

CORPORATE OVERVIEW

May 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; 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, 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, prasinezumab, coramitug, and PRX019; the expected timing of reporting data from clinical trials of PRX012, coramitug, BMS-986446, and PRX019, including multiple data readouts starting in August 2025 and continuing throughout the year from our ongoing Phase 1 clinical trials evaluating PRX012; Roche's plans to work with health authorities to determine next steps for prasinezumab; 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 May 8, 2025, and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. This overview is made as of May 23, 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

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



Transthyretin amyloidosis (ATTR)

450,000

Estimated number of patients worldwide with wtATTR or ATTRv[4-6]

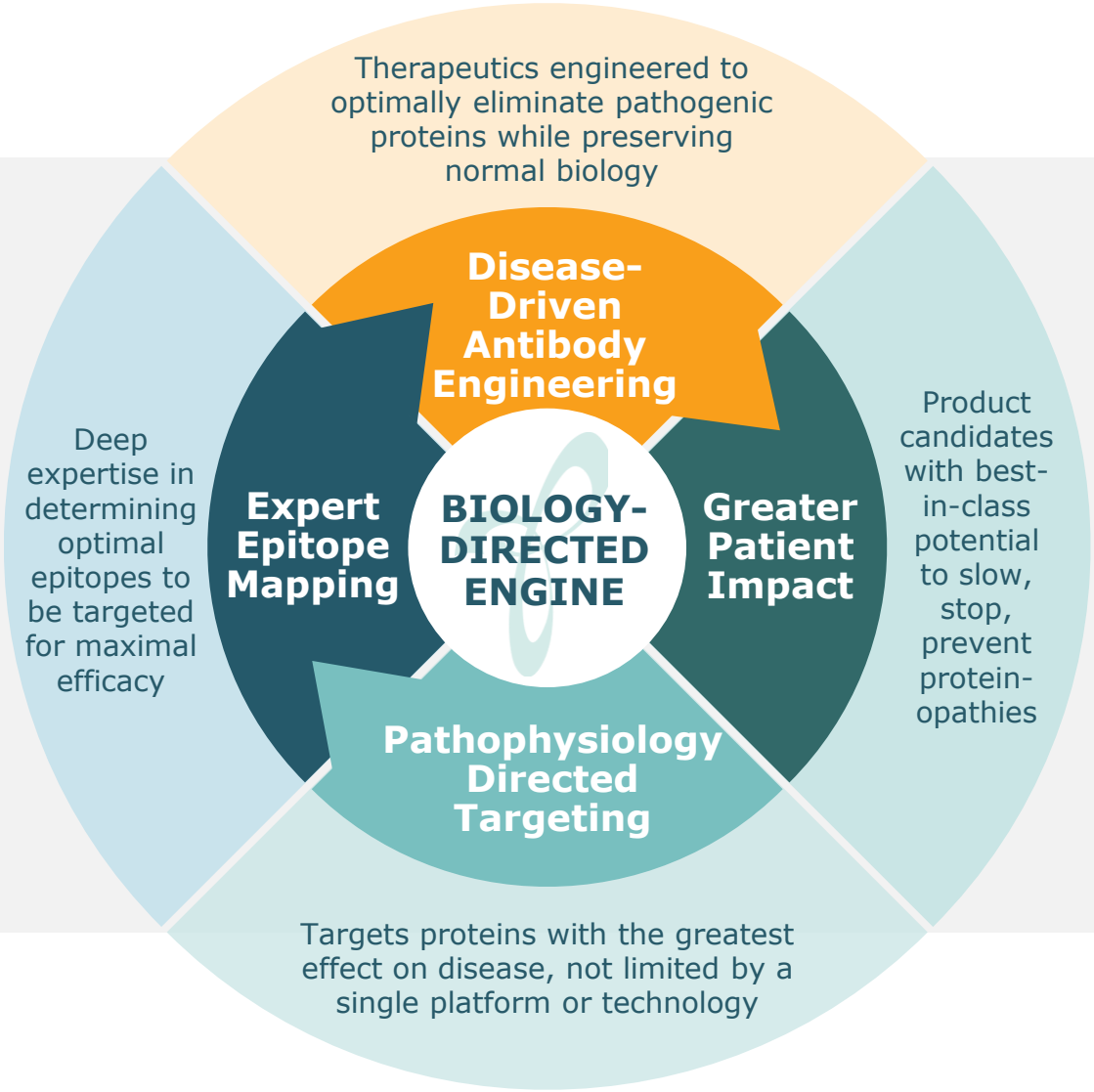
2.08 years

Median overall survival New York Heart Association class III patients with ATTR cardiomyopathy[7,8]

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] González-Duarte A, Conceição I, Amass L, Botteman MF, Carter JA, Stewart M. *Neurol Ther*. 2020;9(1):135-149.
[5] González-López E, Gagliardi C, Dominguez F, et al. *Eur Heart J.* 2017;38(24):1895-1904. [6] Tanskanen M, Peuralinna T, Polvikoski T, et al. *Ann Med.* 2008;40(3):232-239. [7] Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995
[8] 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

Three partnered Phase 2 programs

One partnered Phase 1 program

Wholly-owned Phase 1 program

Strong Collaborations Established

Bristol Myers Squibb

Novo Nordisk[1]

Roche

[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

PROGRAM/ INDICATION	PROTEIN TARGET	DISCOVERY	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	GLOBAL PARTNER[3]
Prasinezumab ***Parkinson's disease***	α-Synuclein (C-terminus)	PASADENA (Phase 2) | PADOVA (Phase 2b)					Roche
Coramitug (PRX004) *ATTR-CM* ODD[1]	Transthyretin (misTTR)	Phase 2					novo nordisk
BMS-986446 (PRX005) *Alzheimer's disease*	Tau (MTBR)	Phase 2					Bristol Myers Squibb
PRX012 *Alzheimer's disease* Fast Track[2]	Aβ (N-terminus)	ASCENT (Phase 1)					
PRX019 *Neurodegeneration*	Undisclosed Target	Phase 1					Bristol Myers Squibb
PRX123 *Alzheimer's disease* Fast Track[2]	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] Orphan Drug Designation granted by FDA & EMA; [2] FDA Fast Track designation;
[3] 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

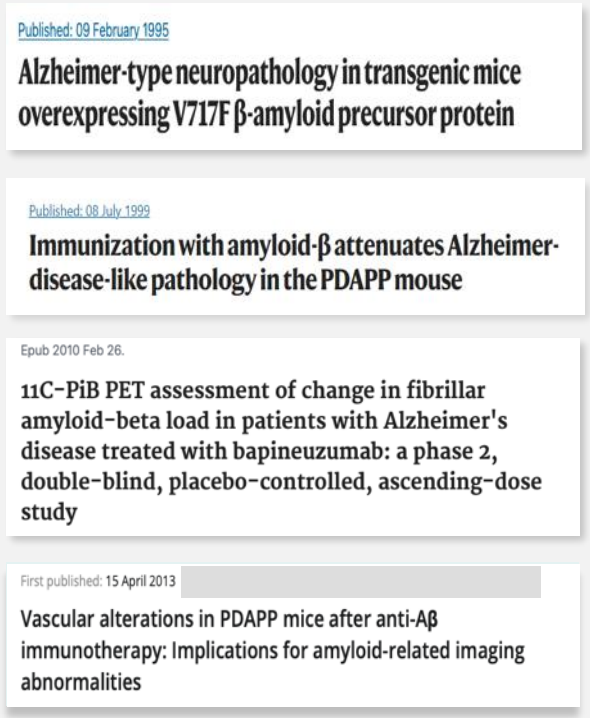
2012
Prothena spins-out from Elan with a wholly-owned drug discovery platform

