



CORPORATE OVERVIEW

February 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 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, discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC, and our Annual Report on Form 10-K to be filed with the SEC for our fiscal year 2025. This overview is made as of February 19, 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

RARE PERIPHERAL AMYLOID



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

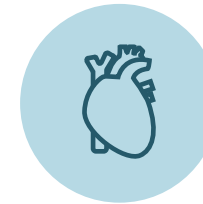
In annual US healthcare costs by 2050 from AD and other dementias³



**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**

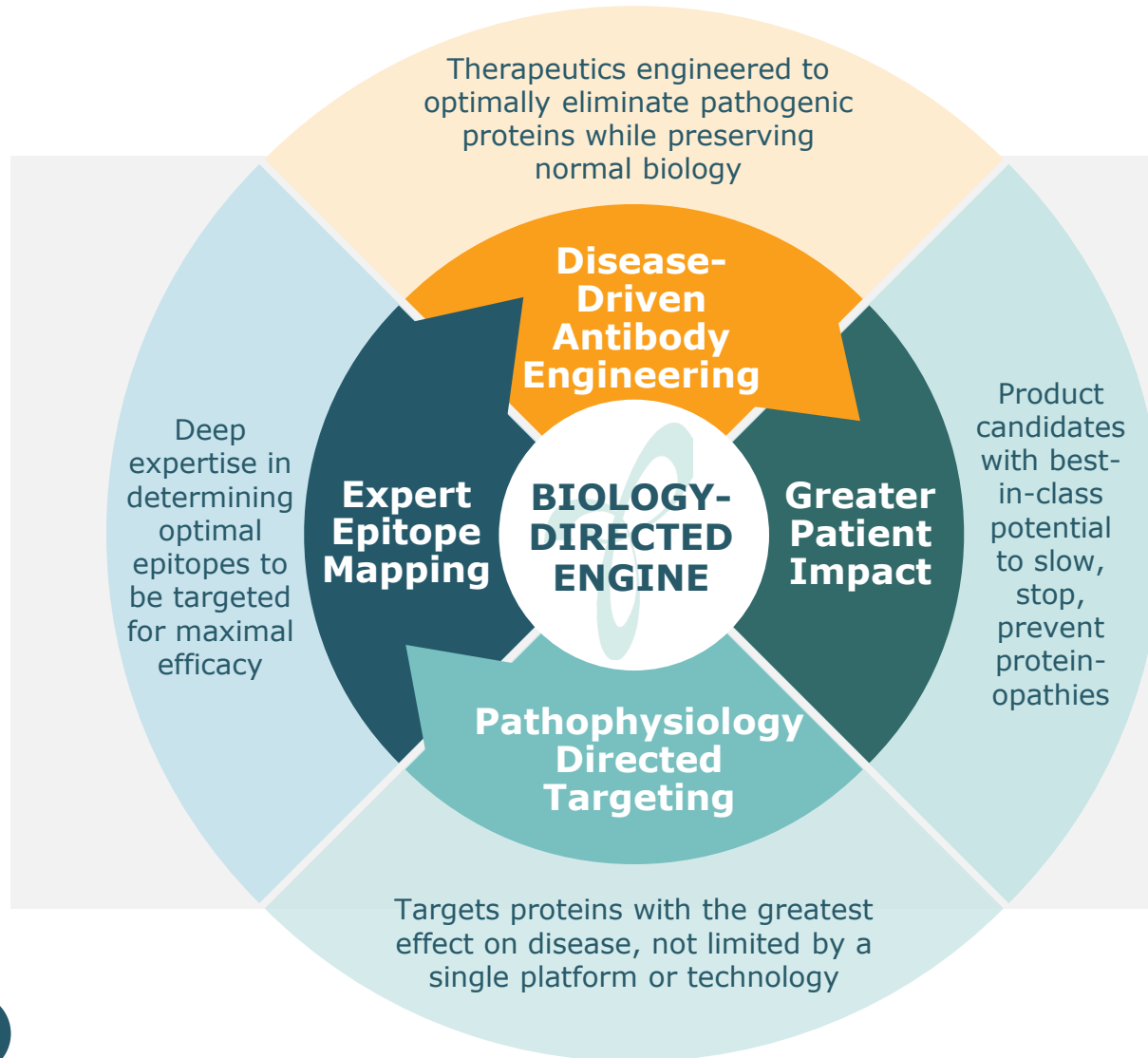
ATTRv: Hereditary amyloid transthyretin; wtATTR: Wild-type ATTR.

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					
WHOLLY OWNED PRECLINICAL PROGRAMS							
TDP-43 CYTOPE[®] <i>ALS</i> (mAb-CYTOPE [®])	pTDP-43						
PRX012-TfR³ <i>Alzheimer's disease</i> (mAb-TfR)	Aβ (N-terminus)						

mAb = monoclonal antibody; TfR = transferrin receptor

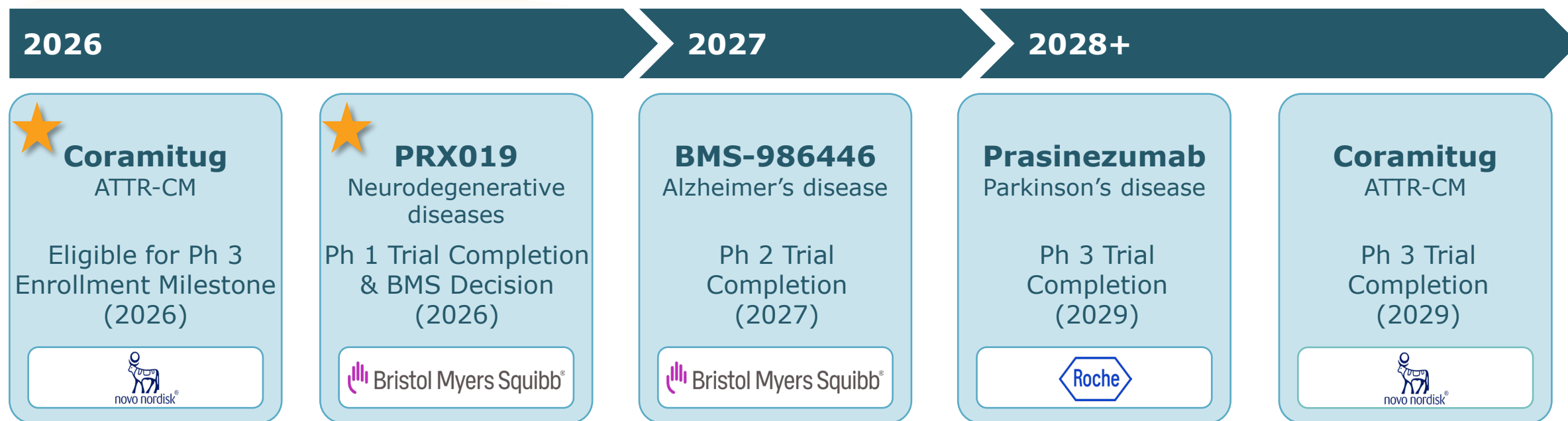
¹ Orphan Drug Designation granted by FDA & EMA; ² FDA Fast Track designation.

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

Future Partner Catalysts

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



Up to ~**\$3 BILLION** aggregate downstream milestones across partnered programs
and **SALES ROYALTIES** from prasinezumab, BMS-986446, and PRX019

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

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



Clear Addressable Unmet Need

- **> 10 million Parkinson's patients** globally, fastest growing neurodegenerative disease¹

