Prothena Fourth Quarter and Year-End 2025 Financial Results

February 19, 2026

4Q and FY25 Earnings Call Agenda

Welcome	**Mark Johnson** | Vice President, Head of Investor Relations
Opening Remarks	**Gene Kinney, Ph.D.** | President and CEO
Clinical Programs	**Chad Swanson, Ph.D.** | Chief Development Officer
Preclinical Programs	**Philip Dolan, Ph.D.** | Vice President, Head of Discovery Research
Financial Results	**Tran Nguyen** | Chief Strategy Officer and Chief Financial Officer
Closing Remarks	**Gene Kinney, Ph.D.** | President and CEO
Q&A Session	**Brandon Smith** | Chief Operating Officer

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; our anticipated net cash burn from operating and investing activities for 2026 and expected cash balance at the end of 2026; our estimated net loss and non-cash share-based compensation expense for 2026. 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 uncertainties related to the completion of operational and financial closing procedures, audit adjustments and other developments that may arise that would require adjustments to the preliminary financial results included in this press release, as well as 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.

Opening Remarks

Gene Kinney, Ph.D.

President and CEO

2025 Achievements Shape Pipeline Progress

PROGRAM INDICATION (MODALITY)	2025 ACHIEVEMENTS	STATUS	GLOBAL RIGHTS[4]
PARTNERED CLINICAL PROGRAMS			
Prasinezumab Parkinson's disease (mAb) Target: α-Syn (C-terminus)	✓ Roche advanced to Phase 3 based on data from two Phase 2 trials & OLEs presented at AD/PD 2025 showing consistent slowing of disease progression	Phase 3	Roche
Coramitug ATTR-CM (mAb) Target: Transthyretin (misTTR) ODD[1]	✓ Novo Nordisk advanced to Phase 3 based on positive Phase 2 results presented at AHA 2025 showing significant reduction in NT-proBNP as well as improvements in functional & echocardiographic measures	Phase 3	novo nordisk®
BMS-986446 Alzheimer's disease (mAb) Target: Tau (MTBR) Fast Track[2]	✓ Bristol Myers Squibb fully enrolled TargetTau-1 Phase 2 trial, presented Phase 1 MAD data at CTAD 2025, and obtained Fast Track Designation	Phase 2	Bristol Myers Squibb®
PRX019 Neurodegeneration diseases (mAb) Target: Undisclosed	✓ Phase 1 ongoing with expected completion on track for 2026	Phase 1	Bristol Myers Squibb®
WHOLLY OWNED PRECLINICAL PROGRAMS			
TDP-43 CYTOPE® ALS (mAb-CYTOPE) Target: pTDP-43	✓ Described CYTOPE® technology and presented innovative preclinical data at Neuroscience 2025 (SfN) & International Symposium on ALS/MND	Preclinical	prothena®
PRX012-TfR[3] Alzheimer's disease (mAb-TfR) Target: Aβ (N-terminus)	✓ Advanced preclinical work to add transferrin receptor technology; Phase 1 ASCENT results demonstrated robust plaque clearance at 400 mg	Preclinical	prothena®

mAb: Monoclonal Antibody; MAD: Multiple Ascending Dose; NT-proBNP: N-terminal Pro-B-type Natriuretic Peptide; 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.

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

- Up to **$105 MILLION** in clinical milestones by YE 2026
  - Coramitug potential milestone after prespecified enrollment criteria are met in the Phase 3 trial
  - PRX019 potential milestone at time of BMS decision to further develop PRX019
- Obtained necessary shareholder approvals at an Extraordinary General Meeting and confirmed by the Irish High Court to support a share redemption program in 2026

