Prothena Fourth Quarter and Year-End 2023 Financial Results

February 15, 2024

4Q and FY23 Earnings Call Agenda

Welcome	**Mark Johnson** | VP of Investor Relations
Opening Remarks	**Gene Kinney, Ph.D.** | President and CEO
Pre-Commercial Planning	**Brandon Smith** | Chief Operating Officer
Clinical Progress	**Hideki Garren, M.D., Ph.D.** | Chief Medical 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 expected timing of reporting data from clinical trials of PRX012, birtamimab, prasinezumab, and NNC6019, including any substantive updates regarding our ongoing Phase 1 clinical trial evaluating PRX012 in 2024 and any topline study results for our Phase 3 AFFIRM-AL clinical trial between 4Q 2024 and 2Q 2025; the treatment potential, designs, proposed mechanisms of action, and potential administration of birtamimab, PRX012, prasinezumab, and NNC6019/PRX004; potential indications (including prevalence) and attributes of epitopes and antibodies we have identified in our programs; our anticipated net cash burn from operating and investing activities for 2024 and expected cash balance at the end of 2024; our estimated net loss and non-cash share-based compensation expense for 2024; plans for ongoing and future clinical trials of birtamimab, PRX012, PRX123, prasinezumab, NNC6019/PRX004, and BMS-986446/PRX005; and the continued advancement of our discovery, preclinical, and clinical pipeline, and expected milestones in 2024, 2025, and beyond. 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 2, 2023, 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 2023. We undertake no obligation to update publicly any forward-looking statements contained in this press release 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	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	COMMERCIAL RIGHTS
Birtamimab *AL amyloidosis*	Kappa & Lambda Light Chain	AFFIRM-AL (Phase 3 clinical trial, under SPA[1] agreement with FDA)					prothena
Prasinezumab *Parkinson's disease*	a-Synuclein (C-terminus)	PASADENA (Phase 2 clinical trial) | PADOVA (Phase 2b clinical trial)					prothena Roche
NNC6019 (PRX004) *ATTR amyloidosis*	Transthyretin (misTTR)	Phase 2 clinical trial					novo nordisk
BMS-986446 (PRX005) *Alzheimer's disease*	Tau (MTBR)	Phase 1 clinical trial					Bristol Myers Squibb
PRX012 *Alzheimer's disease*	Aβ (N-terminus)	ASCENT-1 & ASCENT-2 (Phase 1 clinical trial)					prothena
PRX123 *Alzheimer's disease*	Aβ + Tau	IND cleared					prothena
PRX019 *Neurodegeneration*	Undisclosed Target	IND cleared					Bristol Myers Squibb
TDP-43 *ALS*	TDP-43						Bristol Myers Squibb
Undisclosed *AD in Down syndrome*	Undisclosed Target						prothena

References: mAb | Small Molecule | Vaccine | Undisclosed

[1]Primary endpoint of all-cause mortality at p≤0.10 under the Special Protocol Assessment (SPA) agreement with FDA; Aβ, Abeta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; mAb, monoclonal antibody

