



CORPORATE OVERVIEW

January 2026

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 our broad pipeline, and the potential to advance, initiate, and complete preclinical and IND enabling studies for our early-stage programs, including our TDP-43 CYTOPE® and PRX012-TfR programs; 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; whether potential milestones are achieved and amounts we might receive under our partnerships and collaborations with Roche, BMS, and Novo Nordisk; the treatment potential, designs, proposed mechanisms of action, and potential administration of prasinezumab, coramitug, BMS-986446, TDP-43 CYTOPE®, and PRX012-TfR; 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 prasinezumab, coramitug, BMS-986446, and PRX019; and the potential to partner our early-stage programs, including PRX012-TfR. These statements are based on estimates, projections and assumptions that may prove not to be accurate, and actual results could differ materially from those anticipated due to known and unknown risks, uncertainties and other factors, including but not limited to those described in the “Risk Factors” sections of our Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 6, 2025, and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. This overview is made as of January 11, 2026, 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



Parkinson's disease (PD)

>10 million

People living with PD worldwide¹

Fastest increasing

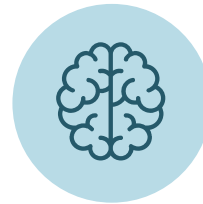
Neurodegenerative disease¹

\$52 billion

In overall economic burden in the US¹



**Prasinezumab
Phase 3**



Alzheimer's disease (AD)

>80 million

People worldwide living with early symptomatic AD²

>315 million

People worldwide living with presymptomatic AD²

\$1 trillion

In annual US healthcare costs by 2050 from AD and other dementias³



**BMS-986446
Phase 2**



**PRX012-TfR
Preclinical**



Transthyretin amyloidosis (ATTR)

450,000

Estimated number of patients worldwide with wtATTR or ATTRv⁴⁻⁶

2.08 years

Median overall survival New York Heart Association class III patients with ATTR cardiomyopathy^{7,8}



**Coramitug
Phase 3**

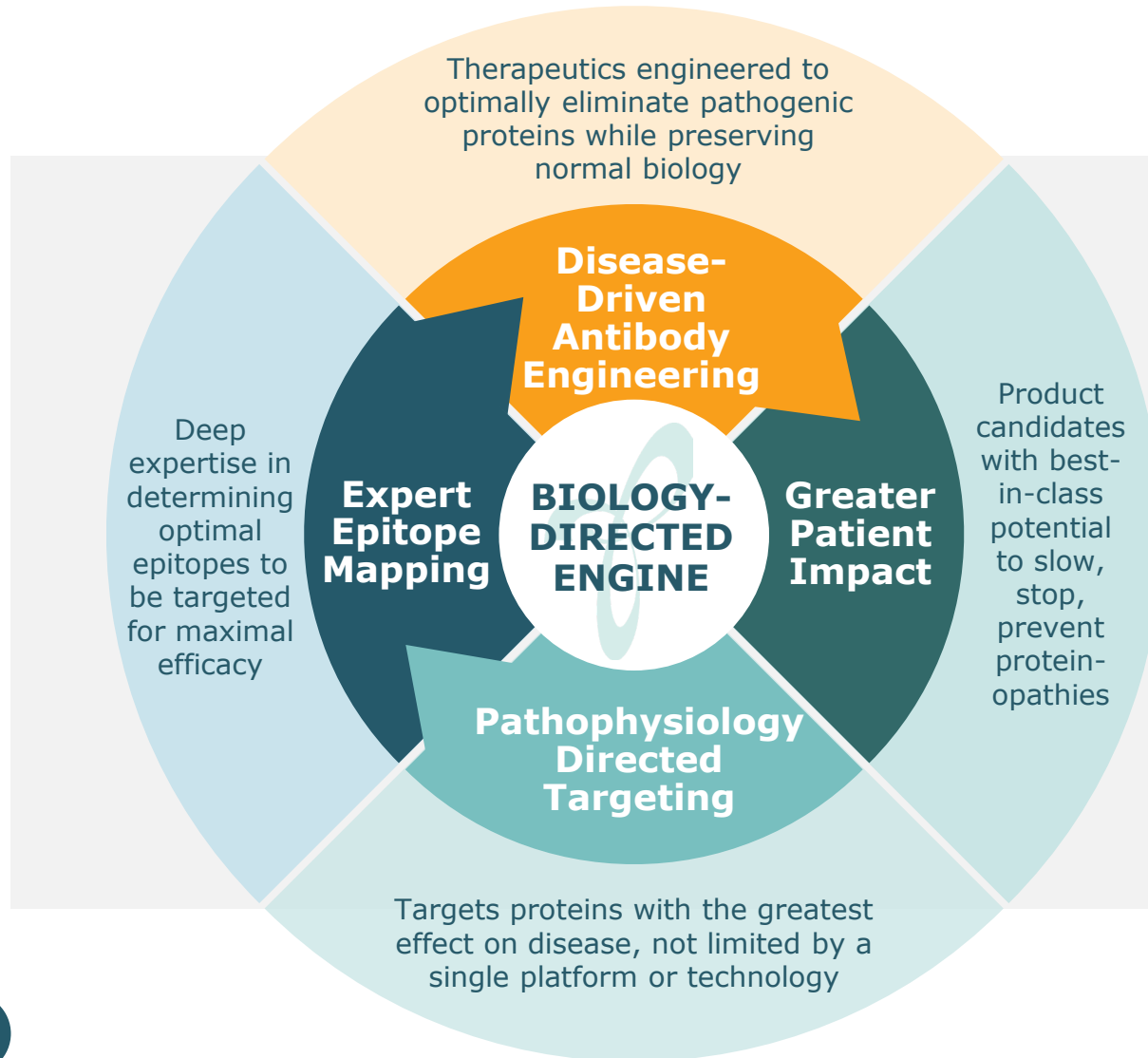
ATTRv: Hereditary amyloid transthyretin; wtATTR: Wild-type ATTR.

¹ Parkinson's Foundation. Understanding Parkinson's. Statistics. Accessed July 17, 2024. <https://www.parkinson.org/understanding-parkinsons/statistics>. ² Gustavsson, A. et al. "Global estimates on the number of persons across the Alzheimer's disease continuum." *Alzheimer's & Dementia* (2022) 1-13. ³ Long S, Benoit C, Weidner W. World Alzheimer Report 2023: Reducing dementia risk: never too early, never too late. London, England: Alzheimer's Disease International. Accessed July 18, 2024. <https://www.alzint.org/u/World-Alzheimer-Report-2023.pdf>. 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, Domínguez 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 Active Clinical Programs

- Two partnered Phase 3 programs
- One partnered Phase 2 program
- One partnered Phase 1 program



Strong Collaborations Established

- Bristol Myers Squibb
- Novo Nordisk¹
- 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 Development Pipeline

PROGRAM INDICATION (MODALITY)	PROTEIN TARGET	DISCOVERY	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	GLOBAL RIGHTS ⁴
Prasinezumab <i>Parkinson's disease</i> (mAb)	α-Synuclein (C-terminus)	Phase 3 PARAISO trial ongoing (NCT07174310)					
Coramitug (PRX004) <i>ATTR-CM</i> (mAb)	Transthyretin (misTTR)	Phase 3 CLEOPATTRA trial ongoing (NCT07207811)					
BMS-986446 (PRX005) <i>Alzheimer's disease</i> (mAb)	Tau (MTBR)	Phase 2 TargetTau-1 to complete in 1H 2027 (NCT06268886)					
PRX019 <i>Neurodegeneration</i> (mAb)	Undisclosed Target	Phase 1 to complete in 2026					
EARLY-STAGE PROGRAMS							
TDP-43 CYTOPE[®] <i>ALS</i> (CYTOPE [®])	pTDP-43						
PRX012-TfR³ <i>Alzheimer's disease</i> (mAb)	Aβ (N-terminus)						

mAb = monoclonal antibody; TfR = transferrin receptor

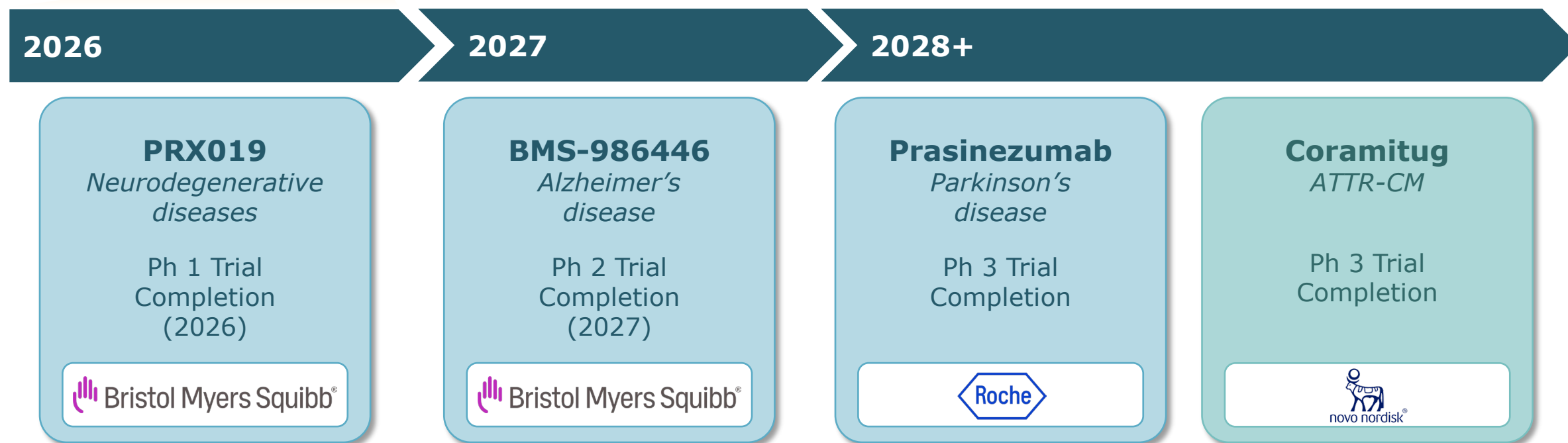
¹ Orphan Drug Designation granted by FDA & EMA; ² FDA Fast Track designation.

