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Prasinezumab Slows Progression on Measures of Parkinson's Disease in Phase 2 PASADENA Study

September 15, 2020

Agenda

- **Introduction and Overview of Results**
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- **Prasinezumab Background**
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- **Phase 2 PASADENA Study Results**
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- **Q&A**
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  - Tran Nguyen, COO & CFO
  - Radhika Tripuraneni, MD, MPH, CDO
  - Wagner Zago, PhD, CSO

Forward-looking Statements

This presentation contains forward-looking statements. These statements relate to, among other things: the treatment potential and proposed mechanisms of action of prasinezumab; plans for the ongoing Phase 2 clinical study of prasinezumab; plans for future clinical studies of prasinezumab; and the continued advancement of our discovery and preclinical pipeline. 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. Prothena undertakes no obligation to update publicly any forward-looking statements contained in this presentation as a result of new information, future events or changes in Prothena's expectations.

Introduction and Overview of Results

Gene Kinney, PhD

President & Chief Executive Officer

Prasinezumab

Alpha-synuclein Immunotherapy for Parkinson's Disease

Part of Prothena's pipeline based on expertise in **protein dysregulation** and focused on **neurodegenerative** and **rare peripheral amyloid diseases**

Potentially disease-modifying therapy is focus of worldwide development and commercialization **collaboration with Roche**

Prothena Summary

Positive clinical results from PASADENA position prasinezumab as the first potentially disease-modifying therapy for Parkinson's disease

PASADENA dataset further validates Prothena's specific and selective targeting approach towards protein dysregulation diseases

Growing and diverse pipeline will generate new preclinical and clinical data over the next 12 months

Phase 2 PASADENA Study

Prasinezumab in Early Parkinson's Disease

- **First potentially disease modifying, anti-alpha-synuclein antibody to demonstrate signals of efficacy on multiple pre-specified secondary and exploratory clinical endpoints, including measures of motor function and biomarkers**
- **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
- **Consistent signal favoring prasinezumab on cognition as well as clinician and patient impression of change endpoints and imaging biomarkers**
- **Low and high doses showed similar safety and efficacy profile, in line with expectations that both doses saturate the target**
- **Prasinezumab showed similar AEs and IRRs compared to placebo**
- **Results support the potential of prasinezumab to slow underlying disease pathophysiology and clinical decline in patients with PD. Further clinical development is warranted**

Prasinezumab Background

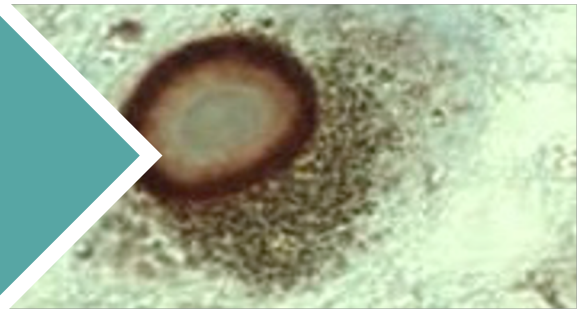
Wagner Zago, PhD
Chief Scientific Officer

α-Synuclein Implicated in Parkinson's Disease

- **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

α-synuclein is the predominant component of Lewy bodies found in PD and other synucleinopathies

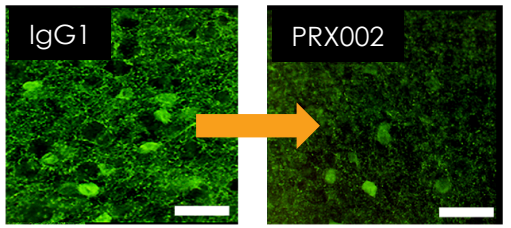


Summary of Effects of 9E4 in Multiple Preclinical Models of Synucleinopathy

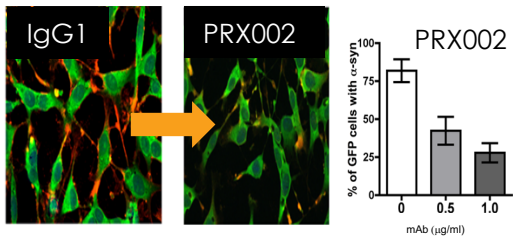
Prasinezumab (murine form of 9E4) demonstrated in multiple in vivo and cellular α-synucleinopathy models to:[1–4]

- ✓ 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

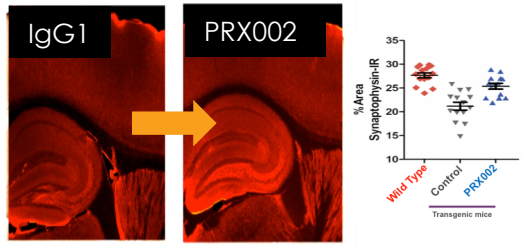
Lowering of α -syn Pathology



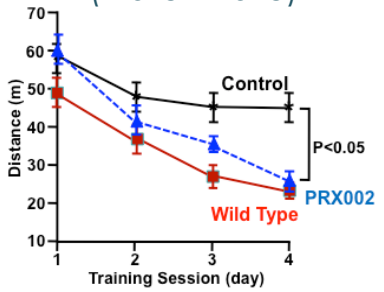
Blockade of cell-to-cell transmission



Protection of Synapses



Improvement in Behavior (water maze)



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; **4.** Spencer B, et al. *Acta Neuropathol Commun*. 2017; 5:7; **5.** Zago et al., 2015

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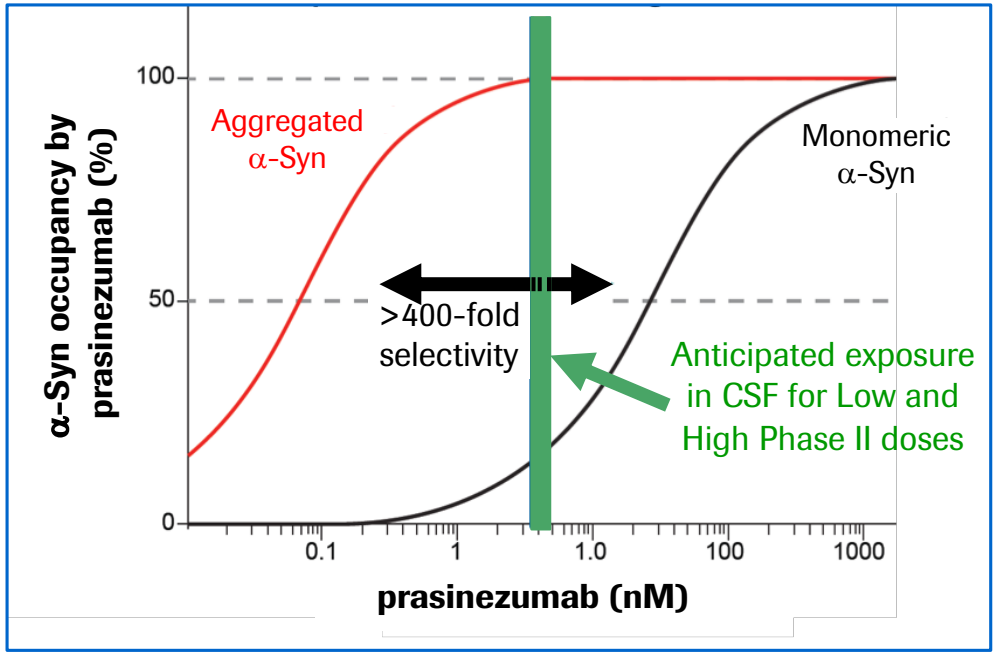
Pharmacokinetic/Pharmacodynamic Framework

Elements determining target-occupancy in CNS

- Relative concentrations of prasinezumab in peripheral and central compartments
- Relative concentrations of α-synuclein in the periphery, CSF, and brain
- Affinity/Avidity of prasinezumab to aggregated α-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

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Phase 2 PASADENA Study Results

Radhika Tripuraneni, MD, MPH
Chief Development Officer

Patient Journey in Parkinson's Disease

Stages of Parkinson's Disease

PASADENA

- Mild/moderate symptoms

Treated:

- Satisfactory control of motor symptoms

Treated:

- Suboptimal control of motor symptoms
- Early response fluctuations

- Fully established motor complications (fluctuations and dyskinesias)
- Advanced PD with motor and non-motor complications

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PASADENA: A Phase 2 study to evaluate the safety and efficacy of prasinezumab in early Parkinson's disease: Part 1 Week-52 results

