

prothena®

CORPORATE OVERVIEW

August 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 pipeline, and expected milestones in 2025, 2026, 2027, and beyond, including the expected timing of (i) the up to $105 million in clinical milestone payments that we may earn from Novo Nordisk and BMS, (ii) reporting initial data from our ongoing Phase 1 clinical trials evaluating PRX012, (iii) completion of our ongoing Phase 1 clinical trial evaluating PRX019, (iv) completion of the ongoing Phase 2 clinical trial evaluating BMS-986446, (v) completion of Phase 3 development for prasinezumab, and (vi) for coramitug, reporting of data from the Phase 2 clinical trial and completion of Phase 3 development; amounts we might receive under our partnerships and collaborations with Roche, BMS, and Novo Nordisk; 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; and plans for ongoing and future clinical trials of PRX012, BMS-986446, prasinezumab, coramitug, and PRX019. 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 4, 2025, and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. This overview is made as of August 6, 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]

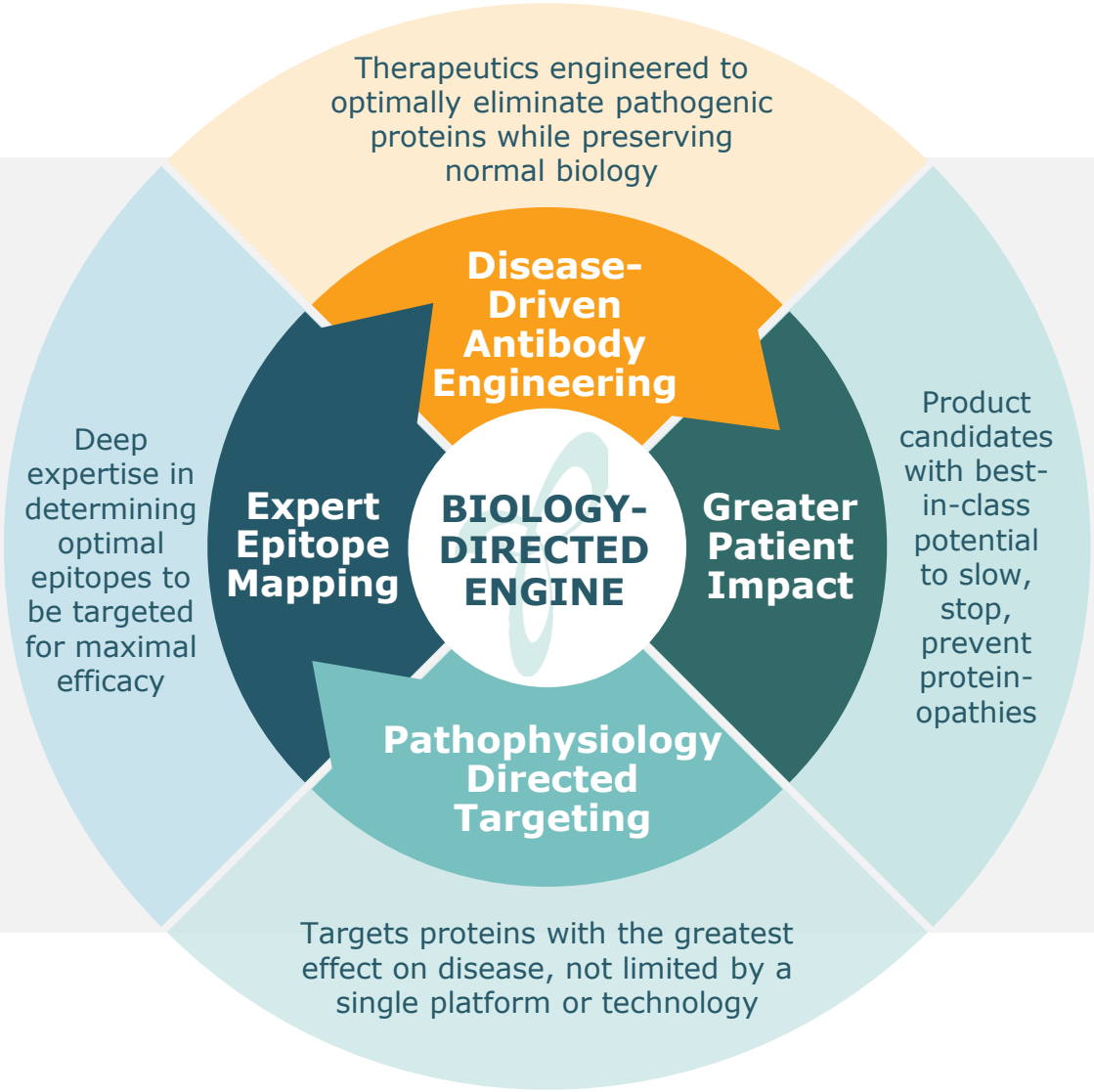
2.08 years

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

Two partnered Phase 3 programs

One partnered Phase 2 program

One partnered Phase 1 program

One 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)	Roche to initiate Phase 3 development by YE 2025					Roche
Coramitug (PRX004) *ATTR-CM* ODD[1]	Transthyretin (misTTR)	Novo to initiate Phase 3 development by YE 2025					novo nordisk®
BMS-986446 (PRX005) *Alzheimer's disease*	Tau (MTBR)	Phase 2 to complete in 2027					Bristol Myers Squibb®
PRX012 *Alzheimer's disease* Fast Track[2]	Aβ (N-terminus)	Phase 1 initial data in August 2025					
PRX019 *Neurodegeneration*	Undisclosed Target	Phase 1 to complete in 2026					Bristol Myers Squibb®
PRX123 *Alzheimer's disease* Fast Track[2]	Aβ + Tau	IND Cleared					

Neurodegenerative | Rare Peripheral

Aβ, Abeta
[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

Potential Value-Creating Milestones

Up to $105 Million in Clinical Milestones in 2026 Related to the Advancement of Coramitug and PRX019[1]

PRX012
Alzheimer's disease
Ph 1 ASCENT initial data (Aug 2025)

PRX019
Neurodegenerative diseases
Ph 1 Trial Completion (2026)

Bristol Myers Squibb®

BMS-986446
Alzheimer's disease
Ph 2 Trial Completion (2027)

Bristol Myers Squibb®

Prasinezumab
Parkinson's disease
Ph 3 Trial Completion

Roche

Coramitug
ATTR-CM
Ph 3 Trial Completion

novo nordisk®

2025 | **2026** | **2027** | **2028+**

Neurodegenerative | Rare Peripheral

[1] Coramitug potential milestone could be achieved after prespecified enrollment criteria are met in the Phase 3 clinical trial. PRX019 potential milestone could be achieved at time of decision to further develop PRX019 expected in 2026.

Prothena Partnerships Expected to Generate Meaningful Value Across Programs

Roche

Up to $755 Million in Total Milestones +Royalties

novo nordisk®

Up to $1.23 Billion in Total Milestones

Bristol Myers Squibb®

Up to $1.55 Billion in Total Milestones + Royalties Across Two Clinical Stage Programs

✓ Upfront Payment + Equity: $150 million[2]

Prasinezumab
Parkinson's disease

- ✓ **$135 million** paid to date
- ❑ **$620 million** remaining in regulatory and sales milestones[1]
- ❑ Up to double digit teen royalties
- ❑ US co-promote option

Coramitug (PRX004)
ATTR-CM

- ✓ **$100 million** paid to date
- ❑ **$1.13 billion** remaining in clinical, regulatory, and sales milestones

BMS-986446
Alzheimer's disease

- ✓ **$135 million** paid to date
- ❑ **$562.5 million** remaining in regulatory and sales milestones
- ❑ Up to high teens royalties on a weighted average basis

PRX019
Neurodegenerative diseases

- ✓ **$80 million** paid to date
- ❑ **$617.5 million** remaining in clinical, regulatory, and sales milestones
- ❑ Up to high teens royalties on a weighted average basis

Neurodegenerative | Rare Peripheral

[1] Includes $5 million clinical milestone payment for an indication outside of Parkinson's Disease.
[2] Bristol Myers Squibb owns approximately 2.2% of Prothena's outstanding shares as of March 3, 2025 ("record date")

Prasinezumab
Parkinson’s Disease

Worldwide Collaboration with Roche

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

Prasinezumab
Parkinson's Disease

Status: Phase 3 initiation by YE 2025

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

- ✓ $135 million paid-to-date
- Up to $620 million in additional milestones
- Up to double-digit teen royalties
- US co-promote option
- Roche: peaks sales potential >$3B (unadjusted)[4]

Phase 2 Clinical Development Programs:

- First anti-α-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 effect observed in population treated with levodopa in the Phase 2b PADOVA trial (~75% of participants)
- The PADOVA study also provided the first biomarker evidence of prasinezumab impacting the underlying disease biology

Next Steps:

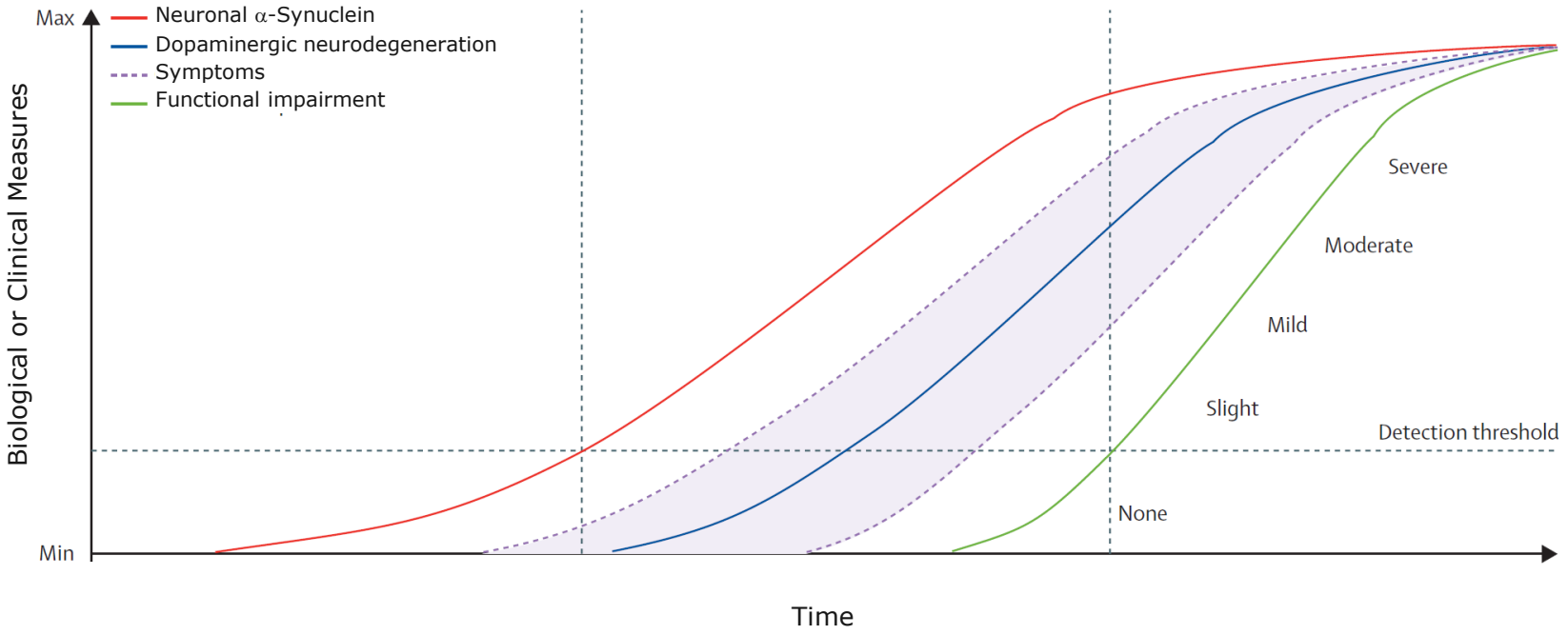
- Roche plans to initiate Phase 3 development for early-stage Parkinson's disease by YE 2025
- Open-label extension studies from both PADOVA and PASADENA ongoing to explore the observed effects

