

CORPORATE OVERVIEW

February 2025

Forward-Looking Statements

This overview contains forward-looking statements. These statements relate to, among other things, the sufficiency of our cash position to fund advancement of a broad pipeline; the continued advancement of our discovery, preclinical, and clinical pipeline, and expected milestones in 2025, 2026, and beyond, including potential launch for birtamimab; our goal to continue building a biology-directed engine targeting protein dysregulation; our potential to advance, initiate, and complete IND enabling studies for our discovery and preclinical programs; the treatment potential, designs, proposed mechanisms of action, and potential administration of PRX012, BMS-986446/PRX005, PRX123, birtamimab, prasinezumab, and coramitug/PRX004; potential indications and attributes of epitopes and antibodies we have identified in our programs, including their potential for a best-in-class profile; plans for ongoing and future clinical trials of PRX012, BMS-986446, birtamimab, prasinezumab, coramitug, and PRX019; the expected timing of reporting data from clinical trials of birtamimab, PRX012, coramitug, BMS-986446, and PRX019, including multiple data readouts starting in mid-2025 and continuing throughout the year from our ongoing Phase 1 clinical trials evaluating PRX012 and topline study results for our Phase 3 AFFIRM-AL clinical trial in 2Q 2025; Roche's plans to work with health authorities to determine next steps for prasinezumab; potential market penetration and opportunity for birtamimab; potential market exclusivity periods for birtamimab; and amounts we might receive under our partnerships and collaborations with Roche, BMS, and Novo Nordisk. These statements are based on estimates, projections and assumptions that may prove not to be accurate, and actual results could differ materially from those anticipated due to known and unknown risks, uncertainties and other factors, including but not limited to those described in the "Risk Factors" sections of our Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 12, 2024, discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC, and our Annual Report on Form 10-K to be filed with the SEC for our fiscal year 2024. This overview is made as of February 20, 2025, and we undertake no obligation to update publicly any forward-looking statements contained in this overview as a result of new information, future events, or changes in our expectations.

Our Mission Today

We are Focused on Delivering Life-Saving Therapies...

…for unmet medical needs caused by **diseases of protein dysregulation**



We are Addressing Devastating Proteinopathies Affecting Millions of Patients and Families Worldwide

prothena®

NEURODEGENERATIVE DISEASES

Alzheimer's disease (AD)

>80 million
People worldwide living with early symptomatic AD[1]

>315 million
People worldwide living with presymptomatic AD[1]

$1 trillion
In annual US healthcare costs by 2050 from AD and other dementias[2]

Parkinson's disease (PD)

>10 million
People living with PD worldwide[3]

Fastest increasing
Neurodegenerative disease[3]

$52 billion
In overall economic burden in the US[3]

RARE PERIPHERAL AMYLOID DISEASES

Amyloid light chain amyloidosis (AL)

150,000-300,000
AL amyloidosis with cardiac involvement patients globally[4-6]

60,000-120,000
Mayo Stage IV AL amyloidosis patients globally[4,5]

5.8 months
Median overall survival in Mayo Stage IV patients with AL amyloidosis[5,7]

Transthyretin amyloidosis (ATTR)

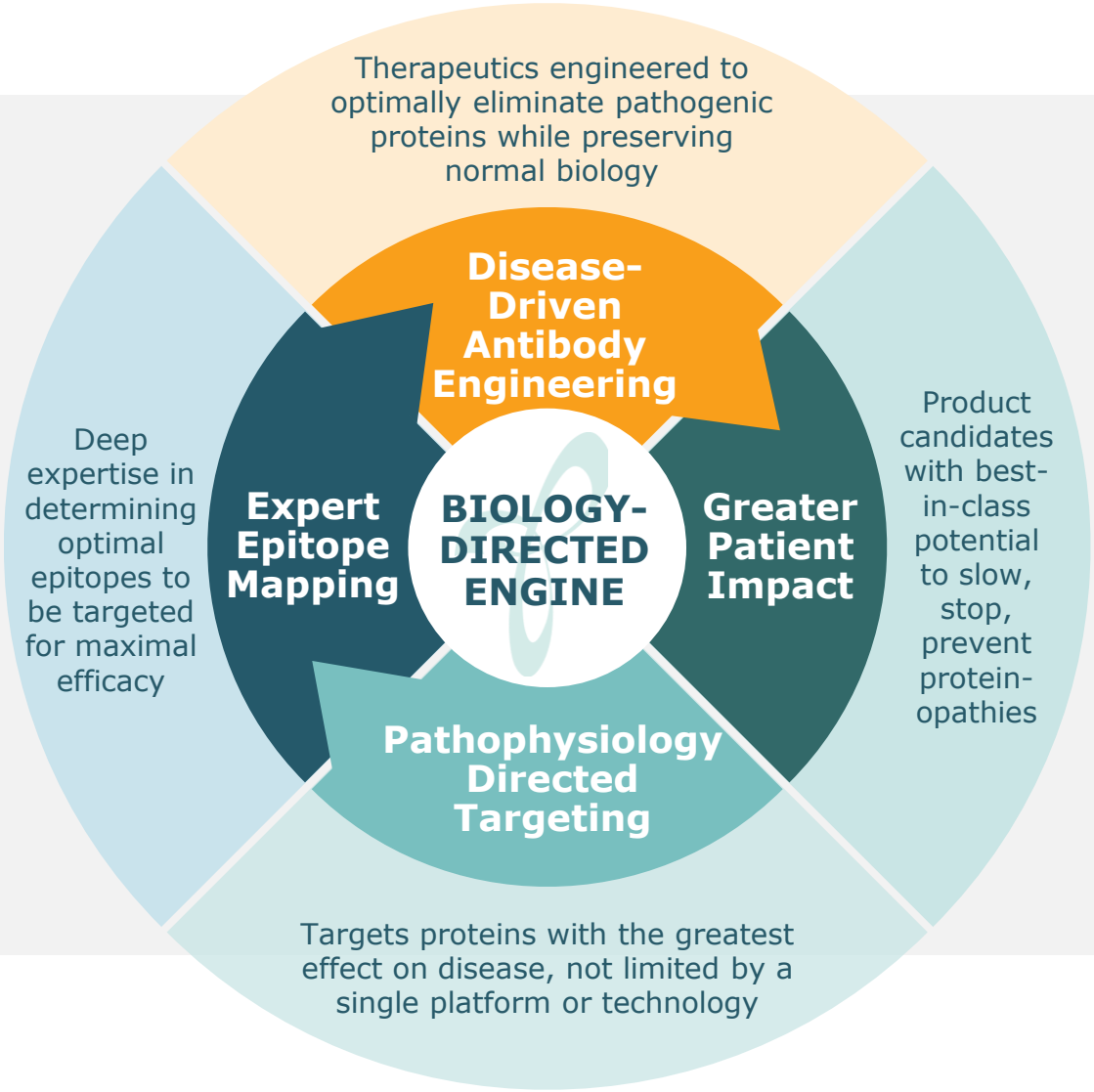
450,000
Estimated number of patients worldwide with wtATTR or ATTRv[8-10]

2.08 years
Median overall survival New York Heart Association class III patients with ATTR cardiomyopathy[5,11]

ATTRv=hereditary amyloid transthyretin; wtATTR=wild-type ATTR.

[1] Gustavsson, A. et al. "Global estimates on the number of persons across the Alzheimer's disease continuum." Alzheimer's & Dementia (2022) 1-13. [2] Long S, Benoist C, Weidner W. World Alzheimer Report 2023: Reducing dementia risk: never too early, never too late. London, England: Alzheimer's Disease International. Accessed July 18, 2024. https://www.alzint.org/u/World-Alzheimer-Report-2023.pdf. [3] Parkinson's Foundation. Understanding Parkinson's. Statistics. Accessed July 17, 2024. https://www.parkinson.org/understanding-parkinsons/statistics. [4] Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis*. 2022;17(1):278. [5] Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995. [6] Merlini G, *Blood*. 2012; 119 (19): 4343–4345. [7] Kyle RA, Gertz MA, Greipp PR, et al. *N Engl J Med*. 1997;336(17):1202-1207. [8] González-Duarte A, Conceição I, Amass L, Botteman MF, Carter JA, Stewart M. *Neurol Ther*. 2020;9(1):135-149. [9] González-López E, Gagliardi C, Dominguez F, et al. *Eur Heart J*. 2017;38(24):1895-1904. [10] Tanskanen M, Peuralinna T, Polvikoski T, et al. *Ann Med*. 2008;40(3):232-239. [11] Lane T, Fontana M, Martinez-Naharro A, et al. *Circulation*. 2019;140(1):16-26.

Our Biology-Directed Engine Propels Prothena's Progress Across our Broad Pipeline



Multiple Clinical Programs Ongoing

Wholly-owned Phase 3 program

Three partnered Phase 2 programs

One partnered Phase 1 program

Wholly-owned Phase 1 program

Strong Collaborations Established

Collaborations with Bristol Myers Squibb, Novo Nordisk[1] and Roche

Leveraging our Phase 3 Rare Peripheral Amyloid Disease Program to Support Commercial Buildout

Transition into a fully integrated commercial biotech through our lead rare disease program

[1] In July 2021 Novo Nordisk acquired coramitug (formerly PRX004) and broader ATTR amyloidosis program and gained full worldwide rights. Prothena is eligible to receive up to $1.23 billion in total consideration.

Robust R&D Pipeline

FOCUSED ON NEURODEGENERATIVE AND RARE PERIPHERAL AMYLOID DISEASES

PROGRAM/ INDICATION	PROTEIN TARGET	DISCOVERY	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	GLOBAL PARTNER[4]
Birtamimab SPA[1] ODD[2] Fast Track[3] *AL amyloidosis*	Light Chain (Kappa & Lambda)	AFFIRM-AL (Phase 3)					
Prasinezumab *Parkinson's disease*	α-Synuclein (C-terminus)	PASADENA (Phase 2) | PADOVA (Phase 2b)					Roche
Coramitug (PRX004) ODD[2] *ATTR-CM*	Transthyretin (misTTR)	Phase 2					novo nordisk
BMS-986446 (PRX005) *Alzheimer's disease*	Tau (MTBR)	Phase 2					Bristol Myers Squibb
PRX012 Fast Track[3] *Alzheimer's disease*	Aβ (N-terminus)	ASCENT (Phase 1)					
PRX019 *Neurodegeneration*	Undisclosed Target	Phase 1					Bristol Myers Squibb
PRX123 Fast Track[3] *Alzheimer's disease*	Aβ + Tau	IND cleared					
Undisclosed *AD in Down syndrome*	Undisclosed Target						

Modalities: mAb | Small Molecule | Vaccine

Aβ, Abeta; AD, Alzheimer's disease; mAb, monoclonal antibody.
[1] Primary endpoint of all-cause mortality at p≤0.10 under the Special Protocol Assessment (SPA) agreement with FDA; [2] Orphan Drug Designation granted by FDA & EMA; [3] FDA Fast Track designation;
[4] In July 2021 Novo Nordisk acquired coramitug (formerly PRX004) and broader ATTR amyloidosis program and gained full worldwide rights. Prothena is eligible to receive up to $1.23 billion in total consideration

Alzheimer’s Disease

Our Team has Pioneered Multiple Scientific Advances in Protein Dysregulation

OUR LEGACY INCLUDES FOUNDATIONAL DISCOVERIES IN THE UNDERSTANDING OF ALZHEIMER'S DISEASE

1986
Athena Neurosciences founded

1996
Athena acquired by Elan

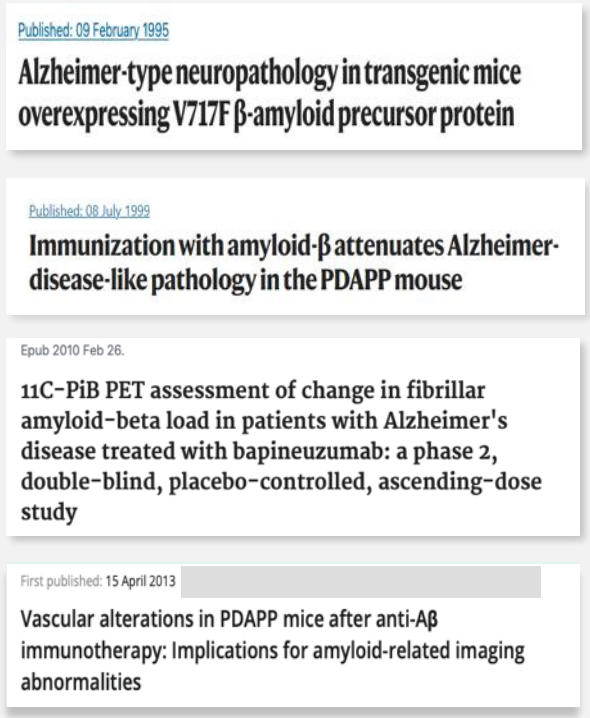
2012
Prothena spins-out from Elan with a wholly-owned drug discovery platform

- **Pioneered fundamental discoveries** elucidating the roles of beta amyloid (Aβ), gamma secretase and beta secretase play in disease[1]
- **First to show** that anti-Aβ immunotherapy prevented and cleared amyloid plaques in the brains of transgenic mice[2]
- **First to demonstrate plaque clearance** by an n-terminus antibody in brains from AD patients[3]
- **Discovered biological cause of ARIA** and vascular recovery following anti-Aβ immunotherapy[4]
- **Developed PRX012, best-in-class anti-Aβ product candidate,** with ~10X greater binding potency to fibrillar Aβ vs. aducanumab[5] and ~20X greater binding potency against protofibrils vs. lecanemab[6]

[1] Games, D., Adams, D., Alessandrini, R. et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein. 1995 Nature; [2] Schenk, D., Barbour, R., Dunn, W. et al. Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. 1999 Nature; [3] Rinne et al, C-BiP PET assessment of change in fibrillar amyloid-b load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending –dose study, 2010, [4] Zago W, Schroeter S, Guido T, et al. Vascular alterations in PDAPP mice after anti-Aβ immunotherapy: Implications for amyloid-related imaging abnormalities. 2013 Alzheimers Dement. [5] PRX012 Induces Microglia-Mediated Clearance of Pyroglutamate-Modified and -Unmodified Aß in Alzheimer's Disease Brain Tissue presented at AAIC 2021; [6] Binding Characteristics of Surrogate PRX012 Demonstrate Potent Engagement of Toxic Abeta Protofibrils and Robust Clearance of Pyroglutamate-Modified Abeta presented at AD/PD 2023

Our Legacy Drives Our Vision to Transform the Care of Alzheimer's Disease

With unparalleled protein dysregulation expertise…



OUR LEGACY [1-4]

…We're uniquely positioned to address Alzheimer's Disease with a best-in-class portfolio

PRX012, anti-Aβ candidate with potential best-in-class, **highly potent binding**; designed for improved patient access via **subcutaneous** delivery[5]

Phase 1

BMS-986446 (PRX005), anti-tau candidate, with **potential to reduce pathogenic tau spread**[6]

Phase 2

PRX123, dual Aβ/tau vaccine candidate designed for **treatment and prevention**

IND cleared

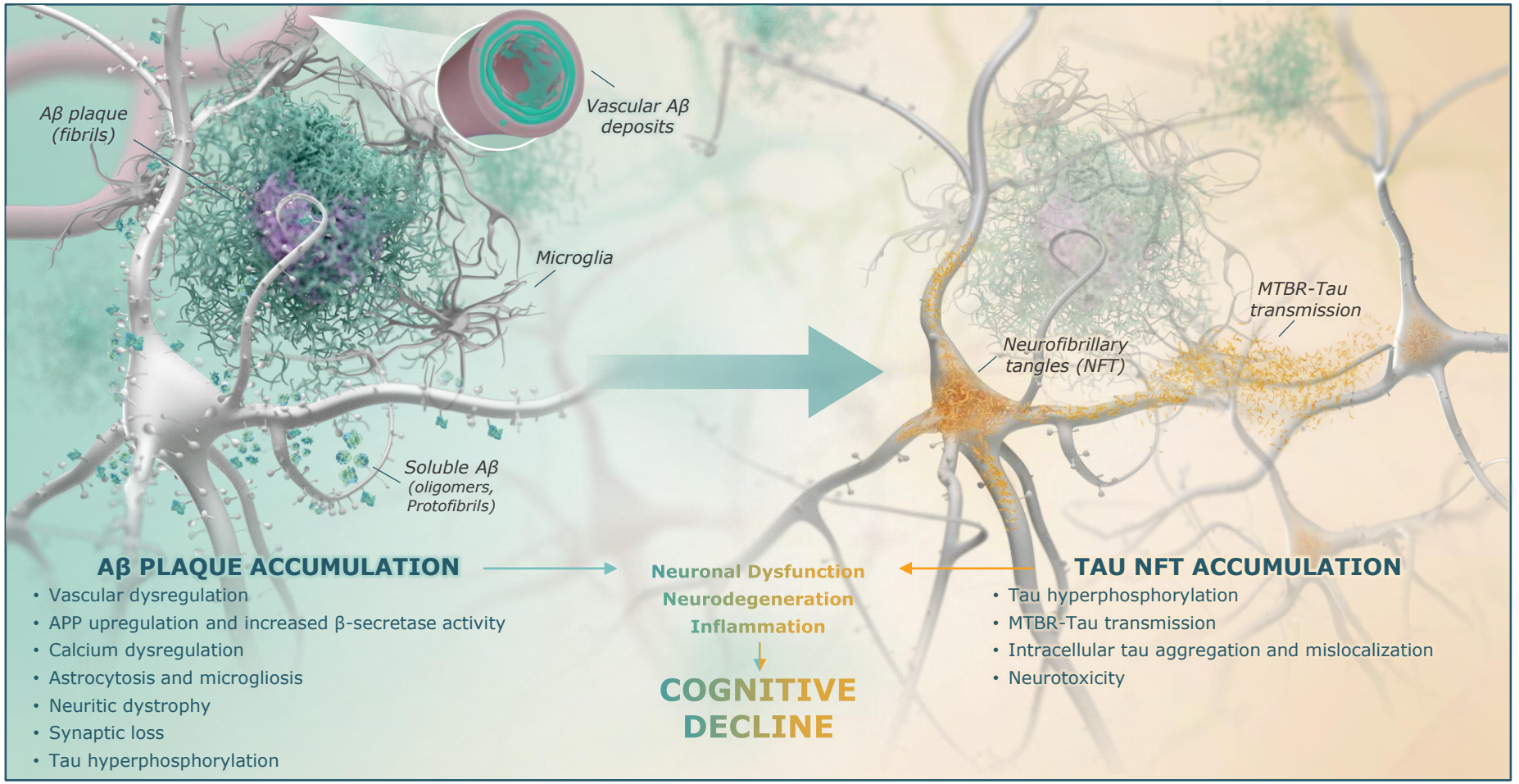
[1] Games D, et al.1995 *Nature*; [2] Zago W, et al. 2013 *Alzheimers Dement*; [3] Schenk D, et al. 1999 *Nature*; [4] Rinne, et al. 2010 *Lancet Neurol*; [5] Skov M, et al. Preclinical data available at: https://tinyurl.com/3zzpmbxh; [6] Dolan P. Preclinical data available at: https://tinyurl.com/3kf7pvnd.

