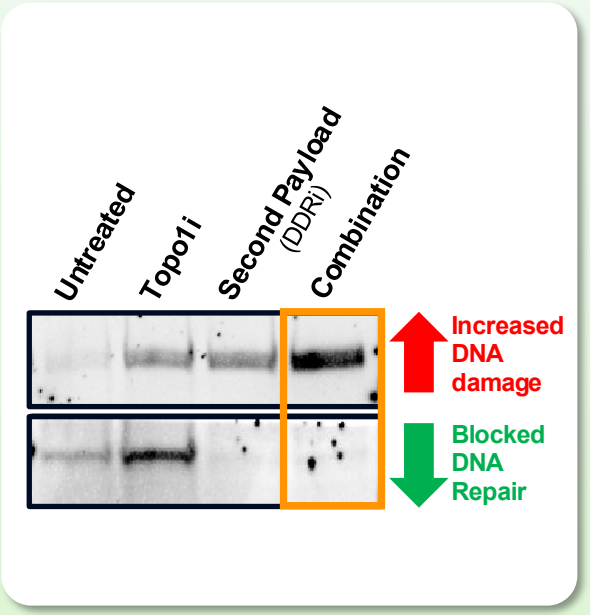
Synthetic Lethality as a Mechanism of Action for Dual-Payload ADCs











Dual-Payload ADC Architecture | **Mechanism of Synergy** | **Payload Synergy Observed at the Molecular Level**

Synergistic ADC Design

Topo1 inhibition and synergistic payloads profoundly inhibit DDR signaling, driving an accumulation of DNA damage that dramatically increases cell killing in rapidly proliferating cancer cells **as well as stimulating an enhanced antitumor immune response**

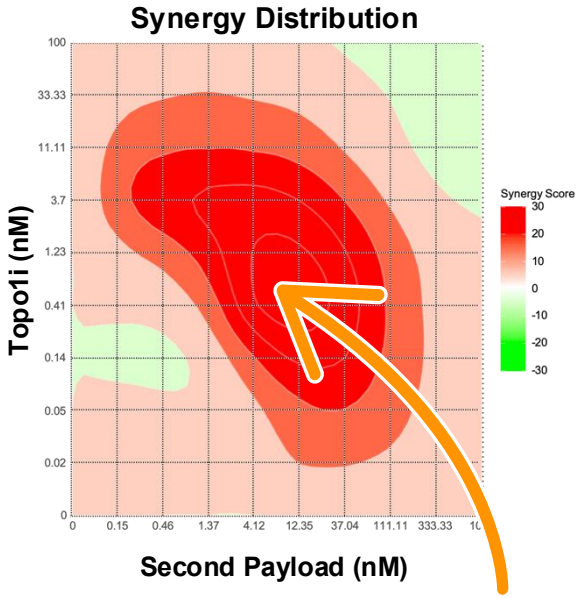
Robust Screening Efforts Identify Payloads That Synergize With Topo1i for Next-Generation Biohaven Dual-Payload ADCs

ONCOLOGY

In vitro cell-based synergy screen identifies compounds that synergize with Topo1i and are suitable for ADC conjugation

Top synergy hits from combination screen demonstrate increased efficacy and DAR4+2 may be optimal

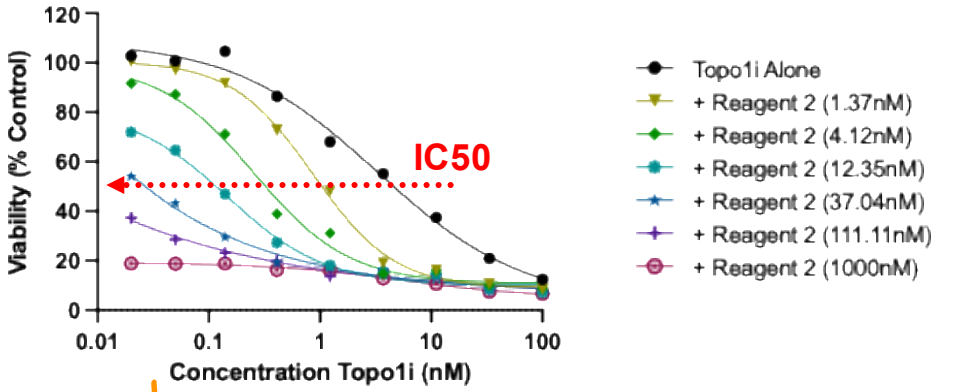
Topo1i + Second Payload Demonstrates Synergistic Interaction

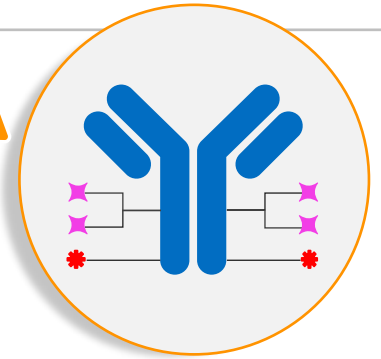


Target synergy partner and concentration range for optimal tumor cell killing

Synergy score to define optimal DAR

Potency Shift of Topo1i in Combination With Second Payload





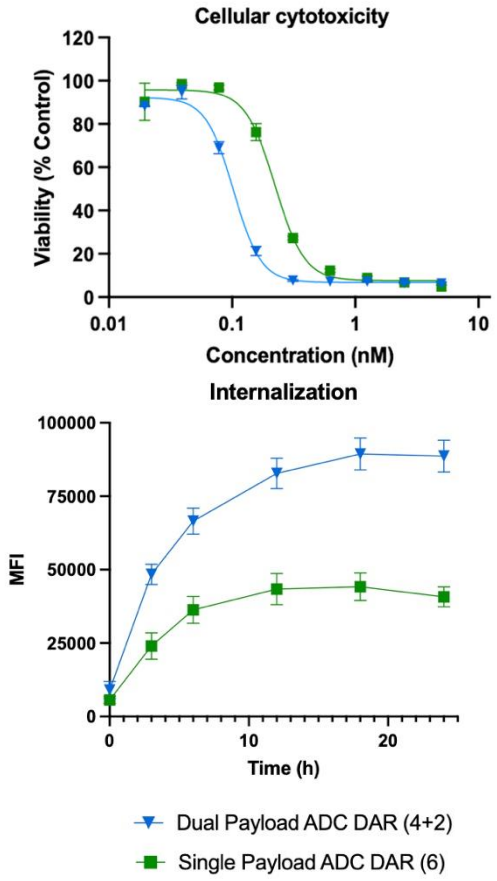
Biohaven Platform Enables the Development of Next-Generation ADCs With Improved Activity and Potential Transformational Functional Properties

ONCOLOGY

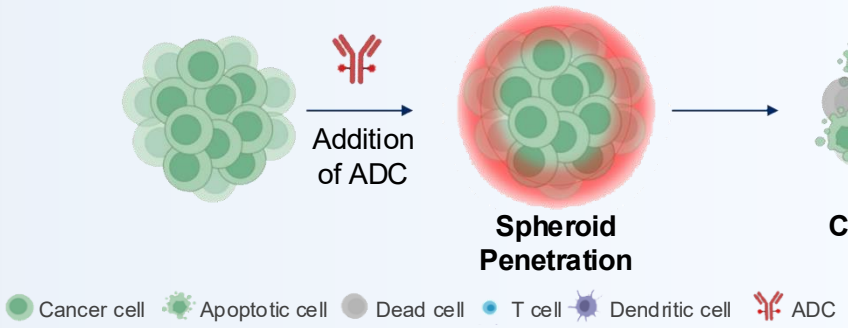
Dual-payload ADC approach demonstrates superiority vs. clinical competitors *in vitro*

Biohaven's Dual-Payload ADC

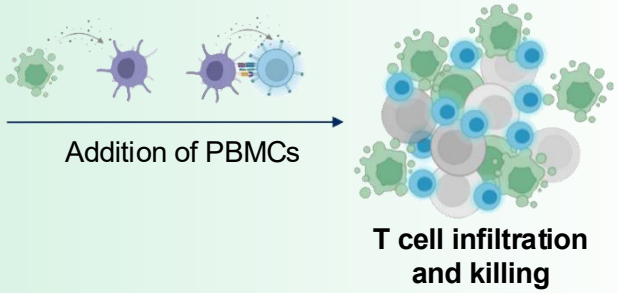
Improved 2D Cytotoxicity and Internalization



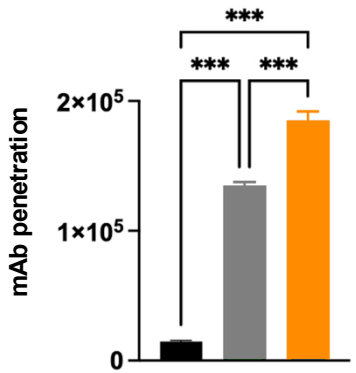
Enhanced 3D Spheroid Penetration



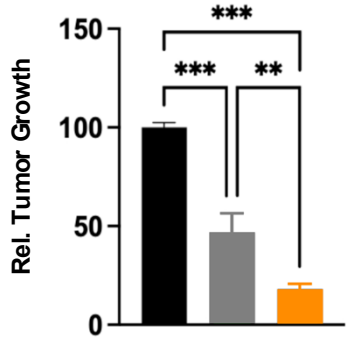
Increased Immunogenic Cell Death



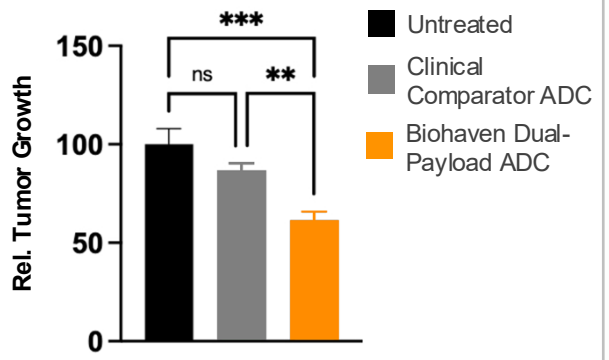
Spheroid Penetration



Spheroid Growth Inhibition



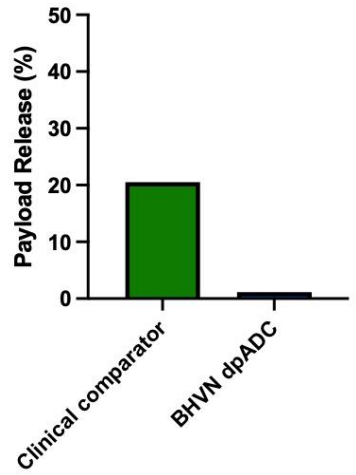
Immune Killing



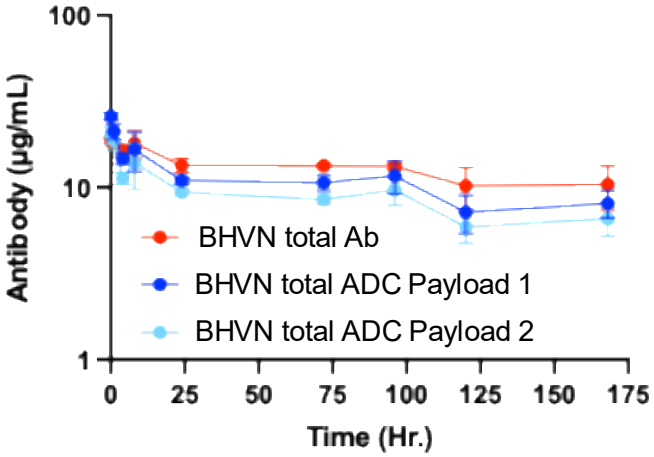
Superior Dual-Payload Path to the Clinic Targeting CRC

ONCOLOGY

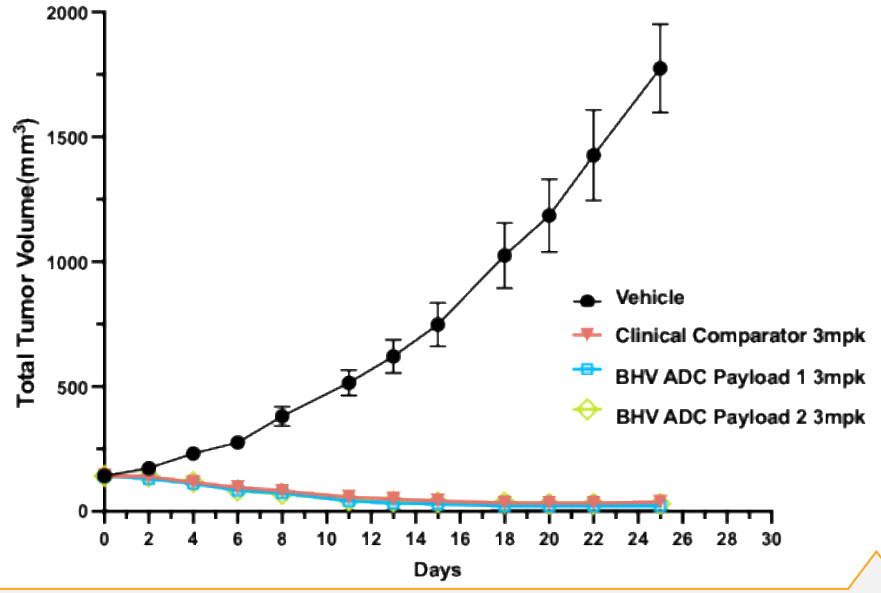
Neutrophil Elastase Mediates Payload Release



Mouse PK: IV Administration 3mg/kg BHVN dpADC DAR (4+2)



Total Tumor Volume



Biohaven dual-payload shows superior stability and half-life >8 days in mice

Biohaven dual-payload shows strong (>98%) tumor growth inhibition

KEY POINTS

- **Serial site-specific conjugations produce highly effective dual-payload ADCs**
- **Stable conjugations expected to improve dose-limiting toxicities driven by premature payload release**

Panel

MODERATOR

Tyler Van Buren

Equity Analyst

TD Cowen

PARTICIPANTS

Brian Lestini, MD, PhD
President, Oncology
Biohaven

Nushmia Khokhar, MD
CMO, Oncology
Biohaven

David Pirman, PhD
SVP and Head of Drug Discovery
Biohaven

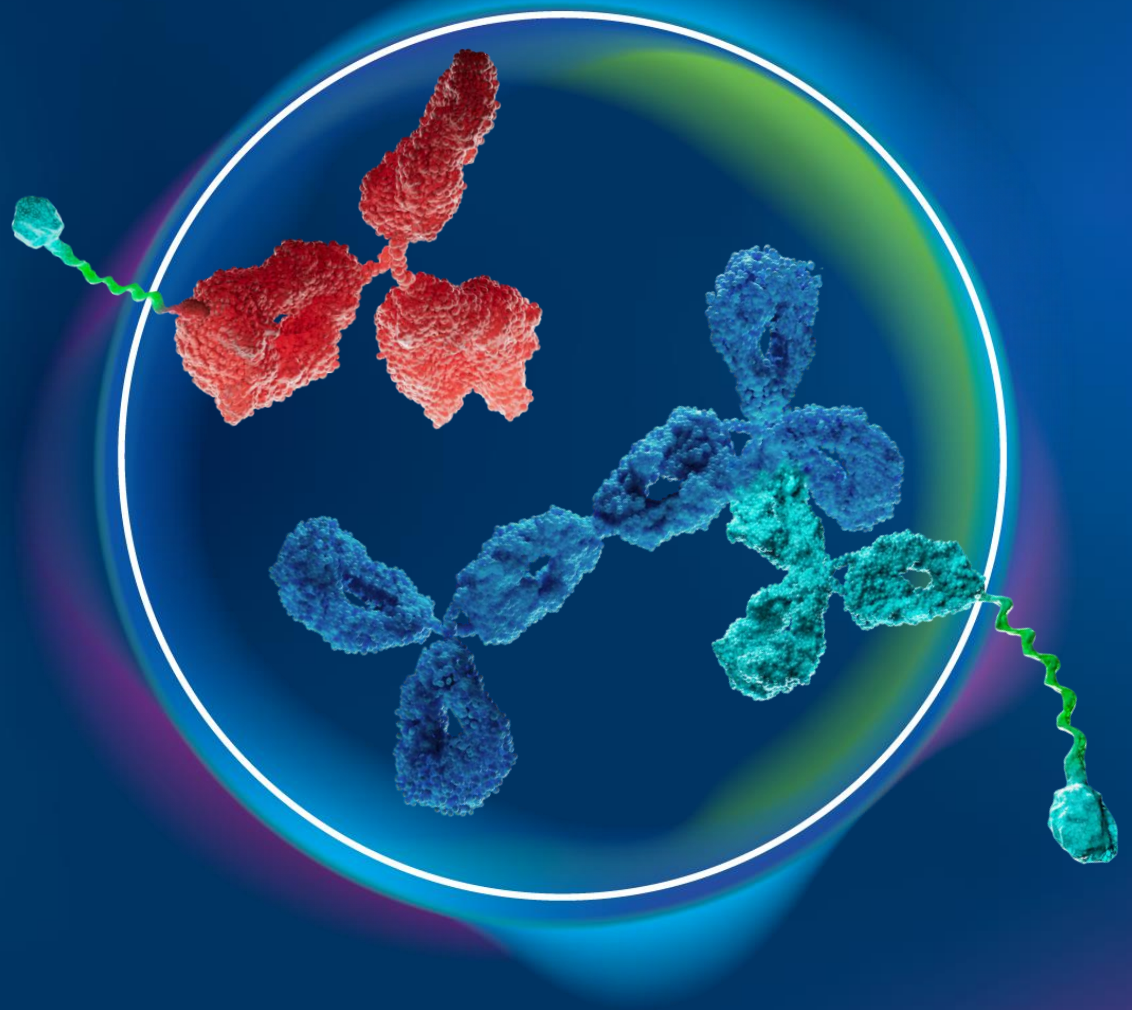
Gopa Iyer, MD
Genitourinary Medical Oncologist
Memorial Sloan Kettering Cancer Center

BHVN
LISTED
NYSE

biohaven®

DEGRADERS: MoDE™ AND TRAP™

Targeting the Root Cause of Autoimmune Disease



Tova Gardin, MD, MPP
Chief Translational Officer

biohaven®

David Pirman, PhD
SVP and Head of Drug Discovery

biohaven®

Malini Gupta, MD, ECNU, FACE, FITS
Director of G2Endo, Endocrinology and Metabolism 2025 AACE Chair

G2ENDO

Professor Jonathan Barratt, PhD, FRCP
The Mayer Professor of Renal Medicine, Department of Cardiovascular Sciences

UNIVERSITY OF LEICESTER

MoDE™ and TRAP™ Degraders

biohaven®

Tova Gardin, MD, MPP
Chief Translational Officer

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MoDE™ and TRAP™ Degraders

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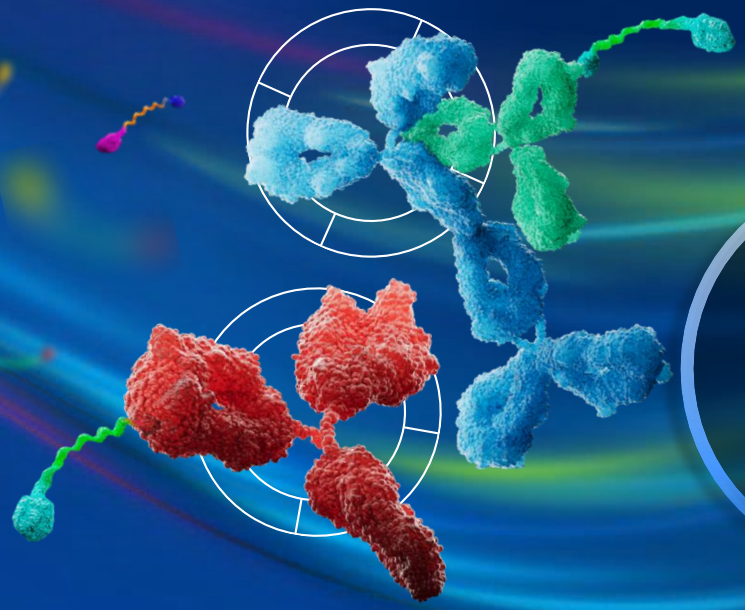
MoDE™ and TRAP™ DEGRADERS

Advancing Potential Paradigm Shifting Extracellular Degraders Into Pivotal Development

PRECISION PLATFORM BUILT ON VALIDATED TARGETS



RAPID, DEEP TARGET REDUCTION

MEANINGFUL CLINICAL OUTCOMES

ADVANCING INTO PIVOTAL STUDIES

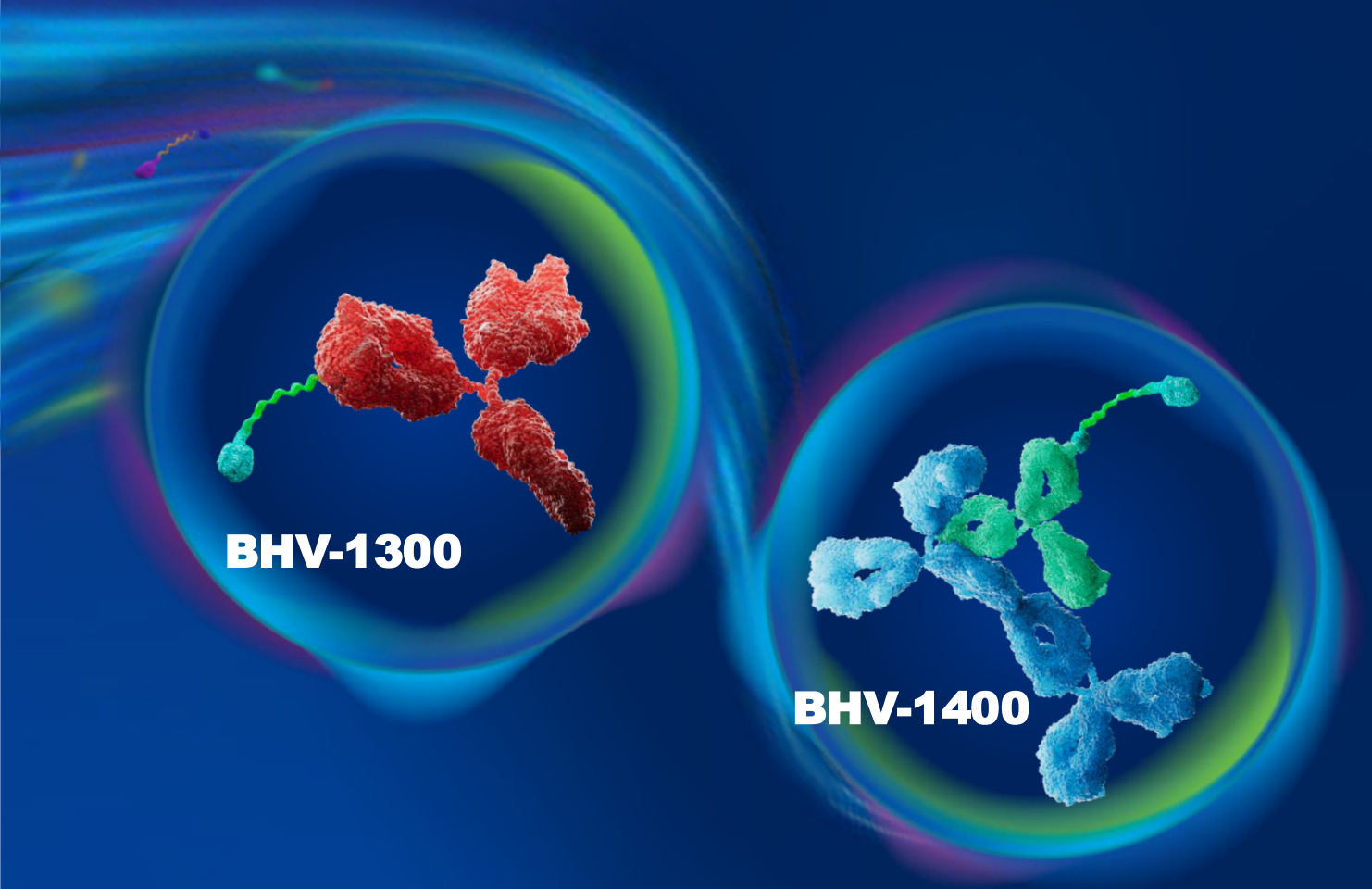
TO TRANSFORM PATIENT OUTCOMES

Engineered for selective removal of disease-causing proteins

BECAUSE DAYS MATTER™

MoDE™ and TRAP™ DEGRADERS

First Extracellular Protein Degraders in the Clinic Demonstrate Rapid and Robust Pharmacodynamic Effects and Compelling Safety in Nearly 200 Individuals Dosed

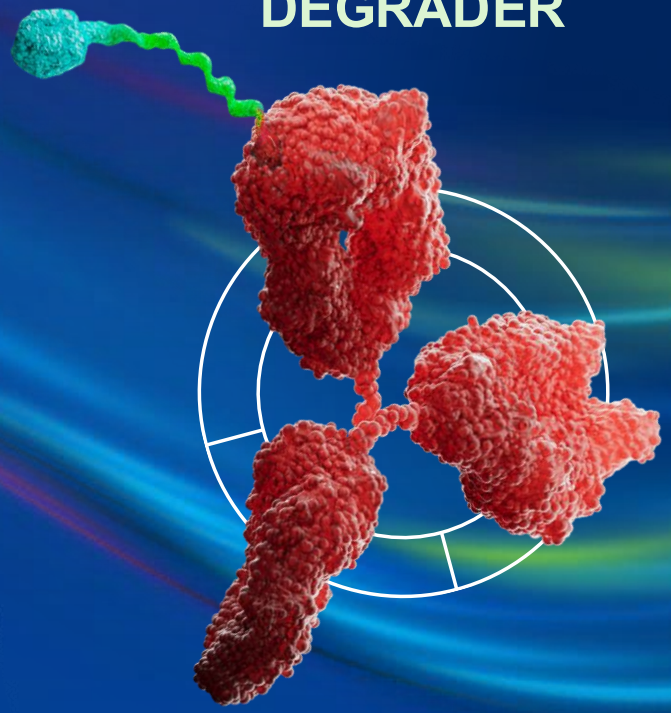


- Safe
- Well-tolerated
- Highly selective
- Deep and rapid lowering
- Patient outcomes
- Pivotal trials mid-2026

BHV-1300 MoDE™
DEGRADER

Designed To Treat the Root Cause of Graves' Disease… Not Just the Symptoms

POTENTIAL FIRST-IN-CLASS EXTRACELLULAR DEGRADER



Degrades TSHR autoantibodies
Normalizes thyroid function

Deep TSHR autoantibody degradation >80%

Normalization of thyroid hormones within weeks

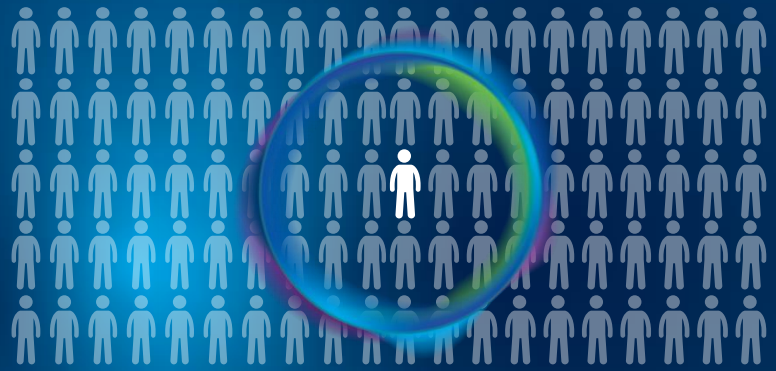
BHV-1300 advances to pivotal trial mid-2026

TO TRANSFORM PATIENT OUTCOMES

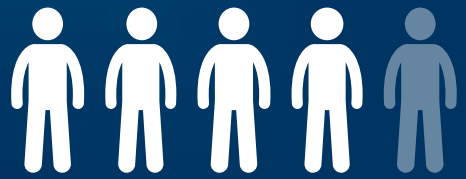
BECAUSE
DAYS MATTER™

Living with Graves' Disease

Graves' disease affects nearly 1 in 100 Americans.[1]



About 4 out of 5 cases of hyperthyroidism in the United States are caused by Graves' disease.[1]

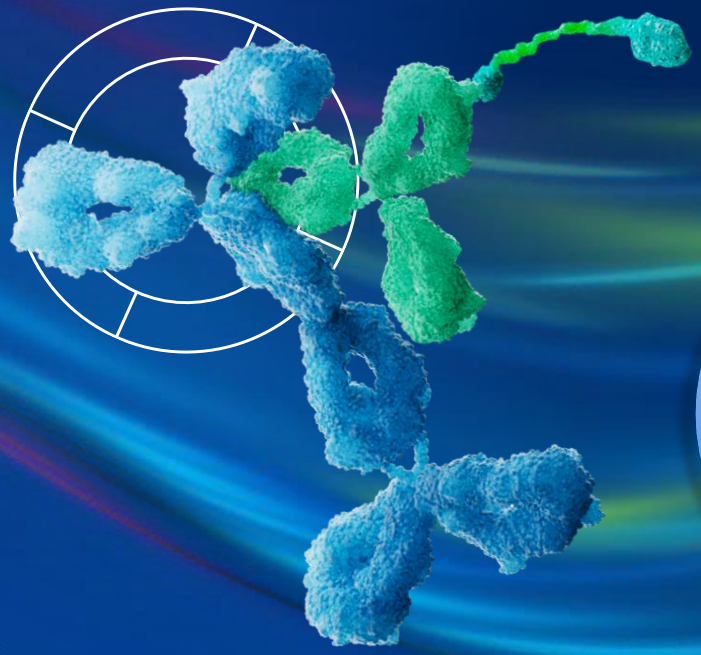


1. Akram S, Elfenbein DM, Chen H, Schneider DF, Sippel RS. Assessing American Thyroid Association guidelines for total thyroidectomy in Graves' disease. Journal of Surgical Research. 2020;245:64–71.

BHV-1400 TRAP™
DEGRADER

Designed To Treat the Root Cause of IgAN… Rapidly and Without Immunosuppression

POTENTIAL FIRST-IN-CLASS EXTRACELLULAR DEGRADER



Degrades Gd-IgA1
Targeting the Disease at its Root

Deep Gd-IgA1 degradation

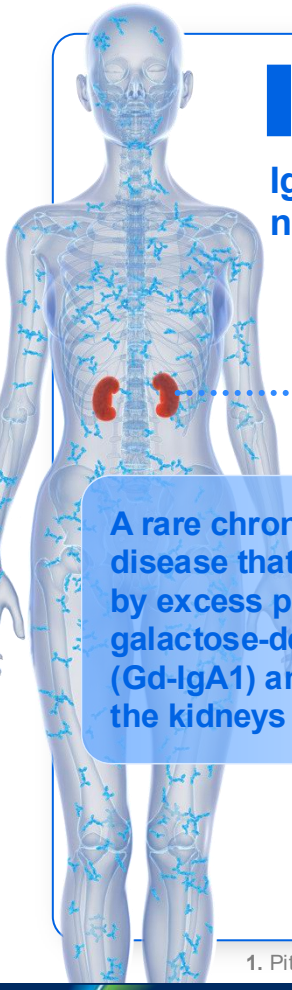
Improvement in hematuria, UPCR and eGFR within weeks

BHV-1400 advances to pivotal trial mid-2026

TO TRANSFORM PATIENT OUTCOMES

BECAUSE
DAYS MATTER™

By the Time IgAN Is Diagnosed, Kidney Function Is Already Significantly Compromised



IgAN

IgA nephropathy

A rare chronic kidney disease that is caused by excess production of galactose-deficient IgA1 (Gd-IgA1) antibodies in the kidneys

IgAN predominantly affects people in their **MOST PRODUCTIVE YEARS OF LIFE**

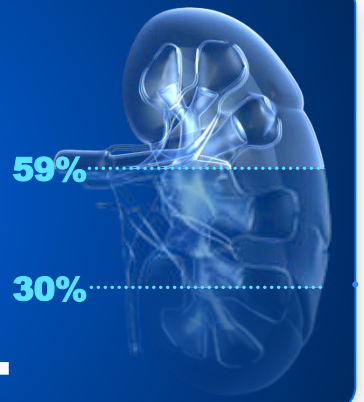
20s	**30s**
MEDIAN AGE AT DIAGNOSIS[1]	MOST COMMON AGE RANGE[1]

CKD STAGE 3

MOST COMMON AT DIAGNOSIS

At diagnosis, kidney function is already reduced to

30–59% OF NORMAL



Camille

Diagnosed with IgAN in 2020 at age 25

IgAN demands rapid intervention and a therapy safe enough to last a lifetime

1. Pitcher. Kidney Int. 2023.

TREATMENT **GOAL**

Every month matters — rapid intervention to preserve kidney function and limited remaining nephrons

MoDE™ and TRAP™ Degraders

PIPELINE ASSETS

8+

BHV degrader programs

ADDRESSABLE PATIENTS

>2M

across lead programs (US)

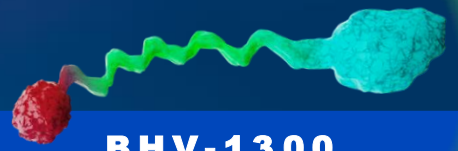
PEAK SALES POTENTIAL

$30B+

combined gross sales

MoDE™

> 1M patients | $7.6B



BHV-1300

IgG degrader

Graves' disease · RA
Sjögren's · Biologic failures

TRAP™

~133K patients | $5.0B

BHV-1400

Gd-IgA1 degrader

IgA nephropathy

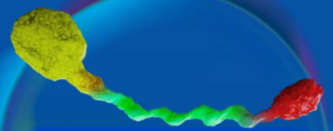
~400K patients | $11.1B

BHV-1310

IgG Degrader

gMG · Systemic sclerosis
AE · ITP

~92K patients | $2.6B

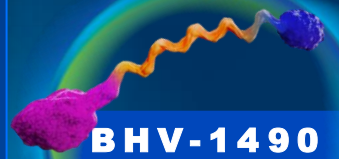


BHV-1450

IgG4 degrader

Pemphigus vulgaris
MuSK MG · IgG4-RD
CIDP

~42K patients | $1.7B



BHV-1490

IgM degrader

Cold agglutinin disease
Anti-MAG
Waldenström's

BHV-1440

TSHR AAb degrader

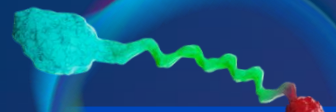
Graves' disease
Thyroid eye disease

~41K patients | $1.3B

BHV-1420

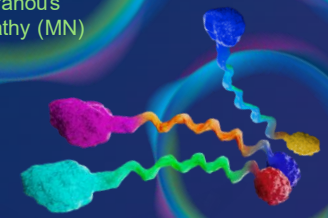
PLA2R AAb Degrader

Membranous
Nephropathy (MN)



BHV-6500

Pro-Insulin/Insulin
AAB Degrader



Addressable patients for each degrader based on internal assessment of potential patient population. Peak sales potential based on addressable patients for each degrader and internal assessment of gross revenue potential (prior to GTN adjustments or any adjustments associated with clinical risk), adjusted for estimated market share / market penetration.













MoDE™ and TRAP™ Degraders

Precision technology to

TRANSFORM LIVES

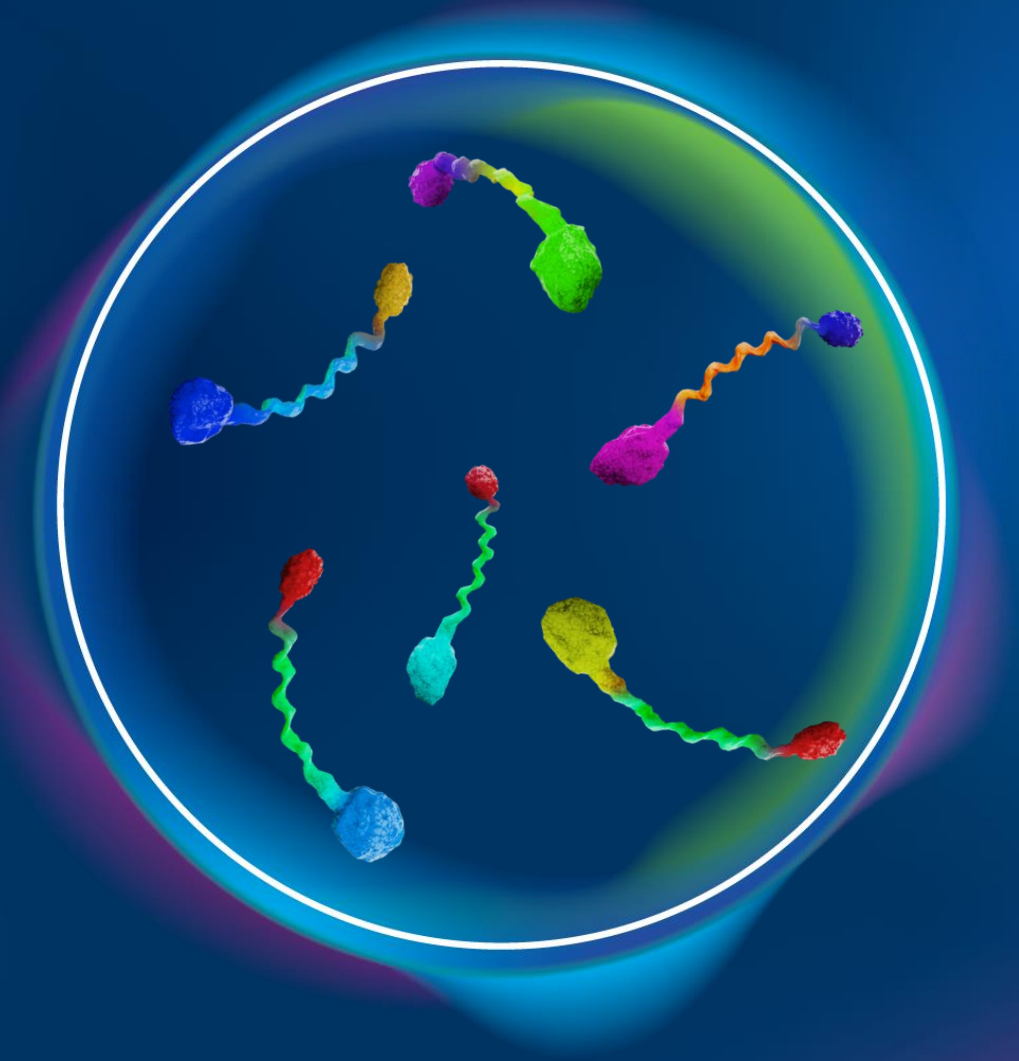
BECAUSE

DAYS MATTER™

biohaven®

NEXT-WAVE DEGRADERS

Novel Assets and Next-Generation Technology



David Pirman, PhD
SVP, Head of Drug Discovery

biohaven®

Next-Generation Degrader Innovation

biohaven®

Current Pre-IND Degrader Programs Offer a Sustainable Portfolio

DISCOVERY | PRECLIN. DEVELOPMENT | CLIN. DEVELOPMENT

DC ····· Discovery to IND <2 years ····· IND ····· Clinical

EFFICIENT/TRUNCATED SAFETY ASSESSMENT

STREAMLINED EFFICACY EVALUATION

MODULAR DRUG DESIGN AND SYNTHESIS

Early Targets + New Technology (catalytic, oral, CNS)

BHV-1490 (IgM)

BHV-1420 (PLA2R)

BHV-1450 (IgG4)

BHV-1440 (TSHR)

BHV-6500 (proinsulin, insulin)

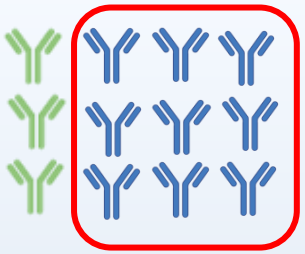
BHV-1300
BHV-1310
BHV-1400
BHV-1600

KEY POINT

Degrader platform produces high value assets with unmatched speed

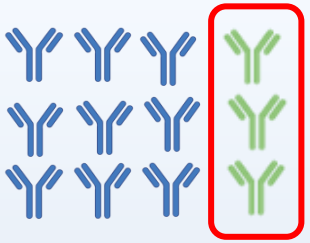
Building an Extensive Asset Platform With MoDEs™ and TRAPs™

DISCOVERY



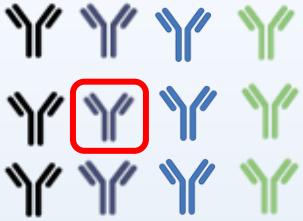
MoDE™

e.g., IgG, IgM



MoDE IgG4 Subclass

e.g., MuSK myasthenia gravis, pemphigus vulgaris



TRAP™ Targeting AAb, Antigen or Protein

e.g., IgAN, Graves', idiopathic membranous nephropathy

Aligning disease indications with appropriate degrader technology

Novel degrader approaches and technologies created to address novel targets and unmet need

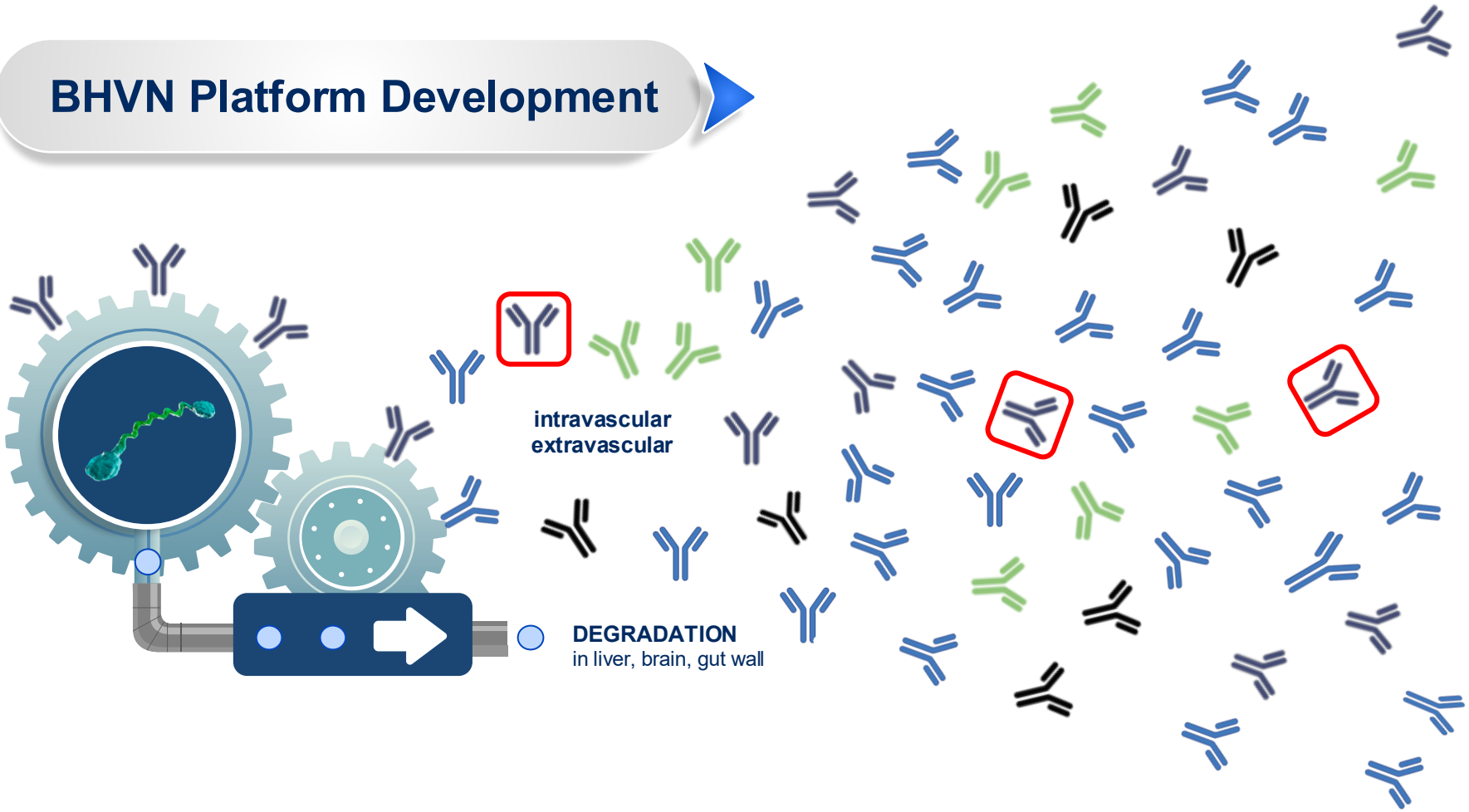
*Indications are exemplary, many of which are early programs

Beyond MoDEs™ and TRAPs™: Novel Technologic Solutions Drive Improved Efficacy and Target Profiles

DISCOVERY

MULTIPLE TECHNOLOGY SOLUTIONS

BHVN Platform Development



- Novel ASGPR ligands
- Oral degraders
- Novel, tissue-specific degradation pathways
- Specific B-cell targeting, tolerizing
- Catalytic degraders

biohaven®

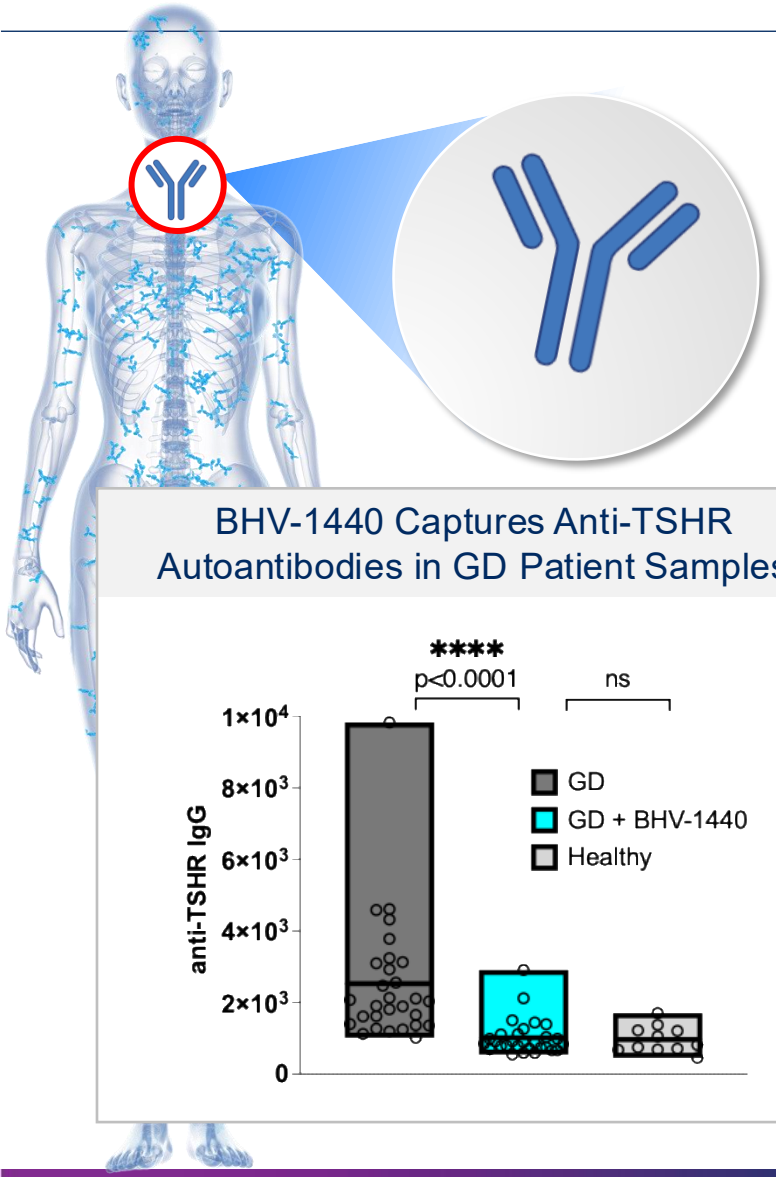
BHV-1440

TSHR TRAP™ Targeting Autoantibodies Driving Graves' Disease

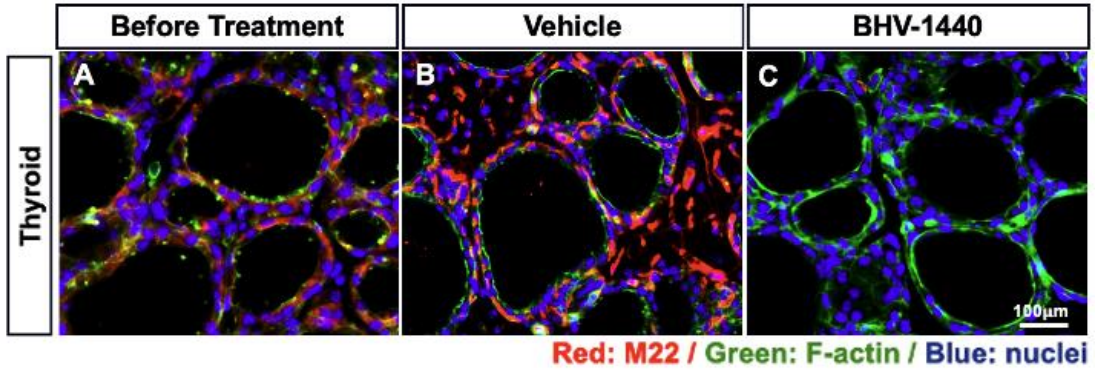
DAYS MATTER™

BHV-1440 Anti-TSHR Auto-Ab TRAP™ Degrader for the Treatment of Graves' Disease

DISCOVERY

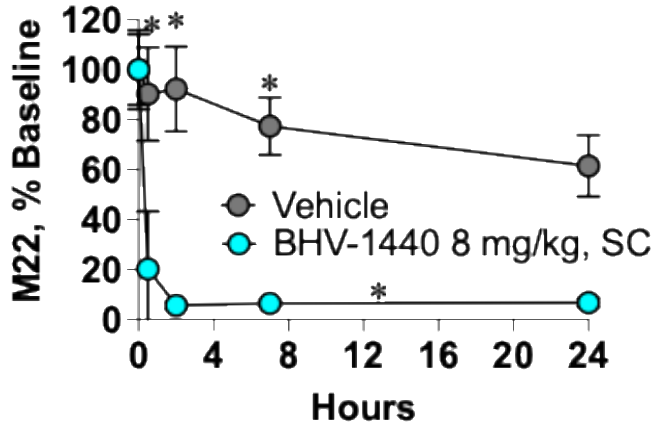


Specific removal of anti-TSHR autoantibody from tissue and circulation

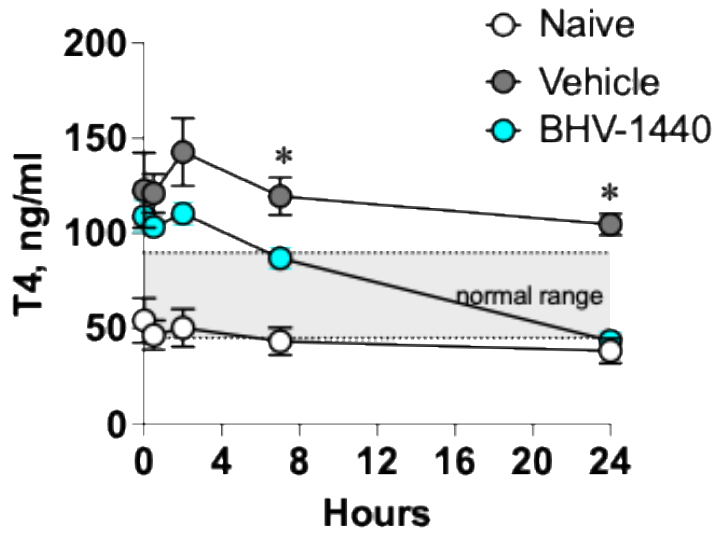


BHV-1440 Captures Anti-TSHR Autoantibodies in GD Patient Samples

BHV-1440 Rapidly Depletes Patient-Derived Anti-TSHR IgG (M22) From Circulation and Normalizes T4 Levels



BHV-1440 Rapidly Normalizes T4 Levels



biohaven®

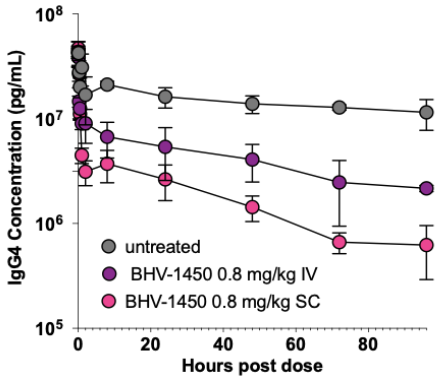
BHV-1450

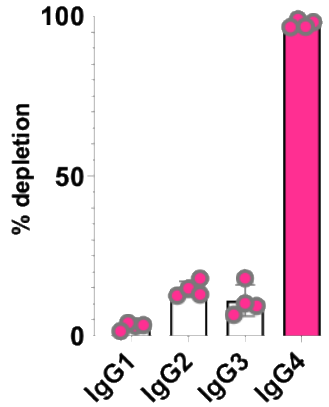
IgG4 MoDE™ Degrader for the Treatment of Pemphigus Vulgaris

DAYS MATTER™

BHV-1450: Deep Removal of IgG4 in IgG4-Mediated Diseases

DISCOVERY





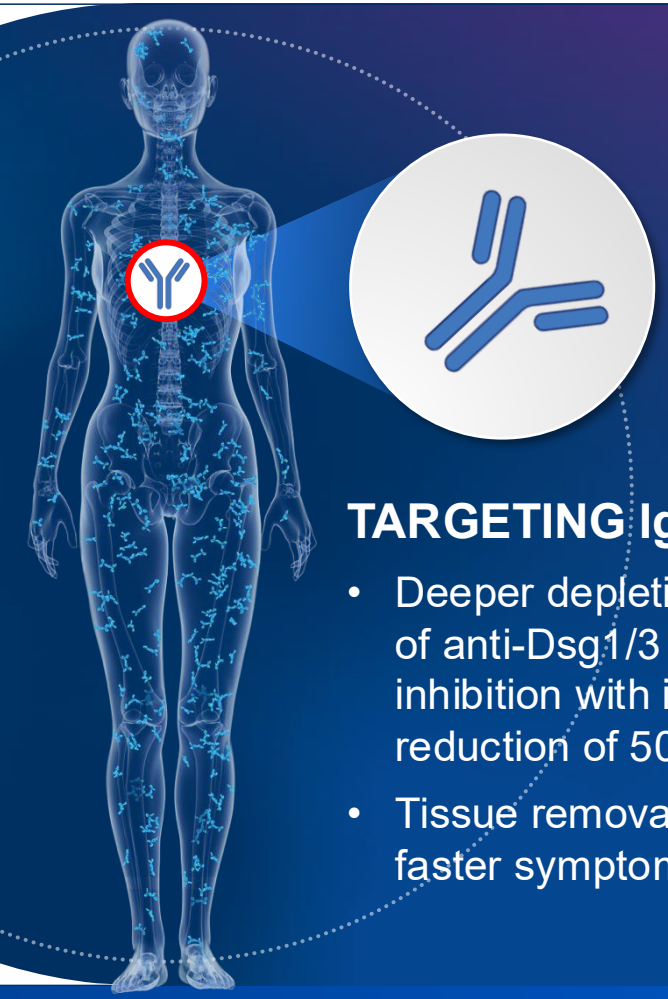
Pemphigus vulgaris

LGI-1 encephalitis

Thrombotic thrombo-cytopenic purpura

MuSK myasthenia gravis

Antidrug antibodies



TARGETING IgG4 ONLY

- Deeper depletion (>80%) of anti-Dsg1/3 than FcRN inhibition with its limited reduction of 50–70%
- Tissue removal facilitates faster symptomatic reversal

Mori. *Am J Pathol*. 2012. Koneczny. *Autoimmun Rev*. 2020. van Sonderen. *Nat Rev Neurol*. 2017.