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] Roche's Half-Year Results 2025 Presentation on July 24, 2025; not a milestone or royalty projection.

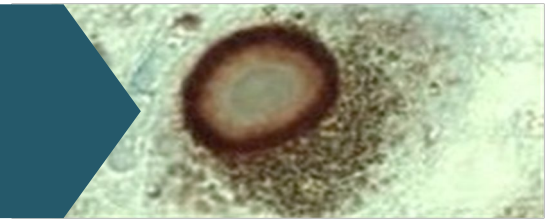
α-Synuclein Pathology is Strongly Implicated in Parkinson's Disease

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



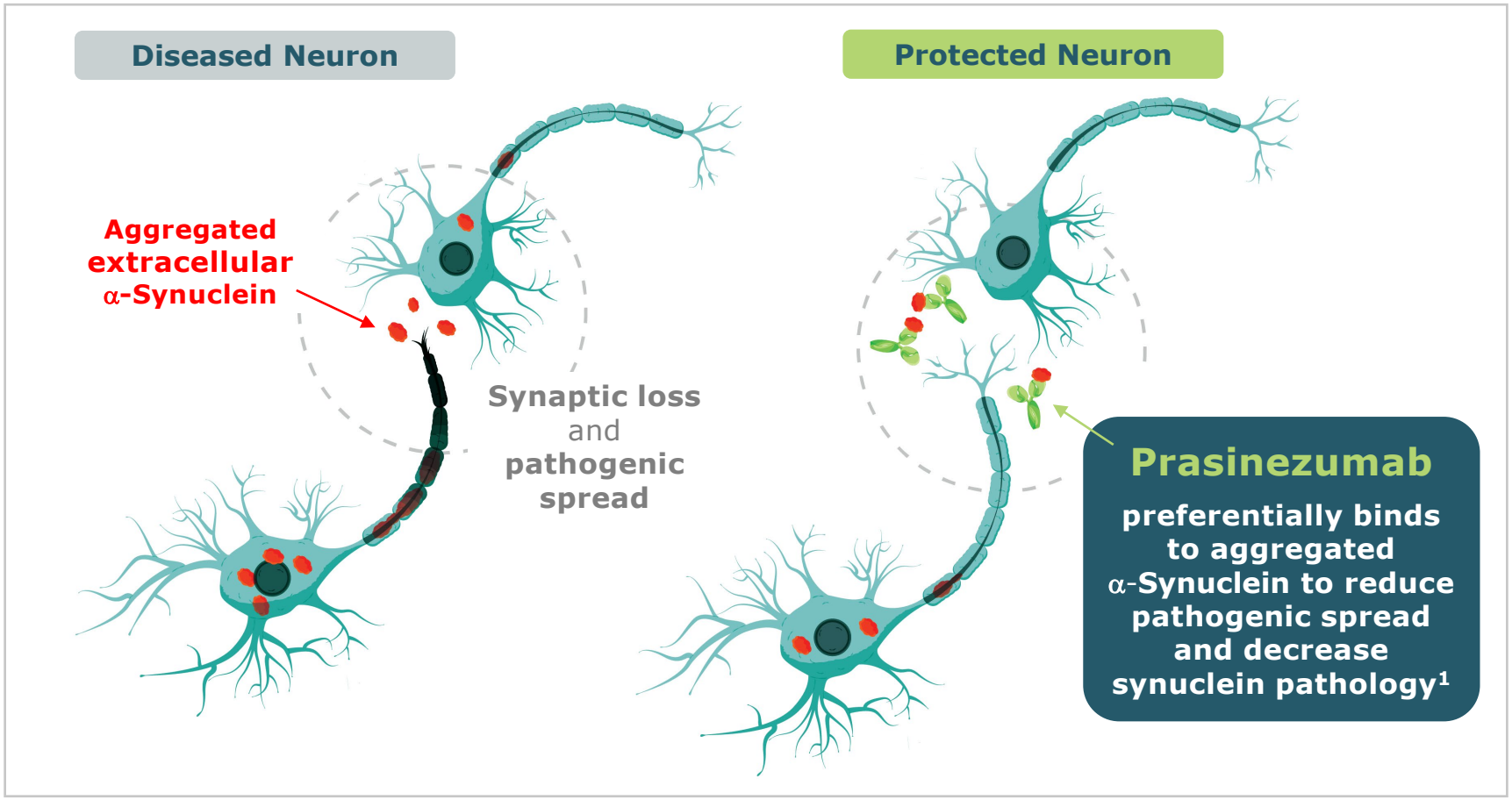
Symptoms: Clinical signs or symptoms attributable to neuronal α-Synuclein disease that can be motor or non-motor (e.g., hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety).
Functional Impairment: Degree of impact on activities of daily living.
Chart adapted from: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

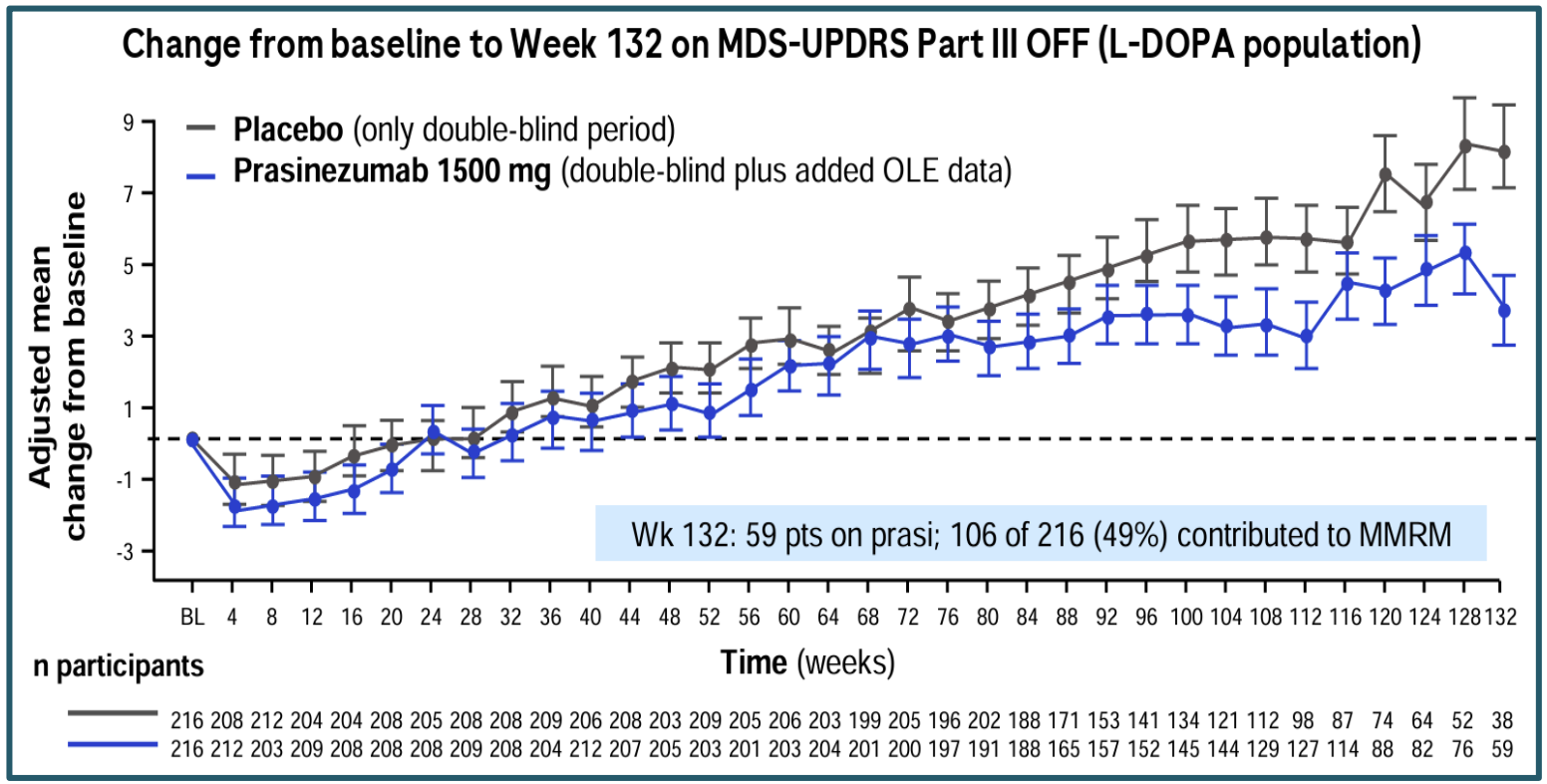


[1] Proposed mechanism of action.

Moving into Phase 3 in Parkinson's Disease

PHASE 2B (PADOVA) AND LONGER FOLLOW-UP DATA SUGGEST CLINICAL BENEFIT IN DELAY OF CONFIRMED MOTOR PROGRESSION

Phase 2b (PADOVA) 2.5 years results[1]



- Multiple endpoints from the PADOVA and OLE study suggest potential clinical benefit of prasinezumab; more pronounced effect in L-DOPA treated pts (~75% of population)
- Positive trends towards reduced motor progression sustained at 2.5 years (incl. OLE data)
- PASADENA and PADOVA OLE studies continuing with high retention / rollover
- Phase 3 to initiate by YE 2025

MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MMRM: Mixed Model Repeated Measures; MRI: Magnetic resonance imaging; OFF: Practically defined OFF state; OLE: Open label extension.