Gennaro Pagano,[1] Kirsten I Taylor,[1,2] Judith Anzures Cabrera,[3] Maddalena Marchesi,[4] Wagner Zago,[5] Radhika Tripuraneni,[5] Anne Boulay,[1] Annamarie Vogt,[1] Frank G Boess,[1] Tania Nikolcheva,[6] Hanno Svoboda,[1] Markus Britschgi,[1] Florian Lipsmeier,[4] Michael Lindemann,[4] Sebastian Dziadek,[4] Jean-Philippe Azulay,[7] Brit Mollenhauer,[8,9] Lydia Lopez Manzanares,[10] David S Russell,[11] James T Boyd,[12] Anthony P Nicholas,[13] María R Luquin,[14] Robert A Hauser,[15] Tanya Simuni,[16] Thomas Gasser,[17,18] Werner Poewe,[19] Gene G Kinney,[5] Rachelle Doody,[4] Paulo Fontoura,[4] Daniel Umbricht,[1] and Azad Bonni[1] for the PASADENA Investigators and Prasinezumab Study Group

1. Roche Pharma Research and Early Development, Neuroscience and Rare Diseases Discovery and Translational Area, Roche Innovation Center, Basel, Switzerland; 2. Faculty of Psychology, University of Basel, Basel, Switzerland; 3. Roche Products Ltd, Welwyn Garden City, UK; 4. F. Hoffmann-La Roche Ltd, Basel, Switzerland; 5. Prothena Biosciences Inc, South San Francisco, CA, USA; 6. F. Hoffmann-La Roche Ltd, Product Development Neuroscience, Basel, Switzerland; 7. Centre Hospitalier de la Timone, Marseille, France; 8. Paracelsus-Elena-Klinik, Kassel, Germany; 9. University Medical Center Göttingen, Göttingen, Germany; 10. Hospital de La Princesa, Madrid, Spain; 11. Institute for Neurodegenerative Disorders, New Haven, CT, USA; 12. University of Vermont Larner College of Medicine, Burlington, VT, USA; 13. University of Alabama Medical Center, Birmingham, AL, USA; 14. University Clinic of Navarra, Pamplona, Navarra, Spain; 15. University of South Florida, Tampa, FL, USA; 16. Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 17. Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany; 18. German Center for Neurodegenerative Diseases (DZNE), Tuebingen, Germany; 19. Department of Neurology, Innsbruck Medical University, Innsbruck, Austria.

Presented at the Virtual 2020 International Congress of Parkinson's Disease and Movement Disorders Society; Sept. 15, 2020

Disclosures

Gennaro Pagano is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd

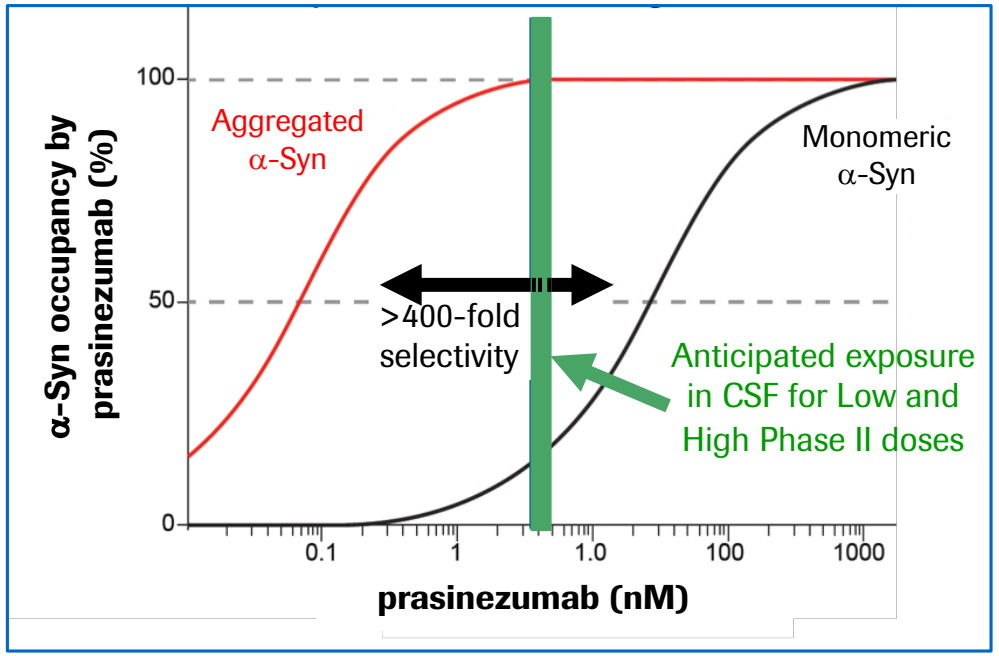
Prasinezumab

Preclinical efficacy and proposed mode of action

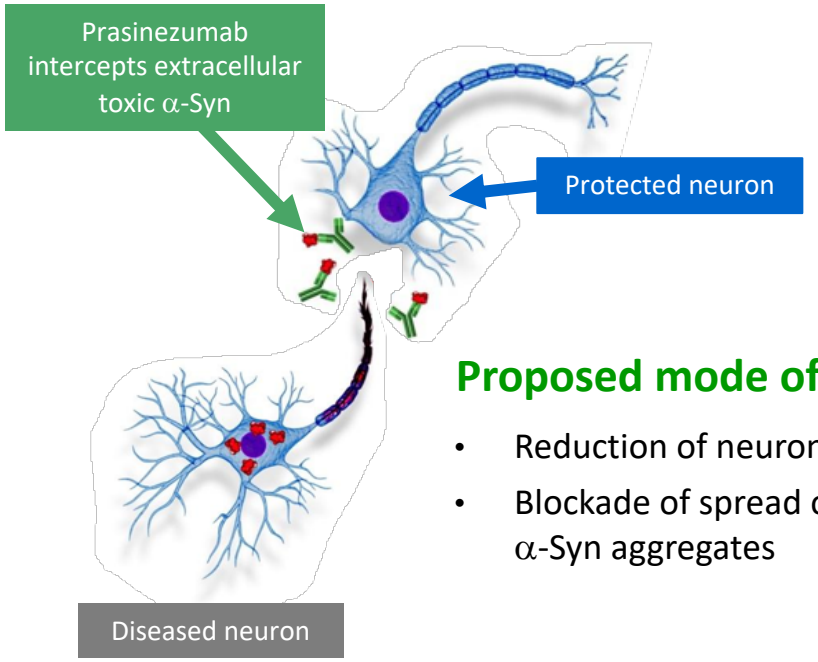
Prasinezumab (PRX002/RG7935 or murine parent 9E4) **demonstrated in multiple *in vivo* and cellular a-synucleinopathy models[1–4] to:**

- Reduce build-up of intracellular α-Syn pathology and protect neurons
- Block cell-to-cell transmission of α-Syn
- Protect synapses and reduce gliosis
- Ameliorate motor and cognitive behavioral deficits

Selectivity towards aggregated α-Syn and doses selected for the PASADENA study expected to saturate aggregated α-Syn in CNS[5]



Slowing disease progression by protecting neurons from toxic α-Syn species[6]



Proposed mode of action

- Reduction of neuronal toxicity
- Blockade of spread of pathogenic α-Syn aggregates

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; 4. Spencer B, et al. *Acta Neuropathol Commun*. 2017; 5:7;
5. Jankovic J et al. *JAMA Neurol*. 2018; 75:1206–1214; 6. Zago W., et al. *Presented at ADPD 2015 International Congress*.

