PRX004, the First Investigational Anti-Amyloid Immunotherapy for the Treatment of ATTR Amyloidosis

9-month results from a Phase 1 long-term extension study

December 9, 2020

Agenda and Speakers

- **Introduction**
  - Gene Kinney, PhD, President & Chief Executive Officer
- **ATTR Amyloidosis Overview**
  - Wagner Zago, PhD, Chief Scientific Officer
- **PRX004 Phase 1 Study Results**
  - Ole Suhr, MD, Senior Professor, Department of Public Health and Clinical Medicine, Umeå University
- **ATTR Amyloidosis Patient Journey – Diagnosis, Treatment Options, and Unmet Need**
  - Daniel Lenihan, MD, Director, Cardio-Oncology Center of Excellence, Cardiovascular Division, Washington University in St. Louis
- **Next Steps and Summary**
  - Radhika Tripuraneni, MD, MPH, Chief Development Officer & ATTR Program Head
- **Concluding Remarks**
  - Gene Kinney, PhD, President & Chief Executive Officer
- **Q&A**
  - Tran Nguyen, Chief Operating Officer & Chief Financial Officer

Forward-looking Statements

This overview contains forward-looking statements. These statements relate to, among other things: the design, proposed mechanism of action and possible clinical benefits of PRX004, and its potential as a treatment for ATTR amyloidosis; the potential of PRX004 to complement proven therapies and offer superior efficacy; the design and capabilities of our misTTR assay for hereditary ATTR; the design of the Phase 1 study of PRX004; the design and timing of future clinical studies of PRX004; the design, proposed mechanism of action and possible clinical benefits of prasinezumab (PRX002/RG7935), and its potential as a treatment for Parkinson's disease; the design and timing of future clinical studies of prasinezumab; amounts we might receive under our collaboration with Roche; the sufficiency of our cash position to fund advancement of a broad pipeline; the continued advancement of our discovery and preclinical pipeline; our goal of building a neurotherapeutics engine; potential Tau and abeta indications; our potential to advance, initiate and complete IND enabling studies for our tau and abeta programs; and our ability to progress our vaccine program. These forward-looking 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 the effects on our business of the worldwide COVID-19 pandemic and the risks, uncertainties and other factors described in the "Risk Factors" sections of our Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 3, 2020, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the SEC. We undertake no obligation to update publicly any forward-looking statements contained in this presentation as a result of new information, future events or changes in our expectations.

Introduction

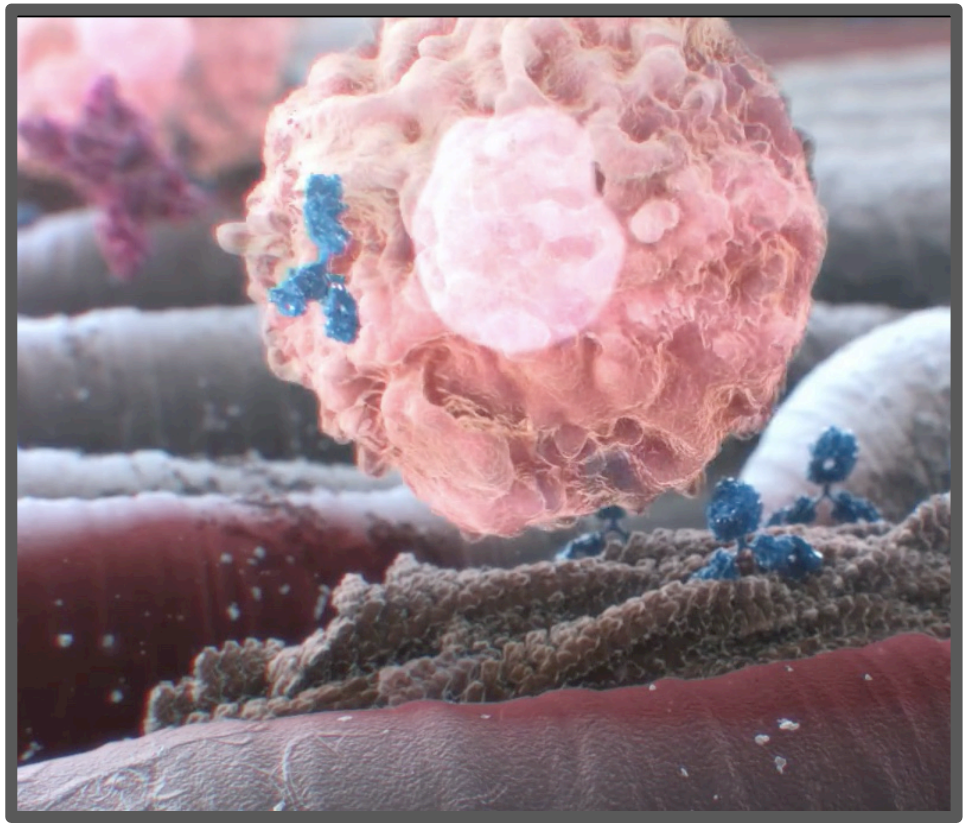
Gene Kinney, PhD

President & CEO

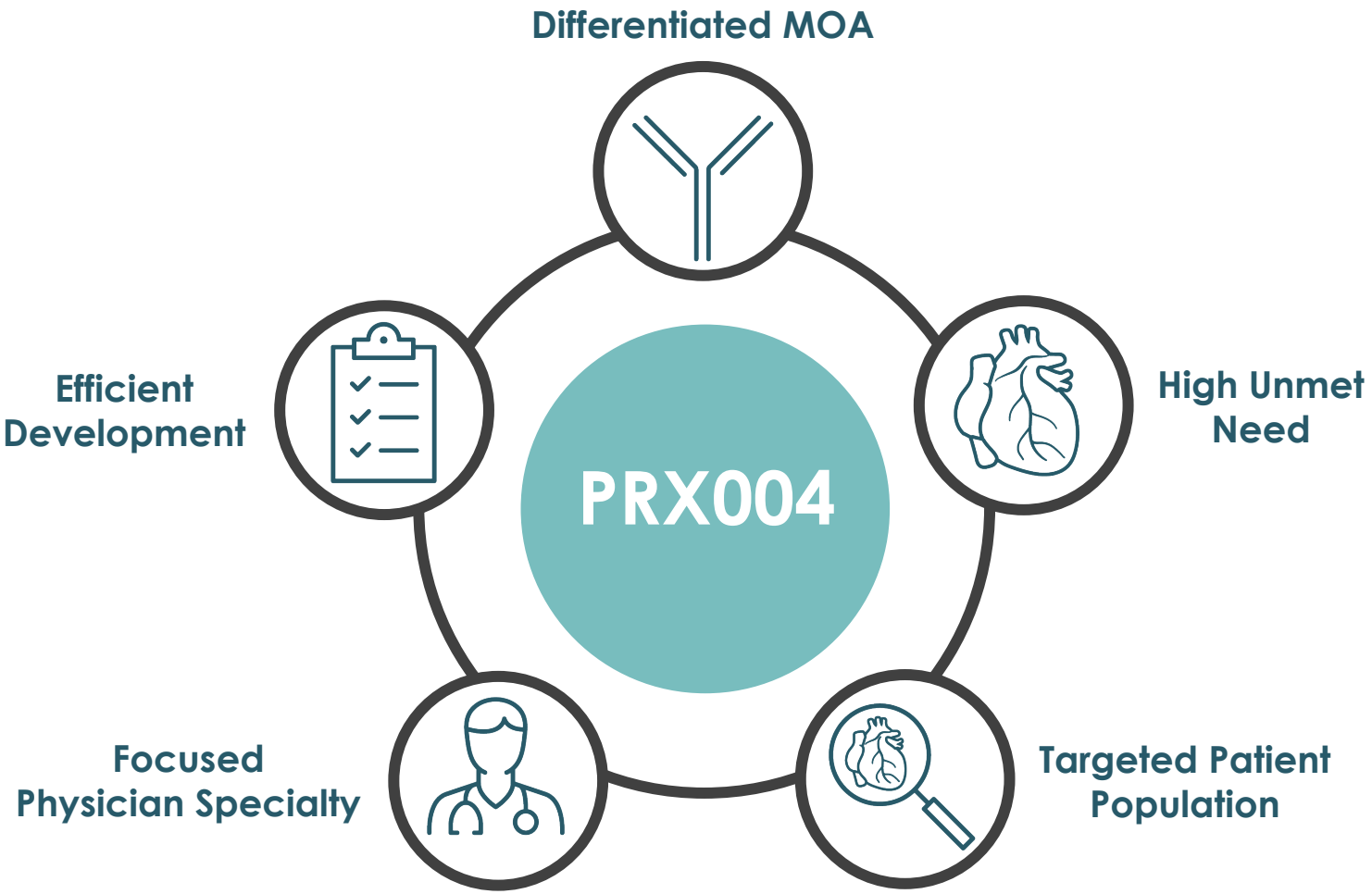
Protein Dysregulation and Amyloid Causes Multiple Fatal Diseases