[1]Roche unpublished data, including up to 6 months OLE data. Slide adapted from Roche's Half-Year Results 2025 Presentation on July 24, 2025.

Roche's Phase 3 Go Decision Based on Meeting the Bar Criteria

INSIGHTS FROM PHASE 2B (PADOVA) AND OPEN LABEL EXTENSION WILL INFORM ROCHE'S PH 3 TRIAL DESIGN

The Bar		Prasinezumab
Answers a clear & addressable unmet need	✓	▪ >10m PD patients globally with no approved DMT to slow/stop progression
Engages a 'foundational target'	✓	▪ α-synuclein is a known biological driver of PD progression, as supported by Ph II studies PADOVA and PASADENA
Possesses worthy pharmacologic & developability characteristics	✓	▪ Innovative clinical endpoints linked to PD progression ▪ Favorable safety and tolerability profile
Achieves meaningful therapeutic differentiation	✓	▪ Potentially first in class anti-α-synuclein antibody
Unlocks a path to value	✓	▪ Peak sales potential >$3B (unadjusted)

✓ Meets the Bar criteria ✓ Doesn't meet the Bar criteria BUT has path to green

DMT: Disease modifying therapy; OLE: Open label extension; PD: Parkinson's disease.
Slide adapted from Roche's Half-Year Results 2025 Presentation on July 24, 2025.

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)

Status: Phase 3 initiation by YE 2025

Differentiated Depleter Mechanism of Action[1]

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

Worldwide Collaboration with Novo Nordisk

- ✓ $100 million paid-to-date
- $1.13 billion in potential additional milestones
- Potential blockbuster therapy

Phase 2 Signal Detection Trial (NCT05442047):

- Trial complete
- N = 105 ATTR-CM patients, 3 arms
- Participants received 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
- Detailed data are expected to be shared at a medical conference in 2H 2025

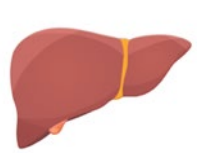
Next Steps:

- Novo Nordisk expects to initiate a Phase 3 program in 2025
- Ongoing open label extension trial (NCT06260709) for participants who completed the Phase 2

[1] Preclinical studies of mPRX004, the murine form of PRX004; Higaki JN et al. *Amyloid*, 2016; Suhr OB et al., *Amyloid*, 2025

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

Preclinical studies of mPRX004, the murine form of PRX004; Higaki JN et al. *Amyloid*, 2016; Suhr OB et al., *Amyloid*, 2025

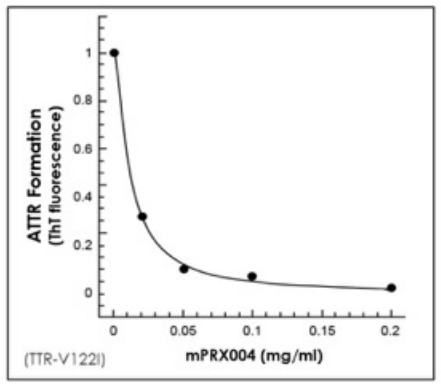
Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF mPRX004

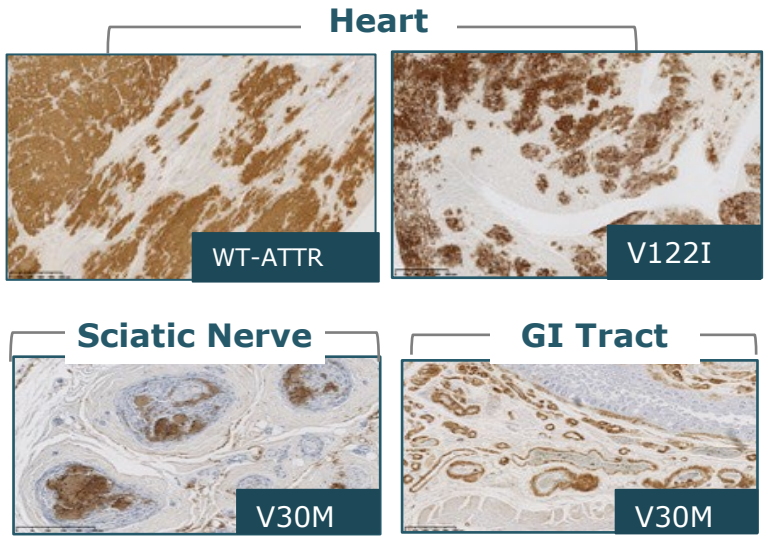
mPRX004 (murine form of PRX004) preclinical results:[1]

- ✓ 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

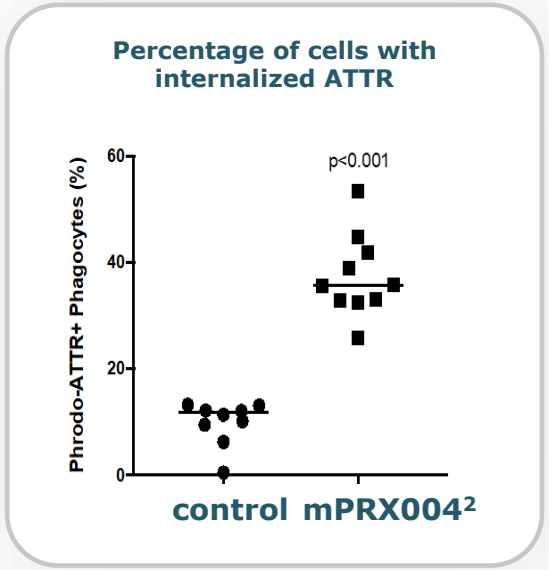
Inhibition of amyloid formation



Specific binding to amyloid



Clearance of amyloid



Preclinical studies of mPRX004, the murine form of PRX004; Higaki JN et al. *Amyloid*, 2016; Suhr OB et al., *Amyloid*, 2025

[2] mPRX004 = murine form of PRX004 (coramitug)

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…

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.

11C-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-Aβ 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-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

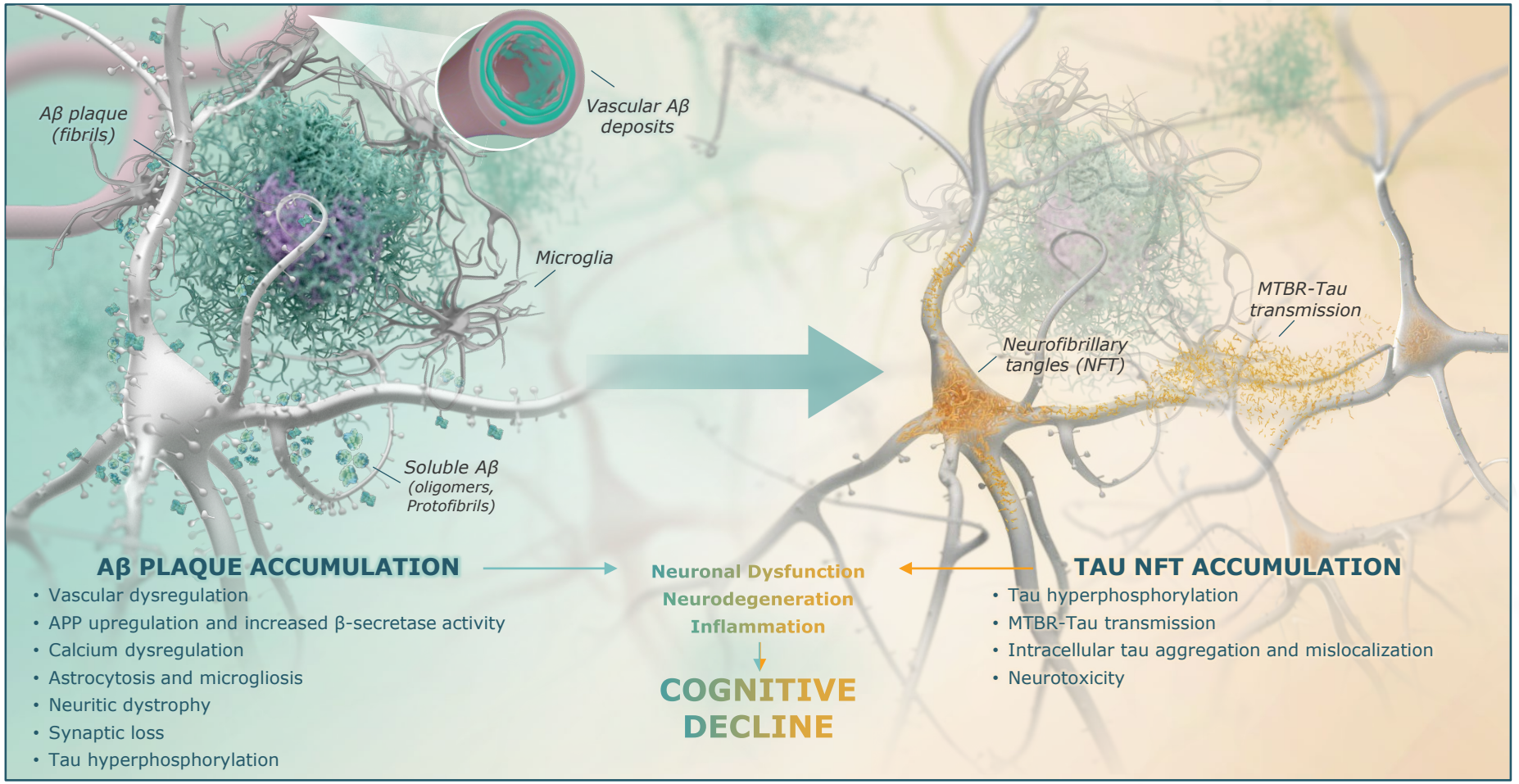
[1] Games D, et al.1995 *Nature*; [2] Zago W, et al. 2013 *Alzheimers Dement*; [3] Schenk D, et al. 1999 *Nature*; [4] Rinne, et al. 2010 *Lancet Neurol*; [5] Skov M, et al. Preclinical data available at: https://tinyurl.com/3zzpmbxh; [6] Dolan P. Preclinical data available at: https://tinyurl.com/3kf7pvnd.

