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AD/PD™ 2021
The 15th International Conference on Alzheimer's & Parkinson's Diseases
March 9-14, 2021 Virtual Conference

Prothena at AD/PD 2021

New Data on PRX005 (Alzheimer's Disease) and Prasinezumab (Parkinson's Disease)

March 11, 2021

Agenda

- **Introduction and highlights**
  - Gene Kinney, PhD, President & CEO
- **New preclinical data from PRX005 (Alzheimer's Disease)**
  - Philip Dolan, PhD, Senior Director & Head of Exploratory Research
- **New analyses from Phase 2 PASADENA study of prasinezumab (Parkinson's Disease)**
  - Radhika Tripuraneni, MD, MPH, CDO
- **Summary**
  - Gene Kinney, PhD, President & CEO
- **Q&A**
  - Tran Nguyen, COO & CFO
  - Wagner Zago, PhD, CSO

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 2021 and beyond; our goal of building a protein dysregulation platform; the treatment potential, designs, and proposed mechanisms of action of birtamimab, prasinezumab, PRX004, PRX005, PRX012 and multi-immunogen Aβ-tau vaccine; plans for future clinical studies of birtamimab, prasinezumab, PRX004, PRX005, and PRX012; amounts we might receive under our collaborations with Roche and Bristol-Myers Squibb; the expected timing of reporting data from prior clinical studies of birtamimab and the Phase 2 clinical study of prasinezumab; potential indications and the potential superior attributes and efficacy of novel epitopes and antibodies we have identified in our programs, including our TDP-43 and undisclosed programs; and our potential to advance, initiate and complete IND enabling studies for our discovery and preclinical programs. 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 February 26, 2021, 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 and Highlights

Gene Kinney, PhD
President & Chief Executive Officer

Summary Highlights
PRX005 and Prasinezumab at AD/PD 2021

PRX005, Alzheimer's Disease (with Bristol Myers Squibb™)

- **Targeting MTBR of tau displays superior activity against tau internalization and neurotoxicity**
- **(m)PRX005 reduces tau pathology and downstream behavioral deficits**
- **Consistent, superior profile across a broad range of *in vitro* and *in vivo* models supports advancing PRX005 into clinical development for AD**
  - IND submission and study initiation expected 3Q21

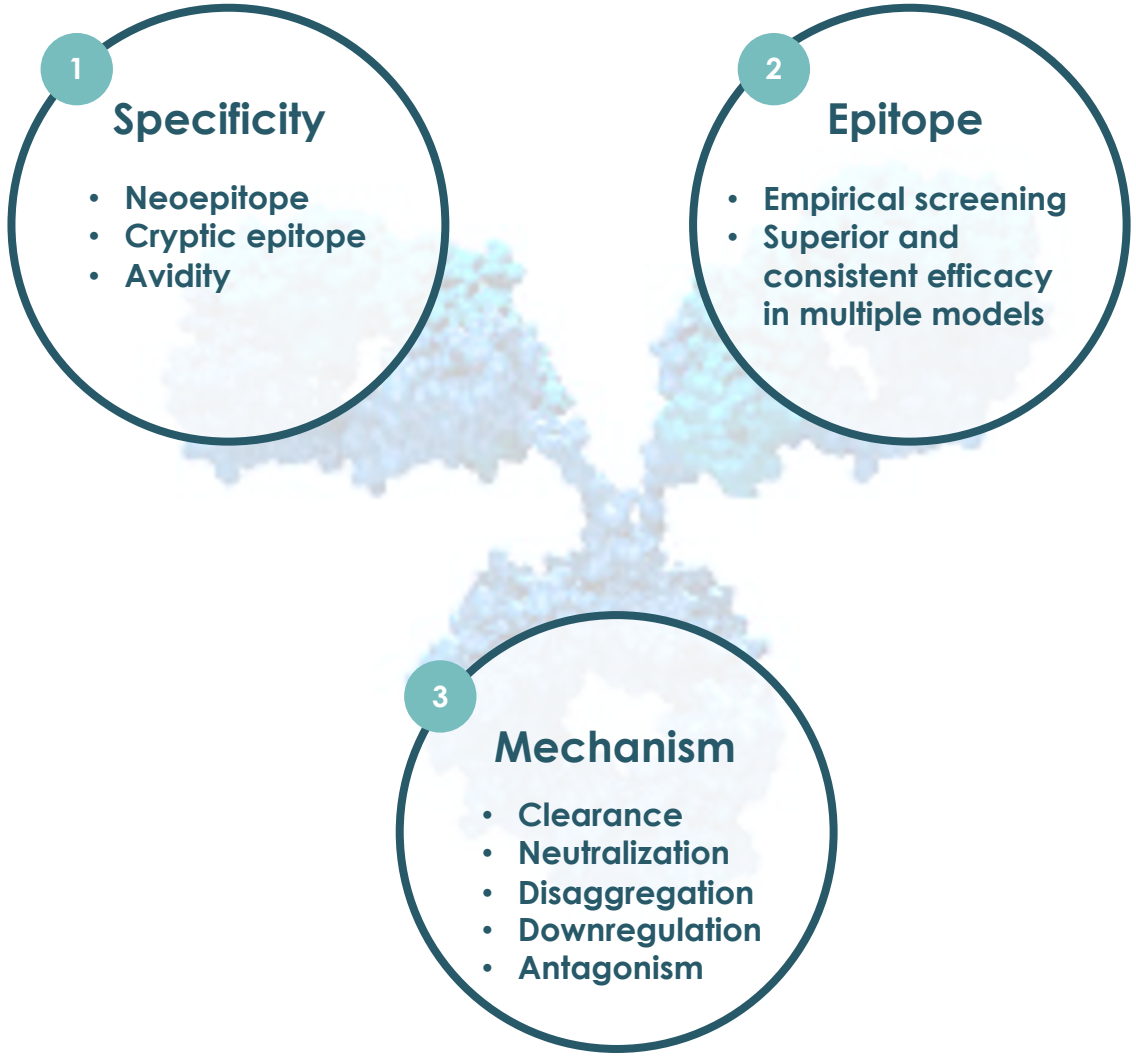
Prasinezumab, Parkinson's Disease (with Roche)

- **First anti-α–synuclein antibody to significantly slow progression on measures of PD**
- **New prespecified subgroup analysis showed greater effect in slowing clinical decline in subgroups with faster disease progression**
- **New digital biomarker results consistent with potential disease modifying effect of prasinezumab in slowing PD progression**
- **Advancing to Phase 2b PADOVA study (N=575)**
  - Study initiation expected 2Q21 (NCT #04777331)

Our Proven Scientific Platform Delivering Transformational Therapeutics

Scientific Platform:

1. **Specificity**: Spare normal biology
2. **Epitope**: Target optimal region
3. **Mechanism**: Engage the right pharmacology



Prothena today:

- **Translation to clinical POC**
- **Blockbuster indications**
- **Strong corporate foundation**

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New Preclinical Data from PRX005

Alzheimer's Disease

Global Neuroscience Collaboration with Bristol Myers Squibb

Philip Dolan, PhD

Senior Director & Head of Exploratory Research

Microtubule Binding Region (MTBR)-Specific Antibody PRX005 Prevents Pathological Tau Progression via Blockade of Neuronal Internalization



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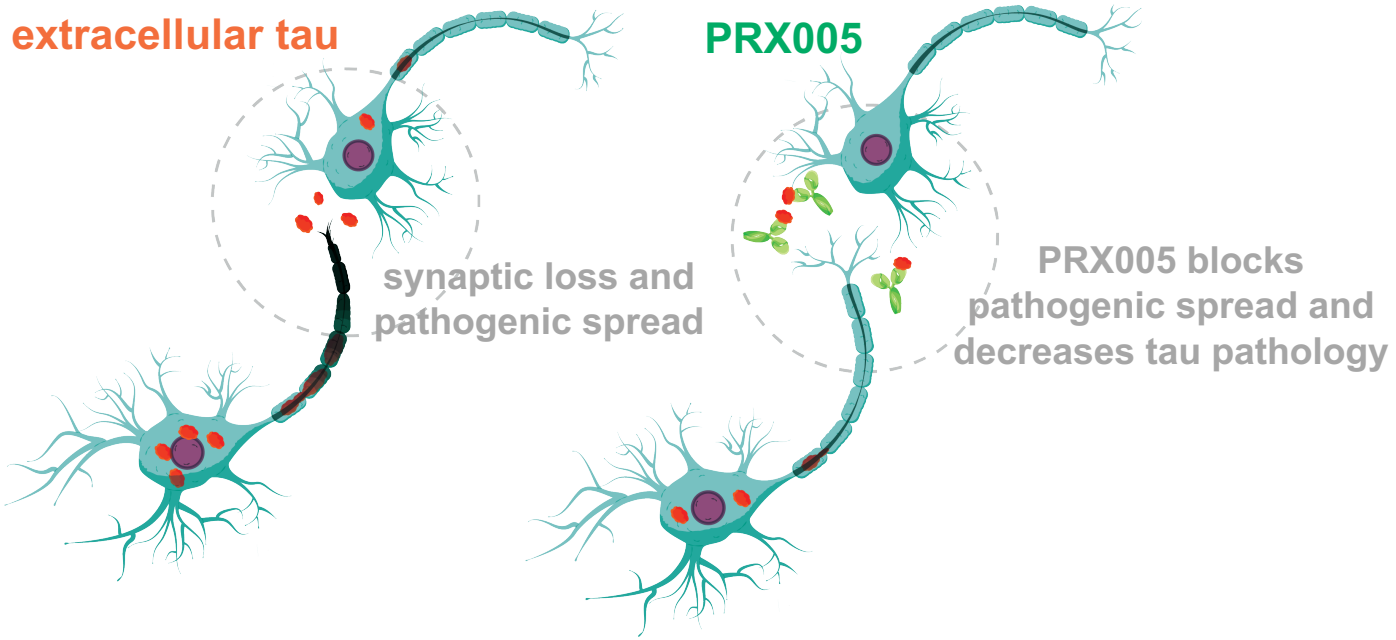
Session: Tau Pathology and Therapeutic Strategies 1
March 11, 2021, 12:00 – 14:00 CET

Tau Immunotherapy

Reduce neurotoxicity, prevent cell-to-cell transmission, promote clearance

- Histopathological and PET studies demonstrate correlation between cognitive function and extent of tau pathology in patients with Alzheimer's disease
- Spatiotemporal staging of tau pathology suggests cell-to-cell transmission of tau pathology
- Mechanistic studies have demonstrated release and transmission of tau *in vitro* and *in vivo* to adjacent and synaptically connected neurons



PRX005 is an IgG1 humanized antibody that binds with high affinity to the MTBR of tau protein and was designed to block cell-to-cell transmission of tau pathology

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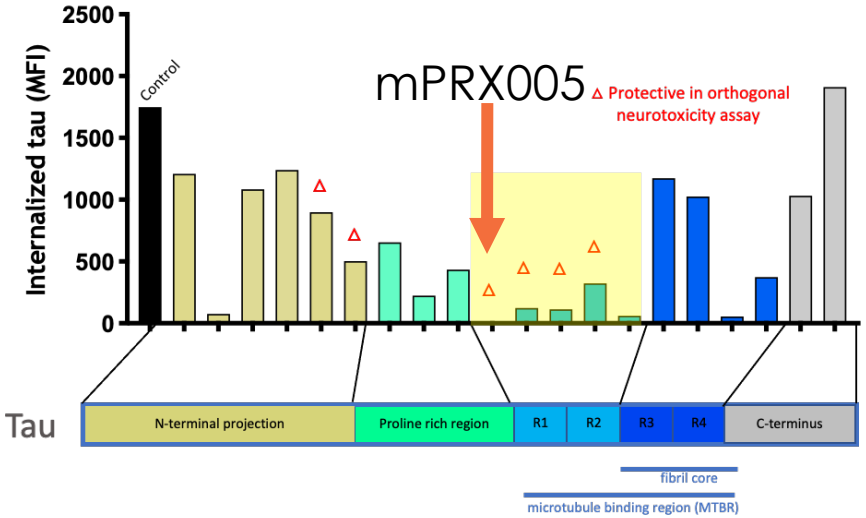
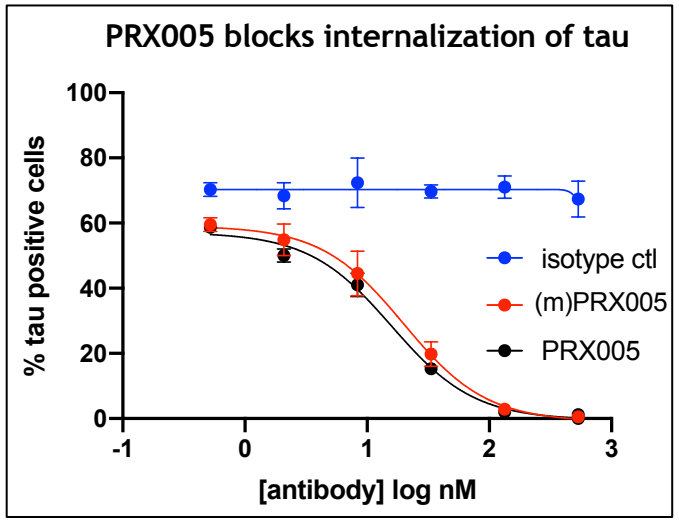
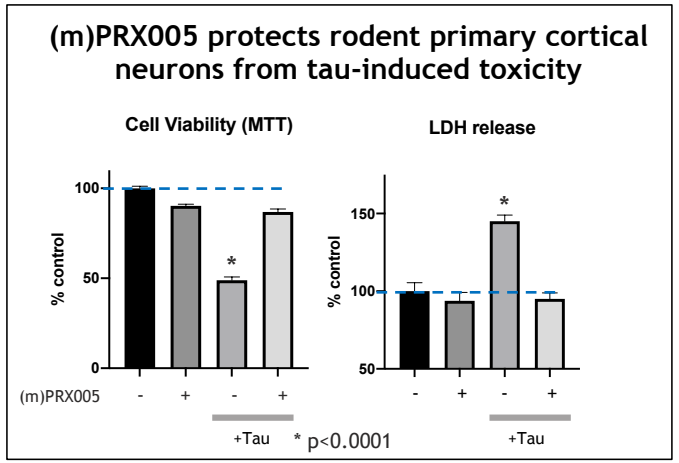
PRX005 is Superior to Other Anti-Tau Antibodies in Blocking Cellular Internalization of Tau and Downstream Neurotoxicity

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



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





All values are mean ± SD (n=3-5)

Internalized pHrodo-tau (pH-sensitive dye) measured by FACS

IC_{50}=9 nM
[tau] = 167nM

(m)PRX005 = murine form of PRX005

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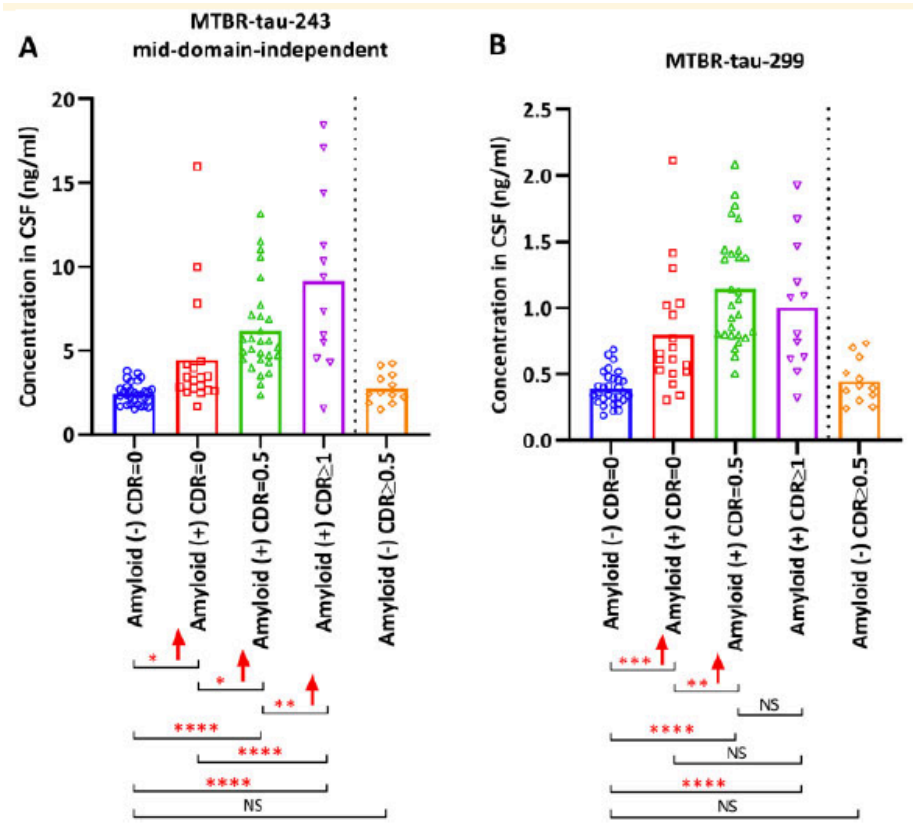
Tau Pathogenesis and the Microtubule Binding Region (MTBR)