Expertise in **protein dysregulation** applied to **rare peripheral amyloid disease** and **neurodegeneration**

- ✓ Understanding protein dysregulation in the context of disease
- ✓ Expertise in targeting toxic proteins to alleviate detrimental effects
- ✓ Translating science into clinical benefit across multiple programs



PRX004: Depleter MOA for ATTR Amyloidosis



Phase 1 results of first-in-class amyloid depleter demonstrate:

- Improvement in neuropathy
- Improvement in cardiac function
- Favorable safety & tolerability

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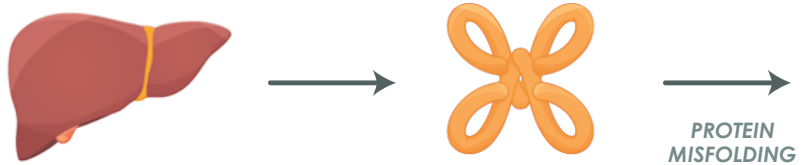
ATTR Amyloidosis Overview

Wagner Zago, PhD,
Chief Scientific Officer

Amyloid Deposition Causes ATTR Amyloidosis

Amyloid accumulates over time and is present in organs at diagnosis

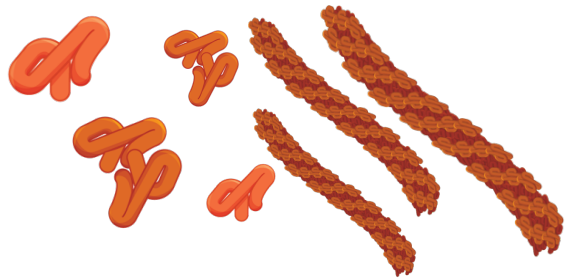
Non-Pathogenic Pathway



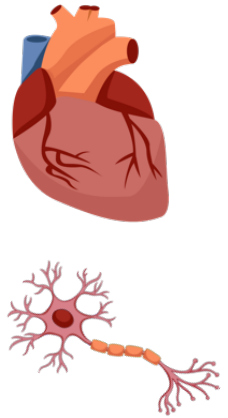
LIVER

FREE
TETRAMER

Pathogenic Pathway



MONOMER, SOLUBLE AGGREGATE
AMYLOID FIBRILS



HEART
Restrictive cardiomyopathy
Heart failure

PERIPHERAL NERVES
Loss of sensation
Loss of reflex
Muscle weakness

Current treatment approach:
Reduce new protein entering pathogenic pathway

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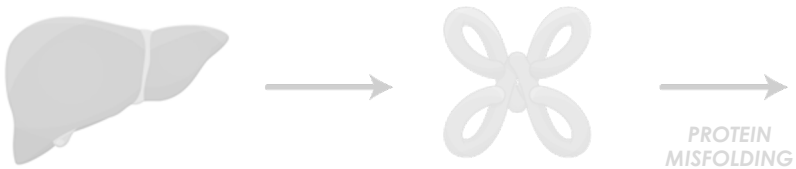
PRX004: Differentiated Depleter MOA

Specifically targets non-native transthyretin (TTR) to clear amyloid

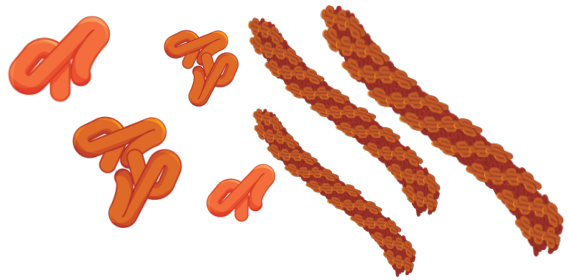
Non-Pathogenic Pathway



LIVER

FREE
TETRAMER

Pathogenic Pathway



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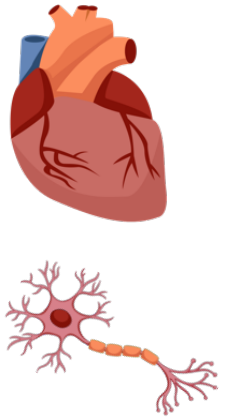

HEART
Restrictive cardiomyopathy
Heart failure

PERIPHERAL NERVES
Loss of sensation
Loss of reflex
Muscle weakness

Current treatment approach:
Reduce new protein entering pathogenic pathway

PRX004:
Amyloid depletion
Uniquely suited for patients at high risk of early mortality

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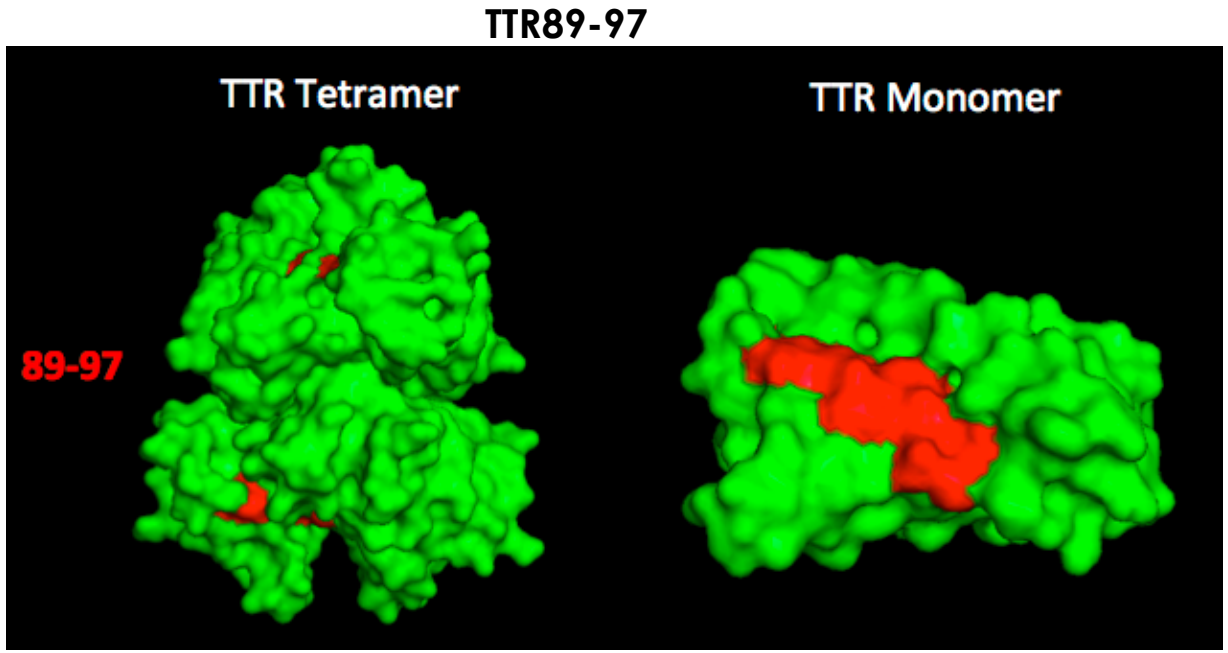
Prothena Developed PRX004 to Target an Epitope Exposed on Pathogenic Forms of TTR[1]