Targeting Alzheimer's Where it Matters

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

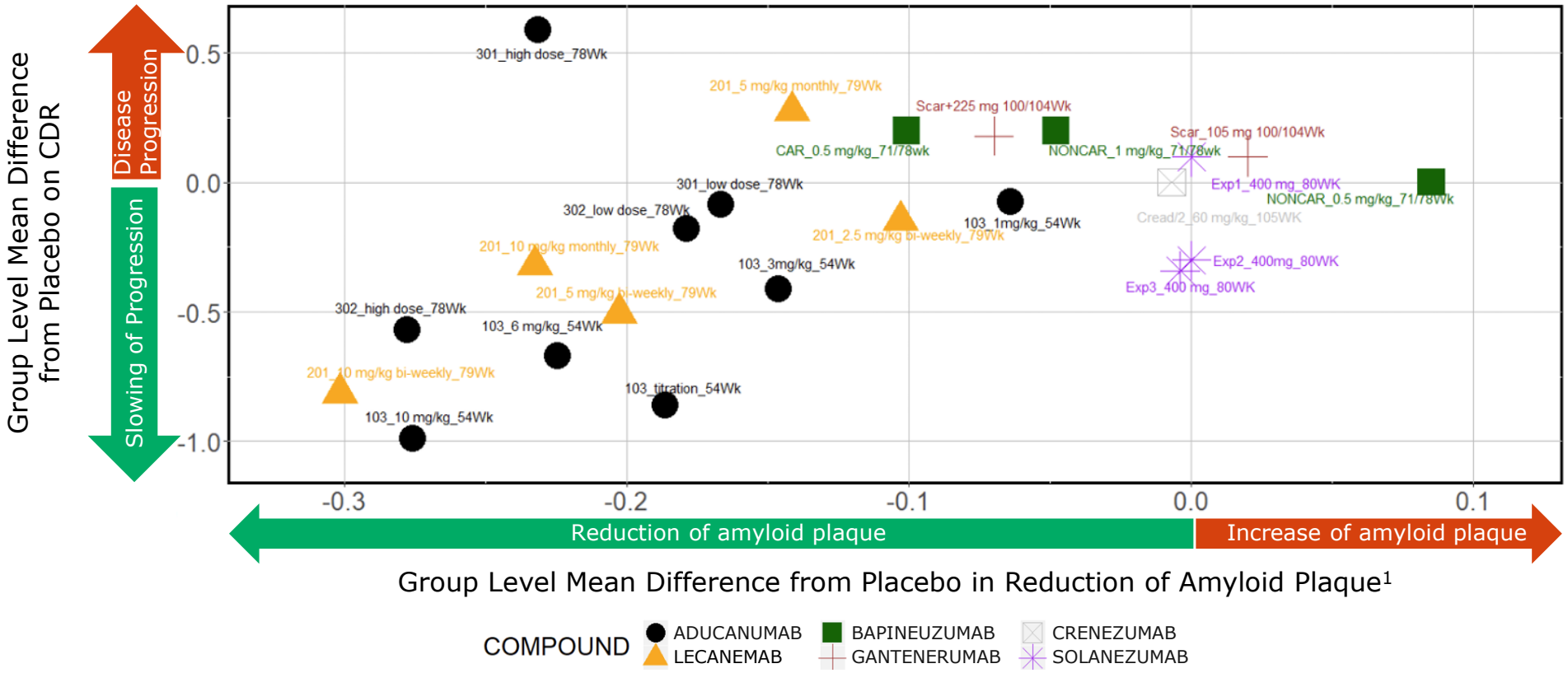
Reduction of Aβ plaque associated with clinically meaningful slowing of disease progression

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



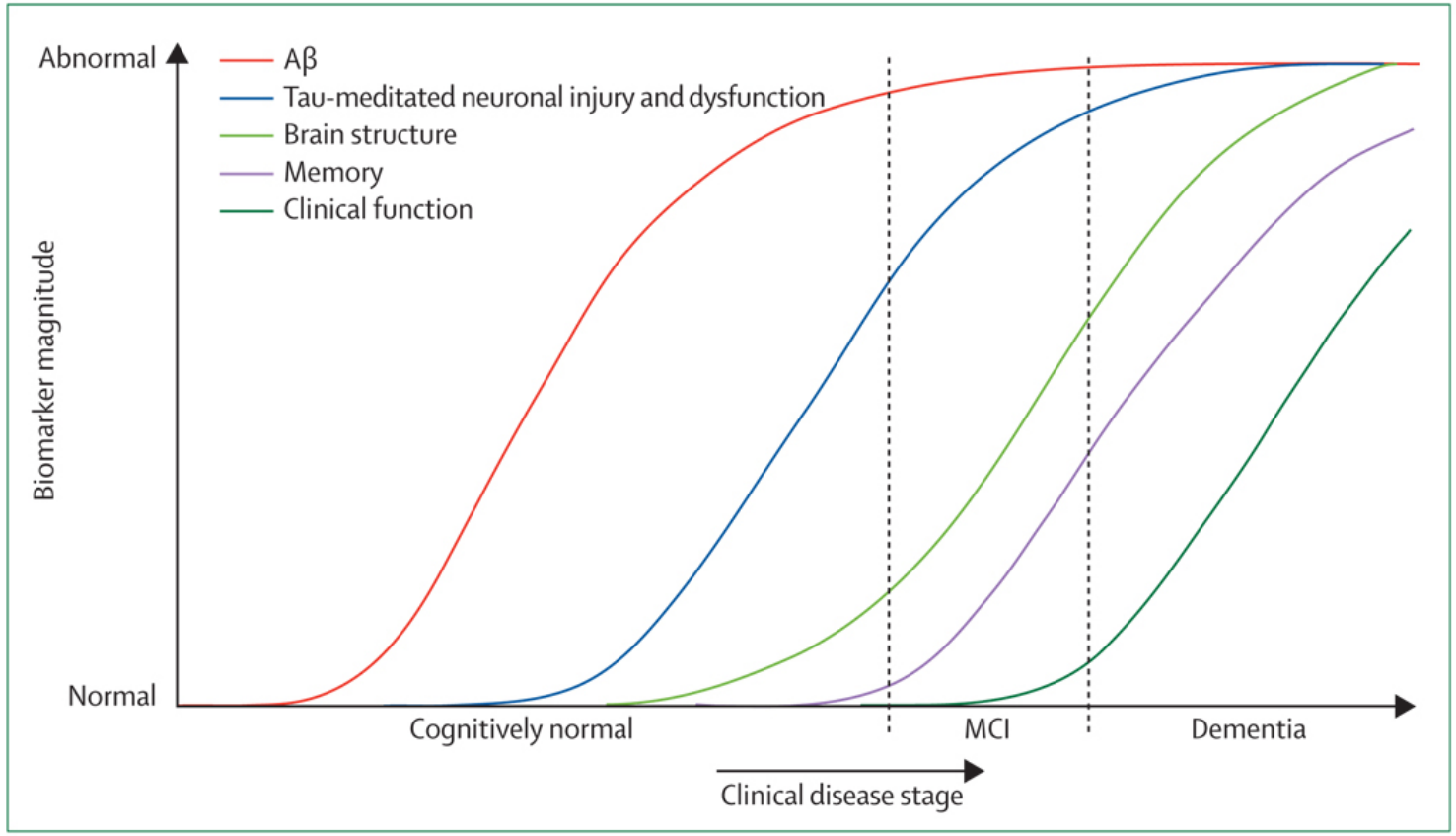
2020 US FDA ANALYSIS: Aβ has been established as a disease modifying target in AD[2,3]

[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]



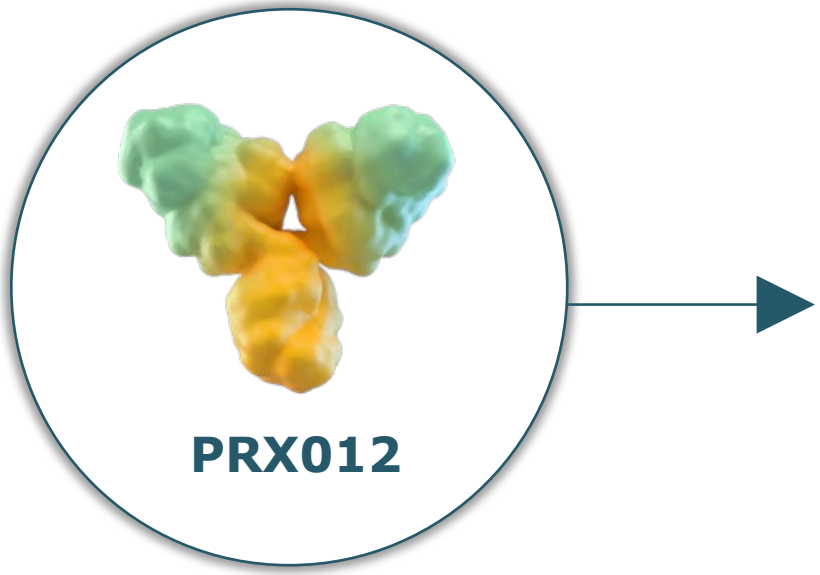
[1] Jack, Clifford et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, 2010 NIH Public Access

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

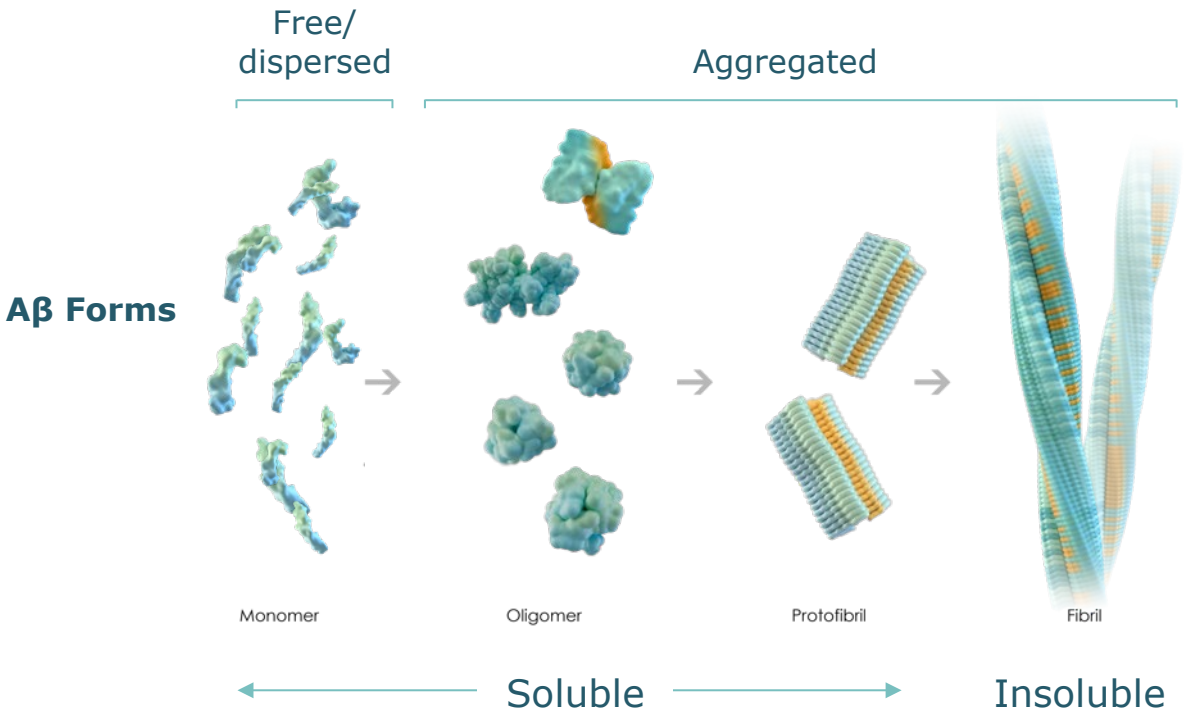
	TARGET PROFILE	ANTIBODY DESIGN ATTRIBUTES
Maintain From First Generation Antibodies	**Effectively clear soluble and insoluble aggregated amyloid**	• N-terminal directed • Full effector-function
Innovations to Minimize Disease and Treatment Burden	**Low-volume subcutaneous (SC) delivery**	• High binding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