KEY POINT

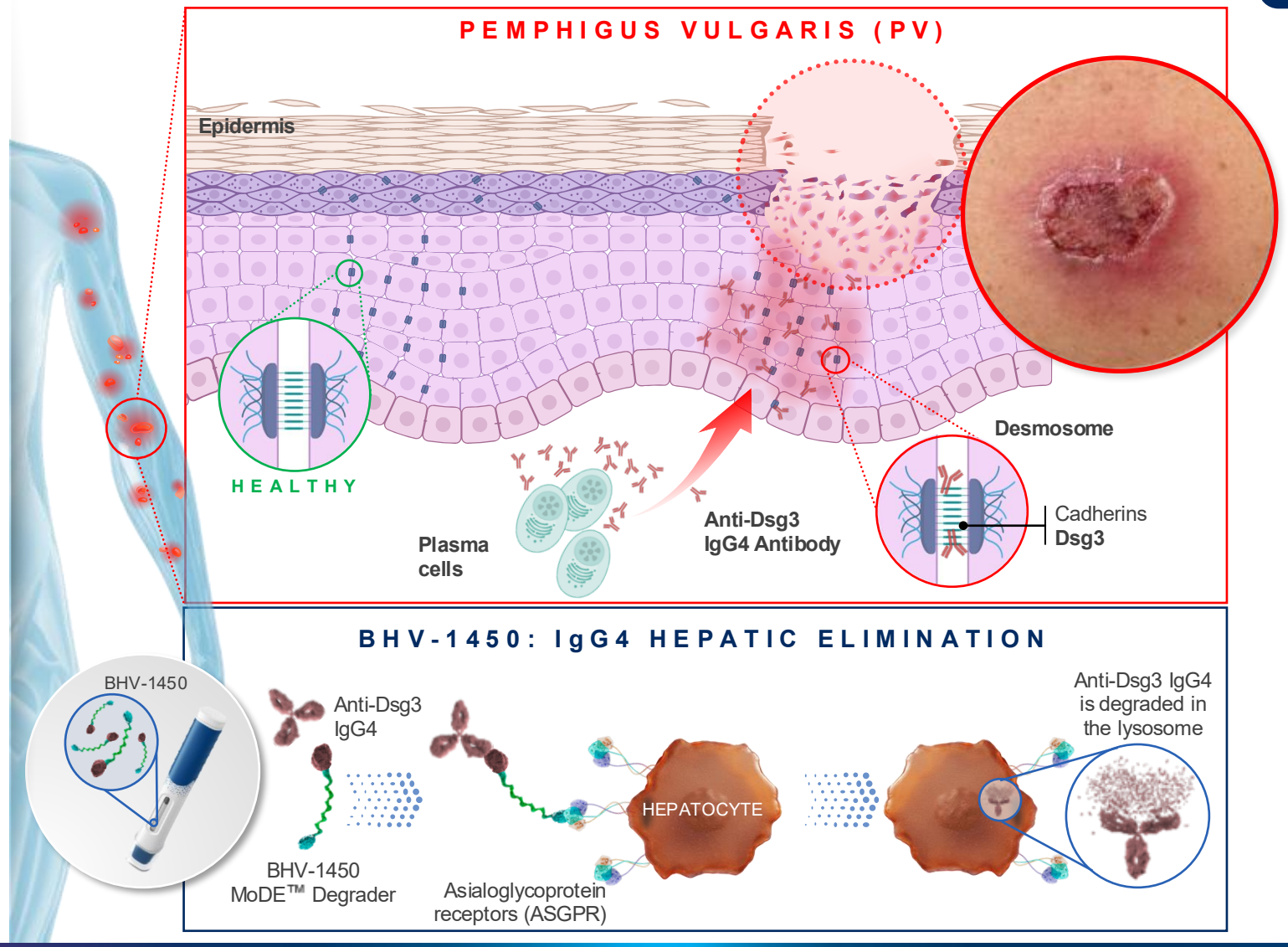
BHV-1450 specifically degrades the IgG4 subclass: IgG1, IgG2 and IgG3 remain
BHV-1450 on track for IND in Q1 2027

BHV-1450, an IgG4 Selective Degrader, Reverses the Anti-Dsg3-Mediated Skin Damage of Pemphigus Vulgaris

DISCOVERY

PEMPHIGUS VULGARIS (PV)

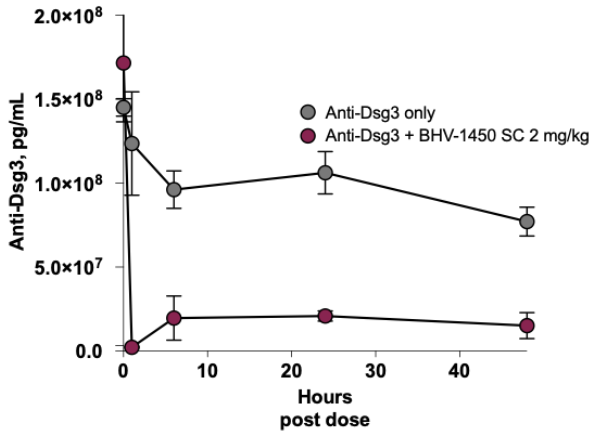
- Impacting 30–50K patients in the US
- PV is a painful, blistering, autoimmune disease with skin and mucous membrane erosions
- IgG4 autoantibodies target desmoglein 3 (Dsg3), essential for keratinocyte cell-cell adhesion



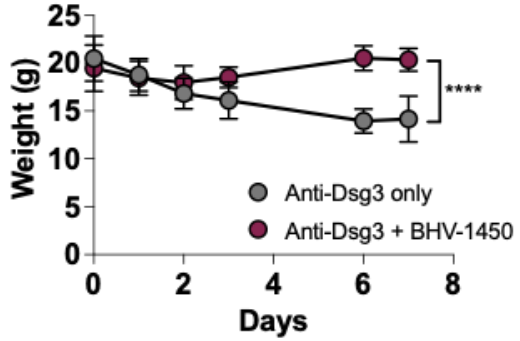
BHV-1450 Rapidly Removes Anti-Desmogleins Which Drive Disease From Circulation and From Tissue

DISCOVERY

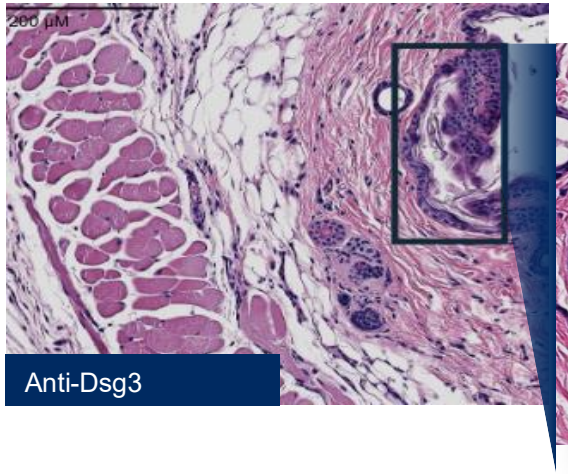
BHV-1450 Removes Anti-Dsg3 Ab From Circulation



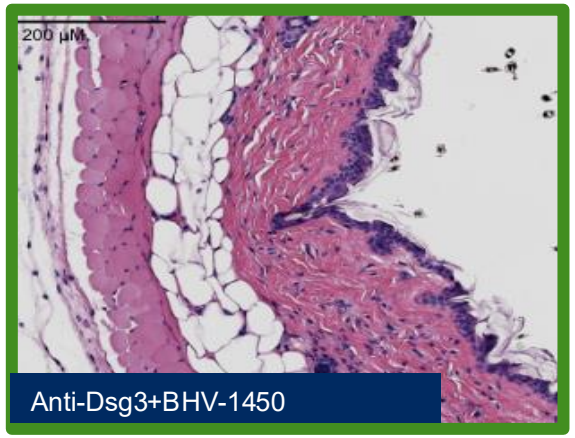
BHV-1450 Rescues Body Weight Loss in PV-like model



BHV-1450 Rescues Blistering Disease Phenotype in a PV-Like Model



Suprabasilar keratinocyte clefts create blistering disease



No observation of any suprabasilar keratinocyte clefts create blistering disease

biohaven®

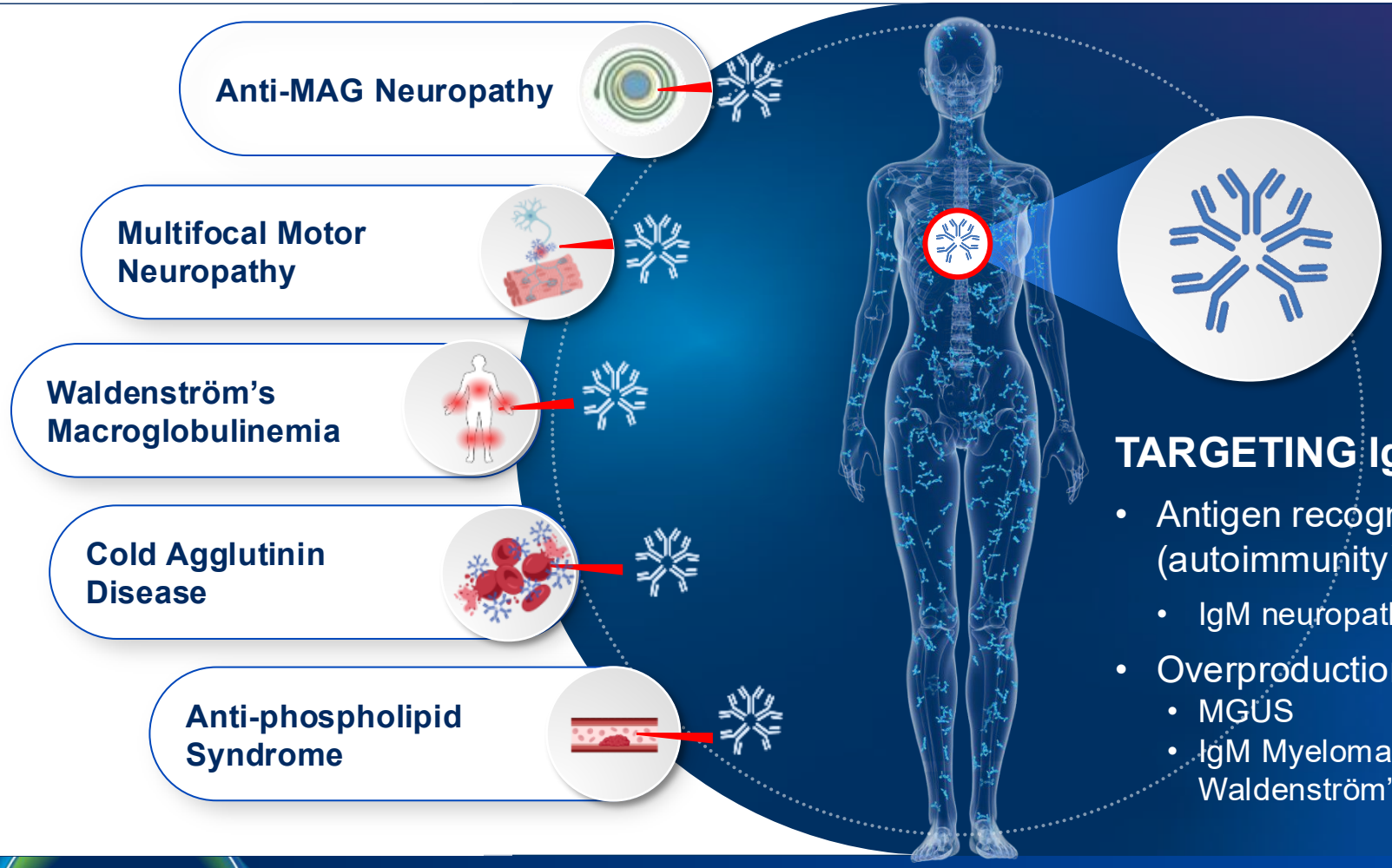
BHV-1490

IgM MoDE™ Degrader Treatment of IgM-Driven Disease

DAYS MATTER™

Removal of IgM Specifically Addresses Several Diseases

DISCOVERY



TARGETING IgM ONLY

- Antigen recognition (autoimmunity)
  - IgM neuropathy, APS (IgM only)
- Overproduction
  - MGUS
  - IgM Myeloma, MyD88, Waldenström's macroglobulinemia

Existing IgM-lowering therapies are immunosuppressants (BLyS/APRIL, rituximab), narrow therapeutic index chemotherapeutics (ibrutinib, bendamustine) or inconvenient (plasmapheresis)

An IgM MoDE™ preserves all non-IgM isotypes and IgG subclasses

KEY POINT

BHV-1490 specifically and deeply degrades the IgM isotype of immunoglobulins

IgM-Mediated Diseases Have Significant Unmet Need and Are Suitable for MoDE™ Degraders

DISCOVERY

IgM-mediated diseases caused by pathogenic autoreactive IgM

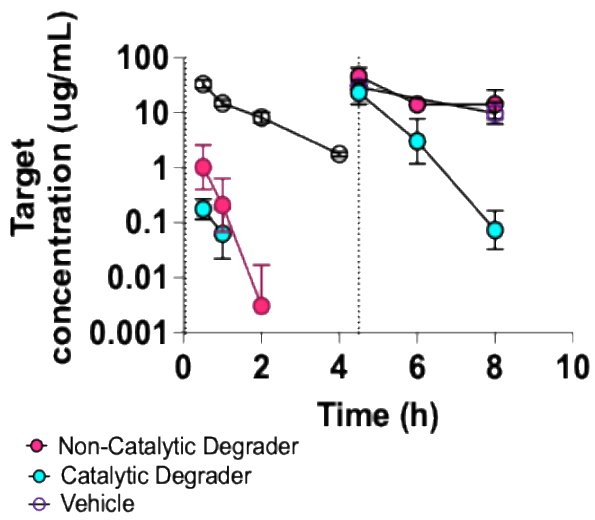
Significant market opportunity in IgM-mediated diseases with unmet clinical need with streamlined clinical path towards POC

Indication	US Patients	IgM Burden	Competition	Rationale and endpoint	Pricing Structure
Anti-MAG neuropathy	5–10K	Low	None approved; rituximab off-label ~$15K	• Anti-MAG titer is low — attractive for SC autoinjector dosing • IgM titer and nerve conduction velocity	Orphan; first-in-class
Multifocal motor neuropathy	3–5K	Low	IVIG ~$136–500K/yr (infusion)	• Anti-GM1 IgM is low-titer monoclonal. Stoichiometric SC weekly dose tractable. • IgM titer and grip strength	SC vs. IVIG cost-effectiveness
APS-IgM only	3–7K	Low	Warfarin <$1K/yr; rivaroxaban ~$5K/yr	• IgM aCL/aβ2GPI titers are low in isolated phenotype — no class-switch • IgM titer-stroke recurrence	First IgM-specific label; stroke value ~$250K
Schnitzler syndrome	200	Very Low	Anakinra off-label ~$80K/yr	• Lowest IgM titer of all indications. MGUS-level monoclonal IgM • IgM titer UAS7, C-reactive protein	Ultra-rare orphan; no approved IgM-directed Rx
Cold agglutinin disease	5K	Medium	Sutimlimab (Enjaymo) $440K/yr WAC	• Monoclonal IgM is high but levels could be assessed and lowered over time • Hemoglobin	Below sutimlimab; SC vs. IV

IgM Degraders: Catalytic and MoDE™ Degraders Provide Optionality Across Indications

DISCOVERY

In Vitro Evidence for Catalytic Degradation of IgM



Biohaven IgM-MoDE Platform

Dual Molecular Architecture

Circulating IgM
Pentameric antibody target

Catalytic Degrader
pH-dep. IgM binder + FcRn recycled
Substoichiometric; multiple rounds

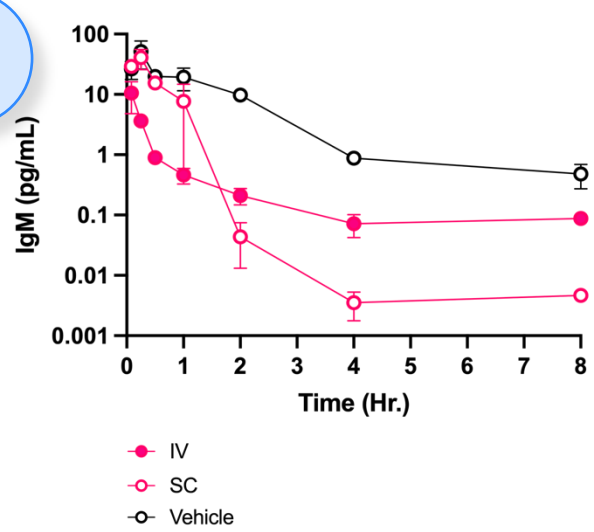
MoDE
GalNAc-linked ASGPR ligand
Stoichiometric; 1:1 IgM removal

FcRn Recycling
Endosome pH release → re-use

Hepatic ASGPR
Lysosomal degradation sink

IgM Degraded
Lysosomal proteolysis

BHV-1490: Human IgM Depletion in Mice



KEY POINT

- **BHV-1490 leverages a novel ASGPR ligand to rapidly remove IgM from circulation**
- **BHV-1490 on track to initiate preclinical development in 2027**

Malini Gupta, MD, ECNU, FACE, FITS
Director of G2Endo, Endocrinology and Metabolism 2025 AACE Chair

G2ENDO

Graves' Disease:
Old Disease, New Therapeutic Landscape

biohaven®

History of Graves' Disease

DEGRADERS

Persian physician Abicenna documented patients with goiter and increased appetite

1000 AD

1100 AD

Sayyid Zayn al-Din Isma'il al-Husayni al-Jurjani (Ismail Gorgani) described this in a medical encyclopedia

1786

Caleb Hillier Parry described hyperthyroidism and goiter in Europe

1835

Karl Adolph van Basedow, described a constellation of symptoms, independently in Germany

1840

Irish surgeon Robert James Graves linked many symptoms with thyroid enlargement in multiple patients in Dublin

Dr. Robert Graves

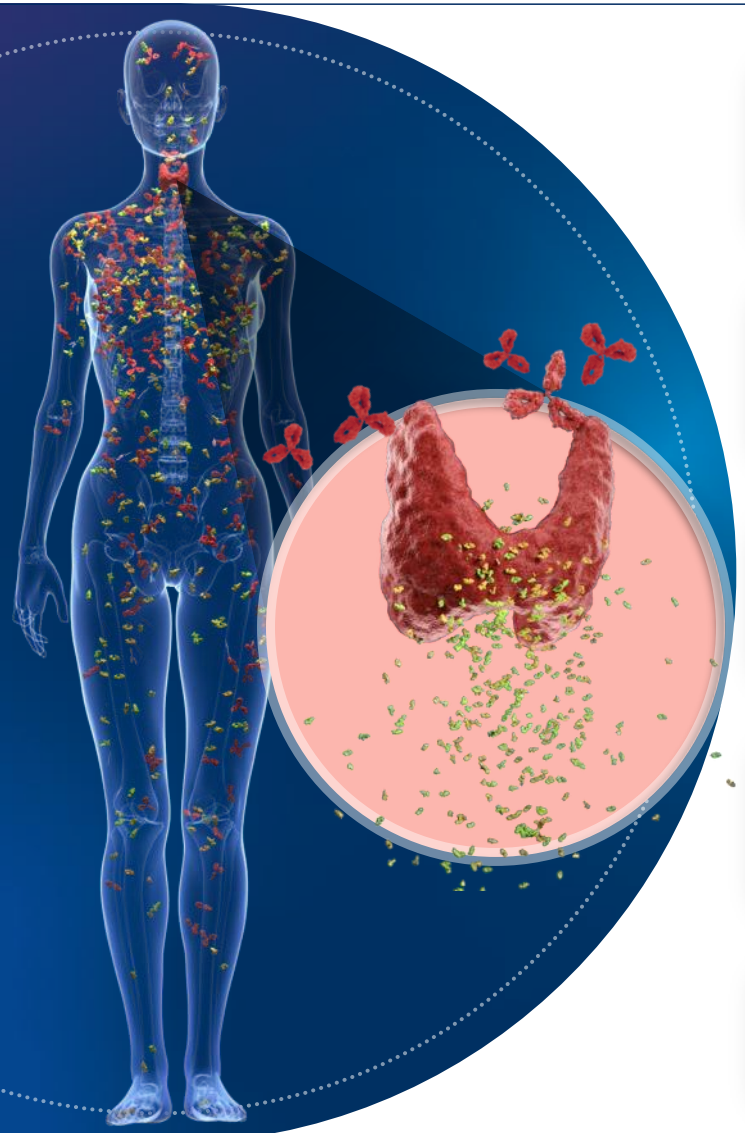
His fame rests chiefly on his Clinical Lectures, which were a model for the day and recommended by Armand Trousseau in France (1801–1867), who suggested the term Graves' disease.

Trousseau was the first in France to perform a tracheotomy, and he wrote a monograph on this as well as intubation in 1851.

What is Graves' Disease?

DEGRADERS

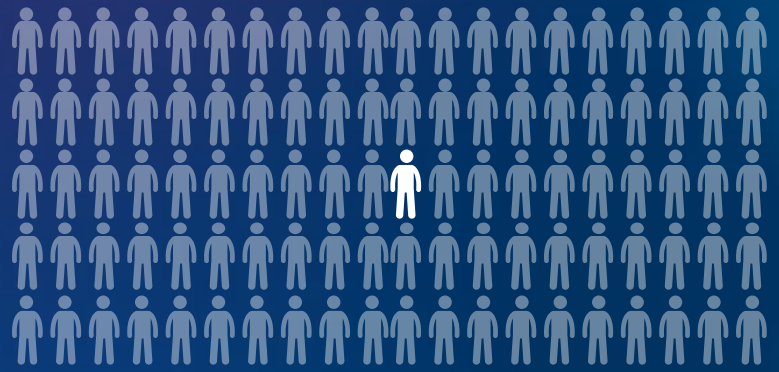
Graves' disease is an immune system disorder that affects the thyroid gland. It causes the body to make too much thyroid hormone.



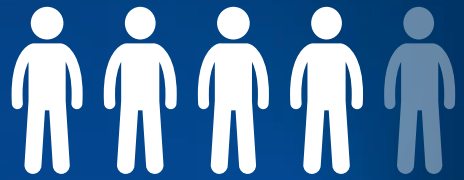
- Nervousness, irritability insomnia, depression
- Broken hair, hair loss
- Weight loss, strong feeling of hunger, diarrhea
- Enlarged thyroid gland
- Fragile fingernails, shaking hands
- Increased heart rate, arrhythmia, high blood pressure
- Warm, moist skin, increased body temperature
- Muscle cramps, muscle weakness
- Miscellaneous cycle disorders

Demographics: Graves' Disease Impacts 1% of the Global Population

Graves' disease affects nearly 1 in 100 Americans.[1]



About 4 out of 5 cases of hyperthyroidism in the United States are caused by Graves' disease.[1]

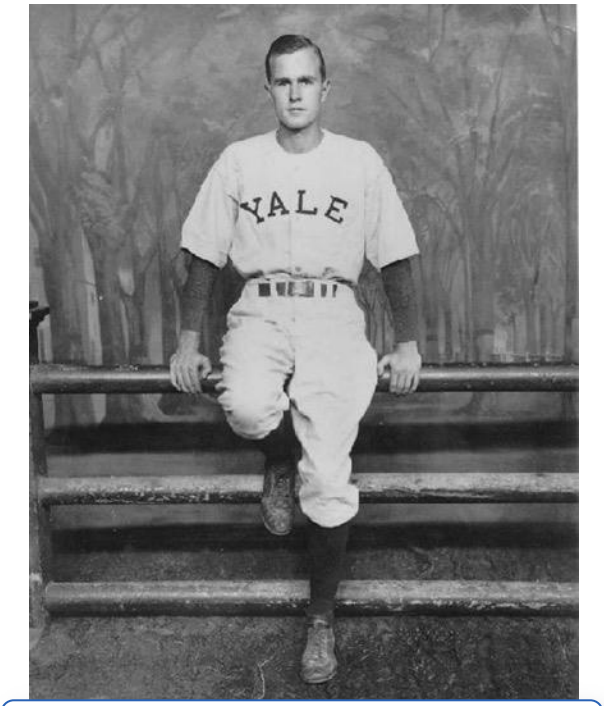


Worldwide incidence of Graves' disease[2]

1. Akram. Journal of Surgical Research. 2020. **2.** McLeod. Endocrine, 2012.

Notable Persons With Graves' Disease

DEGRADERS



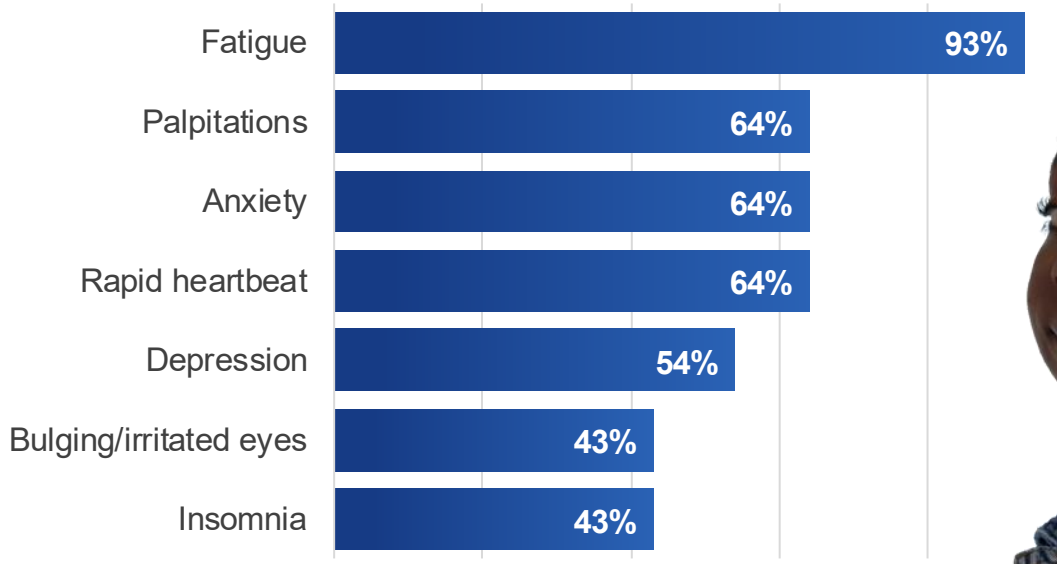
George H.W. Bush

Barbara Bush

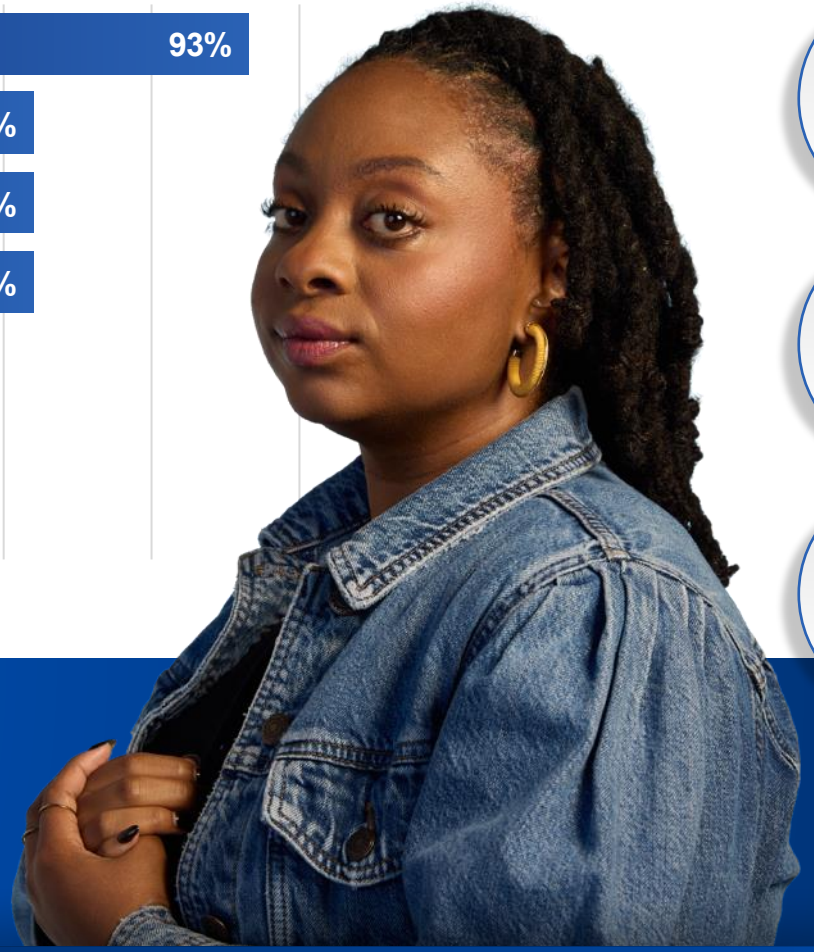
- Actor Marty Feldman
- Actor Rodney Dangerfield
- Sprinter Gail Devers
- Singer Missy Elliott
- Artist Yayoi Kusama
- Actress Dame Maggie Smith

The Under-Recognized Burden of Graves' Disease[1]

DEGRADERS



1. Patient Burden in Graves' Disease: Results From a Mixed Methods Survey



93% report multiple symptoms (≥2)

79% experience 4+ symptoms

72% experience 5+ symptoms

Even among biochemically well-controlled patients, 75% report recurring symptoms — fatigue, palpitations, anxiety, weight gain

Courtnay
Living with Graves' disease

KEY POINT

Current treatments achieve biochemical control but do not address the underlying antibody-driven disease, antibodies continue to circulate, targeting the thyroid, orbit, brain, and crossing the placenta

Living With Graves' Disease — The Human Toll[1]

DEGRADERS

EMOTIONAL TOLL

100% Emotional

57% Physical

50% Social

FUNCTIONAL IMPACT

36% Daily activities

36% Family planning

29% Work/financial

Emma
Living with Graves' disease

> ***The anxiety makes it really hard to do normal people stuff sometimes.*** *I'll drive to the grocery store and then not go inside because I have anxiety for no reason.*
>
> — Patient A

> ***I had to leave my job.*** *I don't get to see my friends as much anymore.*
>
> — Patient B

> *I'm 90% a no on having children… knowing that that's an option* ***being taken away without my choice*** *affects it.*
>
> — Patient C

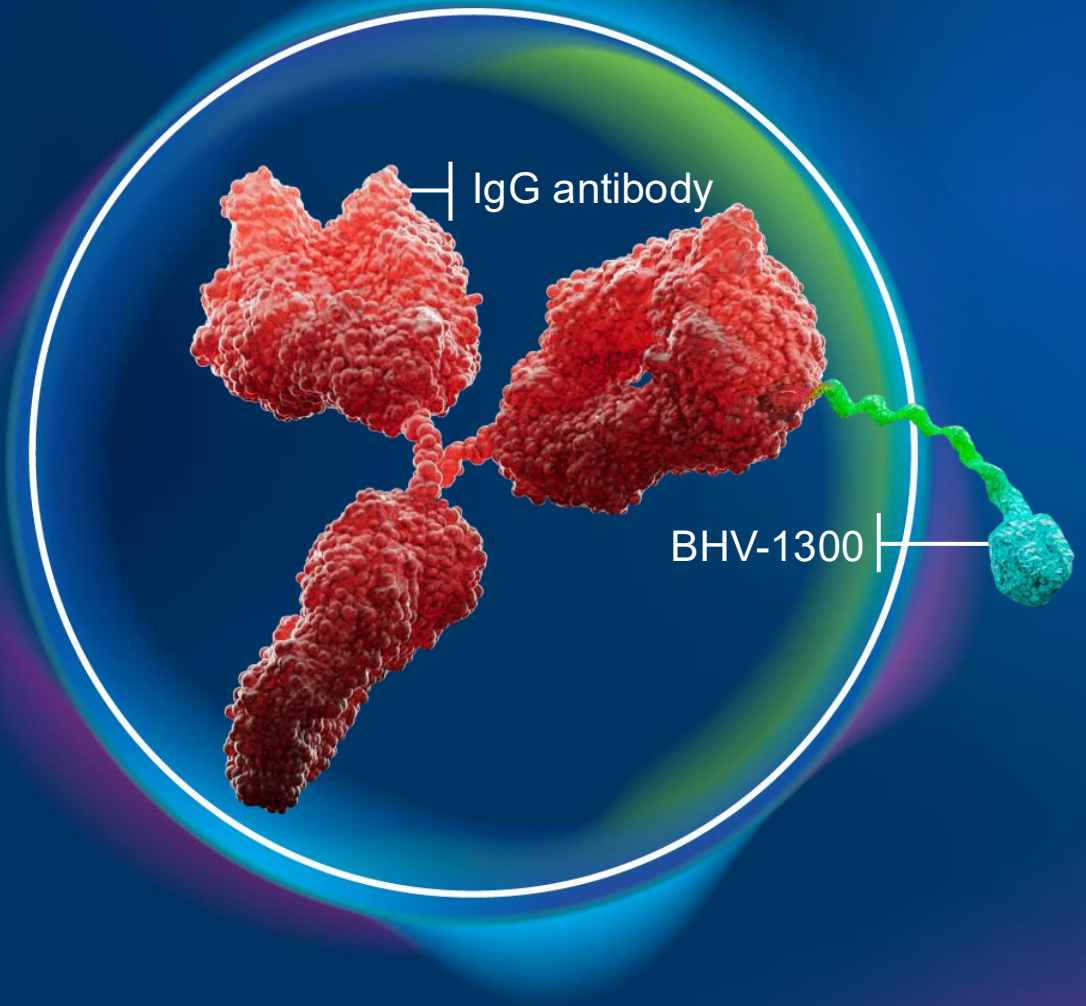
1. Patient Burden in Graves' Disease: Results From a Mixed Methods Survey

KEY POINT

Patients on antithyroid drugs continue to suffer. Symptoms are pervasive and multi-system.

biohaven®

The Science of Graves' Disease



How Is Graves' Disease Diagnosed?

History

- History of symptoms and review of symptoms
- Family history of autoimmune disease, thyroid disease
- Social history

Physical Exam

Including eye and hearing

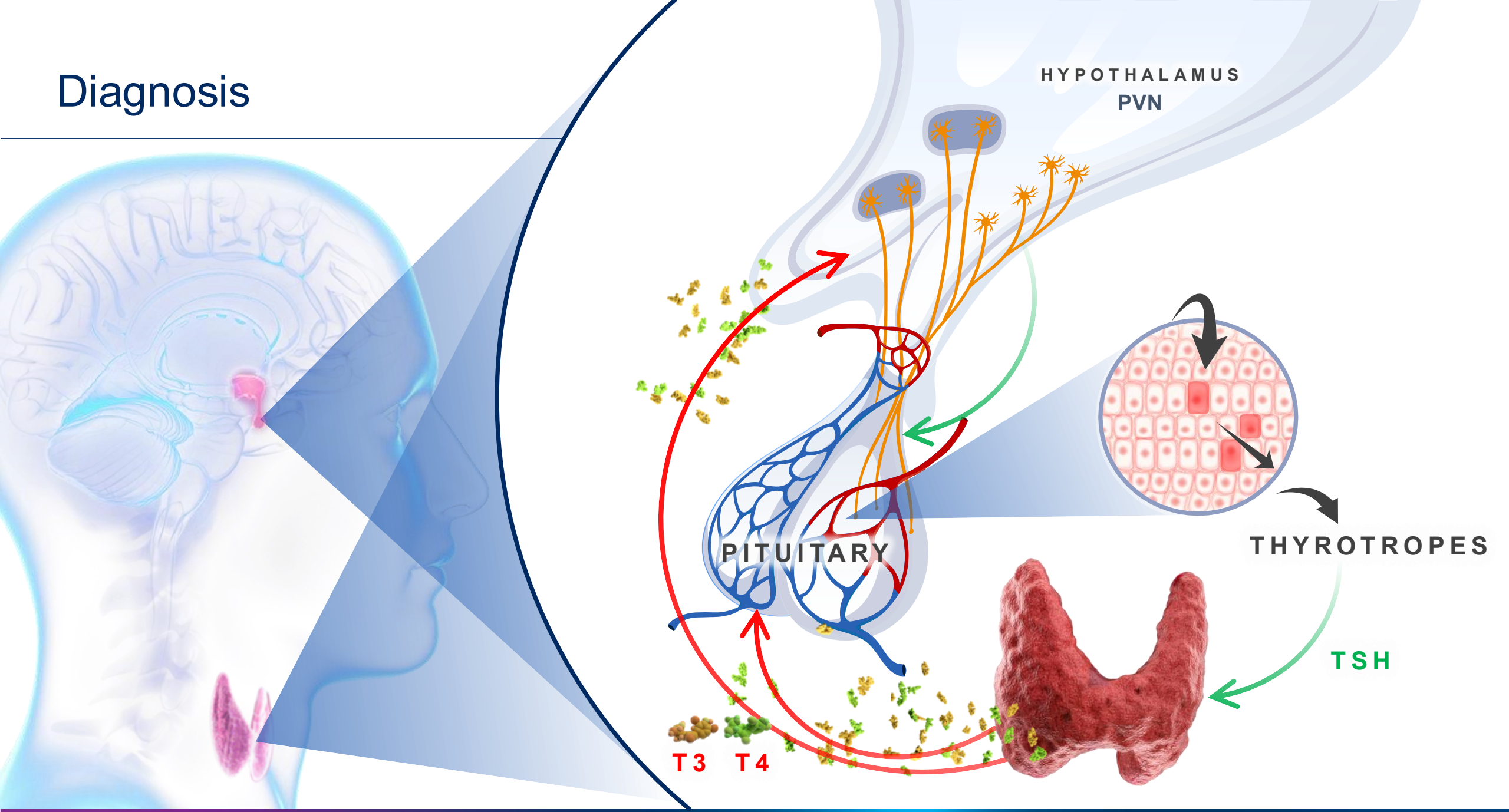
Lab Testing

TSH, free T4, free T3, TRAb, TSI, TPO Ab

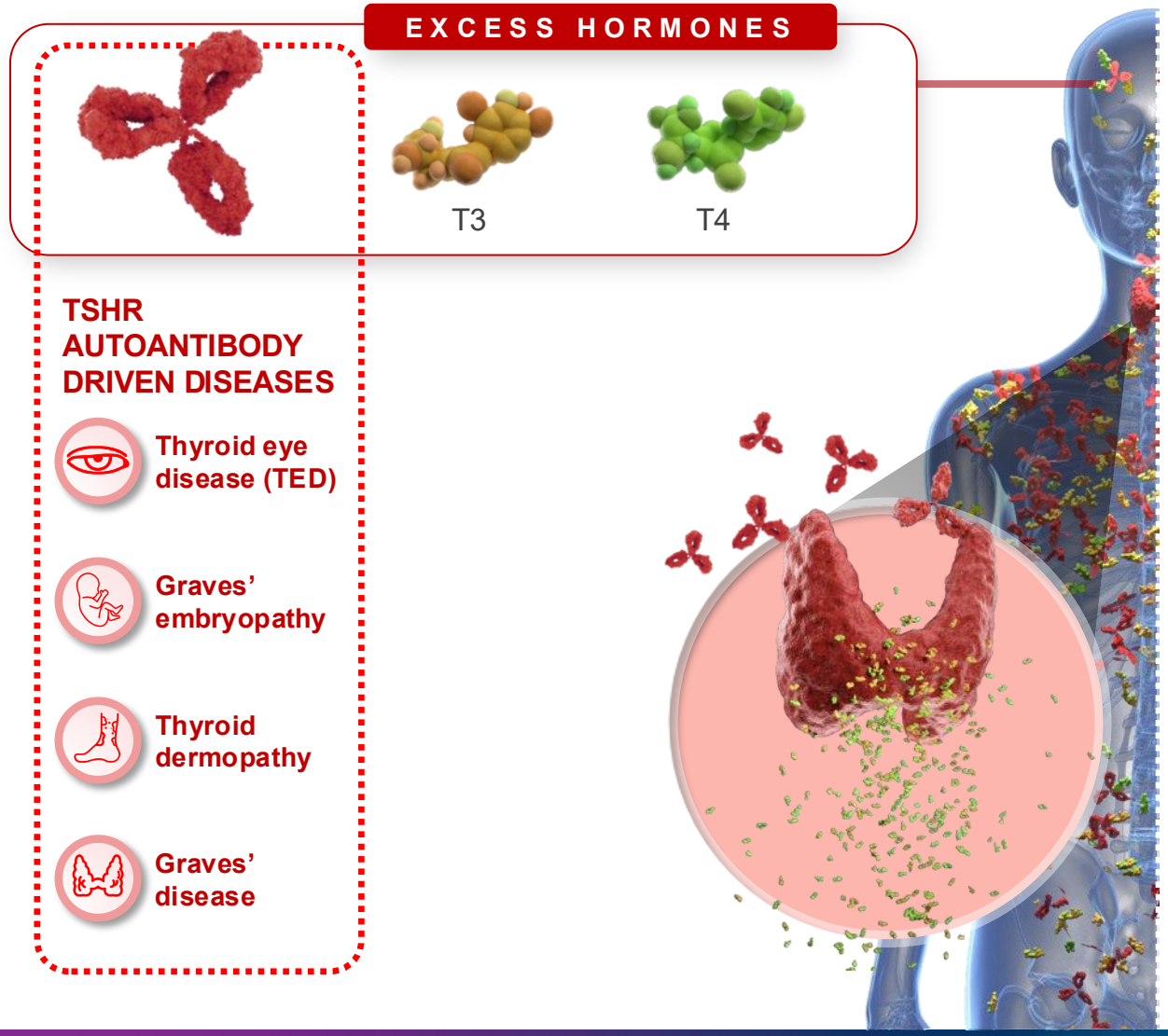
Imaging

Ultrasound, CT, I-123 thyroid uptake and scan

Diagnosis



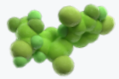
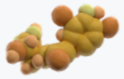
Root Cause of Graves' Disease and Extrathyroidal Manifestations



The TSHR autoantibody causes more than hyperthyroidism

TSHR autoantibodies don't just attack the thyroid, they target TSHR-expressing cells across multiple organs

TSHR Autoantibodies (TSHR-IgG1) Cause Hyperthyroidism

	Hyperthyroidism (from a toxic nodule)	Graves' disease hyperthyroidism	Autoimmune hypothyroidism (Hashimoto's)
Thyroid stimulating hormone (TSH)	↓	↓	↑
Thyroxine (T4) 	↑	↑	↓
Thyronine (T3) 	↑	↑	↓
Thyroid receptor antibody (TRAb)	−	+	−
Thyroid stimulating immunoglobulin (TSI)	−	+	−
Thyroid peroxidase antibody (TPO Ab)	−	+	+

KEY POINT

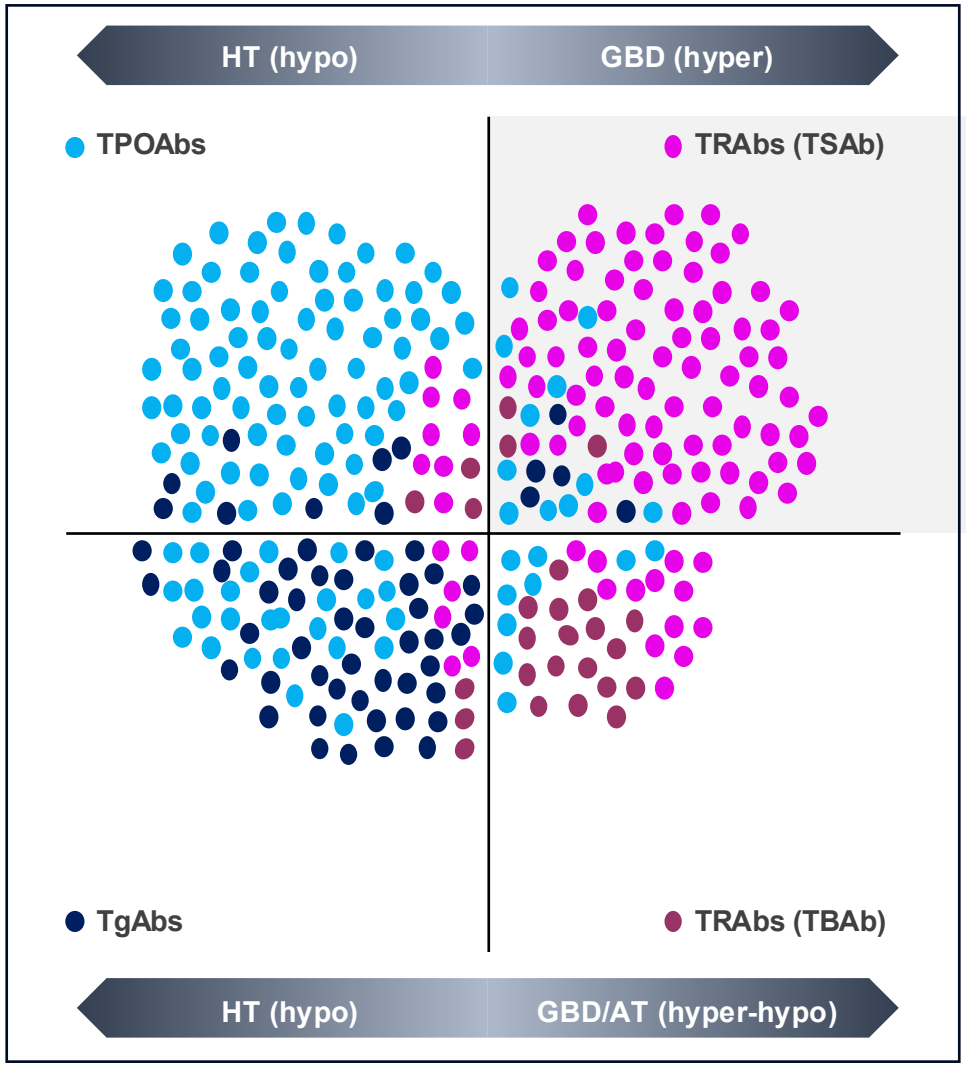
TSHR-IgG1 causes Graves' Hyperthyroidism, the diagnosis of which is made when a patient has elevated thyroid hormones and TSHR autoantibodies present

The Antibody Landscape in Autoimmune Thyroid Disease

DEGRADERS

Most Hashimoto's patients have TPO antibodies, these attack the thyroid and cause it to underproduce hormones (**hypo**thyroidism)

Some Hashimoto's patients also have thyroglobulin antibodies, a second marker, but less common



Graves' patients have stimulating TRAb

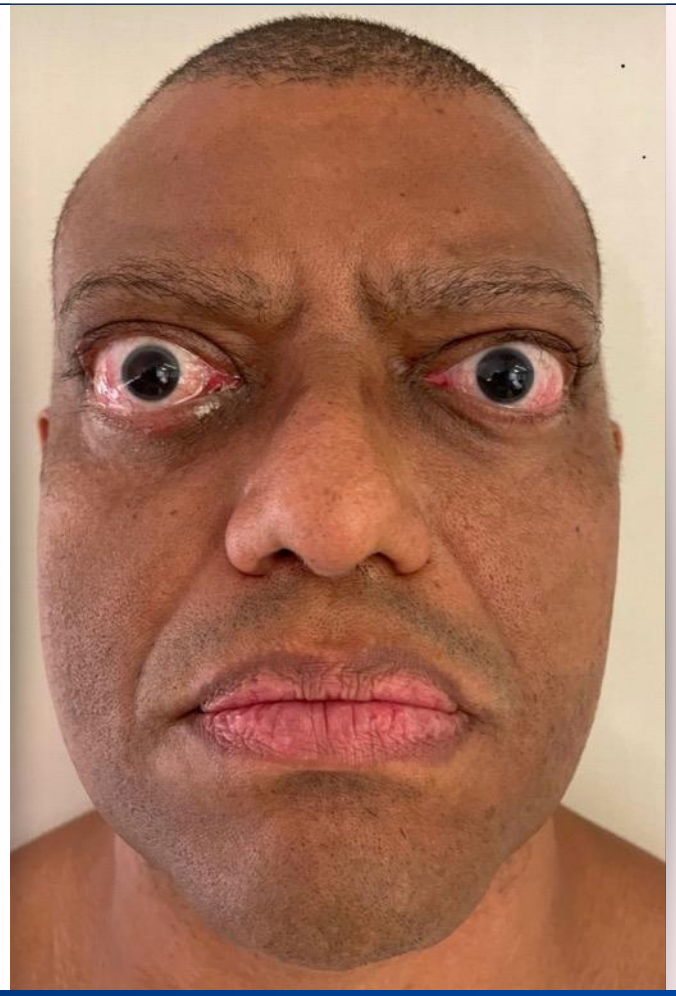
These force the thyroid to overproduce hormones (hyperthyroidism)

A small group also have blocking TRAb, these shut the thyroid down, causing a rare shift from hyper- to hypothyroidism

Adapted from: Vargas-Uricoechea H, Nogueira JP, Pinzón-Fernández MV, Schwarzstein D. The Usefulness of Thyroid Antibodies in the Diagnostic Approach to Autoimmune Thyroid Disease. *Antibodies*. 2023; 12(3):48. https://doi.org/10.3390/antib12030048

Thyroid Eye Disease (TED)

TRAb autoantibodies cross-react with IGF-1R on orbital fibroblasts which leads to inflammation and tissue remodeling



CLINICAL CONSEQUENCES

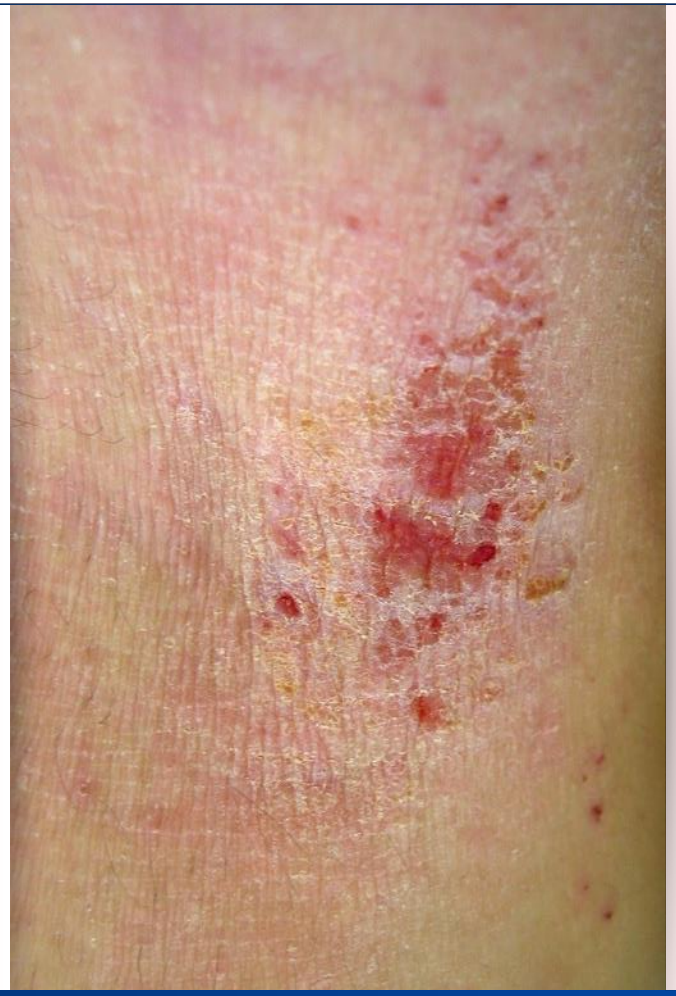
- Proptosis (exophthalmos) — orbital fat expansion pushes the globe forward
- Lid retraction and stare
- Diplopia (double vision)
- Pain and pressure sensation
- Periorbital edema
- Vision loss (severe cases)

KEY POINT

50% of Graves' patients develop TED — it can occur even with normal thyroid function

Pretibial Myxedema, a Form of Graves' Dermopathy

TRAb autoantibodies bind TSHR on dermal fibroblasts which leads to glycosaminoglycan deposition and dermal thickening.



