

prothena®

CORPORATE OVERVIEW

November 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 pipeline, and the potential to advance, initiate, and complete preclinical and IND enabling studies for our preclinical portfolio, including our TDP-43 CYTOPE and PRX012-TfR programs, and CYTOPE internal targets; the continued advancement of our pipeline, and expected milestones in 2027 and beyond, including the expected timing of (i) data readout from the ongoing Phase 2 clinical trial evaluating moponetug in 2027, (ii) completion of the Phase 3 clinical trial for prasinezumab in 2029, and (iii) completion of the Phase 3 clinical trial for coramitug in 2029; whether potential milestones are achieved and amounts we might receive under our partnerships and collaborations with Roche, BMS, and Novo; the treatment potential, designs, proposed mechanisms of action, and potential administration of prasinezumab, coramitug, moponetug, 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, and moponetug; the potential to partner our early-stage programs, including PRX012-TfR; and the potential to return capital to shareholders via a share repurchase program or other permissible means. 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 6, 2026, and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. This overview is made as of November 5, 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 worldwide[1]

Fastest increasing
Neurodegenerative disease[1]

$52 billion
In overall economic burden in the US[1]

Prasinezumab
Phase 3

Alzheimer's disease (AD)

>80 million
People worldwide living with early symptomatic AD[2]

>315 million
People worldwide living with presymptomatic AD[2]

$1 trillion
In annual US healthcare costs by 2050 from AD and other dementias[3]

Moponetug
Phase 2

PRX012-TfR
Preclinical

RARE PERIPHERAL AMYLOID

Transthyretin amyloidosis (ATTR)

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

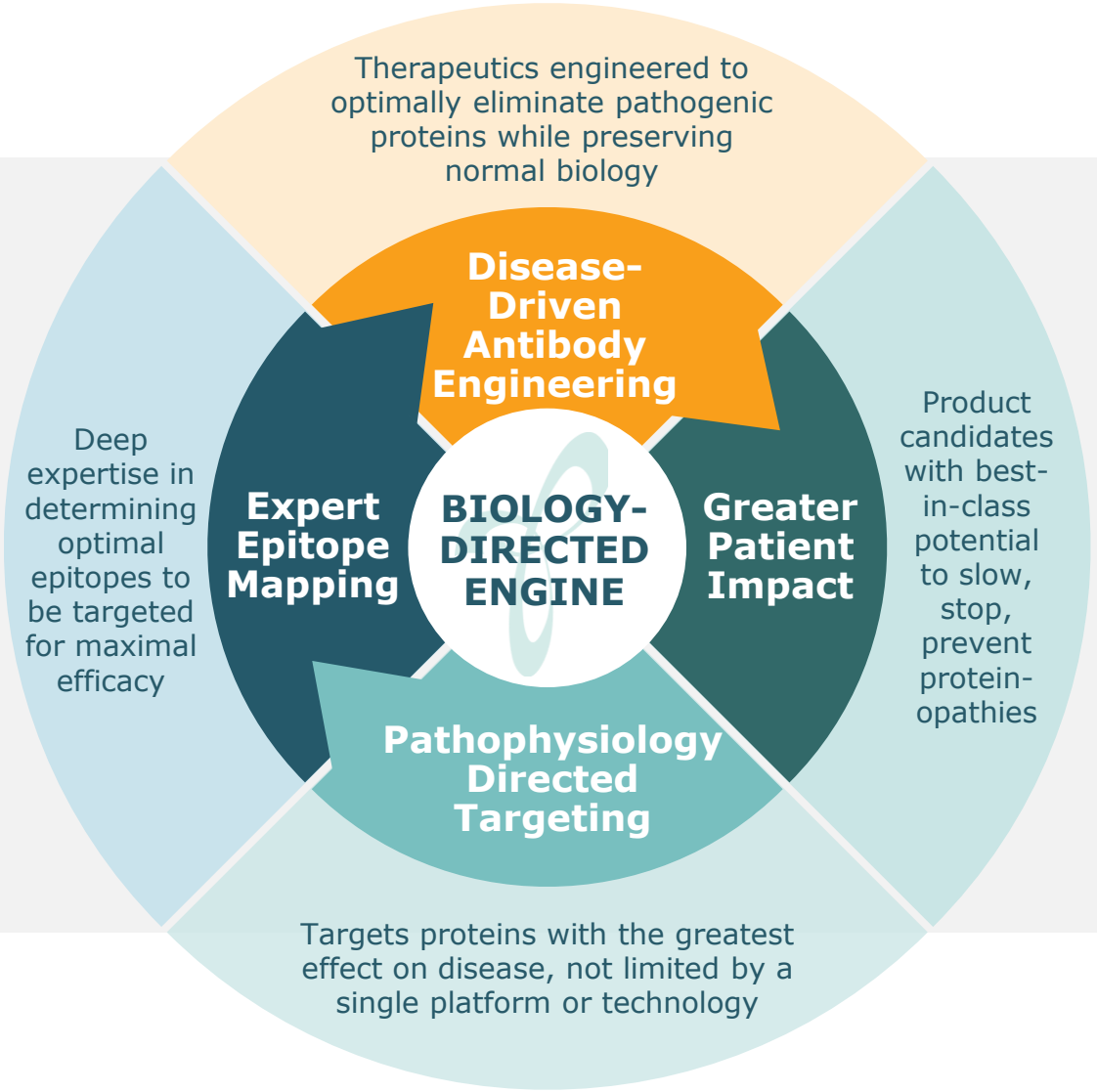
2.08 years
Median overall survival New York Heart Association class III patients with ATTR cardiomyopathy[7,8]

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, 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. [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 Active Clinical Programs

Two partnered Phase 3 programs

One partnered Phase 2 program

Strong Collaborations Established

Bristol Myers Squibb

Novo[1]

Roche

[1] In July 2021 Novo 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.

Research & Development Pipeline

PROGRAM	PROTEIN TARGET	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	GLOBAL RIGHTS
Prasinezumab *Parkinson's disease* *(mAb)*	α-Synuclein (C-terminus)	Phase 3 PARAISO trial ongoing (NCT07174310)				Roche
Coramitug (PRX004) ODD[1] Fast Track[2] *ATTR-CM* *(mAb)*	Transthyretin (misTTR)	Phase 3 CLEOPATTRA trial ongoing (NCT07207811)				novo
Moponetug (PRX005) Fast Track[2] *Alzheimer's disease* *(mAb)*	Tau (MTBR)	Phase 2 TargetTau-1 data expected 1H 2027[5] (NCT06268886)				Bristol Myers Squibb
PRECLINICAL PORTFOLIO						
TDP-43 CYTOPE® *ALS and other TDP-43 proteinopathies* *(mAb-CYTOPE)*	pTDP-43					prothena
PRX012-TfR[3] *Alzheimer's disease* *(mAb-TfR)*	Aβ (N-terminus)					prothena
CYTOPE® Research Collaborations[4] *Ongoing with industry partners in multiple diseases & modalities*	Undisclosed targets					prothena
CYTOPE® Internal Targets[4] *Multiple diseases and modalities*	Undisclosed targets					prothena

mAb: Monoclonal Antibody; TfR: Transferrin Receptor; misTTR: misfolded transthyretin; ATTR-CM: transthyretin amyloid cardiomyopathy; MTBR: microtubule binding region; ALS: amyotrophic lateral sclerosis
[1] Orphan Drug Designation granted by FDA & EMA; [2] FDA Fast Track designation; [3] PRX012 combination with TfR technology; [4] Various applications of CYTOPE® technology.
[5] Data timing based on 3Q 2026 earnings report by Bristol Myers Squibb.

2026 Strategic Priorities



CAPTURE VALUE EMBEDDED IN PARTNERSHIPS & OPTIMIZE CAPITAL STRUCTURE

All partnered assets originated from Prothena's R&D engine & drive meaningful long-term value

- ✓ **$50 MILLION** Phase 3 enrollment milestone achieved for coramitug
- ✓ **$26.6 MILLION** worth of shares repurchased through 9/30/2026 under Share Repurchase Program[1]



ADVANCE R&D TO SUPPORT RESEARCH COLLABORATIONS & LICENSING DEALS

Partnerships provide an efficient path to explore the potential value of early-stage programs

- ✓ Investing in preclinical CYTOPE® technology and PRX012-TfR
- ✓ Multiple research collaborations ongoing with industry partners evaluating our CYTOPE® technology
- ✓ Exploring additional research collaborations and licensing deals for unpartnered programs

[1] Prothena repurchased an aggregate of 2,745,380 ordinary shares during the first nine months of 2026 with $26.6 million, excluding commissions and expenses. Prothena may repurchase the shares from time to time in open market transactions, which may be structured to occur in accordance with the requirements of Rule 10b-18 of the Securities Exchange Act of 1934, as amended. Prothena may also enter into Rule 10b5-1 plans to facilitate repurchases. The timing, number of shares repurchased, and prices paid for the shares under this program will depend on general business and market conditions as well as corporate and regulatory limitations, prevailing share prices, and other considerations. The Share Repurchase Plan allows for up to $100.0 million in share repurchases and will expire on December 31, 2026, may be suspended or discontinued at any time, and does not obligate the company to acquire any amount of ordinary shares. No amount or any amount of outstanding ordinary shares may be acquired by the expiration of the Share Repurchase Plan, at Prothena's sole discretion.

Meaningful Partner Catalysts

2026	2027	2028/2029+
✓ **Coramitug** ATTR-CM $50 Million Phase 3 Enrollment Milestone (2026) novo	**Moponetug** Alzheimer's disease Phase 2 Trial Data Readout (1H 2027) Bristol Myers Squibb®	**Prasinezumab** Parkinson's disease Phase 3 Trial Completion (2029) Roche
		Coramitug ATTR-CM Phase 3 Trial Completion (2029) novo

- ☑ **$650 MILLION** received in upfront / milestones / equity[1] from strategic partners to date
- ❑ **>$2.25 BILLION** in potential milestones across **3** partnered programs
- ❑ **SALES ROYALTIES** from prasinezumab and moponetug

[1] Bristol Myers Squibb owns approximately 2.2% of Prothena's outstanding shares as of March 2, 2026.

Prothena Partnerships Expected to Generate Meaningful Value Across Programs

Up to $755 Million + Royalties

Prasinezumab
Phase 3
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

Up to $1.23 Billion

Coramitug
Phase 3
ATTR-CM

- ✓ **$150 million** paid to date
- ❑ **$1.08 billion** remaining in sales milestones

Up to $697.5 Million + Royalties

Moponetug
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

Collaboration and Other Targets:

- ✓ Additional **$230 million** received (upfront/equity[2]/PRX019)

[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 2, 2026.