- A recent study (right) confirmed the presence of MTBR tau in extracellular fluid (CSF), and correlated MTBR-tau with AD clinical progression[1]
- Correlation of MTBR peptides with dementia stages in AD is superior to other tau markers measured (N-terminal, mid-domain)
- MTBR mediates tau aggregation via nucleation-dependent mechanism[2]
- Another C-terminal tau fragment detected in CSF, tau368, was also correlated with PET tau pathology[3,4], lending further support to the disease relevance of extracellular MTBR



[1]Horie et al., BRAIN 2020

[2]von Bergen et al., 2005
[3]Leuzy et al., 2019
[4]Blennow et al., 2020

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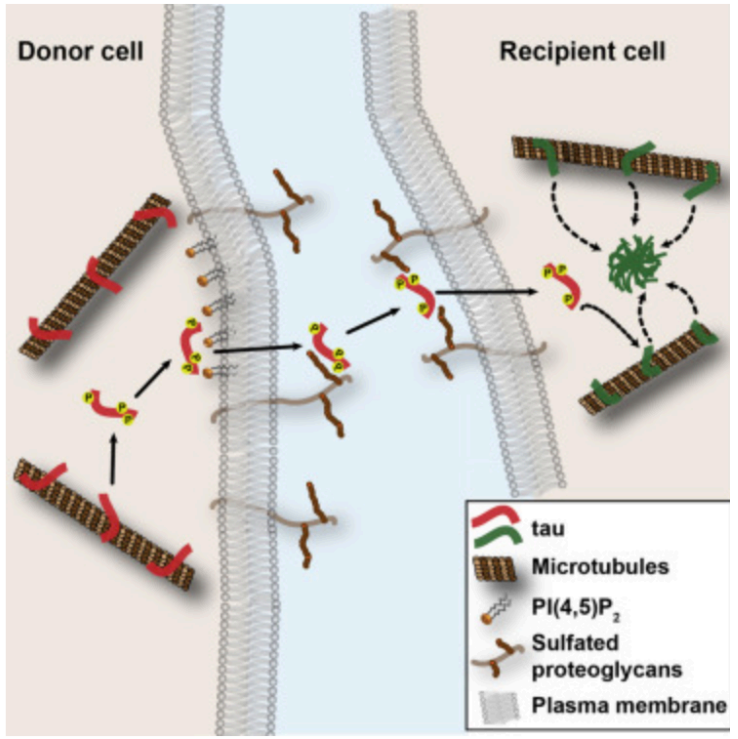
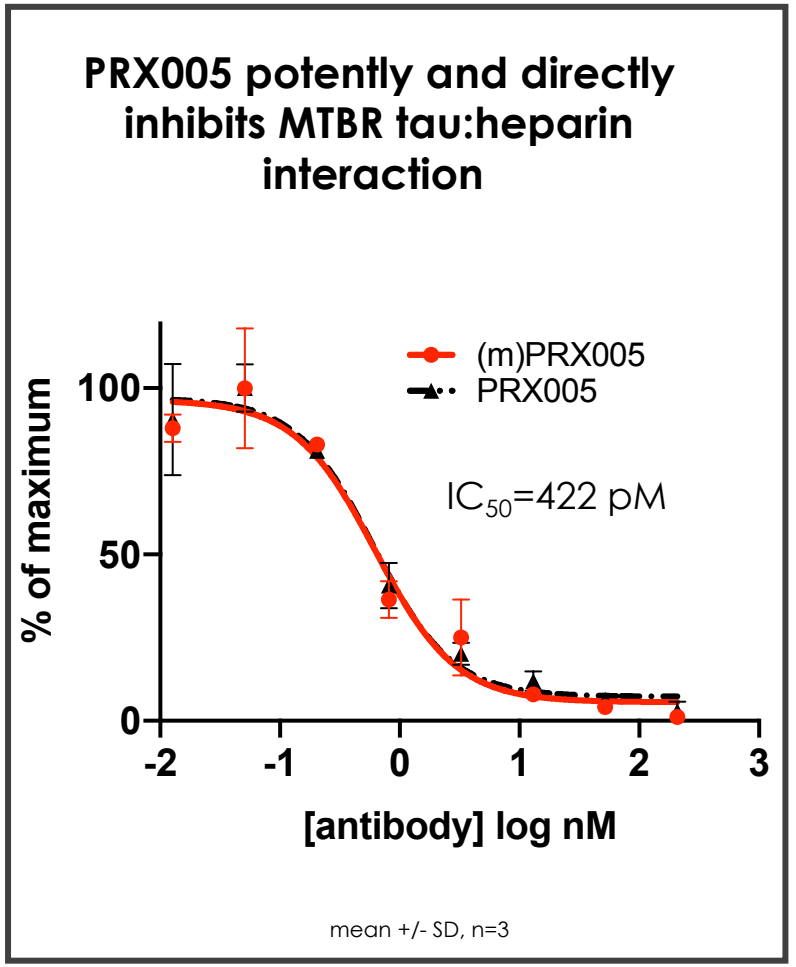
PRX005 Potently Blocks Interaction of a Repeat Region in the MTBR with HSPG Analog

- Tau-HSPG interactions occur across a broad interface, largely within the MTBR
- Tau-HSPG interactions are critical for tau secretion and uptake
- Block of tau-HSPG by PRX005 might prevent tau pathogenesis by blocking tau secretion and cell uptake



Katsinelos et al., 2018



(m)PRX005 = murine form of PRX005

Sibille et al., 2006; Holmes et al., 2013; Zhao et al., 2017; Katsinelos et al., 2018; Merezhko et al., 2018; Stopschinski et al., 2020)

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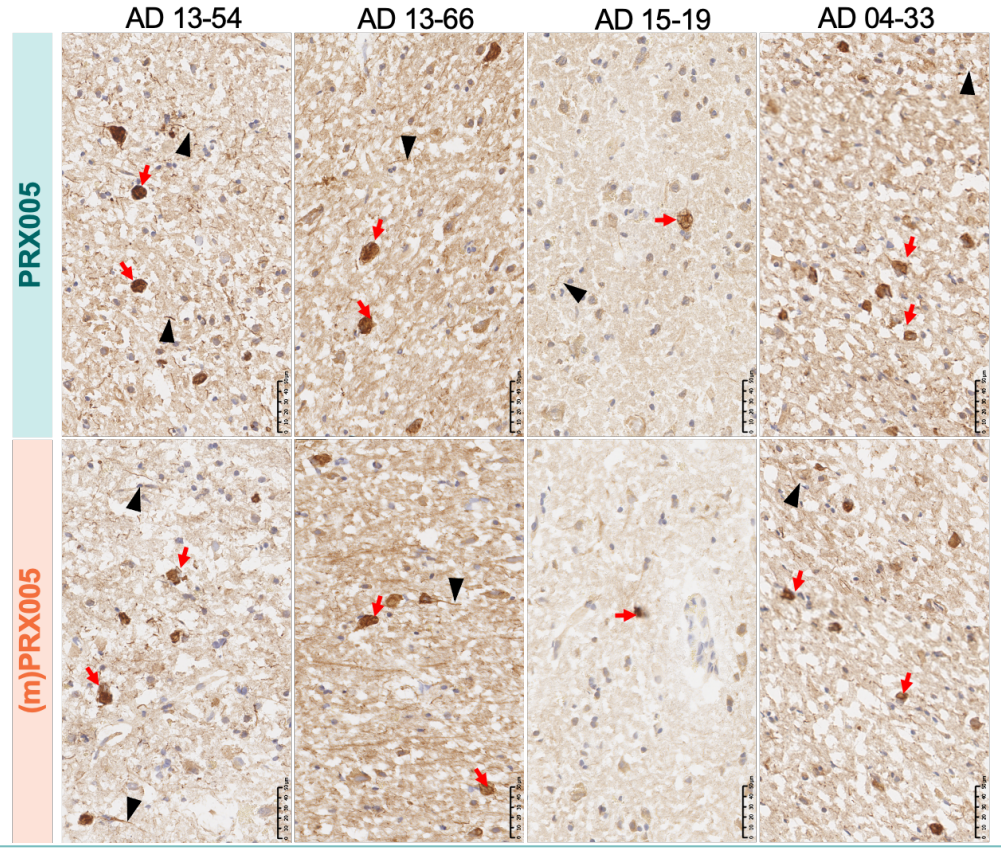
PRX005 Binds Phospho and 3R/4R Isoforms of Tau with High Affinity

- PRX005 equivalently binds phosphorylated and non-phosphorylated tau
- PRX005 binds all splice isoforms of tau

Kinetic binding parameters of PRX005 to 3R- and 4R-tau determined by SPR

	K_D
3R2N-tau	**154** pM
4R2N-tau	**206** pM

PRX005 Binds Alzheimer's disease brain tissue from multiple donors[1]



[1]Subset of tissue panel displayed here
Red arrows: neurofibrillary tangles
Black arrowheads: dystrophic neurites

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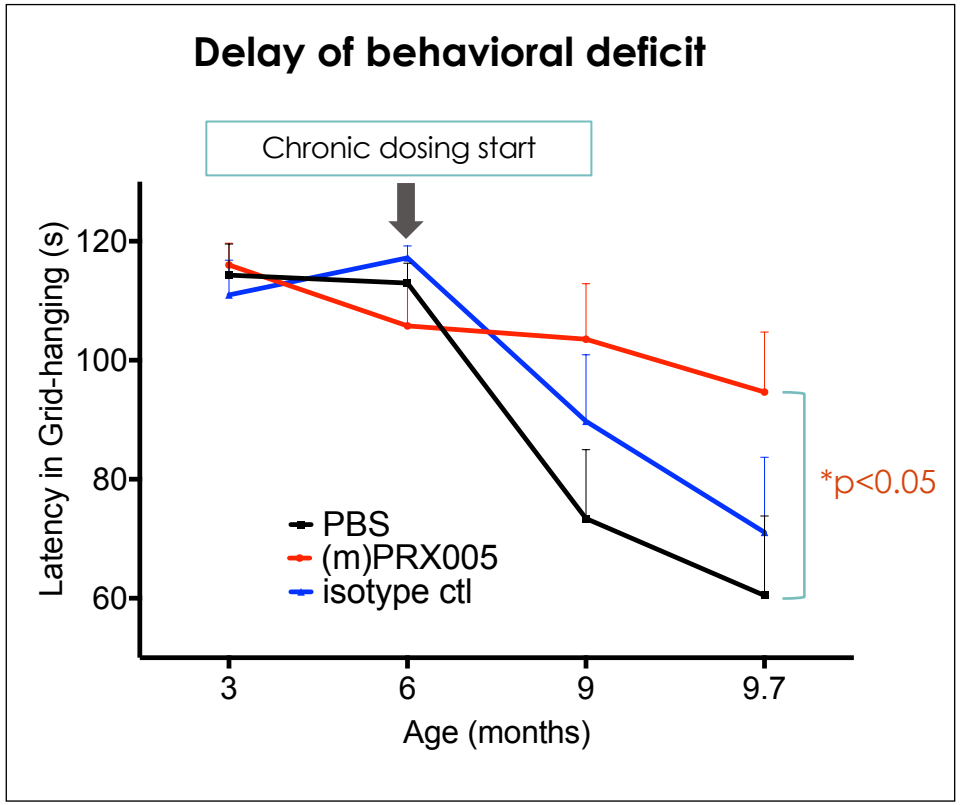
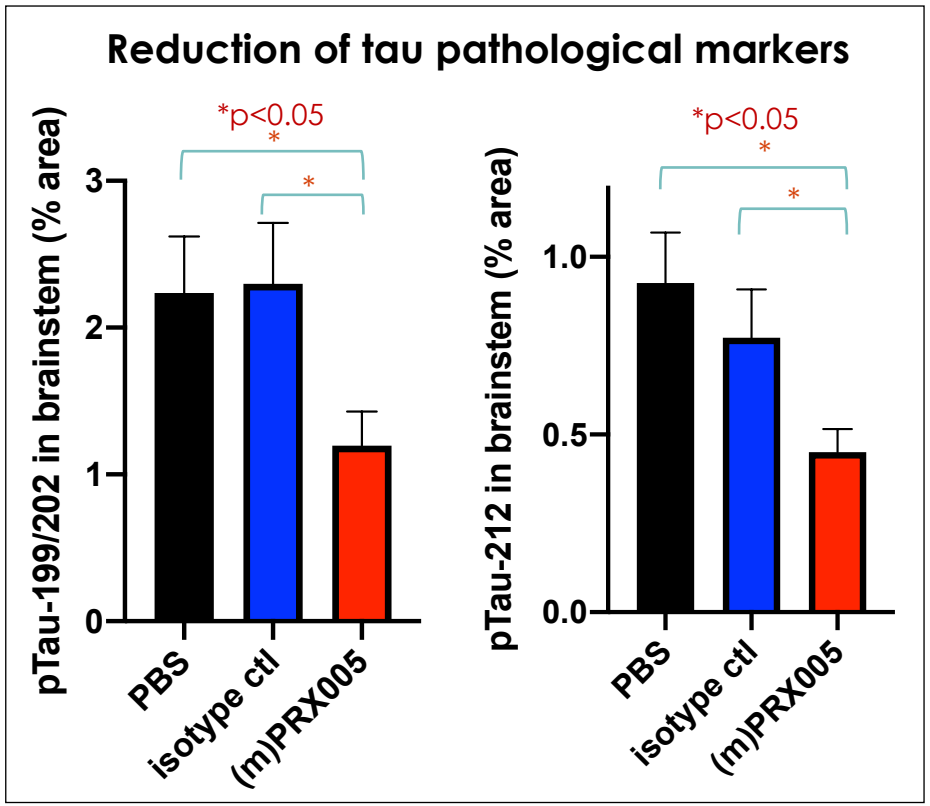
(m)PRX005 Treatment Reduces Pathological Tau and Ameliorates Behavior Deficit in a Transgenic Tau Mouse Model





All values are mean ± SE (n=15-20)

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

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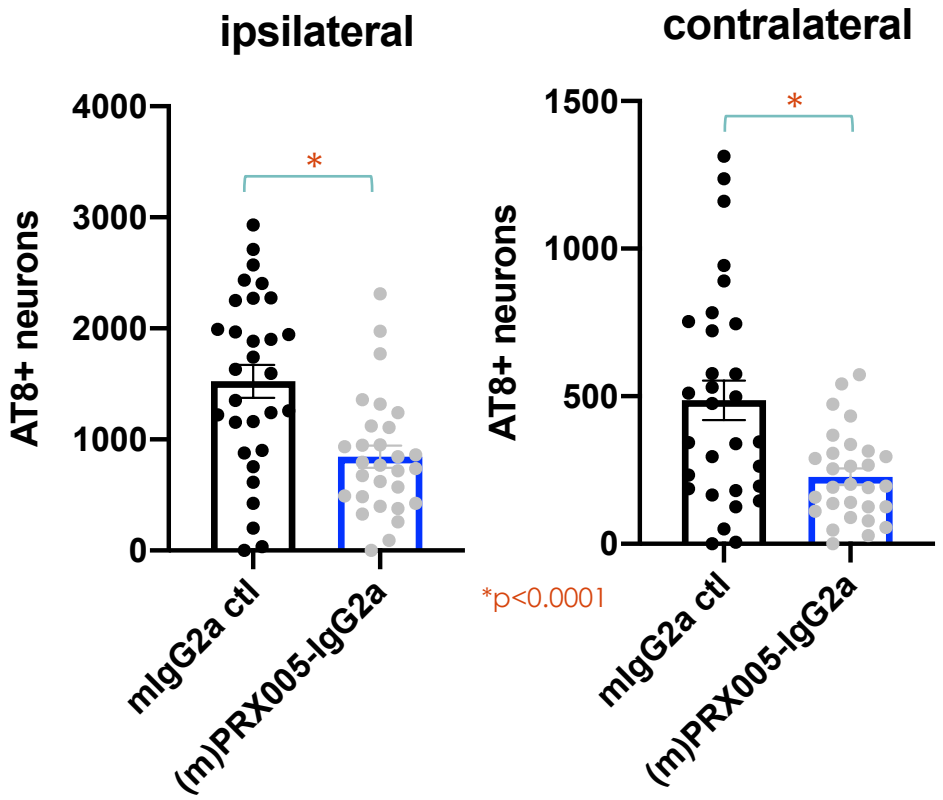
(m)PRX005 Treatment Reduces Pathological Tau Development in an Induced Tau Seeding Model with AD Extracts