ADVANCE R&D TO SUPPORT RESEARCH COLLABORATIONS & LICENSING DEALS

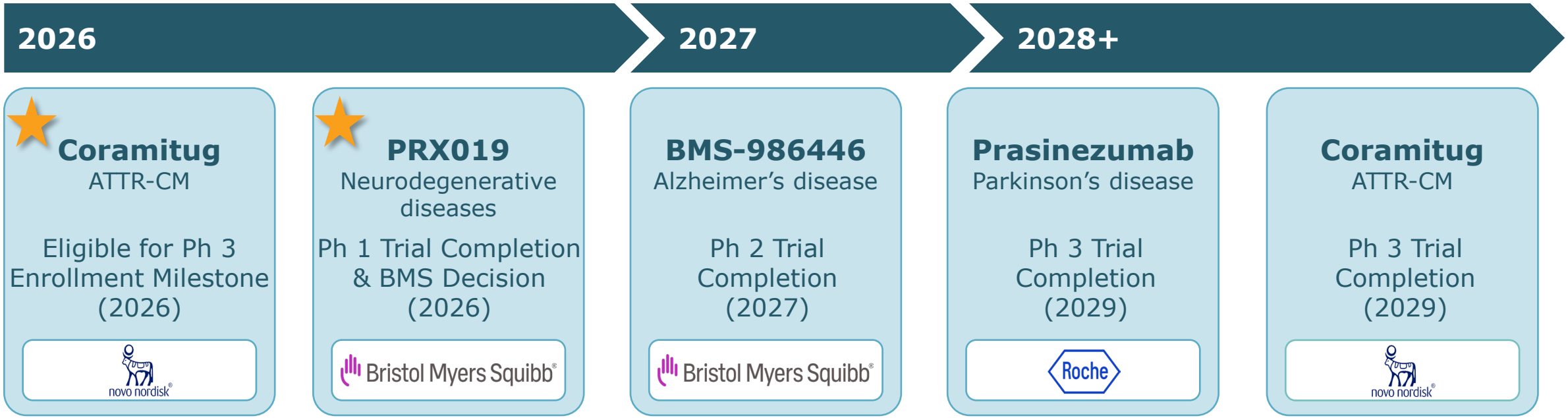
Partnerships provide an efficient path to explore the potential value of early-stage programs

- Investing in preclinical CYTOPE® technology and PRX012-TfR
- Exploring research collaborations and licensing deals for unpartnered programs
- Expanded scientific visibility with additional upcoming congress presentations from preclinical portfolio

Strategic priorities supported by $308.4 M in cash, cash equivalents, and restricted cash as of December 31, 2025

Future Partner Catalysts

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



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

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

Clinical Programs

Chad Swanson, Ph.D.
Chief Development Officer

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]