Differentiated Mechanism of Action²

- 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 Roche³

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

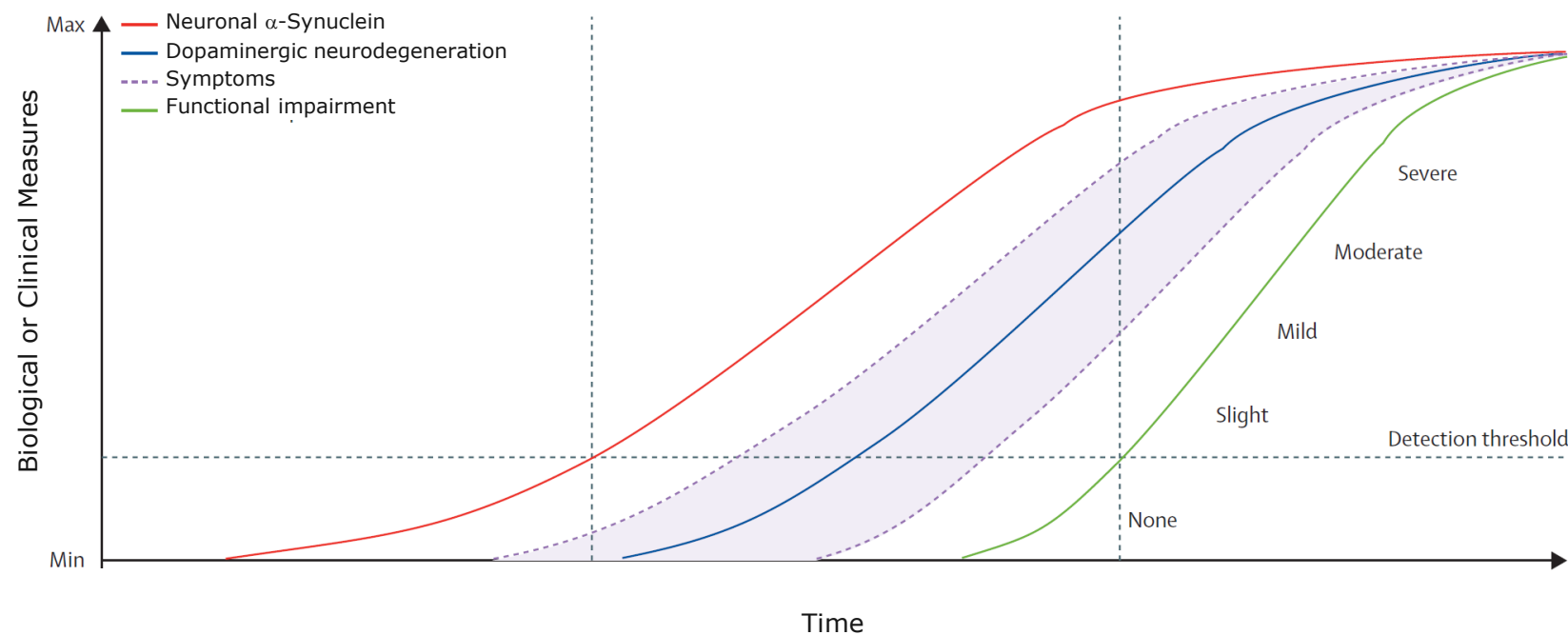
Slide adapted from Roche's Pharma Day 2025 Presentation on September 22, 2025.

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.

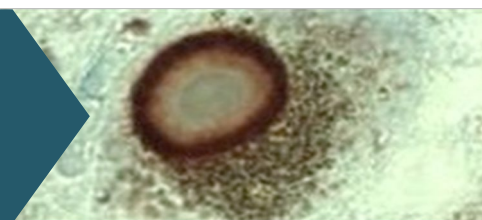
α -Synuclein Pathology is Strongly Implicated in Parkinson's Disease