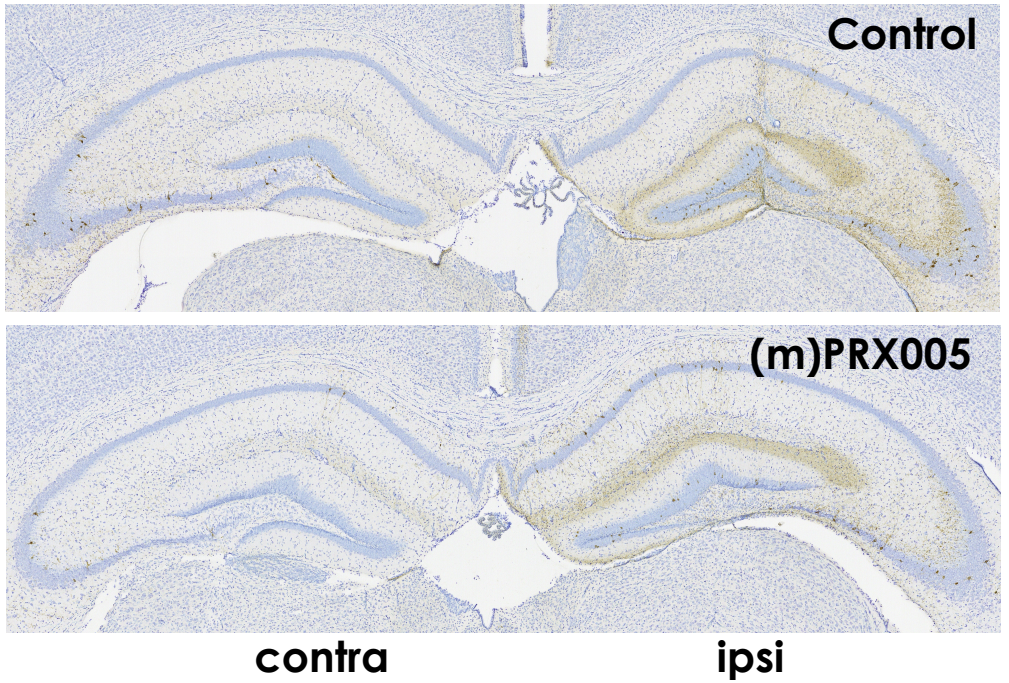


All values are mean ± SE (n=30)

- PS19 mice
- 3m: Unilateral injection of AD material
- 5m: Pathology measurements in ipsilateral and contralateral Hpc
- Tx: i.p. weekly

- Murine IgG2a promotes faster tau clearance by phagocytes *in vitro,* compared to IgG1
- Mouse IgG2a is the closest in function/biology to human IgG1

Representative images



(m)PRX005 = murine form of PRX005

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Summary of Findings

- *In vitro* screening of antibodies spanning the whole length of the tau protein indicated R1/R2 of MTBR displayed superior activity against tau uptake and neurotoxicity

- The murine precursor of PRX005 has a high affinity for MTBR tau epitope and superior profile versus other antibodies
  - Direct inhibition of the tau-HSPG interaction may contribute to blockade of tau internalization, toxicity, and development of intracellular tau pathology

- *In vivo* treatment with (m)PRX005 in transgenic tau mice and a seeding model reduces intraneuronal tau pathology and downstream behavioral deficits

The consistent, superior profile of PRX005 across a broad range of *in vitro* and *in vivo* systems supports advancing PRX005 as a clinical candidate for the potential treatment of Alzheimer's disease

Co-authors

Prothena Biosciences

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- Heather Prill
- Frédérique Bard
- Wagner Zago

We thank our collaborators at Bristol Myers-Squibb

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New Prespecified Subset Analyses from Phase 2 PASADENA Study

Parkinson's Disease
Worldwide Collaboration with Roche

Radhika Tripuraneni, MD, MPH
Chief Development Officer

A Phase 2 Study to Evaluate the Safety and Efficacy of Prasinezumab in Early Parkinson's Disease (PASADENA) Results from Part 1 Week-52

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March 11, 2021, 08:00 - 10:15 CET

Slowing of Clinical Decline with Prasinezumab Even More Evident in Prespecified PASADENA Subgroups

- **Ability to demonstrate the beneficial effect of an intervention depends on the ability to measure disease progression**
- **Progression of MDS-UPDRS total over 1 year is mostly driven by Part III in an early-stage population (PPMI and PASADENA)**
- **Slowing of clinical decline with prasinezumab was even more evident in subgroups with faster disease progression**
  - **MDS-UPDRS Part III: –25%**, Total population; **–39%,** MAO-B inhibitor treated; **–64%,** Diffuse malignant subtype
  - **Digital motor measures: –25%**, Total population; **–26%,** MAO-B inhibitor treated; **–36%,** Diffuse malignant subtype
- **Phase 2b PADOVA study is planned to start in 2Q21 (NCT #04777331)**
  - Early-stage patients requiring stable symptomatic therapy (N=575)

MAO-B, monoamine oxidase B; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale

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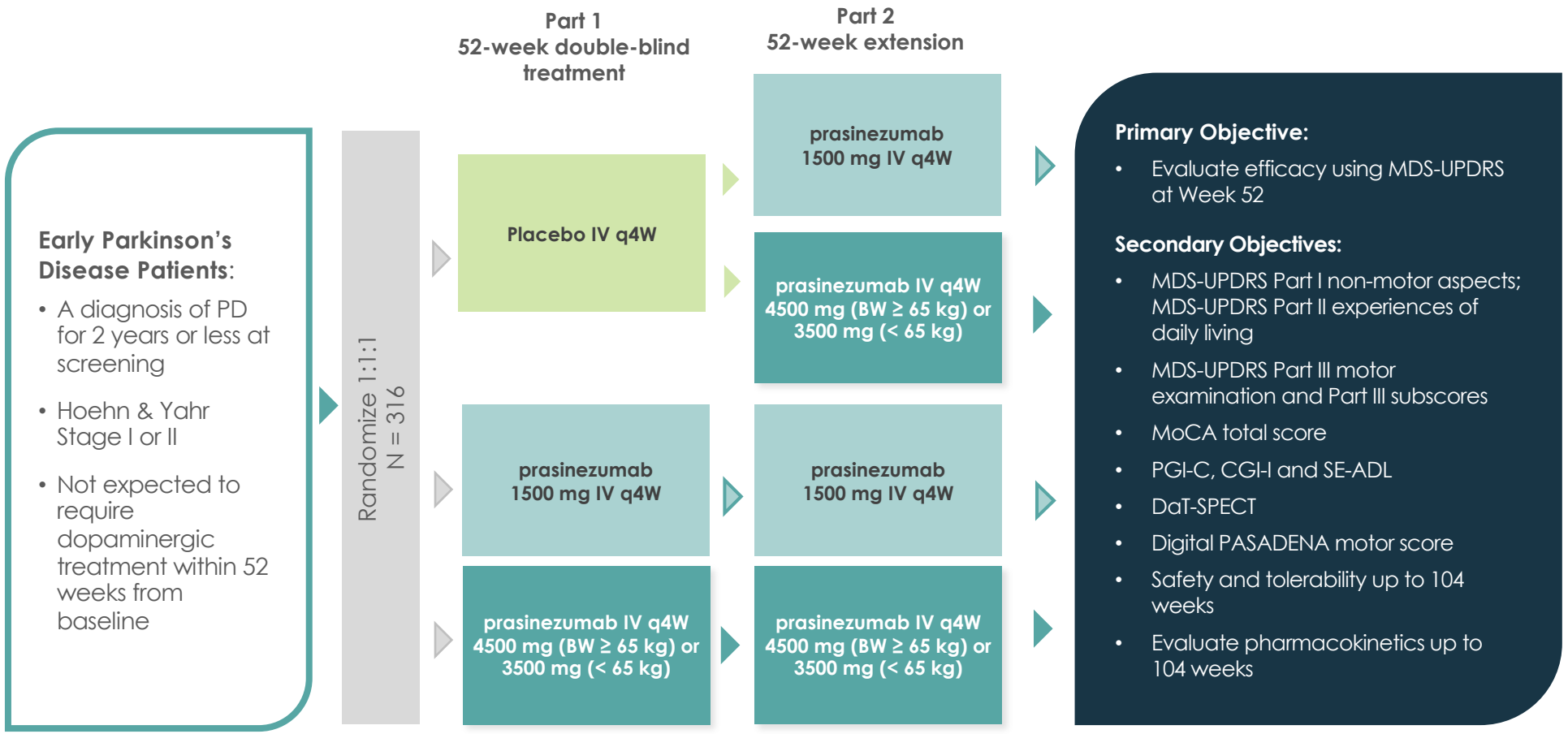
PASADENA Phase 2 Study (NCT03100149)



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

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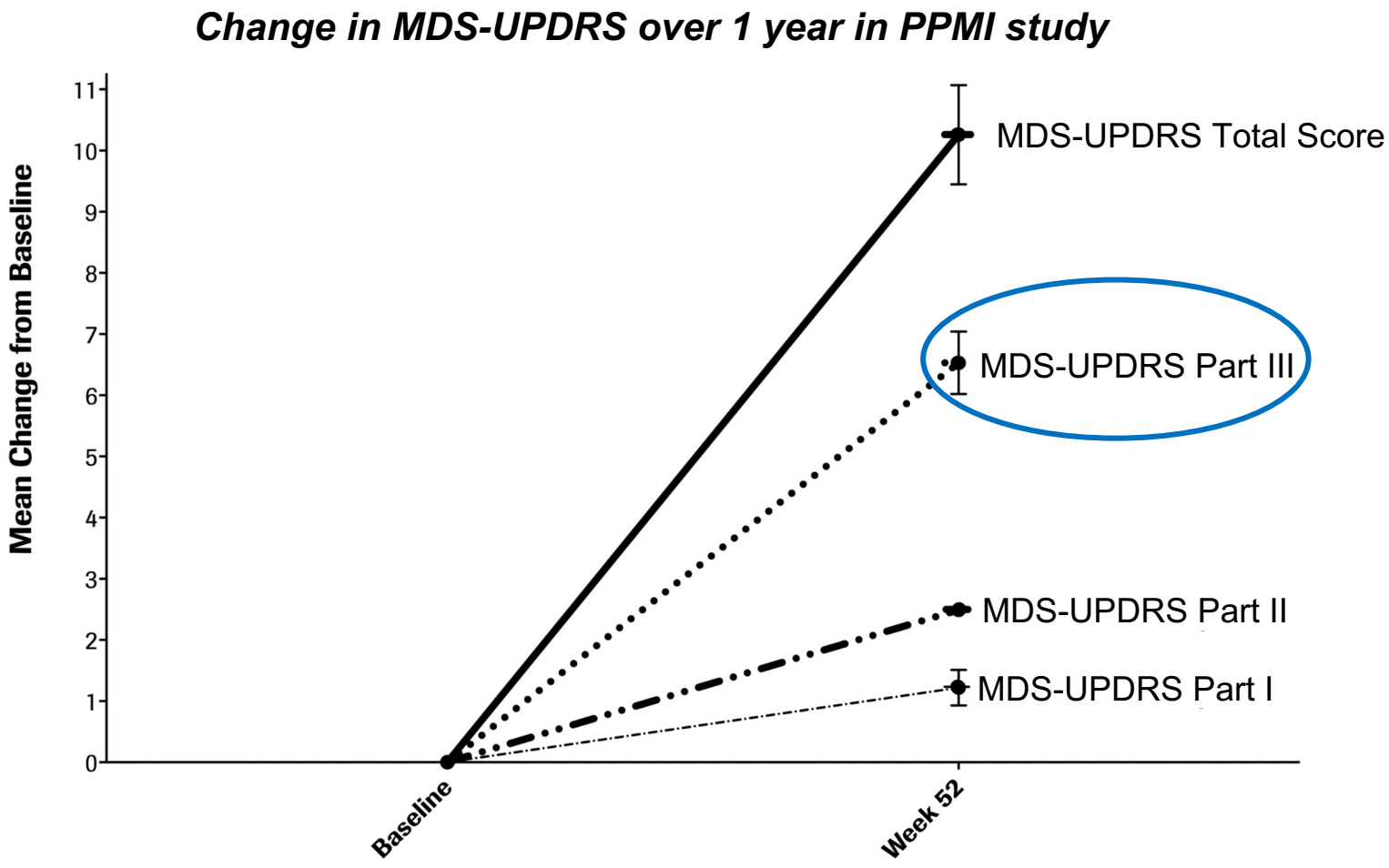
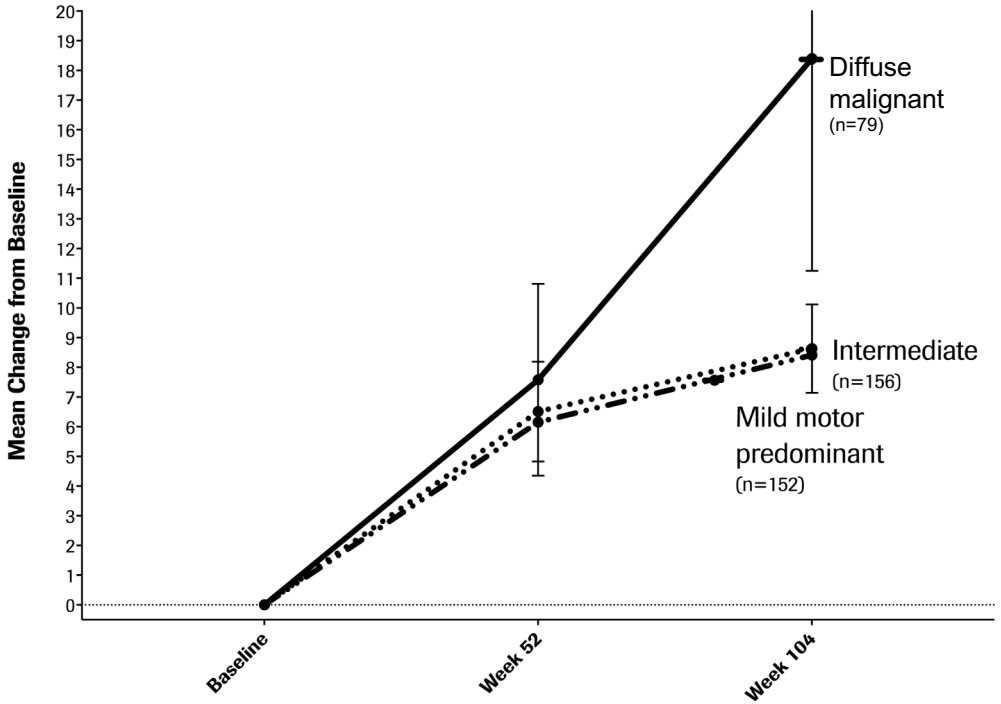
Progression of MDS-UPDRS total over 1 year is mostly driven by MDS-UPDRS Part III in an early stage population (PPMI study)



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).