CLINICAL CONSEQUENCES

- Non-pitting, waxy skin plaques
- Hyperkeratosis and skin thickening
- Cosmetic disfigurement
- Discomfort and reduced mobility (severe)
- Elephantiasic form (rare, most severe)
- **Can extend to feet, ankles, arms and other sites**

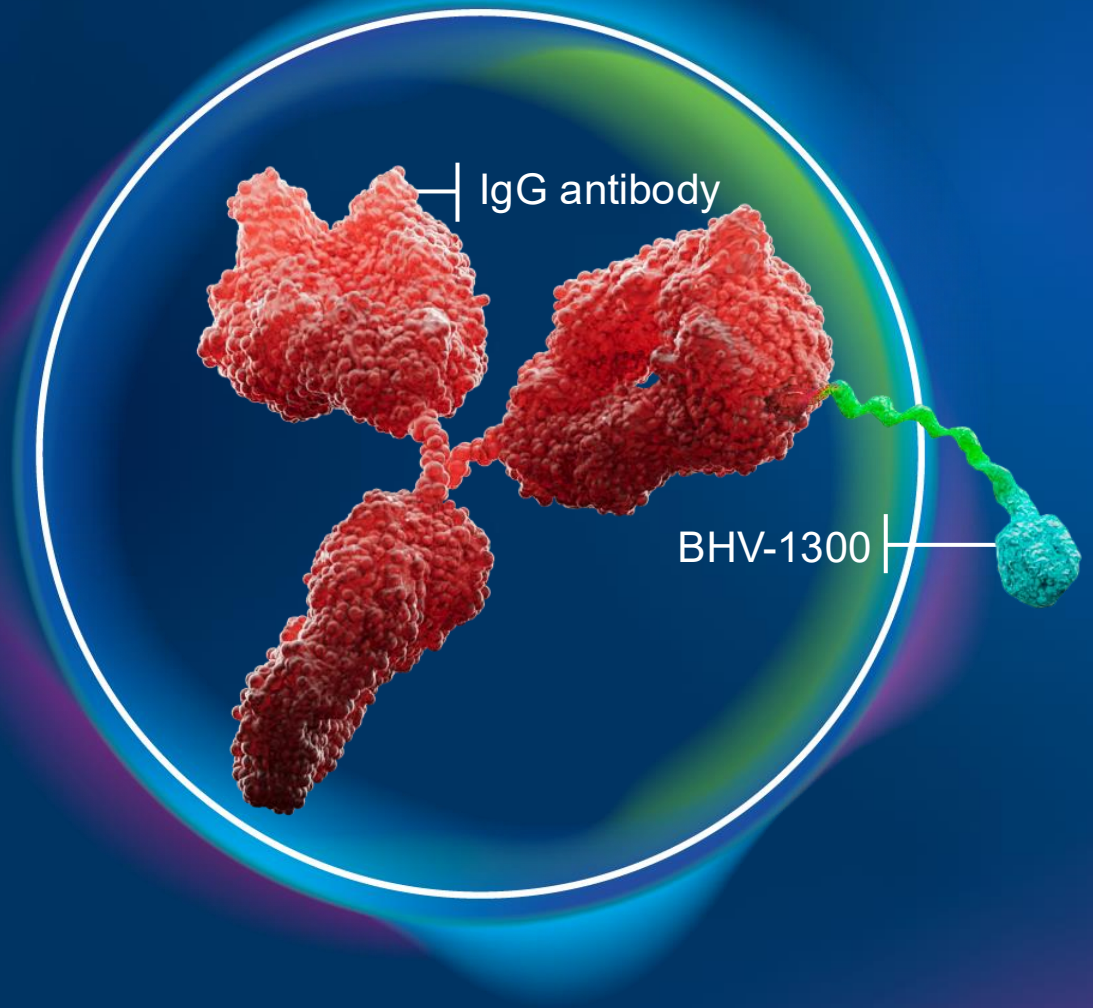
KEY POINT

Like TED, pretibial myxedema is driven by TRAb autoantibodies activating fibroblasts, a shared autoimmune mechanism, different tissue target

biohaven®

NEW TREATMENTS IN GRAVES' DISEASE

The Evolving Therapeutic Landscape



Current Treatments for Graves' Disease

CONSERVATIVE

1. **Use of thionamides**
   (ATDs, like methimazole, carbimazole, and propylthiouracil (PTU)
   Aplastic anemia, granulocytosis, peripheral neuritis, liver issues, secreted in breastmilk
2. **Use of steroids**

ABLATIVE

3. **Surgical removal of the thyroid**
   Lifelong T4 replacement, surgical complications
4. **Use of I-131 radiation treatment**
   Cannot use in pregnancy, TED worsens

BHV-1300 MoDE™ Targets the Root Cause of Graves' Disease and TSHR Autoantibody-Driven Diseases

DEGRADERS

EXCESS HORMONES

T3 T4

TSHR AUTOANTIBODY DRIVEN DISEASES

- Thyroid eye disease
- Graves' embryopathy
- Thyroid dermopathy
- Graves' disease

STABILIZED HORMONES

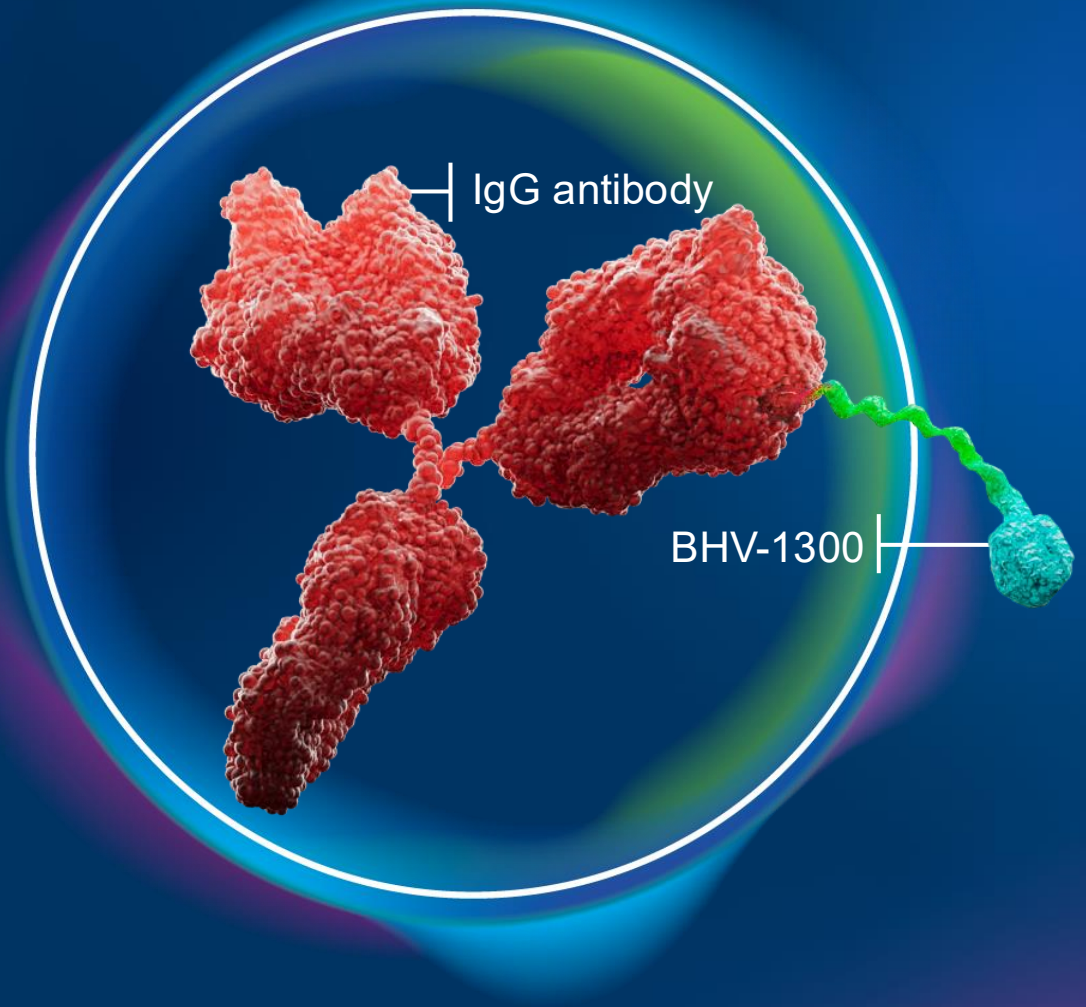
T3 T4

BHV-1300

BHV-1300 degrades disease-causing TSHR-IgG1 antibodies

biohaven®

BHV-1300 in Graves' Disease



Not FcRn Inhibitor: Biohaven IgG MoDE™ Degrader Differentiates as a Novel MOA, Potential Paradigm Shifting Therapy

DEGRADERS

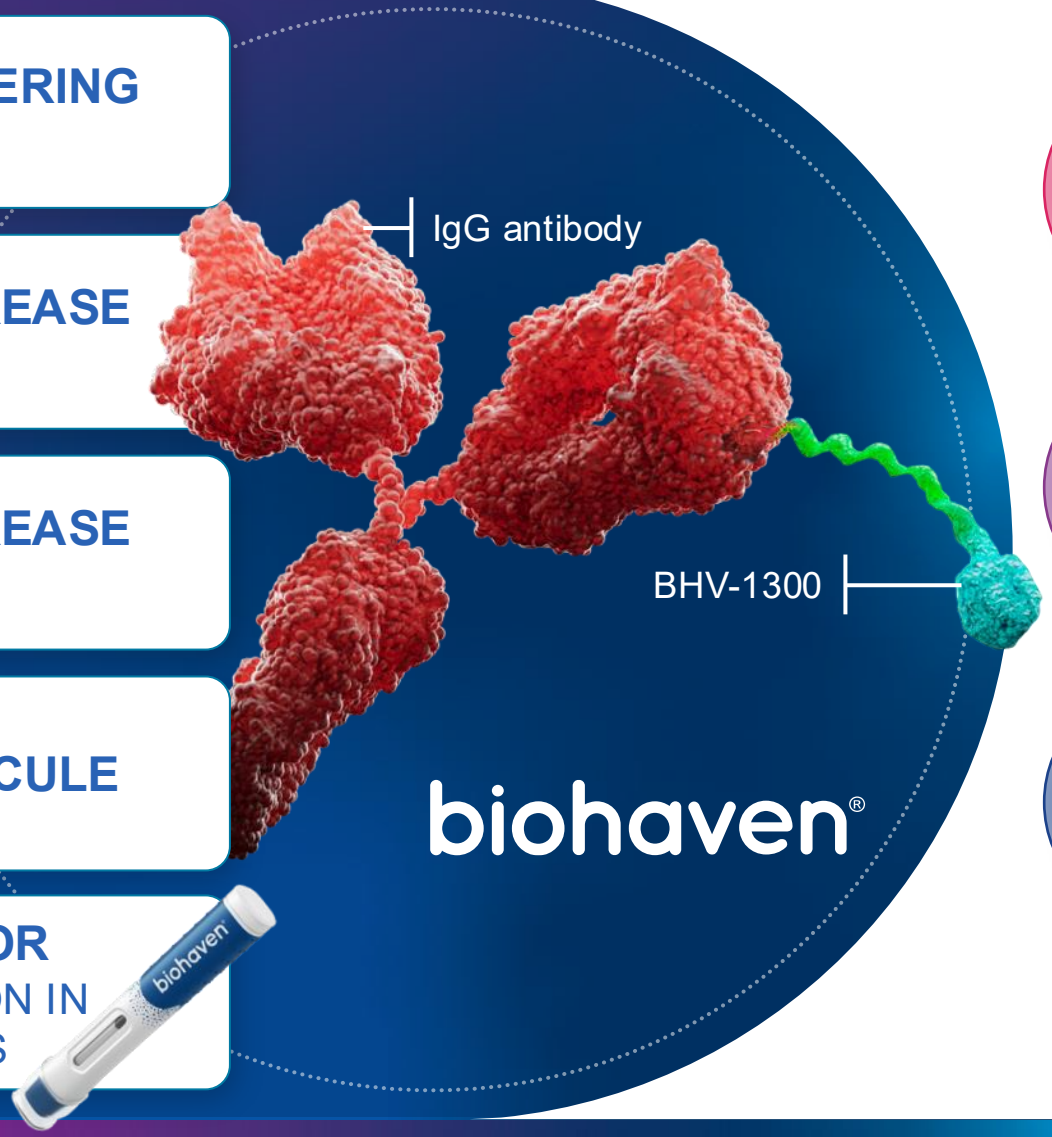
83% IgG LOWERING
BY DAY 18

DID NOT INCREASE
HEADACHES

DID NOT INCREASE
CHOLESTEROL

SMALL MOLECULE

AUTOINJECTOR
ADMINISTRATION IN PIVOTAL TRIALS



IMAAVY™ J&J

- 74.6% IgG lowering after load, 68.8% in maintenance in Vivacity MG-3[1,2]
- **IV infusion**
- Increased cholesterol (24%), muscle spasms (12%), edema (12%)

Vyvgart® argenx

- Approximately 61% IgG lowering at week 4 (VYVGART Hytrulo® in MG trial)[3] (average 75% in MAD)[4]
- Prefilled syringe
- Cyclical dosing can lead to symptom rebound

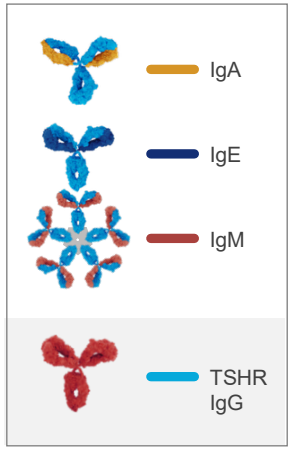
Rystiggo® UCB

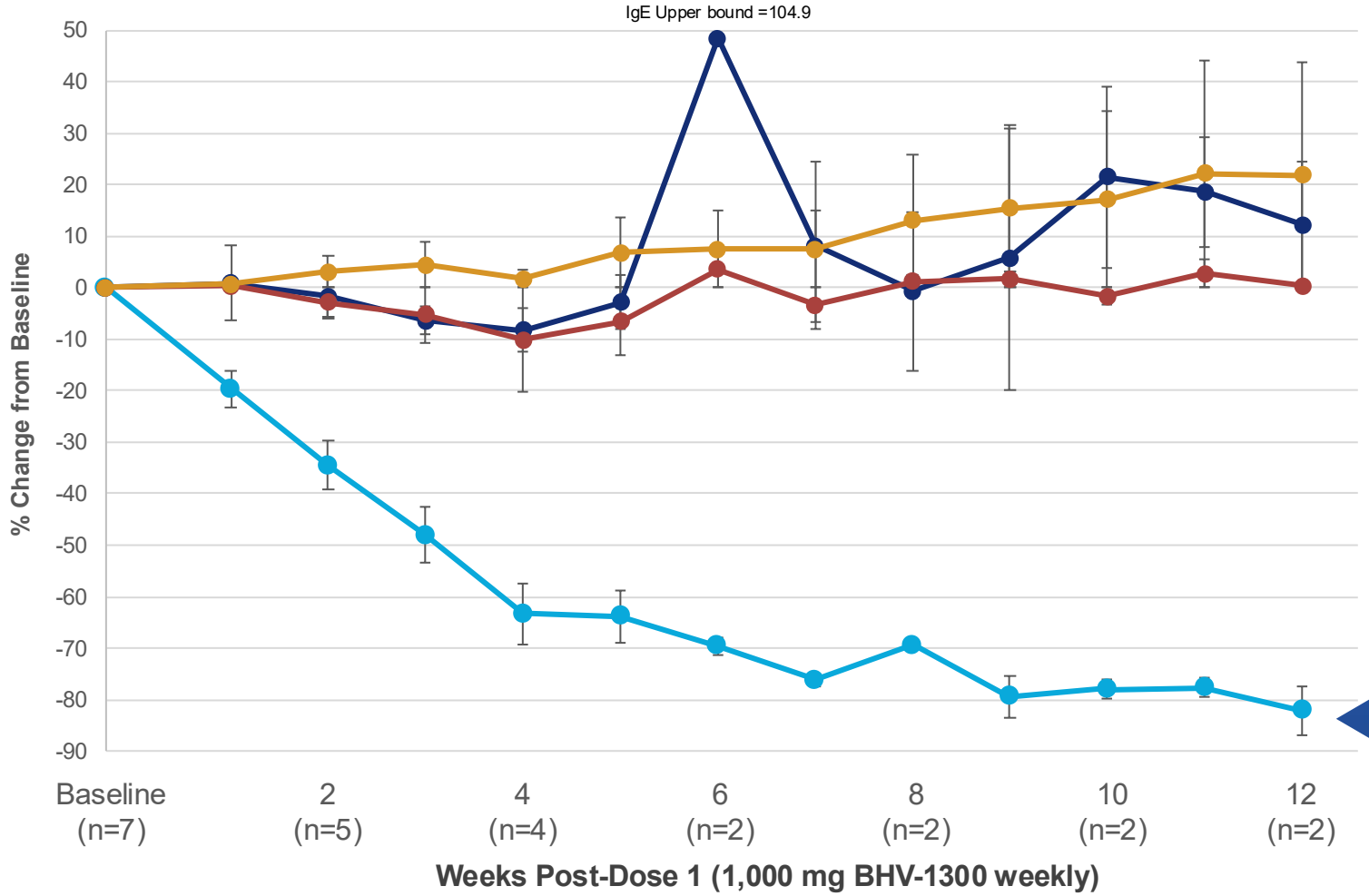
- Approximately 76% IgG lowering in the MycarinG study[5]
- Healthcare administered SC infusion
- **44% headaches**
- Cyclical dosing can lead to symptom rebound

1. Median of the maximal total IgG % change from baseline **2.** 84% IgG lowering (twice the labeled frequency) in Phase 1; Ling. Clin Pharmacol Ther. 2019. **3.** Howard, Jr. ADAPT (SC) Data – 2024; **4.** Ulrichts. J. Clin. Invest. 2018. **5.** MAD data unavailable. MG Data from Bril, Lancet Neurology. 2023 – MyCarinG study.

BHV-1300 Rapidly Degrades Disease-Causing Autoantibodies That Target the Thyroid-Stimulating Hormone Receptors (TSHR) in Patients with Graves' Disease

DEGRADERS

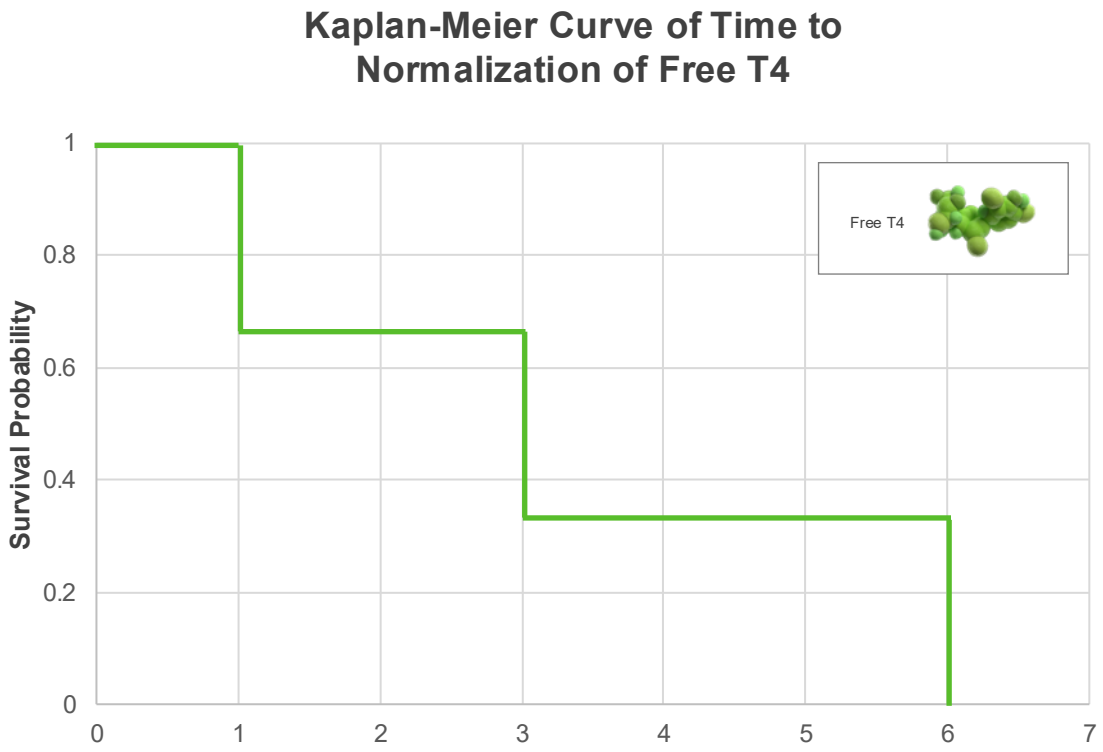


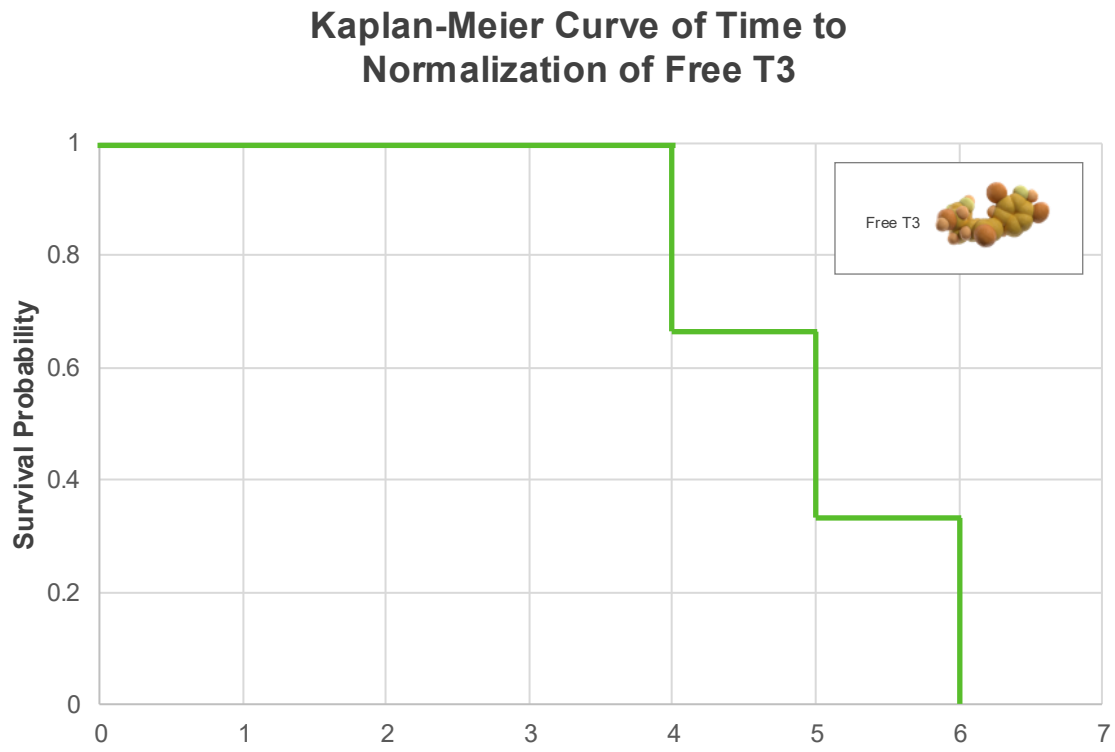


Preliminary data from ongoing study, analysis conducted May 20, 2026. *Graph represents mean in participants administered BHV-1300 1,000 mg SC weekly. Values below the lower limit of quantification were set to a value of LOQ/2.

BHV-1300 Rapidly Normalizes Thyroid Hormones in Patients With Graves' Hyperthyroidism

DEGRADERS





Weeks Post-Dose 1

Preliminary data from ongoing study, analysis conducted April 8, 2026. Graphs represent time to normalization of Free T3 and Free T4 in participants (n=3) with Graves' disease and overt hyperthyroidism at baseline administered BHV-1300 1,000 mg SC weekly for 12 weeks (n=2) or BHV-1300 1000 mg SC weekly for 4 weeks followed by 500 mg SC weekly for 8 weeks (n=1).

KEY POINT

In hyperthyroid patients receiving BHV-1300 1,000 mg SC weekly, Free T4 normalized within an average of 3 weeks and Free T3 normalized within an average of 5 weeks

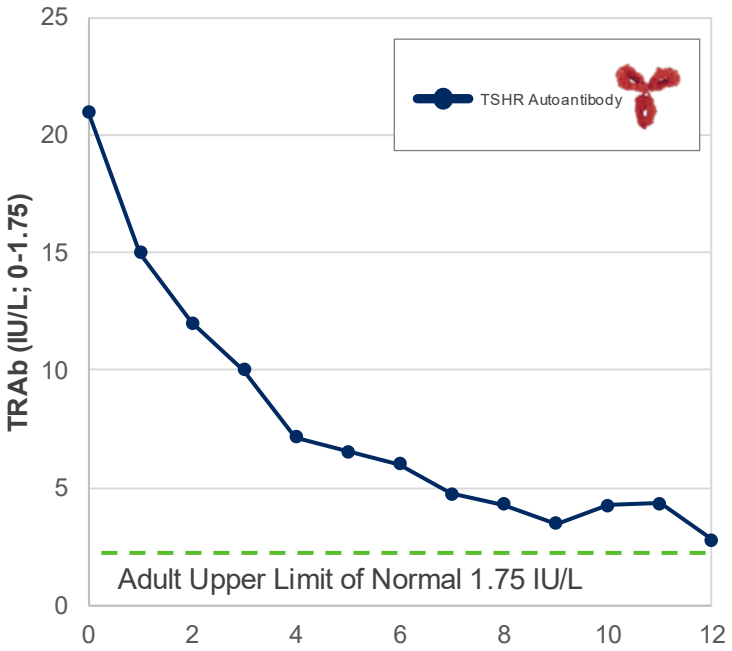
Early Graves' Patient Experience: Most Severely Hyperthyroid Patient BHV-1300 Rapidly Normalizes Thyroid Hormones

DEGRADERS

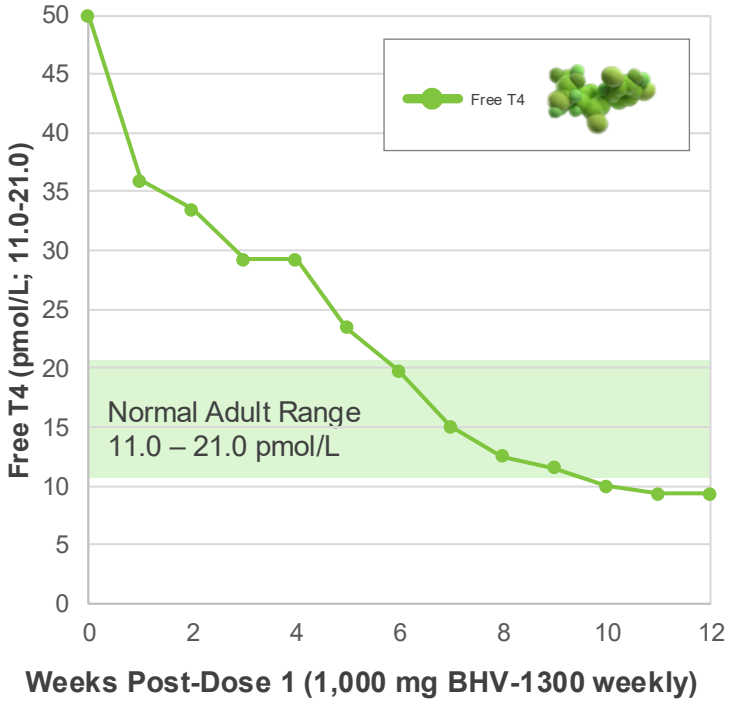
CASE DETAILS

- Male patient in his late 50s
- Severely elevated thyroid hormone levels at baseline
- Patient reported **improvement in sweating, palpitations, diarrhea, fatigue and motivation** at 30 days compared to baseline
- TSH normalized within 12 weeks of BHV-1300 initiation

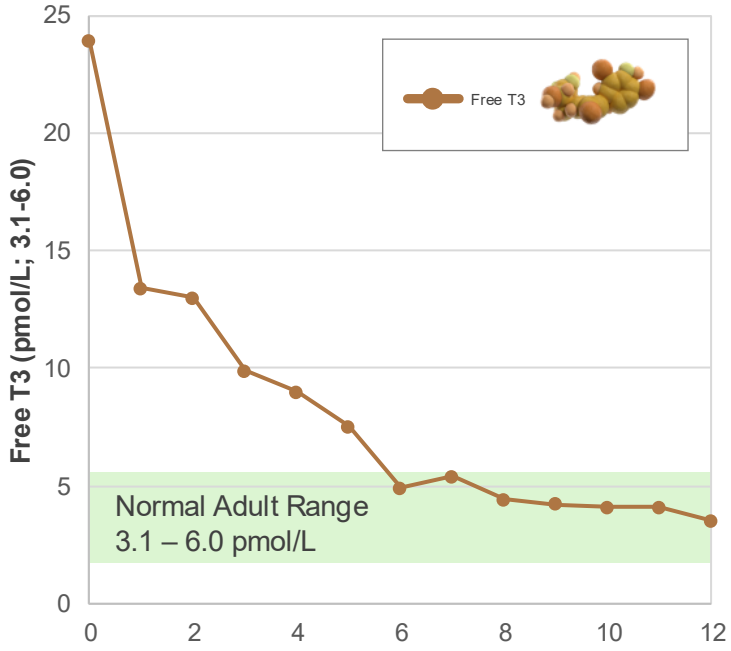
TRAb Change from Baseline



Change from Baseline in Free T4



Change from Baseline in Free T3



Preliminary data from ongoing study, analysis conducted April 8, 2026.

Early Graves' Patient Experience: Severely Hyperthyroid Patient BHV-1300 Rapidly Normalizes TSH and Hyperthyroid Symptoms

DEGRADERS

CASE DETAILS

- Male patient in his late 50s
- Severely elevated thyroid hormone levels at baseline
- Patient reported **improvement in sweating, palpitations, diarrhea, fatigue and motivation** at 30 days compared to baseline
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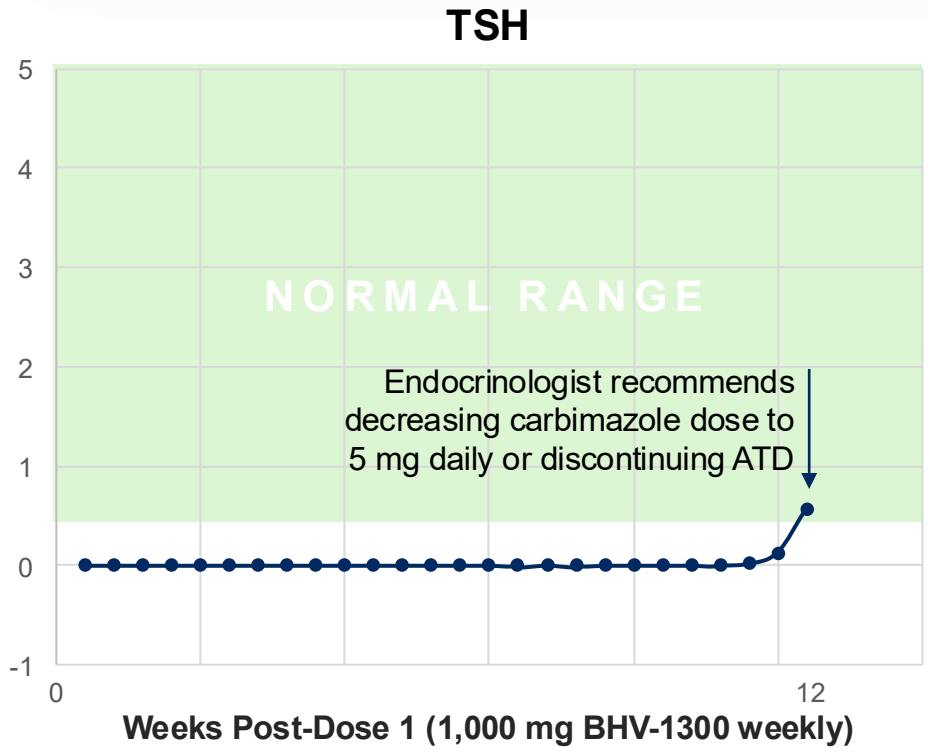


Baseline	Thypro-39 symptoms	End of dosing
	Trembling hands	Resolved
	Sweating	Resolved
	Palpitations	Resolved

Preliminary data from ongoing study, analysis conducted April 8, 2026.

Lead MoDE™ Degrader, BHV-1300, Enters Phase 3

KEY STUDY DETAILS

Study Design: Randomized, double-blind, placebo-controlled trial

Population: Male and female adults with Graves' disease

Endpoints: Normal T3, T4 and TSH off ATD at week 26

ATD, antithyroid drugs

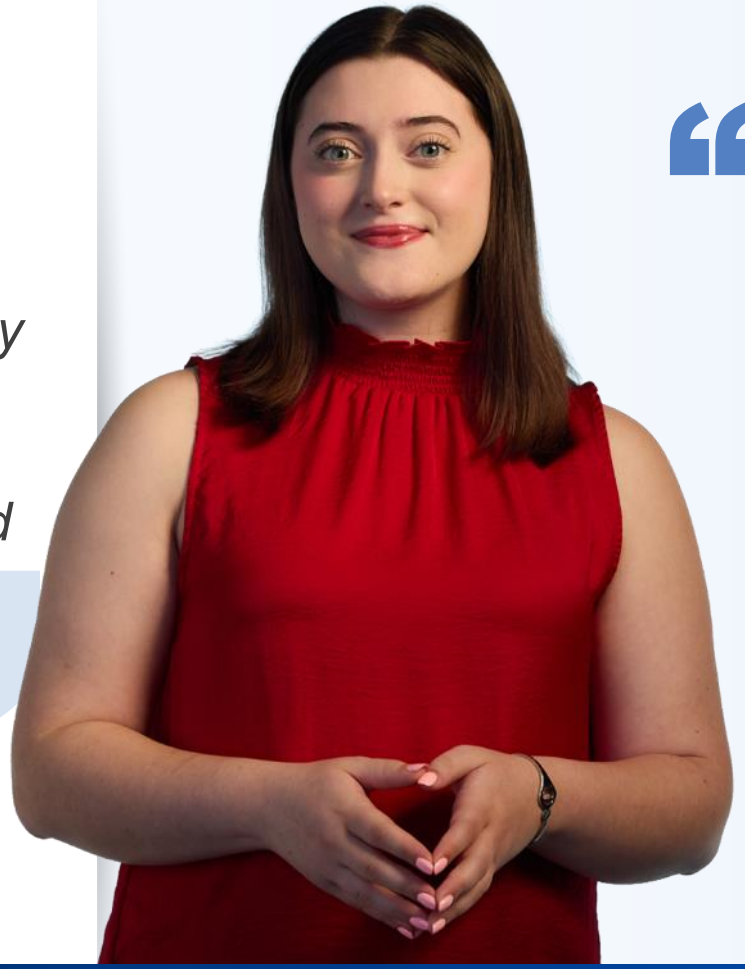
KEY POINT

BHV-1300 pivotal trial in Graves' disease commencing mid-2026

Patients Want To Target the Root Cause[1]

DEGRADERS

> *That's the most attractive thing, **removing the root cause rather than putting a Band-Aid on it**. It's essentially like **repairing the thyroid** or putting it **back into its original coding**, that it should work the way that it was originally designed to do.*



> *Going back to root cause is a pretty big deal. A lot of times, treatments just cover the symptoms. **You're putting a Band-Aid over what is a much larger wound**.*

Paige
Living with Graves' disease

1. Patient Burden in Graves' Disease: Results From a Mixed Methods Survey

KEY POINT

BHV-1300 is a precision degrader designed to target the autoantibody — addressing the root cause of Graves' disease

Professor Jonathan Barratt, PhD, FRCP

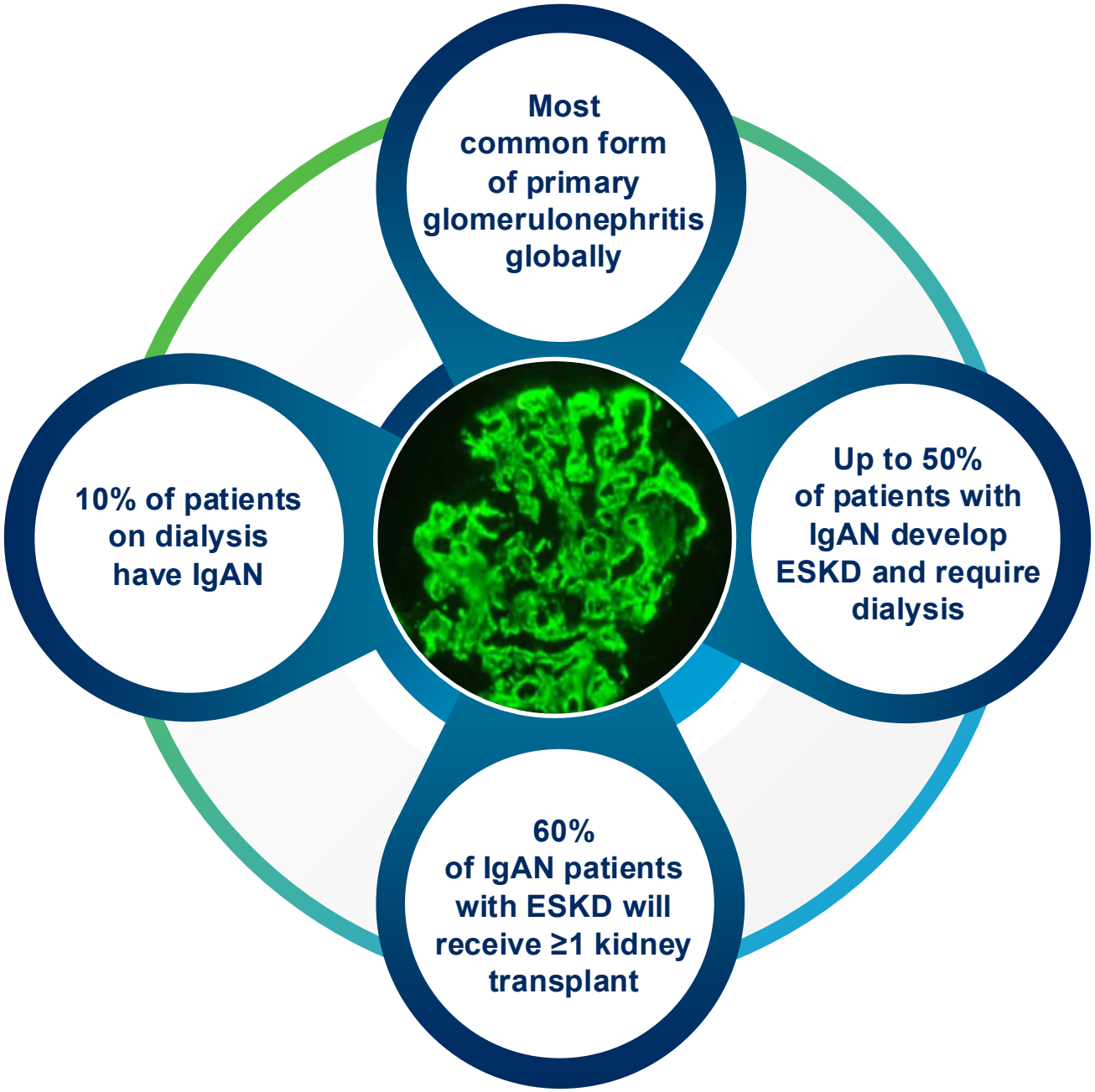
The Mayer Professor of Renal Medicine,
Department of Cardiovascular Sciences

UNIVERSITY OF LEICESTER

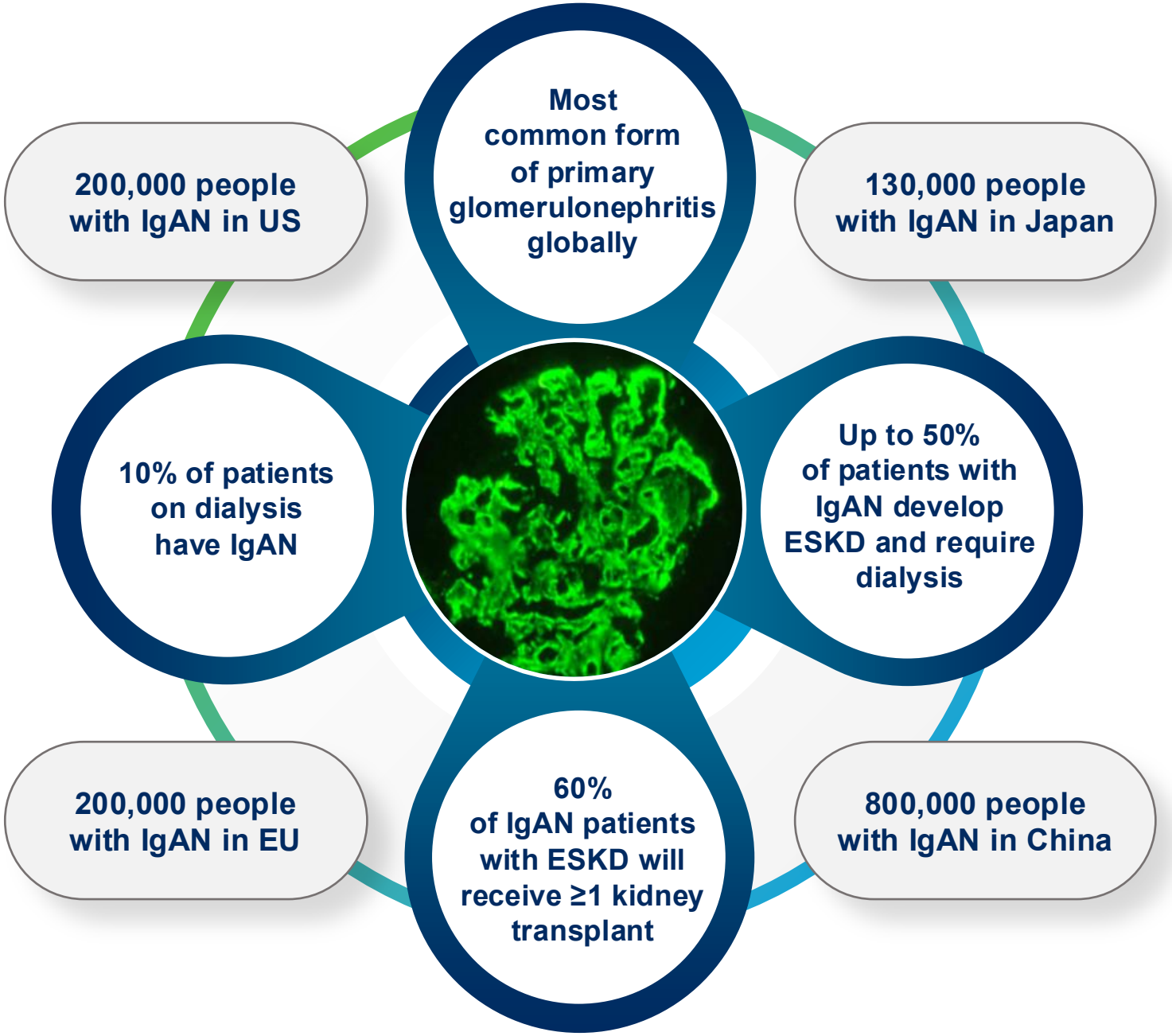
BHV-1400 for IgA Nephropathy

biohaven®

Jonathan Barratt	
Consulting and speaker fees	Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra
Grant support	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra
Clinical trials	ADU-CL-19 and ALIGN (Chinook), APPLAUSE (Novartis), ARTEMIS-IGAN (Omeros), ENVISION (Visterra), NeflgARD (Calliditas), ORIGIN (Vera Therapeutics)
Research projects	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra



Barrett. 2026.



Barrett. 2026.

KDIGO

SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

IMMUNOGLOBULIN A NEPHROPATHY

2.1 Diagnosis

Practice Point 2.1.1: Considerations regarding the diagnosis of immunoglobulin A nephropathy (IgAN):

- **IgAN can only be diagnosed with a kidney biopsy, as there are no validated diagnostic serum or urine biomarkers for IgAN.**
- **To ensure an early diagnosis and prompt treatment of IgAN, a kidney biopsy should be performed in all adults with proteinuria ≥0.5 g/d (or equivalent) in whom IgAN is a possible diagnosis and who do not have a contraindication for kidney biopsy.**
- **Once a diagnosis of IgAN is made, assess for secondary causes.**
- **In cases of primary IgAN, determine the MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.[80]**

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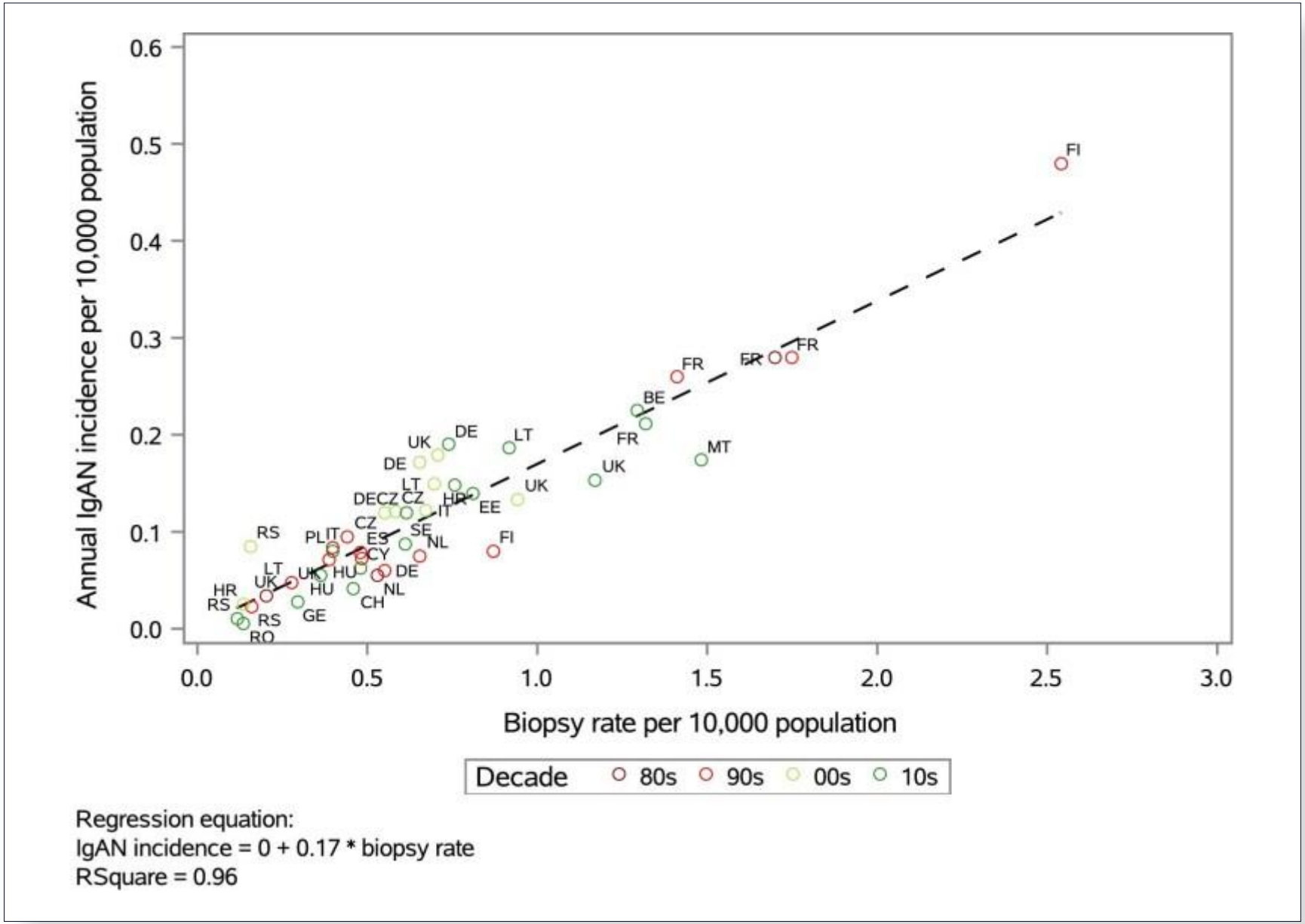

Buisker. Clin Kidney J. 2025.

RaDaR

National Registry of Rare Kidney Diseases

Effects of rare kidney diseases on kidney failure: a longitudinal analysis of the UK National Registry of Rare Kidney Diseases (RaDaR) cohort

*Katie Wong, David Pitcher, Fiona Braddon, Lewis Downward, Retha Steenkamp, Nicholas Annear, Jonathan Barratt, Coralie Bingham, Constantina Chrysochou, Richard J Coward, David Game, Sian Griffin, Matt Hall, Sally Johnson, Durga Kanigicherla, Fiona Karet Frankl, David Kavanagh, Larissa Kerecuk, Eamonn R Maher, Shabbir Moochhala, Jenny Pinney, John A Sayer, Roslyn Simms, Smeeta Sinha, Shalabh Srivastava, Frederick W K Tam, Andrew Neil Turner, Stephen B Walsh, Aoife Waters, Patricia Wilson, Edwin Wong, Christopher Mark Taylor, Dorothea Nitsch, Moin Saleem, Detlef Bockenhauer, Kate Bramham, Daniel P Gale, for the RaDaR consortium**

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Findings Between Jan 18, 2010, and July 25, 2022, 27 285 participants were recruited to RaDaR. Median follow-up time from diagnosis was 9·6 years (IQR 5·9–16·7). RaDaR participants had significantly higher 5-year cumulative incidence of kidney failure than 2·81 million UK patients with all-cause chronic kidney disease (28% *vs* 1%; p<0·0001), but better survival rates (standardised mortality ratio 0·42 [95% CI 0·32–0·52]; p<0·0001). Median age at kidney failure, median age at death, time from start of dialysis to death, time from diagnosis to eGFR thresholds, and therapeutic trial window all varied substantially between rare diseases.

Interpretation Patients with rare kidney diseases differ from the general population of individuals with chronic kidney disease: they have higher 5-year rates of kidney failure but higher survival than other patients with chronic kidney disease stages 3–5, and so are over-represented in the cohort of patients requiring kidney replacement therapy. Addressing unmet therapeutic need for patients with rare kidney diseases could have a large beneficial effect on long-term kidney replacement therapy demand.

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More than 50% of children and those younger than 20 years receiving kidney replacement therapy have a rare kidney disease.[7] In contrast to earlier chronic kidney disease stages, glomerulonephritis (which comprises multiple individually rare disorders) accounts for more UK adults receiving kidney replacement therapy than do common causes of chronic kidney disease, such as

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RaDaR
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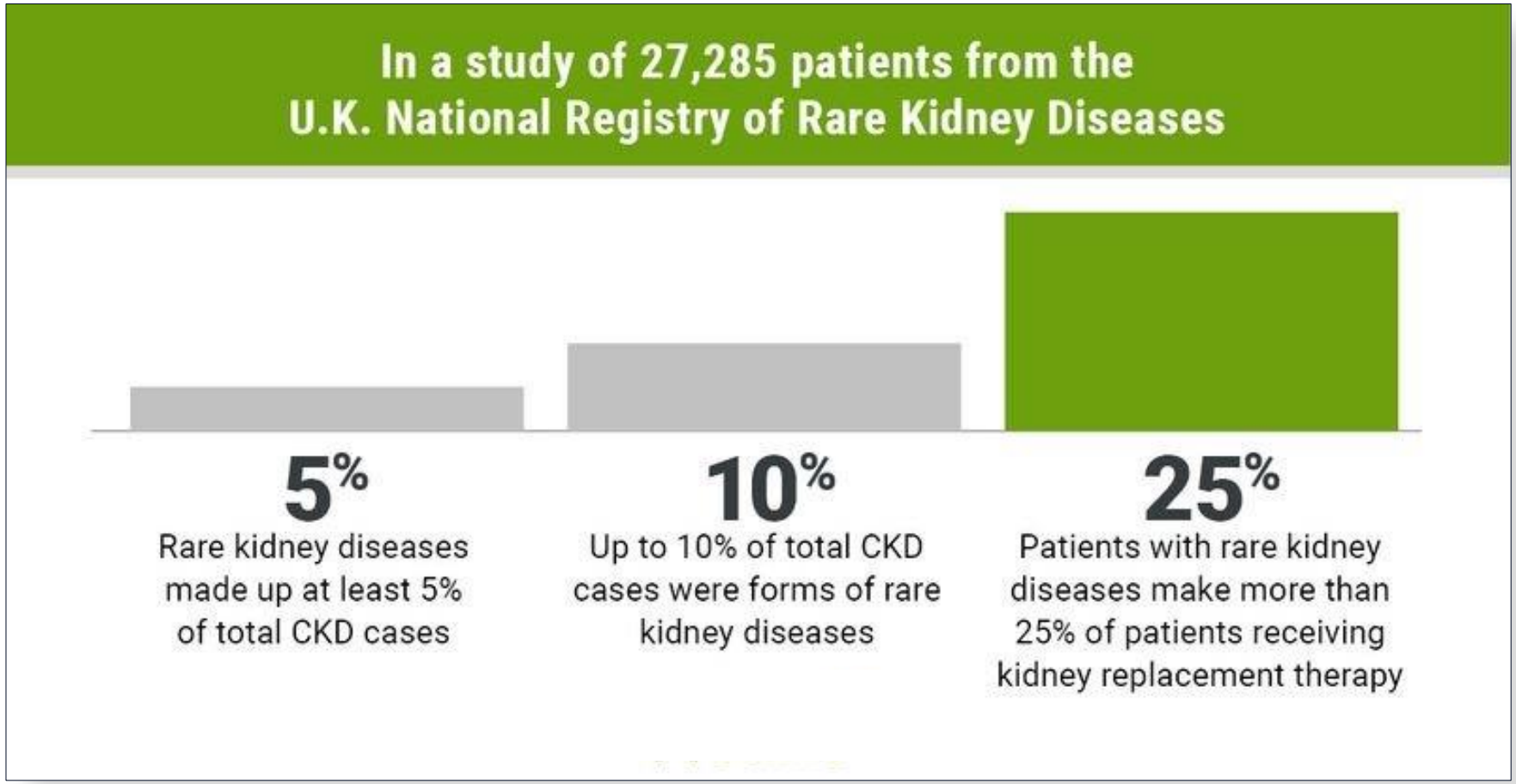

Lancet Pub

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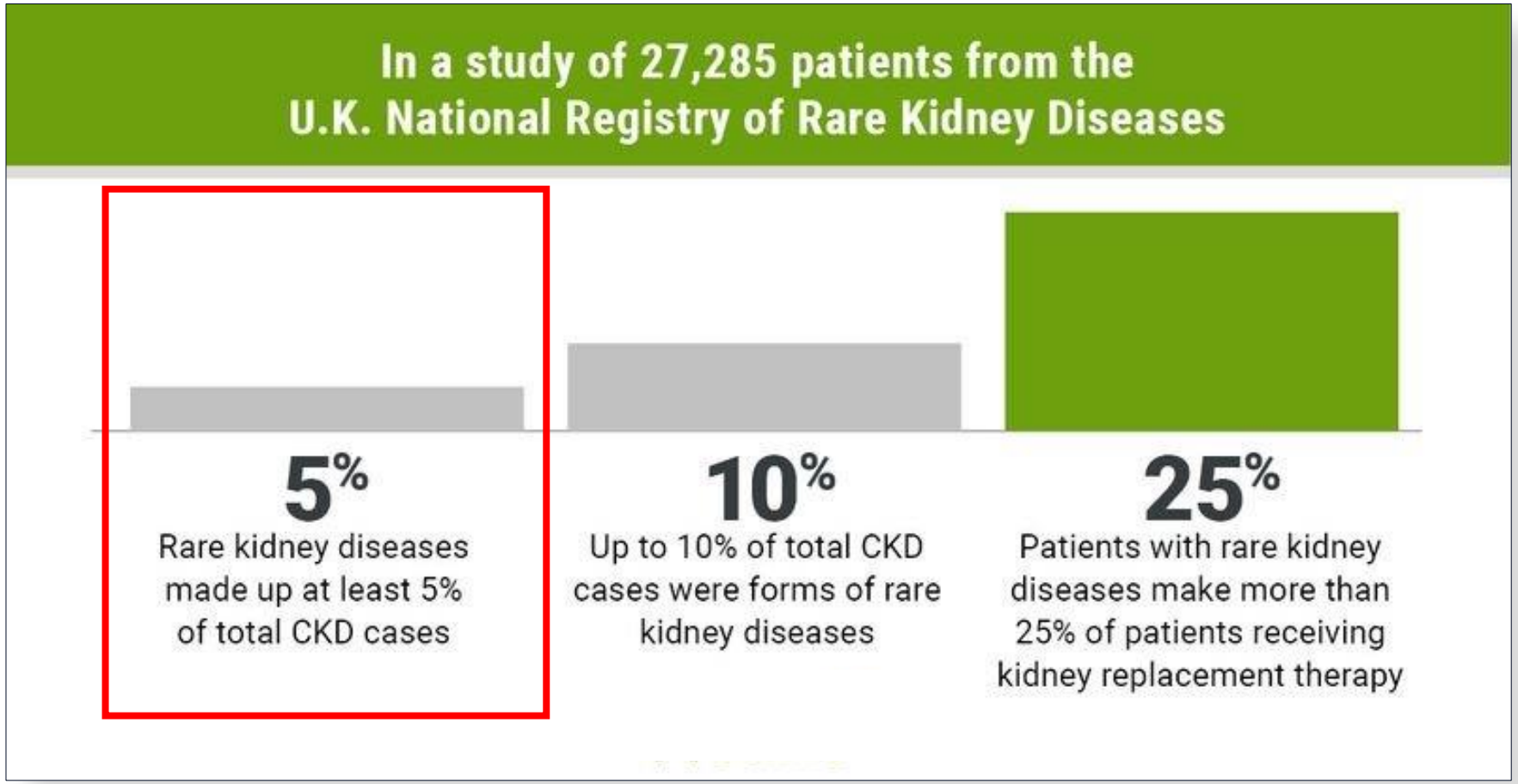

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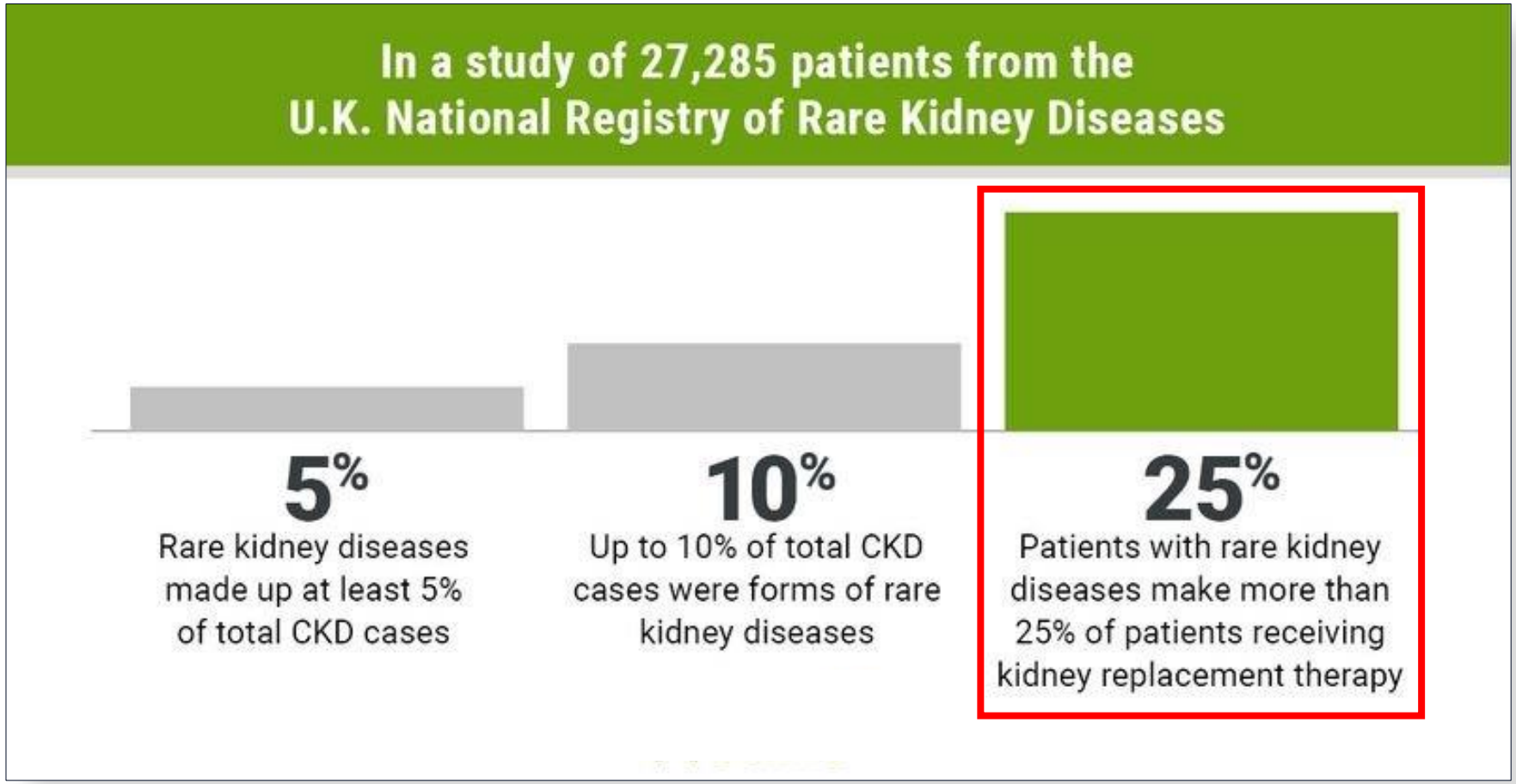

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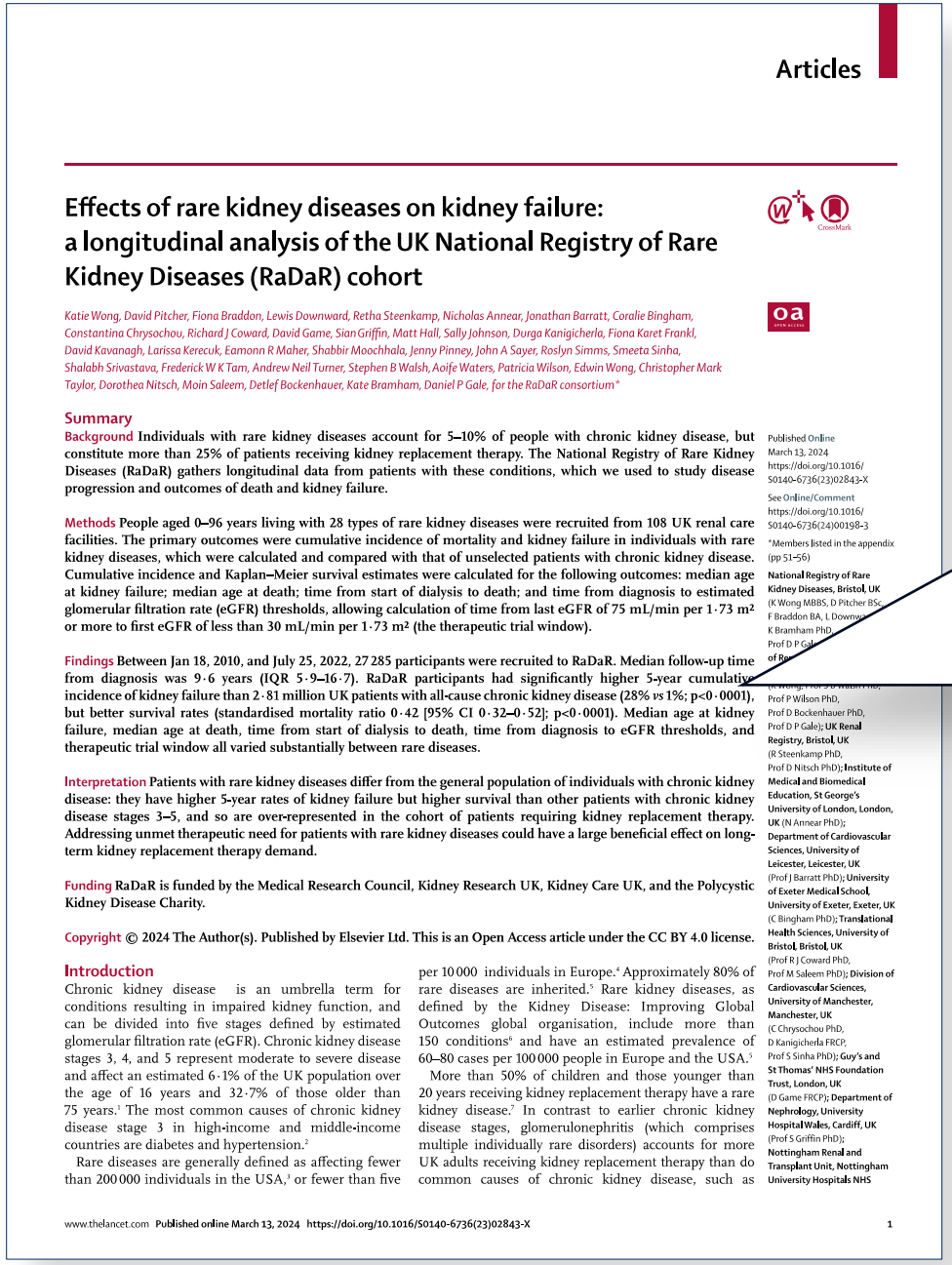

Articles

Effects of rare kidney diseases on kidney failure: a longitudinal analysis of the UK National Registry of Rare Kidney Diseases (RaDaR) cohort

Katie Wong, David Pitcher, Fiona Braddon, Lewis Downward, Retha Steenkamp, Nicholas Annear, Jonathan Barratt, Coralie Bingham, Constantina Chrysochou, Richard J Coward, David Game, Sian Griffin, Matt Hall, Sally Johnson, Durga Kanigicherla, Fiona Karet Frankl, David Kavanagh, Larissa Kerecuk, Eamonn R Maher, Shabbir Moochhala, Jenny Pinney, John A Sayer, Roslyn Simms, Smeeta Sinha, Shalabh Srivastava, Frederick W K Tam, Andrew Neil Turner, Stephen B Walsh, Aoife Waters, Patricia Wilson, Edwin Wong, Christopher Mark Taylor, Dorothea Nitsch, Moin Saleem, Detlef Bockenhauer, Kate Bramham, Daniel P Gale, for the RaDaR consortium*

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OPEN

Long-Term Outcomes in IgA Nephropathy

David Pitcher[1,2], Fiona Braddon[1], Bruce Hendry[3], Alex Mercer[4], Kate Osmaston[1], Moin A. Saleem[5], Retha Steenkamp[1], Katie Wong[1,2], A. Neil Turner[6], Kaijun Wang[7], Daniel P. Gale[2], and Jonathan Barratt[7,8]

Abstract

Background IgA nephropathy can progress to kidney failure, and risk assessment soon after diagnosis has advantages both for clinical management and the development of new therapeutics. We present relationships among proteinuria, eGFR slope, and lifetime risks for kidney failure.