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

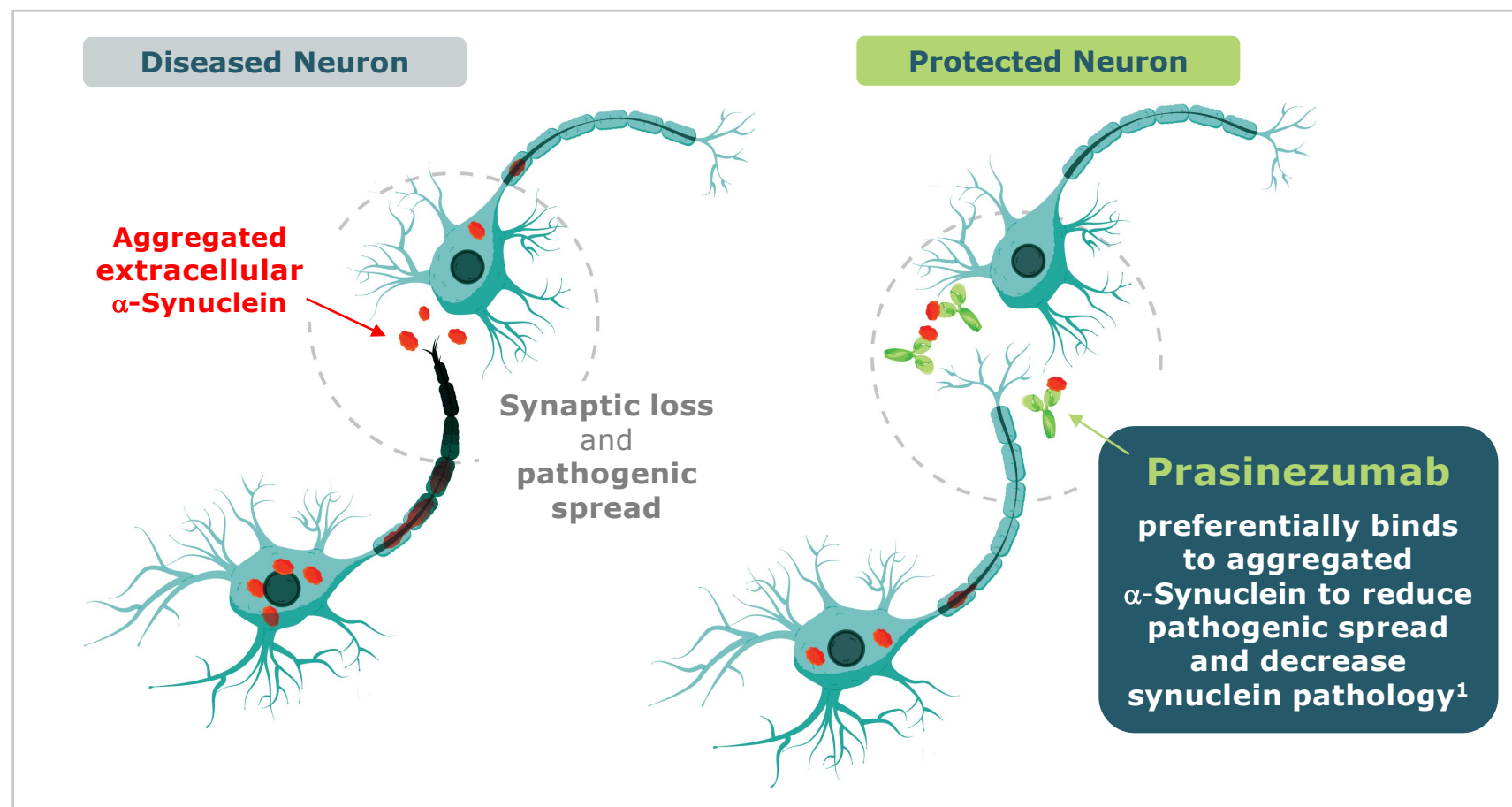


α -Synuclein Immunotherapy

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

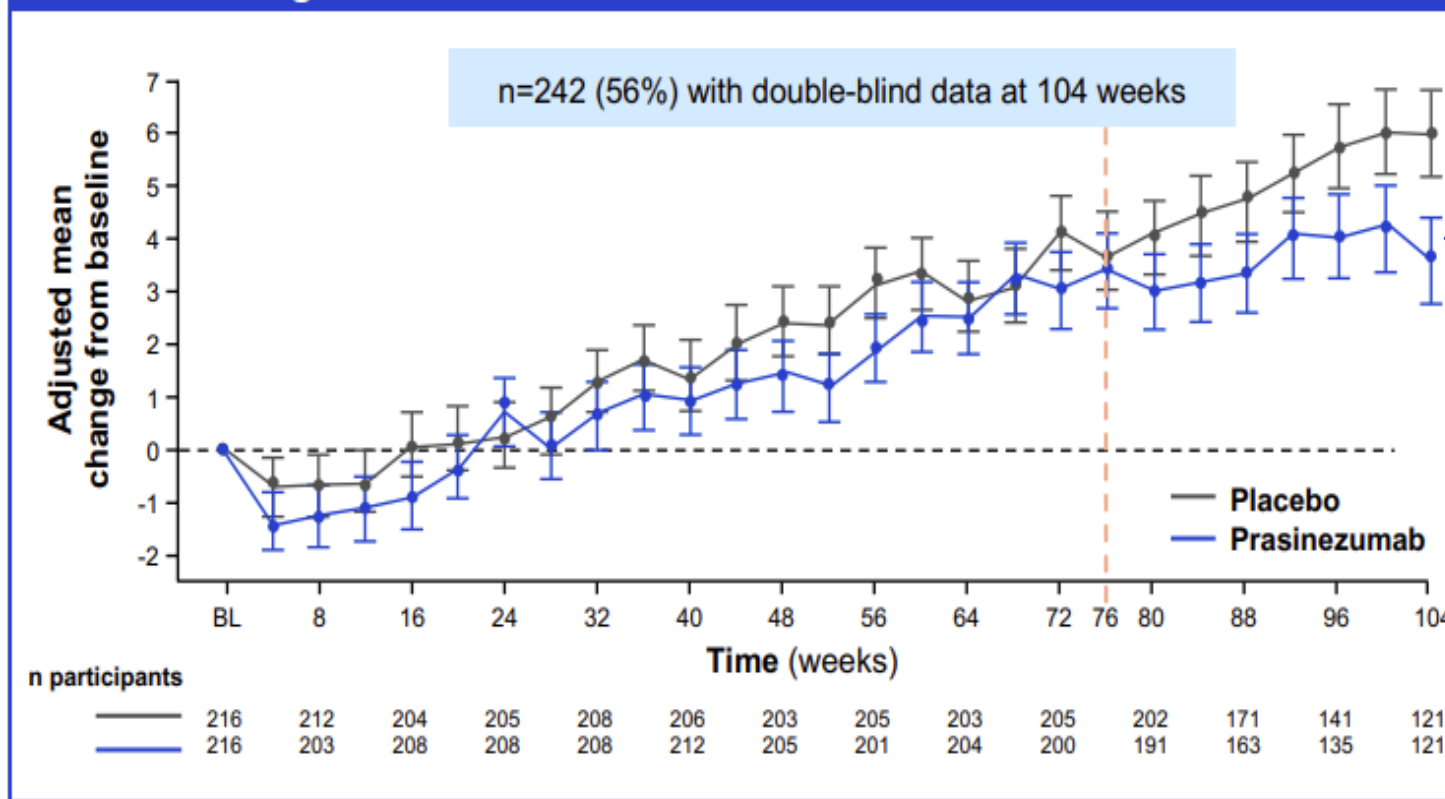


Moving into Phase 3 in Parkinson's Disease

Phase 2b (PADOVA) 2 Year Results

L-DOPA-treated population

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



~40% relative reduction in progression at week 104 vs. placebo
 $p=0.0177^1$

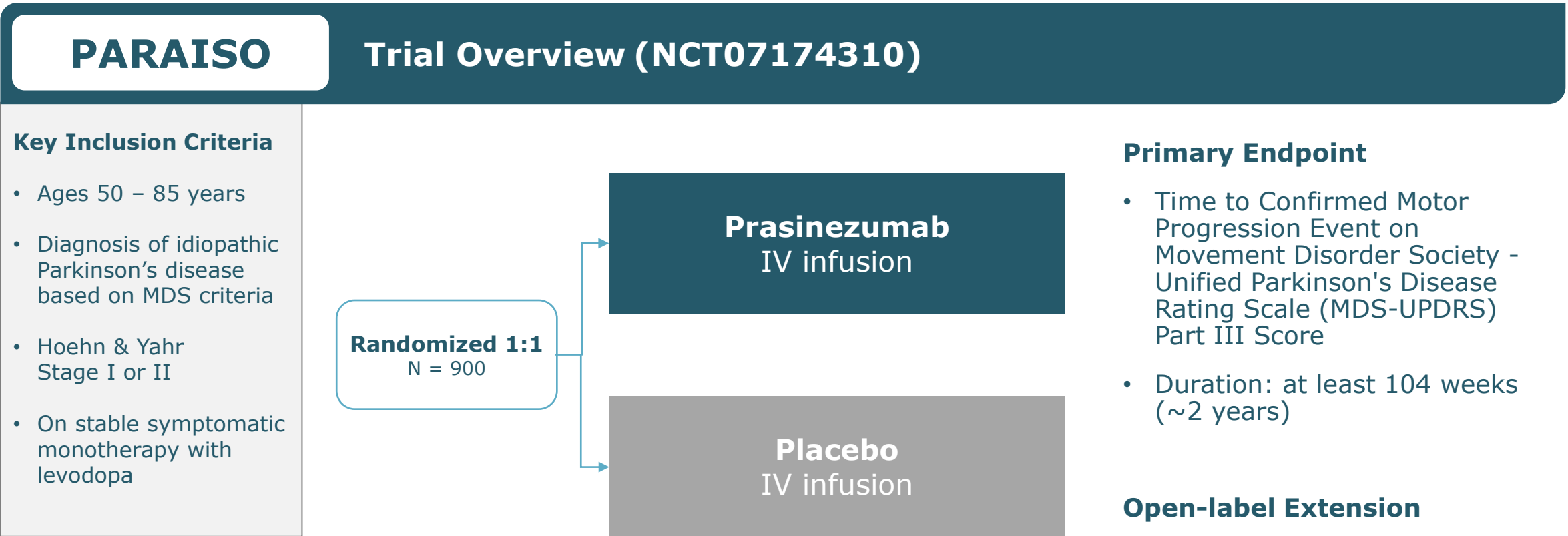
- More pronounced effect in L-DOPA treated patients (~75% of population)
- Results consistent across both PADOVA and PASADENA Phase 2 trials and OLEs
- Phase 3 trial design incorporates:
 - Larger sample size 'n' (~900)
 - Longer duration (2 years)
 - L-DOPA population

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

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

¹ For descriptive purposes, nominal p-values are displayed for 2-year, double-blind data for L-DOPA-treated population.

Phase 3 PARAISO 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: Potential First-in-Class Depleter Treatment for ATTR-CM



Clear Addressable Unmet Need

- **450,000** patients estimated globally with wild-type or hereditary ATTR-CM¹⁻³

Differentiated Mechanism of Action

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

Clinical Support⁴⁻⁵

- **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 Therapy⁴⁻⁵

- Benefits observed in Phase 2 on top of standard of care⁶

Current Status

- Novo Nordisk advanced coramitug into the **Phase 3 CLEOPATTRA** clinical trial in ~1280 patients with ATTR-CM (NCT07207811)

Upcoming Milestones

- Potential milestone in 2026 after prespecified enrollment criteria are met in Phase 3 clinical trial
- Phase 3 trial primary completion expected in 2029

