

prothena®

CORPORATE OVERVIEW

May 2023

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 2023, 2024, and beyond; our goal to continue building a biology-directed engine targeting protein dysregulation; our potential to advance, initiate, and complete IND enabling studies for our discovery and preclinical programs; the treatment potential, designs, proposed mechanisms of action, and potential administration of birtamimab, prasinezumab, NNC6019 (formerly PRX004), PRX005, PRX012, and PRX123; potential indications and attributes of epitopes and antibodies we have identified in our programs; plans for future clinical studies of birtamimab, prasinezumab, NNC6019, PRX005, PRX012, and PRX123 (including the filing of an IND application); and the expected timing of reporting data from clinical studies of birtamimab, prasinezumab, NNC6019, PRX005, and PRX012. 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 May 4, 2023 and discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. This overview is made as of May 4, 2023, and 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.

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

NEUROSCIENCE

Alzheimer's disease (AD)

50 million

People worldwide living with Alzheimer's disease or other dementias[1]

7th

Leading cause of death in United States[5]

$1 trillion

In annual US healthcare costs by 2050 from AD and other dementias[7]

Parkinson's disease (PD)

10 million

People living with PD worldwide[2]

Fastest increasing

Neurodegenerative disease[6]

$52 billion

In overall economic burden in the US[8]

RARE PERIPHERAL AMYLOID DISEASES

Amyloid light chain amyloidosis (AL)

60,000-120,000

Patients with Mayo Stage IV AL amyloidosis globally[3]

5.8 months

Median overall survival in Mayo Stage IV patients with AL amyloidosis

Transthyretin amyloidosis (ATTR)

450,000

Estimated number of patients worldwide with wtATTR or ATTRv[4]

2.08 years

Median overall survival New York Heart Association class III patients with ATTR cardiomyopathy[9]

[1] Patterson C. World Alzheimer Report 2018, [2] Parkinson's Foundation. Understanding Parkinson's. Statistics, [3] Kyle et al Mayo Clin Proc, 2019, [4] Gonzalez-Lopez et al, 2017; Mauer et al, 2016; Gagliardi et al, 2018, [5] 2021 Alzheimer's Disease Fact Sheet, National Institute on Aging, NIH, [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] Alzheimer's Association Facts and Figures Report 2022, [8] The Economic Burden of Parkinson's Disease - The Michael J. Fox Foundation, [9] Kumar et al 2012, Pinney J et al. 2013; Gonzalez-Lopez E et al. 2017

Our Team has Pioneered Multiple Scientific Advances in Protein Dysregulation

OUR LEGACY INCLUDES FOUNDATIONAL DISCOVERIES IN THE UNDERSTANDING OF ALZHEIMER'S DISEASE

1986
Athena Neurosciences founded

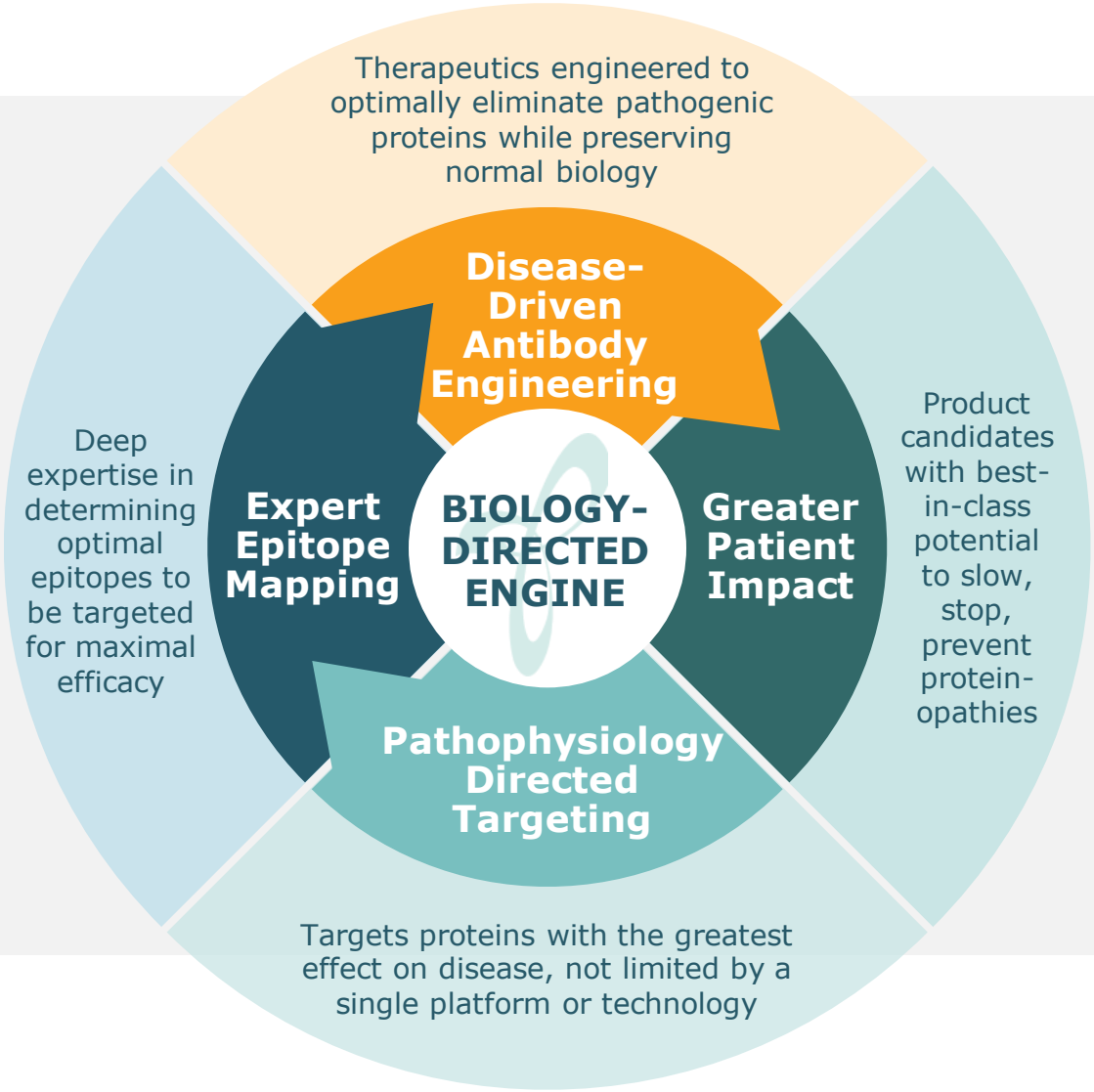
1996
Athena acquired by Elan

2012
Prothena spins-out from Elan with a wholly-owned drug discovery platform

- **Pioneered fundamental discoveries** elucidating the roles amyloid, gamma secretase and beta secretase play in disease[1]
- **First to show** that anti-Ab immunotherapy prevented and cleared amyloid plaques in the brains of transgenic mice[2]
- **First to demonstrate plaque clearance** by an n-terminus antibody in brains from AD patients[3]
- **Discovered biological cause of ARIA** and vascular recovery following anti-Ab immunotherapy[4]
- **Developed PRX012, best-in-class anti-Ab product candidate,** with ~10X greater binding potency vs. aducanumab[5]

[1] Games, D., Adams, D., Alessandrini, R. et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein. 1995 Nature; [2] Schenk, D., Barbour, R., Dunn, W. et al. Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. 1999 Nature; [3] Rinne et al, C-BiP PET assessment of change in fibrillar amyloid-b load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending –dose study, 2010, [4] Zago W, Schroeter S, Guido T, et al. Vascular alterations in PDAPP mice after anti-Aβ immunotherapy: Implications for amyloid-related imaging abnormalities. 2013 Alzheimers Dement. [5] PRX012 Induces Microglia-Mediated Clearance of Pyroglutamate-Modified and -Unmodified Aß in Alzheimer's Disease Brain Tissue presented at AAIC 2021

Our Biology-Directed Engine Propels Prothena's Progress Across our Broad Pipeline



Multiple Clinical Programs Ongoing

Wholly-owned Phase 3 program

Two partnered Phase 2 programs

Two Phase 1 programs

Five potential new INDs from Biology-Directed Engine in the next five years

Strong Collaborations Established

Collaborations with Bristol Myers Squibb, Novo Nordisk[1] and Roche

Leveraging our Rare Disease Portfolio to Support Commercial Buildout

Transition into a fully-integrated commercial biotech through our rare disease portfolio

[1]In July 2021 Novo Nordisk acquired NNC6019 (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.

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 study, under SPA[1] agreement with FDA)					prothena
Prasinezumab *Parkinson's disease*	a-Synuclein (C-terminus)	PASADENA (Phase 2 study) | PADOVA (Phase 2b study)					prothena / Roche
NNC6019 (PRX004) *ATTR amyloidosis*	Transthyretin (misTTR)	Phase 2 study ongoing					novo nordisk
PRX005 *Alzheimer's disease*	Tau (MTBR)	Phase 1 study ongoing					Bristol Myers Squibb
PRX012 *Alzheimer's disease*	Aβ (N-terminus)	Phase 1 study ongoing					prothena
PRX123 *Alzheimer's disease*	Aβ + Tau	Lead prioritized					prothena
PRX019 *Neurodegeneration*	Undisclosed Target	Lead prioritized					Bristol Myers Squibb
TDP-43 *ALS*	TDP-43						Bristol Myers Squibb
Undisclosed *AD in Down syndrome*	Undisclosed Target						prothena

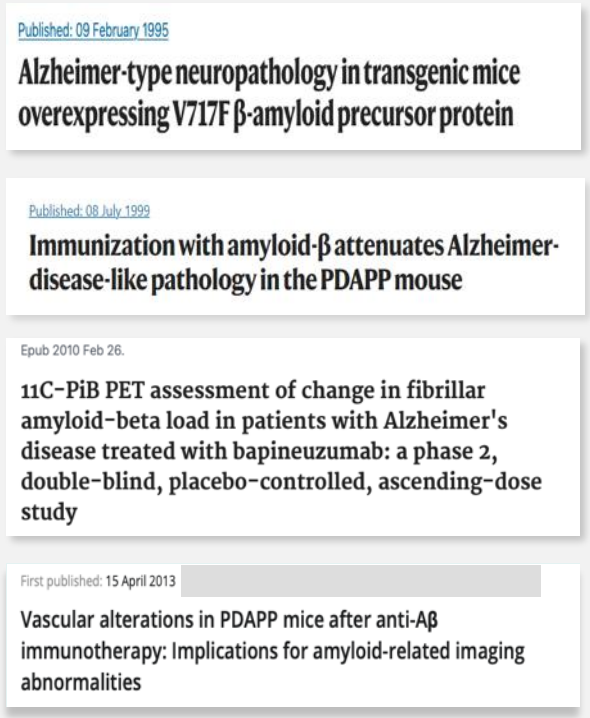
References: mAb | Small Molecule | Vaccine | Undisclosed

[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

Alzheimer’s Disease

Our Legacy Drives Our Vision to Transform the Care of Alzheimer's Disease

With unparalleled protein dysregulation expertise…



OUR LEGACY [1-4]

…We're uniquely positioned to address Alzheimer's Disease with a best-in-class portfolio

PRX012, anti-Aβ product candidate with potential best-in-class, **highly potent binding**; designed for improved patient access via **subcutaneous** delivery[5]

Phase 1

PRX005, anti-tau candidate, with **potential to reduce pathogenic tau spread**[6]

Phase 1

PRX123, dual Aβ/tau vaccine designed for **treatment and prevention**

IND Expected 2023

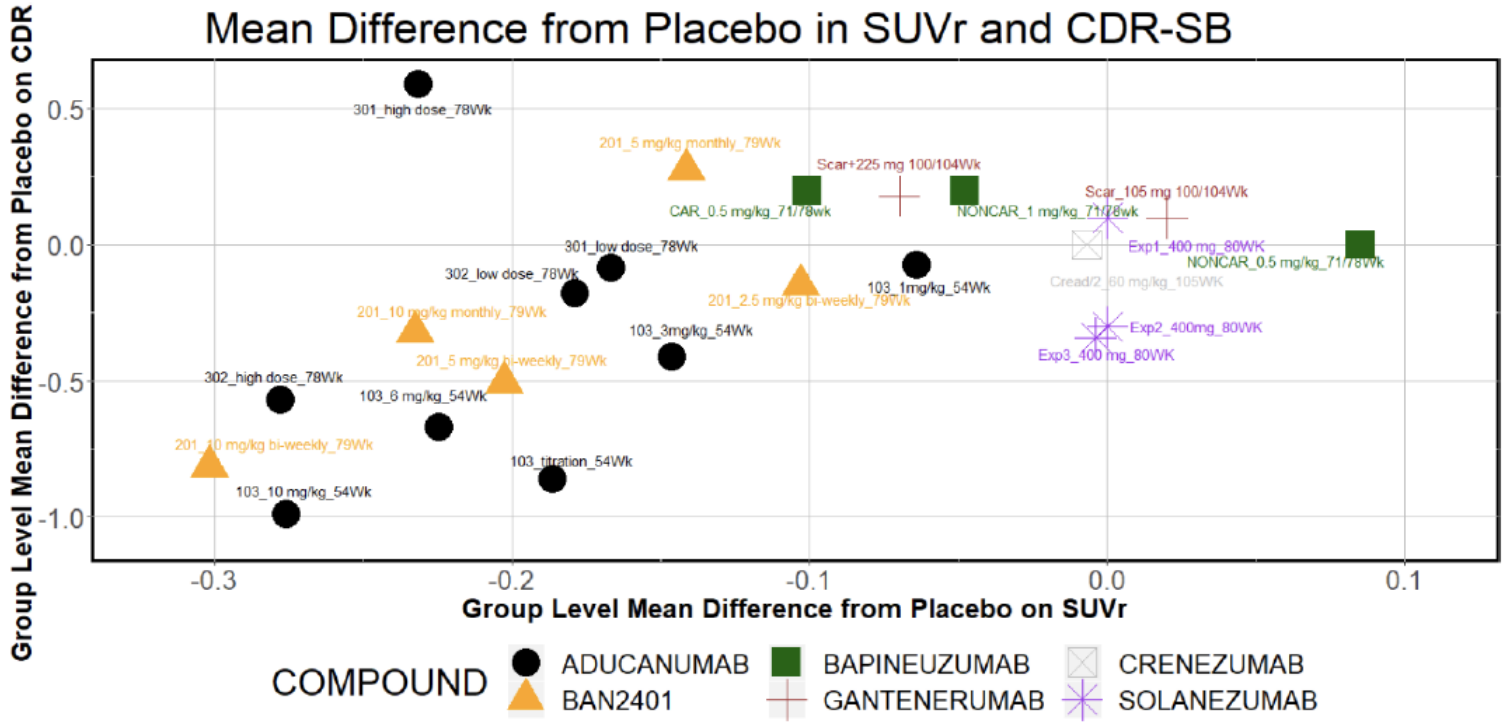
TODAY

[1] Games D, et al.1995 Nature; [2] Zago W, et al. 2013 Alzheimers Dement; [3] Schenk D, et al. 1999 Nature; [4] Rinne, et al. 2010 Lancet Neurol; [5] Skov M, et al. Preclinical data available at: https://tinyurl.com/3zzpmbxh; [6] Dolan P. Preclinical data available at: https://tinyurl.com/3kf7pvnd.

Today's Clinical Science Validates the Mechanism Designed by Us

2020 US FDA ANALYSIS:

Abeta has been validated as a disease modifying target in AD[1,2]



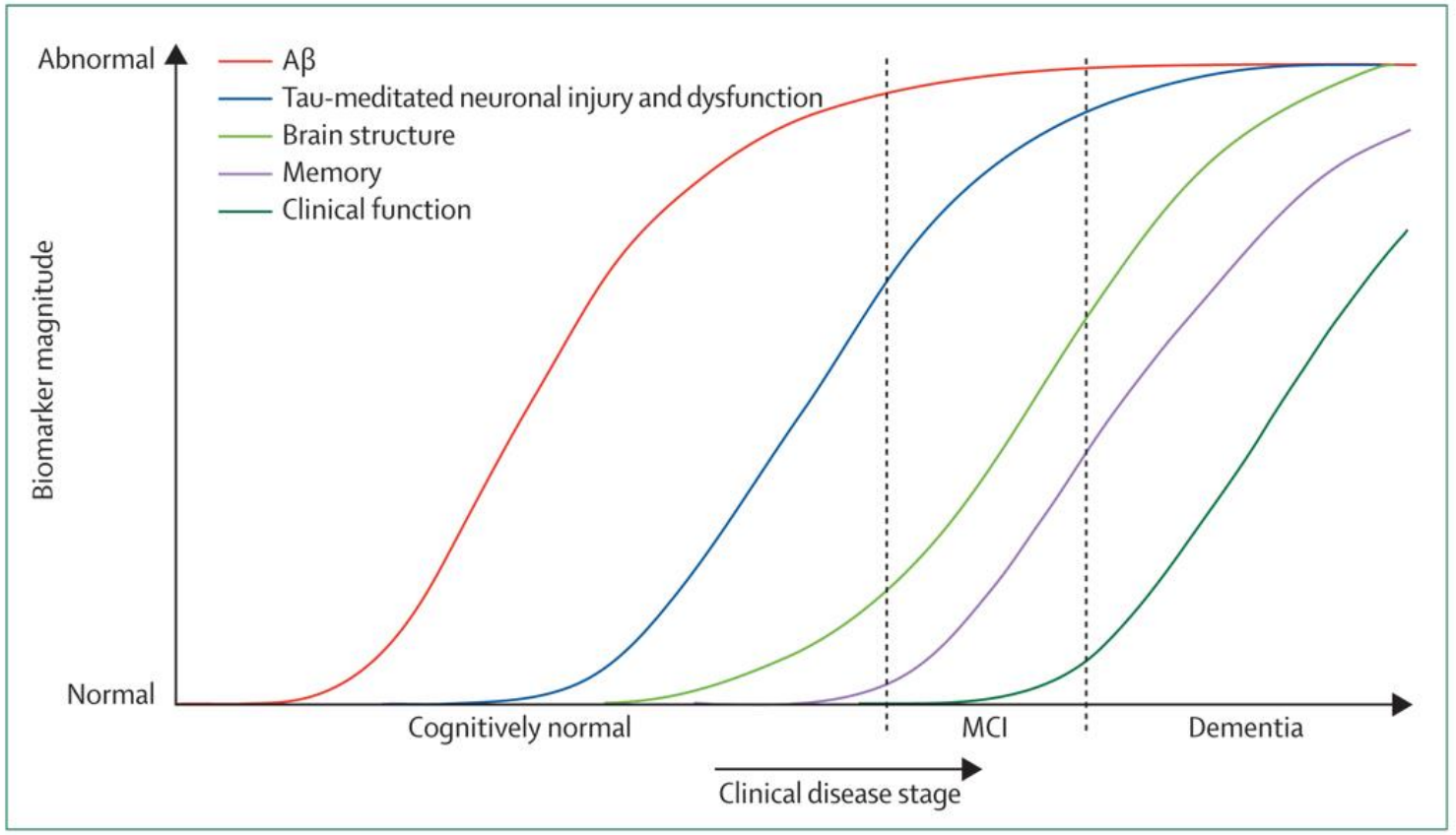
CDR, Clinical Dementia Rating Scale; SUVr, Standardized Uptake Value Ratio.

[1] ADUHELM [prescribing information]. Cambridge, Massachusetts: Biogen Inc; October 2022; [2] US FDA. Clinical Pharmacology and Pharmacokinetics Review(s). July 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000ClinPharm_Redacted.pdf.

Targeting Alzheimer's Where it Matters

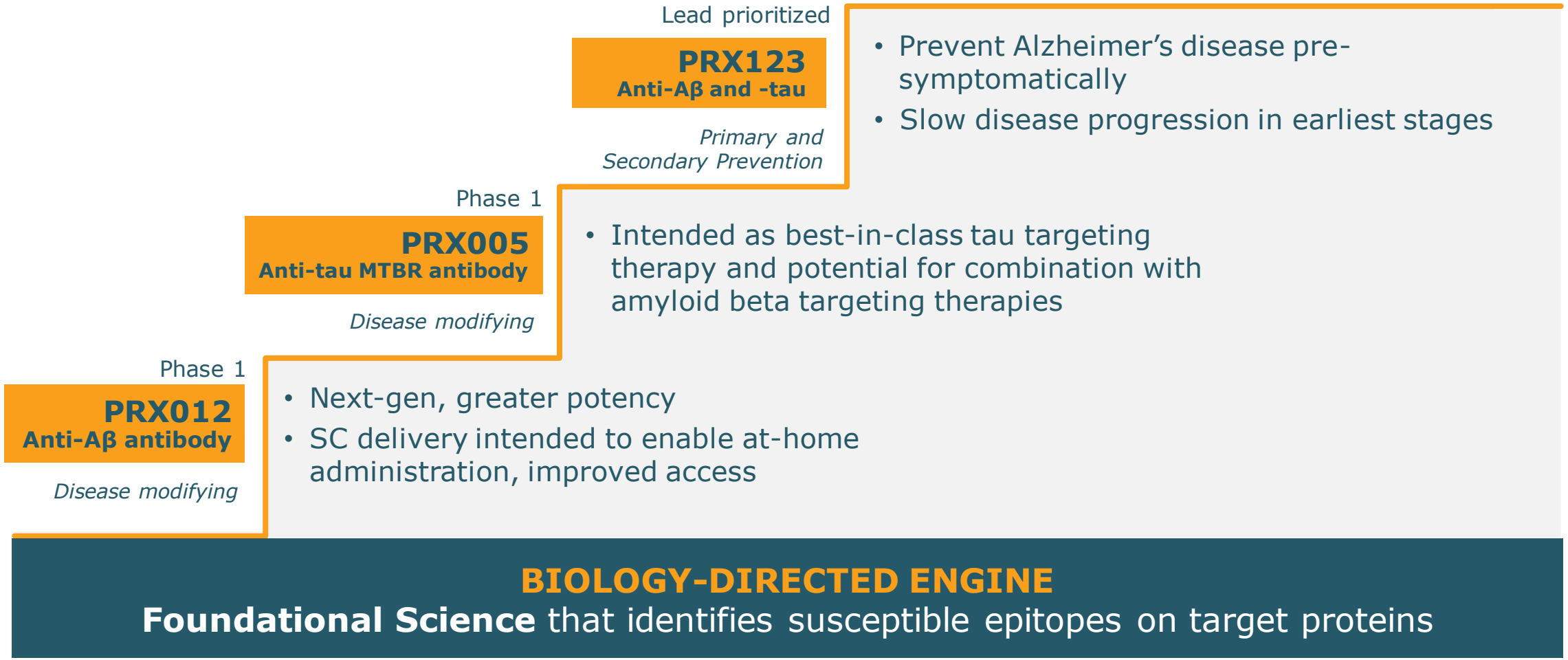
CHANGING THE TREATMENT PARADIGM THROUGH OUR BIOLOGY-DIRECTED ENGINE

Dynamic biomarkers of the Alzheimer's pathological cascade*



*Jack, Clifford et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, 2010 NIH Public Access

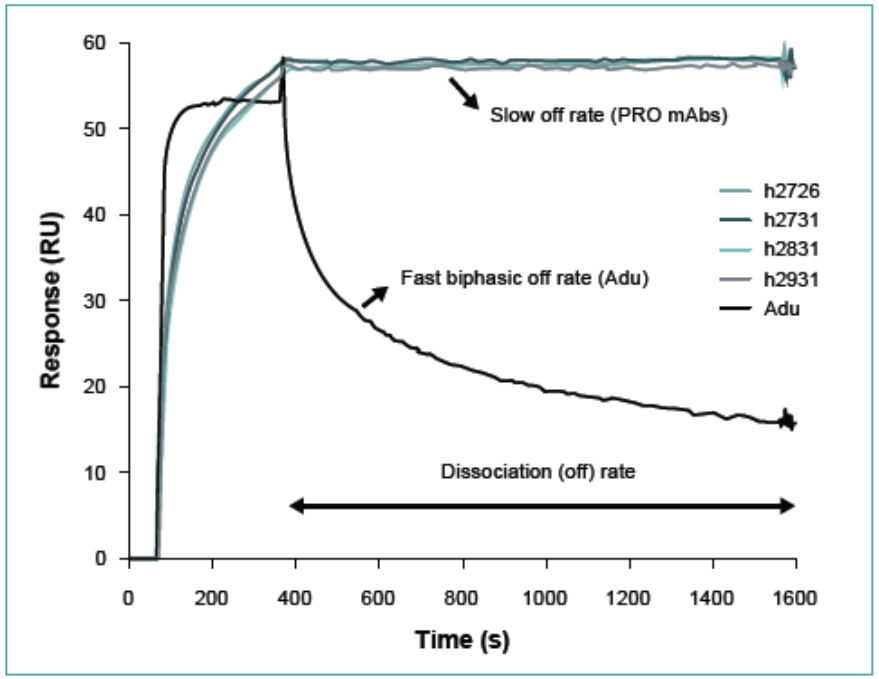
That's Why We're Innovating for Today and Tomorrow —With a Pipeline Designed to Evolve With the Science