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



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

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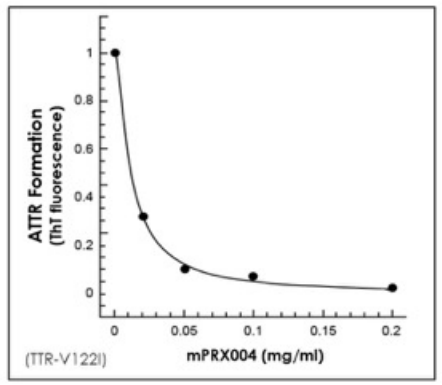
PRX004: Designed to Deplete Amyloid

Summary of preclinical effects of mPRX004

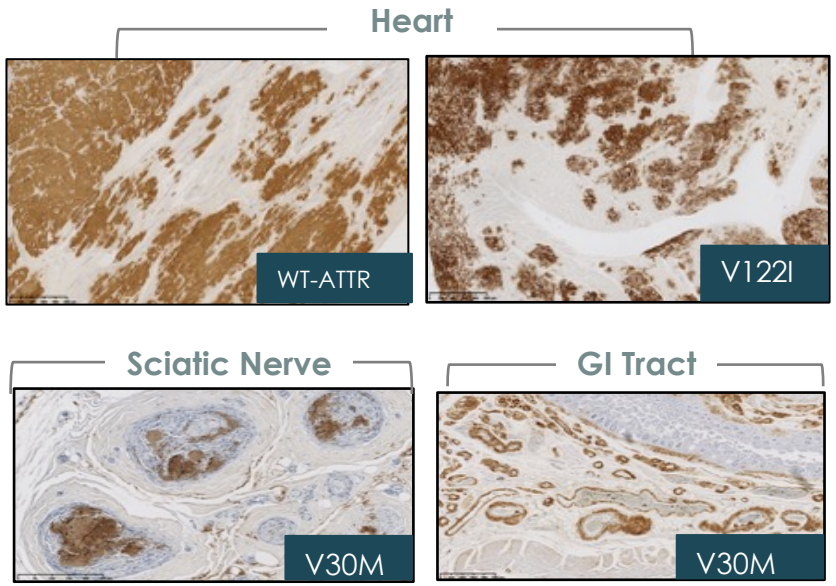
mPRX004 (murine form of PRX004) preclinical results:[1]

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

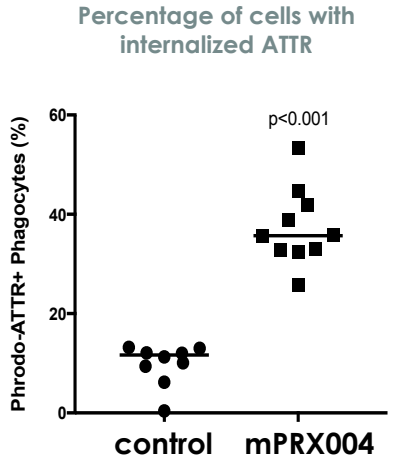
Inhibition of amyloid formation



Specific binding to amyloid



Clearance of amyloid



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

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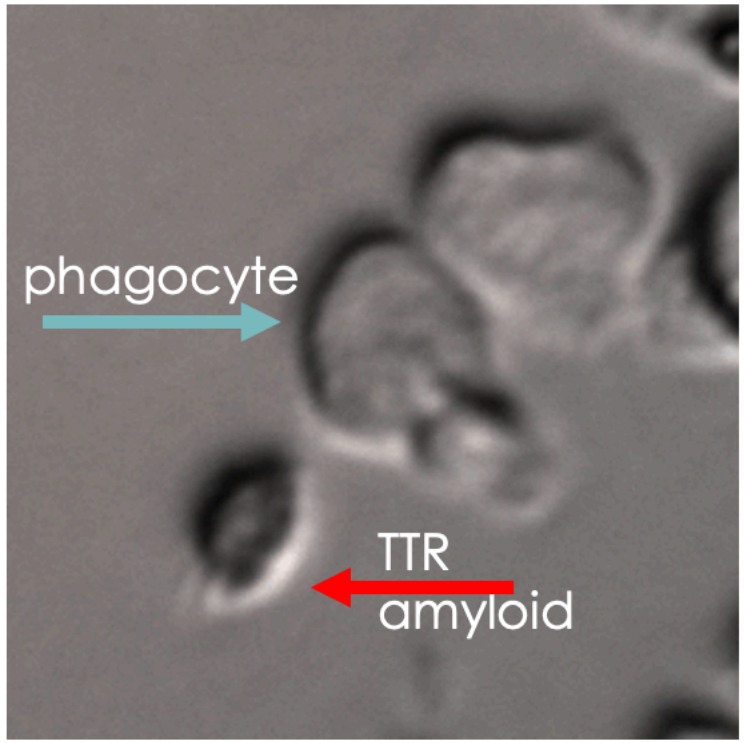
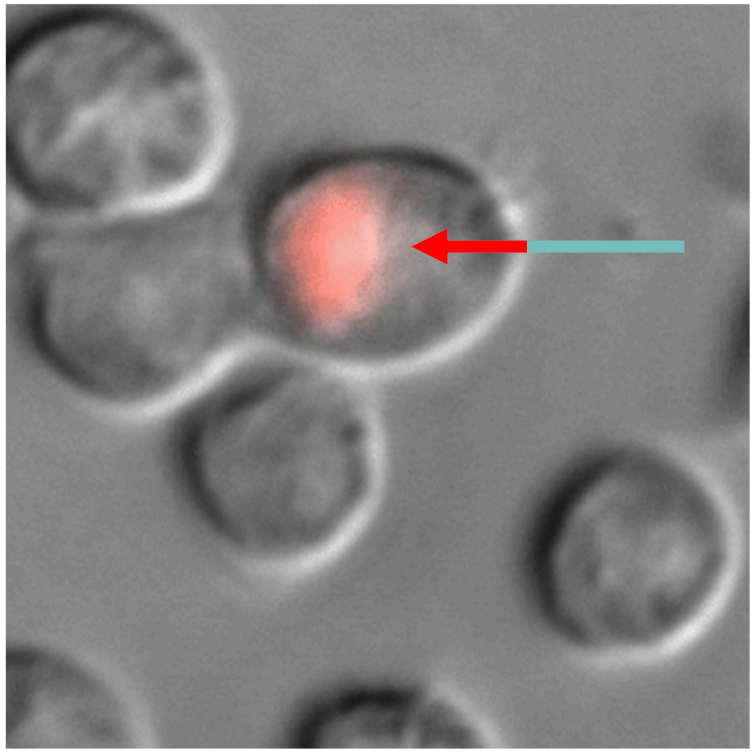
mPRX004* Depletes Amyloid by Phagocytosis In Vitro

Control IgG



mPRX004*



In the presence of PRX004, phagocytes engulf amyloid, indicated by red fluorescence

mPRX004 induces antibody-dependent phagocytosis of ATTR by phagocytes

* Murine form of PRX004

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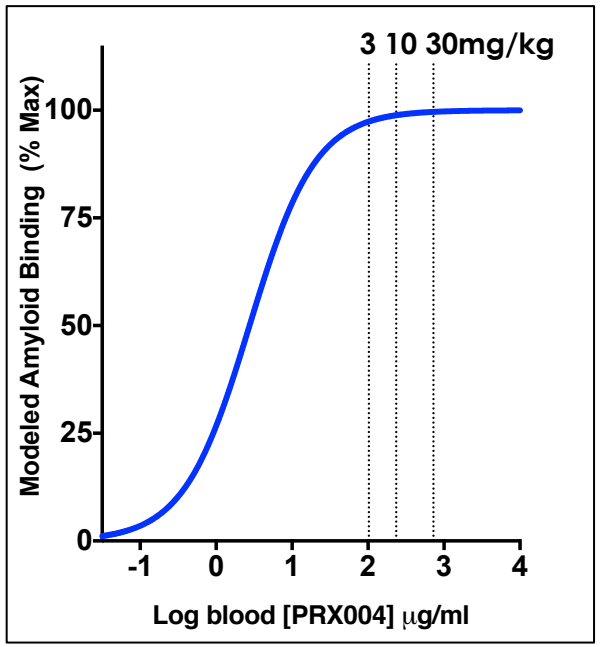
Preclinical PK/PD Dose Selection Model, Confirmed in PRX004–101