PASADENA Part 1 (NCT03100149): A 52-week multicenter, randomized, double-blind, placebo-controlled study

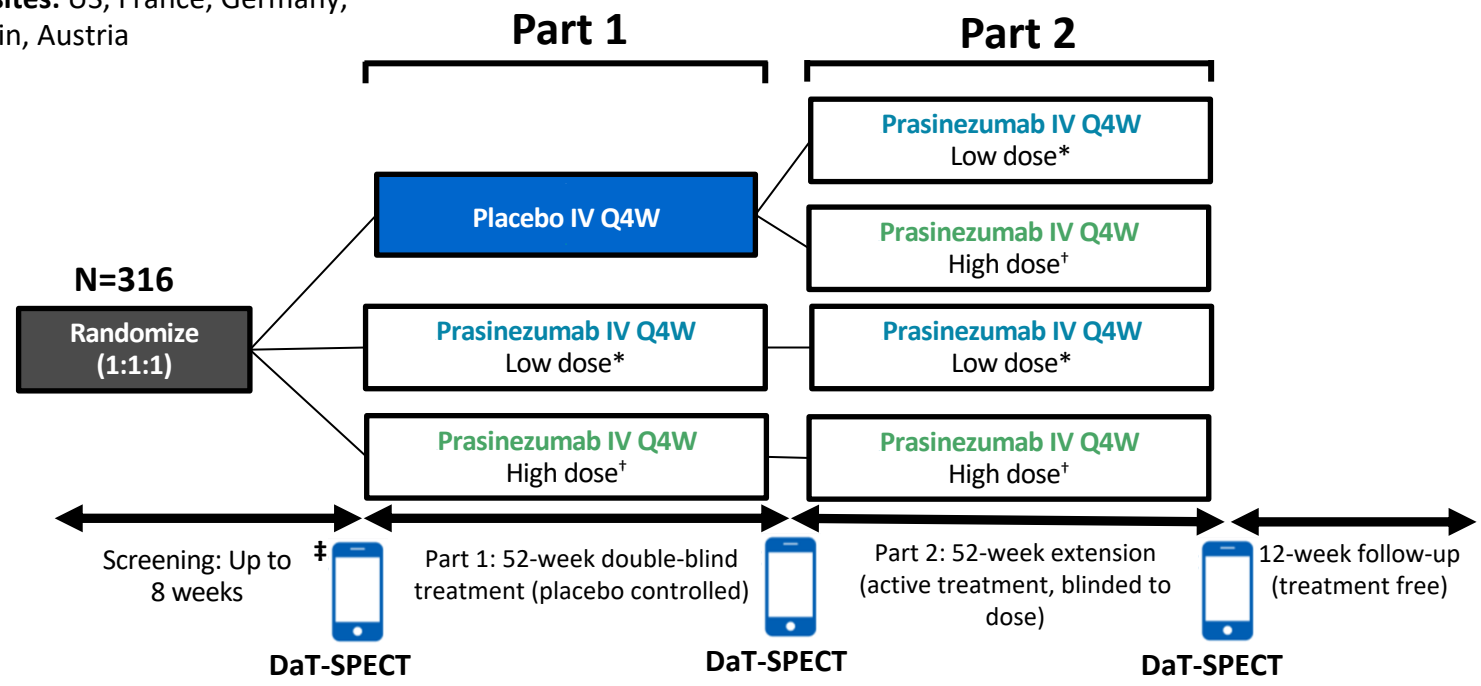
Primary endpoint: Change from baseline to Week 52 in total MDS-UPDRS (sum of Parts I, II and III)

Key secondary and exploratory endpoints:

- **Change from baseline to Week 52 in the following:**
  - MDS-UPDRS Part I non-motor aspects
  - MDS-UPDRS Part II experiences of daily living (motor aspects)
  - MDS-UPDRS Part III motor examination and Part III subscores (bradykinesia, rigidity, tremor, axial signs)
  - MoCA total score
  - PGI-C
  - CGI-I and disability (SE-ADL)
  - Neurodegeneration of dopaminergic terminals (DaT-SPECT)
  - Digital PASADENA motor score
- **Safety**, tolerability, pharmacokinetics and immunogenicity

Two doses versus placebo (1:1:1)

56 sites: US, France, Germany, Spain, Austria



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

*Low dose=1,500 mg, † High dose=4,500 mg for ≥65 kg; 3,500 mg for <65 kg. ‡Digital biomarkers (smartphone and wrist-worn wearable assessments).

CGI-I, Clinical Global Impression of Improvement; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; IV, intravenous; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale MoCA, Montreal Cognitive Assessment; PGI-C, Patient Global Impression of Change; SE-ADL, Schwab and England Activities of Daily Living Scale; Q4W, every month.

NCT03100149. https://clinicaltrials.gov/ct2/show/NCT03100149 (Accessed August 2020).

Baseline characteristics

	Placebo (n=105)*	Low dose (n=105)*	High dose (n=106)*	All patients (N=316)
Age, years Mean (SD)	59.9 (8.7)	60.3 (8.8)	59.4 (9.8)	59.9 (9.1)
Gender, Male N (%)	71 (67.6)	71 (67.6)	71 (67.0)	213 (67.4)
Disease duration Mean (SD)	9.9 (6.8)	10.2 (6.3)	10.1 (6.5)	10.1 (6.5)
MAO-Bi				
Yes	38 (36.2)	38 (36.2)	39 (36.8)	115 (36.4)
No	67 (63.8)	67 (63.8)	67 (63.2)	201 (63.6)
MDS-UPDRS total Mean (SD)	32.01 (12.98)	31.49 (13.32)	30.75 (12.10)	31.41 (12.78)
MDS-UPDRS Part III Mean (SD)	21.54 (9.11)	21.90 (9.14)	20.97 (8.81)	21.47 (9.00)
MDS-UPDRS Part II Mean (SD)	5.55 (4.09)	4.94 (3.99)	5.50 (4.07)	5.33 (4.04)
MDS-UPDRS Part I Mean (SD)	4.91 (3.71)	4.64 (4.16)	4.27 (3.57)	4.61 (3.83)
H&Y Stage category				
I (%)	20 (19.0)	29 (27.6)	29 (27.4)	78 (24.7)
II (%)	85 (81.0)	76 (72.4)	77 (72.6)	238 (75.3)
Patients with evaluable data at Week 52†	76 (72.4)	75 (73.5)	73 (70.9)	224 (70.9)

Baseline characteristics are well balanced among treatment arms

For more details please see the PASADENA results poster. *n represents number of participants contributing to summary statistics. Percentages are based on n. † Visits are time windowed. Non-evaluable data is considered as patient starting symptomatic PD treatment, an increase on MAO-Bi (if the patient was on MAO-Bi at baseline), or withdrawal from the study.

H&Y, Hoehn and Yahr; MAO-Bi, monoamine oxidase B inhibitor; MDS-UPDRS, Movement Disorder Society Unified PD Rating Scale; PD, Parkinson's disease; SD, standard deviation.

Overview of safety data

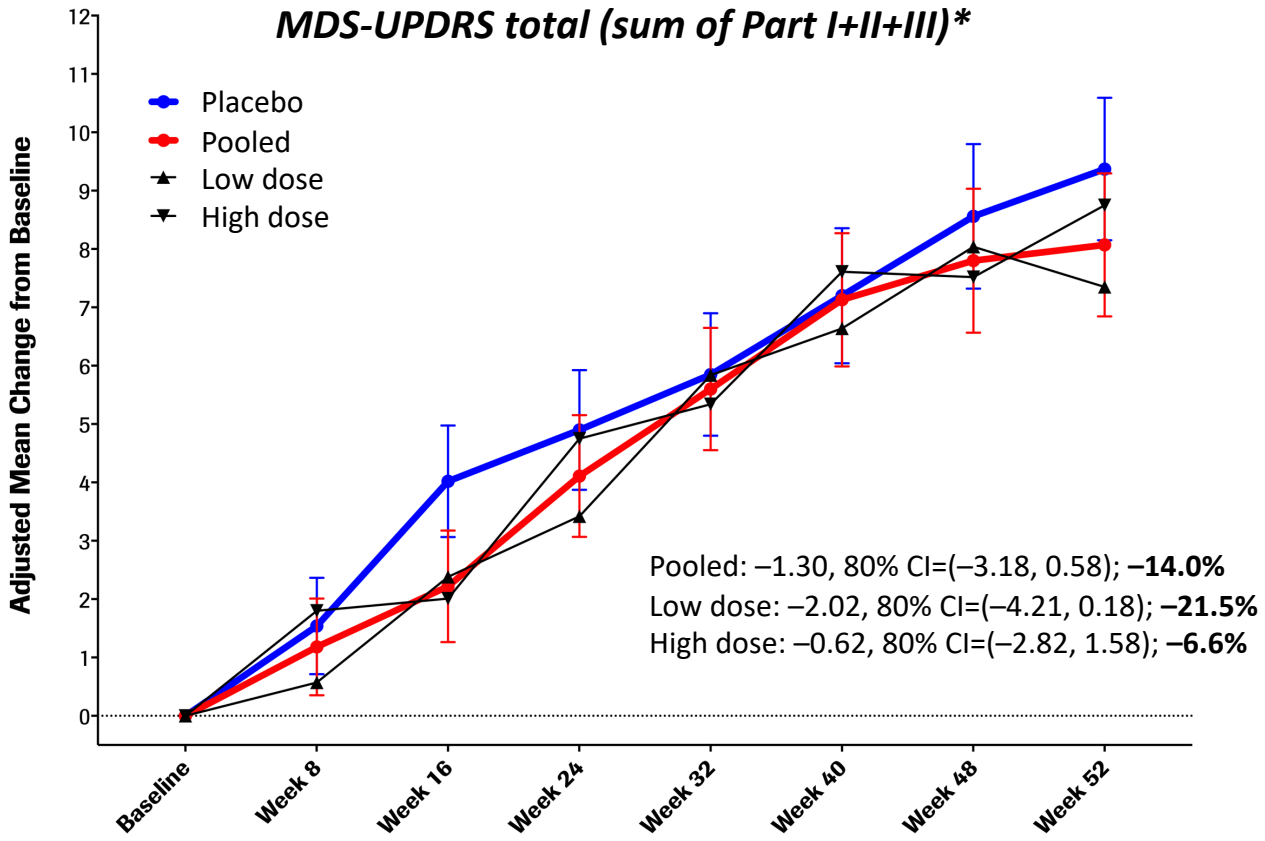
	Placebo (n=105)	Low dose (n=105)	High dose (n=106)	All patients (n=316)
Total number of AEs*	411	428	549	1388
Total number of AE with fatal outcome (Grade 5)*	0	0	0	0
Total number of patients with at least one (%):†				
AE	87 (82.9)	98 (93.3)	97 (91.5)	282 (89.2)
SAE	5 (4.8)	7 (6.7)	8 (7.5)	20 (6.3)
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.

