Prothena Fourth Quarter and Year-End 2024 Financial Results

February 20, 2025

4Q and FY24 Earnings Call Agenda

Welcome	**Mark Johnson** | Vice President of Investor Relations
Opening Remarks	**Gene Kinney, Ph.D.** | President and CEO
R&D Update	**Chad Swanson, Ph.D.** | Chief Development Officer
Commercial Update	**Brandon Smith** | Chief Operating Officer
Financial Results	**Tran Nguyen** | Chief Financial Officer and Chief Strategy Officer
Closing Remarks	**Gene Kinney, Ph.D.** | President and CEO
Q&A Session	

Forward-Looking Statements

This overview contains forward-looking statements. These statements relate to, among other things, the sufficiency of our cash position to fund advancement of a broad pipeline; the continued advancement of our discovery, preclinical, and clinical pipeline, and expected milestones in 2025, 2026, and beyond, including potential launch for birtamimab; the treatment potential, designs, proposed mechanisms of action, and potential administration of birtamimab, PRX012, PRX123, prasinezumab, coramitug/PRX004, BMS-986446/PRX005, and PRX019; 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 birtamimab, PRX012, prasinezumab, coramitug, BMS-986446, and PRX019; the expected timing of reporting data from clinical trials of birtamimab, PRX012, coramitug, BMS-986446, and PRX019, including multiple data readouts starting in mid-2025 and continuing throughout the year from our ongoing Phase 1 clinical trials evaluating PRX012 and topline study results for our Phase 3 AFFIRM-AL clinical trial in 2Q 2025; Roche's plans to work with health authorities to determine next steps for prasinezumab; potential market penetration and opportunity for birtamimab; potential market exclusivity periods for birtamimab; and our anticipated net cash burn from operating and investing activities for 2025 and expected cash balance at the end of 2025; our estimated net loss and non-cash share-based compensation expense for 2025. 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 12, 2024, 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 2024. This overview is made as of February 20, 2025, and we undertake no obligation to update publicly any forward-looking statements contained in this overview as a result of new information, future events, or changes in our expectations.

Opening Remarks

Gene Kinney, Ph.D.

President and CEO

Our Mission Today

We are Focused on Delivering Life-Saving Therapies...

…for unmet medical needs caused by **diseases of protein dysregulation**



Robust R&D Pipeline

FOCUSED ON NEURODEGENERATIVE AND RARE PERIPHERAL AMYLOID DISEASES

PROGRAM/ INDICATION	PROTEIN TARGET	DISCOVERY	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	GLOBAL PARTNER[4]
Birtamimab SPA[1] ODD[2] Fast Track[3] *AL amyloidosis*	Light Chain (Kappa & Lambda)	AFFIRM-AL (Phase 3)					
Prasinezumab *Parkinson's disease*	α-Synuclein (C-terminus)	PASADENA (Phase 2) | PADOVA (Phase 2b)					Roche
Coramitug (PRX004) ODD[2] *ATTR-CM*	Transthyretin (misTTR)	Phase 2					novo nordisk
BMS-986446 (PRX005) *Alzheimer's disease*	Tau (MTBR)	Phase 2					Bristol Myers Squibb
PRX012 Fast Track[3] *Alzheimer's disease*	Aβ (N-terminus)	ASCENT (Phase 1)					
PRX019 *Neurodegeneration*	Undisclosed Target	Phase 1					Bristol Myers Squibb
PRX123 Fast Track[3] *Alzheimer's disease*	Aβ + Tau	IND cleared					
Undisclosed *AD in Down syndrome*	Undisclosed Target						

Modalities: mAb | Small Molecule | Vaccine

Aβ, Abeta; AD, Alzheimer's disease; mAb, monoclonal antibody.
[1] Primary endpoint of all-cause mortality at p≤0.10 under the Special Protocol Assessment (SPA) agreement with FDA; [2] Orphan Drug Designation granted by FDA & EMA; [3] FDA Fast Track designation;
[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

Long-term Value Creation: Wholly-Owned Programs

AL Amyloidosis

Treatment designed to address significant unmet needs for a rare disease population at high risk of early mortality

Birtamimab

- Novel anti-amyloid mechanism with potential to be preferred first-line, standard-of-care treatment
- Only treatment to observe an early survival benefit in Mayo Stage IV patients in RCT (VITAL Phase 3 trial[1,2])
- Confirmatory Phase 3 AFFIRM-AL trial ongoing per FDA SPA with unprecedented P ≤ 0.10

Phase 3 data expected in 2Q 2025

Multi-billion dollar global opportunity

Alzheimer's Disease Portfolio

Treatments designed to address unmet needs for millions of presymptomatic and early symptomatic AD patients

PRX012

- Potential best-in-class, once-monthly, single-injection, SC anti-Aβ mAb
- Phase 1 ASCENT trials ongoing with ~260 patients enrolled