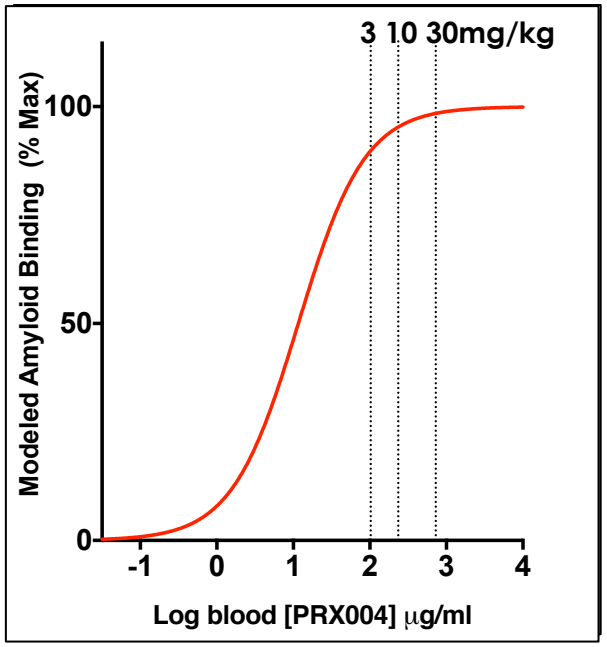
Preclinical PK/PD Model



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

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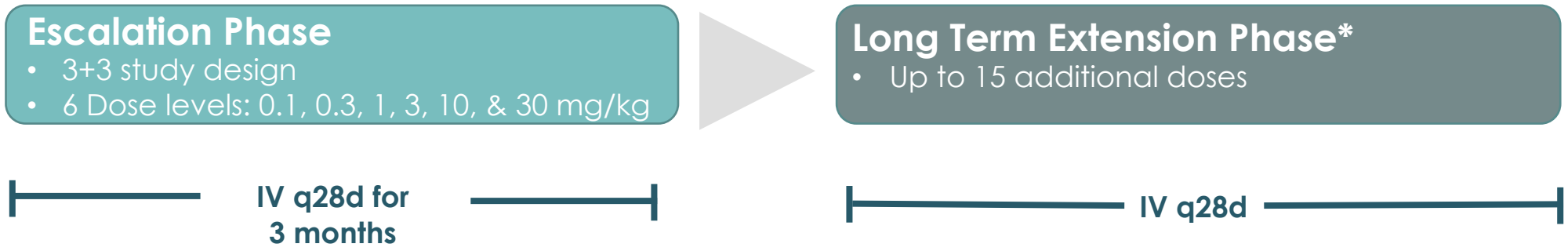
PRX004 Phase 1 Study Results

Ole Suhr, MD

Senior Professor, Department of Public Health and Clinical Medicine, Umeå University

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 hATTR-PN with or without hATTR-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

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PRX004: Summary of Baseline Demographic Data

	PRX004 0.1 mg/kg (n=3)	PRX004 0.3 mg/kg (n=3)	PRX004 1 mg/kg (n=3)	PRX004 3 mg/kg (n=3)	PRX004 10 mg/kg (n=3)	PRX004 30 mg/kg (n=6)	Overall (n=21)
Age Range (years)	68-72	65-68	66-75	58-78	42-75	44-70	42-78
Sex: Male/ (%)	66.7	33.3	66.7	66.7	33.3	83.3	61.9
Race:							
White/Non-white (%)	100	100	100	100	100	83.3/16.7	95.2/4.8
Ethnicity: (%)							
Not Hispanic/Latino	100	100	100	100	100	100	100
Primary Disease*:							
Both CM and PN	2 (66.7%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	5 (83.3%)	11 (52.4%)
Cardiomyopathy only	N/A	1 (33.3%)	2 (66.7%)	N/A	N/A	N/A	3 (14.3%)
Peripheral Neuropathy only	1 (33.3%)	1 (33.3%)	N/A	2 (66.7%)	2 (66.7%)	1 (16.7%)	7 (33.3%)

The 7 patients evaluable for efficacy had similar baseline characteristics

* Defined per the Principal Investigator's clinical impression. Regardless of primary disease, all patients had NYHA assessed during course of study

No Serious Treatment Related AEs

PRX004 exposure and summary of TEAEs

Dose Escalation Phase, Cohorts 1-6, completed (all subjects received at least 3 doses of PRX004)

During the study (end of Long-Term Extension):

- 223 infusions were given over 21 patients
- Patients received between 3-17 infusions

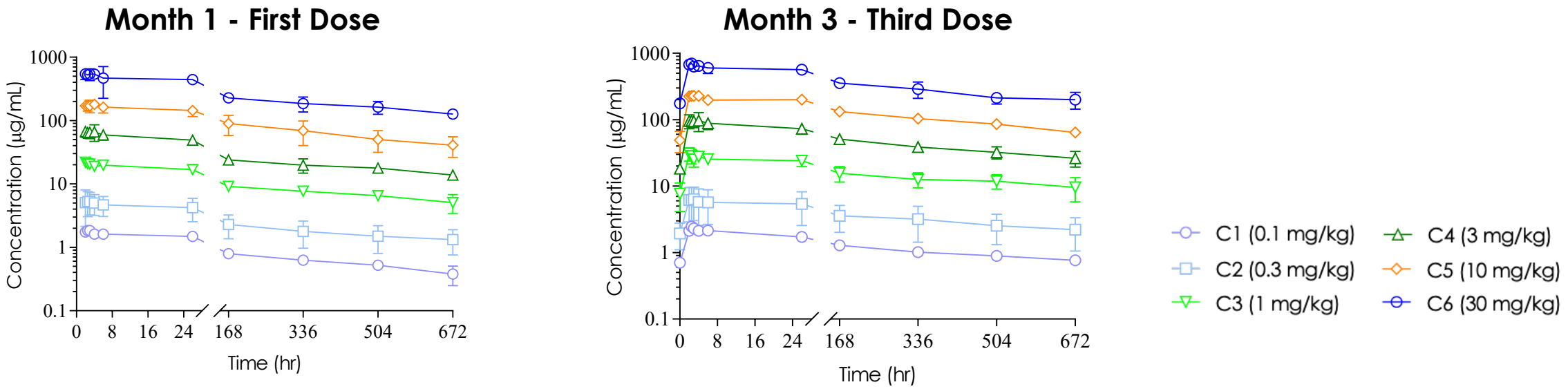
	PRX004 0.1 mg/kg (N=3)	PRX004 0.3 mg/kg (N=3)	PRX004 1 mg/kg (N=3)	PRX004 3 mg/kg (N=3)	PRX004 10 mg/kg (N=3)	PRX004 30 mg/kg (N=6)	Overall (N=21)
Number of Subjects Reporting at Least One:							
TEAE leading to death	0	0	0	0	0	0	0
Total Number of Serious TEAEs:							
Treatment related (# of patients reporting)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not treatment related (# of patients reporting)	0 (0)	0 (0)	2 (1)	0 (0)	3 (2)	5 (2)	10 (5)

PRX004 Safe and Well Tolerated Through LTE

- **For subjects administered PRX004 at all dose levels and time points:**
  - Multiple IV infusions of PRX004 were generally safe and well-tolerated
  - No dose-limiting toxicities, no serious, related TEAEs and no life-threatening or fatal events have been reported
  - One subject had study drug withdrawn due to pregnancy
  - Two subjects had transient ADA findings, with no clinical or PK findings

Overall, no clinical safety trends in clinical laboratory data, vital signs, ECG parameters or echocardiogram were observed in the study

PRX004 Exposure Increases in a Dose Proportional Manner



- Dose-proportional increase in exposure across all 6 dose level cohorts
- Mean observed half-life of ~31 days was similar across all 6 dose level cohorts

