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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 2026, 2027, and beyond, including the expected timing of (i) completion of our ongoing Phase 1 clinical trial evaluating PRX019, (ii) completion of the ongoing Phase 2 clinical trial evaluating BMS-986446, (iii) completion of the Phase 3 clinical trial for prasinezumab, and (iv) completion of the Phase 3 clinical trial for coramitug; 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 prasinezumab, coramitug, and BMS-986446; 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 prasinezumab, coramitug, BMS-986446, 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 27, 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

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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)

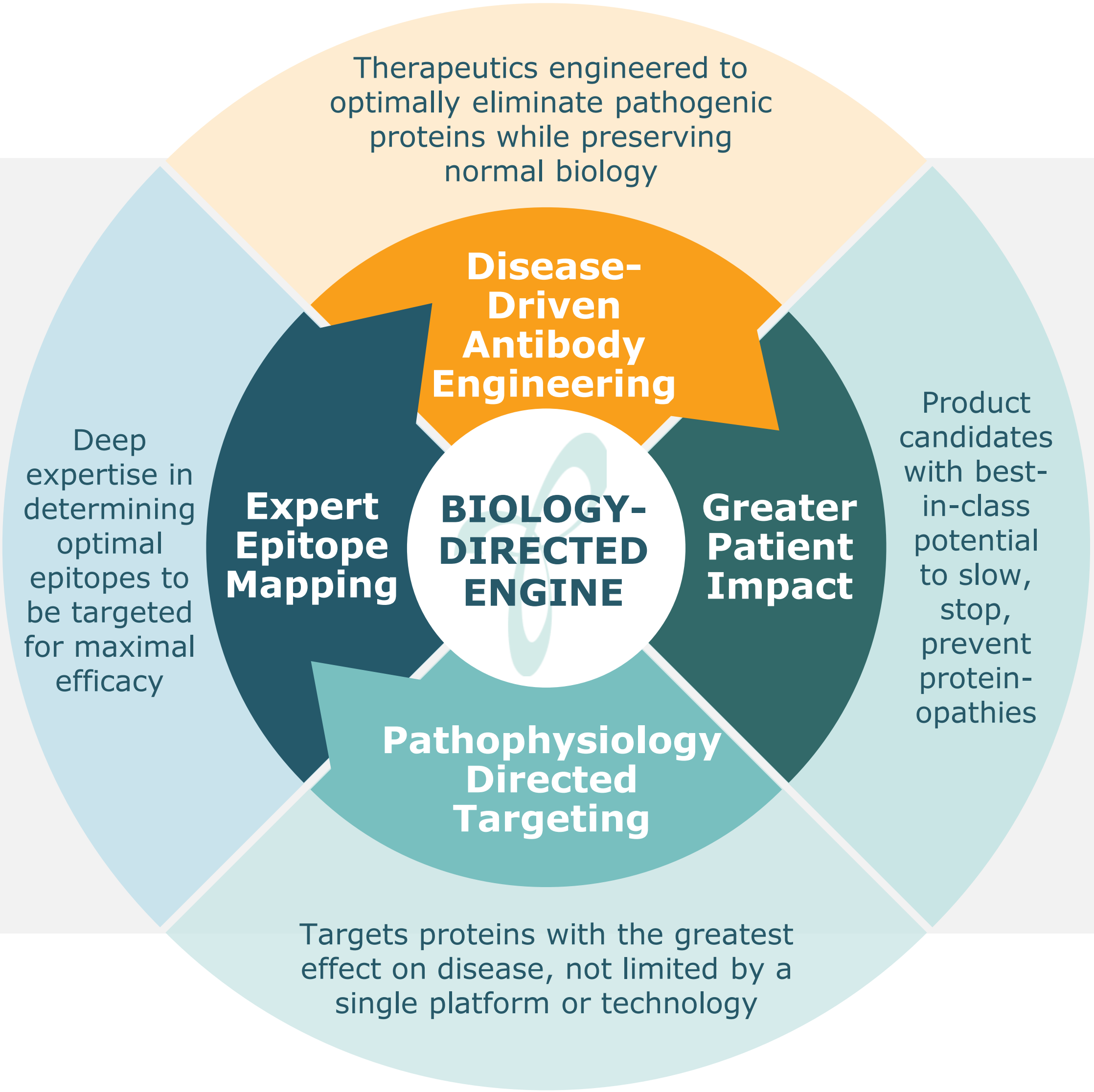
450,000
Estimated number of patients worldwide with wtATTR or ATTRv[4-6]

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

Two partnered Phase 3 programs

One partnered Phase 2 program

One partnered 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.