PRX123

- Potential best-in-class, dual Aβ/tau vaccine designed for treatment and prevention
- IND cleared and Fast Track designation granted by FDA

Multiple data readouts mid-2025 through YE from the ongoing PRX012 Phase 1 trials

SOC = Standard of Care; RCT = Randomized Clinical Trial; mAb = monoclonal antibody; SC = subcutaneous; AD = Alzheimer's disease

[1] Post hoc analyses demonstrated a significant survival benefit with birtamimab and meaningful improvements in QoL and functional capacity in patients at high risk for early mortality (Mayo Stage IV at baseline). [2] Gertz MA, et al. Blood. 2023;142(14):1208-1218

Key: Rare Peripheral Amyloid | Neurodegeneration

Long-term Value Creation: Strategically Partnered Programs

Roche

Prasinezumab
Parkinson's disease

- Potential first-in-class anti-α-synuclein antibody
- Phase 2b PADOVA results suggest possible benefit in early Parkinson's
- Roche to work with health authorities to determine next steps

$755 million in total milestones, plus royalties, and U.S. co-promote option

$135 million paid-to-date

novo nordisk

Coramitug (PRX004)
ATTR-CM

- Potential first-in-class anti-amyloid antibody
- Novo Nordisk initiated Phase 2, ~99 patient trial ongoing; expected to complete in 1H 2025
- Phase 2 results to inform next steps in development

$1.23 billion in total milestones[1]

$100 million paid-to-date

Bristol Myers Squibb

BMS986446 (PRX005)
Alzheimer's disease

- Potential best-in-class anti-tau antibody
- BMS initiated Phase 2 TargetTau-1, ~475 patient trial; expected to complete in 2027

PRX019
Neurodegeneration

- Potential treatment of neurodegenerative diseases
- Prothena initiated Phase 1 trial in 4Q 2024; expected to complete in 2026

$1.55 billion in total milestones, plus royalties

$365 million paid-to-date

[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 (all development and sales milestones).

Key: Rare Peripheral Amyloid | Neurodegeneration

R&D Update

Chad Swanson, Ph.D.
Chief Development Officer

Birtamimab's Anti-Amyloid Mechanism Designed to Address the Unmet Need for Patients

AL Amyloidosis Pathogenic Pathway[1-4]



PLASMA CELL DYSCRASIA[1,2]



SOLUBLE TOXIC LIGHT CHAIN AGGREGATES

INSOLUBLE AMYLOID DEPOSITS



Current plasma cell directed treatments decrease light chain production[2]

Most patients today take some combination of daratumumab + CyBorD[3]

Birtamimab's transformative anti-amyloid MoA[3]:

- ✓ Clears AL amyloid deposits from organs/tissues
- ✓ Neutralizes toxic soluble aggregates

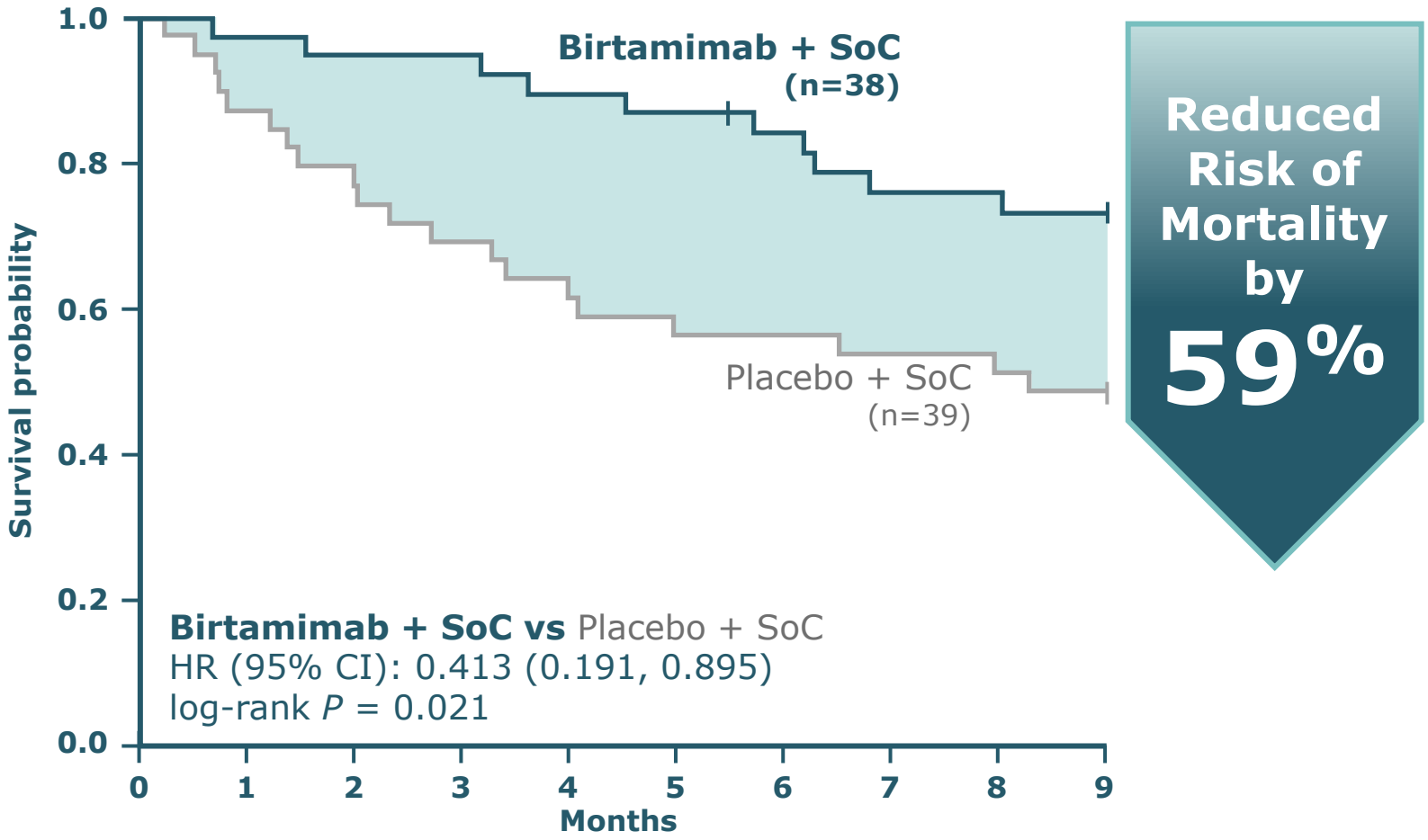
Birtamimab demonstrated significant survival benefit in Phase 3 VITAL post hoc analysis in Mayo Stage IV patients[5]