C = cohort; Only 2 timepoints in Month 2

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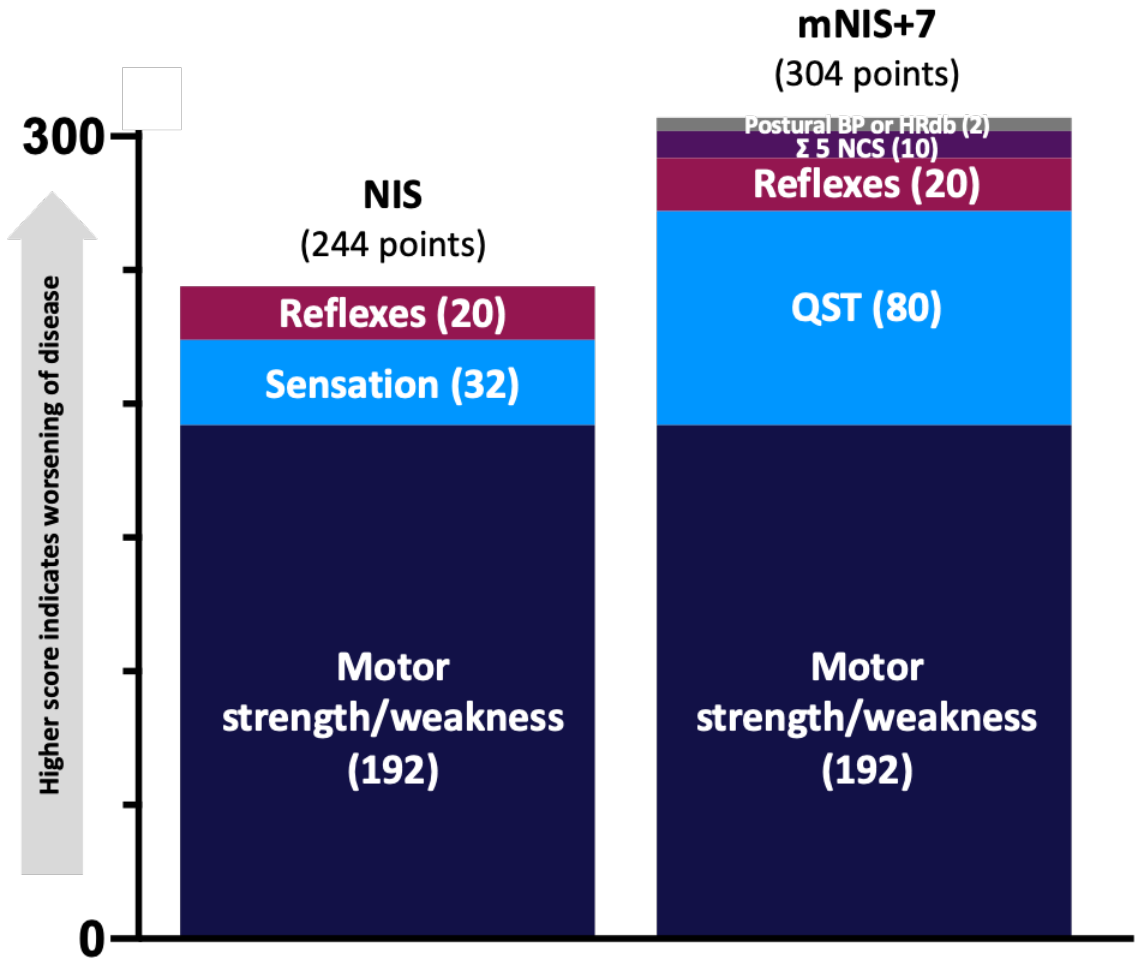
Neuropathy Impairment Assessments in Clinical Studies



BP: Blood Pressure
HRdb: Heart Rate Response to Deep Breathing
NCS: Nerve Conduction Studies
QST: Quantitative Sensory Testing

Adapted from Adams D et al., *Neurology. 2015*

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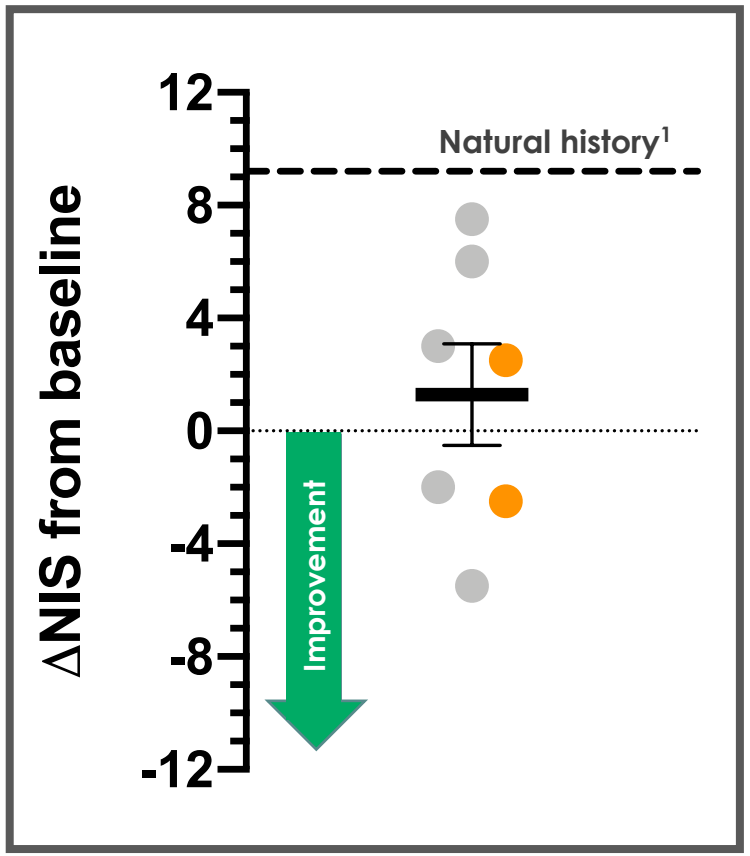
Observed Improvement in Neuropathy with PRX004



- 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	
	All	PRX004 Alone
ΔNIS mean* (n)	**+1.29** (n=7)	**0.00** (n=2)
Time point	9 months	

Natural History[1]	Patisiran[2]
+9.2 (N=349)	**+2.6** (N=27)
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
Error bar = Standard Error of the Mean
Not based on head-to-head studies

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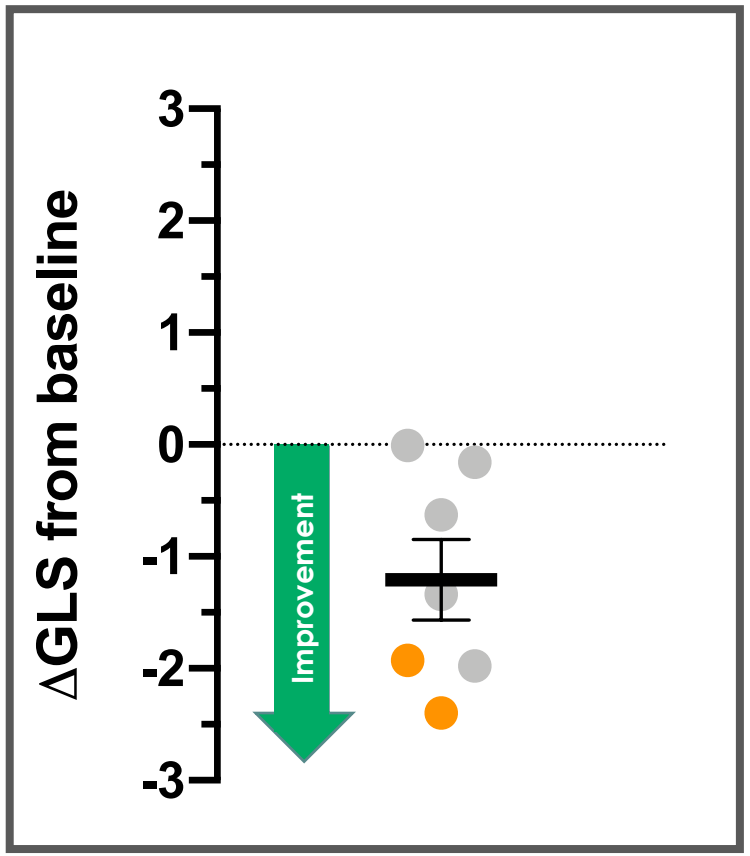
Observed Improvement in Cardiac Systolic Function with PRX004