Active Clinical Development Pipeline

PROGRAM *INDICATION*	PROTEIN TARGET	DISCOVERY	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	GLOBAL PARTNER[2]
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
PRX019 *Neurodegeneration*	Undisclosed Target	Phase 1 to complete in 2026					Bristol Myers Squibb

Neurodegenerative | Rare Peripheral

[1] Orphan Drug Designation granted by FDA & EMA;
[2] 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

Upcoming Partner Milestones

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

2026	2027	2028+	
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

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

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Roche	novo nordisk®	Bristol Myers Squibb®	
Up to $755 Million in Total Milestones + Royalties	***Up to $1.23 Billion in Total Milestones***	***Up to $1.55 Billion in Total Milestones + Royalties Across Two Clinical Stage Programs*** ☑ Upfront Payment + Equity: $150 million[2]	
Prasinezumab *Parkinson's disease*	**Coramitug (PRX004)** *ATTR-CM*	**BMS-986446** *Alzheimer's disease*	**PRX019** *Neurodegenerative diseases*
☑ **$135 million** paid to date ❑ **$620 million** remaining in regulatory and sales milestones[1] ❑ Up to double digit teen royalties ❑ US co-promote option	☑ **$100 million** paid to date ❑ **$1.13 billion** remaining in clinical, regulatory, and sales milestones	☑ **$135 million** paid to date ❑ **$562.5 million** remaining in regulatory and sales milestones ❑ Up to high teens royalties on a weighted average basis	☑ **$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
Phase 3

Worldwide Collaboration with Roche

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

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Roche

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:

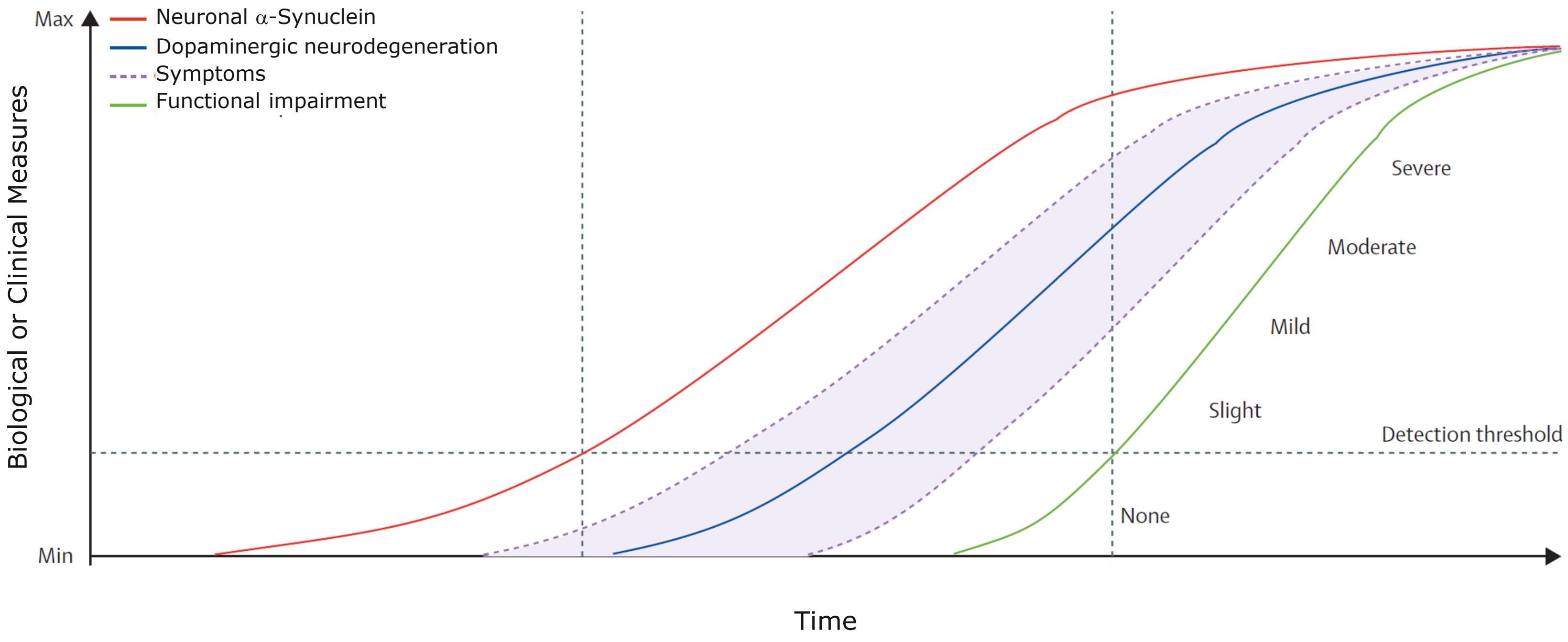
- Roche plans to initiate Phase 3 development for early-stage Parkinson's disease by YE 2025
- Open-label extension studies from both PADOVA and PASADENA ongoing to explore the observed effects