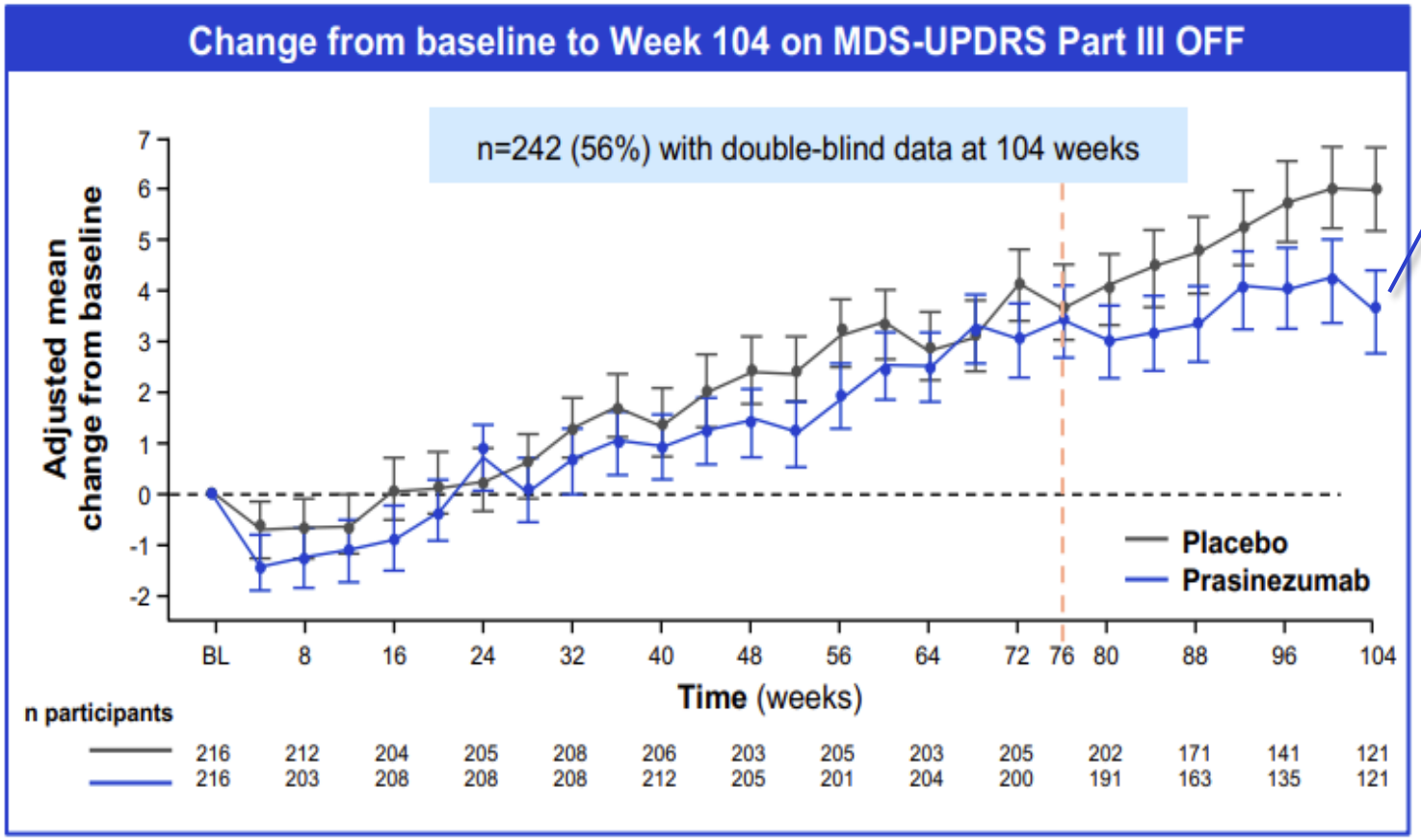
Partnership Economics with Roche

- ☑ **$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.

Moving into Phase 3 in Parkinson's Disease

Phase 2b (PADOVA) 2 Year Results
L-DOPA-treated population



~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

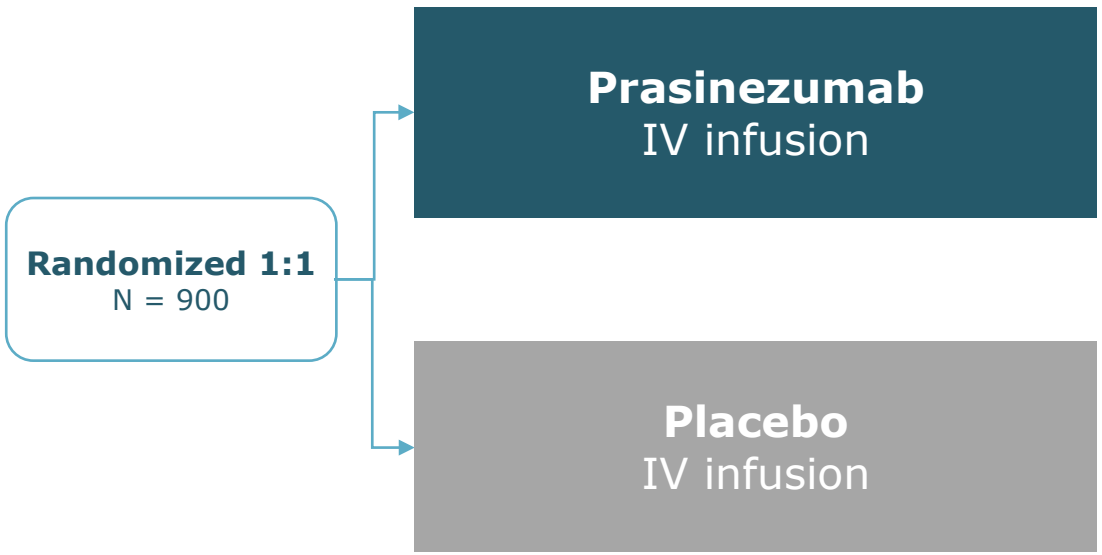
Slide adapted from Roche's presentation at ADPD 2025 in Vienna, Austria April 1-5, 2025.
MDS-UPDRS: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; OFF: Practically defined OFF state; OLE: Open-label Extension.
[1] For descriptive purposes, nominal p-values are displayed for 2-year, double-blind data for L-DOPA-treated population.

Phase 3 PARAISO Trial Design

PARAISO Trial Overview (NCT07174310)

Key Inclusion Criteria

- Ages 50 – 85 years
- Diagnosis of idiopathic Parkinson's disease based on MDS criteria
- Hoehn & Yahr Stage I or II
- On stable symptomatic monotherapy with levodopa



Primary Endpoint

- Time to Confirmed Motor Progression Event on Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Score
- Duration: at least 104 weeks (~2 years)

Open-label Extension

- Patients may continue into an optional OLE

Trial design slide adapted from information available on posting on clinicaltrials.gov.
MDS: Movement Disorder Society; OLE: Open-label Extension.