Targeting Alzheimer's Where it Matters

Aβ has been established as a disease modifying target in Alzheimer's disease

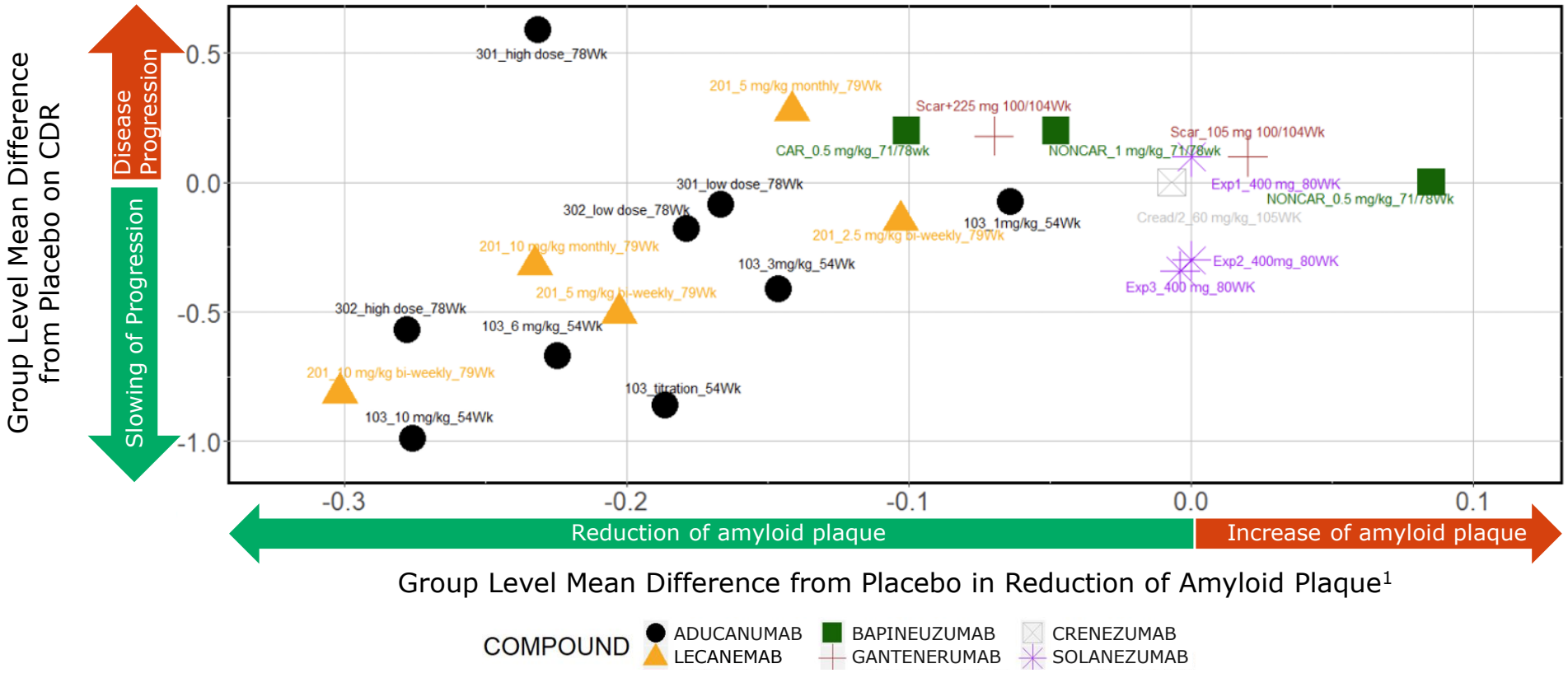
Reduction of Aβ plaque associated with clinically meaningful slowing of disease progression

Presence of tau pathology strongly correlates with neurodegeneration and cognitive impairment in Alzheimer's disease



Today's Clinical Science Validates the Mechanism Designed by Our Team

Mean Difference from Placebo in Reduction of Amyloid Plaque[1] and CDR-SB



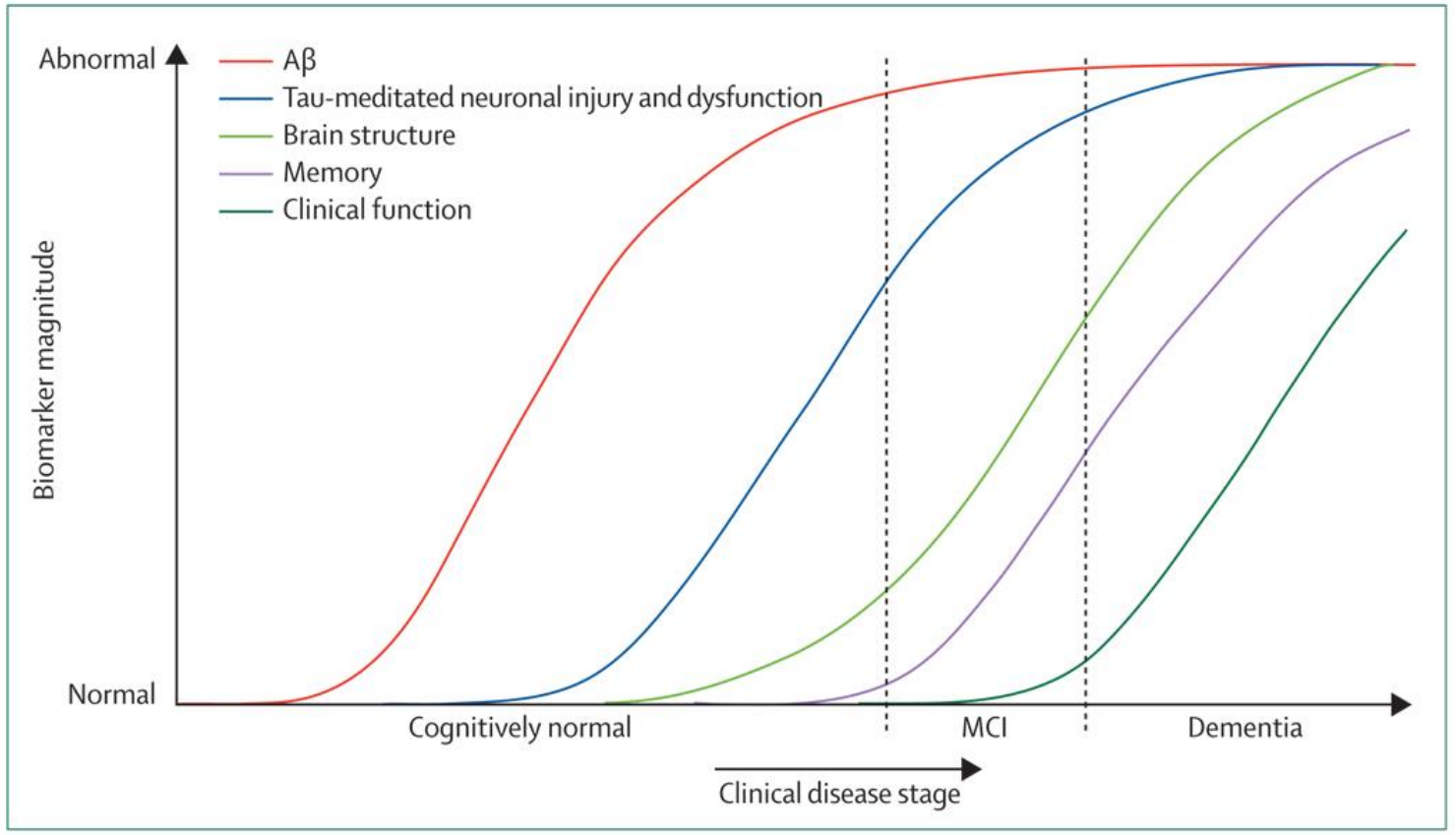
2020 US FDA ANALYSIS: Aβ has been established as a disease modifying target in AD[2,3]

[1] Reduction of Amyloid Plaque as measured by SUVr, Standardized Uptake Value Ratio; CDR, Clinical Dementia Rating Scale.
[2] ADUHELM [prescribing information]. Cambridge, Massachusetts: Biogen Inc; October 2022; [3] US FDA. Clinical Pharmacology and Pharmacokinetics Review(s). July 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000ClinPharm_Redacted.pdf.

Targeting Alzheimer's Where it Matters

CHANGING THE TREATMENT PARADIGM THROUGH OUR BIOLOGY-DIRECTED ENGINE

Dynamic biomarkers of the Alzheimer's pathological cascade[1]



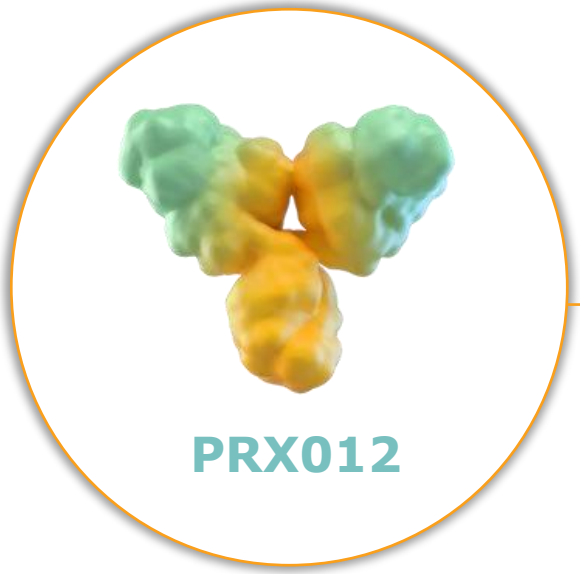
[1] Jack, Clifford et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, 2010 NIH Public Access

PRX012

Alzheimer’s Disease

PRX012: Leading a Paradigm Shift in the Treatment of Alzheimer's Disease

300+ iterative antibody design and optimization campaigns led to…



…potential best-in-class, subcutaneous, once-monthly anti-Aβ product candidate

Key Antibody Design Attributes

HUMANIZED IgG1 monoclonal antibody with low immunogenicity

TARGETS a key epitope at the N-terminus of Aβ protein

HIGH AFFINITY AND AVIDITY to Aβ for extended binding time and opsonization efficiency

SLOW OFF RATE / slow & steady dissociation translates to consistent target exposure and potential safety advantages

HIGHLY POTENT BINDING, designed for subcutaneous administration

Translating Patient Needs Into Antibody Engineering

PATIENT-CENTRIC DESIGN STRATEGY FOR PRX012

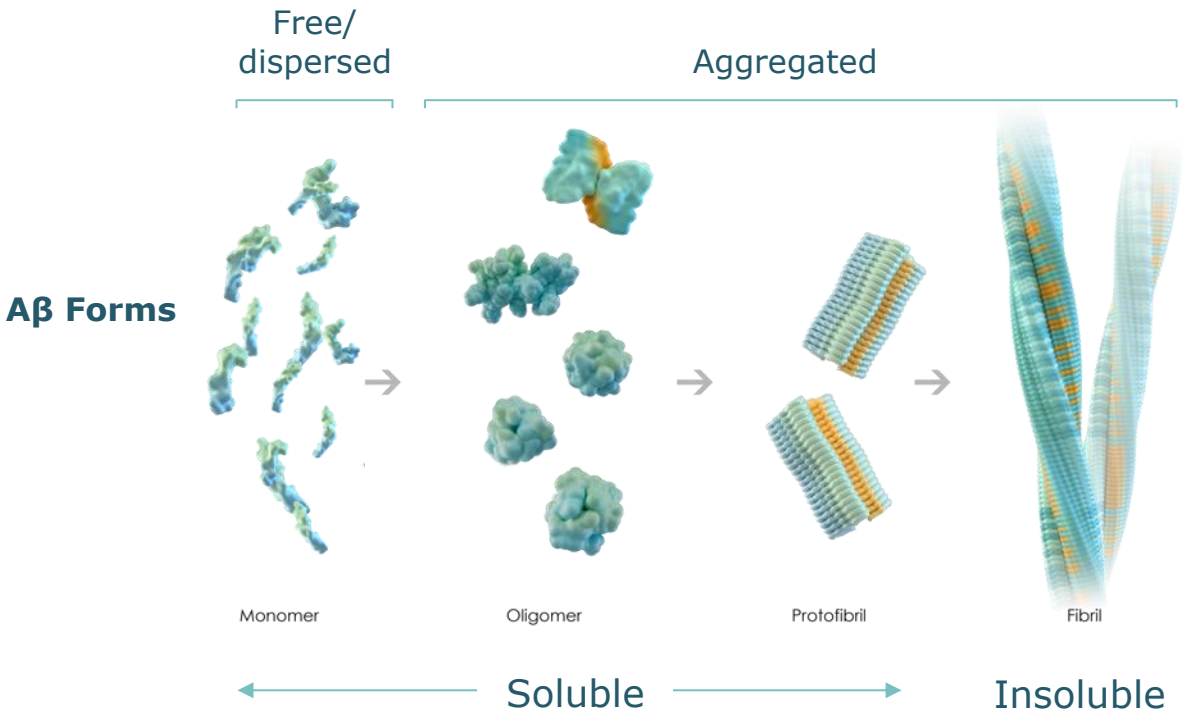
	TARGET PROFILE	ANTIBODY DESIGN ATTRIBUTES
Maintain From First Generation Antibodies	**Effectively clear soluble and insoluble aggregated amyloid**	• N-terminal directed • Full effector-function
Innovations to Minimize Disease and Treatment Burden	**Low-volume subcutaneous (SC) delivery**	• High binding potency • Stability in high concentrations for single syringe use
	Once-monthly dosing	• Optimize pharmacokinetic profile and immunogenicity • Optimal bioavailability
	At-home administration	• Optimal biophysical qualities

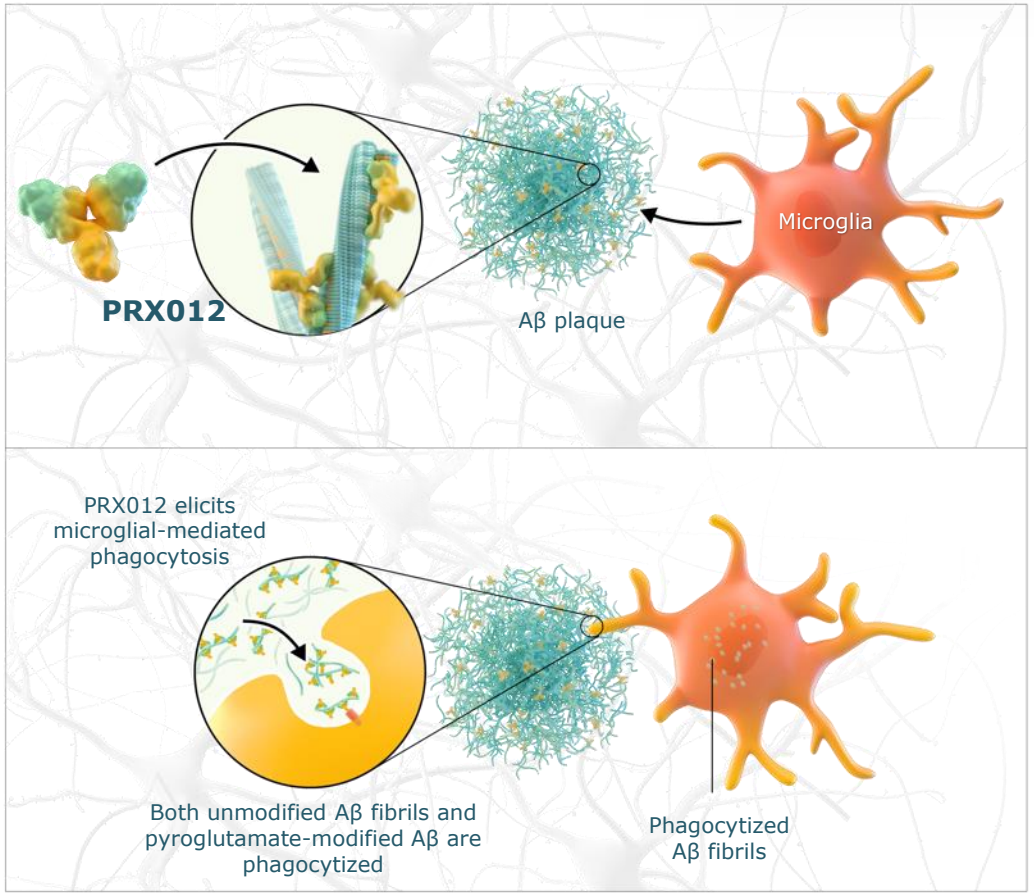
OUR MISSION

- Improve patient outcomes
- Increase accessibility
- Minimize treatment burden
- Enable patients and care partners to take anti-Aβ treatment into their own hands

PRX012: Promotes Comprehensive Clearance of Amyloid Plaques and Neutralization of Oligomers

Designed to target and clear toxic aggregated forms of Aβ



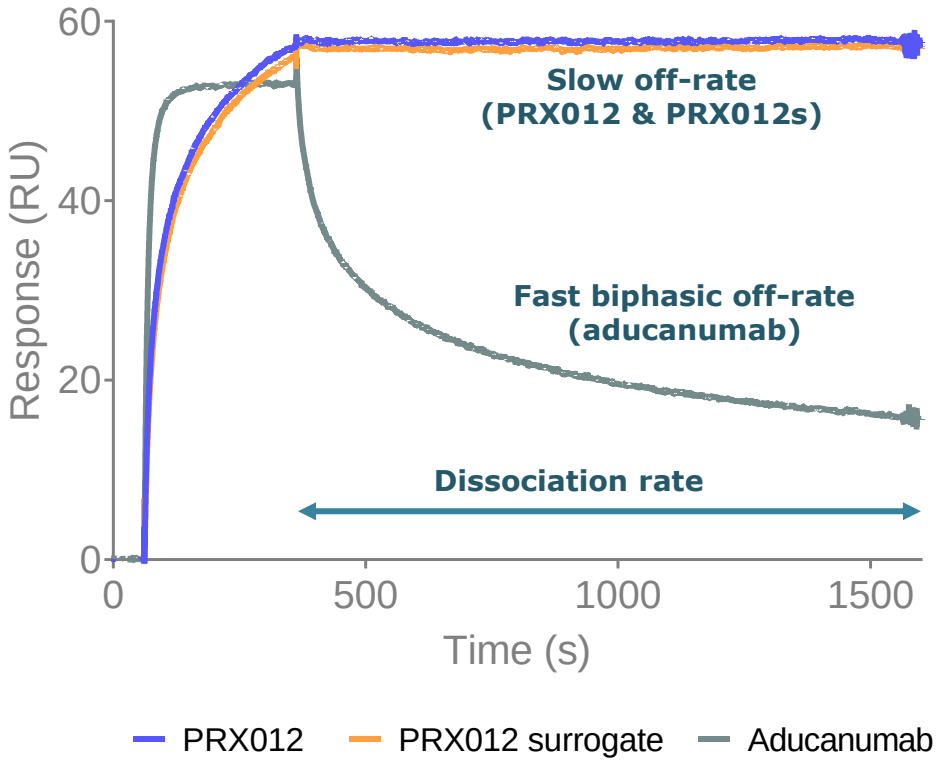


Microglia recognize and engulf PRX012-opsonized Aβ fibrils

Note: Based on preclinical data. Visuals not to scale.