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.

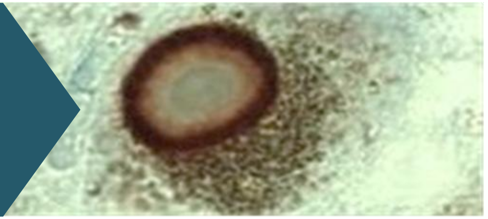
α-Synuclein Pathology is Strongly Implicated in Parkinson's Disease

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



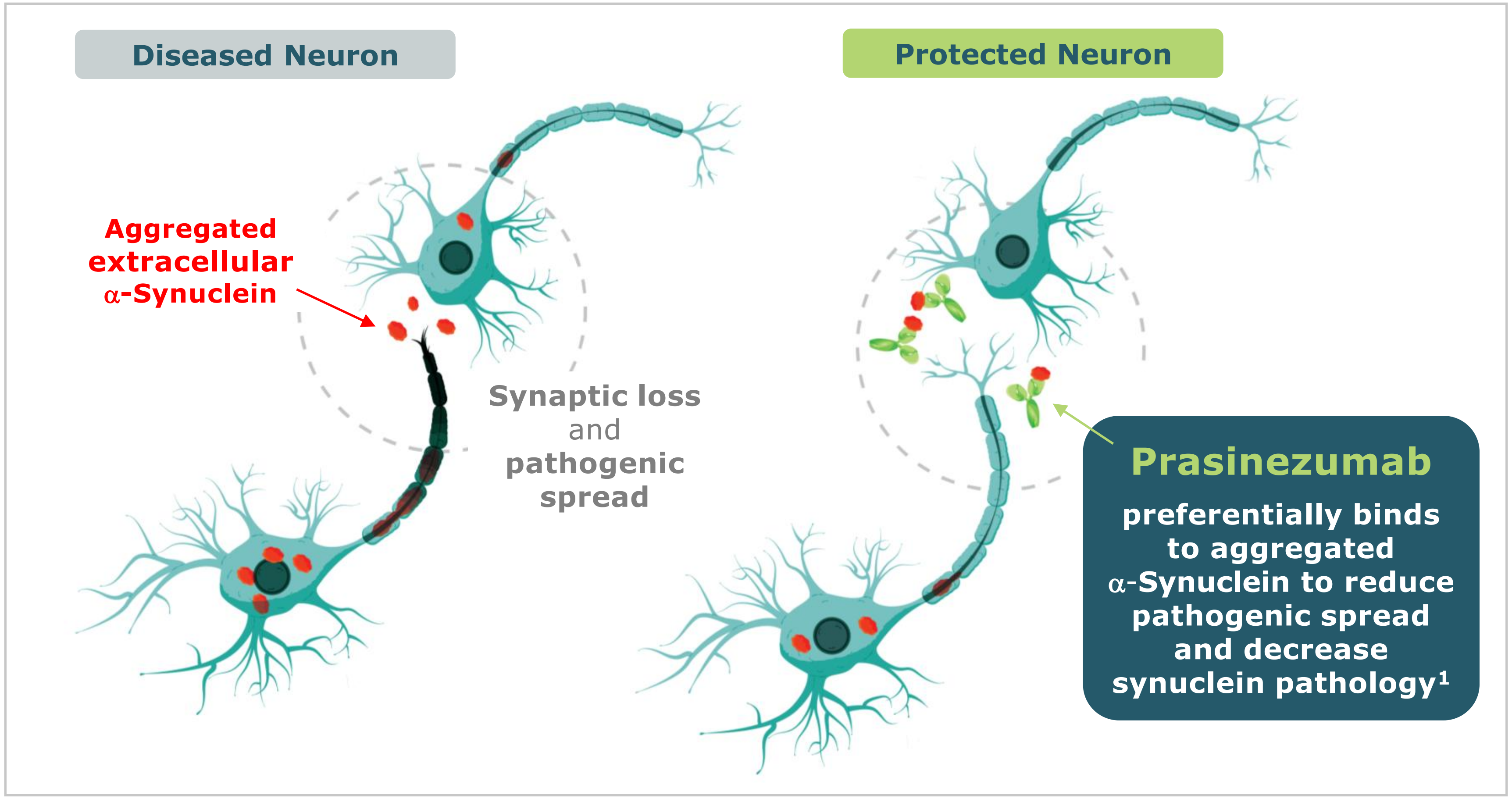
Symptoms: Clinical signs or symptoms attributable to neuronal α-Synuclein disease that can be motor or non-motor (e.g., hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety).
Functional Impairment: Degree of impact on activities of daily living.
Chart adapted from: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

