



CORPORATE OVERVIEW

August 2024

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 2024, 2025, and beyond; 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, coramitug/PRX004, and prasinezumab; potential indications (including prevalence) and attributes of epitopes and antibodies we have identified in our programs; plans for ongoing and future clinical trials of PRX012, BMS-986446/PRX005, birtamimab, prasinezumab, coramitug/PRX004, PRX123, and PRX019; the expected timing of reporting data from clinical trials of birtamimab, PRX012, prasinezumab, and coramitug, including any updates regarding our ongoing Phase 1 clinical trial evaluating PRX012 in 2024 and any topline study results for our Phase 3 AFFIRM-AL clinical trial between 4Q 2024 and 2Q 2025; 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 August 8, 2024, and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. This overview is made as of August 8, 2024, and we undertake no obligation to update publicly any forward-looking statements contained in this press release 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



NEURODEGENERATIVE DISEASES



Alzheimer's disease (AD)

55 million

People worldwide living with Alzheimer's disease or other dementias¹

7th

Leading cause of death in United States¹

\$1 trillion

In annual US healthcare costs by 2050 from AD and other dementias¹



Parkinson's disease (PD)

10 million

People living with PD worldwide²

Fastest increasing

Neurodegenerative disease²

\$52 billion

In overall economic burden in the US²

RARE PERIPHERAL AMYLOID DISEASES



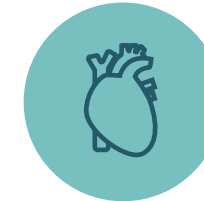
Amyloid light chain amyloidosis (AL)

60,000-120,000

Patients with Mayo Stage IV AL amyloidosis globally^{3,4}

5.8 months

Median overall survival in Mayo Stage IV patients with AL amyloidosis^{4,5}



Transthyretin amyloidosis (ATTR)

450,000

Estimated number of patients worldwide with wtATTR or ATTRv⁶⁻⁸

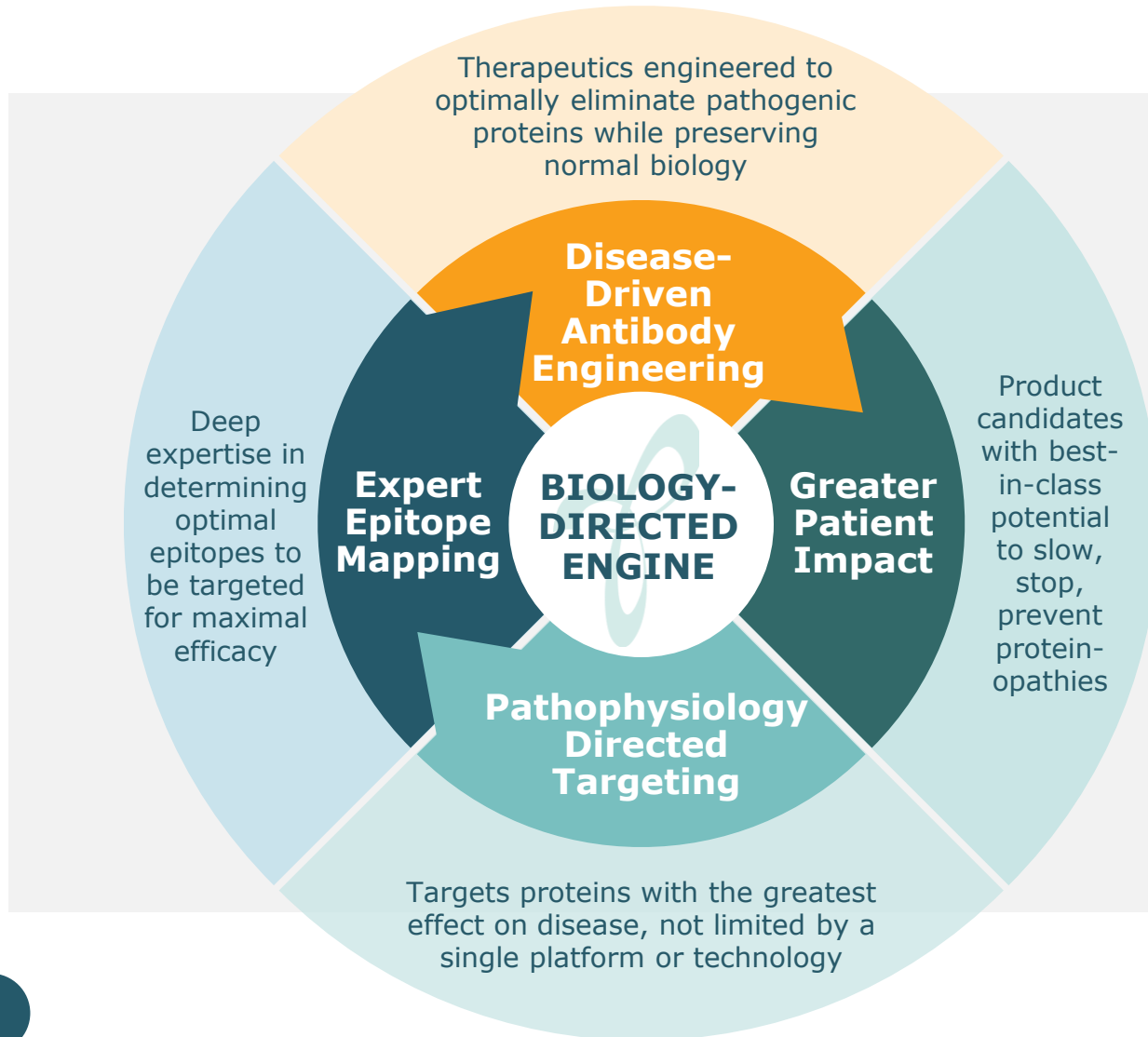
2.08 years

Median overall survival New York Heart Association class III patients with ATTR cardiomyopathy^{4,9}

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

¹ Long S, Benoit 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>. ² Parkinson's Foundation. Understanding Parkinson's. Statistics. Accessed July 17, 2024. <https://www.parkinson.org/understanding-parkinsons/statistics>. ³ Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis*. 2022;17(1):278. ⁴ Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995. ⁵ Kyle RA, Gertz MA, Greipp PR, et al. *N Engl J Med*. 1997;336(17):1202-1207. ⁶ González-Duarte A, Conceição I, Amass L, Botteman MF, Carter JA, Stewart M. *Neurol Ther*. 2020;9(1):135-149. ⁷ González-López E, Gagliardi C, Dominguez F, et al. *Eur Heart J*. 2017;38(24):1895-1904. ⁸ Tanskanen M, Peuralinna T, Polvikoski T, et al. *Ann Med*. 2008;40(3):232-239. ⁹ 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
- Wholly-owned Phase 1 program
- Two new INDs cleared by FDA

✓ **Strong Collaborations Established**

- Collaborations with Bristol Myers Squibb, Novo Nordisk¹ 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 <i>AL amyloidosis</i> SPA ¹ ODD ² Fast Track ³	Kappa & Lambda Light Chain	AFFIRM-AL (Phase 3)						
Prasinezumab <i>Parkinson's disease</i>	α-Synuclein (C-terminus)	PASADENA (Phase 2) PADOVA (Phase 2b)						
Coramitug (PRX004) <i>ATTR amyloidosis</i>	Transthyretin (misTTR)	Phase 2						
BMS-986446 (PRX005) <i>Alzheimer's disease</i>	Tau (MTBR)	Phase 2						
PRX012 <i>Alzheimer's disease</i> Fast Track ³	Aβ (N-terminus)	ASCENT (Phase 1)						
PRX123 <i>Alzheimer's disease</i> Fast Track ³	Aβ + Tau	IND cleared						
PRX019 <i>Neurodegeneration</i>	Undisclosed Target	IND cleared						
Undisclosed <i>AD in Down syndrome</i>	Undisclosed Target							

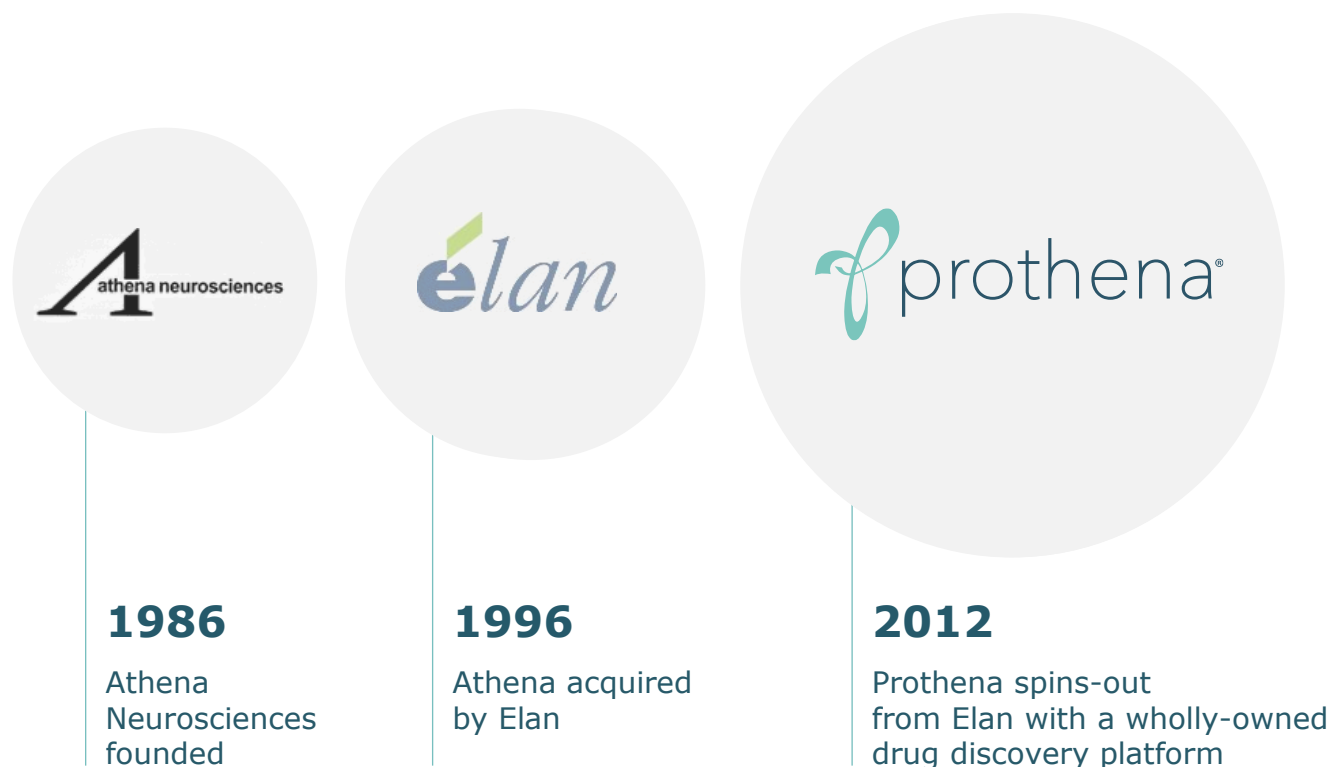
Modalities: mAb Small Molecule Vaccine

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



- ✓ **Pioneered fundamental discoveries** elucidating the roles of beta amyloid ($A\beta$), gamma secretase and beta secretase play in disease¹
- ✓ **First to show** that anti- $A\beta$ immunotherapy prevented and cleared amyloid plaques in the brains of transgenic mice²
- ✓ **First to demonstrate plaque clearance** by an n-terminus antibody in brains from AD patients³
- ✓ **Discovered biological cause of ARIA** and vascular recovery following anti- $A\beta$ immunotherapy⁴
- ✓ **Developed PRX012, best-in-class anti- $A\beta$ product candidate**, with $\sim 10X$ greater binding potency to fibrillar $A\beta$ vs. aducanumab⁵ and $\sim 20X$ greater binding potency against protofibrils vs. lecanemab⁶

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- $A\beta$ immunotherapy: Implications for amyloid-related imaging abnormalities. 2013 Alzheimers Dement. ⁵ PRX012 Induces Microglia-Mediated Clearance of Pyroglutamate-Modified and -Unmodified $A\beta$ 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...

Published: 09 February 1995

Alzheimer-type neuropathology in transgenic mice overexpressing V717F β -amyloid precursor protein

Published: 08 July 1999

Immunization with amyloid- β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Epub 2010 Feb 26.

^{11}C -PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

First published: 15 April 2013

Vascular alterations in PDAPP mice after anti-A β immunotherapy: Implications for amyloid-related imaging abnormalities

OUR LEGACY ¹⁻⁴

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



PRX012, anti-A β candidate with potential best-in-class, **highly potent binding**; designed for improved patient access via **subcutaneous** delivery⁵



Phase 1

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



Phase 2

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



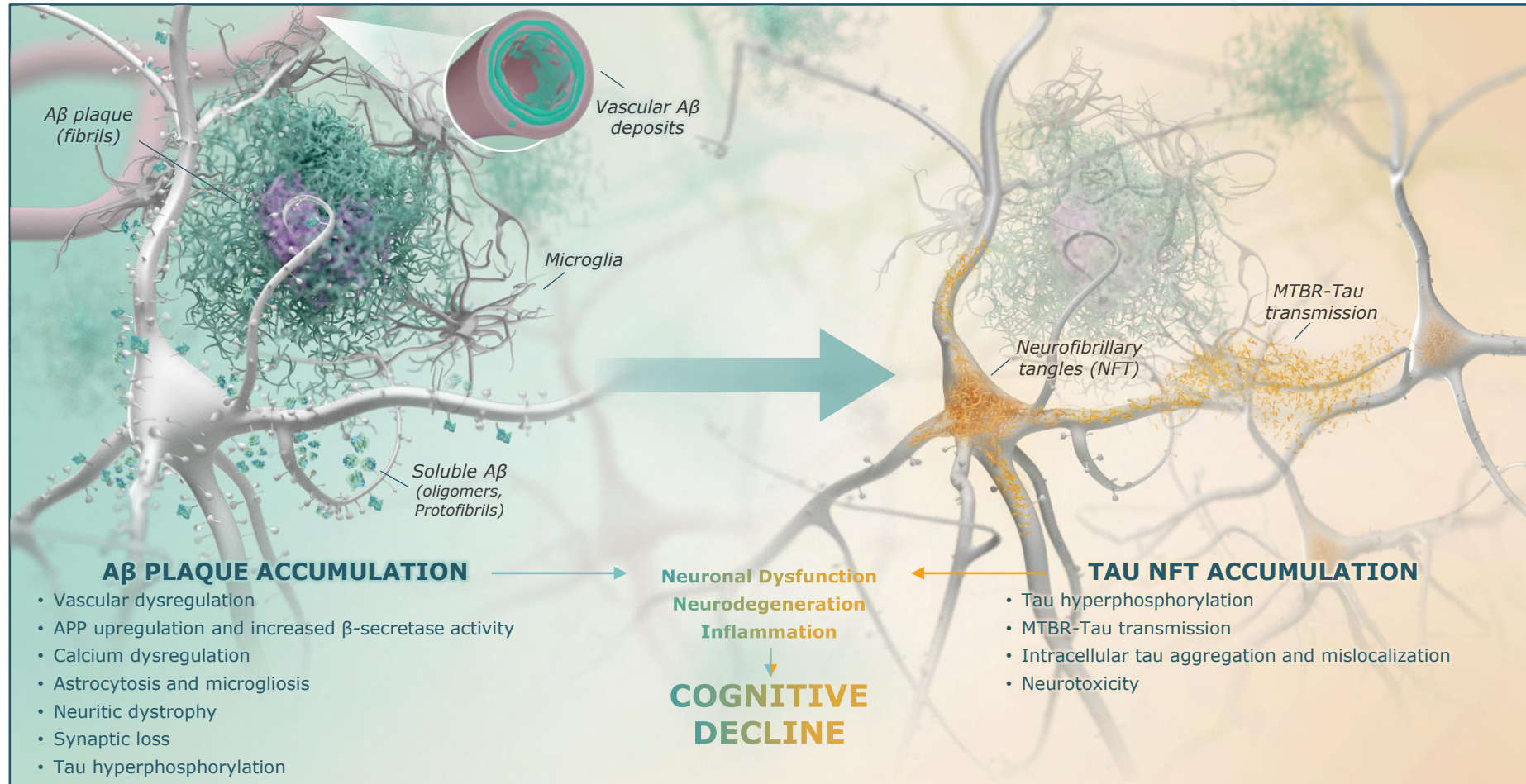
IND cleared

Targeting Alzheimer's Where it Matters

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

Reduction of A β plaque associated with clinically meaningful slowing of disease progression