³ PRX012 has completed Phase 1b ASCENT program; PRX012 combination with transferrin receptor technology (PRX012-TfR) is in preclinical development

⁴ In July 2021 Novo Nordisk acquired coramitug (formerly PRX004) and broader ATTR amyloidosis program and gained full worldwide rights. Prothena is eligible to receive up to \$1.23 billion in total consideration

Upcoming Partner Milestones

**★ Up to \$105 Million in Clinical Milestones by YE 2026
Related to the Advancement of Coramitug and PRX019¹**



Neurodegenerative Rare Peripheral

Prothena Partnerships Expected to Generate Meaningful Value Across Programs



Up to \$755 Million in Total Milestones + Royalties

Prasinezumab

Phase 3
Parkinson's disease

- ✓ **\$135 million** paid to date
- ❑ **\$620 million** remaining in regulatory and sales milestones¹
- ❑ Up to double digit teen royalties
- ❑ US co-promote option



Up to \$1.23 Billion in Total Milestones

Coramitug (PRX004)

Phase 3
ATTR-CM

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



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

✓ Upfront Payment + Equity: \$150 million²

BMS-986446

Phase 2
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

Phase 1
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

Phase 3

Worldwide Collaboration with Roche

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



Prasinezumab *Parkinson's Disease*

Status: Phase 3, completion in 2029

Anti- α -synuclein Antibody

- Preferentially binds to aggregated α -synuclein, designed to reduce pathogenic spread and decrease synuclein pathology¹

Rapidly Growing Parkinson's Patient Population

- 10 million patients globally²
- Fastest increasing neurodegenerative disease³

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 >\$3.5B (unadjusted)⁴

Phase 3 Clinical Program:

- Roche initiated Phase 3 PARAISO trial (NCT07174310) in ~900 participants with early-stage Parkinson's disease on stable symptomatic levodopa monotherapy
- Primary endpoint: Time to confirmed motor progression event on MDS-UPDRS Part III score at least 2 years

Phase 2 Clinical Program Results:

- 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 Phase 2b PADOVA (~75% of participants)
- PADOVA trial provided the first biomarker evidence of prasinezumab impacting the underlying disease biology
- OLE studies from both PADOVA and PASADENA ongoing and data support slowing of disease progression

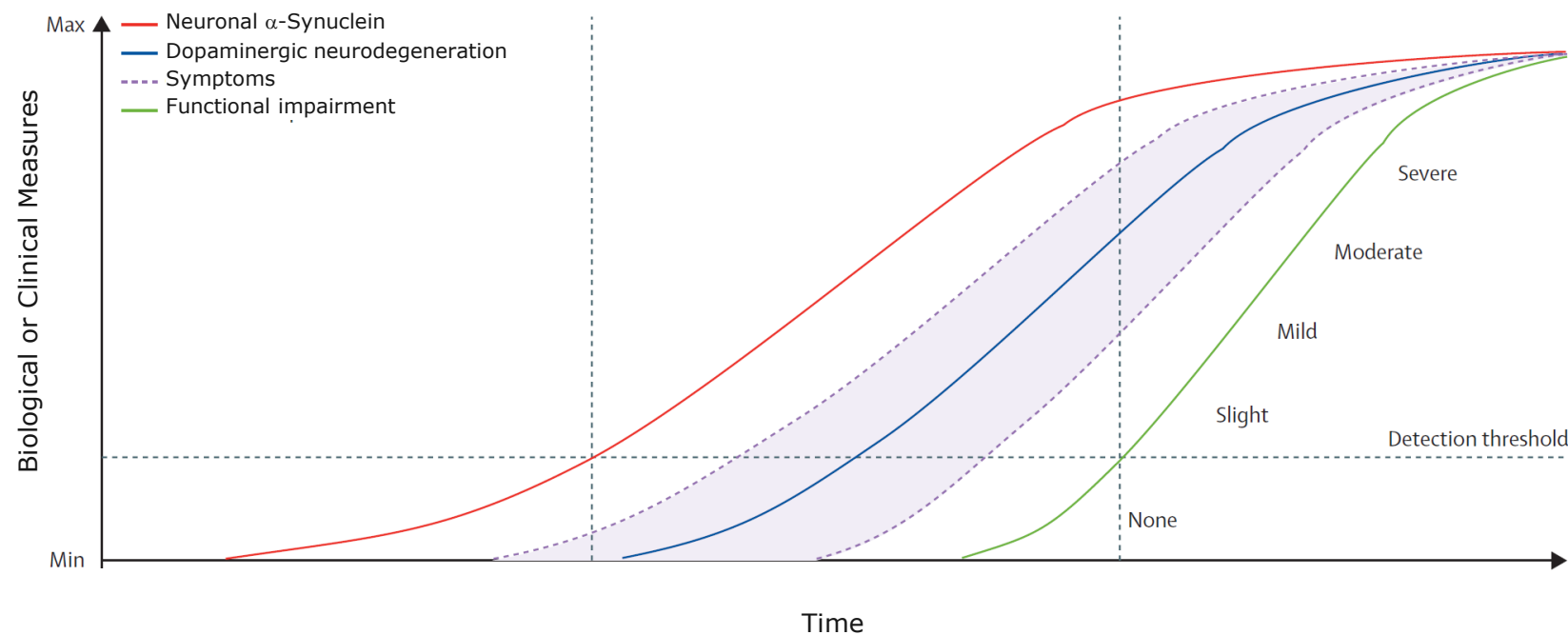
MDS-UPDRS: Movement Disorder Society – Unified Parkinson's Disease Rating Scale.

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 Pharma Day 2025 Presentation on September 22, 2025; not a milestone or royalty projection. Roche states >3B CHF in their 9/22/2025 Pharma Day presentation; conversion rate of 1 CHF = 1.26 USD (as of October 22, 2025) equates to ~3.77B USD.

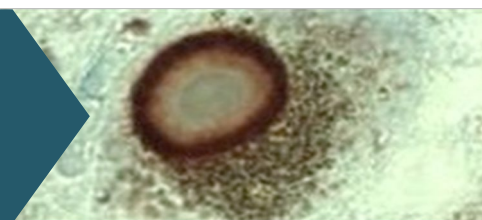
α -Synuclein Pathology is Strongly Implicated in Parkinson's Disease