PRX012

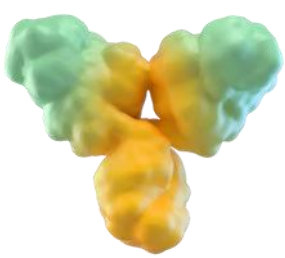
Alzheimer’s Disease

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



~10X greater binding potency vs. aducanumab

300+ iterative antibody design and optimization campaigns led to…



PRX012

…best-in-class anti-Aβ product candidate

HUMANIZED IgG1 monoclonal antibody with low immunogenicity

TARGETS all N-terminal epitopes of Aβ protein

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

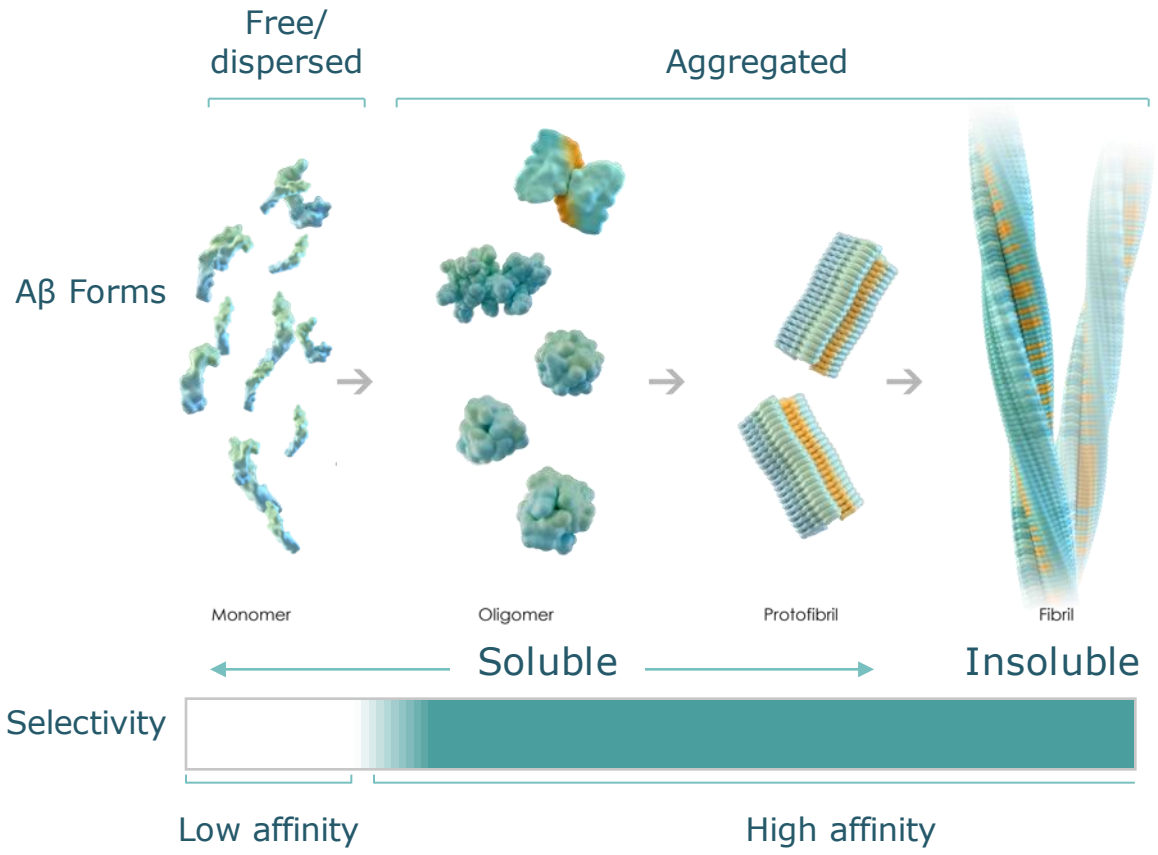
SLOW OFF RATE / slow & steady dissociation translates to consistent target exposure and potential safety advantages

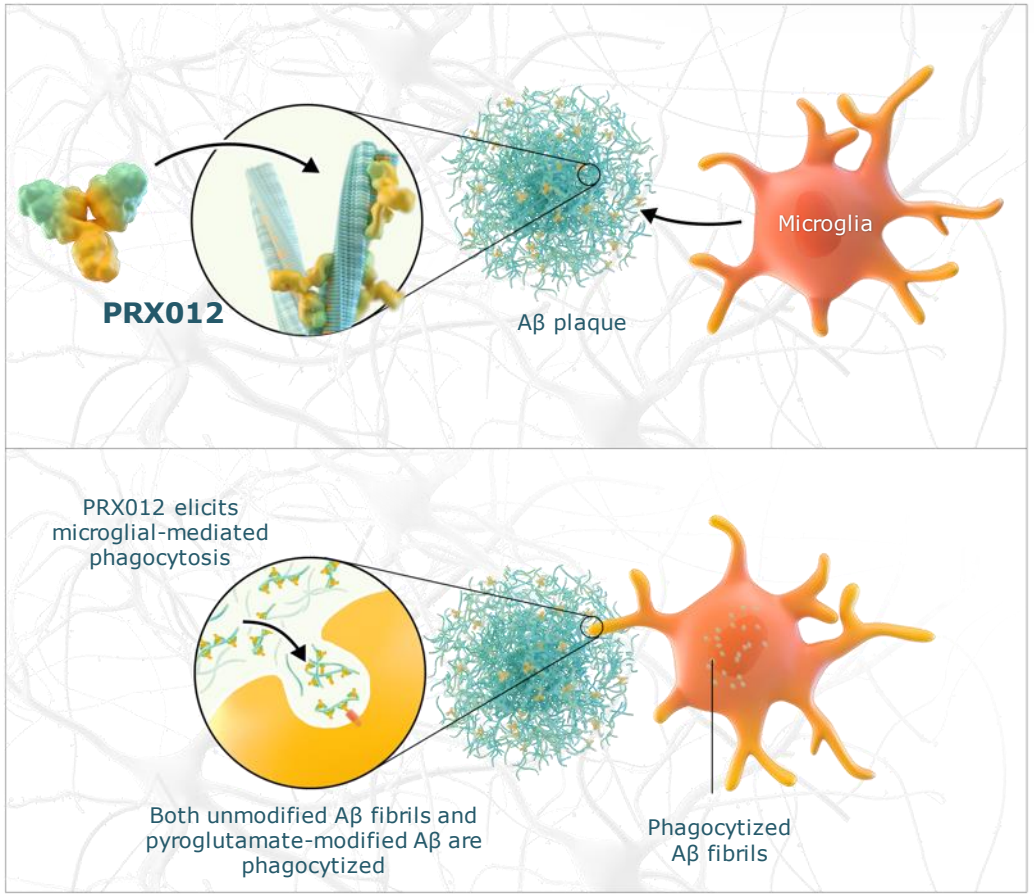
HIGHLY POTENT BINDING, designed for subcutaneous administration

Adu, aducanumab; PRO, Prothena.

PRX012: Promotes Comprehensive Clearance of Amyloid Plaques and Neutralization of Oligomers

Designed to target and clear all toxic aggregated forms of Aβ





Microglia recognize and engulf PRX012-opsonized Aβ fibrils

Note: Based on preclinical data. Visuals not to scale.

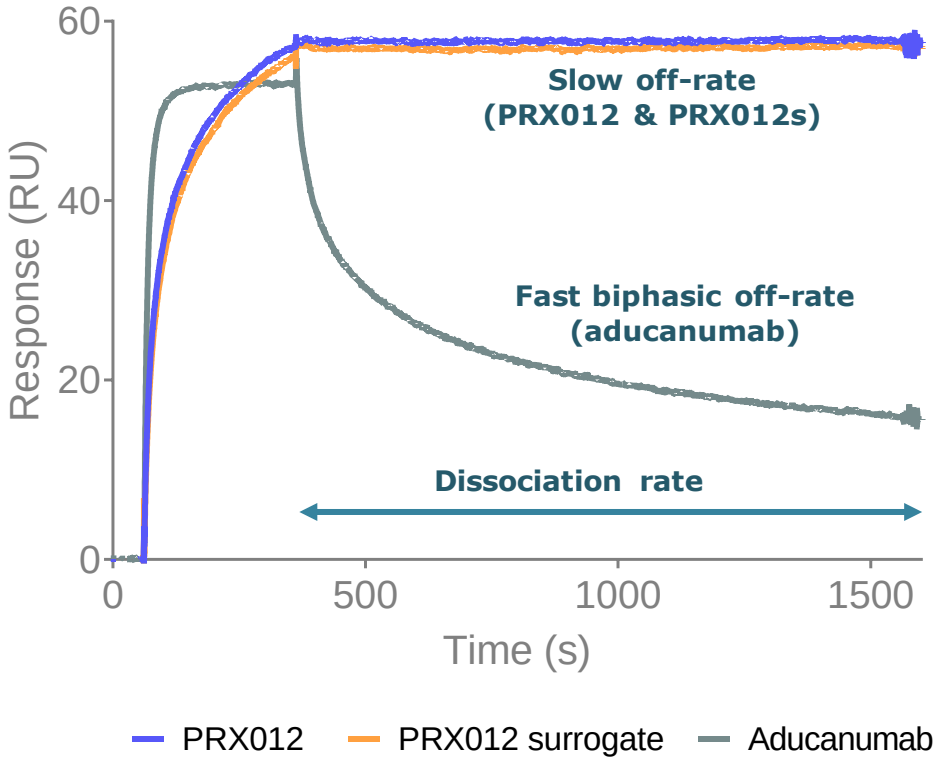
Translating Patient Needs Into Antibody Engineering

PATIENT-CENTRIC DESIGN STRATEGY FOR PRX012

	TARGET PROFILE	ANTIBODY DESIGN ATTRIBUTES	POTENTIAL IMPLICATIONS FOR PATIENTS
Maintain From First Generation Antibodies	**Effectively clear soluble and insoluble aggregated amyloid**	• N-terminal directed	• Associated with efficacy
Innovations to Support Patient Needs	**Low-volume subcutaneous (SC) delivery**	• High binding potency • Stability in high concentrations for single syringe use	• Simplicity for patient and caretaker • More convenient • Increases access • Minimizes treatment burden • Less time-consuming • Infrequent dosing • Potential for at-home use
	Designed for monthly dosing	• Optimize pharmacokinetic profile and immunogenicity • Optimal bioavailability	
	Treatment outside infusion centers	• Optimal biophysical qualities	

PRX012 and Surrogate Demonstrate Equivalent Potent Binding Affinity for Aβ

Surface Plasmon Resonance (SPR) Aβ Fibrils



Affinity for Aβ Species

Compound	Fibril/Plaque	N3pE-Aβ
PRX012	0.070[a]	>67[b]
PRX012s	0.054[a]	>67[b]

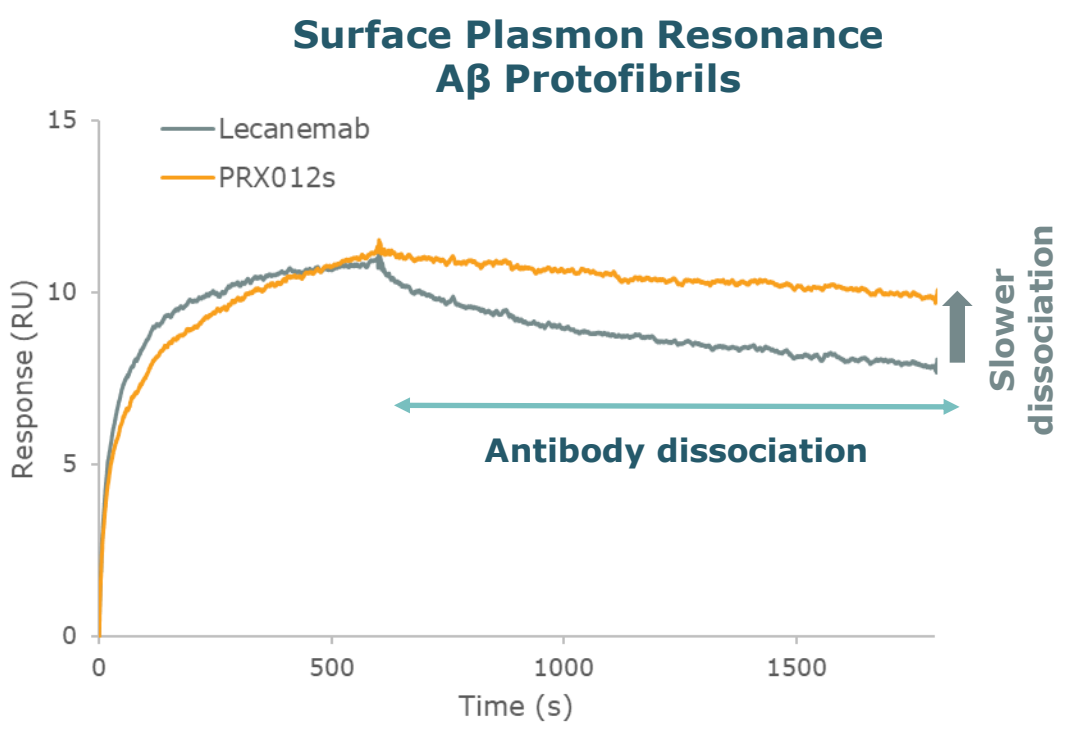
Data represent K_D values from SPR[a] (nM) or IC50 from ELISA[b] (nM).

- **Potent binding strength of PRX012 and its surrogate (PRX012s) to fibrillar Aβ are equivalent, both demonstrating a very slow rate of dissociation**
  - PRX012 and PRX012s share >99.5% sequence homology
- **How does binding to protofibrils compare?**



Aβ, amyloid beta; N3pE-Aβ, pyroglutamate-modified Aβ; SPR, surface plasmon resonance.
PRX012s: "Surrogate" is defined as an antibody with >99.5% homology, the same binding epitope and equivalent binding profile to different forms of Aβ where directly compared. Aducanumab was generated from a publicly available sequence.

PRX012s Binds Aβ Protofibrils With Very High Affinity



SPR protofibril binding was performed as described in Tucker et al., 2015[1]

Antibody	Relative Affinity (K_{D1})
Lecanemab[1] (Tucker et al., 2015)	1.97 nM
Lecanemab*	1.91 nM
PRX012s	0.0975 nM

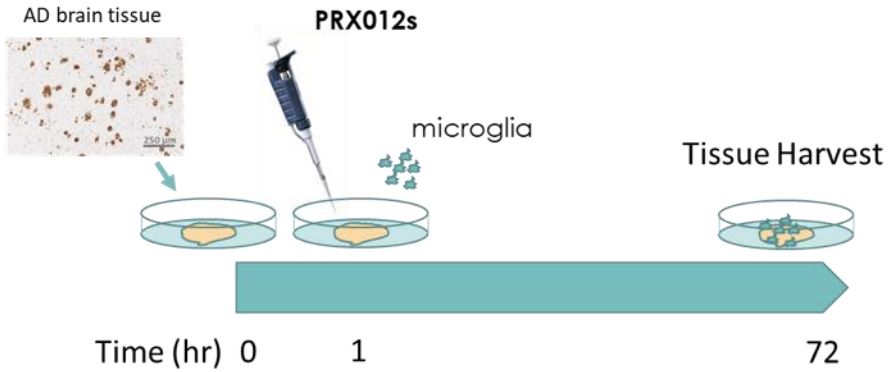
SPR Binding Kinetics

	ka1 (1/Ms)	kd1 (1/s)	K_{D1}
Lecanemab[1] (Tucker et al., 2015)	6.60E+05	1.30E-03	1.97E-09
Lecanemab*	1.80E+05	3.42E-04	1.91E-09
PRX012s	1.63E+05	1.59E-05	9.75E-11

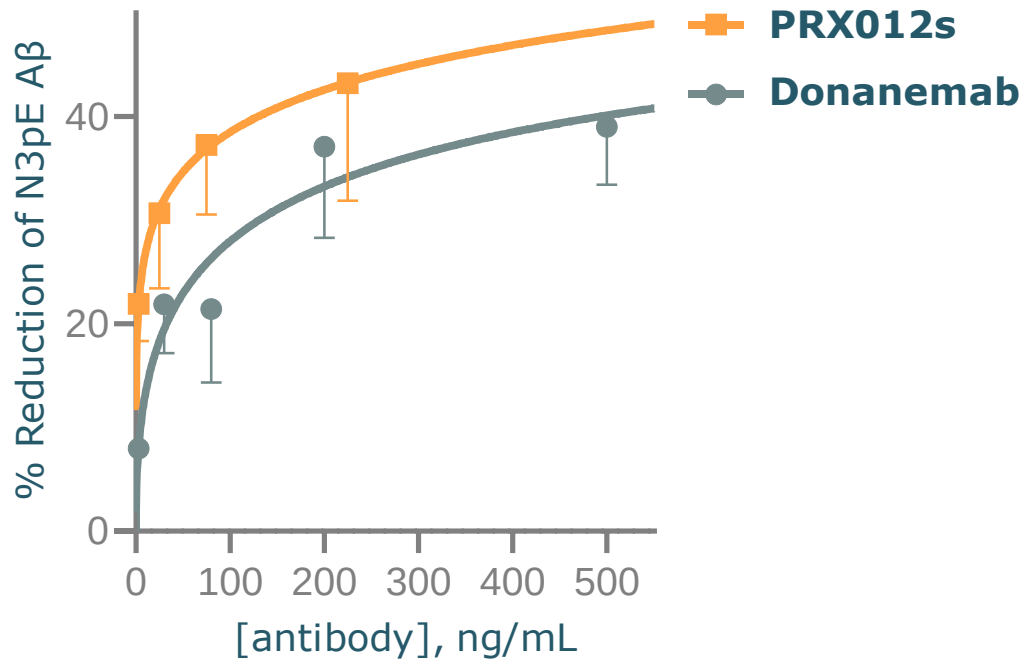
- **PRX012s binds to Aβ protofibrils with approximately 20-fold greater affinity than lecanemab when tested under the same conditions**
- **Greater affinity is driven largely by a slower binding dissociation**

Aβ, amyloid beta; ka, association constant; kd, dissociation constant; KD, equilibrium constant; SPR, surface plasmon resonance.
*Determined by Prothena.
[1] Tucker S, et al. *J Alzheimers Dis.* 2015;43:575-588.
Lecanemab and donanemab were generated from publicly available sequences.

PRX012s Induced Potent and Robust Clearance of Pyroglutamate-modified Aβ



	Study Conditions
Tissue	Post-mortem AD brain tissue (same donor used for all conditions)
Treatment	PRX012s, donanemab, or IgG1 isotype control
Microglia	Primary mouse microglia (800,000 cells/mL)
Culture time	72 hours at 37°C

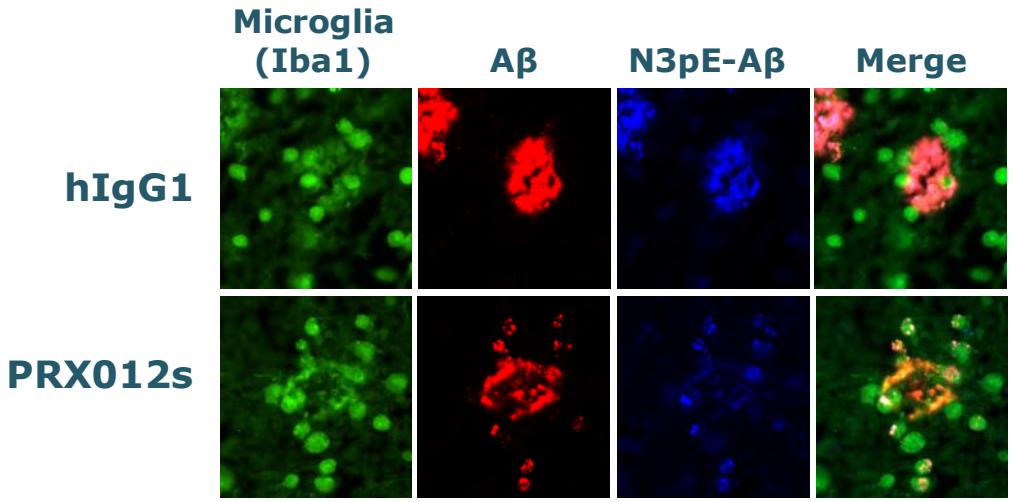


- **PRX012s facilitates concentration-dependent clearance of pyroglutamate-modified Aβ (N3pE-Aβ) at concentrations that may be relevant for PRX012 clinical exposure**
- **PRX012s clears equivalent or more N3pE-Aβ at ~3–8x lower concentrations than donanemab**

Aβ, amyloid beta; AD, Alzheimer's disease; IgG, immunoglobulin; N3pE-Aβ, pyroglutamate-modified Aβ.
Lecanemab and donanemab were generated from publicly available sequences.

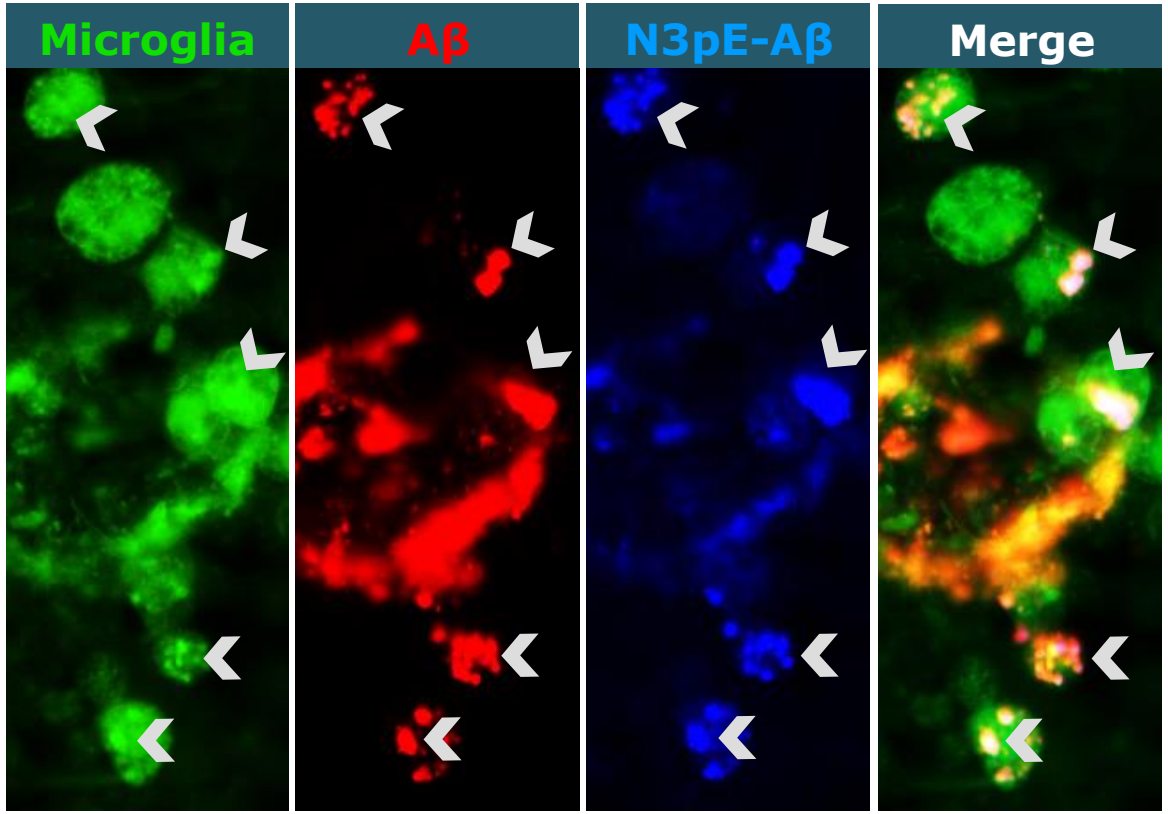


PRX012s Promotes Simultaneous Microglia-Mediated Phagocytosis of Aβ and N3pE-Aβ in Post-mortem Brain Tissue From AD Subjects



Microglia (Iba1: green) simultaneously phagocytose Aβ (red) and pyroglutamate-modified Aβ ($Aβ_{pE3-42}$: blue) in the presence of PRX012 surrogate, indicating that opsonization of plaques is sufficient to clear both species.