Prasinezumab
Parkinson's Disease
Phase 3

Worldwide Collaboration with Roche

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

Clear Addressable Unmet Need

- **> 10 million Parkinson's patients** globally, fastest growing neurodegenerative disease[1]

Differentiated Mechanism of Action[2]

- Potential **first-in-class** disease-modifying anti-α-synuclein antibody
- α-synuclein is a known biological driver of PD progression, as supported by preclinical data and two Phase 2 clinical trials

Clinical Support

- **Two Phase 2 clinical trials and OLEs** demonstrate consistent effects on slowing of disease progression
- Favorable safety and tolerability profile

Combination Therapy

- Prasinezumab benefits demonstrated on top of symptomatic treatments (e.g., levodopa/carbidopa)

Current Status

- Roche advanced prasinezumab into the **Phase 3 PARAISO** clinical trial in ~900 patients with early PD on stable levodopa therapy (NCT07174310)

Upcoming Milestones

- Phase 3 trial primary completion expected in 2029

Market Opportunity

- **>$3.5 billion** global peak sales per Roche[3]

Partnership Economics with Roche

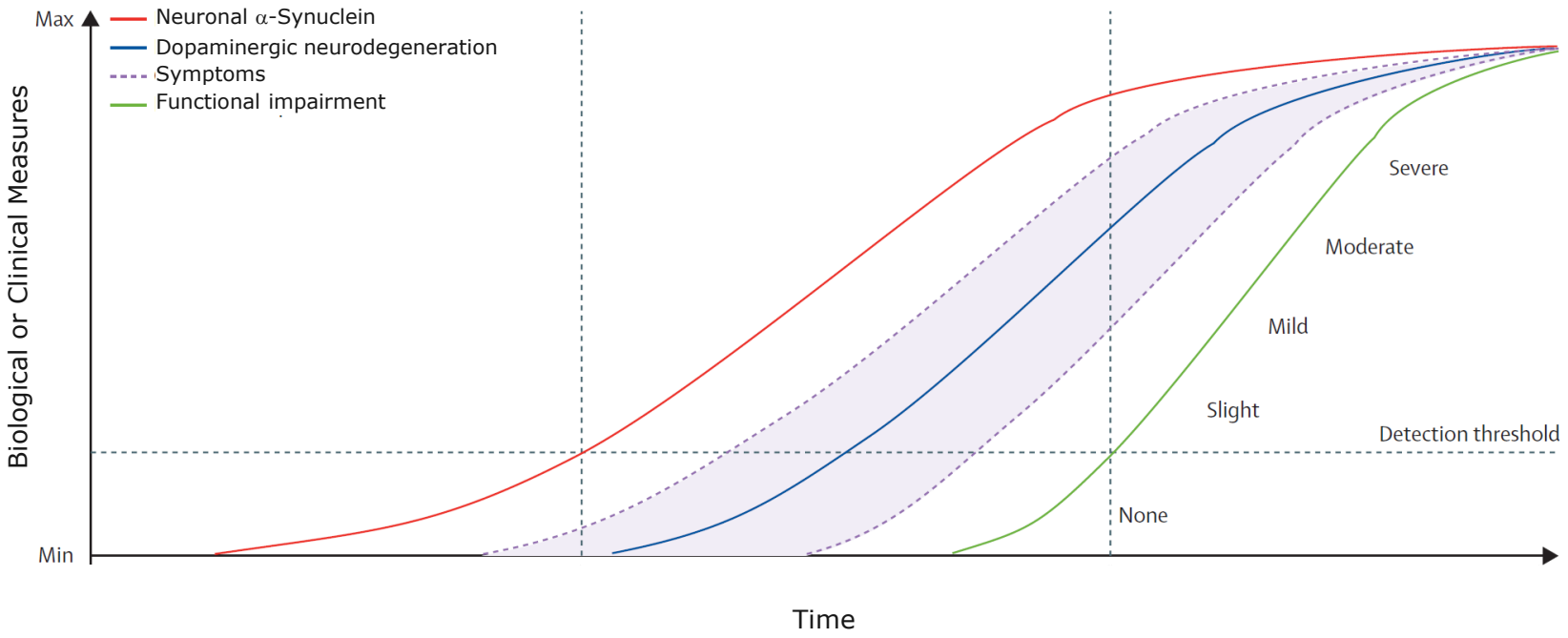
- ☑ **$135 million** paid to date
- ❑ **$620 million** remaining in regulatory and sales milestones
- ❑ **Up to high teen royalties**
- ❑ US co-promote option

Slide adapted from Roche's Pharma Day 2025 Presentation on September 22, 2025.
OLE: Open-label Extension; PD: Parkinson's Disease.
[1] Parkinson's Foundation. Understanding Parkinson's. Statistics. Accessed July 17, 2024. [2] Jankovic J et al. *JAMA Neurol*. 2018; 75:1206–1214. [3] Roche states >3B CHF in their 1/29/2026 FY 2025 Earnings presentation; conversion rate of 1 CHF = 1.28 USD (as of January 31, 2026) equates to ~3.85B 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

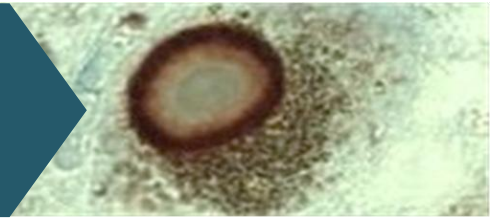


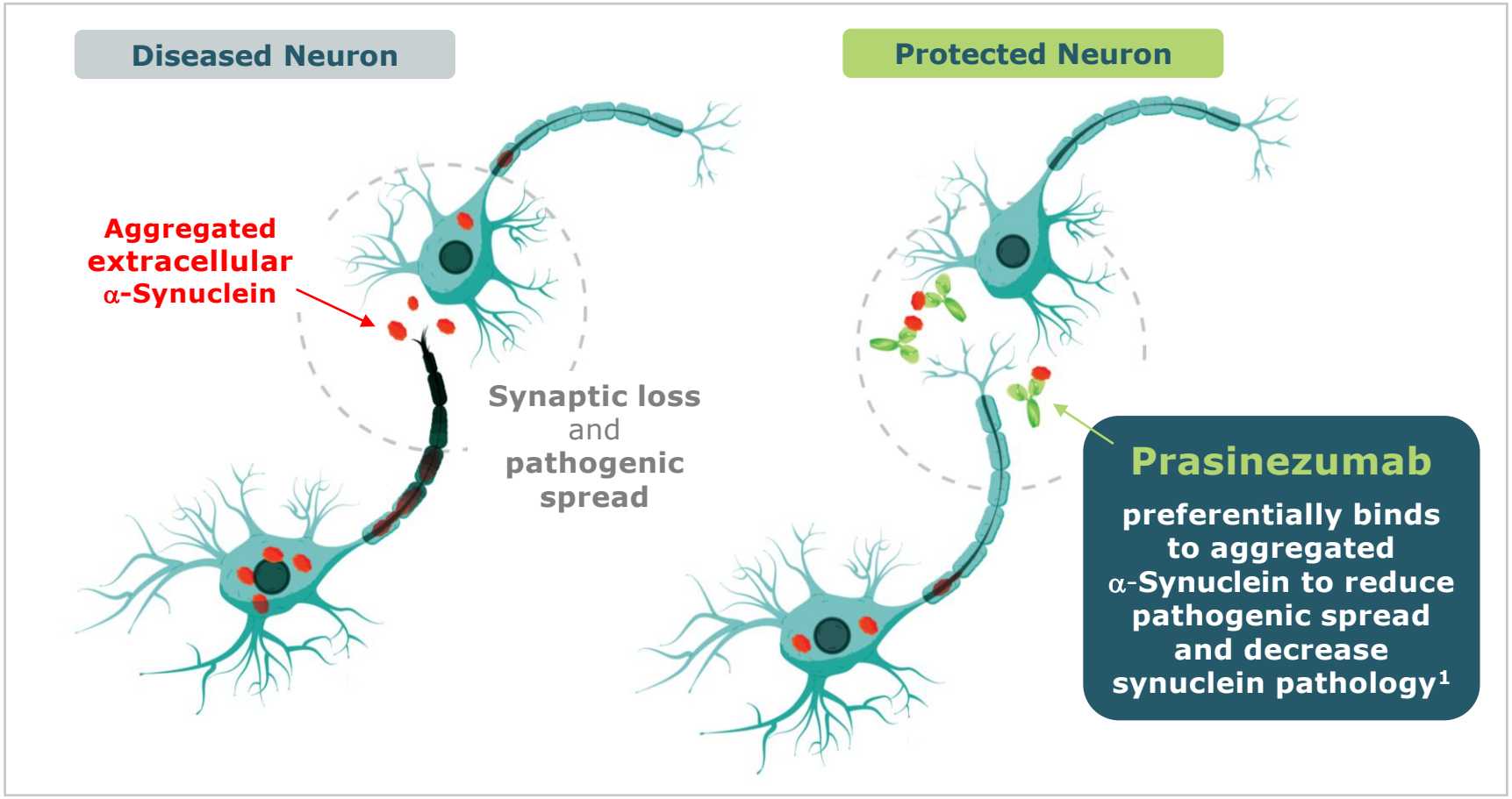
Chart adapted from: Simuni, Tanya et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. *Lancet Neurol* 2024.
Symptoms: Clinical signs or symptoms attributable to neuronal α-Synuclein disease that can be motor or non-motor (e.g., hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety); Functional Impairment: Degree of impact on activities of daily living.

Immunotherapy Designed to Selectively Bind Aggregated α-Synuclein

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.

Phase 2 Results Support Moving Prasinezumab into Phase 3 in Parkinson's Disease

MULTIPLE ENDPOINTS FROM PHASE 2 STUDIES (PASADENA & PADOVA) AND OLES 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)*

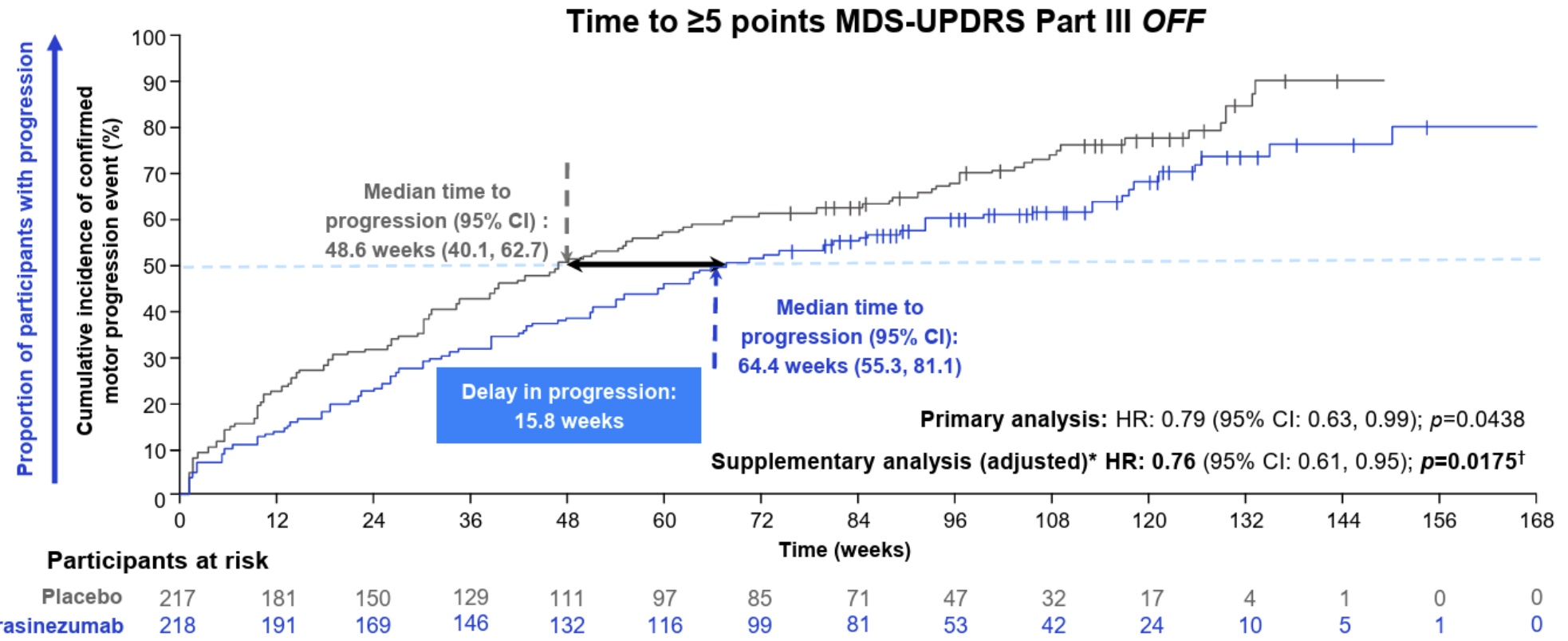
Slide adapted from Roche's Pharma Day 2025 Presentation on September 22, 2025.
OLE: Open-label Extension; PD: Parkinson's Disease.
* Roche states >3B CHF in their 9/22/2025 Pharma Day presentation; conversion rate of 1 CHF = 1.26 USD (as of October 22, 2025) equates to ~3.77B USD.