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-CM[1-3]

Differentiated Mechanism of Action

- Potential **first-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

- 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

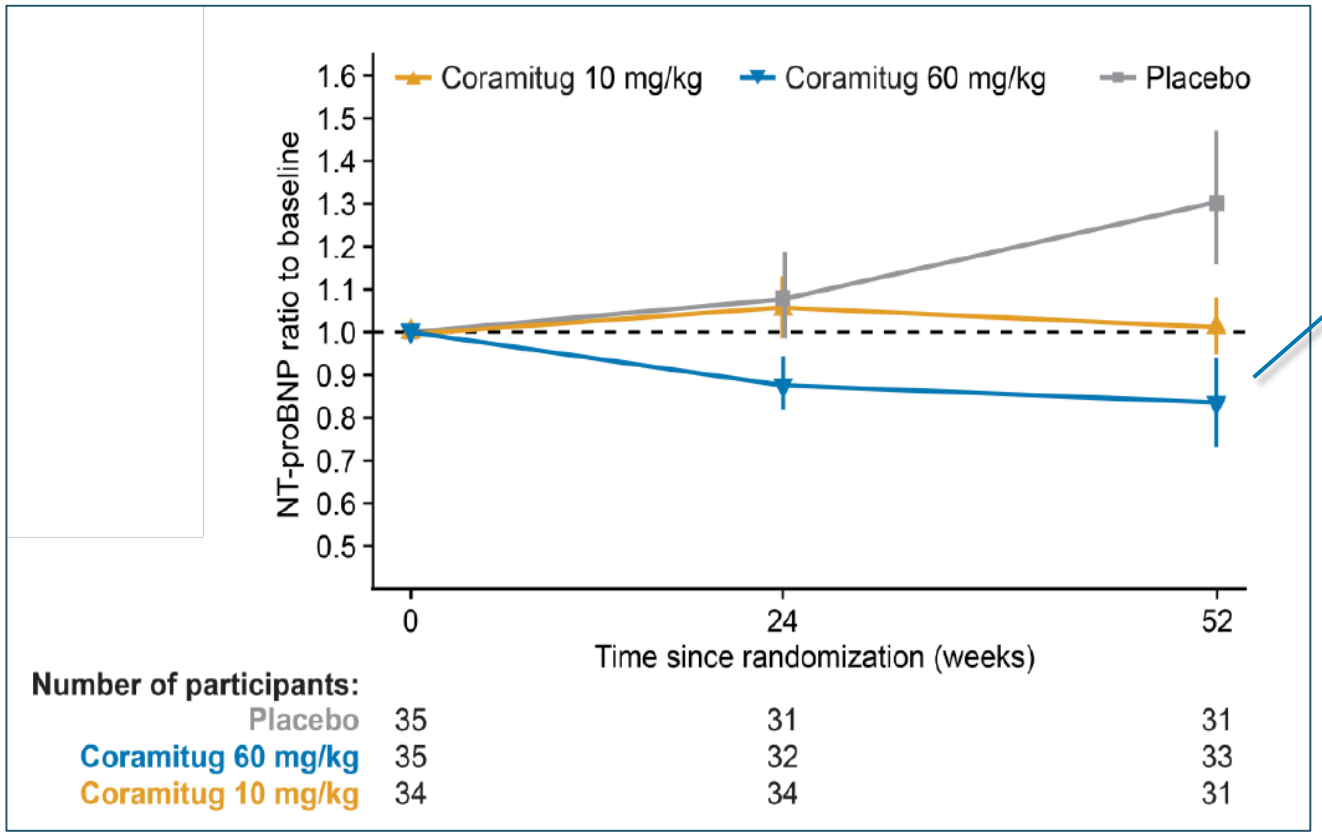
Partnership Economics with Novo Nordisk

- ☑ **$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.

Moving 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 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