Methods The IgA nephropathy cohort (2299 adults and 140 children) of the UK National Registry of Rare Kidney Diseases (RaDaR) was analyzed. Patients enrolled had a biopsy-proven diagnosis of IgA nephropathy plus proteinuria >0.5 g/d or eGFR <60 ml/min per 1.73 m². Incident and prevalent populations and a population representative of a typical phase 3 clinical trial cohort were studied. Analyses of kidney survival were conducted using Kaplan–Meier and Cox regression. eGFR slope was estimated using linear mixed models with random intercept and slope.

Results The median (Q1, Q3) follow-up was 5.9 (3.0, 10.5) years; 50% of patients reached kidney failure or died in the study period. The median (95% confidence interval [CI]) kidney survival was 11.4 (10.5 to 12.5) years; the mean age at kidney failure/death was 48 years, and most patients progressed to kidney failure within 10–15 years. On the basis of eGFR and age at diagnosis, almost all patients were at risk of progression to kidney failure within their expected lifetime unless a rate of eGFR loss ≤1 ml/min per 1.73 m² per year was maintained. Time-averaged proteinuria was significantly associated with worse kidney survival and more rapid eGFR loss in incident, prevalent, and clinical trial populations. Thirty percent of patients with time-averaged proteinuria of 0.44 to <0.88 g/g and approximately 20% of patients with time-averaged proteinuria <0.44 g/g developed kidney failure within 10 years. In the clinical trial population, each 10% decrease in time-averaged proteinuria from baseline was associated with a hazard ratio (95% CI) for kidney failure/death of 0.89 (0.87 to 0.92).

Conclusions Outcomes in this large IgA nephropathy cohort are generally poor with few patients expected to avoid kidney failure in their lifetime. Significantly, patients traditionally regarded as being low risk, with proteinuria <0.88 g/g (<100 mg/mmol), had high rates of kidney failure within 10 years.

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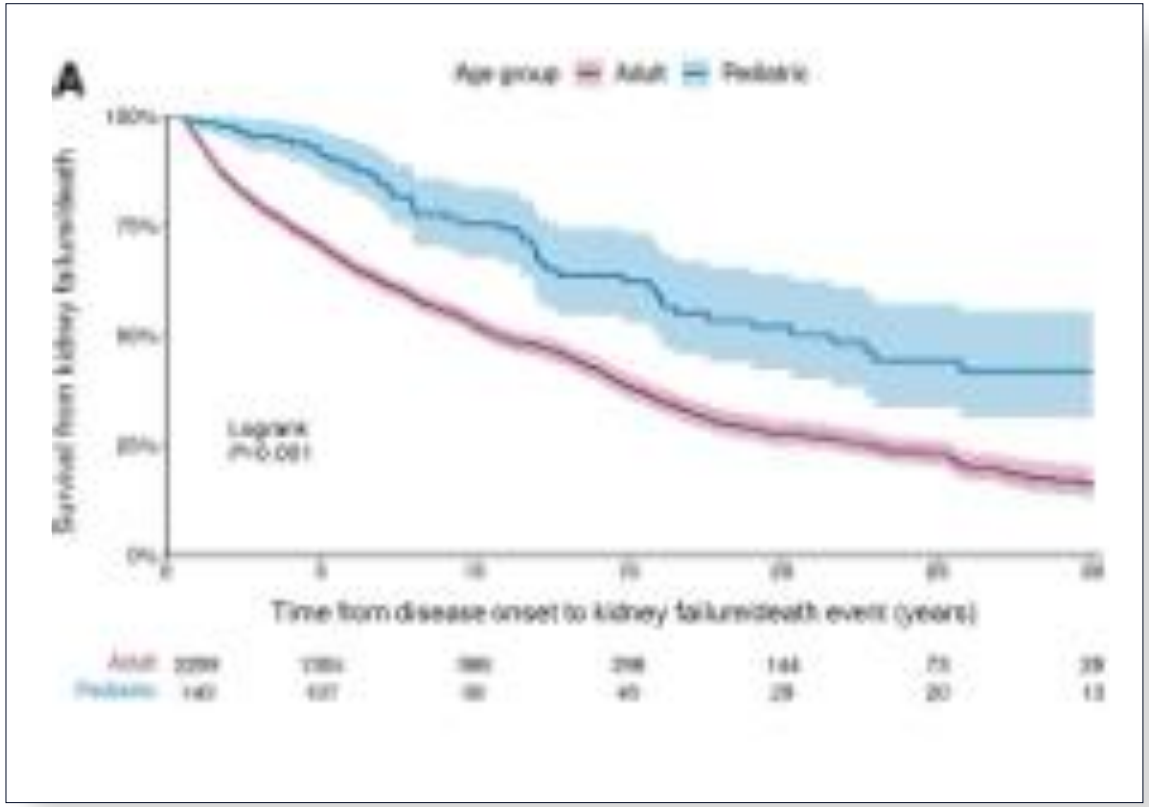
Introduction

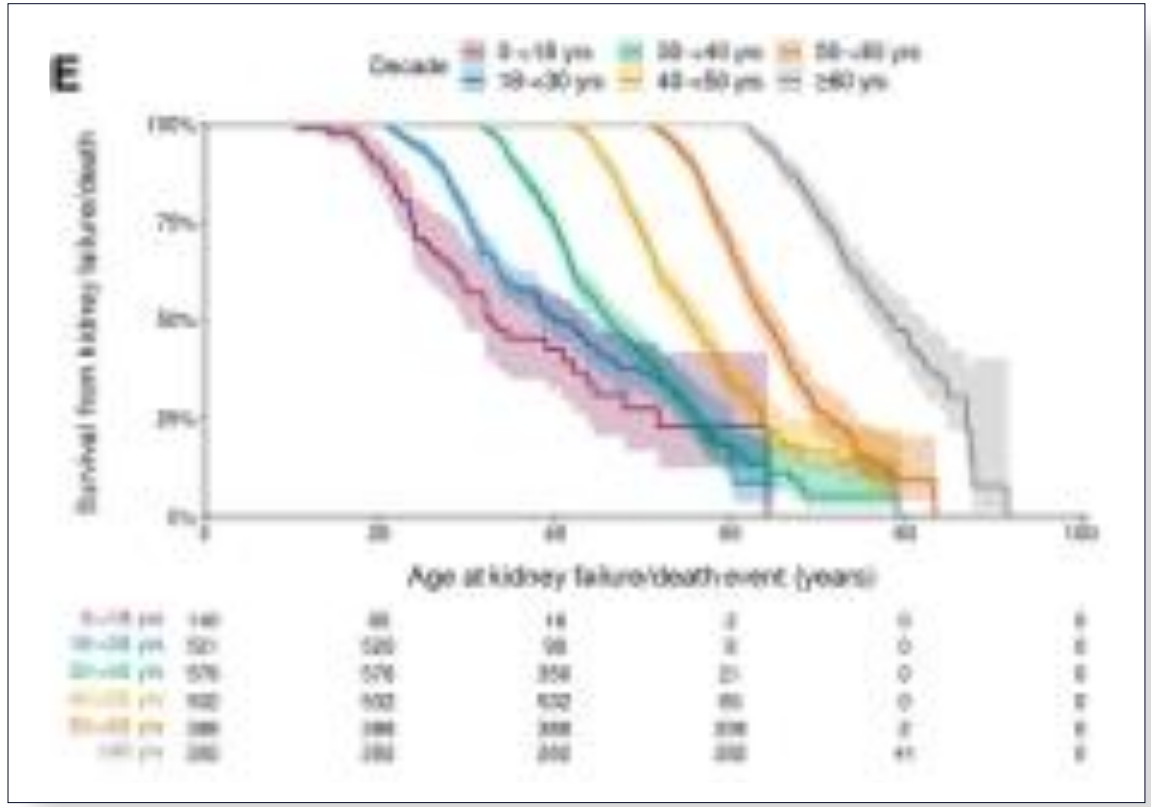
IgA nephropathy is the most common form of primary glomerulonephritis and a major cause of CKD and kidney failure worldwide.[1,2] Most patients are diagnosed before age 40 years.[3–5] Life expectancy in countries where IgA nephropathy is commonly encountered varies from 70 to 85 years.[6] Current perceptions of risk of progression are based on outcome data typically spanning 10 or 15 years,[8,9] a relatively short period that represents less than half the remaining lifespan of the typical patient with IgA nephropathy.

To facilitate investment in new therapies, a focus of recent research has been to identify surrogate end points that predict long-term clinical outcomes.[8,9] Reduction in proteinuria has recently been accepted by regulatory authorities as a reasonably likely surrogate end point for IgA nephropathy.[10] The design of ongoing phase 2 and 3 randomized controlled trials (RCTs) focuses on generating data over a 1- to 2-year period for proteinuria and rate of eGFR loss. After the inception of this approach, more than 15 phase 2 or 3 RCTs for new therapeutic approaches for IgA nephropathy are in progress in 2022.

Outstanding questions are first, the extent to which such short-term proteinuria and eGFR data predict the long-term rate of eGFR loss and risk of kidney failure in IgA nephropathy, and second, the degree of proteinuria reduction that would be associated with slowing eGFR decline so that kidney failure is not reached during a patient's lifetime. According to the Kidney Disease Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases,[11] a reduction of proteinuria to <1 g/d is considered as a reasonable treatment target in patients with IgA nephropathy. However, long-term outcomes for patients with proteinuria <1 g/d need to be better understood.

RaDaR
National Registry of Rare Kidney Diseases





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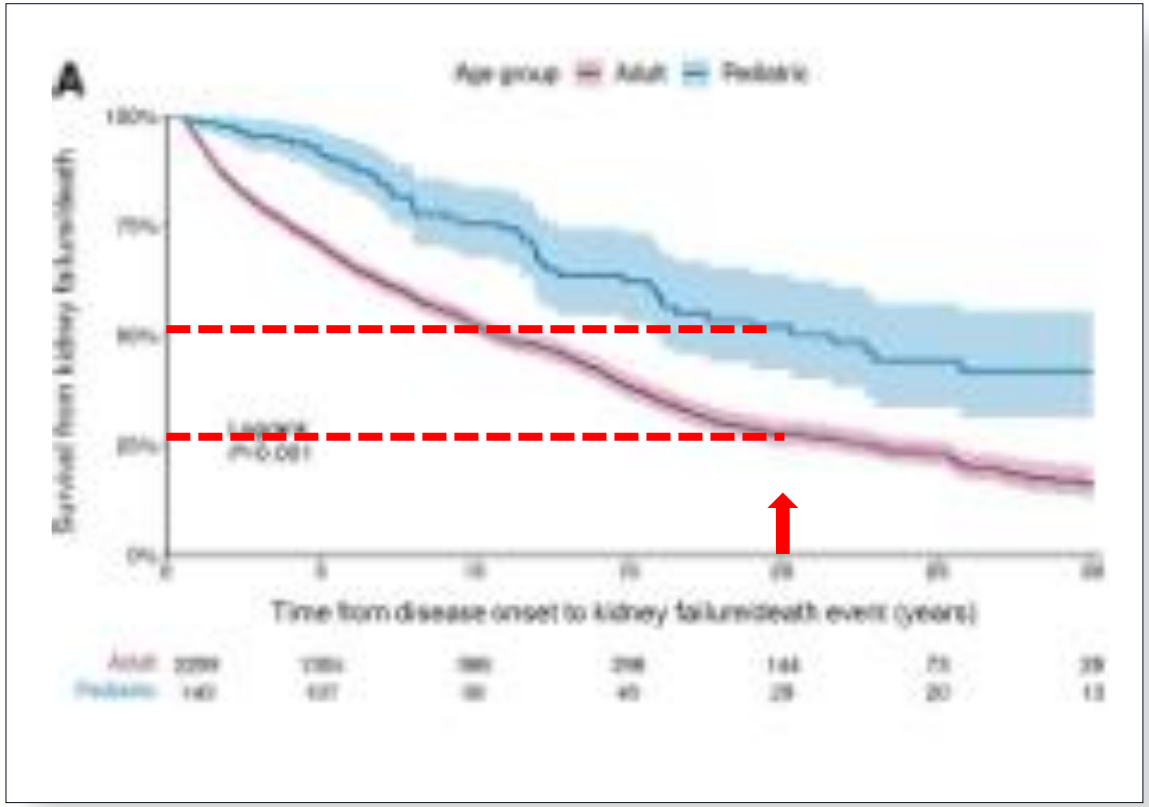

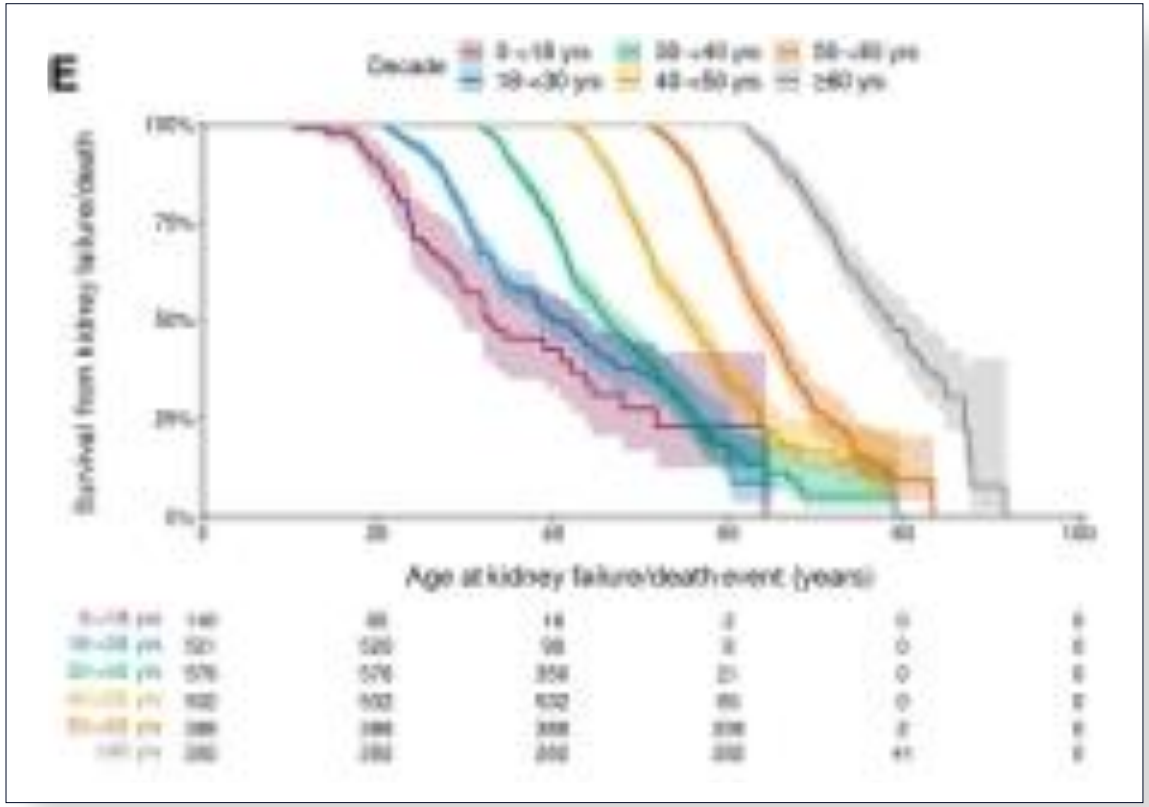

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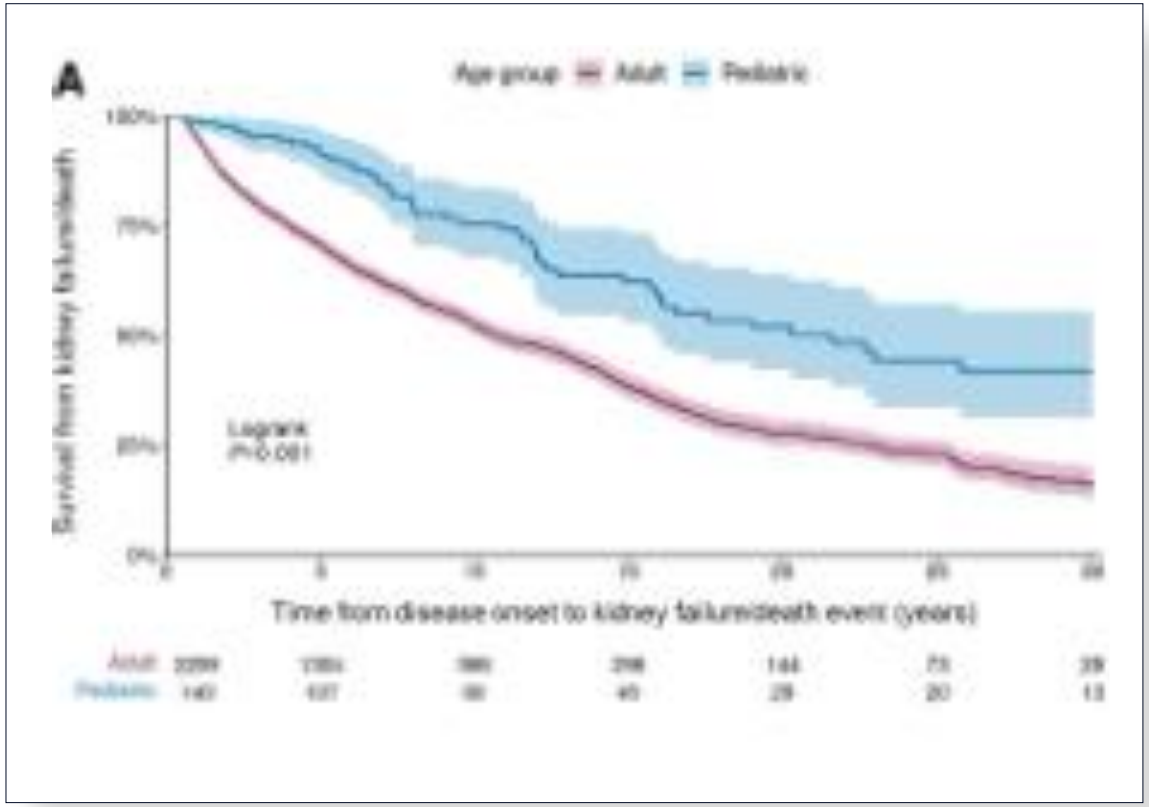

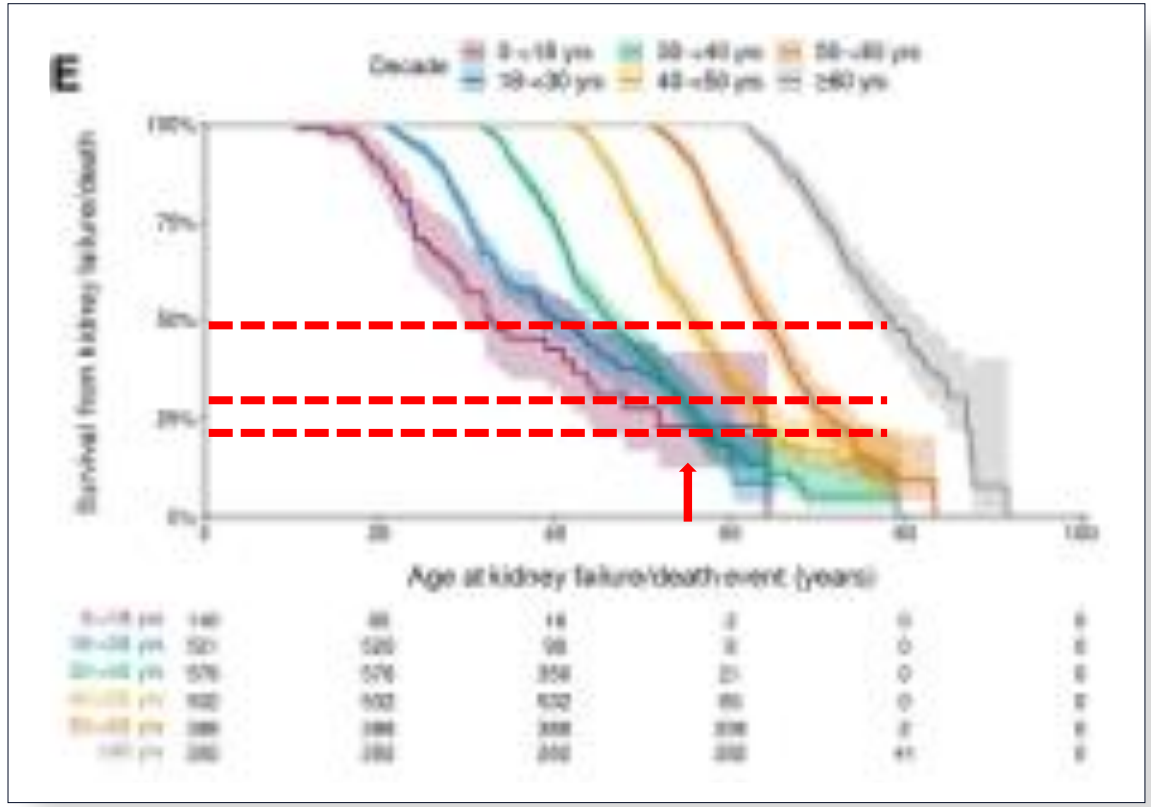

Extent of proteinuria predicts how quickly you develop kidney failure

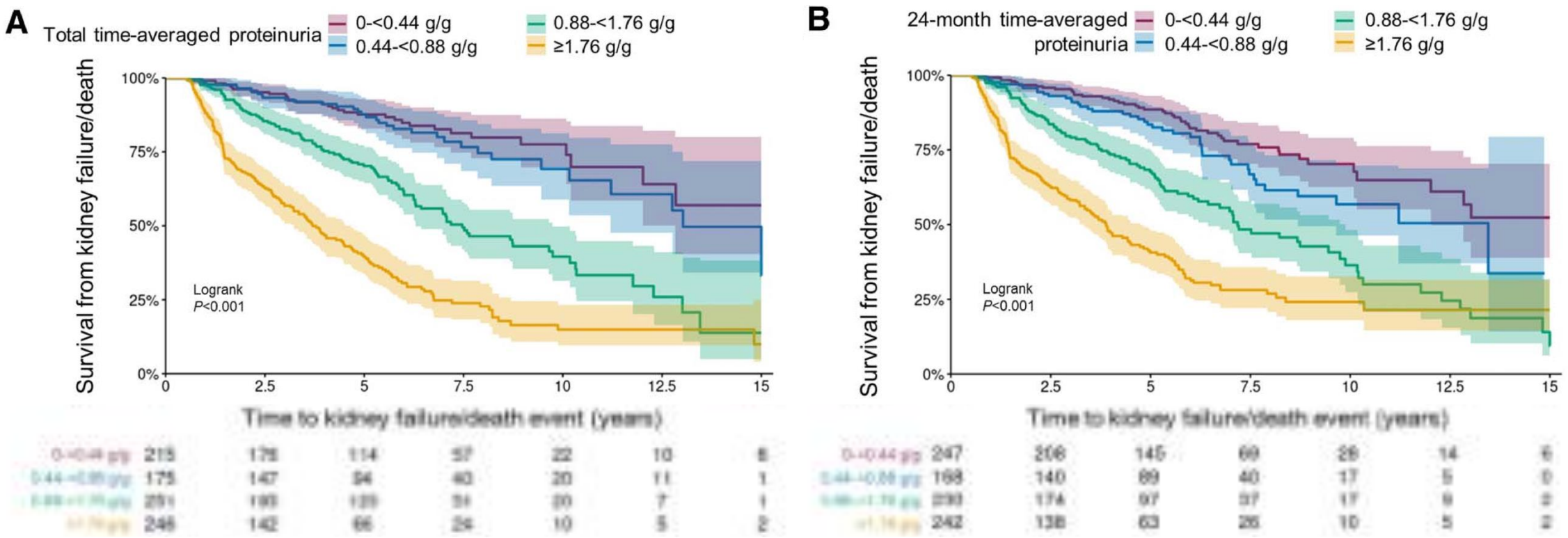

Figure 2. Kaplan–Meier survival curves of time to kidney failure/death event in population 1. (A) Using total follow-up time-averaged proteinuria. (B) Using 24-month time-averaged proteinuria. 0.44 g/g=50 mg/mmol; 0.88 g/g=100 mg/mmol; 1.76 g/g=200 mg/mmol.

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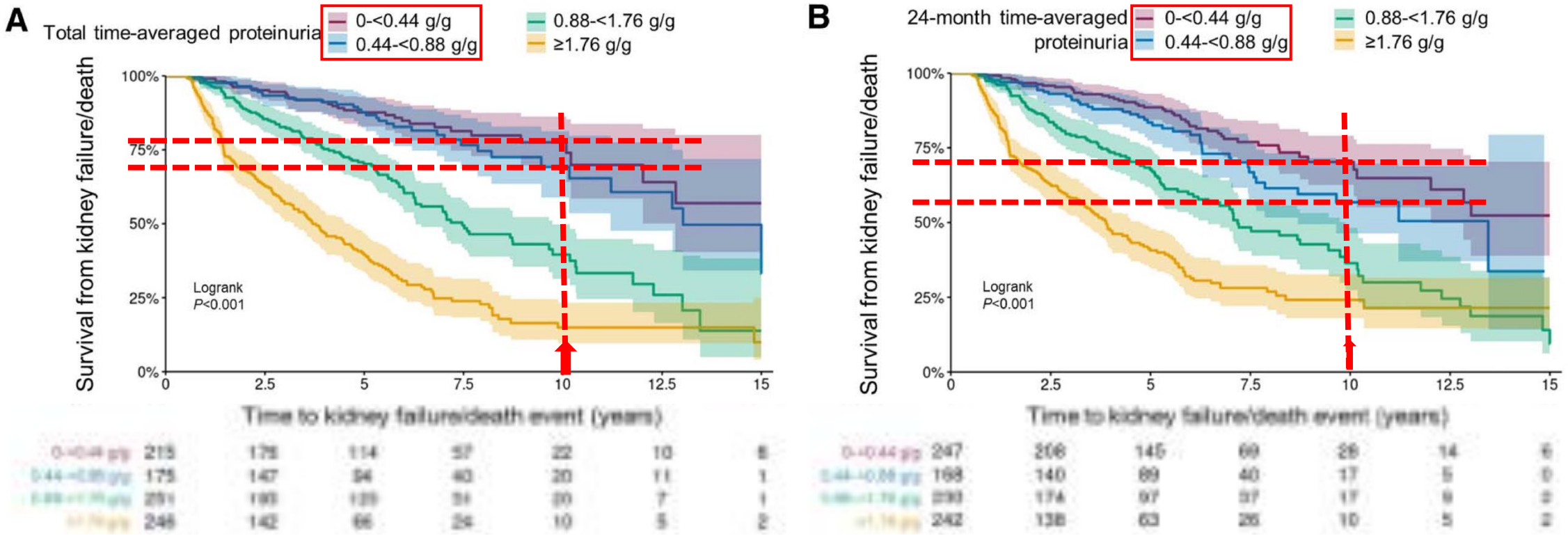

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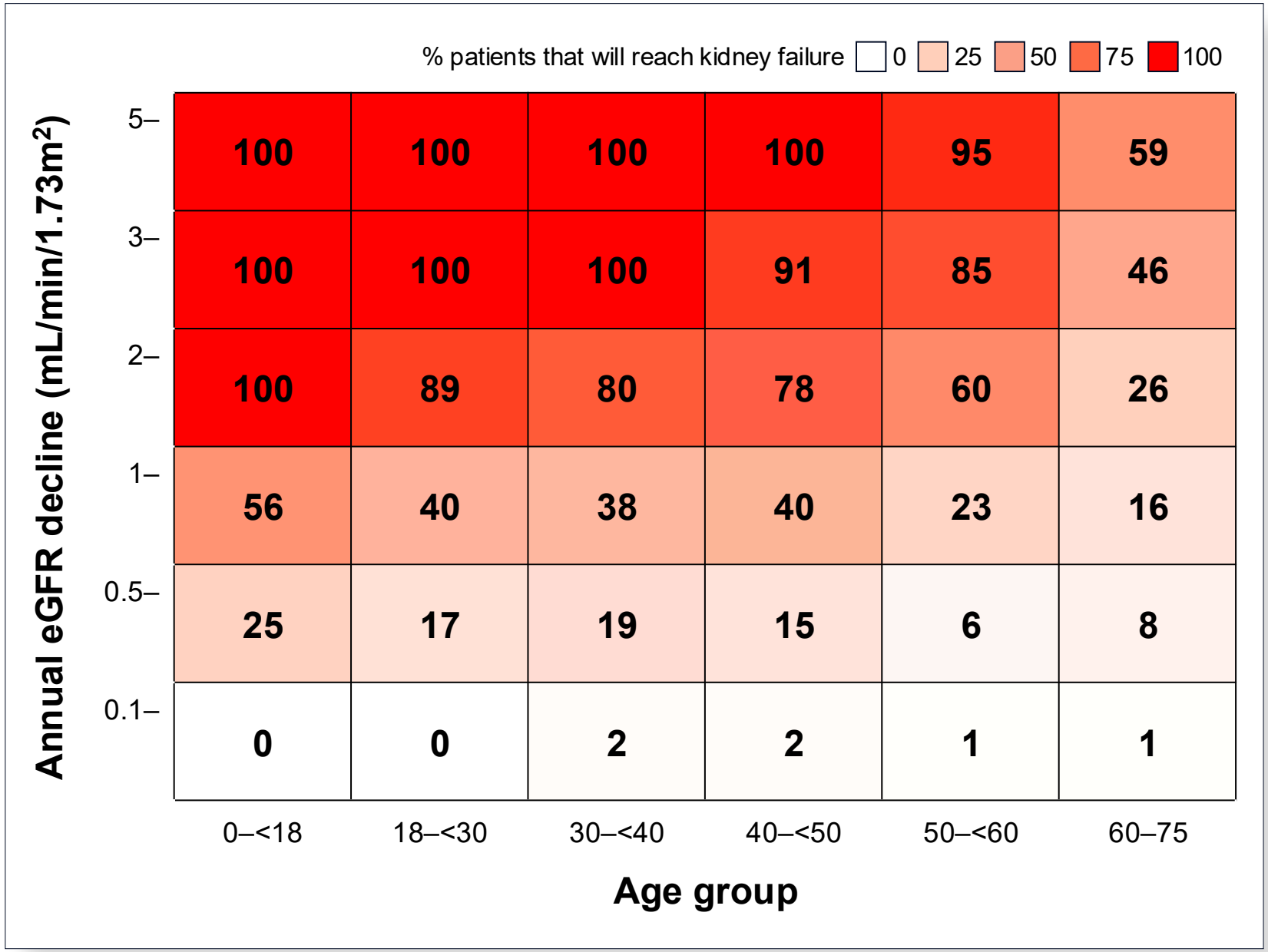

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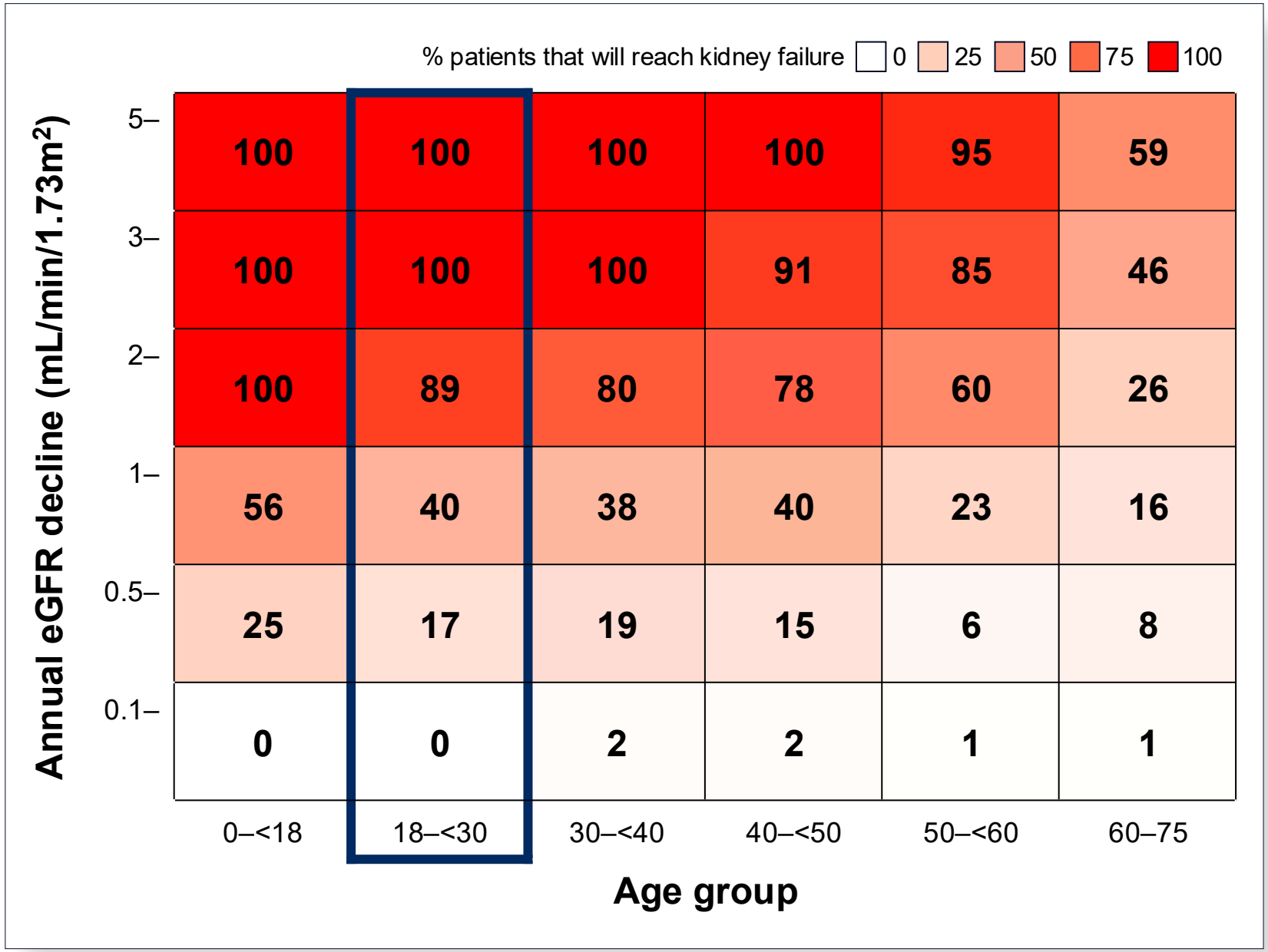

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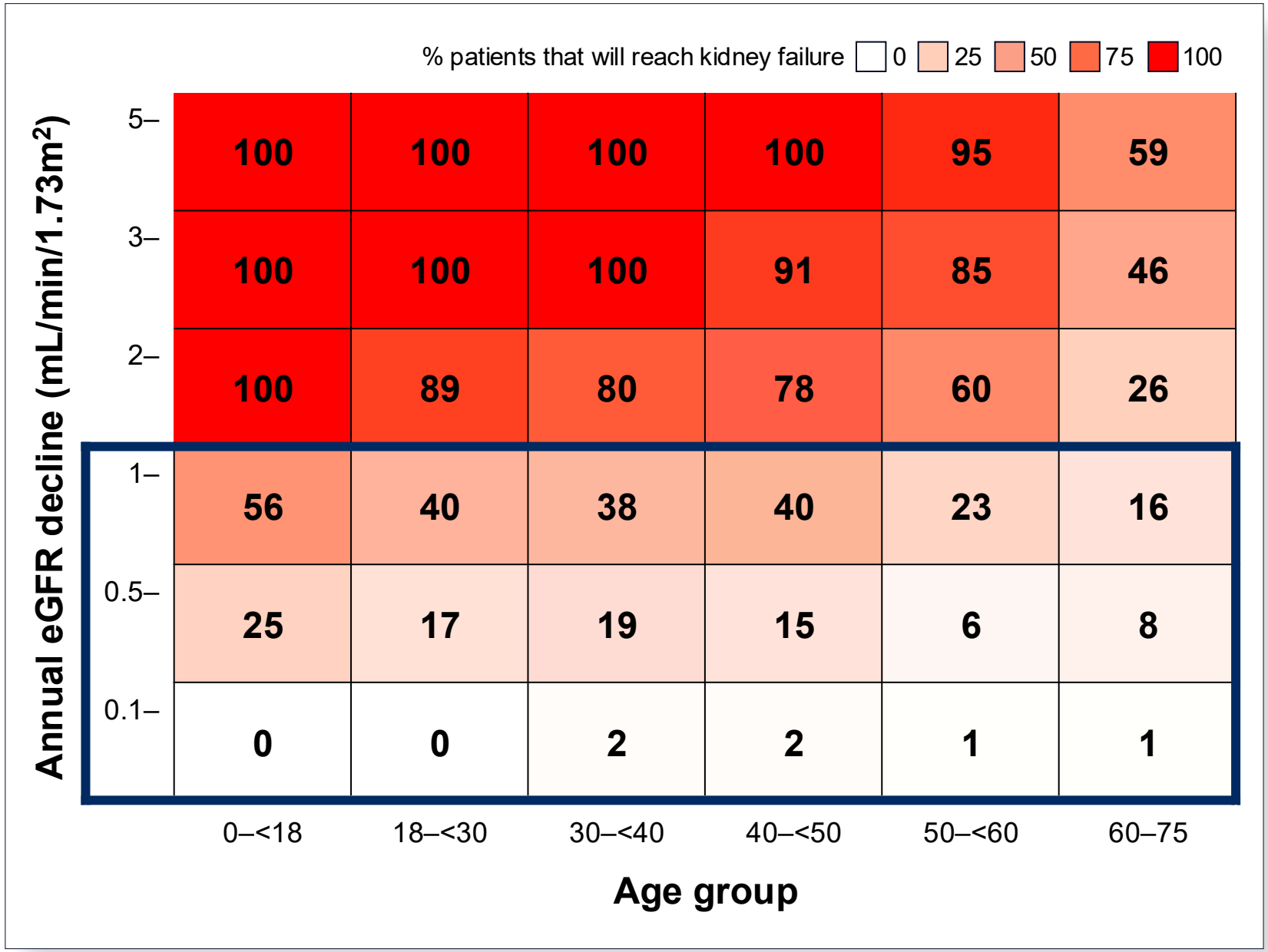
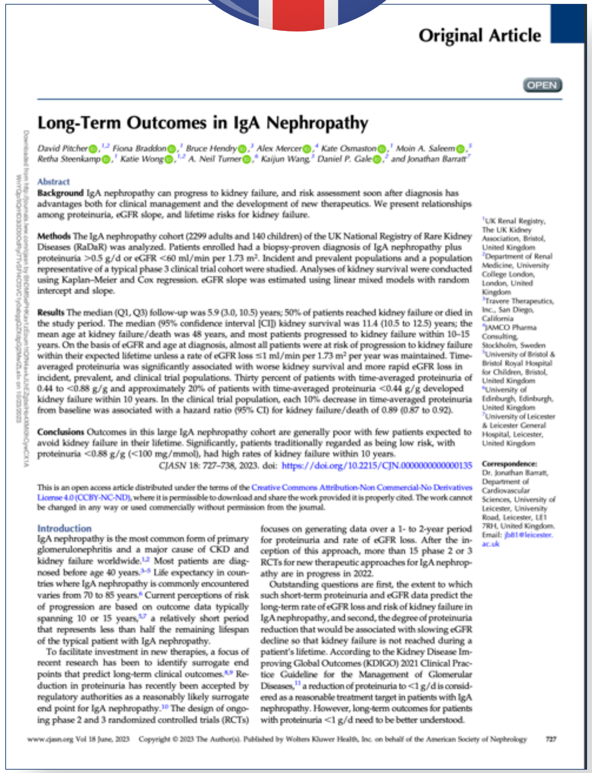




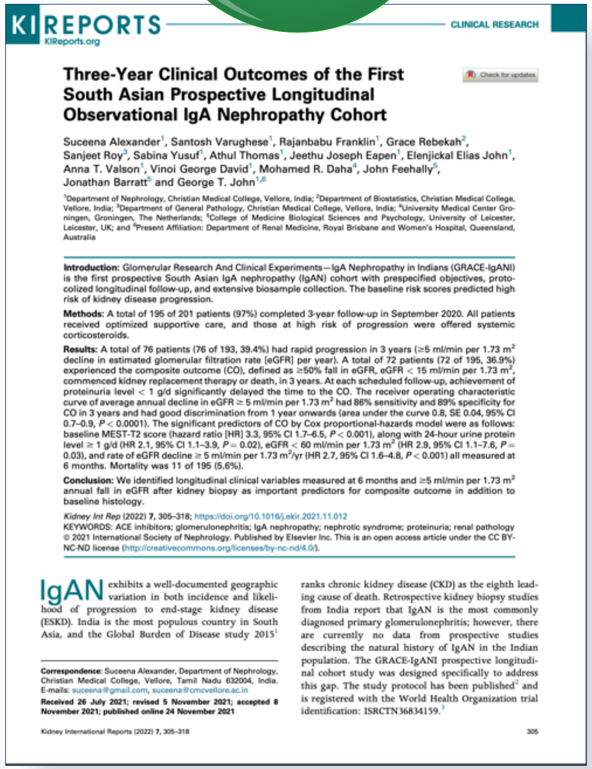
Original Article

OPEN

Long-Term Outcomes in IgA Nephropathy

David Pitcher, Fiona Braddon, Bruce Hendry, Alex Mercer, Kate Osmaston, Moin A. Saleem, Retha Steenkamp, Katie Wong, A. Neil Turner, Kaijun Wang, Daniel P. Gale, and Jonathan Barratt

CJASN 18: 727–738, 2023. doi: https://doi.org/10.2215/CJN.0000000000000135



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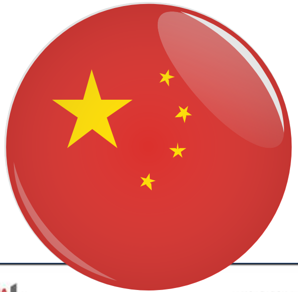
CLINICAL RESEARCH

Three-Year Clinical Outcomes of the First South Asian Prospective Longitudinal Observational IgA Nephropathy Cohort

Suceena Alexander, Santosh Varughese, Rajanbabu Franklin, Grace Rebekah, Sanjeet Roy, Sabina Yusuf, Athul Thomas, Jeethu Joseph Eapen, Elenjickal Elias John, Anna T. Valson, Vinoi George David, Mohamed R. Daha, John Feehally, Jonathan Barratt and George T. John

Kidney Int Rep (2022) 7, 305–318; https://doi.org/10.1016/j.ekir.2021.11.012



OXFORD ERA ndt

Nephrol Dial Transplant, 2025, 40, 1137–1146

https://doi.org/10.1093/ndt/gfae252

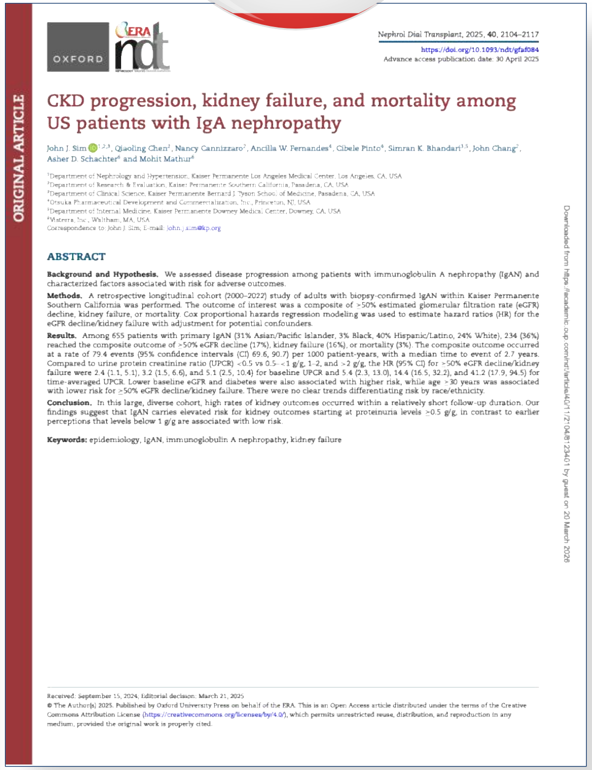
Advance access publication date: 18 November 2024

ORIGINAL ARTICLE

Long-term outcomes of IgA nephropathy in China

Xue Shen, Pei Chen, Muqing Liu, Lijun Liu, Sufang Shi, Xujie Zhou, Jicheng Lv and Hong Zhang

ABSTRACT



OXFORD ERA ndt

Nephrol Dial Transplant, 2025, 40, 2104–2117

https://doi.org/10.1093/ndt/gfaf084

Advance access publication date: 30 April 2025

ORIGINAL ARTICLE

CKD progression, kidney failure, and mortality among US patients with IgA nephropathy

ABSTRACT

KDIGO

2.3 Treatment

2.3.1 Defining patients with IgAN at risk of progressive loss of kidney function requiring treatment

Practice Point 2.3.1.1: A patient with IgAN is at risk of progressive loss of kidney function if they have proteinuria ≥0.5 g/d (or equivalent), while on or off treatment for IgAN, and treatment/additional treatment should be started in all cases.

2.3.2 Defining a treatment goal in patients with IgAN at risk of progressive loss of kidney function

Practice Point 2.3.2.1: The treatment goal in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of loss of kidney function to <1 ml/min per year for the rest of the patient's life. The only validated early biomarker to help guide clinical decision-making is urine protein excretion, which should be maintained at <0.5 g/d (or equivalent), preferably <0.3 g/d (or equivalent), accepting that in some patients with extensive kidney scarring this may not be possible and that multiple drugs are likely to be needed to achieve this.

Practice Point 2.3.2.2: Treatment of patients with IgAN wh
kidney function decline and do not have a variant form

- **The focus of management in most patie**
  - **Prevent or reduce IgA imm**
    mediated glomerular i
  - **In parallel, ma**
- **Reduction**
  treatments that have been proven to reduce pathogen
  measured as galactose deficient IgA1 [gd-IgA1]).
- **Prevention of immune complex-mediated injury shou**
  proven anti-inflammatory effects, and ideally should
  and not as a replacement for, treatments that prevent
  complex formation.
- **Management of the consequences of IgAN-induced nephron loss should include:**
  - **Lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise, as appropriate,**
  - **Control of blood pressure with a target of ≤120/70 mm Hg,**
  - **Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade or dual endothelin angiotensin receptor antagonism (DEARA), and sodium-glucose cotransporter-2 inhibition (SGLT2i), and**
  - **A thorough cardiovascular risk assessment and commencement of appropriate interventions, as necessary.**

4

2.3.1 Defining patients with IgAN at risk of progressive loss of kidney function requiring treatment

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Practice Point 1.3.2: The initial assessment of the patient with IgAN is shown in Figure 2.

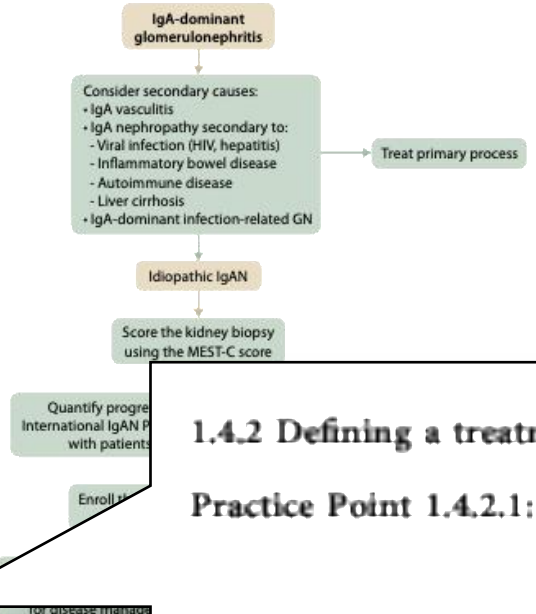

Figure 2| Initial assessment and management of
human immunodeficiency virus; MEST-C, mesangial
atrophy (T), and crescents (C).