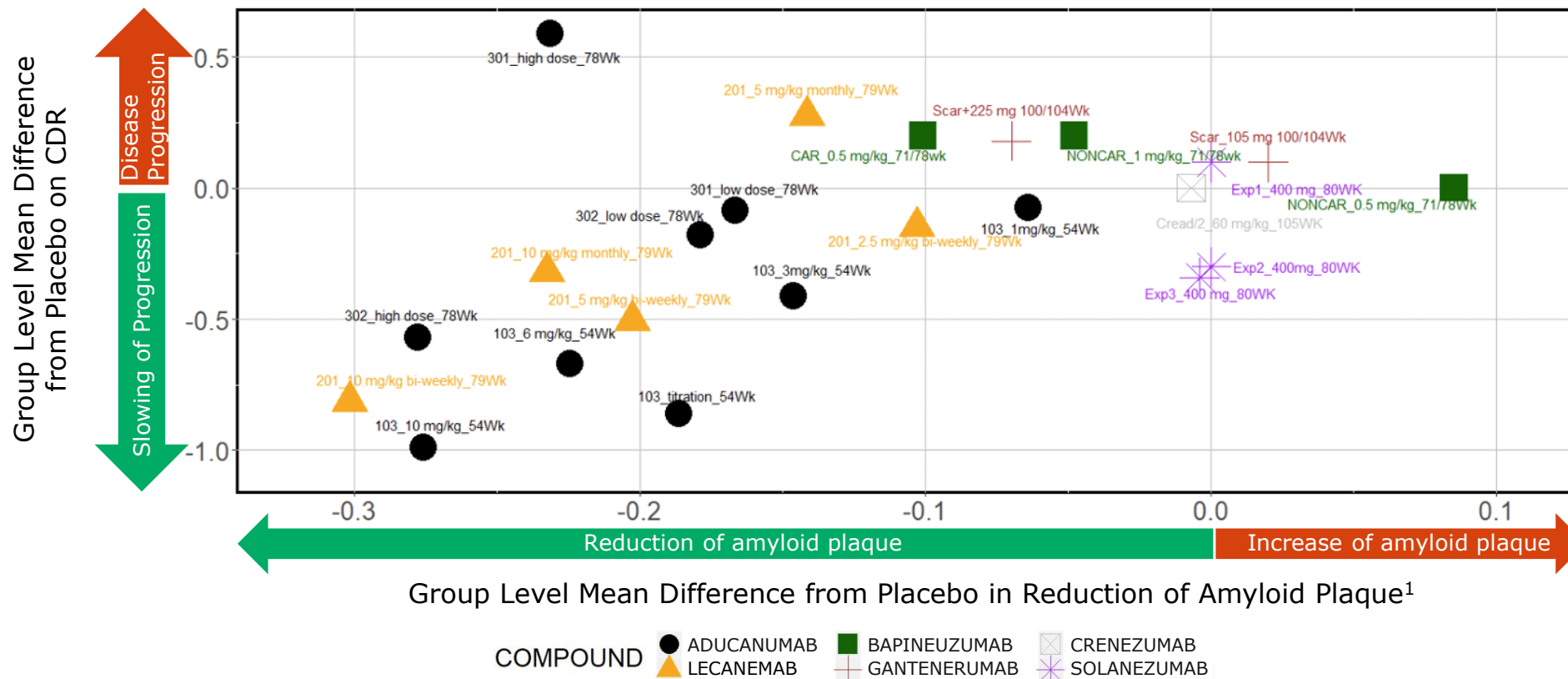
Presence of tau pathology strongly correlates with neurodegeneration and cognitive impairment in Alzheimer's disease



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



Mean Difference from Placebo in Reduction of Amyloid Plaque¹ and CDR-SB



2020 US FDA ANALYSIS: A β has been established as a disease modifying target in AD^{2,3}

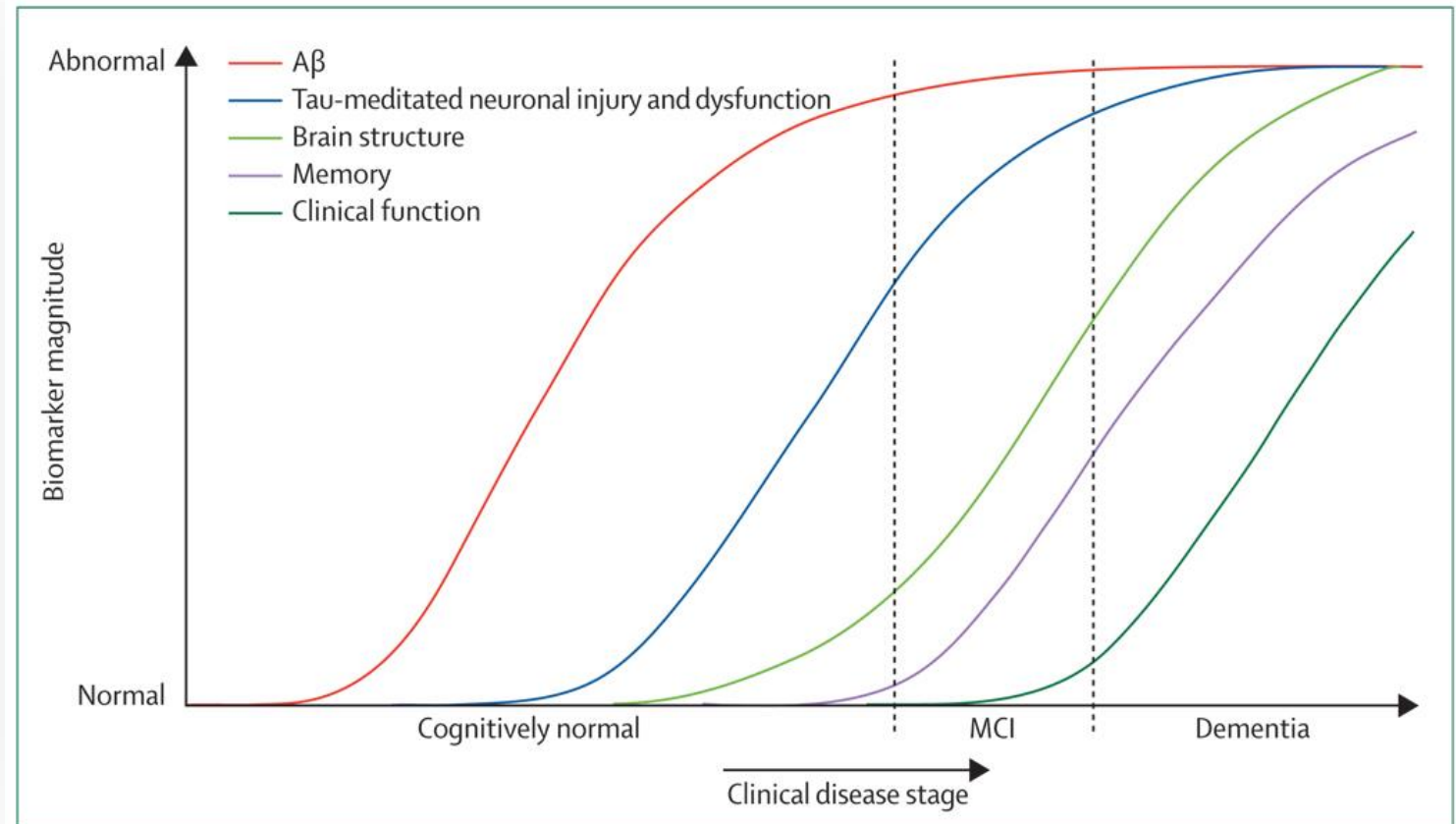
¹ Reduction of Amyloid Plaque as measured by SUVr, Standardized Uptake Value Ratio; CDR, Clinical Dementia Rating Scale.

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 cascade¹



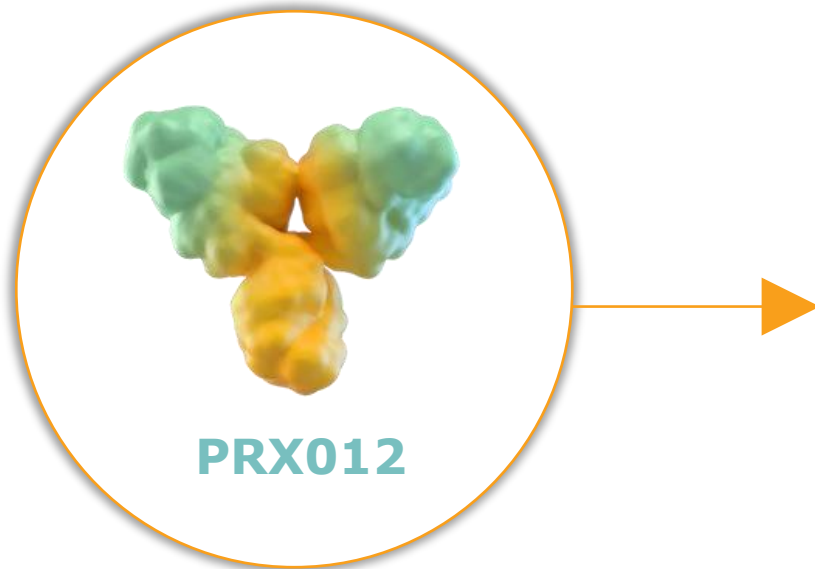
PRX012

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-A β product candidate

Key Antibody Design Attributes

HUMANIZED IgG1 monoclonal antibody with low immunogenicity

TARGETS a key epitope at the N-terminus of A β protein

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

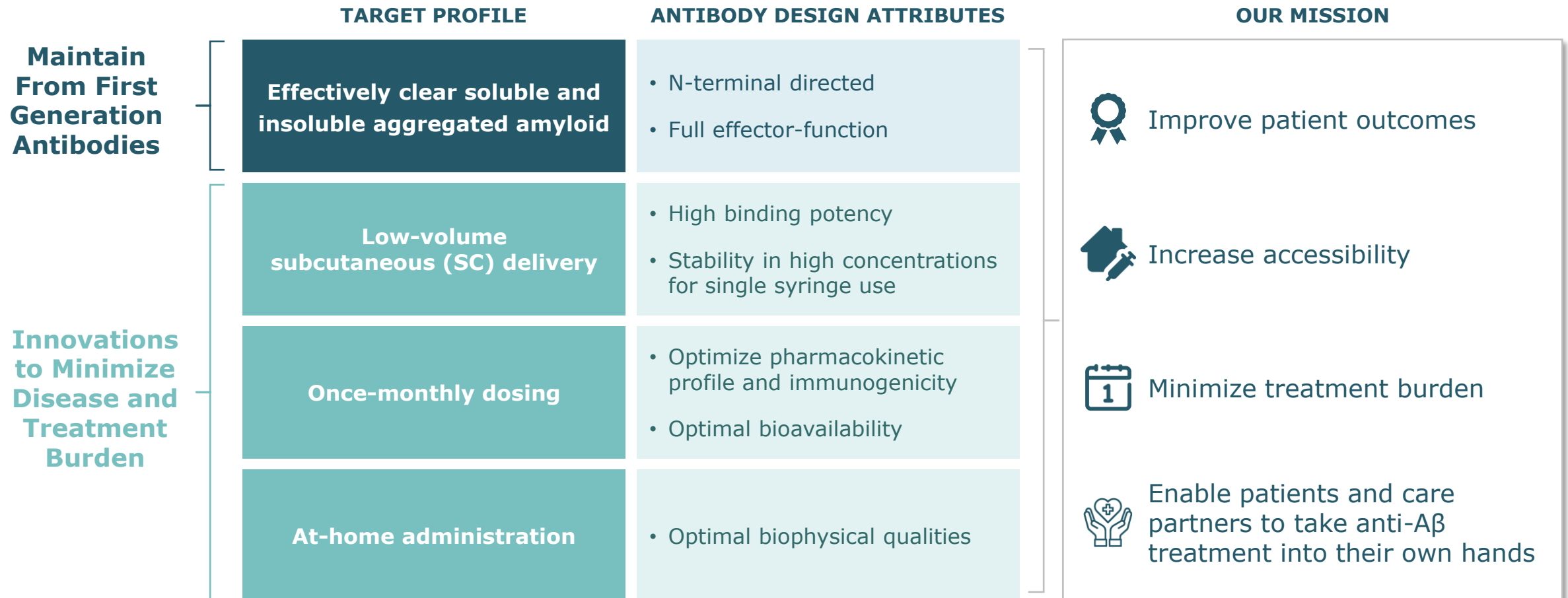
SLOW OFF RATE / slow & steady dissociation translates to consistent target exposure and potential safety advantages