MOA=mechanism of action. Current standard of care treatments include daratumumab and cyclophosphamide, bortezomib, and dexamethasone (CyBorD).

[1] Koike H, Katsuno M. *Molecules*. 2021;26(15):4611. [2] Merlini G. *Am Soc Hematol* Educ *Program*. 2017;2017:1-12. [3] Palladini G, et al. Leukemia & Lymphoma. 2024;1–11. [4] Maritan M, Romeo M, Oberti L, et al. *J Mol Biol*. 2020;432:845-860. [5] Gertz MA, et al. *Blood*. 2023;142(14):1208-1218.

Previous Phase 3 VITAL Trial Demonstrated Significant Survival Benefit in Mayo Stage IV[1]

Time to All-Cause Mortality (ACM) in Mayo Stage IV Patients[2]



Post Hoc Analyses of Initial Phase 3 Randomized Trial (VITAL) in Mayo Stage IV Patients

Efficacy

- Unparalleled early and sustained survival benefit (HR = 0.413)
- Meaningful improvements in functional (6MWT) and quality of life (SF-36v2 PCS) endpoints, at 9 months ($P < 0.05$)

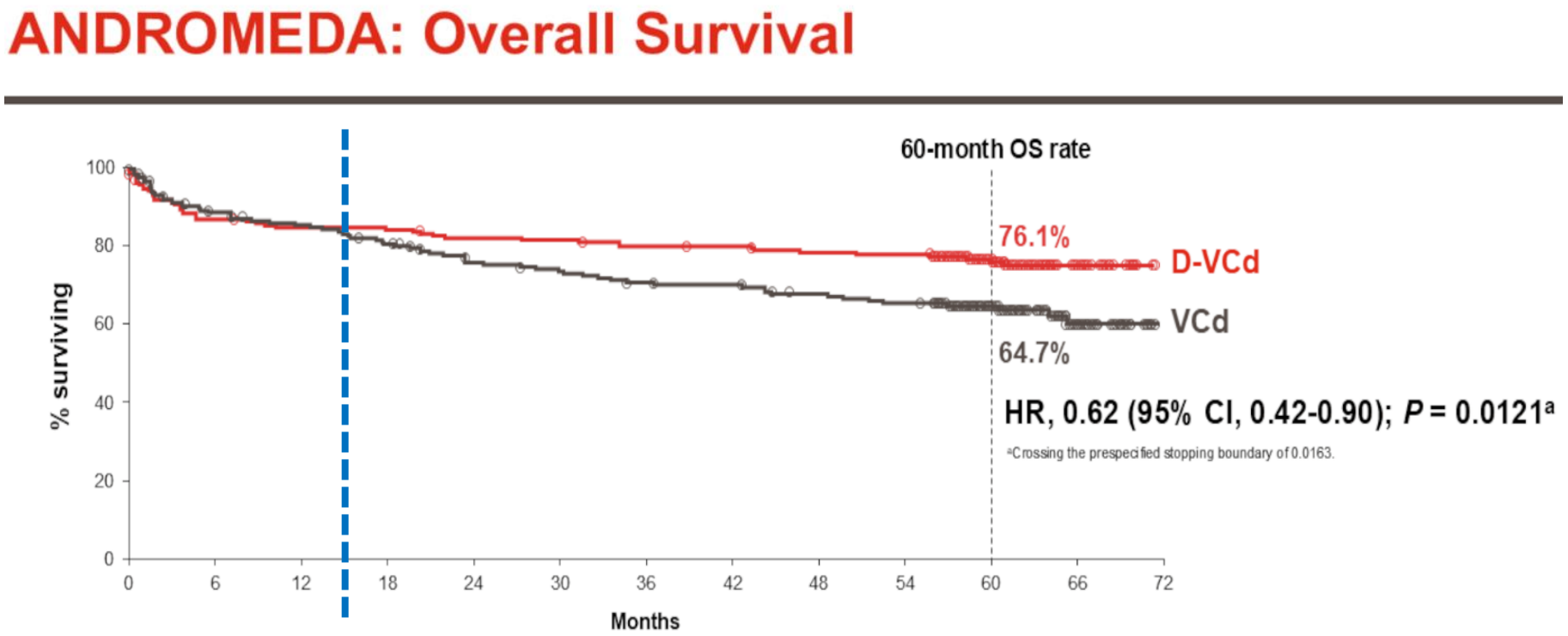
Safety

- Treatment-related grade ≥3 TEAE: 3% (birtamimab + SoC) vs 10% (placebo + SoC)
- Common treatment-emergent adverse event rate similar to placebo + SoC