PRX012 and Surrogate Demonstrate Equivalent Potent Binding Affinity for Aβ

Surface Plasmon Resonance (SPR) Aβ Fibrils



Affinity for Aβ Species

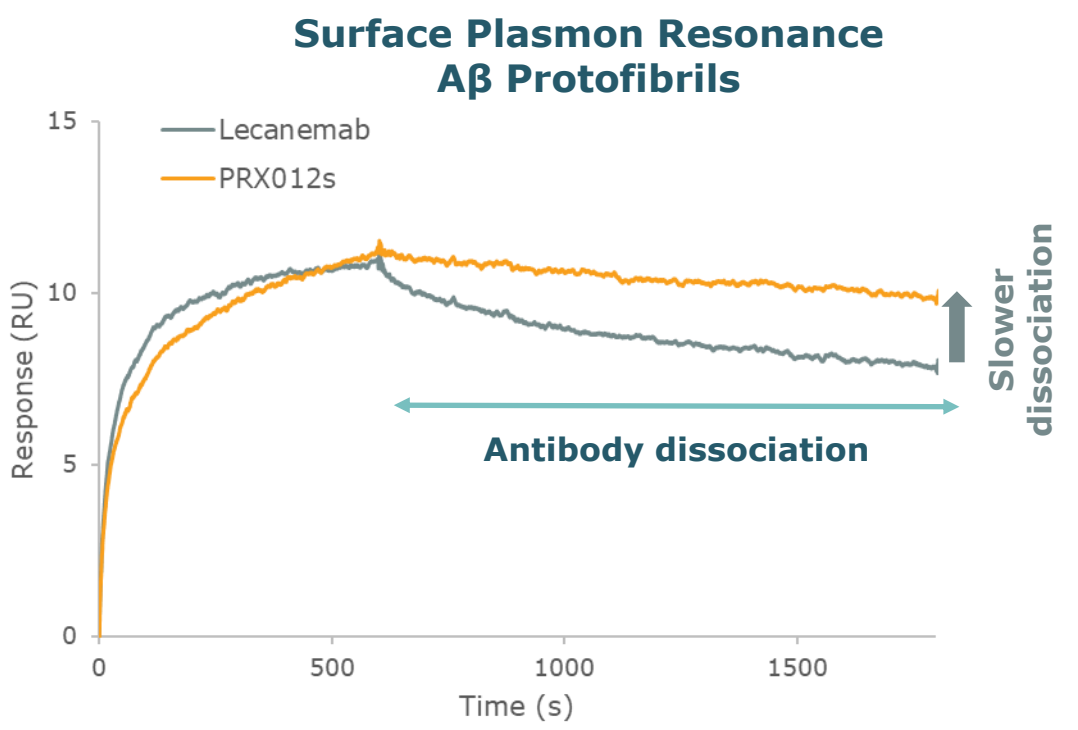
Compound	Fibril/Plaque	N3pE-Aβ
PRX012	0.070[a]	>67[b]
PRX012s	0.054[a]	>67[b]

Data represent K_D values from SPR[a] (nM) or IC50 from ELISA[b] (nM).

- **Potent binding strength of PRX012 and its surrogate (PRX012s) to fibrillar Aβ are equivalent, both demonstrating a very slow rate of dissociation**
  - PRX012 and PRX012s share >99.5% sequence homology
- **How does binding to protofibrils compare?**

N3pE-Aβ, pyroglutamate-modified Aβ; SPR, surface plasmon resonance.
PRX012s: "Surrogate" is defined as an antibody with >99.5% homology, the same binding epitope and equivalent binding profile to different forms of Aβ where directly compared.
Aducanumab was generated from a publicly available sequence.

PRX012s Binds Aβ Protofibrils With Very High Affinity



SPR protofibril binding was performed as described in Tucker et al., 2015[1]

Antibody	Relative Affinity (K_{D1})
Lecanemab[1] **(Tucker et al., 2015)**	1.97 nM
Lecanemab[2]	1.91 nM
PRX012s	0.0975 nM

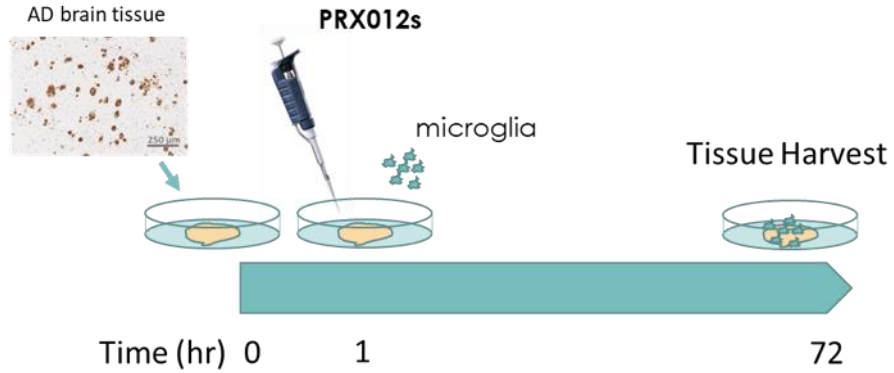
SPR Binding Kinetics

	ka1 (1/Ms)	kd1 (1/s)	K_{D1}
Lecanemab[1] **(Tucker et al., 2015)**	6.60E+05	1.30E-03	1.97E-09
Lecanemab[2]	1.80E+05	3.42E-04	1.91E-09
PRX012s	1.63E+05	1.59E-05	9.75E-11

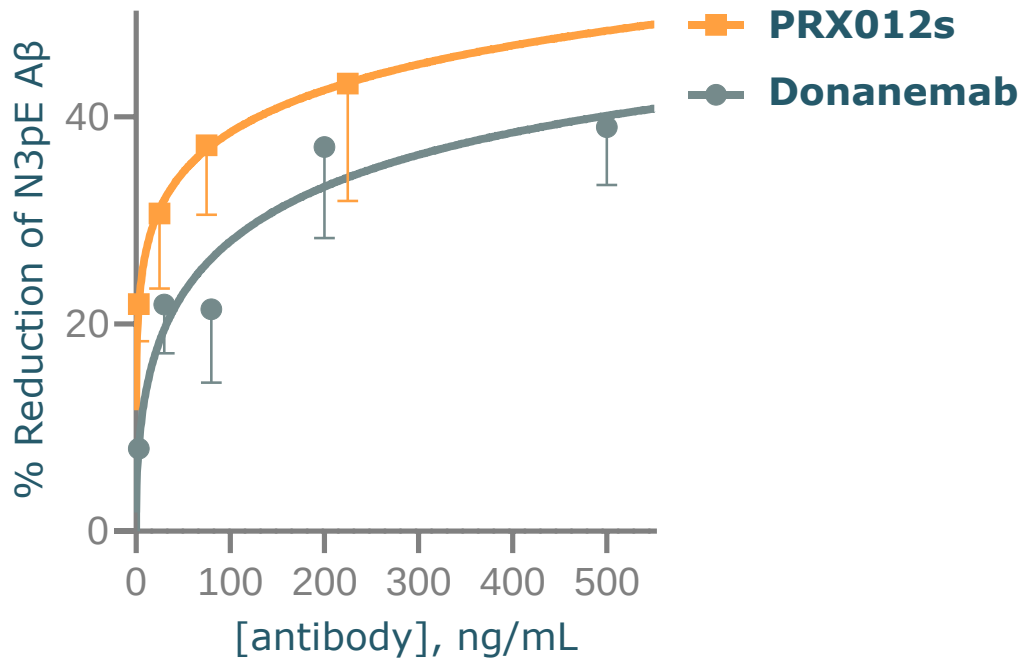
- **PRX012s binds to Aβ protofibrils with approximately 20-fold greater affinity than lecanemab when tested under the same conditions**
- **Greater affinity is driven largely by a slower binding dissociation**

ka, association constant; kd, dissociation constant; KD, equilibrium constant; SPR, surface plasmon resonance.
[1] Tucker S, et al. *J Alzheimers Dis.* 2015;43:575-588.
[2] Determined by Prothena.
Lecanemab was generated from a publicly available sequence.

PRX012s Induced Potent and Robust Clearance of Pyroglutamate-modified Aβ



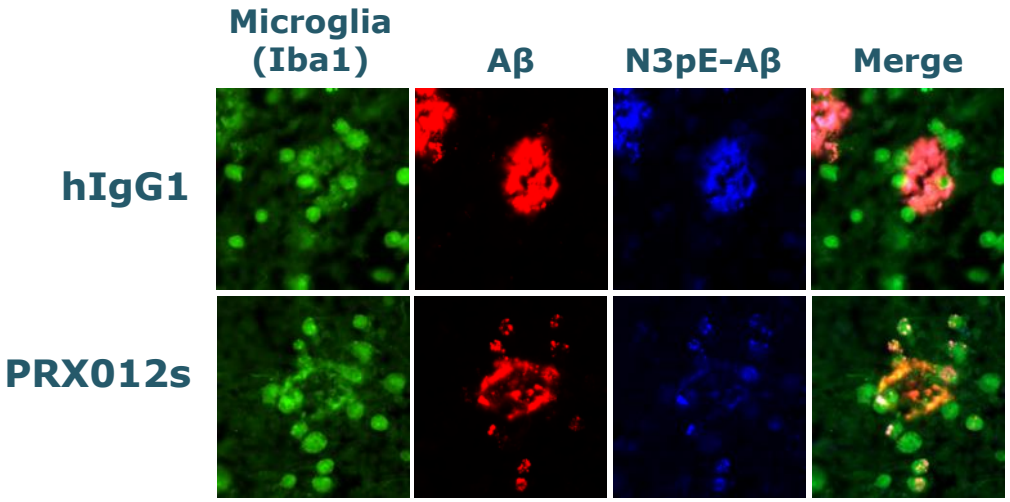
	Study Conditions
Tissue	Post-mortem AD brain tissue (same donor used for all conditions)
Treatment	PRX012s, donanemab, or IgG1 isotype control
Microglia	Primary mouse microglia (800,000 cells/mL)
Culture time	72 hours at 37°C



- **PRX012s facilitates concentration-dependent clearance of pyroglutamate-modified Aβ (N3pE-Aβ) at concentrations that may be relevant for PRX012 clinical exposure**
- **PRX012s clears equivalent or more N3pE-Aβ at ~3–8x lower concentrations than donanemab**

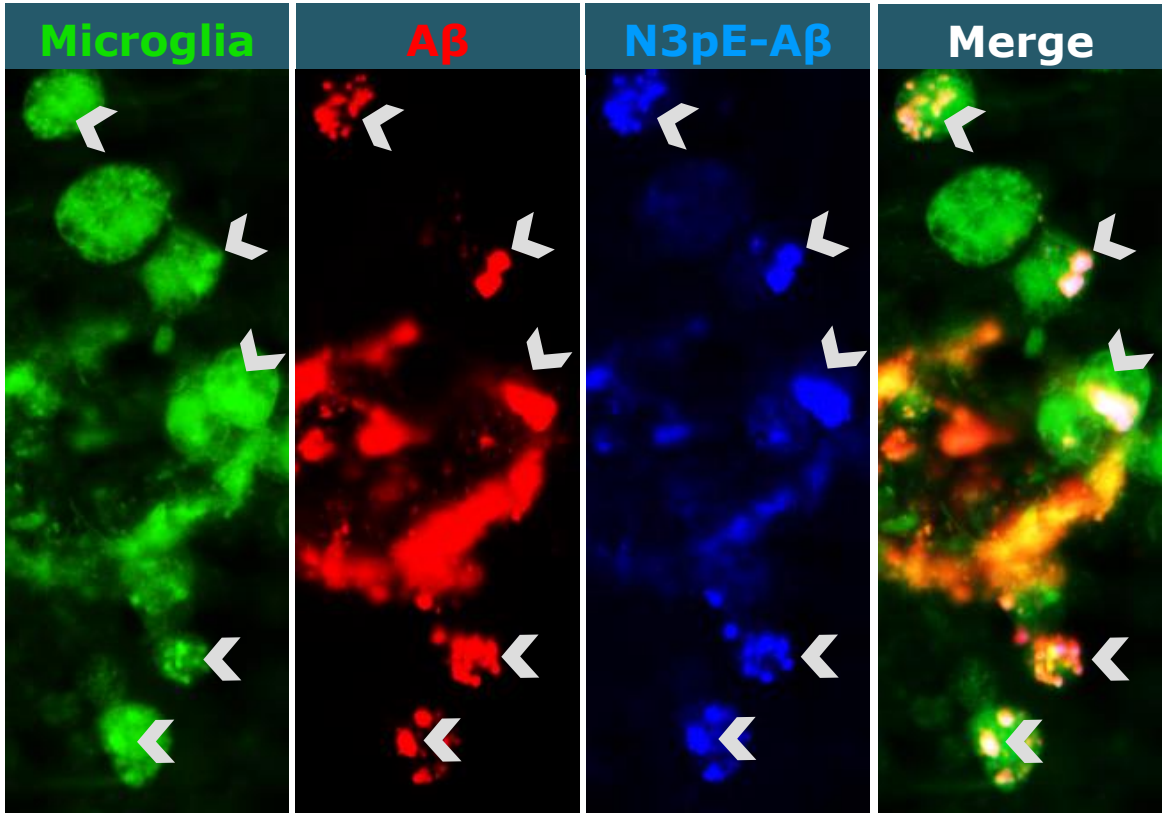
IgG, immunoglobulin; N3pE-Aβ, pyroglutamate-modified Aβ.
Donanemab was generated from a publicly available sequence.

PRX012s Promotes Simultaneous Microglia-Mediated Phagocytosis of Aβ and N3pE-Aβ in Post-mortem Brain Tissue From AD Subjects



Microglia (Iba1: green) simultaneously phagocytose Aβ (red) and pyroglutamate-modified Aβ ($Aβ_{pE3-42}$: blue) in the presence of PRX012 surrogate, indicating that opsonization of plaques is sufficient to clear both species.

PRX012s promoted microglia-mediated phagocytosis of Aβ and pyroglutamate-modified Aβ (N3pE-Aβ) simultaneously



Arrows indicate examples of phagocytosed Aβ and N3pE-Aβ that co-localize inside microglia cells (immunostained with anti-Iba1 antibody).

Aβ, amyloid beta; AD, Alzheimer's disease; IgG, immunoglobulin; N3pE-Aβ, pyroglutamate-modified Aβ.

PRX012 Phase 1 SAD Design

Healthy Volunteer Cohorts

- Age 20 – 45 years

70 mg	200 mg
n ~ 8 (3:1)	n ~ 8 (3:1)

Early Alzheimer's Disease Cohorts

- Ages 60 – 85 years
- Amyloid PET positive
- MMSE ≥ 18

70 mg	200 mg	400 mg
n ~ 8 (3:1)	n ~ 8 (3:1)	n ~ 8 (3:1)

Trial Design | ascent-1

- Phase 1, randomized 3:1, double-blind, placebo-controlled, single ascending dose trial
- 1 subcutaneous dose of PRX012 or placebo
- Evaluate the safety, tolerability, immunogenicity, and pharmacokinetics of PRX012 in healthy volunteers and patients with Alzheimer's disease

MMSE: Mini Mental State Examination.

PRX012 Phase 1 Multiple Dose Design

ascent-2 Trial Overview[1]

Key Inclusion Criteria

- Patients with early AD
- Ages 55 – 85 years
- Amyloid PET positive
- MMSE ≥ 18

Dose Escalation: "A" and "B" Cohorts[2,3]

Randomized 3:1
Active to Placebo
(n ~ 263)

- **45 mg A Cohort (n~32)** SC 6X Q4W
- **70 mg A Cohort (n~32)** SC 6X Q4W
- **200 mg A Cohort (n~32)** SC 6X Q4W
- **400 mg A Cohort (n~32)** SC 6X Q4W
- **45 mg B Cohort (n~12)** SC 6X Q4W
- **70 mg B Cohort (n~12)** SC 6X Q4W
- **200 mg B Cohort (n~12)** SC 6X Q4W

Dose Expansion

- **200 mg Expansion A Cohort (n~99)** SC 6X Q4W

Key Objectives

- Evaluate the safety, tolerability, and immunogenicity
- Effect on brain amyloid plaque
- Incidence of radiographic amyloid-related imaging abnormalities

Open-label Extension

- Patients may continue into an optional OLE for 12 months, an additional 12 doses (SC 12X Q4W)

ascent-3

[1] Presented at: The 2024 AAIC Annual Meeting; July 28, 2024; Philadelphia, PA.
[2] "A" dose cohorts include only APOε4 non-carrier or heterozygous AD patients
[3] "B" dose cohorts include only APOε4 homozygous AD patients
AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SC, subcutaneous injection; Q4W, every 4 weeks.