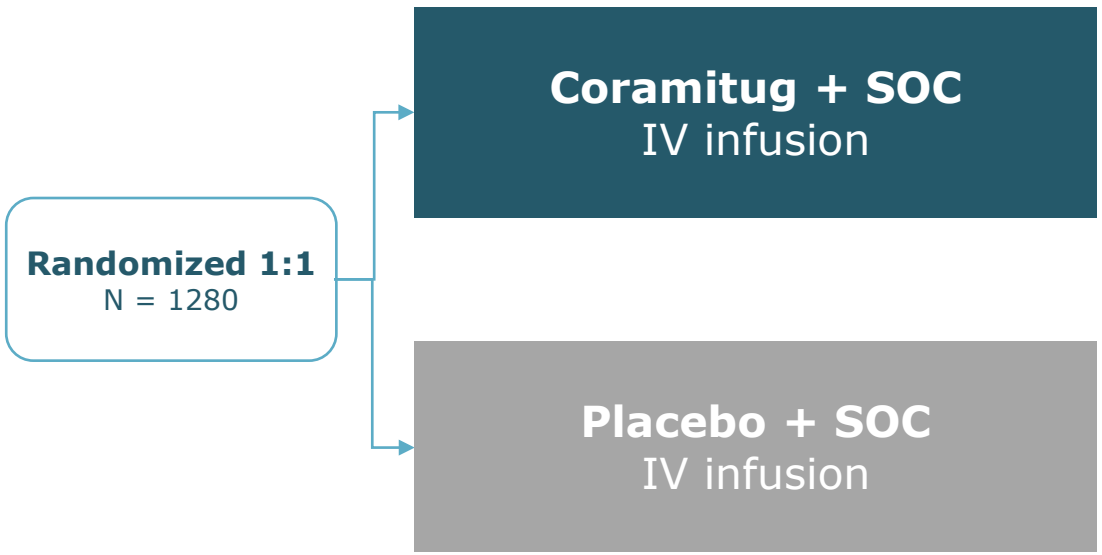
LV: Left Ventricle; NT-proBNP: N-terminal Pro-B-type Natriuretic Peptide; RV: Right Ventricle; TTR: Transthyretin; 6MWT: 6-Minute Walk Test.
[1] Phase 2 Results Presented During Late-Breaking Session of The American Heart Association Scientific Sessions 2025; November 10, 2025; New Orleans, LA. [2] Phase 2 Results Published November 10, 2025. Edition of *Circulation*: https://doi.org/10.1161/CIRCULATIONAHA.125.077304.

Phase 3 CLEOPATTRA Trial Design

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.

BMS-986446: 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
- 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

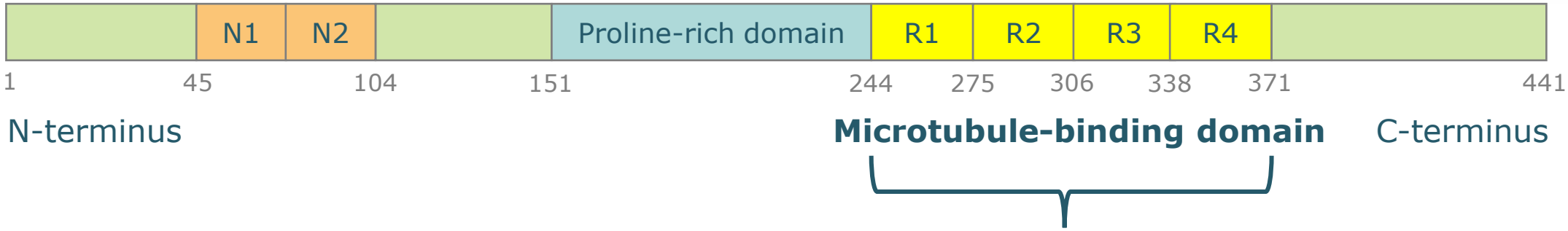
- **Multi-billion** global peak sales potential

Partnership Economics with BMS[2]

- ☑ **$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 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[5,7]
- Clinical: Trials ongoing, early clinical data from MTBR-targeting antibodies has shown positive trends on biomarkers including MTBR-tau243 and tau-PET[6]