Phase 2 Results Support Moving Prasinezumab into Phase 3 in Parkinson's Disease

Phase 2b PADOVA Primary Endpoint (L-Dopa Subgroup)

Prasinezumab showed a trend towards delaying motor progression on top of effective symptomatic therapy

- Signal of efficacy more pronounced in pre-specified L-DOPA subgroup (~74% of total study population)

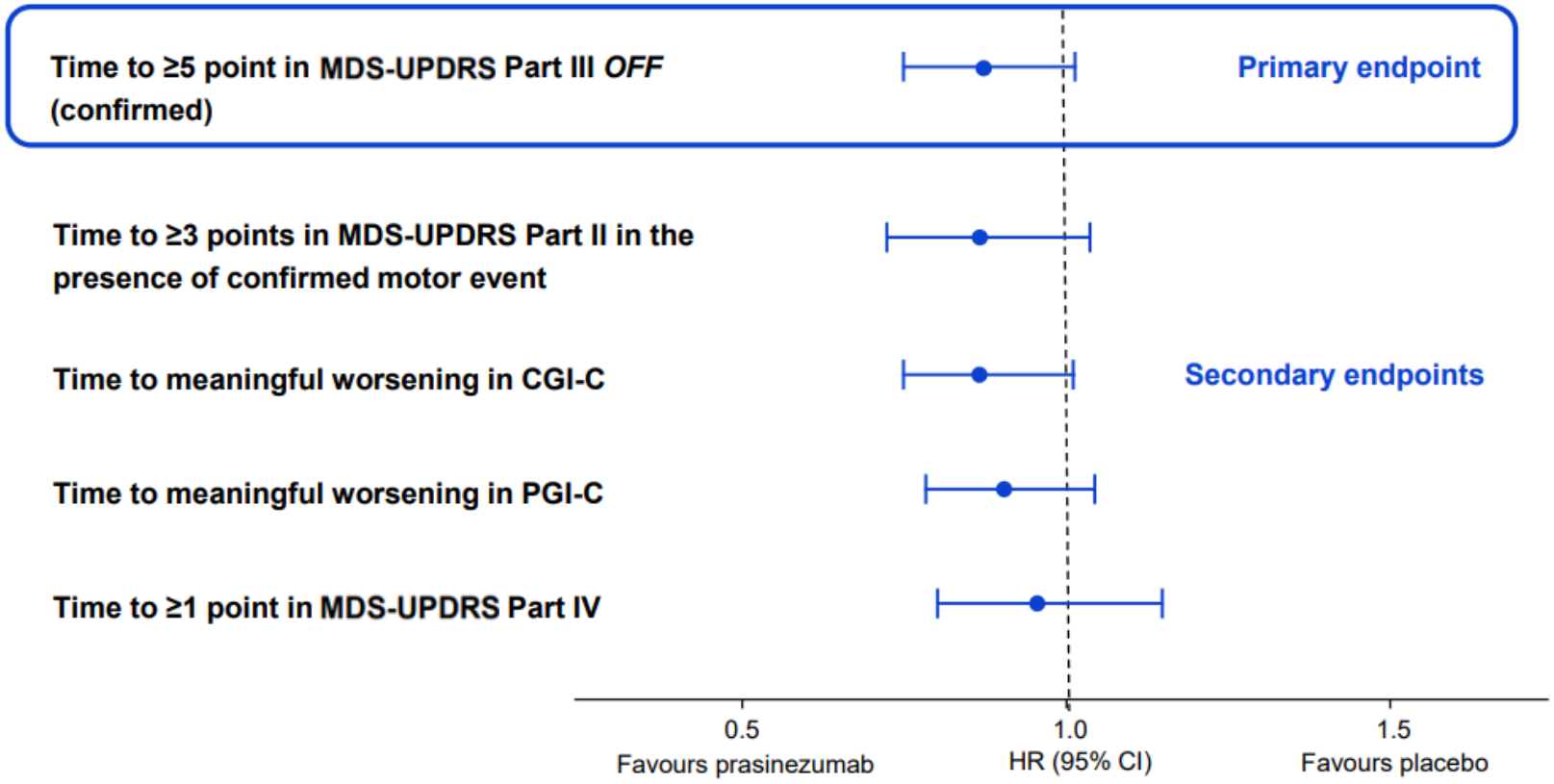


Slide adapted from Roche's presentation at AD/PD 2026 in Copenhagen, Denmark March 17 -21, 2026.
Participants received prasinezumab 1500 mg or placebo Q4W. *Covariates used for adjustment: H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral, age (<60 vs ≥60), sex (male vs female), BL MDS-UPDRS Part III. The intercurrent events of treatment discontinuation and LEDD increase prior to event are handled with the treatment policy strategy; †For descriptive purposes, nominal p-values are displayed.
BL, baseline; CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn and Yahr; HR, hazard ratio; L-DOPA, levodopa; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; Q4W, every four weeks.

Phase 2 Results Support Moving Prasinezumab into Phase 3 in Parkinson's Disease

Phase 2b PADOVA Primary & Secondary Endpoints

Consistent trends in favor of prasinezumab across TTE endpoints with clinical signals extending beyond motor signs



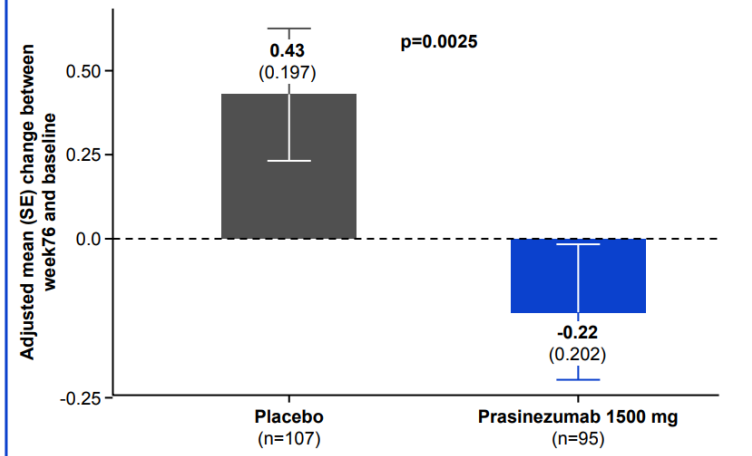
Slide adapted from Roche's presentation at AD/PD 2026 in Copenhagen, Denmark March 17 -21, 2026.
Participants received prasinezumab 1500 mg or placebo Q4W.
CGI-C, Clinical Global Impression of Change; CI, confidence interval; HR, hazard ratio; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PGI-C, Patient Global Impression of Change; Q4W, every four weeks; TTE, time-to-event.

Phase 2 Results Support Moving Prasinezumab into Phase 3 in Parkinson's Disease

Phase 2b PADOVA Exploratory Endpoints

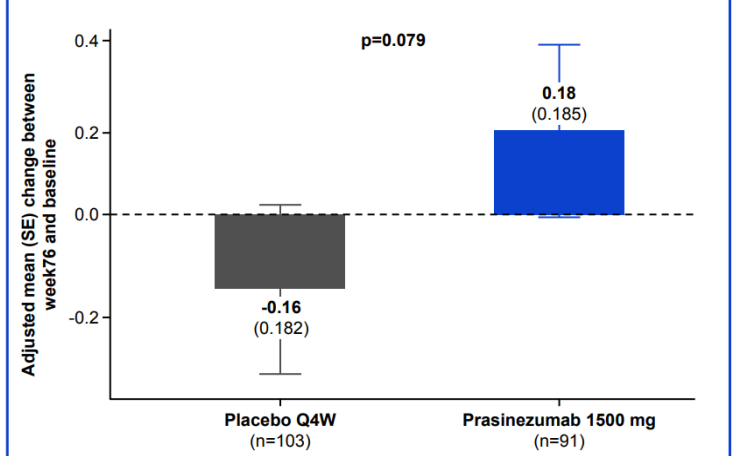
Biomarker evidence suggest impact on underlying disease pathology and potential link to clinical changes

Iron (R2*) putamen (Average)



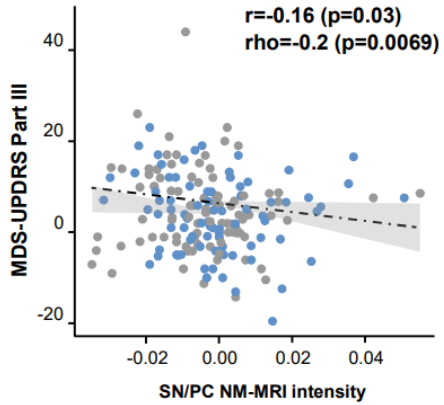
- **Iron:** Prasinezumab treatment was associated with a decrease in substania nigra pars compacta iron (SNpc) and showed significantly reduced iron accumulation in the putamen versus placebo

Neuromelanin MRI at Week 76
Substantia nigra pars compacta intensity



- **Neuromelanin (NM):** Prasinezumab treatment slowed the loss of NM signal in the SNpc as shown by an increase in NM intensity and volume

Longitudinal NM MRI changes correlate with MDS-UPDRS III



- Individuals with slowed decrease of NM-MRI also progressed slower on MDS-UPDRS III
- Cross-sectionally, these correlations were not observed

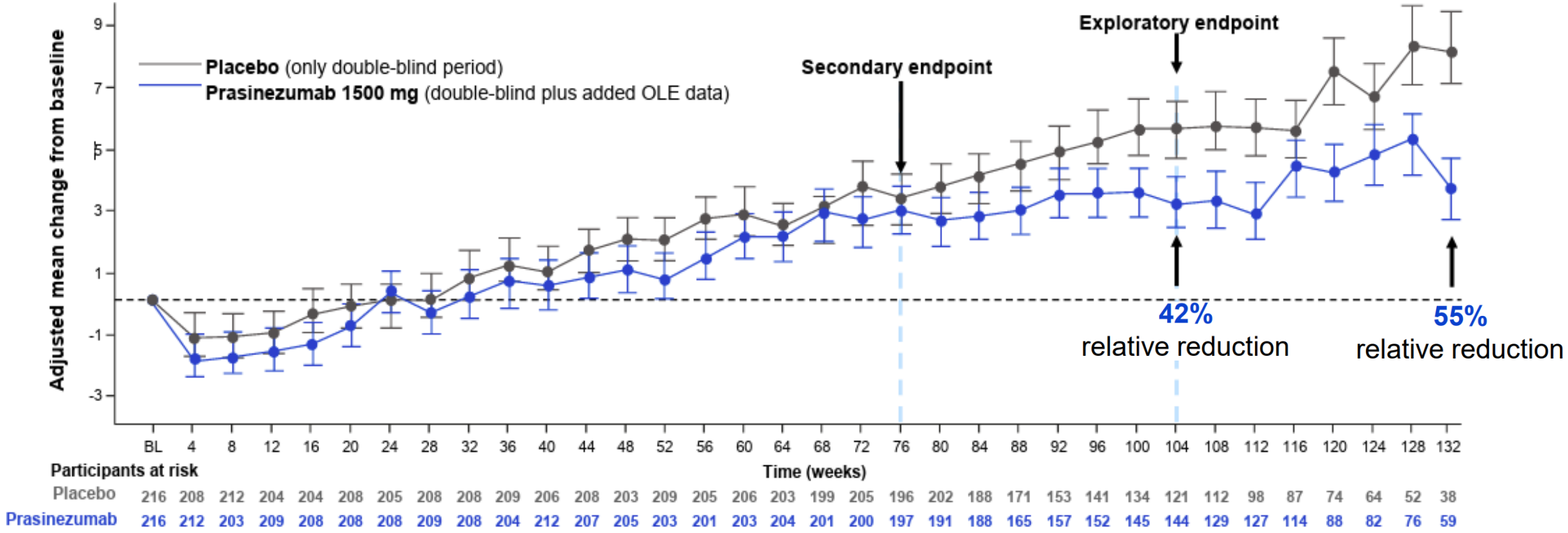
- Structural imaging changes correlated with MDS-UPDRS Part III scores, linking biological impact to clinical motor progression

Slide adapted from Roche's presentation at AD/PD 2026 in Copenhagen, Denmark March 17 -21, 2026.
Error bars represent SE; p-values are nominal.
*R2 MRI sequence used for imaging.
NM, neuromelanin; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MRI, magnetic resonance imaging; PD, Parkinson's disease; r, Pearson correlation; rho, Spearman rank correlation; SE, standard error; SN/PC, substantia nigra pars compacta.