[1] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218. Post hoc analyses demonstrated a significant survival benefit with birtamimab and significant improvements in QoL and functional capacity in patients at high risk for early mortality (Mayo Stage IV).
[2] Adapted from Gertz et al. *Blood*. 2023.

Unmet Need: Early Mortality

Phase 3 ANDROMEDA Study: *Daratumumab (D) + Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) in AL Amyloidosis Patients*[1]



Highlights urgent need to increase early survival for patients with cardiac involvement

[1] Adapted from presentation by E Kastritis at the 66th American Society of hematology (ASH) Annual Meeting & Exposition; December 7-10; San Diego, CA USA; dotted blue line and takeaway comment added by Prothena

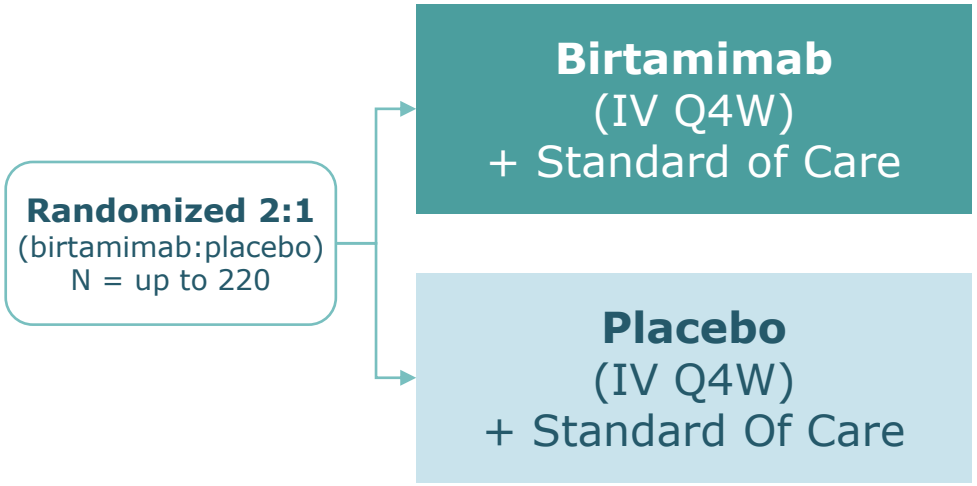
Birtamimab: Confirmatory Phase 3 AFFIRM-AL Trial Design

AFFIRM-AL Trial Overview (NCT04973137)[1]

Key Eligibility Criteria

- Confirmed diagnosis of AL amyloidosis
- Patients with significant cardiac involvement (Mayo Stage IV)

- ✓ **SPA Agreement**
- ✓ **FDA Fast Track Designation**
- ✓ **Orphan Drug Designation (FDA and EMA)**