Market Opportunity

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

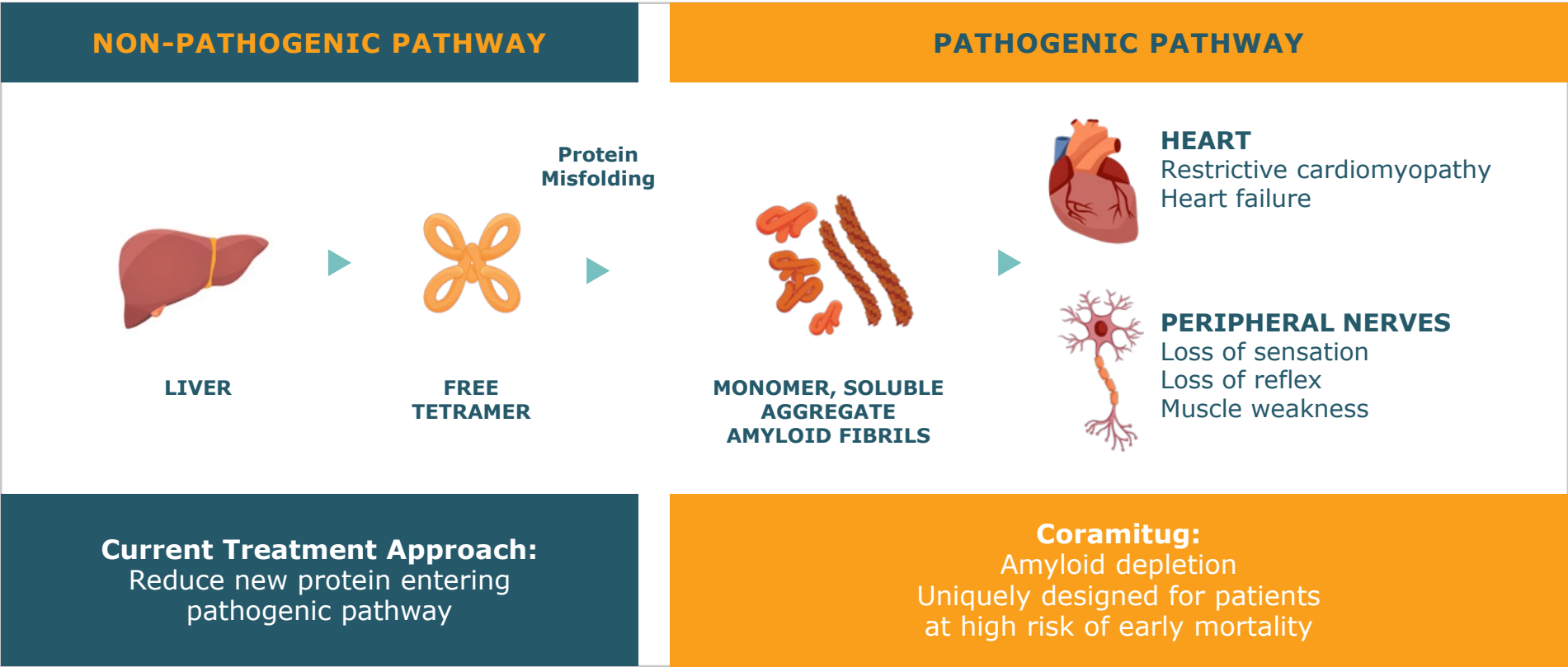
Partnership Economics with Novo Nordisk

☒ **\$100 million** paid to date

☐ **\$1.13 billion** remaining in clinical, regulatory, and 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

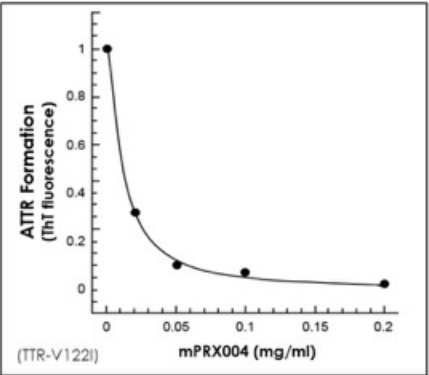
Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF mPRX004

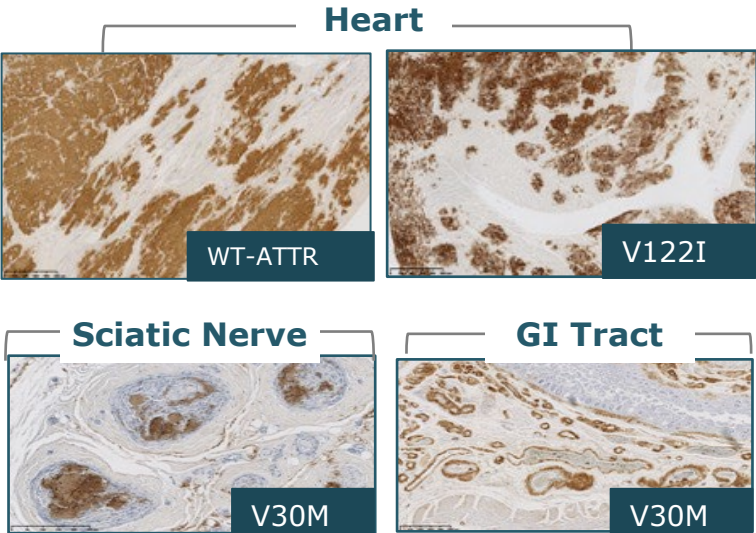
mPRX004 (murine form of PRX004) preclinical results:¹