PRX012s promoted microglia-mediated phagocytosis of Aβ and pyroglutamate-modified Aβ (N3pE-Aβ) simultaneously



Arrows indicate examples of phagocytosed Aβ and N3pE-Aβ that co-localize inside microglia cells (immunostained with anti-Iba1 antibody).

Aβ, amyloid beta; AD, Alzheimer's disease; IgG, immunoglobulin; N3pE-Aβ, pyroglutamate-modified Aβ.

PRX012 Phase 1 SAD

Phase 1 Study Design:

- Randomized, double-blind, placebo-controlled, SAD study
- Up to 6 dose cohorts in healthy volunteer (HV) subjects and subjects with biologically confirmed Alzheimer's disease
- To assess safety and tolerability

Randomize 3:1
N = ~ 50 total subjects and patients

Healthy Volunteers (SubQ single dose)

AD Patients (SubQ single dose)

Primary Objective:

- To evaluate the safety and tolerability of PRX012 when administered as a single dose

Secondary Objectives:

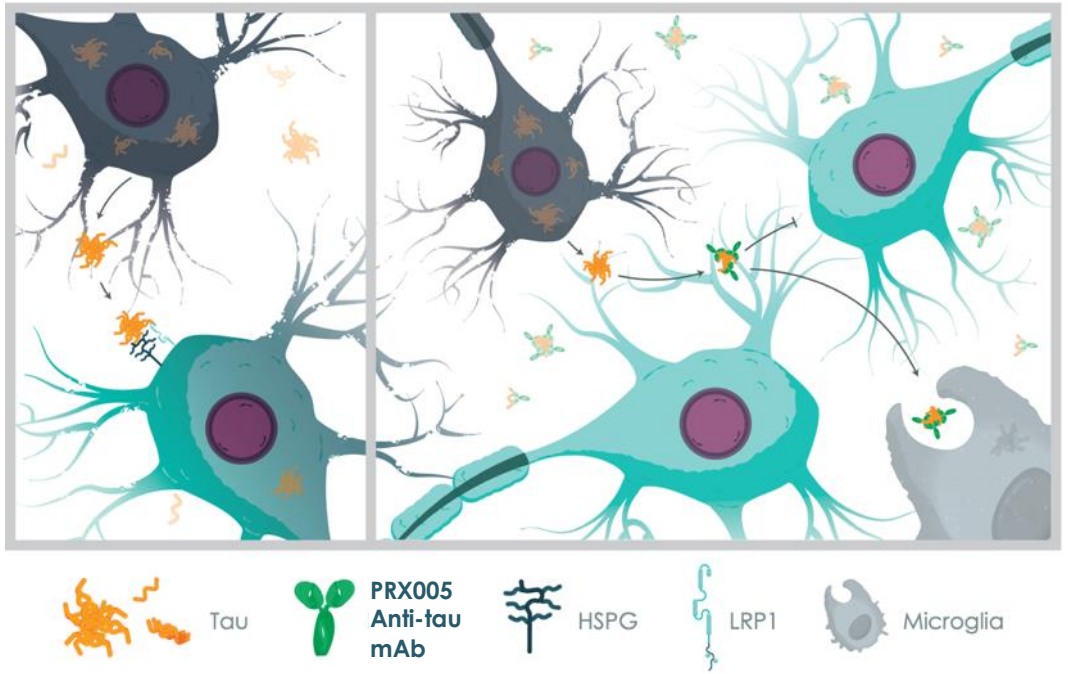
- To characterize the plasma PK profile of PRX012 and cerebrospinal fluid PK profile of PRX012 after subcutaneous administration as a single dose

PRX005
Alzheimer's Disease

Global Neuroscience Collaboration
with Bristol Myers Squibb

PRX005: MTBR-Specific Anti-Tau Designed to be Best-in-Class

- **PRX005, a differentiated tau antibody that targets an optimal tau region within the MTBR**
  - Recent publications strongly suggest that tau appears to spread throughout the brain via synaptically-connected pathways[1]
  - This propagation of pathology is thought to be mediated by tau "seeds" containing the MTBR of tau[2]
- **Potential for best-in-class efficacy**
  - Preclinical evaluation of our antibodies in our AD models demonstrated that MTBR-specific antibodies are superior to non-MTBR tau antibodies in blocking tau uptake and neurotoxicity
  - Demonstrated significant inhibition of cell-to-cell transmission and neuronal internalization in vitro and in vivo and slowed pathological progression in a tau transgenic mouse model
- **Phase 1 SAD data in HVs demonstrated dose-proportional PRX005 concentrations in plasma with robust CNS penetration and generally safe and well tolerated**
- **Topline Phase 1 MAD data expected YE23**

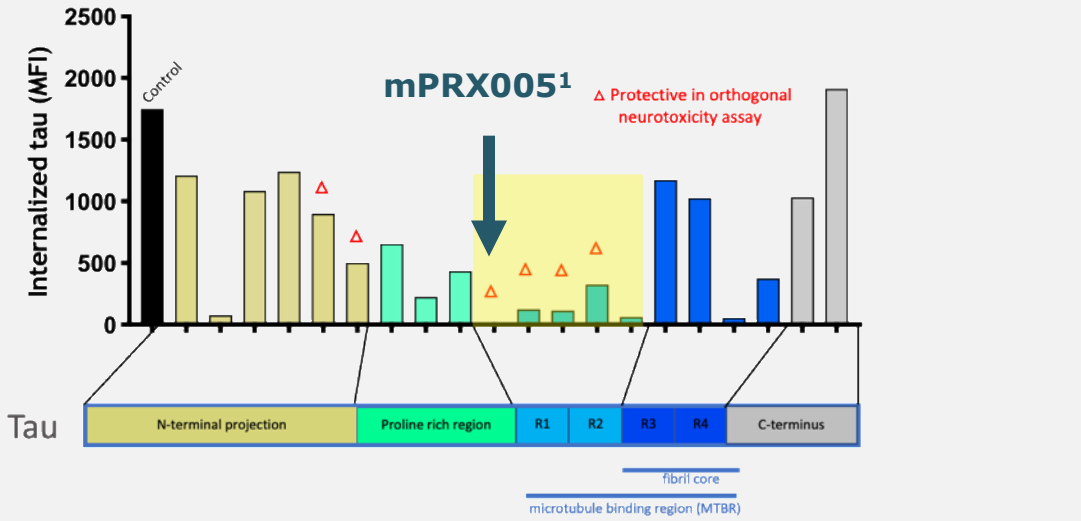


PRX005: Potential Best-in-Class MTBR-Specific Anti-Tau Antibody to Reduce Pathogenic Tau Spread

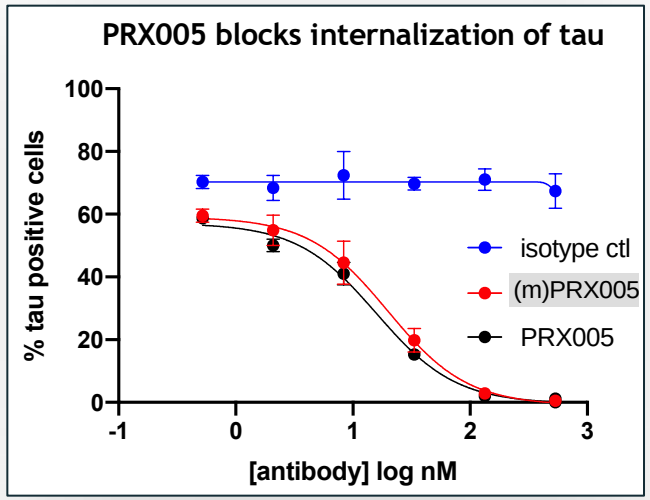
[1] Ahmed, Z., Cooper, J.. et al. A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity. 2014 Acta Neuropathol; [2] Horie, k., Barthelemy, H., Bateman, R.J. CSF tau microtubule binding region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

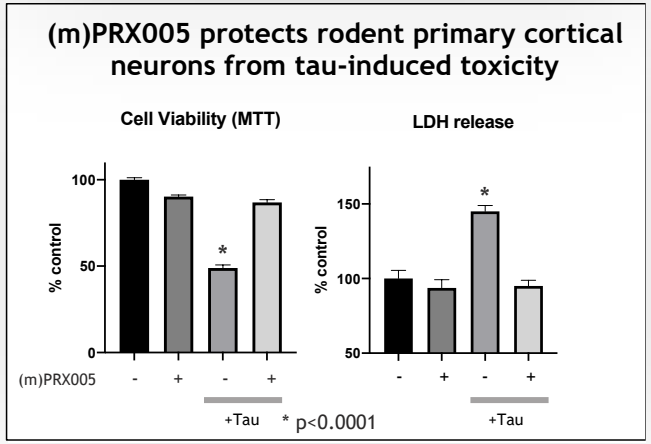
PRX005: Superior in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity Compared to Other Anti-tau Antibodies

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



- Panel of Prothena antibodies targeted throughout the tau molecule were screened for optimal affinity and epitope
- These were tested *in vitro* for their ability to block internalization and toxicity



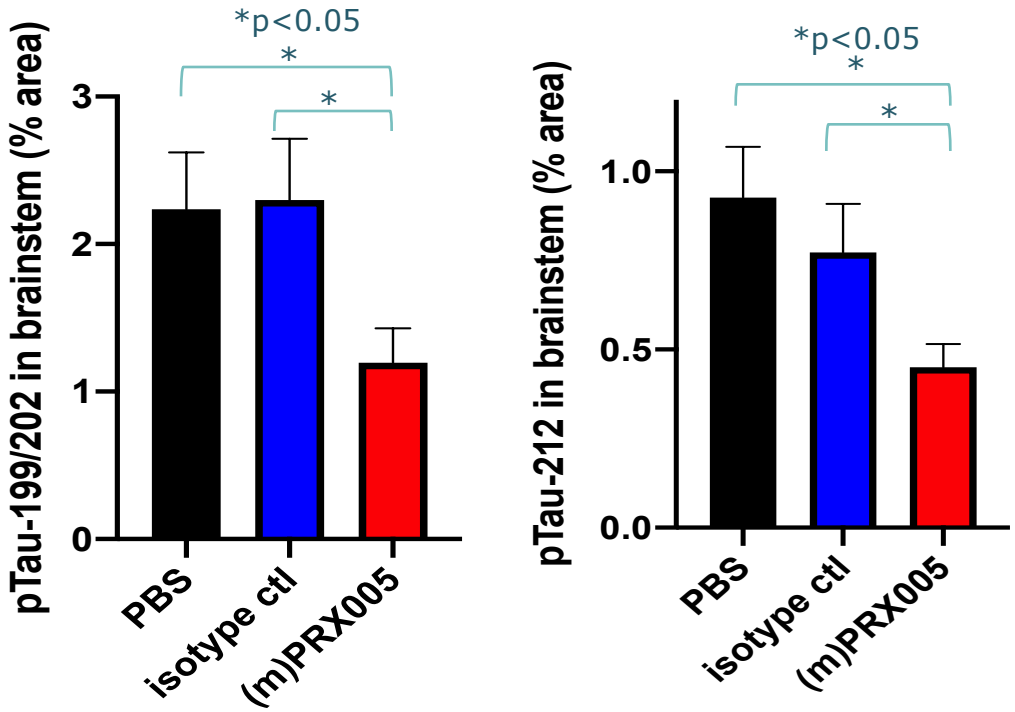


[1] (m)PRX005 = murine form of PRX005

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

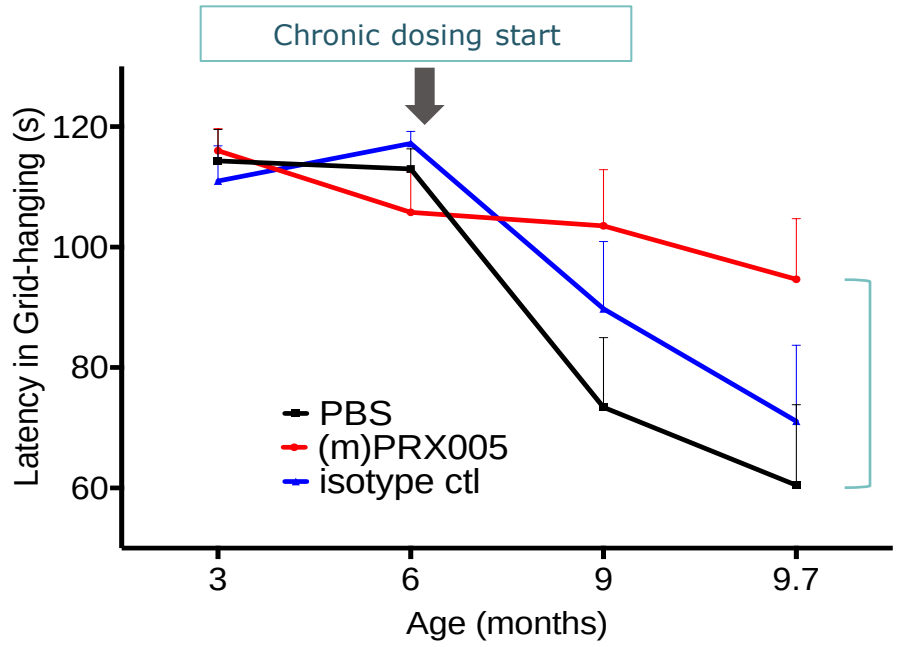
All values are mean ± SE (n=15-20)

Reduction of tau pathological markers



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

Delay of behavioral deficit



- Initiation of treatment (weekly i.p.) at the onset of pathological development (treatment mode) with (m)PRX005 delays brainstem tau pathology and consequent behavioral deficits

(m)PRX005 = murine form of PRX005

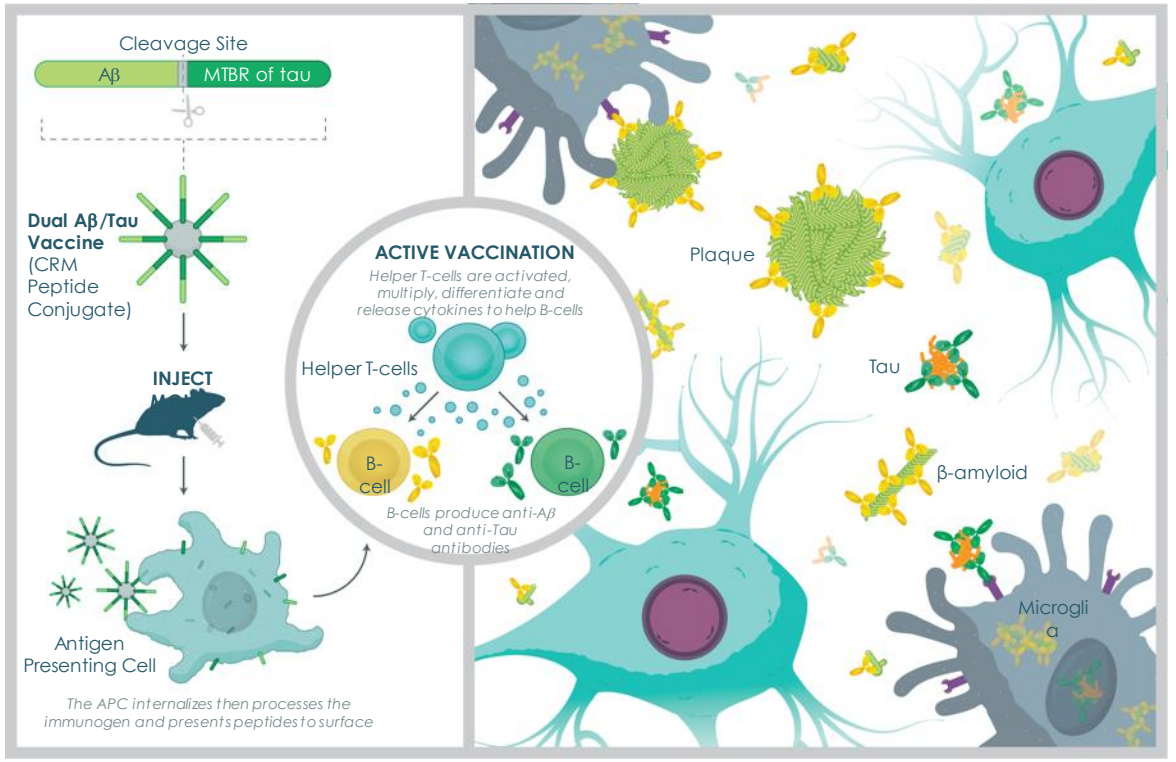
PRX123

Alzheimer’s Disease

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

PROTHENA IS PIONEERING THE DEVELOPMENT OF DUAL AB/TAU VACCINE CANDIDATE PRX123

- **Synergistic mechanism designed for increased efficacy over single-target vaccines**
  - Strong evidence from preclinical models suggests that Aβ and tau may act synergistically in the development of AD
  - Prothena's dual Aβ/tau vaccine program aims to induce optimal (quantity and quality) and balanced immune response to both targets, while avoiding cytotoxic t-cell response
- **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
  - The immune animal sera reacted to Aβ and tau, induced Ab phagocytosis, and blocked tau interaction with a key mediator of cellular release and cell-to-cell transmission
- **IND filing expected YE2023**



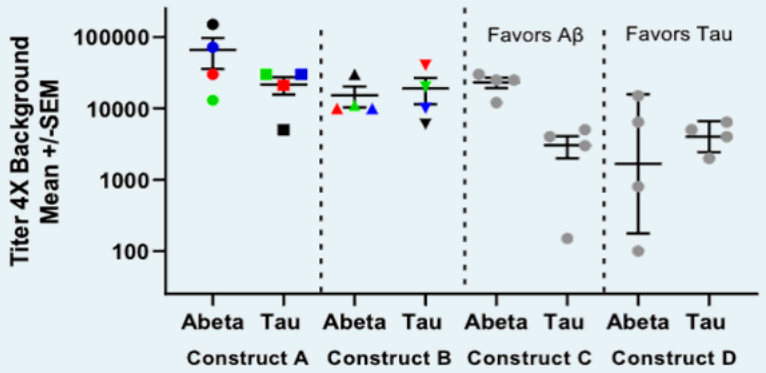
Desirable Attributes of Ab/Tau Vaccines and Prothena's Design Strategies

		Design Strategy	Desirable Output
1 Quantity	**RESPONSE** Antibody levels, balanced Ab/tau, persistency	• Linear peptides, proprietary cleavable linkers • Optimal carriers, immunization schedule, adjuvant	✓ Optimal antigen presentation with persistent immune response ✓ Overcomes immunodominance and immunosenescence
2 Quality	**EFFICACY** Isotypes, binding, Ab clearance, tau neutralization	• Optimal Aβ and tau epitopes • Elements for induction of mature TH response	✓ Antibodies bind the right epitopes on pathogenic proteins ✓ IgG switch and affinity maturation
3 Safety	**SAFETY** Cytotoxic T-cell avoidance, target-specificity	• Short Aβ/tau epitopes not recognizable by cytotoxic T-cells • No off-target binding risk based on peptide sequences	✓ No cytotoxic T-cell responses ✓ Specific antibodies

Preclinical data presentation titles: Development of a Dual Aβ/Tau Vaccine for the Treatment and Prevention of Alzheimer's Disease presented at ADPD 2022

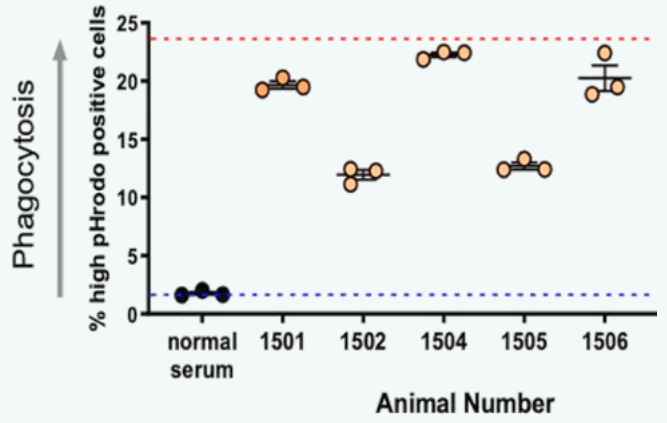
Prothena's Dual Aβ/Tau Vaccines Demonstrate Desirable Quantity, Quality and Safety

Quantity



✓ High, Balanced, Consistent

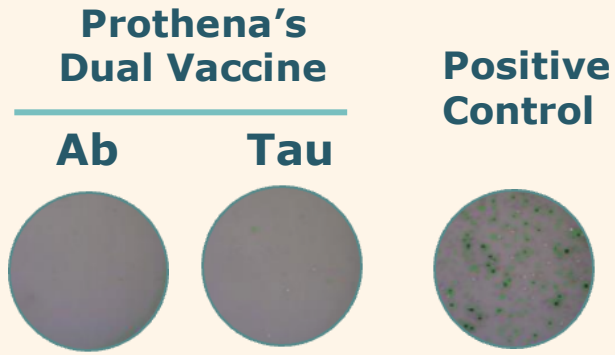
Quality



✓ Epitope, affinity, Ab clearance, Tau neutralization

Safety

Unable to induce measurable cytotoxic T-cell activity against Ab and tau in Non-human primates (ELISpot)

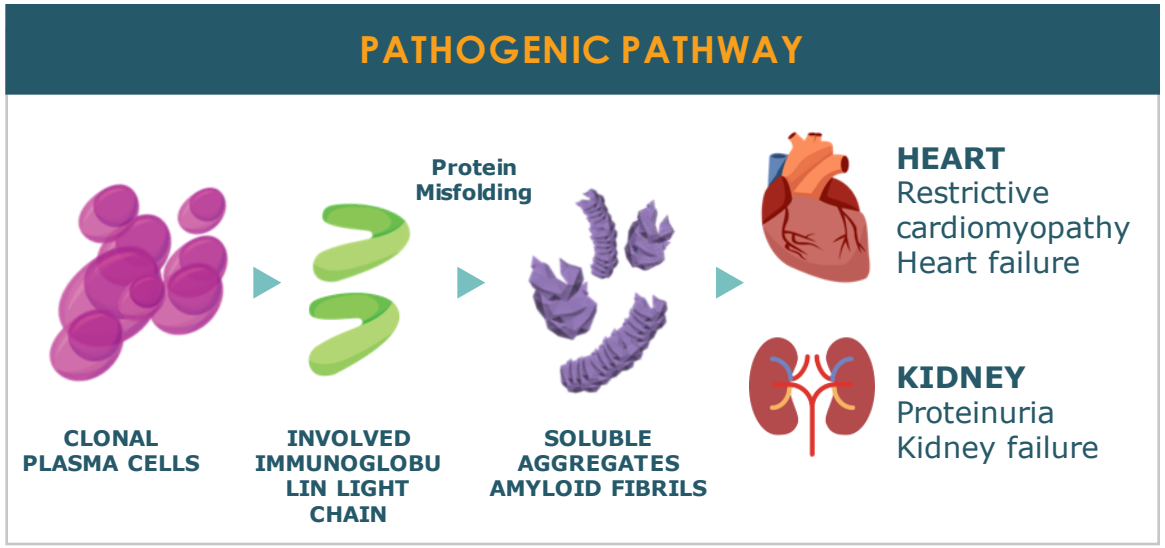


✓ Avoids T-cell response observed in other vaccines

Preclinical data presentation titles: Development of a Dual Aβ/Tau Vaccine for the Treatment and Prevention of Alzheimer's Disease presented at ADPD 2022

Rare Peripheral Amyloid Diseases

AL Amyloidosis:
A Rare, Progressive, and Fatal Disease



- Caused by misfolded κ or λ immunoglobulin light chains resulting from underlying plasma cell dyscrasia[1,2]
- Misfolded proteins clump together into fibrils that aggregate in vital organs, particularly the heart[3]

The four stages (Mayo Stages I–IV) of AL amyloidosis: life expectancy decreases as the disease progresses[4,5]

Mayo Stage	Biomarkers Impacted*	Life Expectancy
I	0/3	<8 years
II	1/3	<3.5 years
III	2/3	<14 months
IV	3/3	<6 months

There are an estimated 60,000 to 120,000 patients globally with Mayo Stage IV AL amyloidosis[6]

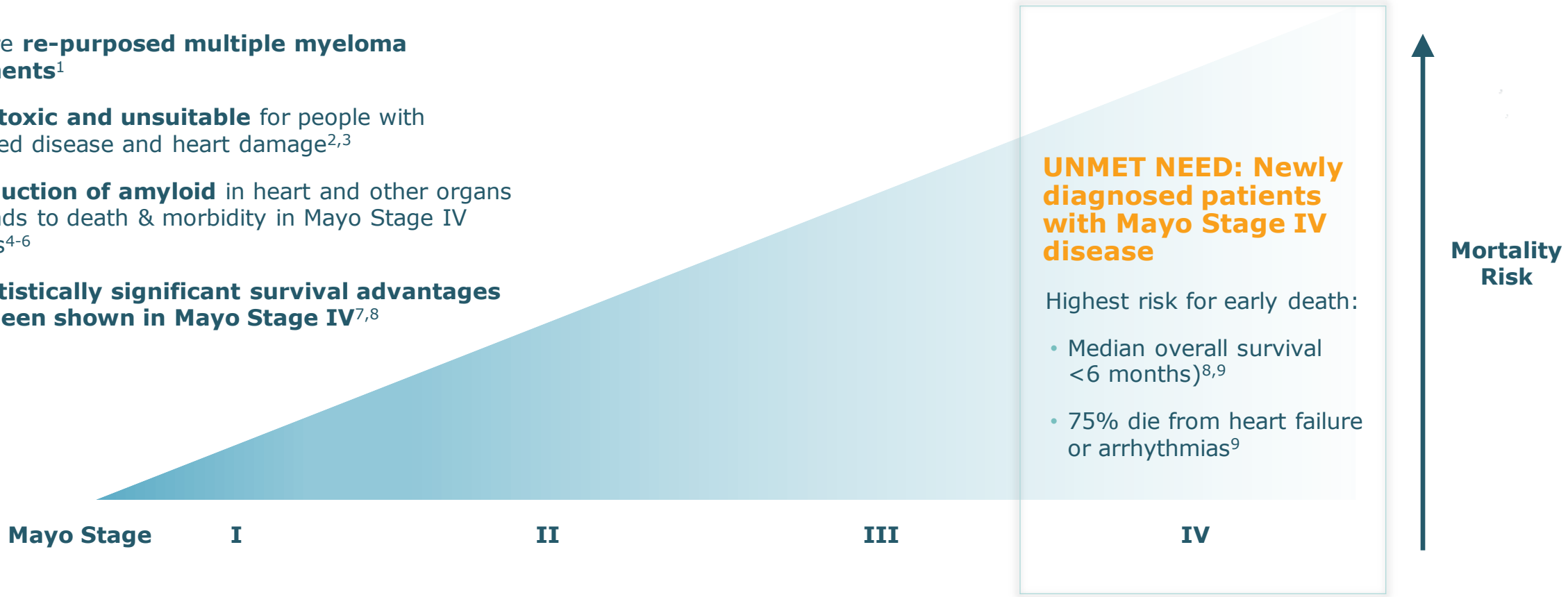
*Biomarkers are: NT-proBNP (1,800 nanograms/liter); cTnT (0.025 nanograms/mL; dFLC (180 mg/L).