- **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		Placebo-treated[1]	Patisiran[1]
	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

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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

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
- **Depleter MOA may provide a new treatment paradigm for patients at high risk of early mortality due to amyloid deposition**

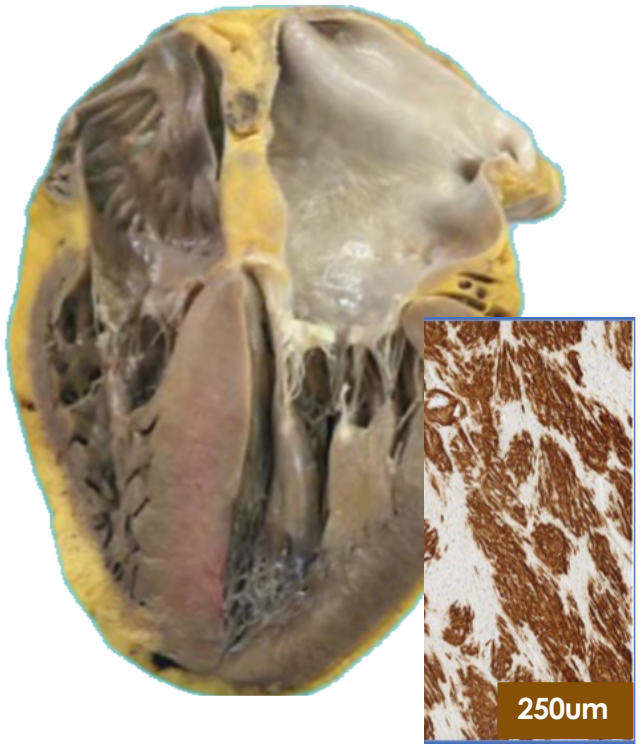
ATTR Amyloidosis Patient Journey – Diagnosis, Treatment Options, and Unmet Need

Daniel Lenihan, MD

Director, Cardio-Oncology Center of Excellence
Cardiovascular Division, Washington University in St. Louis

ATTR Amyloidosis is Caused by Amyloid Deposition

- ATTR amyloidosis is a rare, progressive, and fatal disease caused by amyloid deposition leading to organ dysfunction and failure
- In amyloidosis, proteins misfold, form toxic aggregates and deposit as amyloid in vital organs
  - Most commonly the heart and peripheral nerves
- Clinical manifestations of the disease depend on impacted organs and degree of deposition
- Morbidity and mortality is driven by restrictive cardiomyopathy and progressive heart failure



By the time they are diagnosed, patients have accumulated significant cardiac amyloid deposition

Photo: Clevelandclinic.org

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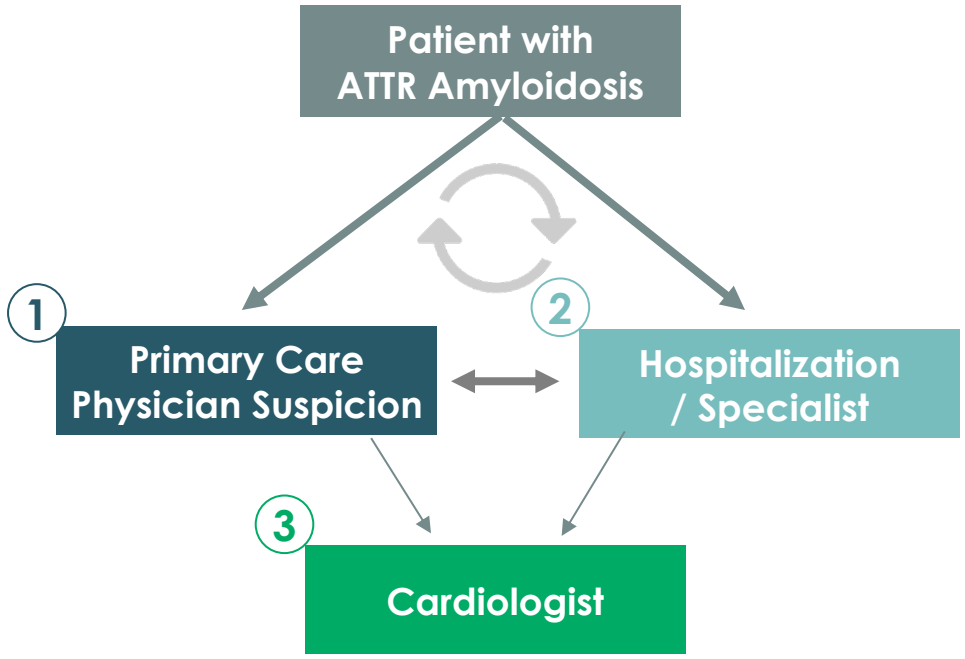
Patients Often Present with Advanced Cardiac Disease



1 Patients may present with symptoms attributed to other cardiovascular conditions

- ATTR suggested as significant underlying cause of heart failure with preserved ejection fraction (HFpEF)
- ~35% of ATTR patients misdiagnosed with other CV conditions

2 Patients are often hospitalized with diastolic heart failure and are referred to multiple specialists before definitive diagnosis

- ATTR patients often see 3-5 specialists prior to diagnosis
- ATTR Amyloidosis symptoms typically progress more slowly than AL Amyloidosis, delaying time to diagnosis

3 Cardiologists typically lead diagnosis and management, often with multidisciplinary team support

Gonzalez-Lopez et al. 2015; Gonzalez-Lopez et al. 2017; Decision Resources 2018

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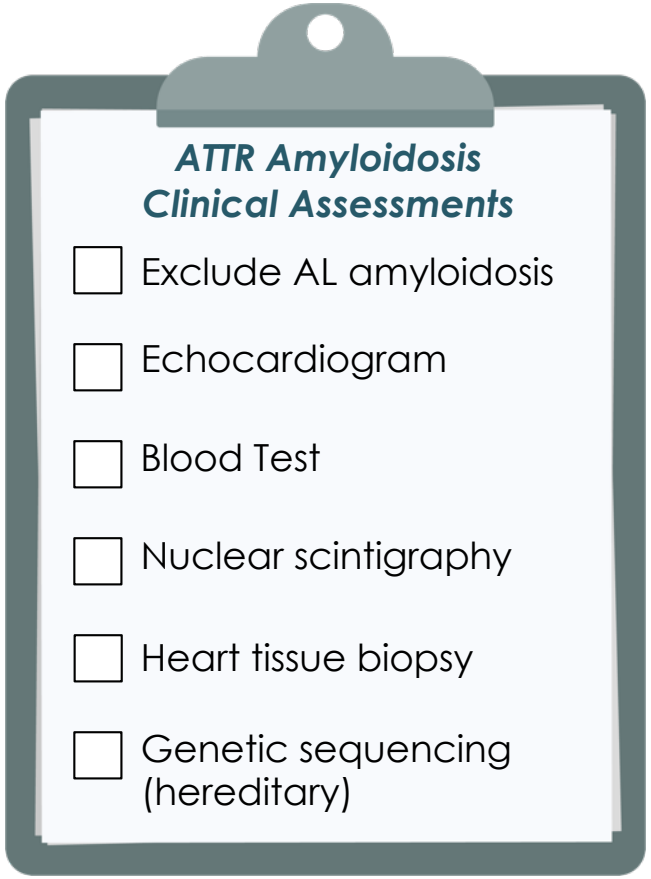
Confirming ATTR Amyloidosis Diagnosis Requires Piecing Together a Patchwork of Clinical Assessments