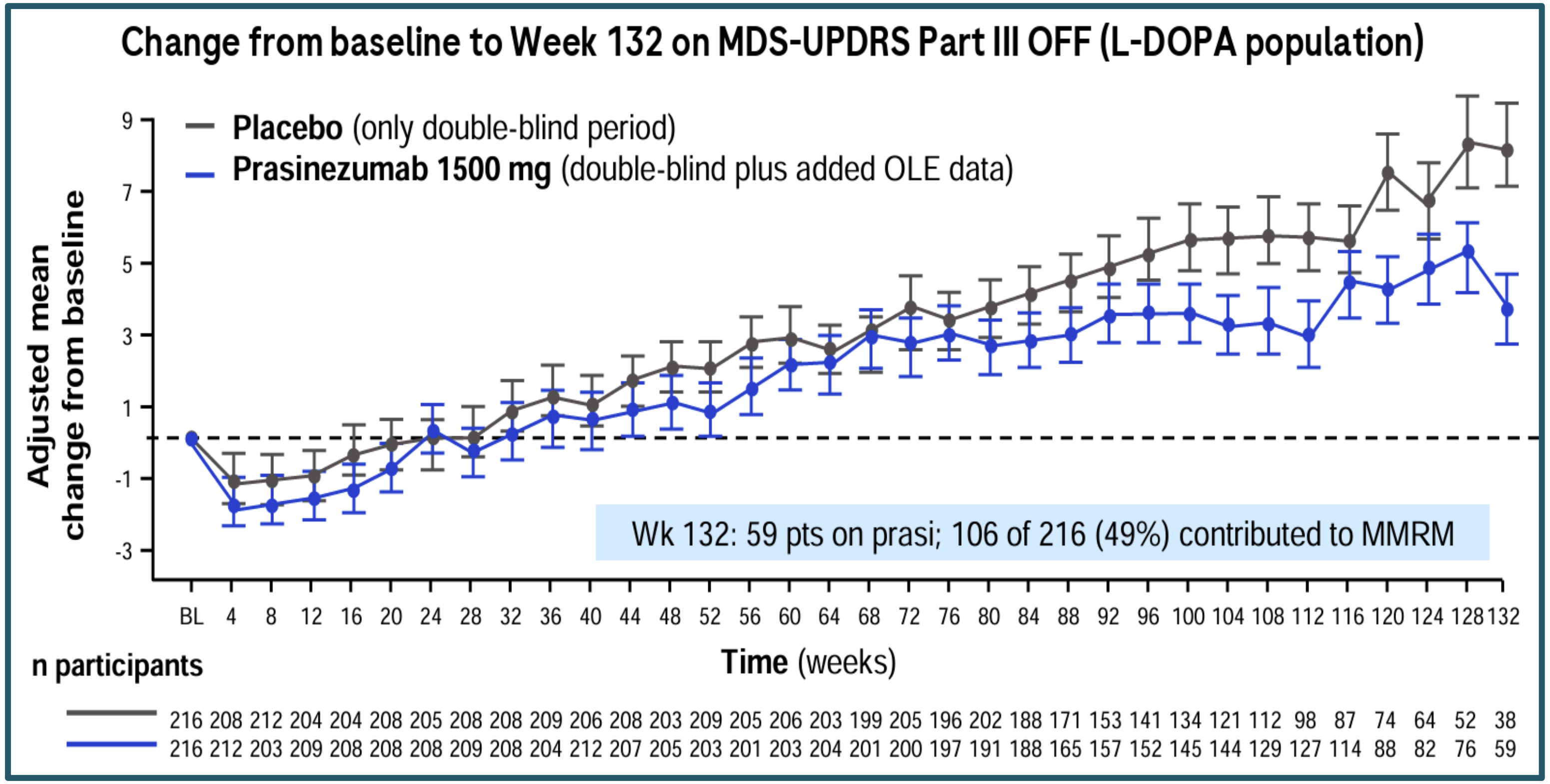


[1] Proposed mechanism of action.