[1] Dittrich T, et al. 2020 *Acta Haematol*. [2] Muchtar E, et al. 2021 *Mayo Clin Proc*. [3] Cleveland Clinic. Available at: https://my.clevelandclinic.org/health/diseases/15718-amyloidosis-al-amyloid-light chain#:~:text=AL%20amyloidosis%20(amyloid%20light%20chain%20or%20primary%20amyloidosis)%20is%20a,cause%20life-threatening%20medical%20conditions. [4] Palladini G, et al. 2019 *Haematologica*; [5] Levin M, et al. Available at: https://www.myamyloidosisteam.com/resources/stages-of-amyloidosis; [6] Kyle et al Mayo Clin Proc, 2019.

AL Amyloidosis Treatments Are at a Roadblock

Currently available AL treatments have not shown survival benefit in AL patients

- Most are **re-purposed multiple myeloma treatments**[1]
- **Cardiotoxic and unsuitable** for people with advanced disease and heart damage[2,3]
- **No reduction of amyloid** in heart and other organs that leads to death & morbidity in Mayo Stage IV patients[4-6]
- **No statistically significant survival advantages have been shown in Mayo Stage IV**[7,8]



[1] American Cancer Society. Available from: https://www.cancer.org/cancer/multiple-myeloma/treating/chemotherapy.html; [2] Alsomali D, et al. 2022 *Clin Adv Hematol Oncol;* [3] Czyżewska E, et al. 2021 *J Clinical Med*; [4] Palladini G, et al. 2019 *Haematologica*; [5] Levin M, et al. Available at: https://www.myamyloidosisteam.com/resources/stages-of-amyloidosis; mayoclinic.org/diseases-conditions/amyloidosis/diagnosis-treatment/drc-20353183; [6] Cleveland Clinic. Available at: https://my.clevelandclinic.org/health/diseases/15718-amyloidosis-al-amyloid-light-chain#:~:text=AL%20amyloidosis%20(amyloid%20light%20chain%20or%20primary%20amyloidosis)%20is%20a,cause%20life-threatening%20medical%20conditions; [7] Gertz M, et al. 2021 *Blood.* [Abstract and Poster]; [8] Kumar S, et al. 2012 *J Clin Oncol;* [9] Czyżewska E, et al. 2021 *J Clinical Med*.

Birtamimab

AL Amyloidosis

Birtamimab: Pioneering a New Class of Amyloid-Depleting Therapies for Advanced AL Amyloidosis

Addresses acute unmet needs in Mayo Stage IV AL amyloidosis

- Ongoing Phase 3 trial designed per FDA Special Protocol Assessment (SPA)
- Amyloid depleter MoA
  - Clears insoluble AL amyloid deposits clogging vital organs
  - Slows toxic amyloid build-ups
- Humanized mAb
  - Reduced immunogenicity
  - Normal half-life, enabling convenient (1x/month) administration



BINDS only to misfolded light chain isoforms; leaves normal proteins intact

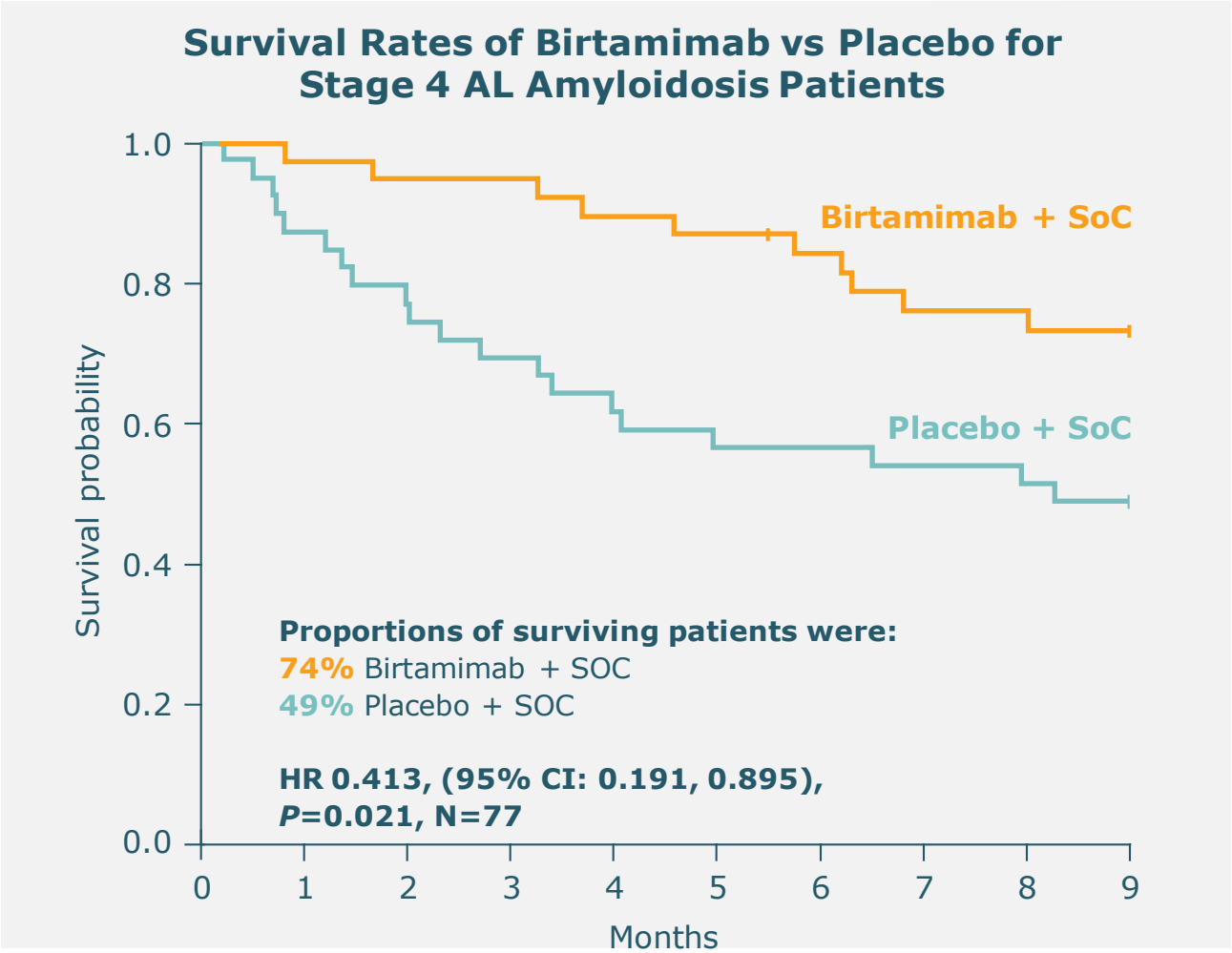
NEUTRALIZES toxic circulating kappa and lambda light chain aggregates

DEPLETES accumulated amyloid in heart & other organs via macrophage-induced phagocytosis

CLEARS amyloid deposits and circulating light chains in all patients, regardless of disease stage

Birtamimab: The Only Clinical Candidate Demonstrating a Significant Survival Benefit in Stage IV AL Amyloidosis

- **More than 300 patients treated in clinical trials as of 2022**
- Post hoc analyses of initial Phase 3 RCT (VITAL Study):
  - **Survival benefit in Mayo IV** (74% vs. 49% for placebo)
  - Meaningful **improvements in** health-related **quality of life** (SF-36v2) and **functional** endpoints (6MWT) at 9 months (*P*< 0.05)
- Common treatment-emergent adverse event rate similar to placebo



Gertz MA et al. Presented at: Annual Meeting of the American Society of Hematology; December 10-13, 2022; New Orleans, Louisiana, USA.

AFFIRM-AL Study: Confirmatory Phase 3 Trial Underway

FDA Fast Track Designation

Orphan Drug Designation (FDA and EMA)

Special Protocol Assessment (SPA)

AFFIRM-AL

SPA agreement with FDA on trial design

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

Ongoing enrollment

- Toplines results 2024

Key Eligibility Criteria

- 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
- All-Cause Mortality

Secondary Endpoints
- SF-36v2 PCS
- 6MWT

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.

Mayo Stage IV Patients are Primarily Treated in Amyloidosis Centers

TREATMENT SETTING	MAYO STAGE IV PATIENTS
Amyloidosis Centers of Excellence (COEs)	15-27%
Amyloidosis Specialty Academic Centers	43-51%
Community Centers/ Private Practice	24-40%

~75% of US and EU patients primarily treated in ~500 Amyloidosis COE and specialty centers

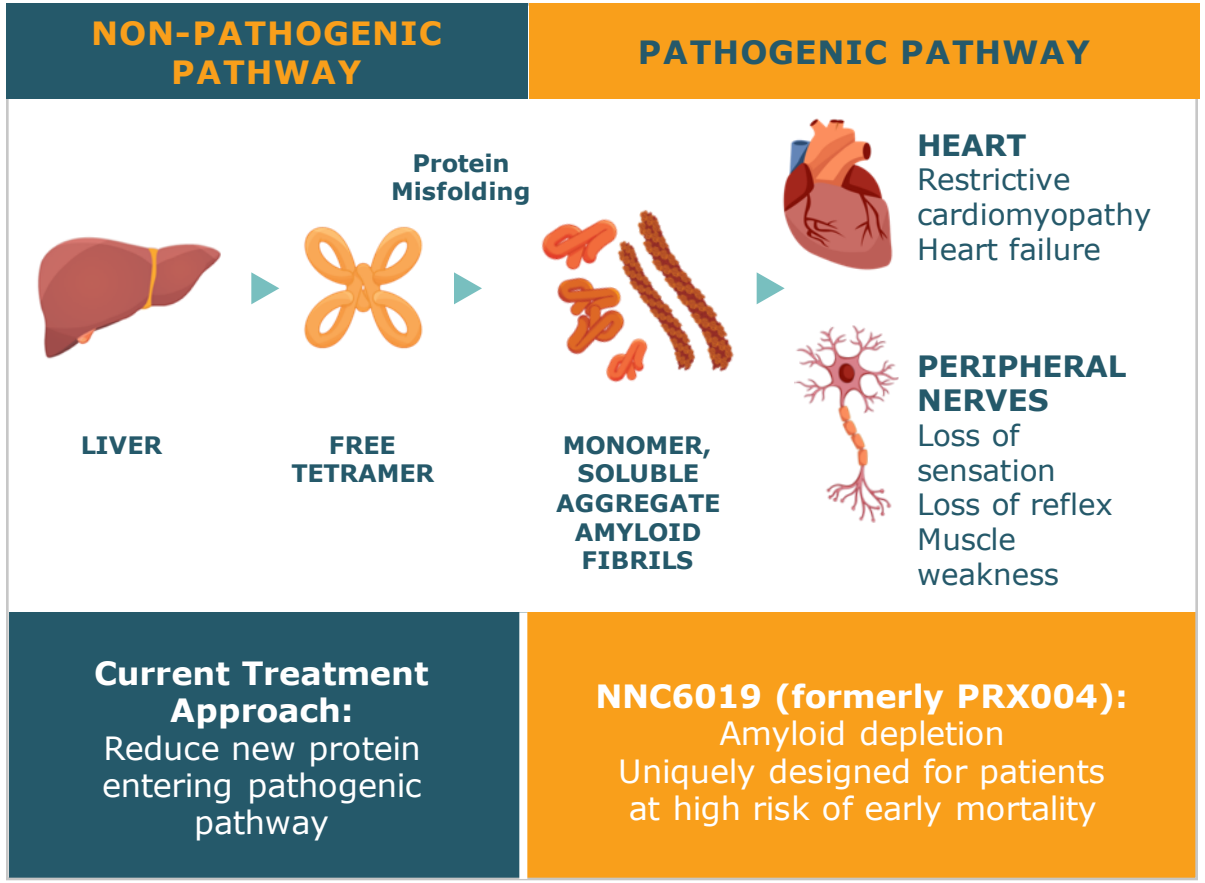
Estimates based on US/EU/UK Market Research, LEK Analysis

NNC6019
(formerly PRX004)
ATTR Amyloidosis

ATTR Business Acquired by Novo Nordisk

NNC6019 (formerly PRX004): Potential First-in-Class Treatment for ATTR Amyloidosis

- **Differentiated depleter uniquely designed for patients at high risk of early mortality**
- **mPRX004 (murine form of PRX004) preclinical results:[1]**
  - Inhibits fibril formation and specifically binds to pathogenic TTR
  - Reacts to amyloid deposits in multiple organs in both wtATTR and ATTRv patients
  - Promotes in vivo ATTR amyloid clearance
- **ATTR amyloidosis program acquired by Novo Nordisk**
  - Prothena is eligible to receive a total aggregate of up to $1.23 billion
  - Includes $60 million upfront payment
- **Phase 1 study identified that all six dose levels of PRX004 found to be generally safe and well-tolerated**
  - Positive results on neuropathy and cardiac function
- **Novo Nordisk is conducting a Phase 2 study in patients with ATTR cardiomyopathy (NCT05442047); topline data expected in 2024**



NNC6019: Depleter MoA May Provide a New Treatment Paradigm for Patients at High-risk of Early Mortality Due to Amyloid Deposition

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

Parkinson’s Disease

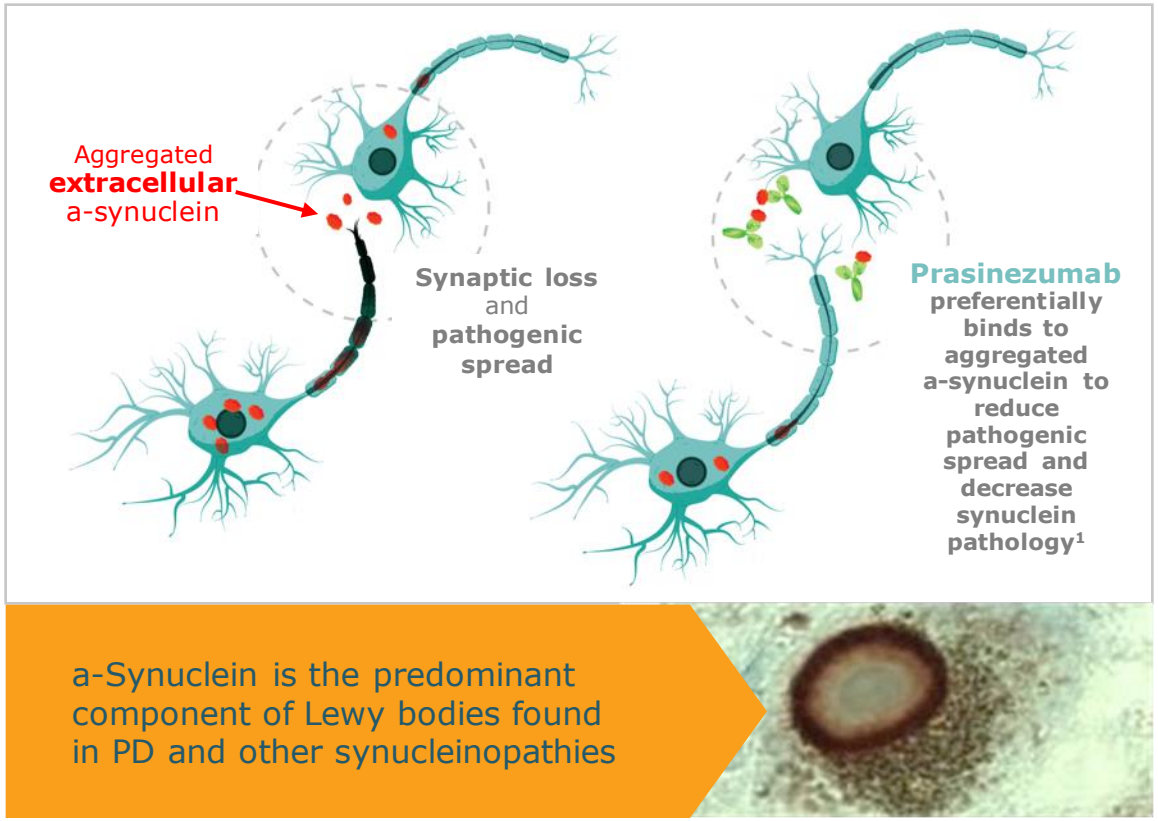
Prasinezumab
Parkinson's Disease

Worldwide Collaboration with Roche

Prasinezumab: a-Synuclein Immunotherapy

REDUCE NEURONAL TOXICITY AND PREVENT CELL-TO-CELL TRANSMISSION1

- **α-Synuclein pathology is strongly implicated in PD**
  - 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 disease: missense mutations and duplication/triplication
- **α-Synuclein as an extracellular target during pathogenesis**
  - Caudal-rostral staging, host-to-graft transfer, various propagation models
- **Prasinezumab is the first anti-α-synuclein antibody to significantly slow progression on measures of PD, supporting disease modification, in a Phase 2 study**
- **Phase 2b PADOVA study results expected 2024**
  - Being conducted by Roche



a-Synuclein is the predominant component of Lewy bodies found in PD and other synucleinopathies

Prasinezumab: Preferentially Binds to Aggregated α-Synuclein to Reduce Pathogenic Spread and Decrease Synuclein Pathology[1]

[1] Proposed mechanism of action

Upcoming Milestones

Upcoming Potential Milestones

TRANSFORMATIONAL PERIOD AHEAD

PRX012 for potential treatment of Alzheimer's disease

- **YE22** ✓ Phase 1 multiple ascending dose study initiation
- **1Q23** ✓ Oral presentation of preclinical data showing superior binding characteristics of PRX012 at AD/PD 2023
- **YE23** ❑ Topline Phase 1 SAD and MAD data

PRX005 for potential treatment of Alzheimer's disease (Bristol Myers Squibb)

- **1Q23** ✓ Topline Phase 1 SAD data
- **YE23** ❑ Topline Phase 1 MAD data

PRX123, dual Aβ/Tau vaccine for potential treatment and prevention of Alzheimer's disease

- **YE23** ❑ IND filing

Prasinezumab for potential treatment of Parkinson's disease (Roche)

- **2024** ❑ Phase 2b PADOVA study topline data

Birtamimab for potential treatment of AL amyloidosis

- **2024** ❑ Confirmatory Phase 3 AFFIRM-AL topline data

NNC6019/PRX004 for potential treatment of ATTR-cardiomyopathy (Novo Nordisk)

- **2024** ❑ Topline Phase 2 data

APPENDIX

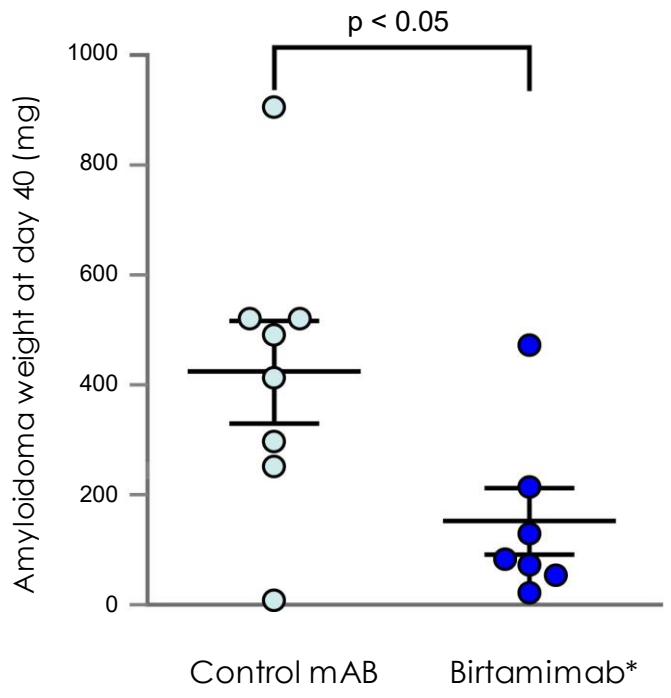
prothena®

Birtamimab

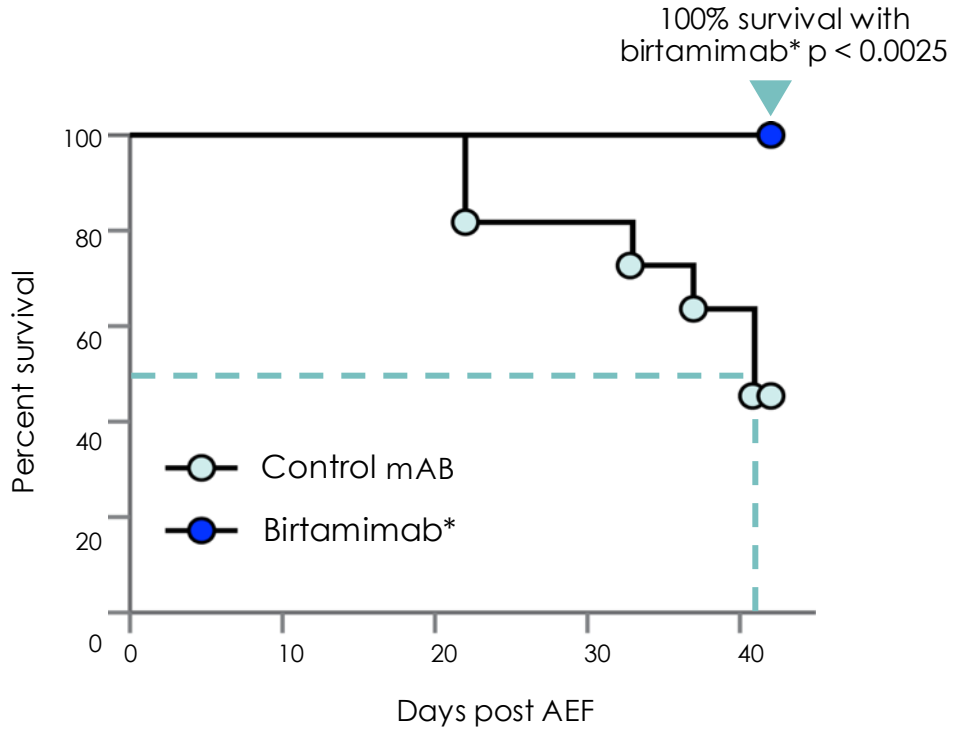
Supplemental Information

Birtamimab* Demonstrated Significant Amyloid Clearance and Prolonged Survival in Preclinical Model