ATTR Amyloidosis Diagnostic Dynamics

- Most patients are admitted to the hospital with a clinical event that sparks suspicion (NYHA Classification III and IV)
- No single blood test will point to diagnosis of ATTR
  - Blood tests and fat pad aspiration used to rule out AL Amyloidosis
  - Diagnosis requires heart tissue biopsy or, more recently, nuclear scintigraphy
- Blood tests, echocardiogram and genetic sequencing inform extent of disease progression and hereditary nature

Amyloidosis Foundation; Decision Resources 2018

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Tafamidis Showed Little/No Benefit in NYHA Class III ATTR Amyloidosis Patients; NYHA Class IV Not Studied

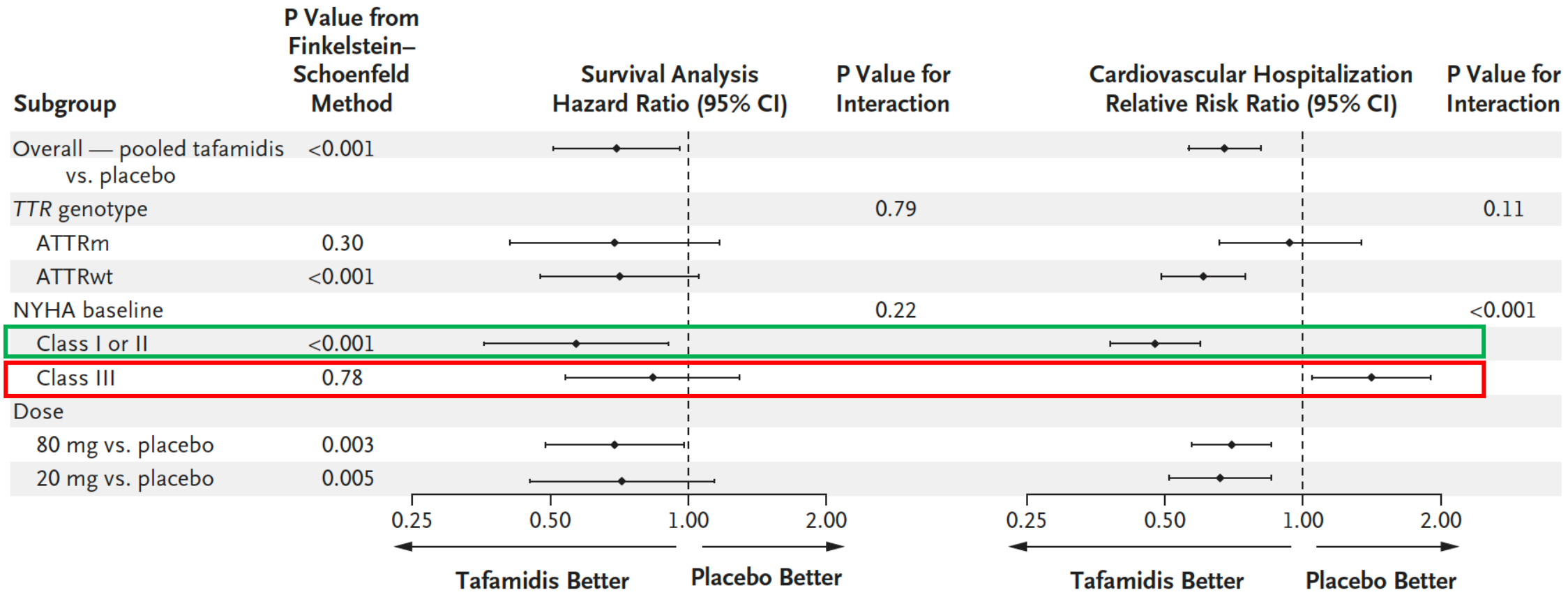

Figure 3. Overall and Subgroup Results as Calculated with the Use of the Finkelstein–Schoenfeld Method, All-Cause Mortality, and Cardiovascular-Related Hospitalizations.

Source: Maurer M et al. 2018; ATTR-ACT Phase 3 Study

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Next Steps and Summary

Radhika Tripuraneni, MD, MPH

Chief Development Officer

NYHA Class III and IV Patients Lack Effective Treatment Options

Representing 130k-490k Patients Globally

HFpEF Patients

11m patients[1]

4-13%[2,3]

ATTR-CM Patients

400k-1.4m patients

32-34%[4,5,6]

NYHA Class III-IV

130-490k patients

Urgent need in significant patient population for amyloid targeting therapy

HFpEF: Heart failure with preserved ejection fraction; [1]GlobalData epidemiology for major markets (US, EU5, Japan, China);
[2] Pfizer estimate; [3] Gonzalez-Lopez et al, 2015; [4]Gonzalez-Lopez et al, 2017; [5]Mauer et al, 2016; [6]Gagliardi et al, 2018

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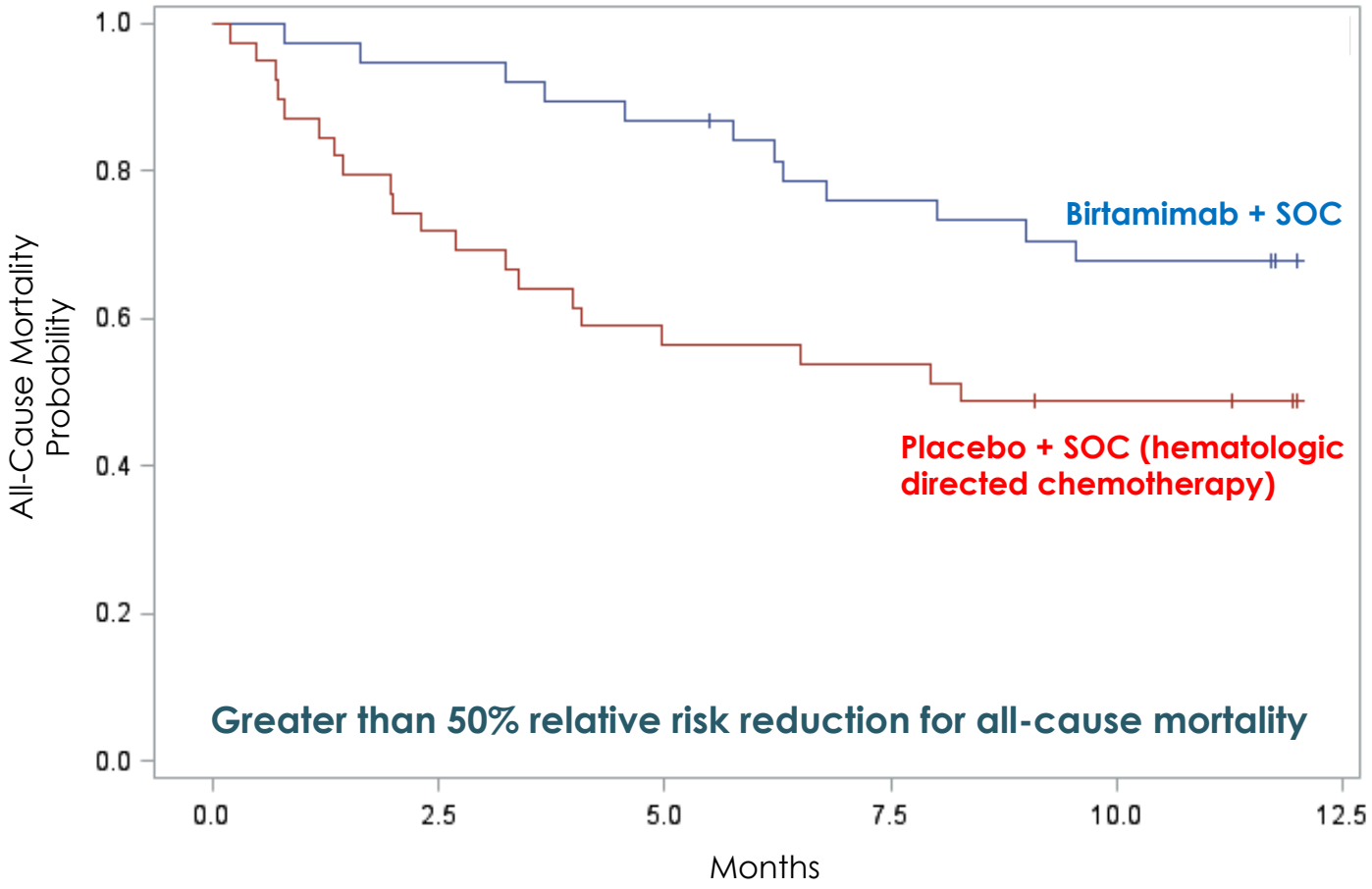
Phase 3 Study of Birtamimab in AL Amyloidosis: All-Cause Mortality, Mayo Stage IV (n=77)