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

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

✔ (green) Meets the Bar criteria ✔ (yellow) 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
Phase 3

ATTR Business Acquired by Novo Nordisk

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

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novo nordisk®

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

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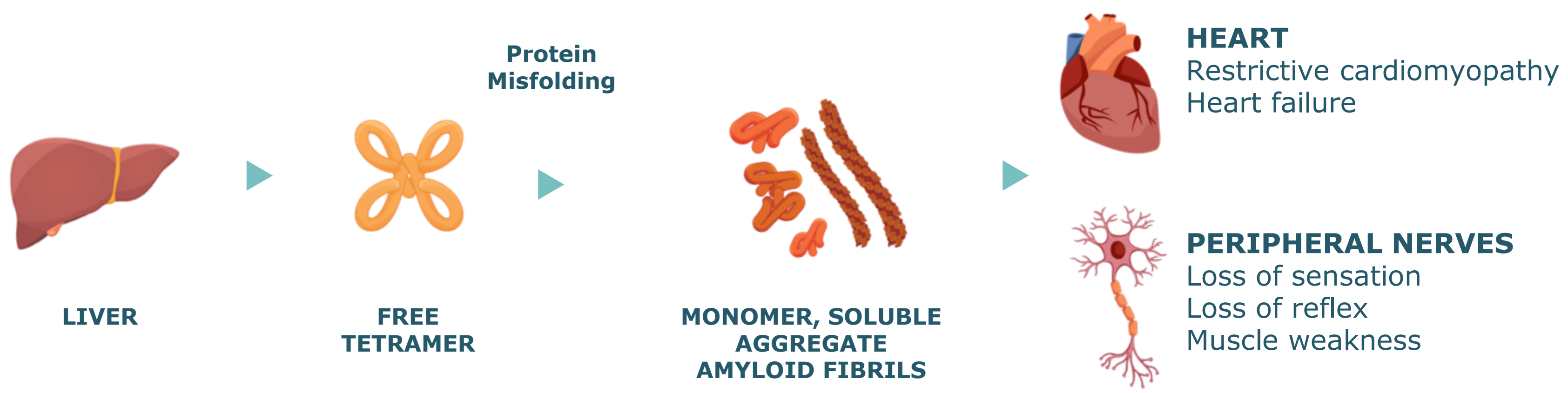
Differentiated Mechanism for ATTR-CM

NON-PATHOGENIC PATHWAY | **PATHOGENIC PATHWAY**



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

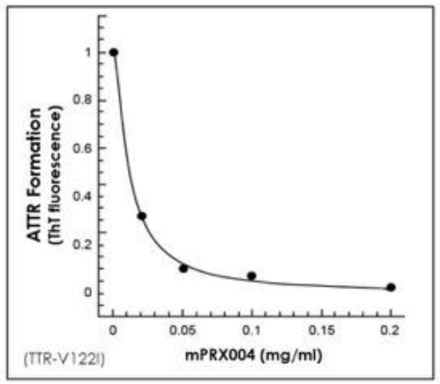
Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF mPRX004

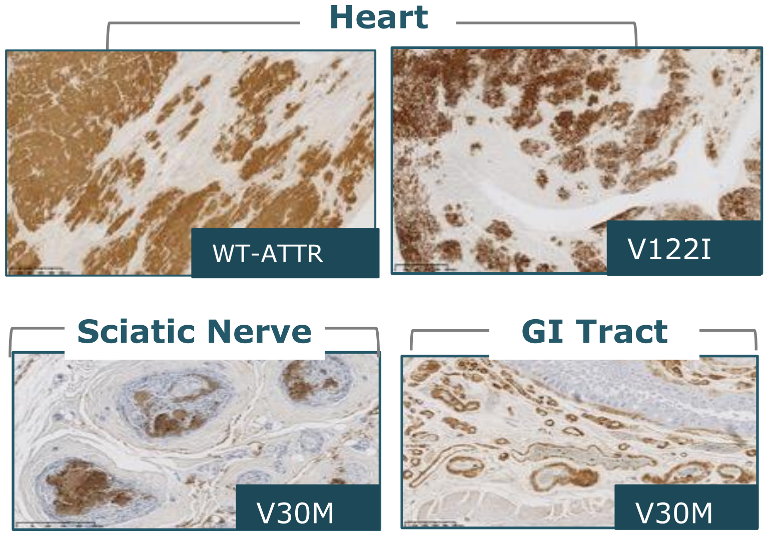
mPRX004 (murine form of PRX004) preclinical results:[1]