Birtamimab* Removes Amyloid In Vivo



Birtamimab* Prolongs Survival in Transgenic Mouse Model



*murine version of birtamimab, 2A4
Wall et al., PLOS ONE, 2012, data on file

Phase 3 VITAL Study Overview

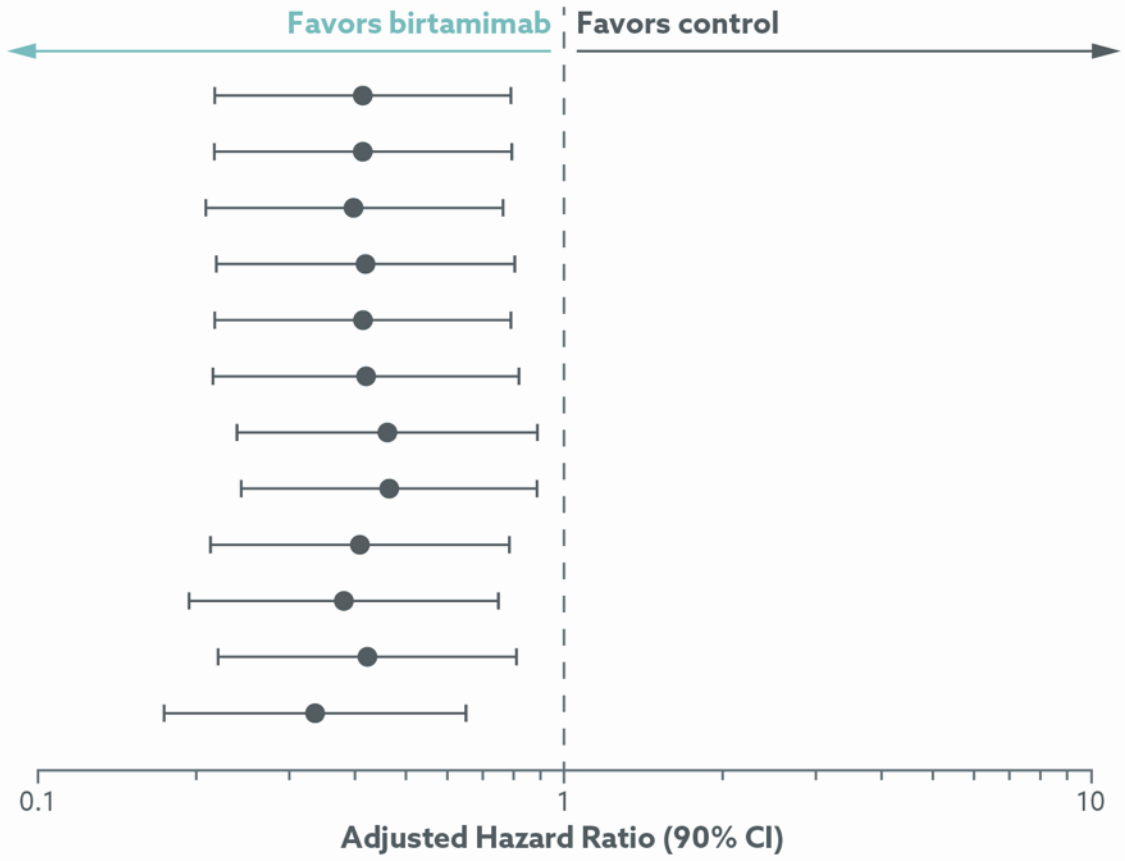
- **Global, randomized, double-blinded, placebo-controlled study**
  - Sample size and randomization
    - N=260
    - 1:1
  - Key eligibility criteria
    - Confirmed diagnosis of AL amyloidosis
    - Newly diagnosed and treatment naïve
    - Cardiac involvement
  - Treatment regimen
    - Birtamimab 24 mg/kg vs. placebo, with concurrent standard of care (SoC) in both arms
- **Primary endpoint**
  - Composite endpoint of time to all-cause mortality or time to cardiac hospitalizations (≥90 days) as adjudicated by the Clinical Events Committee
- **Secondary endpoints**
  - Quality of life: SF-36v2 PCS
  - Functional capacity: 6MWT
- **Randomization stratification**
  - Mayo Stage I-II vs III-IV, renal stage I vs II-III and 6MWT distance < 300 m vs ≥ 300m

- **30% of patients enrolled in VITAL (N=77) were characterized as Mayo Stage IV at baseline**
  - 38 in birtamimab + SoC arm
  - 39 in placebo + SoC arm
- **Primary reason for patient discontinuation post ~12 months was study termination by sponsor**

SF-36v2 PCS = Short Form-36 Physical Component Score; 6MWT = 6-Minute Walk Test

Birtamimab Survival Benefit Adjusted for Key Baseline Variables for Mayo Stage IV Patients

Baseline variable	Adjusted HR
Age	0.414
Sex	0.415
Race	0.399
Ethnicity	0.419
Age at diagnosis	0.414
Duration since diagnosis (months)	0.420
NT-proBNP	0.460
dFLC	0.465
FLC	0.410
NYHA class	0.381
Troponin-T	0.422
6MWT distance	0.336



Post hoc analysis: Cox Proportional Hazards Model for all-cause mortality through the first 9 months of treatment, adjusted for randomization stratification factors (Renal Stage and 6MWT distance category); VITAL Phase 3 study; 2022.

Mayo Stage IV Patients in Major Markets

TARGETED OPPORTUNITY IN ORPHAN POPULATION

					
AL Amyloidosis Dx Prevalence	**~13,000**	**~17,500**	**~4,500**	**~30,500** Urban Only	**~6,800**
Mayo Stage IV Dx Prevalence	**~3,900**	**~5,200**	**~1,300**	**~9,100**	**~2,000**

Kyle Mayo Clin Proc. 2019; Kyle Blood 1992; Quock Blood Adv. 2018; Shimazaki The Japanese Journal of Clinical Hematology. 2018; Duhamel Blood 2017; Hemminki BMC Public Health 2012; Pinney BJ Haem 2013; Merlini Nature 2018; Desport Orphanet J Rare Diseases 2012; Schulman Eur J Haematol 2020; Zhang J CLML 2019; VITAL study; World Bank Databank; ClearView Analysis

Improvements in Hematological Response Have Not Been Shown to Impact Survival in AL Amyloidosis

Table 3. Univariate and multivariate analysis for OS

Model 2: Non-ASCT patients

	Univariate analysis			Multivariate analysis A			Multivariate analysis B		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Period									
2010-2014	Reference				Not significant			Not significant	
2005-2009	1.1	0.9-1.3	.3						
2000-2004	1.8	1.5-2.2	**<.001**						
Age ≥ 65 y	1.2	1. 1-1.4	**.005**	1.2	1.1-1.4	**.009**	1.3	1.04-1.5	**.01**
>2 organs involved	1.4	1.1-1.6	**<.001**	1.4	1.2-1.7	**<.001**	1.3	1.04-1.5	**.01**
BMPCs ≥10%	1.3	1.1-1.5	**.002**	1.2	1.1-1.4	**.008**		NS	
dFLC ≥18 mg/dL	1.6	1.3-1.8	**<.001**		NI		1.4	1.1-1.6	**.001**
Treatment category									
MDex	Reference			Reference			Reference		
MP	1.9	1.6-2.4	**<.001**	1.6	1.2-2.1	**<.001**	2.0	1.4-2.8	**<.001**
Bortezomib-based	1.0	0.8-1.2	.98	1.1	0.8-1.4	.58	1.0	0.8-1.4	.77
IMiD-based	1.0	0.7-1.3	.87	1	0.7-1.4	.92	1.2	0.8-1.7	.34
Dexamethasone alone	2.1	1.5-2.9	**<.001**	2.0	1.4-2.9	**<.001**	1.9	1.1-3.0	**.02**
Troponin T ≥0.035 ng/mL	2.2	1.9-2.7	**<.001**		NI		2.2	1.8-2.6	**<.001**
eGFR <30 mL/min per 1.73 m^2	0.9	0.8-1.1	.53		NI			NI	

Boldface indicates significance at $P < .05$.
RR, risk ratio.

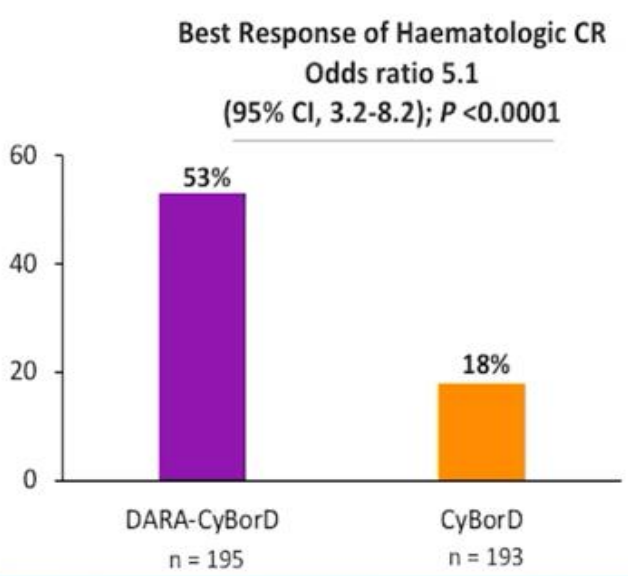
blood BLOOD, 13 APRIL 2017 • VOLUME 129, NUMBER 15

Primary Results from the Daratumumab Phase 3 ANDROMEDA Study, Presented at EHA June 2020

EUROPEAN HEMATOLOGY ASSOCIATION

EHA25 VIRTUAL

Haematologic CR: Primary Endpoint

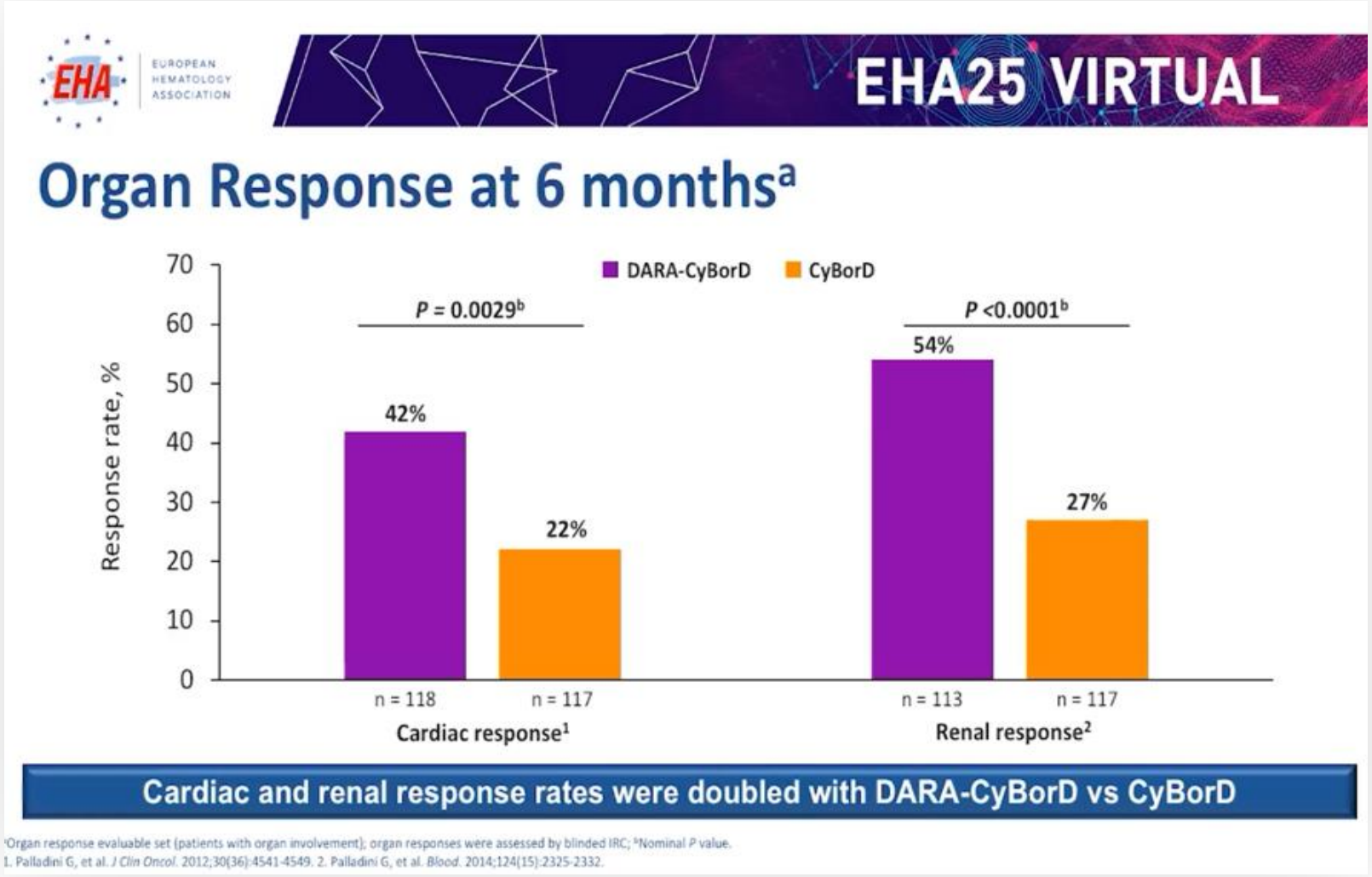


- Assessed by blinded Independent Review Committee
- CR per Comenzo criteria[1] with clarifications:
  - Abnormal FLC ratio does not preclude CR[2]
  - CR requires confirmation
- The CR rate at 6 months was consistent with overall CR rate
  - 50% DARA-CyBorD vs 14% CyBorD (odds ratio 6.1; *P* <0.0001)
- Median time to CR[a]:
  - DARA-CyBorD: 60 days
  - CyBorD: 85 days

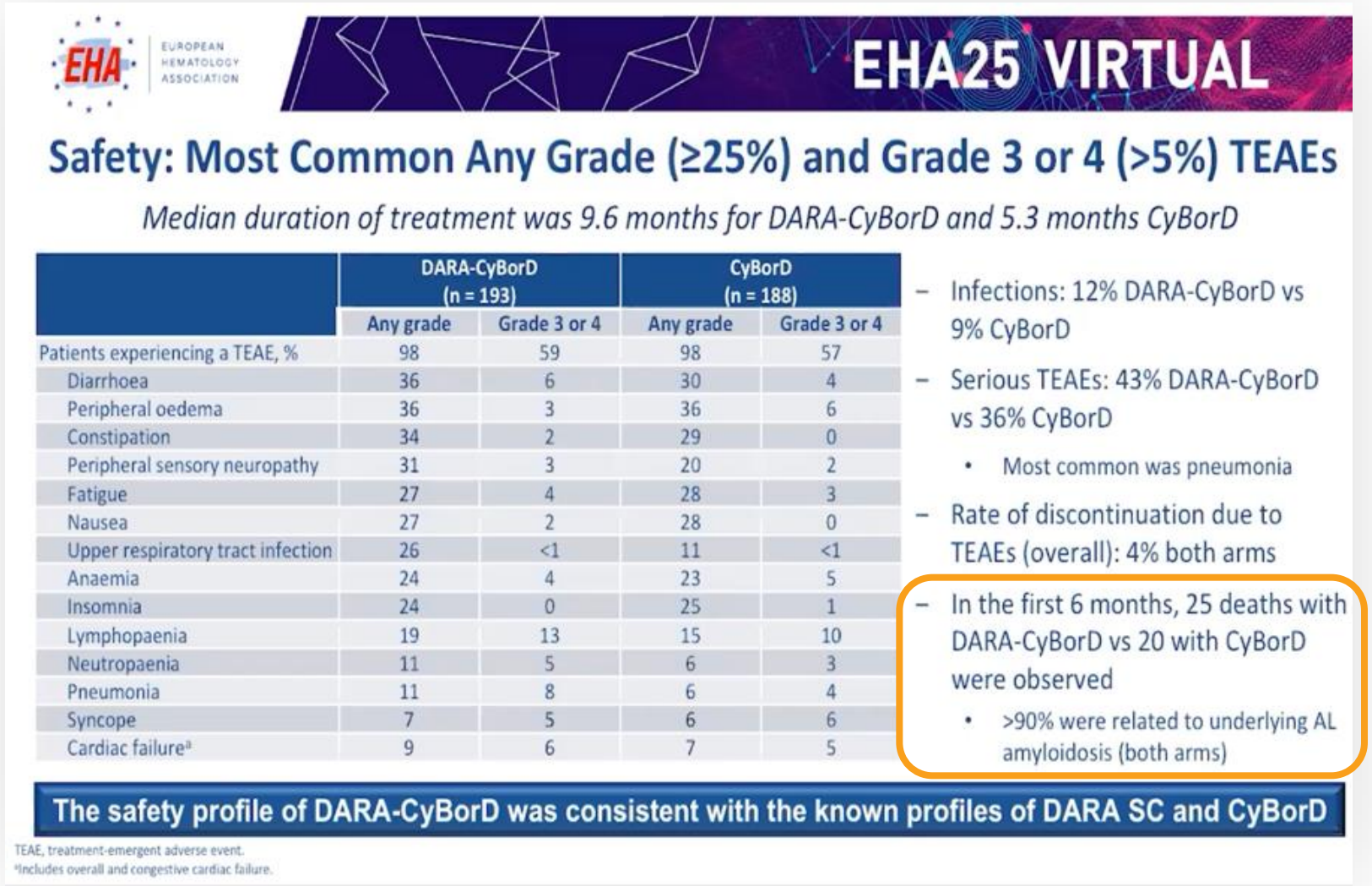
Responses with DARA-CyBorD were deeper and achieved more rapidly

CI, confidence interval; FLC, free light chain.
[a]Among CR responders (DARA-CyBorD, n = 104; CyBorD, n = 35).
1. Comenzo RL, et al. *Leukemia*. 2012;26(11):2317-2325. 2. Sidana S, et al. *Leukemia*. 2019;34(5):1472-1475.

Primary Results from the Daratumumab Phase 3 ANDROMEDA Study, Presented at EHA June 2020



Primary Results from the Daratumumab Phase 3 ANDROMEDA Study, Presented at EHA June 2020



Safety: Most Common Any Grade (≥25%) and Grade 3 or 4 (>5%) TEAEs

Median duration of treatment was 9.6 months for DARA-CyBorD and 5.3 months CyBorD

	DARA-CyBorD (n = 193)		CyBorD (n = 188)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Patients experiencing a TEAE, %	98	59	98	57
Diarrhoea	36	6	30	4
Peripheral oedema	36	3	36	6
Constipation	34	2	29	0
Peripheral sensory neuropathy	31	3	20	2
Fatigue	27	4	28	3
Nausea	27	2	28	0
Upper respiratory tract infection	26	<1	11	<1
Anaemia	24	4	23	5
Insomnia	24	0	25	1
Lymphopaenia	19	13	15	10
Neutropaenia	11	5	6	3
Pneumonia	11	8	6	4
Syncope	7	5	6	6
Cardiac failure[a]	9	6	7	5

- Infections: 12% DARA-CyBorD vs 9% CyBorD
- Serious TEAEs: 43% DARA-CyBorD vs 36% CyBorD
  - Most common was pneumonia
- Rate of discontinuation due to TEAEs (overall): 4% both arms
- In the first 6 months, 25 deaths with DARA-CyBorD vs 20 with CyBorD were observed
  - >90% were related to underlying AL amyloidosis (both arms)

The safety profile of DARA-CyBorD was consistent with the known profiles of DARA SC and CyBorD

TEAE, treatment-emergent adverse event.
[a]Includes overall and congestive cardiac failure.

The Path Leading to AFFIRM-AL

VITAL results analyzed

- Results **analyzed** with **input from external advisors** and **KOLs**
- **Greater than 50% relative risk reduction on all-cause mortality** in Mayo Stage IV patients at high risk for early mortality

Collaboration and alignment with FDA

- Multiple **in-depth discussions** with FDA
- **VITAL data enables path forward under SPA for AFFIRM-AL**

AFFIRM-AL

- **Confirmatory Phase 3 global study of birtamimab in Mayo Stage IV patients** with AL amyloidosis
- **Primary endpoint all-cause mortality**
- **SPA** agreement with significance level of **$p \leq 0.10$**

NNC6019
(formerly PRX004)

Supplemental Information

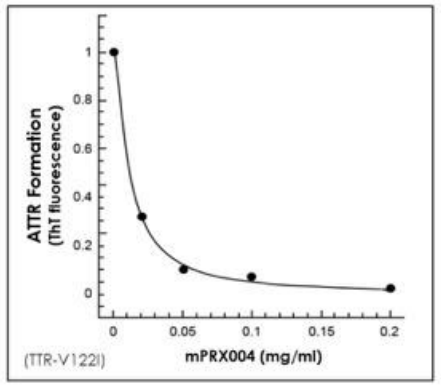
PRX004: Designed to Deplete Amyloid

SUMMARY OF PRECLINICAL EFFECTS OF MPRX004

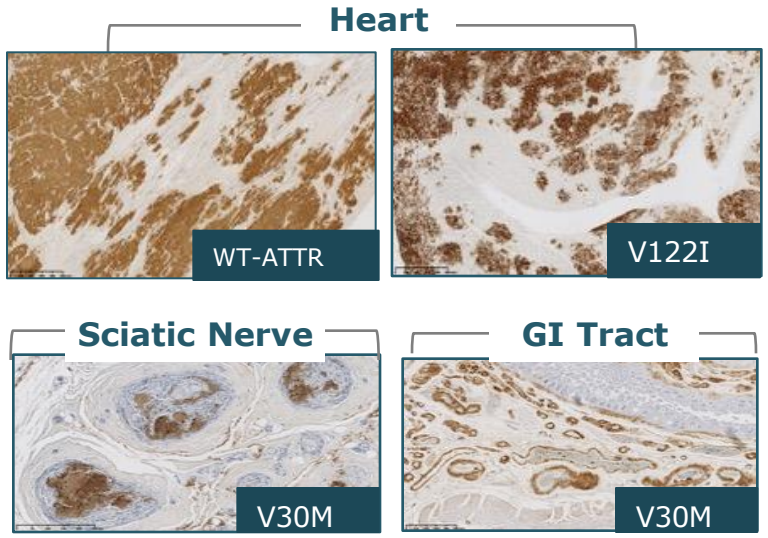
mPRX004 (murine form of PRX004) preclinical results:[1]

- ✓ Inhibits fibril formation
- ✓ Specifically binds to pathogenic TTR
- ✓ Reacts to amyloid deposits in multiple organs in both wtATTR and ATTRv patients
- ✓ Promotes in vivo ATTR amyloid clearance