Phase 2 Results Support Moving Prasinezumab into Phase 3 in Parkinson's Disease

Phase 2b PADOVA 6-month OLE (L-DOPA Subgroup)

Persistent reduction of motor progression over 2.5 years; mirrors PASADENA results

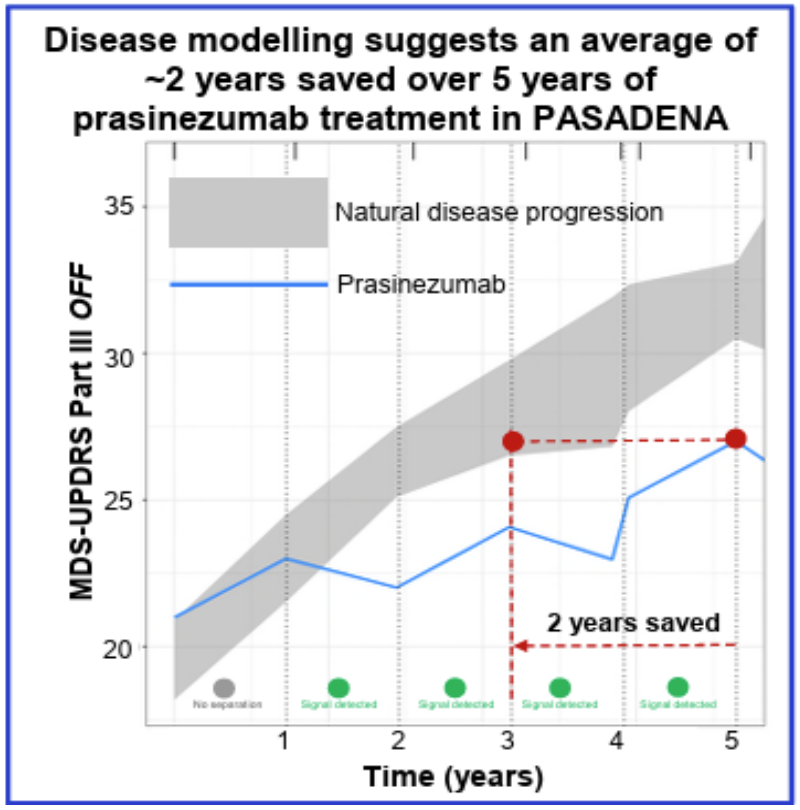


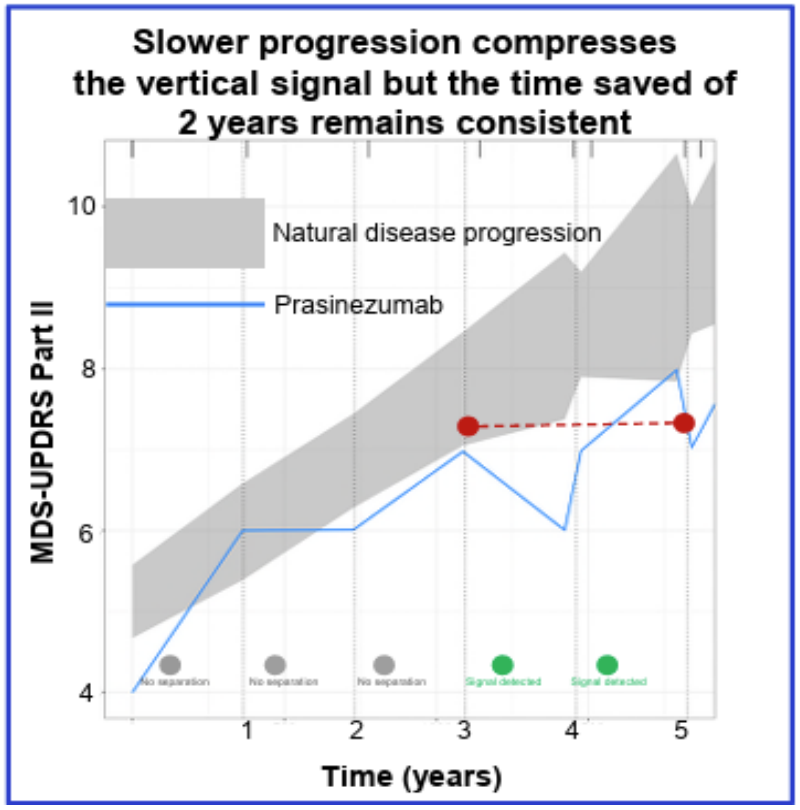
Slide adapted from Roche's presentation at AD/PD 2026 in Copenhagen, Denmark March 17 – 21, 2026.
Covariates used for adjustment in MMRM model: medication at baseline (MAO-Bi vs L-DOPA), H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral, age (<60 vs ≥60), sex (male vs female), MDS-UPDRS Part III.
BL: Baseline; DaT-SPECT: Dopamine Transporter Imaging with Single-photon Emission Computed Tomography; H&Y: Hoehn & Yahr; L-DOPA: Levodopa; MAO-Bi: Monoamine Oxidase Type B Inhibitor; MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MMRM: Mixed Model for Repeated Measures; OLE: Open-label Extension.

Additional Phase 2 Data Demonstrates Potential for Prasinezumab to Delay Parkinson's Disease Progression

Phase 2 PASADENA Disease Progression Model

PASADENA OLE vs. PPMI-based Virtual Comparator





- Observed PASADENA outcomes were better than model-predicted progression over time, consistent with a sustained treatment effect
- Participants showed ~2 years of 'time gained' versus the virtual comparator over 5 years of treatment, suggesting a ~2-year delay in disease progression
- A similar effect was observed across both motor and functional domains

No separation Signal detected

Slide adapted from Roche's presentation at AD/PD 2026 in Copenhagen, Denmark March 17 – 21, 2026.
MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; OLE: Open-label Extension; PPMI: Parkinson's Progression Markers Initiative.

Phase 3 PARAISO Trial Design

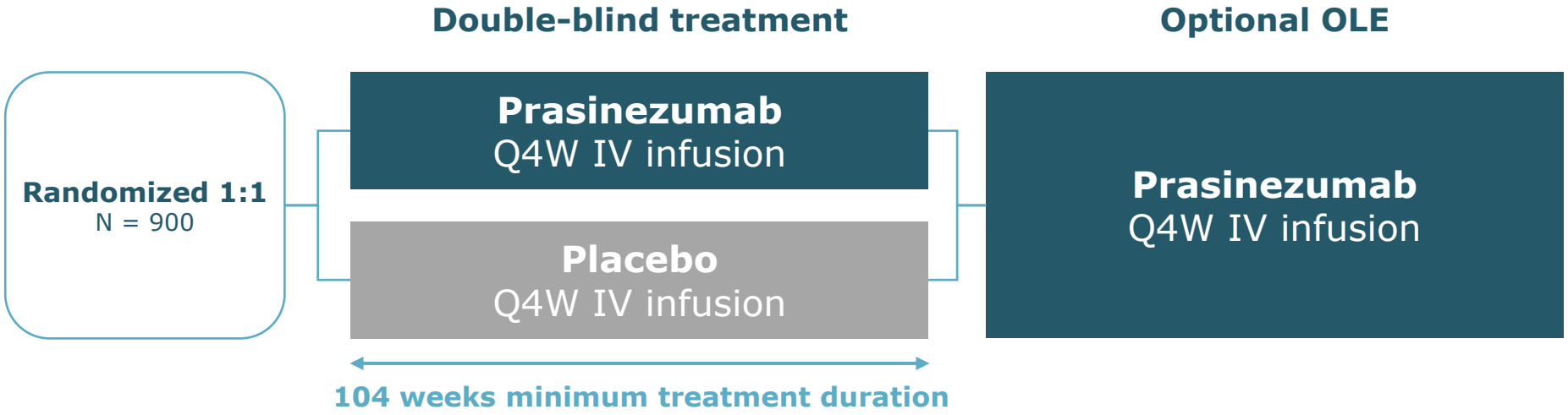
PARAISO Trial Overview (NCT07174310)

Key Inclusion Criteria

- Early-stage PD on stable L-DOPA monotherapy (excludes MAO-B inhibitors)

Primary Endpoint

- Time to confirmed motor progression (MDS-UPDRS Part III OFF*)



PARAISO builds on learnings from the PADOVA trial:

- Larger sample size 'n' of 900 vs. 586 in Phase 2b PADOVA
- Longer primary treatment duration of 2 years minimum vs. 18 months in Phase 2b PADOVA
- L-DOPA treatment required vs. ~74% on L-DOPA treatment in Phase 2b PADOVA

Trial design slide adapted from information available on posting on clinicaltrials.gov.
*Practically defined OFF-medication state (≥12 hours since the last dose of L-DOPA).
MDS: Movement Disorder Society; OLE: Open-label Extension.

Coramitug (formerly PRX004)
ATTR Amyloidosis with Cardiomyopathy
Phase 3

ATTR Business Acquired by Novo

Coramitug: Potential Best-in-Class Depleter Treatment for ATTR-CM

Clear Addressable Unmet Need

- **450,000** patients estimated globally with wild-type or hereditary ATTR-CM[1-3]

Differentiated Mechanism of Action

- Potential **best-in-class** depleter for ATTR-CM
- Designed to inhibit fibril formation and specifically deplete pathogenic TTR

Clinical Support[4-5]

- **Positive Phase 2** results presented at AHA 2025
- 60 mg/kg reduced NT-proBNP levels from baseline at month 12 and by 48% compared to placebo (*p=0.0017*)
- Favorable safety and tolerability profile

Combination Therapy[4-5]

- Benefits observed in Phase 2 on top of standard of care[6]

Current Status

- **Phase 3 CLEOPATTRA** clinical trial ongoing in ~1280 patients with ATTR-CM (NCT07207811); primary completion expected in 2029
- Open-label Phase 1 to evaluate the biodistribution of 89Zr-coramtiug and investigate the effects of coramitug on depleting TTR amyloid deposits in myocardial tissues using PET/CT imaging in ATTR-CM (NCT07448623); primary completion expected in 2027
- Obtained Fast Track Designation from the FDA