Primary Endpoint

- Time to all-cause mortality

Secondary Endpoints

- 6MWT at month 9
- SF-36v2 PCS at month 9

SPA Agreement with FDA

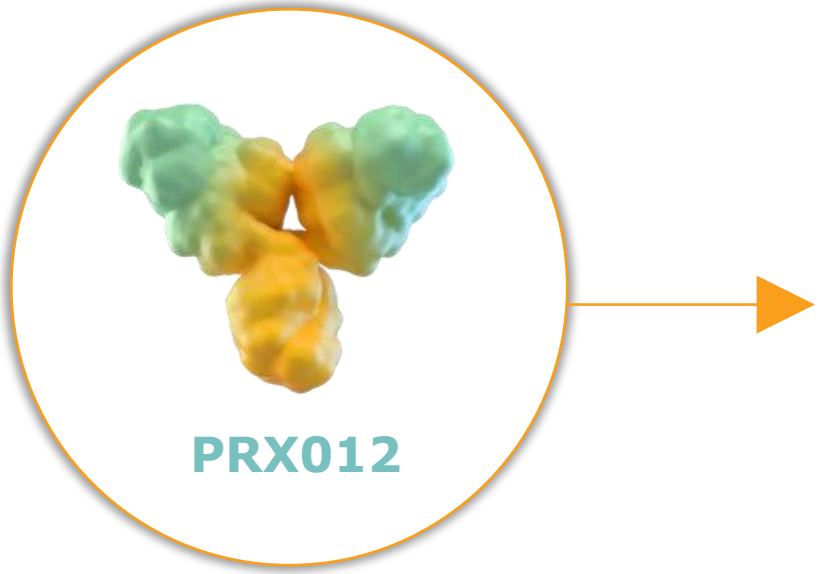
- Based on VITAL results, SPA agreement with FDA at unprecedented $P \leq 0.10$

Topline Results Expected 2Q 2025

Mayo Stage IV patients have all 3 biomarkers elevated: NT-proBNP (≥1,800 pg/mL); cTnT (≥0.025 ng/mL); dFLC (≥180 mg/dL)
Standard of care: bortezomib-containing chemotherapy (required) +/- daratumumab (at investigator's discretion).
[1] Gertz MA, et al. Birtamimab in patients with Mayo stage IV AL amyloidosis: Rationale for confirmatory affirm-AL phase 3 study. Presented at: The 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, USA.

PRX012: Leading a Paradigm Shift in the Treatment of Alzheimer's Disease

300+ iterative antibody design and optimization campaigns led to…



…potential best-in-class, subcutaneous, once-monthly anti-Aβ product candidate

Key Antibody Design Attributes

HUMANIZED IgG1 monoclonal antibody with low immunogenicity

TARGETS a key epitope at the N-terminus of Aβ protein

HIGH AFFINITY AND AVIDITY to Aβ for extended binding time and opsonization efficiency

SLOW OFF RATE / slow & steady dissociation translates to consistent target exposure and potential safety advantages

HIGHLY POTENT BINDING, designed for subcutaneous administration

PRX012 Phase 1 Multiple Dose Design

ascent-2 Trial Overview[1]

Key Inclusion Criteria

- Patients with early AD
- Ages 55 – 85 years
- Amyloid PET positive
- MMSE ≥ 18

Dose Escalation: "A" and "B" Cohorts[2,3]

Randomized 3:1
Active to Placebo
(n ~ 263)

- **45 mg A Cohort (n~32)** SC 6X Q4W
- **70 mg A Cohort (n~32)** SC 6X Q4W
- **200 mg A Cohort (n~32)** SC 6X Q4W
- **400 mg A Cohort (n~32)** SC 6X Q4W
- **45 mg B Cohort (n~12)** SC 6X Q4W
- **70 mg B Cohort (n~12)** SC 6X Q4W
- **200 mg B Cohort (n~12)** SC 6X Q4W

Dose Expansion

- **200 mg Expansion A Cohort (n~99)** SC 6X Q4W

Key Objectives

- Evaluate the safety, tolerability, and immunogenicity
- Effect on brain amyloid plaque
- Incidence of radiographic amyloid-related imaging abnormalities

Open-label Extension

- Patients may continue into an optional OLE for 12 months, an additional 12 doses (SC 12X Q4W)

ascent-3

[1] Presented at: The 2024 AAIC Annual Meeting; July 28, 2024; Philadelphia, PA.
[2] "A" dose cohorts include only APOε4 non-carrier or heterozygous AD patients
[3] "B" dose cohorts include only APOε4 homozygous AD patients
AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SC, subcutaneous injection; Q4W, every 4 weeks.