- ✓ 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

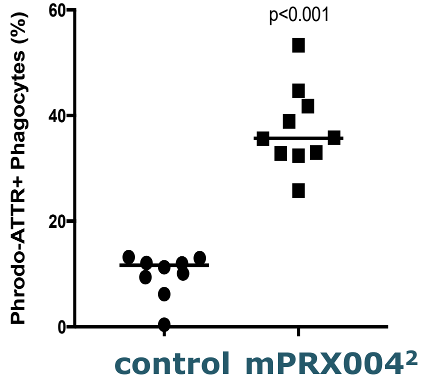
Inhibition of amyloid formation



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)

BMS-986446 (formerly PRX005)
Alzheimer's Disease
Phase 2

Global Neuroscience Collaboration
with Bristol Myers Squibb

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

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Bristol Myers Squibb®

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.

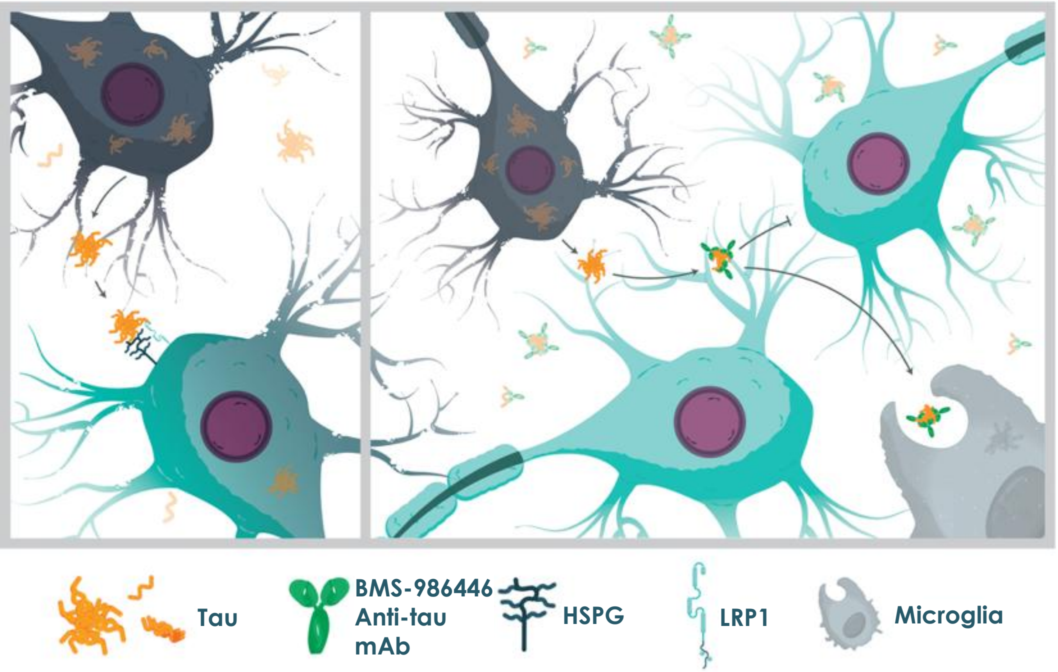
BMS-986446: MTBR-Specific Anti-Tau Antibody