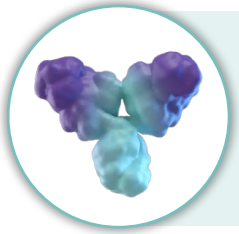
Potential Upcoming Clinical Readouts

	WHOLLY OWNED	STRATEGICALLY PARTNERED
NEURODEGENERATIVE DISEASES	**PRX012** *Alzheimer's disease* ascent CLINICAL TRIALS • Potential best-in-class, next generation, subcutaneous anti-Aβ antibody • Phase 1 ASCENT-1 & ASCENT-2 trials ongoing; expect to update in 2024	**Prasinezumab** *Parkinson's disease* Roche • Potential first-in-class anti-α-synuclein antibody • Phase 2b PADOVA trial ongoing (conducted by Roche); (NCT04777331) • Topline results expected in 2024
RARE PERIPHERAL AMYLOID DISEASES	**Birtamimab** *AL Amyloidosis* AFFIRM-AL • Potential best-in-class amyloid depleter antibody • Confirmatory Phase 3 AFFIRM-AL trial ongoing; (NCT04973137) • Topline results expected between 4Q24 and 2Q25	**NNC6019** (PRX004) *ATTR Amyloidosis* novo nordisk® • Potential first-in-class amyloid depleter antibody • Phase 2 trial ongoing (conducted by Novo Nordisk); (NCT05442047) • Topline results expected in 1H 2025

Pre-Commercial Planning

Brandon Smith
Chief Operating Officer

Birtamimab: Differentiated Approach to AL Amyloidosis



Birtamimab
AL Amyloidosis

Anti-Amyloid Mechanism of Action

- Clears insoluble AL amyloid deposits that cause vital organ dysfunction and failure[1]
- Neutralizes toxic soluble amyloid species circulating in the blood[2]

Addresses Acute Unmet Need in Mayo Stage IV AL Amyloidosis

- Patients with significant cardiac involvement are at highest risk for early mortality[3,4]
- Currently approved treatments have no survival advantages in Mayo Stage IV[5,6]

Ongoing Phase 3 AFFIRM-AL (NCT04973137)

- Trial designed per FDA Special Protocol Assessment (SPA) with unprecedented significance level of $P \leq 0.10$
- Primary Endpoint: Time to all-cause mortality
- Topline results expected between 4Q 2024 and 2Q 2025

VITAL Phase 3 Post Hoc Analyses Showed Significant Survival Benefit in Mayo Stage IV[7]

- 59% relative risk reduction of all-cause-mortality (HR 0.413, $P = 0.021$)
- Rapid response with clear and sustained separation by month 2
- Significantly improved physical function and quality of life

[1] Murine version of birtamimab, 2A4; Wall et al., PLOS ONE, 2012, data on file. [2] Renz M, et al. Amyloid. 2016;23:168-177.
[3] Palladini G, et al. 2019 *Haematologica*; [4] Kumar S, et al. 2012 *J Clin Oncol.*; [5] Gertz M, et al. 2021 *Blood.* [Abstract and Poster]; [6] Kumar S, et al. 2012 *J Clin Oncol*; [7] Gertz et al. 2023 *Blood*.

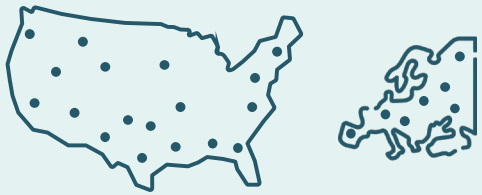
Defined Patient Population and Consolidated Prescriber Base Enable Birtamimab Market Penetration with Focused Launch

Significant Unmet Need



- Urgent need for immediate intervention in advanced patients
- Median overall survival <6 months[1,2]

Defined Patient Population[2-6]



- 60 – 120 K Mayo Stage IV patients globally
- >20 K Mayo Stage IV patients across major global markets
  - US (4 K); EU (5 K)

Consolidated Prescriber Base



- ~75% US and EU Mayo Stage IV patients primarily treated in ~500 Amyloidosis specialty centers[7]
- Patients are primarily treated by hematologists and cardiologists

Focused Opportunity and Commercial Approach

[1] Levin M, et al. Available at: https://www.myamyloidosisteam.com/resources/stages-of-amyloidosis; [2] Kumar S, et al. 2012 *J Clin Oncol.;* [3] Kumar N, et al. 2022 *Orphanet J Rare Dis*; [4] Quock T, et al. 2018 *Blood Advances*; [5] Gertz M, et al. 2023 *Blood*; [6] Shimazaki. 2018 *The Japanese Journal of Clinical Hematology*; [7] Estimates based on US/EU/UK Market Research, LEK Analysis.