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

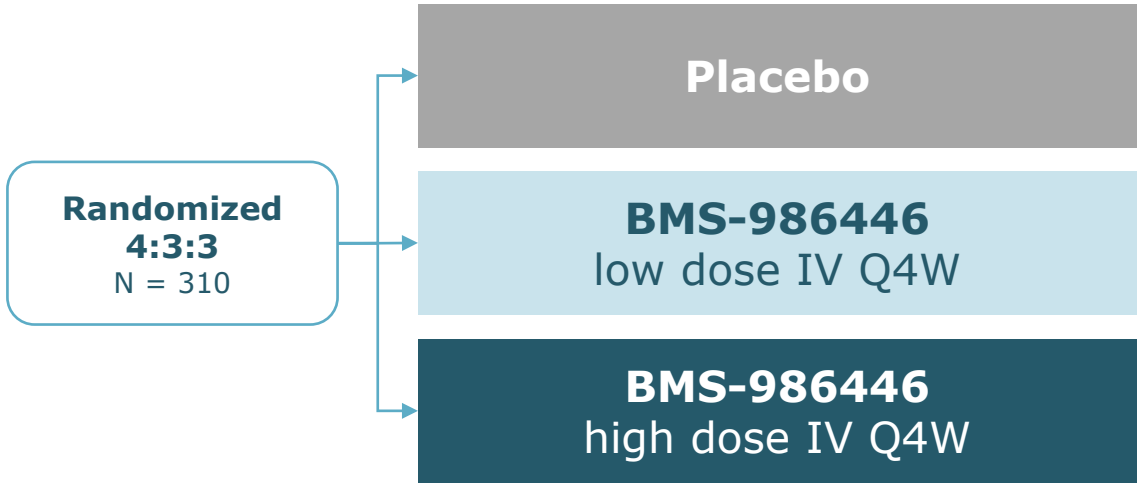
[1] Holmes BB, Diamond MI et al. Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. 2013 *Proc Natl Acad Sci U S A*. [2] Annadurai N, et al. Tau R2 and R3 are essential regions for tau aggregation, seeding and propagation. 2022 *Biochimie.* [3] Horie 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.

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

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 BMS[1]

- ✓ **$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

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

Preclinical Programs

Philip Dolan, Ph.D.
VP, Head of Discovery Research

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

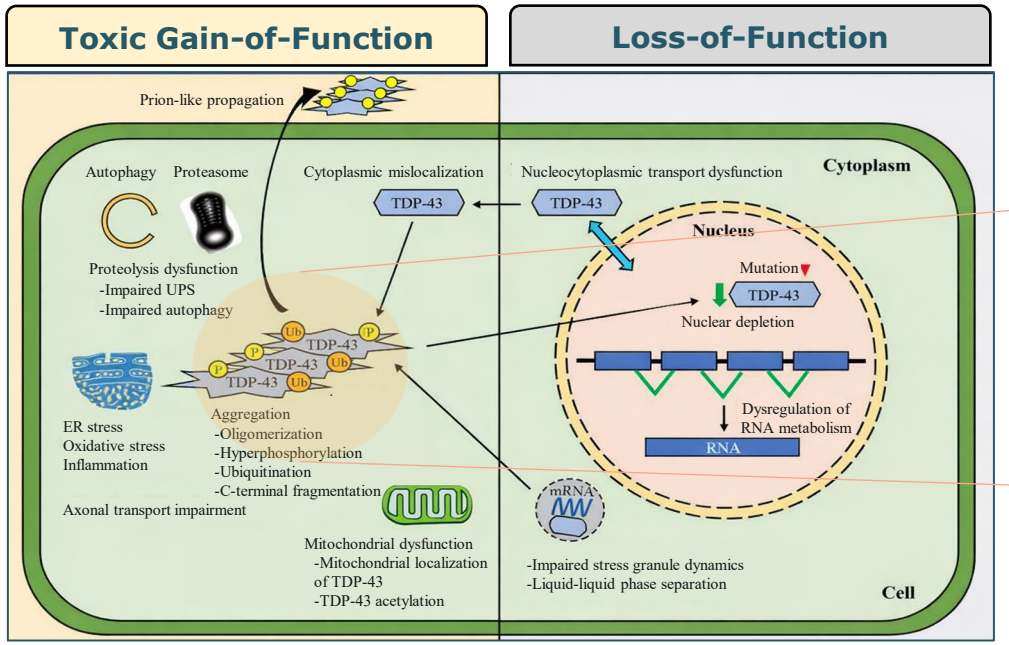
prothena®

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

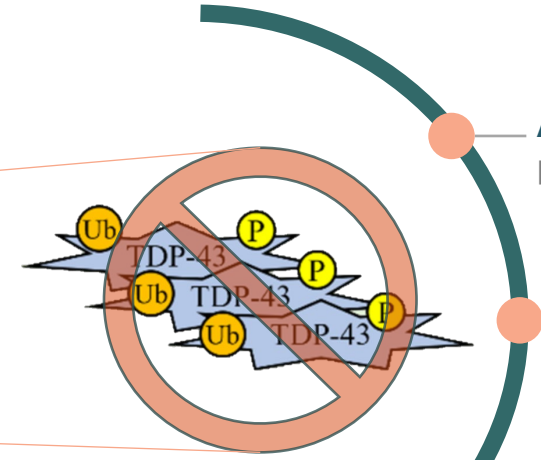
- Delivery: Intracellular target expressed broadly in CNS & periphery
- Specificity: Targeting pTDP-43 is critical; broad TDP-43 KD disrupts global RNA processing, leading to cell death