BMS-986446
(formerly PRX005)
Alzheimer's Disease

Global Neuroscience Collaboration
with Bristol Myers Squibb

BMS-986446: Potential Best-in-Class anti-Tau antibody for Alzheimer's Disease

BMS-986446

Alzheimer's disease

Current Status: Phase 2

Anti-Tau Mechanism of Action

- Designed to specifically bind with high affinity to a key epitope within the microtubule binding region (MTBR) of tau, a protein implicated in the causal pathophysiology of Alzheimer's disease

Global Rights Deal for BMS-986446[1]

- $135 million paid-to-date for global rights
- BMS funds all development and commercialization
- Up to $563 million in regulatory/sales milestones
- Tiered royalties

Phase 2 Trial (NCT06268886): Ongoing

- Global, double-blind, placebo-controlled
- 475 participants with early AD
- Randomized, 3 arms (two doses and placebo)
- Primary Endpoint: Mean change from baseline in CDR-SB score at 18 months
- Primary completion expected in 2027

Phase 1 Trial:

- Phase 1 SAD data in healthy volunteers demonstrated dose-proportional concentrations in plasma with robust CNS penetration
- Phase 1 data supportive of Phase 2
- Generally safe and well-tolerated

[1] Global Neuroscience Research and Development Collaboration with BMS for three programs (BMS-986446, PRX019, TDP-43) also included $100 million upfront payment and a $50 million equity investment in Prothena.
CDR-SB, Clinical Dementia Rating Scale Sum of Boxes

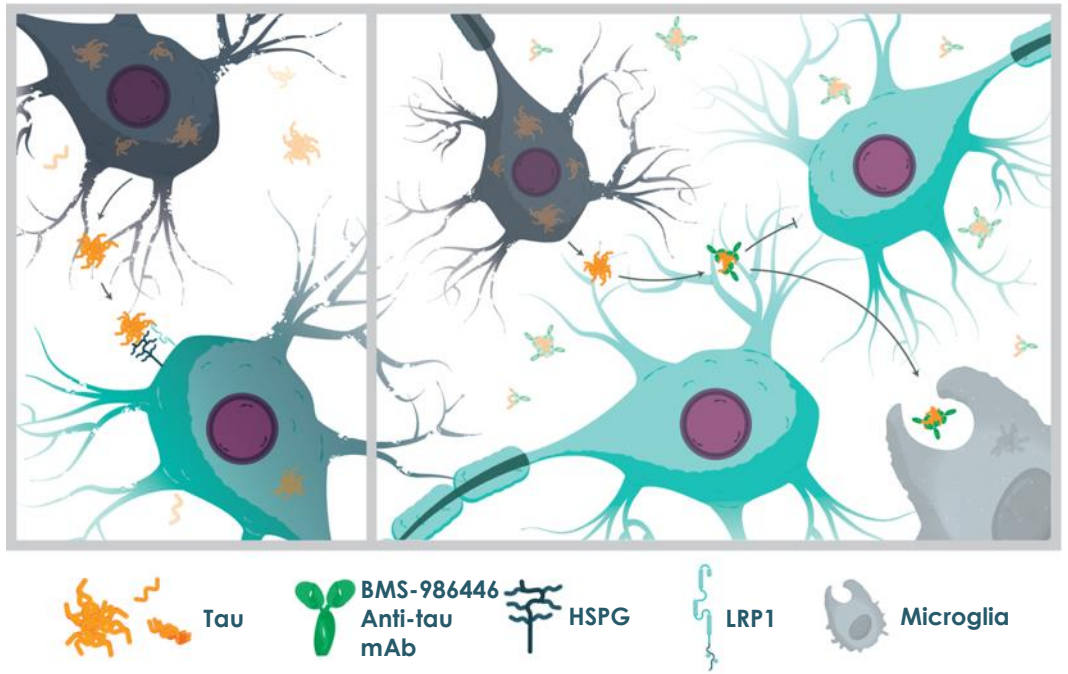
BMS-986446: MTBR-Specific Anti-Tau Antibody

BMS-986446, a differentiated tau antibody that targets an optimal tau region within the MTBR

- Recent publications strongly suggest that tau appears to spread throughout the brain via synaptically-connected pathways[1]
- This propagation of pathology is thought to be mediated by tau "seeds" containing the MTBR of tau[2]

Potential for best-in-class efficacy

- Preclinical evaluation of our antibodies in our AD models demonstrated that MTBR-specific antibodies are superior to non-MTBR tau antibodies in blocking tau uptake and neurotoxicity
- Demonstrated significant inhibition of cell-to-cell transmission and neuronal internalization in vitro and in vivo and slowed pathological progression in a tau transgenic mouse model

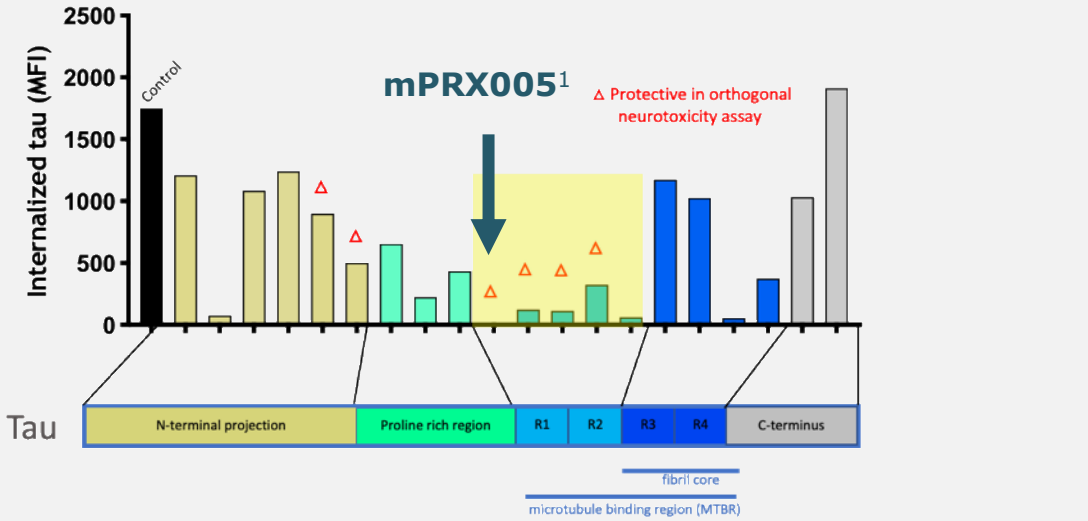


BMS-986446: Potential Best-in-Class MTBR-Specific Anti-Tau Antibody to Reduce Pathogenic Tau Spread

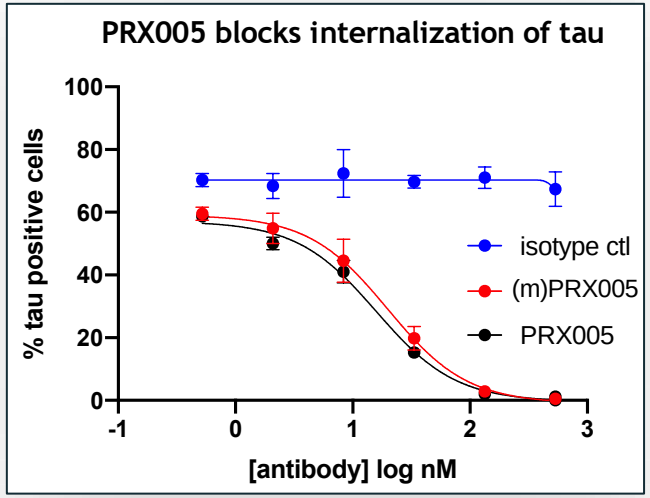
[1] Ahmed, Z., Cooper, J.. et al. A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. 2014 *Acta Neuropathol*;
[2] Horie, k., Barthelemy, H., Bateman, R.J. CSF tau microtubule binding region identifies tau tangle and clinical stages of Alzheimer's disease. 2021 *Brain*

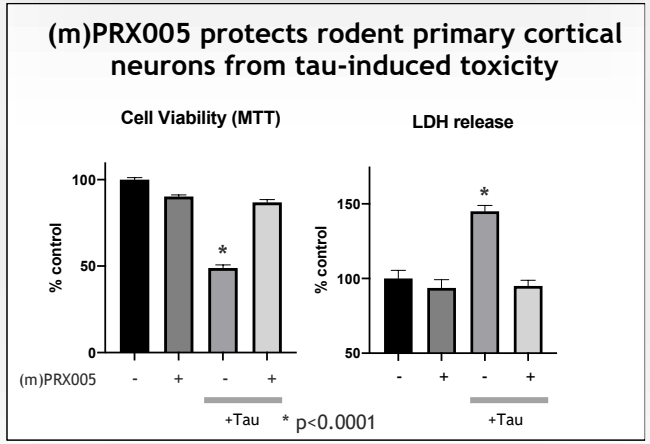
BMS-986446 (PRX005): Superior in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity Compared to Other Anti-Tau Antibodies

Repeats 1 and 2 defined as the strongest inhibitory regions in screening with cellular internalization and neurotoxicity assays



- Panel of Prothena antibodies targeted throughout the tau molecule were screened for optimal affinity and epitope
- These were tested *in vitro* for their ability to block internalization and toxicity



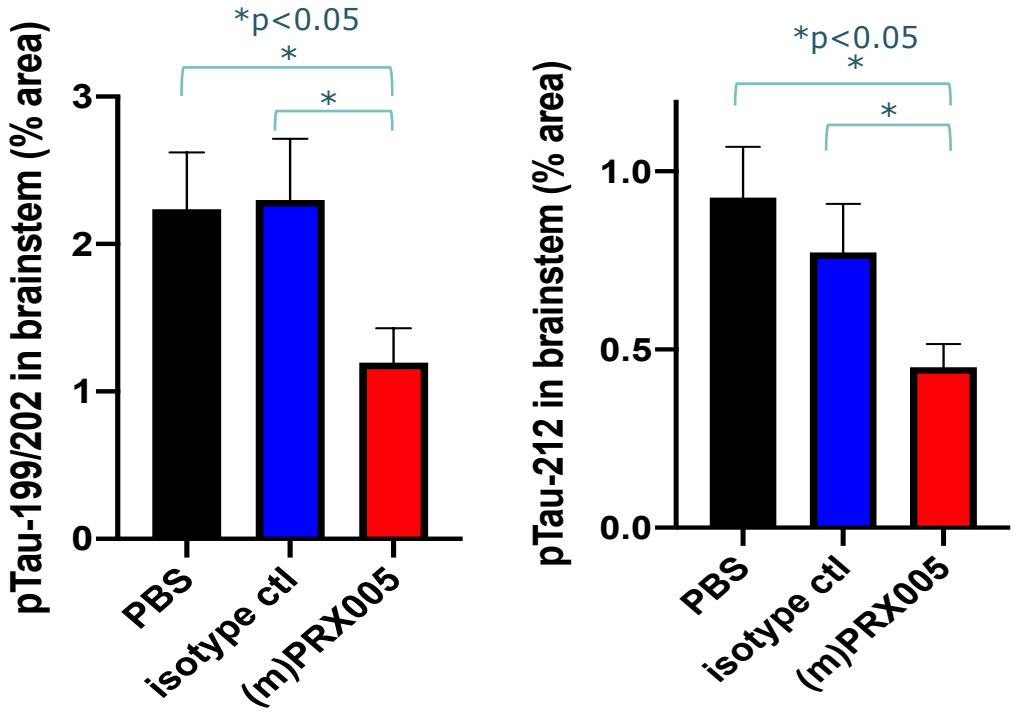


[1] (m)PRX005 = murine form of PRX005 (BMS-986446)

(m)PRX005 Treatment Reduces Pathological Tau and Ameliorates Behavioral Deficit in Transgenic Tau Mouse Model

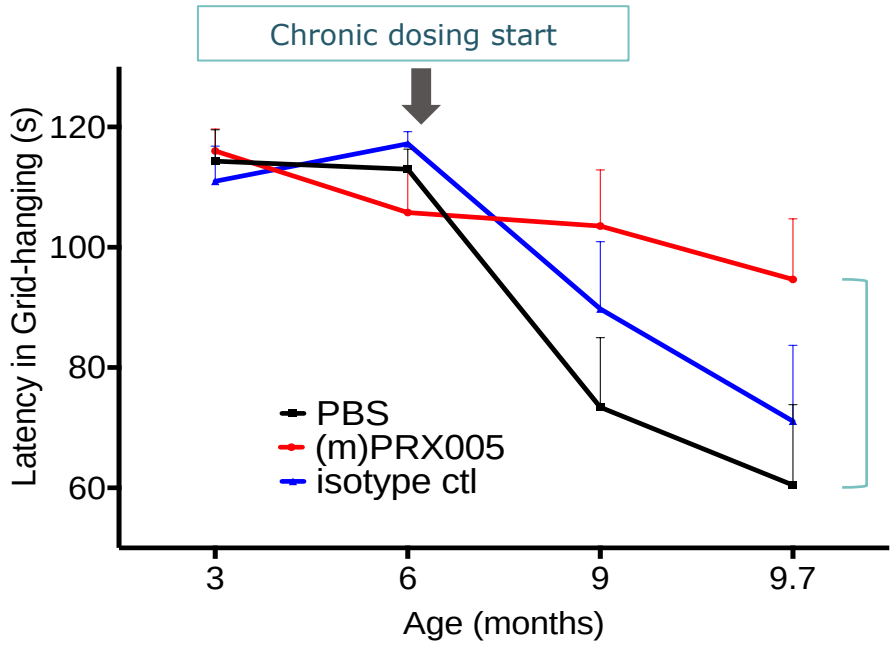
All values are mean ± SE (n=15-20)

Reduction of tau pathological markers



- PS19 transgenic mice overexpressing tau mutation (P301S) cause high levels of neuronal tau pathology and resultant behavioral deficits

Delay of behavioral deficit



- Initiation of treatment (weekly i.p.) at the onset of pathological development (treatment mode) with (m)PRX005 delays brainstem tau pathology and consequent behavioral deficits

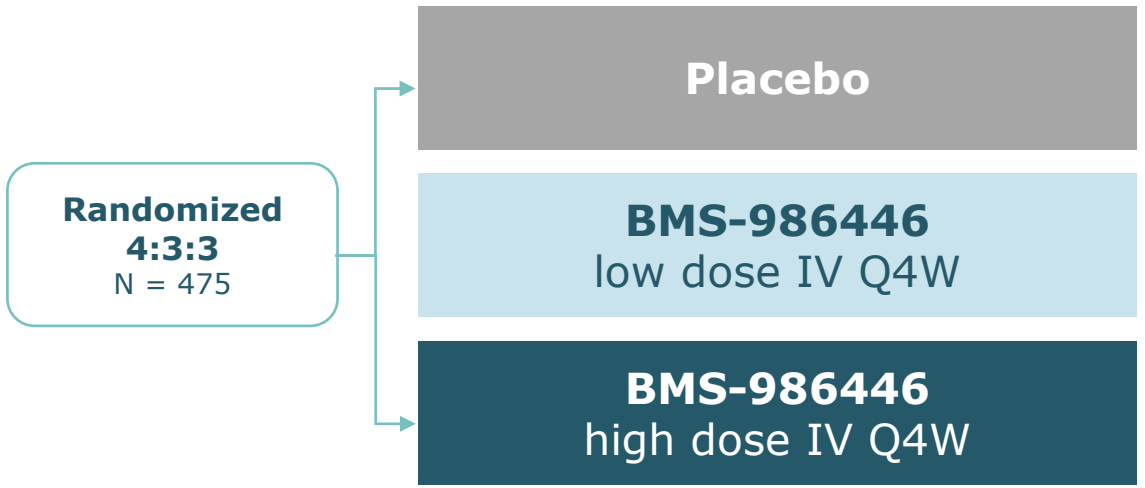
(m)PRX005 = murine form of PRX005 (BMS-986446)

BMS-986446: TargetTau-1 Phase 2 Trial Design

TargetTau-1 Trial Overview (NCT06268886)[1]

Key Inclusion Criteria

- Ages 50 – 80 years
- MCI due to AD or mild AD dementia
- Objective episodic memory impairment
- MMSE score 22–30
- AD pathology confirmed by plasma biomarkers and positive tau PET imaging



Key Assessments

- Tau PET imaging
- Cognitive assessments
- AD biomarkers[2]
- MRI

Primary Endpoint

- Mean change from baseline in CDR-SB score vs. placebo at 76 weeks

Secondary Endpoints

- Mean change from baseline in brain tau deposition, iADRS, MMSE, ADAS-Cog14, & ADCS-iADL vs. placebo at 76 weeks

Open-label Extension

- Patients may continue into an optional OLE for 96 weeks

[1] Presented at: The 2024 AAIC Annual Meeting; July 28, 2024; Philadelphia, PA.
[2] Standard bFluid-based biomarkers include total tau, p181tau, p217tau, Aβ [1-42], Aβ [1-40], neurofilament light chain, and glial fibrillary acidic protein.
AD, Alzheimer's disease; ADAS-Cog14,14-item Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-iADL, Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living Scale; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; IV, intravenous; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; OLE, open-label extension; PET, positron emission tomography; Q4W, every 4 weeks.

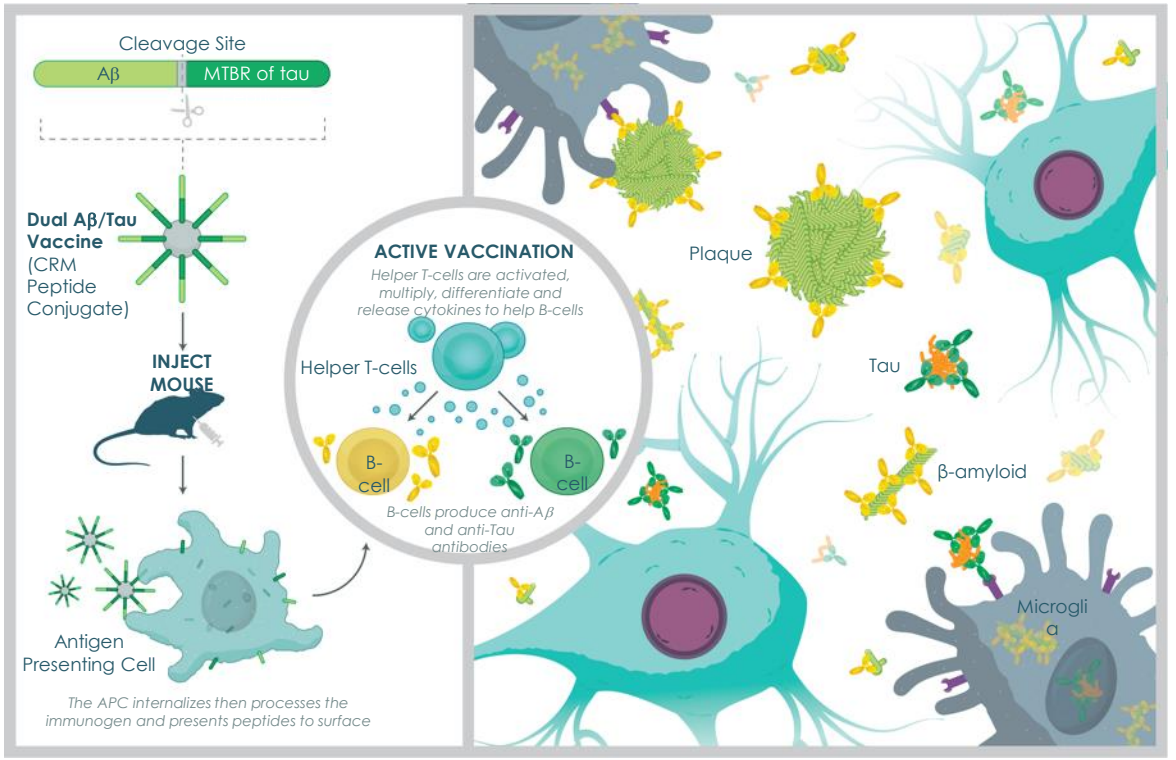
PRX123

Alzheimer’s Disease

Vaccine Constructs: Potential Best-in-class Dual Aβ/Tau Vaccine for the Treatment & Prevention of AD

PROTHENA IS PIONEERING THE DEVELOPMENT OF DUAL Aβ/TAU VACCINE CANDIDATE PRX123

- **Synergistic mechanism designed for increased efficacy over single-target vaccines**
  - Strong evidence from preclinical models suggests that Aβ and tau may act synergistically in the development of AD
  - Prothena's dual Aβ/tau vaccine program aims to induce optimal (quantity and quality) and balanced immune response to both targets, while avoiding cytotoxic t-cell response
- **Potential treatment & prevention**
  - Dual vaccine constructs were shown to generate balanced titers to Aβ and tau in non-human primates and Guinea pigs as measured by ELISA
  - The immune animal sera reacted to Aβ and tau, induced Aβ phagocytosis, and blocked tau interaction with a key mediator of cellular release and cell-to-cell transmission
- **IND cleared by FDA**
- **Fast Track designation granted by FDA**