1.4 Treatment

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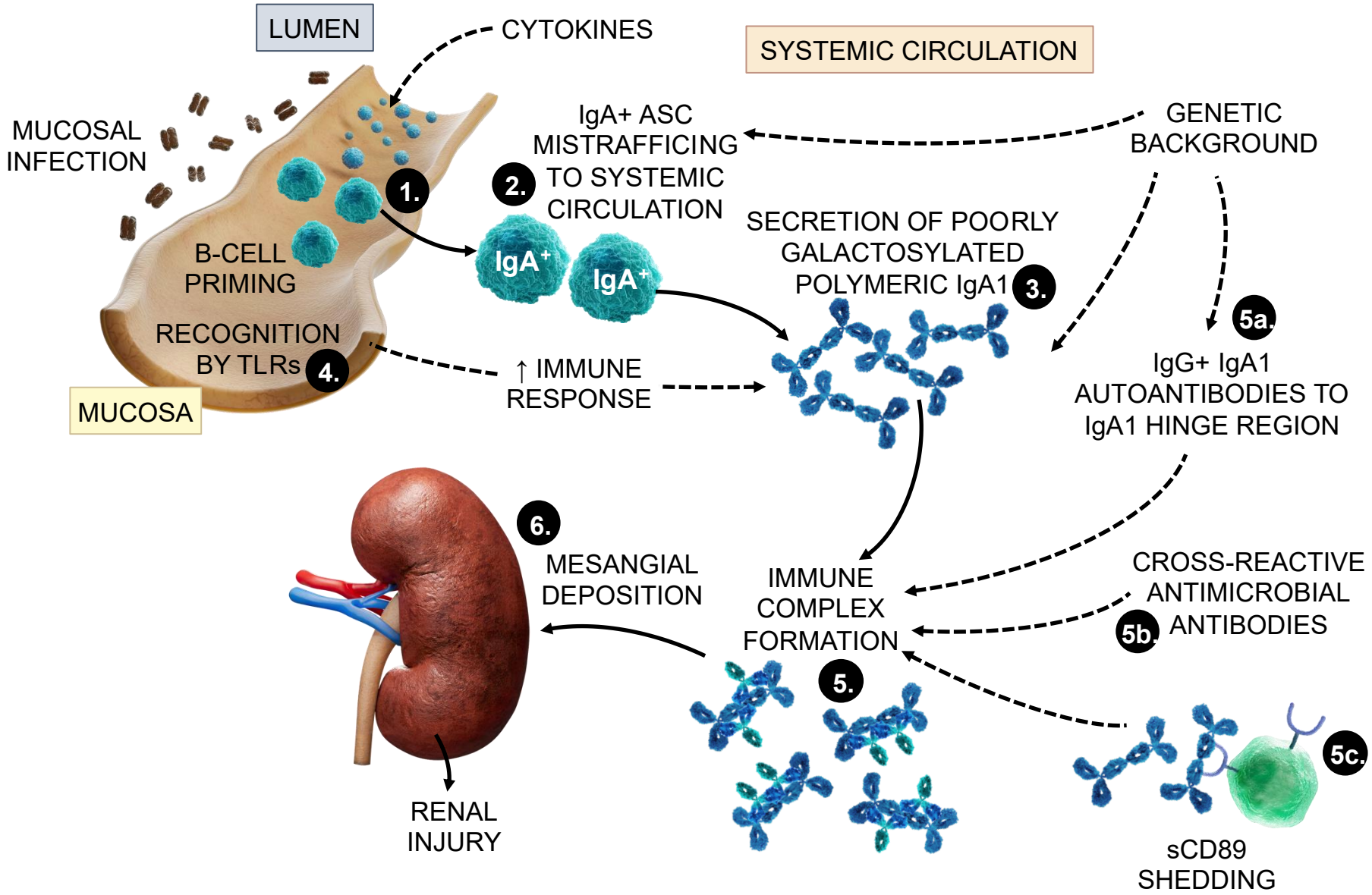
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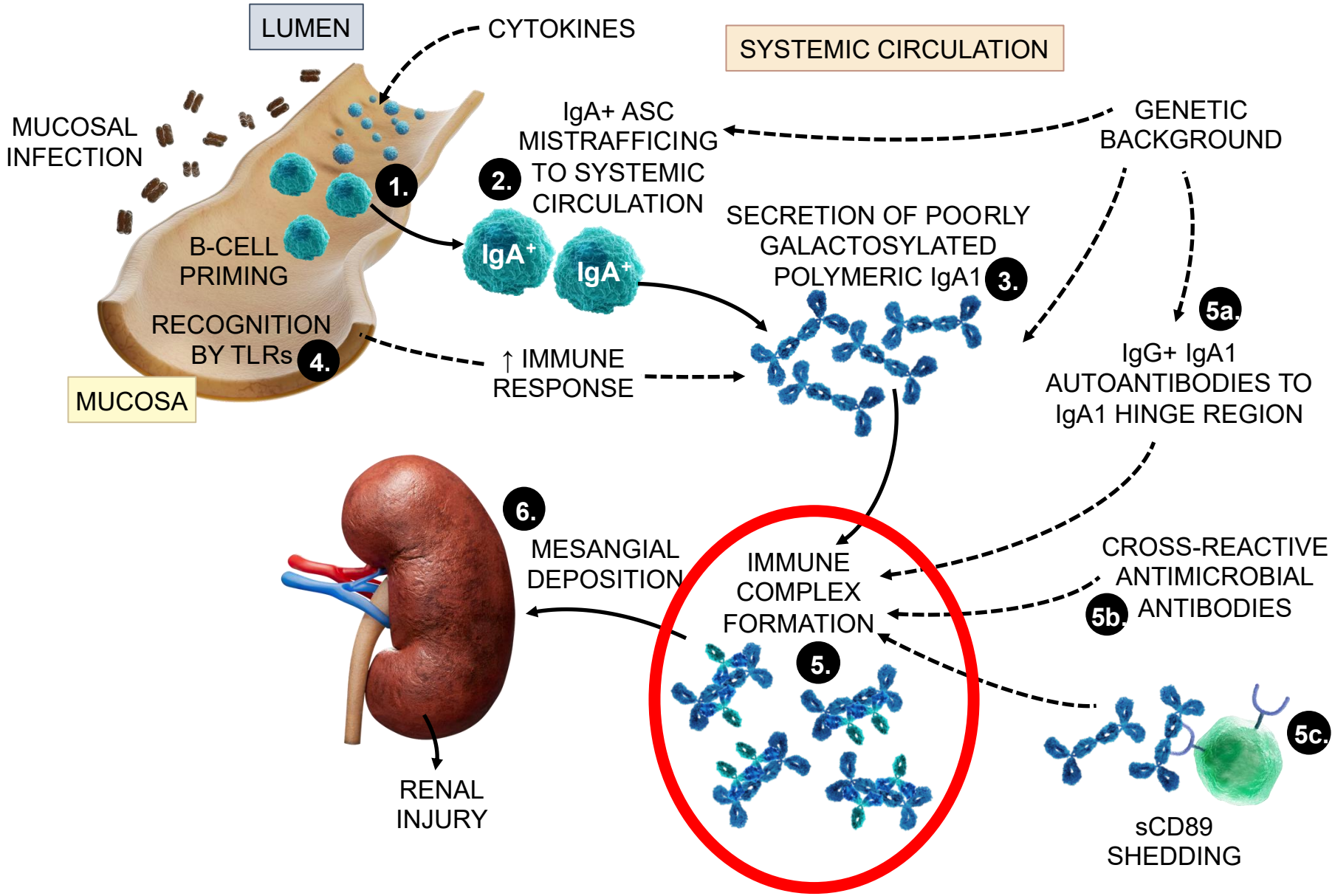
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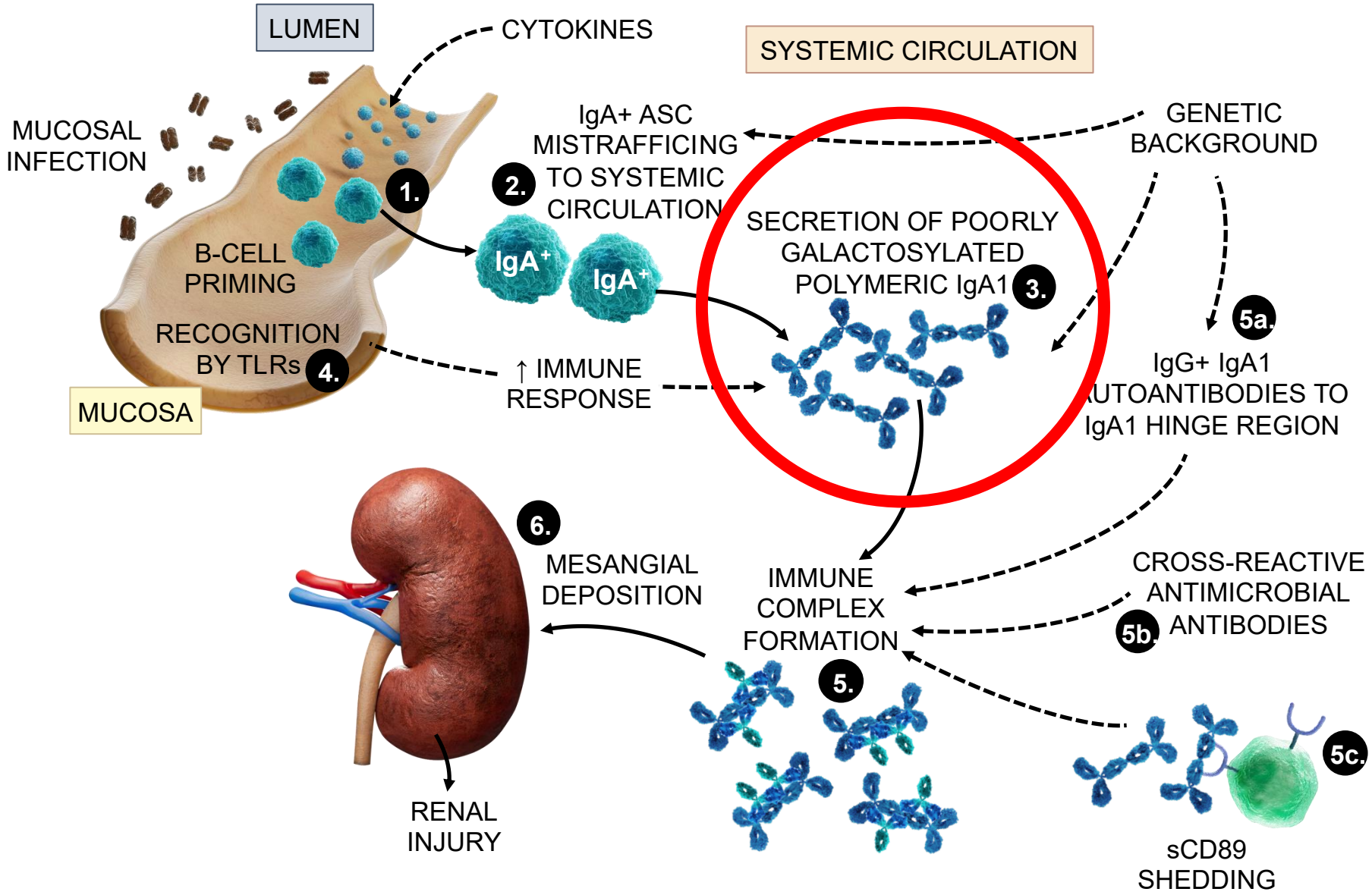
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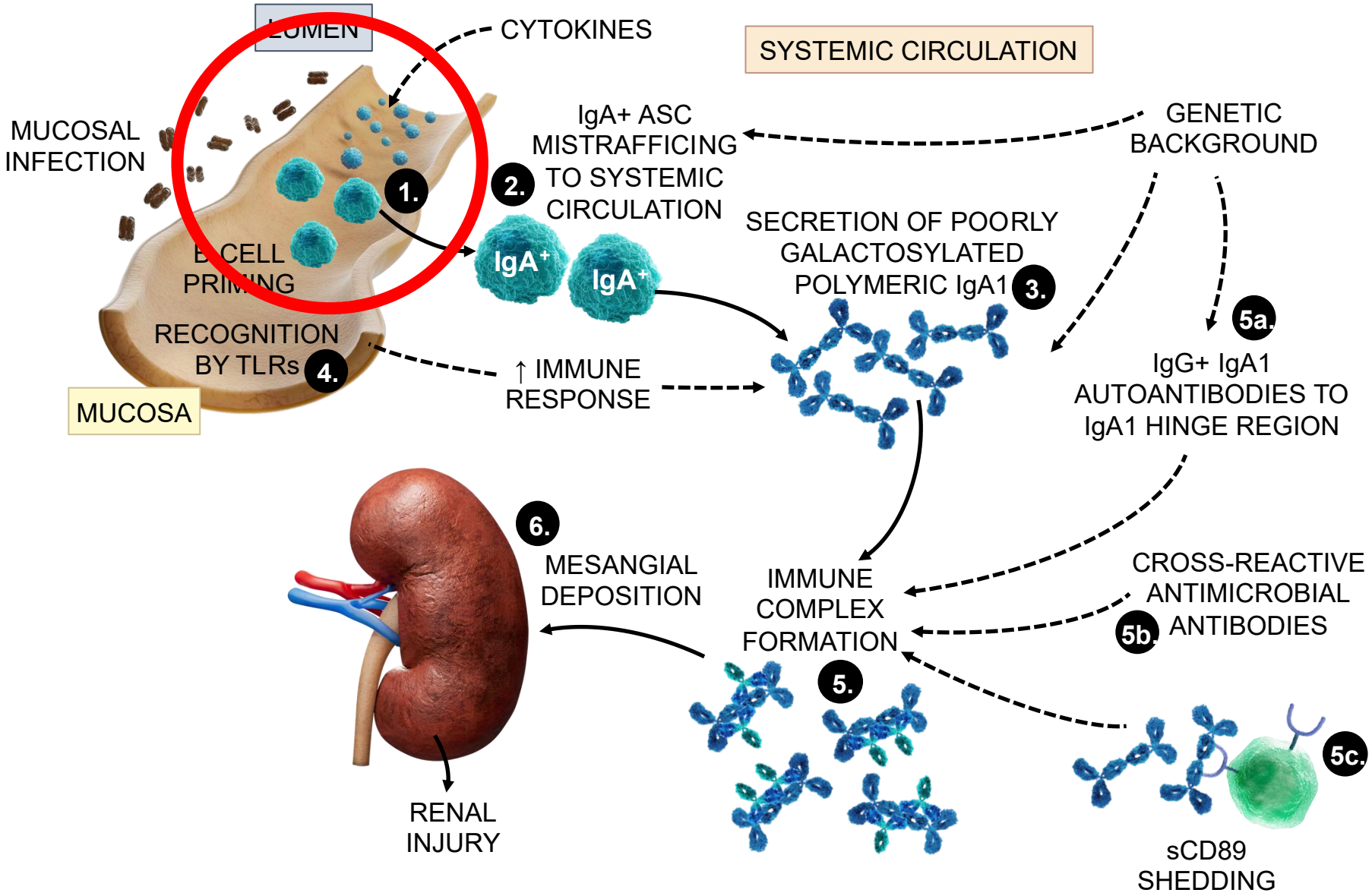
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KDIGO

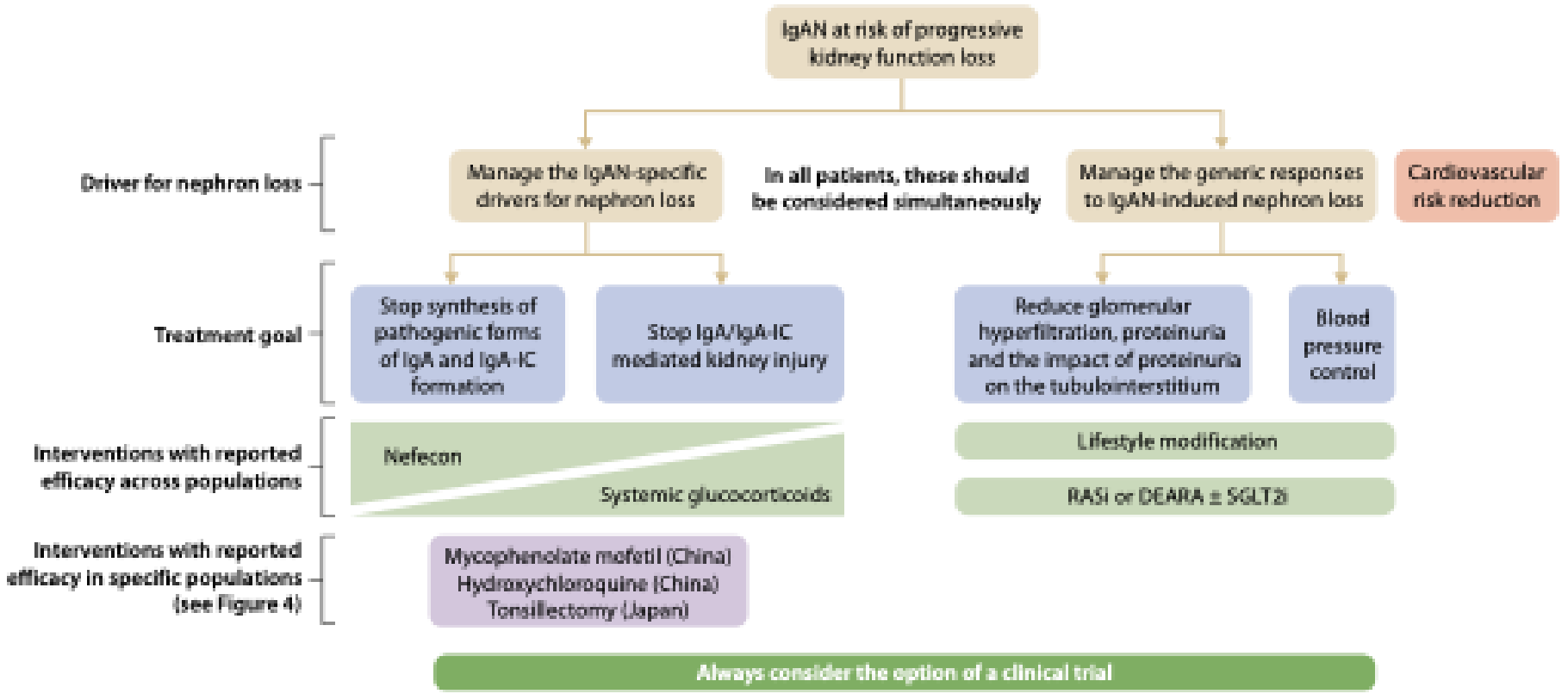

Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline. Reflecting current understanding, Nefecon is shown as having a predominant effect on the production of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs), with an undetermined direct effect of systemically absorbed budesonide on the kidneys. Systemic glucocorticoids have a well-documented anti-inflammatory effect within the kidneys and an undetermined direct effect on the production of pathogenic forms of IgA and IgA-ICs. Strategies to manage the generic response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in selected patients. DEARA, dual endothelin angiotensin receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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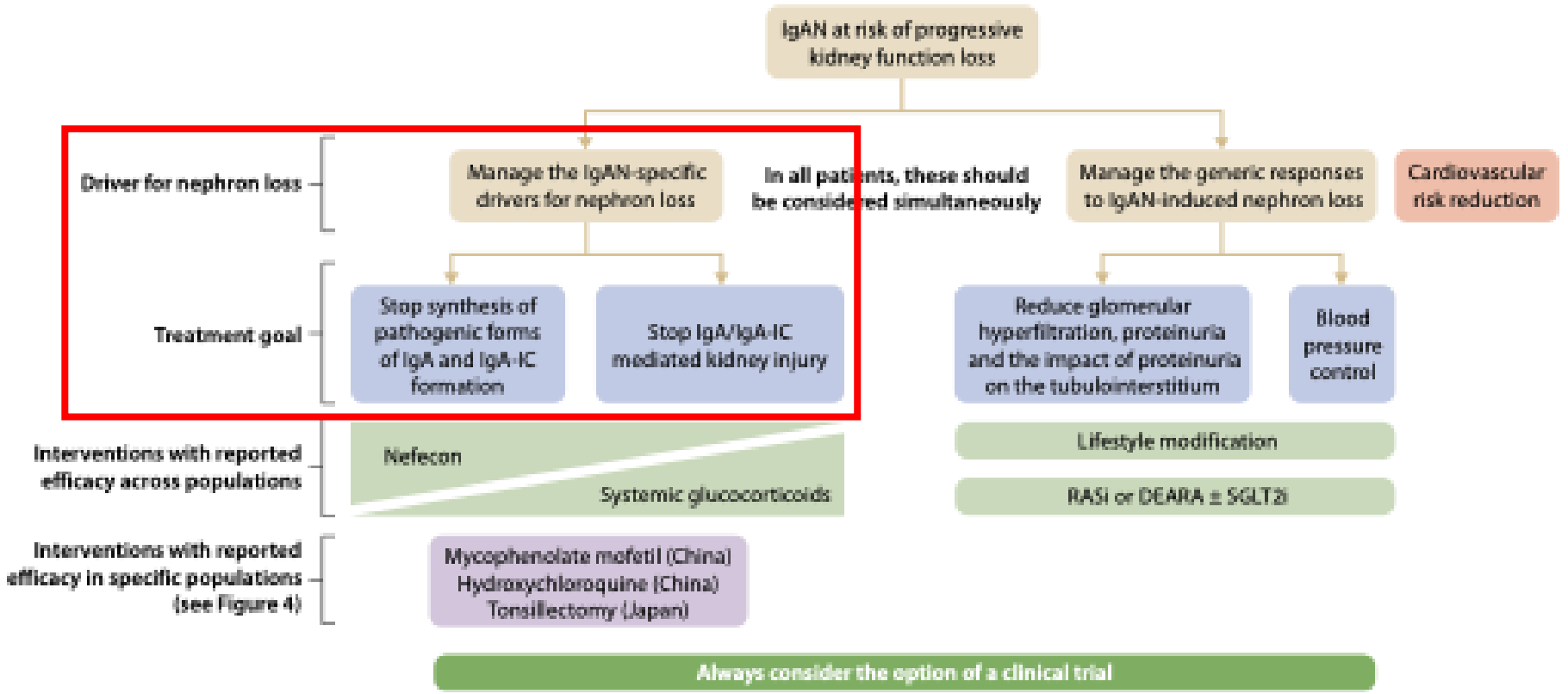

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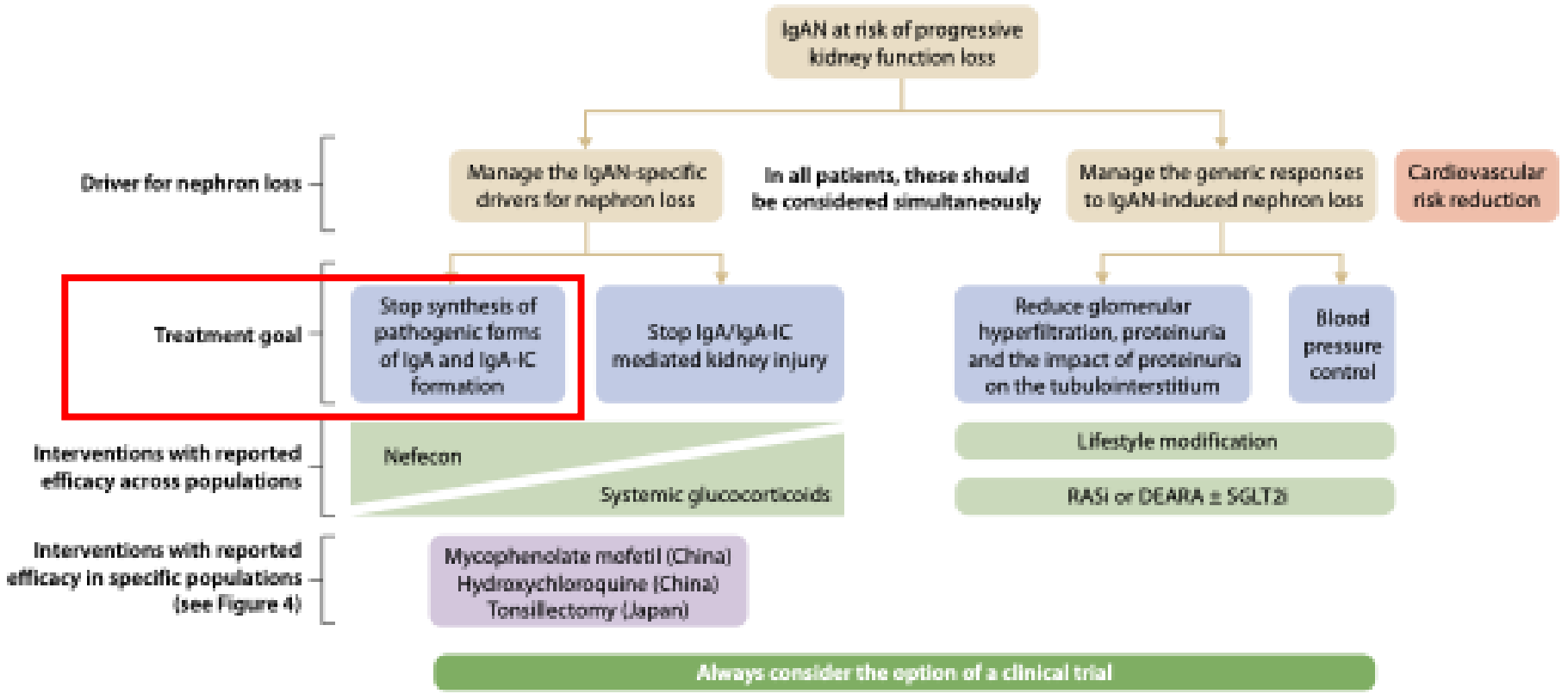

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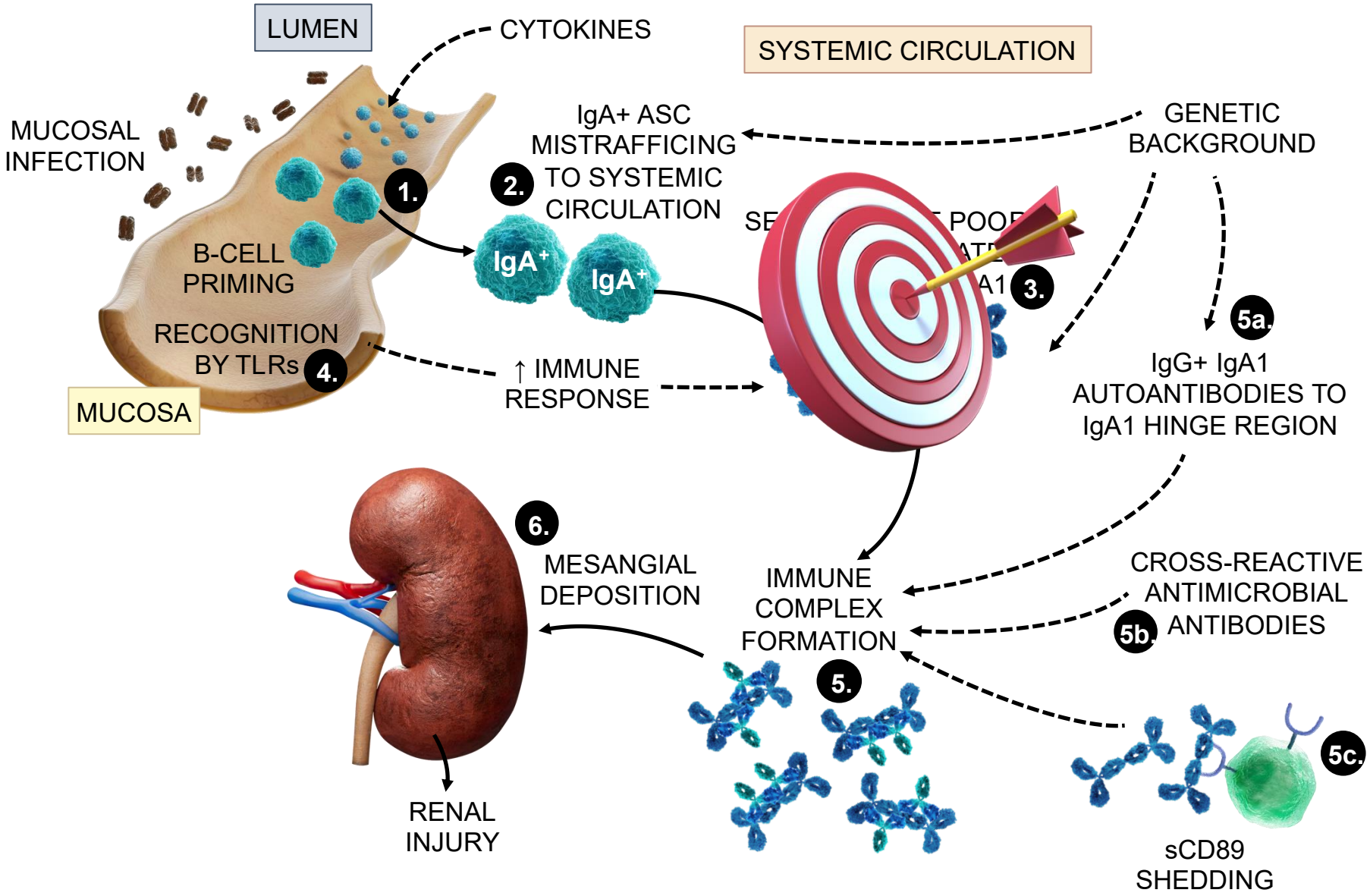
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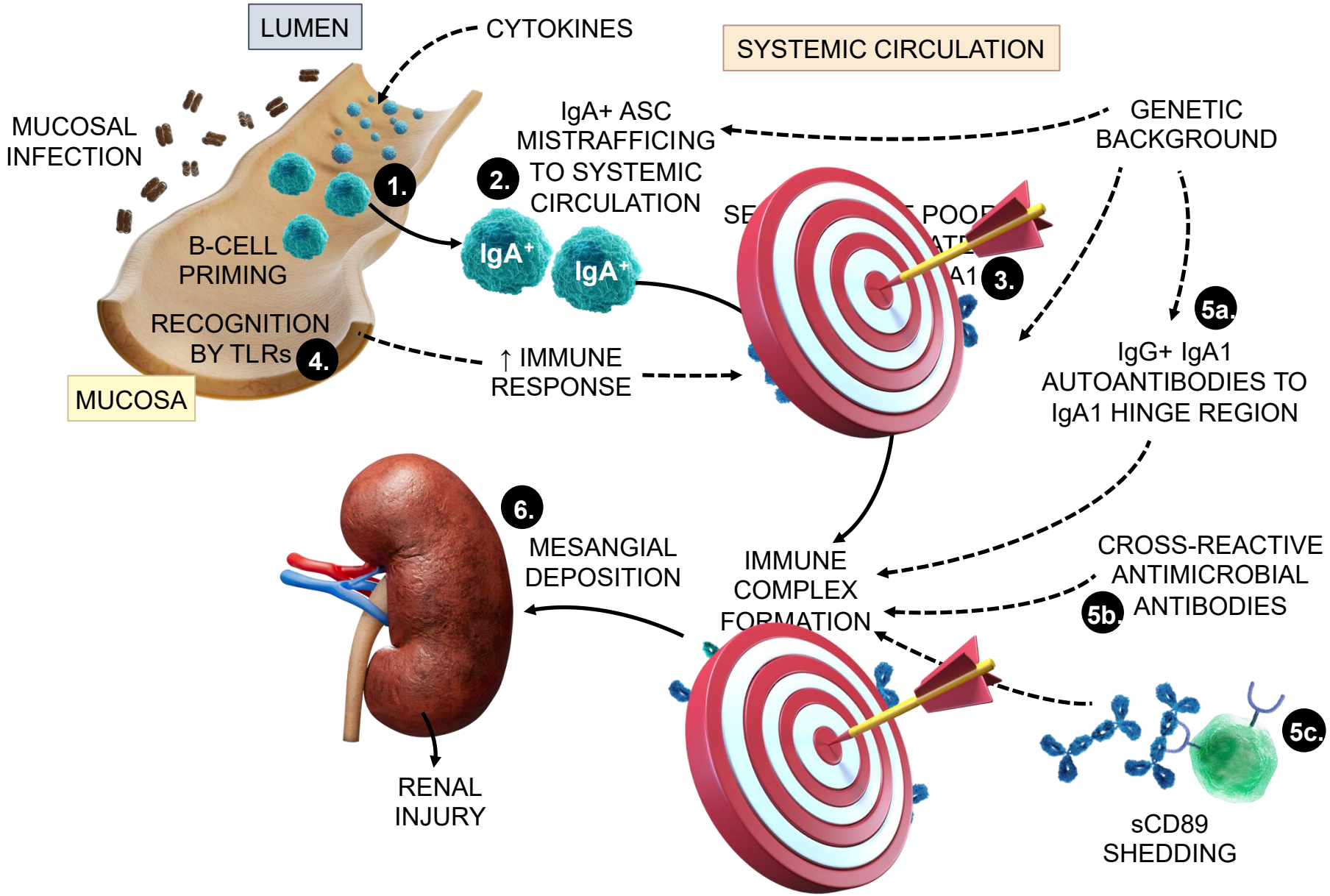
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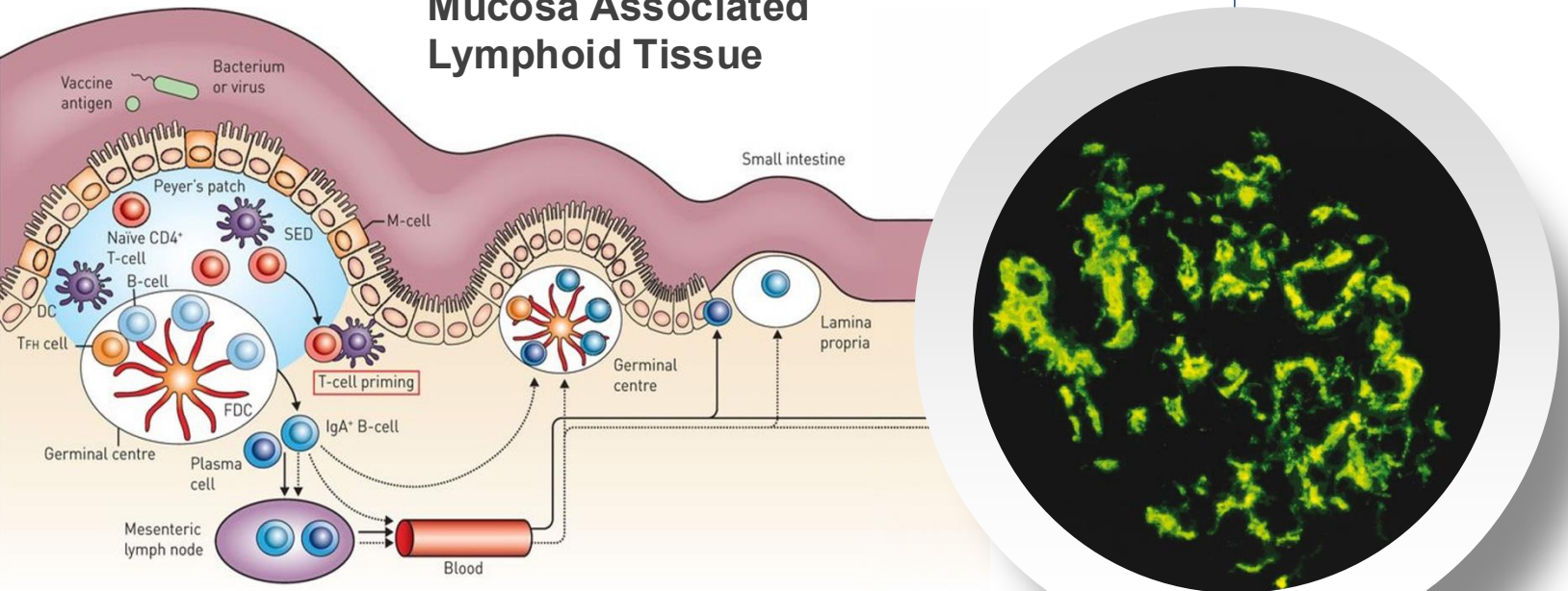
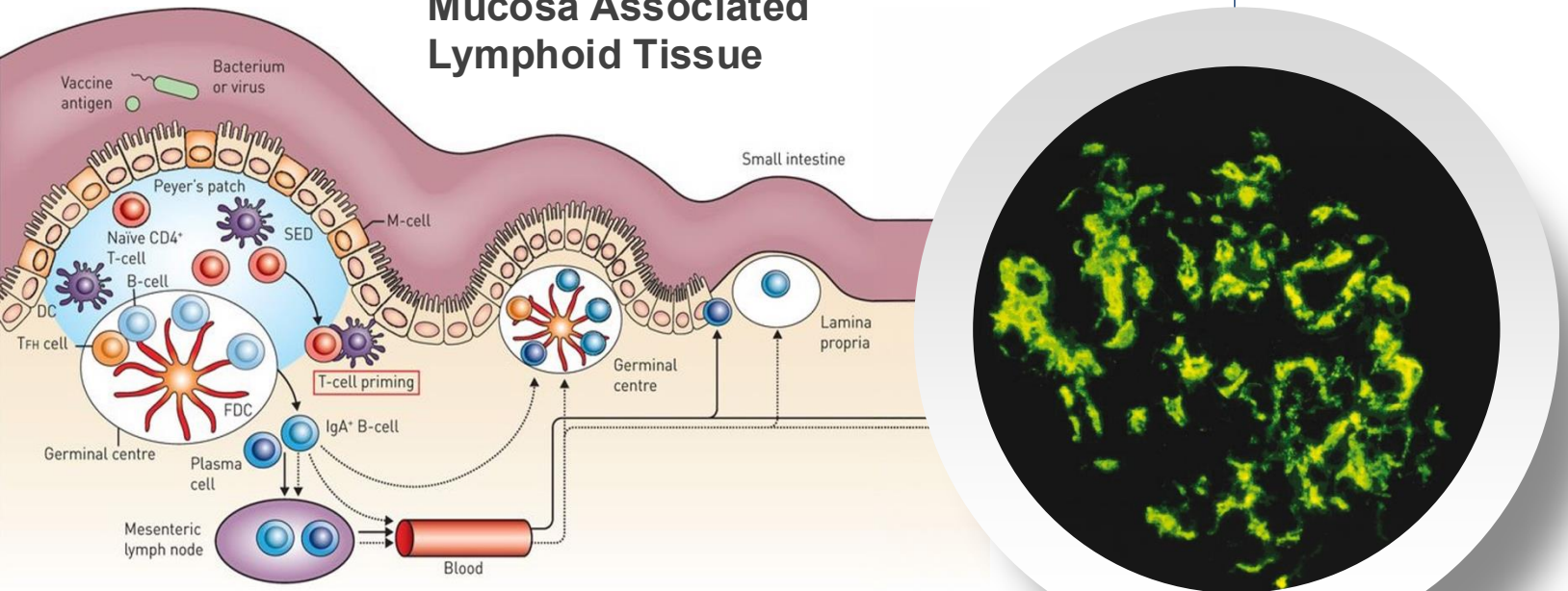
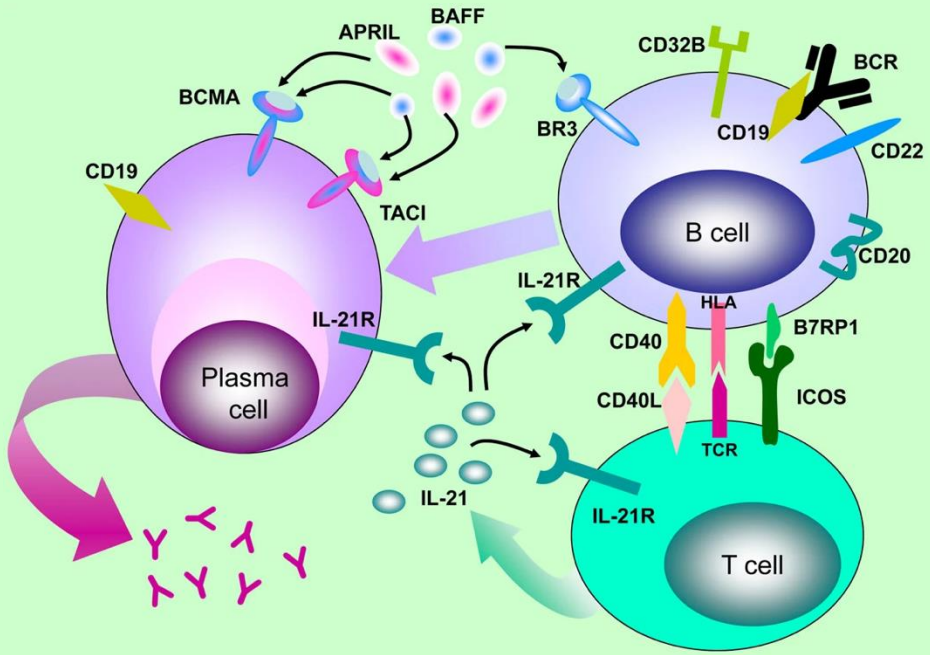
6.
MESANGIAL DEPOSITION
RENAL INJURY

Mucosa Associated Lymphoid Tissue

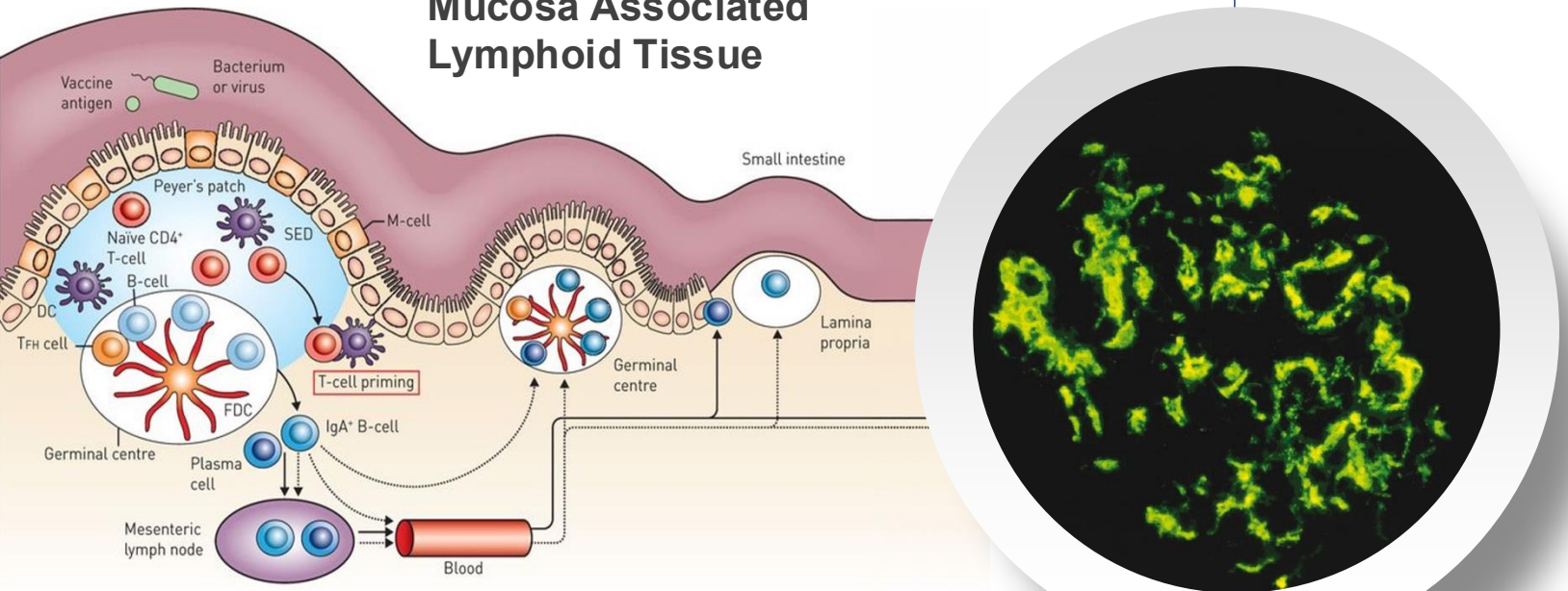


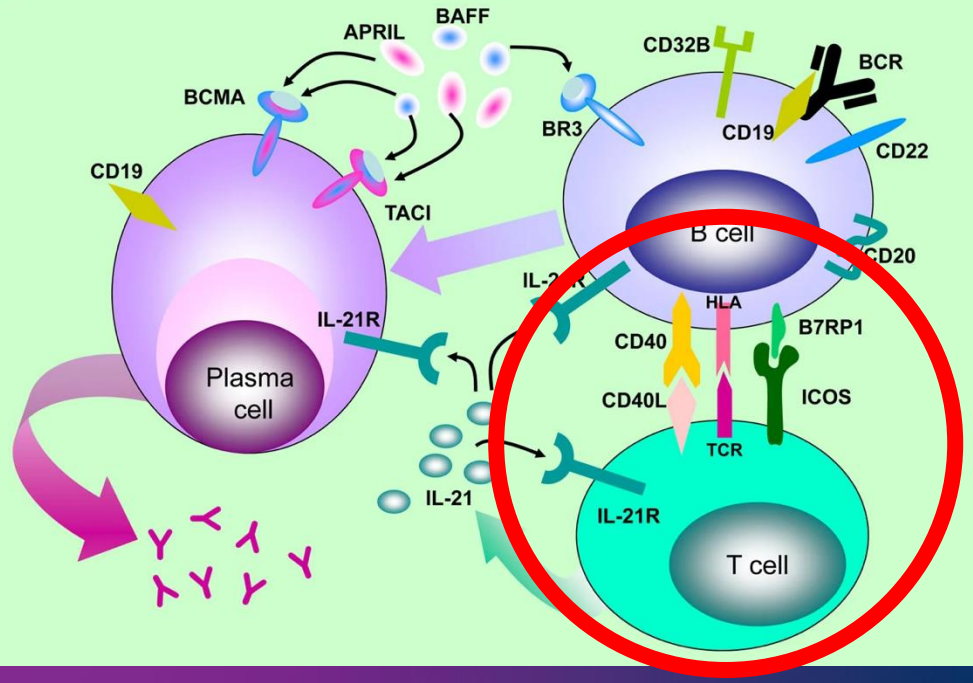
Mucosa Associated Lymphoid Tissue



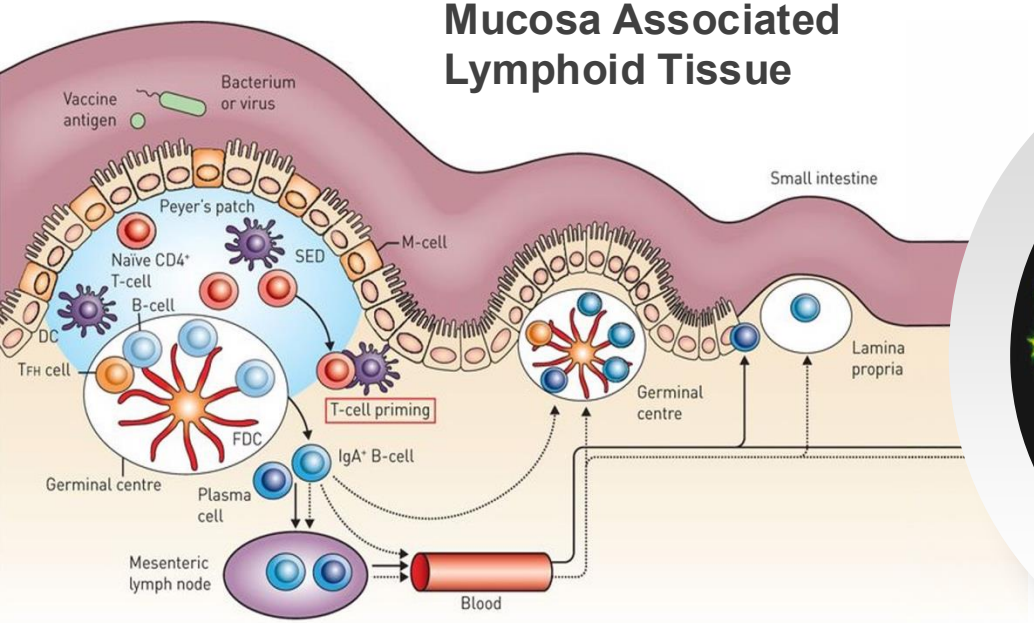


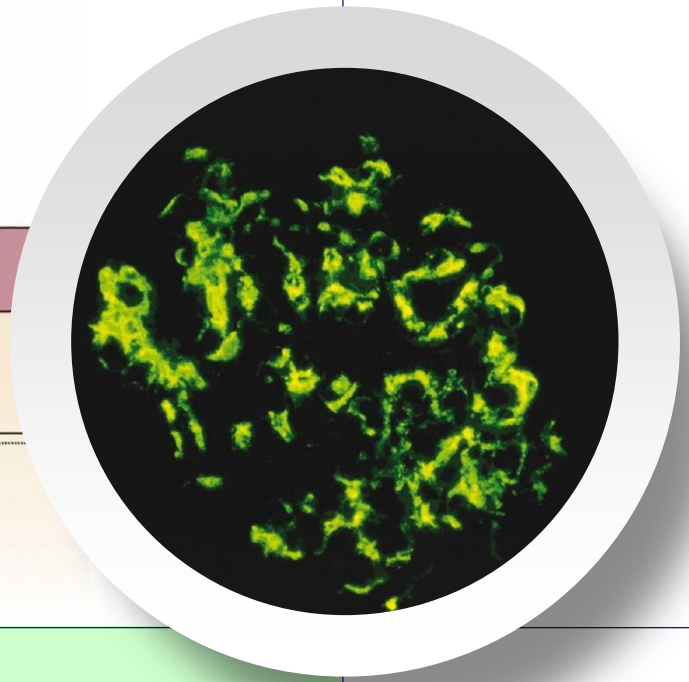
Mucosa Associated Lymphoid Tissue

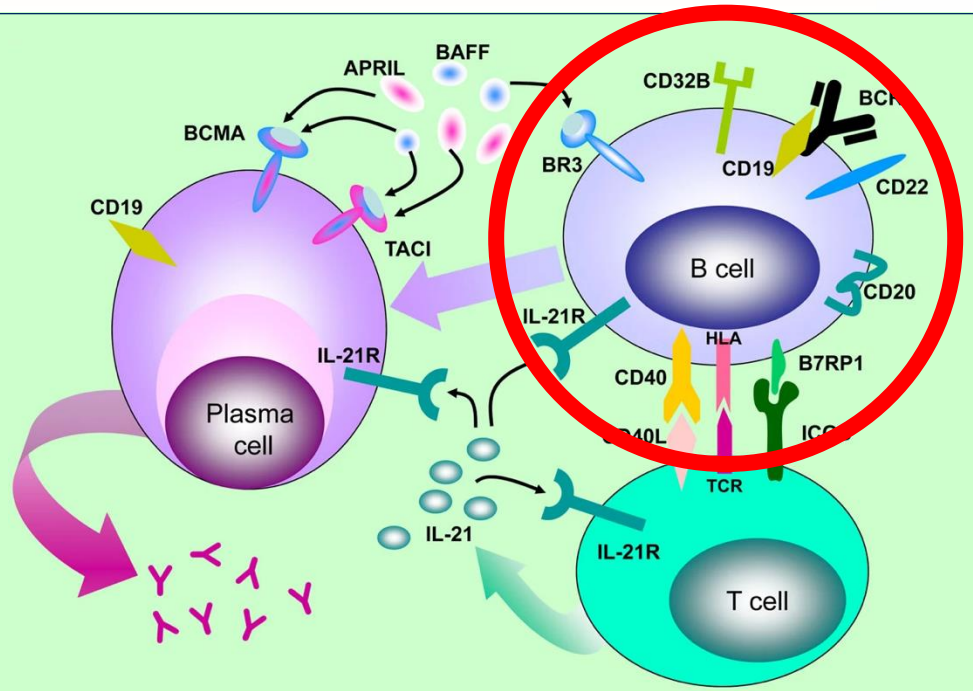




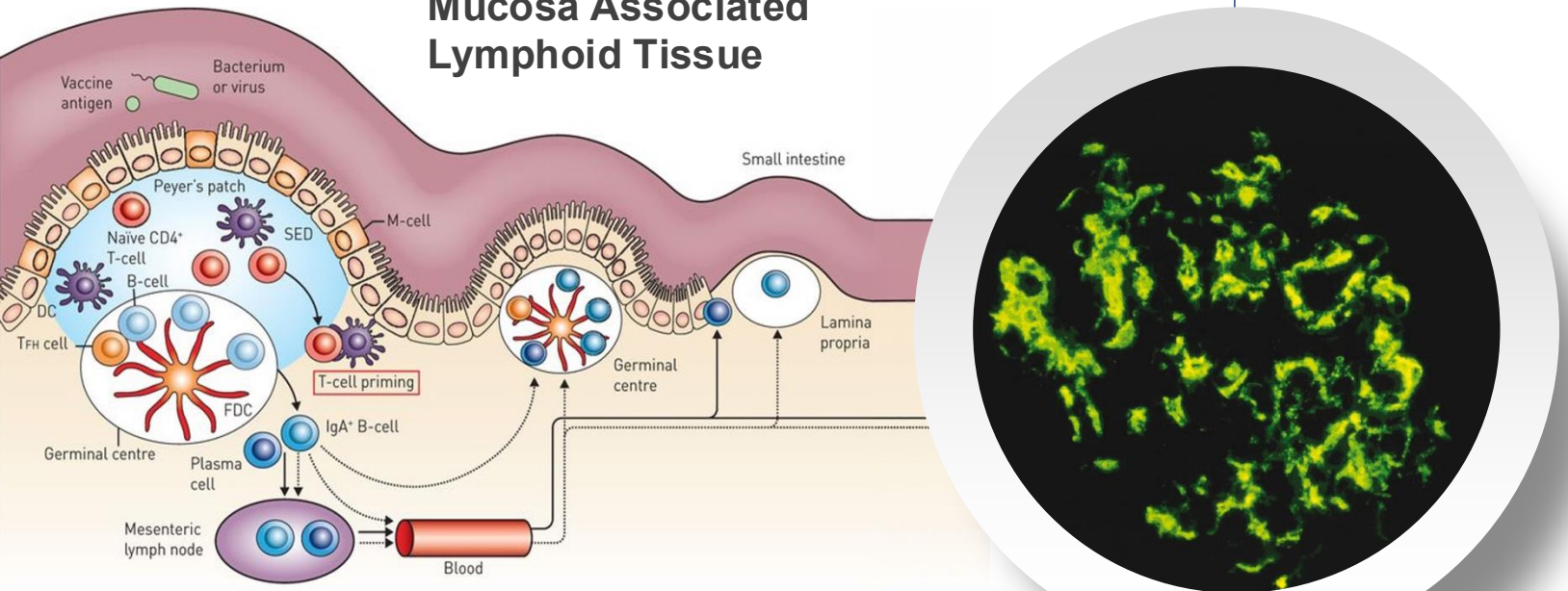
Mucosa Associated Lymphoid Tissue

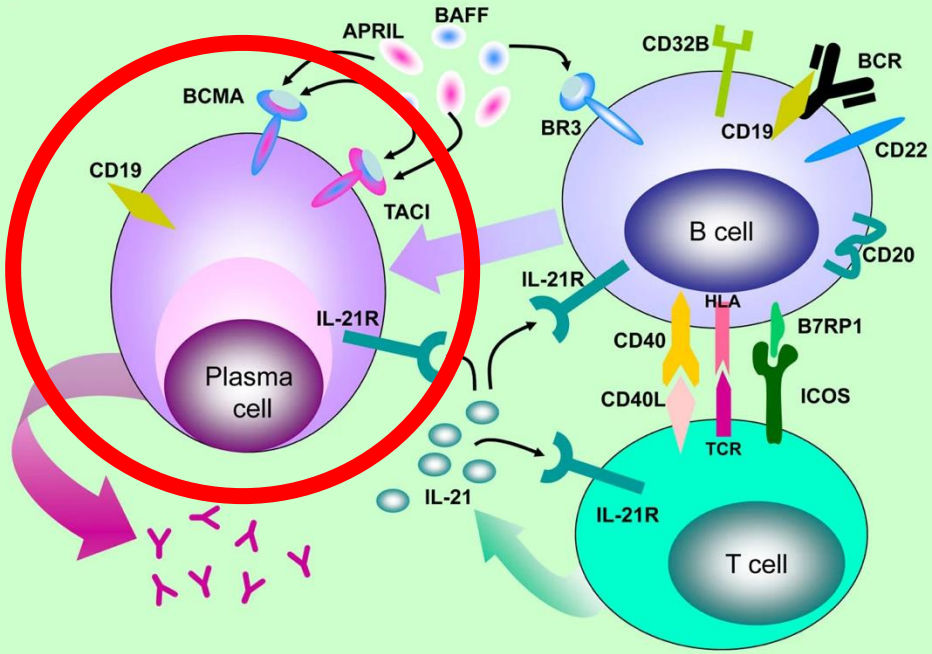




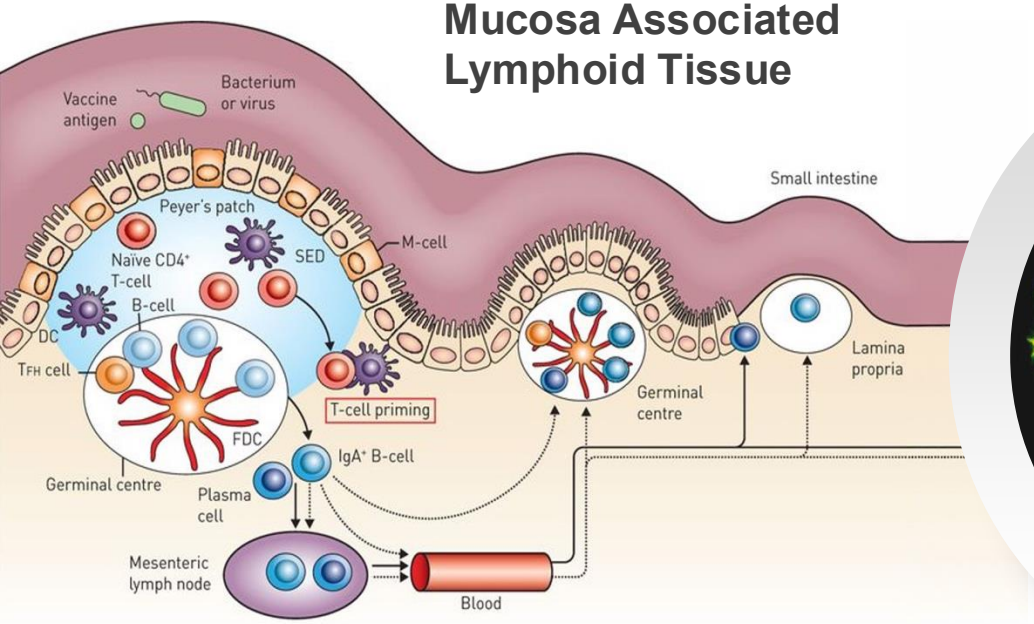


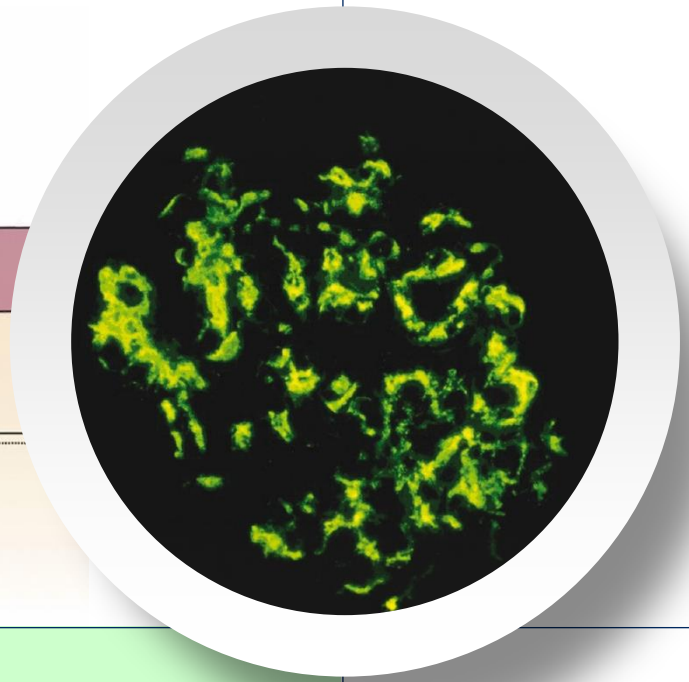
Mucosa Associated Lymphoid Tissue

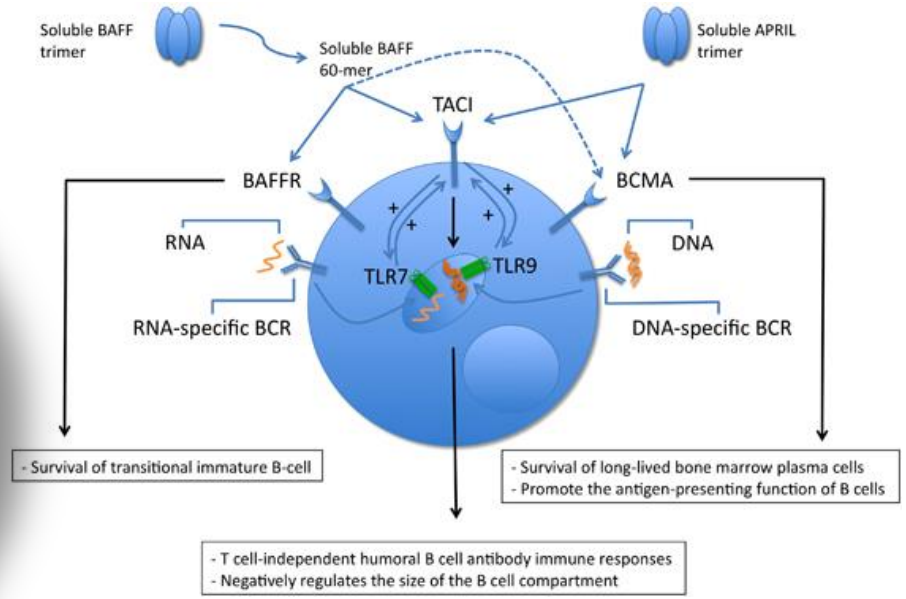


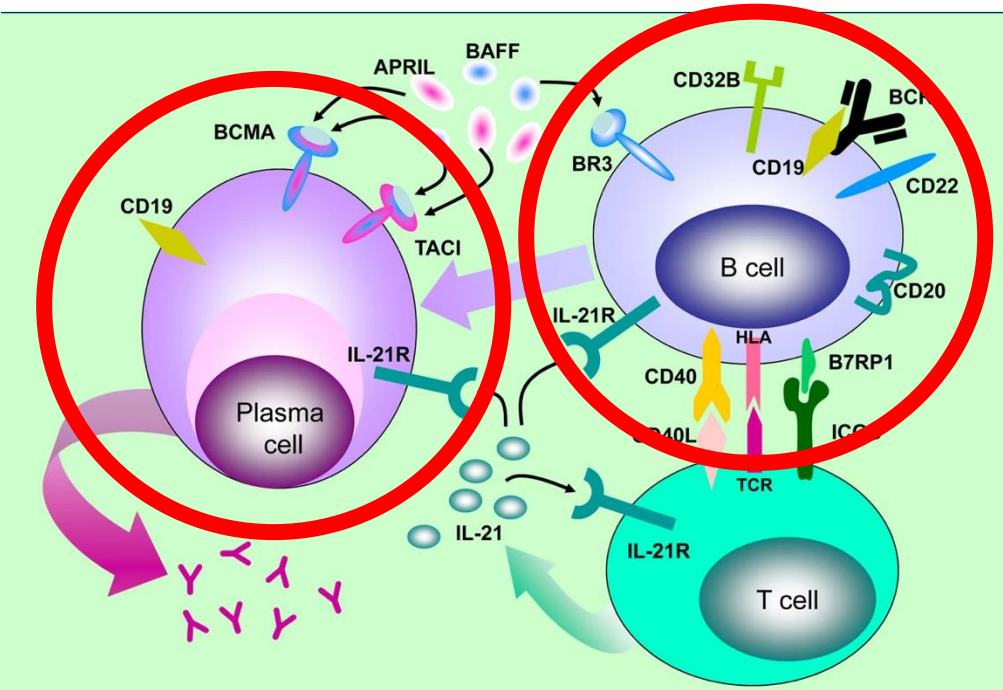


Mucosa Associated Lymphoid Tissue









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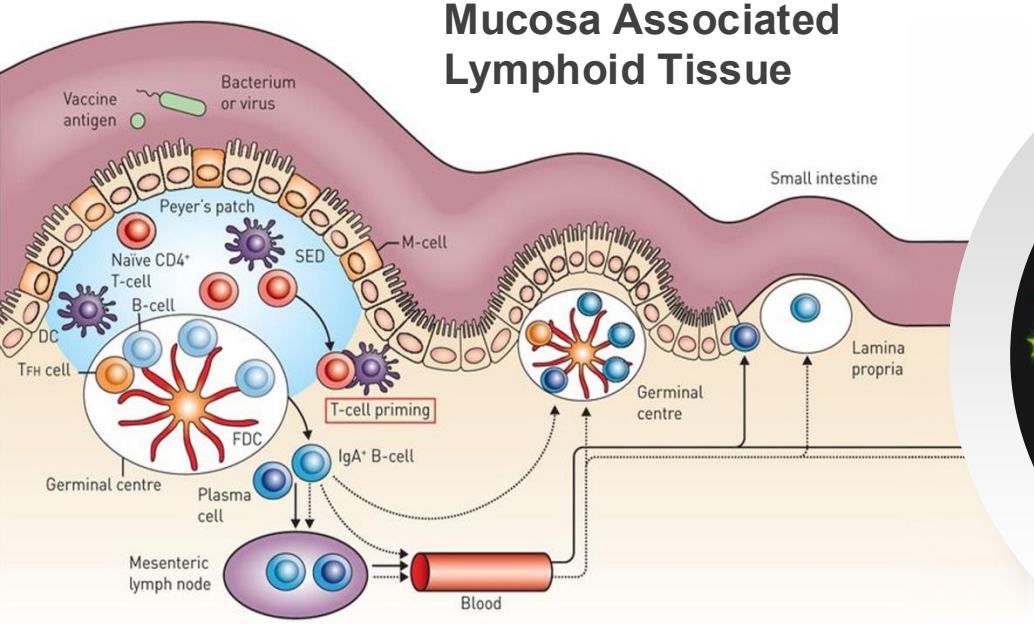