Market Opportunity

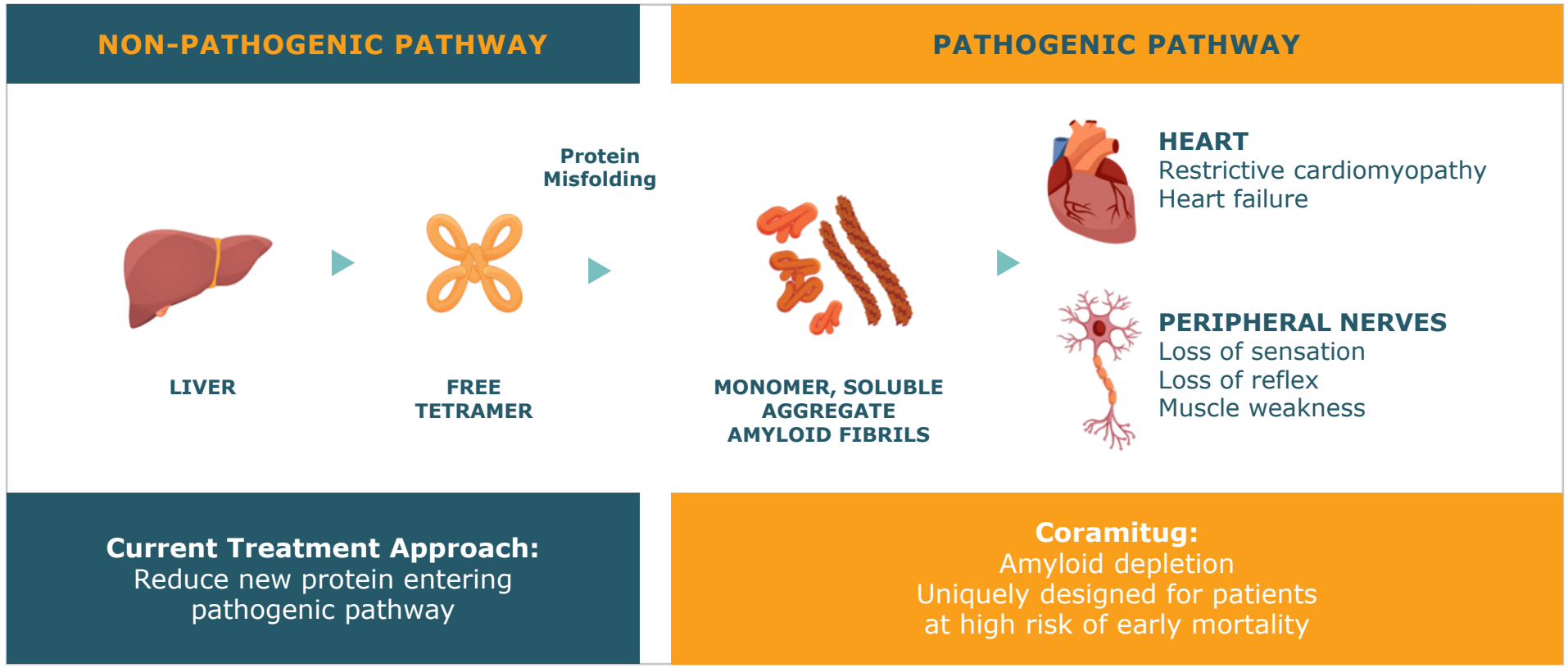
- **Multi-billion dollar** global peak sales potential

Partnership Economics with Novo

- ☑ **$150 million** paid to date
- ☐ **$1.08 billion** remaining in sales milestones

[1] González-Duarte A, Conceição I, Amass L, Botteman MF, Carter JA, Stewart M. *Neurol Ther*. 2020;9(1):135-149. [2] González-López E, Gagliardi C, Dominguez F, et al. *Eur Heart J.* 2017;38(24):1895-1904. [3] Lane T, Fontana M, Martinez-Naharro A, et al. *Circulation*. 2019;140(1):16-26. [4] Phase 2 Results Presented During Late-Breaking Session of The American Heart Association Scientific Sessions 2025; November 10, 2025; New Orleans, LA. [5] Phase 2 Results Published in November 10, 2025 Edition of *Circulation*: https://doi.org/10.1161/CIRCULATIONAHA.125.077304. [6] Standard of care as recommended by their medical health professional; >80% of patients on stabilizers in addition to either coramitug or placebo.

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.

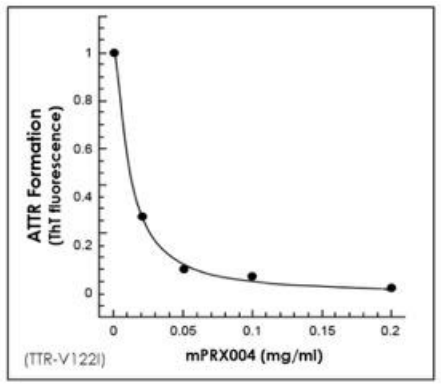
Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF mPRX004

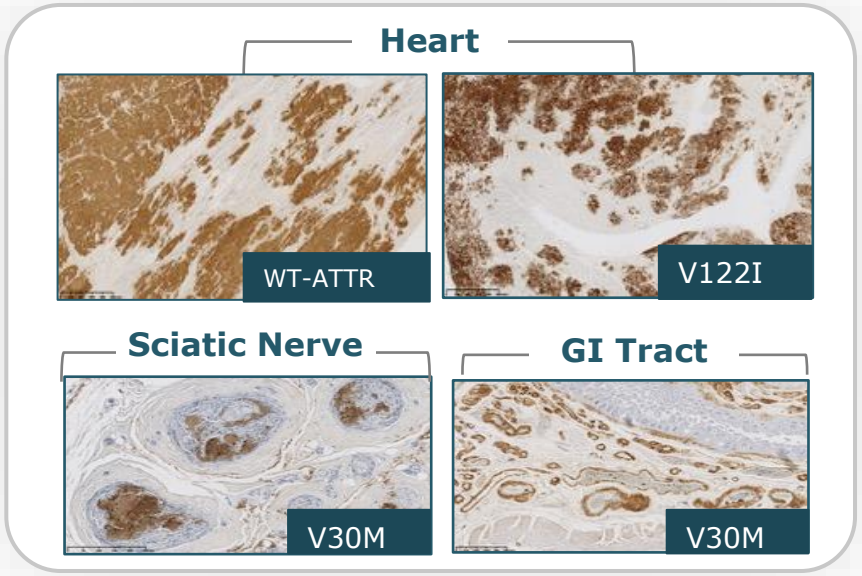
mPRX004 (murine form of PRX004) preclinical results:[1]

- ✓ 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

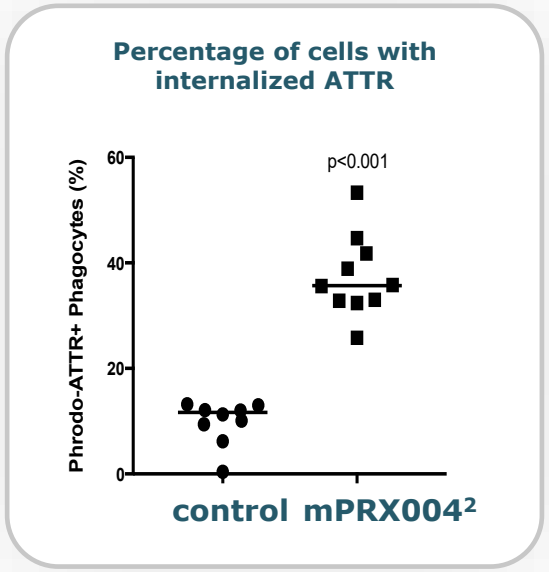
Inhibition of amyloid formation



Specific binding to amyloid



Clearance of amyloid



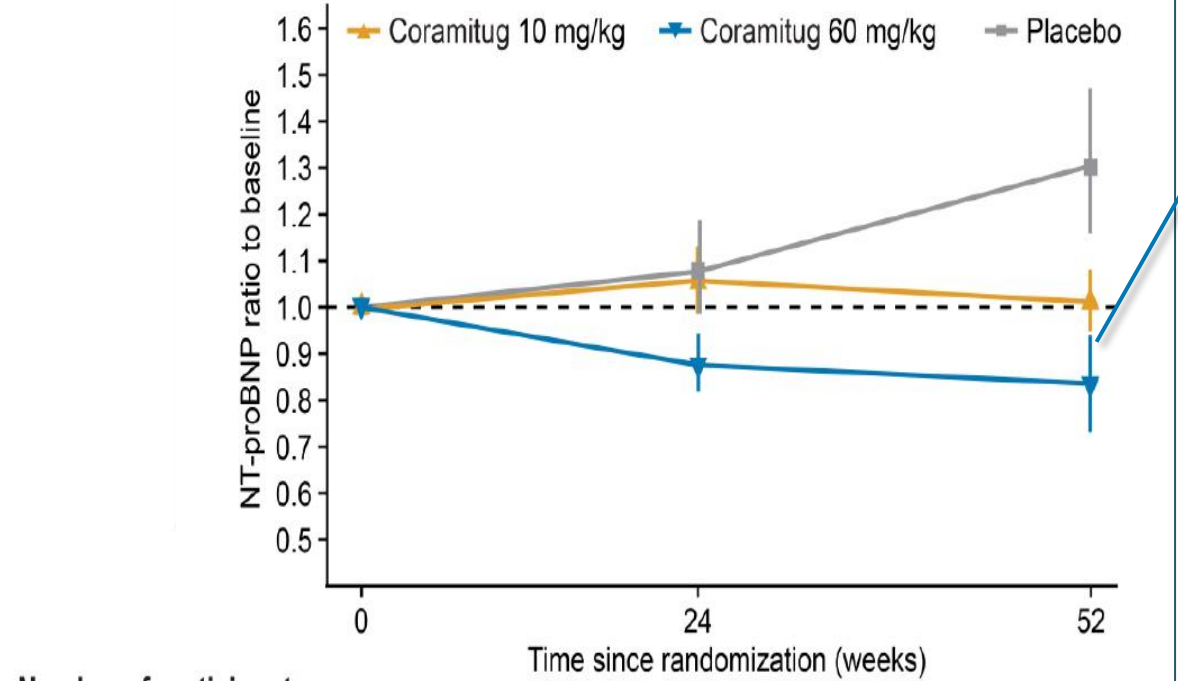
[2]

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

Phase 2 Results Support Moving Coramitug into Phase 3 in ATTR-CM

Phase 2 Results[1-2]

105 patients / 3-arms / 12 months



Coramitug 60 mg/kg reduced NT-proBNP levels from baseline at 12 months and by 48% vs. placebo
p=0.0017

- Coramitug 60 mg/kg showed a treatment difference of 13.45 m in 6MWT vs. placebo at 12 months
- Coramitug 60 mg/kg was associated with improvements vs. placebo across a wide range of echocardiogram parameters suggestive of favorable cardiac remodeling at 12 months
  - Improved measures include LV & RV systolic function, diastolic function, & estimated pulmonary arterial pressures
- Post hoc analyses showed a reduction in the inflammatory biomarker hsCRP by ~8% with coramitug treated patients vs. ~33% increase in placebo treated patients at 12 months[3]
  - Pooled coramitug dose groups (10 and 60 mg/kg) vs. placebo (treatment ratio 0.66; nominal *p=0.0269)*
- Favorable safety and tolerability profile

LV: Left Ventricle; NT-proBNP: N-terminal Pro-B-type Natriuretic Peptide; RV: Right Ventricle; TTR: Transthyretin; 6MWT: 6-Minute Walk Test; hsCRP: high-sensitivity C-reactive protein.

[1] Phase 2 Results Presented During Late-Breaking Session of The American Heart Association Scientific Sessions 2025; November 10, 2025; New Orleans, LA. [2] Phase 2 Results Published November 10, 2025. Edition of *Circulation*: https://doi.org/10.1161/CIRCULATIONAHA.125.077304.