HIGHLY POTENT BINDING, designed for subcutaneous administration

Translating Patient Needs Into Antibody Engineering



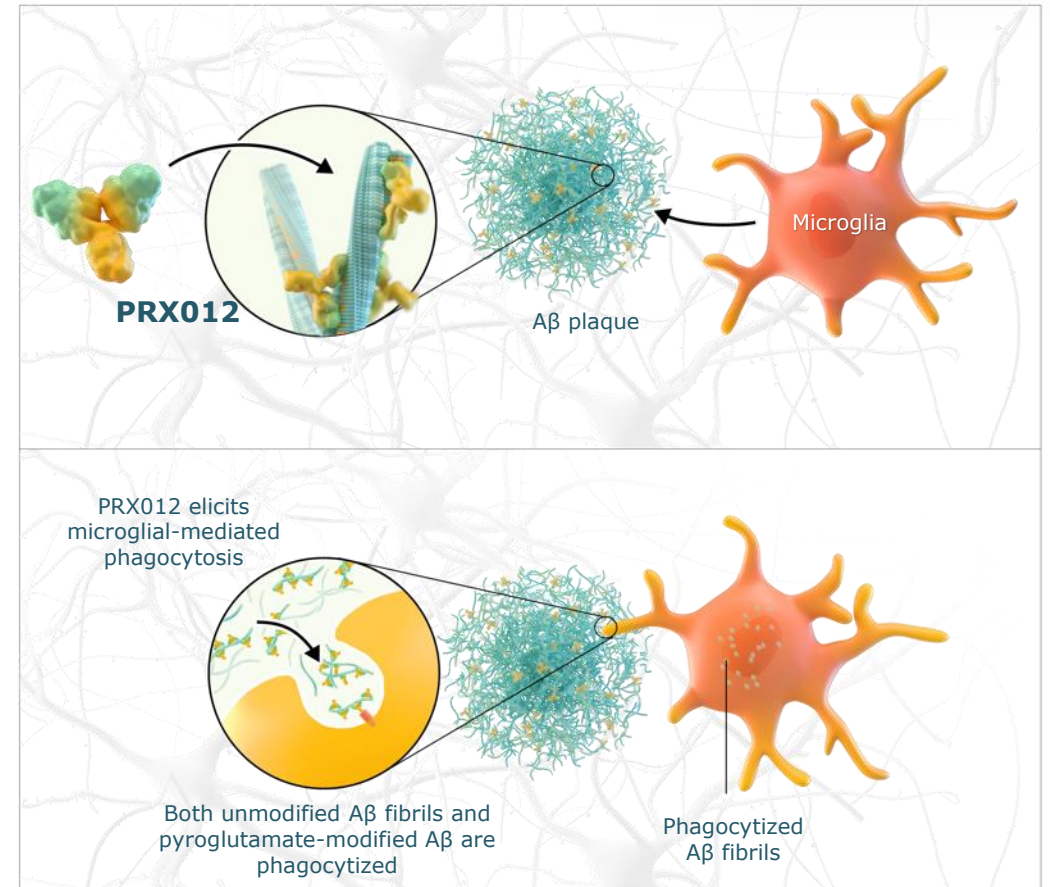
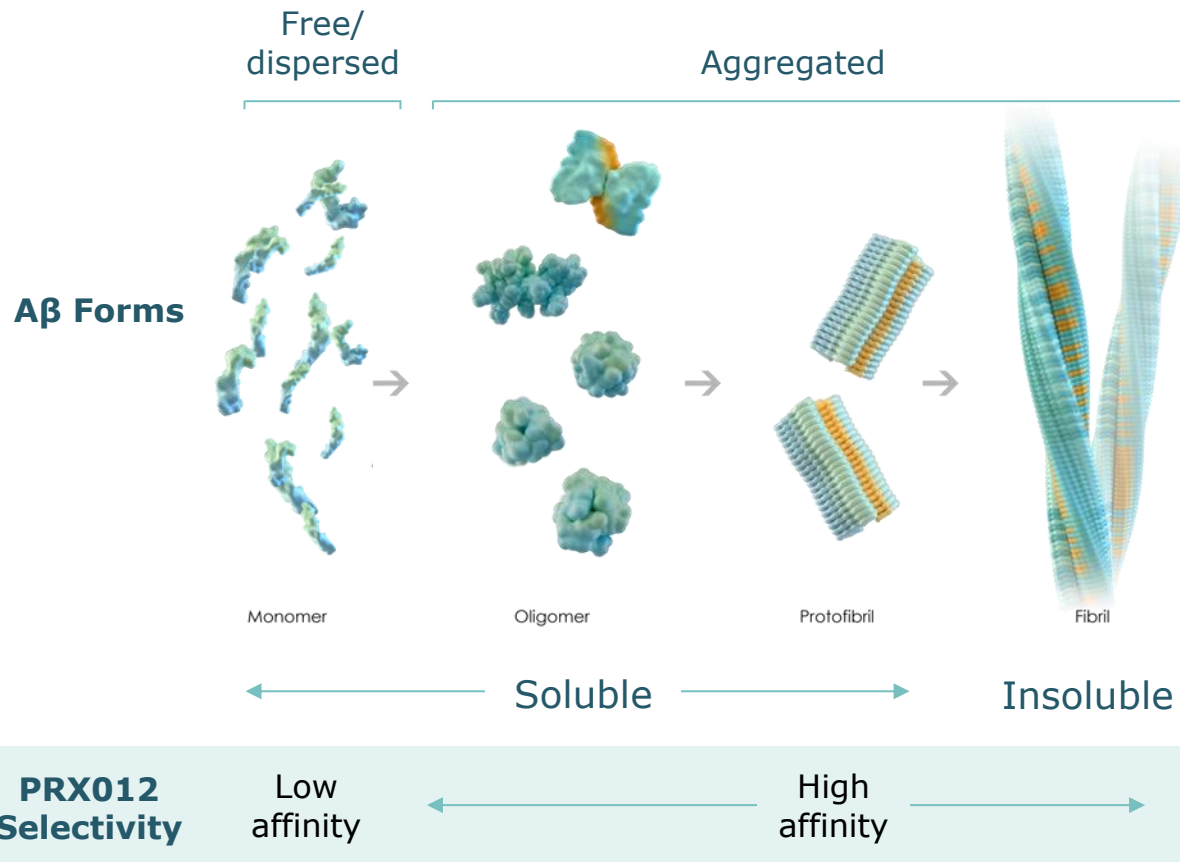
PATIENT-CENTRIC DESIGN STRATEGY FOR PRX012



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

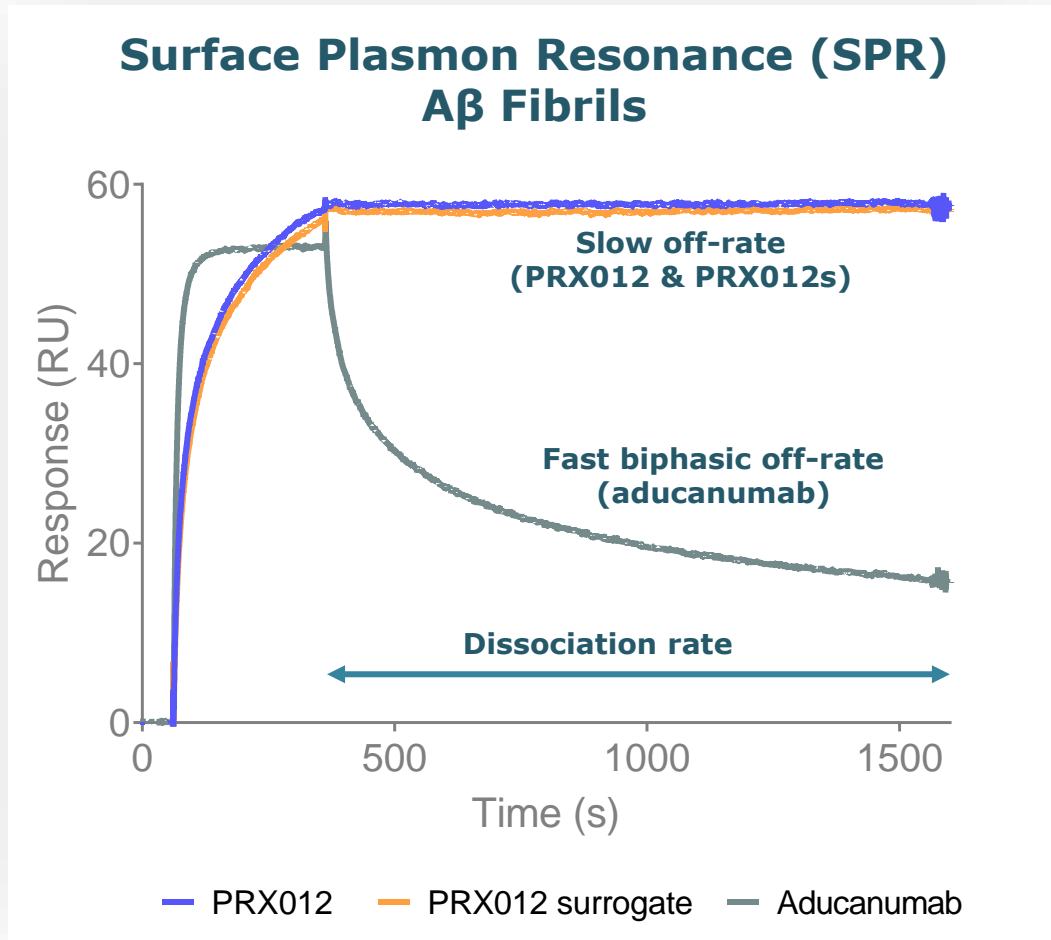


Designed to target and clear toxic aggregated forms of A β



Microglia recognize and engulf PRX012-opsonized A β fibrils

PRX012 and Surrogate Demonstrate Equivalent Potent Binding Affinity for A β



Affinity for A β Species

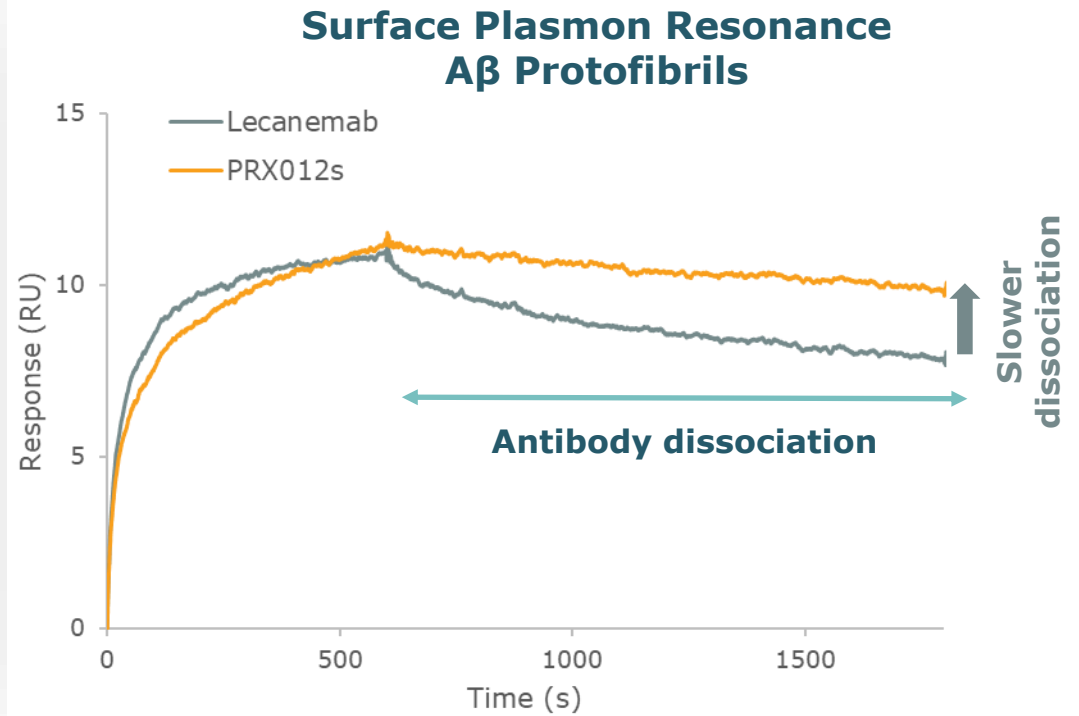
Compound	Fibril/Plaque	N3pE-A β
PRX012	0.070 ^a	>67 ^b
PRX012s	0.054 ^a	>67 ^b

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 A β 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-A β , pyroglutamate-modified A β ; 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 A β where directly compared.
 Aducanumab was generated from a publicly available sequence.

PRX012s Binds A β Protofibrils With Very High Affinity



SPR protofibril binding was performed as described in Tucker et al., 2015¹

Antibody	Relative Affinity (K_{D1})
Lecanemab¹ (Tucker et al., 2015)	1.97 nM
Lecanemab²	1.91 nM
PRX012s	0.0975 nM

SPR Binding Kinetics

	k_{a1} (1/Ms)	k_{d1} (1/s)	K_{D1}
Lecanemab¹ (Tucker et al., 2015)	6.60E+05	1.30E-03	1.97E-09
Lecanemab²	1.80E+05	3.42E-04	1.91E-09
PRX012s	1.63E+05	1.59E-05	9.75E-11



PRX012s binds to A β 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

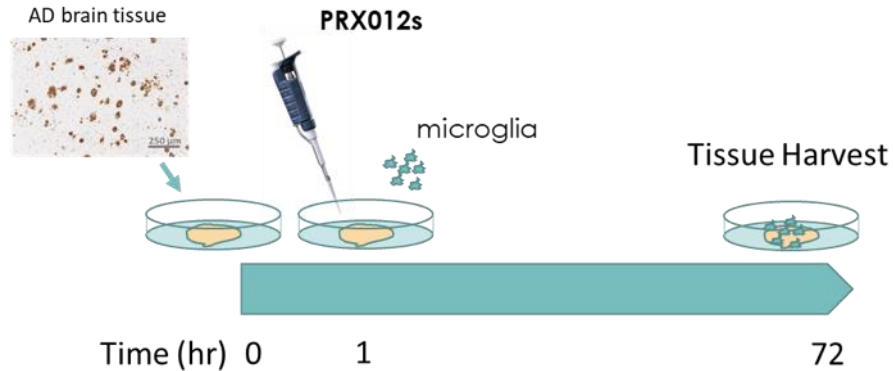
k_a , association constant; k_d , dissociation constant; K_D , equilibrium constant; SPR, surface plasmon resonance.

¹Tucker S, et al. *J Alzheimers Dis.* 2015;43:575-588.

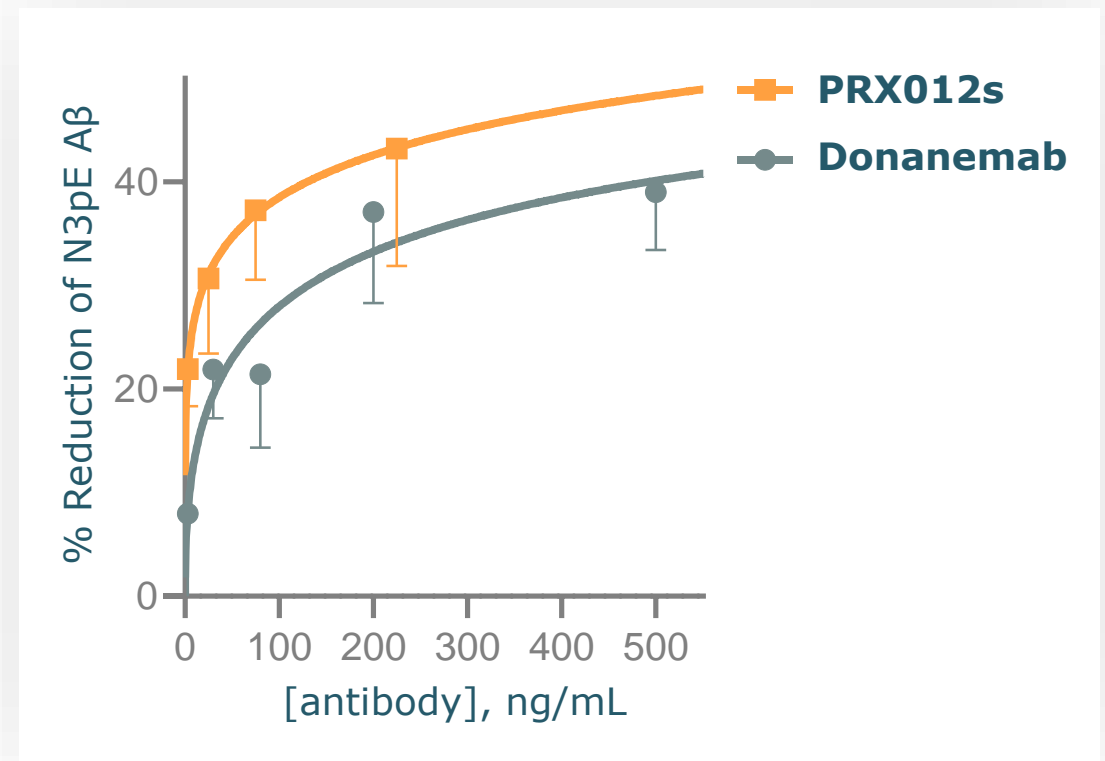
² Determined by Prothena.