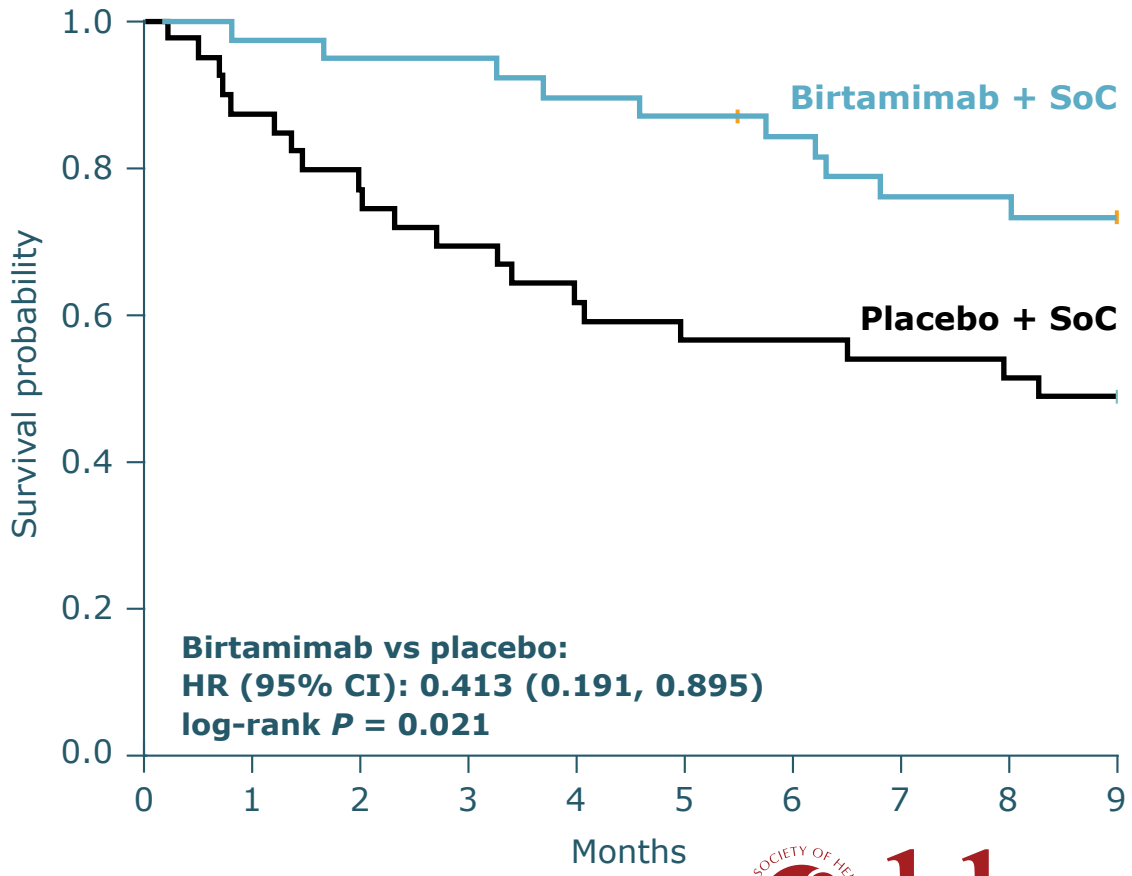
Clinical Progress

Hideki Garren, M.D., Ph.D.
Chief Medical Officer

Significant Survival Benefit in Mayo Stage IV AL Amyloidosis in Randomized Clinical Trial[1]

- Post hoc analyses of initial Phase 3 randomized clinical trial (VITAL):
  - **Survival benefit in Mayo Stage IV** (74% vs. 49% for placebo)
  - Meaningful **improvements** in health-related **functional** endpoints (6MWT) and **quality of life** (SF-36v2) at 9 months ($P < 0.05$)
- Treatment-emergent adverse event rate similar to placebo

Survival Rates of Birtamimab vs Placebo for Mayo Stage IV AL Amyloidosis Patients[2]



SoC = Standard of Care.