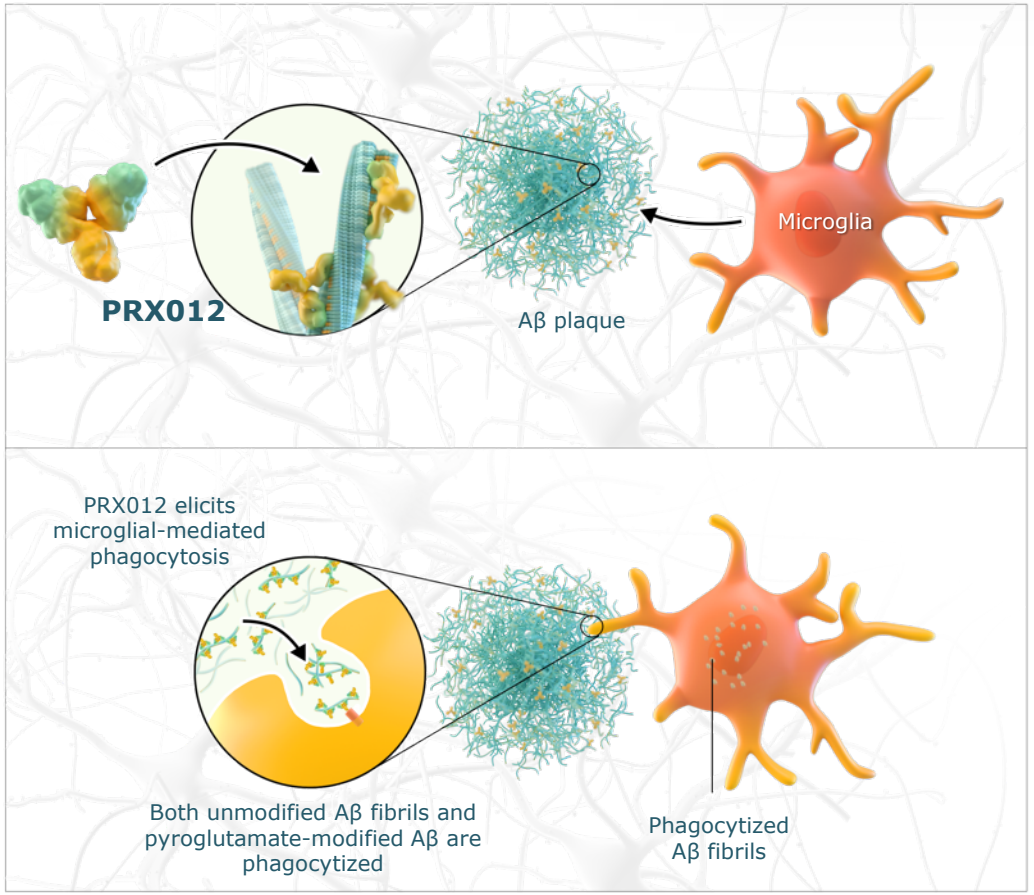
OUR MISSION

- 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



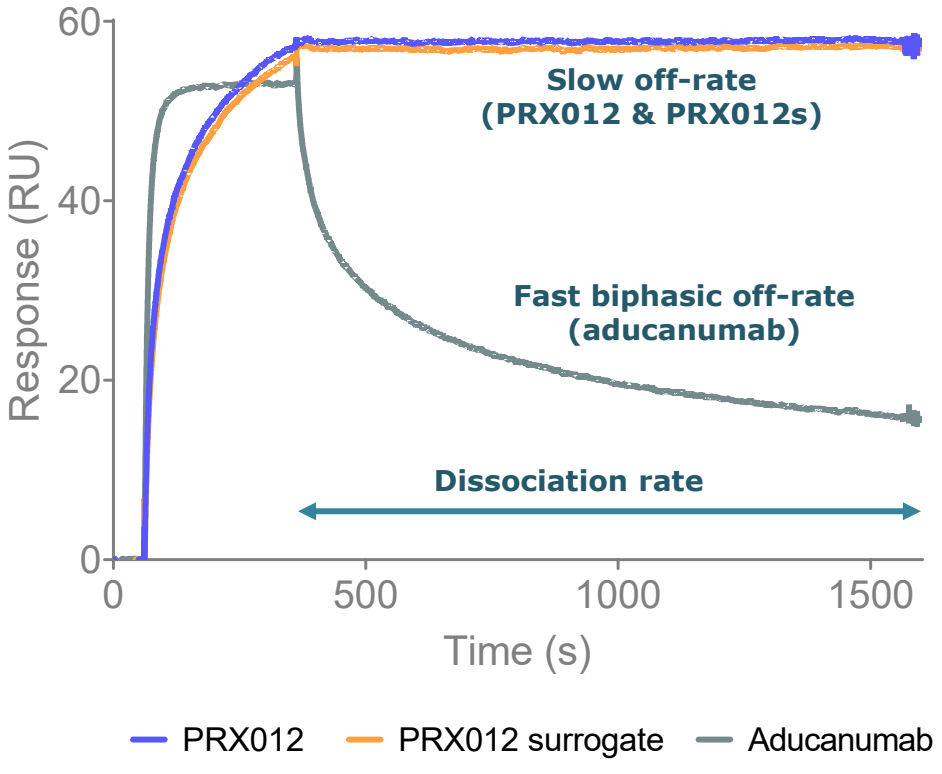


Microglia recognize and engulf PRX012-opsonized Aβ fibrils

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

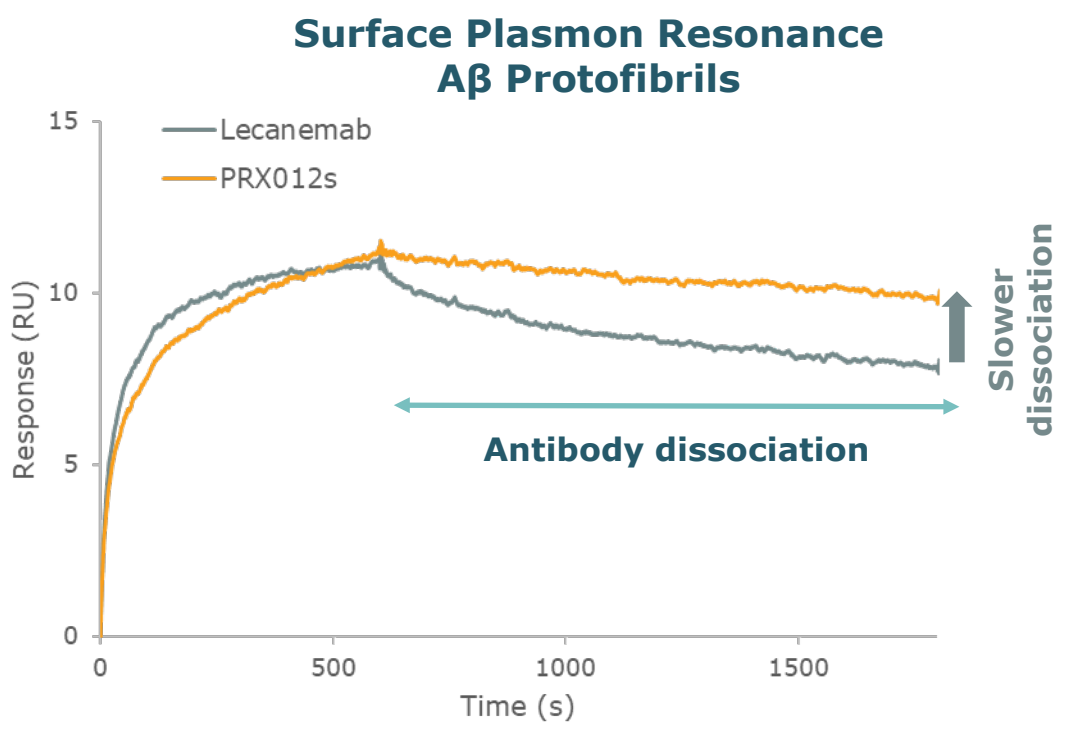
Compound	Fibril/Plaque	N3pE-Aβ
PRX012	0.070[a]	>67[b]
PRX012s	0.054[a]	>67[b]