Lecanemab was generated from a publicly available sequence.

PRX012s Induced Potent and Robust Clearance of Pyroglutamate-modified A β

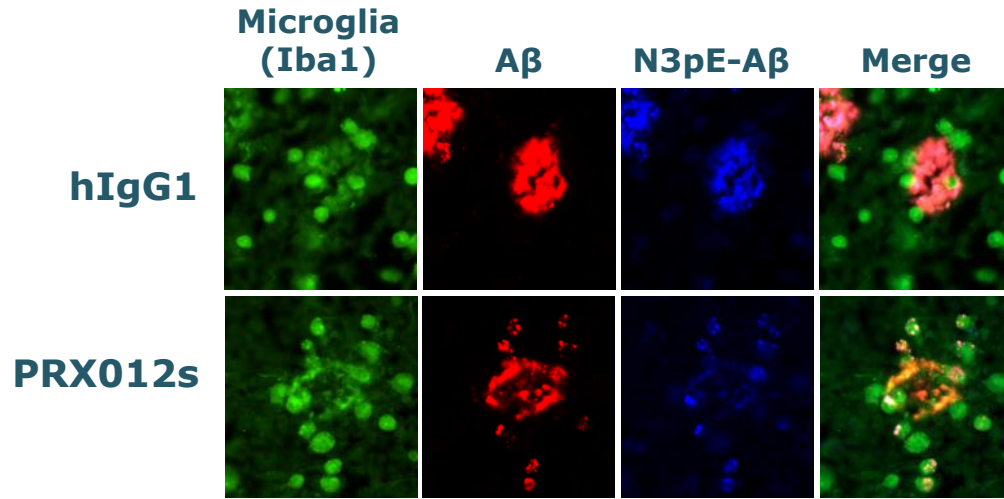


Study Conditions	
Tissue	Post-mortem AD brain tissue (same donor used for all conditions)
Treatment	PRX012s, donanemab, or IgG1 isotype control
Microglia	Primary mouse microglia (800,000 cells/mL)
Culture time	72 hours at 37°C



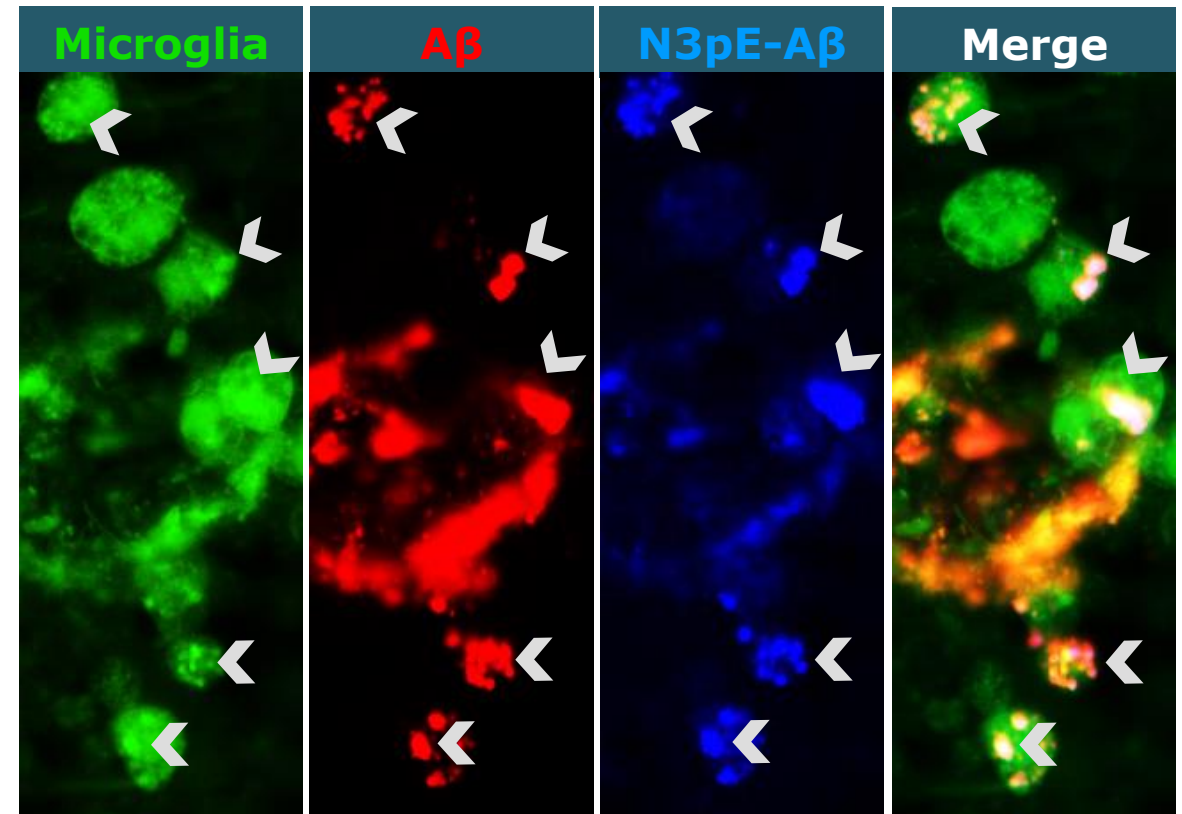
- ✓ PRX012s facilitates concentration-dependent clearance of pyroglutamate-modified A β (N3pE-A β) at concentrations that may be relevant for PRX012 clinical exposure
- ✓ PRX012s clears equivalent or more N3pE-A β at ~3–8x lower concentrations than donanemab

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



Microglia (Iba1: green) simultaneously phagocytose A β (red) and pyroglutamate-modified A β (A β _{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 A β and pyroglutamate-modified A β (N3pE-A β) simultaneously



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

PRX012 Phase 1 SAD Design

SINGLE ASCENDING DOSE (SAD) COHORTS

Healthy Volunteer Cohorts

- Age 20 – 45 years

70 mg
n = ~8
(3:1)

200 mg
n = ~8
(3:1)

Early Alzheimer's Disease Cohorts

- Ages 60 – 85 years
- Amyloid PET positive
- MMSE \geq 18

70 mg
n = ~8
(3:1)

200 mg
n = ~8
(3:1)

400 mg
n = ~8
(3:1)

Trial Design

 ascent-1

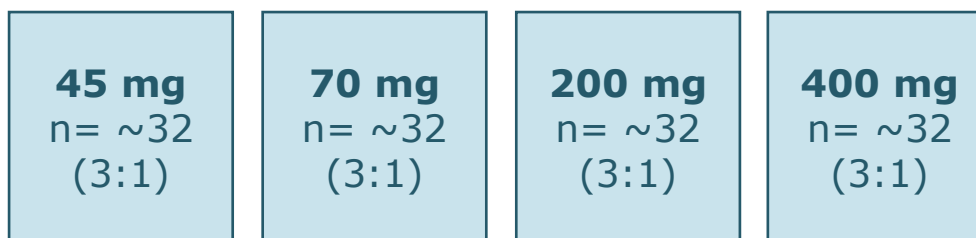
- Phase 1, randomized 3:1, double-blind, placebo-controlled, single ascending dose trial
- 1 subcutaneous dose of PRX012 or placebo
- Evaluate the safety, tolerability, immunogenicity, and pharmacokinetics of PRX012 in healthy volunteers and patients with Alzheimer's disease

PRX012 Phase 1 Multiple Dose Design

MULTIPLE DOSE ACTIVE COHORTS

Early Alzheimer's Disease "A" Cohorts

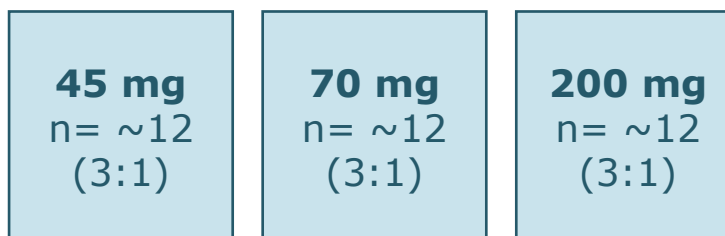
- Ages 55 – 85 years
- Amyloid PET positive
- MMSE \geq 18
- "A" cohorts: APO ϵ 4 non-carrier or heterozygous



Optional Expansion Cohorts¹
 Further evaluate selected doses from the "A" cohorts

Early Alzheimer's Disease "B" Cohorts

- Ages 55 – 85 years
- Amyloid PET positive
- MMSE \geq 18
- "B" cohorts: APO ϵ 4 homozygous



Trial Design



- Phase 1, randomized 3:1, double-blind, placebo-controlled, multiple dose trial
- Q4W (once monthly) subcutaneous dosing for 6 doses total (6 months)
- Evaluate the safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of PRX012 in patients with early Alzheimer's disease
- ASCENT-1 and ASCENT-2 patients may continue into an open-label extension (**ASCENT-3**) for 12 doses (Q4W) of PRX012

¹ There is currently one optional expansion cohort active. MMSE: Mini Mental State Examination.

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-986446¹

- \$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

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

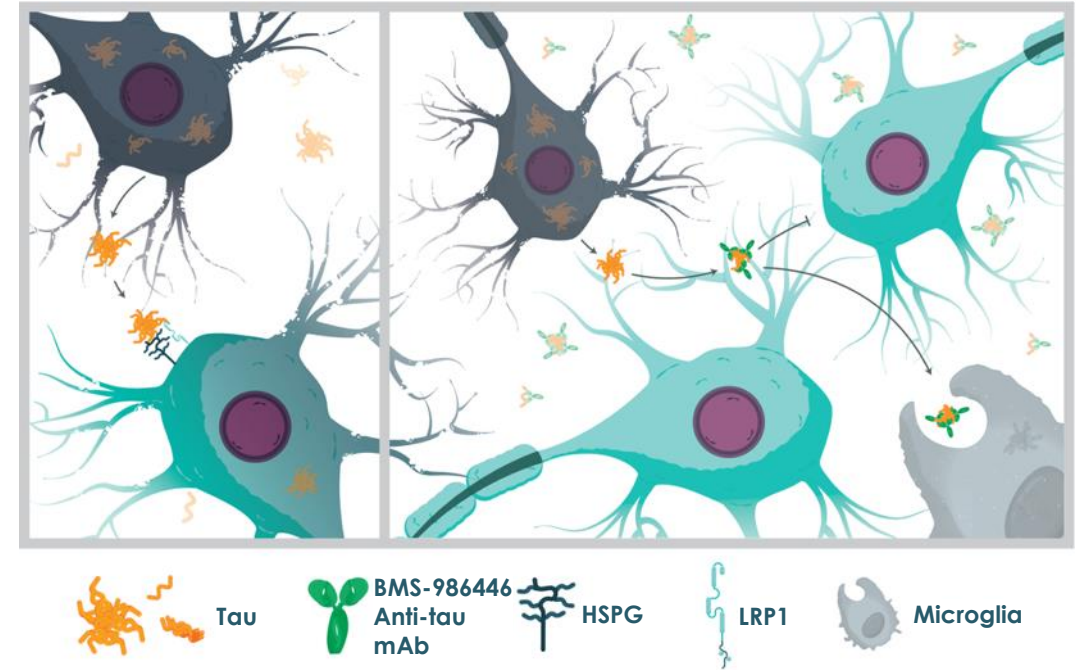
BMS-986446: MTBR-Specific Anti-Tau Antibody

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 pathways¹
- This propagation of pathology is thought to be mediated by tau “seeds” containing the MTBR of tau²

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

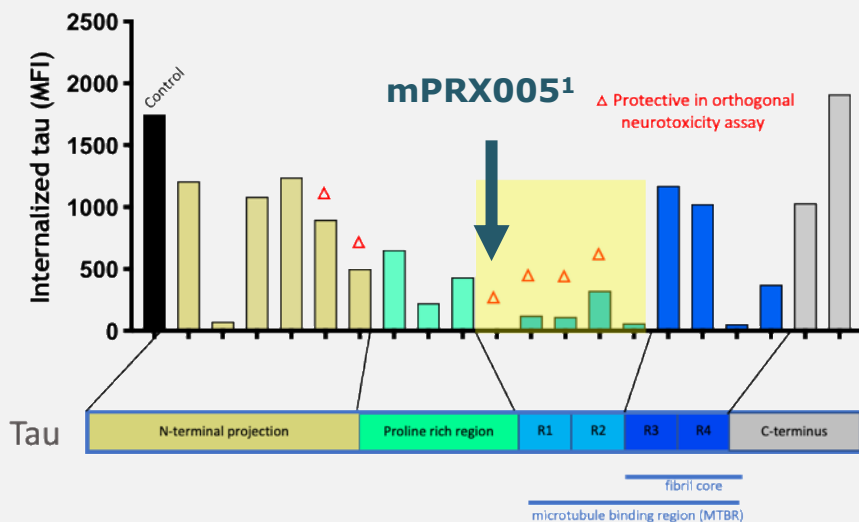


BMS-986446: Potential Best-in-Class MTBR-Specific Anti-Tau Antibody to Reduce Pathogenic Tau Spread

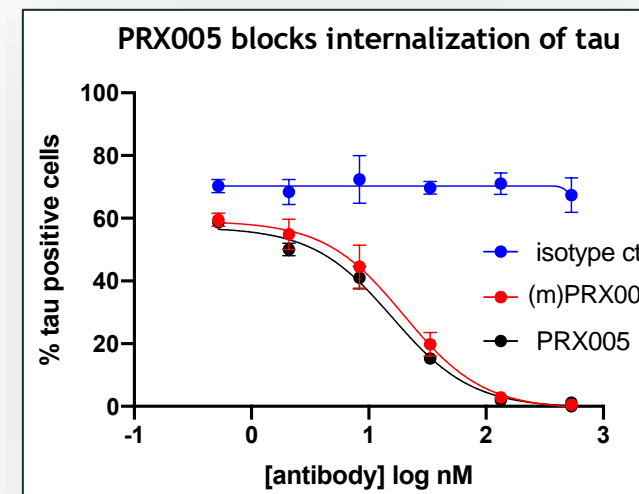
BMS-986446 (PRX005): Superior in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity Compared to Other Anti-Tau Antibodies



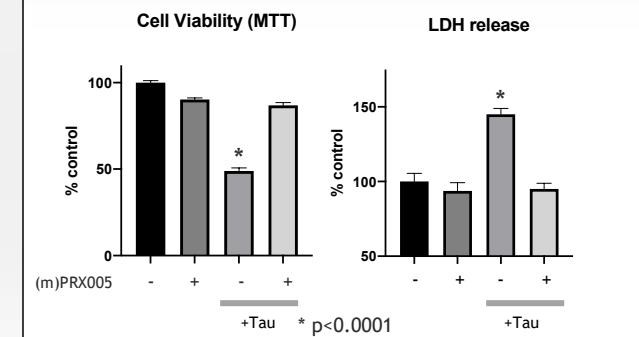
Repeats 1 and 2 defined as the strongest inhibitory regions in screening with cellular internalization and neurotoxicity assays