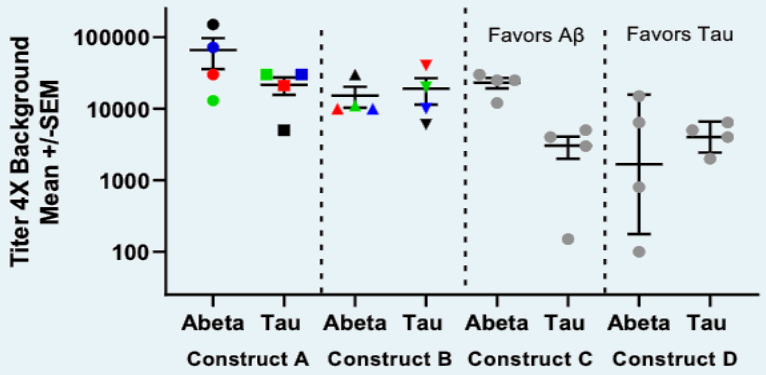
Desirable Attributes of Aβ/Tau Vaccines and Prothena's Design Strategies

		Design Strategy	Desirable Output
1 Quantity	**RESPONSE** Antibody levels, balanced Aβ/tau, persistency	• Linear peptides, proprietary cleavable linkers • Optimal carriers, immunization schedule, adjuvant	✓ Optimal antigen presentation with persistent immune response ✓ Overcomes immunodominance and immunosenescence
2 Quality	**EFFICACY** Isotypes, binding, Aβ clearance, tau neutralization	• Optimal Aβ and tau epitopes • Elements for induction of mature TH response	✓ Antibodies bind the right epitopes on pathogenic proteins ✓ IgG switch and affinity maturation
3 Safety	**SAFETY** Cytotoxic T-cell avoidance, target-specificity	• Short Aβ/tau epitopes not recognizable by cytotoxic T-cells • No off-target binding risk based on peptide sequences	✓ No cytotoxic T-cell responses ✓ Specific antibodies

Preclinical data presentation titles: Development of a Dual Aβ/Tau Vaccine for the Treatment and Prevention of Alzheimer's Disease presented at ADPD 2022

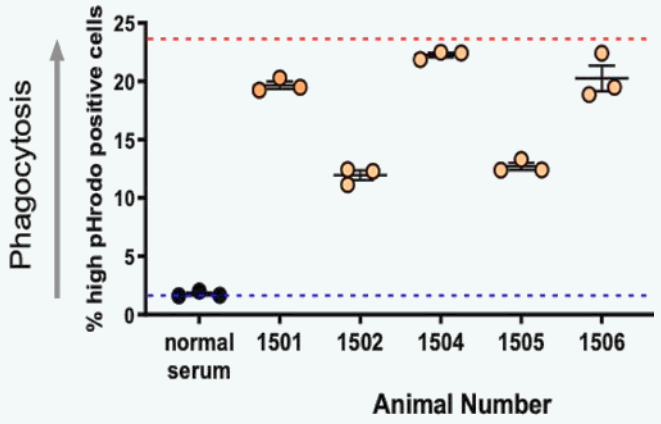
Prothena's Dual Aβ/Tau Vaccines Demonstrate Desirable Quantity, Quality and Safety

Quantity



✓ High, balanced, consistent

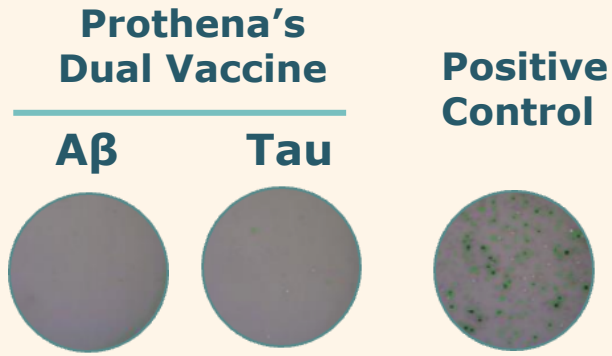
Quality



✓ Epitope, affinity, Aβ clearance, tau neutralization

Safety

Unable to induce measurable cytotoxic T-cell activity against Aβ and tau in Non-human primates (ELISpot)



✓ Avoids T-cell response observed in other vaccines

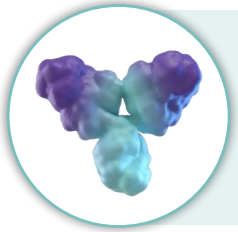
Preclinical data presentation titles: Development of a Dual Aβ/Tau Vaccine for the Treatment and Prevention of Alzheimer's Disease presented at ADPD 2022

prothena®

Birtamimab

AL Amyloidosis

Birtamimab: Differentiated Approach to AL Amyloidosis



Birtamimab
AL amyloidosis
Current Status: Phase 3

Anti-Amyloid Mechanism of Action

- Designed to neutralize toxic soluble species and clear insoluble AL amyloid deposits that cause vital organ dysfunction and failure[1-4]

Addresses Acute Unmet Need

- Patients with significant cardiac involvement are at high risk for early mortality[2]

Favorable Safety Profile

- Birtamimab was well tolerated with a favorable safety profile across multiple clinical trials[5]

Phase 3 AFFIRM-AL (NCT04973137): Ongoing[6]

- Trial designed per FDA Special Protocol Assessment (SPA) with unprecedented $P \leq 0.10$
- Primary Endpoint: Time to all-cause mortality
- Top-line results expected 1H 2025
- Potential Launch: 2026

Phase 3 VITAL: Post hoc analysis[7]

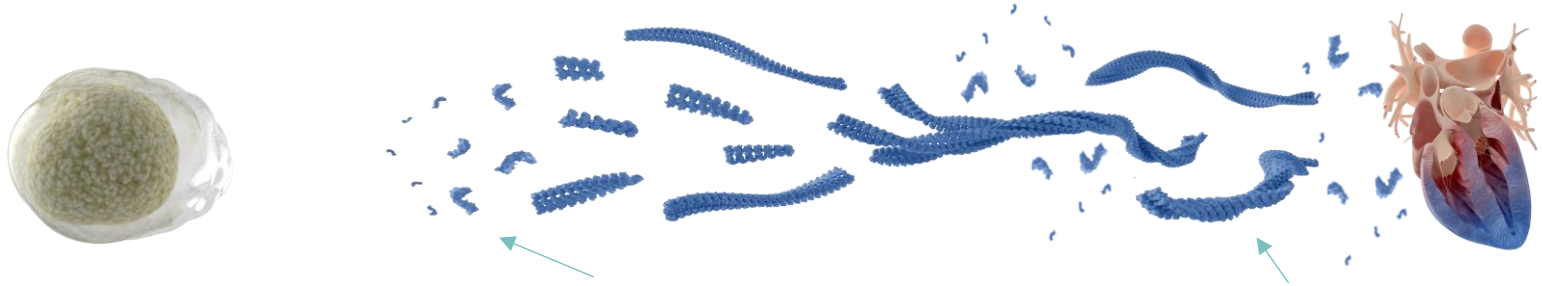
- Significant survival benefit in Mayo Stage IV
- Birtamimab + SoC reduced the risk of mortality by 59% compared to placebo + SoC (HR 0.413, $P = 0.021$)
- Rapid response with clear and sustained separation by month 2
- Meaningful improvement on measures of physical function and quality of life

HR=Hazard Ratio; SoC=Standard of care. Mayo Stage IV patients have all 3 biomarkers elevated: NT-proBNP (≥1,800 pg/mL); cTnT (≥0.025 ng/mL); dFLC (≥180 mg/dL).

[1] Murine version of birtamimab, 2A4
[2] Palladini G, et al. *Leukemia & Lymphoma*. 2024;1–11. [3] Wall JS, Kennel SJ, Williams A, et al. *PLoS One*. 2012;7(12):e52686. [4] Renz M, Torres R, Dolan PJ, et al. *Amyloid*. 2016;23(3):168-177. [5] Sanchorawala V, et al. Pooled analysis of safety from birtamimab Phase 1-3 studies in patients with light chain (AL) amyloidosis. Presented at the 65th ASH Annual Meeting; December 9-12, 2023; San Diego, CA, USA. [6] Gertz MA, et al. Birtamimab in patients with Mayo stage IV AL amyloidosis: Rationale for confirmatory affirm-AL phase 3 study. Presented at: The 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, USA. [7] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218.

Abnormal Light Chains Deposit As Amyloid in Vital Organs, Most Commonly the Heart[1]

AL Amyloidosis Pathogenic Pathway



PLASMA CELL DYSCRASIA[1,2]

SOLUBLE TOXIC LIGHT CHAIN AGGREGATES[2,3]

INSOLUBLE AMYLOID DEPOSITS[2]

CARDIAC DYSFUNCTION & EARLY MORTALITY[2,3]

Light chains misfold and aggregate[2,3]

Continuous accumulation of toxic amyloid in heart, other organs, and surrounding tissues leads to organ dysfunction and failure[1,3,4]

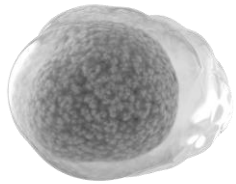
Early Disease[1] → ***Advanced Disease with Cardiac Involvement***[1,2,5]

Of Patients with Cardiac Involvement, the Most Severe Have Median Survival of <6 Months[6,7]

[1] Koike H, Katsuno M. *Molecules*. 2021;26(15):4611. [2] Merlini G. *Am Soc Hematol* Educ *Program*. 2017;2017:1-12. [3] Maritan M, Romeo M, Oberti L, et al. *J Mol Biol*. 2020;432:845-860. [4] Lavatelli F. *Hemato*. 2022;3(1):47-62. [5] Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis*. 2022;17(1):278. [6] Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995. [7] Kyle RA, Gertz MA, Greipp PR, et al. *N Engl J Med*. 1997;336(17):1202-1207.

Birtamimab's Anti-Amyloid Mechanism Designed to Address the Unmet Need for Patients

AL Amyloidosis Pathogenic Pathway[2-4]



PLASMA CELL DYSCRASIA



SOLUBLE TOXIC LIGHT CHAIN AGGREGATES

INSOLUBLE AMYLOID DEPOSITS



Current plasma cell directed treatments decrease light chain production[2]

Most patients today take some combination of daratumumab + CyBorD[1]

Birtamimab's transformative anti-amyloid MoA[1]:

- ✓ Clears AL amyloid deposits from organs/tissues
- ✓ Neutralizes toxic soluble aggregates

Birtamimab demonstrated significant survival benefit in Phase 3 VITAL post hoc analysis in Mayo Stage IV patients[5]

MOA=mechanism of action.
Current standard of care treatments include daratumumab and cyclophosphamide, bortezomib, and dexamethasone (CyBorD).
[1] Palladini G, et al. *Leukemia & Lymphoma*. 2024;1–11. [2] Merlini G. *Am Soc Hematol* Educ *Program*. 2017;2017:1-12. [3] Koike H, Katsuno M. *Molecules*. 2021;26(15):4611. [4] Maritan M, Romeo M, Oberti L, et al. *J Mol Biol*. 2020;432:845-860. [5] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218.

Birtamimab Designed to Address Unmet Need

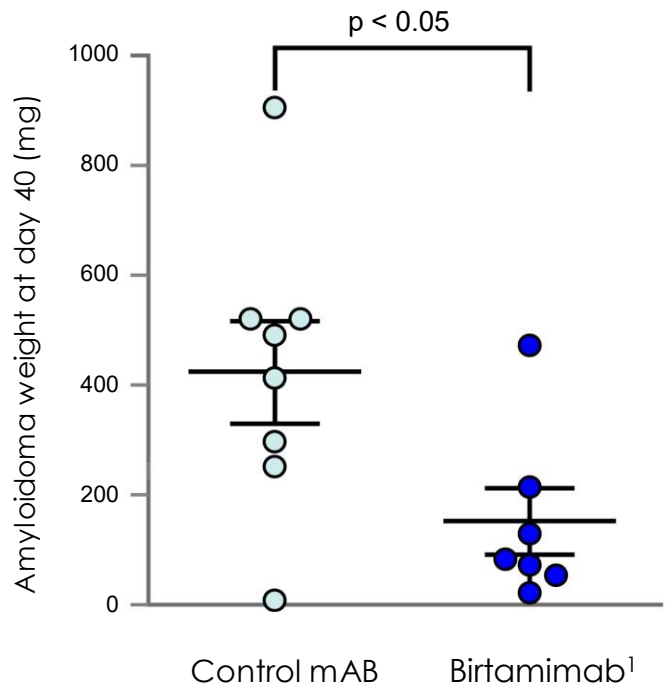
	Birtamimab[1,2] (Prothena)	CAEL-101[3-5] (AZ/Alexion)	Daratumumab[1,6,7] (Janssen)
Anti-Fibril mAb	✓	✓	✗
Demonstrated Early Survival Benefit in a Randomized Clinical Trial[8]	✓	✗	✗
MOA: Clears Insoluble Deposits	✓	✓	✗
MOA: Neutralizes Soluble Aggregates	✓	?	✗
Monthly Dosing	✓	✗	✗
Humanized	✓	✗	✓

Addition of Birtamimab could significantly improve survival in patients with cardiac involvement[2]

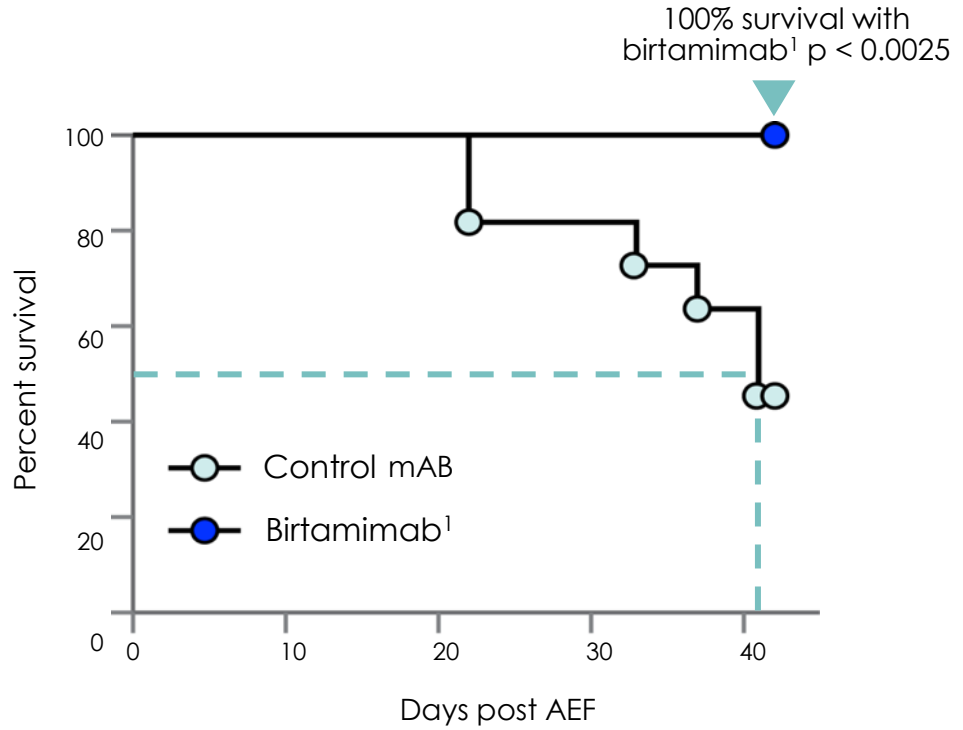
[1] Palladini G, et al. *Leukemia & Lymphoma*. 2024;1–11. [2] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218. [3] Edwards CV, Rao N, Bhutani D, et al. *Blood*. 2021;138(25):2632-2641. [4] Hughes MS, et al. Updated OS of patients with AL amyloidosis after CAEL-101. Presented at: The 2023 ASCO Annual Meeting; June 2-6, 2023; Chicago, IL, USA. [5] Valent J, Silowsky J, Kurman MR, et al. *Blood* (2020) 136 (Supplement 1): 26–27. [6] Kastritis E, Palladini G, Minnema MC, et al. *N Engl J Med*. 2021;385(1):46-58. [7] Muchtar E, Dispenzieri A, Gertz MA, et al. *Mayo Clin Proc.* 2021;96(6):1546-1577.
[8] Post-hoc analyses demonstrated a significant survival benefit with birtamimab and meaningful improvements in QoL and functional capacity in patients at high risk for early mortality (Mayo Stage IV at baseline).

Birtamimab[1] Demonstrated Significant Amyloid Clearance and Prolonged Survival in Preclinical Model

Birtamimab[1] Removes Amyloid In Vivo



Birtamimab[1] Prolongs Survival in Transgenic Mouse Model



[1] murine version of birtamimab, 2A4
Wall et al., PLOS ONE, 2012, data on file

Phase 3 VITAL Trial Overview[1]

Global, randomized, double-blinded, placebo-controlled clinical trial

- Sample size and randomization
  - N=260
  - 1:1
- Key eligibility criteria
  - Confirmed diagnosis of AL amyloidosis
  - Newly diagnosed and treatment naïve
  - Cardiac involvement
- Treatment regimen
  - Birtamimab 24 mg/kg vs placebo, with concurrent standard of care (SoC) in both arms

- **Primary endpoint**
  - Composite endpoint of time to all-cause mortality or time to cardiac hospitalizations (≥90 days) as adjudicated by the Clinical Events Committee
- **Secondary endpoints**
  - Quality of life: SF-36v2 PCS
  - Functional capacity: 6MWT
- **Randomization stratification**
  - Mayo Stage I-II vs III-IV, renal stage I vs II-III and 6MWT distance < 300 m vs ≥ 300m

30% of patients enrolled in VITAL (N=77) were characterized as Mayo Stage IV at baseline

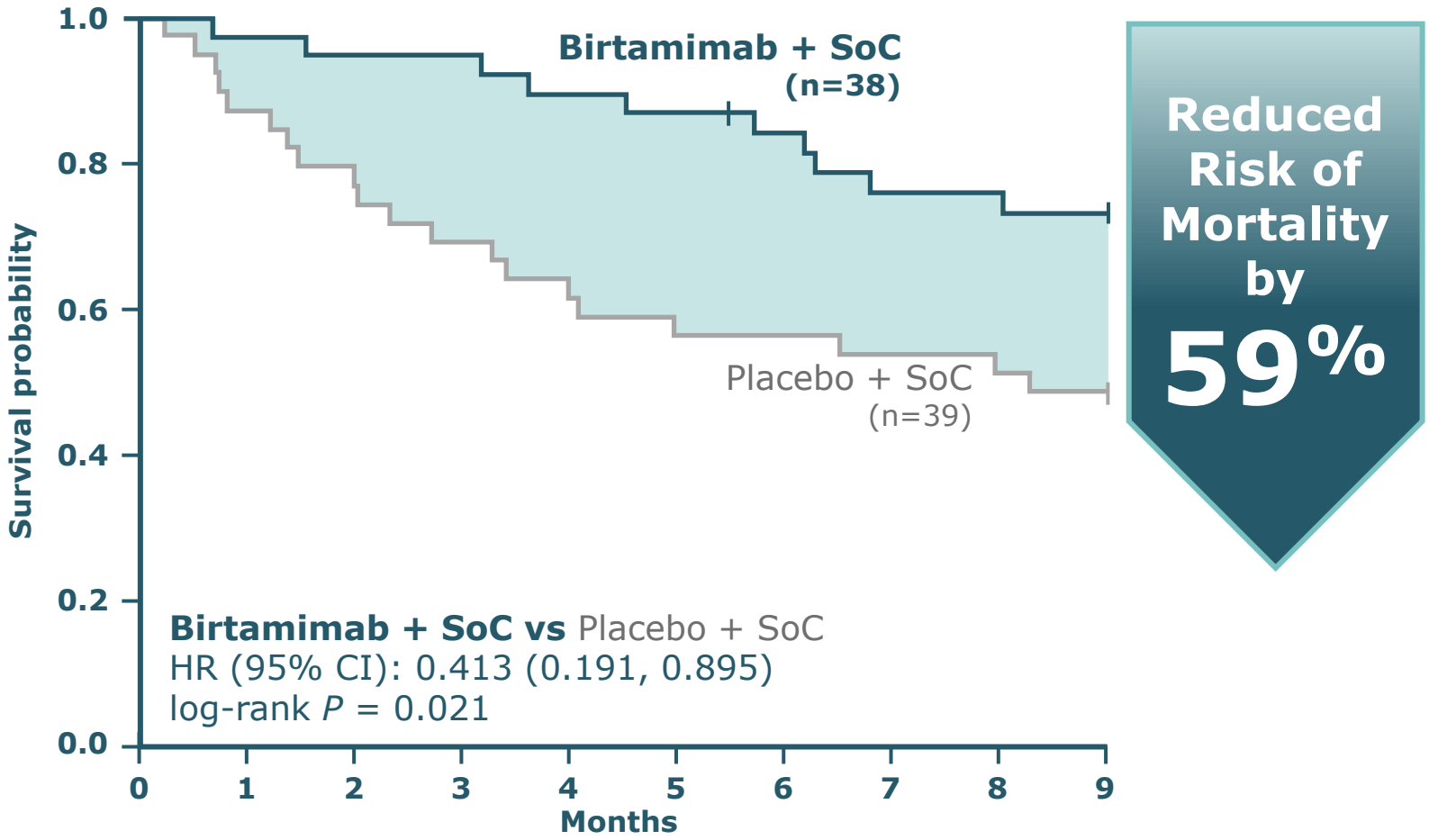
- 38 in birtamimab + SoC arm
- 39 in placebo + SoC arm

6MWT=6-Minute Walk Test; SF-36v2 PCS=Short Form-36 Physical Component Score.