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

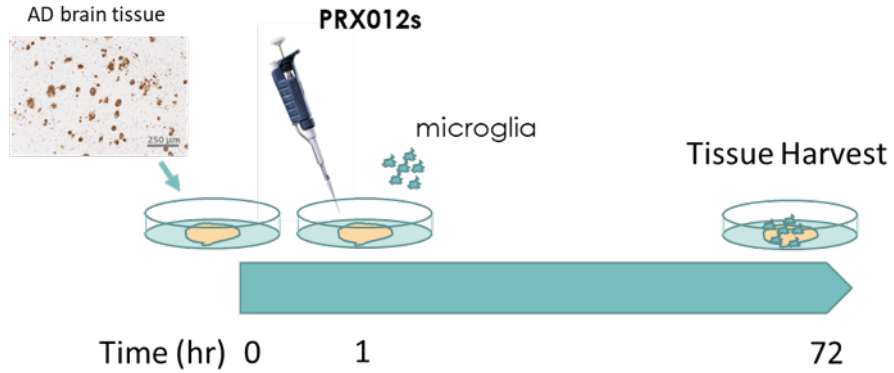
SPR Binding Kinetics

	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

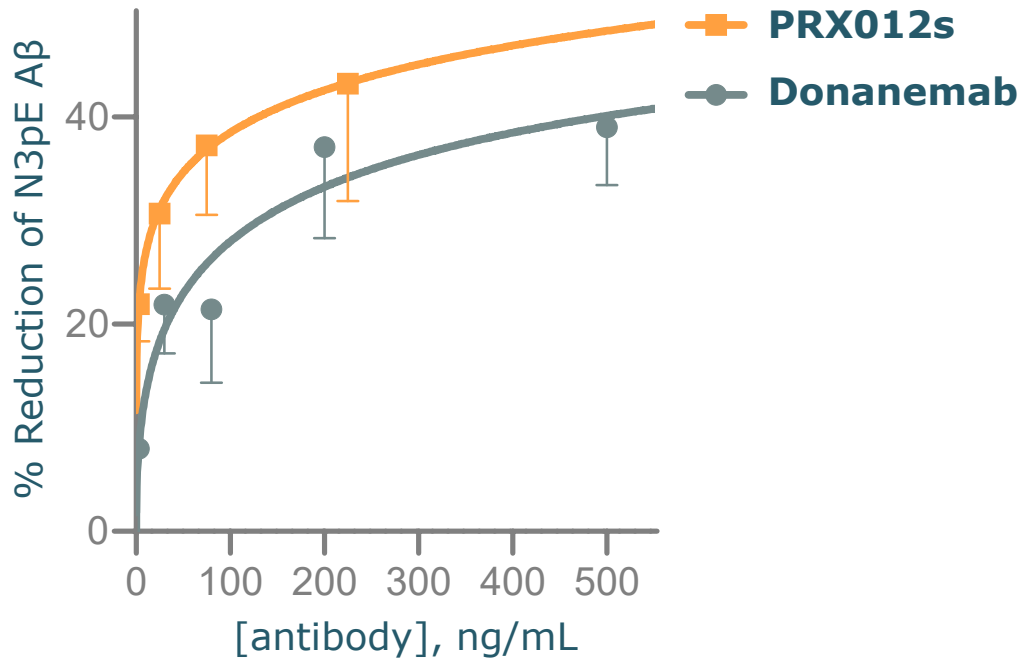
- **PRX012s binds to Aβ protofibrils with approximately 20-fold greater affinity than lecanemab when tested under the same conditions**
- **Greater affinity is driven largely by a slower binding dissociation**

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



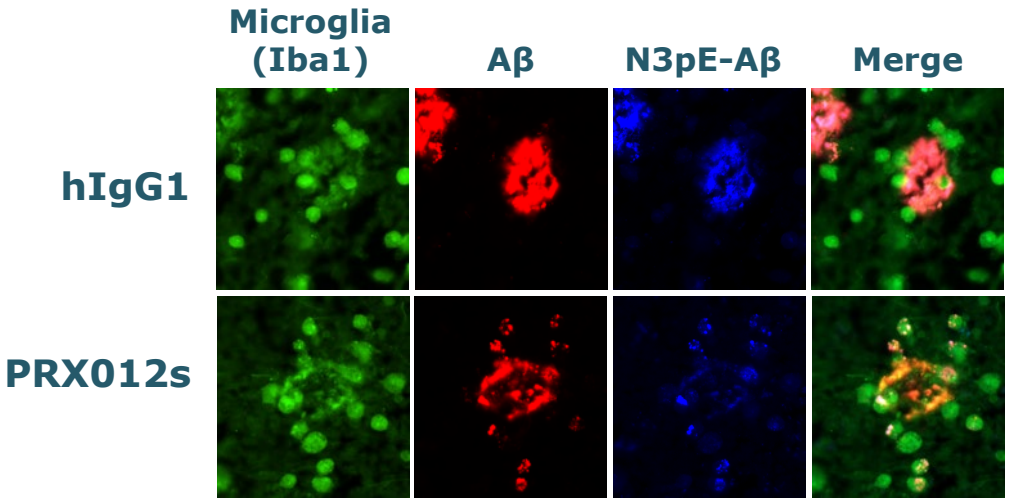
Study Conditions	
Tissue	Post-mortem AD brain tissue (same donor used for all conditions)
Treatment	PRX012s, donanemab, or IgG1 isotype control
Microglia	Primary mouse microglia (800,000 cells/mL)
Culture time	72 hours at 37°C



- **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**

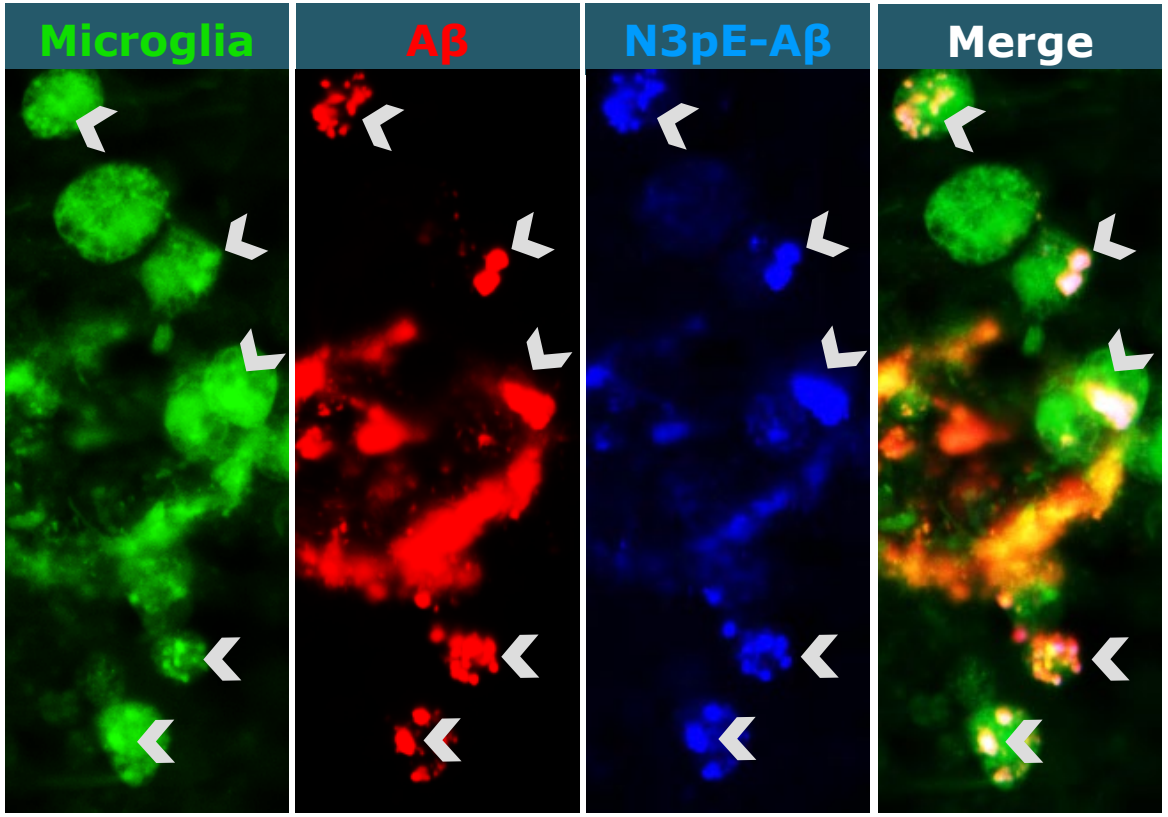
IgG, immunoglobulin; N3pE-Aβ, pyroglutamate-modified Aβ.
Donanemab was generated from a publicly available sequence.

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

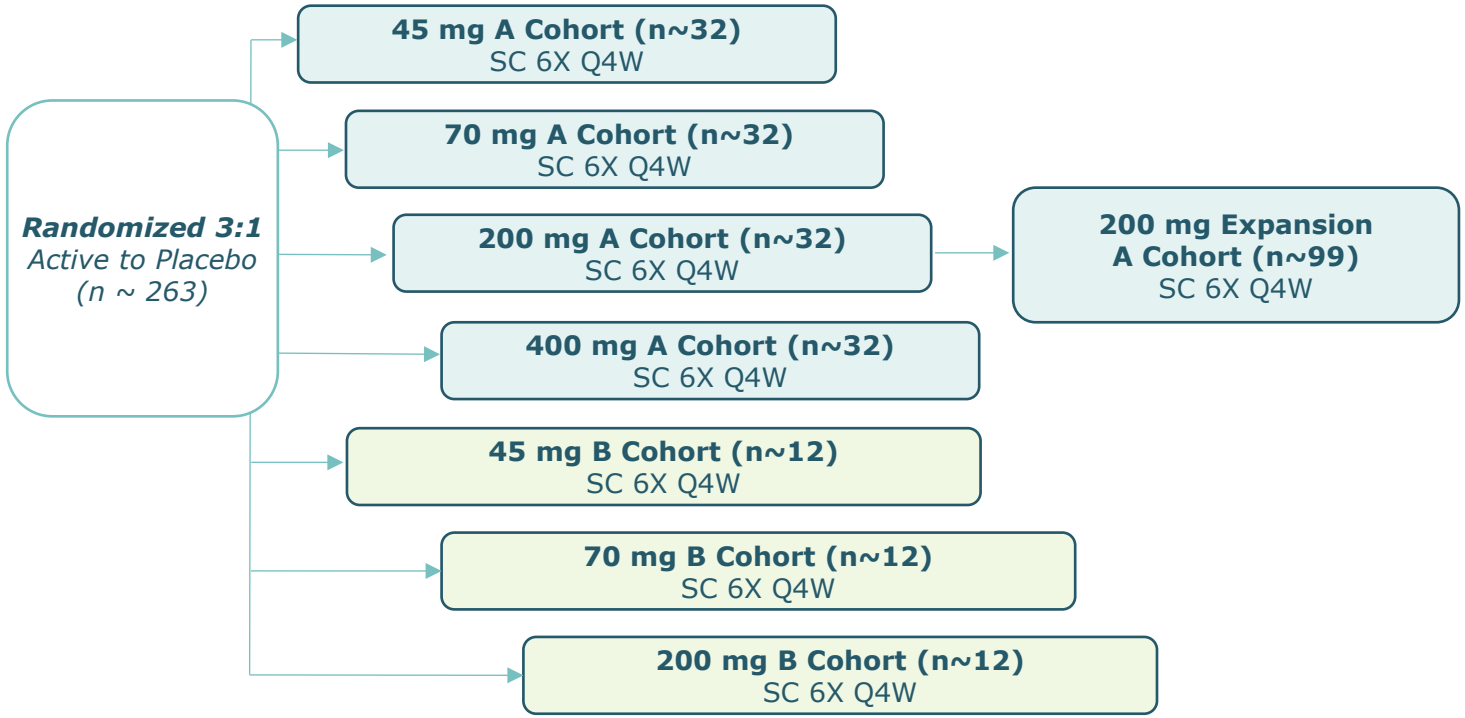
ascent-2 Trial Overview[1]

Key Inclusion Criteria

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

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

Dose Expansion



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

Status: Phase 2, completion 2027

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 $562.5 million in regulatory/sales milestones
- Up to high teens royalties on a weighted average basis
- Potential blockbuster therapy

Phase 2 Trial (NCT06268886): Ongoing

- Global, double-blind, placebo-controlled
- 310 participants with early AD
- Randomized, 3 arms (two doses and placebo)
- Primary Endpoint: Change from baseline in brain tau deposition as measured by PET at week 76
- Secondary endpoints include change from baseline in CDR-SB score at week 76
- Primary completion expected in 2027

Phase 1 Trial (NCT06955741): Ongoing

- Open-label single-dose study to assess PK, tolerability, and bioavailability of subcutaneous administration
- Primary completion expected in 2H 2025

[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.