- 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



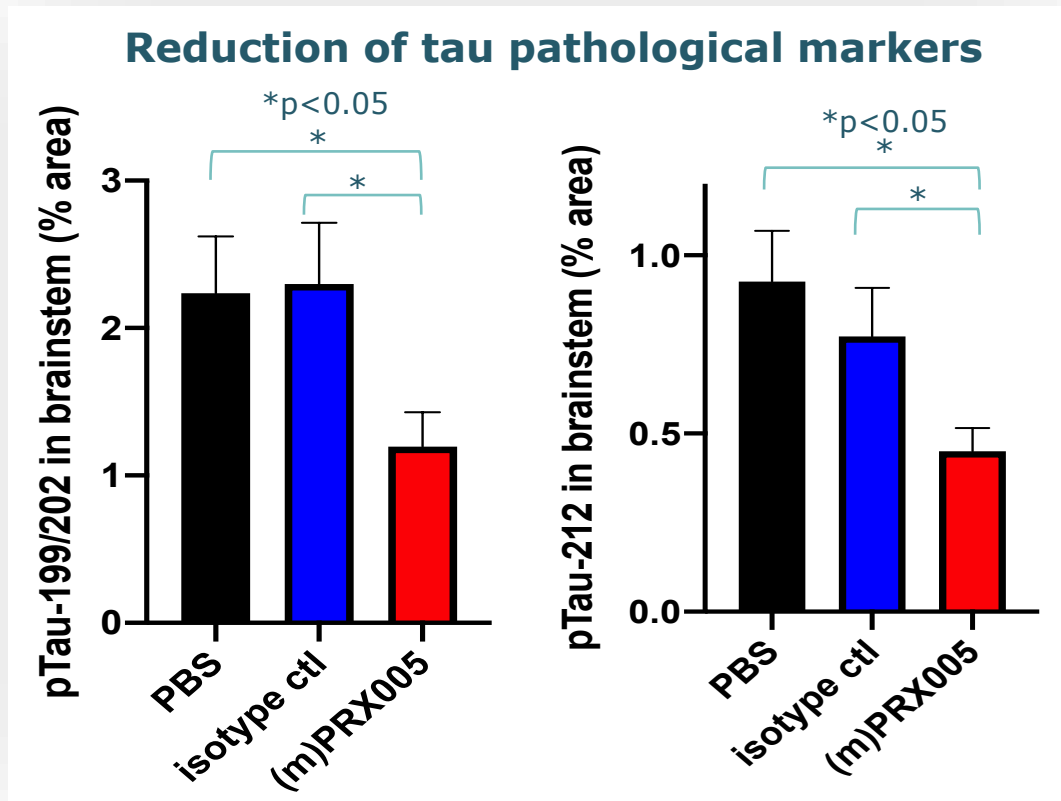
(m)PRX005 protects rodent primary cortical neurons from tau-induced toxicity



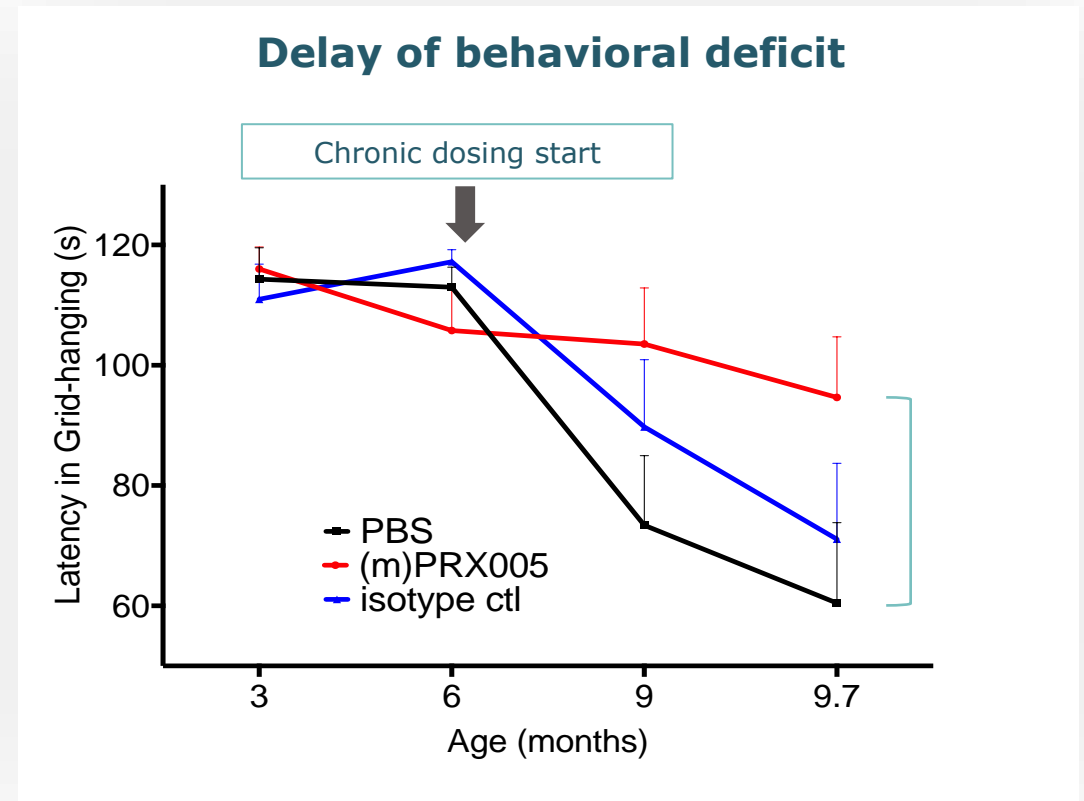
(m)PRX005 Treatment Reduces Pathological Tau and Ameliorates Behavioral Deficit in Transgenic Tau Mouse Model



All values are mean ± SE (n=15-20)



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



- 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

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

Randomized
4:3:3
N = 475

Placebo

BMS-986446
low dose IV Q4W

BMS-986446
high dose IV Q4W

Key Assessments

- Tau PET imaging
- AD biomarkers²
- Cognitive assessments
- 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, A β [1-42], A β [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 A β /Tau Vaccine for the Treatment & Prevention of AD

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

- **Synergistic mechanism designed for increased efficacy over single-target vaccines**

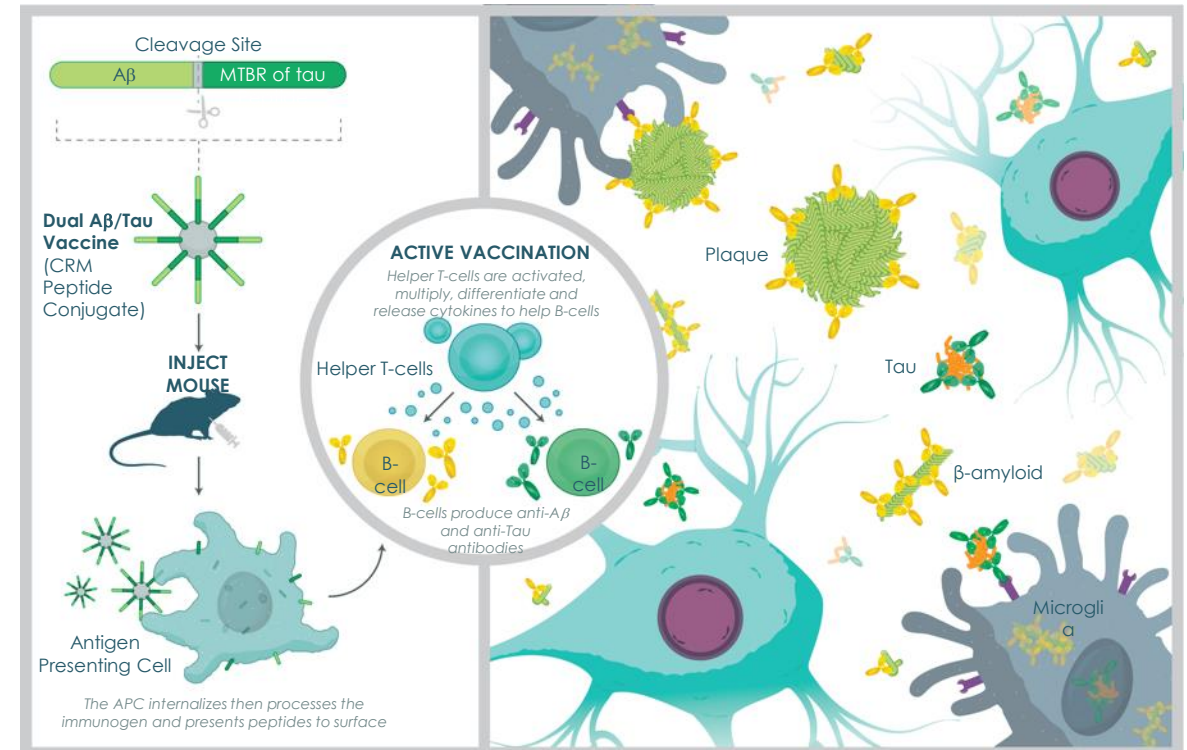
- Strong evidence from preclinical models suggests that A β and tau may act synergistically in the development of AD
- Prothena's dual A β /tau vaccine program aims to induce optimal (quantity and quality) and balanced immune response to both targets, while avoiding cytotoxic t-cell response

- **Potential treatment & prevention**

- Dual vaccine constructs were shown to generate balanced titers to A β and tau in non-human primates and Guinea pigs as measured by ELISA
- The immune animal sera reacted to A β and tau, induced A β 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 A β /Tau Vaccines and Prothena's Design Strategies

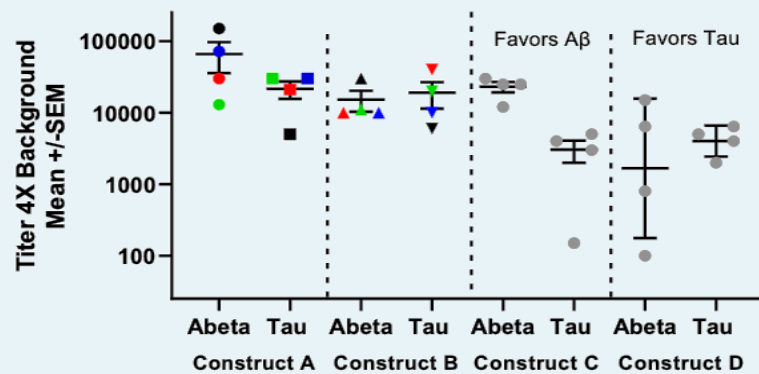


		Design Strategy	Desirable Output
1 Quantity	RESPONSE Antibody levels, balanced A β /tau, persistency	<ul style="list-style-type: none"> Linear peptides, proprietary cleavable linkers Optimal carriers, immunization schedule, adjuvant 	<ul style="list-style-type: none"> ✓ Optimal antigen presentation with persistent immune response ✓ Overcomes immunodominance and immunosenescence
2 Quality	EFFICACY Isotypes, binding, A β clearance, tau neutralization	<ul style="list-style-type: none"> Optimal Aβ and tau epitopes Elements for induction of mature TH response 	<ul style="list-style-type: none"> ✓ Antibodies bind the right epitopes on pathogenic proteins ✓ IgG switch and affinity maturation
3 Safety	SAFETY Cytotoxic T-cell avoidance, target-specificity	<ul style="list-style-type: none"> Short Aβ/tau epitopes not recognizable by cytotoxic T-cells No off-target binding risk based on peptide sequences 	<ul style="list-style-type: none"> ✓ No cytotoxic T-cell responses ✓ Specific antibodies

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

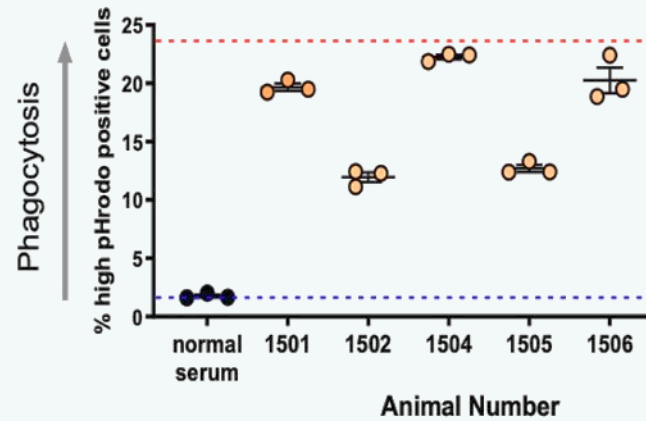


Quantity



✓ High, balanced, consistent

Quality



✓ Epitope, affinity, A β clearance, tau neutralization

Safety

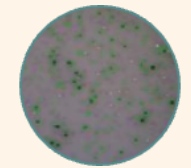
Unable to induce measurable cytotoxic T-cell activity against A β and tau in Non-human primates (ELISpot)

Prothena's Dual Vaccine

A β

Tau

Positive Control



✓ Avoids T-cell response observed in other vaccines

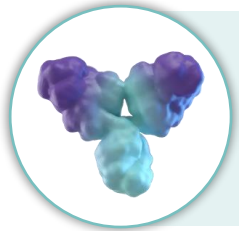
A large, dark teal, stylized leaf-like logo that occupies the left side of the slide. It consists of several overlapping, curved lines that form a complex, organic shape.

Birtamimab

AL Amyloidosis

TM

Birtamimab: Differentiated Approach to AL Amyloidosis



Birtamimab AL amyloidosis

Current Status: Phase 3

Anti-Amyloid Mechanism of Action

- Clears insoluble AL amyloid deposits that cause vital organ dysfunction and failure^{a,1,2}
- Neutralizes toxic soluble amyloidogenic species^{a,2,3}

Addresses Acute Unmet Need

- Patients with significant cardiac involvement are at high risk for early mortality¹
- Currently approved treatments have not demonstrated any survival benefit in Mayo Stage IV^{b,1,4,5}

Phase 3 AFFIRM-AL (NCT04973137): Ongoing⁶

- 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 between 4Q 2024 and 2Q 2025

Phase 3 VITAL: Post hoc analysis⁷

- 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.

^a Murine version of birtamimab, 2A4.

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

¹ Palladini G, et al. *Leukemia & Lymphoma*. 2024;1-11. ² Wall JS, Kennel SJ, Williams A, et al. *PLoS One*. 2012;7(12):e52686. ³ Renz M, Torres R, Dolan PJ, et al. *Amyloid*. 2016;23(3):168-177. ⁴ Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995. ⁵ Kyle RA, Gertz MA, Greipp PR, et al. *N Engl J Med*. 1997;336(17):1202-1207. 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.