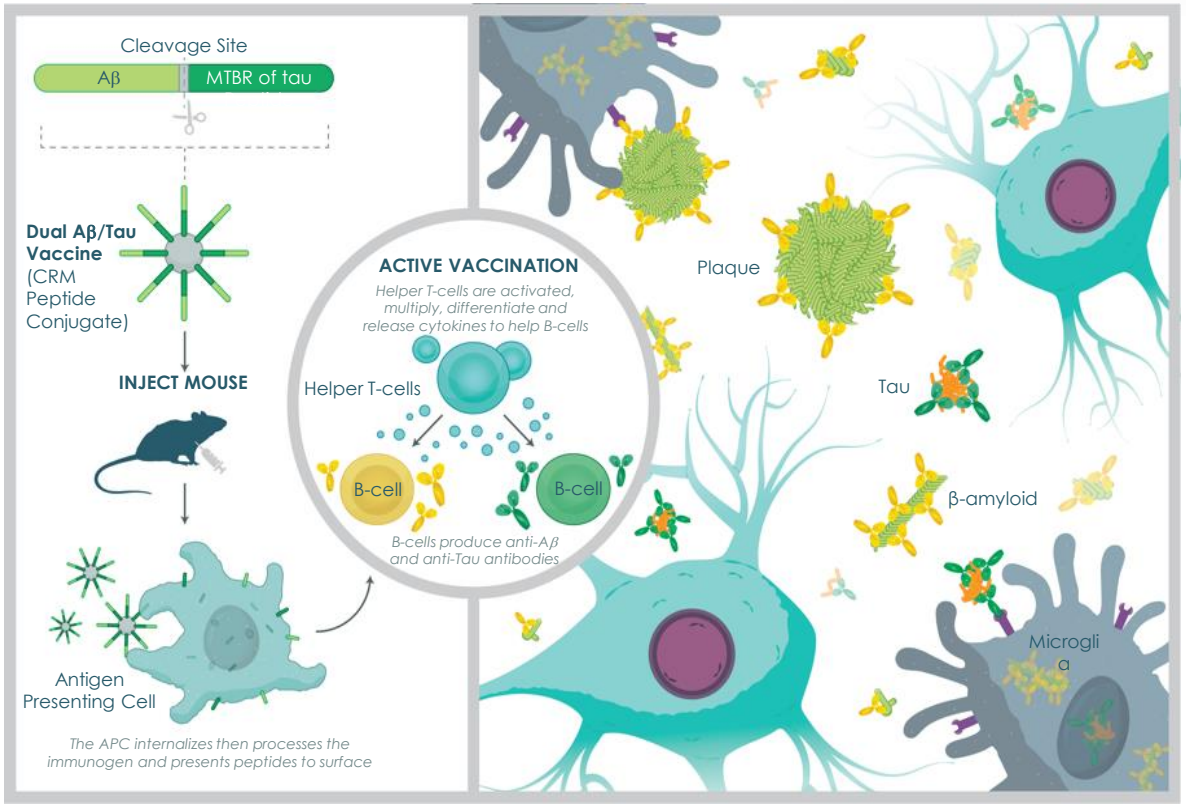
PRX123: Potential Best-in-class Dual Aβ/Tau Vaccine for the Treatment & Prevention of AD

Mechanism of Action: Need for Dual Targets

- PRX123 targets key epitopes within the N-terminus of Aβ and MTBR of tau designed to promote amyloid clearance and block the transmission of pathogenic tau
- Strong evidence from preclinical models suggests Aβ and tau act synergistically in the development of AD

Potential treatment & prevention

- Dual vaccine constructs were shown to generate balanced titers to Aβ and tau in non-human primates and Guinea pigs as measured by ELISA
- Immune animal sera reacted to Aβ and tau, induced Aβ phagocytosis, and blocked tau interaction with a key mediator of cellular release and cell-to-cell transmission



Fast Track Designation Granted by the FDA; IND Cleared

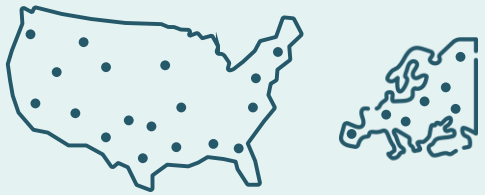
MTBR=Microtubule binding region

Commercial Update

Brandon Smith
Chief Operating Officer

Established Patient Population and Consolidated Prescriber Base Enable Birtamimab Market Penetration with Focused Launch

Established Patient Population[1-6]



Treated AL amyloidosis patients with cardiac involvement:

- US (~13K) and EU (~15K)

Mayo Stage IV patients:

- US (~5K) and EU (>5K)

Consolidated Prescriber Base[6]



- 75% US + EU patients primarily treated in ~500 amyloidosis COEs and specialty centers
- Birtamimab would be administered as an in-office infusion treatment
- Relatively favorable safety profile[7]

Regulatory and IP Positioning



- ✓ SPA agreement with FDA
- ✓ FDA Fast Track designation
- ✓ FDA/EMA: Orphan Drug Designation
- ✓ ≥12 years U.S. market exclusivity
- ✓ ≥10 years E.U. market exclusivity

Potential for very high peak penetration rates in Mayo Stage IV

EU: References the top 5 European markets including the United Kingdom, Germany, France, Spain and Italy.