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

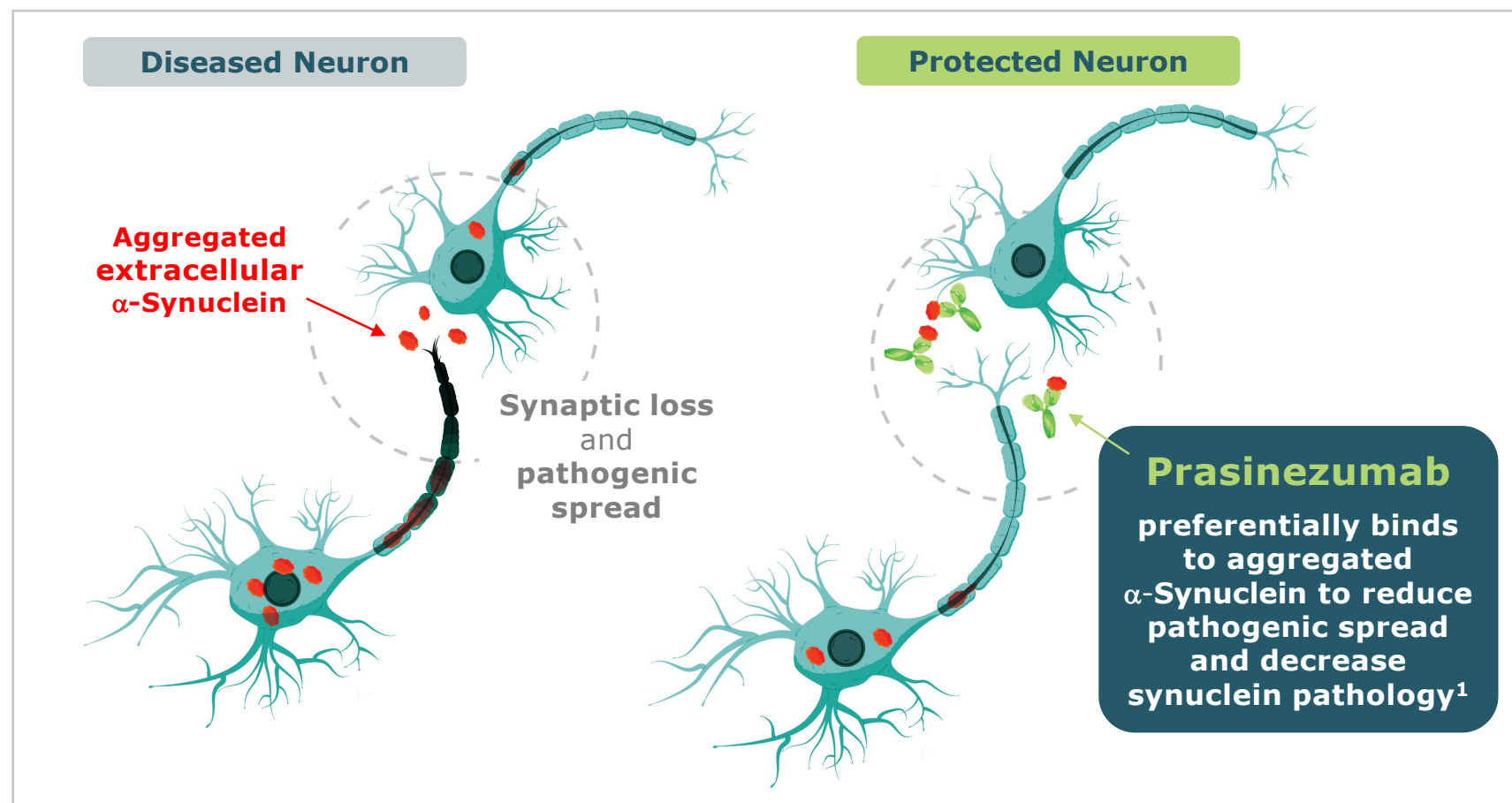


Prasinezumab: α -Synuclein Immunotherapy

REDUCE NEURONAL TOXICITY AND PREVENT CELL-TO-CELL TRANSMISSION¹

α -Synuclein as an extracellular target during pathogenesis

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

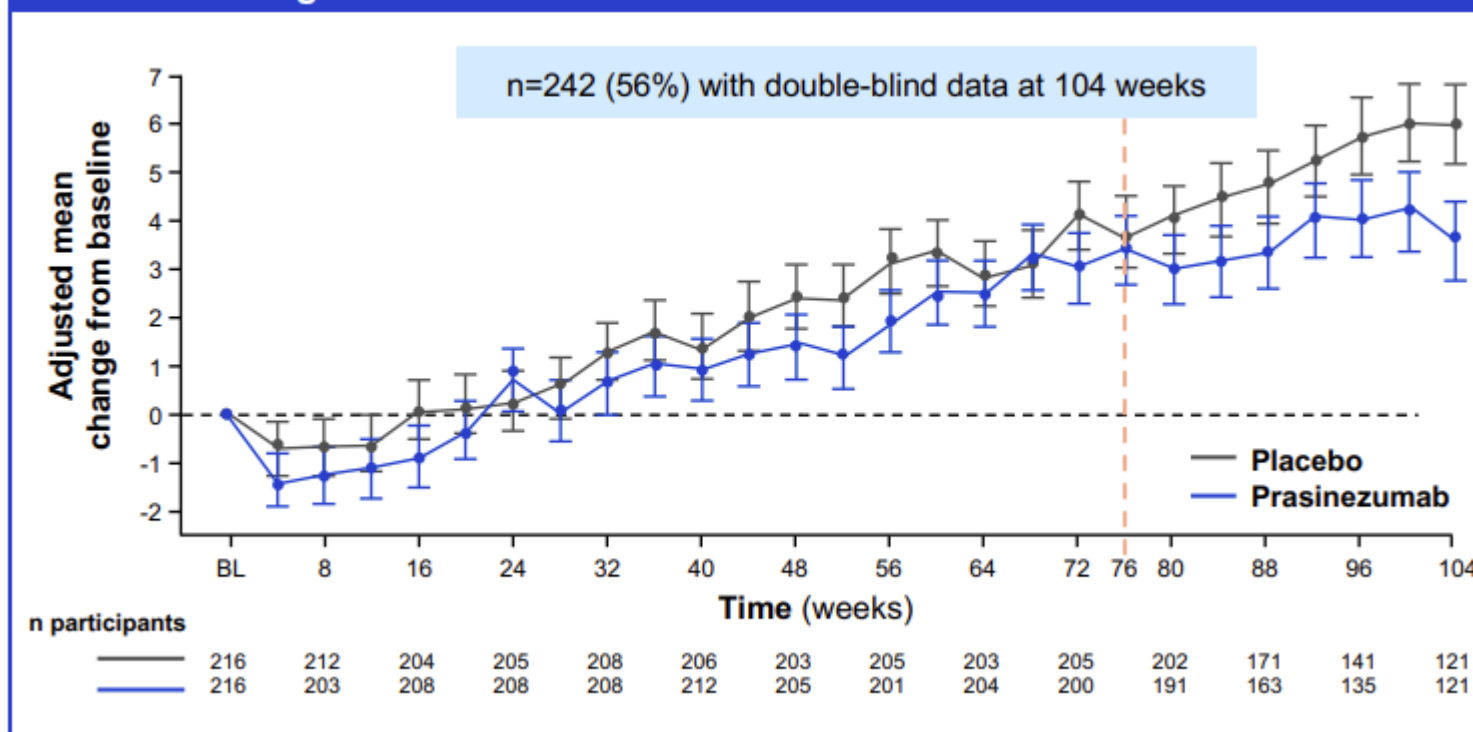


Moving into Phase 3 in Parkinson's Disease

Phase 2b (PADOVA) 2 Year Results¹

L-DOPA-treated population

Change from baseline to Week 104 on MDS-UPDRS Part III OFF



~40% relative reduction vs placebo
p=0.0177²

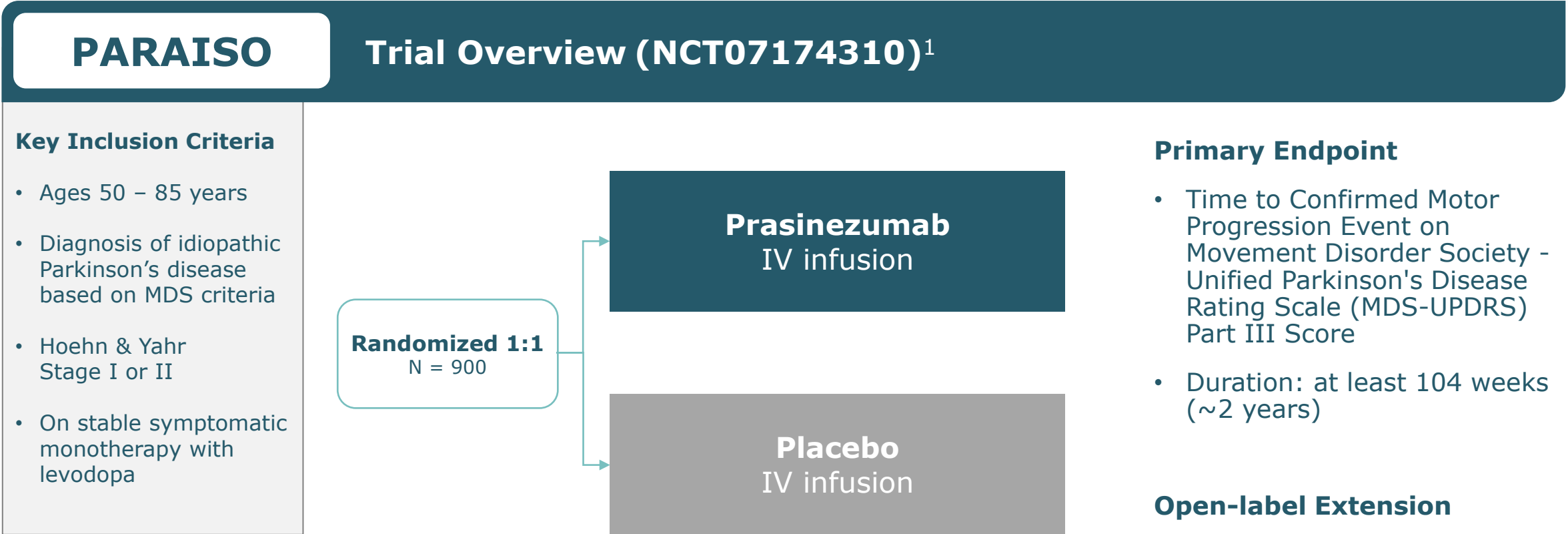
- More pronounced effect in L-DOPA treated patients (~75% of population)
- Treatment duration longer than 18 months may be needed to measure treatment effect
- Phase 3 trial design incorporates:
 - Larger sample size 'n' (~900)
 - Longer treatment duration (2 years)
 - L-DOPA population

MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; OFF: Practically defined OFF state

¹ Slide adapted from Roche's presentation at ADPD 2025 in Vienna, Austria April 1-5, 2025.