- ✓ 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

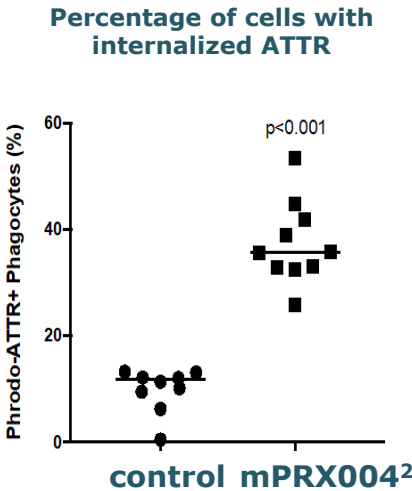
Inhibition of amyloid formation



Specific binding to amyloid

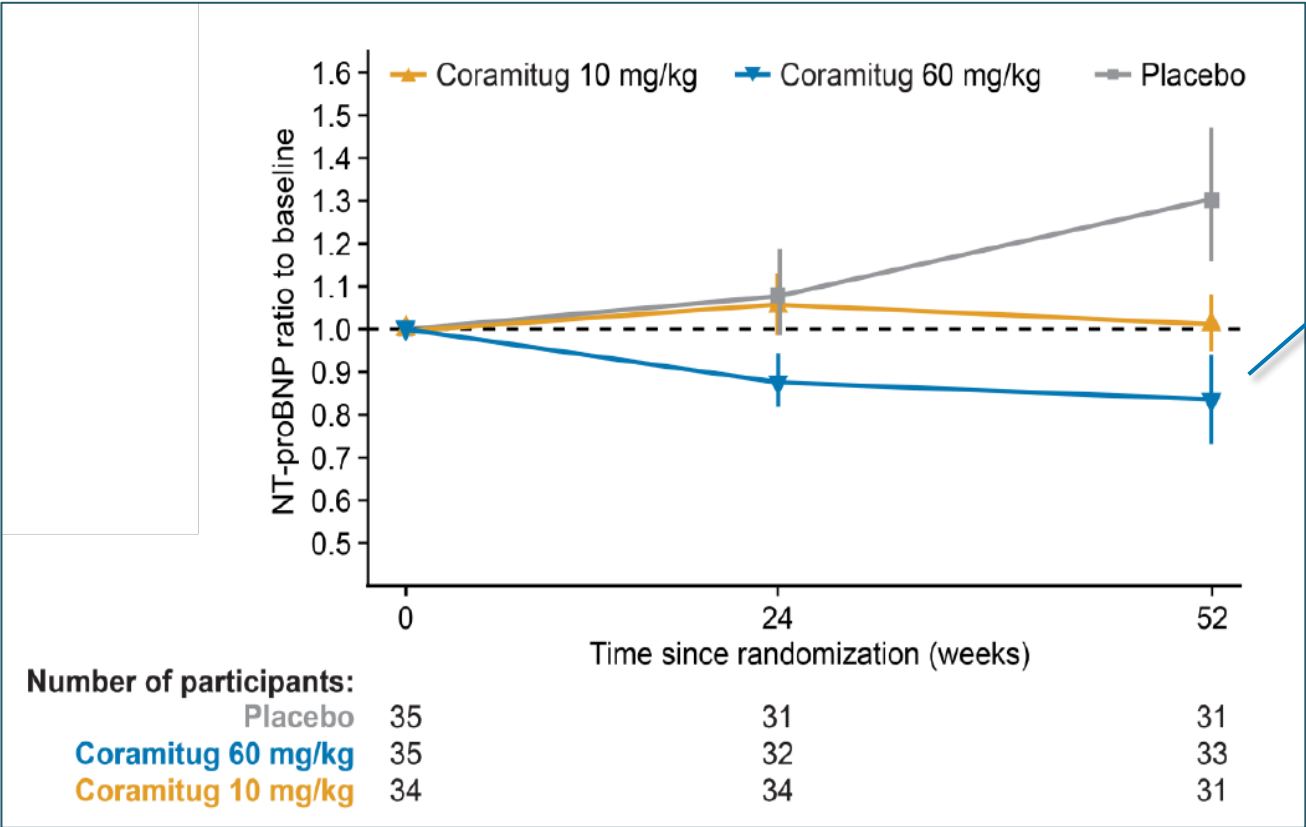


Clearance of amyloid



Moving into Phase 3 in ATTR-CM

Phase 2 Results¹⁻² 105 patients / 3-arms / 12 months

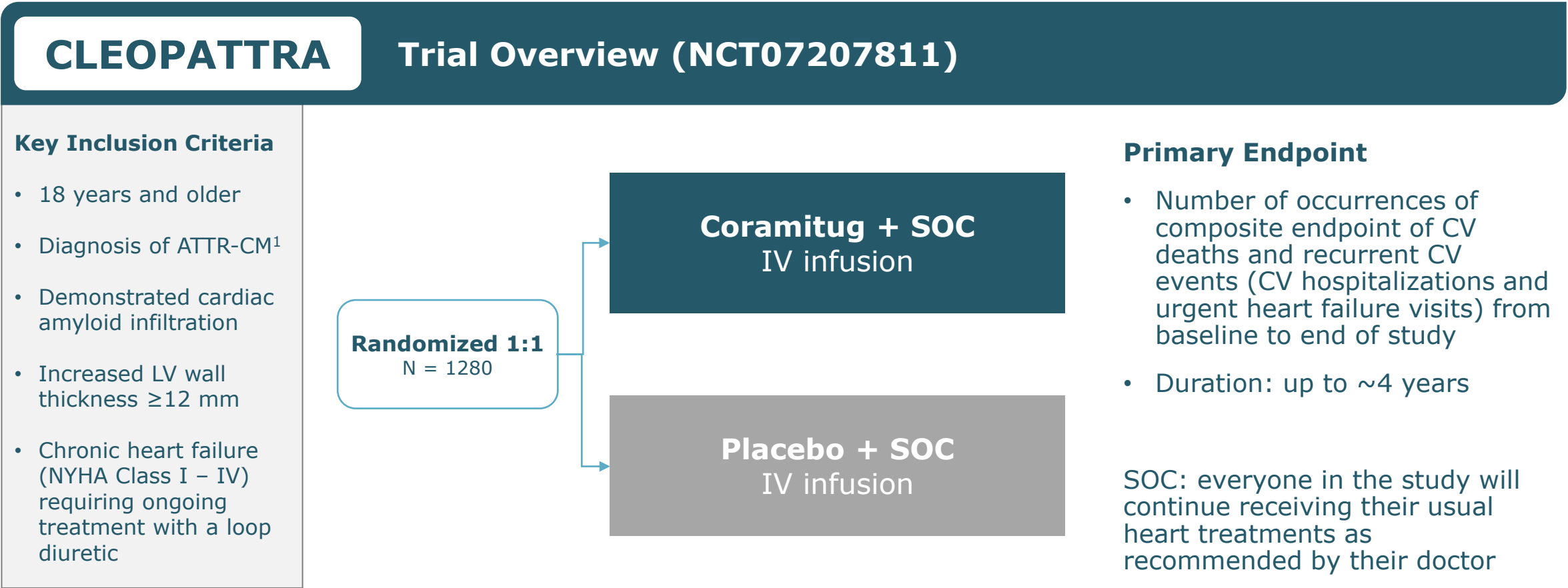


Coramitug 60 mg/kg reduced NT-proBNP levels from baseline at 12 months and by 48% vs. placebo
p=0.0017

- 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 versus placebo across a wide range of echocardiogram parameters suggestive of favorable cardiac remodeling at 12 months
 - Improved measures include LV and RV systolic function, diastolic function, and estimated pulmonary arterial pressures
- 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.
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>.

Phase 3 CLEOPATTRA Trial Design



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 resuitment is ~15% of the study population.

BMS-986446 (formerly PRX005)

Alzheimer's Disease

Phase 2

Global Neuroscience Collaboration
with Bristol Myers Squibb

BMS-986446: Potential First-In-Class anti-Tau mAb for Alzheimer’s Disease



Clear Addressable Unmet Need

- **> 80 million Alzheimer’s patients** globally¹

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
- Open-label single-dose Phase 1 study to assess a subcutaneous administration conducted in 2025
- Favorable safety and tolerability profile

Current Status

- Bristol completed enrollment in the **Phase 2 TargetTau-1** clinical trial in ~310 patients with early Alzheimer’s disease (NCT06268886)
- Obtained Fast Track Designation from the FDA

Upcoming Milestones

- Phase 2 trial primary completion expected in 2027

Market Opportunity

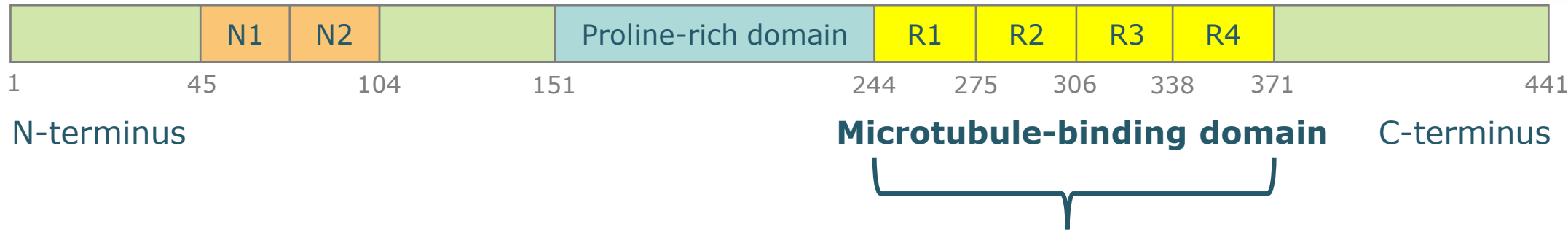
- **Multi-billion** global peak sales potential

Partnership Economics with BMS²

- ✓ **\$135 million** paid to date
- ❑ **\$562.5 million** remaining in regulatory and 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 and a \$50 million equity investment in Prothena.

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-tau243 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-tau243 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.



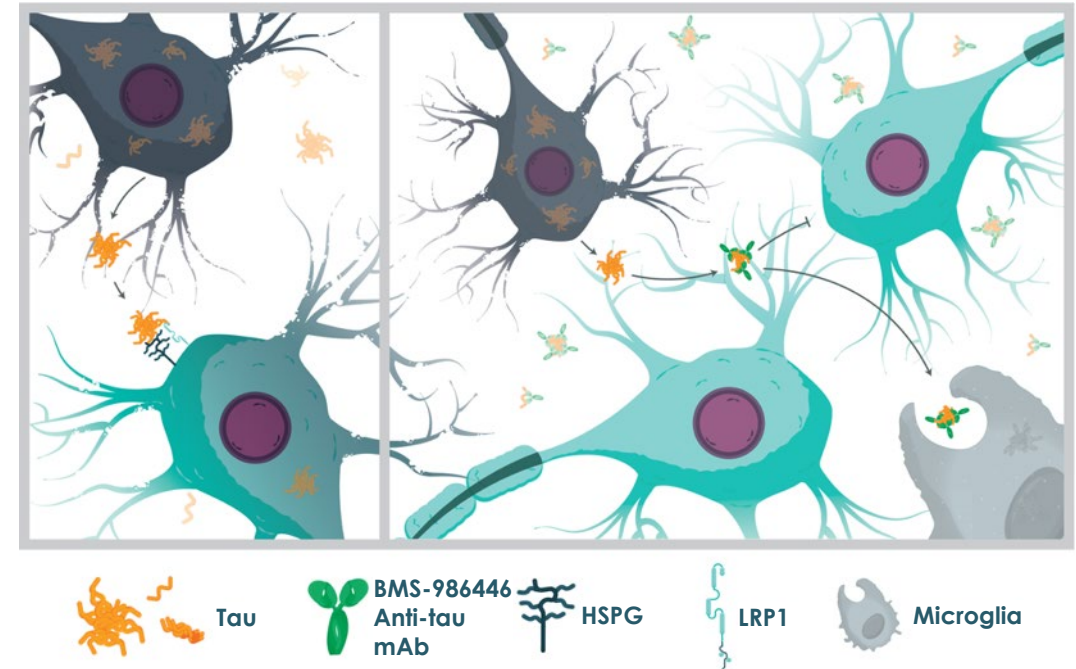
MTBR-Specific Anti-Tau Antibody

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

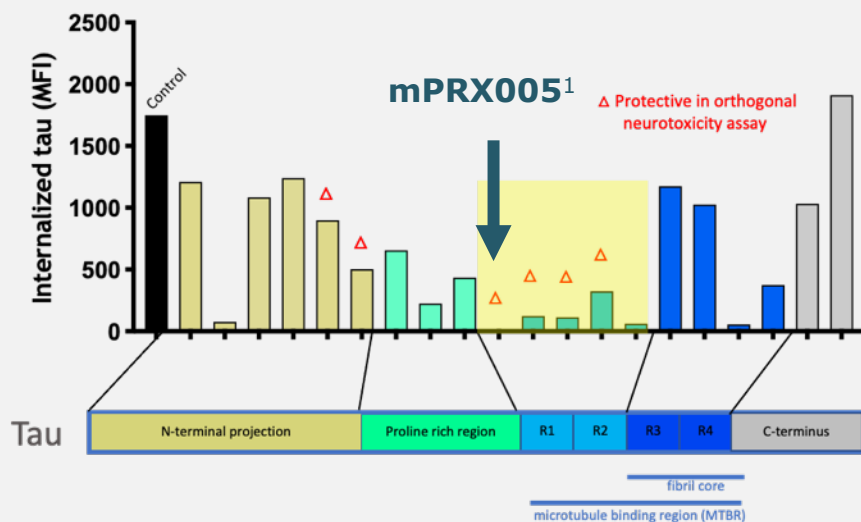
- Preclinical evaluation of our antibodies in our AD models demonstrated that MTBR-specific antibodies are superior to non-MTBR tau antibodies in blocking tau uptake and neurotoxicity
- Demonstrated significant inhibition of cell-to-cell transmission and neuronal internalization in vitro and in vivo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