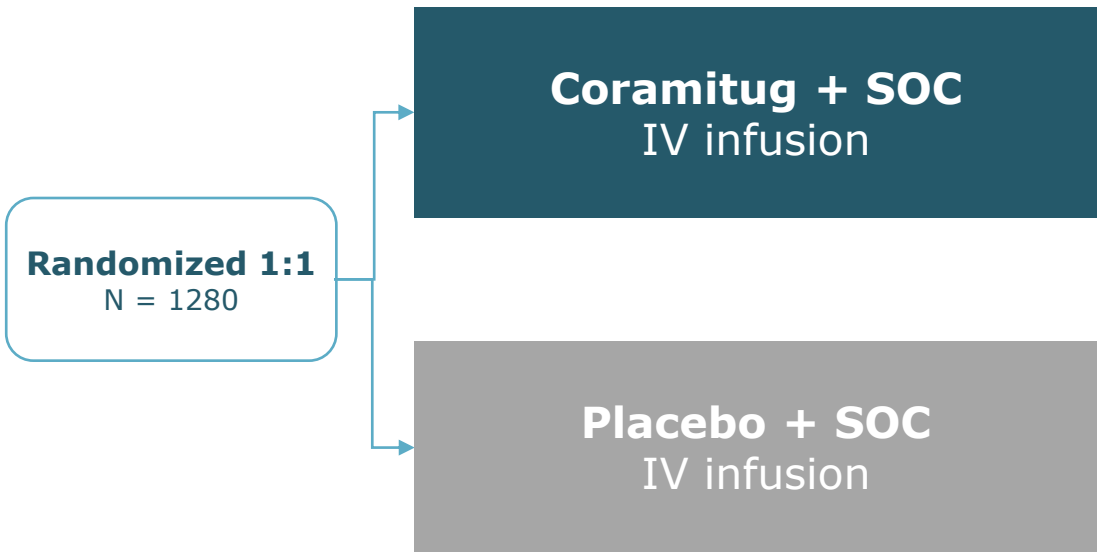
[3] N Fine et al. *Inflammatory biomarkers in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) treated with coramitug: post hoc analysis of a phase 2 randomized trial.* Poster presented at the Heart Failure Society of America (HFSA) Annual Scientific Meeting 2026, October 9–12, 2026, Phoenix, AZ, USA. The findings are exploratory and hypothesis-generating; the trial was not specifically powered to detect differences in inflammatory biomarkers.

Phase 3 CLEOPATTRA Trial Design

CLEOPATTRA Trial Overview (NCT07207811)

Key Inclusion Criteria

- 18 years and older
- Diagnosis of ATTR-CM[1]
- Demonstrated cardiac amyloid infiltration
- Increased LV wall thickness ≥12 mm
- Chronic heart failure (NYHA Class I – IV) requiring ongoing treatment with a loop diuretic



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

SOC: everyone in the study will continue receiving their usual heart treatments as recommended by their doctor

Trial design slide adapted from information available on posting on clinicaltrials.gov.
CV: Cardiovascular; NYHA: New York Heart Association; SOC: Standard of Care (as recommended by their medical health professional).
[1] ATTR-CM includes wild-type ATTR (ATTRwt) or variant ATTR (ATTRv); target ATTRv resruitment is ~15% of the study population.

Moponetug (formerly PRX005)
Alzheimer's Disease
Phase 2

Global Neuroscience Collaboration
with Bristol Myers Squibb

Moponetug: Potential First-In-Class anti-Tau mAb for Alzheimer's Disease

Clear Addressable Unmet Need

- **> 80 million Alzheimer's patients** globally[1]

Differentiated Mechanism of Action

- Potential **first-in-class** anti-tau antibody
- 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

Clinical Support

- Phase 1 MAD data presented at CTAD 2025
- Phase 1 data presented at AD/PD 2026
- Open-label single-dose Phase 1 study to assess a subcutaneous administration conducted in 2025
- Favorable safety and tolerability profile

Current Status

- **Phase 2 TargetTau-1** clinical trial in ~310 patients with early Alzheimer's disease is fully enrolled; data readout expected in 1H 2027 (NCT06268886)
- Open-label Phase 1 study evaluating IV/SC moponetug PK, bioavailability, safety, tolerability and immunogenicity in healthy adults and participants with early AD; primary completion expected mid-2027 (NCT07780383)
- Obtained Fast Track Designation from the FDA

Market Opportunity

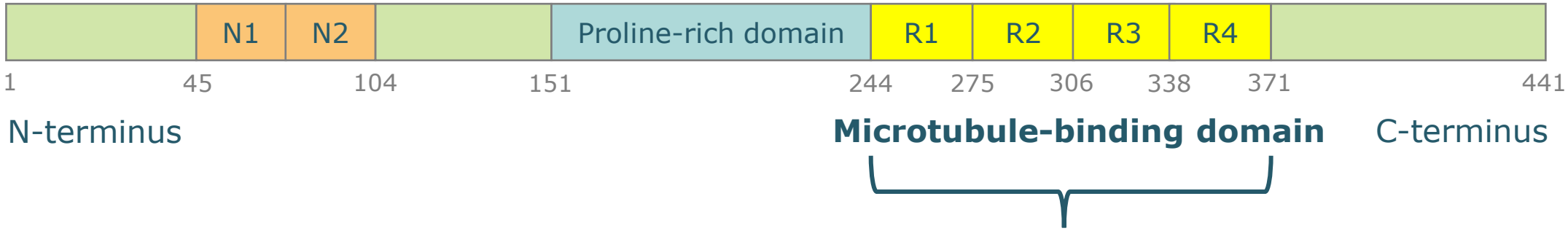
- **Multi-billion dollar** global peak sales potential

Partnership Economics with BMS[2]

- ☑ **$135 million** paid to date
- ❑ **$562.5 million** future regulatory/sales milestones
- ❑ **Up to high teen royalties** on a weighted average basis

MAD: Multiple Ascending Dose. [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] Global Neuroscience Research and Development Collaboration with BMS also included $100 million upfront payment, $50 million equity investment in Prothena and $80 million upfront for PRX019 global license.

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 pathology[1-2]
- Biomarkers: MTBR-tau243 highly correlated with tau-PET and disease progression[3-4]
- Preclinical: MTBR-targeting antibodies have demonstrated blocking of internalization and spread of tau, leading to the reduction of tau pathology[5,6]
- Clinical: Trials ongoing, early clinical data from MTBR-targeting antibodies has shown positive trends on biomarkers including MTBR-tau243 and tau-PET[7]

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] Prothena data on file. [7] Eisai presentation on E2814 at CTAD 2025.

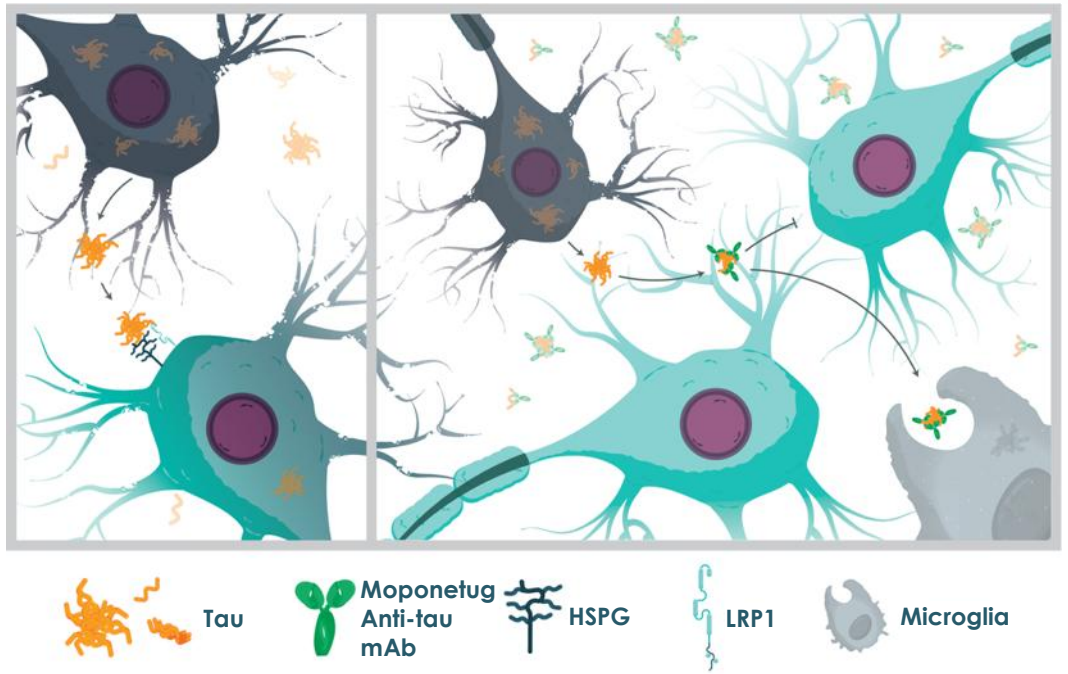
MTBR-Specific Anti-Tau Antibody

Moponetug, 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

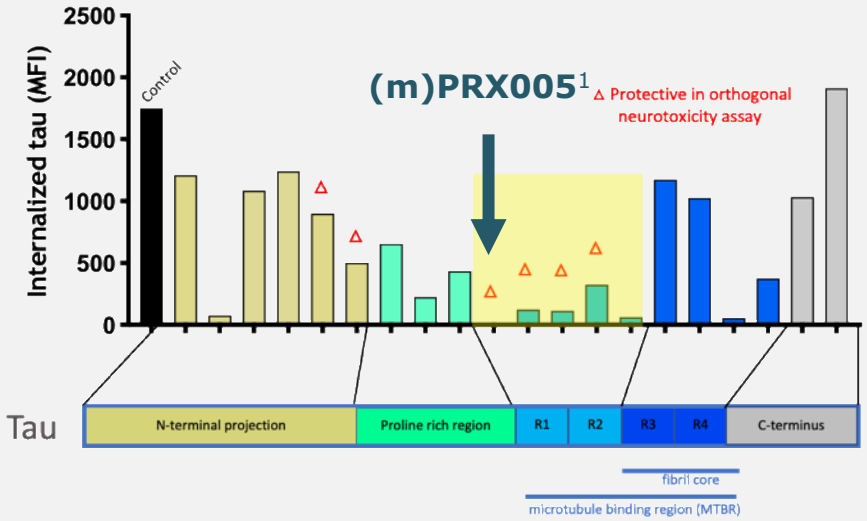


Moponetug: Potential Best-in-Class MTBR-Specific Anti-Tau Antibody to Reduce Pathogenic Tau Spread

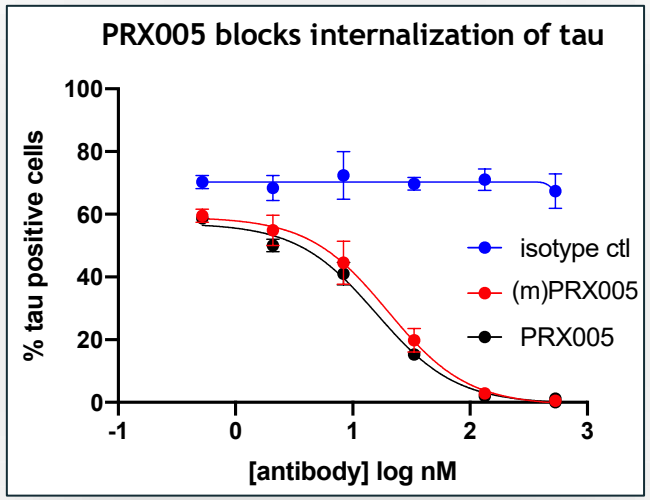
[1] Ahmed, Z., Cooper, J.. et al. A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. 2014 *Acta Neuropathol*;
[2] Horie, k., Barthelemy, H., Bateman, R.J. CSF tau microtubule binding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