² For descriptive purposes, nominal p-values are displayed for 2-year, double-blind data for L-DOPA-treated population

Prasinezumab: PARAISO Phase 3 Trial Design



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



MULTIPLE ENDPOINTS FROM PHASE 2 STUDIES (PASADENA & PADOVA) AND OLE SUGGEST POTENTIAL TO DELAY MOTOR PROGRESSION

The Bar 	Prasinezumab
 Answers a clear & addressable unmet need	>10m Parkinson's disease patients globally; no approved disease modifying therapy to slow/stop progression
 Engages a 'foundational target'	α-synuclein is a known biological driver of PD progression, as supported by preclinical data and Ph II clinical studies (e.g., PADOVA and PASADENA)
 Possesses worthy pharmacologic & developability characteristics	- Potentially first in class anti-α-synuclein antibody - Favorable safety and tolerability profile (PADOVA and PASADENA)
 Achieves meaningful therapeutic differentiation	- Evidence of delayed motor progression - Effect on top of effective symptomatics, i.e. L-DOPA (PADOVA)
 Unlocks a path to value	Peak sales potential >\$3.5B (unadjusted)*

OLE: Open label extension; PD: Parkinson's disease.
 Slide adapted from Roche's Pharma Day 2025 Presentation on September 22, 2025.
 * Roche states >3B CHF in their 9/22/2025 Pharma Day presentation; conversion rate of 1 CHF = 1.26 USD (as of October 22, 2025) equates to ~3.77B USD

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



Coramitug
*ATTR amyloidosis with
cardiomyopathy (ATTR-CM)*

Status: Phase 3, completion in 2029

Differentiated Depleter Mechanism of Action¹

- 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 3 Clinical Program:

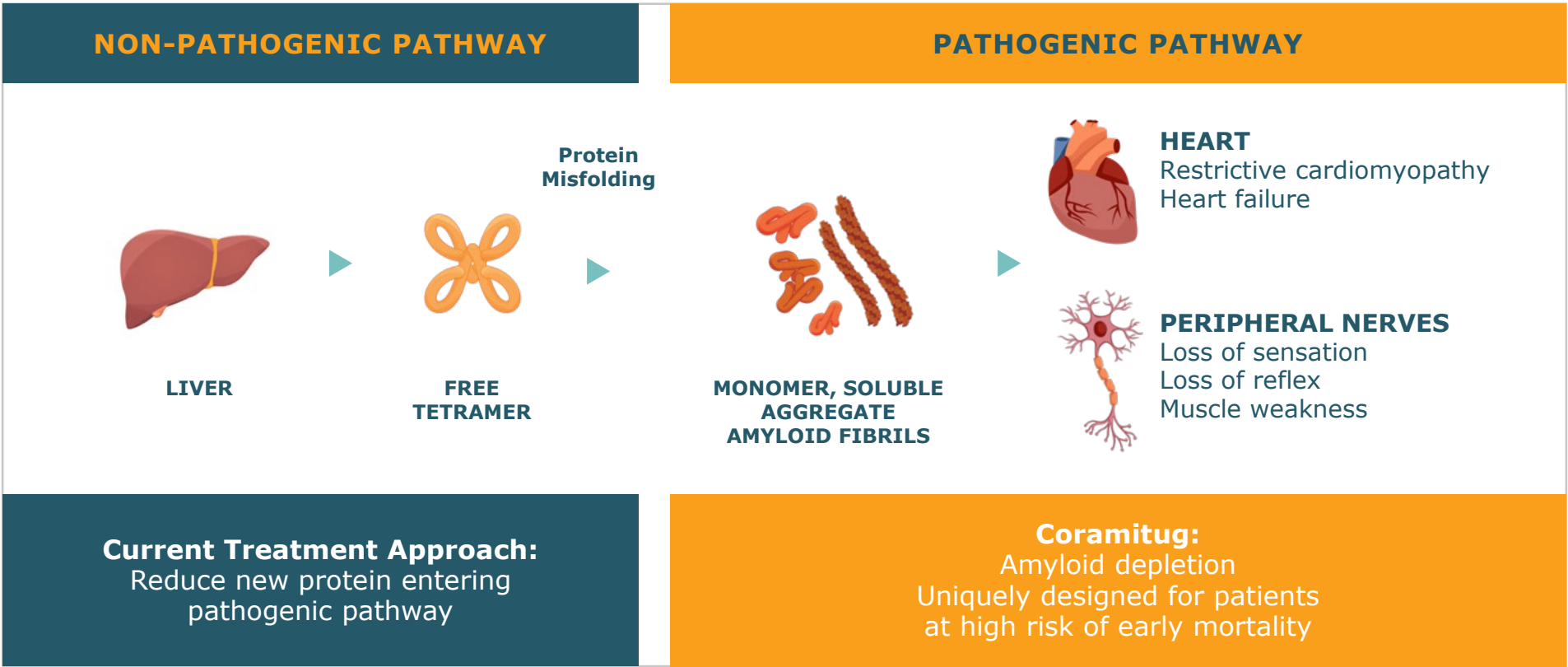
- Novo Nordisk initiated the Phase 3 CLEOPATTRA trial (NCT07207811) in ~1280 participants with ATTR-CM
- NYHA Class I-IV patients randomized 1:1 to coramitug with continued SOC vs. placebo with continued SOC
- Primary endpoint: Number of occurrences of composite endpoint of CV deaths and recurrent CV events (CV hospitalizations and urgent heart failure visits) up to ~4 years

Phase 2 Signal Detection Trial:

- Phase 2 trial in 105 ATTR-CM patients (NCT05442047)
- Participants received IV infusion Q4W of 10 mg/kg or 60 mg/kg of coramitug or placebo added to SOC
- Positive results support Phase 3 development and were shared in a late-breaker presentation at the AHA Scientific Sessions and published in *Circulation*²

CV: Cardiovascular; SOC: Standard of care.
¹ Preclinical studies of mPRX004, the murine form of PRX004; Higaki JN et al. *Amyloid*, 2016; Suhr OB et al., *Amyloid*, 2025
² Fontana M et al. *Circulation*, 2025; <https://doi.org/10.1161/CIRCULATIONAHA.125.077304>

Differentiated Mechanism for ATTR-CM



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

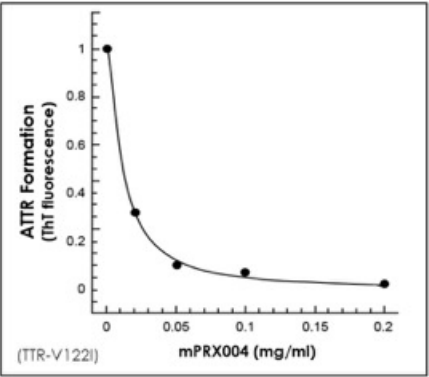
Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF mPRX004

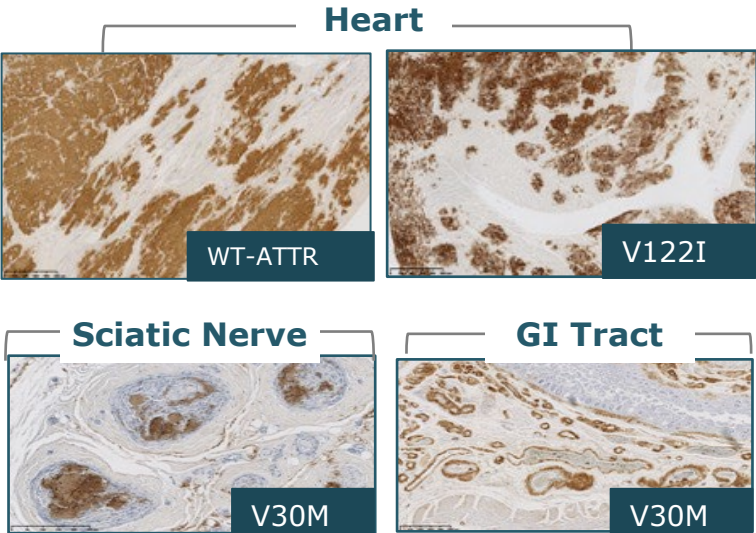
mPRX004 (murine form of PRX004) preclinical results:¹