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

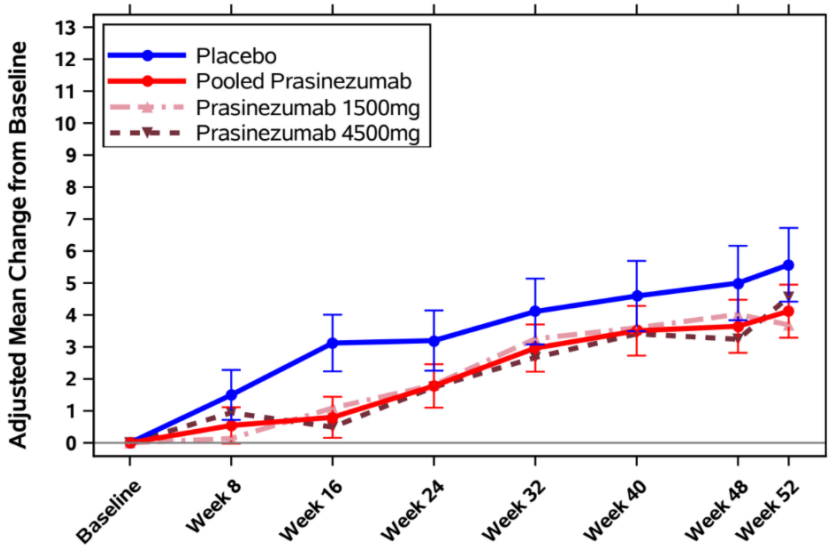
For the derivations of the data-driven sub-phenotypes, scales were classified into; motor scales (MDS-UPDRS Part II and MDS-UPDRS-Part III) and non-motor scales (SCOPA-AUT, RBDSQ and MoCA).
* Please note, the population sizes in the subgroup analyses are small. MAO-B monoamine oxidase B; MDS-UPDRS, Movement 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)

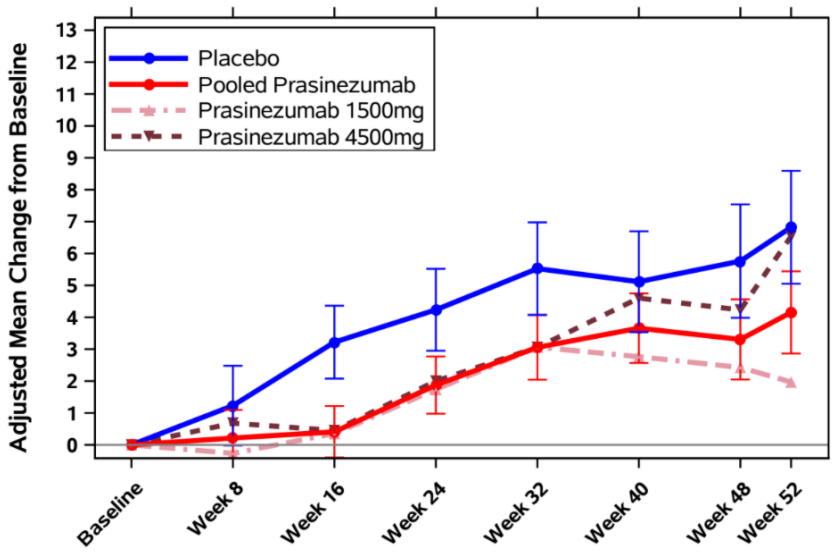
Change at Week 52 (placebo) = **5.57** points



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)

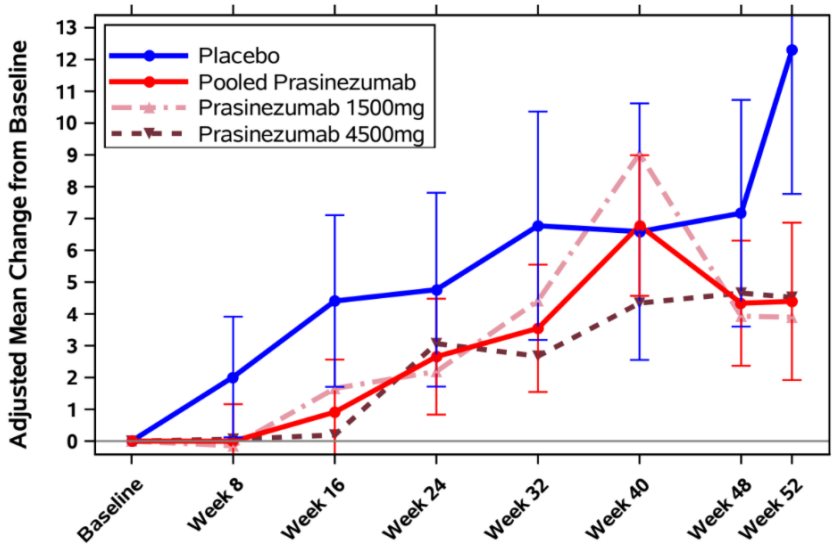
Change at Week 52 (placebo) = **6.82** points



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



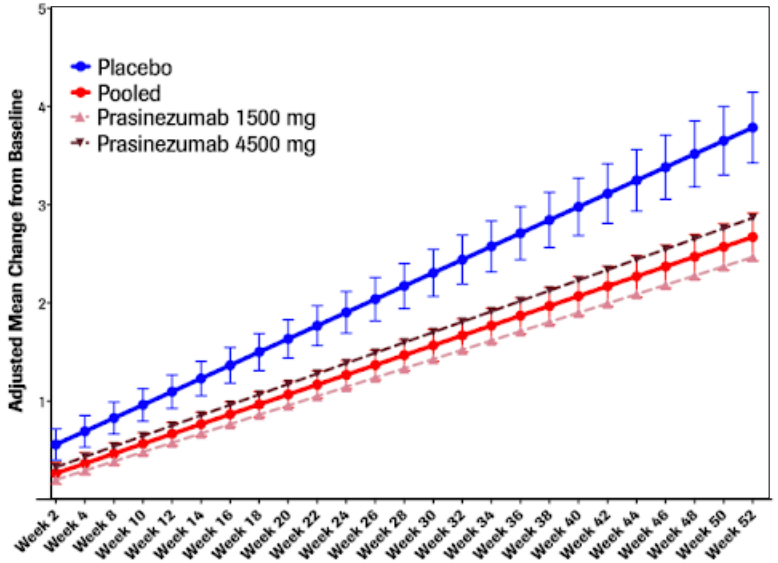
Pooled: –7.86, 80% CI=(–12.9, –2.82); **–63.9%**,
Prasinezumab 1500 mg: –8.4, 80% CI=(–14.2, –2.59); **–68.3%**
Prasinezumab 4500 mg: –7.77, 80% CI=(–13.4, –2.14); **–63.2%**

*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

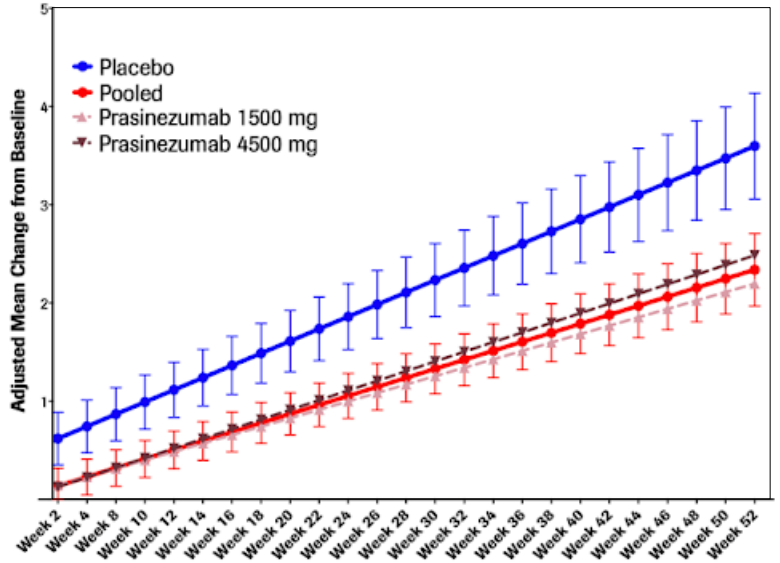
PASADENA Digital Motor Score

Total population (N=316)



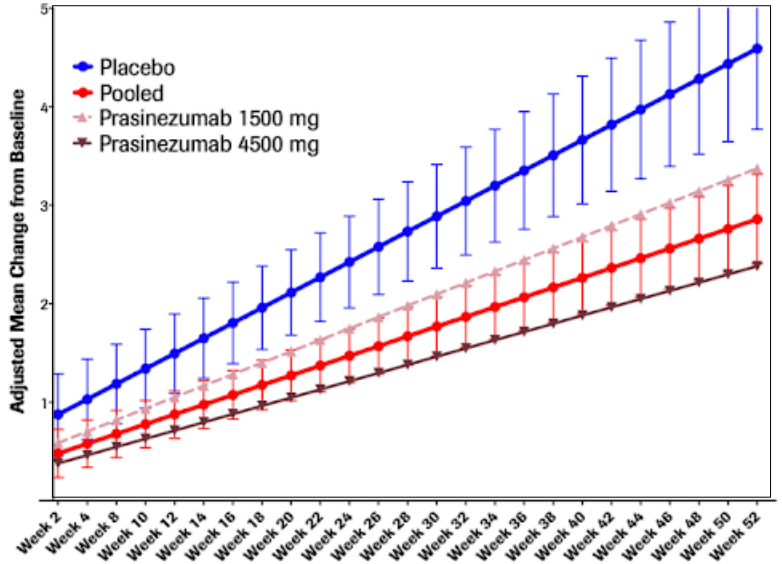
Pooled: –0.030, 80% CI=(–0.050, –0.010); **–25.0%**
Prasinezumab 1500 mg: –0.040, 80% CI=(–0.063, –0.017); **–30.3%**
Prasinezumab 4500 mg: –0.029, 80% CI= (–0.052, –0.006); **–21.5%**

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.

Roche PD Mobile Application V2 Detects Slowing of Early Parkinson's Disease Progression Under Prasinezumab: PASADENA Phase 2 Part 1 Results



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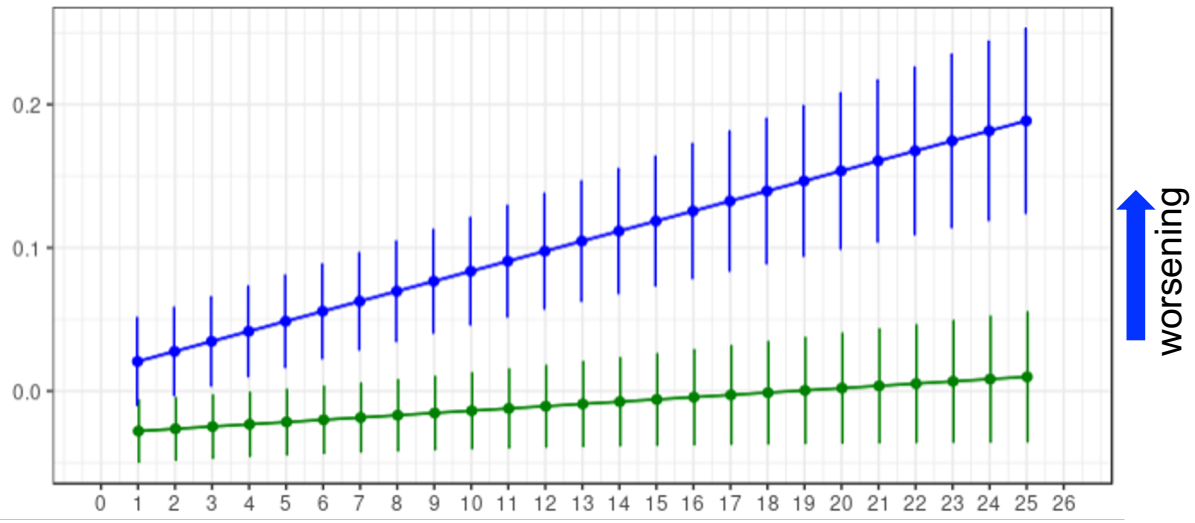
Remote Monitoring App Detects Slowing of Early Parkinson's Disease Progression with Prasinezumab in PASADENA

- **Roche mobile application designed to measure core motor signs of Parkinson's disease remotely, continuously and objectively**
  - Enables modelling of slopes of motor sign progression
  - 17 pre-specified sensor features*, one per task/side and from passive monitoring
  - Sensor features aggregated (median) over all data points within each two-week window** over entire 52 weeks of study
- **Daily quantification via the Roche PD mobile application in early-stage PD demonstrated a divergence of slopes in bradykinesia progression favoring prasinezumab**
- **Results consistent with a potential disease modifying effect of prasinezumab in slowing PD progression, in line with PASADENA results**

*median gesture power of passively monitored gestures, median turn speed in U-turn test and passively monitored gait, jerk in balance test, mel frequency cepstrum 2 in speech test, voice jitter in sustained phonation, number correct in Symbol Digit Modalities Test; for least and most affected sides separately: speeded tapping variability, maximum speed of hand-turning, spiral celerity in draw-a-shape task, median squared energy in rest and postural tremor tasks.
** If <3 data points per fortnight, then missing
PD = Parkinson's disease

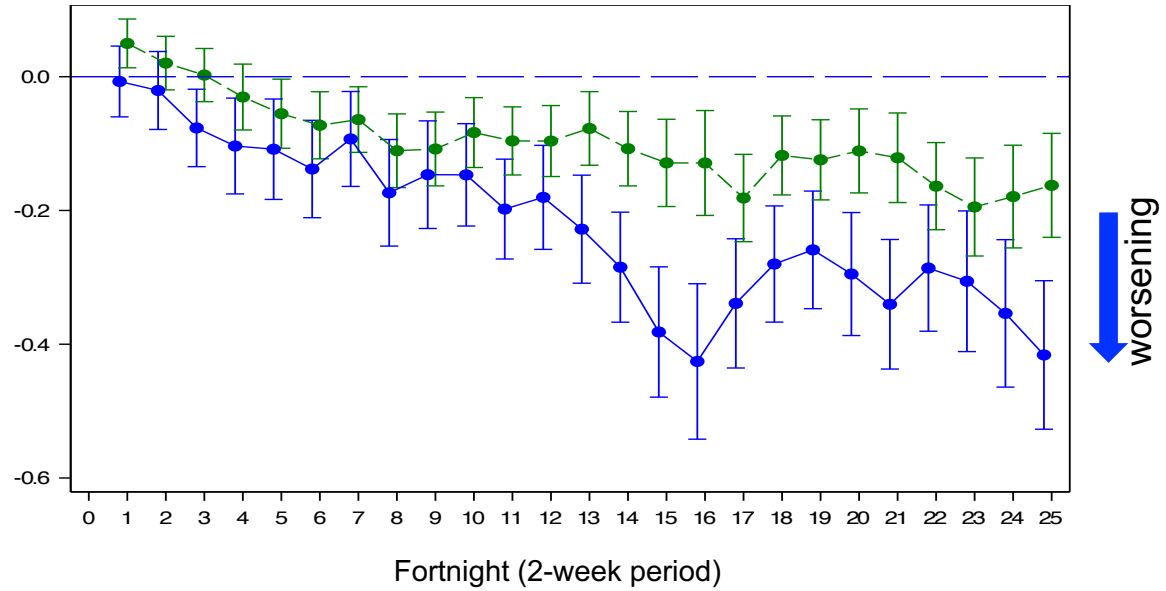
Less bradykinesia progression in treatment group

Speeded tapping variability, less affected side[1]



Placebo Pooled prasinezumab

Passively monitored hand gesture power[2]



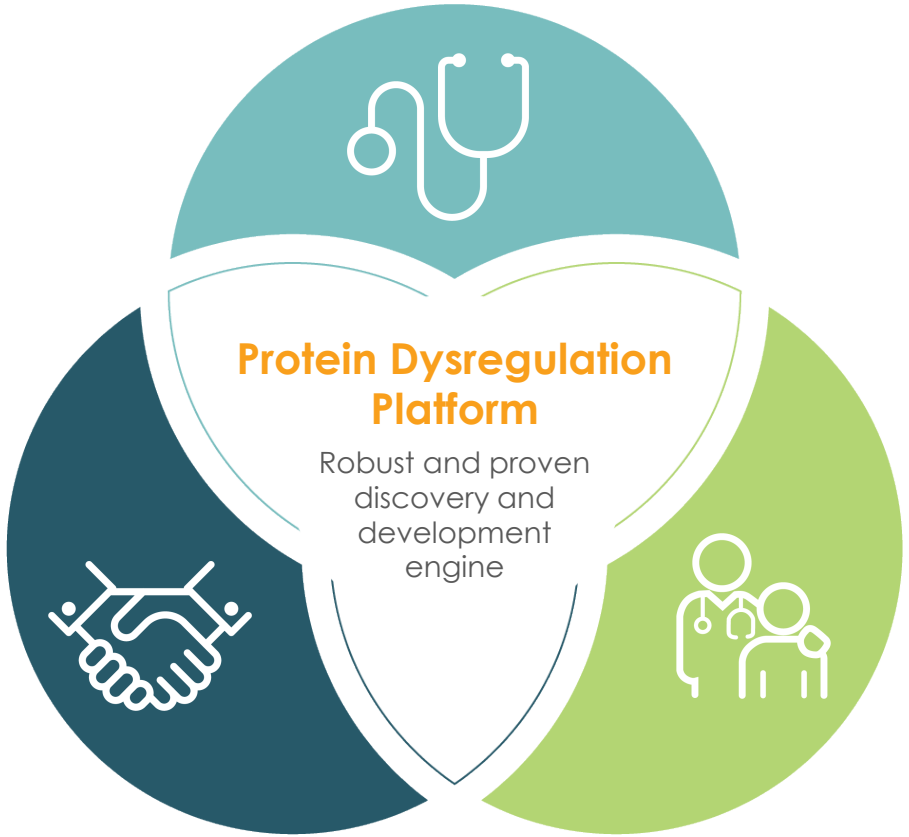
Placebo Pooled prasinezumab

[1]Results of Linear Mixed Effect model (80% CI)
[2]Result of Mixed Model with Repeated Measures (80% CI)

Summary

Gene Kinney, PhD
President & Chief Executive Officer

Path for Sustainable Growth



Clinical

3 Late-stage programs

6 Potential INDs from internal discovery engine

Collaboration

Strong collaborations with Roche and Bristol-Myers Squibb

Significant potential partner payments add to current cash of $298 million[1]

Commercial

Transition to fully-integrated commercial biotech

[1]Includes cash, cash equivalents and restricted cash at end of 4Q20

prothena

Upcoming R&D Milestones and Expected Timing

Birtamimab for potential treatment of AL amyloidosis

mid-2021	❑ Phase 3 AFFIRM-AL Study initiation
2021	❑ VITAL study 9-month results presented at medical conference

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

1Q21	✓ New pre-specified exploratory subgroup analyses from Part 1 of the Phase 2 PASADENA study presented at AD/PD
2Q21	❑ $60 million clinical milestone payment upon first patient dosed in Phase 2b PADOVA study
TBA	❑ Results from Part 2 of the Phase 2 PASADENA study presented at a medical conference

PRX004 for potential treatment of ATTR-cardiomyopathy

2Q21	❑ Phase 1 study results presented at medical conference
4Q21	❑ Initiation of Phase 2/3 study