[1] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218.

Previous Phase 3 VITAL Trial Demonstrated Significant Survival Benefit in Mayo Stage IV[1-2]

Time to All-Cause Mortality (ACM) in Mayo Stage IV Patients[3]



Post Hoc Analyses of Initial Phase 3 Randomized Trial (VITAL) in Mayo Stage IV Patients

Efficacy

- Unparalleled early and sustained survival benefit (HR = 0.413)
- Meaningful improvements in functional (6MWT) and quality of life (SF-36v2 PCS) endpoints, at 9 months ($P < 0.05$)

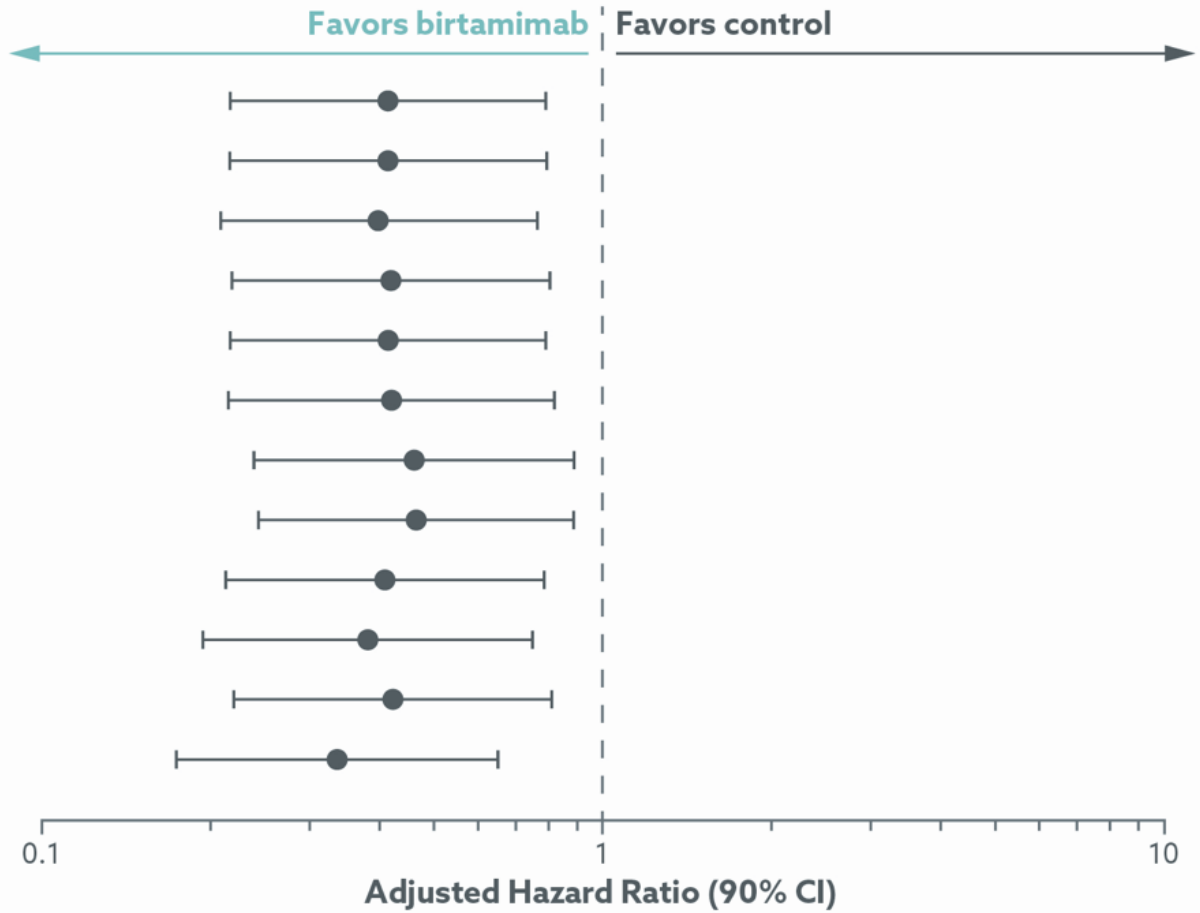
Safety

- Treatment-related grade ≥3 TEAE: 3% (birtamimab + SoC) vs 10% (placebo + SoC)
- Common treatment-emergent adverse event rate similar to placebo + SoC

[1] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218.
[2] Post hoc analyses demonstrated a significant survival benefit with birtamimab and significant improvements in QoL and functional capacity in patients at high risk for early mortality (Mayo Stage IV).
[3] Adapted from Gertz et al. *Blood*. 2023.

Birtamimab Survival Benefit Persists When Adjusted for Key Baseline Variables (Mayo Stage IV)[1-2]

Baseline variable	Adjusted HR
Age	0.414
Sex	0.415
Race	0.399
Ethnicity	0.419
Age at diagnosis	0.414
Duration since diagnosis (months)	0.420
NT-proBNP	0.460
dFLC	0.465
FLC	0.410
NYHA class	0.381
Troponin-T	0.422
6MWT distance	0.336



[1] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218.
[2] Adapted from Gertz et al. *Blood*. 2023.

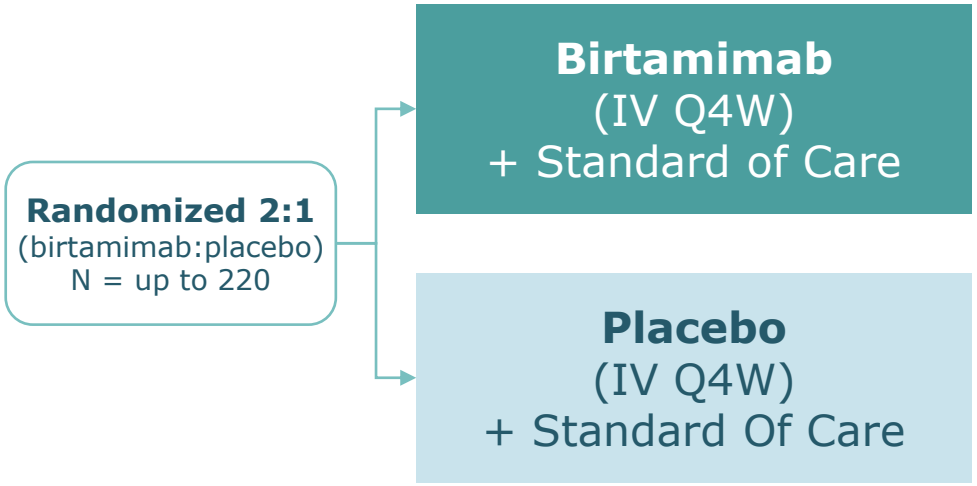
Birtamimab: Confirmatory Phase 3 AFFIRM-AL Trial Design

AFFIRM-AL Trial Overview (NCT04973137)[1]

Key Eligibility Criteria

- Confirmed diagnosis of AL amyloidosis
- Patients with significant cardiac involvement (Mayo Stage IV)

- ✓ **SPA Agreement**
- ✓ **FDA Fast Track Designation**
- ✓ **Orphan Drug Designation (FDA and EMA)**



Primary Endpoint

- Time to all-cause mortality

Secondary Endpoints

- 6MWT at month 9
- SF-36v2 PCS at month 9

SPA Agreement with FDA

- Based on VITAL results, SPA agreement with FDA at unprecedented $P \leq 0.10$

Mayo Stage IV patients have all 3 biomarkers elevated: NT-proBNP (≥1,800 pg/mL); cTnT (≥0.025 ng/mL); dFLC (≥180 mg/dL)
Standard of care was bortezomib-containing chemotherapy (required) +/- daratumumab (at investigator's discretion).

[1] Gertz MA, et al. Birtamimab in patients with Mayo stage IV AL amyloidosis: Rationale for confirmatory affirm-AL phase 3 study. Presented at: The 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, USA.

AL Amyloidosis Patients Require Urgent Treatment Upon Diagnosis[1,2]

PRESENTATION[2-3]

PCP

SYMPTOMS/SIGNS INCLUDE:

- Stiff heart
- Shortness of breath
- Blood pressure changes
- Kidney issues
- Weight loss
- Dizziness
- Fatigue
- Pain

DIAGNOSIS JOURNEY[2,4]

CARDIOLOGIST

NEPHROLOGIST

NEUROLOGIST

OTHER SPECIALISTS

TREATMENT[5]

HEMATOLOGIST/ONCOLOGIST

Normal Heart[6,10]



Amyloidosis Heart[7,11]

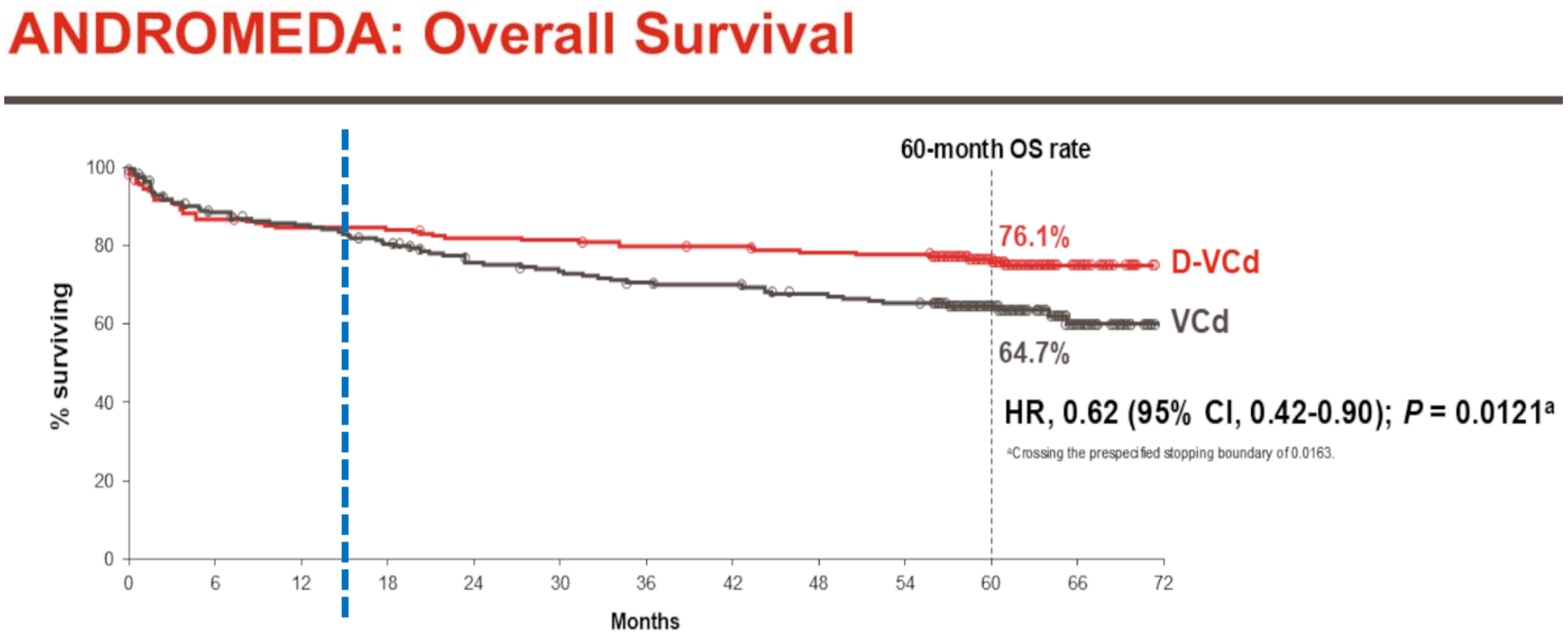


- Symptoms and signs of AL amyloidosis are common to many other conditions[1,3]
- Patients typically see a variety of specialists on their journey to diagnosis[4,5]
- Definitive diagnosis usually not made until they meet with a hematologist/oncologist[2]
- By the time of diagnosis, patients have accumulated significant cardiac amyloid deposition[8,9]
- **Urgent treatment is required**, and hematologists/oncologists are the primary treaters with support from cardiologists[5]

[1] Milani P, Merlini G, Palladini G. *Mediterr J Hematol Infect Dis*. 2018;10(1):e2018022. [2] Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. *Adv Ther*. 2015;32(10):920-928. [3] Muchtar E, Dispenzieri A, Gertz MA, et al. *Mayo Clin Proc*. 2021;96(6):1546-1577. [4] Lousada I, et al. Amyloidosis Research Consortium Cardiac Amyloidosis Survey: Results From Patients With AL Amyloidosis and Their Caregivers. Presented at: The 22nd European Hematology Association Congress; June 22-25, 2017; Madrid, Spain. [5] Stern LK, Patel J. *Methodist Debakey Cardiovasc J*. 2022;18(2):59-72. [6] Basso C, Michaud K, d'Amati G, et al. *Virchows Arch*. 2021;479(1):79-94. [7] Seward JB, Casaclang-Verzosa G. *J Am Coll Cardiol*. 2010;55(17):1769-1779. [8] Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis*. 2022;17(1):278. [9] Muchtar E, Gertz MA, Kyle RA, et al. *Mayo Clin Proc*. 2019;94(3):472-483.
[10] Adapted from Basso, et al. *Virchows Arch*. 2021.
[11] Adapted with permission from Seward JB, et al. *J Am Coll Cardiol*. 2010.

Unmet Need: Early Mortality

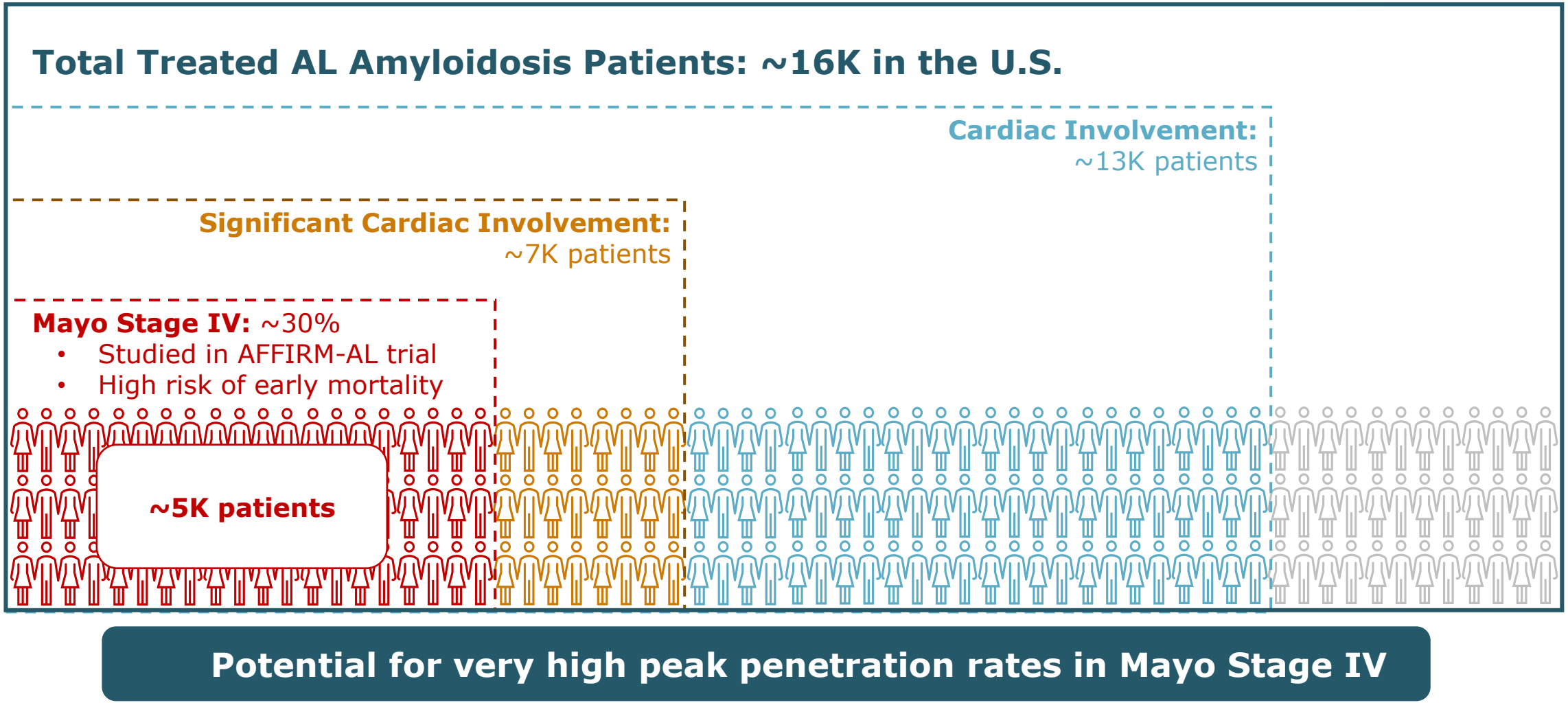
Phase 3 ANDROMEDA Study: *Daratumumab (D) + Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) in AL Amyloidosis Patients*[1]



Highlights urgent need to increase early survival for patients with cardiac involvement

[1] Adapted from presentation by E Kastritis at the 66th American Society of hematology (ASH) Annual Meeting & Exposition; December 7-10; San Diego, CA USA; dotted blue line and takeaway comment added by Prothena

Established Market: Significant opportunity of currently treated patients with high unmet need[1-6]



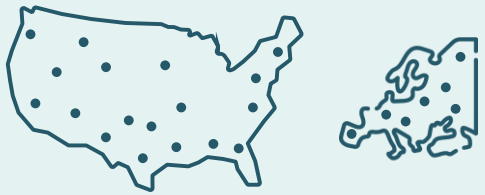
Potential for very high peak penetration rates in Mayo Stage IV

Mayo Stage IV patients have all 3 biomarkers elevated: NT-proBNP (≥1,800 pg/mL); cTnT (≥0.025 ng/mL); dFLC (≥180 mg/dL)

[1] Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995. [2] Kyle RA, Gertz MA, Greipp PR, et al. *N Engl J Med*. 1997;336(17):1202-1207. [3] Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis*. 2022;17(1):278. [4] Merlini G, *Blood*. 2012; 119 (19): 4343–4345. [5] Gertz MA, et al. *Blood*. 2023;142(14):1208-1218. [6] Market research and data on file. Prothena Biosciences. Brisbane, CA.