- **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

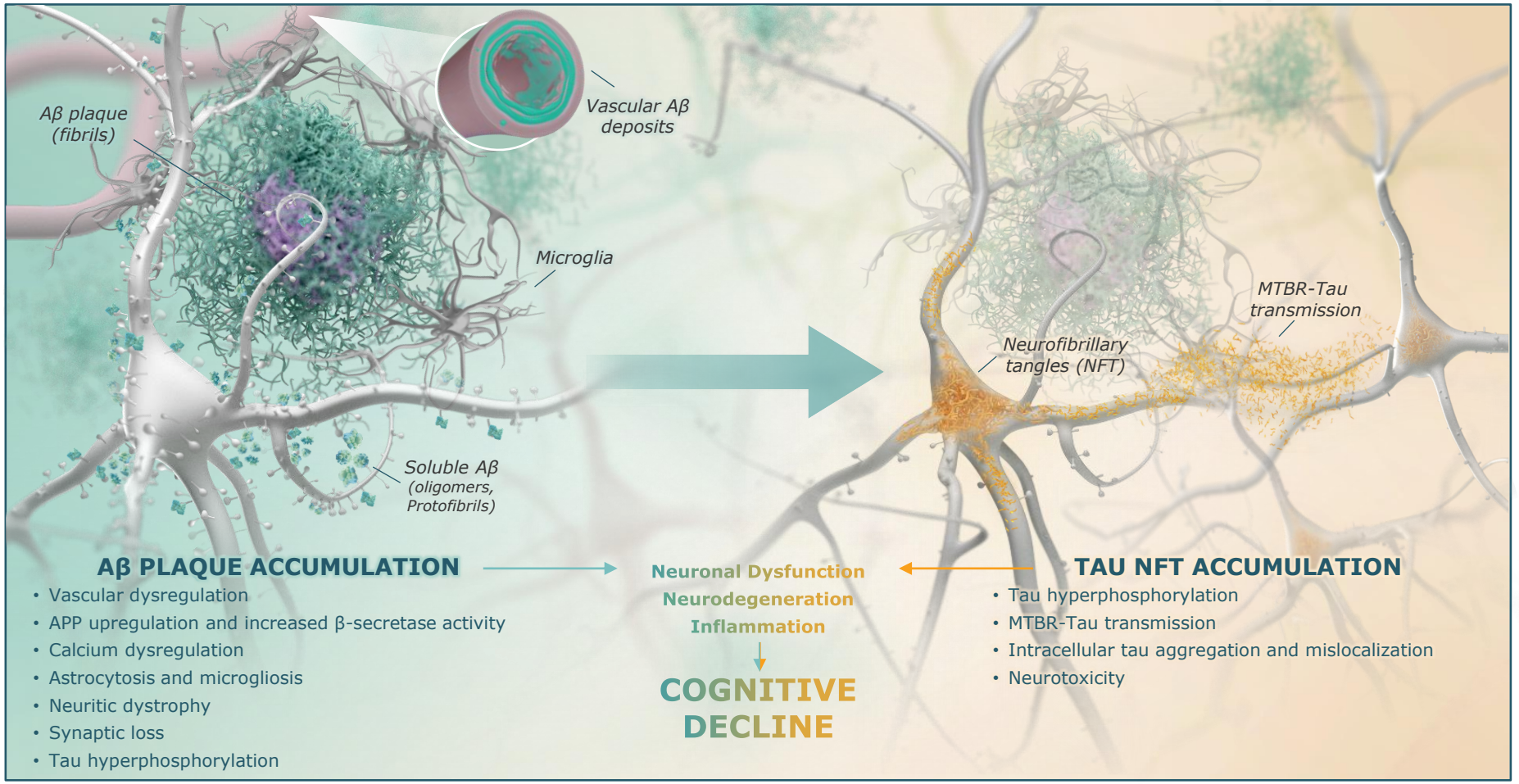
[1] Games D, et al.1995 *Nature*; [2] Zago W, et al. 2013 *Alzheimers Dement*; [3] Schenk D, et al. 1999 *Nature*; [4] Rinne, et al. 2010 *Lancet Neurol*; [5] Skov M, et al. Preclinical data available at: https://tinyurl.com/3zzpmbxh; [6] Dolan P. Preclinical data available at: https://tinyurl.com/3kf7pvnd.

Targeting Alzheimer's Where it Matters

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

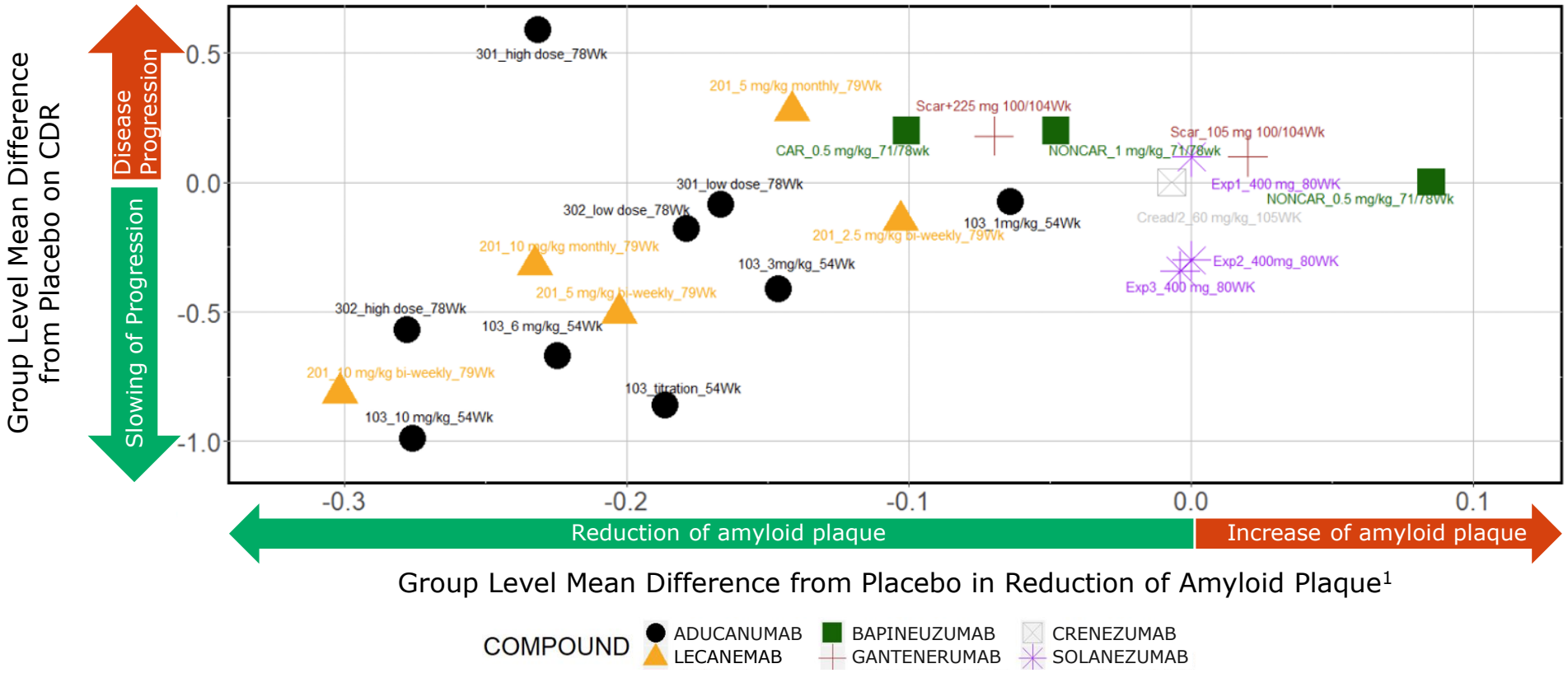
Reduction of Aβ plaque associated with clinically meaningful slowing of disease progression

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



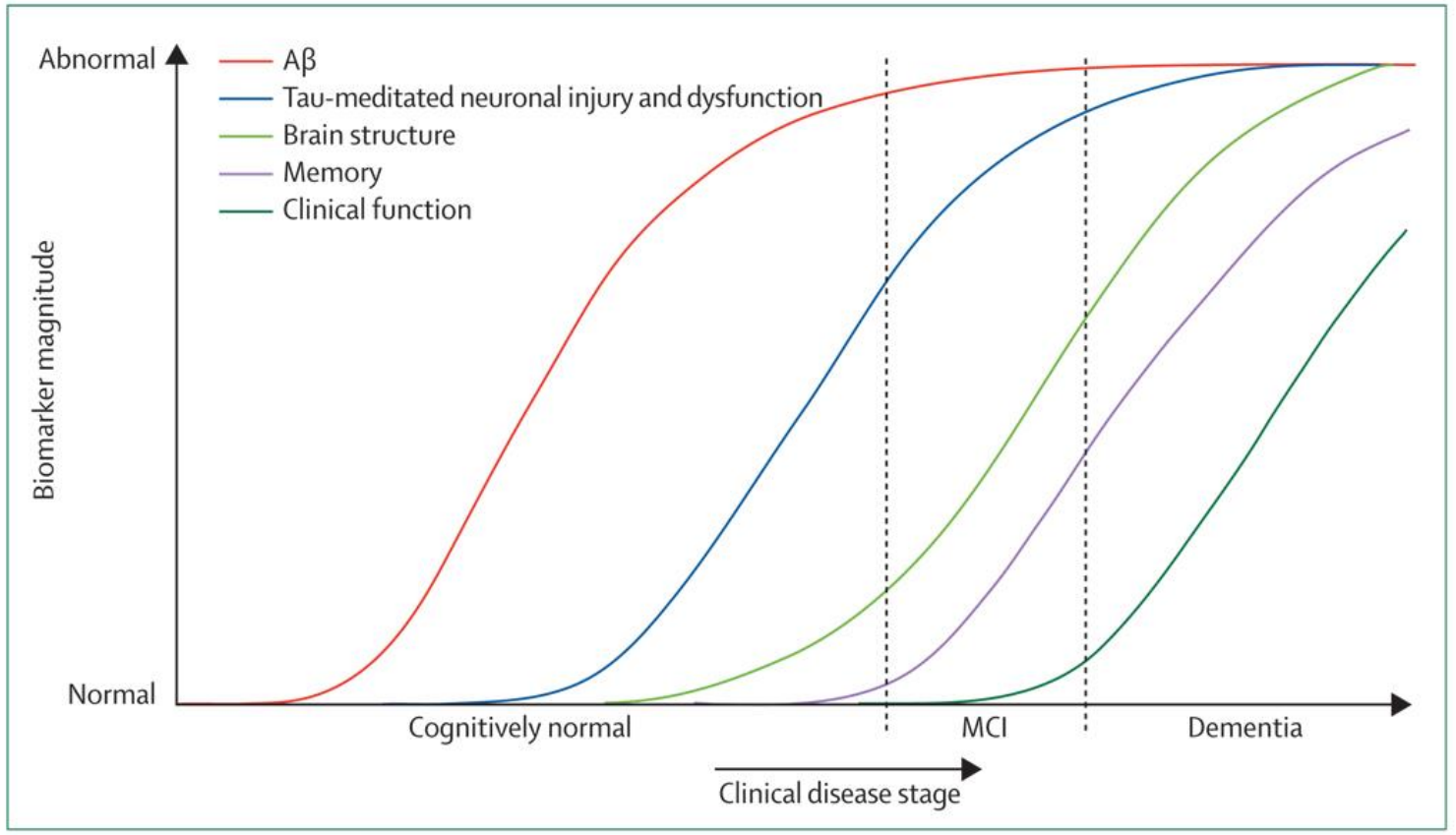
2020 US FDA ANALYSIS: Aβ has been established as a disease modifying target in AD[2,3]