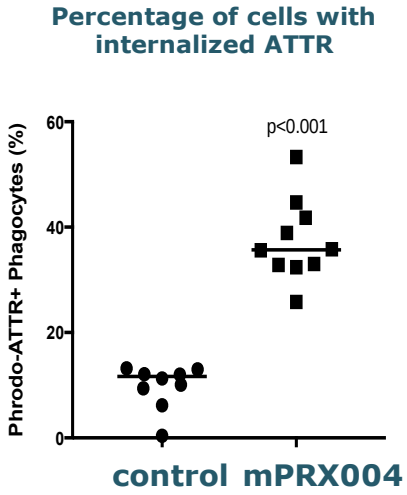
Inhibition of amyloid formation



Specific binding to amyloid



Clearance of amyloid

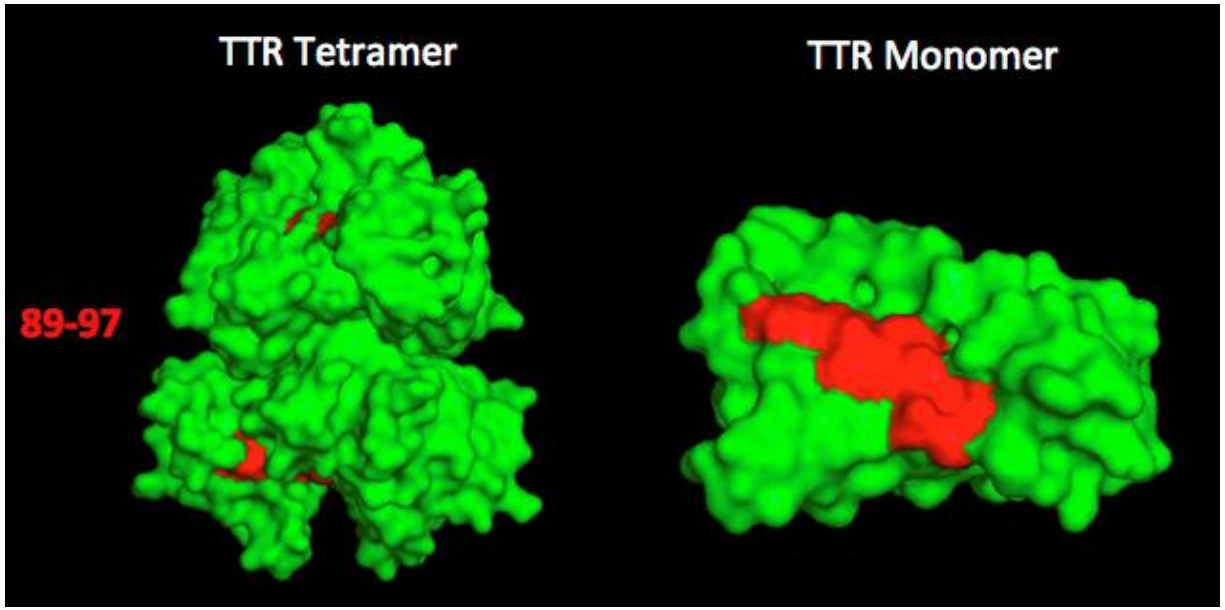


[1] Higaki JN et al. Amyloid, 2016; Preclinical studies of mPRX004, the murine form of PRX004

Prothena Developed PRX004 to Target an Epitope Exposed on Pathogenic Forms of TTR[1]

Epitope recognized by PRX004 is hidden in the TTR tetramer, but exposed in monomeric and aggregated forms of both ATTRv and wtATTR[2]

TTR89-97

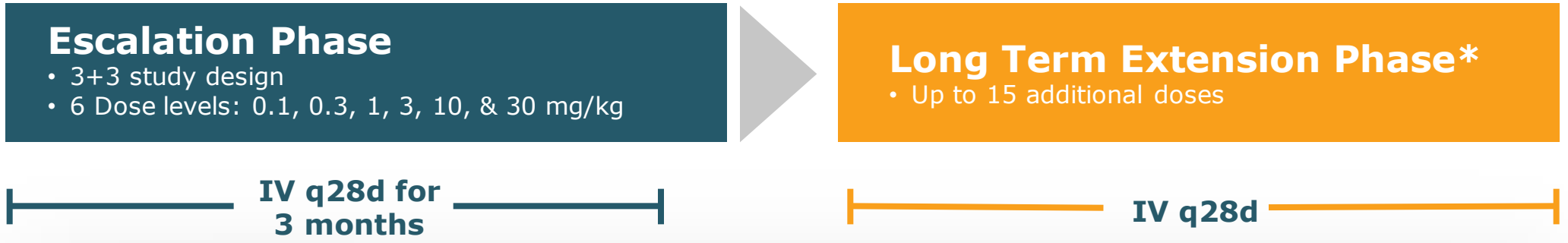


1-GPTGTGESKC PLMVKVLDAV RGSPAINVAV HVFRKAADDT WEPFASGKTS-50
51-ESGELHGLTT EEEFVEGIYK VEIDTKSYWK ALGISPFHEH AEVVFTANDS-100
101-GPRRYTIAAL LSPYSYSTTA VVTNPKE-127

[1] Higaki JN et al. 2016. In collaboration with Avi Chakrabartty (University of Toronto) [2] Ihse E et al. 2011

PRX004 Phase 1 Study Design

NCT03336580



Primary Objectives:

- Evaluate safety, tolerability, PK and target engagement (misTTR assay)
- Determine MTD or RP2D(s)

Secondary Objective:

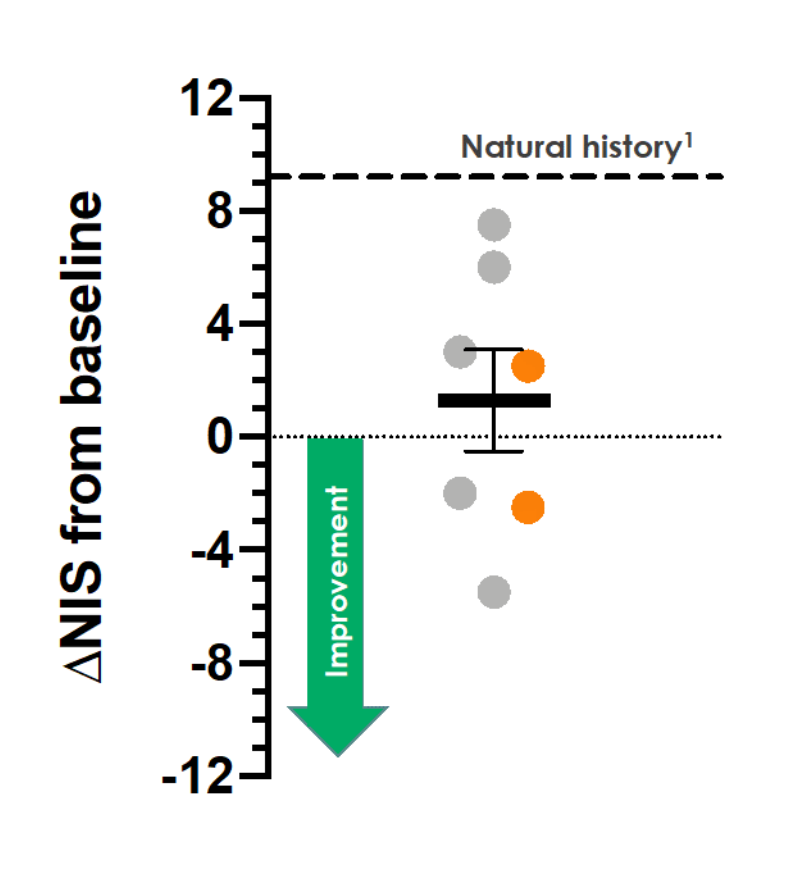
- Evaluate immunogenicity

Exploratory Objective:

- Characterize efficacy (NIS) in patients with ATTRv-PN with or without ATTRv-CM (Cohorts 4-6)

*After 3 months of infusions, patients may be eligible to enroll in long-term extension (LTE); LTE phase was terminated due to COVID-19
7 patients from cohorts 4, 5 and 6 received all infusions through 9 months and were therefore considered evaluable for NIS assessment
Patients on tafamidis and/or diflunisal allowed if dose stable for 6 months; patients on patisiran or inotersen excluded if treated within 90 days
MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose

Observed Improvement in Neuropathy with PRX004

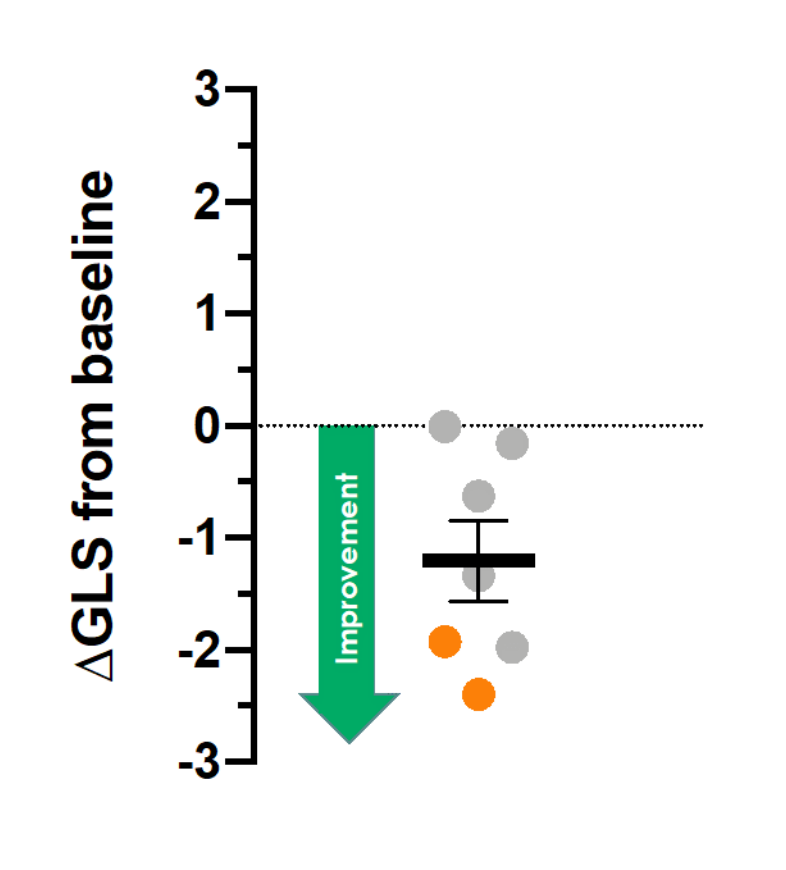


- NIS for each of the 7 evaluable patients was more favorable than published historical data
- 3 of these 7 patients demonstrated improvement in neuropathy with a mean change in NIS of –3.33 points

	PRX004 Phase 1		Natural History[1]	Patisiran[2]
	All	PRX004 Alone		
ΔNIS mean* (n)	**+1.29** (n=7)	**0.00** (n=2)	**+9.2** (N=349)	**+2.6** (N=27)
Time point	9 months		9 months	18 months

*Baseline NIS range 9-55 (median: 17.5), PRX004 alone is a subset of evaluable patients
[1] 9-month values based on linear interpolation from 12-month NIS longitudinal datasets: Adams D et al., *Neurology*. 2015); Berk JL et al., JAMA. 2013 (N=283, n=66) [2] Coelho et al. Orphanet *Journal of Rare Diseases*, 2020; Onpattro EPAR public assessment report EMA/55462/2018 October 30, 2018, Patisiran CDER Multi-Discipline Review, NDA 210922 August 10, 2018,
Error bar = Standard Error of the Mean
Not based on head-to-head studies

Observed Improvement in Cardiac Systolic Function with PRX004



- Improvement in GLS in all 7 evaluable patients
- In the 3 patients who improved on NIS, GLS improvement was more pronounced, with a mean change of –1.51%

	PRX004 Phase 1		Natural History[1]	Patisiran[2]
	All	PRX004 Alone		
ΔGLS mean* (n)	**–1.21%** (n=7)	**–2.16%** (n=2)	**+1.46%** (n=36)	**+0.08%** (N=27)
Time point	9 months		18 months	

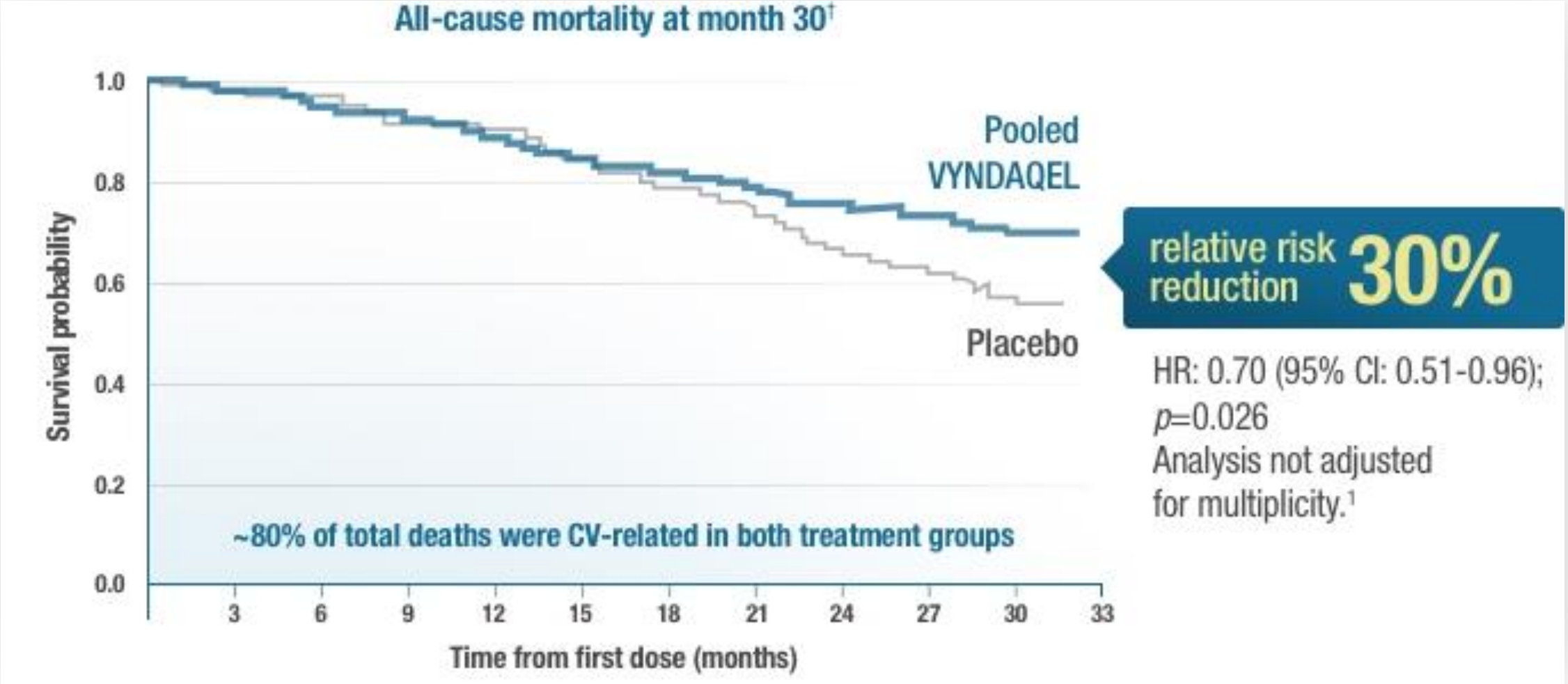
GLS= Global longitudinal strain
*Mean GLS value at baseline -18.34 (range -15.59 to -19.29); PRX004 alone is a subset of evaluable patients
[1] Solomon et al. Circulation. 2019
Error bar = Standard Error of the Mean
Not based on head-to-head studies

NYHA Classification Remained Stable with PRX004

- **Classification at baseline:**
  - NYHA I (n=6)
  - NYHA II (n=1)
- **All patients (n=7) were stable at their last assessed timepoint**
  - 5 patients with NYHA I at baseline remained stable at month 9
  - 1 patient with NYHA I at baseline transiently moved to NYHA II at month 9, but later returned to NYHA I
  - 1 patient with NYHA II at baseline remained stable at month 9

NYHA CLASS	PATIENT SYMPTOMS
I	**No limitation of physical activity**. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea
II	**Slight limitation of physical activity**. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea
III	**Marked limitation of physical activity.** Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	**Unable to carry on any physical activity without discomfort.** Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

Trend for Survival Does Not Show Clear Separation Until ~18 Months After Start of Tafamidis Treatment



Source: Maurer M et al. 2018

ATTR-ACT Phase 3 Study: Tafamidis Showed Little/No Effect in NYHA Class III ATTR Amyloidosis Patients

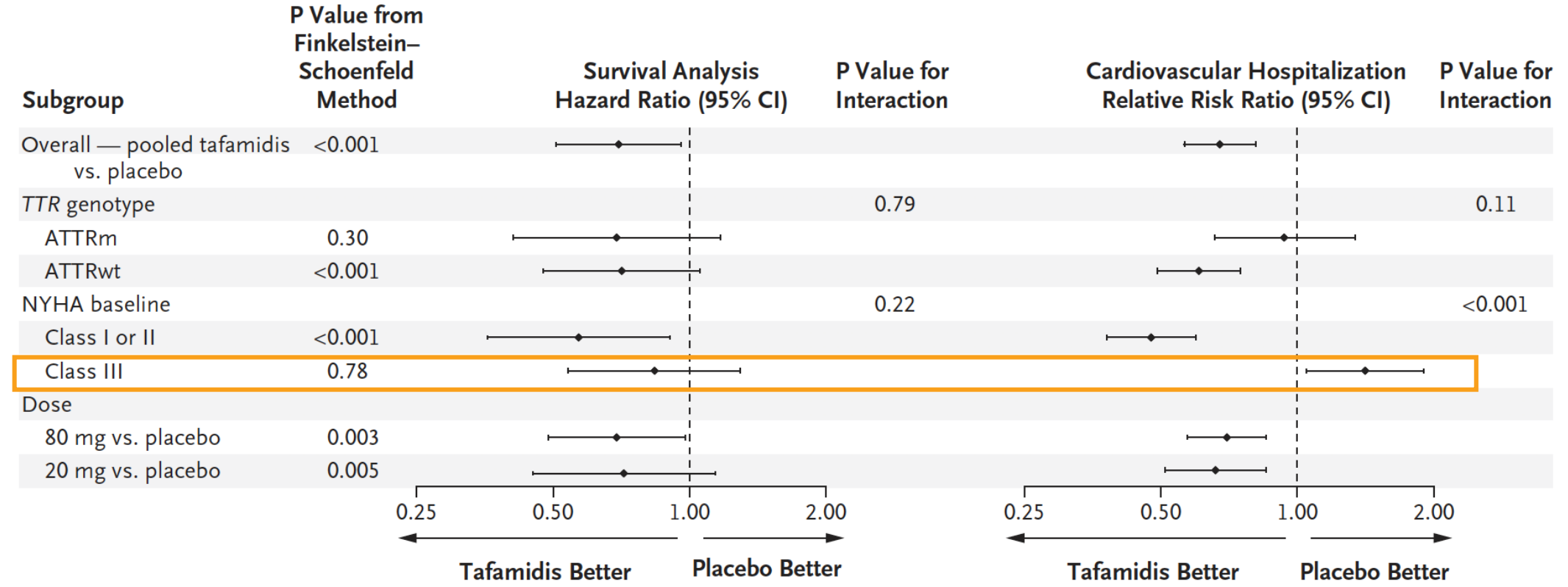
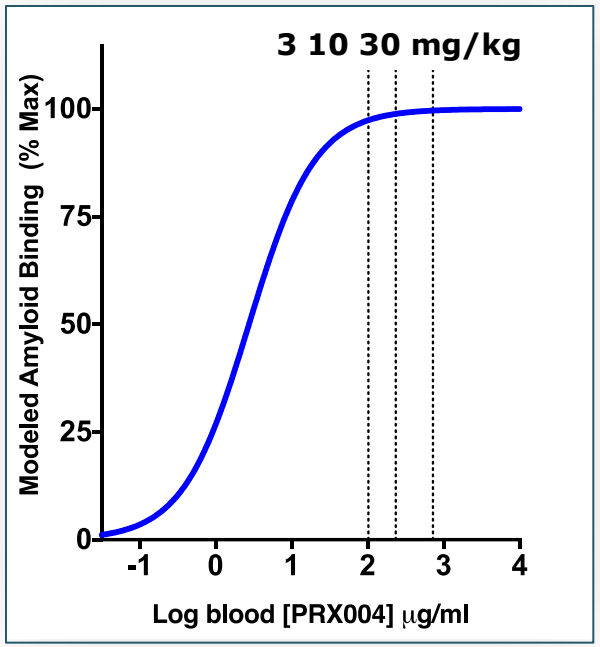


Figure 3. Overall and Subgroup Results as Calculated with the Use of the Finkelstein–Schoenfeld Method, All-Cause Mortality, and Cardiovascular-Related Hospitalizations.

Source: Maurer M et al. 2018

Preclinical PK/PD Dose Selection Model, Confirmed in PRX004–101

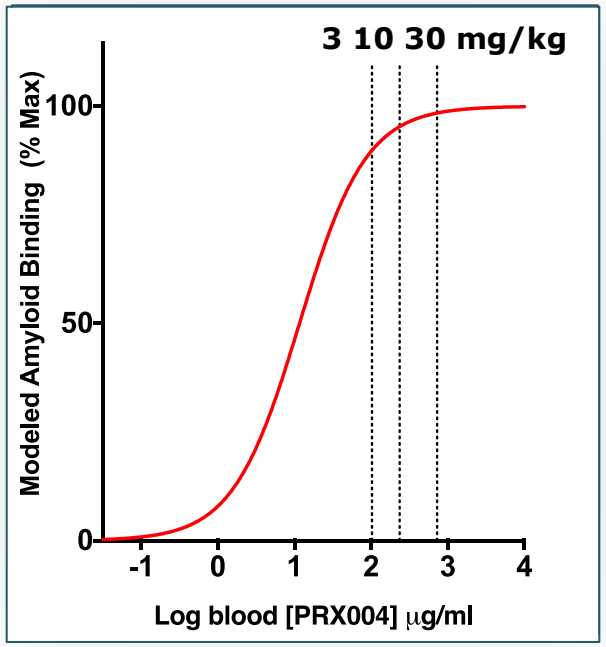
Preclinical PK/PD Model



Variables

- Binding kinetics and immunoreactivity to patient derived amyloid
- Antibody exposure in heart

Clinical Confirmation of Preclinical PK/PD Model



Variables

- Reduction in free non-native TTR by PRX004 (P1), accounting for plasma dilution and binding kinetics to amyloid vs. plasma monomers
- Antibody exposure in heart

PRX004 doses ≥3mg/kg expected to reach exposures to occupy >90% of amyloid

Prasinezumab

Supplemental Information

Phase 2b PADOVA Study (NCT04777331)

Early Parkinson's Disease Patients:

- A diagnosis of PD for at least 6 months to maximum 3 years at screening
- Hoehn & Yahr Stage I or II in ON and OFF states
- On symptomatic PD medication for at least 6 months, with stable doses for 3 months prior to baseline
- No anticipated changes in PD medication from baseline throughout the study duration
- DaT-SPECT imaging consistent with dopamine transporter deficit

Randomize 1:1
N = 575

Placebo (IV q4W)

Prasinezumab (IV q4W)

Primary Objective:

- Time to meaningful progression on motor signs as assessed by ≥5 point increase in MDS-UPDRS Part III score from baseline

Secondary Objectives:

- Time-to-worsening of motor function as reported by participant in MDS-UPDRS Part II and confirmed by clinician in MDS-UPDRS Part III
- Time to meaningful worsening in PGI
- Time to meaningful worsening in CGI
- Change in motor function from baseline to week 76, as measured by MDS-UPDRS Part III total score
- Change in bradykinesia from baseline to week 76, as measured by MDS-UPDRS Part III bradykinesia subscore
- Change in motor aspects of Experiences of Daily Living from baseline to Week 76, as measured by MDS-UPDRS Part II

PD, Parkinson's disease; IV, intravenous; q4W, infusion once every 4 weeks; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PGI, Patient Global Impression of Change; CGI, Clinician Global Impression of Change

Phase 2 PASADENA Study Summary of Part 1 & 2 Results

PRASINEZUMAB IN EARLY PARKINSON'S DISEASE

- **First anti-α-synuclein antibody to significantly slow progression on measures of PD; results support the potential of prasinezumab to slow underlying disease pathophysiology and clinical decline in patients with PD**
- **Slowed disease progression on measures of motor function**
  - Reduced decline in motor function by 35% vs. placebo at one year on MDS-UPDRS Part III, confirmed by site and central rating, Bradykinesia sub-score, and digital measures of motor function
- **Delayed time to clinically meaningful worsening of motor progression**
  - Reduced risk on time to worsening of motor signs
- **Prespecified subgroup analysis showed greater effect in slowing clinical decline in subgroups with faster disease progression**
- **Consistent signal favoring prasinezumab on cognition as well as clinician and patient impression of change endpoints and imaging biomarkers**
- **Generally safe and well tolerated, majority of AEs mild or moderate and similar across placebo and both treatment arms**
- **Participants who were treated with prasinezumab for 2 years (early-start group) are on a more favorable trajectory compared with participants treated with prasinezumab for 1 year (delayed-start group), as indicated by the signal of change from baseline in Movement Disorder Society-Unified PD Rating Scale Part III score, suggesting a potential effect of prasinezumab on delaying motor progression; this signal would need to be confirmed with additional studies.**
- **Progression in the early-start group was slower at Week 104 versus Week 52, suggesting a potential prolonged treatment effect**