Primary endpoint

Change in total MDS-UPDRS score (Parts I+II+III) from baseline to Week 52



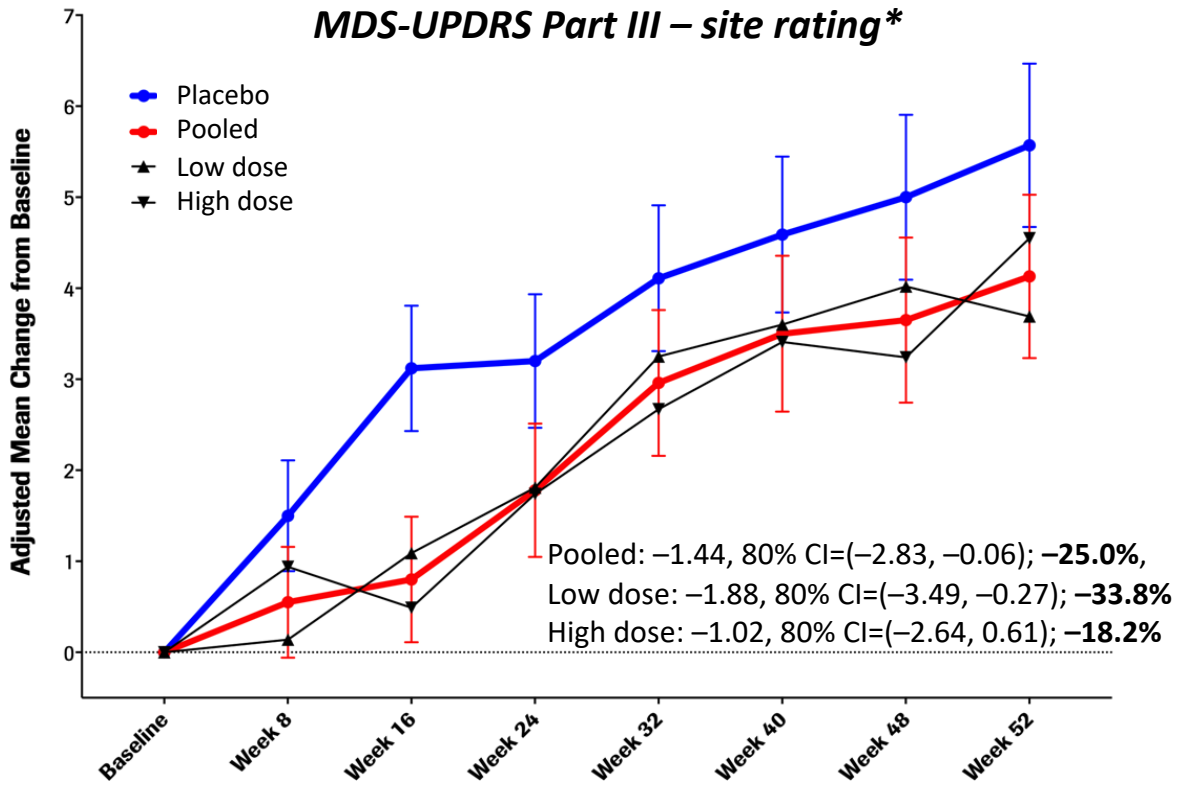
Primary endpoint not met

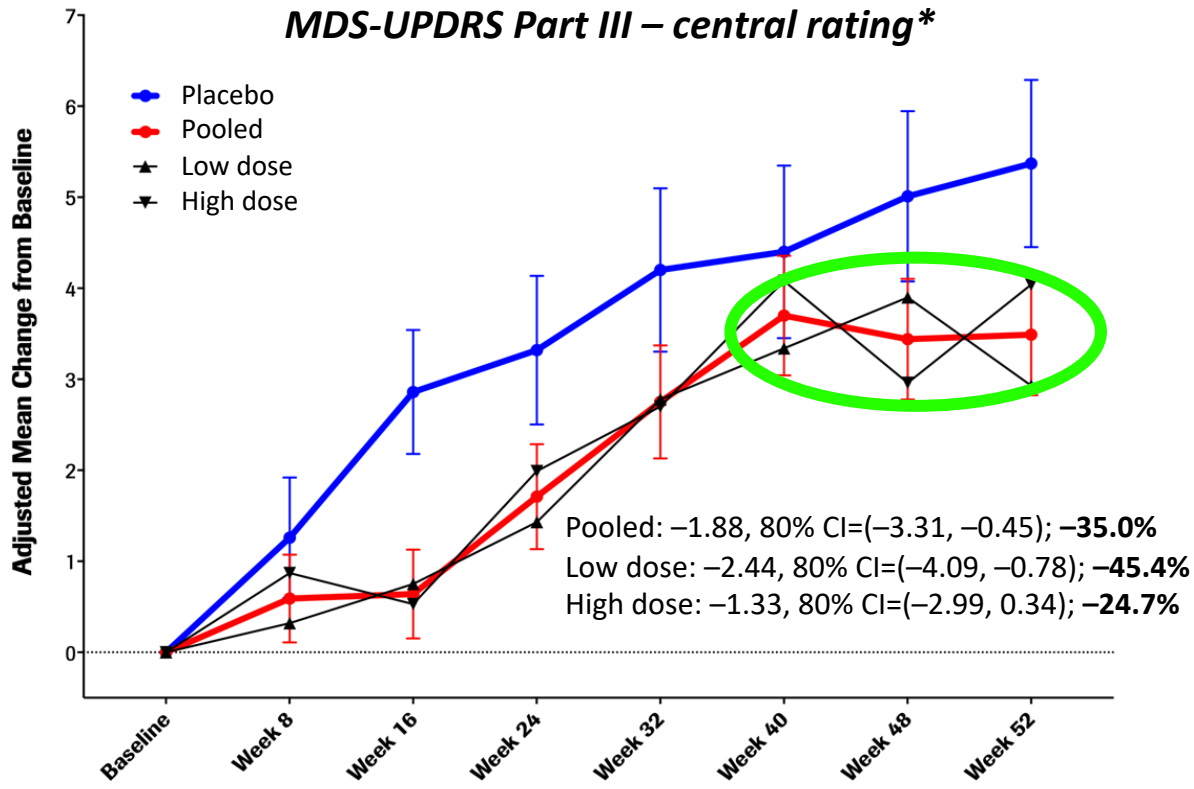
*Patients who started symptomatic PD treatment contribute until the last visit before symptomatic PD treatment is started. Bars represent 80% CI. Estimates are based on a MMRM with the following covariates: MAO-Bi at baseline (y/n), treatment, week, age <60 vs. ≥60, sex, DaT-SPECT putamen binding ratio (contralateral to most clinically affected side), baseline MDS-UPDRS corresponding endpoint.

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. Pooled dose analysis is a pre-specified exploratory endpoint.