[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]



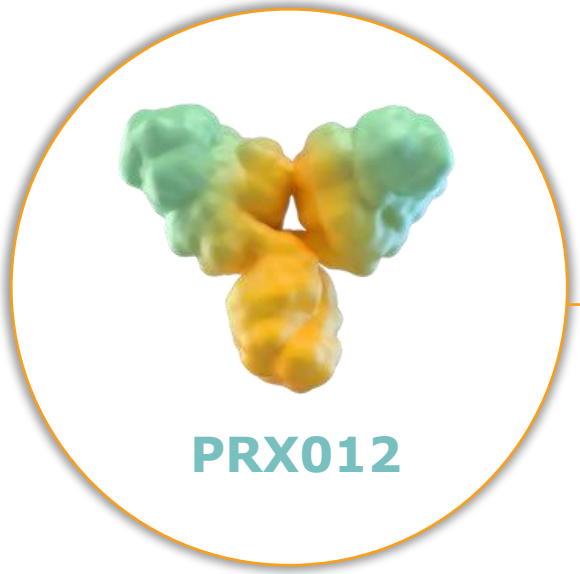
[1] Jack, Clifford et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, 2010 NIH Public Access

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

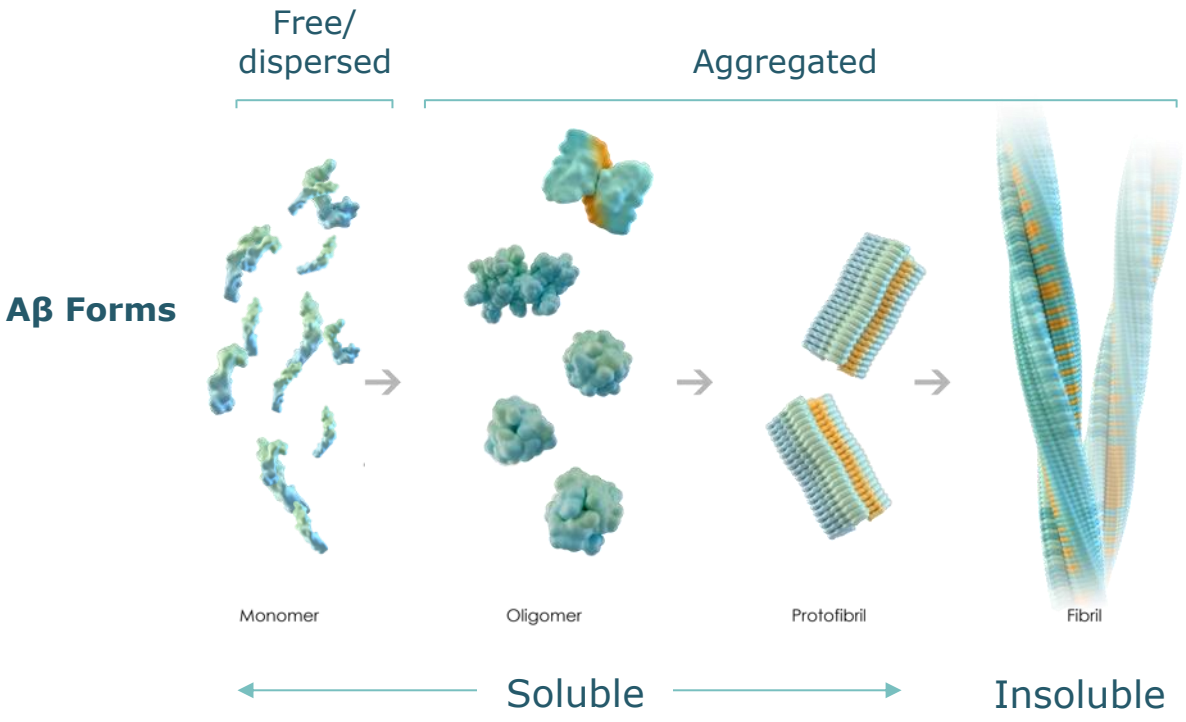
	TARGET PROFILE	ANTIBODY DESIGN ATTRIBUTES
Maintain From First Generation Antibodies	**Effectively clear soluble and insoluble aggregated amyloid**	• N-terminal directed • Full effector-function
Innovations to Minimize Disease and Treatment Burden	**Low-volume subcutaneous (SC) delivery**	• High binding 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