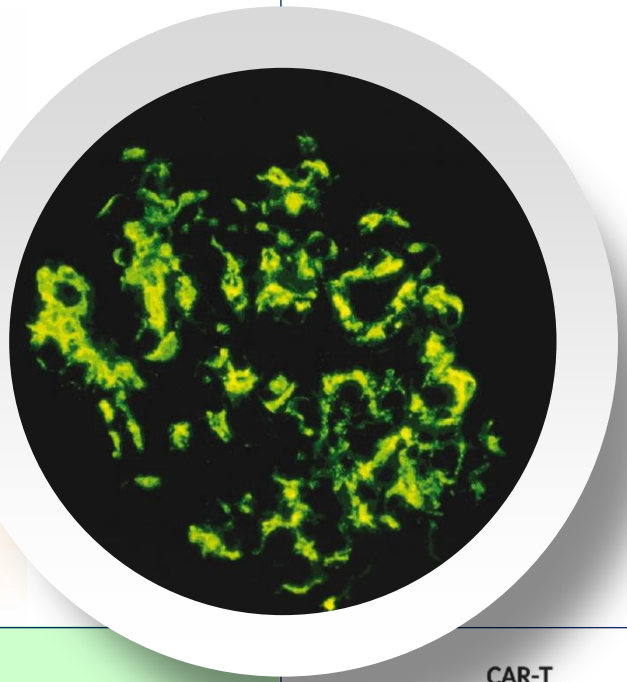

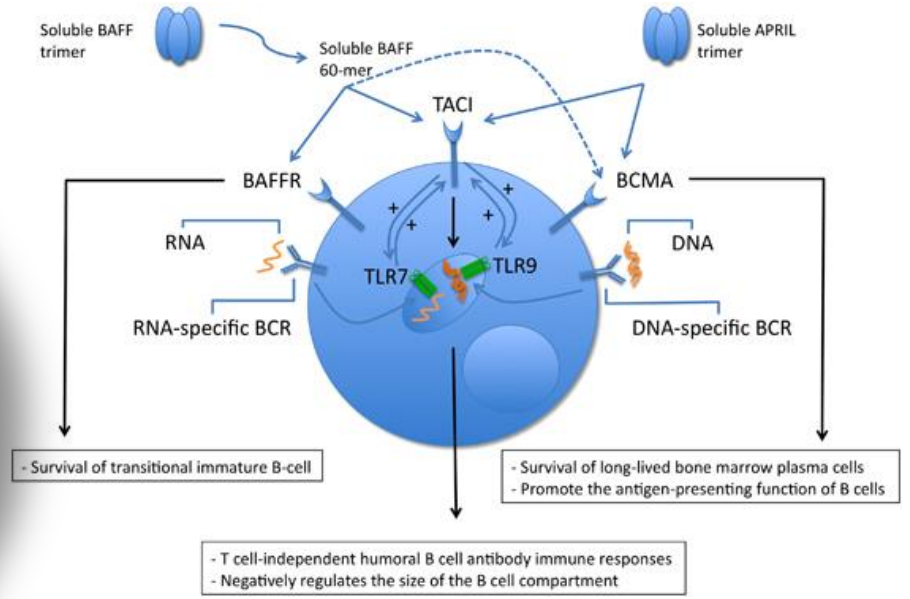

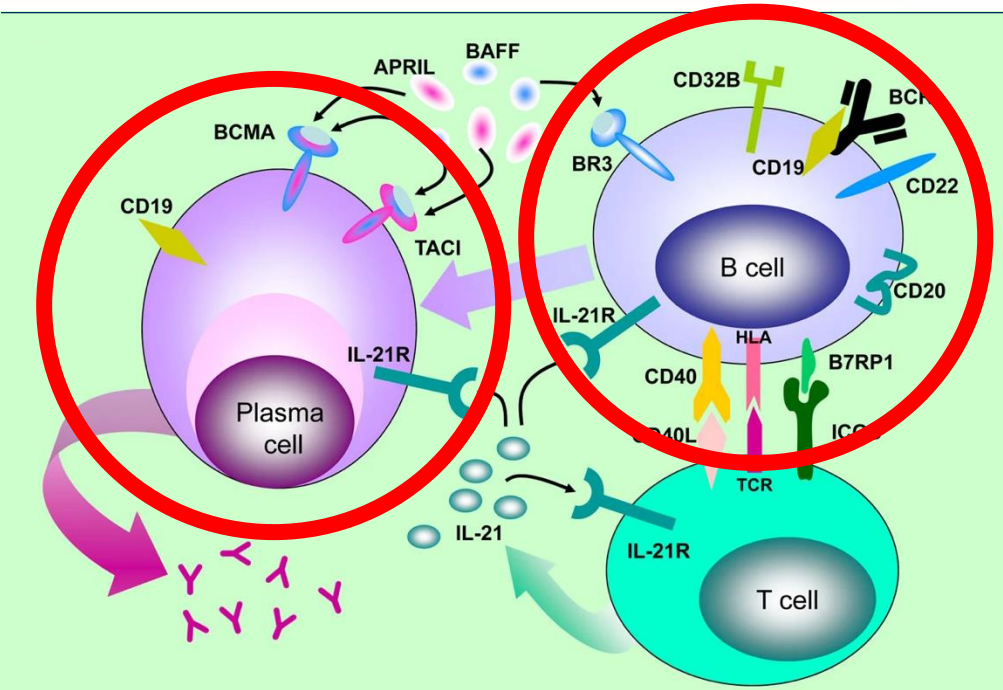

CAR-T

BCMA
-JNJ-68284528
-bb21217
NY-ESO-1
-GSK3377794
BCMA/CD19
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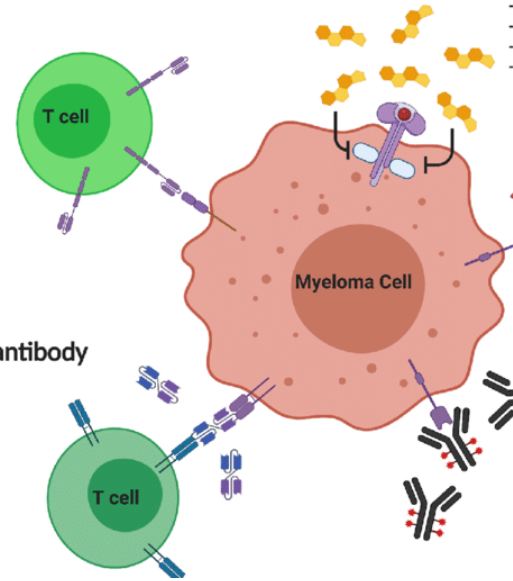
BCMA/CD38
-BM 38CAR
Allogenic
-ALLO-715

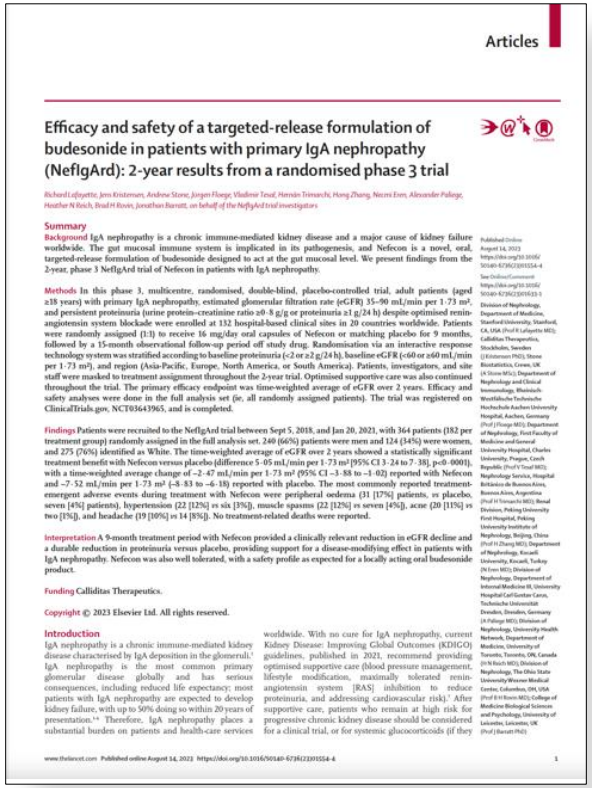


Small molecule inhibitor
-BCL-2 inhibition
-HDAC inhibition
-Cereblon E3 ligase modulation
-MEK/BRAF inhibition

Monoclonal antibody
CD38
-TAK-079, TAK-573
-SAR442085

Bispecific antibody
BCMA x CD3
-Teclistamab
-CC-93269
-PF-06863135
-TNB383B
-REGN5458
GPRC5D x CD3
-Talquetamab
FcRH5 x CD3
-BFCR4350A

Antibody drug conjugate
BCMA-targeted
-MEDI2228
-TAK-169



Articles

Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial

Richard Lafayette, Jens Kristensen, Andrew Stone, Jürgen Floege, Vladimir Tesař, Hernán Trimarchi, Hong Zhang, Necmi Eren, Alexander Pallone, Heather N Reich, Brad H Rovin, Jonathan Barratt, on behalf of the NefIgArd trial investigators

Summary

Background IgA nephropathy is a chronic immune-mediated kidney disease and a major cause of kidney failure worldwide. The gut mucosal immune system is implicated in its pathogenesis, and Nefecon is a novel, oral, targeted-release formulation of budesonide designed to act at the gut mucosal level. We present findings from the 2-year, phase 3 NefIgArd trial of Nefecon in patients with IgA nephropathy.

Methods In this phase 3, multicentre, randomised, double-blind, placebo-controlled trial, adult patients (aged ≥18 years) with primary IgA nephropathy, estimated glomerular filtration rate (eGFR) 35–90 mL/min per 1·73 m², and persistent proteinuria (urine protein–creatinine ratio ≥0·8 g/g or proteinuria ≥1 g/24 h) despite optimised renin-angiotensin system blockade were enrolled at 132 hospital-based clinical sites in 20 countries worldwide. Patients were randomly assigned (1:1) to receive 16 mg/day oral capsules of Nefecon or matching placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Randomisation via an interactive response technology system was stratified according to baseline proteinuria (<2 or ≥2 g/24 h), baseline eGFR (<60 or ≥60 mL/min per 1·73 m²), and region (Asia-Pacific, Europe, North America, or South America). Patients, investigators, and site staff were masked to treatment assignment throughout the 2-year trial. Optimised supportive care was also continued throughout the trial. The primary efficacy endpoint was time-weighted average of eGFR over 2 years. Efficacy and safety analyses were done in the full analysis set (ie, all randomly assigned patients). The trial was registered on ClinicalTrials.gov, NCT03643965, and is completed.

Findings Patients were recruited to the NefIgArd trial between Sept 5, 2018, and Jan 20, 2021, with 364 patients (182 per treatment group) randomly assigned in the full analysis set. 240 (66%) patients were men and 124 (34%) were women, and 275 (76%) identified as White. The time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit with Nefecon versus placebo (difference 5·05 mL/min per 1·73 m² [95% CI 3·24 to 7·38], p<0·0001), with a time-weighted average change of −2·47 mL/min per 1·73 m² (95% CI −3·88 to −1·02) reported with Nefecon and −7·52 mL/min per 1·73 m² (−8·83 to −6·18) reported with placebo. The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] patients, *vs* placebo, seven [4%] patients), hypertension (22 [12%] *vs* six [3%]), muscle spasms (22 [12%] *vs* seven [4%]), acne (20 [11%] *vs* two [1%]), and headache (19 [10%] *vs* 14 [8%]). No treatment-related deaths were reported.

Interpretation A 9-month treatment period with Nefecon provided a clinically relevant reduction in eGFR decline and a durable reduction in proteinuria versus placebo, providing support for a disease-modifying effect in patients with IgA nephropathy. Nefecon was also well tolerated, with a safety profile as expected for a locally acting oral budesonide product.

Funding Calliditas Therapeutics.

Introduction

IgA nephropathy is a chronic immune-mediated kidney disease characterised by IgA deposition in the glomeruli.[1] IgA nephropathy is the most common primary glomerular disease globally and has serious consequences, including reduced life expectancy; most patients with IgA nephropathy are expected to develop kidney failure, with up to 50% doing so within 20 years of presentation.[2,3] Therefore, IgA nephropathy places a substantial burden on patients and health-care services worldwide. With no cure for IgA nephropathy, current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, published in 2021, recommend providing optimised supportive care (blood pressure management, lifestyle modification, maximally tolerated renin-angiotensin system [RAS] inhibition to reduce proteinuria, and addressing cardiovascular risk).[3] After supportive care, patients who remain at high risk for progressive chronic kidney disease should be considered for a clinical trial, or for systemic glucocorticoids (if they

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ORIGINAL ARTICLE

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

V. Perkovic, J. Barratt, B. Rovin, N. Kashihara, B. Maes, H. Zhang, H. Trimarchi, D. Kollins, O. Papachristofi, S. Jacinto-Sanders, T. Merkel, N. Gueyard, R. Renfurm, T. Hach, and D.V. Rizk, for the APPLAUSE-IgAN Investigators*

ABSTRACT

BACKGROUND

The alternative complement pathway plays a key role in the pathogenesis of IgA nephropathy. Iptacopan specifically binds to factor B and inhibits the alternative pathway.

METHODS

In this phase 3, double-blind, randomized, placebo-controlled trial, we enrolled adults with biopsy-confirmed IgA nephropathy and proteinuria (defined as a 24-hour urinary protein-to-creatinine ratio of ≥1 [with protein and creatinine both measured in grams]) despite optimized supportive therapy. Patients were randomly assigned, in a 1:1 ratio, to receive oral iptacopan (200 mg) or placebo twice daily for 24 months while continuing to receive supportive therapy. The primary objective of this prespecified interim analysis was to assess the efficacy of iptacopan as compared with that of placebo in reducing proteinuria at month 9; the primary end point was the change from baseline in the 24-hour urinary protein-to-creatinine ratio at month 9. The proportion of patients who had a 24-hour urinary protein-to-creatinine ratio of less than 1 at month 9 without receiving rescue or alternative medication or undergoing kidney-replacement therapy (dialysis or transplantation) was a secondary end point. Safety was also assessed. The effect of iptacopan on kidney function will be assessed at the end of the 2-year double-blind treatment period.

RESULTS

The main trial population included 222 patients in the iptacopan group and 221 in the placebo group. The interim efficacy analysis included the first 250 patients who underwent randomization in the main trial population (125 patients in each group) and who remained in the trial until month 9 or discontinued the trial by month 9. Safety was assessed in all the patients in the main trial population. At month 9, the adjusted geometric mean 24-hour urinary protein-to-creatinine ratio was 38.3% (95% confidence interval, 26.0 to 48.6; two-sided P<0.001) lower with iptacopan than with placebo. The reduction in proteinuria was supported by consistent results in secondary end point analyses. There were no unexpected safety findings with iptacopan. The incidence of adverse events that occurred during the treatment period was similar in the two groups; most events were mild to moderate in severity and reversible. No increased risk of infection was observed.

CONCLUSIONS

Among patients with IgA nephropathy, treatment with iptacopan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo. (Funded by Novartis; APPLAUSE-IgAN ClinicalTrials.gov number, NCT04578834.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Perkovic can be contacted at vlado.perkovic@unsw.edu.au or at the University of New South Wales, Sydney, NSW 2052, Australia.

*A complete list of the APPLAUSE-IgAN Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 25, 2024, and updated on November 7, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2410026

ORIGINAL ARTICLE

Sibeprenlimab in IgA Nephropathy — Interim Analysis of a Phase 3 Trial

V. Perkovic,[1] H. Trimarchi,[2] V. Tesar,[3] R. Lafayette,[4] M.G. Wong,[5] J. Barratt,[6] Y. Suzuki,[7] A. Liew,[8] H. Zhang,[9] K. Carroll,[10] V. Jha,[11,12] A. Quevedo,[13] S.H. Han,[13] M. Praga,[14] B. Chacko,[15] M. Sahay,[16] C.K. Cheung,[17] L. Kooienga,[18] M. Walsh,[19,20] J. Xia,[21] C. Fajardo,[22] L. Shah,[22] J. Hafkin,[23] and D.V. Rizk,[23] for the VISIONARY Trial Investigators Group*

ABSTRACT

BACKGROUND

The cytokine A proliferation-inducing ligand (APRIL) is considered a key driver of the pathogenesis of IgA nephropathy. Sibeprenlimab, a humanized IgG2 monoclonal antibody, selectively binds to and inhibits APRIL.

METHODS

In this phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we assigned adults with biopsy-confirmed IgA nephropathy in a 1:1 ratio to receive either subcutaneous sibeprenlimab at a dose of 400 mg or placebo administered every 4 weeks for 100 weeks. The primary end point for this interim analysis was the 24-hour urinary protein-to-creatinine ratio at 9 months as compared with baseline. The key secondary end point, to be reported at trial completion, is the annualized slope of estimated glomerular filtration rate over 24 months. Other secondary end points included the change in the level of serum immunoglobulin and safety. Exploratory end points included the change in galactose-deficient IgA1 and APRIL concentrations, the spot 24-hour urinary protein-to-creatinine ratio, hematuria, and remission of proteinuria.

RESULTS

A total of 510 patients underwent randomization — 259 to the sibeprenlimab group and 251 to the placebo group. The prespecified interim analysis included the first 320 patients (152 who received sibeprenlimab and 168 who received placebo) who had the opportunity to complete the 9-month evaluation of the 24-hour urinary protein-to-creatinine ratio. At 9 months, a significant reduction in 24-hour urinary protein-to-creatinine ratio was observed with sibeprenlimab (−50.2%) as compared with an increase with placebo (2.1%), corresponding to an adjusted geometric least-squares mean 24-hour urinary protein-to-creatinine ratio that was 51.2% (96.5% confidence interval [CI], 42.9 to 58.2) lower with sibeprenlimab than with placebo (P<0.001). The levels of APRIL and pathogenic galactose-deficient IgA1 at week 48 were reduced from baseline by 95.8% and 67.1%, respectively, with sibeprenlimab. The safety profile appeared to be similar with sibeprenlimab and placebo. No deaths were reported, and the incidence of serious adverse events that occurred during the treatment period was 3.5% with sibeprenlimab and 4.4% with placebo.

CONCLUSIONS

Sibeprenlimab resulted in a significant reduction in proteinuria as compared with placebo in patients with IgA nephropathy. (Funded by Otsuka Pharmaceutical Development and Commercialization. VISIONARY ClinicalTrials.gov number, NCT05248646.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Vlado Perkovic can be contacted at vlado.perkovic@unsw.edu.au or at University of New South Wales, Sydney, NSW 2052, Australia.

*A list of the VISIONARY trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 8, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2512133

ORIGINAL ARTICLE

A Phase 3 Trial of Atacicept in Patients with IgA Nephropathy

Richard Lafayette, M.D.,[1] Sean J. Barbour, M.D.,[2] Robert M. Brenner, M.D.,[3] Kirk N. Campbell, M.D.,[4] Tom Doan,[5] Necmi Eren, M.D.,[6] Jürgen Floege, M.D.,[4] Vivekanand Jha, M.B., B.S., M.D., D.M.,[7] Beom Seok Kim, M.D., Ph.D.,[8] Adrian Liew, M.D.,[9] Bart Maes, M.D., Ph.D.,[10] Atanu Pal, M.D., D.M.,[11] Roberto Pecoits-Filho, M.D., Ph.D.,[12,13] Richard K.S. Phoon, M.D.,[14,15] Dana V. Rizk, M.D.,[16] Hitoshi Suzuki, M.D., Ph.D.,[17] Vladimír Tesař, M.D., Ph.D.,[18] Hernán Trimarchi, M.D., Ph.D.,[19] Xuelian Wei, Ph.D.,[5] Hong Zhang, M.D., Ph.D.,[20] and Jonathan Barratt, Ph.D.,[21] for the ORIGIN Phase 3 Trial Investigators*

ABSTRACT

BACKGROUND

IgA nephropathy, the most common primary glomerulopathy worldwide, is a kidney disorder of B-cell origin characterized by mesangial accumulation of IgA-containing immune complexes. In at least 50% of patients, IgA nephropathy leads to kidney failure or death within 10 to 20 years after diagnosis. Atacicept is a native human transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI)–Fc fusion protein that inhibits two key immunoregulatory cytokines — B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) — that are thought to be central to the pathophysiology of IgA nephropathy.

METHODS

In this ongoing, phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we assigned patients with IgA nephropathy in a 1:1 ratio to receive atacicept at a dose of 150 mg once weekly, administered subcutaneously by patients at home, or matching placebo. The primary end point was the percentage change from baseline in the 24-hour urinary protein-to-creatinine ratio at week 36. Safety was also evaluated.

RESULTS

A total of 203 patients were included in the prespecified interim analysis: 106 patients in the atacicept group and 97 in the placebo group. At week 36, the percentage reduction from baseline in the urinary protein-to-creatinine ratio was 45.7% in the atacicept group and 6.8% in the placebo group, with a geometric mean between-group difference of 41.8 percentage points (95% confidence interval, 28.9 to 52.3; P<0.001). Adverse events were observed in 59.3% of the patients in the atacicept group and in 50.0% in the placebo group; most were mild or moderate in severity.

CONCLUSIONS

In this prespecified interim analysis, treatment with atacicept resulted in a significantly greater reduction in proteinuria than placebo at week 36 in patients with IgA nephropathy. (Funded by Vera Therapeutics; ORIGIN 3 ClinicalTrials.gov number, NCT04716231.)

Author affiliations are listed at the end of the article. Richard Lafayette can be contacted at czar@stanford.edu or at Stanford University, Nephrology, 300 Pasteur Dr., Suite A175, MC 5309, Stanford, CA 94305.

*A list of investigators and collaborators for the ORIGIN 3 trial is provided in the Supplementary Appendix.

This article was published on November 6, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2510198

KEY POINT

In all immune modulating therapies approved or in development, disease recurs upon cessation of therapy

Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial

Richard Lafayette, Jens Kristensen, Andrew Stone, Jürgen Floege, Vladimir Tesař, Hernán Trimarchi, Hong Zhang, Necmi Eren, Alexander Paliege, Heather N Reich, Brad H Rovin, Jonathan Barratt, on behalf of the NefIgArd trial investigators

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Methods In this phase 3, multicentre, randomised, double-blind, placebo-controlled trial, adult patients (aged ≥18 years) with primary IgA nephropathy, estimated glomerular filtration rate (eGFR) 35–90 mL/min per 1·73 m², and persistent proteinuria (urine protein–creatinine ratio ≥0·8 g/g or proteinuria ≥1 g/24 h) despite optimised renin-angiotensin system blockade were enrolled at 132 hospital-based clinical sites in 20 countries worldwide. Patients were randomly assigned (1:1) to receive 16 mg/day oral capsules of Nefecon or matching placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Randomisation via an interactive response technology system was stratified according to baseline proteinuria (<2 or ≥2 g/24 h), baseline eGFR (<60 or ≥60 mL/min per 1·73 m²), and region (Asia-Pacific, Europe, North America, or South America). Patients, investigators, and site staff were masked to treatment assignment throughout the 2-year trial. Optimised supportive care was also continued throughout the trial. The primary efficacy endpoint was time-weighted average of eGFR over 2 years. Efficacy and safety analyses were done in the full analysis set (ie, all randomly assigned patients). The trial was registered on ClinicalTrials.gov, NCT03643965, and is completed.

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Interpretation A 9-month treatment period with Nefecon provided a clinically relevant reduction in eGFR decline and a durable reduction in proteinuria versus placebo, providing support for a disease-modifying effect in patients with IgA nephropathy. Nefecon was also well tolerated, with a safety profile as expected for a locally acting oral budesonide product.

Funding Calliditas Therapeutics.

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158 (87%) of 182 patients in the Nefecon group and 165 (91%) of 182 in the placebo group received 9 months of randomised treatment. Compliance with study treatment was high (171 [94%] patients in each treatment group took at least 80% of the total capsules). The overall rate of study completion was high and similar in both

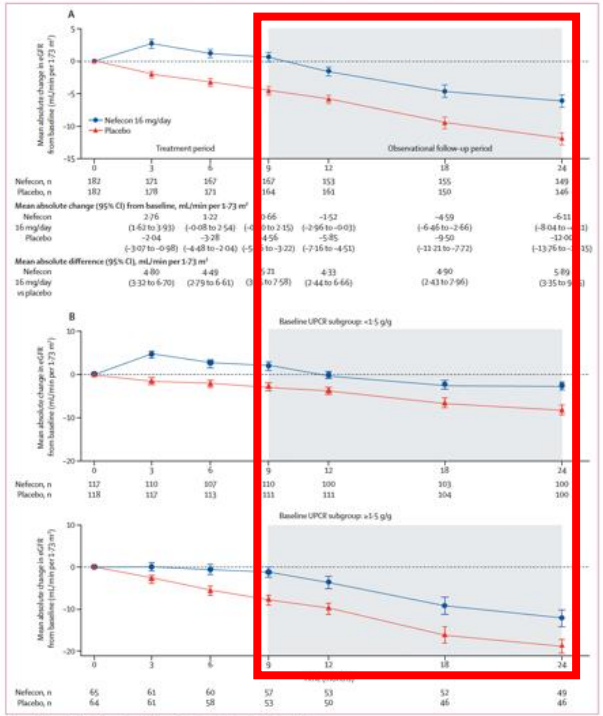

Figure 1: Mean absolute change in eGFR from baseline to 24 months (full analysis set)
All patients (A) and patients stratified according to baseline UPCR, <1·5 g/g and ≥1·5 g/g (B). Estimated mean absolute change (and standard error) was calculated from multiple-imputation robust regression analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months, and transformed back into the original scale. eGFR was calculated by the central laboratory with the Chronic Kidney Disease Epidemiology Collaboration formula.[24] Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. eGFR=estimated glomerular filtration rate. UPCR=urine protein–creatinine ratio.

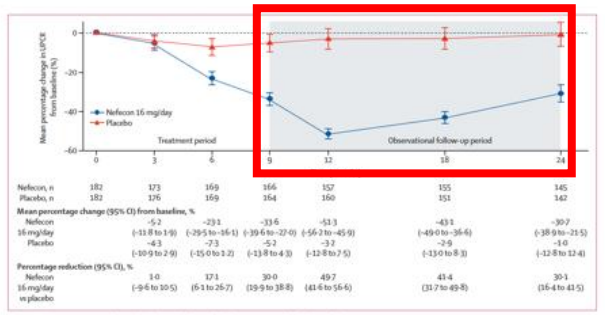

Figure 2: Mean percentage change in UPCR (g/g) from baseline to 24 months (full analysis set)
Estimated geometric mean percentage change (and standard error) was calculated from a mixed-effects model for repeated measures of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months. Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. The corresponding percentage reduction and confidence interval was derived from (1−ratio of geometric least squares means) × 100. UPCR=urine protein–creatinine ratio.

12 months, with a reduction in UPCR of 49·7% (41·6–56·6).

Results from the UACR analysis were consistent with those for UPCR, with the Nefecon group showing a 46·3% (36·5–54·5) reduction in time-averaged UACR between 12 and 24 months compared with the placebo group (p<0·0001; appendix p 11). The proportion of patients without microhaematuria during the observational follow-up period was significantly higher in the Nefecon group than in the placebo group (in patients with two or more urine dipstick results during the observational period, 94 [59%] of 158 *vs* 59 [39%] of 152; odds ratio for Nefecon *vs* placebo 2·5 [95% CI 1·6–4·1], p=0·0001; appendix p 12). Results of other secondary efficacy analyses were generally supportive of the overall beneficial effect of Nefecon treatment (appendix pp 13–14).

During the 9-month treatment period, Nefecon 16 mg/day was well tolerated, with a safety profile as expected for a locally acting oral budesonide product. Discontinuations due to treatment-emergent adverse events occurred in 17 (9%) of 182 patients in the Nefecon group and three (2%) of 182 in the placebo group (table 3). Treatment-emergent serious adverse events were reported in 18 (10%) patients in the Nefecon group and nine (5%) patients in the placebo group, with most considered unrelated to study treatment (table 3), and no discernible patterns in terms of body system or organ (appendix p 15). During the 15-month observational follow-up, the incidence of treatment-emergent adverse events and treatment-emergent serious adverse events was similar between the groups.

One death due to SARS-CoV-2 infection was reported during Nefecon treatment in a patient with several risk factors for COVID-19 mortality, and another patient treated with Nefecon died from a cerebral haemorrhage 10·5 months after their last dose. Neither death was considered to be related to study treatment. No treatment-emergent adverse events leading to death were reported in the placebo group.

The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] of 182 patients *vs* placebo, seven [4%] of 182 patients), hypertension (22 [12%] *vs* six [3%]), muscle spasms (22 [12%] *vs* seven [4%] patients), acne (20 [11%] *vs* two [1%]), and headache (19 [10%] *vs* 14 [8%]); appendix p 15). These were generally non-serious adverse events and were of mild severity, and reversible during or after treatment. In the Nefecon group, two patients had hypertension events, and one patient had both peripheral and face oedema events, all of which were classed as serious; a fourth patient had a peripheral oedema event that was graded as severe (appendix p 15). During the observational follow-up, frequencies of the most commonly reported treatment-emergent adverse events were similar in both treatment groups, including of SARS-CoV-2 infection, which was the most frequently reported event (26 [15%] of 175 patients in the Nefecon group and 30 [17%] of 174 in the placebo group), among patients who had a study visit during the observational follow-up; appendix p 16).

The incidence of infections during treatment was similar between treatment groups (63 [35%] of 182 patients

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Beyond Nephrology

in collaboration with Österreichische Gesellschaft für Nephrologie

Effect of iptacopan discontinuation on proteinuria and complement biomarkers in patients with immunoglobulin A nephropathy (IgAN): a *post hoc* analysis from a Phase II trial

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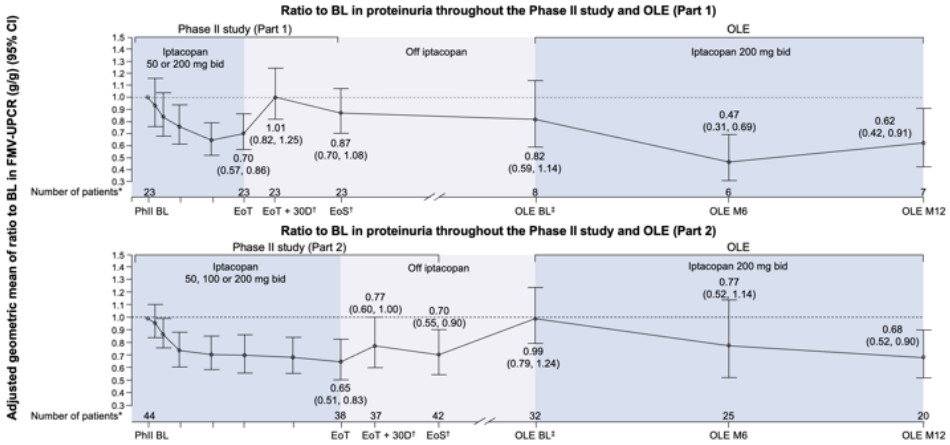
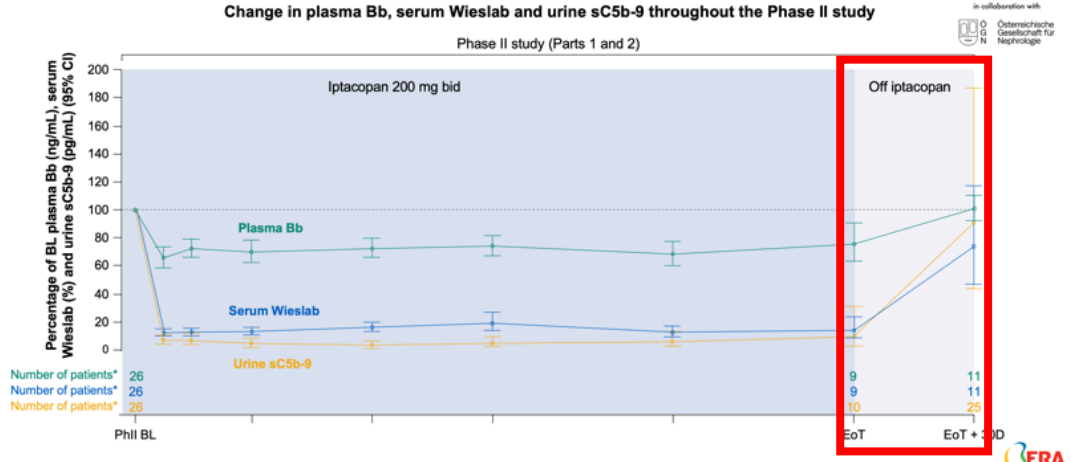
[1]The Mayer IgA Nephropathy Laboratories, University of Leicester, Leicester, UK; [2]The John Walls Renal Unit, Leicester General Hospital, Leicester, UK; [3]University of Alabama at Birmingham, Birmingham, AL, USA; [4]Peking University First Hospital, Beijing, China; [5]AZ Delta, Roeselare, Belgium; [6]Kawasaki Medical School, Okayama, Japan; [7]The Ohio State University Wexner Medical Center, Columbus, OH, USA; [8]Hospital Británico de Buenos Aires, Buenos Aires, Argentina; [9]Novartis Pharma AG, Basel, Switzerland; [10]University of New South Wales, Sydney, NSW, Australia

Proteinuria increased after iptacopan discontinuation, and decreased upon its reinitiation to a similar extent as during initial treatment



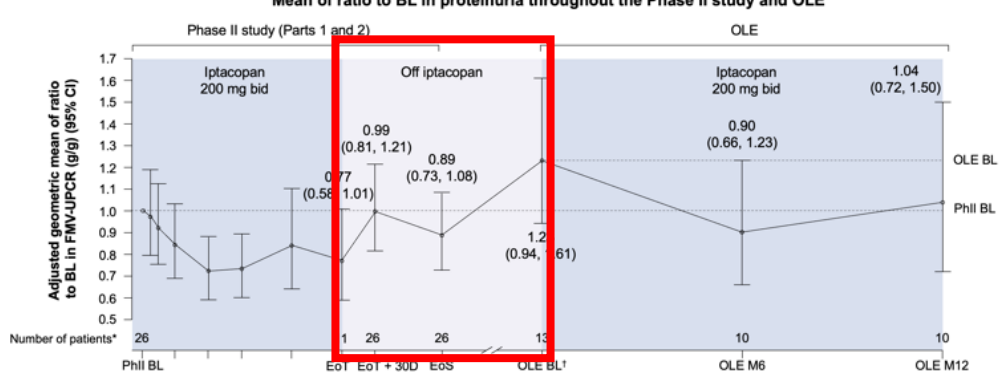
*The number of patients with non-missing values at each study visit; †Five patients (two from Part 1 and three from Part 2) initiated systemic steroids and/or immunosuppressants during the off-iptacopan period. In a sensitivity analysis, the use of steroids/immunosuppressants did not influence the UPCR results; ‡The time between the PhII EoS visit and OLE BL visit varied between patients. As such, this period of the x-axis is not drawn to scale
CI, confidence interval; PhII, Phase II

When iptacopan 200 mg bid was discontinued, there was an increase in AP biomarker activity



*The number of patients with non-missing values at each study visit

In the pooled iptacopan 200 mg bid arms, proteinuria decreased with iptacopan treatment, increased following discontinuation, and decreased again upon reinitiation



*The number of patients with non-missing values at each study visit; †The time between the PhII EoS visit and OLE BL visit varied between patients. As such, this period of the x-axis is not drawn to scale

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

Mathur M et al. DOI: 10.1056/NEJMoa2305635

CLINICAL PROBLEM

Among patients with IgA nephropathy, kidney failure develops in ≥30% within 20 to 30 years, despite the receipt of optimized standard care. A critical step in the pathogenesis of IgA nephropathy is the production of galactose-deficient IgA1 and resulting autoantibody release. Sibeprenlimab is a humanized IgG2 monoclonal antibody that binds to and neutralizes a proliferation-inducing ligand (APRIL), a member of the tumor necrosis factor α superfamily that regulates IgA production.

CLINICAL TRIAL

Design: A phase 2, multicenter, double-blind, randomized, placebo-controlled, multiple-dose trial examined the efficacy and safety of sibeprenlimab in adults with IgA nephropathy at high risk for disease progression.

Intervention: 155 patients were assigned to receive intravenous sibeprenlimab at a dose of 2, 4, or 8 mg per kilogram of body weight or placebo once monthly for 12 months. The primary end point was the change from baseline to month 12 in the log-transformed 24-hour urinary protein-to-creatinine ratio.

RESULTS

Efficacy: The 24-hour urinary protein-to-creatinine ratio decreased significantly more in the sibeprenlimab groups than in the placebo group. The decreases in the sibeprenlimab groups were dose-dependent.

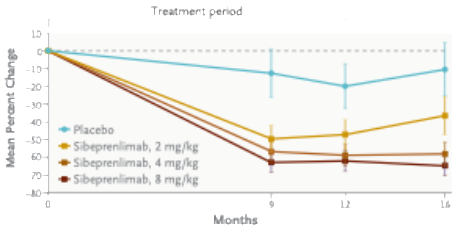
Safety: The incidence of adverse events, including serious adverse events, was similar in the sibeprenlimab groups and the placebo group.

LIMITATIONS AND REMAINING QUESTIONS

- Evidence of a return to baseline levels of APRIL in the 4 months after discontinuation of sibeprenlimab suggests that ongoing treatment will be needed.
- A phase 3 trial has been started to confirm these results in a larger patient population.

Links: Full Article | NEJM Quick Take | Editorial

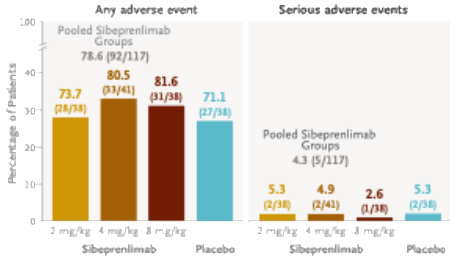
Change in 24-Hr Urinary Protein-to-Creatinine Ratio



Geometric Mean Percent Reduction in 24-Hr Urinary Protein-to-Creatinine Ratio

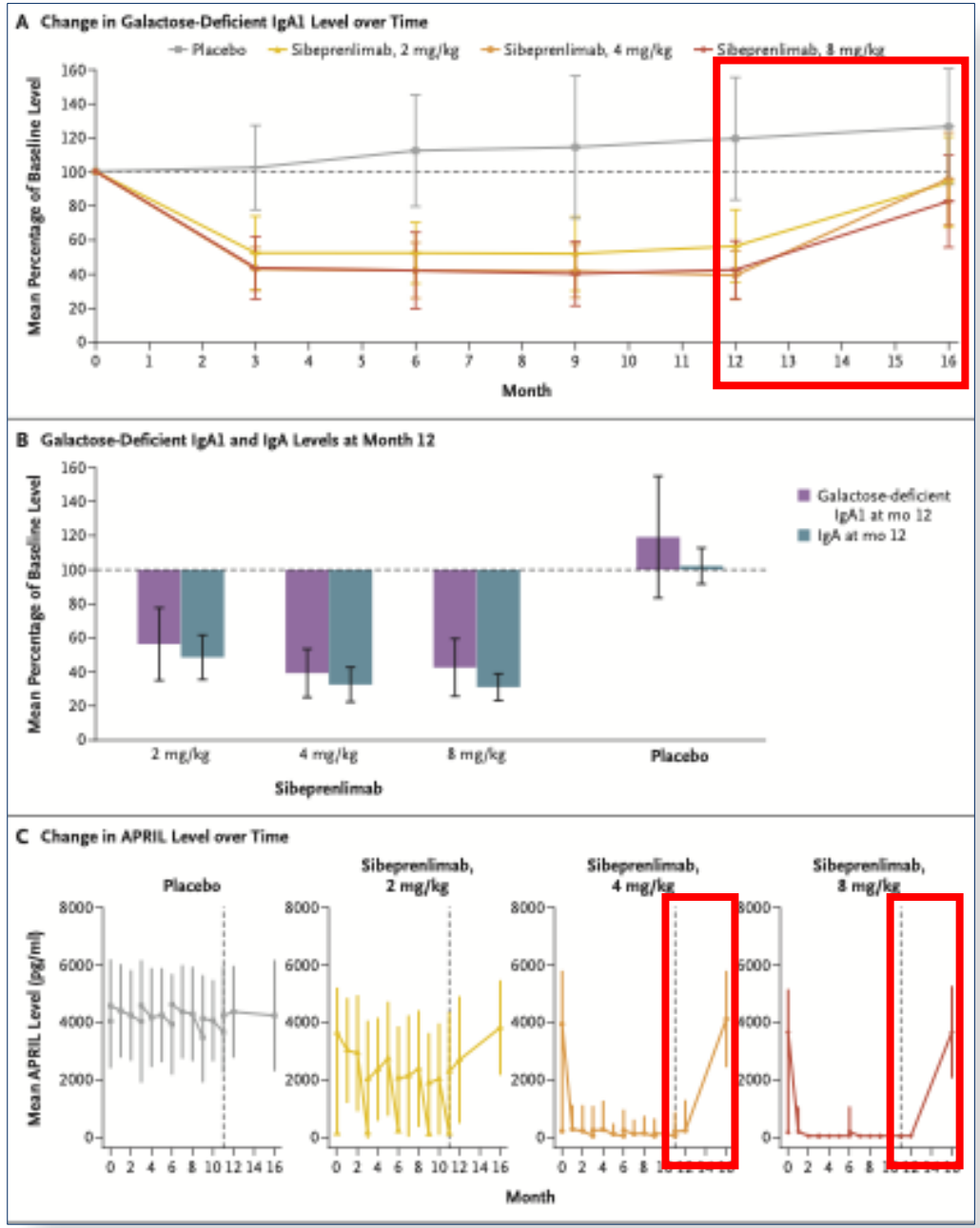
End Point	Sibeprenlimab 2 mg/kg (N=38)	Sibeprenlimab 4 mg/kg (N=41)	Sibeprenlimab 8 mg/kg (N=38)	Placebo (N=38)
Month 9	49.6±7.7	56.7±6.2	62.8±5.5	12.7±13.4
Month 12	**47.2±8.2**	**58.8±6.1**	**62.0±5.7**	**20.0±12.6**
Month 16	36.5±10.6	58.0±6.6	64.6±5.7	10.6±15.0

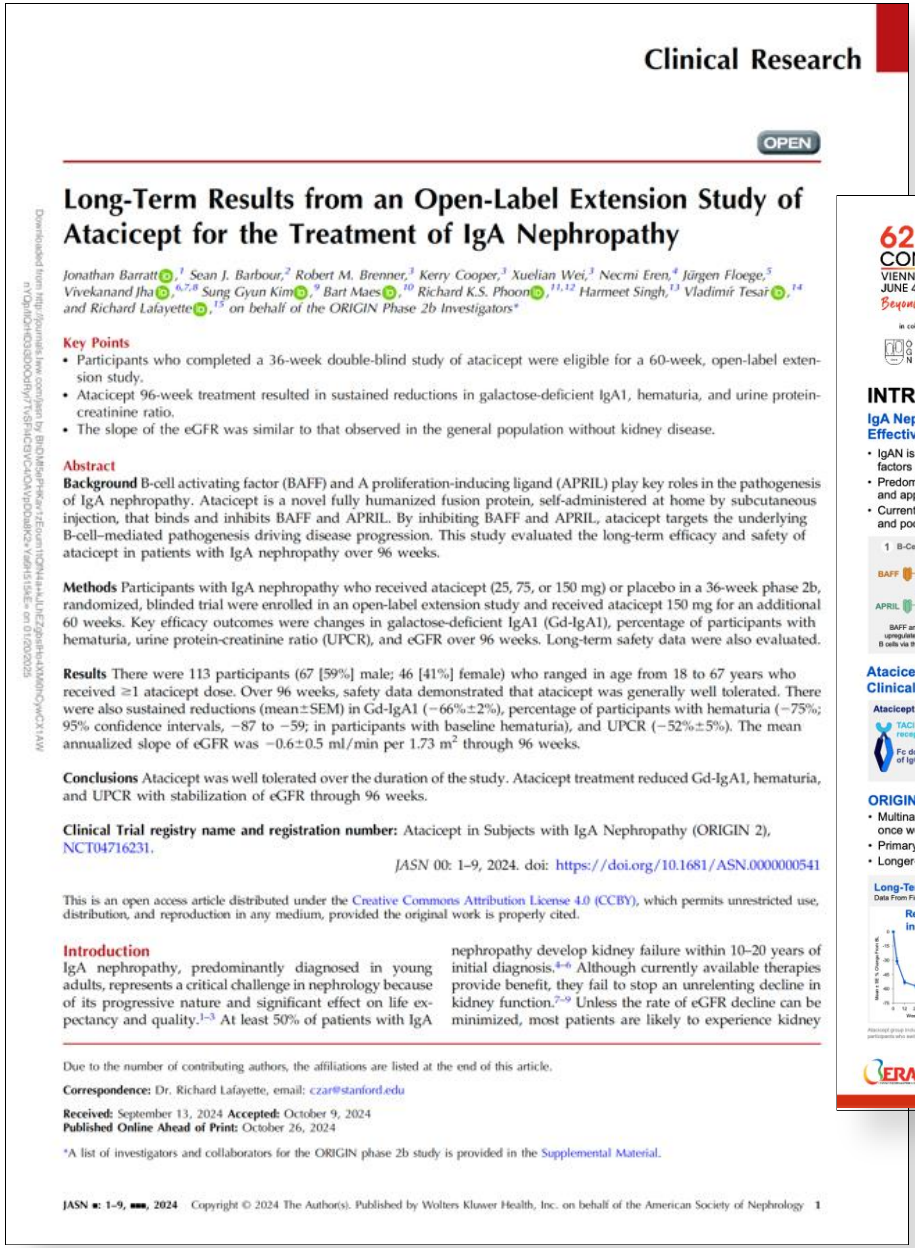
Adverse Events



CONCLUSIONS

Among patients with IgA nephropathy at high risk for disease progression, 12 months of treatment with sibeprenlimab resulted in a significantly greater reduction in proteinuria than placebo.




Clinical Research

OPEN

Long-Term Results from an Open-Label Extension Study of Atacicept for the Treatment of IgA Nephropathy

Jonathan Barratt,[1] Sean J. Barbour,[2] Robert M. Brenner,[3] Kerry Cooper,[3] Xuelian Wei,[3] Necmi Eren,[4] Jürgen Floege,[5] Vivekanand Jha,[6,7,8] Sung Gyun Kim,[9] Bart Maes,[10] Richard K.S. Phoon,[11,12] Harmeet Singh,[13] Vladimír Tesař,[14] and Richard Lafayette,[15] on behalf of the ORIGIN Phase 2b Investigators*

Key Points

- Participants who completed a 36-week double-blind study of atacicept were eligible for a 60-week, open-label extension study.
- Atacicept 96-week treatment resulted in sustained reductions in galactose-deficient IgA1, hematuria, and urine protein-creatinine ratio.
- The slope of the eGFR was similar to that observed in the general population without kidney disease.

Abstract

Background B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL) play key roles in the pathogenesis of IgA nephropathy. Atacicept is a novel fully humanized fusion protein, self-administered at home by subcutaneous injection, that binds and inhibits BAFF and APRIL. By inhibiting BAFF and APRIL, atacicept targets the underlying B-cell–mediated pathogenesis driving disease progression. This study evaluated the long-term efficacy and safety of atacicept in patients with IgA nephropathy over 96 weeks.

Methods Participants with IgA nephropathy who received atacicept (25, 75, or 150 mg) or placebo in a 36-week phase 2b, randomized, blinded trial were enrolled in an open-label extension study and received atacicept 150 mg for an additional 60 weeks. Key efficacy outcomes were changes in galactose-deficient IgA1 (Gd-IgA1), percentage of participants with hematuria, urine protein-creatinine ratio (UPCR), and eGFR over 96 weeks. Long-term safety data were also evaluated.

Results There were 113 participants (67 [59%] male; 46 [41%] female) who ranged in age from 18 to 67 years who received ≥1 atacicept dose. Over 96 weeks, safety data demonstrated that atacicept was generally well tolerated. There were also sustained reductions (mean±SEM) in Gd-IgA1 (−66%±2%), percentage of participants with hematuria (−75%; 95% confidence intervals, −87 to −59; in participants with baseline hematuria), and UPCR (−52%±5%). The mean annualized slope of eGFR was −0.6±0.5 ml/min per 1.73 m^2 through 96 weeks.

Conclusions Atacicept was well tolerated over the duration of the study. Atacicept treatment reduced Gd-IgA1, hematuria, and UPCR with stabilization of eGFR through 96 weeks.

Clinical Trial registry name and registration number: Atacicept in Subjects with IgA Nephropathy (ORIGIN 2), NCT04716231.

JASN 00: 1–9, 2024. doi: https://doi.org/10.1681/ASN.0000000541

Introduction

IgA nephropathy, predominantly diagnosed in young adults, represents a critical challenge in nephrology because of its progressive nature and significant effect on life expectancy and quality.[1–3] At least 50% of patients with IgA nephropathy develop kidney failure within 10–20 years of initial diagnosis.[4–6] Although currently available therapies provide benefit, they fail to stop an unrelenting decline in kidney function.[7–9] Unless the rate of eGFR decline can be minimized, most patients are likely to experience kidney

Due to the number of contributing authors, the affiliations are listed at the end of this article.

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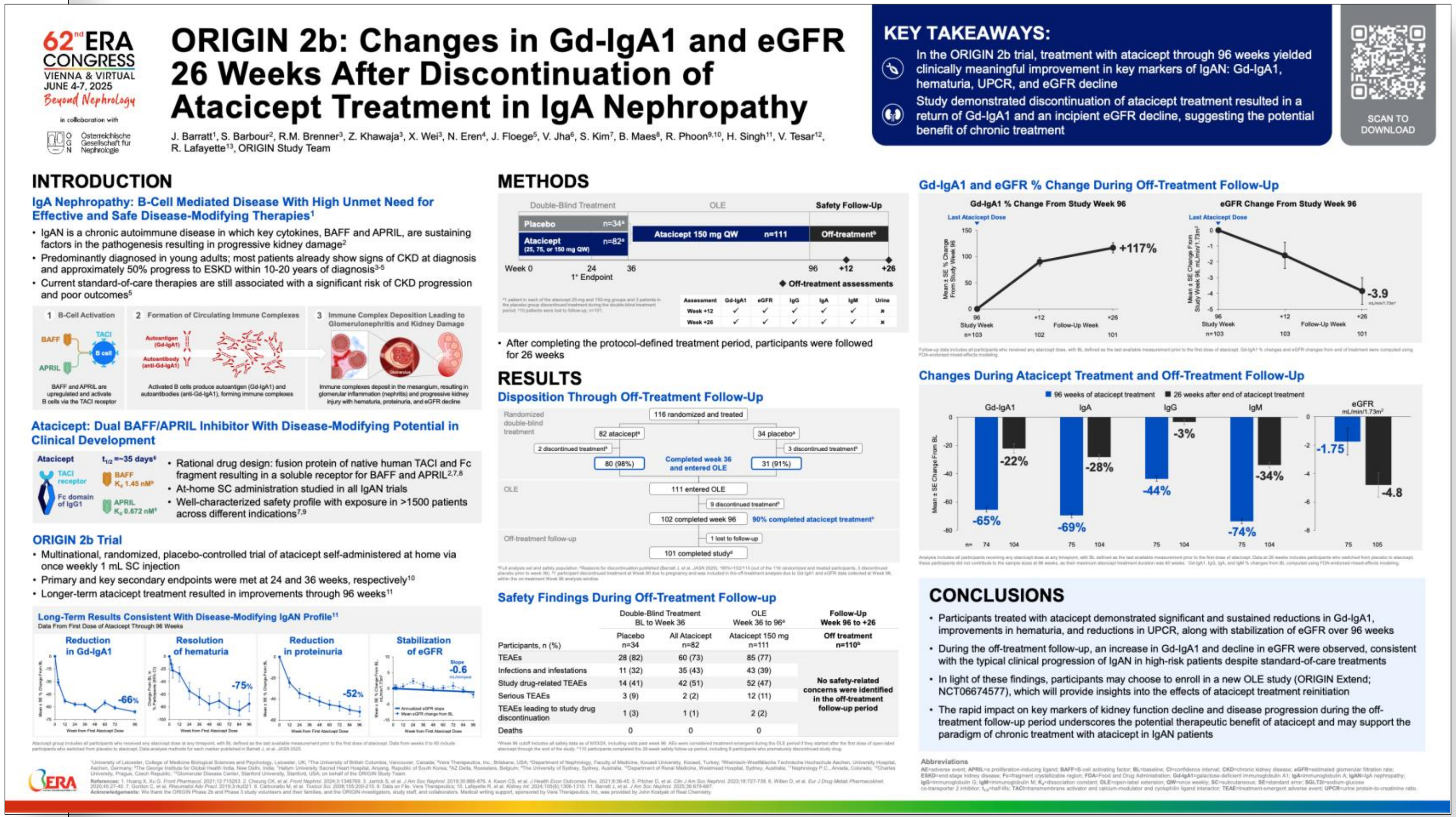
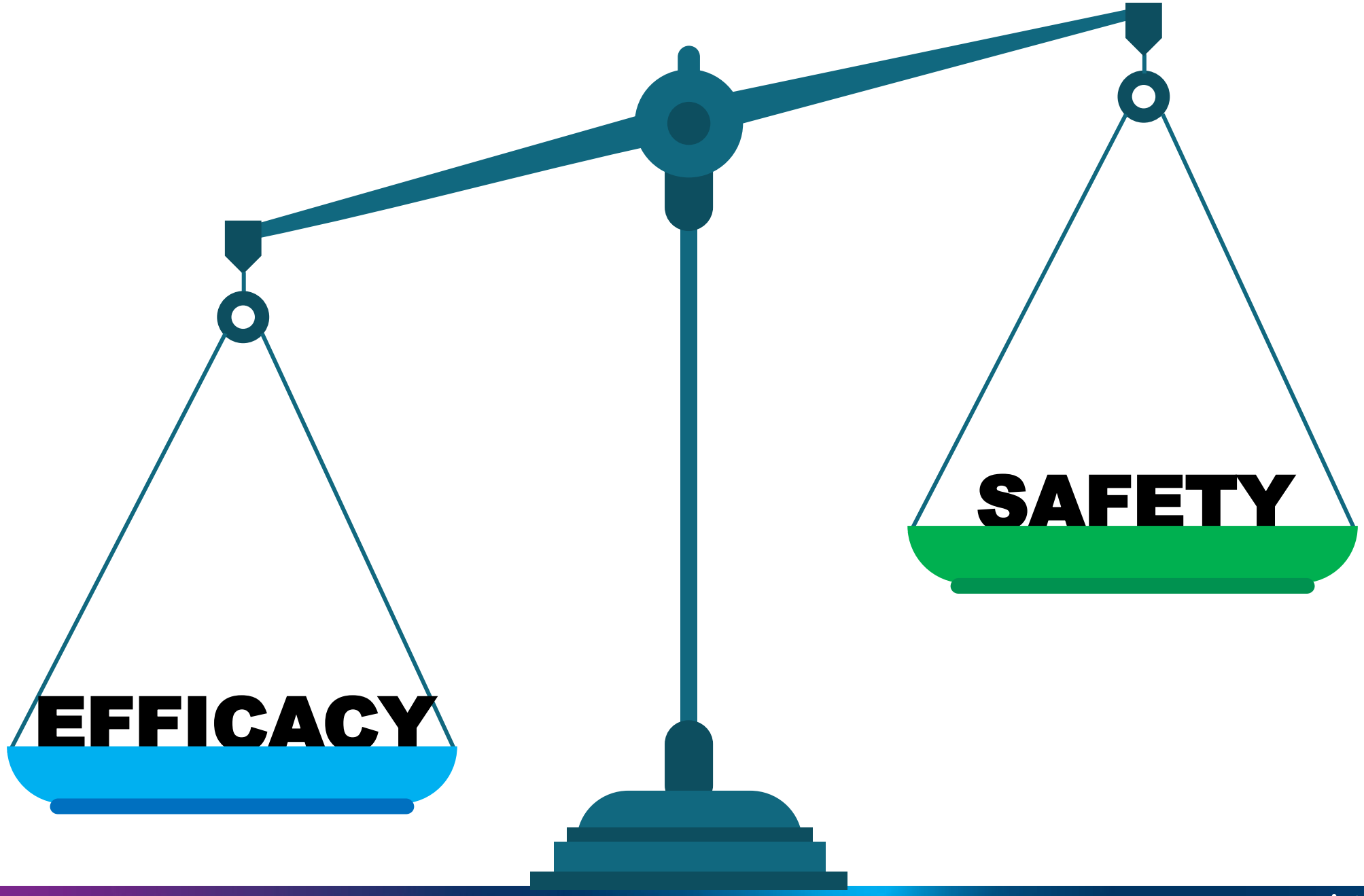
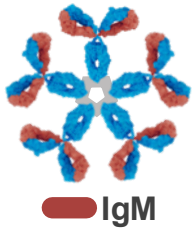
*A list of investigators and collaborators for the ORIGIN phase 2b study is provided in the Supplemental Material.