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

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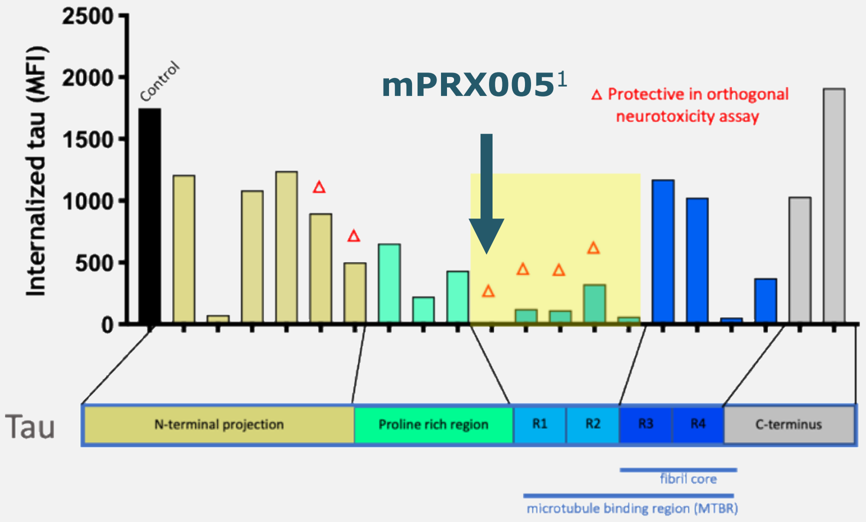
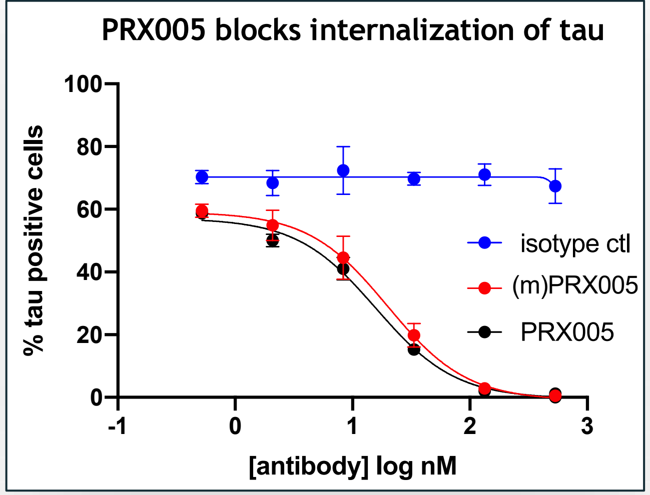
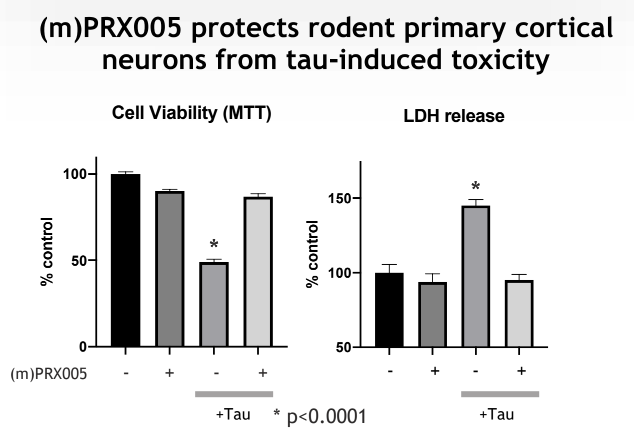
Repeats 1 and 2 defined as the strongest inhibitory regions in screening with cellular internalization and neurotoxicity assays



- 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)