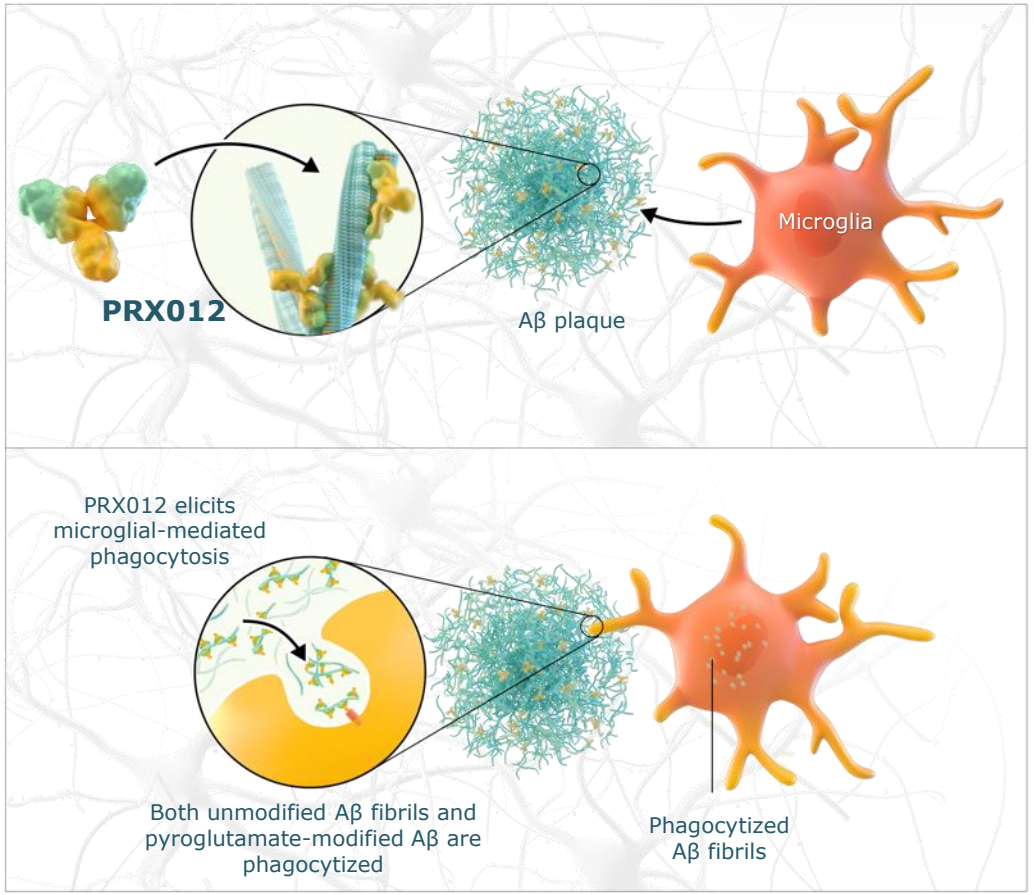
OUR MISSION

- 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



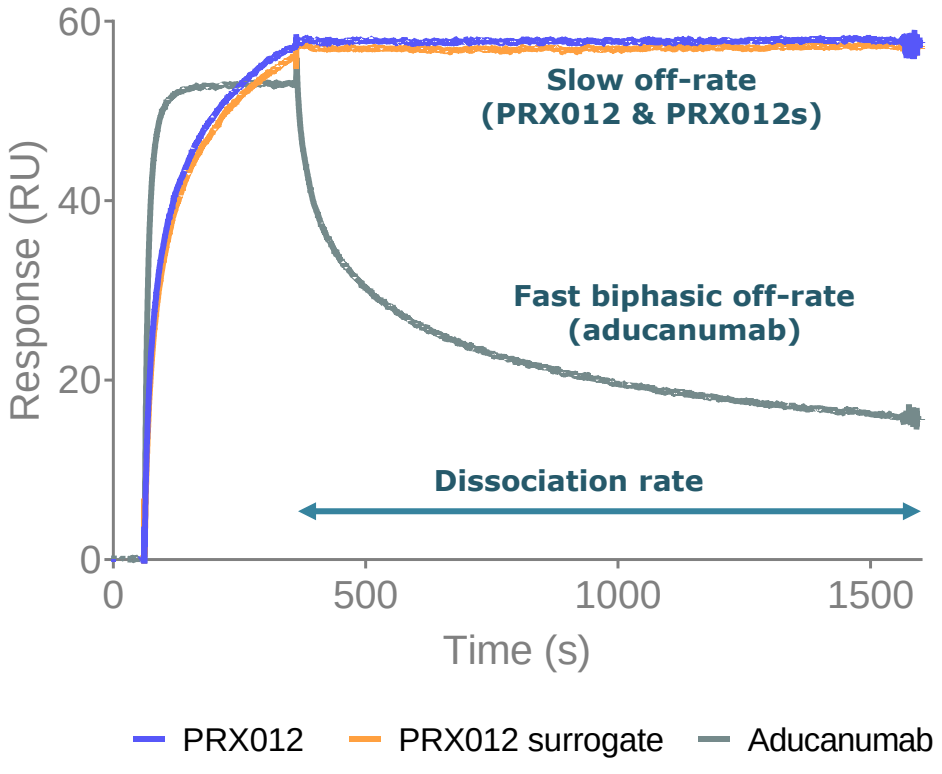


Microglia recognize and engulf PRX012-opsonized Aβ fibrils

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

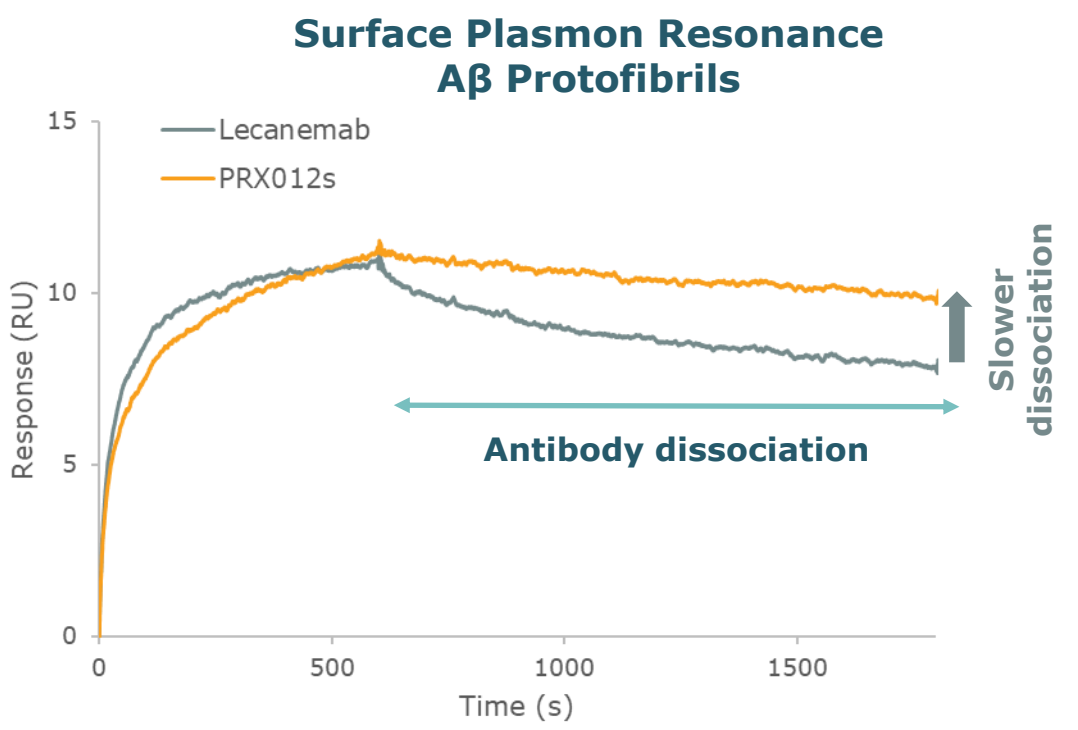
Compound	Fibril/Plaque	N3pE-Aβ
PRX012	0.070[a]	>67[b]
PRX012s	0.054[a]	>67[b]

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

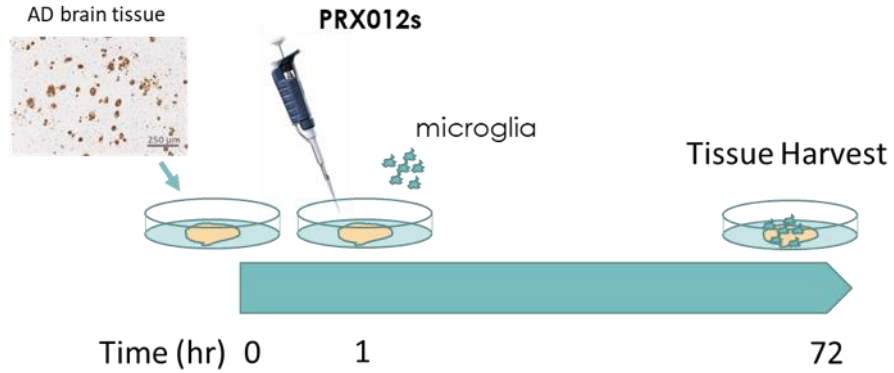
SPR Binding Kinetics

	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

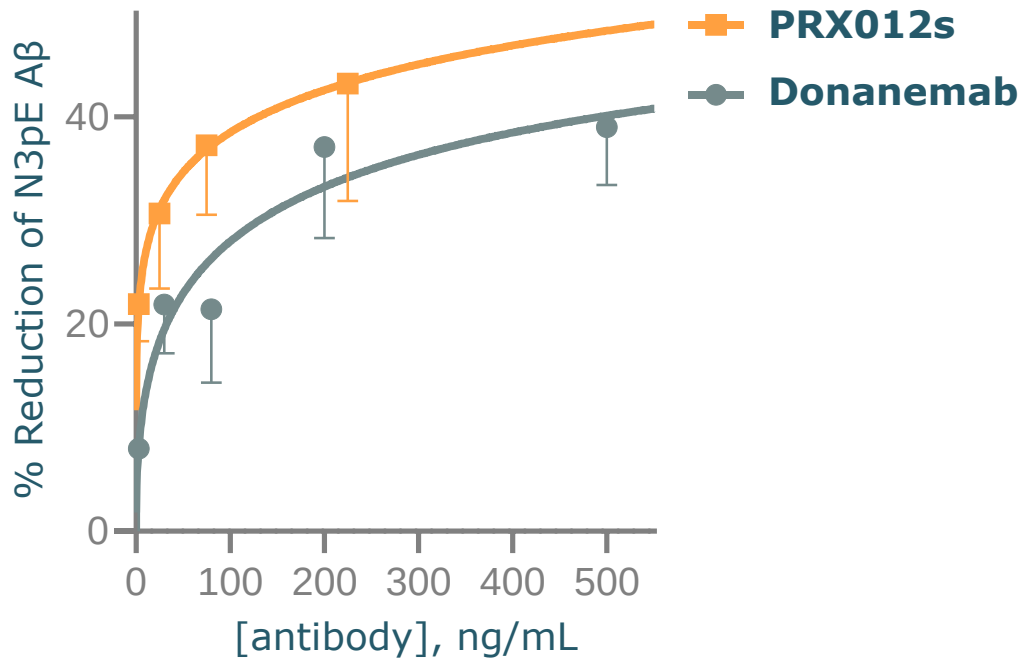
- **PRX012s binds to Aβ protofibrils with approximately 20-fold greater affinity than lecanemab when tested under the same conditions**
- **Greater affinity is driven largely by a slower binding dissociation**

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



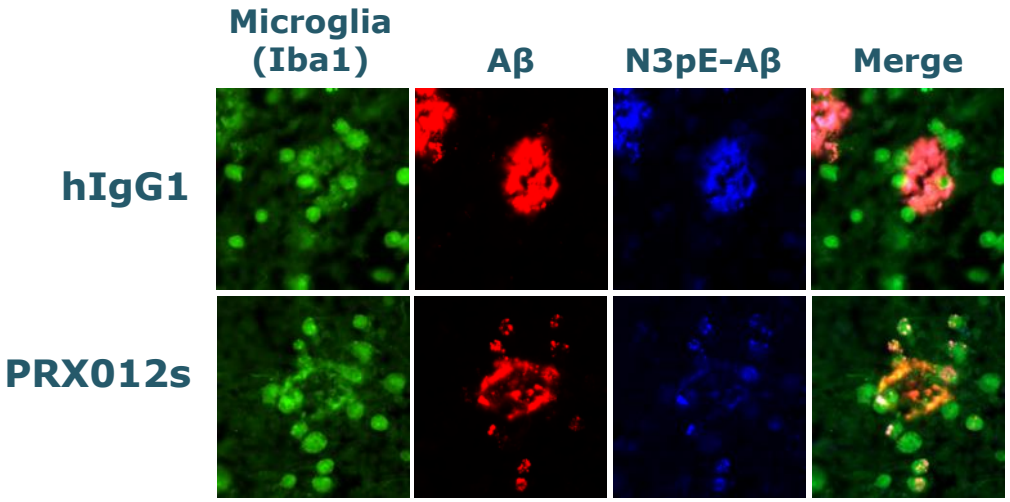
	Study Conditions
Tissue	Post-mortem AD brain tissue (same donor used for all conditions)
Treatment	PRX012s, donanemab, or IgG1 isotype control
Microglia	Primary mouse microglia (800,000 cells/mL)
Culture time	72 hours at 37°C