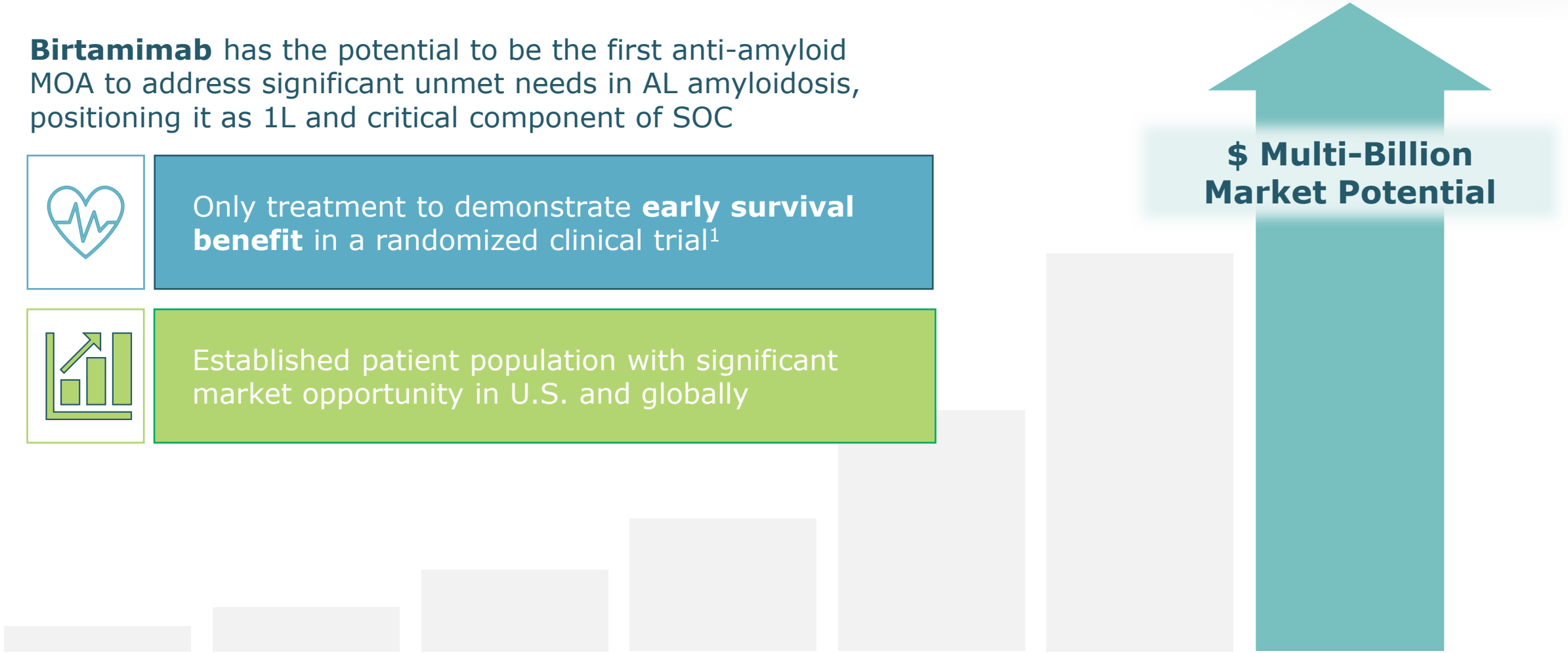
[1] Kumar S, Dispenzieri A, Lacy MQ, et al. *J Clin Oncol*. 2012;30(9):989-995. [2] Kyle RA, Gertz MA, Greipp PR, et al. *N Engl J Med.* 1997;336(17):1202-1207. [3] Kumar N, Zhang NJ, Cherepanov D, Romanus D, Hughes M, Faller DV. *Orphanet J Rare Dis*. 2022;17(1):278. [4] Merlini G, *Blood*. 2012; 119 (19): 4343–4345. [5] Gertz MA, et al. *Blood*. 2023;142(14):1208-1218. [6] Market research and data on file. Prothena Biosciences. Brisbane, CA. [7] Sanchorawala V, et al. Pooled analysis of safety from birtamimab Phase 1-3 studies in patients with light chain (AL) amyloidosis. Presented at the 65th ASH Annual Meeting; December 9-12, 2023; San Diego, CA, USA.

Birtamimab: Large Global Market Opportunity

Birtamimab has the potential to be the first anti-amyloid MOA to address significant unmet needs in AL amyloidosis, positioning it as 1L and critical component of SOC