Amyloidosis Type	AL	ATTR
Cause	Amyloid deposition in vital organs	Amyloid deposition in vital organs
Involved protein	Light chain	Transthyretin
Clinical presentation (cardiac)	Progressive restrictive cardiomyopathy	Progressive restrictive cardiomyopathy
Classification at-risk	Mayo Stage IV	NYHA Class III - IV
Median OS	~6 months[1]	1.3 – 2.1 years[2]

[1] Kumar et al, 2012, [2]Pinney J et al. 2013; Gonzalez-Lopez E et al. 2017
Birtamimab (NEOD001) Phase 3 VITAL study was discontinued for futility; results including Mayo Stage IV mITT analysis announced April 18, 2019, www.prothena.com
SOC = Standard of Care; All-cause mortality regardless of prior cardiac hospitalization OS = Overall Survival

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Planning Moderate-to-Advanced ATTR-CM Study with PRX004

- **Planning underway for next study, to initiate in 2021**
  - Depleter MOA designed to clear amyloid deposition responsible for early mortality
  - Expanding patient population due to increased awareness
  - Significant need for therapies that improve survival
  - Focused study design in a targeted cardiomyopathy population at high risk for early mortality

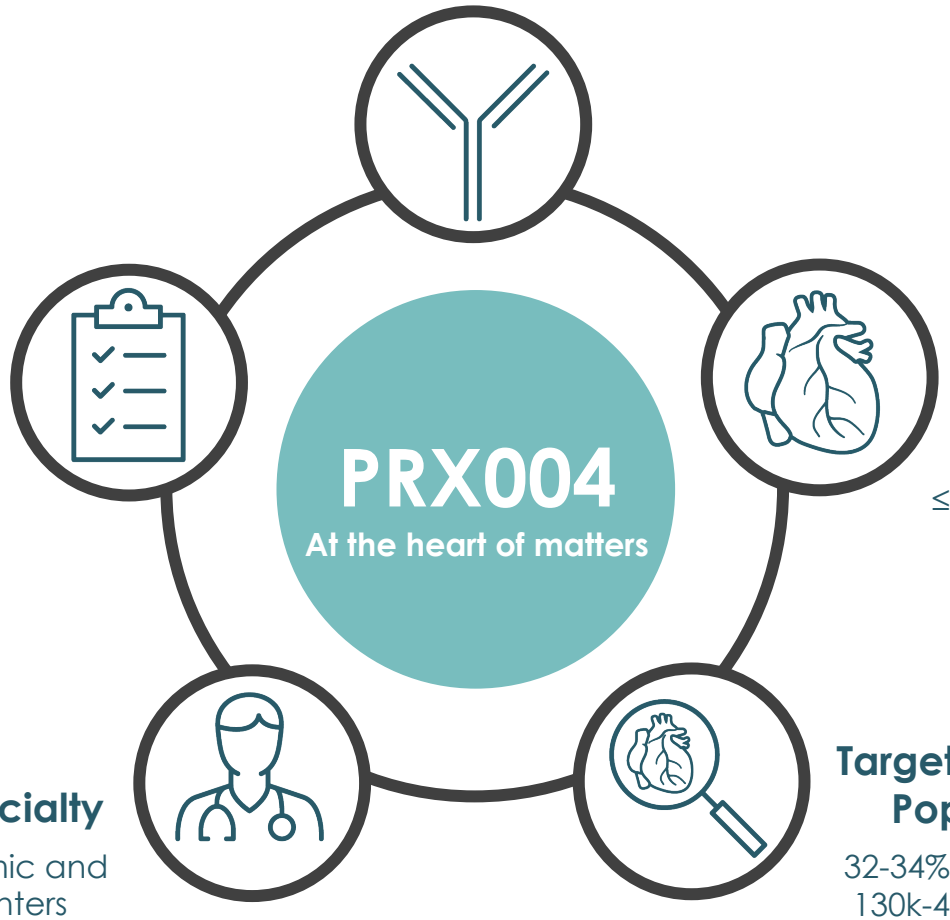
Thank you to the patients, investigators and study site staff who participated in PRX004-101

Concluding Remarks

Gene Kinney, PhD

President & CEO

PRX004: Uniquely Positioned to Change the Treatment Paradigm in ATTR-Cardiomyopathy



- **PRX004 demonstrated clinical benefit**
  - Improvement in neuropathy and cardiac function
  - Safe and well-tolerated
- **Further studies planned in moderate-to-advanced ATTR-CM**
- **Opportunity to establish premium position in orphan disease with blockbuster potential**

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Robust R&D Pipeline

Focused on neurodegenerative and rare peripheral amyloid diseases

Program / Target	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Biomarker Enabled	Commercial Rights
Prasinezumab / α–synuclein *Parkinson's Disease*	PASADENA (Phase 2)					✓ MRI-ASL	prothena / Roche
PRX004 / TTR *ATTR Amyloidosis*	Phase 1					✓ Non-native TTR*	prothena
PRX005 / Tau *AD, PSP, FTD, CTE*	Preclinical					✓ PET-tau	Bristol Myers Squibb
PRX012 / Aβ *AD*	Preclinical					✓ PET-Aβ	prothena
TDP-43 *ALS, FTD*	Discovery						Bristol Myers Squibb
Undisclosed *Neurodegeneration*	Discovery					✓	Bristol Myers Squibb
Vaccine / Aβ + Tau *AD*	Discovery					✓ PET-imaging	prothena
Undisclosed *AD/Down Syndrome*	Discovery					✓ CSF	prothena

*Prothena's proprietary assay for non-native TTR in hereditary ATTR Amyloidosis (hATTR)
Aβ, Abeta; AD, Alzheimer's disease; PSP, progressive supranuclear palsy; FTD, frontotemporal dementia; CTE, chronic traumatic encephalopathy ALS, amyotrophic lateral sclerosis; MRI-ASL, magnetic resonance-arterial spin labelling.PET, positron emission tomography; mAb, monoclonal antibody

mAb | Vaccine | Small Molecule

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Upcoming R&D Milestones

- **Prasinezumab for the potential treatment of PD (worldwide collaboration with Roche)**
  - ✓ Part 1 of the Phase 2 PASADENA study in patients with early PD (N=316) showed signals of efficacy. Results presented as an oral Top Abstract presentation at virtual MDS Congress 2020. Part 2 of the PASADENA study is ongoing
  - ✓ Announced plans to advance prasinezumab into a Phase 2b study in patients with early PD
  - ❑ $60 million clinical milestone payment upon first patient dosed in P2b; further details expected in 1H 2021
- **PRX004 for the potential treatment of ATTR amyloidosis**
  - ✓ Interim data from first five of six dose-level cohorts including safety, tolerability and target engagement, reported in 4Q 2019
  - ✓ Additional dose-escalation and long-term extension data, as well as an update on next steps for clinical development, expected to be reported in 4Q 2020
- **Tau, a protein implicated in a number of neurodegenerative diseases (worldwide collaboration with Bristol-Myers Squibb)**
  - ✓ Advance IND-enabling activities for the internally discovered tau antibody in 2020
  - ❑ IND filing expected in 2021
- **Aβ, a protein implicated in Alzheimer's disease**
  - ✓ Initiated cell line development of a lead candidate in 4Q 2019
  - ✓ Presented preclinical data at CTAD 2020
  - ✓ Initiated IND-enabling studies for the internally discovered Aβ antibody
  - ❑ IND filing expected in 2021

Q&A