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

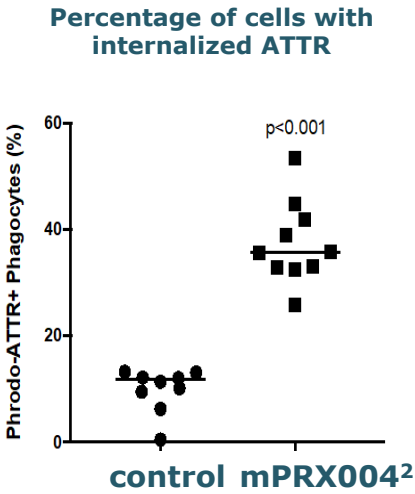
Inhibition of amyloid formation



Specific binding to amyloid

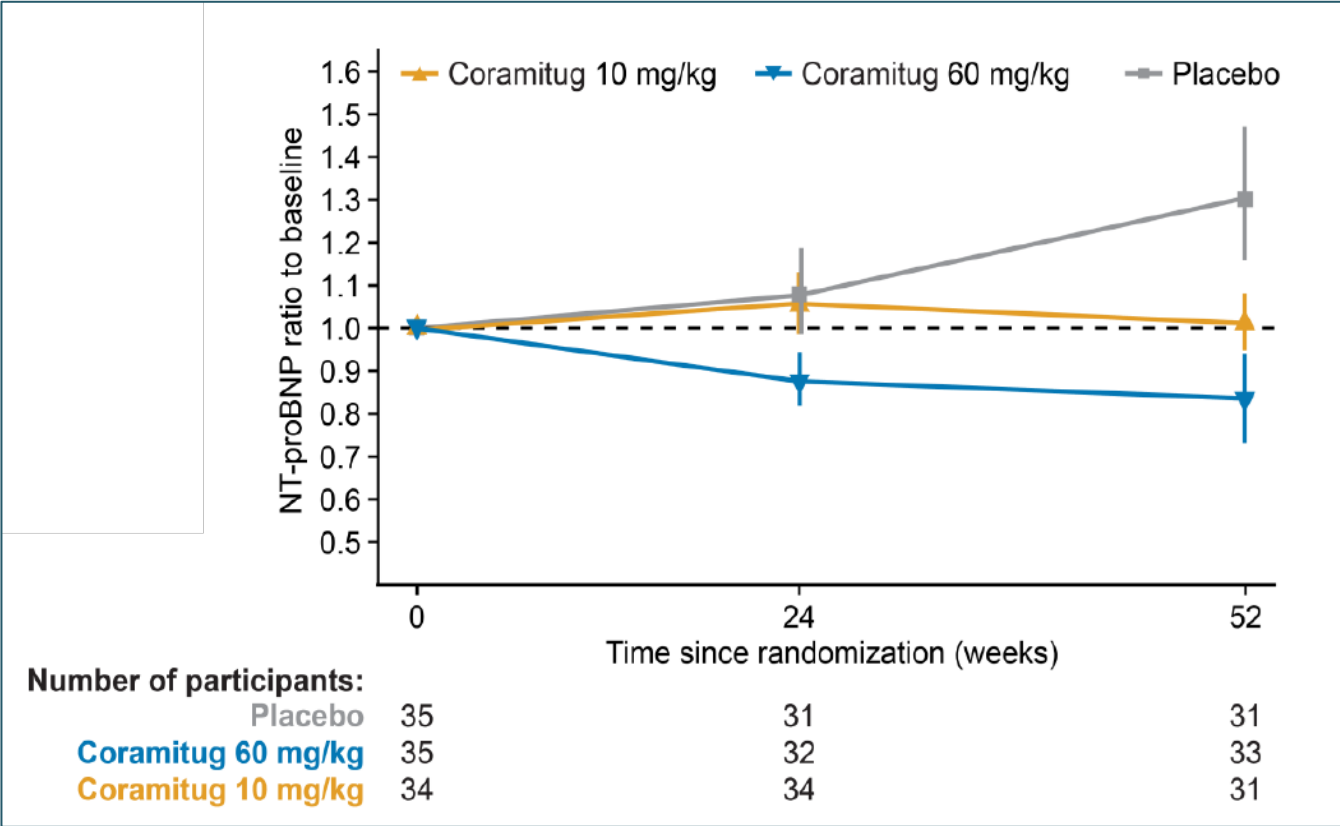


Clearance of amyloid



Phase 2 Signal Detection Study Results

Phase 2 Results: Change in NT-proBNP



60 mg/kg reduced NT-proBNP levels from baseline at month 12 and by 48% compared to placebo
p=0.0017

- Statistically significant reduction in NT-proBNP achieved at 12 months in a 105-patient, 3-arm trial
- Reduction achieved on top of background use of standard-of-care TTR stabilizers:
 - 80% patients on TTR stabilizers in the coramitug 60 mg/kg arm
 - 85.7% patients on TTR stabilizers in the placebo arm



Phase 2 Results Support Advancement to Phase 3

PH 2 DATA PRESENTED AT LATE-BREAKING SESSION AT AHA 2025 AND PUBLISHED IN *CIRCULATION*

- ✓ Treatment with coramitug 60 mg/kg resulted in a statistically significant reduction in NT-proBNP levels compared with placebo (**-48%; p=0.0017**) over 52 weeks with a reduction from baseline
 - Notably, favorable reduction was achieved on top of background use of standard-of-care TTR stabilizers in most patients (80% in the coramitug 60 mg/kg group and 85.7% in the placebo group)
- ✓ Coramitug 60 mg/kg showed an estimated treatment difference of 13.45 m in 6MWT vs. placebo
 - Statistical significance not achieved, potentially due to the small sample size and relatively short study duration
- ✓ Across a wide range of echocardiographic parameters - including measures of LV and RV systolic function, diastolic function, and estimated pulmonary arterial pressures - coramitug 60 mg/kg was associated with improvements versus placebo, suggestive of favorable cardiac remodeling
- ✓ Coramitug demonstrated an acceptable safety profile and was generally well tolerated

Coramitug for ATTR-CM represents a potential multi-billion dollar global market opportunity

Coramitug: CLEOPATTRA Phase 3 Trial Design

CLEOPATTRA

Trial Overview (NCT07207811)¹

Key Inclusion Criteria

- 18 years and older
- Diagnosis of ATTR-CM²
- Demonstrated cardiac amyloid infiltration
- Increased LV wall thickness ≥ 12 mm
- Chronic heart failure (NYHA Class I – IV) requiring ongoing treatment with a loop diuretic

Randomized 1:1
N = 1280

Coramitug
IV infusion

Placebo
IV infusion

Primary Endpoint

- Number of occurrences of composite endpoint of CV deaths and recurrent CV events (CV hospitalizations and urgent heart failure visits) from baseline to end of study
- Duration: up to ~4 years

Everyone in the study will continue receiving their usual heart treatments as recommended by their doctor

CV: Cardiovascular; NYHA: New York Heart Association.
¹ Trial design slide adapted from information available on posting on clinicaltrials.gov.
² ATTR-CM includes wild-type ATTR (ATTRwt) or variant ATTR (ATTRv); target ATTRv resuitment is ~15% of the study population.

BMS-986446 (formerly PRX005)

Alzheimer's Disease

Phase 2

Global Neuroscience Collaboration
with Bristol Myers Squibb

Bristol Myers Squibb®

BMS-986446
Alzheimer's disease

Status: Phase 2, completion in 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-986446¹

- ✓ \$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

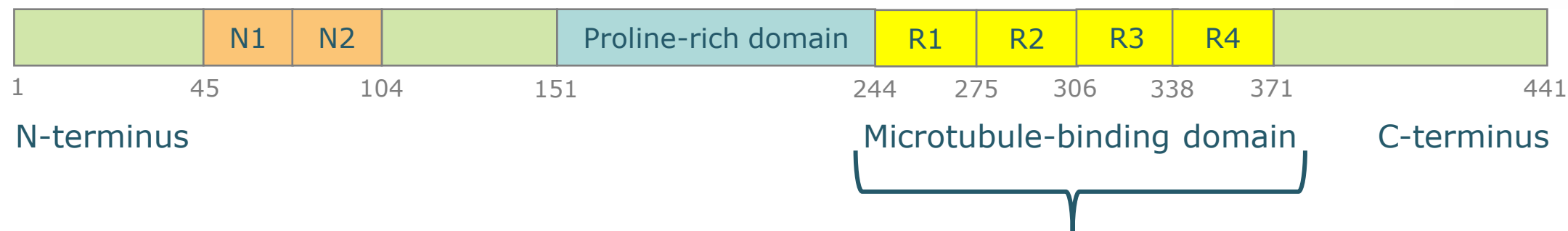
Phase 2 Trial (NCT06268886): Ongoing

- Global, double-blind, placebo-controlled
- Randomized, 3 arms (two doses and placebo) in 310 participants with early AD, IV administration
- 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 Trials: Complete

- Double-blind, placebo-controlled, multiple-ascending-dose (IV) Phase 1 study results presented at CTAD 2025
- Open-label single-dose Phase 1 study (NCT06955741) to assess PK, tolerability, and bioavailability of subcutaneous administration completed in 2H 2025

Microtubule Binding Region (MTBR) of Tau



Rationale for Targeting Microtubule Binding Region (MTBR) of Tau:

- Pathology: MTBR is central to fibril formation, seeding and cell-to-cell transmission of tau pathology¹⁻²
- Biomarkers: MTBR-tau 243 highly correlated with tau-PET and disease progression³⁻⁴
- Preclinical: MTBR-targeting antibodies have demonstrated blocking of internalization and spread of tau, leading to the reduction of tau pathology^{5,7}
- Clinical: Trials ongoing, early clinical data from MTBR-targeting antibodies has shown positive trends on biomarkers including MTBR-tau 243 and tau-PET⁶

N1/N2 = represent the two n-terminal domains; R1-R4 represents the four MTBR domains.