Secondary endpoint

Change in total MDS-UPDRS Part III from baseline to Week 52 – Site and central rating





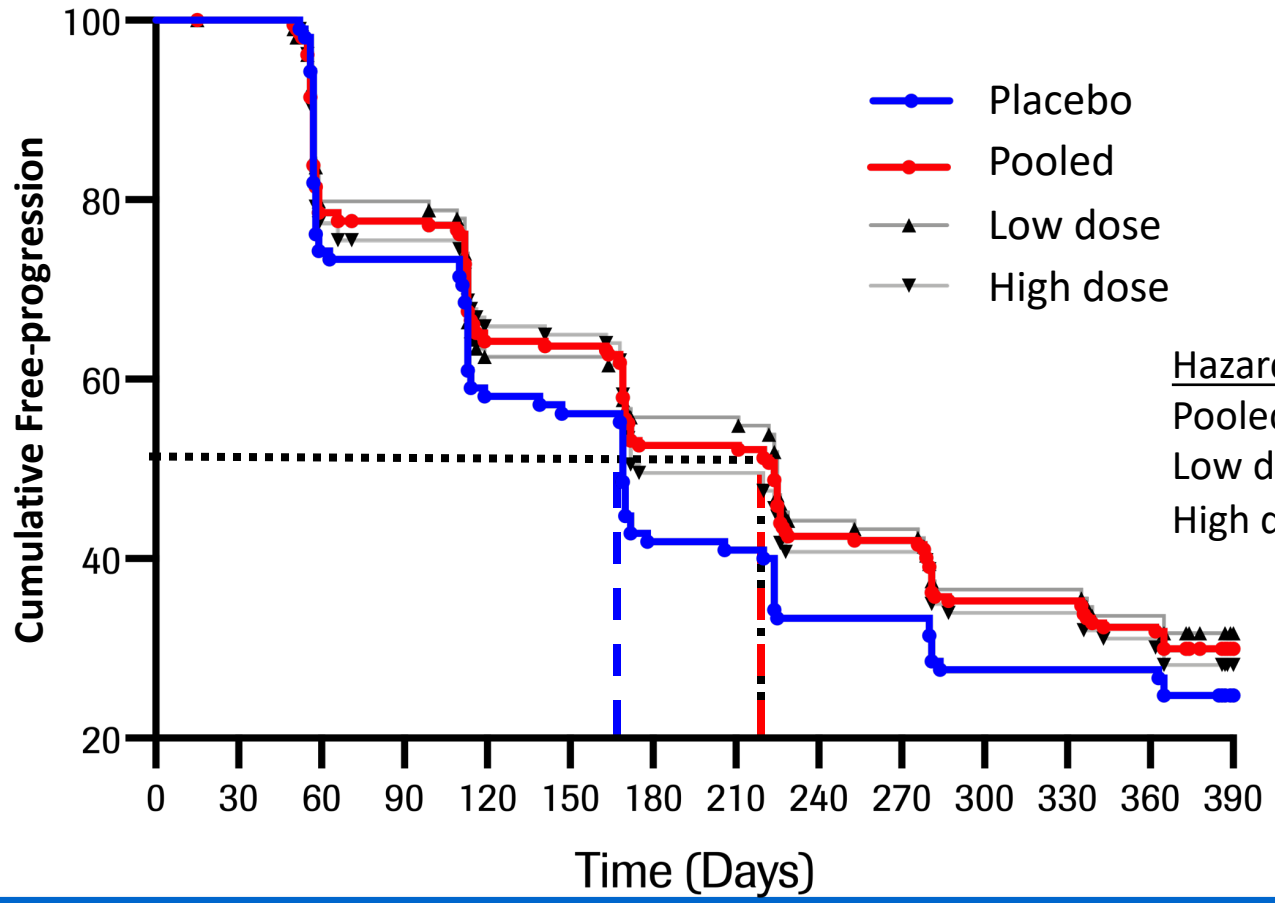
Reduced decline in progression of MDS-UPDRS Part III, confirmed by central rating

*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.

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.

Exploratory endpoint

Time to worsening of motor function (+5 points MDS-UPDRS Part III)



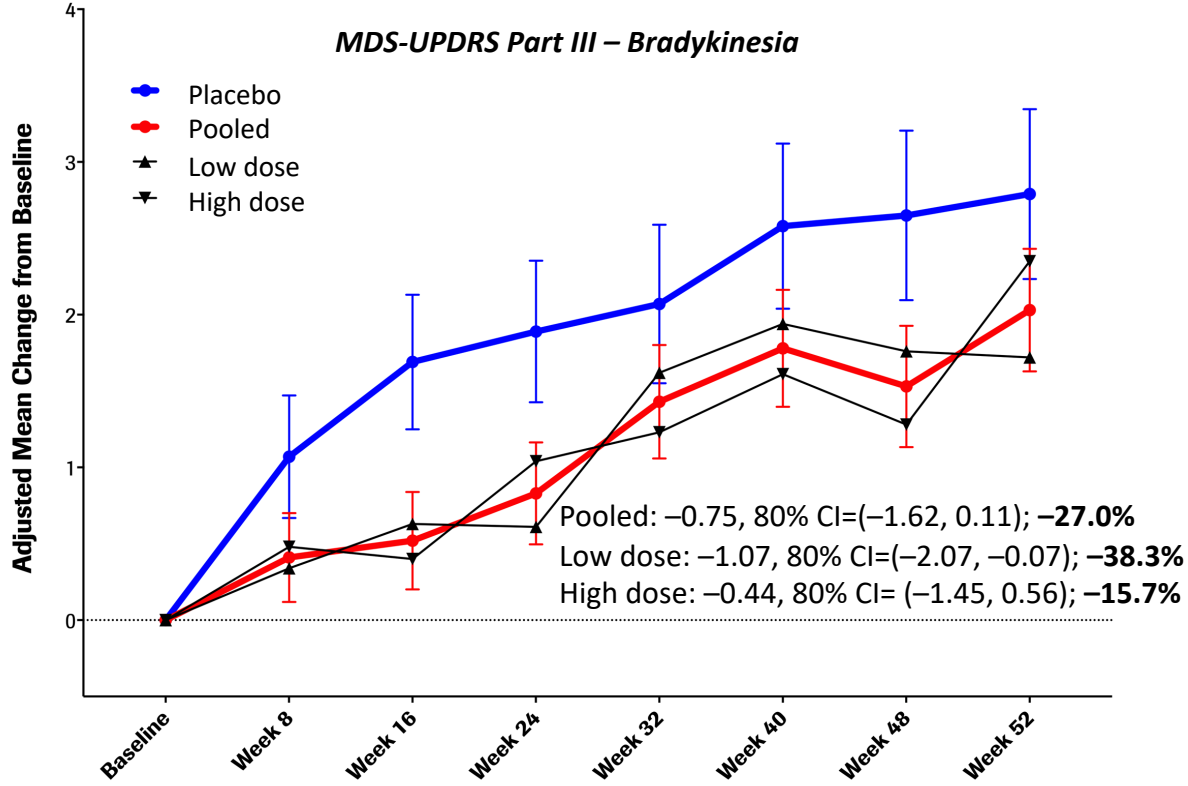
Hazard ratio* comparison to placebo:
Pooled: 0.82, 80% CI=0.64 to 0.99
Low dose: 0.77, 80% CI=0.63 to 0.96
High dose: 0.87, 80% CI=0.70 to 1.07