PRX005 for potential treatment of Alzheimer's disease (collaboration with BMS)

1Q21	✓ Preclinical data to be presented at AD/PD
3Q21	❑ IND submission and study initiation, with potential $80 million US option payment

PRX012 for potential treatment of Alzheimer's disease

1Q22	❑ IND filing

Q&A

Appendix

Robust R&D Pipeline

Focused on rare peripheral amyloid and neurodegenerative diseases

Program/Target	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Commercial Rights	Next Milestone
Birtamimab / AL *AL Amyloidosis*					AFFIRM-AL (Phase 3, under SPA[1] agreement with FDA)	prothena	• P3 initiation mid-2021
Prasinezumab / α–Syn *Parkinson's Disease*				PASADENA (Phase 2)		prothena Roche	✓ AD/PD oral presentation March • P2b initiation 2Q21; $60M at FPI[2]
PRX004 / ATTR *ATTR Amyloidosis*			Phase 1 Complete			prothena	• P2/3 initiation 4Q21
PRX005 / Tau *Alzheimer's Disease*		Preclinical				Bristol Myers Squibb™	✓ AD/PD oral presentation in March • IND and study initiation 3Q21; $80M U.S. opt-in[3]
PRX012 / Aβ *Alzheimer's Disease*		Preclinical				prothena	• IND 1Q22
Undisclosed *AD in Down Syndrome*	Discovery					prothena	• IND 2022
Undisclosed *Neurodegeneration*	Discovery					Bristol Myers Squibb™	• IND
Vaccine / Aβ + Tau *Alzheimer's Disease*	Discovery					prothena	• IND
TDP-43 *ALS*	Discovery					Bristol Myers Squibb™	• IND

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; [2] $60 million milestone payment at Phase 2b first patient dosed; [3] $80 million potential option payment for US rights
Aβ, Abeta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; mAb, monoclonal antibody

prothena

Appendix

Prasinezumab Presentations at AD/PD 2021

A Phase II study to evaluate the safety and efficacy of prasinezumab in early Parkinson's disease (PASADENA): Results from Part 1 Week 52

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*

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Disclosures and Disclaimer

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

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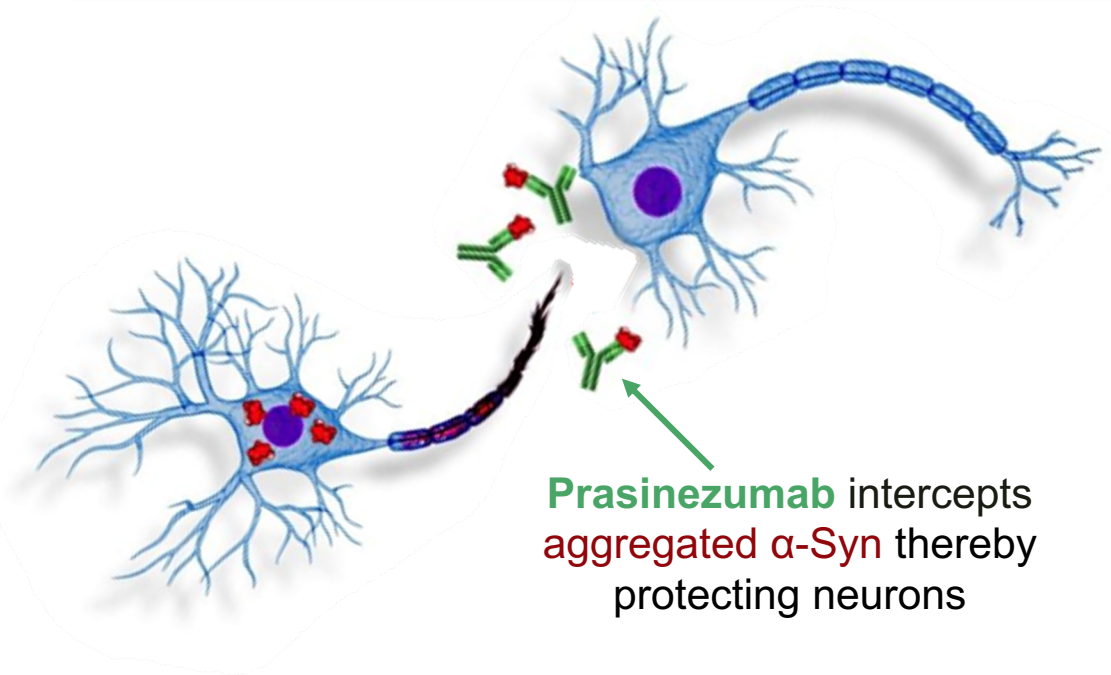
Prasinezumab is a humanized monoclonal antibody, designed to target aggregated α-Syn in PD

No treatments exist that can affect the underlying cause of PD[1–3]
Currently available treatments have powerful effects on symptoms but do not prevent or slow disease progression[2,3]



- **α-Syn** is genetically and neuropathologically validated as a **key target in PD[4]**
- **Prasinezumab binds aggregated α-Syn at the C-terminus[5–7]**
  - The targeted epitope results in higher selectivity for aggregated α-Syn, as well as consistently high levels of efficacy across several preclinical models
- **Prasinezumab demonstrated efficacy in multiple *in vivo* and cellular α-synucleinopathy models:[5–9]**
  - Reducing build-up of intracellular α-Syn pathology and protecting neurons
  - Blocking cell-to-cell transmission of α-Syn
  - Protecting synapses and reduceing gliosis
  - Ameliorating motor and cognitive behavioral deficits

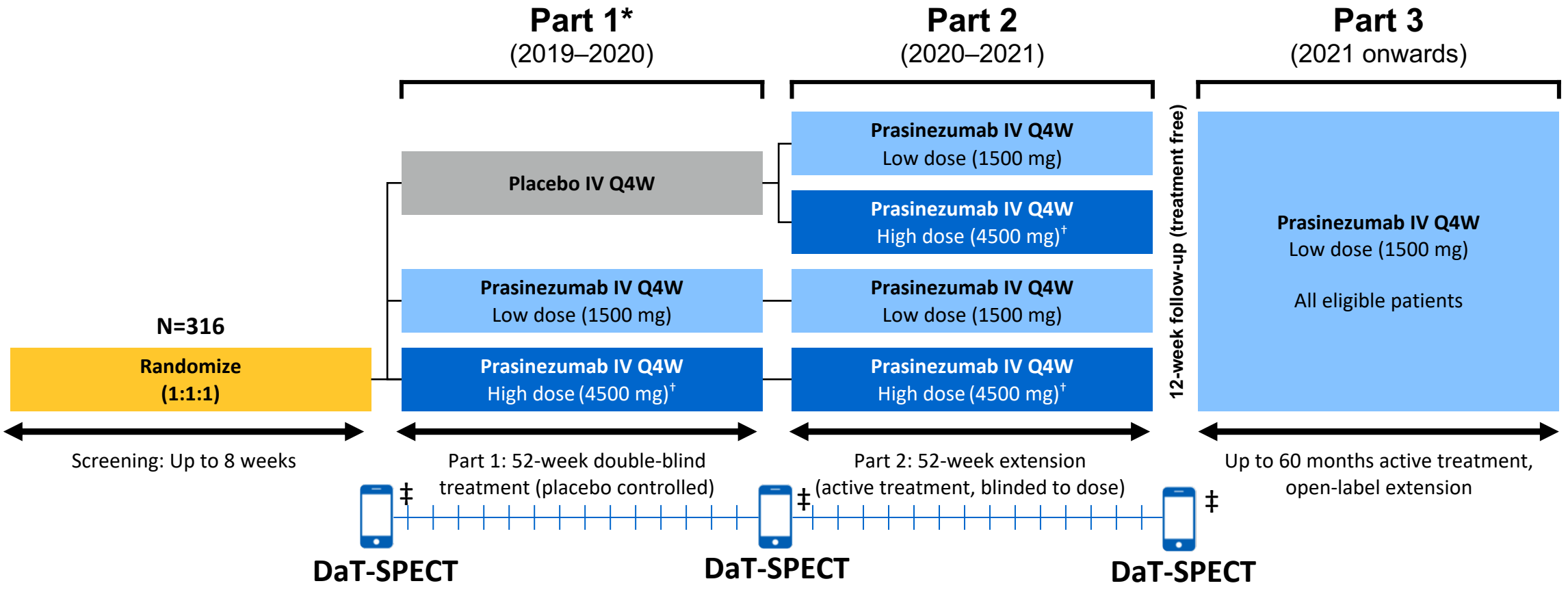
Prasinezumab has the potential to slow disease progression by protecting neurons from toxic α-Syn species

α-Syn, alpha-synuclein; PD, Parkinson's disease.

1. Verschuur CVM, et al. *N Engl J Med*. 2019; 380:315–324; 2. Lang AE & Espay AJ. *Mov Disord*. 2018; 33:660–677; 3. Cheng H, et al. *Ann Neurol*. 2010; 67: 715–725; 4. Dehay B, et al. *Lancet* Neurol. 2015; 14:855–866; 5. Masliah E, et al. *Neuron*. 2005; 46:857–868; 6. Masliah E, et al. *PLoS ONE*. 2011; 6:e19338; 7. Games D, et al. *J Neurosci*. 2014; 34:9441–9454; 8. Spencer B, et al. *Acta Neuropathol Commun*. 2017; 5:7; 9. Jankovic J et al. *JAMA Neurol*. 2018; 75:1206–1214.

PASADENA Phase II study in individuals with early PD

A 52-week multicenter, randomized, double-blind, placebo-controlled study



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

*COVID-19 did not affect assessments during PASADENA Part 1 as these were completed before the pandemic. †High dose = 4500 mg for ≥65 kg; 3500 mg for <65 kg. ‡Digital biomarkers (smartphone and wrist-worn wearable assessments). COVID-19, coronavirus disease 2019; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; IV, intravenous; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; PD, Parkinson's disease; Q4W, every month. ClinicalTrials.gov. NCT03100149. (Accessed February 2021).

The mentioned compounds and their use are investigational and have not yet received regulatory approval in any country.

PASADENA Phase II study in individuals with early PD

Endpoints and inclusion/exclusion criteria

Primary endpoint

- Change from baseline at Week 52 in MDS-UPDRS Total score (sum of Parts I, II and III)

Key secondary endpoints

- Change from baseline at 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 sub-scores (bradykinesia, rigidity, tremor, axial signs)
  - MoCA total score
  - PGI-C, CGI-C and disability (SE-ADL)

Key exploratory endpoints

- Neurodegeneration of dopaminergic terminals (DaT-SPECT)
- Digital PASADENA Motor Score
- ASL-MRI for cerebral blood flow

Safety, tolerability, pharmacokinetics and immunogenicity

Key inclusion criteria

- Idiopathic PD with bradykinesia and one of the other cardinal signs of PD (resting tremor, rigidity) and no other known or suspected cause of PD
- Aged 40–80 years
- DaT-SPECT screening consistent with PD
- Either treatment naïve or on a stable dose of a MAO-B inhibitor for at least 90 days*

Key exclusion criteria

- Medical history indicating a Parkinson syndrome other than idiopathic PD
- Known carriers of certain familial PD genes (*Parkin, PINK1, DJ1*)
- MMSE ≤25

* Use of any of the following is not allowed for more than a total of 60 days or within 60 days of baseline: catechol-O-methyl transferase inhibitors (entacapone, tolcapone), amantadine or anticholinergics, or dopaminergic medication (levodopa and both ergot and non-ergot [pramipexole, ropinirole, rotigotine] dopamine agonists). Prior participation in any prasinezumab study is exclusionary.

ASL-MRI, arterial spin labelling-magnetic resonance imaging; CGI-C, Clinical Global Impressions-Change scale; DaT-SPECT, dopamine transporter single-photon emission computed tomography; MAO-B, monoamine oxidase B; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; PGI-C, Patient Global Impressions-Change scale; SE-ADL, Schwab and England Activities of Daily Living.

PASADENA Phase II study in individuals with early PD

New data from subgroup analyses

Primary endpoint

- Change from baseline at Week 52 in MDS-UPDRS Total score (sum of Parts I, II and III)

Key secondary endpoints

- Change from baseline at 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 sub-scores (bradykinesia, rigidity, tremor, axial signs)
  - MoCA total score
  - PGI-C, CGI-C and disability (SE-ADL)

Key exploratory endpoints

- Neurodegeneration of dopaminergic terminals (DaT-SPECT)
- Digital PASADENA Motor Score
- ASL-MRI for cerebral blood flow

Safety, tolerability, pharmacokinetics and immunogenicity

Clinical pre-specified Subgroups at baseline

- **MAO-B Inhibitor-treated**
- **Diffuse malignant** vs. mild motor-predominant vs. intermediate sub-phenotypes (Data-driven)
- H&Y Stage (1 vs. 2)
- Presence of probable RBD (RBDSQ ≥5 vs. <5)

ASL-MRI, arterial spin labelling magnetic resonance imaging; CGI-C, Clinical Global Impressions scale - Change; DaT-SPECT, dopamine transporter single-photon emission computed tomography; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; MAO-B, monoamine oxidase-B; MMSE, Mini Mental State Examination; PD, Parkinson's disease; PGI-C, Patient Global Impressions scale - Change; SE-ADL, Schwab and England Activities of Daily Living; RBD, Rapid Eye Movement Sleep Behavior Disorder; RBDSQ, RBD Screening Questionnaire.

Baseline characteristics are generally well balanced among treatment arms

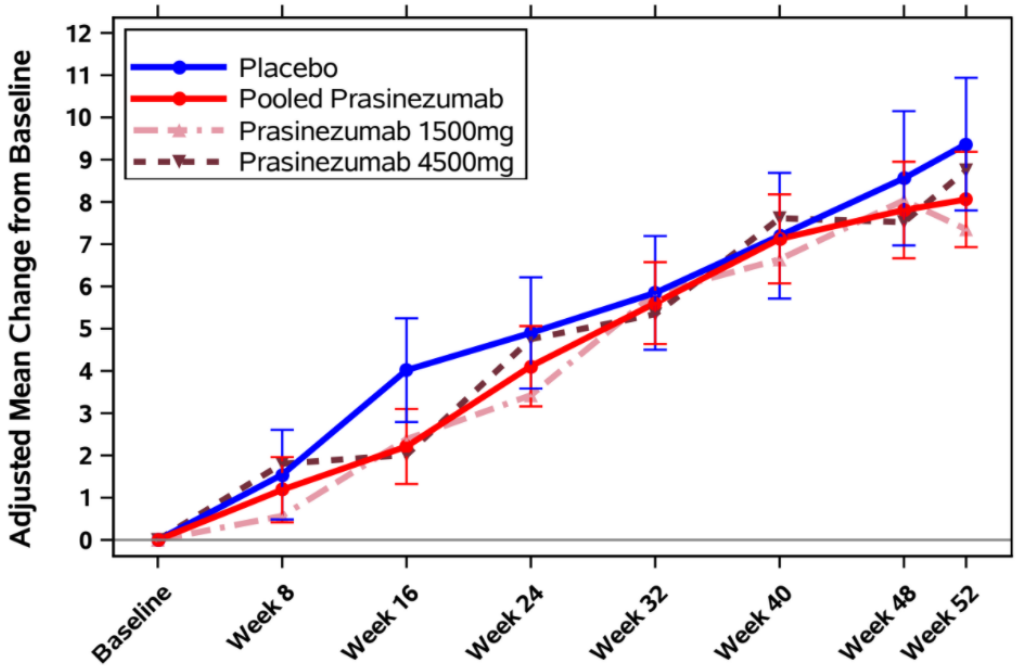
	Placebo (n=105)*	Prasinezumab 1500 mg (n=105)*	Prasinezumab 4500 mg† (n=106)*	All patients (N=316)
Age, years Mean (SD)	59.9 (8.7)	60.3 (8.8)	59.4 (9.8)	59.9 (9.1)
Gender, Male N (%)	71 (67.6)	71 (67.6)	71 (67.0)	213 (67.4)
Time from diagnosis Mean (SD)	9.9 (6.8)	10.2 (6.3)	10.1 (6.5)	10.1 (6.5)
MAO-B inhibitor				
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)
Sub-phenotypes				
Diffuse malignant	15 (14.3)	21 (20.0)	23 (21.7)	59 (18.7)
Mild motor predominant	39 (37.1)	28 (26.7)	39 (36.8)	106 (33.5)
Intermediate	51 (48.6)	56 (53.3)	44 (41.5)	151 (47.8)
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)

*n represents number of participants contributing to summary statistics. Percentages are based on n. †3500 mg for <65 kg. ‡Visits are time windowed. Non-evaluable data are considered as patient starting symptomatic PD treatment, an increase on MAO-B inhibitor (if the patient was on MAO-B inhibitor at baseline), or withdrawal from the study.