- **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**

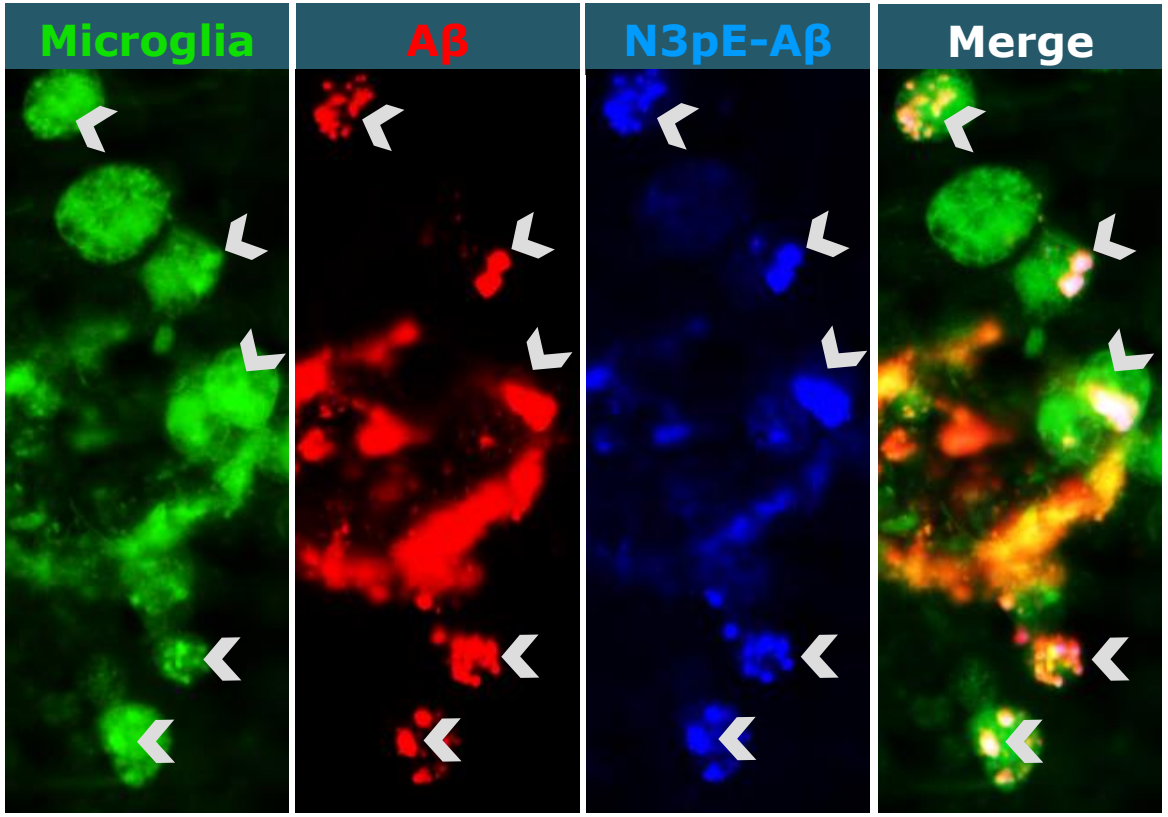
IgG, immunoglobulin; N3pE-Aβ, pyroglutamate-modified Aβ.
Donanemab was generated from a publicly available sequence.

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
- Up to high teens royalties on a weighted average basis

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 also included $100 million upfront payment and a $50 million equity investment in Prothena
CDR-SB, Clinical Dementia Rating Scale Sum of Boxes

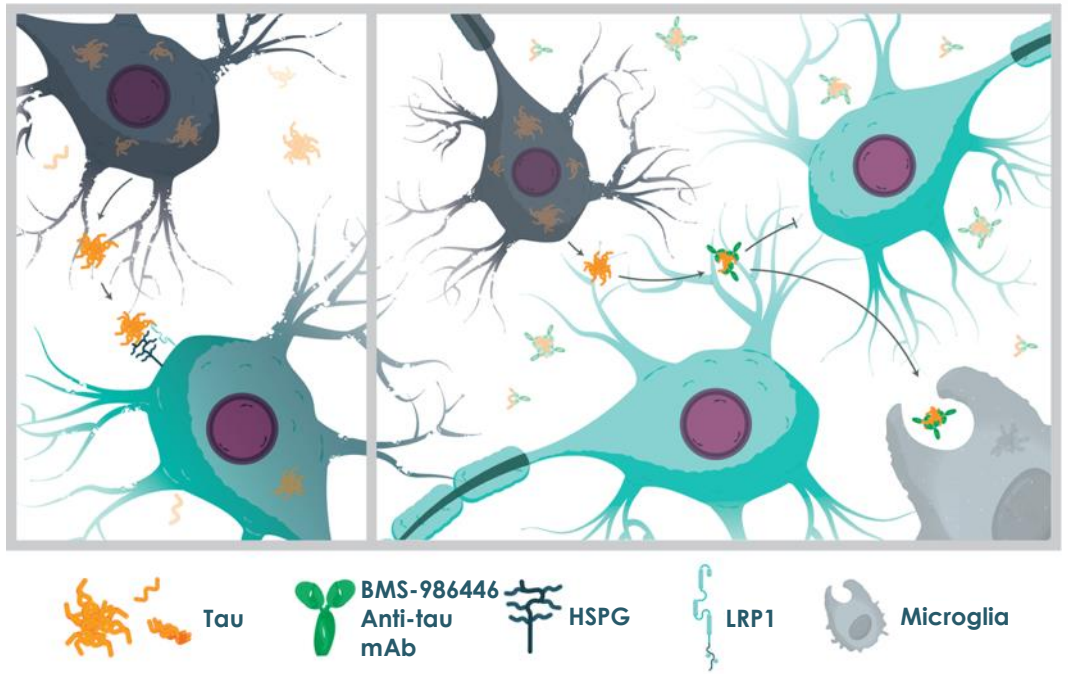
BMS-986446: MTBR-Specific Anti-Tau Antibody

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

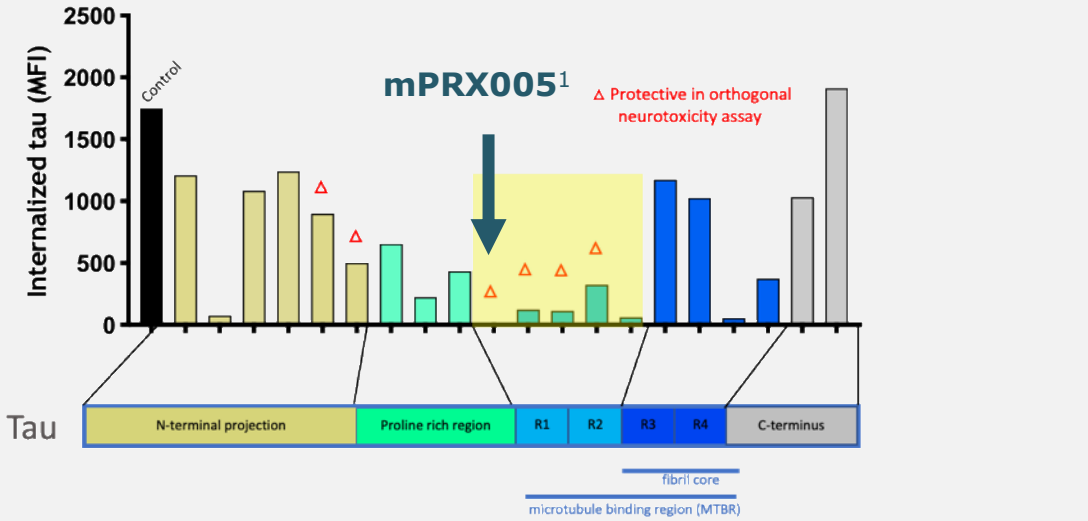


BMS-986446: Potential Best-in-Class MTBR-Specific Anti-Tau Antibody to Reduce Pathogenic Tau Spread

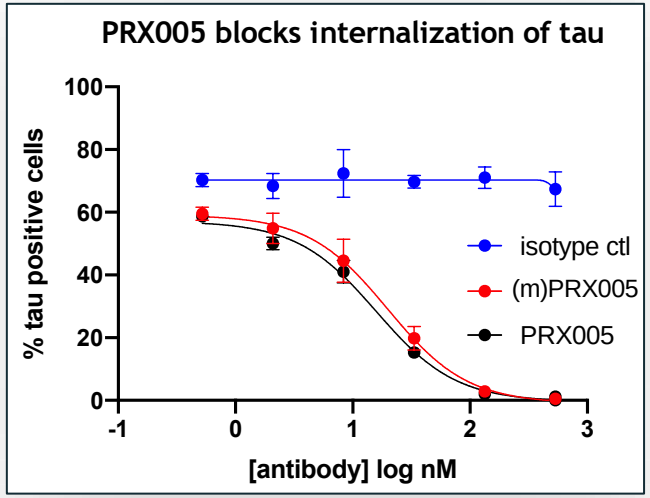
[1] Ahmed, Z., Cooper, J.. et al. A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. 2014 *Acta Neuropathol*;
[2] Horie, k., Barthelemy, H., Bateman, R.J. CSF tau microtubule binding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

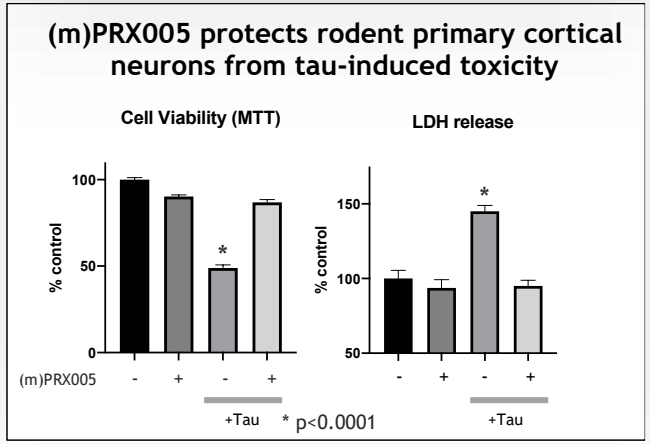
BMS-986446 (PRX005): Superior in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity Compared to Other Anti-Tau Antibodies