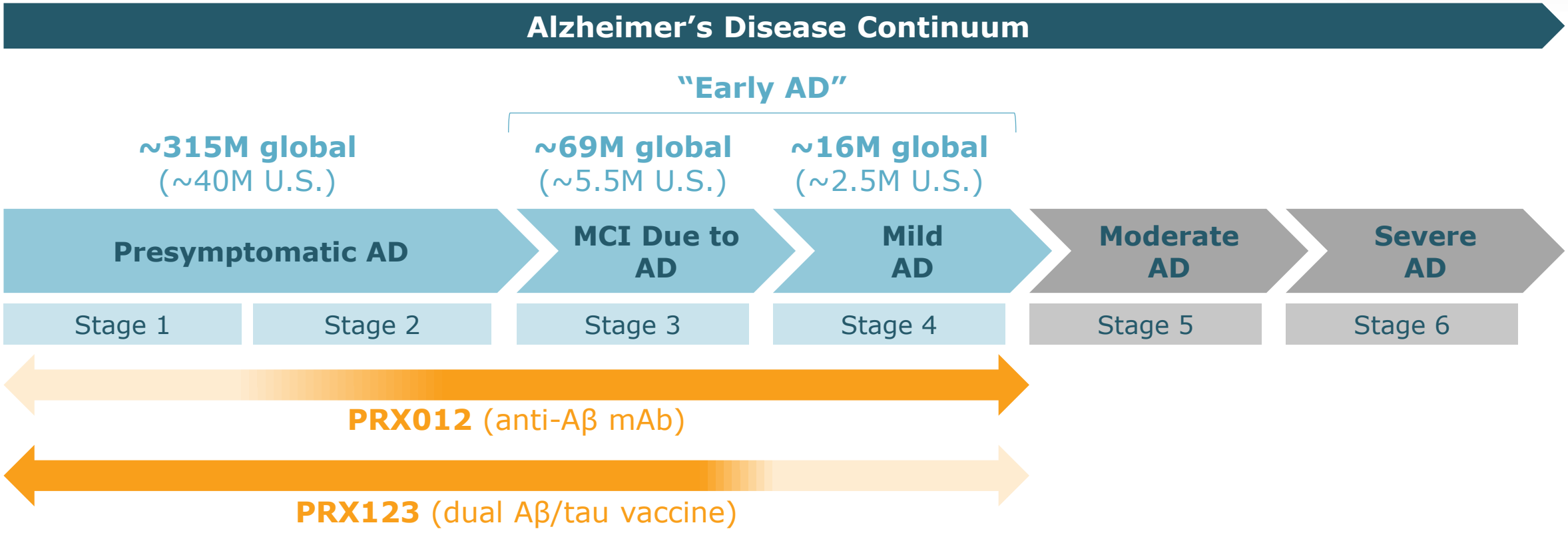
Only treatment to demonstrate **early survival benefit** in a randomized clinical trial[1]

Established patient population with significant market opportunity in U.S. and globally



[1] Gertz MA, et al. *Blood.* 2023;142(14):1208-1218; Post-hoc analyses demonstrated a significant survival benefit with birtamimab and meaningful improvements in QoL and functional capacity in patients at high risk for early mortality (Mayo Stage IV at baseline).
*graphics for illustrative purposes only

Alzheimer's Pipeline: Well-Positioned to Address Presymptomatic & Early AD Patient Population



Significant Unmet Need in a Massive and Growing Global AD Market

Sources: Gustavsson et al., 2022; Yuan et al., 2021 and UN estimates of populations (2020)
FDA Guidance on AD Diagnostic Criteria:
Stage 1: Patients with characteristic pathophysiological changes of AD but no evidence of clinical impact
Stage 2: Patients with characteristic pathophysiological changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures or subjective complaints of mild cognitive symptoms but no functional impairment
Stage 3: Patients with characteristic pathophysiological changes of AD, generally more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment
Stage 4-6: Patients with overt dementia, progressing through mild, moderate, and severe stages

Financial Results

Tran Nguyen
Chief Strategy Officer and Chief Financial Officer

2024 Actual vs. Guidance

	FY 2024 Actuals	FY 2024 Guidance	Commentary
Net Cash Used in Operating and Investing Activities	$150.3 M	$148 –160 M	✓ In-line
Net Loss	$122.3 M[1]	$120 –135 M	✓ In-line
Year End Cash Balance[2]	$472.2 M	$468 M	✓ In-line

[1] Includes non-cash share-based compensation expense of $46 million. [2] Includes cash, cash equivalents, and restricted cash

2025 Financial Guidance

	FY 2025 Guidance
Net Cash Used in Operating and Investing Activities	$168 – 175 M
Net Loss	$197 – 205 M[1]
Year End Cash Balance[2] (midpoint)	$301 M

[1] Includes an estimated $41 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

Meaningful Clinical Catalysts Ahead

Wholly-owned Programs

Birtamimab
AL Amyloidosis

2Q25	Topline results from confirmatory Phase 3 AFFIRM-AL with SPA agreement of $P \leq 0.1$ (NCT04973137)

PRX012 and PRX123
Alzheimer's disease portfolio

Mid-25 to YE25	Multiple data readouts starting in mid-2025 and continuing throughout the year from PRX012 Phase 1 ASCENT clinical trials
2025	Update on PRX123 clinical development

Partnered Programs

Coramitug (PRX004)
ATTR-CM

2025	Completion and results of ongoing Phase 2 trial (NCT05442047)

Prasinezumab
Parkinson's disease

2025	Roche to determine next steps

BMS-986446 (PRX005)
Alzheimer's disease

2027	Completion of ongoing Phase 2 trial (NCT06268886)

PRX019
Neurodegeneration

2026	Completion of ongoing Phase 1 trial

Q&A