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

Primary endpoint not met and favorable safety profile in study

MDS-UPDRS Total (sum of Part I+II+III)*
Site rating

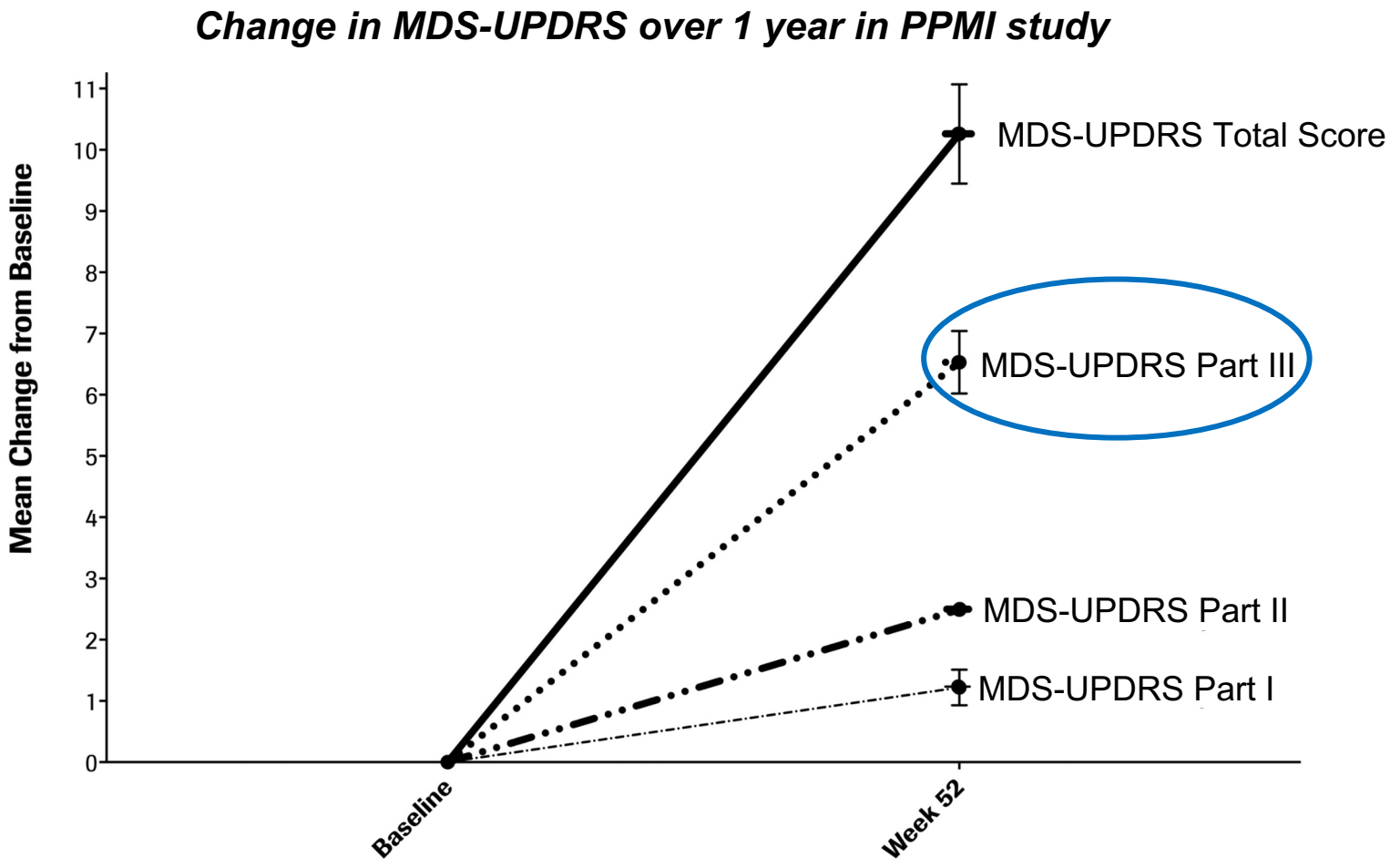


Pooled: –1.30, 80% CI=(–3.18, 0.58); **–14.0%**
Prasinezumab 1500 mg: –2.02, 80% CI=(–4.21, 0.18); **–21.5%**
Prasinezumab 4500 mg: –0.62, 80% CI=(–2.82, 1.58); **–6.6%**

	Placebo (n=105)	1500 mg (n=105)	4500 mg (n=106)
Total number of AEs†	411	428	549
Total number of AE with fatal outcome (Grade 5)*	0	0	0
Total number of patients with at least one (%):‡			
AE	87 (82.9)	98 (93.3)	97 (91.5)
SAE	5 (4.8)	7 (6.7)	8 (7.5)
Grade 3–5 AE	8 (7.6)	4 (3.8)	8 (7.5)
AE leading to withdrawal from treatment or dose interruption	1 (1.0)	2 (1.9)	5 (4.7)
All Grade IRR	17 (16.2)	20 (19.0)	36 (33.9)
Grade 1–2 IRR	17 (16.2)	20 (19.0)	35 (33.0)
Grade 3 IRR	0	0	1 (0.9)

*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 (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 analysis is a prespecified exploratory analysis. 4500 mg for ≥65 kg; 3500 mg for <65 kg. †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 4500 mg dose group (no patients in the 1500 mg 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. 4500 mg for ≥65 kg; 3500 mg for <65 kg. AE, adverse event; CI, confidence interval; DaT-SPECT, dopamine transporter single-photon emission computed tomography; IRR, infusion-related reaction; MAO-B, monoamine oxidase B; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; MMRM, mixed-effect model repeated measures; PD, Parkinson’s disease. SAE, serious AE.

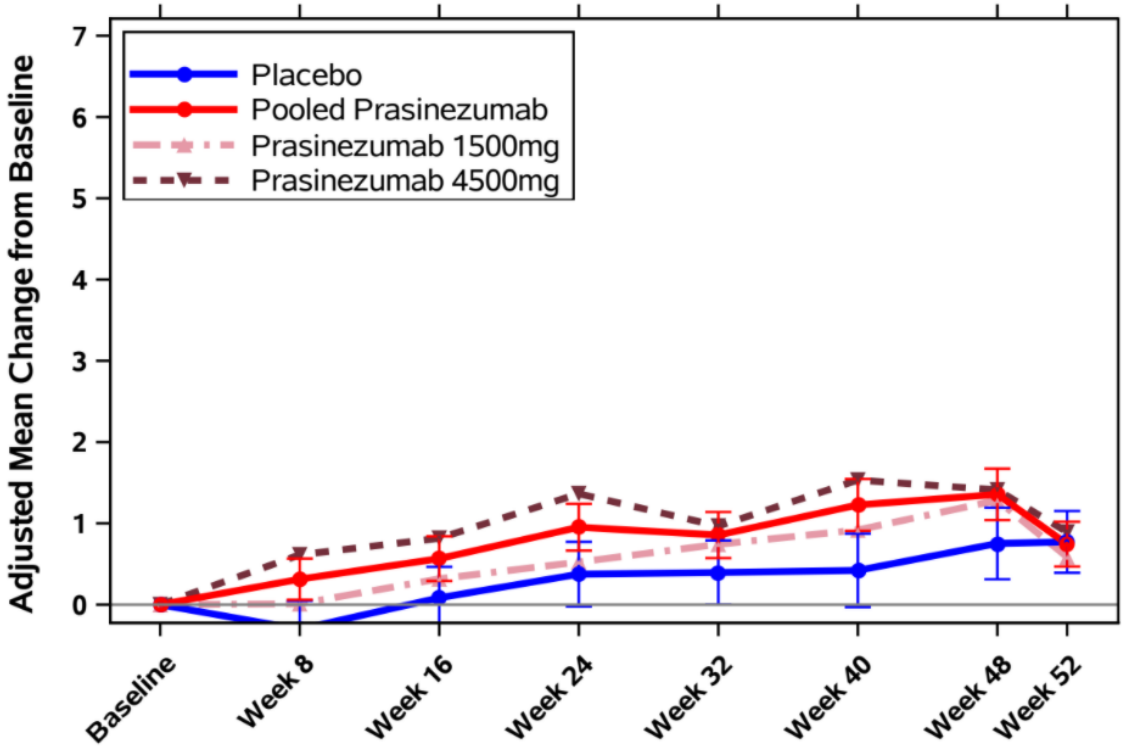
Progression of MDS-UPDRS total over 1 year is mostly driven by MDS-UPDRS Part III in an early stage population (PPMI study)



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).

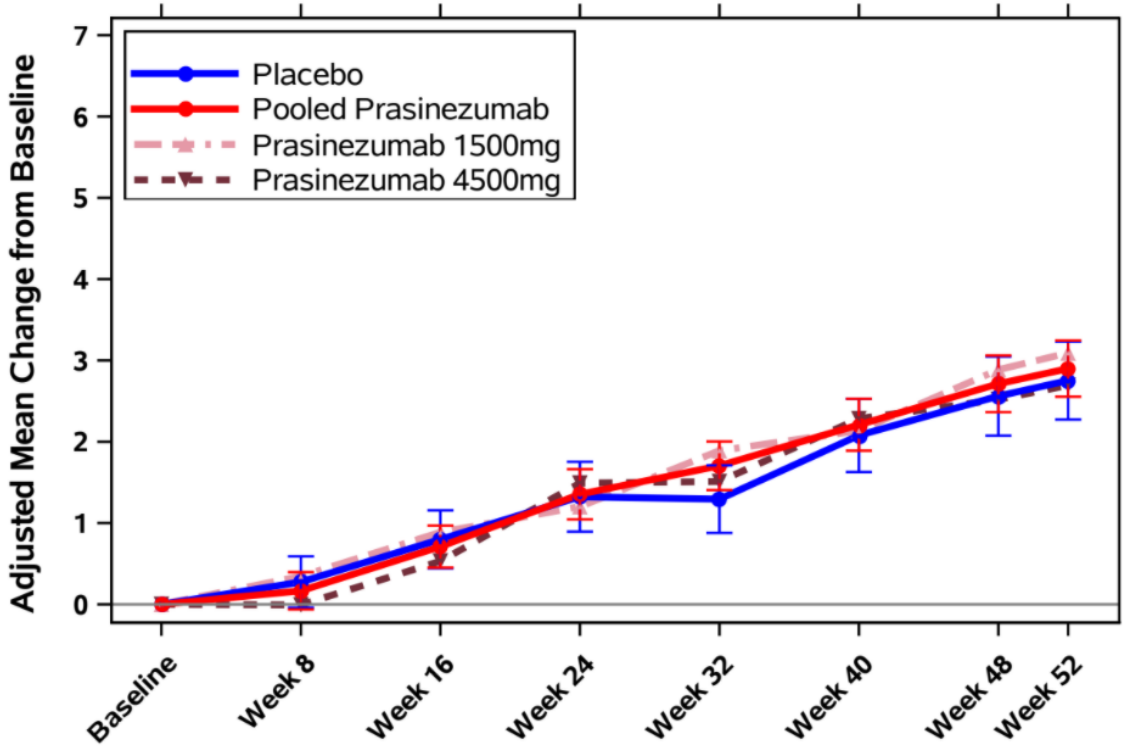
Progression on MDS-UPDRS Part I and II, on which to assess treatment effect, was minimal over the trial period

MDS-UPDRS Part I*



Pooled: –0.03, 80% CI=(–0.49, 0.43); **–3.9%**
Prasinezumab 1500 mg: –0.19, 80% CI=(–0.71, 0.34); **–24.7%**
Prasinezumab 4500 mg: 0.12, 80% CI=(–0.41, 0.65); **+15.6%**

MDS-UPDRS Part II*

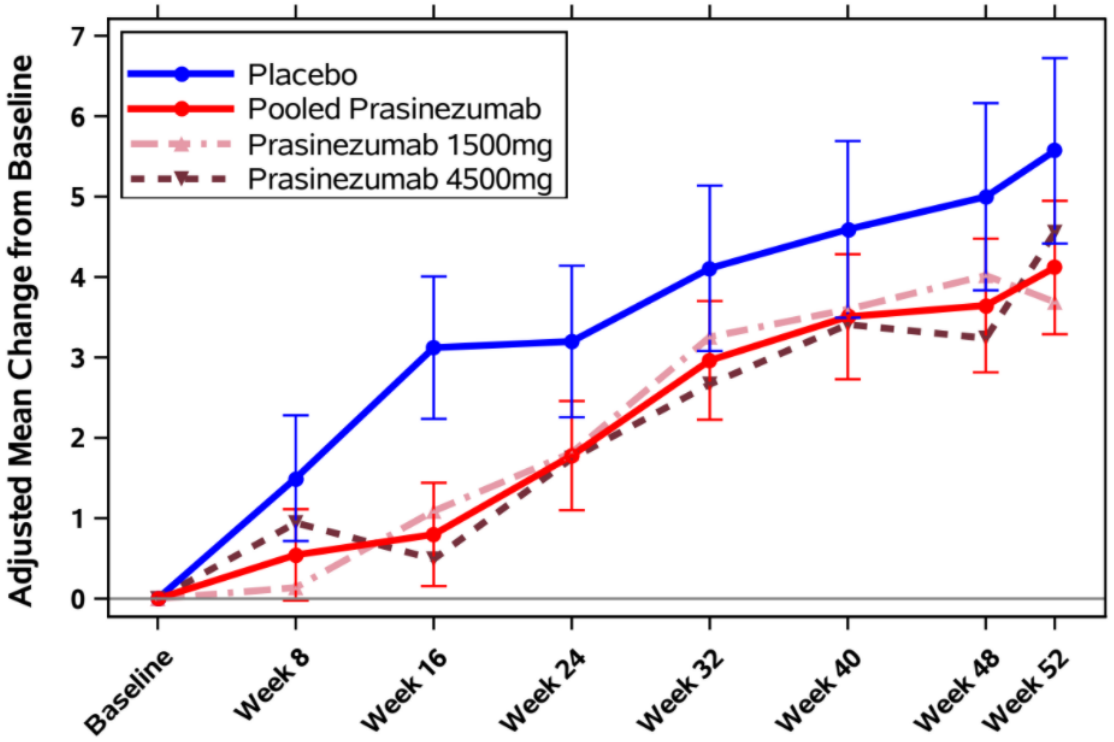


Pooled: 0.14, 80% CI=(–0.44, 0.73); **+6.1%**
Prasinezumab 1500 mg: 0.34, 80% CI=(–0.33, 1.01); **+12.4%**
Prasinezumab 4500 mg: –0.06, 80% CI=(–0.73, 0.61); **–2.0%**

*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.

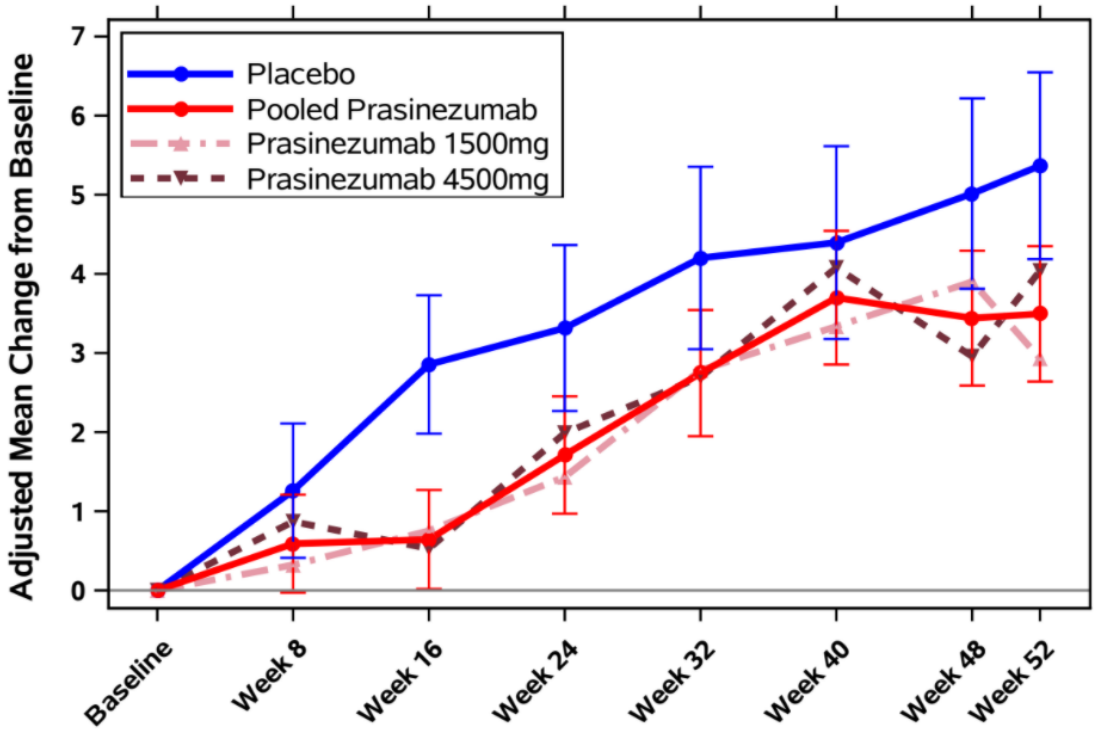
Prasinezumab reduced clinical decline in motor assessments compared to placebo, confirmed by central rating

MDS-UPDRS Part III*
Site rating



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%**

MDS-UPDRS Part III*
Central rating



Pooled: –1.88, 80% CI=(–3.31, –0.45); **–35.0%**
Prasinezumab 1500 mg: –2.44, 80% CI=(–4.09, –0.78); **–45.4%**
Prasinezumab 4500 mg: –1.33, 80% CI=(–2.99, 0.34); **–24.7%**

*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.