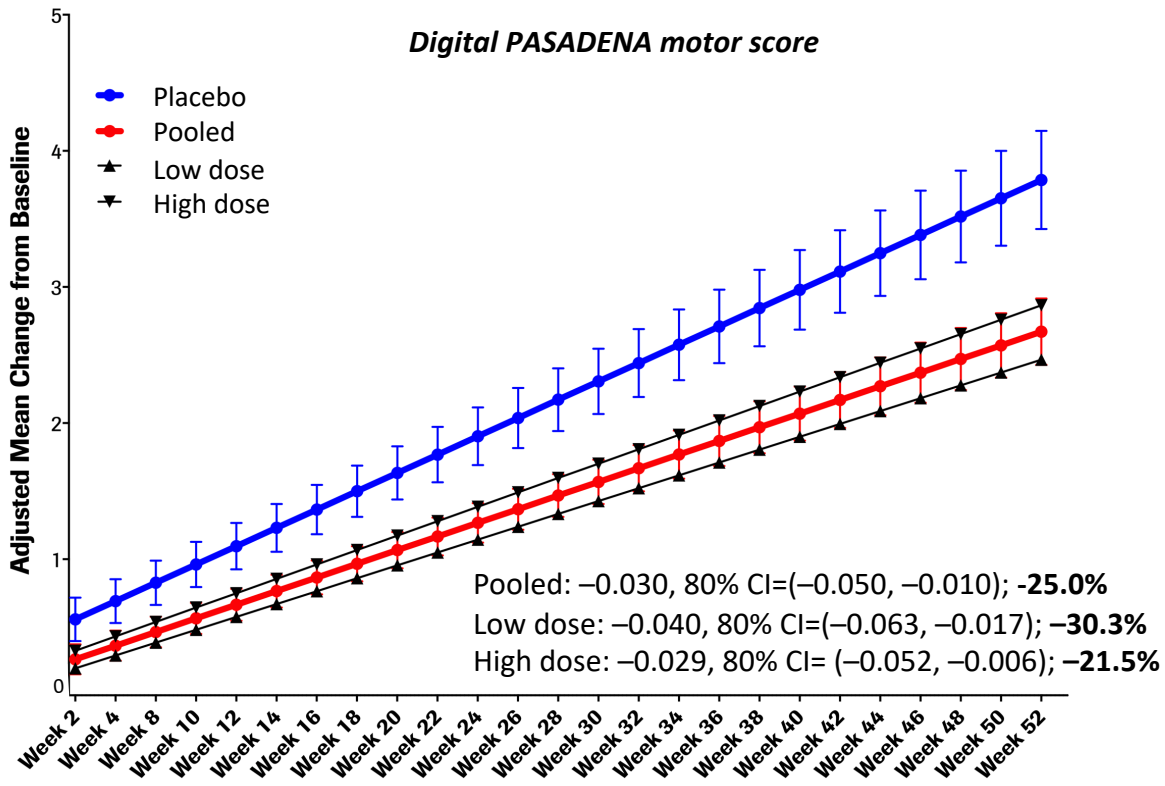
Reduced risk on time to worsening of motor function with delay of progression to clinically meaningful decline

*Wald CI/test.
CI, confidence interval; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale.

Secondary and exploratory endpoints

Change in MDS-UPDRS Part III – Bradykinesia and digital PASADENA motor score from baseline to Week 52



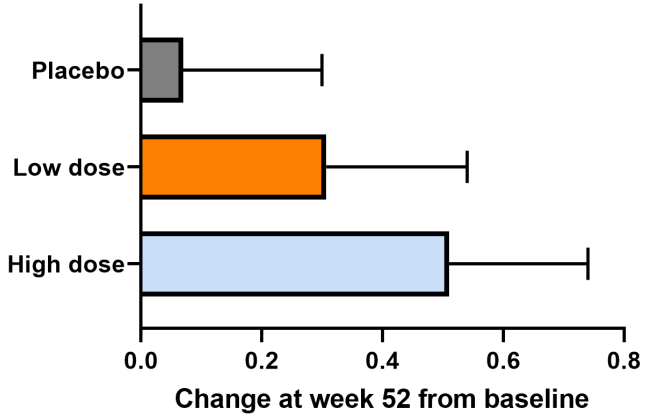


Reduced clinical decline in bradykinesia, confirmed by digital measures of progression (slope analysis)

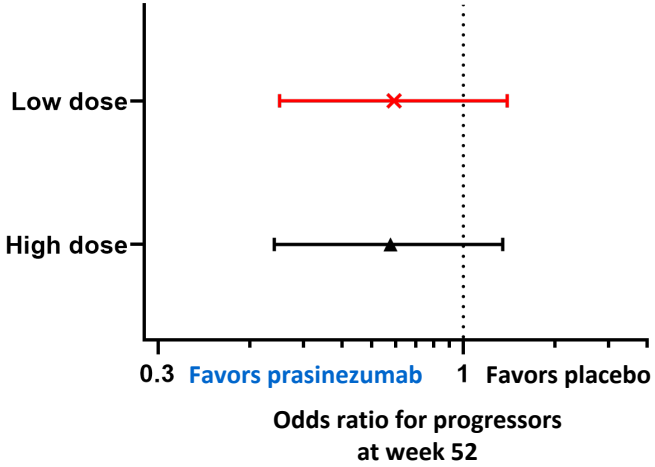
Pooled dose analysis for digital PASADENA motor score is a post-hoc analysis.
The digital PASADENA motor score was built from 80% bradykinesia features and 20% resting tremor features using blinded data from 150 PASADENA patients prior to unblinding.
CI, confidence interval; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale.

Secondary endpoints

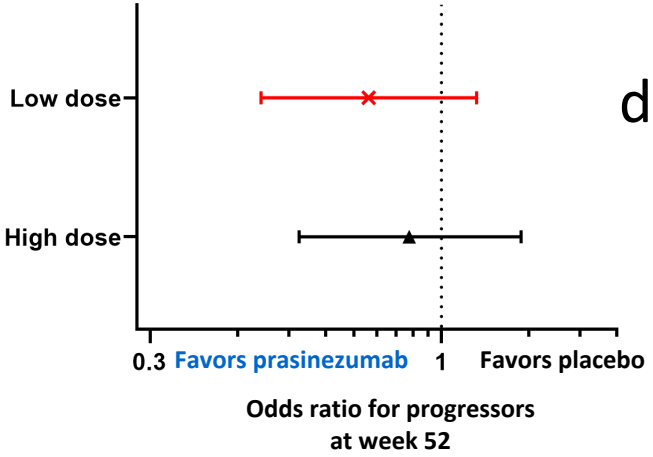
a. MoCA
Change in cognitive function



b. CGI-I
Change in clinical impression

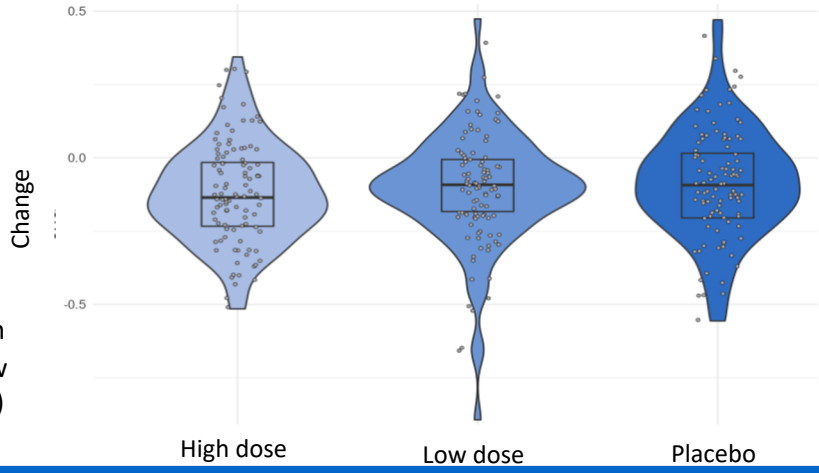


c. PGI-C
Change in patient's impression



d. DaT-SPECT
Change in dopaminergic terminals

DaT-SPECT progression was highly variable and less than expected (Placebo –8%, Low dose–10%, High dose –11%)