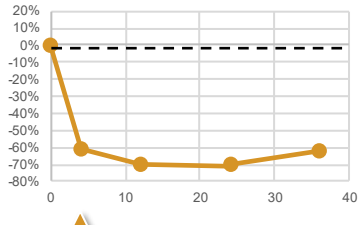

62nd ERA CONGRESS
VIENNA & VIRTUAL
JUNE 4-7, 2025
Beyond Nephrology
ORIGIN 2b: Changes in Gd-IgA1 and eGFR 26 Weeks After Discontinuation of Atacicept Treatment in IgA Nephropathy
J. Barratt1, S. Barbour2, R.M. Brenner3, Z. Khawaja3, X. Wei3, N. Eren4, J. Floege5, V. Jha6, S. Kim7, B. Maes8, R. Phoon9,10, H. Singh11, V. Tesar12, R. Lafayette13, ORIGIN Study Team
KEY TAKEAWAYS:
In the ORIGIN 2b trial, treatment with atacicept through 96 weeks yielded clinically meaningful improvement in key markers of IgAN: Gd-IgA1, hematuria, UPCR, and eGFR decline
Study demonstrated discontinuation of atacicept treatment resulted in a return of Gd-IgA1 and an incipient eGFR decline, suggesting the potential benefit of chronic treatment
SCAN TO DOWNLOAD
INTRODUCTION
IgA Nephropathy: B-Cell Mediated Disease With High Unmet Need for Effective and Safe Disease-Modifying Therapies
IgAN is a chronic autoimmune disease in which key cytokines, BAFF and APRIL, are sustaining factors in the pathogenesis resulting in progressive kidney damage
Predominantly diagnosed in young adults; most patients already show signs of CKD at diagnosis and approximately 50% progress to ESKD within 10-20 years of diagnosis
Current standard-of-care therapies are still associated with a significant risk of CKD progression and poor outcomes
1 B-Cell Activation
2 Formation of Circulating Immune Complexes
3 Immune Complex Deposition Leading to Glomerulonephritis and Kidney Damage
Atacicept: Dual BAFF/APRIL Inhibitor With Disease-Modifying Potential in Clinical Development
Rational drug design: fusion protein of native human TACI and Fc fragment resulting in a soluble receptor for BAFF and APRIL
At-home SC administration studied in all IgAN trials
Well-characterized safety profile with exposure in >1500 patients across different indications
ORIGIN 2b Trial
Multinational, randomized, placebo-controlled trial of atacicept self-administered at home via once weekly 1 mL SC injection
Primary and key secondary endpoints were met at 24 and 36 weeks, respectively
Longer-term atacicept treatment resulted in improvements through 96 weeks
Long-Term Results Consistent With Disease-Modifying IgAN Profile
Reduction in Gd-IgA1
Resolution of hematuria
Reduction in proteinuria
Stabilization of eGFR
-66%
-75%
-52%
-0.6
METHODS
Double-Blind Treatment
OLE
Safety Follow-Up
Placebo n=34
Atacicept (25, 75, or 150 mg QW) n=82
Atacicept 150 mg QW n=111
Off-treatment
Week 0
24 1° Endpoint
36
96
+12
+26
Off-treatment assessments
After completing the protocol-defined treatment period, participants were followed for 26 weeks
RESULTS
Disposition Through Off-Treatment Follow-Up
116 randomized and treated
82 atacicept
34 placebo
2 discontinued treatment
3 discontinued treatment
80 (98%)
Completed week 36 and entered OLE
31 (91%)
111 entered OLE
9 discontinued treatment
102 completed week 96
90% completed atacicept treatment
1 lost to follow-up
101 completed study
Safety Findings During Off-Treatment Follow-up
Gd-IgA1 and eGFR % Change During Off-Treatment Follow-Up
Gd-IgA1 % Change From Study Week 96
+117%
eGFR Change From Study Week 96
-3.9
Changes During Atacicept Treatment and Off-Treatment Follow-Up
96 weeks of atacicept treatment
26 weeks after end of atacicept treatment
Gd-IgA1 IgA IgG IgM eGFR
-65% -22% -69% -28% -44% -3% -74% -34% -1.75 -4.8
CONCLUSIONS
Participants treated with atacicept demonstrated significant and sustained reductions in Gd-IgA1, improvements in hematuria, and reductions in UPCR, along with stabilization of eGFR over 96 weeks
During the off-treatment follow-up, an increase in Gd-IgA1 and decline in eGFR were observed, consistent with the typical clinical progression of IgAN in high-risk patients despite standard-of-care treatments
In light of these findings, participants may choose to enroll in a new OLE study (ORIGIN Extend; NCT06674577), which will provide insights into the effects of atacicept treatment reinitiation
The rapid impact on key markers of kidney function decline and disease progression during the off-treatment follow-up period underscores the potential therapeutic benefit of atacicept and may support the paradigm of chronic treatment with atacicept in IgAN patients


EFFICACY
SAFETY

Competitors Show Long-Term Immunosuppression[1,2]

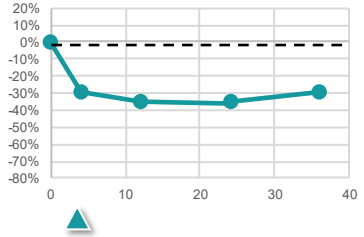


Mezagitamab 600 mg SC[2,4]



62% DROP FROM BASELINE MONTH 36

61% DROP MONTH 4

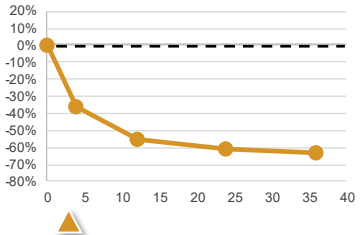


30% DROP FROM BASELINE MONTH 36

30% DROP MONTH 4

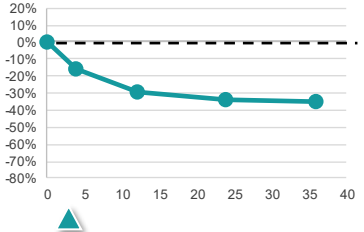
IgM Data not Reported

Atacicept 150 mg[2,5]



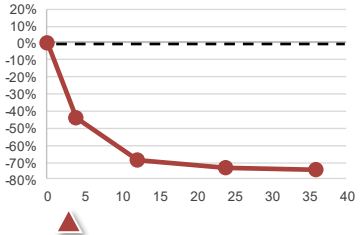
64% DROP FROM BASELINE WEEK 36

36% DROP DAY 30



35% DROP FROM BASELINE WEEK 36

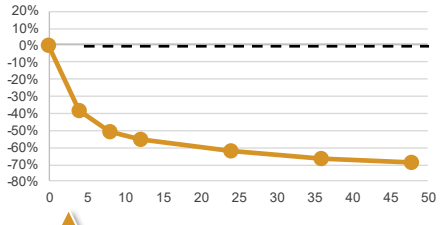
16% DROP DAY 30



75% DROP FROM BASELINE WEEK 36

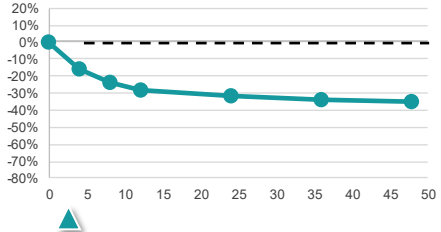
44% DROP DAY 30

VOYXACT SC[2,6]



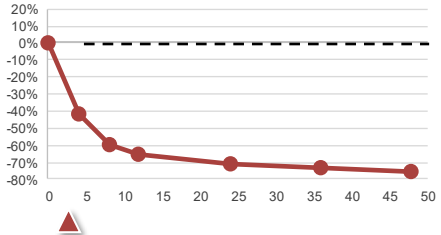
69% DROP FROM BASELINE WEEK 48

38% DROP DAY 30



35% DROP FROM BASELINE WEEK 48

16% DROP DAY 30



75% DROP FROM BASELINE WEEK 48

42% DROP DAY 30

VOYXACT FDA LABEL[7]

WARNINGS AND PRECAUTIONS

Immunosuppression and Increased Risk of Infections
VOYXACT suppresses the immune system by reducing antibody production, which may increase the risk of infections.

Immunosuppression and Immunization Risks
Because of its mechanism of action, VOYXACT may interfere with the immune responses to vaccines and increase the risk of infection from live vaccines.

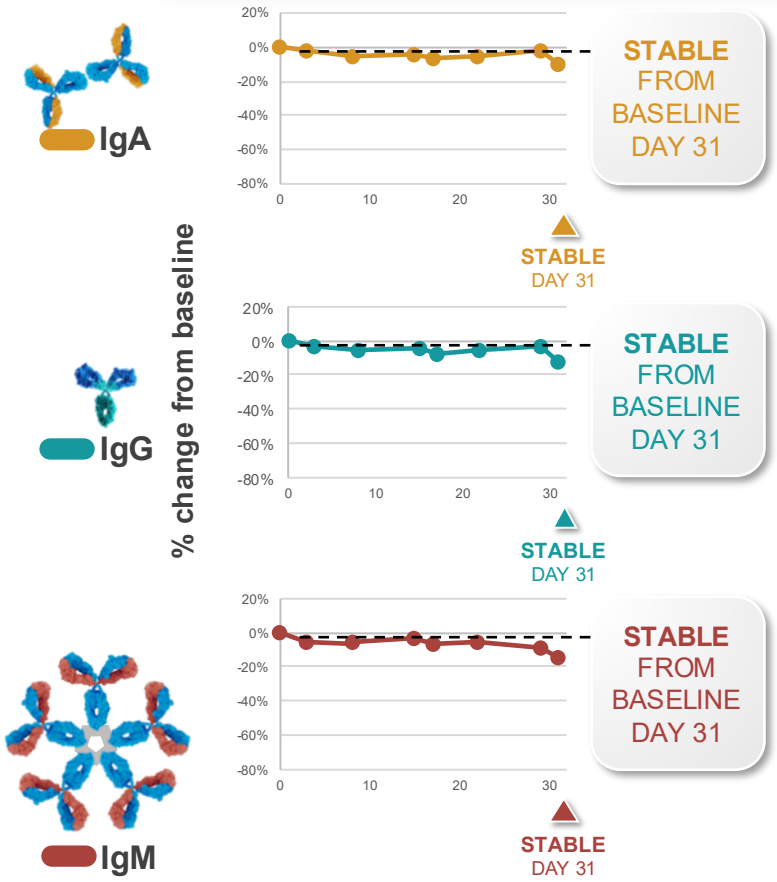
Months **Weeks** **Weeks**

1. Competitors did not report IgE. **2.** All competitor data presented herein are derived from publicly available sources only. Certain data points have been reconstructed or estimated from published graphical information. No confidential, non-public, or proprietary information was used. This analysis has not been reviewed or validated by the referenced companies. **3.** Solid dots represent the mean of the maximal total IgG % change from baseline 4. Barratt. American Society of Nephrology Kidney Week 2025. Poster FP-PO0808. **5.** Lafayette. Kidney International. 2024 **6**. Lafayette. NEJM. 2025. **7**. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761434s000lbl.pdf

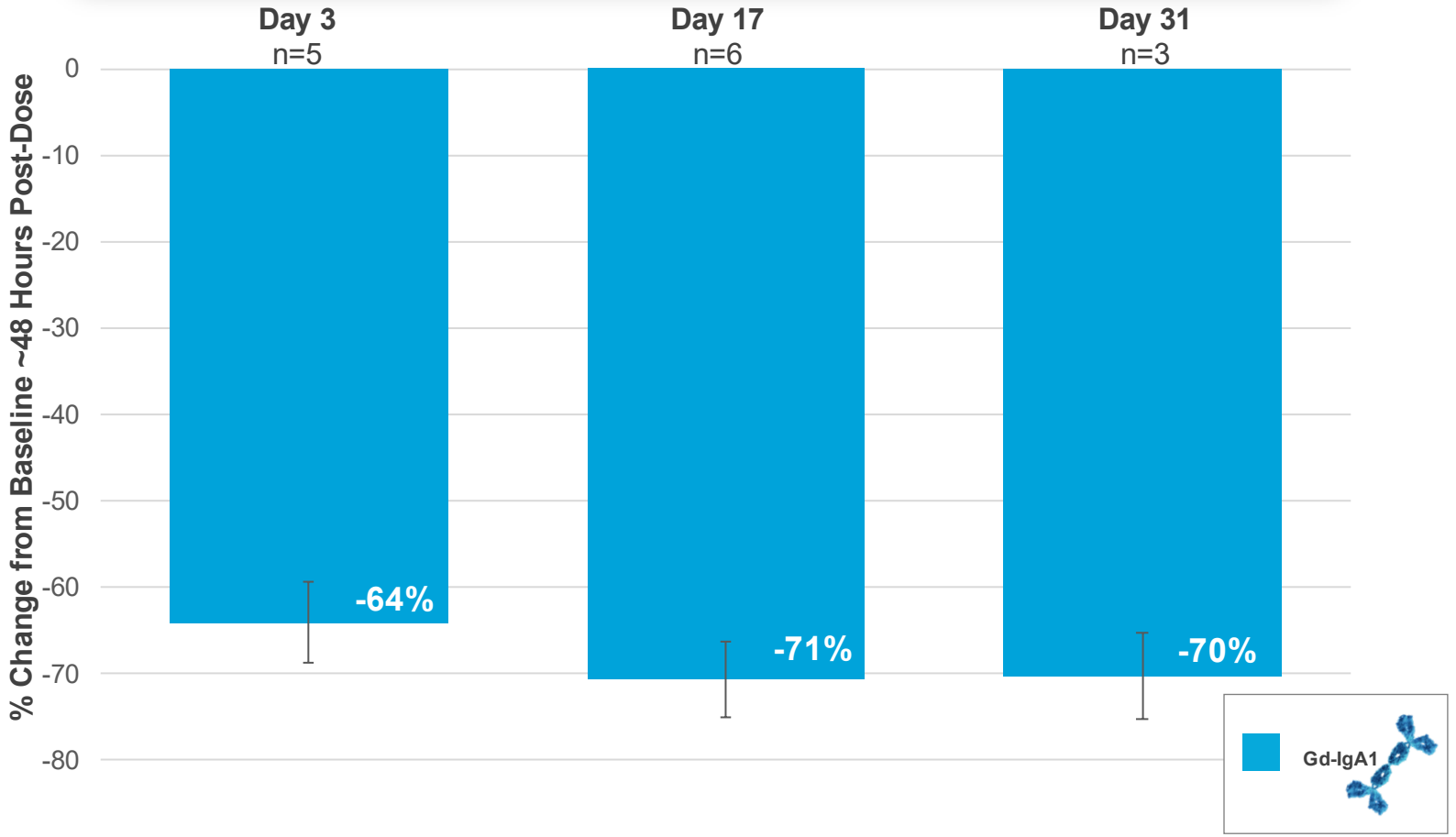
BHV-1400 500 mg SC Bi-Monthly Deeply and Selectively Removes Gd-IgA1 Without Suppression of Normal Healthy IgA in Patients With IgAN

DEGRADERS

Healthy Immunoglobulins



Gd-IgA1



Preliminary data from ongoing study. Data represents mean % change in immunoglobulins in patients with IgAN administered one month of BHV-1400 500 mg every two weeks. Error bars represent standard error.

Practice Point 1.4.2.2: Treatment of patients with IgAN who are at risk of progressive loss of kidney function and do not have a variant form (Section 1.5) of primary IgAN (Figure 3):

- The focus of management in most patients should be to ***simultaneously***:
  - Prevent or reduce immunoglobulin A–containing immune complex (IgA-IC) formation and IgA-IC–mediated glomerular injury (whether this requires lifelong or intermittent therapy is currently unknown)
  - Manage the consequences of existing IgAN-induced nephron loss (likely lifelong)
- Reduction or prevention of IgA-IC formation should incorporate treatments that have been proven to reduce pathogenic forms of IgA (commonly measured as galactose-deficient IgA1 [gd-IgA1]).
- Prevention of IgA-IC–mediated injury should incorporate treatments with proven anti-inflammatory and/or antifibrotic effects and ideally should be used in combination with, and not as a replacement for, treatments that prevent or reduce IgA-IC formation.
- Management of the consequences of IgAN-induced nephron loss should include:
  - Lifestyle advice, including information on dietary sodium restriction (<2 g/d), smoking and vaping cessation, weight control, and endurance exercise, as appropriate
  - Control of blood pressure with a target of ≤120/70 mm Hg
  - Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using renin-angiotensin system (RAS) blockade or dual endothelin angiotensin receptor antagonism, [illegible] hibitor (SGLT2i)
  - A thorough cardiovasc[illegible] as per local guidelines
- Enrollment in a clini[illegible] increase in the [illegible] from the [illegible] dard [illegible]

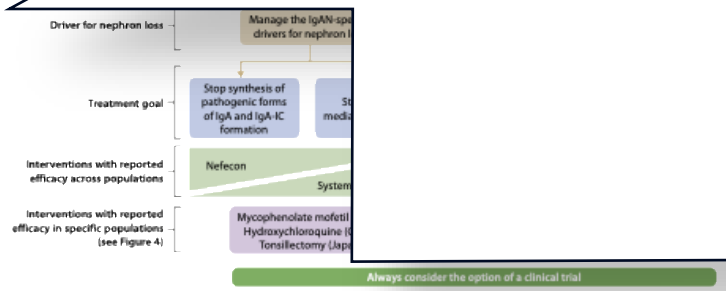


Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline. Reflecting current understanding, Nefecon is shown as having a predominant effect on the production of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs), with an undetermined direct effect of systemically absorbed budesonide on the kidneys. Systemic glucocorticoids have a well-documented anti-inflammatory effect within the kidneys and an undetermined direct effect on the production of pathogenic forms of IgA and IgA-ICs. Strategies to manage the generic response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in selected patients. DEARA, dual endothelin angiotensin receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

1.4.2 Defining a treatment goal in patients with IgAN at risk of progressive loss of kidney function

Practice Point 1.4.2.1: The treatment goal in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of loss of kidney function to the physiological state (i.e., <1 ml/min/yr for most adults) for the rest of the patient's life. The only validated early biomarker to help guide clinical decision-making is urine protein excretion, which should be maintained at a minimum of <0.5 g/d (or equivalent), and ideally at <0.3 g/d (or equivalent), accepting that in some patients with extensive kidney scarring, this may not be possible and that multiple treatment strategies, including non-pharmacologic interventions, may be needed to achieve this.

KDIGO

summary of recommendation statements and practice points www.kidney-international.org

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receptor antagonism, singly
hibitor (SGLT2i)

- A thorough cardiovascular ri
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  from the current 2-year, placeb
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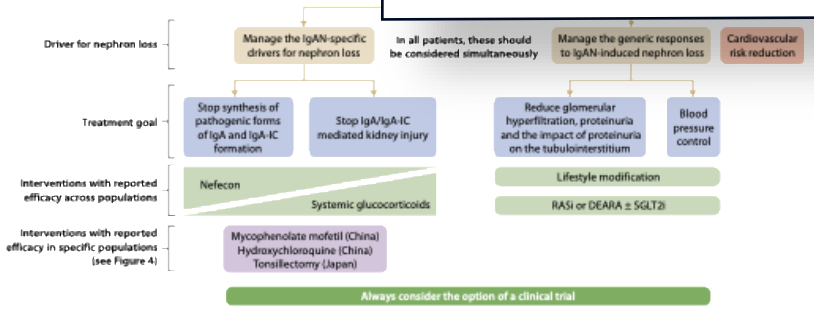

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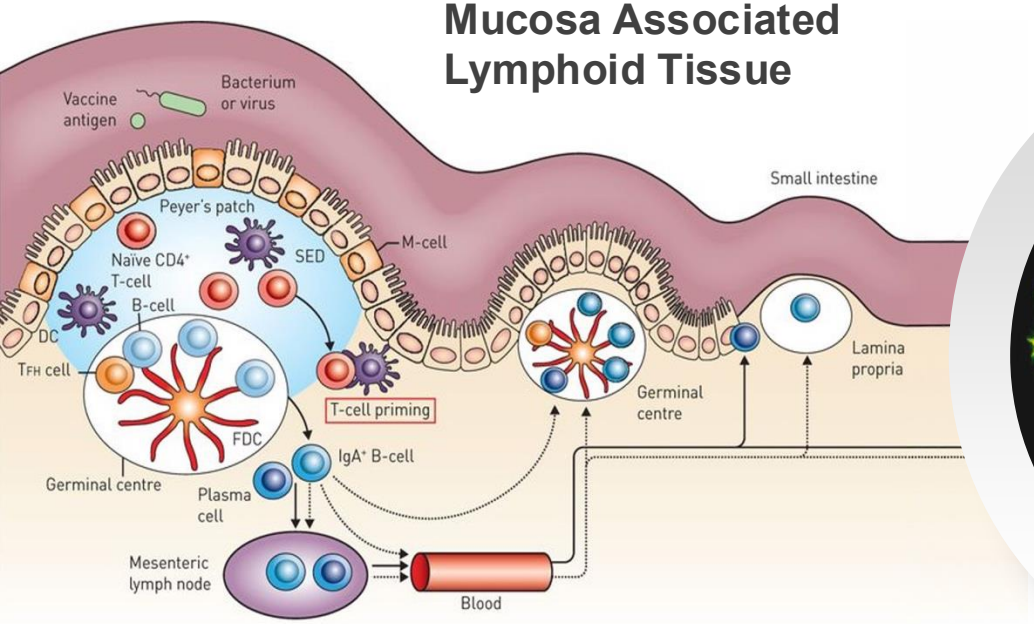
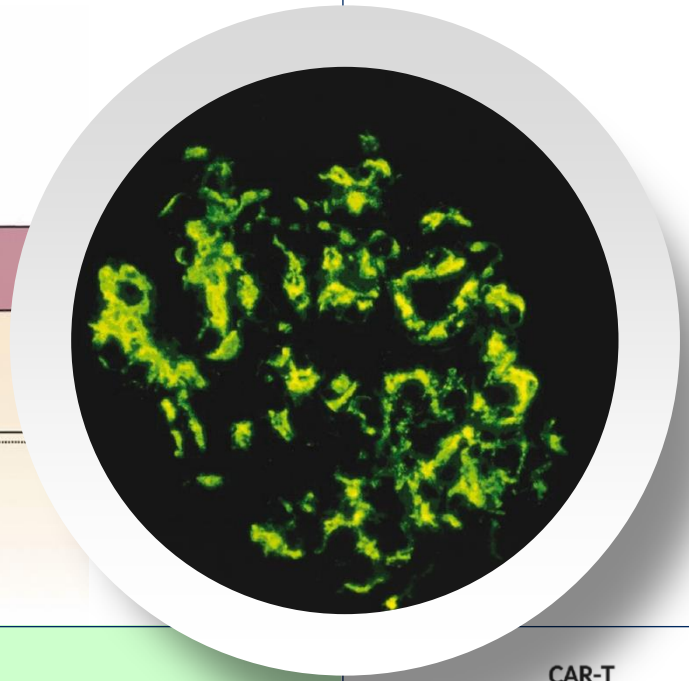
In few patients, competitors achieve guideline proteinuria threshold goal

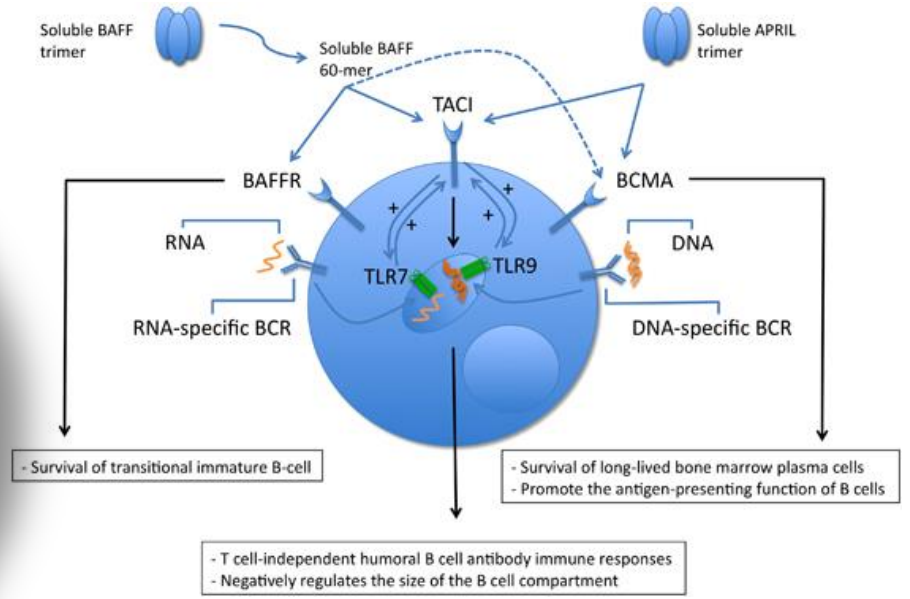
VOYXACT®[1]	**FILSPARI®[2]**
Sibeprenlimab	Sparsentan
By month 12, 34.3% vs 12.7% placebo <0.5 g/d	By month 9, 11% <0.3 g/d

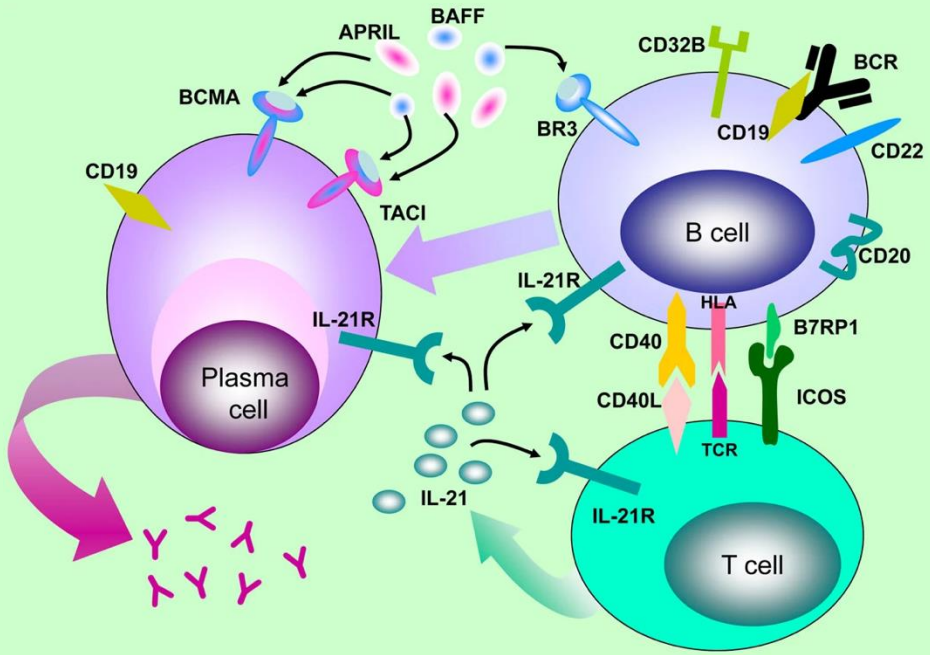

UNMET
NEED

Mucosa Associated Lymphoid Tissue







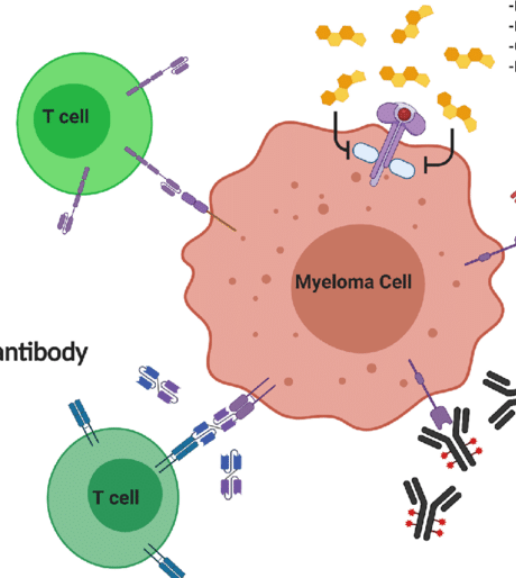


CAR-T

BCMA
-JNJ-68284528
-bb21217
NY-ESO-1
-GSK3377794
BCMA/CD19
-GC012F
BCMA/CD38
-BM 38CAR
Allogenic
-ALLO-715

Small molecule inhibitor

-BCL-2 inhibition
-HDAC inhibition
-Cereblon E3 ligase modulation
-MEK/BRAF inhibition



Monoclonal antibody

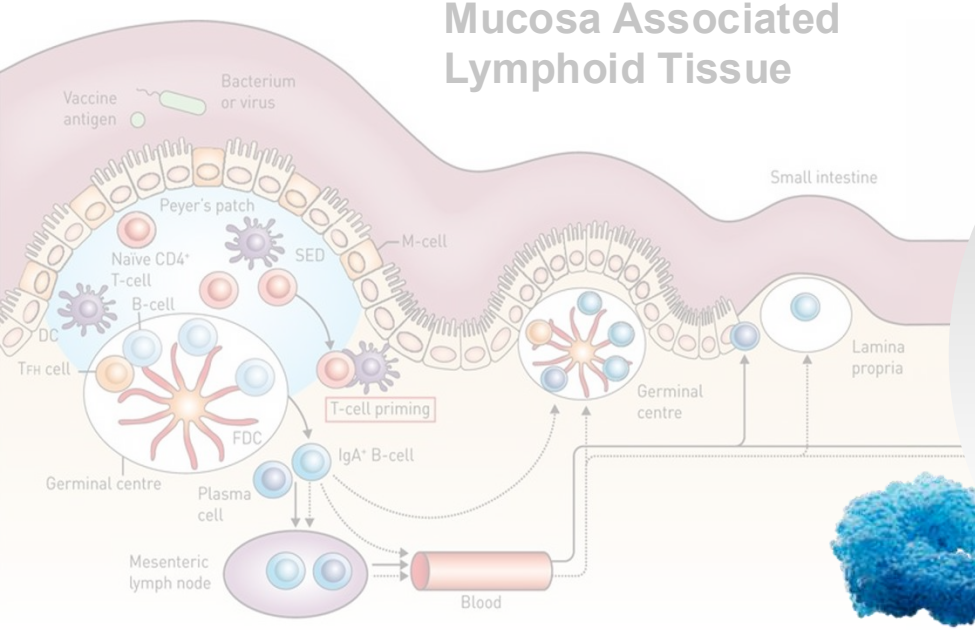
CD38
-TAK-079, TAK-573
-SAR442085

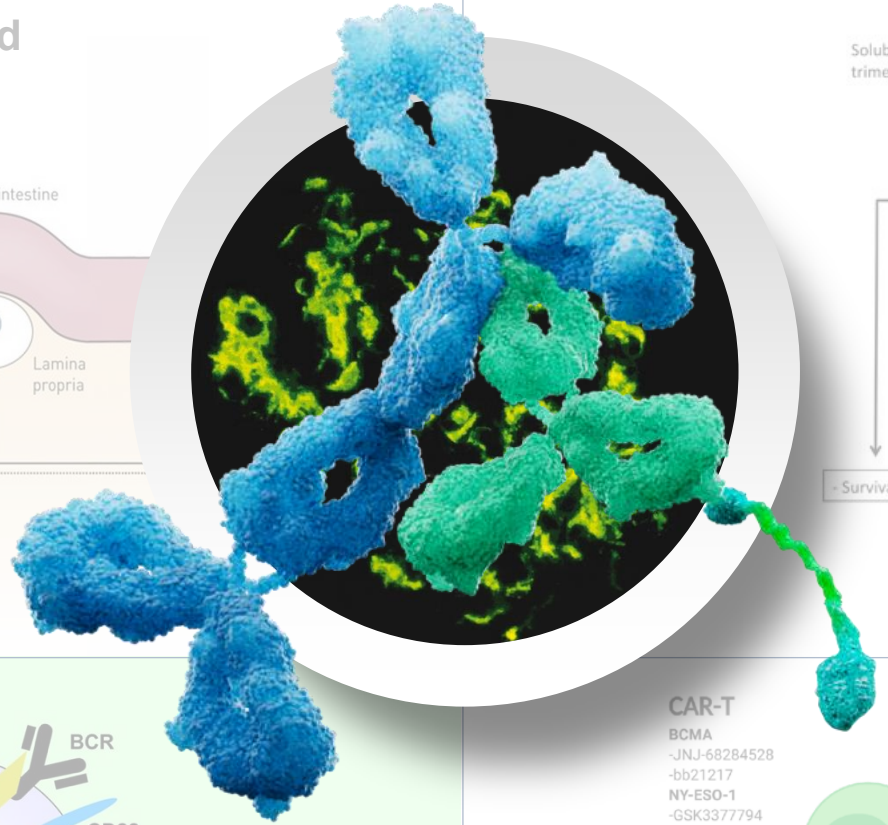
Bispecific antibody

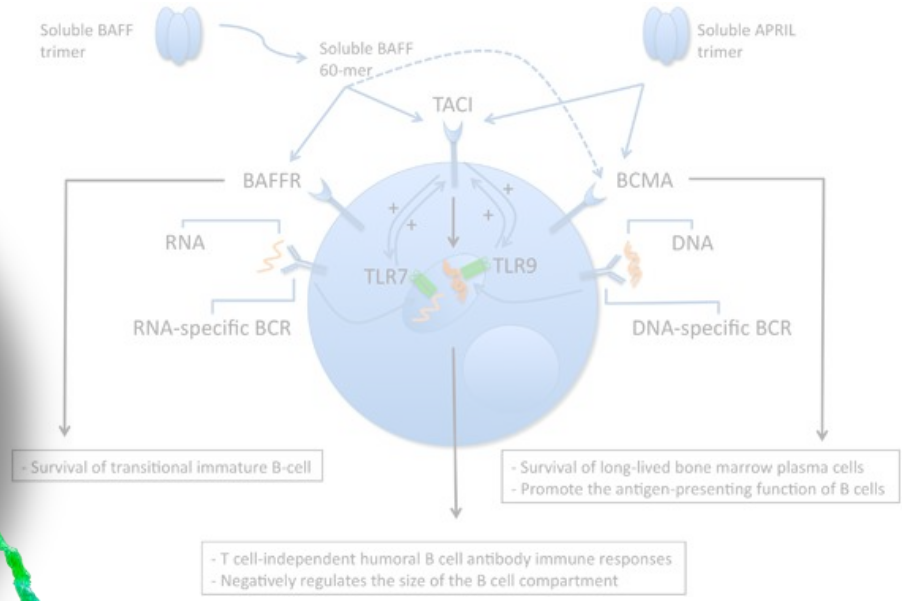
BCMA x CD3
-Teclistamab
-CC-93269
-PF-06863135
-TNB383B
-REGN5458
GPRC5D x CD3
-Talquetamab
FcRH5 x CD3
-BFCR4350A

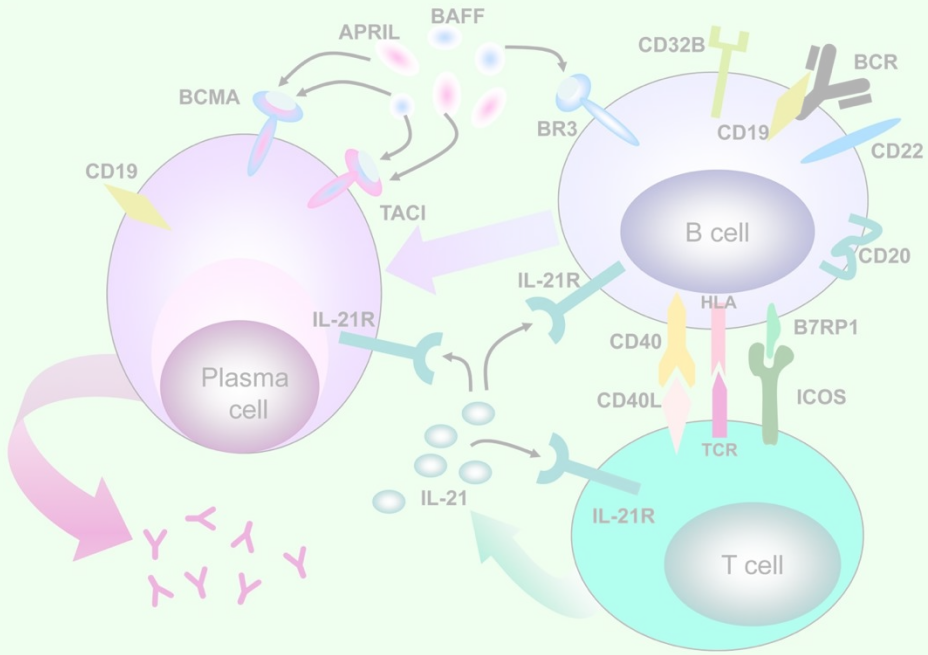
Antibody drug conjugate

BCMA-targeted
-MEDI2228
-TAK-169



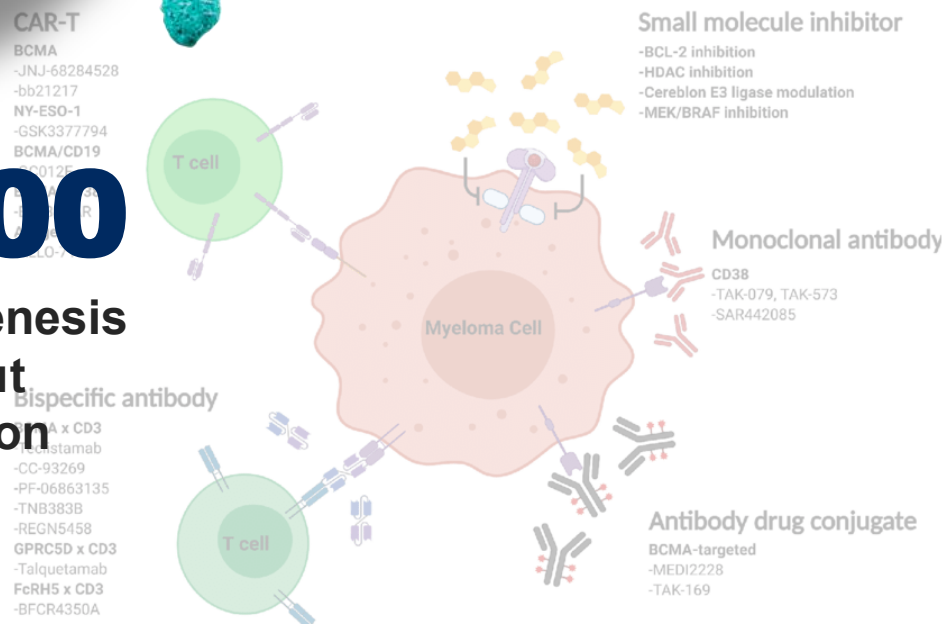






BHV-1400

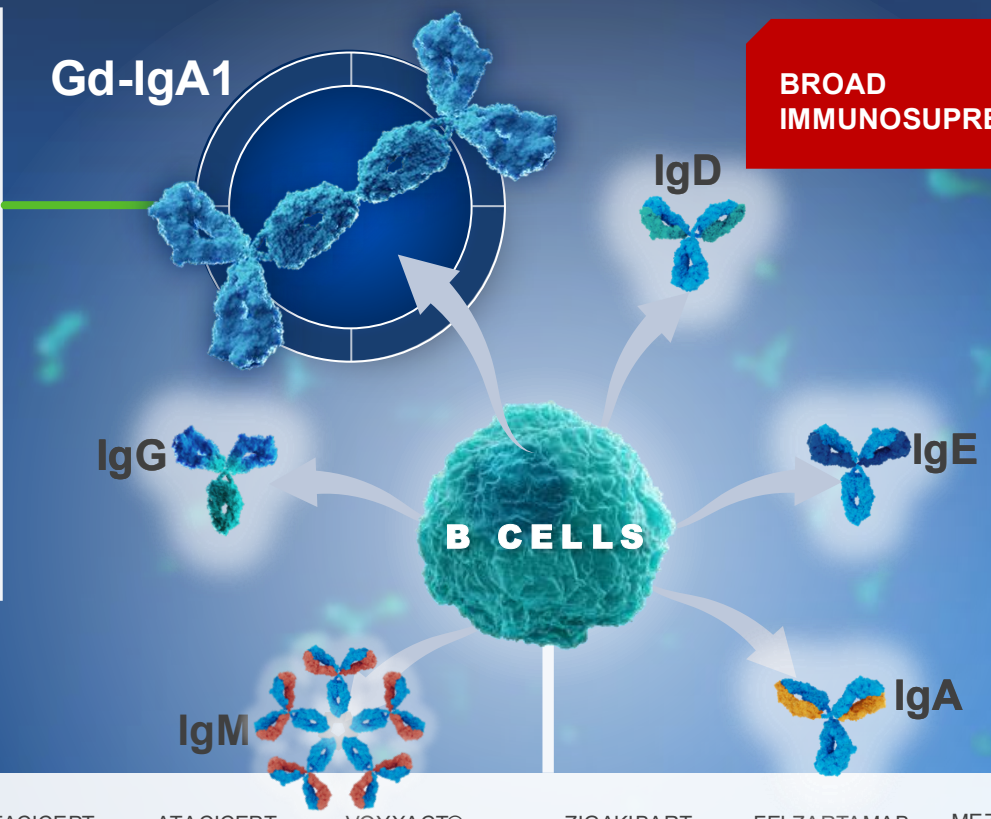
Targeting the pathogenesis of disease without immunosuppression



BHV-1400: Selective Removal of Disease-Causing Gd-IgA1 Without Immunosuppression Compared to Market Competitors

DEGRADERS

TRAP™ Degrader
BHV-1400 SELECTIVELY DEGRADES ONLY Gd-IgA1
Targeting the pathogenesis of disease without immunosuppression



BROAD IMMUNOSUPRESSION
TARPEVO®
calliditas

INHIBIT COMPLEMENT SYSTEM
WITH BROAD IMMUNOSUPPRESSION
FABHALTA® NOVARTIS
SEFAXERSEN IONIS Roche
ULTOMIRIS® CHINOOK NOVARTIS

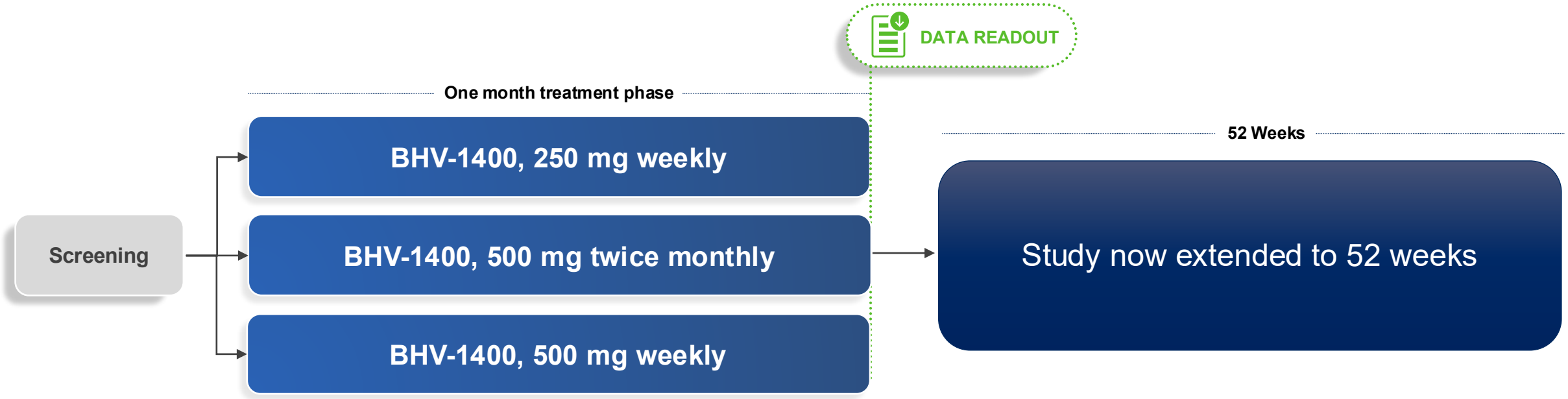
TARGET B CELLS
WITH GLOBAL IMMUNOGLOBULIN SUPPRESSION
POVETACICEPT ALPINE VERTEX
ATACICEPT vera therapeutics
VOYXACT® Otsuka
ZIGAKIBART CHINOOK NOVARTIS
FELZARTAMAB Biogen
MEZAGITAMAB Takeda

TARGET ENDOTHELIAN RECEPTOR
FILSPARI® TRAVERE THERAPEUTICS
VANRAFIA® CHINOOK NOVARTIS

KEY POINT

BHV-1400 is the only therapy designed to remove pathogenic Gd-IgA1, the root cause of IgA, while preserving healthy immune function

IgAN Patient Expansion Cohort Study Design



KEY STUDY DETAILS

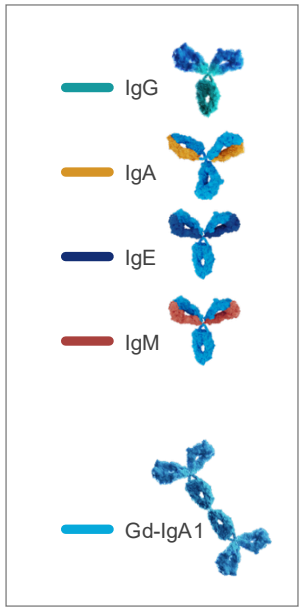
Study Design: Open-label, n=10, potential to increase

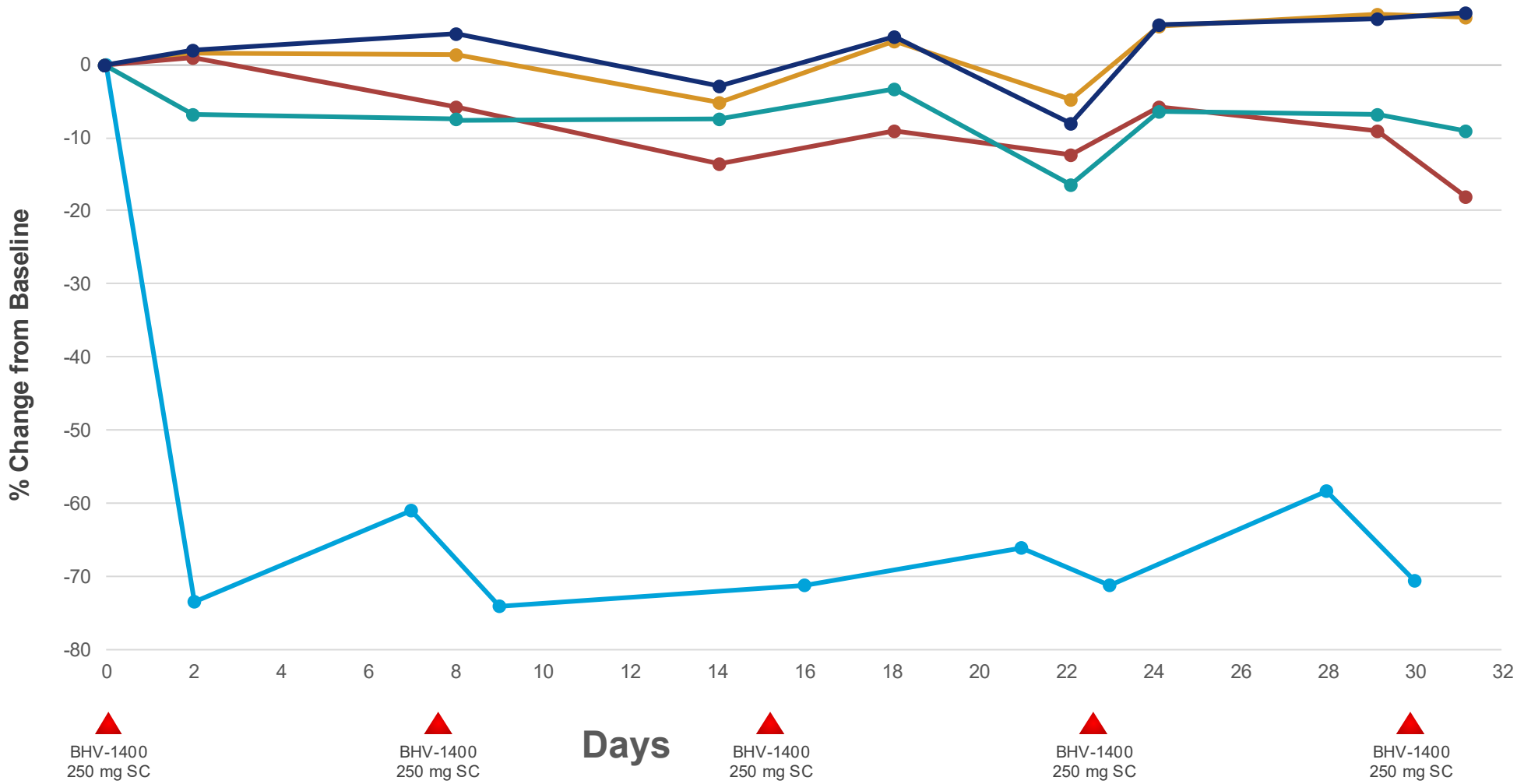
Population: Male and female adults with biopsy proven IgAN, UPCR ≥ 0.5 g/d, eGFR ≥ 30

Endpoints: Primary safety, pharmacodynamic measures

IgAN Patient Expansion Cohort Site Map

Dr. Barratt's First Patient With IgAN Dosed: BHV-1400 SC Delivers Rapid, Selective, Deep and Sustained Removal of Gd-IgA1 Over First Month





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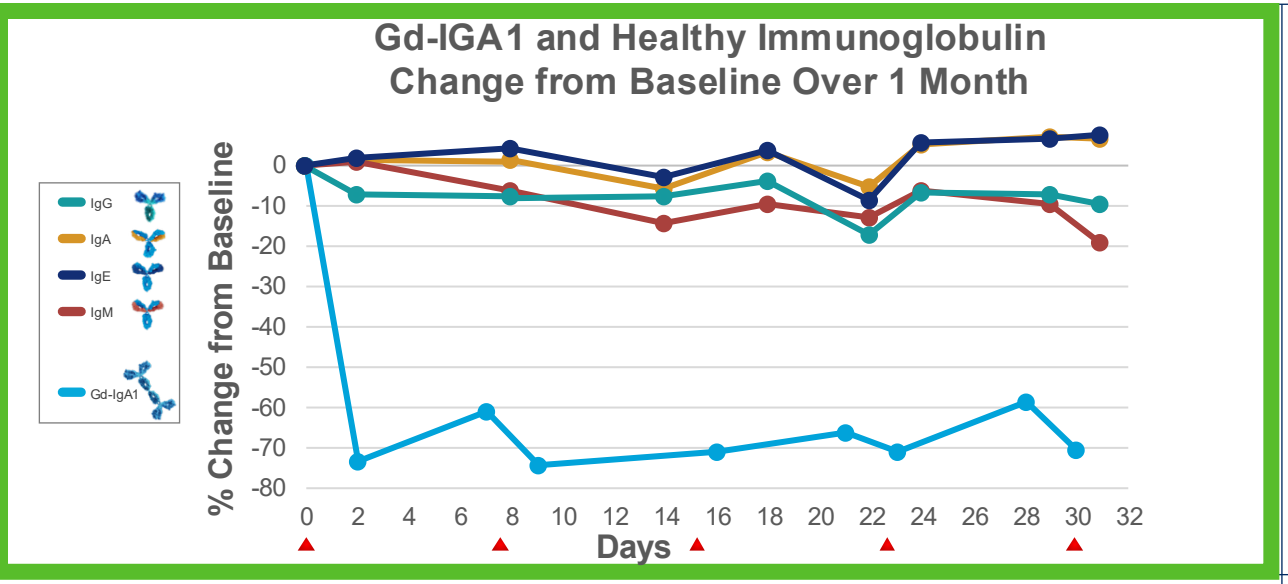
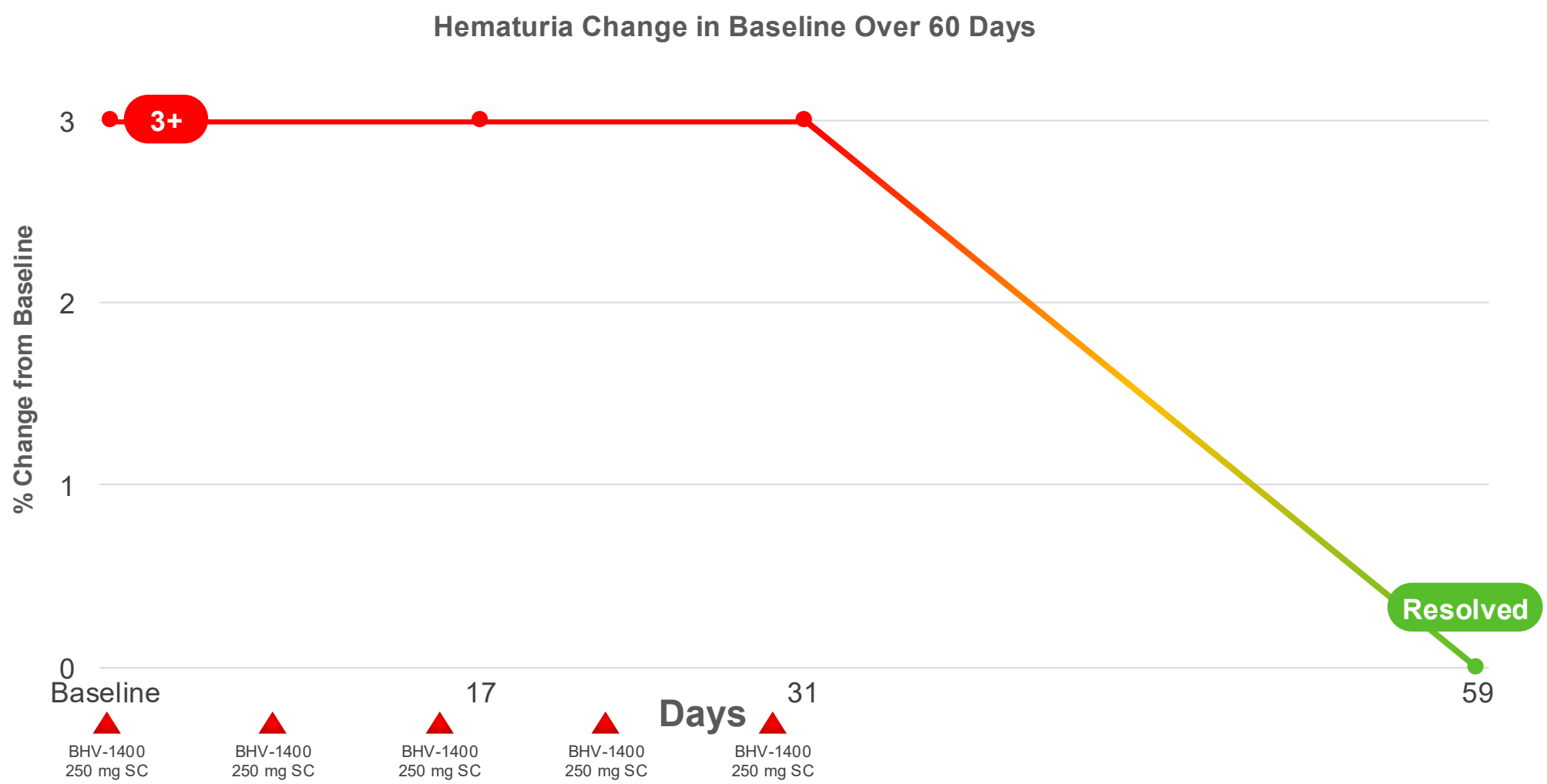