¹ Holmes BB, Diamond MI et al. Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. 2013 *Proc Natl Acad Sci U S A*. ² Annadurai N, et al. Tau R2 and R3 are essential regions for tau aggregation, seeding and propagation. 2022 *Biochimie*. ³ Horie K, Bateman RJ et al. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. 2023 *Nat Med*. ⁴ Horie K, Bateman RJ et al. Plasma MTBR-tau243 biomarker identifies tau angle pathology in Alzheimer's disease. 2025 *Nat Med*. ⁵ Roberts M, de Silva R et al. Pre-clinical characterisation of E2814, a high-affinity antibody targeting the microtubule-binding repeat domain of tau for passive immunotherapy in Alzheimer's disease. 2020 *Acta Neuropathol Commun*. ⁶ Eisai presentation on E2814 at CTAD 2025 ⁷ Prothena data on file



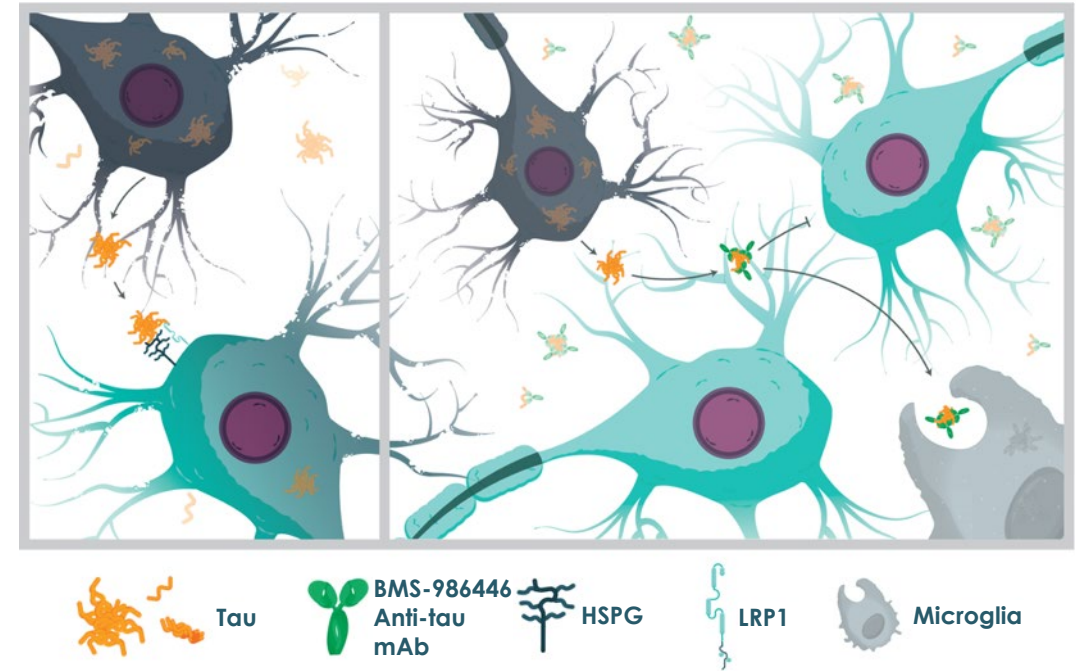
BMS-986446: MTBR-Specific Anti-Tau Antibody

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

- Recent publications strongly suggest that tau appears to spread throughout the brain via synaptically-connected pathways¹
- This propagation of pathology is thought to be mediated by tau “seeds” containing the MTBR of tau²

Potential for best-in-class efficacy

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



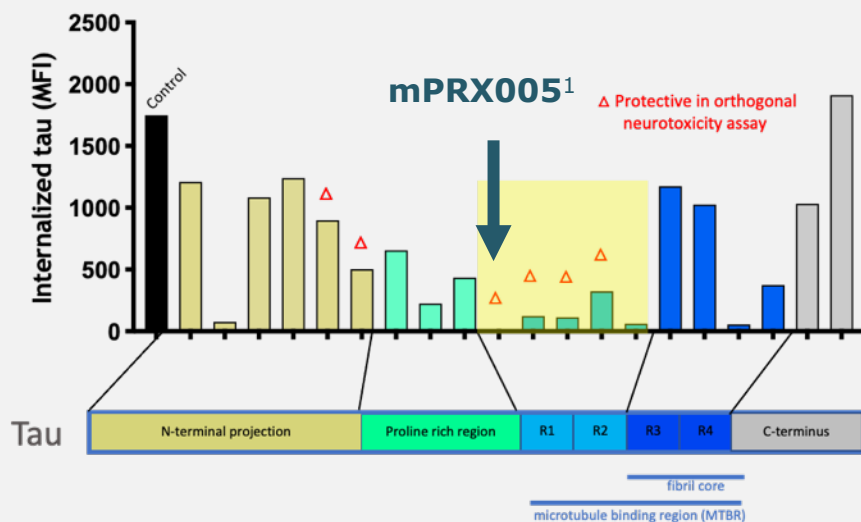
BMS-986446: Potential Best-in-Class MTBR-Specific Anti-Tau Antibody to Reduce Pathogenic Tau Spread

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*;

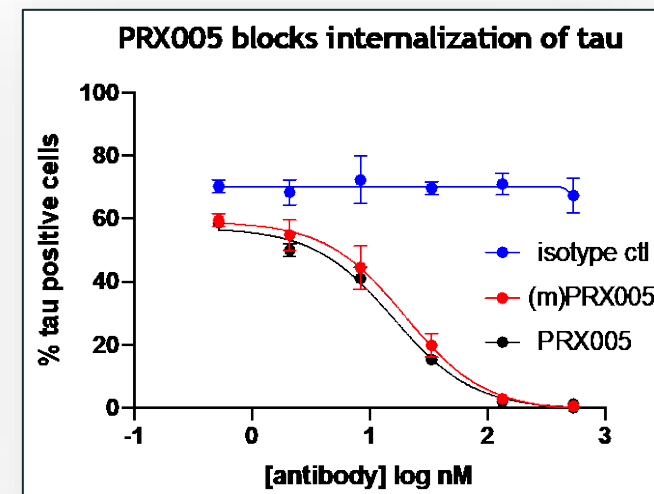
² Horie, K., Barthelemy, H., Bateman, R.J. CSF tau microtubule binding region identifies tau tangle and clinical stages of Alzheimer's disease. 2021 *Brain*

BMS-986446 (PRX005): Superior in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity

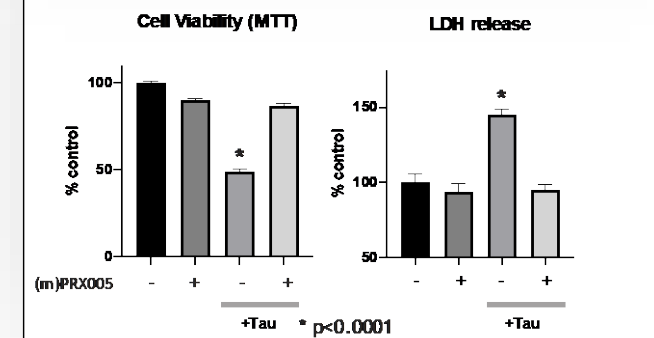
Repeats 1 and 2 defined as the strongest inhibitory regions in screening with cellular internalization and neurotoxicity assays



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



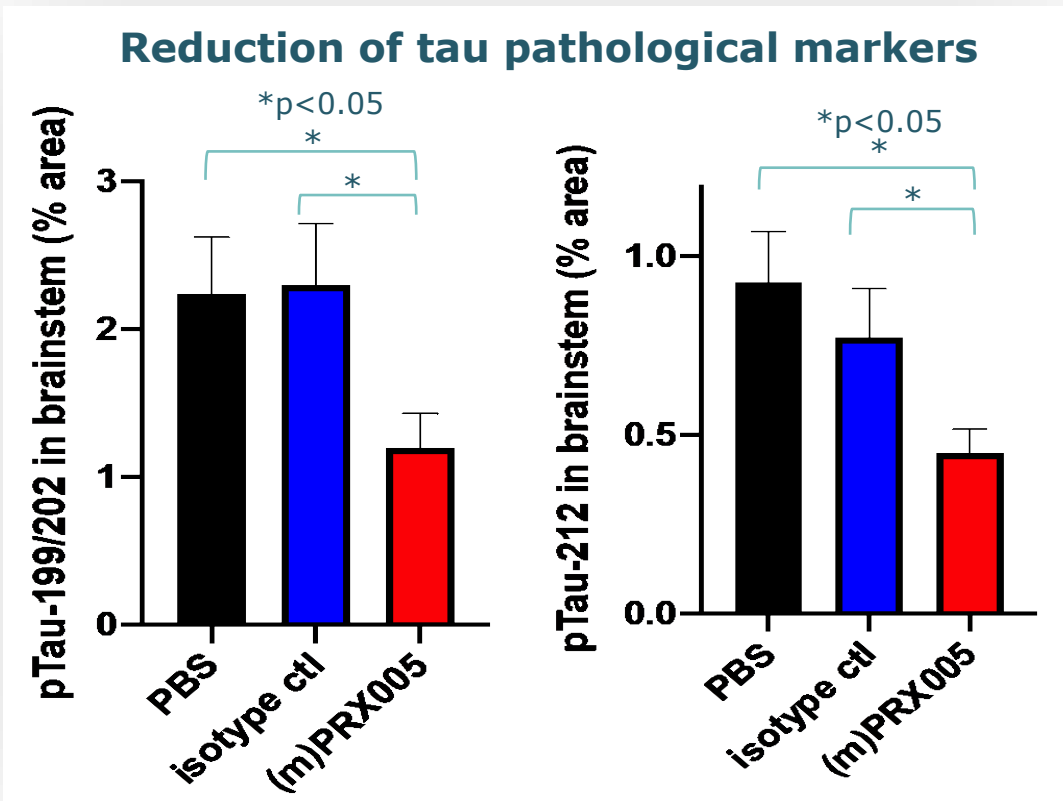
(m)PRX005 protects rodent primary cortical neurons from tau-induced toxicity