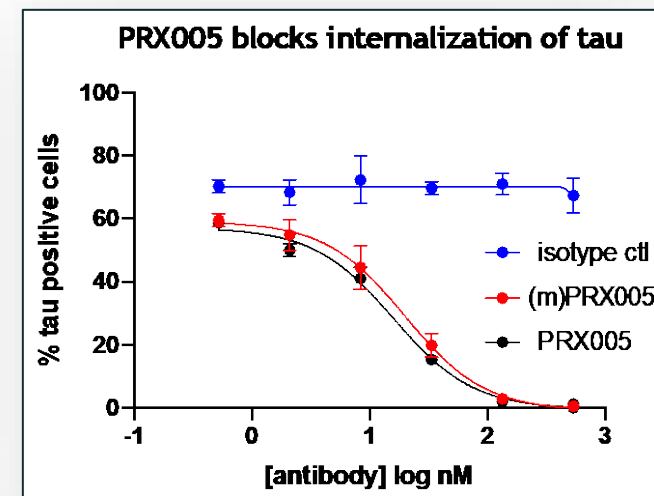
BMS-986446: Potential Best-in-Class MTBR-Specific Anti-Tau Antibody to Reduce Pathogenic Tau Spread

Superior in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity

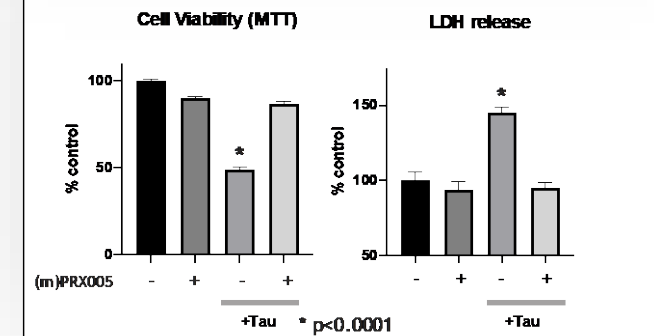
Repeats 1 and 2 defined as the strongest inhibitory regions in screening with cellular internalization and neurotoxicity assays



- 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



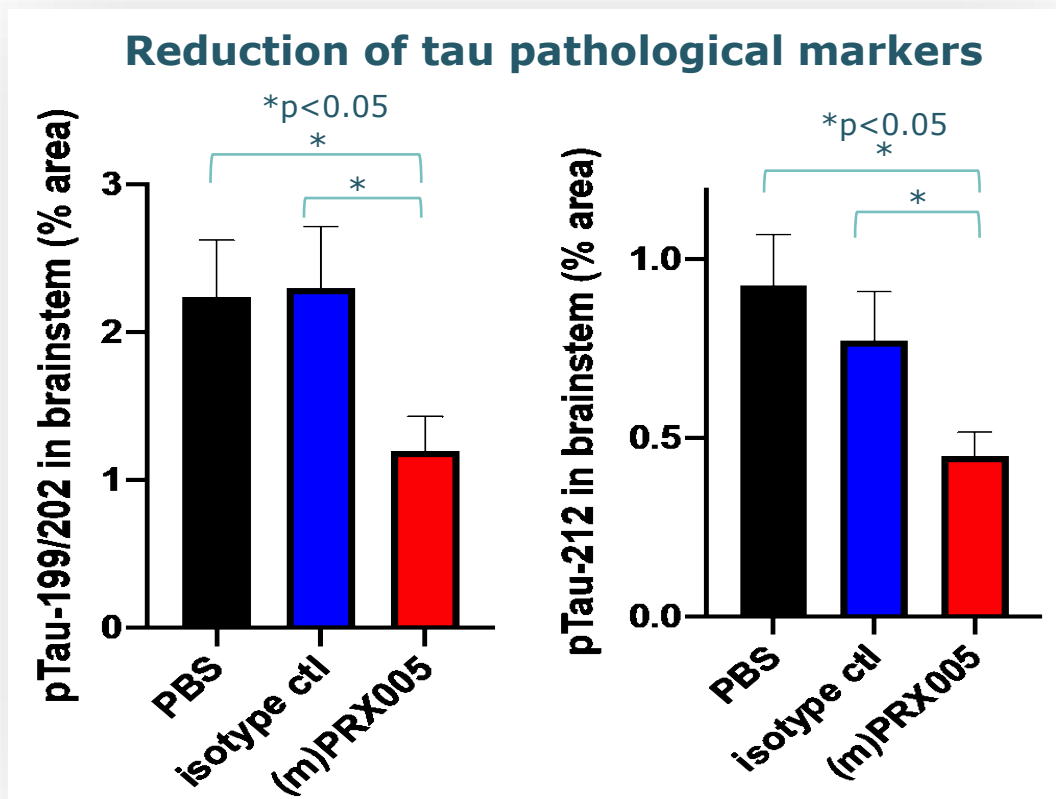
(m)PRX005 protects rodent primary cortical neurons from tau-induced toxicity



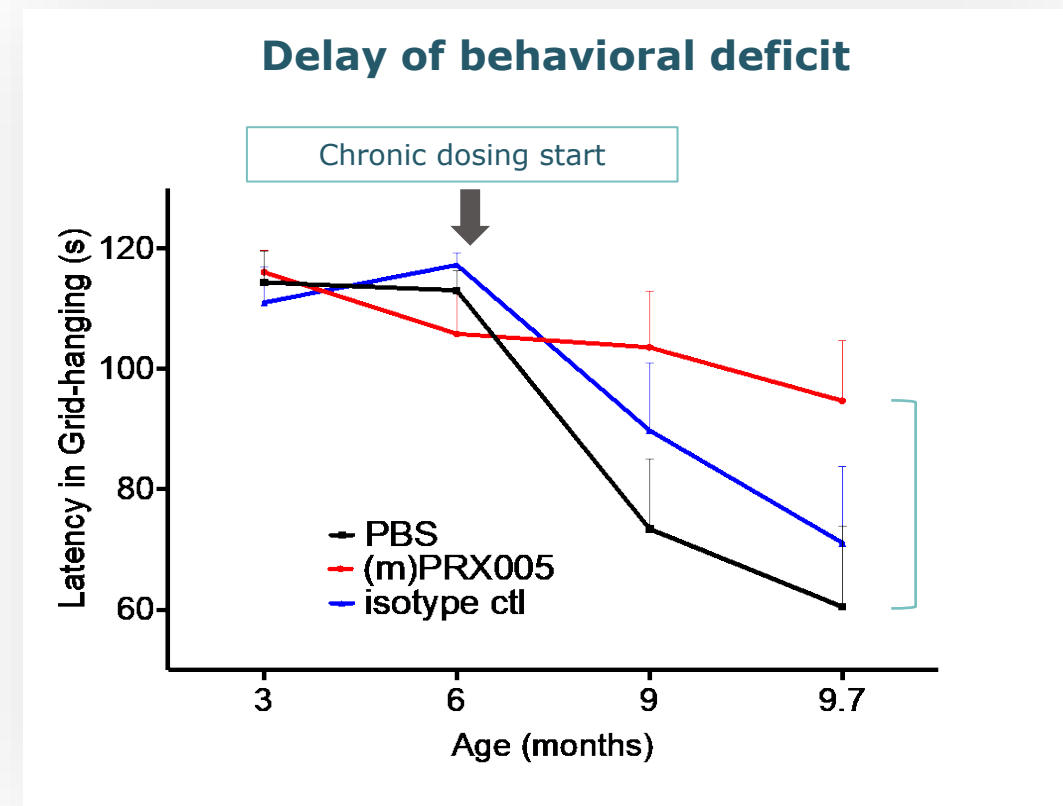
¹ (m)PRX005: murine form of PRX005 (BMS-986446)
Prothena data on file

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

All values are mean $\pm$ SE (n=15-20)