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



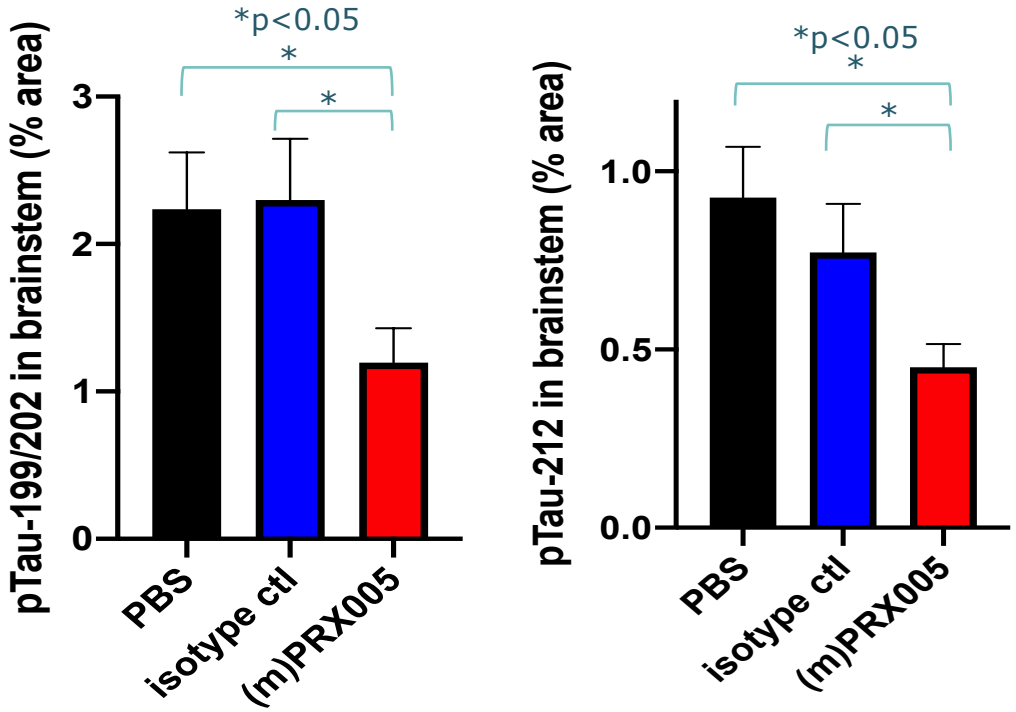


[1] (m)PRX005 = murine form of PRX005 (BMS-986446)

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

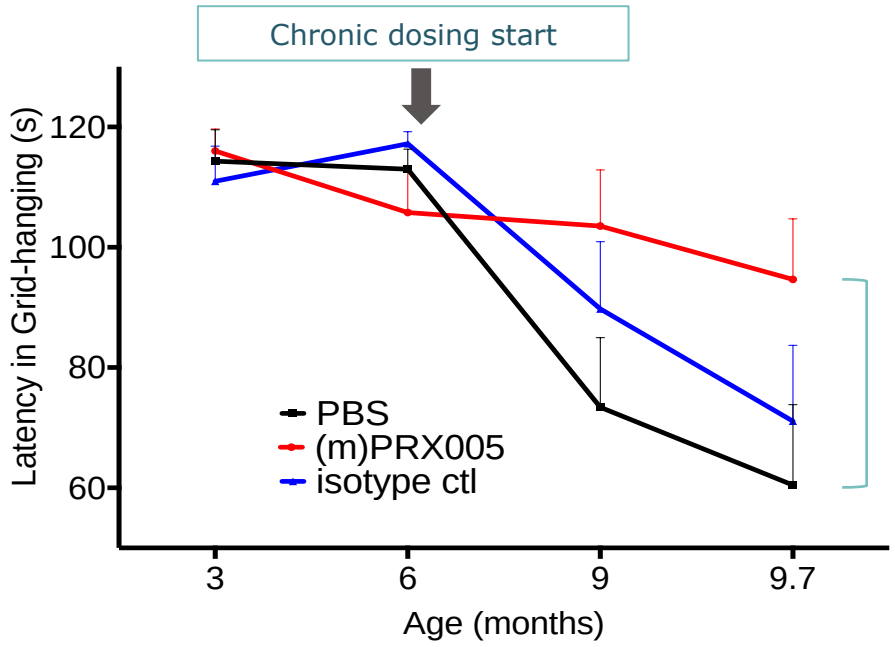
All values are mean ± SE (n=15-20)

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

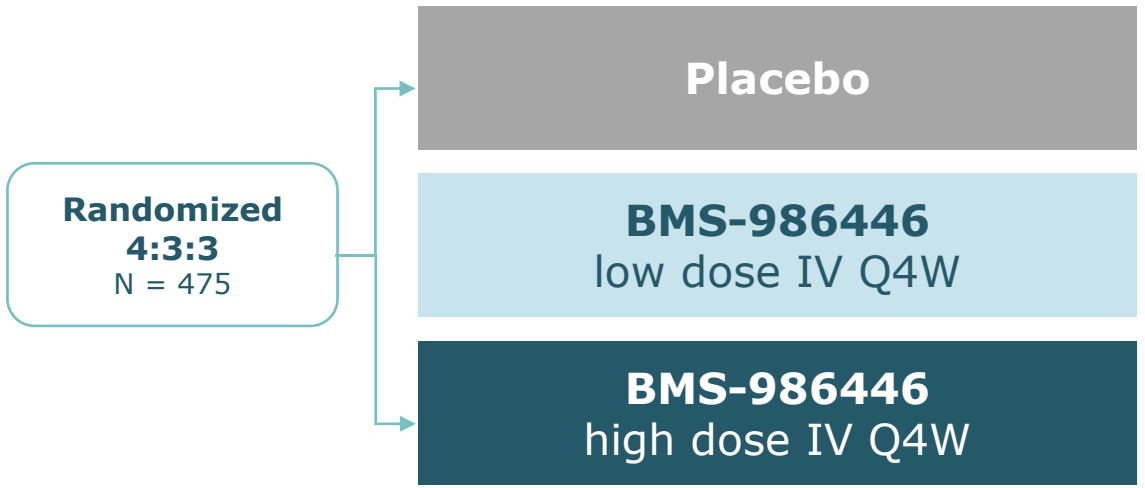
(m)PRX005 = murine form of PRX005 (BMS-986446)

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.

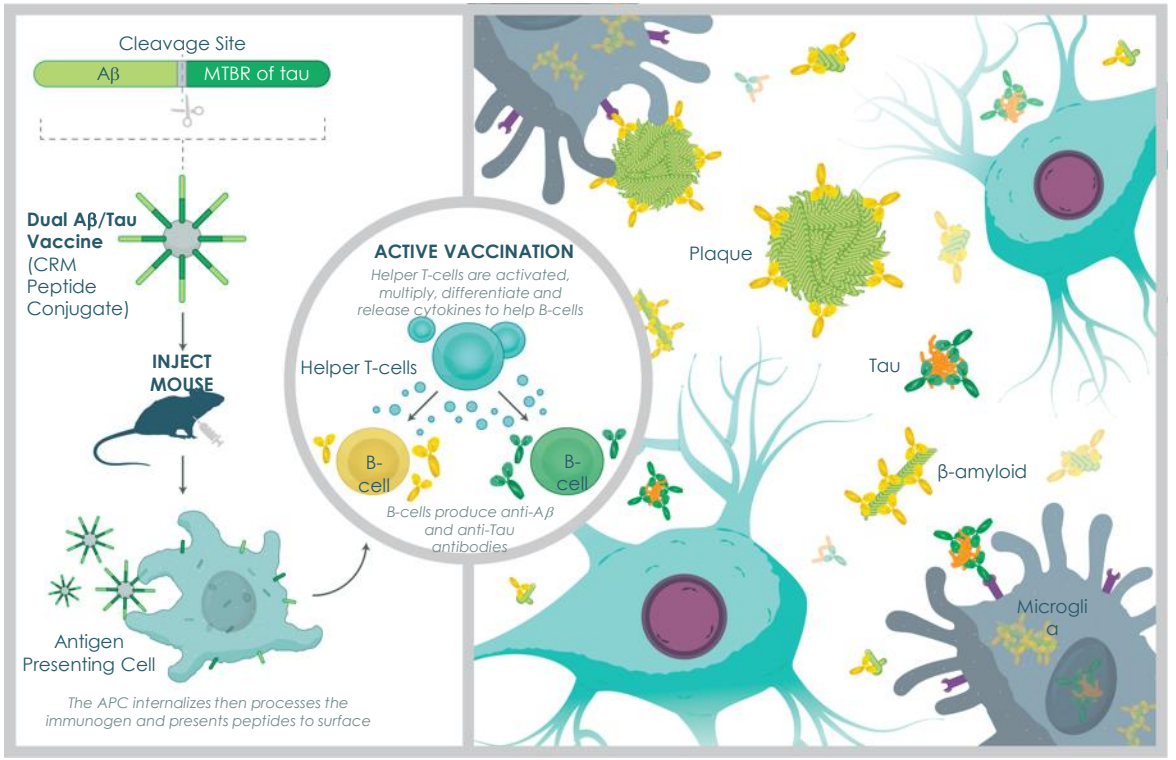
PRX123

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**



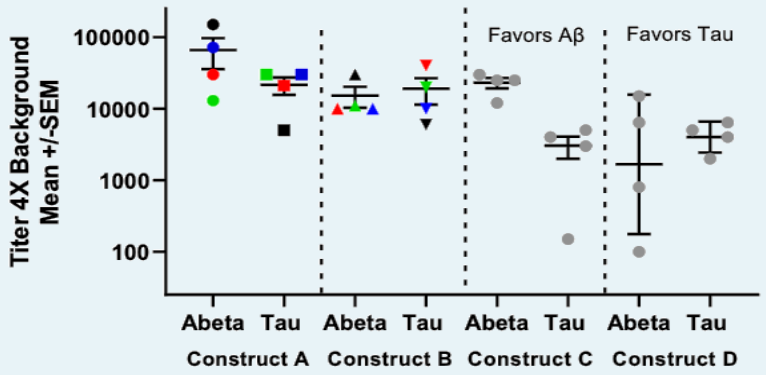
Desirable Attributes of Aβ/Tau Vaccines and Prothena's Design Strategies