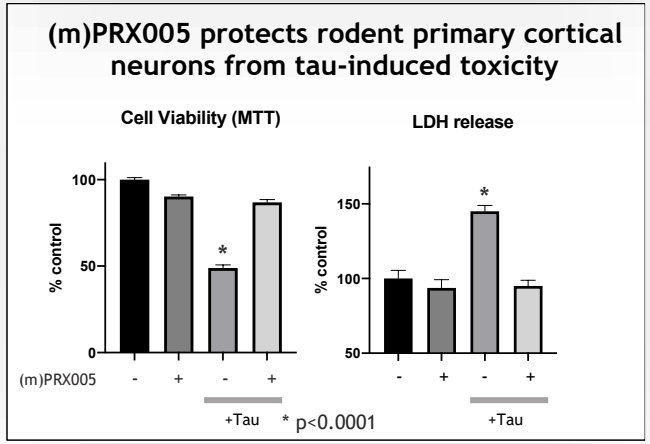
Superior in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity

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



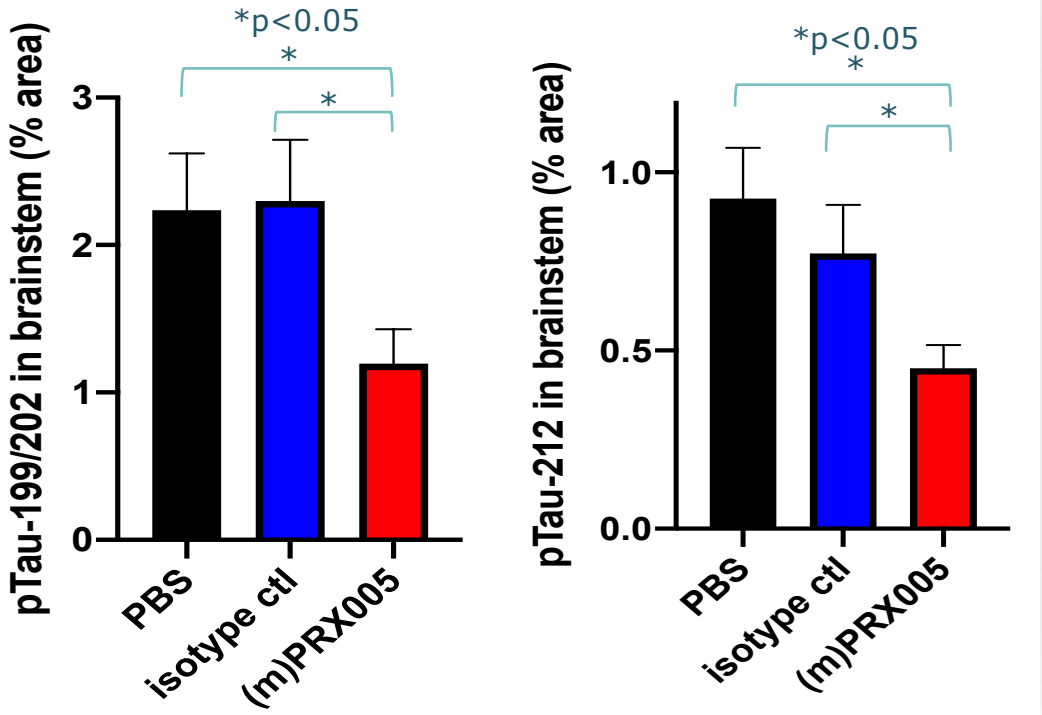


[1] (m)PRX005: murine form of PRX005 (moponetug/BMS-986446). Prothena data on file.

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

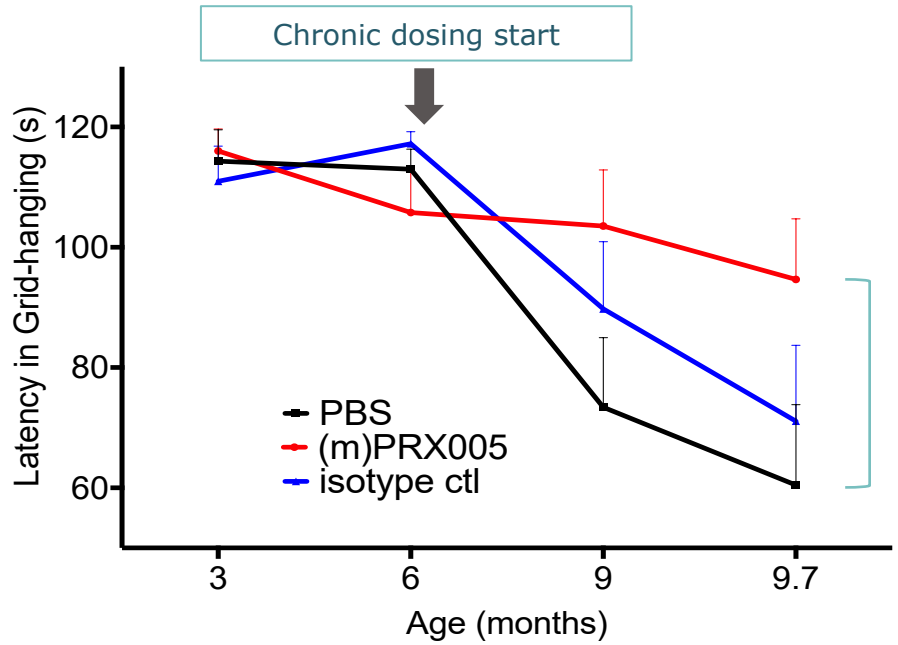
All values are mean ± SE (n=15-20)

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

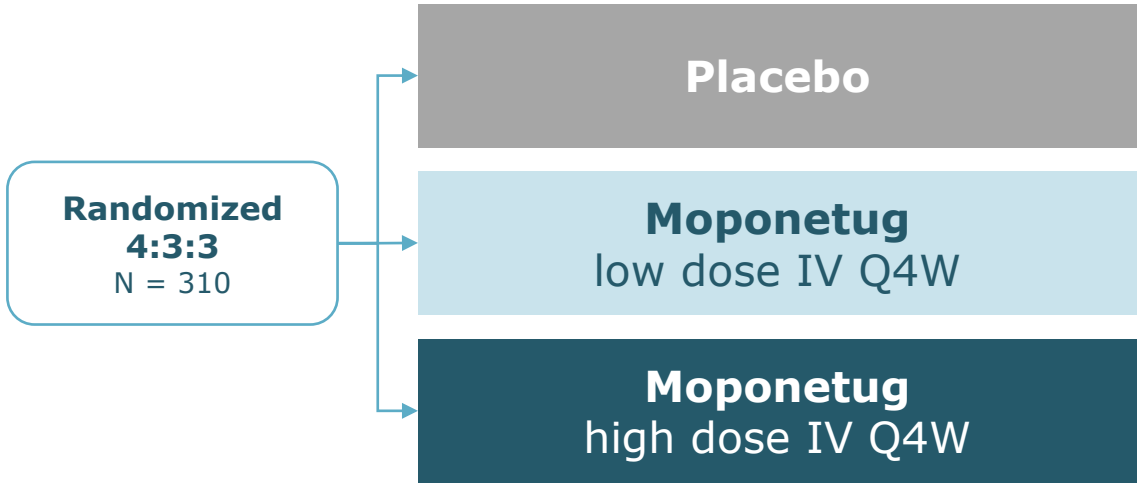
(m)PRX005: murine form of PRX005 (moponetug/BMS-986446).
Prothena data on file.

Phase 2 TargetTau-1 Trial Design

TargetTau-1 Trial Overview (NCT06268886)

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[1]
- 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

Trial design slide adapted from presentation at The 2024 AAIC Annual Meeting (July 28, 2024) and clinicaltrials.gov.
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] Standard Fluid-based biomarkers include total tau, p181tau, p217tau, Aβ [1-42], Aβ [1-40], neurofilament light chain, & glial fibrillary acidic protein.

TDP-43 CYTOPE®

ALS

Preclinical

Unpartnered Program

CYTOPE®: A Breakthrough in Intracellular Therapeutics

CYTOPE® is an **innovative intracellular drug targeting technology** designed at Prothena to reach virtually any cell-type, enable precise targeting of intracellular disease pathways, and to **unlock therapeutic access** to targets where conventional modalities fall short

CYTOPE Elements

Delivery Element



Proprietary Cell Internalizing Technology

\+

Targeting Element



Macromolecule (e.g., mAb)

+/-

Optional Elements



Receptor binding Fab fragment

Compatibility with Add-on Elements

- Demonstrated to efficiently **target intracellular disease pathways in multiple cell-types & tissues**, to cross the blood-brain-barrier, and to achieve **activity in brain & periphery with infrequent, systemic administration**[1]
- Utilizes **endosomal escape mechanism** for cytosolic delivery while preserving membrane and vesicle integrity (non-endolytic) designed for safety & performance

- **Compatible with add-on elements** such as a receptor-mediated technology to enable delivery to specific cells / tissues

Fab: Fragment antigen-binding region. [1] Poster presentation at Society for Neuroscience (SfN) November 2025 titled: *Treatment with a Cell-Internalizing CYTOPE® Targeting pTDP-43 Reduces Intraneuronal Pathology in a Mouse Model of ALS.*

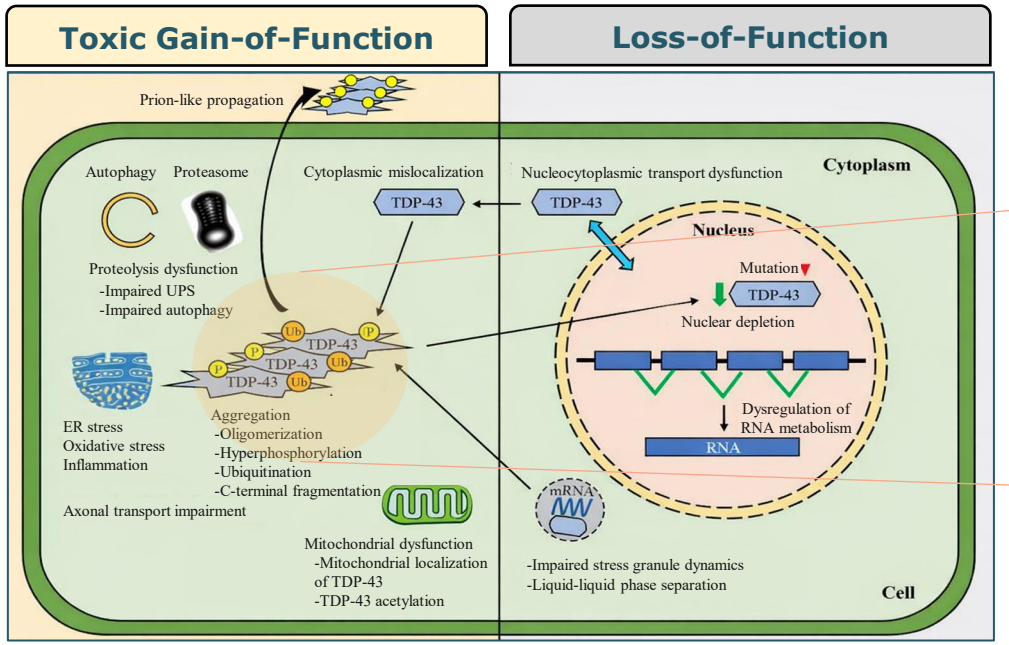
pTDP-43 is a Core Driver of ALS Pathogenesis that is an Undruggable Target with Current Modalities

pTDP-43: Hallmark of ALS Pathology

- ~97% of ALS cases show TDP-43 nuclear-to-cytoplasmic mislocalization where it forms toxic aggregates
- pTDP-43 aggregates trigger both **toxic gain-of-function** and **loss-of-function** consequences

Challenges in Targeting pTDP-43

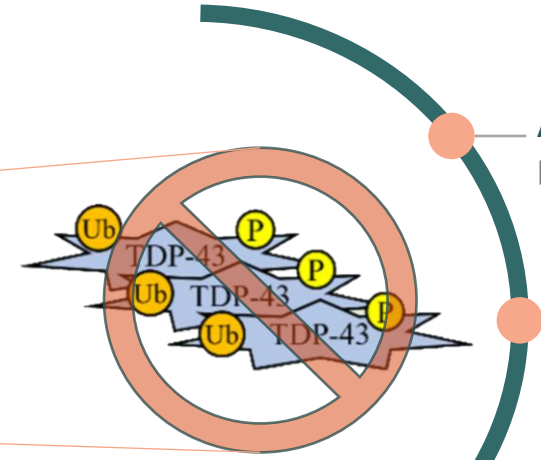
- Delivery: Intracellular target expressed broadly in CNS & periphery
- Specificity: Targeting pTDP-43 is critical; broad TDP-43 KD disrupts global RNA processing, leading to cell death



Graphic modified from Tamaki et al. *Int. J. Mol. Sci.* 2022.