Dr. Jonathan Barratt's First Patient With IgAN Dosed: Removal of Gd-IgA1Translating Into Rapid Resolution of Hematuria



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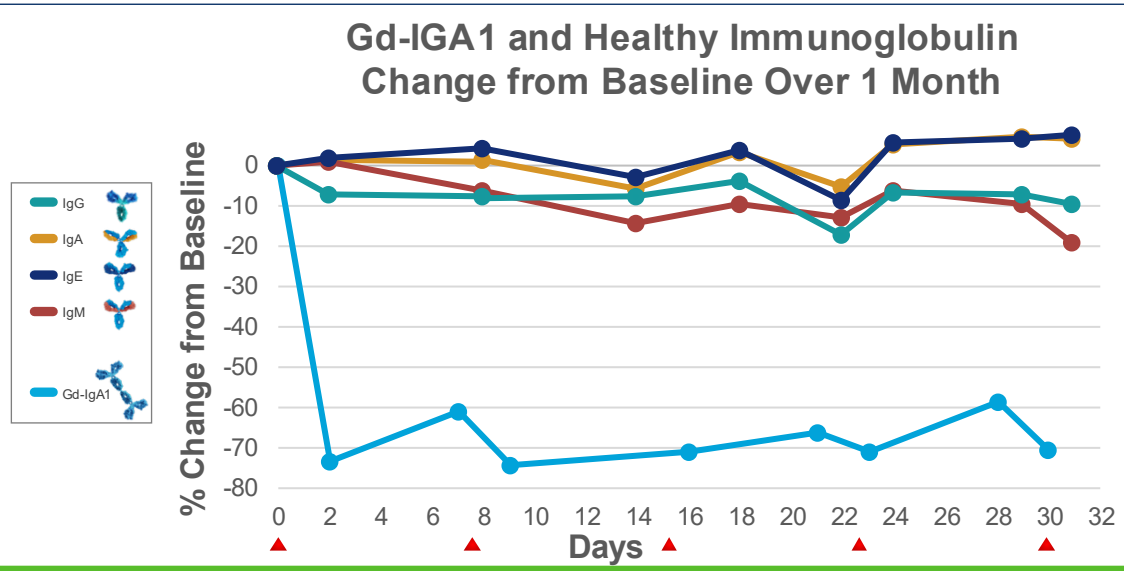
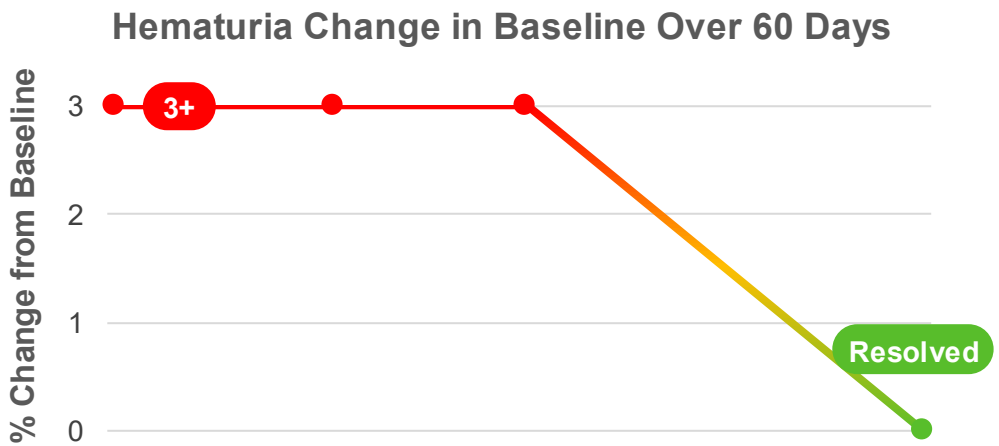
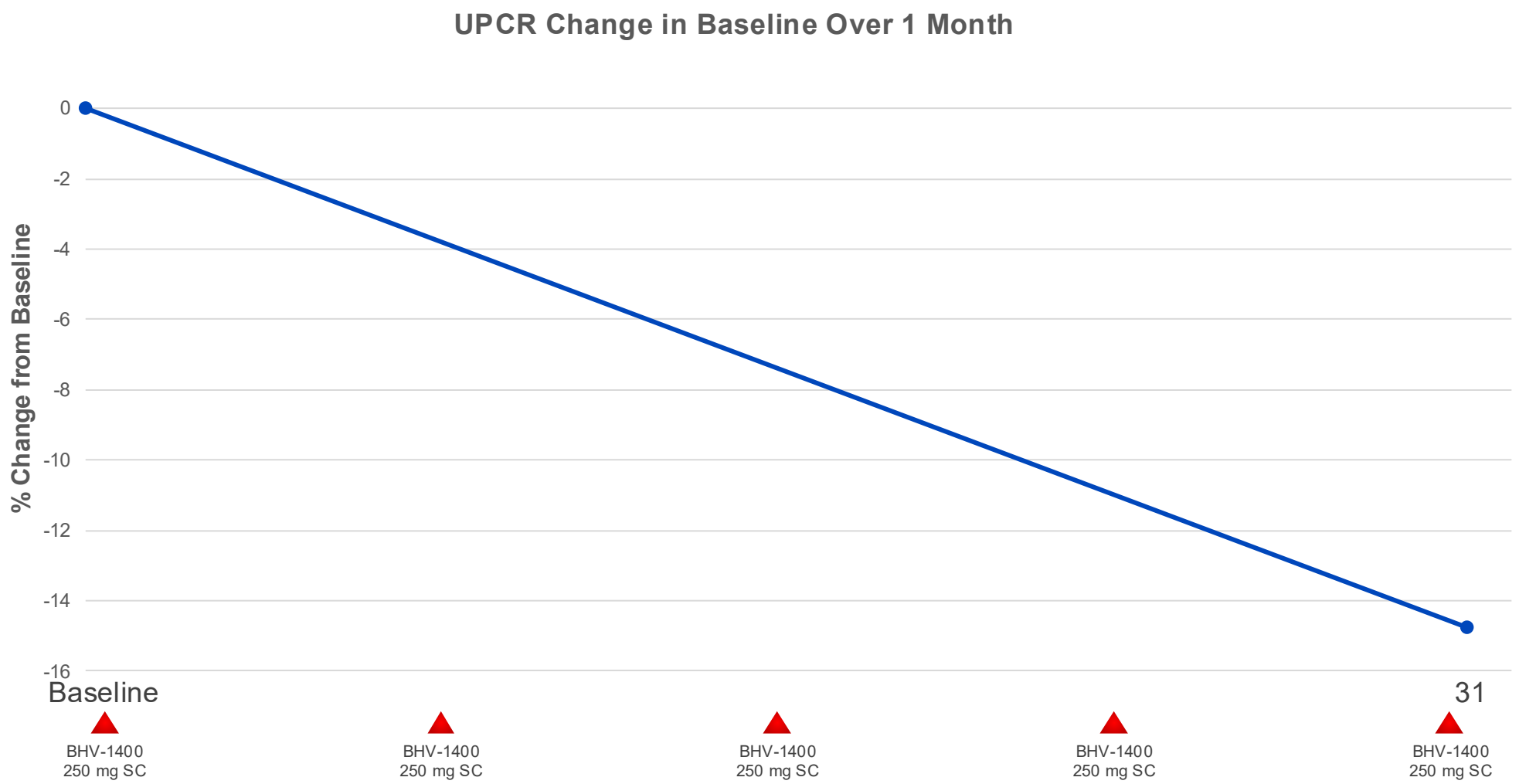




Dr. Jonathan Barratt's First Patient With IgAN Dosed: BHV-1400 SC Delivers Rapid Removal of Gd-IgA1Translating Into Rapid Improvement of Proteinuria



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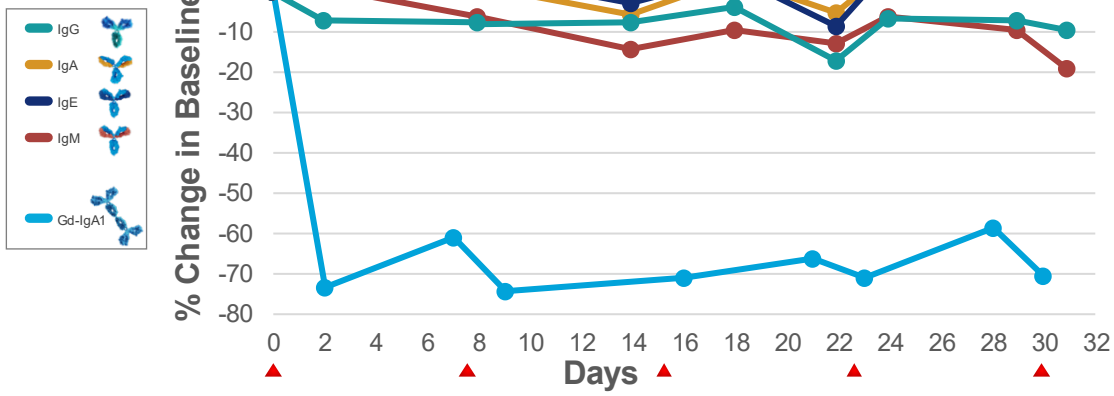
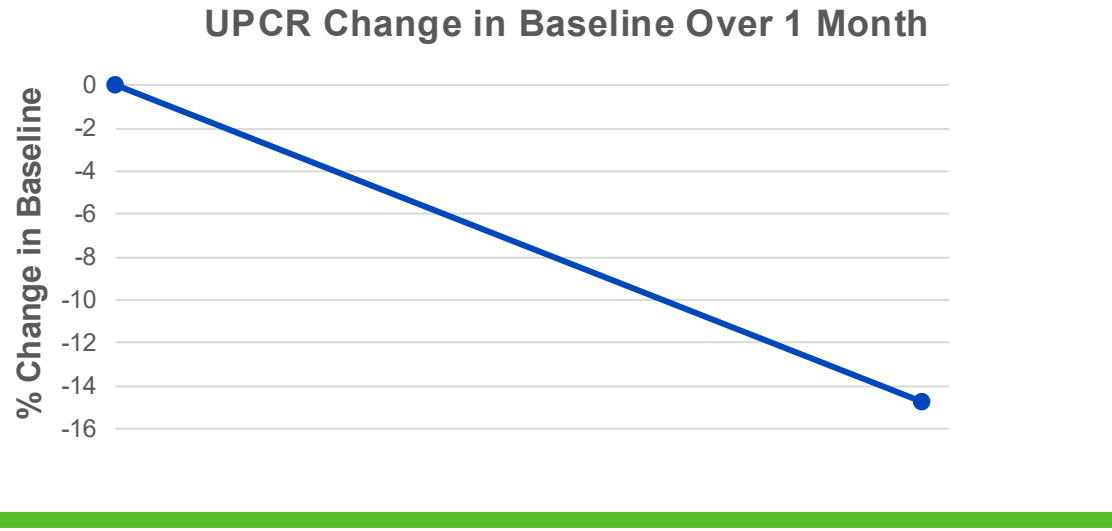
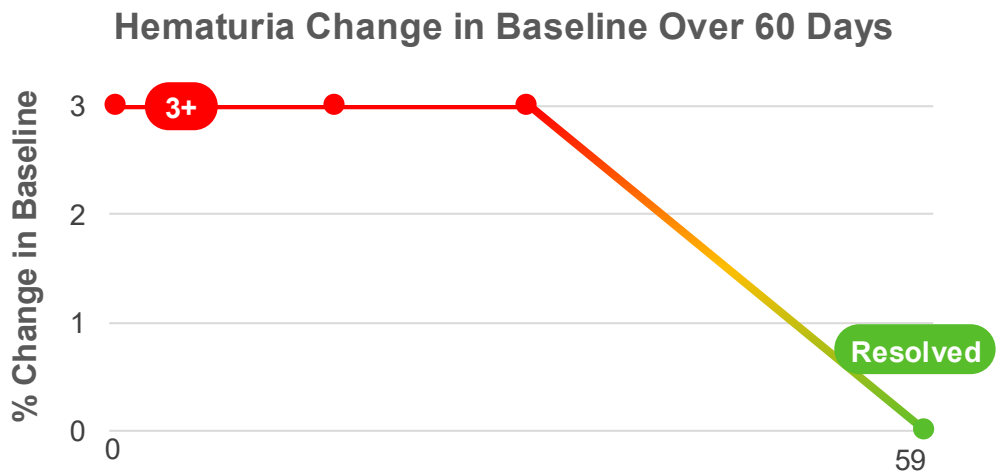
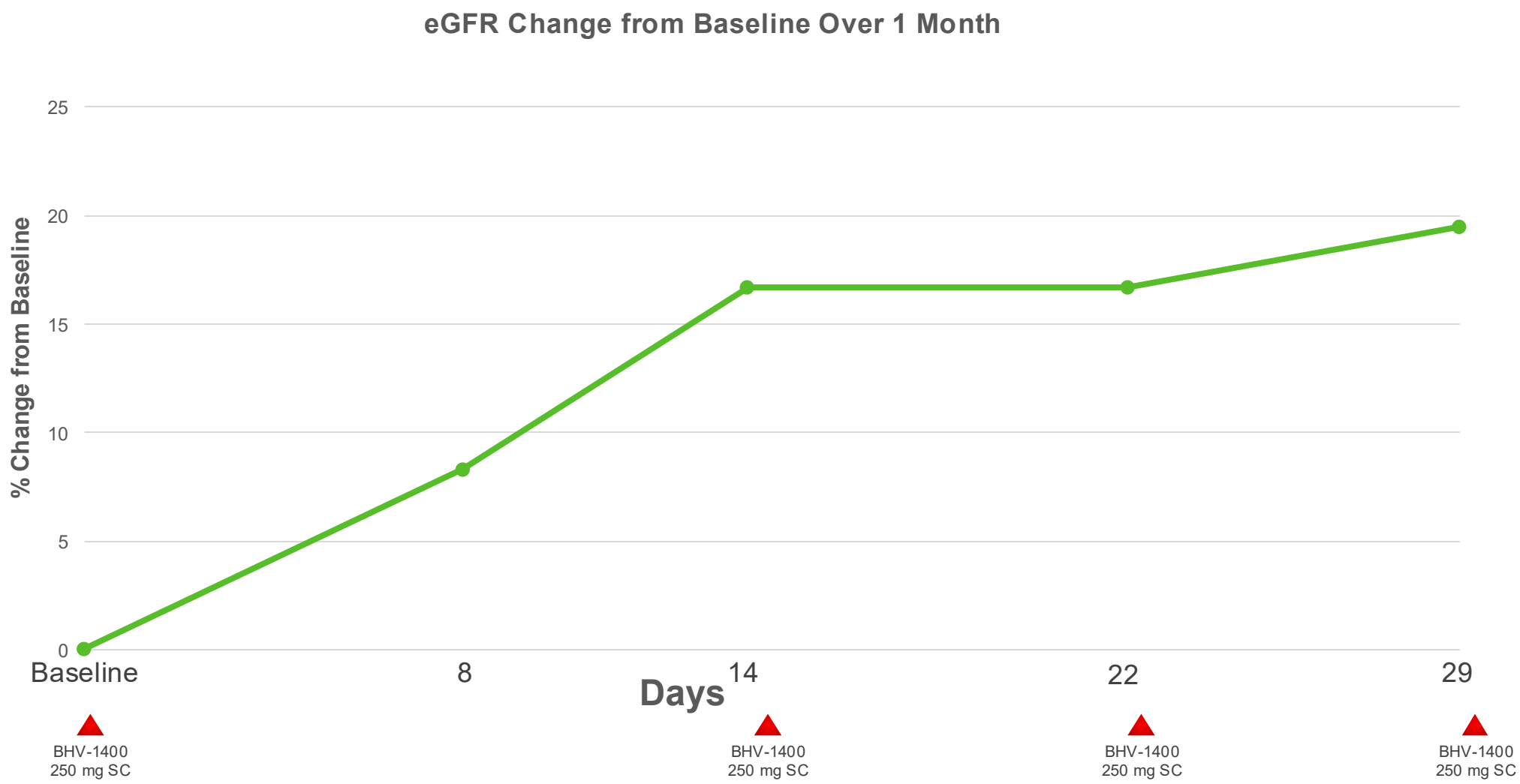






Dr. Jonathan Barratt's First Patient With IgAN Dosed: BHV-1400 SC Delivers Rapid Removal of Gd-IgA1Translating Into Rapid Improvement in Kidney Function (eGFR)



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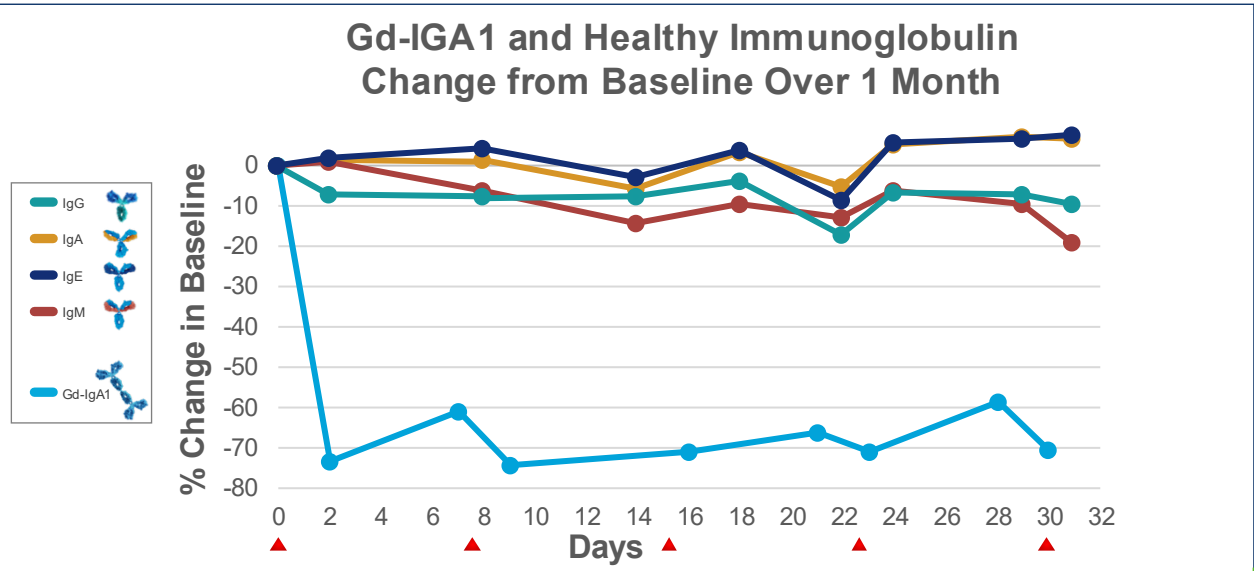
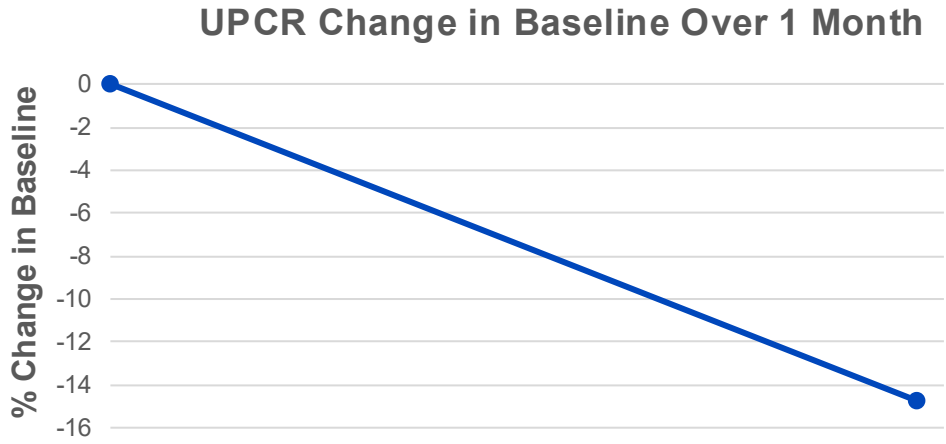
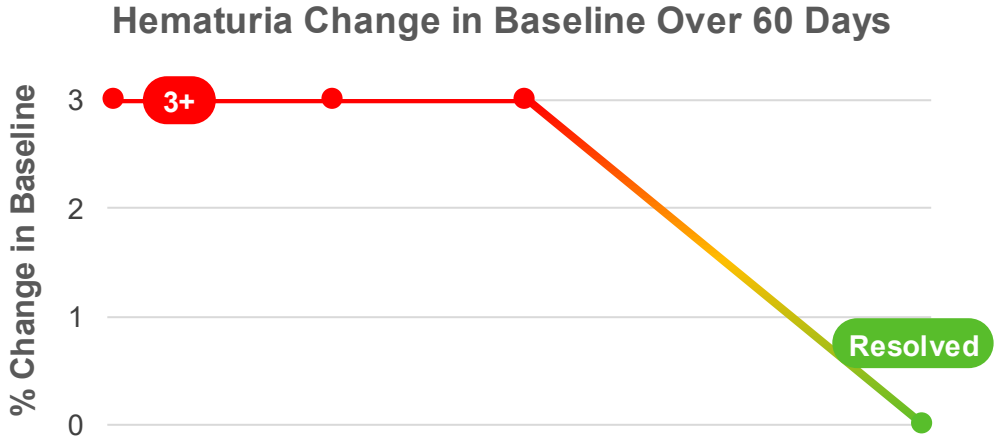
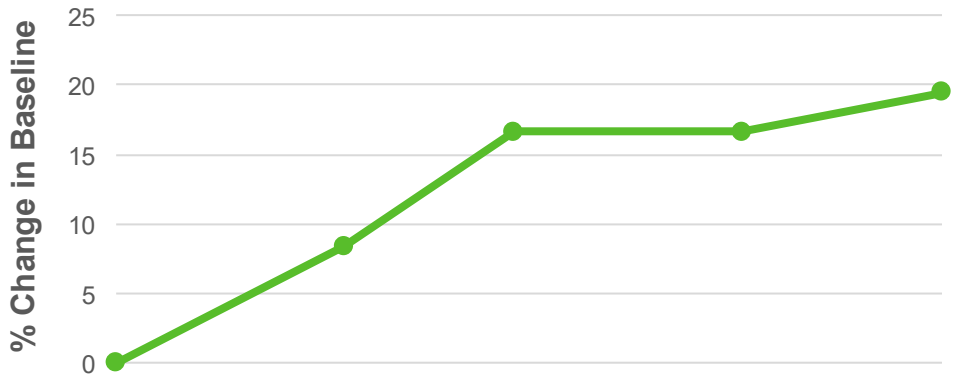








Demographic and Clinical Characteristics of the Patients Receiving BHV-1400 at Baseline

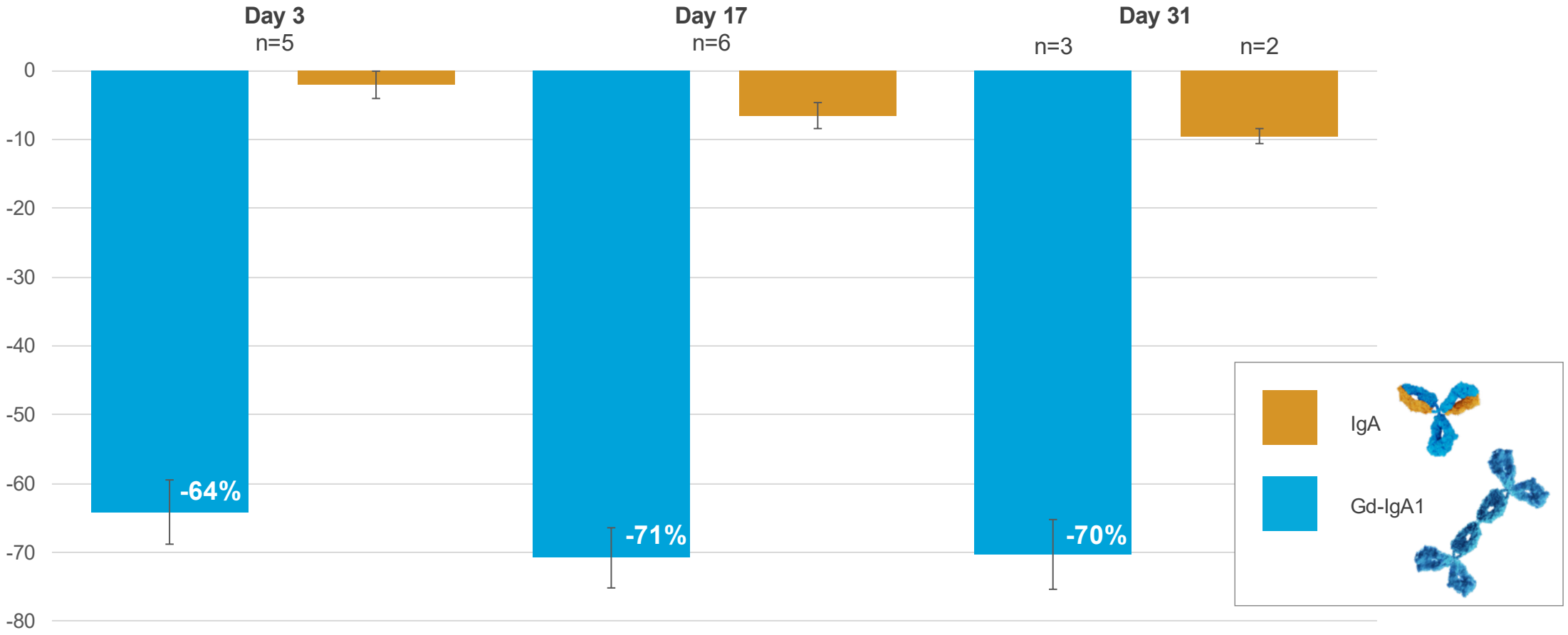
DEGRADERS

Characteristics	Overall (n=10)
Age (yrs) Mean [Min, Max]	43.6 [27, 65]
Sex n (%) Male Female	 6 (60%) 4 (40%)
Race n (%) Asian White Unknown	 3 (30%) 6 (60%) 1 (10%)
Spot UPCR* (mg/g) Mean [Min, Max]	766.4 [213–2144]
eGFR** (ml/min/1.73 m^2) Mean [Min, Max]	67 [33–124]
Hematuria (1+, 2+, or 3+) n (%)	2 (20%)
Time from Biopsy (yrs) Mean [Min, Max]	3.03 [0.3, 8.9]

UPCR, urinary protein-to-creatinine ratio. **eGFR:** estimated glomerular filtration rate.

BHV-1400 500 mg SC Q2WK Deeply and Selectively Removes Gd-IgA1 Without Suppression of Normal Healthy IgA in Patients With IgAN

DEGRADERS



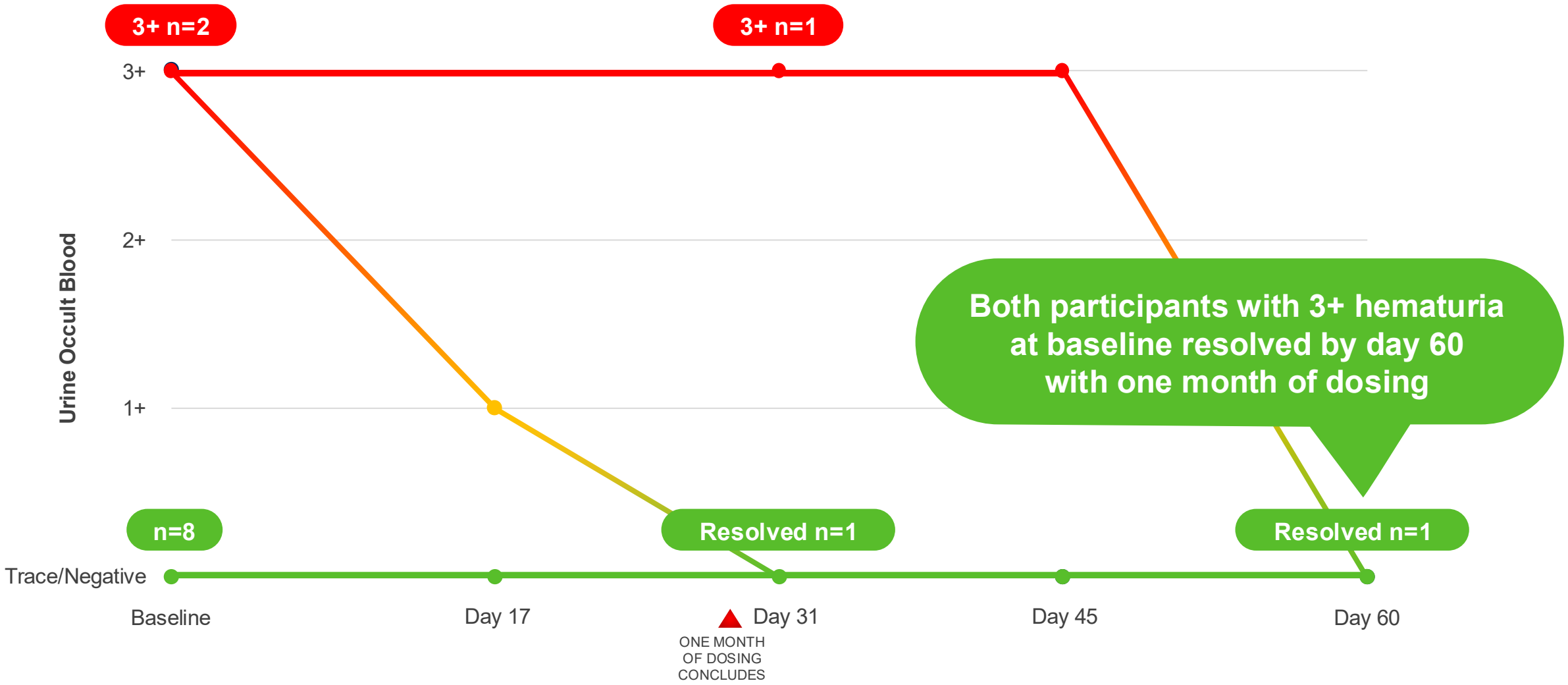
Preliminary data from ongoing study. Graph represents the mean and standard error of % change in Gd-IgA1 from baseline at each time-point in patients with IgAN receiving BHV-1400 500 mg every two weeks.

BREAKING NEWS

Patients with IgAN administered BHV-1400 achieved deep lowering within hours and 70% lowering within one month of dosing.

Hematuria Change With One Month of Dosing BHV-1400 SC

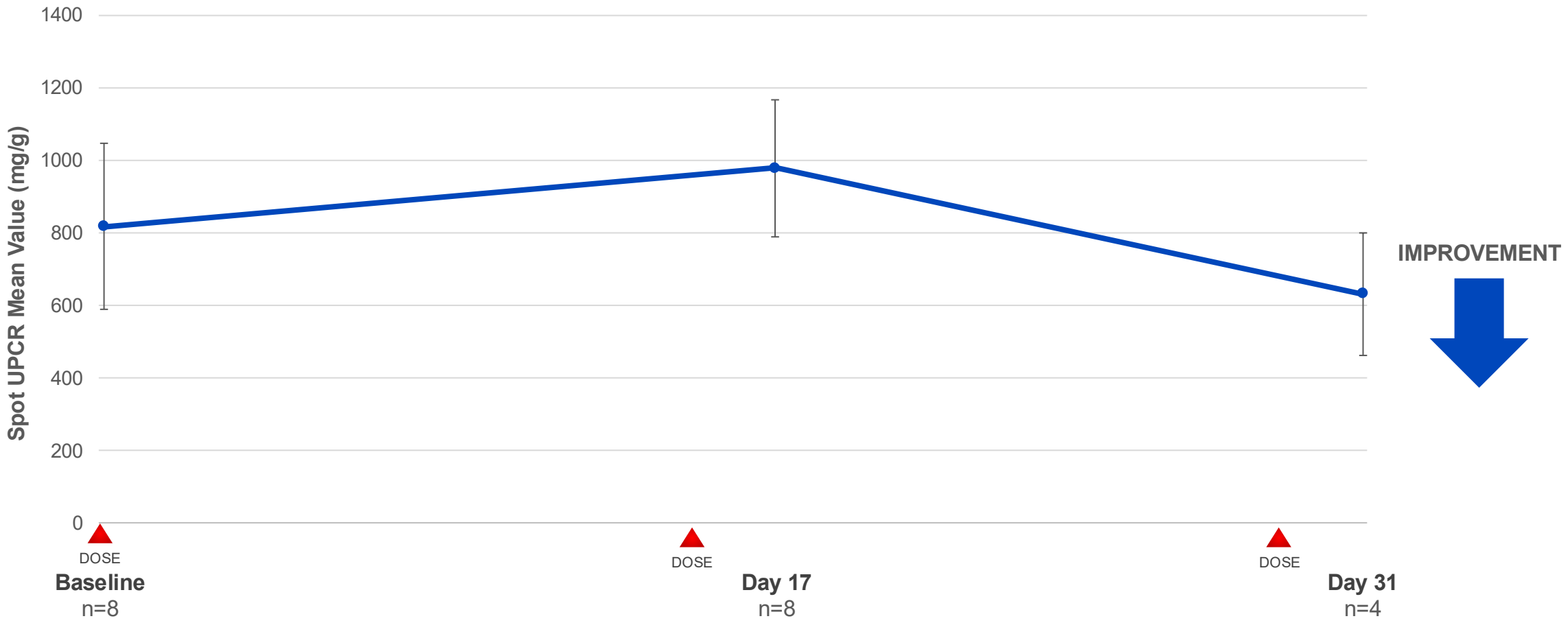
DEGRADERS



Preliminary data from ongoing study. Graph represents hematuria values for participants with IgAN (n=10) receiving BHV-1400 SC for one month of dosing.

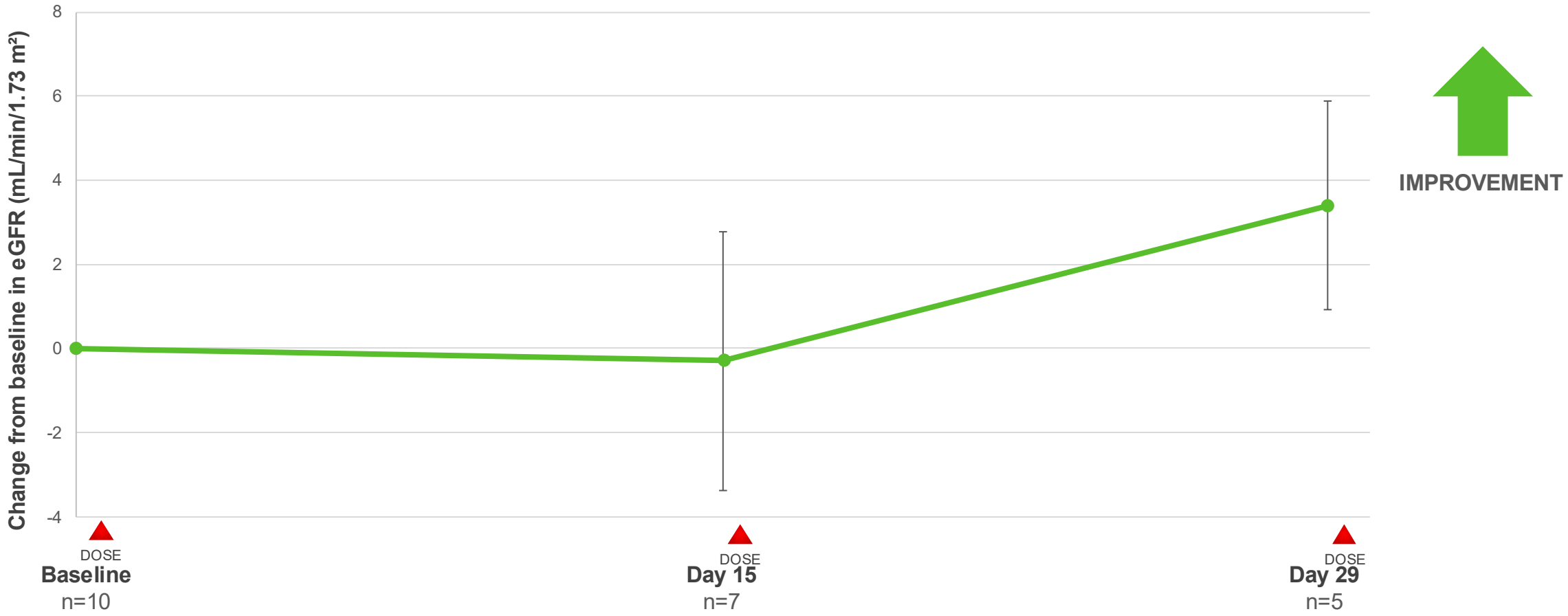
UPCR Change With One Month of Dosing BHV-1400 SC

DEGRADERS



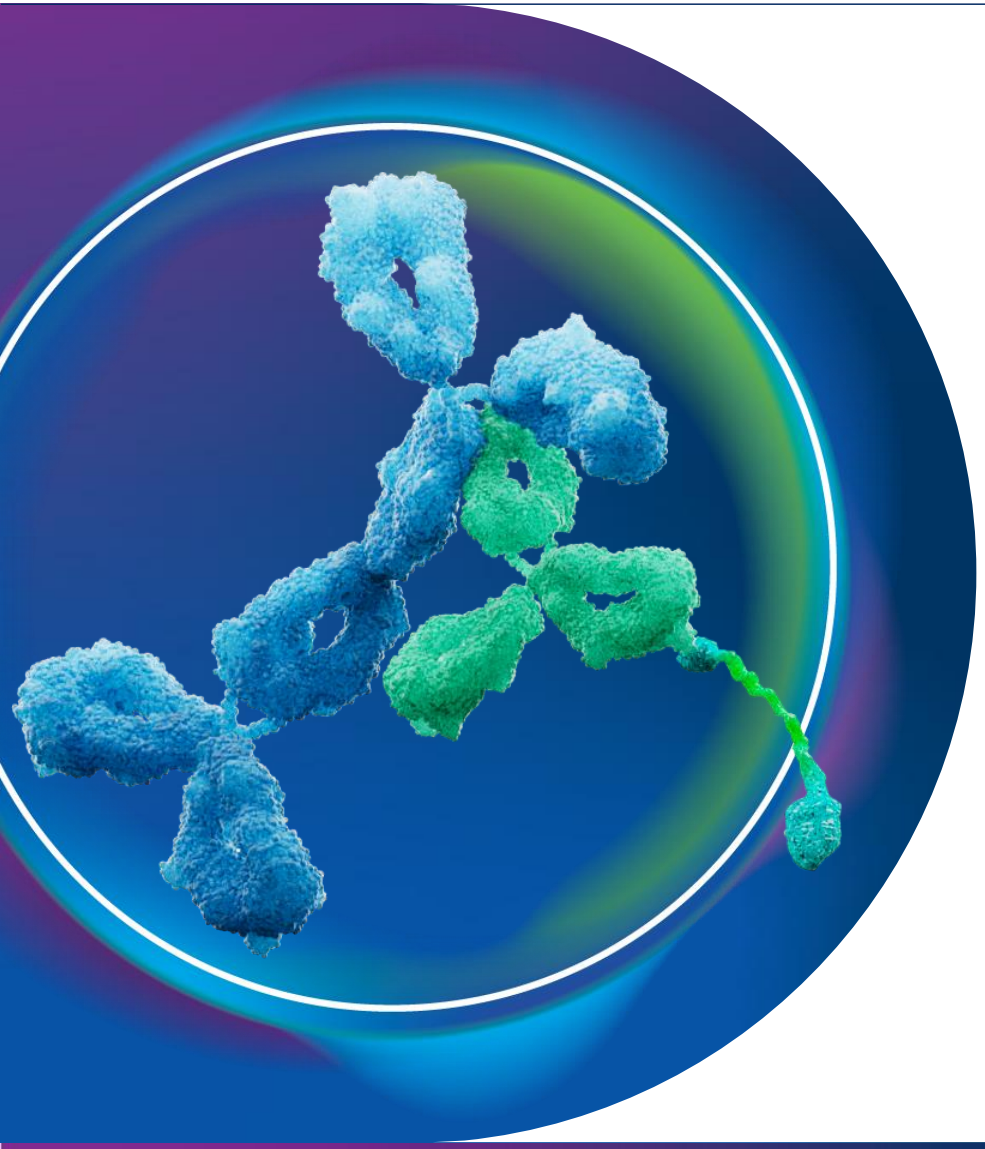
Preliminary data from ongoing study. Graph represent mean and standard error of spot UPCR in participants with IgAN (n=8) receiving BHV-1400 SC for one month of dosing.

eGFR Change With One Month of Dosing BHV-1400 SC



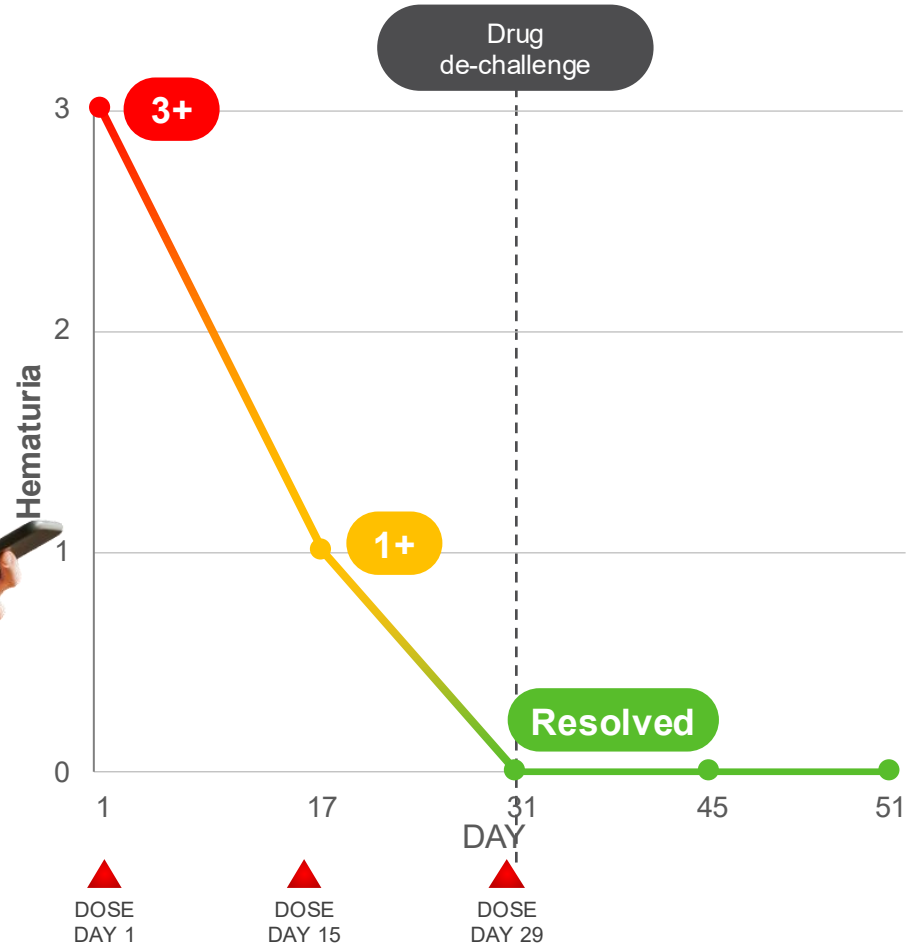
Preliminary data from ongoing study. Graph represent mean and standard error of eGFR in participants with IgAN (n=10) receiving BHV-1400 SC for one month of dosing.

BHV-1400 Phase 1/2 IgAN Patient Cohort — Safety Summary



- 10 participants with IgA Nephropathy
- Most AEs were mild and self-resolving
- No treatment discontinuations for adverse events
- No clinically significant trends in vitals, ECGs, or labs (including AST/ALT/Tbili)
- No clinical evidence of cardiovascular, renal, hepatic, or hematologic toxicity
- Preservation of IgA, IgG, IgM, IgE
- No SAEs, severe AEs, or AEs resulting in discontinuation of therapy

BHV-1400 Early Disease Clinical Experience: Rapid, Complete Resolution of Hematuria Within Weeks of Initial Dosing



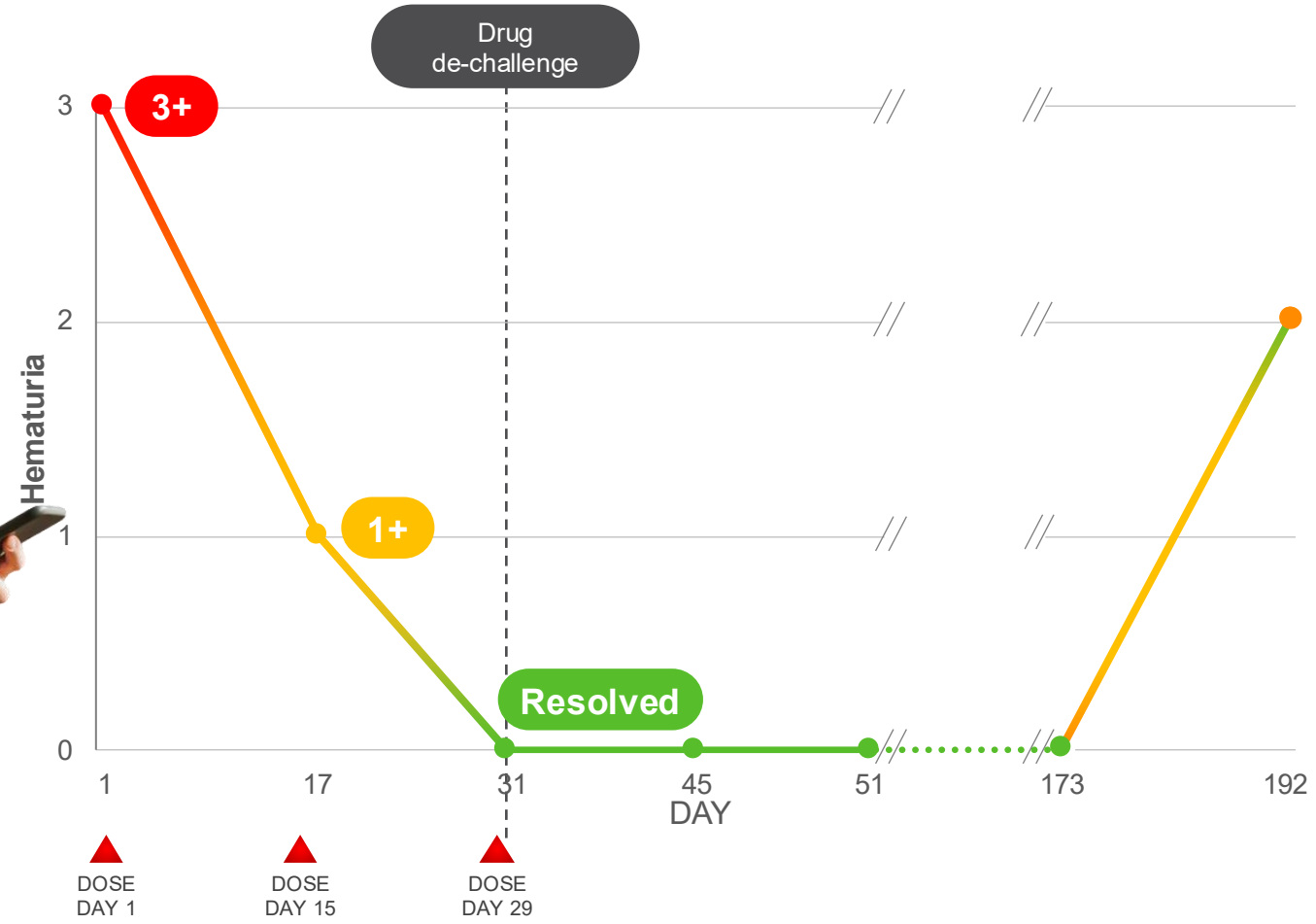
CASE REPORT:
Initial IgAN Patient Dosed

- Young female patient
- Normal eGFR
- Chronic hematuria
- Active lifestyle
- Significant fatigue
- Comorbid diabetes

KEY POINT

BHV-1400 500 mg SC every other week delivers rapid and complete resolution of hematuria

BHV-1400 Durable Response:
Off-Treatment Remission Observed Months After Final Study Dose

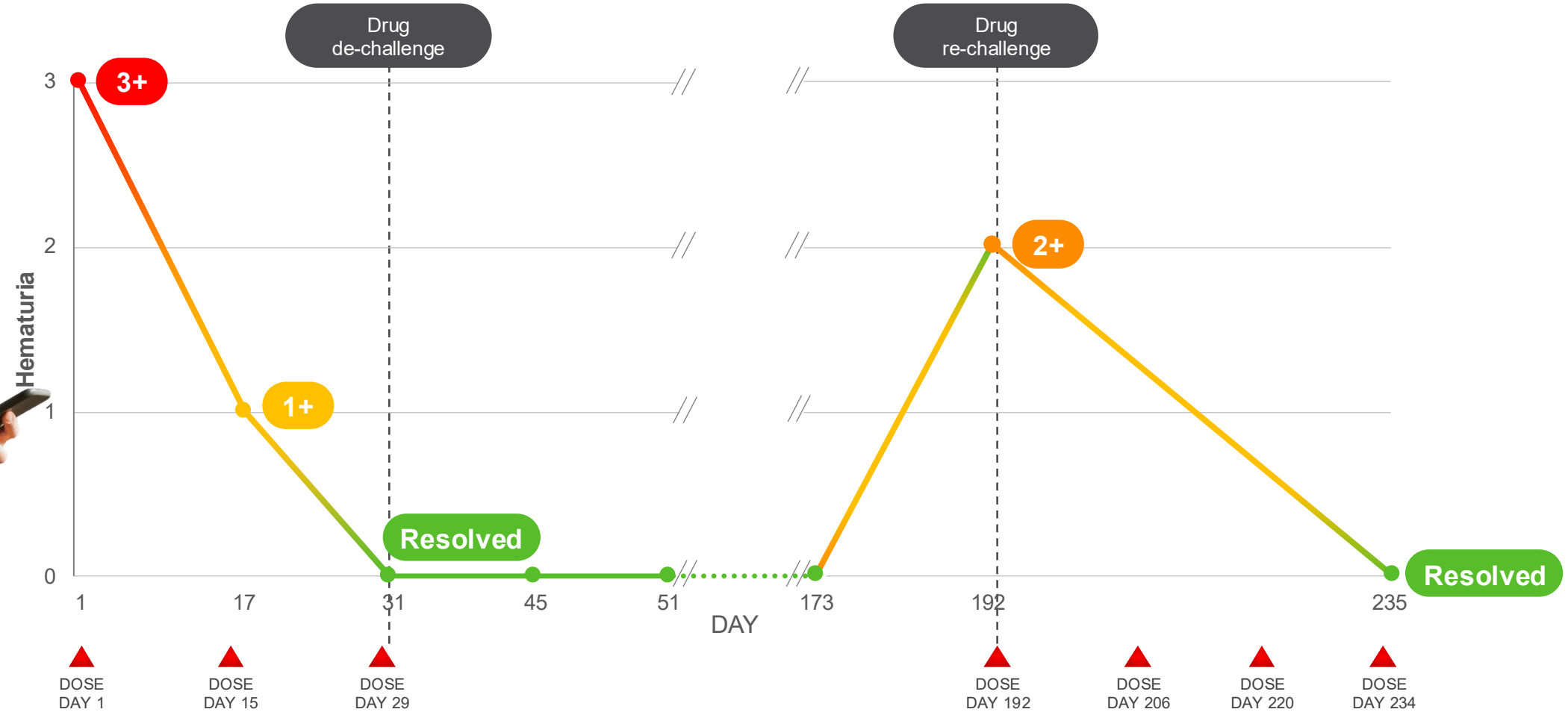


Disease Recurrence observed after extended off-treatment period

KEY POINTS

- **Re-treatment initiated upon disease recurrence after extended off-treatment period**
- **Durability observed well beyond active treatment window**

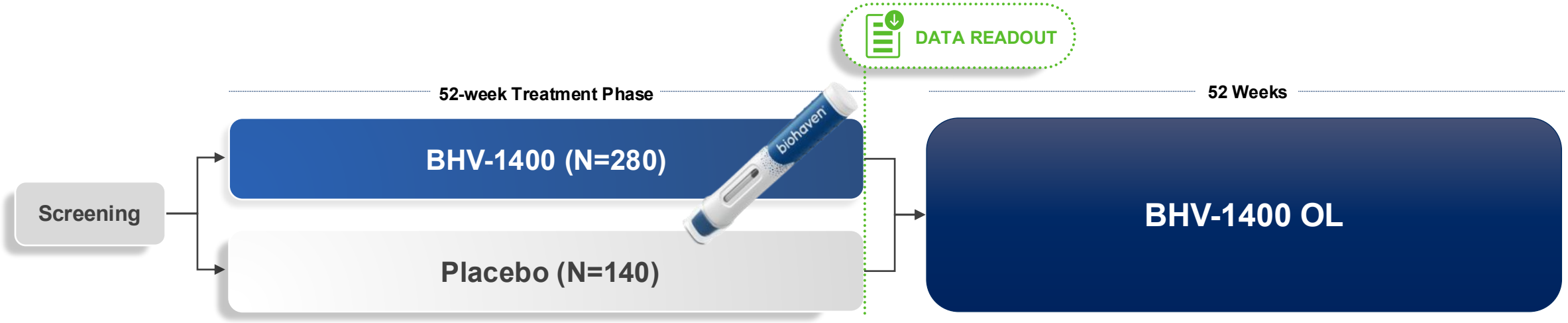
BHV-1400 Re-Treatment:
Re-Challenge Recaptures Complete Hematuria Resolution



KEY POINTS

- **Re-treatment with BHV-1400 500 mg every two weeks initiated upon disease recurrence after extended off-treatment period**
- **Complete resolution of hematuria re-achieved within weeks of reinitiation**

Lead TRAP Degrader BHV-1400 Enters Phase 3



KEY STUDY DETAILS

Study Design: Randomized, double-blind, placebo-controlled trial

Population: Male and female adults with biopsy proven IgAN

Dose: 500 mg bimonthly, at home administration

Endpoints: Δ UPCR, Δ in eGFR, Δ in Gd-IgA1 at week 52

ATD, antithyroid drugs

KEY POINT

BHV-1400 pivotal trial in IgA nephropathy commencing mid-2026

Panel

MODERATOR

Corine Johnson
Equity Analyst
Goldman Sachs

PANELISTS

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Key Milestones Anticipated in 2026

			1H 2026	2H 2026
INFLAMMATION & IMMUNOLOGY	**Gd-IgA1 Degrader | BHV-1400**	IgA Nephropathy	Initiate Pivotal IgAN	
	IgG Degrader | BHV-1300	Common Disease (Graves', RA)	Initiate Pivotal Graves'	
	TYK2/JAK1 Inhibitor | BHV-8000 (brain-penetrant)	Parkinson's Disease	Ongoing Phase 2/3 Trial	
MYOSTATIN ACTIVIN	**Taldefgrobep Alfa | BHV-2000**	Obesity		Phase 2 Topline
ION CHANNEL	**Kv7 Activator | Opakalim**	Focal Epilepsy		Pivotal Topline
ONCOLOGY	**Trop2 ADC +/- PD-1 | BHV-1510**	Advanced or Metastatic Epithelial Tumors	Initiate expansion cohort in endometrial cancer	
	FGFR3 ADC | BHV-1530	Urothelial Cancer and Other Tumors	Phase 1 in urothelial cancer	


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