Phase 2 PASADENA study did not meet its primary endpoint; results presented at the virtual 2020 International Congress of Parkinson's Disease and Movement Disorders Society September 15, 2020, www.prothena.com

PASADENA Phase 2 Study (NCT03100149)

Early Parkinson's Disease Patients:

- A diagnosis of PD for 2 years or less at screening
- Hoehn & Yahr Stage I or II
- Not expected to require dopaminergic treatment within 52 weeks from baseline

Randomize 1:1:1
N = 316

Part 1 – Complete 52-week double-blind treatment

- Placebo IV q4W
- prasinezumab 1500 mg IV q4W
- prasinezumab IV q4W 4500 mg (BW ≥ 65 kg) or 3500 mg (< 65 kg)

Part 2 - Ongoing 52-week complete

- prasinezumab 1500 mg IV q4W
- prasinezumab IV q4W 4500 mg (BW ≥ 65 kg) or 3500 mg (< 65 kg)
- prasinezumab 1500 mg IV q4W
- prasinezumab IV q4W 4500 mg (BW ≥ 65 kg) or 3500 mg (< 65 kg)

Primary Objective:

- Evaluate efficacy using MDS-UPDRS at Week 52

Secondary Objectives:

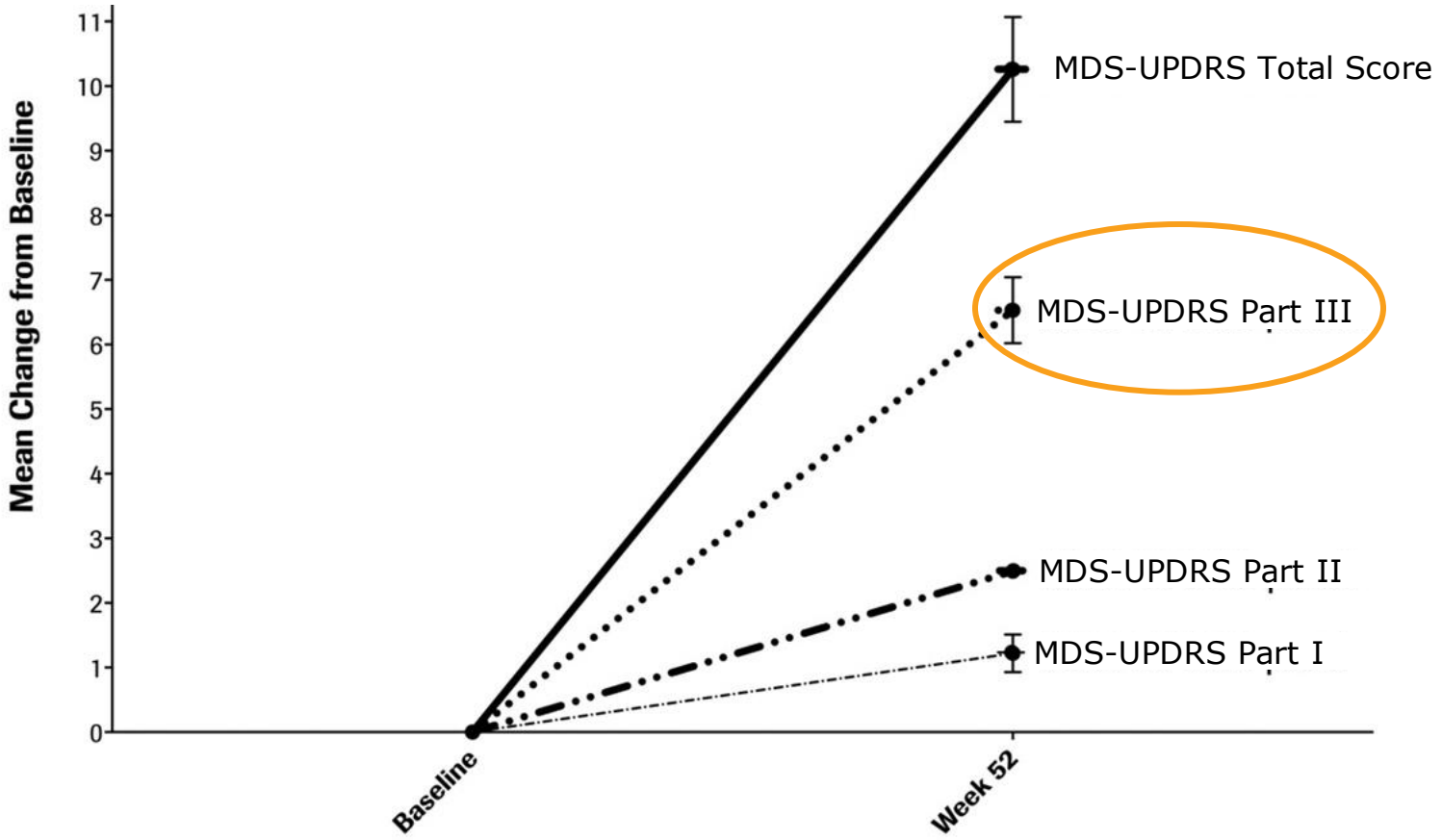
- MDS-UPDRS Part I non-motor aspects; MDS-UPDRS Part II experiences of daily living
- MDS-UPDRS Part III motor examination and Part III subscores
- MoCA total score
- PGI-C, CGI-I and SE-ADL
- DaT-SPECT
- Digital PASADENA motor score
- Safety and tolerability up to 104 weeks
- Evaluate pharmacokinetics up to 104 weeks

Signal-detection study designed to include 100 patients/arm, resulting in 80% power and two-sided alpha of 0.20, to detect a 37.5% relative change in MDS-UPDRS total score between groups from baseline to Week 52

IV, intravenous; q4W, infusion once every 4 weeks; BW, body weight

Progression of MDS-UPDRS Total Over 1 Year is Mostly Driven by MDS-UPDRS Part III in an Early-Stage Population (PPMI study)

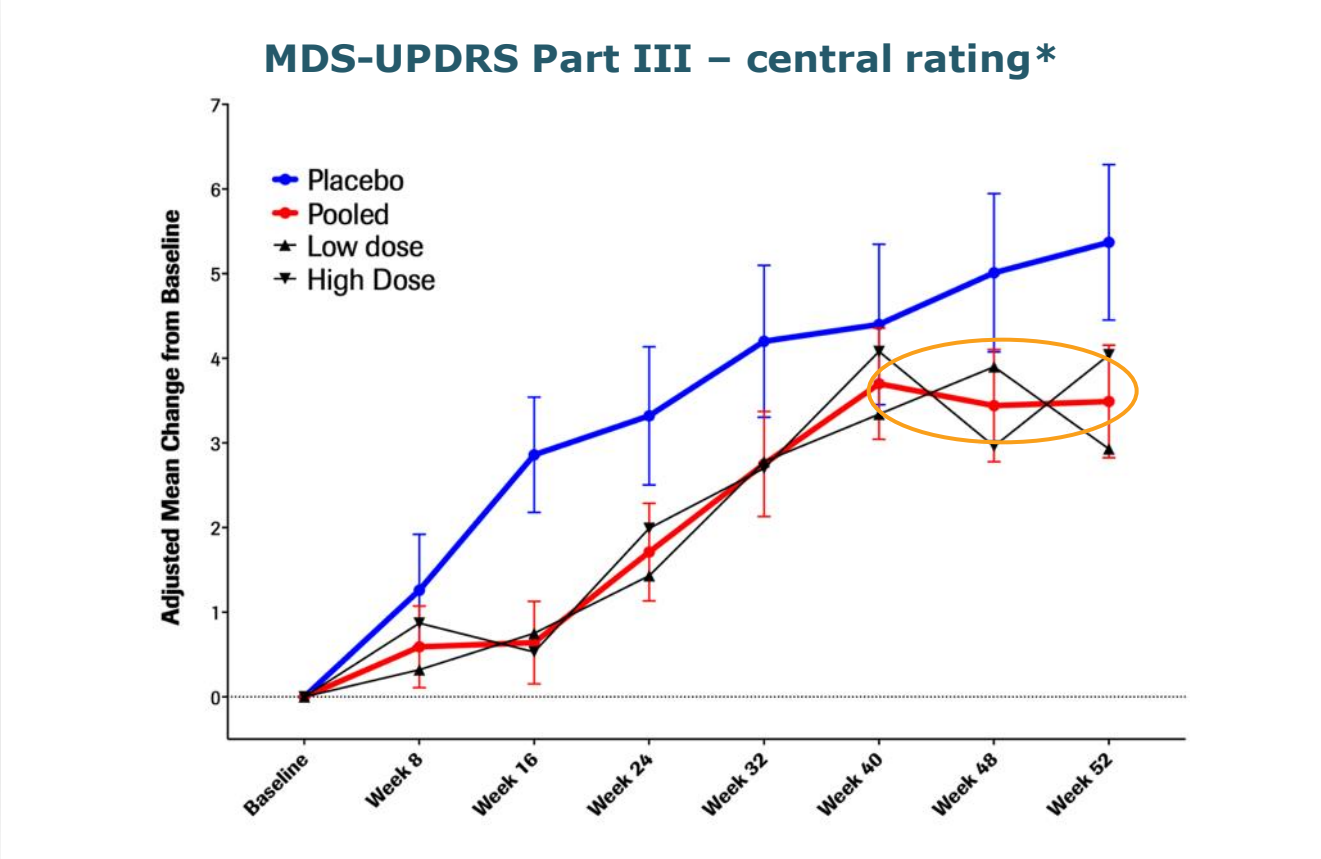
Change in MDS-UPDRS over 1 year in PPMI study



MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Marker Initiative
Graph developed using raw data, downloaded from the PPMI website (https://www.ppmi-info.org/) (Accessed February 2021)

PASADENA Phase 2

SIGNIFICANTLY SLOWED PROGRESSION OF MDS-UPDRS PART III



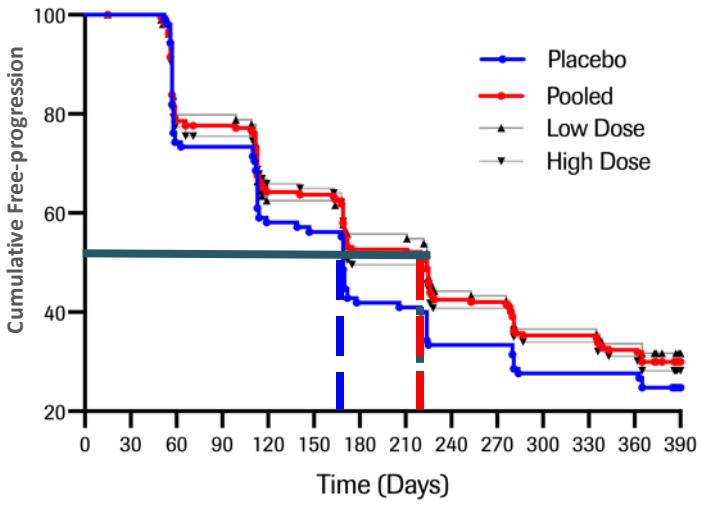
SECONDARY ENDPOINT:
Change in total MDS-UPDRS Part III from baseline to Week 52

*Patients who started symptomatic PD treatment contribute until the last visit before symptomatic PD treatment is started. Bars represent 80% CI. Estimates are based on a MMRM with the following covariates: MAO-Bi at baseline (y/n), treatment, week, age <60 vs ≥60, sex, DaT-SPECT putamen binding ratio (contralateral to most clinically affected side), baseline MDS-UPDRS corresponding endpoint.
Pooled dose level p=0.09, statistical analyses conducted in alignment with powering to detect changes at a two-sided alpha of 0.20; p-values below 0.20 are considered significant. Comparing the results of the pooled treatment arms vs. placebo was a prespecified exploratory analysis of MDS-UPDRS
CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; MAO-Bi, monoamine oxidase B inhibitor; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMRM, mixed-effect model repeated measures; PD, Parkinson's disease.

PASADENA Phase 2

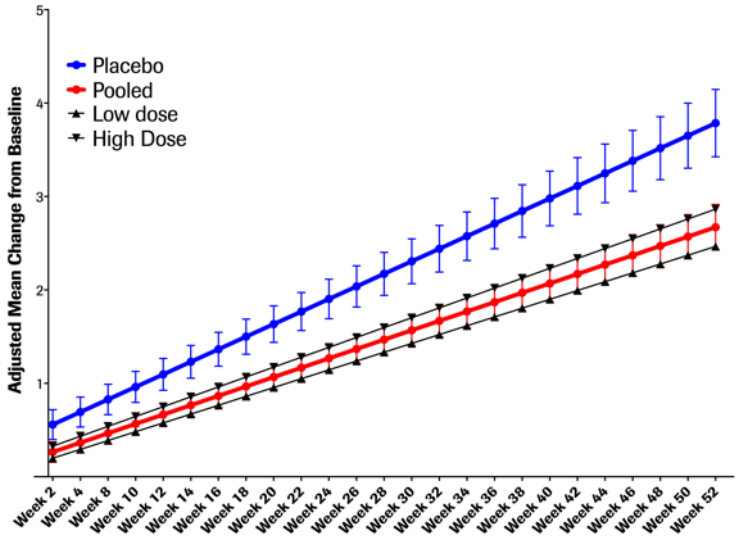
SIGNIFICANTLY DELAYED TIME TO WORSENING OF MOTOR FUNCTION, CONFIRMED BY DIGITAL MEASURES OF PROGRESSION

Exploratory Endpoint: **Time to worsening of motor function** (≥5 points MDS-UPDRS Part III)



Hazard ratio* comparison to placebo:
Pooled: **0.82**, 80% CI=0.64 to 0.99
Low dose: **0.77**, 80% CI=0.63 to 0.96
High dose: **0.87**, 80% CI=0.70 to 1.07

Exploratory Endpoint: **Digital PASADENA motor score** from baseline to Week 52

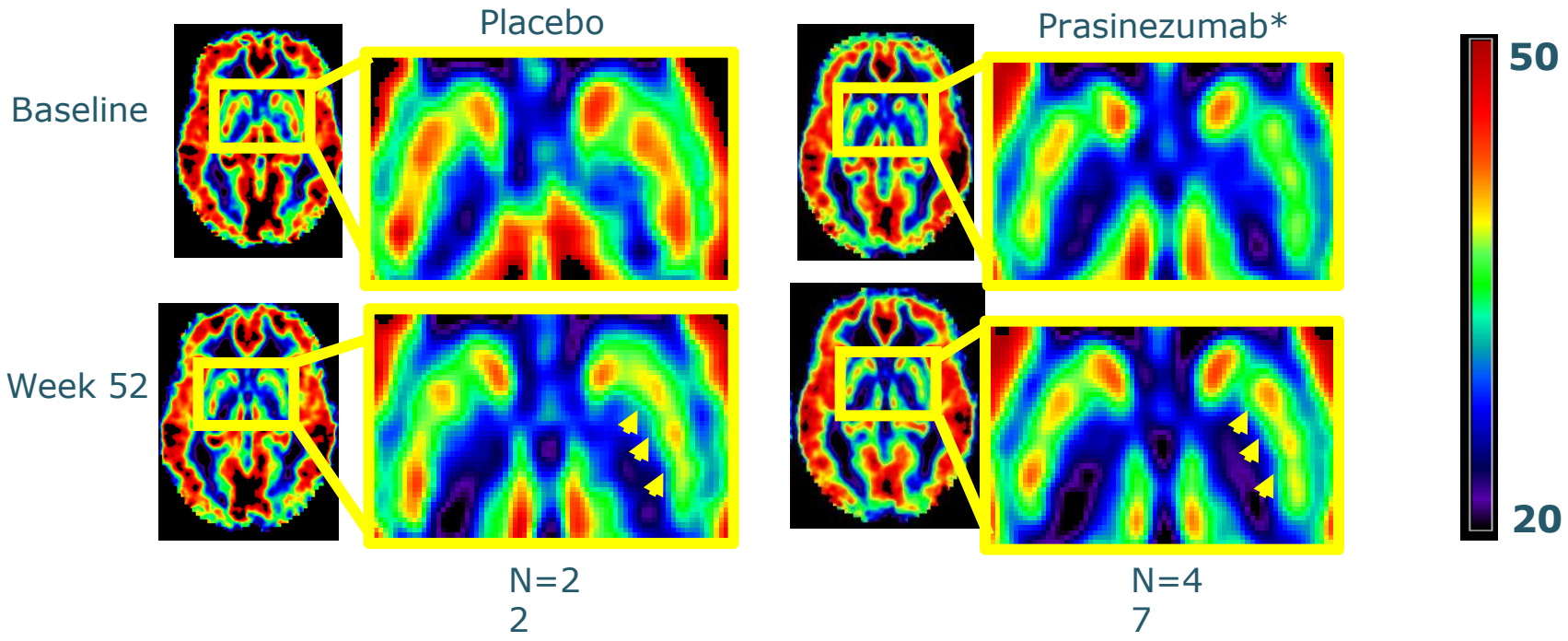


Pooled: –0.030, 80% CI=(–0.050, –0.010); **-25.0%**
Low dose: –0.040, 80% CI=(–0.063, –0.017); **–30.3%**
High dose: –0.029, 80% CI= (–0.052, –0.006); **–21.5%**

*Wald CI/test. Pooled dose level on time to worsening of motor function, p=0.17, statistical analyses conducted in alignment with powering to detect changes at a two-sided alpha of 0.20; p-values below 0.20 are considered significant. Comparing the results of the pooled treatment arms vs. placebo was a prespecified exploratory analysis of MDS-UPDRS.
Pooled dose analysis for digital PASADENA motor score is a post-hoc analysis. The digital PASADENA motor score was built from 80% bradykinesia features and 20% resting tremor features using blinded data from 150 PASADENA patients prior to unblinding.
CI, confidence interval; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale.

PASADENA Phase 2

IMPROVEMENT IN CEREBRAL BLOOD FLOW IN THE PUTAMEN

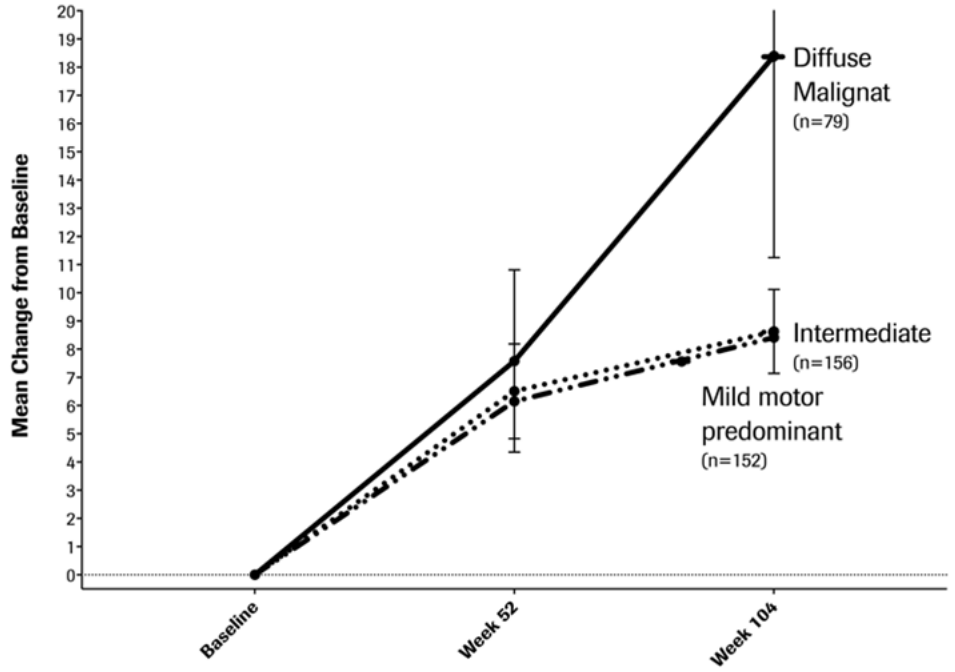


Exploratory endpoint: change in cerebral blood flow in the brain regions from baseline to Week 52 (MRI-ASL)

Images from a subset of all individuals treated with prasinezumab (Low/High dose). Images are a composite of all patients overlaid to create a mean image
MRI-ASL, magnetic resonance-arterial spin labelling

Opportunity to Detect Treatment Effect is Increased in Fast-Progressing Individuals

Sub-phenotype progression in PPMI population[1]



In the PASADENA study population, the following subgroups* were defined for further analyses:

Mild motor predominant (n=106)
Motor and all non-motor scores <75th percentile

Diffuse malignant (n=59)
Score on motor scales > 75th percentile AND at least 1 score on a non-motor scale >75th percentile; OR all 3 non-motor scales > 75th percentile

Intermediate (n=151)
All other individuals

Treatment naive (n=201)

MAO-B inhibitor treated (n=115)

Diffuse malignant sub-phenotype showed faster motor progression on MDS-UPDRS Part III in PPMI[1,2]
PASADENA analyses were performed in diffuse malignant and MAO-B inhibitor subgroups

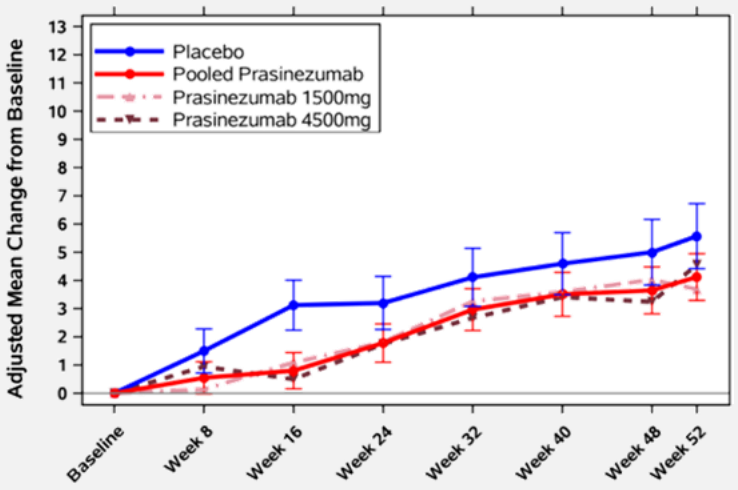
For the derivations of the data-driven sub-phenotypes, scales were classified into; motor scales (MDS-UPDRS Part II and MDS-UPDRS-Part III) and non-motor scales (SCOPA-AUT, RBDSQ and MoCA).
*Please note, the population sizes in the subgroup analyses are small. MAO-B monoamine oxidase B; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; PPMI, Parkinson's Progression Marker Initiative; RBDSQ, Rapid Eye Movement Sleep Behaviour Disorder Questionnaire.
[1] Pagano et al. PPMI Unpublished; [2] Fereshtehnejad S, et al. JAMA Neurol. 2015; 72:863-873.