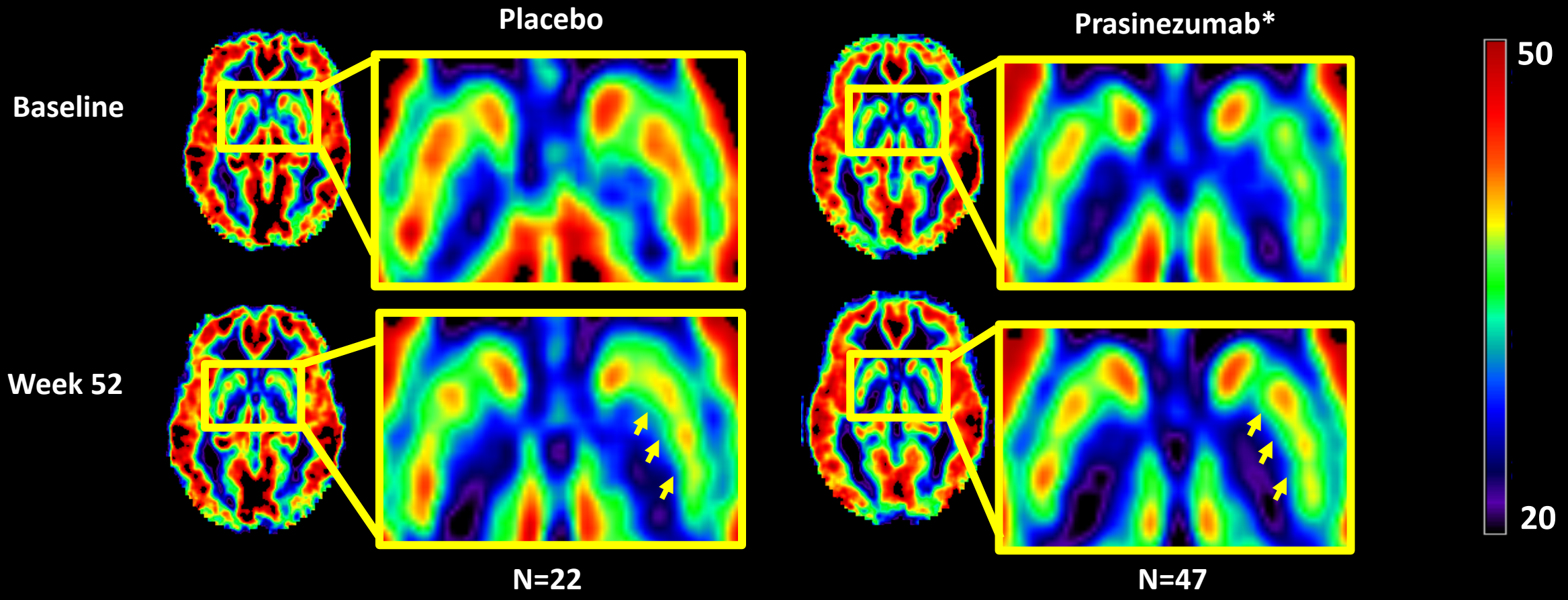


MoCA score increased in a cognitively normal range
Reduced risk of worsening on CGI-I and PGI-C
No effect on DaT-SPECT, but progression slower than expected in the placebo arm

CGI-I, Clinical Global Impression of Improvement; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; MoCA, Montreal Cognitive Assessment; PGI-C, Patient Global Impression of Change. Progressors on CGI-I-C and PGI-C are classed as patients with score of 5-7 (i.e., rated as "minimally worse", "much worse" or "very much worse")

Exploratory endpoint

Change in cerebral blood flow in the brain regions from baseline to Week 52 (MRI-ASL)



Reduced decline in cerebral blood flow in the putamen

*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.

Summary of results

- The PASADENA Part 1 study did not meet its primary endpoint
- **Safety**: Prasinezumab showed similar AEs and IRRs to placebo
- **Efficacy**: Prasinezumab showed:
  - Reduced decline in progression of MDS-UPDRS Part III – site and central rating and Bradykinesia subscore
  - Reduced risk on time to worsening of motor signs (+5 points on MDS-UPDRS Part III)
  - Reduced decline in digital measures of motor function (digital biomarker motor score) with divergence of slopes
  - MoCA score increased in a cognitively normal range
  - Reduced risk of worsening on CGI-I and PGI-C
  - Reduced decline in cerebral blood flow in the putamen (MRI-ASL)
- Prasinezumab did not show an effect on:
  - DaT-SPECT, but progression slower than expected in the placebo arm
  - MDS-UPDRS Part II, Part I, SE-ADL, time to start dopaminergic therapy, time to worsening on non-motor or motor aspects of daily living (+3 points on MDS-UPDRS Part I or II)
- Low and high doses showed similar safety and efficacy profile, in line with the expectations (both doses saturate the target)
- **Conclusion:** Our findings support the potential of prasinezumab to slow underlying disease pathophysiology and clinical decline in patients with PD. Further investigations are warranted.

AE, adverse event; CGI-C, Clinical Global Impression of Improvement; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; IRR, infusion-related reaction; MDS-UPDRS, Movement Disorder Society Unified PD Rating Scale; MoCA, Montreal Cognitive Assessment; MRI-ASL, magnetic resonance-arterial spin labelling; PD, Parkinson's disease; PGI-C, Patient Global Impression of Change.

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PASADENA investigators: Jean-Philippe Azulay, Ernest Balaguer Martinez, James Boyd, Matthew Brodsky, Anthony Ciabarra, Joseph Classen, Robert Coleman, Jean-Christophe Corvol, Nabila Dahodwala, Philippe Damier, Moro Elena, Karla Maria Eggert, Aaron Ellenbogen, Alexandra Foubert Samier, Franck Durif, John Fang, Samuel Frank, Jose Manuel Garcia Moreno, Thomas Gasser, Caroline Giordana, Ira Goodman, Robert Hauser, Jorge Hernandez-Vara, Guenter Hoeglinger, Jean-Luc Houeto, Jennifer Hui, Stuart Isaacson, Joseph Jankovic, Maria Jose Marti Domenech, Srinath Kadimi, R. Jan Kassubek, Kevin Klos, Andrea Kuhn, Jaime Kulisevsky Bojarsky, Rajeev Kumar, Peter Le Witt, Gurutz Linazasoro Cristobal, Irene Litvan, Oren Levy, Lydia Lopez Manzanares, Maria Luquin Piudo, David Maltete, Brit Mollenhauer, Anthony Nicholas, Rajesh Pahwa, Elizabeth Peckham, Werner Poewe, Olivier Rascol, Philippe Remy, Irene Richard, David Russell, Julie Schwartzbard, Tanya Simuni, Alfons Schnitzler, Caroline Tanner, Lydia Vela, Ryan Walsh

Prasinezumab Study Group: Markus Abt, Teresa Barata, Nicholas Barbet, Frank Boess, Azad Bonni, Edilio Borroni, Anne Boulay, Valerie Cosson, Christian Czech, Dennis Deptula, Cheikh Diack, Rachelle Doody, Giulia D'Urso, Chris Edgar, Beki Finch, Paulo Fontoura, Waltraud Gruenbauer, Stefan Holiga, Michael Honer, Shirin Jadidi, Timothy Kilchenmann, Thomas Kremer, Thomas Kustermann, Claire Landsdall, Michael Lindemann, Florian Lipsmeier, Cecile Luzy, Meret Martin-Facklam, Markus Niggli, Tania Nikolcheva, Susanne Ostrowitzki, Gennaro Pagano, Megana Prasad, Anke Post, Nathalie Pross, Benedicte Ricci, Jeff Sevigny, Kaycee Sink, Hannah Staunton, Hanno Svoboda, Dylan Trundell, Daniel Umbricht, Lynne Verselis, Ferenc Martenyi, Daniel K Ness, Tiffany Quock, Ellen Rose, Radhika Tripuraneni, Annamarie Vogt, Wagner Zago

Next Steps and Summary

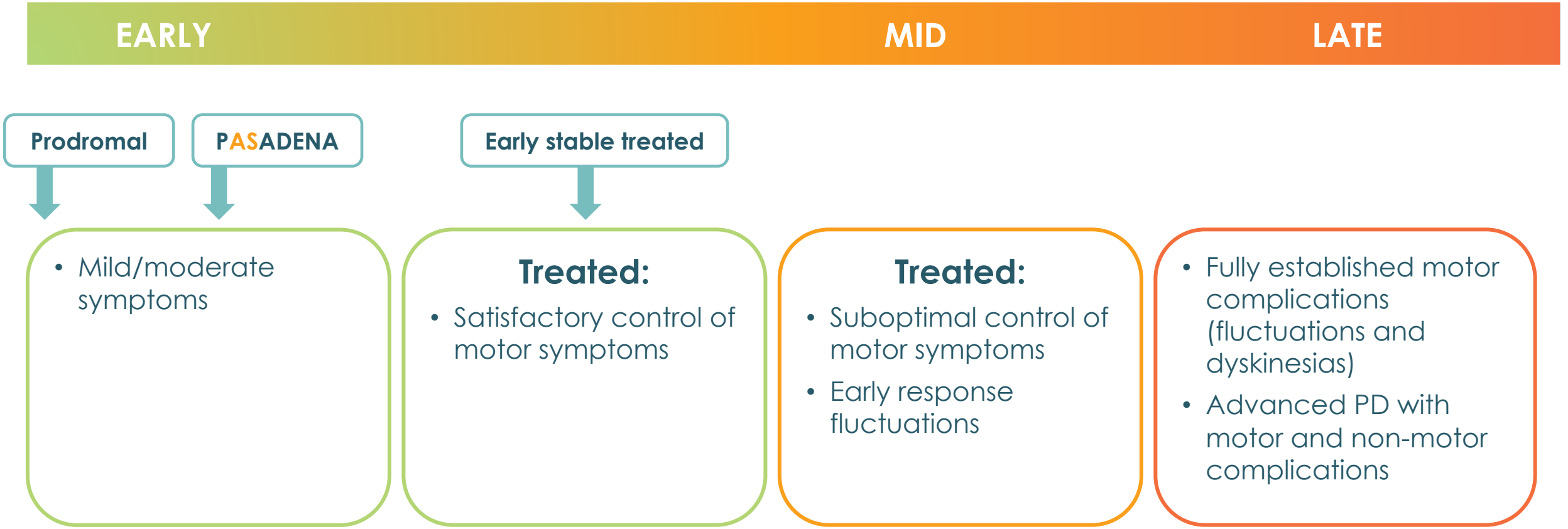
Gene Kinney, PhD

President & Chief Executive Officer

Next Steps

Potential Populations for Further Clinical Development

Stages of Parkinson's Disease



Per collaboration agreement, decisions regarding prasinezumab development are made through the Joint Steering Committee, with Roche having the ultimate tie breaking decision.