[1] Post-hoc analyses demonstrated a significant survival benefit with birtamimab in patients at the highest risk for early mortality (Mayo Stage IV);

[2] Gertz et al. Birtamimab plus standard of care in light chain amyloidosis: the phase 3 randomized placebo-controlled VITAL trial. *Blood* 2023.

Birtamimab: Confirmatory Phase 3 AFFIRM-AL Trial Design

FDA Fast Track Designation

Orphan Drug Designation (FDA and EMA)

FDA Special Protocol Assessment (SPA)

AFFIRM-AL

SPA agreement with FDA

- Based on VITAL results in this population, SPA agreement with FDA at unprecedented significance level of $P \leq 0.10$

Timeline

- Topline results expected between 4Q 2024 and 2Q 2025

Key Eligibility Criteria

- Consistent with VITAL study
- Newly diagnosed and treatment naïve
- Confirmed diagnosis of AL amyloidosis with cardiac involvement
- Mayo Stage IV

Randomize 2:1 N = 150

Birtamimab (IV q28d) + SoC n = 100

Placebo (IV q28d) + SoC n = 50

Primary Endpoint

- Time to All-Cause Mortality

Secondary Endpoints

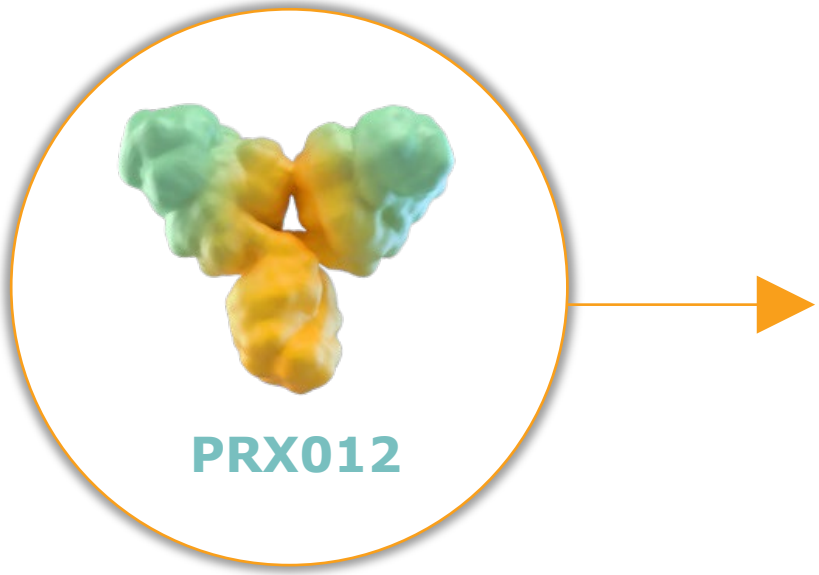
- 6MWT
- SF-36v2 PCS

Interim analysis when ~50% events have occurred

A Study to Evaluate the efficacy and Safety of birtamimab in Mayo Stage IV Patients with AL Amyloidosis (AFFIRM-AL). ClinicalTrials.gov Identifier: NCT04973137.

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 SAD Design

SINGLE ASCENDING DOSE (SAD) COHORTS

Healthy Volunteer Cohorts

- Age 20 – 45 years

70 mg	200 mg
n= ~8 (3:1)	n= ~8 (3:1)

Early Alzheimer's Disease Cohorts

- Ages 60 – 85 years
- Amyloid PET positive
- MMSE ≥ 18

70 mg	200 mg	400 mg
n= ~8 (3:1)	n= ~8 (3:1)	n= ~8 (3:1)

Trial Design | ascent-1

- Phase 1, randomized 3:1, double-blind, placebo-controlled, single ascending dose trial
- 1 subcutaneous dose of PRX012
- Evaluate the safety, tolerability, immunogenicity, and pharmacokinetics of PRX012 in healthy volunteers and patients with Alzheimer's disease

MMSE: Mini Mental State Examination.