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

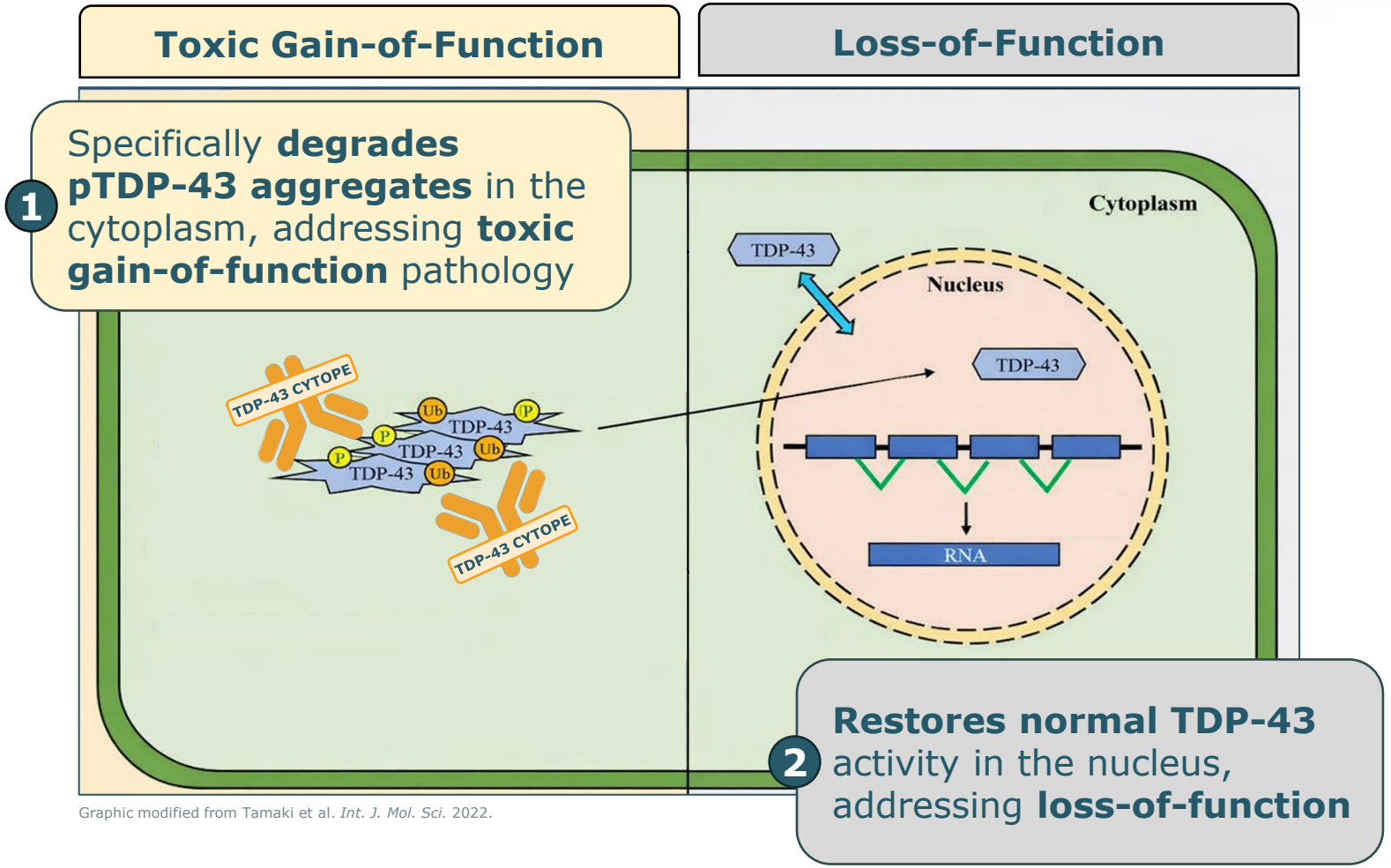
ASOs/siRNAs lack specificity
Targeting only pTDP-43 without wildtype knockdown is not feasible (post-translational modification)

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

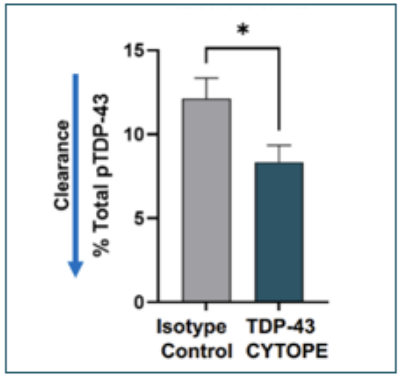


Graphic modified from Tamaki et al. *Int. J. Mol. Sci.* 2022.