Slowing of Clinical Decline with Prasinezumab was More Evident in Individuals with Faster Disease Progression

MDS-UPDRS Part III*

Total population (N=316)

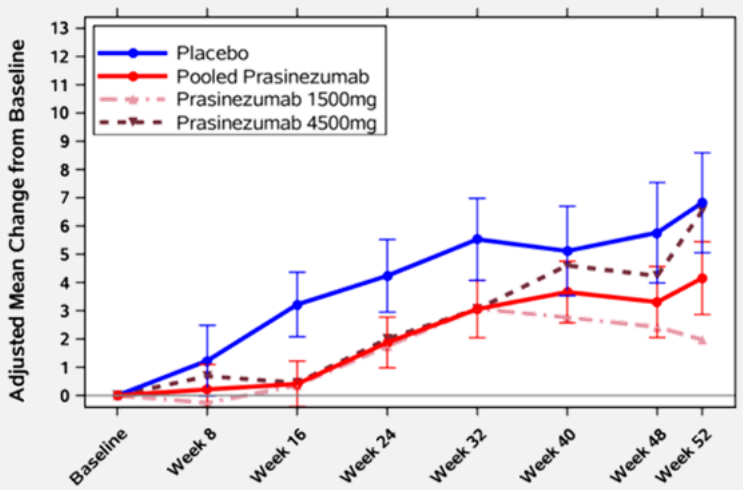
Change at Week 52 (placebo) = **5.57** points



Pooled: −1.44, 80% CI=(−2.83, −0.06); **−25.0%**
Prasinezumab 1500 mg: −1.88, 80% CI=(−3.49, −0.27); **−33.8%**
Prasinezumab 4500 mg: −1.02, 80% CI=(−2.64, 0.61); **−18.2%**

MAO-B inhibitor treated (n=115)

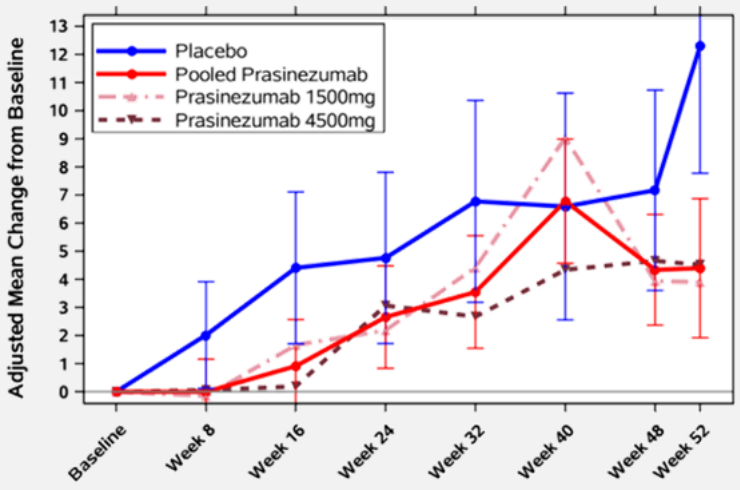
Change at Week 52 (placebo) = **6.82** points



Pooled: −2.66, 80% CI=(−4.87, −0.45); **−39.0%**
Prasinezumab 1500 mg: −4.85, 80% CI=(−7.33, −2.37); **−71.1%**
Prasinezumab 4500 mg: −0.28, 80% CI=(−2.82, 2.25); **−4.0%**

Diffuse malignant (n=59)

Change at Week 52 (placebo) = **12.29** points



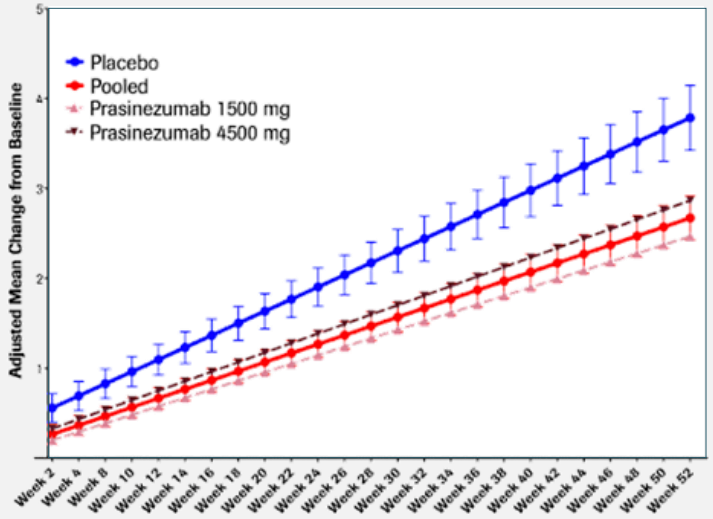
Pooled: −7.86, 80% CI=(−12.9, −2.82); **−63.9%**,
Prasinezumab 1500 mg: −8.4, 80% CI=(−14.2, −2.59); **−68.3%**
Prasinezumab 4500 mg: −7.77, 80% CI=(−13.4, −2.14); **−63.2%**

*Patients who started symptomatic PD treatment contribute until the last visit before symptomatic PD treatment is started. Bars represent 80% CI. Estimates are based on a MMRM with the following covariates: MAO-B inhibitor at baseline (yes/no), treatment, week, age <60 vs ≥60, sex, DaT-SPECT putamen binding ratio (contralateral to most clinically affected side), baseline MDS-UPDRS corresponding endpoint. Pooled-dose analysis is a pre-specified exploratory analysis. 4500 mg for ≥65 kg; 3500 mg for <65 kg. CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; MAO-B, monoamine oxidase B; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; MMRM, mixed-effect model repeated measures; PD, Parkinson's disease.

Slowing of Clinical Decline with Prasinezumab was More Evident in Individuals with Faster Progression in Digital Motor Measures

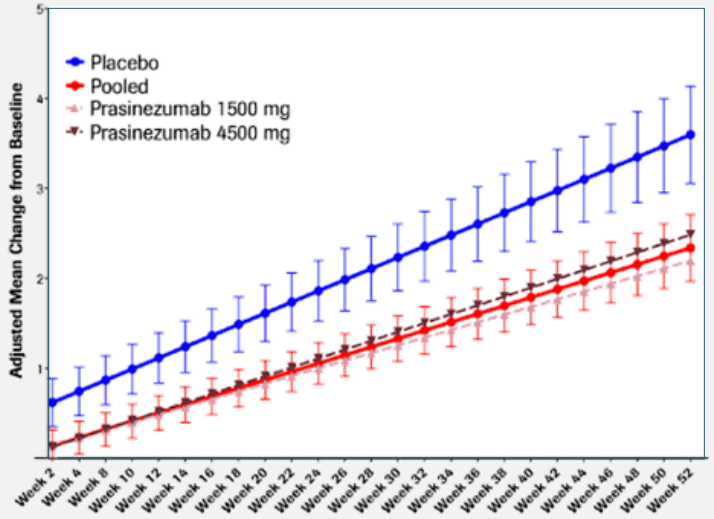
PASADENA Digital Motor Score

Total population (N=316)



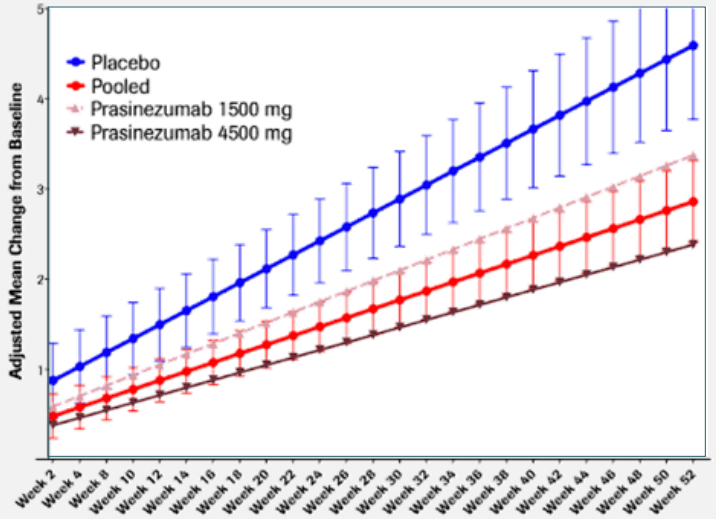
Pooled: −0.030, 80% CI=(−0.050, −0.010); **−25.0%**
Prasinezumab 1500 mg: −0.040, 80% CI=(−0.063, −0.017); **−30.3%**
Prasinezumab 4500 mg: −0.029, 80% CI= (−0.052, −0.006); **−21.5%**

MAO-B inhibitor treated (n=115)



Pooled: −0.032, 80% CI=(−0.062, −0.003); **−26.0%**
Prasinezumab 1500 mg: −0.039, 80% CI=(−0.072, −0.049); **−31.0%**
Prasinezumab 4500 mg: −0.026, 80% CI= (−0.060, 0.008); **−20.9%**

Diffuse malignant (n=56)



Pooled: −0.055, 80% CI=(−0.105, −0.005); **−35.7%**
Prasinezumab 1500 mg: −0.039, 80% CI=(−0.094, 0.017); **−25.2%**
Prasinezumab 4500 mg: −0.071, 80% CI= (−0.126, −0.017); **−46.2%**

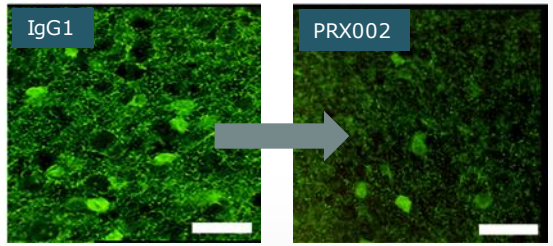
*Patients who started symptomatic PD treatment contribute until the last visit before symptomatic PD treatment is started. Bars represent 80% CI. Estimates are based on a MMRM with the following covariates: MAO-B inhibitor at baseline (yes/no), treatment, week, age <60 vs ≥60, sex, DaT-SPECT putamen binding ratio (contralateral to most clinically affected side), baseline MDS-UPDRS corresponding endpoint. Pooled-dose analysis is a pre-specified exploratory analysis. 4500 mg for ≥65 kg; 3500 mg for <65 kg. CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; MAO-B, monoamine oxidase B; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; MMRM, mixed-effect model repeated measures; PD, Parkinson's disease.

Summary of Effects of Prasinezumab in Multiple Preclinical Models of Synucleinopathy

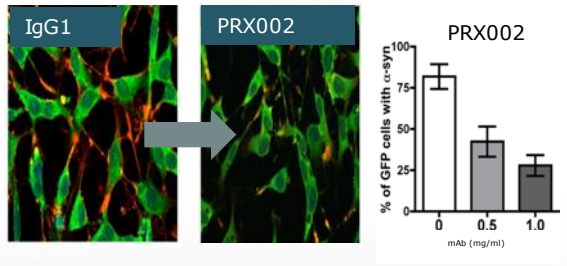
Prasinezumab (murine form of 9E4) demonstrated in multiple in vivo and cellular α-synucleinopathy models to:[1–3]

- ✓ Reduce build-up of intracellular α-Syn pathology and protect neurons
- ✓ Block cell-to-cell transmission of α-Syn
- ✓ Co-localize with intracellular lysosomes and autophagosomes
- ✓ Protect synapses
- ✓ Reduce gliosis
- ✓ Ameliorate motor and cognitive behavioral deficits

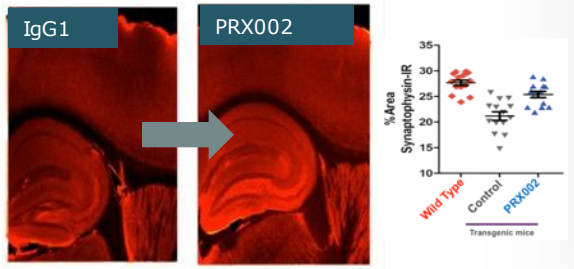
Lowering of α-Syn Pathology



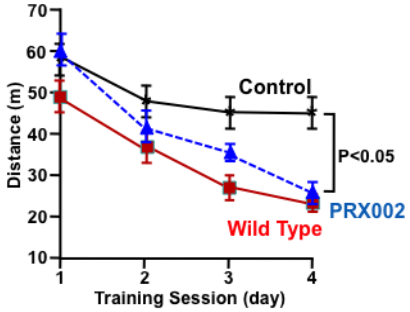
Blockade of cell-to-cell transmission



Protection of Synapses



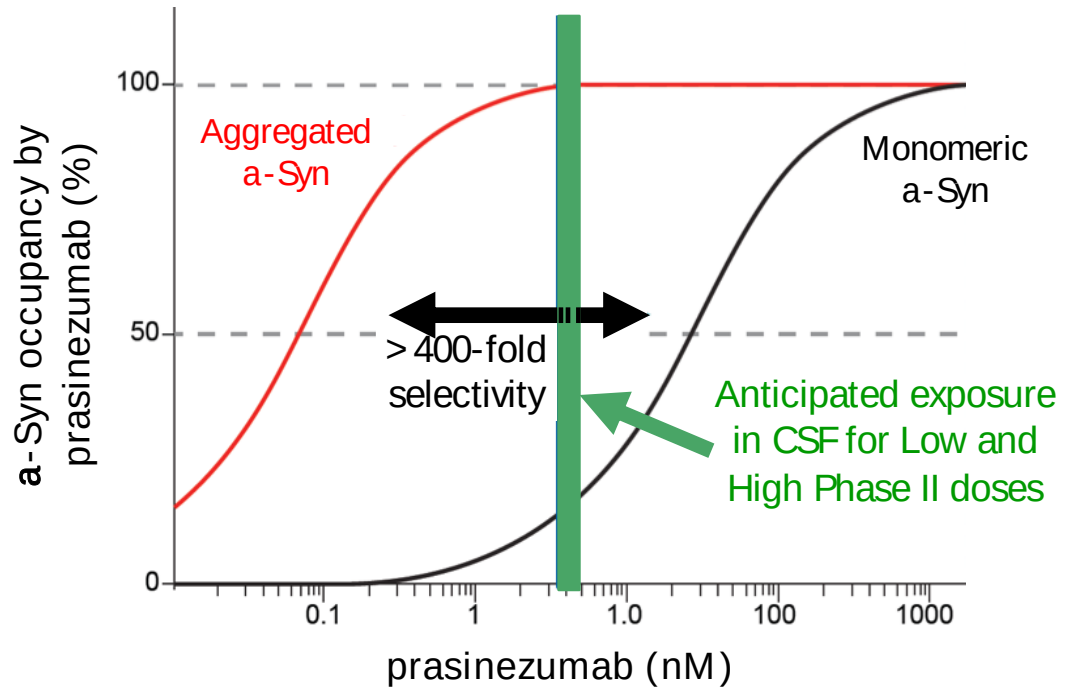
Improvement in Behavior (water maze)



Preclinical models are 9E4, the murine form of prasinezumab
α-Syn, alpha-synuclein; CNS, central nervous system.
[1] Masliah E, et al. *Neuron*. 2005; 46:857–868; [2] Masliah E, et al. *PLoS ONE*. 2011; 6:e19338; [3] Games D, et al. *J Neurosci*. 2014; 34:9441–9454

Pharmacokinetic/Pharmacodynamic Framework

BOTH PHASE 2 DOSE LEVELS SATURATE THE TARGET



Elements determining target-occupancy in CNS

- Relative concentrations of prasinezumab in peripheral and central compartments
- Relative concentrations of a-synuclein in the periphery, CSF, and brain
- Affinity/Avidity of prasinezumab to aggregated a-synuclein at the relevant site of action in the brain

CSF, cerebral spinal fluid; ISF, interstitial fluid
Jankovic J et al. *JAMA Neurol*. 2018; 75:1206–1214

PASADENA Phase 2 Baseline Demographics

PRESENTED AT AAT-AD/PD, APRIL 2020

Baseline data (1/2)

	PASADENA All patients (n=316)	PASADENA patients on MAO-Bi (n=115)	PASADENA drug-naive patients (n=201)	PPMI PASADENA-like PD patients* (n=337)
Age, years				
Mean (SD)	59.9 (9.1)	58.2 (9.0)	60.8 (9.0)	61.3 (9.7)
Gender				
Male	213 (67.4%)	74 (64.3%)	139 (69.2%)	221 (65.6%)
Female	103 (32.6%)	41 (35.7%)	62 (30.8%)	116 (34.4%)
Disease duration, months				
Mean (SD)	10.1 (6.5)	12.0 (6.1)	9.1 (6.5)	6.4 (6.3)
Education, years				
Mean (SD)	15.6 (5.0)	15.8 (5.6)	15.5 (4.5)	15.5 (3.0)
Hoehn–Yahr Stage				
I	78 (24.7%)	32 (27.8%)	46 (22.9%)	139 (41.2%)
II	238 (75.3%)	83 (72.2%)	155 (77.1%)	197 (58.5%)
MDS-UPDRS total				
Mean (SD)	31.4 (12.8)	30.2 (12.0)	32.1 (13.2)	32.6 (13.0)
MDS-UPDRS Part II				
Mean (SD)	5.3 (4.0)	5.2 (3.9)	5.4 (4.1)	6.1 (4.2)
MDS-UPDRS Part III				
Mean (SD)	21.5 (9.0)	20.5 (8.9)	22.0 (9.1)	20.9 (8.9)

*PD patients identified using PASADENA criteria for the diagnosis of PD.
MAO-Bi, monoamine oxidase B inhibitor; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative; SD, standard deviation.

PASADENA Phase 2 Baseline Demographics

PRESENTED AT AAT-AD/PD, APRIL 2020

Baseline data (2/2)

	PASADENA All patients (n=316)	PASADENA patients on MAO-Bi (n=115)	PASADENA drug-naive patients (n=201)	PPMI PASADENA-like PD patients* (n=337)
MDS-UPDRS Part I				
Mean (SD)	4.6 (3.8)	4.5 (3.4)	4.7 (4.1)	5.6 (3.9)
MoCA				
Mean (SD)	27.9 (2.0)	28.3 (2.0)	27.7 (2.0)	27.2 (2.3)
REM sleep behaviour disorder				
Positive (≥5)	85 (27.0%)	33 (28.7%)	52 (26.0%)	126 (37.6%)
Negative (<5)	230 (73.0%)	82 (71.3%)	148 (74.0%)	209 (62.4%)
SCOPA-AUT				
Mean (SD)	8.1 (5.7)	7.7 (4.8)	8.3 (6.6)	9.7 (6.2)
DaT-SPECT Putamen Contralateral				
Mean (SD)	0.80 (0.25)	0.81 (0.25)	0.78 (0.24)	0.68 (0.27)
DaT-SPECT Putamen Ipsilateral				
Mean (SD)	1.06 (0.39)	1.09 (0.33)	1.02 (0.30)	0.96 (0.39)

*PD patients identified using PASADENA criteria for the diagnosis of PD.
DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; MAO-Bi, monoamine oxidase B inhibitor;
MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease;
PPMI, Parkinson's Progression Markers Initiative; REM, rapid eye movement; SCOPA-AUT, Scales for outcomes in Parkinson's disease autonomic dysfunction; SD, standard deviation.

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PASADENA Phase 2 Overview of Safety Data

	PLACEBO (N=105)	LOW DOSE (N=105)	HIGH DOSE (N=106)	ALL PATIENTS (N=316)
Total number of AEs*	411	428	549	1388
Total number of AE with fatal outcome (Grade 5)*	0	0	0	0
Total number of patients with at least one (%):†				
AE	87 (82.9)	98 (93.3)	97 (91.5)	282 (89.2)
SAE	5 (4.8)	7 (6.7)	8 (7.5)	20 (6.3)
Grade 3–4 AE	8 (7.6)	4 (3.8)	8 (7.5)	20 (6.3)
AE leading to withdrawal from treatment or dose interruption	1 (0.9)	2 (1.9)	5 (4.7)	8 (2.5)
All Grade IRR	17 (16.2)	20 (19.0)	36 (33.9)	73 (23.1)
Grade 1–2 IRR	17 (16.2)	20 (19.0)	35 (33)	72 (22.8)
Grade 3 IRR	0	0	1 (0.9)	1 (0.3)

Similar AEs and IRRs profile across Low-High dose and placebo

*Most AEs were Grade 1–2. Only one Grade 4 AE (suicide attempt) was reported and considered unrelated to study treatment (High-dose group). The most frequently reported (>1.0%) Grade 3–4 AEs were: radius fracture - two patients (1.9%) in the Placebo group (but no patient in the prasinezumab-treated groups) and anxiety - two patients (1.9%) in the High-dose group (no patient in the Low-dose or Placebo group).
†Percentages are based on N in the column headings. Only treatment-emergent AEs are displayed where the study medication adjustment case report form question is answered as "drug withdrawn". For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. AE, adverse event; IRR, infusion-related reaction; SAE, serious AE.

NNC6019/PRX004

Supplemental Information

Summary of Phase 1 Study Results

PRX004* IN ATTR AMYLOIDOSIS

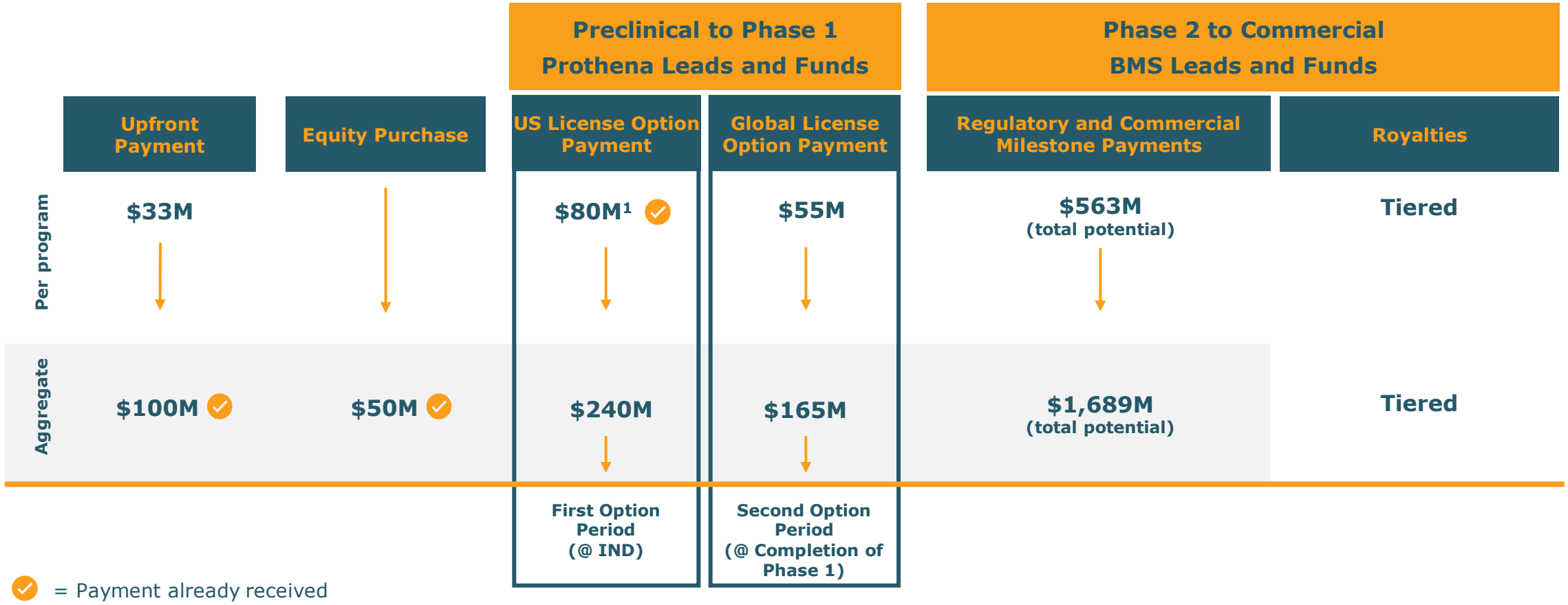
- **First clinical results from a depleter mechanism of action in ATTR amyloidosis**
  - 223 total doses administered through the end of the study
  - Patient received between 3 – 17 doses
- **All six dose levels of PRX004 found to be generally safe and well-tolerated**
- **Positive results on neuropathy and cardiac function**
  - Mean change in NIS of +1.29 points in all 7 evaluable patients was more favorable than the expected +9.2 points based on published historical data
  - Change in NIS for each of the 7 evaluable patients was also more favorable than published historical data
  - Improvement of neuropathy in 3 of 7 evaluable patients, with a mean change in NIS of –3.33 points
  - Improvement in cardiac systolic function in all 7 evaluable patients, with a mean change in GLS of –1.21%
  - All 7 evaluable patients remained stable on NYHA Class

*PRX004 is also known as NNC6019

Partnerships and Collaboration Details

Global Neuroscience R&D Collaboration with Bristol Myers Squibb

INCLUDES PRX005 (TAU), TDP-43 AND PRX019



*BMS = Bristol-Myers Squibb; collaboration with BMS, following its acquisition of Celgene in November 2019; total of up to $2.2 billion, including upfront payment and equity investment, future potential option payments and regulatory and commercial milestones, plus potential additional U.S. and global product sales royalties

[1] U.S. license option payment received for tau program; first of three total potential US License Option payments

Worldwide Collaboration with Roche

Total Milestones	prothena®	Roche
	$755M	**$--**
✓ Upfront, P1, P2 and P2b milestones	**135M***	--
☐ Clinical, regulatory & first sale	290M	--
☐ U.S. sales milestones	155M	--
☐ Ex-U.S. sales milestones	175M	–
• U.S.	• Up to double digit teen royalties	• Leads clinical development
• U.S. co-promote	• Ability to opt-in	• Will lead commercialization
• Ex-U.S.	• Up to double digit teen royalties	• Sole responsibility to develop and commercialize

First Patient Dosed in Phase 2b PADOVA Study in May 2021;
$60 Million Milestone Earned From Roche

*Includes $60 million milestone announced in May 2021 from Roche as earned (received in June 2021)