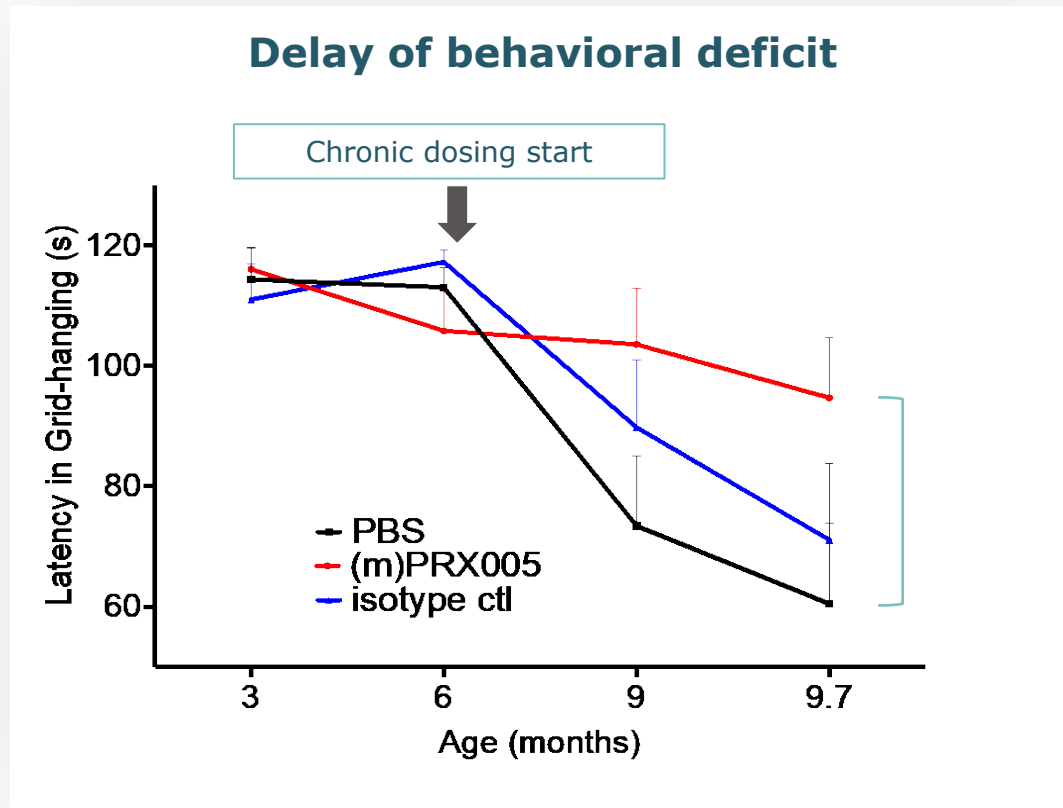
¹ (m)PRX005: murine form of PRX005 (BMS-986446)
Prothena data on file

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

All values are mean ± SE (n=15-20)

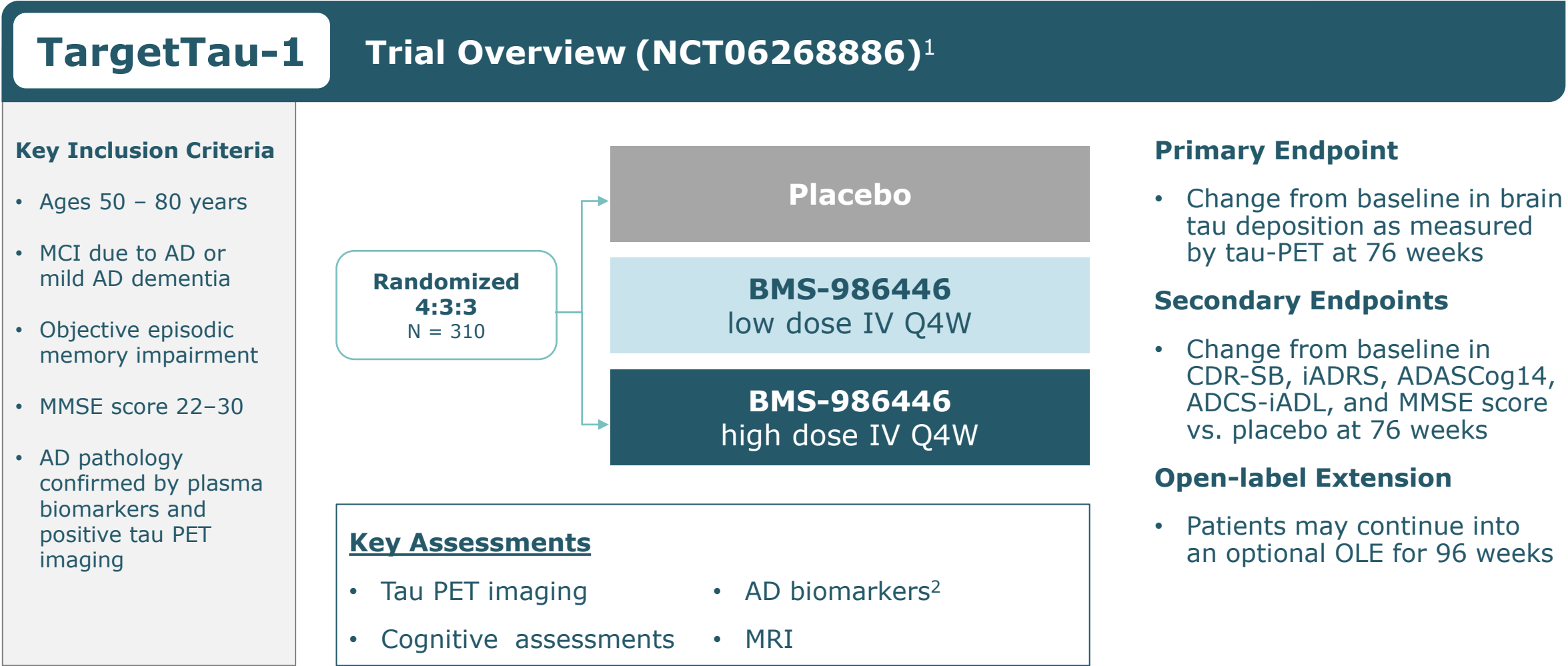


- PS19 transgenic mice overexpressing tau mutation (P301S) cause high levels of neuronal tau pathology and resultant behavioral deficits



- 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

BMS-986446: TargetTau-1 Phase 2 Trial Design



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.
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.

PRX019

Neurodegenerative Diseases

Phase 1

Global Neuroscience Collaboration
with Bristol Myers Squibb

PRX019: Potential Treatment of Neurodegenerative Diseases



PRX019

Neurodegenerative diseases

Status: Phase 1, completion in 2026

Global Rights Deal for PRX019¹

- ✓ \$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
 - Pharmacodynamics
- Trial expected to complete in 2026

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

TDP-43 CYTOPE®

ALS

Preclinical

Unpartnered Program

A Vast Number of Disease Targets Remain Untreatable by Today's Modalities

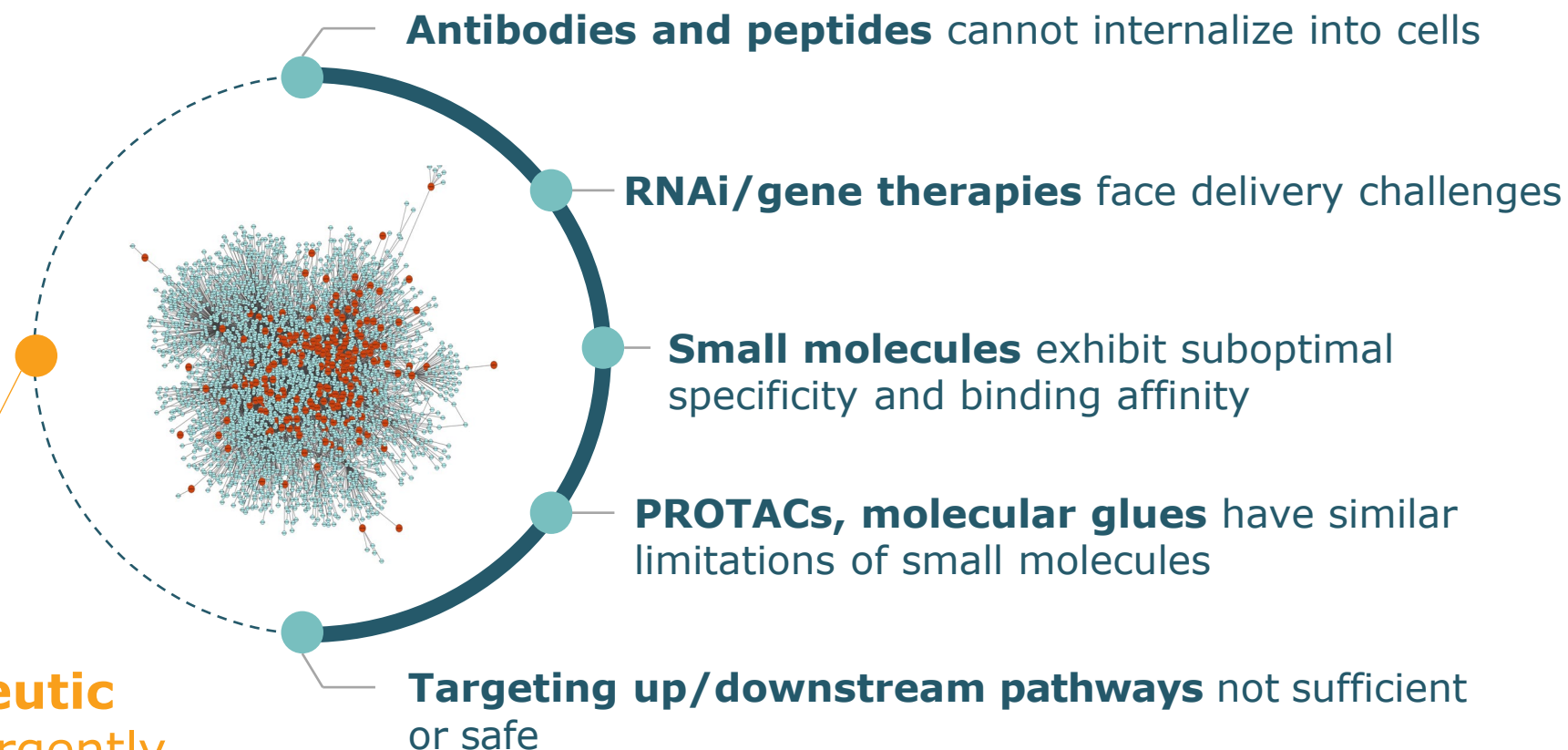
Why Current Modalities Fall Short?