Toxic pTDP-43 aggregation in cytoplasm leads to neuron death

Loss of normal nuclear TDP-43 leads to aberrant RNA splicing



Antibodies cannot reach
pTDP-43 aggregates are cytosolic

Small Molecules cannot bind
pTDP-43 aggregates lack specific binding pockets

ASOs/siRNAs lack specificity
Targeting only pTDP-43 without wildtype knockdown is not feasible (post-translational modification)

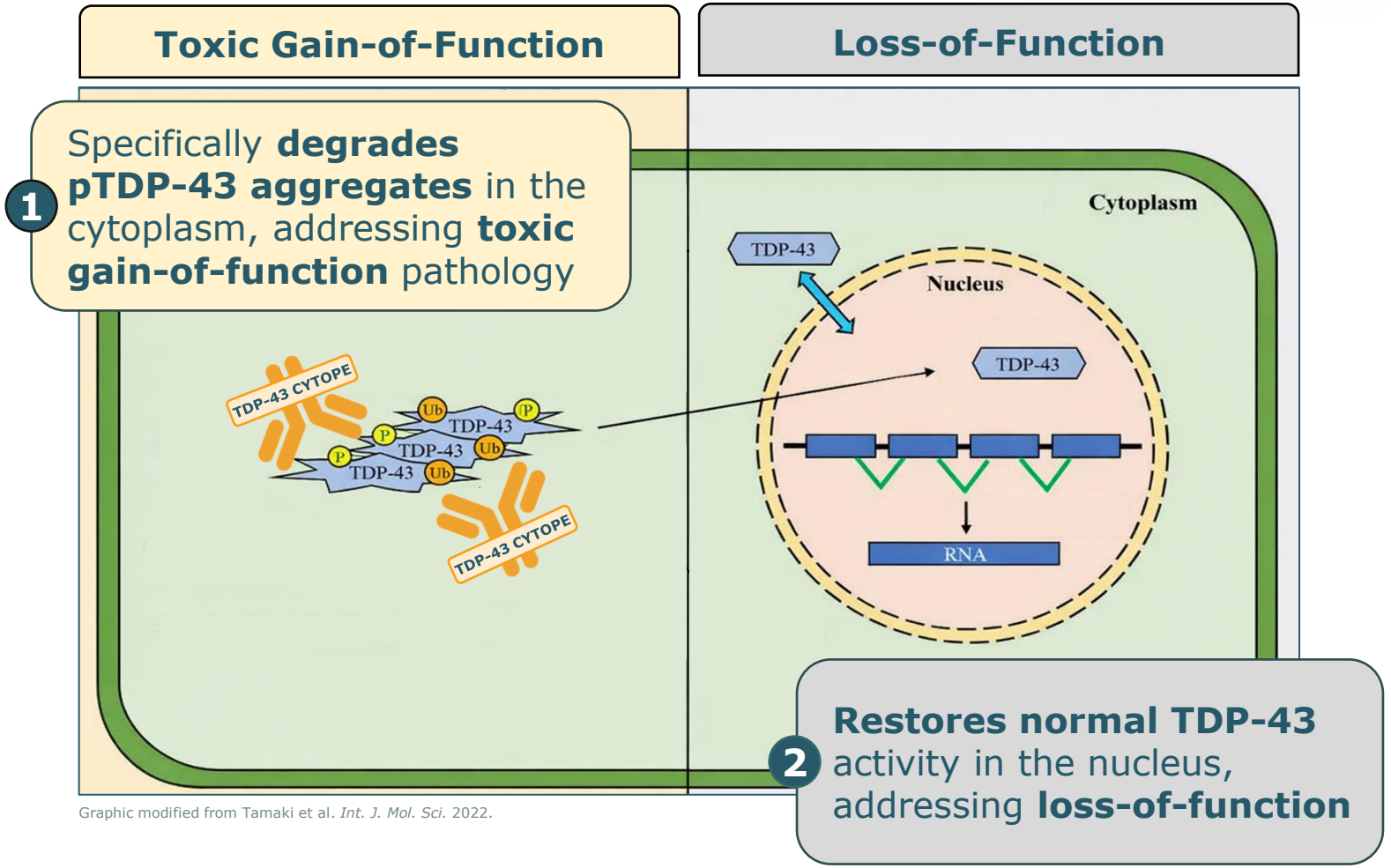
KD: Knockdown. Ling et al. *Neuron.* 2013; Tamaki et al. *Int. J. Mol. Sci.* 2022.

TDP-43 CYTOPE® is Designed to Address Toxic Gain-of-Function and Loss-of-Function Pathology

TDP-43 CYTOPE®



TDP-43 CYTOPE was designed to specifically bind to and degrade intracellular pTDP-43 aggregates that are central to ALS pathology

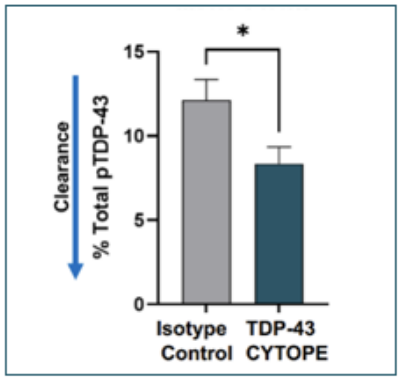


Graphic modified from Tamaki et al. *Int. J. Mol. Sci.* 2022.

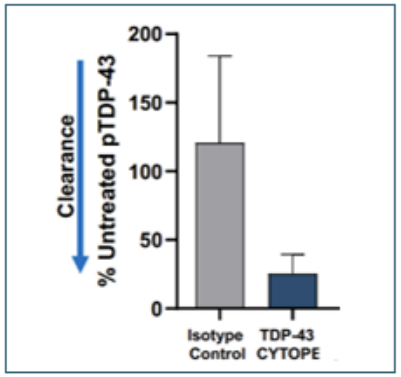
TDP-43 CYTOPE® Preclinical Data Demonstrates Potential of CYTOPE Technology

1 Addresses Toxic Gain-of-Function: Significantly Reduced pTDP-43 Aggregates

Motor Cortex



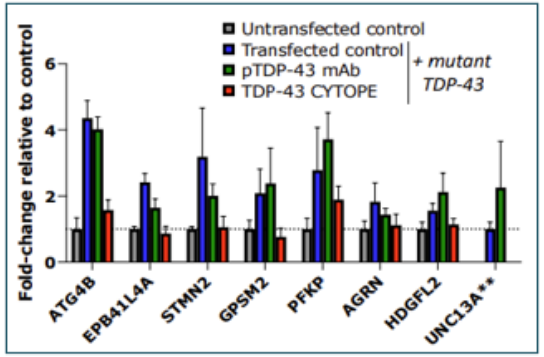
Skeletal Muscle



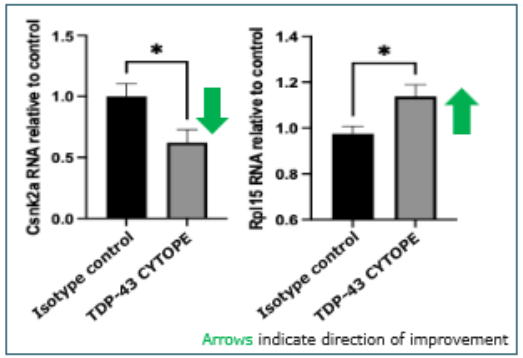
(Left) % Total pTDP-43 staining in motor cortex of rNLS8 nice after 4 weekly IV doses of TDP-43 CYTOPE. *p<0.05. *(Right)* % Untreated pTDP-43 staining in skeletal muscle of rNLS8 mice 72 hours post treatment with a single IV dose of TDP-43 CYTOPE; sample size (n) did not support statistical analysis.

2 Addresses Loss-of-Function: Attenuated ALS-Related Splicing Defects

Human Neuronal Cells



rNLS8 Mice



(Left) SH-SY5Y cells transfected with mutant TDP-43 to induce cytoplasmic aggregates for 24h; cells treated with indicated antibodies for an additional 24h. **UNC13A levels were undetectable in transfected and TDP-43 treated samples; values normalized to transfected samples. *(Right)* 4-week treatment of rNLS8 mice with TDP-43 CYTOPE. *p<0.05.

TDP-43 CYTOPE® significantly reduced brain & muscle pathology in a severe ALS mouse model after systemic administration

- These findings are particularly compelling given rapid, persistent, and aggressive accumulation of pathogenic aggregates in the rNLS8 transgenic mouse model of ALS

TDP-43 CYTOPE attenuated RNA mis-splicing caused by cytoplasmic pTDP-43 aggregates in human neurons & mice

- Species-specific splicing necessitates analysis in both human cells & mice; rNLS8 mice do not replicate human ALS splicing defects, but they do express dysregulated transcriptomics due to pTDP-43 pathology (↑Csn2a; ↓Rpl15 mRNA)[1,2]

Poster presentation at Society for Neuroscience (SfN) November 2025 titled: *Treatment with a Cell-Internalizing CYTOPE® Targeting pTDP-43 Reduces Intraneuronal Pathology in a Mouse Model of ALS*.
[1] Eck et al., 2025; [2] Riemenschneider et al., 2023.

PRX012-TfR
Alzheimer's Disease
Preclinical

Unpartnered Program

Potential of TfR for PRX012

Rationale for Transferrin Receptor Technology:

- The addition of transferrin targeting to gantenerumab has been demonstrated to:
  - 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-Aβ mAb with its TfR-1 technology:

	Gantenerumab[1] Phase 3 GRADUATE I and II		**Trontinemab**[2,3] Phase 1b/2
Dose level (monthly)	~15mg/kg[4]	⇨	3.6 mg/kg
Subjects amyloid negative (<24 CL)	~27-28%	⇨	~91%
Timepoint	116 weeks	⇨	28 weeks
ARIA-E incidence	24.9%	⇨	<5%

ARIA: Amyloid-Related Imaging Abnormalities; CL: Centiloid; PET: Positron Emission Tomography. [1] Bateman RJ et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. 2023 NEJM. M[2] Roche 2025 Pharma Day presentation: https://www.roche.com/investors/events/roche-pharma-day-2025. [3] Trontinemab administered intravenously every four weeks: Kulic L et al., AAIC 2025. [4] 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 results[1] 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
  - 16.0 mean CL at month 18
  - 9 of 12 participants reached amyloid negativity (<24.1 CL) within 18 months
- ARIA-E rates were non-competitive relative to FDA approved anti-Aβ 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 demonstrated[2]:
  - Substantially increased brain exposure
  - Facilitated rapid targeting of Aβ plaques
- Additional preclinical studies ongoing to further elucidate the potential of PRX012-TfR

Prothena is exploring partnership interest in the program

ARIA: Amyloid-Related Imaging Abnormalities; CL: Centiloid; PET: Positron Emission Tomography. [1] Prothena data on file. Preliminary 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 Aβ-transferrin receptor antibody in an APP/PS1 transgenic mouse model.