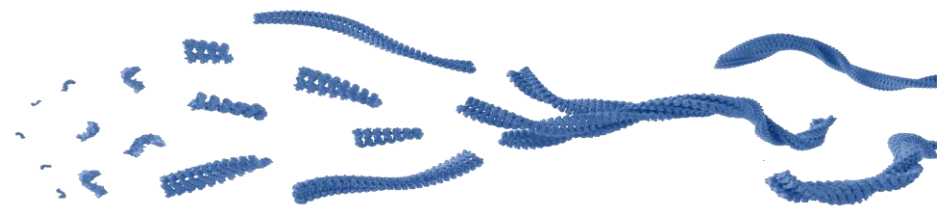
Abnormal Light Chains Deposit As Amyloid in Vital Organs, Most Commonly the Heart¹



AL AMYLOIDOSIS PATHOGENIC PATHWAY



PLASMA CELL DYSCRASIA^{1,2}



SOLUBLE TOXIC AMYLOIDGENIC LIGHT CHAIN AGGREGATES^{2,3}

INSOLUBLE AMYLOID DEPOSITS²



CARDIAC DYSFUNCTION & EARLY MORTALITY^{2,3}

Amyloidogenic 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 Disease¹

Advanced Disease with Cardiac Involvement^{1,2,5}

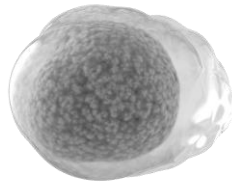
Of Patients with Cardiac Involvement, the Most Severe Have Median Survival of <6 Months^{6,7}

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 PATHWAY²⁻⁴



PLASMA CELL DYSCRASIA



Current plasma cell directed treatments decrease light chain production^{a,2}

Most patients today take some combination of daratumumab + CyBorD^{a,1}

Birtamimab's transformative anti-amyloid MoA¹:

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

Birtamimab demonstrated significant survival benefit in Phase 3 VITAL post hoc analysis in Mayo Stage IV patients⁵

MOA=mechanism of action.

^a 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 Survival Benefit in a Randomized Clinical Trial^a	✓	✗	✗
MOA: Clears Insoluble Deposits	✓	✓	✗
MOA: Neutralizes Soluble Aggregates	✓	?	✗
Monthly Dosing	✓	✗	✗
Humanized	✓	✗	✓

Addition of Birtamimab could significantly improve survival in patients with cardiac involvement²

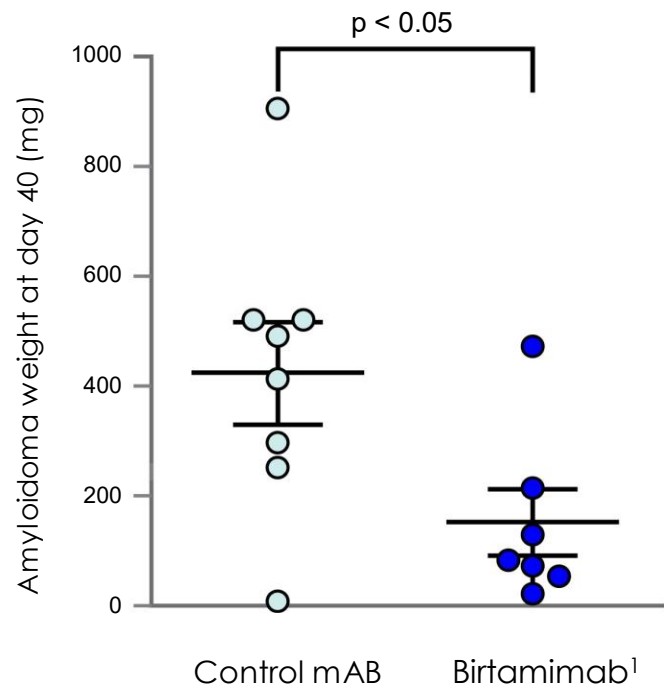
^aPost-hoc analyses demonstrated a significant survival benefit with birtamimab and meaningful improvements in QoL and functional capacity in patients at high risk for early mortality (Mayo Stage IV at baseline).

¹Palladini G, et al. *Leukemia & Lymphoma*. 2024;1-11. ²Gertz MA, et al. *Blood*. 2023;142(14):1208-1218. ³Edwards CV, Rao N, Bhutani D, et al. *Blood*. 2021;138(25):2632-2641. ⁴Hughes 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. ⁵Valent J, Silowsky J, Kurman MR, et al. *Blood* (2020) 136 (Supplement 1): 26-27. ⁶Kastritis E, Palladini G, Minnema MC, et al. *N Engl J Med*. 2021;385(1):46-58. ⁷Muchtar E, Dispenzieri A, Gertz MA, et al. *Mayo Clin Proc*. 2021;96(6):1546-1577.

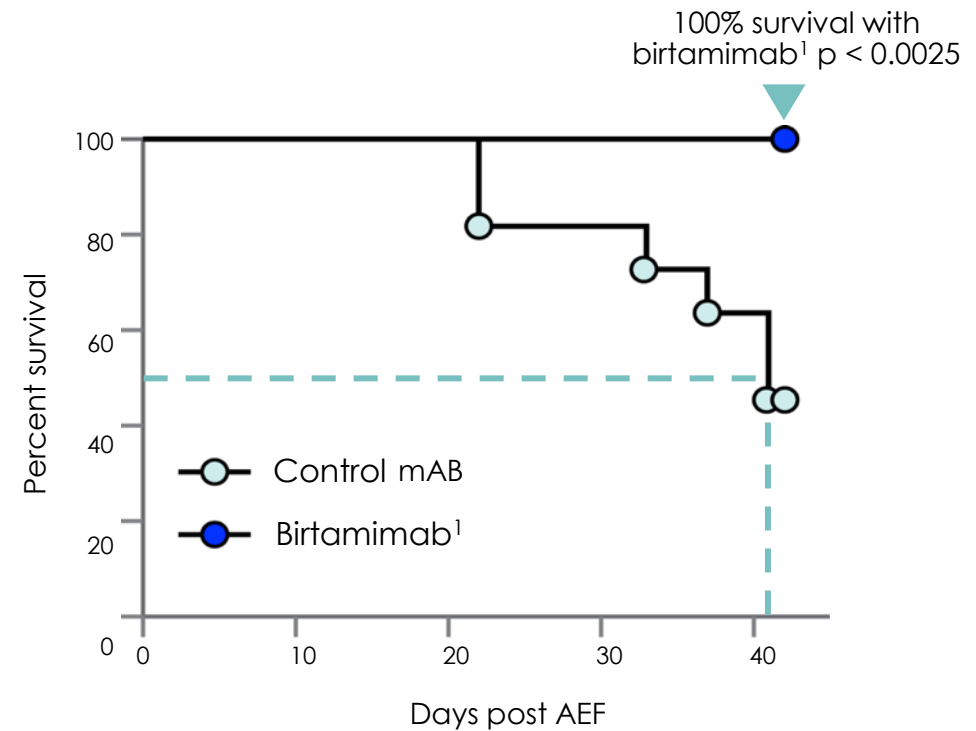
Birtamimab¹ Demonstrated Significant Amyloid Clearance and Prolonged Survival in Preclinical Model



Birtamimab¹ Removes Amyloid In Vivo



Birtamimab¹ Prolongs Survival in Transgenic Mouse Model



Phase 3 VITAL Trial Overview¹

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

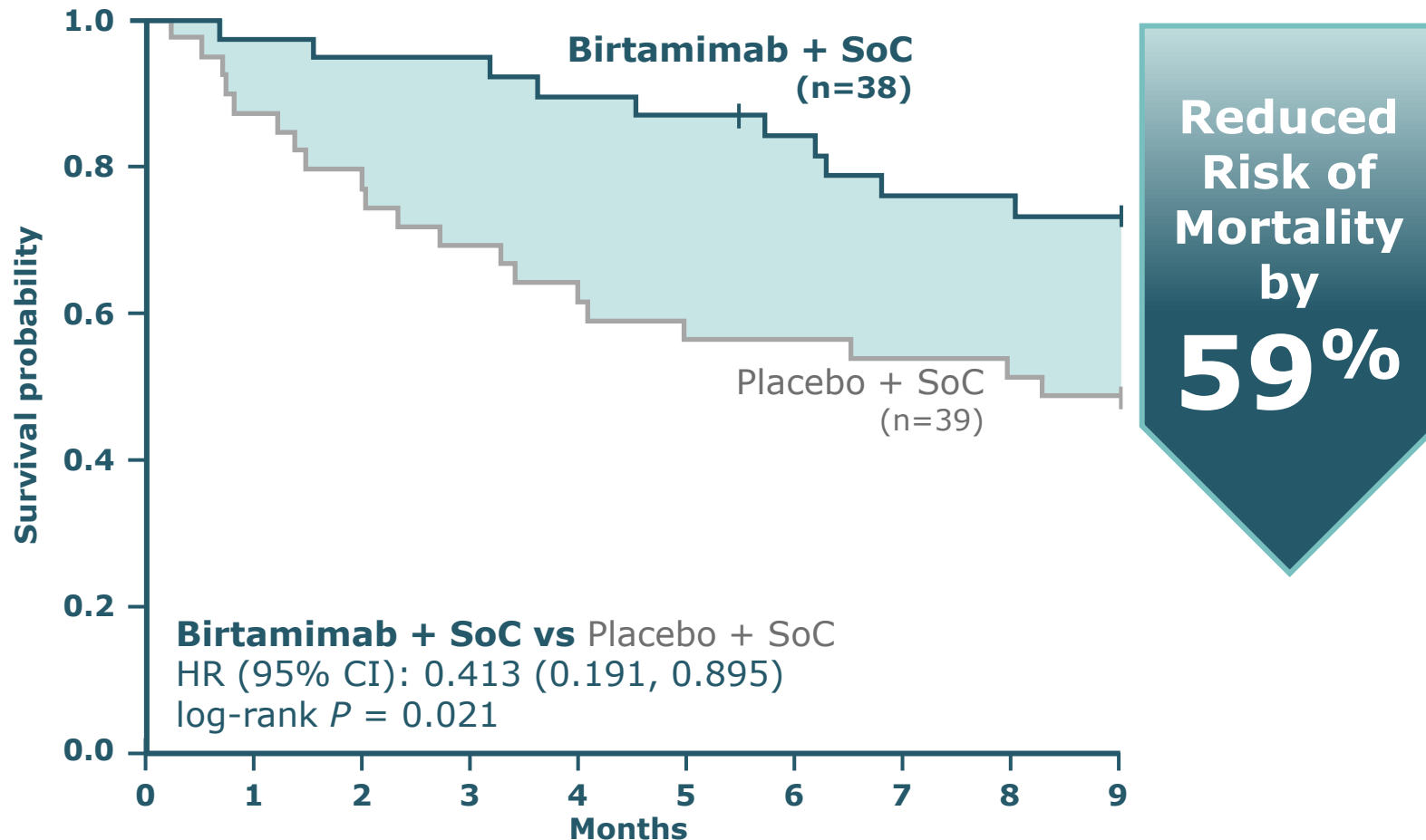
30% of patients enrolled in VITAL (N=77) were characterized as Mayo Stage IV at baseline

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

Previous Phase 3 VITAL Trial Demonstrated Significant Survival Benefit in Mayo Stage IV^{a,1}



Time to All-Cause Mortality (ACM) in Mayo Stage IV Patients^b



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

^a 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).

^b Adapted from Gertz et al. *Blood*, 2023.

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

Birtamimab Survival Benefit Persists When Adjusted for Key Baseline Variables (Mayo Stage IV)^{a,1}



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

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)

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

Randomized 2:1
(birtamimab:placebo)
N = up to 220

Birtamimab
(IV Q4W)
+ Standard of Care^a

Placebo
(IV Q4W)
+ Standard Of Care^a

Primary Endpoint

- Time to all-cause mortality

Secondary Endpoints

- 6MWT
- SF-36v2 PCS

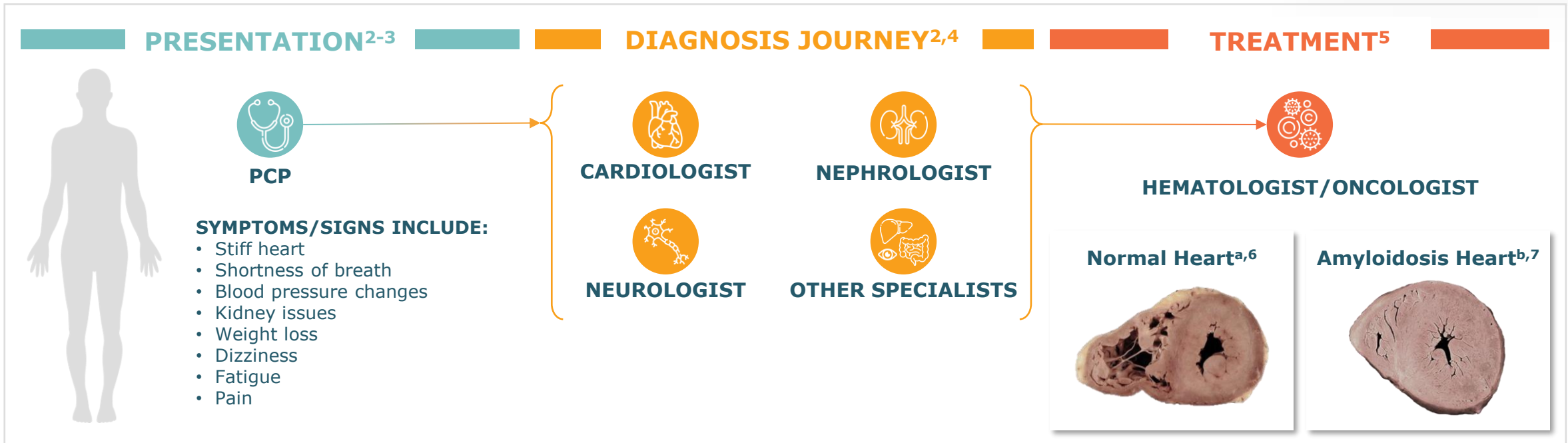
SPA Agreement with FDA

- Based on VITAL results, SPA agreement with FDA at unprecedented $P \leq 0.10$
- Interim analysis when ~50% events have occurred

^a 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}



- 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/oncologist²

- 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 cardiologists⁵

¹ Adapted from Basso, et al. *Virchows Arch.* 2021.

² Adapted with permission from Seward JB, et al. *J Am Coll Cardiol.* 2010.

³ Milani P, Merlini G, Palladini G. *Mediterr J Hematol Infect Dis.* 2018;10(1):e2018022. ⁴ Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. *Adv Ther.* 2015;32(10):920-928. ⁵ Muchtar E, Dispenzieri A, Gertz MA, et al. *Mayo Clin Proc.* 2021;96(6):1546-1577. ⁶ 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. ⁷ Stern LK, Patel J. *Methodist DeBakey Cardiovasc J.* 2022;18(2):59-72. ⁸ Basso C, Michaud K, d'Amati G, et al. *Virchows Arch.* 2021;479(1):79-94. ⁹ Seward JB, Casaclang-Verzosa G. *J Am Coll Cardiol.* 2010;55(17):1769-1779. ¹⁰ Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis.* 2022;17(1):278. ¹¹ Muchtar E, Gertz MA, Kyle RA, et al. *Mayo Clin Proc.* 2019;94(3):472-483.