BMS-986446

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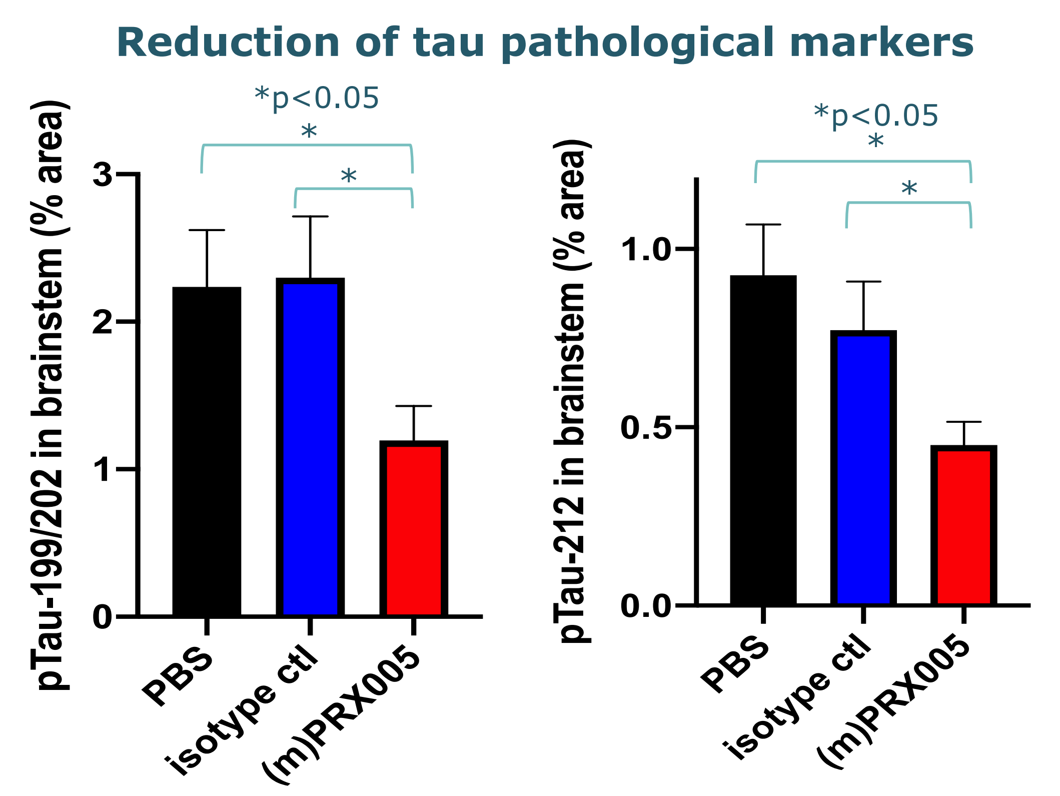
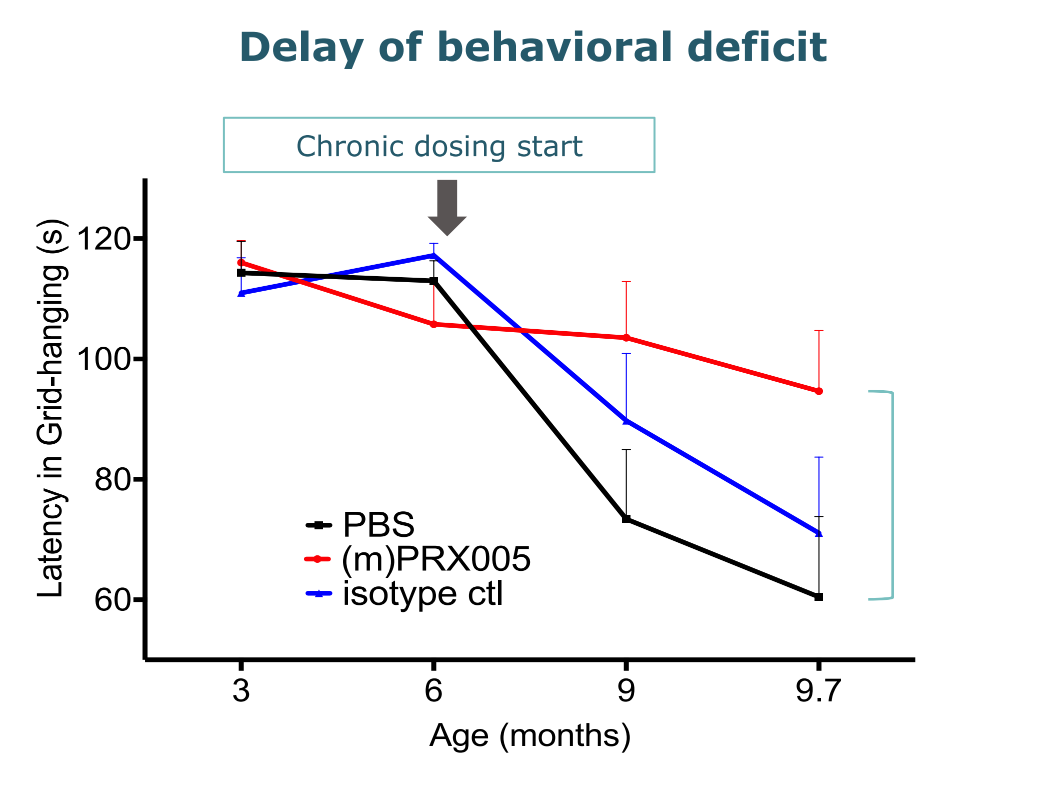
(m)PRX005 Reduces Pathological Tau and Ameliorates Behavioral Deficit in Transgenic Tau Mouse Model

All values are mean ± SE (n=15-20)





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

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

(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

Randomized 4:3:3
N = 310

- **Placebo**
- **BMS-986446** low dose IV Q4W
- **BMS-986446** high dose IV Q4W

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.

PRX019
Neurodegenerative Diseases
Phase 1

Global Neuroscience Collaboration
with Bristol Myers Squibb

PRX019: Potential Treatment of Neurodegenerative Diseases

Bristol Myers Squibb®

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