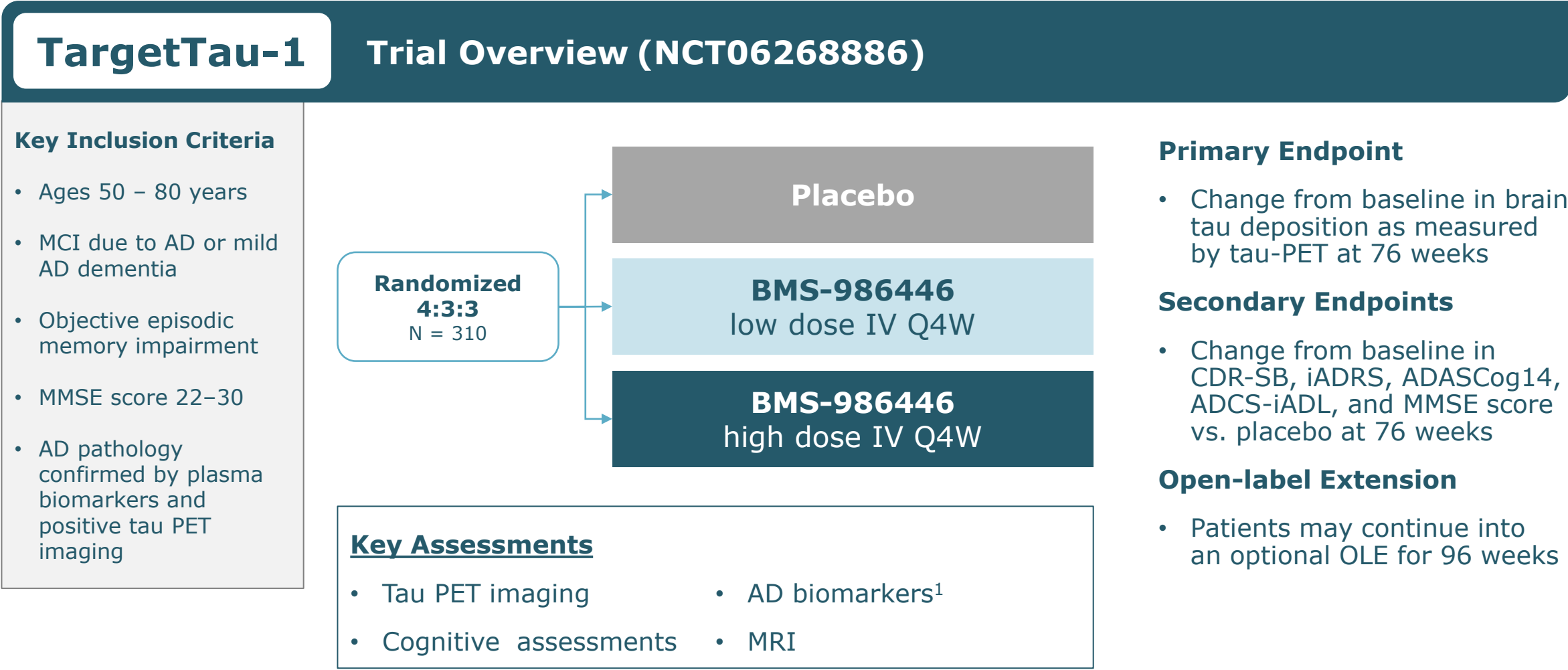


- PS19 transgenic mice overexpressing tau mutation (P301S) cause high levels of neuronal tau pathology and resultant behavioral deficits



- 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

Phase 2 TargetTau-1 Trial Design



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 bFluid-based biomarkers include total tau, p181tau, p217tau, Aβ [1-42], Aβ [1-40], neurofilament light chain, & glial fibrillary acidic protein.

PRX019

Neurodegenerative Diseases

Phase 1

Global Neuroscience Collaboration
with Bristol Myers Squibb



PRX019: Potential Treatment of Neurodegenerative Diseases



Current Status

- Phase 1 clinical trial being conducted by Prothena (NCT06699680)
- Single ascending dose and multiple ascending dose in healthy adults
- Phase 1 trial to evaluate:
 - Safety
 - Tolerability
 - Immunogenicity
 - Pharmacokinetics
 - Pharmacodynamics

Upcoming Milestones

- Phase 1 trial primary completion expected in 2026
- Eligible for potential milestone at time of BMS decision to further develop PRX019 expected by YE 2026

Partnership Economics with BMS¹

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

TDP-43 CYTOPE[®]

ALS

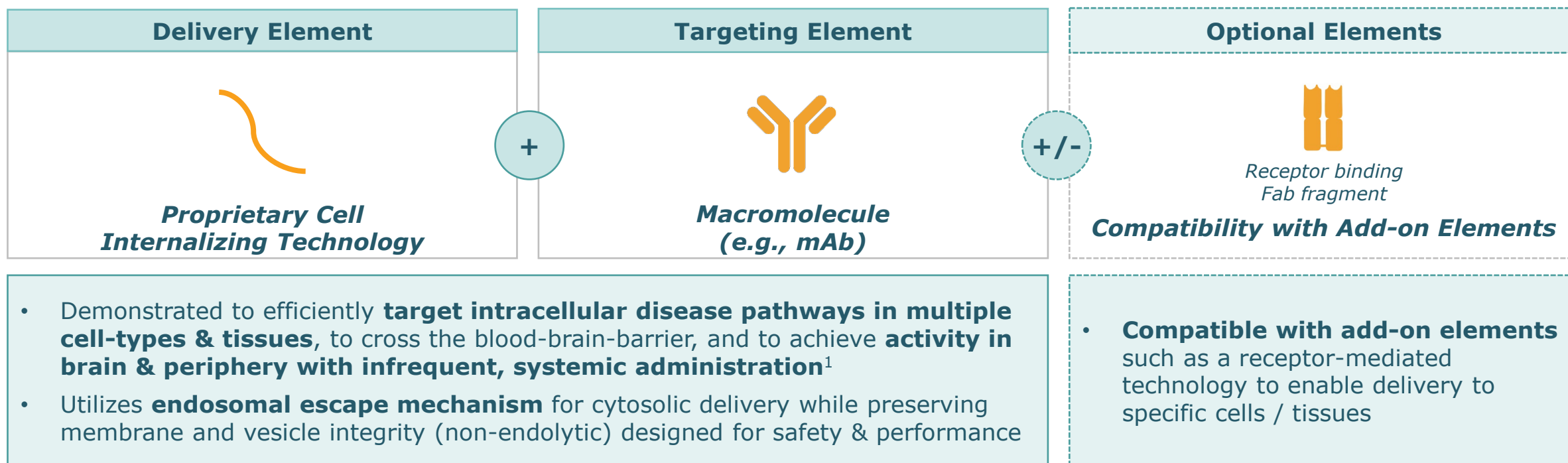
Preclinical

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



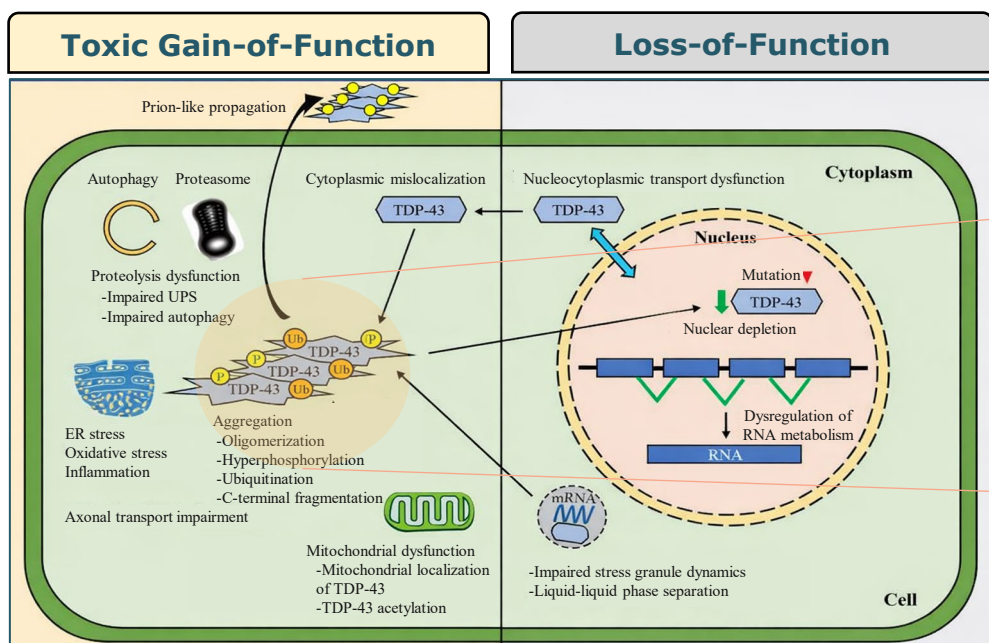
pTDP-43 is a Core Driver of ALS Pathogenesis that is an Undruggable Target with Current Modalities