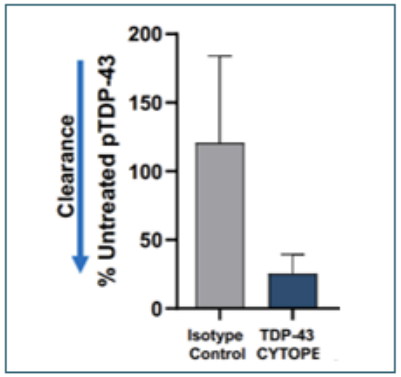
TDP-43 CYTOPE® Preclinical Data Demonstrates Potential of CYTOPE Technology

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

Motor Cortex



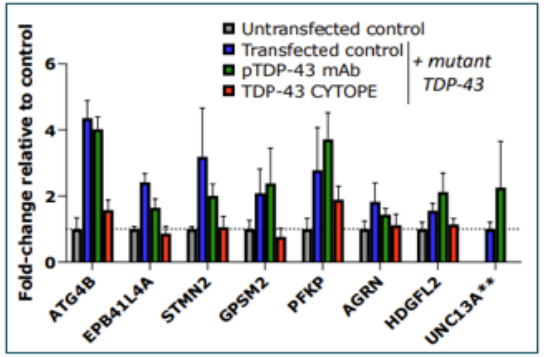
Skeletal Muscle



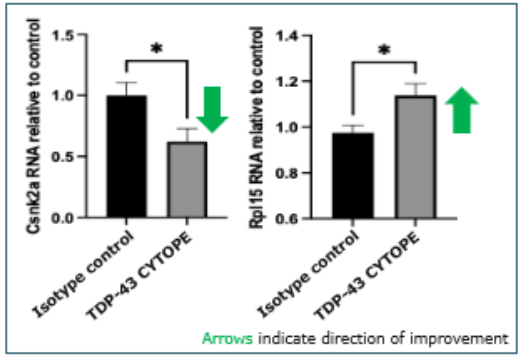
(Left) % Total pTDP-43 staining in motor cortex of rNLS8 nice after 4 weekly IV doses of TDP-43 CYTOPE. *p<0.05. *(Right)* % Untreated pTDP-43 staining in skeletal muscle of rNLS8 mice 72 hours post treatment with a single IV dose of TDP-43 CYTOPE; sample size (n) did not support statistical analysis.

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.

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 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.

Financial Results

Tran Nguyen
Chief Strategy Officer and Chief Financial Officer

2025 Actual vs. Guidance

	FYE 2025 Actuals	FYE 2025 Guidance	Performance
Net Cash Used in Operating and Investing Activities	$163.7 M	$170 – 178 M	✓ Favorable
Net Loss	$244.1 M[1]	$240 – 248 M	✓ In-line
Year End Cash Balance[2]	$308.4 M	$298 M	✓ Favorable

[1] Includes non-cash share-based compensation expense of $37.6 million. [2] Includes cash, cash equivalents, and restricted cash.

2026 Financial Guidance

	FYE 2026 Guidance
Net Cash Used in Operating and Investing Activities	$50 – 55 M
Net Loss	$67 – 72 M[1]
Year End Cash Balance[2] (midpoint)	$255 M[2]

Financial guidance does not include the potential to earn up to $105 million of aggregate clinical milestone payments from strategic partners in 2026

[1] Includes an estimated $24 million of non-cash share-based compensation expense. [2] Includes cash, cash equivalents, and restricted cash.

Closing Remarks

Gene Kinney, Ph.D.

President and CEO

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

- Up to **$105 MILLION** in clinical milestones by YE 2026
  - Coramitug potential milestone after prespecified enrollment criteria are met in the Phase 3 trial
  - PRX019 potential milestone at time of BMS decision to further develop PRX019
- Obtained necessary shareholder approvals at an Extraordinary General Meeting and confirmed by the Irish High Court to support a share redemption program in 2026

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
- Exploring research collaborations and licensing deals for unpartnered programs
- Expanded scientific visibility with additional upcoming congress presentations from preclinical portfolio

Strategic priorities supported by $308.4 M in cash, cash equivalents, and restricted cash as of December 31, 2025

Q&A