Established Patient Population and Consolidated Prescriber Base Enable Birtamimab Market Penetration with Focused Launch

Established Patient Population[1-6]



Treated AL amyloidosis patients with cardiac involvement:

- US (~13K) and EU (~15K)

Mayo Stage IV patients:

- US (~5K) and EU (>5K)

Consolidated Prescriber Base[6]



- ~75% US + EU patients primarily treated in ~500 amyloidosis specialty centers
- Birtamimab would be administered as an in-office infusion treatment
- Relatively favorable safety profile[7]

Regulatory and IP Positioning



- ✓ SPA agreement with FDA
- ✓ FDA Fast Track designation
- ✓ FDA/EMA: Orphan Drug Designation
- ✓ ≥12 years U.S. market exclusivity
- ✓ ≥10 years E.U. market exclusivity

Focused Opportunity and Commercial Approach

EU: References the top 5 European markets including the United Kingdom, Germany, France, Spain and Italy.

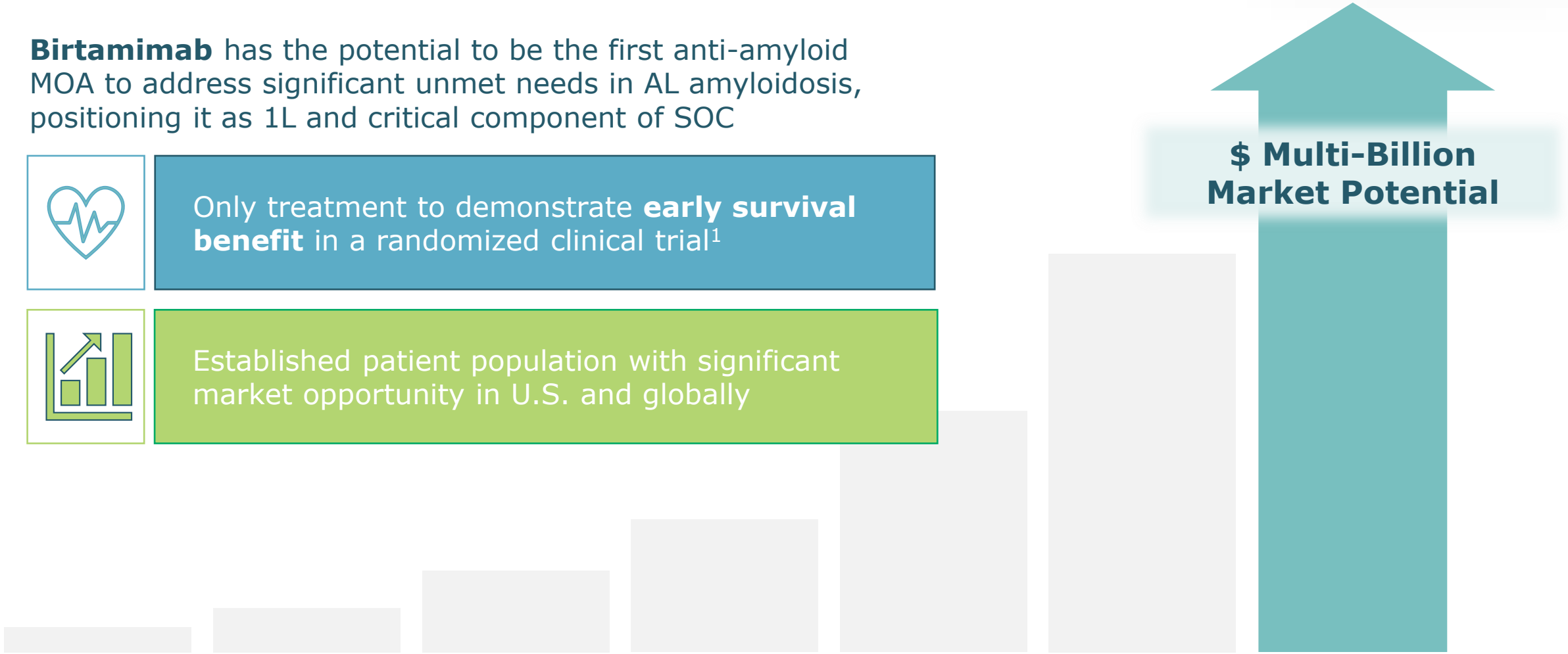
[1] Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995. [2] Kyle RA, Gertz MA, Greipp PR, et al. *N Engl J Med.* 1997;336(17):1202-1207. [3] Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis*. 2022;17(1):278. [4] Merlini G, *Blood*. 2012; 119 (19): 4343–4345. [5] Gertz MA, et al. *Blood*. 2023;142(14):1208-1218. [6] Market research and data on file. Prothena Biosciences. Brisbane, CA. [7] Sanchorawala V, et al. Pooled analysis of safety from birtamimab Phase 1-3 studies in patients with light chain (AL) amyloidosis. Presented at the 65th ASH Annual Meeting; December 9-12, 2023; San Diego, CA, USA.

Birtamimab: Global Commercial Opportunity

Birtamimab has the potential to be the first anti-amyloid MOA to address significant unmet needs in AL amyloidosis, positioning it as 1L and critical component of SOC

Only treatment to demonstrate **early survival benefit** in a randomized clinical trial[1]

Established patient population with significant market opportunity in U.S. and globally



[1] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218; Post-hoc analyses demonstrated a significant survival benefit with birtamimab and meaningful improvements in QoL and functional capacity in patients at high risk for early mortality (Mayo Stage IV at baseline).
*graphics for illustrative purposes only

Prasinezumab
Parkinson's Disease

Worldwide Collaboration with Roche

Prasinezumab: Potential First-in-Class Treatment for Parkinson's Disease

Prasinezumab
Parkinson's Disease

Current Status: Phase 2b Complete

Anti-α-synuclein Antibody

- Preferentially binds to aggregated α-synuclein, designed to reduce pathogenic spread and decrease synuclein pathology[1]

Rapidly Growing Parkinson's Patient Population

- 10 million patients globally[2]
- Fastest increasing neurodegenerative disease[3]

Worldwide Collaboration with Roche

- Up to $620 million in additional milestones
- $135 million paid-to-date
- Up to double-digit teen royalties
- US co-promote option

Phase 2 Clinical Development Program:

- First anti-a-synuclein antibody to slow progression on measures of PD
- Consistent positive trends across multiple endpoints observed in both Phase 2b PADOVA (NCT04777331) and Phase 2 PASADENA (NCT03100149) trials
- More pronounced efficacy observed in population treated with levodopa in the Phase 2b PADOVA trial (~75% of participants)

Next Steps:

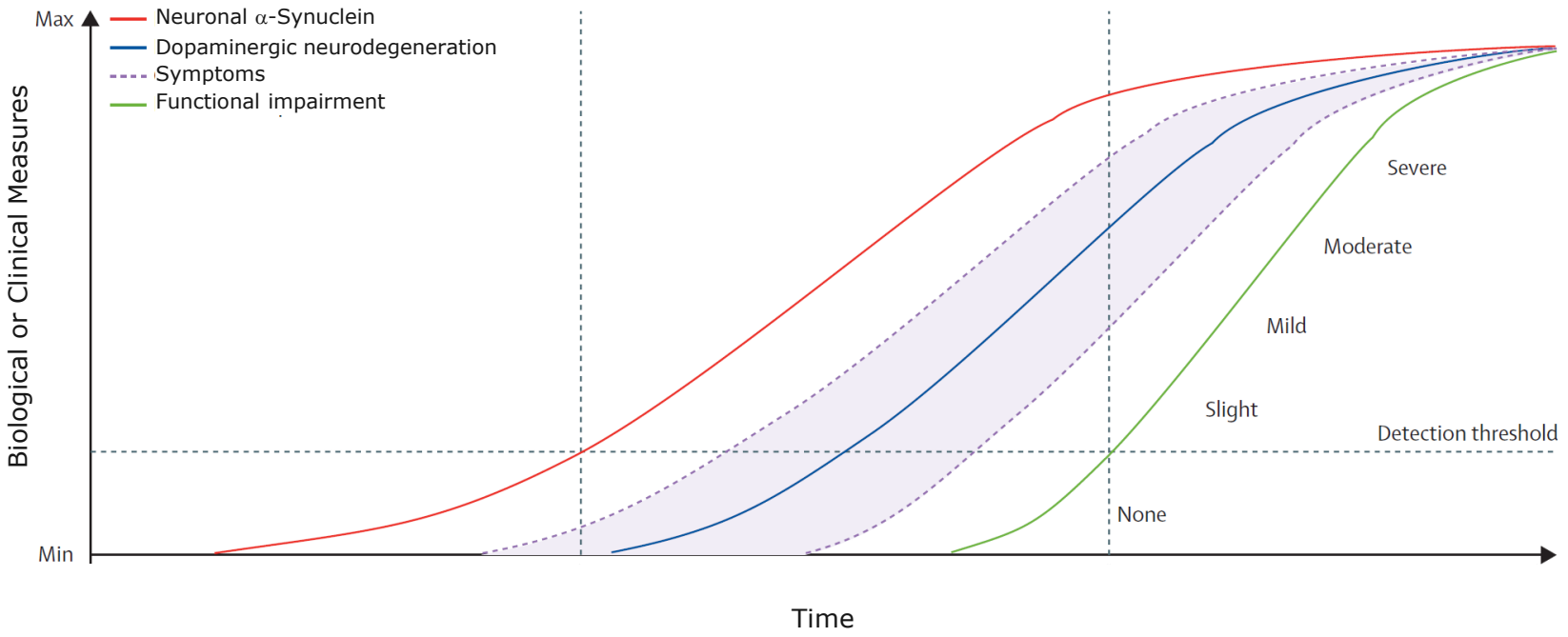
- Open-label extension studies from both PADOVA and PASADENA ongoing to explore the observed effects
- PASDAENA OLE showed slowing of motor progression vs. matched RWD PPMI cohort[4]
- Roche will continue to evaluate the data and work together with health authorities to determine next steps

MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; RWD: Real World Data; PPMI: Parkinson's Progression Markers Initiative.
[1] Jankovic J et al. *JAMA Neurol*. 2018; 75:1206–1214; [2] Parkinson's Foundation. Understanding Parkinson's. Statistics; [3] GBD 2015 Neurological Disorders Collaborator Group (2017) Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol* 16, 877-897. [4] Pagano G et al. Sustained effect of prasinezumab on Parkinson's disease motor progression in the open-label extension of the PASADENA trial. *Nat Med* (2024)

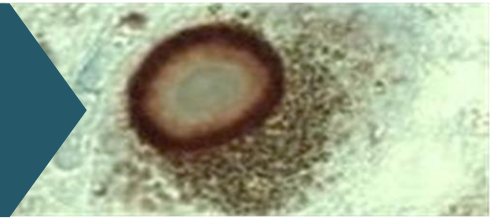
α-Synuclein Pathology is Strongly Implicated in Parkinson's Disease

Accumulation of α-Synuclein is a predominant neuropathological feature and follows the topological progression of disease

Genetically validated target with evidence favoring a prominent role for α-Synuclein in early PD: missense mutations and duplication/triplication



α-Synuclein is the predominant component of Lewy bodies found in Parkinson's disease and other synucleinopathies



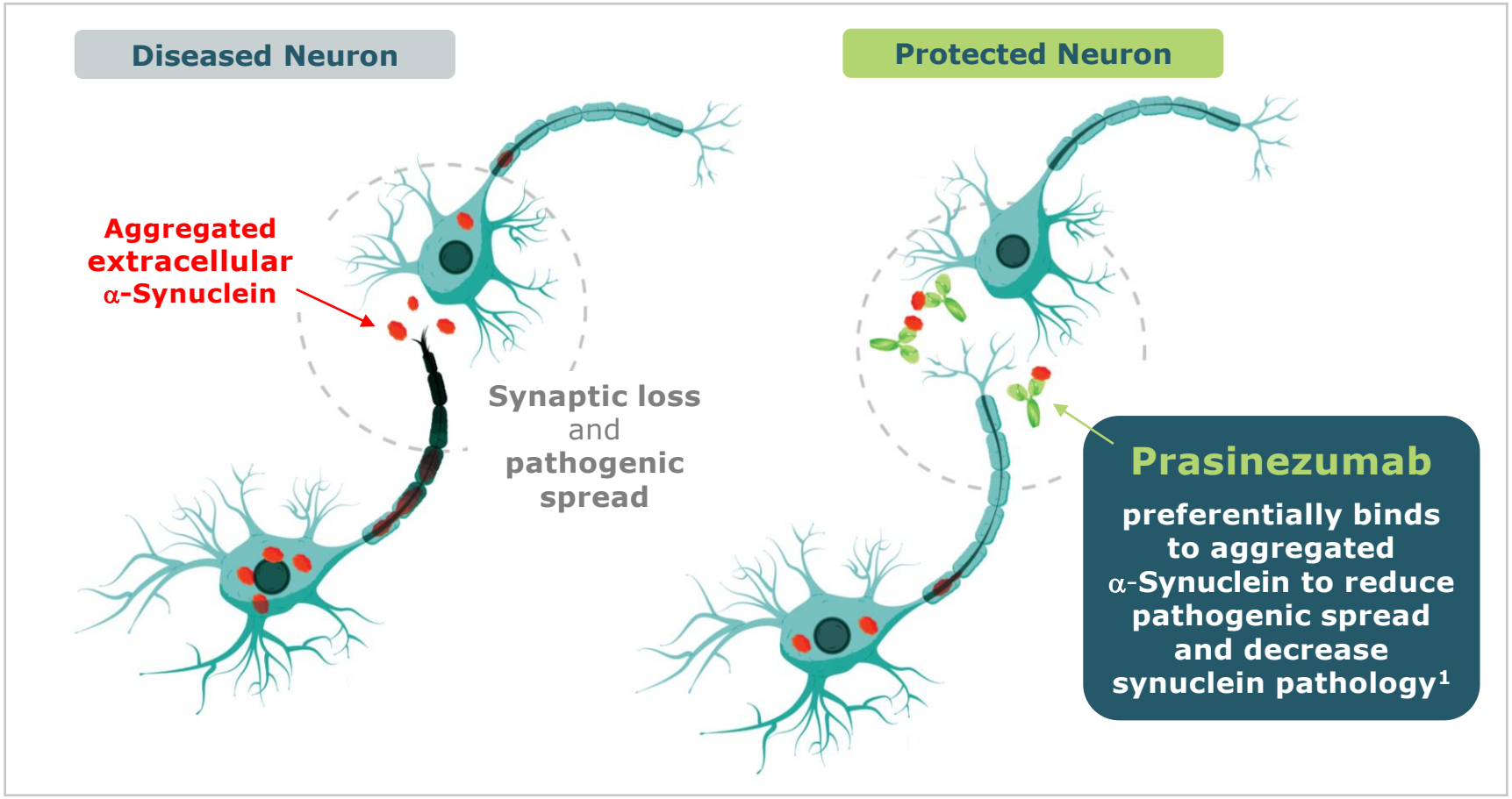
Symptoms: Clinical signs or symptoms attributable to neuronal α-Synuclein disease that can be motor or non-motor (e.g., hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety).
Functional Impairment: Degree of impact on activities of daily living.
Chart adapted from: Simuni, Tanya et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. *Lancet Neurol* 2024.

Prasinezumab: α-Synuclein Immunotherapy

REDUCE NEURONAL TOXICITY AND PREVENT CELL-TO-CELL TRANSMISSION[1]

α-Synuclein as an extracellular target during pathogenesis

- Caudal-rostral staging, host-to-graft transfer, various propagation models



[1] Proposed mechanism of action.

Prasinezumab: Clinical Development Program for Early Parkinson's Disease

prothena®

Phase 2 PASADENA (NCT03100149)

- N=316, randomized 1:1:1 (1500 mg, 4500 mg, placebo), Q4W IV dosing for 52 weeks (Part 1), followed by a 52-week extension (Part 2)
- **Study Population:** Hoehn & Yahr Stage I or II
  - H&Y Stage I = 24.7%
  - H&Y Stage II = 75.3%
  - **Age:** 40 – 80 years; mean = 59.9 years
  - **Time from diagnosis:** ≤ 2 years; mean = 10.1 months
  - **Concomitant medication:** Treatment naïve or stable dose of MAO-B inhibitor and not expected to change within 52 wks

Primary Endpoint:

- Change from baseline at Week 52 in MDS-UPDRS sum of Parts I + II + III vs. placebo

Phase 2b PADOVA (NCT04777331)

- N=586, randomized 1:1 (1500 mg, placebo), Q4W IV dosing for at least 76 weeks and confirmed number of events[1]
- **Study Population:** Hoehn & Yahr Stage I or II
  - H&Y Stage I = 13.8%
  - H&Y Stage II = 85%[2]
  - **Age:** Age 50 to 85 years; mean = 64.2 years of age
  - **Time from diagnosis:** ≤ 3 years; mean = 18.6 months
  - **Concomitant medication:** On a stable dose of levodopa or MAO-B inhibitor for ≥3 months prior to baseline

Primary Endpoint:

- Time to confirmed motor progression event (≥5 point increase in MDS-UPDRS Part III score from baseline)

PADOVA study population more advanced than the PASADENA population

PADOVA to focus on evaluation of motor progression as measured by MDS-UPDRS Part III

[1] At least 76 weeks and ≥248 events of confirmed motor progression (≥5 point on MDS-UPDRS Part III)
[2] 7 patients were randomized in PADOVA with H-Y Stage III.
Source: Pagano et al. *A study to evaluate the efficacy and safety of intravenous prasinezumab in participants with early Parkinson's disease (PADOVA): Rationale, design, and baseline data.* Presented at the AD/PD™ 2024 International Conference on Alzheimer's and Parkinson's Diseases in Lisbon, Spain. March 5-9, 2024.