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

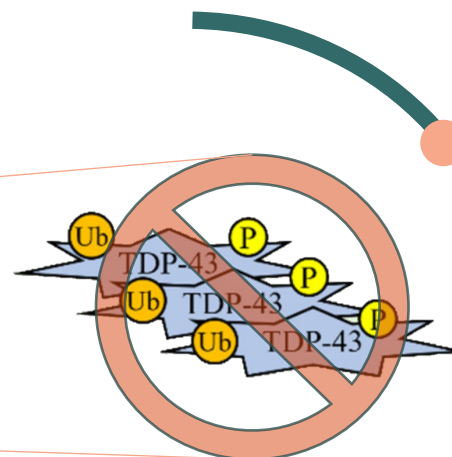
- Delivery: Intracellular target expressed broadly in CNS & periphery
- Specificity: Targeting pTDP-43 is critical; broad TDP-43 KD disrupts global RNA processing, leading to cell death



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)

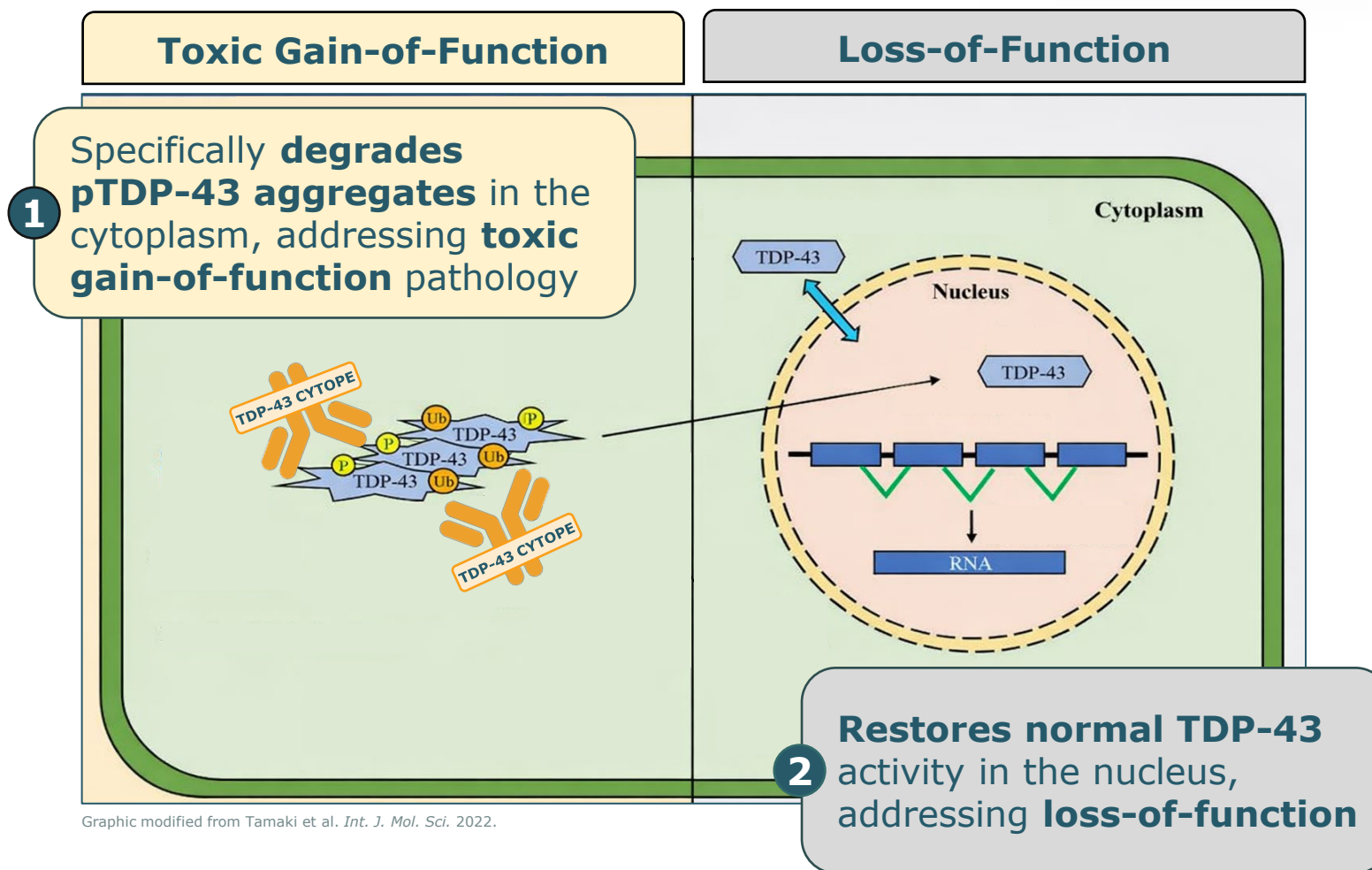
TDP-43 CYTOPE® is Designed to Address Toxic Gain-of-Function and Loss-of-Function Pathology



TDP-43 CYTOPE®



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



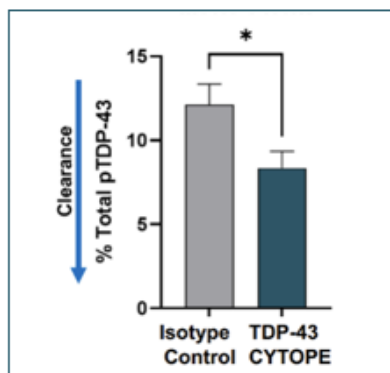
TDP-43 CYTOPE® Preclinical Data Demonstrates Potential of CYTOPE Technology



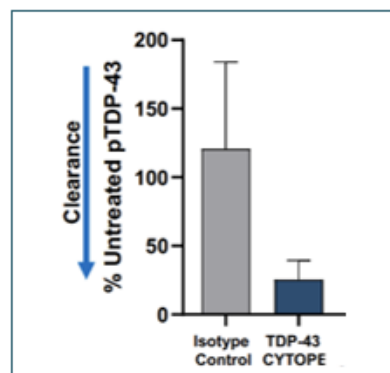
1

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

Motor Cortex



Skeletal Muscle



(Left) % Total pTDP-43 staining in motor cortex of rNLS8 mice 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.

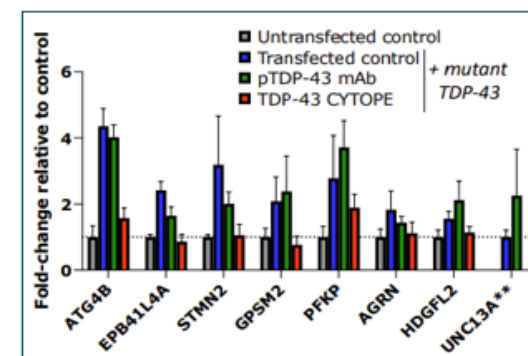
TDP-43 CYTOPE® significantly reduced brain & muscle pathology in a severe ALS mouse model after systemic administration

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

2

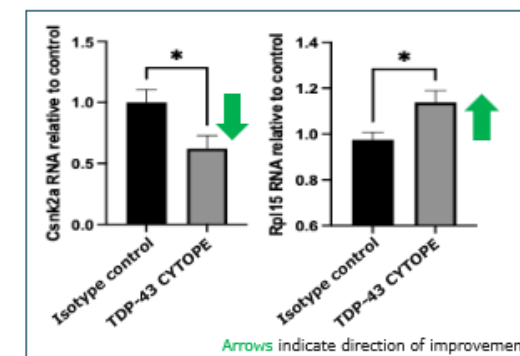
Addresses Loss-of-Function: Attenuated ALS-Related Splicing Defects

Human Neuronal Cells



(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. * $p < 0.05$.

rNLS8 Mice



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 ($\uparrow$ Csn2a; $\downarrow$ Rpl15 mRNA)^{1,2}

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. 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 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
 - 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-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 elucidate the potential of PRX012-TfR

Prothena is exploring partnership interest in the program