PRX012 Phase 1 MAD Design

MULTIPLE ASCENDING DOSE (MAD) COHORTS

Early Alzheimer's Disease "A" Cohorts

- Ages 55 – 85 years
- Amyloid PET positive
- MMSE ≥ 18
- "A" cohorts: APOε4 non-carrier or heterozygous

45 mg	70 mg	200 mg	400 mg
n= ~32 (3:1)	n= ~32 (3:1)	n= ~32 (3:1)	n= ~32 (3:1)

Early Alzheimer's Disease "B" Cohorts

- Ages 55 – 85 years
- Amyloid PET positive
- MMSE ≥ 18
- "B" cohorts: APOε4 homozygous

45 mg	70 mg	200 mg
n= ~12 (3:1)	n= ~12 (3:1)	n= ~12 (3:1)

Trial Design | ascent-2

- Phase 1, randomized 3:1, double-blind, placebo-controlled, MAD trial
- Q4W (once monthly) subcutaneous dosing for 6 doses total (6 months)
- Evaluate the safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of PRX012 in patients with Alzheimer's disease
- After first 6 doses, patients may continue in an open-label extension for 6 additional doses (Q4W) of PRX012

MMSE: Mini Mental State Examination.

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

Prasinezumab
Parkinson's Disease

Anti-α-synuclein Antibody

- Preferentially binds to aggregated α-synuclein to reduce pathogenic spread and decrease synuclein pathology[1-4]

Rapidly Growing Parkinson's Disease Patient Population

- **10 million** patients globally[5]
- Fastest increasing neurodegenerative disease[6]

Worldwide Collaboration with Roche

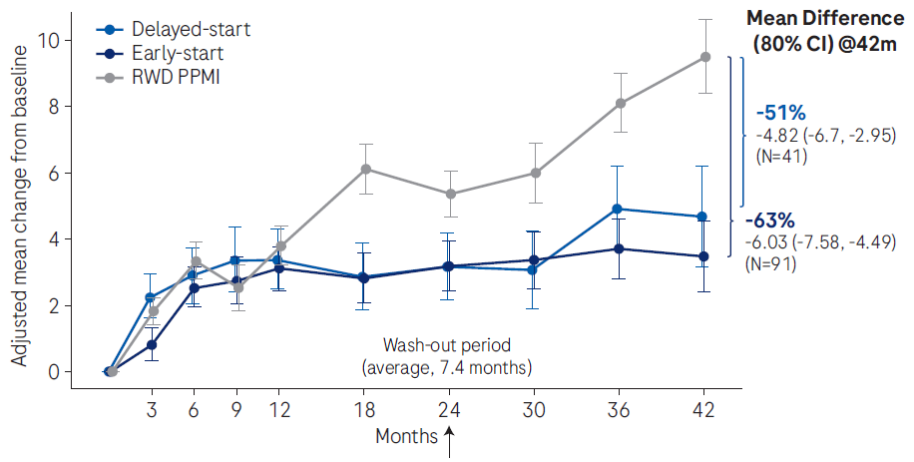
- Up to $620 million in additional milestones
- $135 million paid-to-date
- Up to double-digit teen royalties

Ongoing Phase 2b PADOVA (NCT04777331)

- N = 586 early Parkinson's disease patients
- Primary Endpoint: Time to confirmed motor progression event
- Topline results expected in 2024

Phase 2 PASADENA OLE Showed Slowing of Motor Progression vs. Matched RWD PPMI Cohort

3-year change from baseline in MDS-UPDRS Part III OFF score[7]



MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; RWD: Real World Data; PPMI: Parkinson's Progression Markers Initiative.