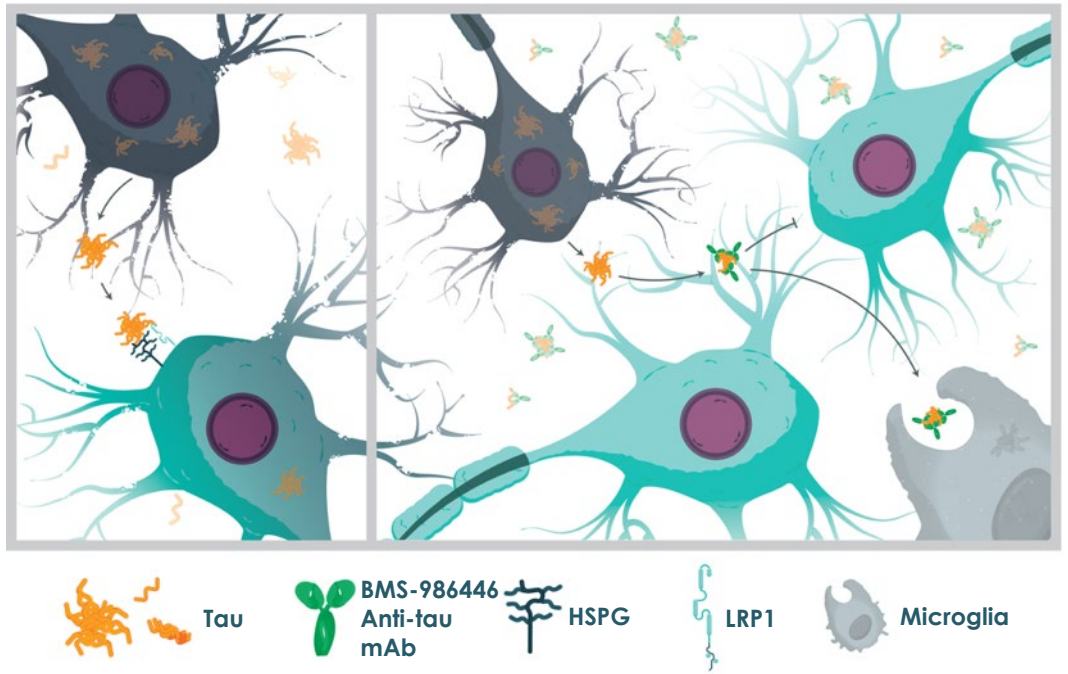
BMS-986446: MTBR-Specific Anti-Tau Antibody

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

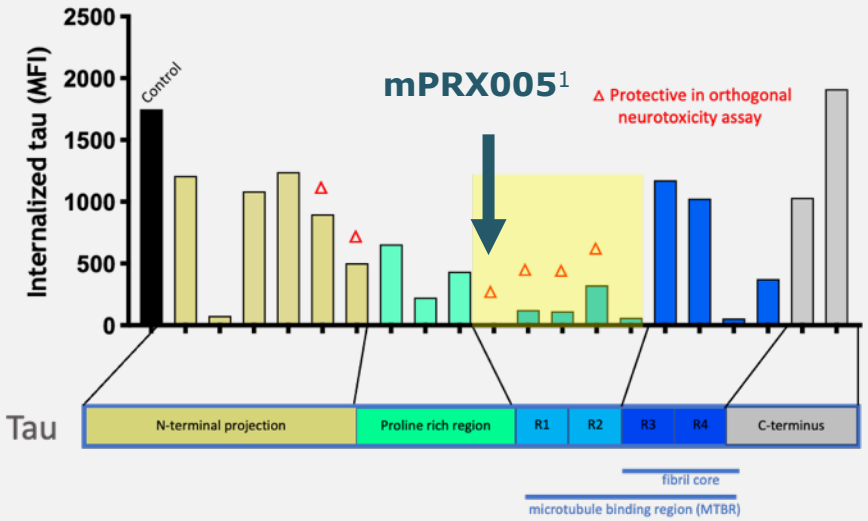


BMS-986446: Potential Best-in-Class MTBR-Specific Anti-Tau Antibody to Reduce Pathogenic Tau Spread

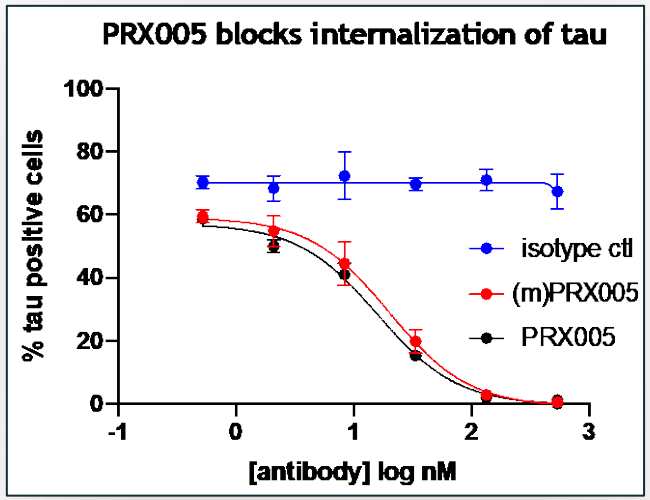
[1] Ahmed, Z., Cooper, J.. et al. A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. 2014 *Acta Neuropathol*;
[2] Horie, k., Barthelemy, H., Bateman, R.J. CSF tau microtubule binding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

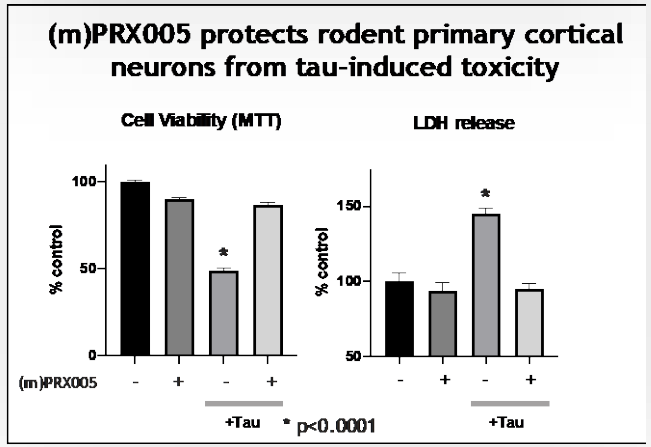
BMS-986446 (PRX005): Superior in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity Compared to Other Anti-Tau Antibodies

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



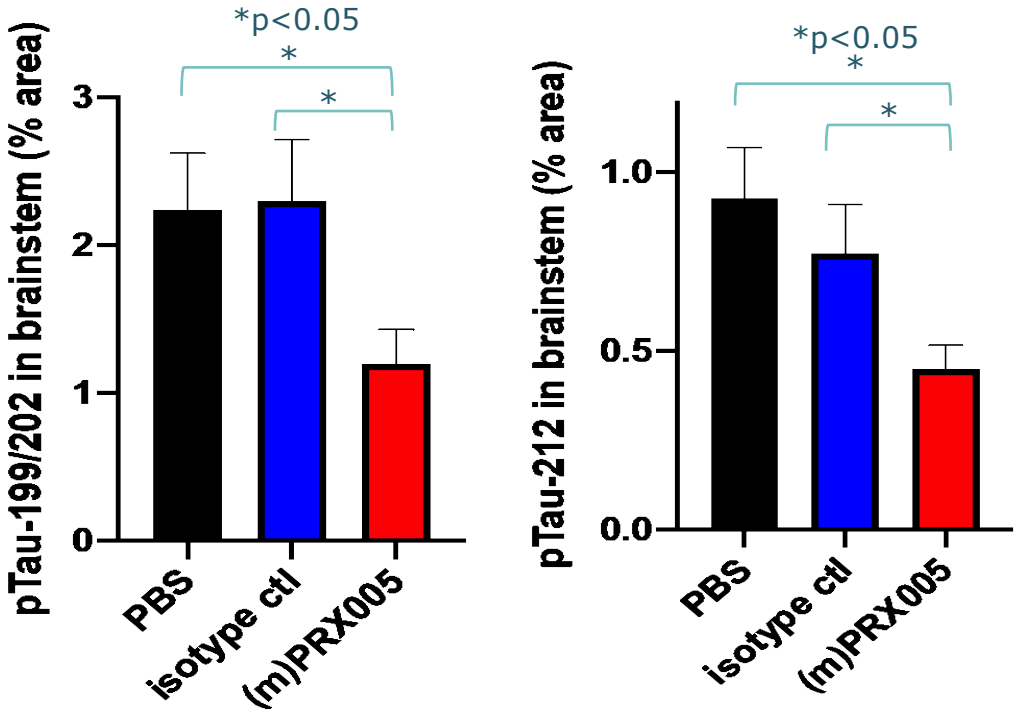


[1] (m)PRX005 = murine form of PRX005 (BMS-986446)