Prasinezumab reduced clinical decline confirmed by digital measures of progression (slope analysis)

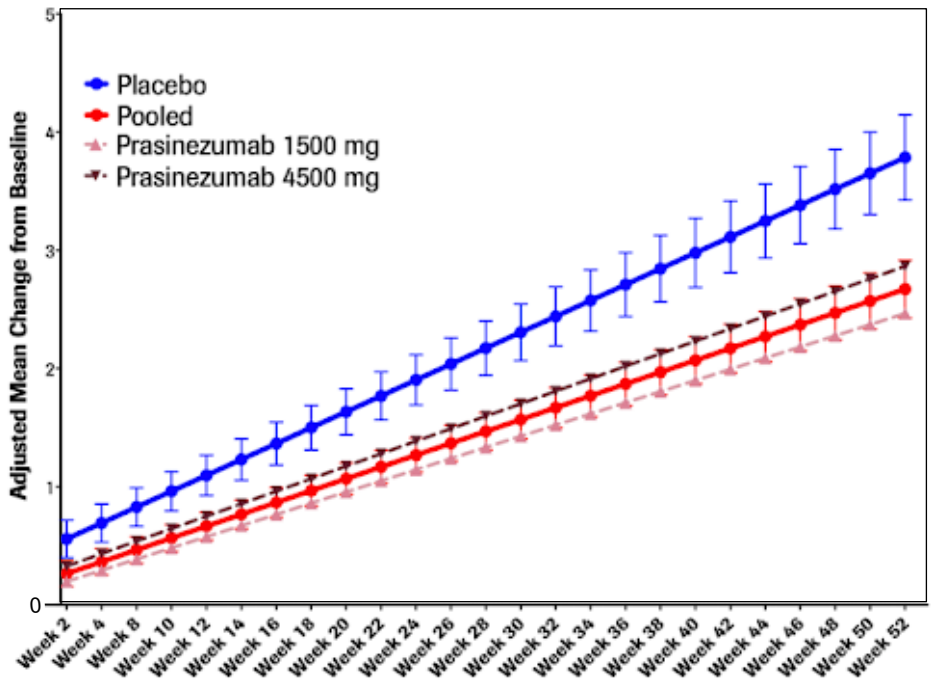
Digital measures included in the Roche Parkinson's Disease Mobile Application v2



PASSIVE MONITORING		
Bradykinesia and Activities of Daily Living		
Gait	Arm Swing & Tremor	Mobility & Sociability
Daily	Daily	Daily

ACTIVE TESTS									
Bradykinesia			*Tremor/ Bradykinesia*	*Tremor*			*Rigidity/ Postural Instability*		*Cognition*
Draw A Shape	Dexterity	Hand Turning	Speech	Phonation	Postural Tremor	Rest Tremor	Balance	U-Turn	Cognitive Test (SDMT)
Bradykinesia Days (Every 2nd Day)			Alternating		Tremor and Stability Days (Every 2nd Day)				Fortnightly

Digital PASADENA Motor Score



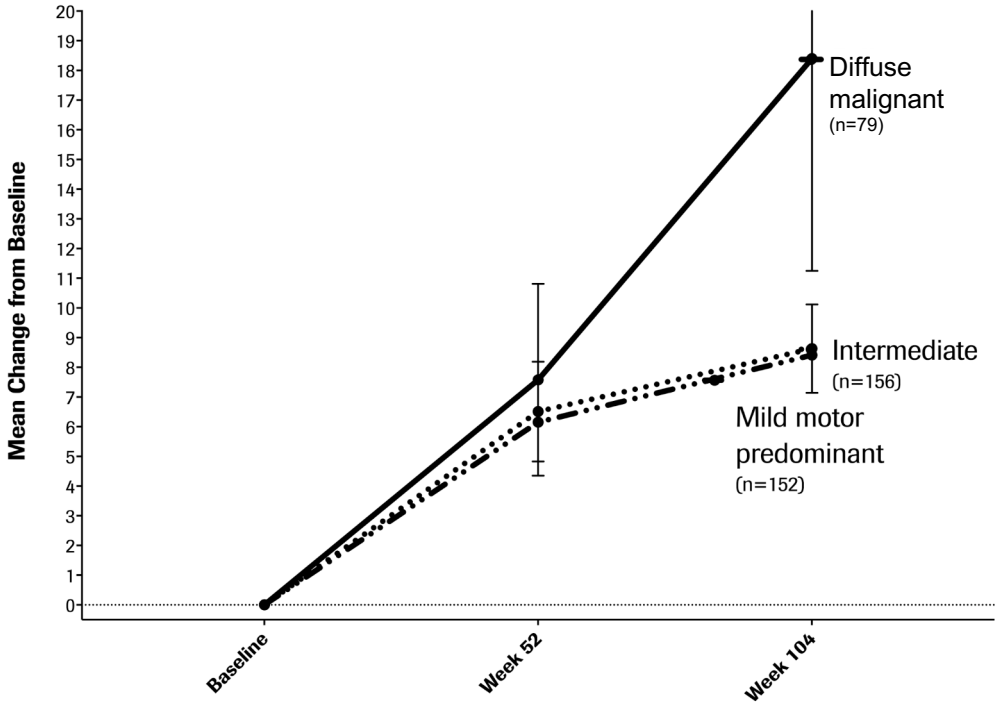
Pooled: –0.030, 80% CI=(–0.050, –0.010); **–25.0%**
Prasinezumab 1500 mg: –0.040, 80% CI=(–0.063, –0.017); **–30.3%**
Prasinezumab 4500 mg: –0.029, 80% CI= (–0.052, –0.006); **–21.5%**

Pooled-dose analysis is a pre-specified exploratory analysis. 4500 mg for ≥65 kg; 3500 mg for <65 kg.
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; SDMT, Symbol Digit Modalities Test.

For further details on the PASADENA Digital Motor Score please see the presentation by Kirsten Taylor, et al. via the following link; https://bit.ly/370A68G

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)

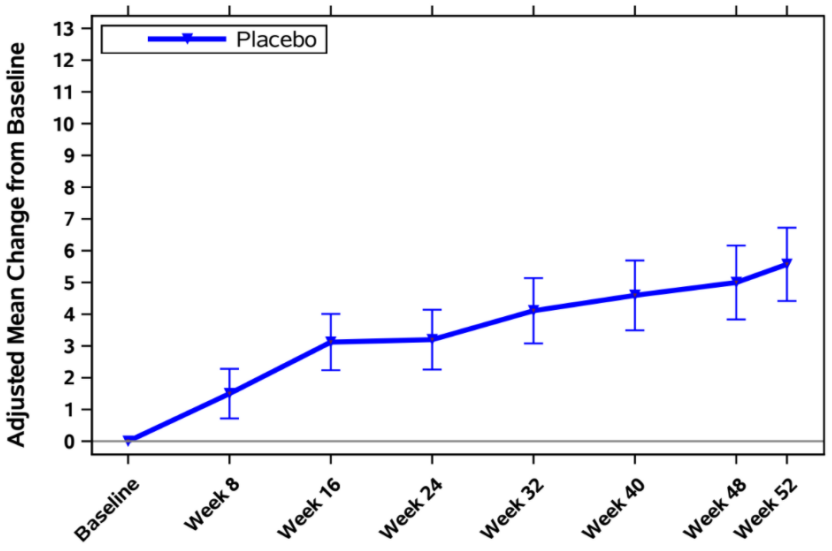
Diffuse malignant sub-phenotype showed faster motor progression on MDS-UPDRS Part III in PPMI[1,2]
PASADENA analyses were performed in diffuse malignant and MAO-B inhibitor subgroups

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.

MAO-B inhibitors-treated and diffuse malignant sub-phenotype showed faster disease progression on MDS-UPDRS Part III

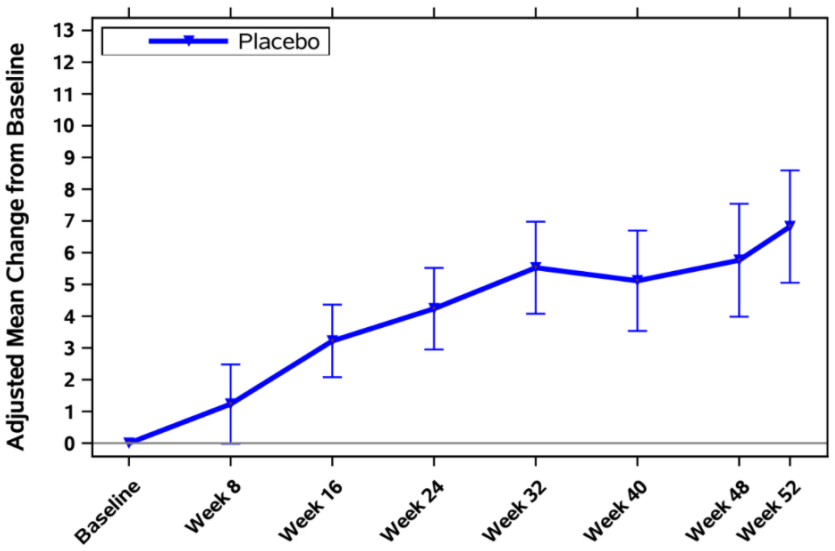
MDS-UPDRS Part III*

Total population – Placebo (n=105)



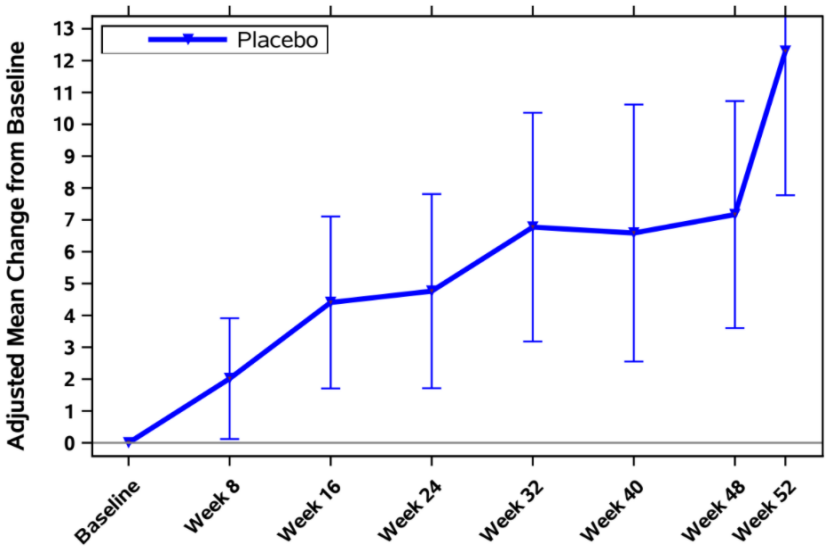
Change at Week 52 = **5.57** points (placebo)

MAO-B inhibitor treated – Placebo (n=38)



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

Diffuse malignant– Placebo (n=15)



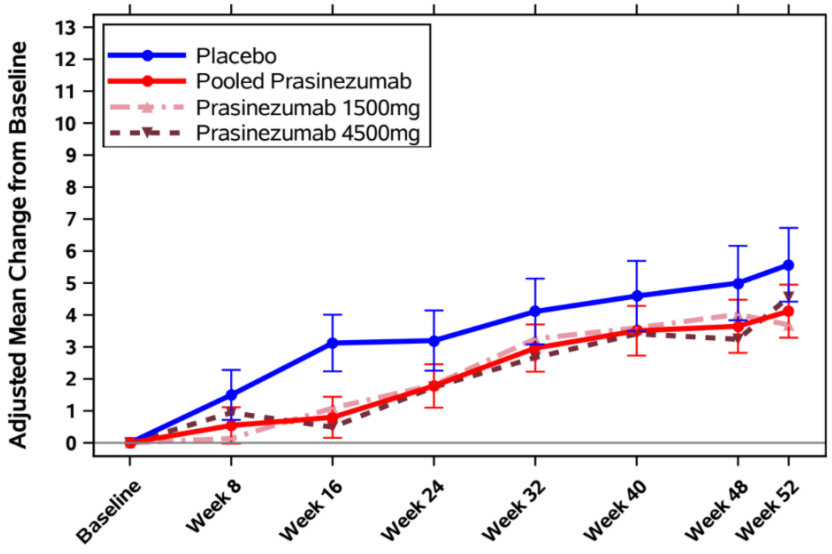
Change at Week 52 = **12.29** points (placebo)

*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 disease progression

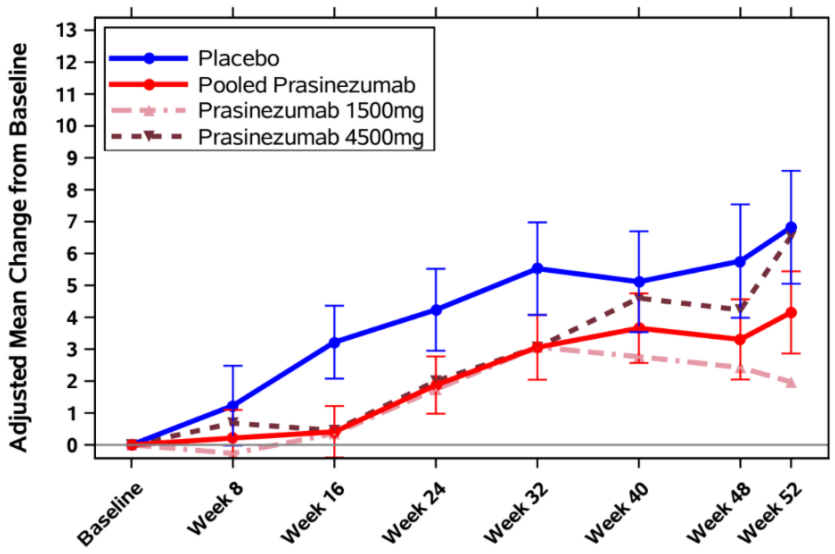
*MDS-UPDRS Part III**

Total population (N=316)



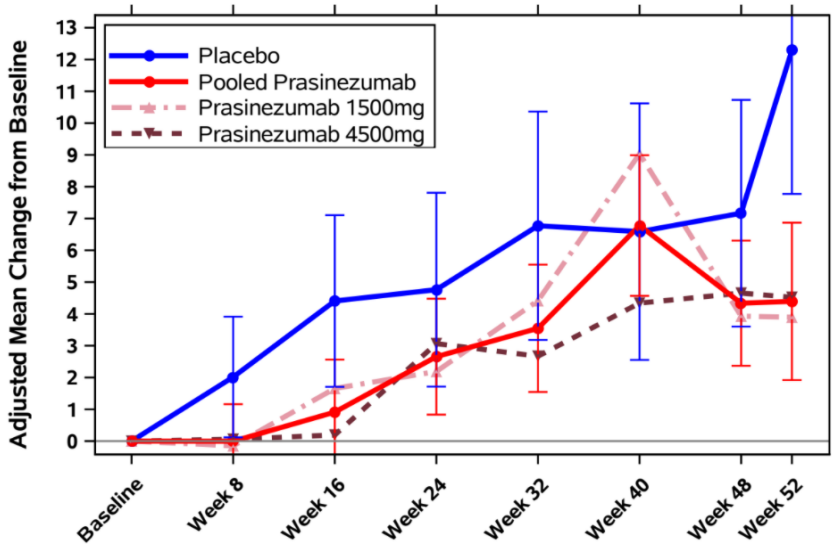
Pooled: –1.44, 80% CI=(–2.83, –0.06); **–25.0%**
Prasinezumab 1500 mg: –1.88, 80% CI=(–3.49, –0.27); **–33.8%**
Prasinezumab 4500 mg: –1.02, 80% CI=(–2.64, 0.61); **–18.2%**

MAO-B inhibitor treated (n=115)



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)