		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

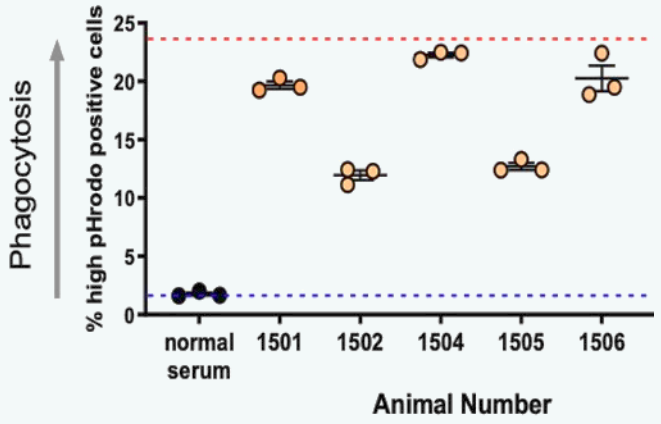
Prothena's Dual Aβ/Tau Vaccines Demonstrate Desirable Quantity, Quality and Safety

Quantity



✓ High, balanced, consistent

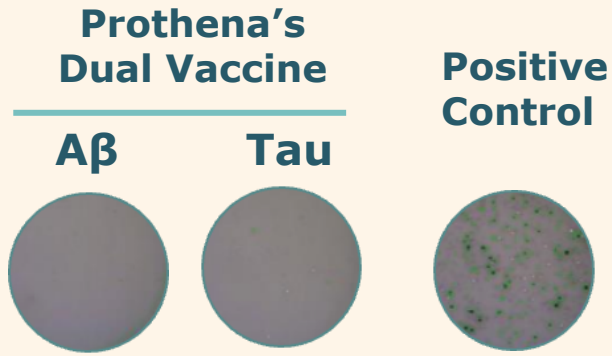
Quality



✓ 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

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:

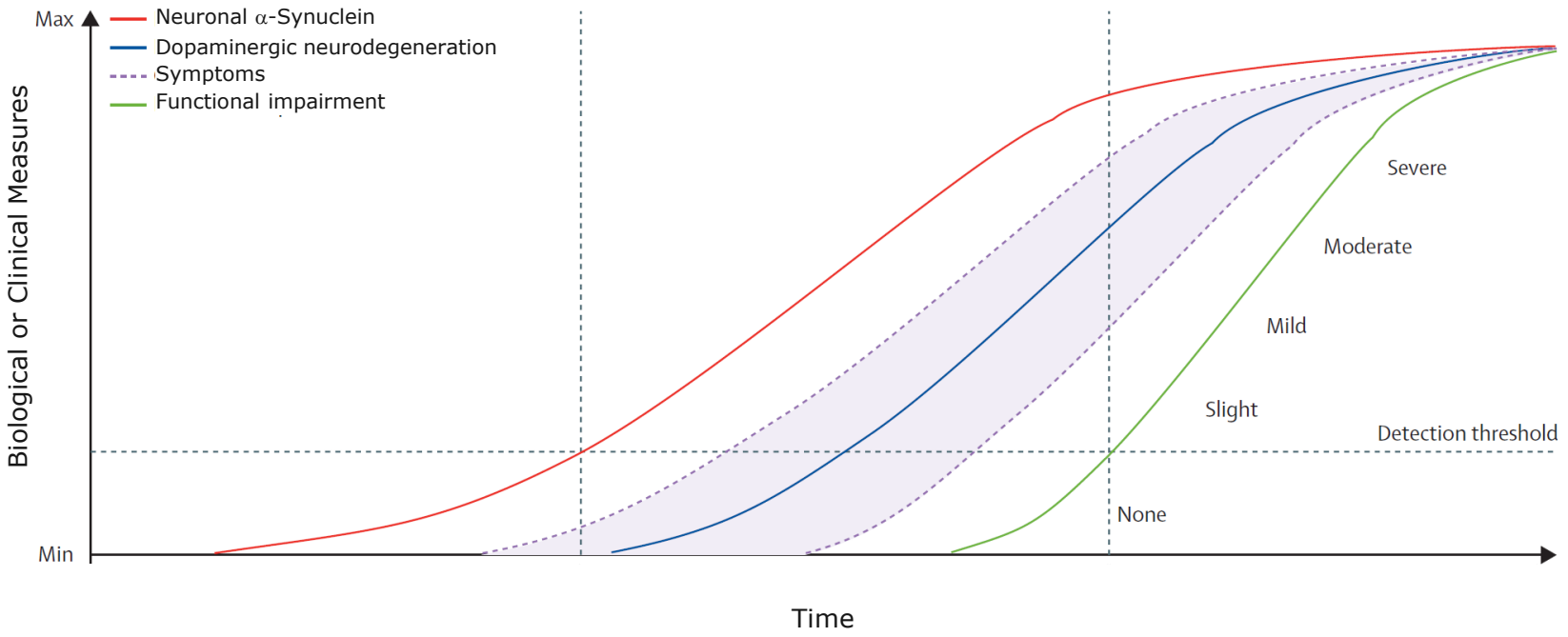
- Open-label extension studies from both PADOVA and PASADENA ongoing to explore the observed effects
- PASDAENA OLE showed slowing of motor progression vs. matched RWD PPMI cohort[4]
- Roche will continue to evaluate the data and work together with health authorities to determine next steps

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)

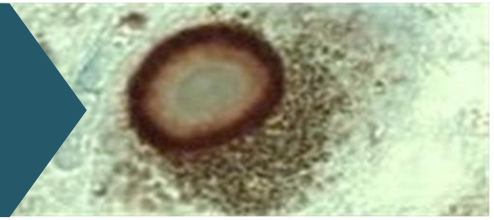
α-Synuclein Pathology is Strongly Implicated in Parkinson's Disease

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



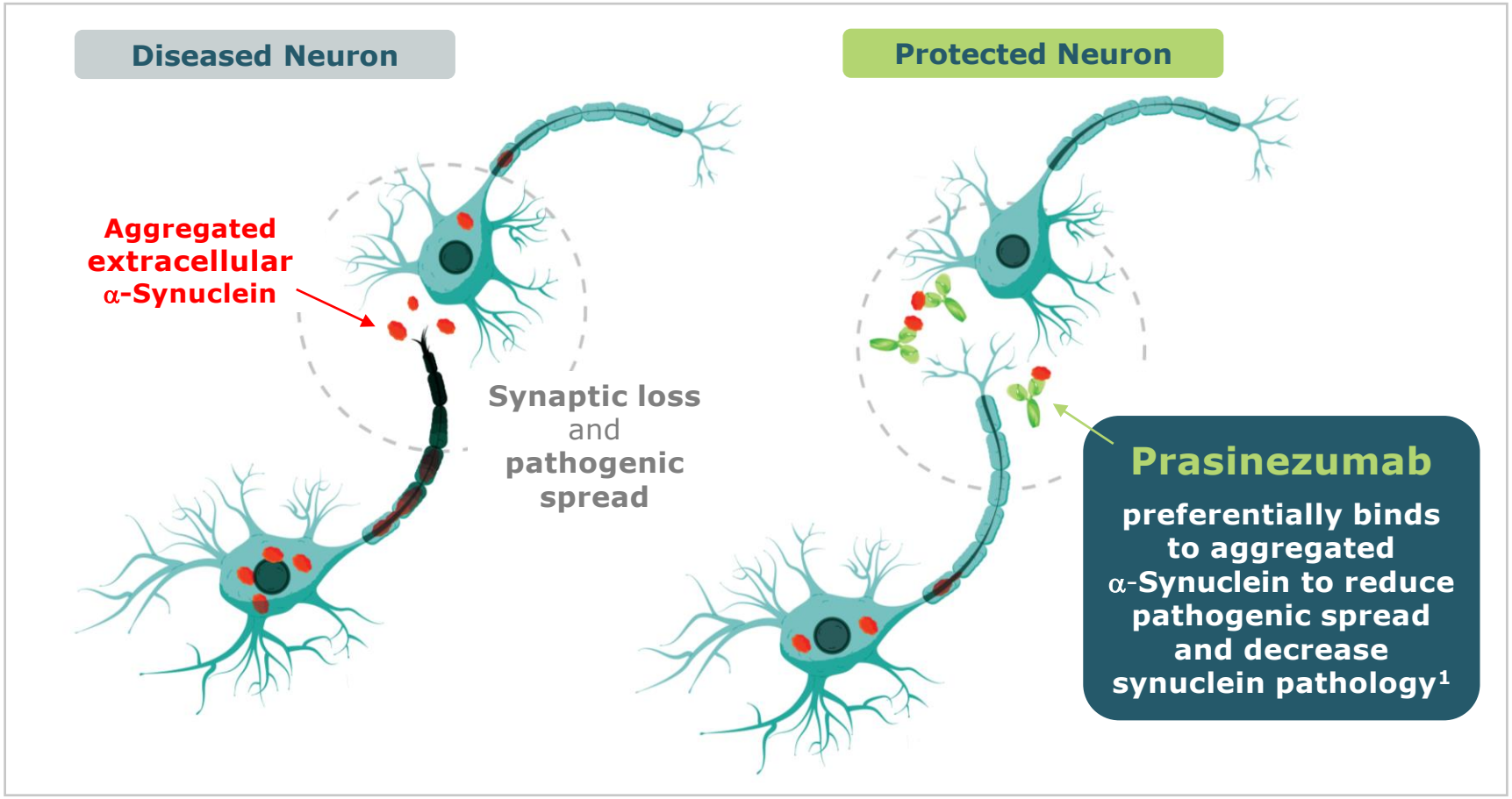
Symptoms: Clinical signs or symptoms attributable to neuronal α-Synuclein disease that can be motor or non-motor (e.g., hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety).
Functional Impairment: Degree of impact on activities of daily living.
Chart adapted from: 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)	**Phase 2b PADOVA** (NCT04777331)
• 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)	• 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 = 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	• **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
PADOVA study population more advanced than the PASADENA population	
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 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