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

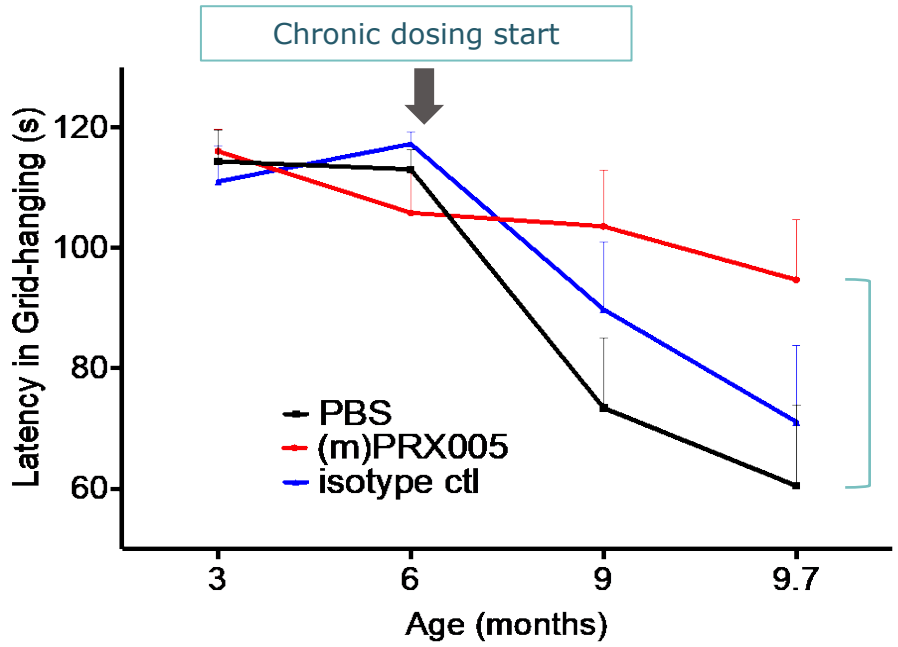
All values are mean ± SE (n=15-20)

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

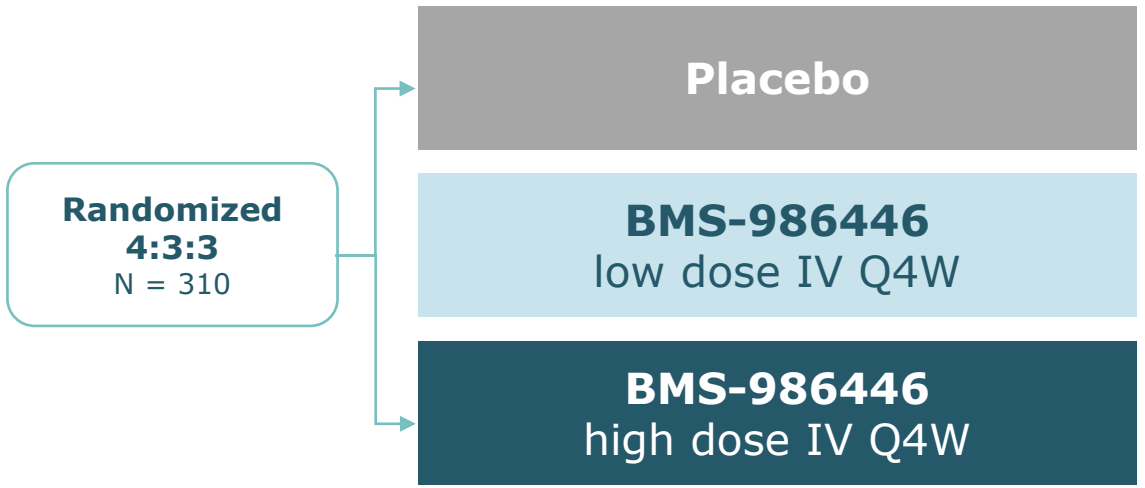
(m)PRX005 = murine form of PRX005 (BMS-986446)

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

- Change from baseline in brain tau deposition as measured by tau PET at 76 weeks

Secondary Endpoints

- Change from baseline in CDR-SB, iADRS, ADASCog14, ADCS-iADL, and MMSE score 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. Clinicaltrials.gov.
[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.

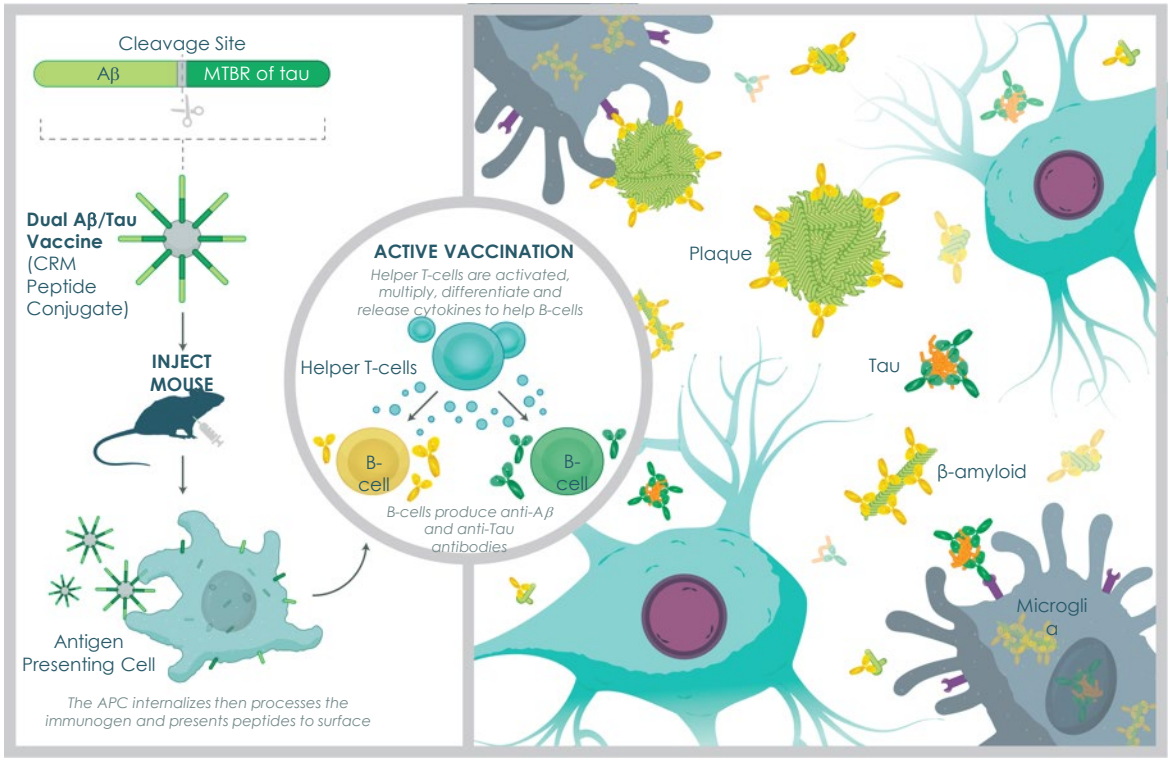
PRX123

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**



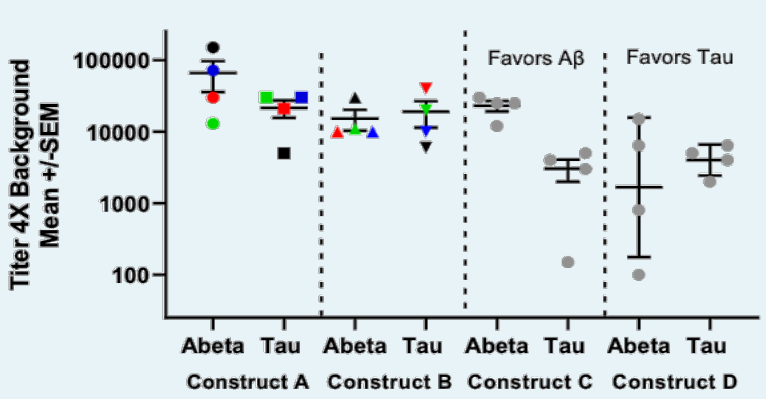
Desirable Attributes of Aβ/Tau Vaccines and Prothena's Design Strategies

			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

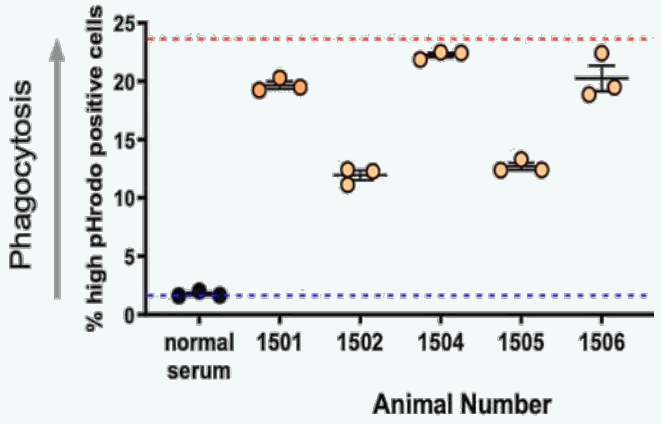
Prothena's Dual Aβ/Tau Vaccines Demonstrate Desirable Quantity, Quality and Safety

Quantity



✓ High, balanced, consistent

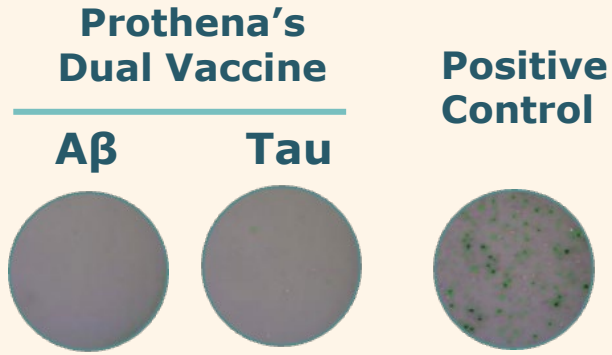
Quality



✓ 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

PRX019
Neurodegenerative Diseases

Global Neuroscience Collaboration
with Bristol Myers Squibb

PRX019: Potential Treatment of Neurodegenerative Diseases

PRX019

Neurodegenerative diseases

Status: Phase 1, completion 2026

Global Rights Deal for PRX019[1]

- ✓ $80 million paid-to-date for global rights
- Up to $617.5 million remaining in clinical, regulatory, and sales milestones
- Up to high teens royalties on a weighted average basis

Phase 1 Trial: Ongoing

- Phase 1 clinical trial being conducted by Prothena
- Single ascending dose and multiple ascending dose in healthy adults
- Phase 1 trial to evaluate:
  - Safety
  - Tolerability
  - Immunogenicity
  - Pharmacokinetics
- Trial expected to complete in 2026

Potential Clinical Milestone Could be Achieved at Time of BMS Decision to Further Develop PRX019; Expected in 2026

[1] Global Neuroscience Research and Development Collaboration with BMS also included $100 million upfront payment and a $50 million equity investment in Prothena