Phase 2b PADOVA Trial Summary of Results

PRASINEZUMAB IN EARLY PARKINSON'S DISEASE

- **First anti-α-synuclein antibody to slow progression on measures of PD**
  - ✓ Prasinezumab showed potential clinical effect in the primary endpoint of time to confirmed motor progression with a HR=0.84 [0.69-1.01] and p=0.0657
  - ✓ The effect of prasinezumab was more pronounced in a pre-specified analysis in the population treated with levodopa (75% of participants), HR=0.79 [0.63-0.99] and nominal p=0.0431
  - ✓ Pre-specified supplementary covariate-adjusted[1] analyses of these endpoints demonstrated nominally significant effects:
    - Primary endpoint (HR=0.81 [0.67-0.98]; nominal p=0.0334)
    - Primary endpoint/levodopa subgroup (HR=0.76 [0.61-0.95]; nominal p=0.0175)
  - ✓ Consistent positive trends across multiple secondary and exploratory endpoints were also observed
- Prasinezumab generally safe and well-tolerated

Results support the potential of prasinezumab to slow underlying disease pathophysiology and clinical decline in patients with PD

[1] Covariates used for adjustment: Medication at baseline, H&Y stage, DaT-SPECT, Age, Sex, Baseline dependent parameter

Phase 2 PASADENA Trial Summary of Results

PRASINEZUMAB IN EARLY PARKINSON'S DISEASE

- **First anti-α-synuclein antibody to slow progression on measures of PD**
  - ✓ Part 1: **35% less progression** vs. placebo at **1 year** on MDS-UPDRS Part III[1]
    - Greater slowing of motor progression in subpopulations of individuals with rapidly progressing disease[2]
  - ✓ Part 2: **Less progression** on MDS-UPDRS Part III in early-start vs. delayed-start group at 2 years[3]
  - ✓ OLE: **65% less progression** vs. matched RWD PPMI cohort at **4 years** on MDS-UPDRS Part III (OFF state) with early-start treatment group[3]
  - ✓ OLE: **118% less progression** vs. matched RWD PPMI cohort at **4 years** on MDS-UPDRS Part III (ON state) with early-start treatment group[3]
- Prasinezumab generally safe and well-tolerated

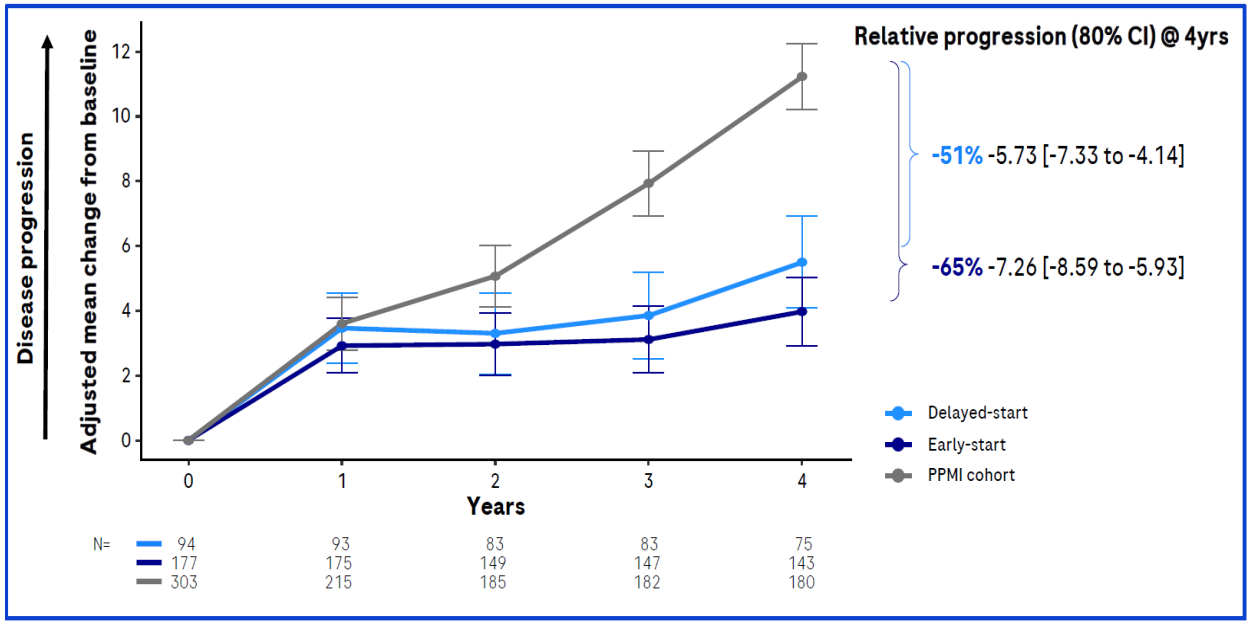
Results support the potential of prasinezumab to slow underlying disease pathophysiology and clinical decline in patients with PD

[1] Primary Endpoint: Change from baseline at Week 52 in MDS-UPDRS sum of Parts I + II + III vs. placebo; Pagano et al. *N Engl J Med* 2022;387:421-32. [2] Pagano, G., Taylor, K.I., Anzures Cabrera, J. et al. *Nat Med* 30, 1096–1103 (2024).
[3] Pagano et al. *Delayed start analysis of PASADENA: A randomised Phase II study to evaluate the safety and efficacy of prasinezumab in early Parkinson's disease; Part 2 Week 104 results.* Presented at the AD/PD™ 2022 International Conference on Alzheimer's and Parkinson's Diseases in Barcelona, Spain. March 15-20, 2022. [4] Compared prasinezumab population with a propensity score-balanced cohort of real-world data (RWD) Parkinson's Progression Markers Initiative (PPMI); Source: Pagano et al. *PASADENA long-term open-label extension continue to show reduced motor and functional progression in prasinezumab-treated individuals with early-stage Parkinson's disease compared to a real-world data arm.* Presented at the AD/PD™ 2024 International Conference on Alzheimer's and Parkinson's Diseases in Lisbon, Spain. March 5-9, 2024.

PASADENA Open-Label Extension

PRASINEZUMAB CONTINUED TO SLOW PROGRESSION OF MOTOR DEFICITS IN EARLY-STAGE PD

4-year change from baseline on MDS UPDRS Part III OFF score[1]



PASADENA: Open-Label Extension

Compared prasinezumab population with a propensity score-balanced cohort of real-world data (RWD) Parkinson's Progression Markers Initiative (PPMI)

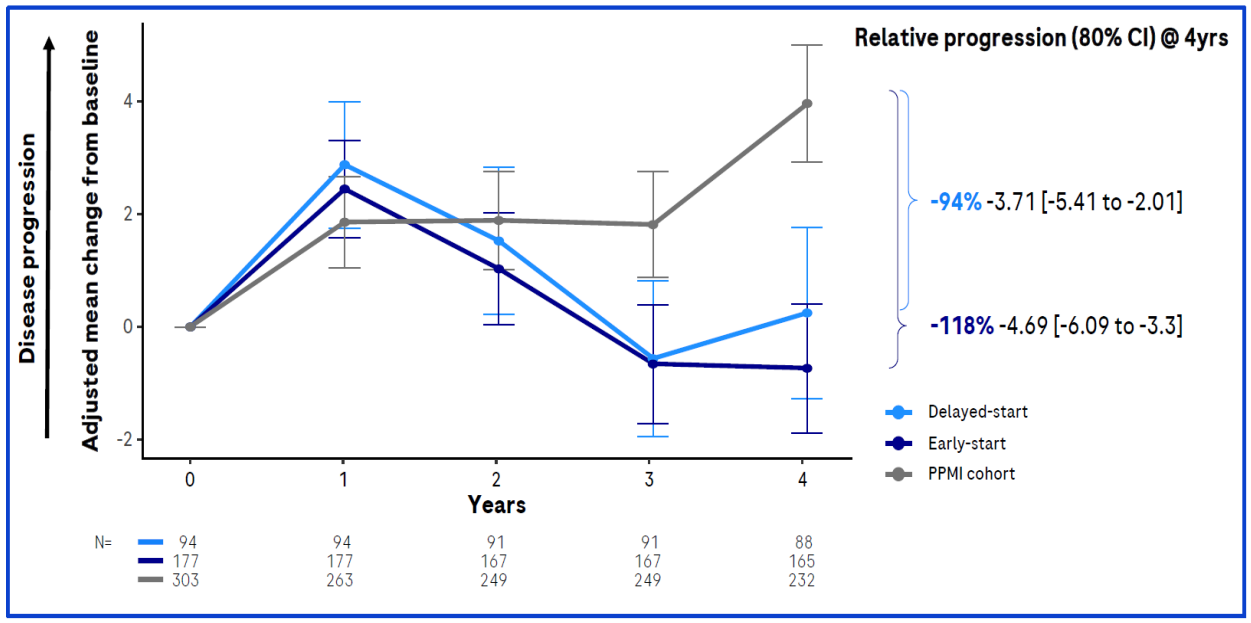
The data suggests that prasinezumab slowed the progression of motor deficits (MDS-UPDRS Part III OFF score) in early-stage Parkinson's disease

[1] CI, confidence interval; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative; RWD, real-world data.
Data from ongoing 5 year open-label extension trial with patients receiving 1500 mg dose of Prasinezumab Q4W IV dosing.
Source: Pagano G et al. Sustained effect of prasinezumab on Parkinson's disease motor progression in the open-label extension of the PASADENA trial. *Nat Med* (2024)

PASADENA Open-Label Extension

PRASINEZUMAB CONTINUED TO SLOW PROGRESSION OF MOTOR DEFICITS IN EARLY-STAGE PD

4-year change from baseline on MDS UPDRS Part III ON score[1]



PASADENA: Open-Label Extension

The data suggests that prasinezumab slowed the progression of motor deficits (MDS-UPDRS Part III ON score) in early-stage PD patients when receiving benefit from symptomatic treatment

[1] CI, confidence interval; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative; RWD, real-world data.
Data from ongoing 5 year open-label extension trial with patients receiving 1500 mg dose of Prasinezumab Q4W IV dosing.
Source: Pagano G et al. Sustained effect of prasinezumab on Parkinson's disease motor progression in the open-label extension of the PASADENA trial. *Nat Med* (2024)

Coramitug
(formerly PRX004)
ATTR Amyloidosis with Cardiomyopathy

ATTR Business Acquired by Novo Nordisk

Coramitug (formerly PRX004): Potential First-in-Class Treatment for ATTR-CM

Coramitug
ATTR amyloidosis with cardiomyopathy (ATTR-CM)

Current Status: Phase 2

Differentiated Depleter Mechanism of Action

- Designed to inhibit fibril formation and specifically bind to pathogenic TTR[1]
- Uniquely designed for patients at high risk of early mortality due to amyloid deposition

Worldwide Collaboration with Novo Nordisk

- $1.13 billion in potential additional milestones
- $100 million paid-to-date

Phase 2 Signal Detection Trial (NCT05442047): Ongoing

- N = ~99 ATTR-CM patients, 3 arms
- Participants receive IV infusion Q4W of 10 mg/kg or 60 mg/kg of coramitug or placebo added to SOC until week 52
- Co-primary Endpoints: Change from baseline in 6MWT and in NT-proBNP levels
- Trial completion expected in 1H 2025

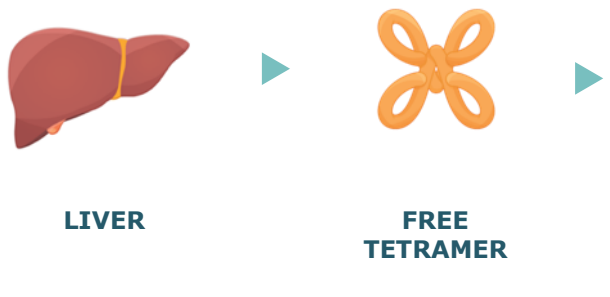
Phase 1 Trial:

- All six dose levels of coramitug found to be generally safe and well-tolerated
- Positive results on neuropathy and cardiac function
- Data supportive of advancing to Phase 2

[1] Higaki JN et al. *Amyloid*, 2016; Preclinical studies of mPRX004, the murine form of PRX004.

Differentiated Mechanism for ATTR-CM

NON-PATHOGENIC PATHWAY	PATHOGENIC PATHWAY



HEART
Restrictive cardiomyopathy
Heart failure

PERIPHERAL NERVES
Loss of sensation
Loss of reflex
Muscle weakness

Current Treatment Approach: Reduce new protein entering pathogenic pathway	**Coramitug:** Amyloid depletion Uniquely designed for patients at high risk of early mortality

Coramitug: Depleter MoA May Provide a New Treatment Paradigm for Patients at High-risk of Early Mortality Due to Amyloid Deposition

Higaki JN et al. Amyloid, 2016; Preclinical studies of mPRX004, the murine form of PRX004

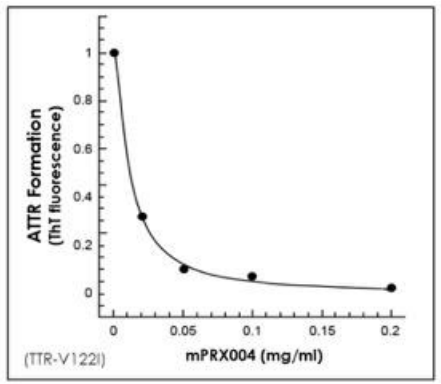
Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF mPRX004

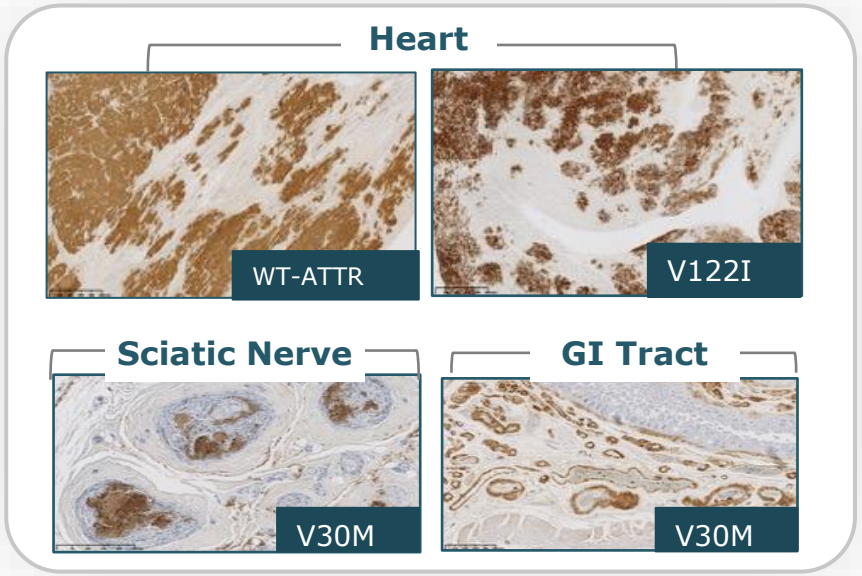
mPRX004 (murine form of PRX004) preclinical results:[1]

- ✓ Inhibits fibril formation
- ✓ Specifically binds to pathogenic TTR
- ✓ Reacts to amyloid deposits in multiple organs in both wtATTR and ATTRv patients
- ✓ Promotes in vivo ATTR amyloid clearance

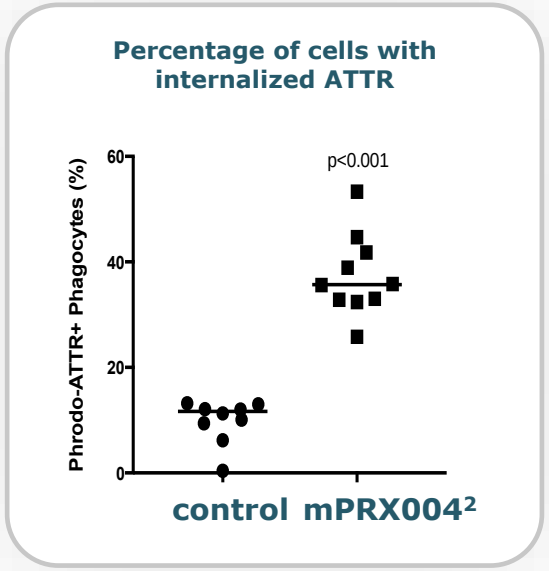
Inhibition of amyloid formation



Specific binding to amyloid



Clearance of amyloid



[1] Higaki JN et al. Amyloid, 2016; Preclinical studies of mPRX004, the murine form of PRX004
[2] mPRX004 = murine form of PRX004 (coramitug)

Upcoming Milestones

Meaningful Clinical Catalysts Ahead

Wholly-owned Programs

Birtamimab
AL Amyloidosis

2Q25	Topline results from confirmatory Phase 3 AFFIRM-AL with SPA agreement of $P \leq 0.1$ (NCT04973137)

PRX012 and PRX123
Alzheimer's disease portfolio

Mid-25 to YE25	Multiple data readouts starting in mid-2025 and continuing throughout the year from PRX012 Phase 1 ASCENT clinical trials
2025	Update on PRX123 clinical development

Partnered Programs

Coramitug (PRX004)
ATTR-CM

2025	Completion and results of ongoing Phase 2 trial (NCT05442047)

Prasinezumab
Parkinson's disease

2025	Roche to determine next steps

BMS-986446 (PRX005)
Alzheimer's disease

2027	Completion of ongoing Phase 2 trial (NCT06268886)

PRX019
Neurodegeneration

2026	Completion of ongoing Phase 1 trial

APPENDIX: Partnership and Collaboration Details

Bristol Myers Squibb Collaboration: Advancing Two Clinical Stage Programs

BMS Collaboration[1]: Up to $1.55 Billion + Royalties

- ☑ $365 million earned to date (includes $100 million upfront and $50 million equity purchase)
- ☐ $1.18 billion in additional milestones available ($562.5 million for BMS-986446 and $617.5 million for PRX019)

BMS-986446 (PRX005)

Status: Phase 2 Ongoing

- ☑ $135 million in option payments received
- ☐ $562.5 million in potential regulatory and commercial milestones
- ☐ Tiered Royalties

BMS leading and funding further development and commercial

PRX019[2]

Status: Initiate Phase 1 by YE24

- ☑ $80 million option exercised
- ☐ $242.5 million in potential development and regulatory milestones
- ☐ $375 million in potential commercial milestones
- ☐ Tiered Royalties

Prothena to conduct Phase 1

[1] BMS = Bristol Myers Squibb collaboration following its acquisition of Celgene in November 2019; total of up to $1.55 billion, including upfront payment and equity investment, future potential development, regulatory and commercial milestones, plus potential additional U.S. and global product sales royalties

[2] Future milestone and royalty payments would be reduced in the case where BMS is successful in developing a modified version of PRX019 that achieves certain specified improved metrics

Worldwide Collaboration with Roche

Total Milestones	prothena	Roche
	$755 million	**$--**
✓ Upfront, P1, P2 and P2b milestones	**$135 million**[1]	--
☐ Clinical, regulatory & first sale	$290 million	--
☐ U.S. sales milestones	$155 million	--
☐ Ex-U.S. sales milestones	$175 million	–
• U.S.	• Up to double digit teen royalties	• Leads clinical development
• U.S. co-promote	• Ability to opt-in	• Will lead commercialization
• Ex-U.S.	• Up to double digit teen royalties	• Sole responsibility to develop and commercialize

[1] Includes $60 million milestone announced in May 2021 from Roche as earned (received in June 2021)