1) Intracellular Delivery

2) Precision Requirement

- Exceptional specificity
- Fine-tuned modulation

A new therapeutic breakthrough is urgently needed



CYTOPE® – A Breakthrough in Intracellular Therapeutics



CYTOPE

- An **innovative intracellular drug delivery technology** designed at Prothena to transport complex molecules into virtually any cell-type, to enable precise targeting of intracellular disease pathways and **to unlock therapeutic access** to targets where conventional modalities fall short
- A proprietary modality utilizing an **endosomal escape mechanism** for cytosolic delivery while preserving membrane and vesicle integrity (non-endolytic) designed for safety and performance

Versatile Plug-&-Play Technology



Reach of Delivery

- Demonstrated to efficiently achieve **intracellular delivery into multiple cell-types** and tissues, to cross blood-brain-barrier, and to achieve **activity in brain and periphery with infrequent, systemic administration**¹
- Modular design enables optional targeted delivery to specific tissues/cells via receptor mediated endocytosis and trafficking to sub-cellular compartments

TDP-43 CYTOPE® Preclinical Data Demonstrates Potential of CYTOPE Technology



Preclinical Data Presented at SfN 2025:

1. Systemic administration

2. Internalization into the cell

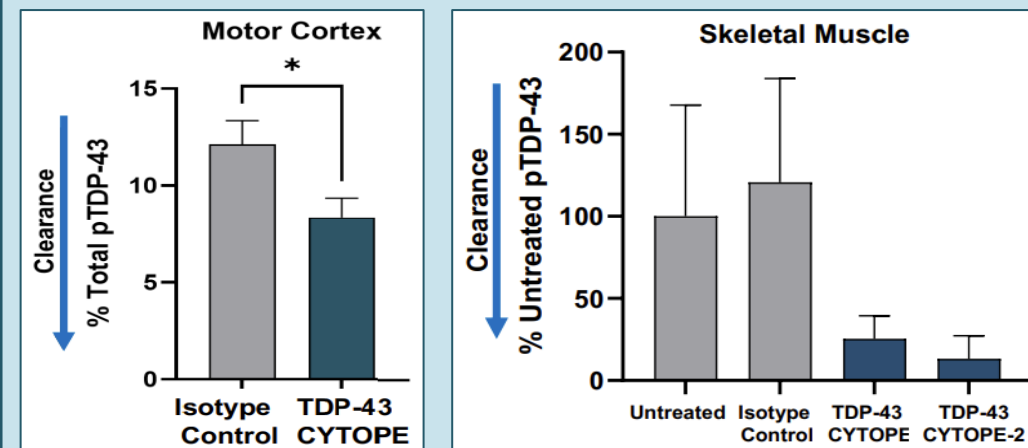
- *In vivo*: rapidly and efficiently distributed to the brain, internalized into the cytosol and colocalized with intracellular pTDP-43 pathology in rNLS8 mice
- *In vitro*: rapidly and efficiently internalized into the cytosol and colocalized with pre-formed cytosolic pTDP-43 aggregates

3. Significantly reduced pathology in brain and in the periphery (toxic gain of function)

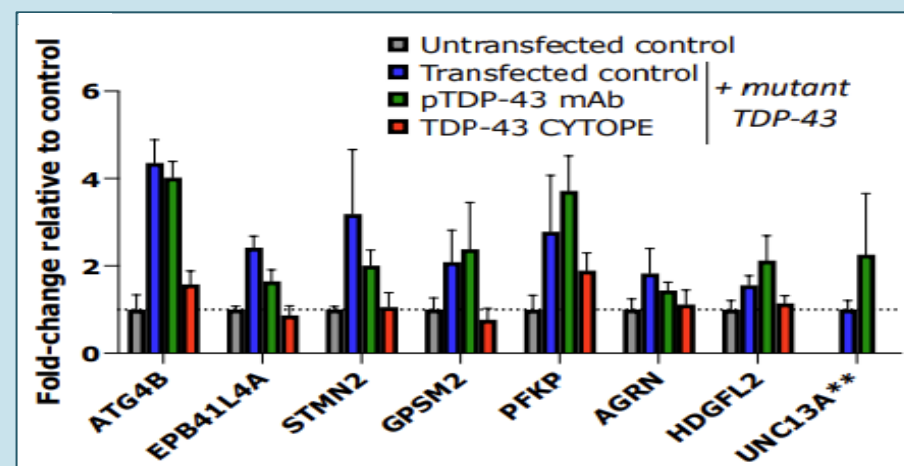
4. Meaningfully reduced RNA dysregulation driven by cryptic exon inclusions (loss of function)

5. Safely preserved membrane and vesicle integrity

3.



4.



PRX012-TfR

Alzheimer's Disease

Preclinical

Unpartnered Program

Potential of TfR for PRX012

Rationale for Transferrin Receptor Technology:

- The addition of transferrin targeting to an anti-A β mAb has been demonstrated to:
 - Lower dose levels needed by an order-of-magnitude
 - Significantly decrease the time required to achieve meaningful amyloid reduction
 - Substantially lower risk of ARIA-E associated with amyloid-targeting antibodies

Roche effectively improved the profile of its anti-A β mAb with its TfR-1 technology:

	Gantenerumab ¹ Phase 3 GRADUATE I and II		Trontinemab ² Phase 1b/2
Dose level (monthly)	~15mg/kg ³	➡	3.6 mg/kg
Subjects amyloid negative (<24 CL)	~27-28%	➡	~91%
Timepoint	116 weeks	➡	28 weeks
ARIA-E incidence	24.9%	➡	<5%

¹ Bateman RJ et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer’s Disease. 2023 *NEJM*

² Roche 2025 Pharma Day presentation: <https://www.roche.com/investors/events/roche-pharma-day-2025>

³ During the double-blind treatment period, the gantenerumab dose was increased over a period of 36 weeks to a target level of 510 mg every 2 weeks, 1020 mg every 4 weeks or roughly 15mg/kg per month.



PRX012-TfR for Alzheimer's Disease

PRX012 Antibody Profile

- Phase 1 ASCENT top-line results¹ support once-monthly, subcutaneous PRX012 with dose- and time-dependent reductions in amyloid plaque
- At the 400 mg dose level, PRX012 demonstrated a mean reduction in amyloid PET to:
 - 27.5 mean centiloids (CL) at month 12
 - 14.8 mean CL at month 18
 - 9 of 11 participants reached amyloid negativity (<24.1 CL) within 18 months
- ARIA-E rates were non-competitive relative to FDA approved anti-A β antibodies



PRX012-TfR Antibody

- PRX012-TfR may lower the risk of ARIA, lower dose level of PRX012 and more rapidly reduce amyloid plaque with a once-monthly subcutaneous administration
- Initial preclinical studies demonstrated²:
 - Substantially increased brain exposure
 - Facilitated rapid targeting of A β plaques
- Additional preclinical studies ongoing to further validate potential of PRX012-TfR

**Prothena is exploring partnership interest
to further advance the program**

¹ Prothena data on file. Top-line results reported above. 12 and 18 months mean CL top-line data includes only participants who were randomized to PRX012 in ASCENT-2 and rolled over to ASCENT-3 (OLE) as those participants had the opportunity to reach month 12 and only those participants had the opportunity to reach month 18 dosing.

² Prothena data on file for surrogate A β -transferrin receptor antibody in an APP/PS1 transgenic mouse model.