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Prothena Summary

Positive clinical results from PASADENA position prasinezumab as the first potentially disease-modifying therapy for Parkinson's disease

PASADENA dataset further validates Prothena's specific and selective targeting approach towards protein dysregulation diseases

Growing and diverse pipeline will generate new preclinical and clinical data over the next 12 months

Protein Dysregulation

Advancing the Scientific Landscape

Optimizing the molecule (epitope matters)

- Targeting appropriate epitope to optimize engagement with both soluble and insoluble pathogenic species
- Engineering for optimal binding characteristics (e.g., neoepitopes, avidity optimization, etc.)

Clinical study design and patient selection

- Endpoints need to be increasingly sensitive and customized
- Advances in imaging, fluid and other biomarkers for inclusion/exclusion criteria enable testing in the patient population most appropriate for evaluation

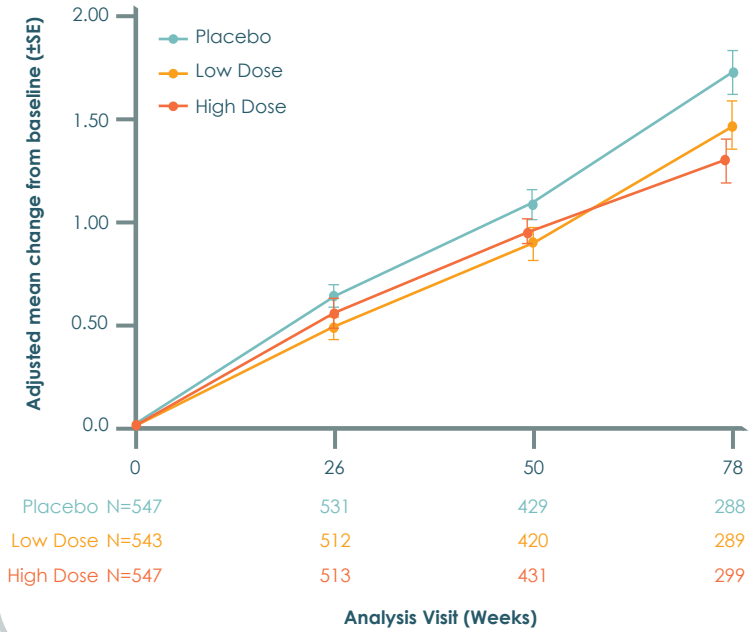
The macro environment

- Regulators are sophisticated in their view of diseases and clinical study design
- Governments are more aware of the potential cost and societal burden of diseases in the aging population

Growing Body of Clinical Evidence Supporting Targeting Proteinopathies

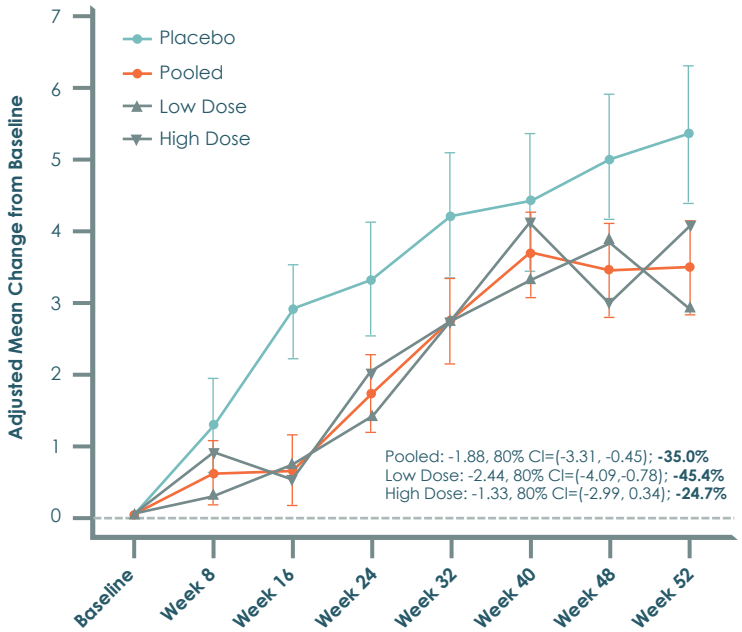
Aducanumab
Target: Aβ

EMERGE: Longitudinal change from baseline in CDR-SB



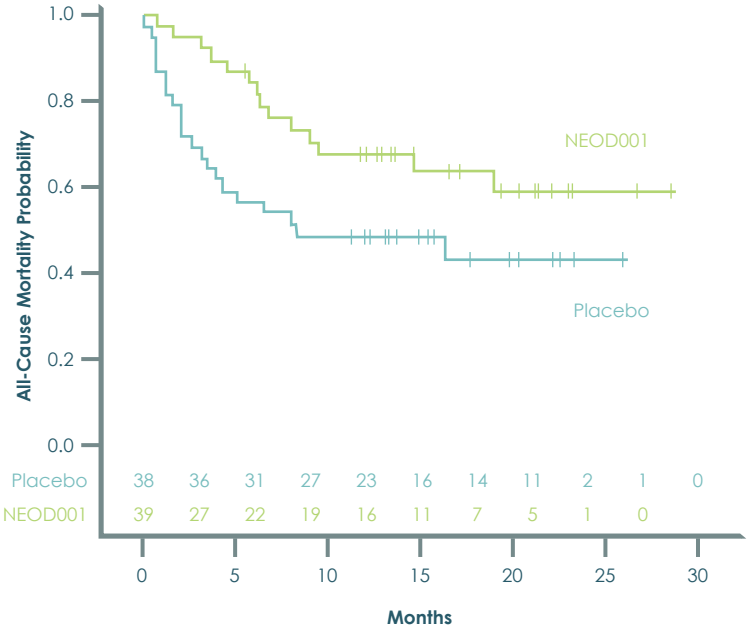
Prasinezumab
Target: Alpha-synuclein

PASADENA Phase 2
MDS-UPDRS Part III – central rating



Birtamimab (NEOD001)
Target: Amyloid Light Chain

VITAL Study All-Cause Mortality in Mayo Stage IV Subgroup (N=77)



All-cause mortality regardless of prior cardiac hospitalization

Biogen aducanumab data; Prothena/Roche prasinezumab data; Prothena birtamimab data

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Prothena's Robust Pipeline

Program/Target	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Biomarker Enabled	Commercial Rights
Prasinezumab (PRX002/RG7935) α–synuclein *Parkinson's Disease*	PASADENA (Phase 2)					✓ MRI-ASL	prothena Roche
PRX004 misTTR *ATTR Amyloidosis*			Phase 1			✓ misTTR*	prothena
Aβ *AD*		Preclinical				✓ PET-Aβ	prothena
Tau *AD, PSP, FTD, CTE*		Preclinical				✓ PET-tau	Bristol Myers Squibb**
TDP-43 *ALS, FTD*	Discovery						Bristol Myers Squibb**
Undisclosed *Neurodegeneration*	Discovery					✓	Bristol Myers Squibb**
Vaccine program *AD*	Discovery					✓ PET-imaging	prothena
Undisclosed *AD/Down Syndrome*	Discovery					✓ CSF	prothena

*Prothena's proprietary assay for misTTR (non-native TTR) in hereditary ATTR Amyloidosis (hATTR)
**Collaboration with Bristol-Myers Squibb, following its acquisition of Celgene in November 2019

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 labeling; PET, positron emission tomography

mAb | Vaccine | Small Molecule

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