[1] Jankovic J et al. JAMA Neurol. 2018; 75:1206–1214. [2] Masliah E, et al. Neuron. 2005; 46:857–868; [3] Masliah E, et al. PLoS ONE. 2011; 6:e19338; [4] Games D, et al. J Neurosci. 2014; 34:9441–9454
[5] Parkinson's Foundation. Understanding Parkinson's. Statistics; [6] GBD 2015 Neurological Disorders Collaborator Group (2017) Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 16, 877-897. [7] Pagano et al. *PASADENA Open-Label Extension: Results After an Additional Year of Treatment with Prasinezumab*. Presented at the International Congress of Parkinson's Disease and Movement Disorders (MDS), Copenhagen, Denmark. August 27–31, 2023.

NNC6019: Potential First-in-Class Treatment for ATTR Amyloidosis

NNC6019
ATTR Amyloidosis

Differentiated Depleter Mechanism of Action

- Inhibits fibril formation and specifically binds to pathogenic TTR[1]
- Uniquely designed for patients at high risk of early mortality due to amyloid deposition

Rare Transthyretin amyloidosis (ATTR) Patient Population

Worldwide Collaboration with Novo Nordisk

- $1.13 billion in additional milestones
- $100 million paid-to-date

Ongoing Phase 2 (NCT05442047)

- N = 99 ATTR-CM patients, 3 arms
- Participants receive IV infusion Q4W of 10 mg/kg or 60 mg/kg of NNC6019 or placebo added to SOC until week 52
- Primary Endpoints: Change from baseline in 6MWT and in NT-proBNP levels
- Trial has fully recruited patients; topline results expected in 1H 2025

Phase 1 Results

- All six dose levels of NNC6019 found to be generally safe and well-tolerated
- Positive results on neuropathy and cardiac function
- Data supportive of advancing to Phase 2

[1] Higaki JN et al. Amyloid, 2016; Preclinical studies of mPRX004, the murine form of PRX004.

Financial Results

Tran Nguyen
Chief Strategy Officer and Chief Financial Officer

2023 Actual vs. Guidance

	FY 2023 Actuals	FY 2023 Guidance	Commentary
Net Cash Used in Operating and Investing Activities	$136.7 M	$148 –161 M	Favorable
Net Loss	$147.0 M[1]	$153 –171 M	Favorable
Year End Cash Balance[2]	$621.0 M	$600 M	Favorable

[1] Includes non-cash share-based compensation expense of $40.9 million. [2] Includes cash, cash equivalents, and restricted cash

2024 Financial Guidance

	FY 2024 Guidance
Net Cash Used in Operating and Investing Activities	$208 – 225 M
Net Loss	$229 – 255 M[1]
Year End Cash Balance[2] (midpoint)	$405 M

[1] Includes an estimated $51 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

Upcoming Potential Milestones

TRANSFORMATIONAL PERIOD AHEAD

Wholly-owned Programs	
Birtamimab for potential treatment of AL amyloidosis	
4Q24 – 2Q25	❑ Confirmatory Phase 3 AFFIRM-AL topline data (NCT04973137)
PRX012 for potential treatment of Alzheimer's disease	
2024	❑ Ongoing Phase 1 trial update
PRX123, dual Aβ/Tau vaccine for potential treatment and prevention of Alzheimer's disease	
2024	❑ Phase 1 timeline update
Partnered Programs	
Prasinezumab for potential treatment of Parkinson's disease (Roche)	
2024	❑ Phase 2b PADOVA clinical trial topline data (NCT04777331)
NNC6019/PRX004 for potential treatment of ATTR-cardiomyopathy (Novo Nordisk)	
1H25	❑ Topline Phase 2 data (NCT05442047)
BMS-986446/PRX005 for potential treatment of Alzheimer's disease (Bristol Myers Squibb)	
2024	❑ Bristol Myers Squibb to initiate a Phase 2 clinical trial

Q&A