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



Significant Unmet Need



Mayo Stage IV AL amyloidosis:

- Urgent need for immediate intervention¹
- Median overall survival <6 months^{2,3}

Defined Patient Population²⁻⁶



Mayo Stage IV AL amyloidosis diagnosed patients:^{2,4}

- >20K across major global markets
 - US (4K); EU (5K)

Consolidated Prescriber Base



- ~75% US and EU Mayo Stage IV patients primarily treated in ~500 amyloidosis specialty centers⁵
- Patients are primarily treated by hematologists and cardiologists⁵

Focused Opportunity and Commercial Approach

¹ Palladini G, et al. *Leukemia & Lymphoma*. 2024;1-11. ² Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995. ³ Kyle RA, Gertz MA, Greipp PR, et al. *N Engl J Med*. 1997;336(17):1202-1207. ⁴ Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis*. 2022;17(1):278. ⁵ Data on file. Prothena Biosciences. Brisbane, CA.

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

Anti- α -synuclein Antibody

- Preferentially binds to aggregated α -synuclein to reduce pathogenic spread and decrease synuclein pathology¹⁻⁴

Rapidly Growing Parkinson's Disease Patient Population

- 10 million patients globally⁵
- Fastest increasing neurodegenerative disease⁶

Worldwide Collaboration with Roche

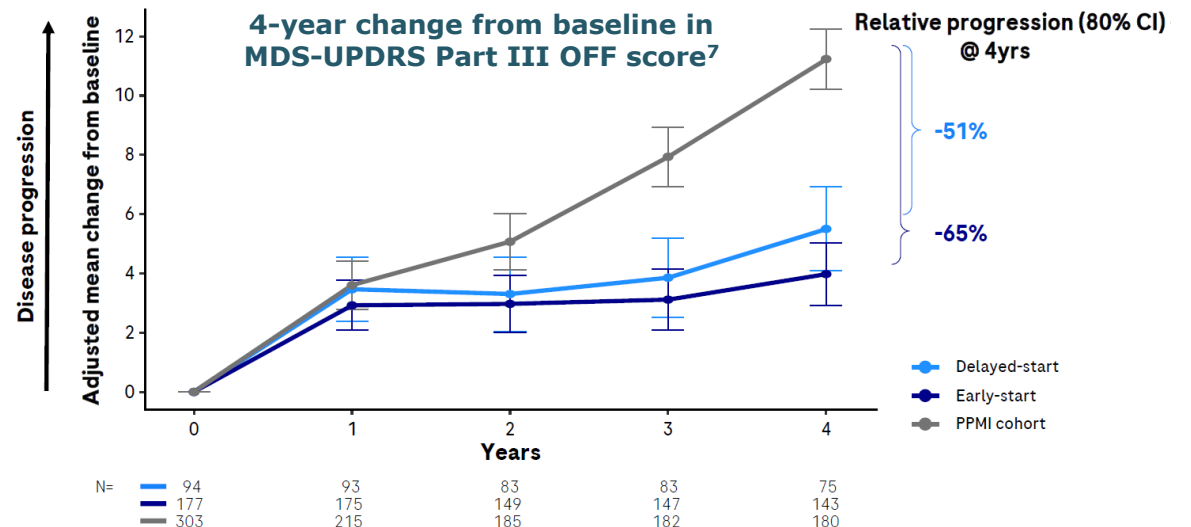
- Up to \$620 million in additional milestones
- \$135 million paid-to-date
- Up to double-digit teen royalties
- US co-promote option

Phase 2b PADOVA (NCT04777331): Ongoing

- N = 586 early Parkinson's disease patients
- Primary Endpoint: Time to confirmed motor progression event (≥ 5 point on MDS-UPDRS Part III)
- Topline results expected in 2H 2024

Phase 2 PASADENA (NCT03100149): OLE Ongoing

- OLE showed slowing of motor progression vs. matched RWD PPMI cohort



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 Masliah E, et al. *Neuron.* 2005; 46:857-868; ³ Masliah E, et al. *PLoS ONE.* 2011; 6:e19338; ⁴ Games D, et al. *J Neurosci.* 2014; 34:9441-9454

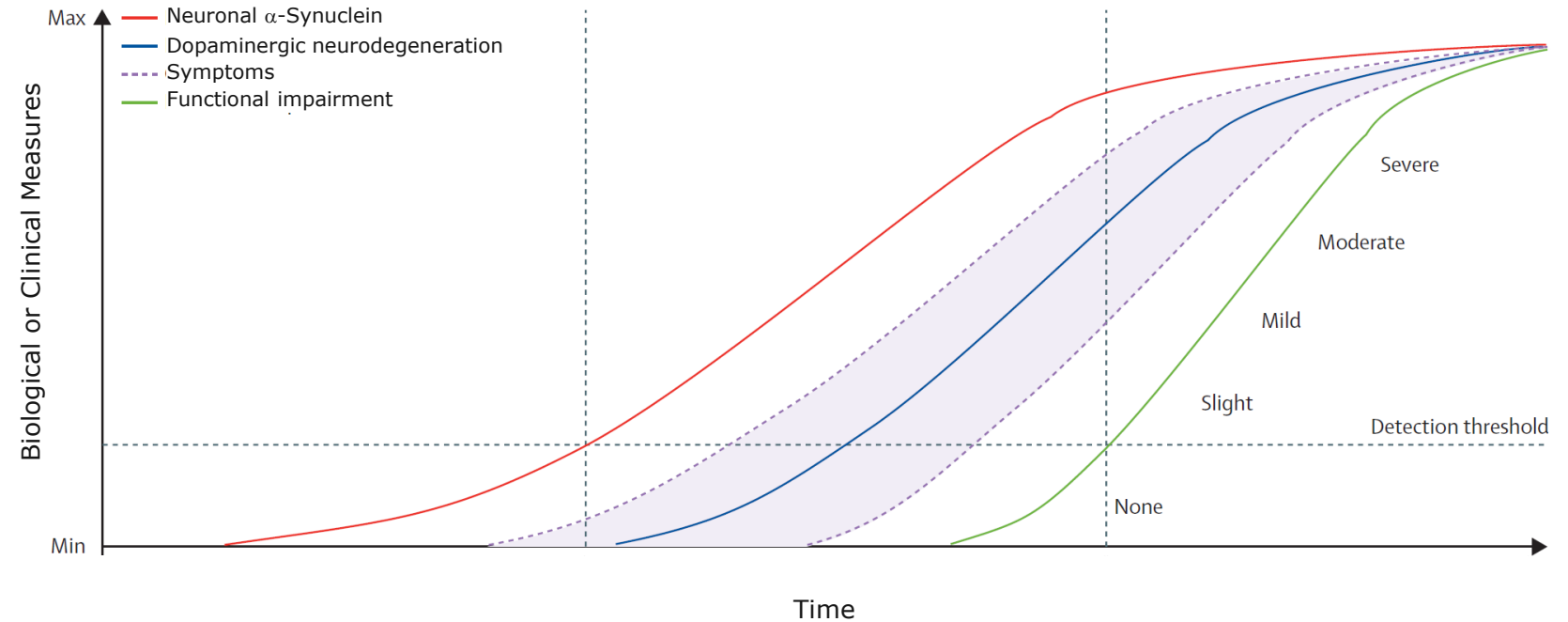
⁵ Parkinson's Foundation. Understanding Parkinson's. Statistics; ⁶ GBD 2015 Neurological Disorders Collaborator Group (2017) Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol* 16, 877-897. ⁷ 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.

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

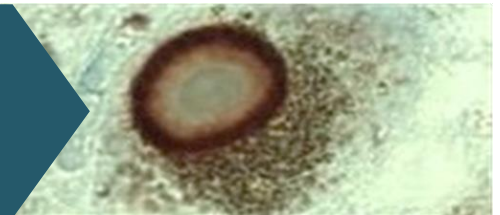


Accumulation of α -Synuclein is a predominant neuropathological feature and follows the topological progression of disease

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



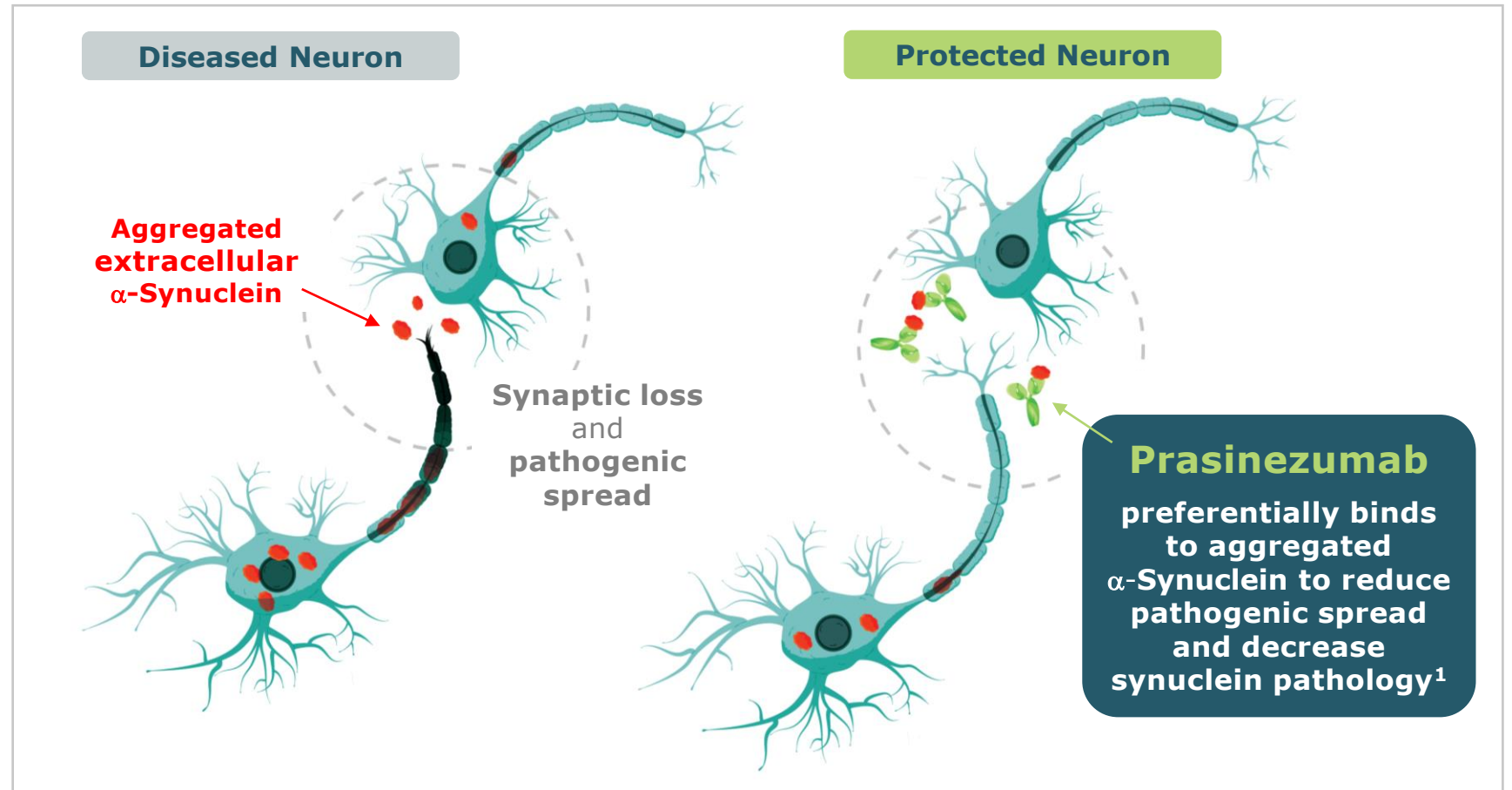
Symptoms: Clinical signs or symptoms attributable to neuronal α -Synuclein disease that can be motor or non-motor (e.g., hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety).
Functional Impairment: Degree of impact on activities of daily living.
Chart adapted from: 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 TRANSMISSION¹

α -Synuclein as an extracellular target during pathogenesis

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



Prasinezumab: Clinical Development Program for Early Parkinson's Disease



Completed 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

PADOVA study population more advanced than the PASADENA population

Ongoing Phase 2b PADOVA (NCT04777331)

- N=586, randomized 1:1 (1500 mg, placebo), Q4W IV dosing for at least 76 weeks and confirmed number of events¹
- **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:

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

Primary Endpoint:

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

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 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 III¹
 - ✓ Greater slowing of motor progression in subpopulations of individuals with rapidly progressing disease²
 - ✓ Part 2: **Less progression** on MDS-UPDRS Part III in early-start vs. delayed-start group at 2 years³
 - ✓ OLE: **65% less progression** vs. matched RWD PPMI cohort at **4 years** on MDS-UPDRS Part III (OFF state) with early-start treatment group³
 - ✓ OLE: **118% less progression** vs. matched RWD PPMI cohort at **4 years** on MDS-UPDRS Part III (ON state) with early-start treatment group³
- Generally safe and well tolerated, majority of AEs mild of moderate and similar across placebo and both treatment arms

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

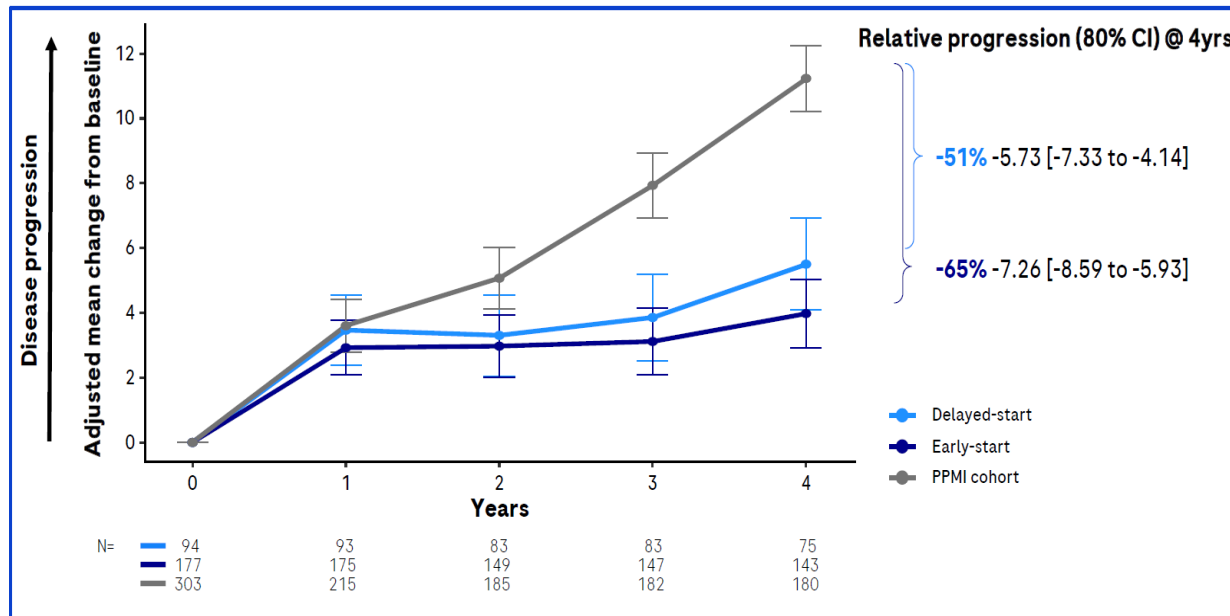
¹ Primary Endpoint: Change from baseline at Week 52 in MDS-UPDRS sum of Parts I + II + III vs. placebo; Pagano et al. *N Engl J Med* 2022;387:421-32. ² Pagano, G., Taylor, K.I., Anzures Cabrera, J. et al. *Nat Med* 30, 1096-1103 (2024).