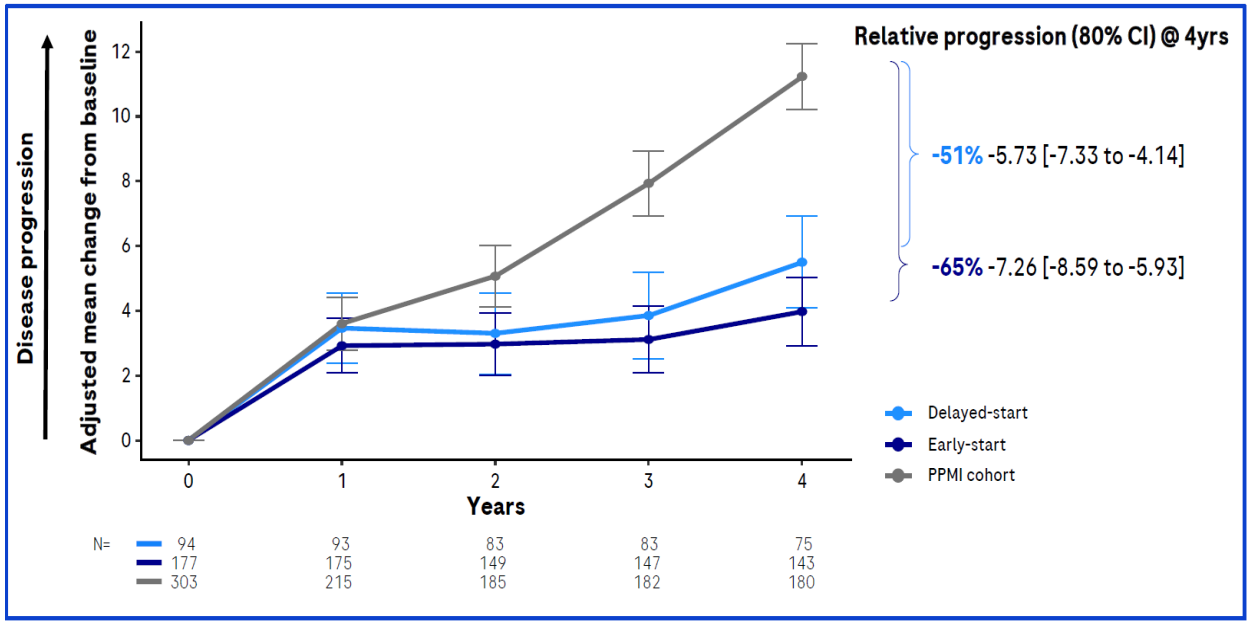
Results support the potential of prasinezumab to slow underlying disease pathophysiology and clinical decline in patients with PD

[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)

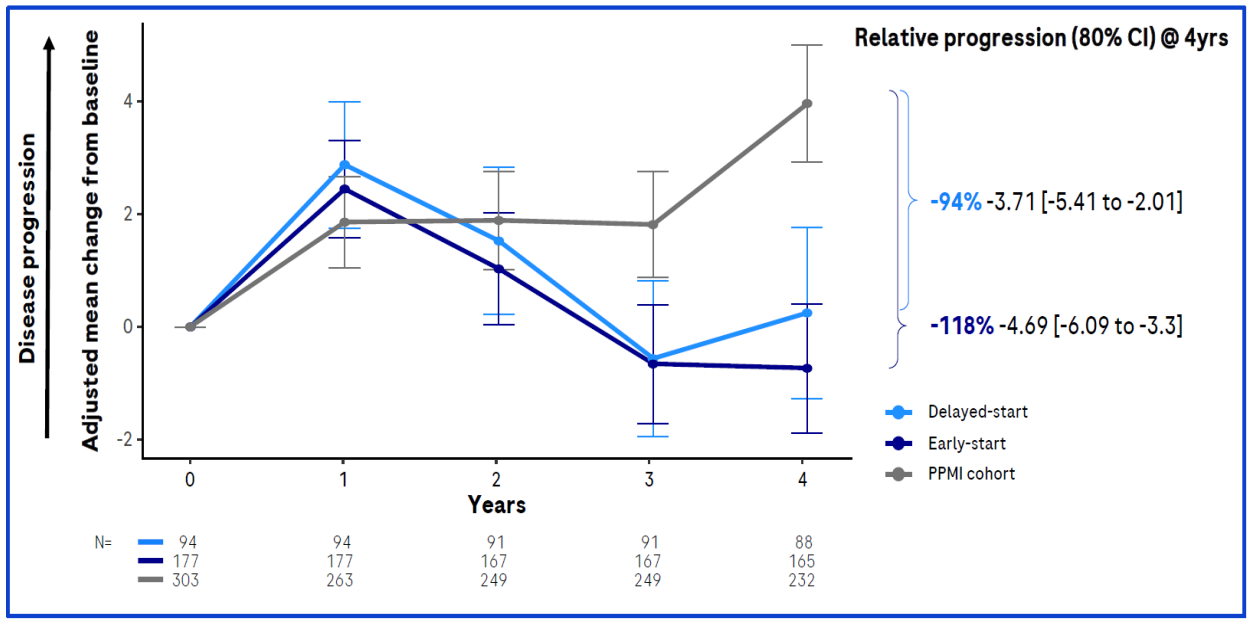
The data suggests that prasinezumab slowed the progression of motor deficits (MDS-UPDRS Part III OFF score) in early-stage Parkinson's disease

[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; results expected in 2H 2025

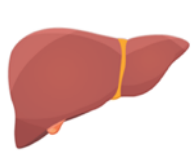
Phase 1 Trial:

- 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



LIVER



FREE TETRAMER

Protein Misfolding



MONOMER, SOLUBLE AGGREGATE AMYLOID FIBRILS



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

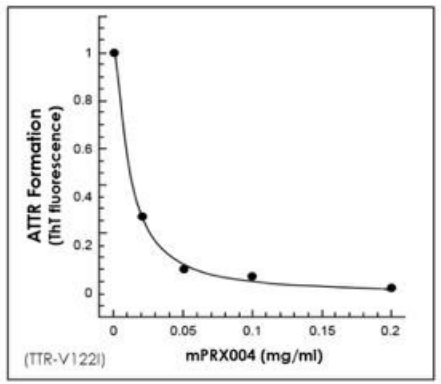
Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF mPRX004

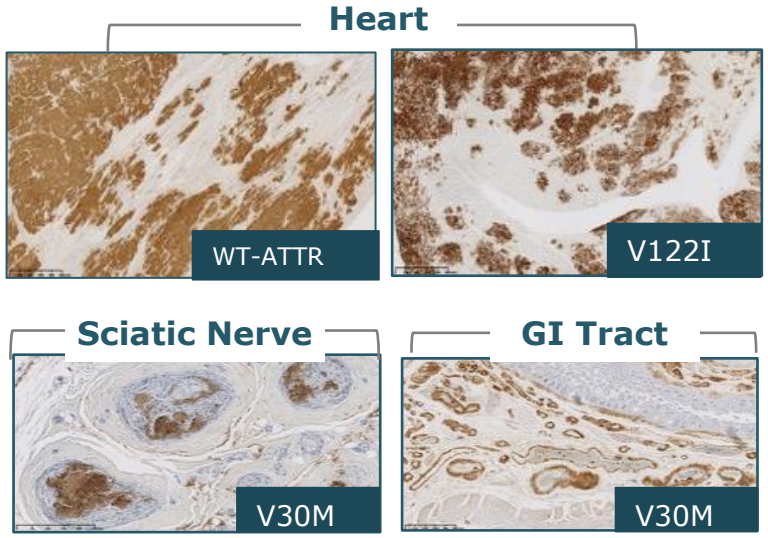
mPRX004 (murine form of PRX004) preclinical results:[1]

- ✓ 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

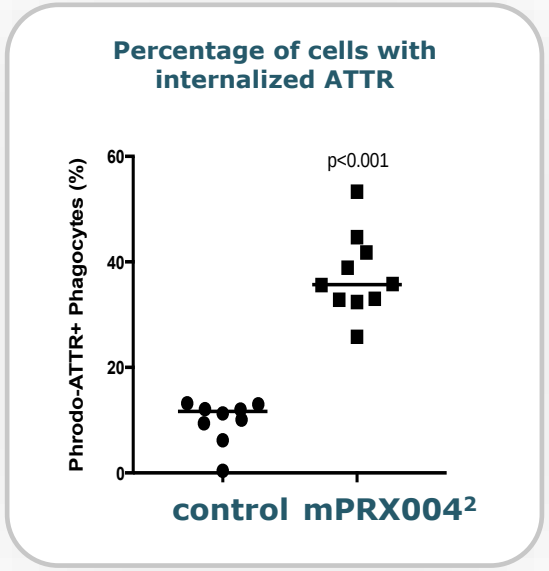
Inhibition of amyloid formation



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

PRX012
Alzheimer's disease

August 2025 to YE25	Multiple data readouts starting August 2025 and continuing throughout the year from PRX012 Phase 1 ASCENT clinical trials

PRX123
Alzheimer's disease portfolio

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

Mid-25	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
- ☐ Up to high teens royalties on a weighted average basis

BMS leading and funding further development and commercial

PRX019[2]

Status: Phase 1 Ongoing

- ☑ $80 million option exercised
- ☐ $242.5 million in potential development and regulatory milestones
- ☐ $375 million in potential commercial milestones
- ☐ Up to high teens royalties on a weighted average basis

Prothena conducting ongoing Phase 1 trial

[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)