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 score¹



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.

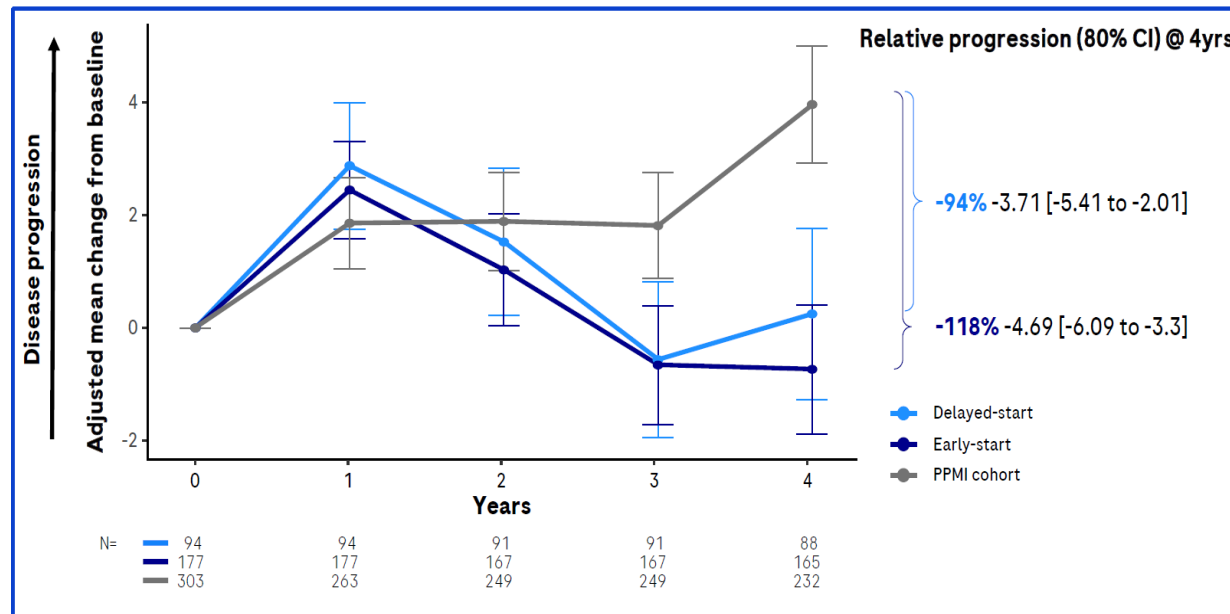
Source: Pagano et al. PASADENA long-term open-label extension continue to show reduced motor and functional progression in prasinezumab-treated individuals with early-stage Parkinson's disease compared to a real-world data arm.

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 ON score¹



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 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.

Coramitug (formerly PRX004) ATTR Amyloidosis

ATTR Business Acquired by Novo Nordisk

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



Coramitug ATTR Amyloidosis

Current Status: Phase 2

Differentiated Deleter Mechanism of Action

- Inhibits fibril formation and specifically binds to pathogenic TTR¹
- Uniquely designed for patients at high risk of early mortality due to amyloid deposition

Rare Transthyretin amyloidosis (ATTR) Patient Population

Worldwide Collaboration with Novo Nordisk

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

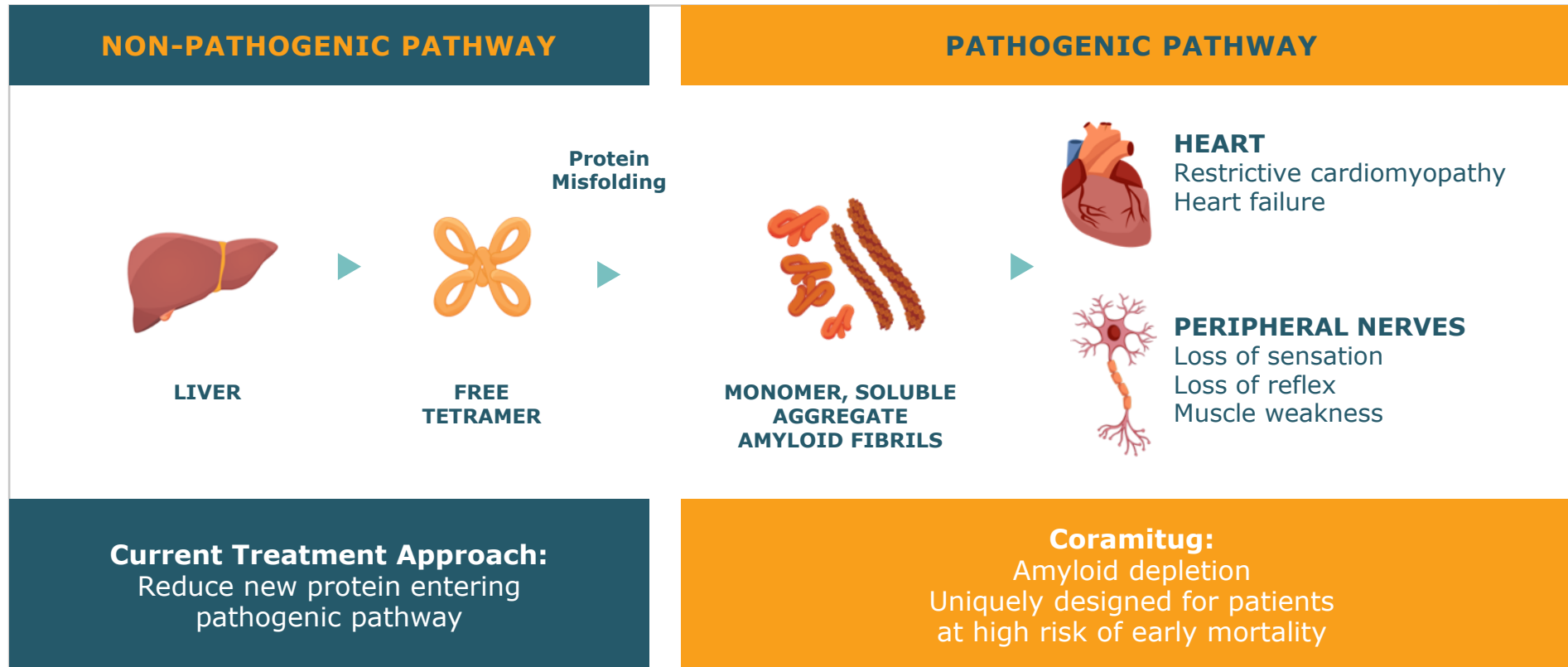
Phase 2 Signal Detection Trial (NCT05442047): Ongoing

- 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 has completed enrollment; topline results 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

Differentiated Mechanism for Treatment of ATTR Amyloidosis



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

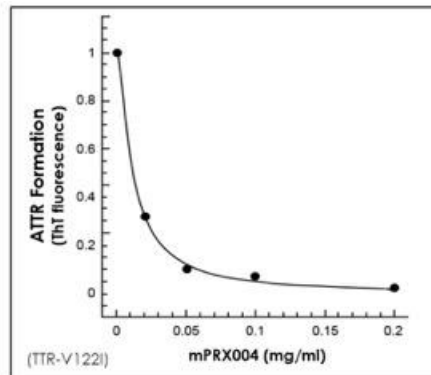
Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF mPRX004

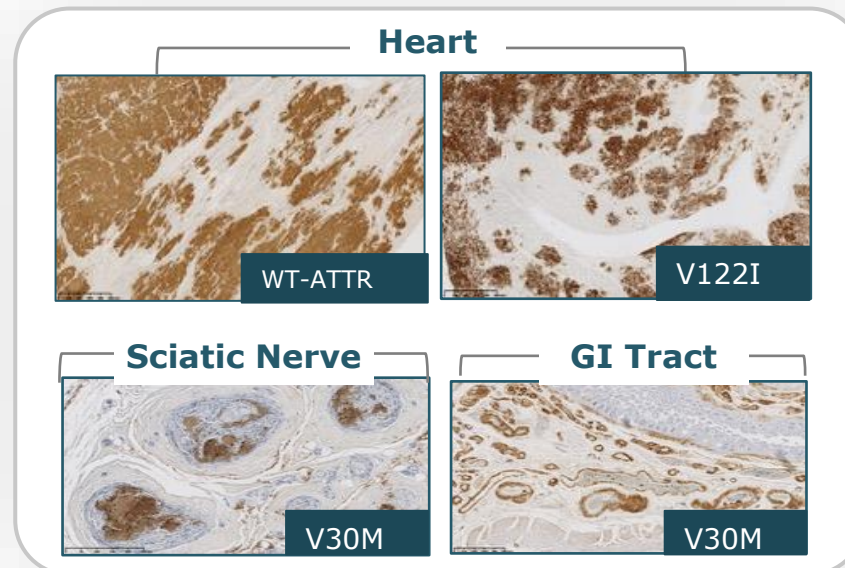
mPRX004 (murine form of PRX004) preclinical results:¹

- ✓ 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

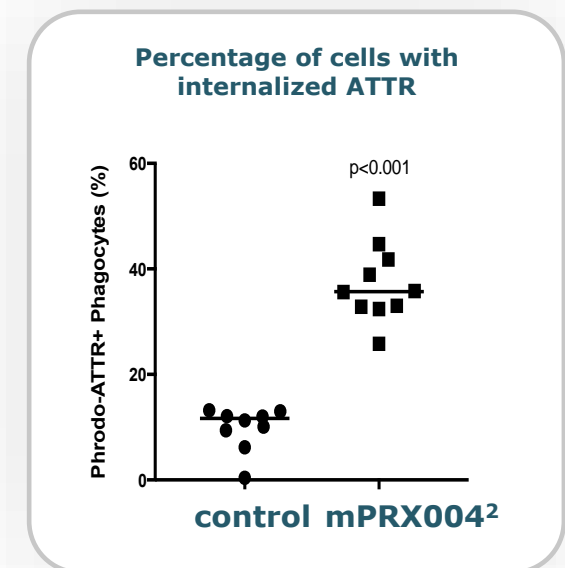
Inhibition of amyloid formation



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

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TM

Upcoming Potential Milestones

TRANSFORMATIONAL PERIOD AHEAD

Wholly-owned Programs

Birtamimab for potential treatment of AL amyloidosis

4Q24 – 2Q25 Confirmatory Phase 3 AFFIRM-AL topline data (NCT04973137)

PRX012 for potential treatment of Alzheimer's disease

2024 Ongoing Phase 1 trial update

PRX123, dual A β /Tau vaccine for potential treatment and prevention of Alzheimer's disease

2024 Phase 1 timeline update

Partnered Programs

Prasinezumab for potential treatment of Parkinson's disease (Roche)

2H24 Phase 2b PADOVA clinical trial topline data (NCT04777331)

Coramitug/PRX004 for potential treatment of ATTR-cardiomyopathy (Novo Nordisk)

1H25 Topline Phase 2 data (NCT05442047)

BMS-986446/PRX005 for potential treatment of Alzheimer's disease (Bristol Myers Squibb)

1H24 Bristol Myers Squibb initiated a Phase 2 clinical trial (NCT06268886)

PRX019 for potential treatment of neurodegenerative diseases (Bristol Myers Squibb)

2024 Prothena to initiate a Phase 1 clinical trial

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APPENDIX: Partnership and Collaboration Details

Bristol Myers Squibb Collaboration: Advancing Two Clinical Stage Programs



BMS Collaboration¹: 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

PRX019²

Status: Initiate Phase 1 by YE24

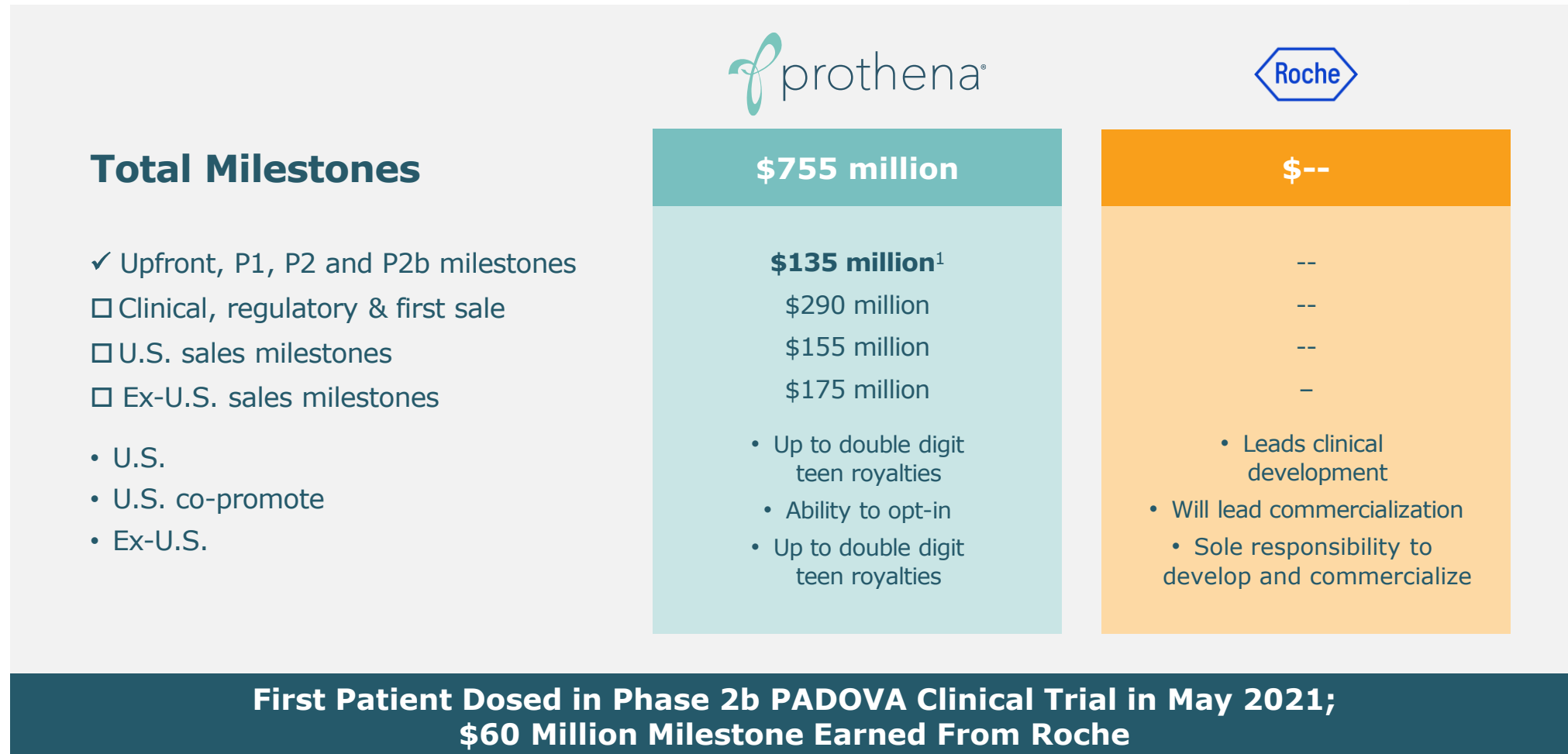
- ☑ \$80 million option exercised
- ☐ \$242.5 million in potential development and regulatory milestones
- ☐ \$375 million in commercial milestones
- ☐ Tiered Royalties

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



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