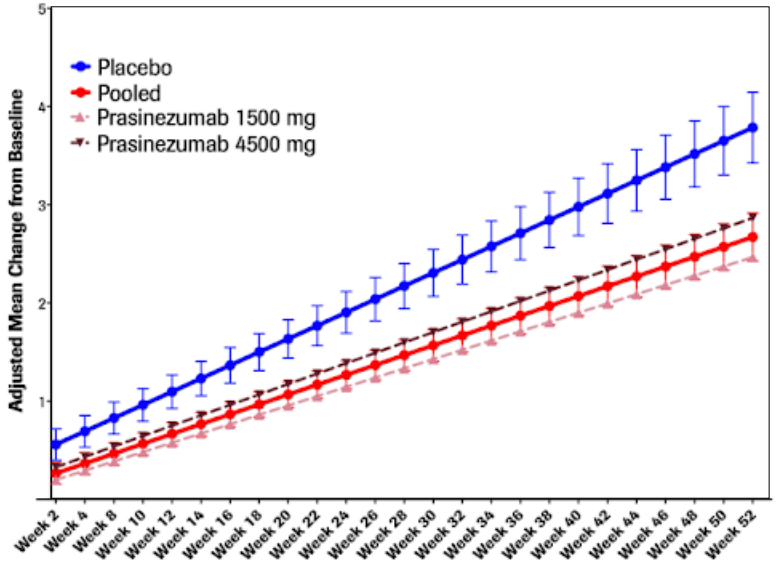
Pooled: –7.86, 80% CI=(–12.9, –2.82); **–63.9%**,
Prasinezumab 1500 mg: –8.4, 80% CI=(–14.2, –2.59); **–68.3%**
Prasinezumab 4500 mg: –7.77, 80% CI=(–13.4, –2.14); **–63.2%**

*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

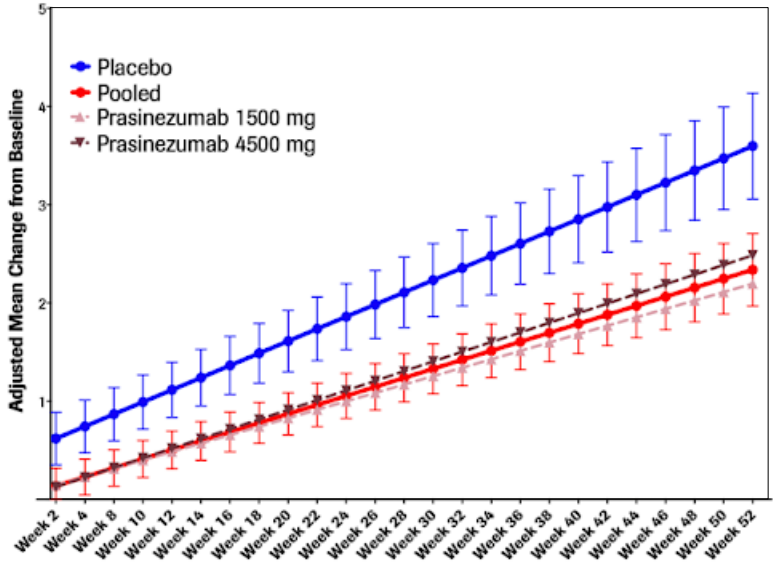
PASADENA Digital Motor Score

Total population (N=316)



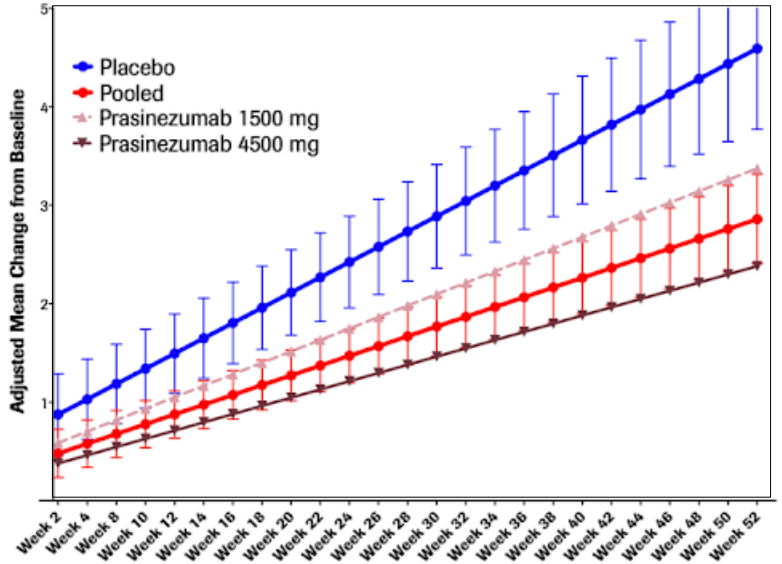
Pooled: –0.030, 80% CI=(–0.050, –0.010); **–25.0%**
Prasinezumab 1500 mg: –0.040, 80% CI=(–0.063, –0.017); **–30.3%**
Prasinezumab 4500 mg: –0.029, 80% CI= (–0.052, –0.006); **–21.5%**

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.

Conclusions

- Motor progression of PD in an untreated, early stage population is generally slow (≈5 points per year on MDS-UPDRS Part III)[1]

- Progression is faster in individuals requiring symptomatic therapy, such as MAO-B inhibitors (≈7 points per year), or in the diffuse malignant sub-phenotype (≈10 points per year)
  - Ability to demonstrate the beneficial effect of an intervention depends on the ability to measure disease progression

- Results of the PASADENA Part 1 study with prasinezumab showed greater effect in slowing clinical decline in subgroup populations with faster disease progression

- Based on these findings, a new Phase IIb (PADOVA) study is planned to start in 2021
  - The PADOVA study will test efficacy and safety of prasinezumab in an early stage population requiring symptomatic therapy
  - Across sites in North America (US and Canada) and Europe (UK, France, Spain, Italy, Austria and Poland).

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MAO-B, monoamine oxidase B; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; PD, Parkinson's disease.

1. Simuni T, et al. *Mov Disord.* 2018; 33:771–782.

Acknowledgments

We thank all participants and their families, without whom completion of this and future studies would not be possible, the PASADENA investigators and the Prasinezumab Study Group for their cooperation and support with this study

PASADENA investigators: Claudia Altendorf, Chareyna Anandan, Giulia Andrews, Solène Ansquer, Raphaele Arrouasse, Sana Aslam, Jean-Philippe Azulay, Jeanette Baker, Ernest Balaguer Martinez, Shadi Barbu, Kara Bardram, Danny Bega, Helena Bejr-Kasem Marco, Isabelle Benatru, Eve Benchetrit, Felix Bernhard, Amit Besharat, Sagari Bette, Amelie Bichon, Andrew Billnitzer, Sophie Blondeau, Thomas Boraud, Freiderike Borngräber, James Boyd, Kathrin Brockmann, Matthew Brodsky, Ethan Brown, Christof Bruecke, Fabienne Calvas, Monica Canelo, Federico Carbone, Claire Carroll, Laura Casado Fernandez, Catherine Casse-Parrot, Anna Castrioto, Helene Catala, Justine Chan, Samia Cheriet, Anthony Ciabarra, Joseph Classen, Juliana Coleman, Robert Coleman, Yaroslau Compta, Jean-Christophe Corvol, Mariana Cosgaya, Nabila Dahodwala, Philippe Damier, Elodie David, Thomas Davis, Marissa Dean, Berengere Debilly, Janell DeGiorgio, Andres Deik, Laure Delaby, Marie-Helene Delfini, Pascal Derkinderen, Philipp Derost, Maria de Toledo, Lisa Deuel, Ann Marie Diaz-Hernandez, Cameron Dietiker, Karina Dimenshteyn, Julio Dotor, Franck Durif, Jens Ebentheuer, Karla Maria Eggert, Sara Eichau Madueño, Claudia Eickoff, Aaron Ellenbogen, Philipp Ellmerer, Ines Esparragosa Vazquez, Alexandre Eusebio, Siobhan Ewert, John Fang, Danielle Feigenbaum, Frederique Fluchere, Alexandra Foubert-Samier, Marie Fournier, Anne Fradet, Valerie Fraix, Samuel Frank, Franka Fries, Anne Gaille Corbille, Monique Gailitzky, Marisol Gallardó Pérez, Jose Manuel Garcia Moreno, Carmen Gasca, Thomas Gasser, Joyce Gibbons, Caroline Giordana, Alicia Gonzalez Martinez, Ira Goodman, Arantza Gorospe, Marie Goubeaud, David Grabli, Mangone Graziella, Stephan Grimaldi, Jeffrey Gross, Raquel Guimaraes-Costa, Andreas Hartmann, Christian Hartmann, Travis Hassell, Robert Hauser, Antonio Hernandez, Jorge Hernandez-Vara, Guenter Hoeglinger, Christian Homedes, Andrea Horta, Jean-Luc Houeto, Julius Huebl, Jennifer Hui, Stuart Isaacson, Joseph Jankovic, Annette Janzen, Junior Jauregui, Jocelyne Jiao, Maria Jose Marti Domenech, Xavier Joseph, Srinath Kadimi, Pat Kaminski, Silja Kannenberg, R. Jan Kassubek, Maya Katz, Kevin Klos, Shannon Klos, Christopher Kobet, Jennifer Koebert, Patricia Krause, Andrea Kuhn, Jaime Kulisevsky Bojarsky, Rajeev Kumar, Martin Kunz, Lille Kurvits, Kimberly Kwei, Simon Laganiere, Brice Laurens, Johannes Levin, Oren Levy, Peter Le Witt, Gurutz Linazasoro Cristobal, Irene Litvan, Karlo Lizarraga, Katherine Longardner, Rocio Lopez, Lydia Lopez Manzanares, Sara Lucas del Pozo, Maria Rosario Luquin Puido, Nijee Luthra, Kelly Lyons, Sylvia Maass, Gerrit Machetanz, Yolanda Macias, David Maltete, Jorge Uriel Manez Miro, Louis-Laure Mariani, Juan Marin, Kathrin Marini, Ana Marques, Gloria Marti, Maria Jose Marti Domenech, Saul Martinez, Wassilios Meissner, Sara Meoni, Brit Mollenhauer, Dunia Mon Martinez, Johnson Moon, Elena Moro, Peter Morrison, Christoph Muehlberg, Manpreet Multani, Christine Murphy, Anthony Nicholas, Rajesh Pahwa, Antonio Palasi, Heidi Pape, Prity Patel, Neepa Patel, Marina Peball, Elizabeth Peckham, Terry Peery, Rafael Perez, Jesus Perez, Alisa Petit, Elmar Pinkhardt, Werner Poewe, Elsa Pomies, Cecile Preterre, Joseph Quinn, Olivier Rascol, Philippe Remy, Emily Reuther, Irene Richard, Benjamin Roeben, Jost-Julian Rumpf, David Russell, Hayet Salhi, Daniela Samaniego, Alexandra Samier-Foubert, Antonio Sanchez, Emmanuelle Schmitt, Alfons Schnitzler, Oliver Schorr, Julie Schwartzbard, Kerstin Schweyer, Klaus Seppi, Victoria Sergo, Holly Shill, Andrew Siderowf, Tanya Simuni, Umberto Spampinato, Ashok Sriram, Natividad Stover, Caroline Tanner, Arjun Tarakad, Carolyn Taylor, Claire Thalamus, Thomas Toothaker, Nadege Van Blercom, Nora Vanegas-Arrogave, Lydia Vela, Sylvian Vergnet, Tiphaine Vidal, Jonathan Voeglein, Ryan Walsh, Cheryl Waters, Mirko Wegschneider, Endy Weidinger, Caroline Weill, Gregor Wenzel, Tatiana Witjas, Isabel Wurster, Brenton Wright, Milan Zimmermann, Rafael Zuzuarregui.

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Roche PD Mobile Application v2 Detects Slowing of Early Parkinson's Disease Progression under Prasinezumab: PASADENA Phase II Part 1 Results

***Kirsten I. Taylor*[1,2], *Florian Lipsmeier*[1], *Ekaterina Volkova-Volkmar*[1], *Daria Rukina*[1], *Judith Anzures Cabrera, Laurent Essioux, Markus Abt*[1], *Ben van Lier*[1], *Alessandra E. Thomann*[1], *Hanno Svoboda*[1], *Wagner Zago*[3], *Gennaro Pagano*[1], *Ronald B. Postuma*[4] *& Michael Lindemann*[1]**

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[4] *Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada*

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Disclosures

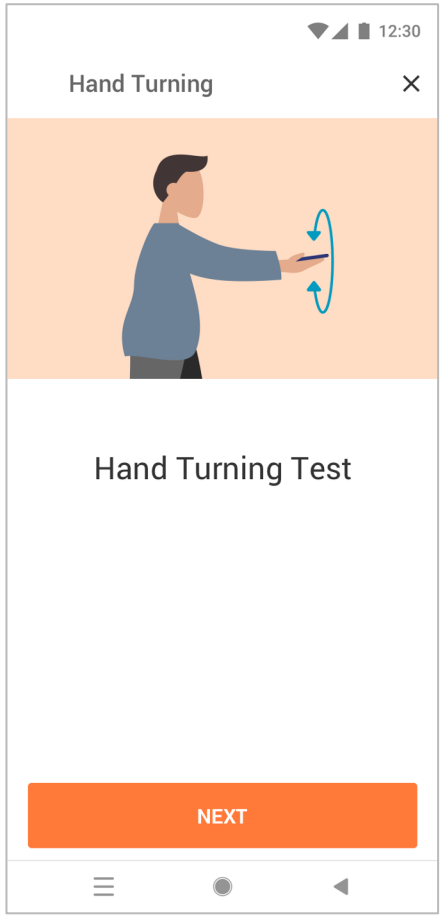
Kirsten I. Taylor is a full-time employee and shareholder of F. Hoffmann-La Roche Ltd.

Introduction

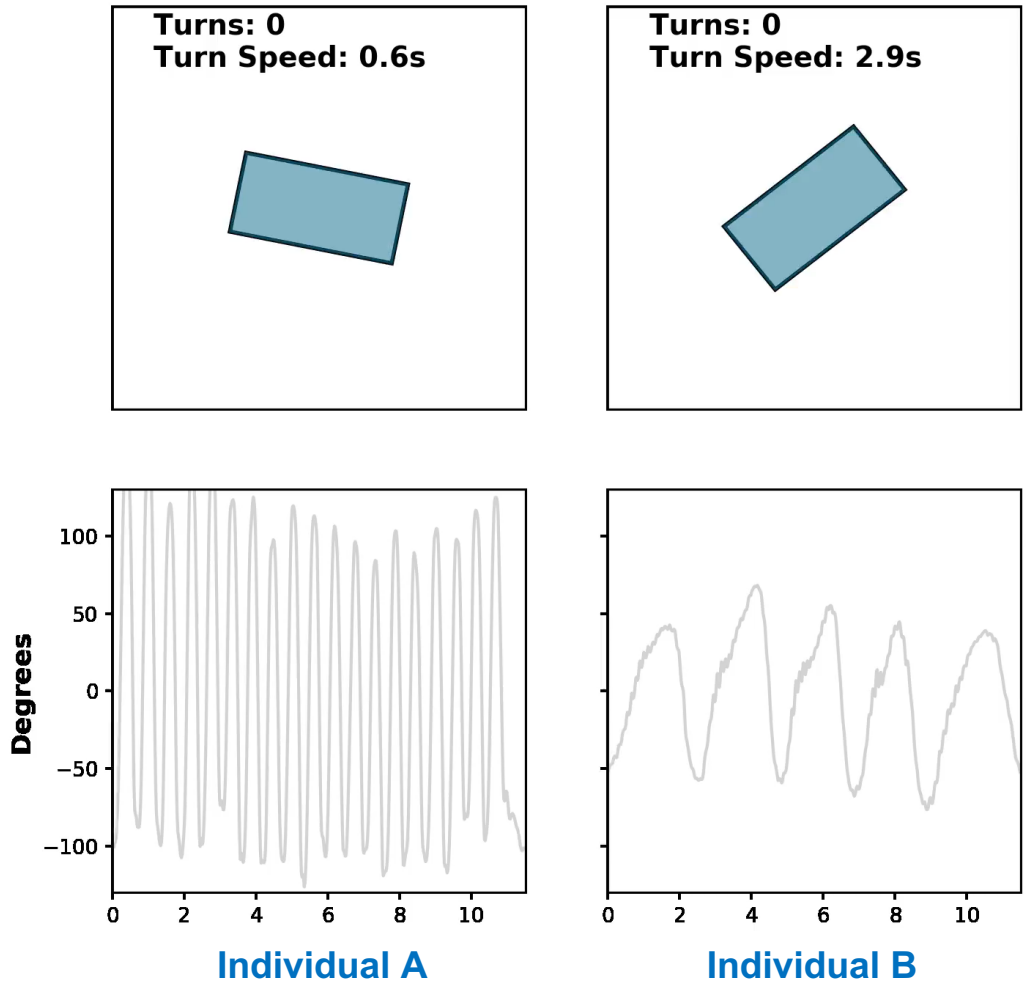
- The fluctuating nature of Parkinsonian symptoms make it difficult to measure potential treatment effects from infrequent clinic visit data.
- Digital Health Technology tools (DHTTs) enable remote and therefore frequent assessments
  - Ecological validity: in environments where individuals live and work
  - Sensors highly sensitive to motor manifestations

Quantifying bradykinesia with smartphone sensors

example: Hand-turning test



Accelerometer output during hand turning task in less (Individual A) and more (Individual B) affected individuals with PD



Introduction

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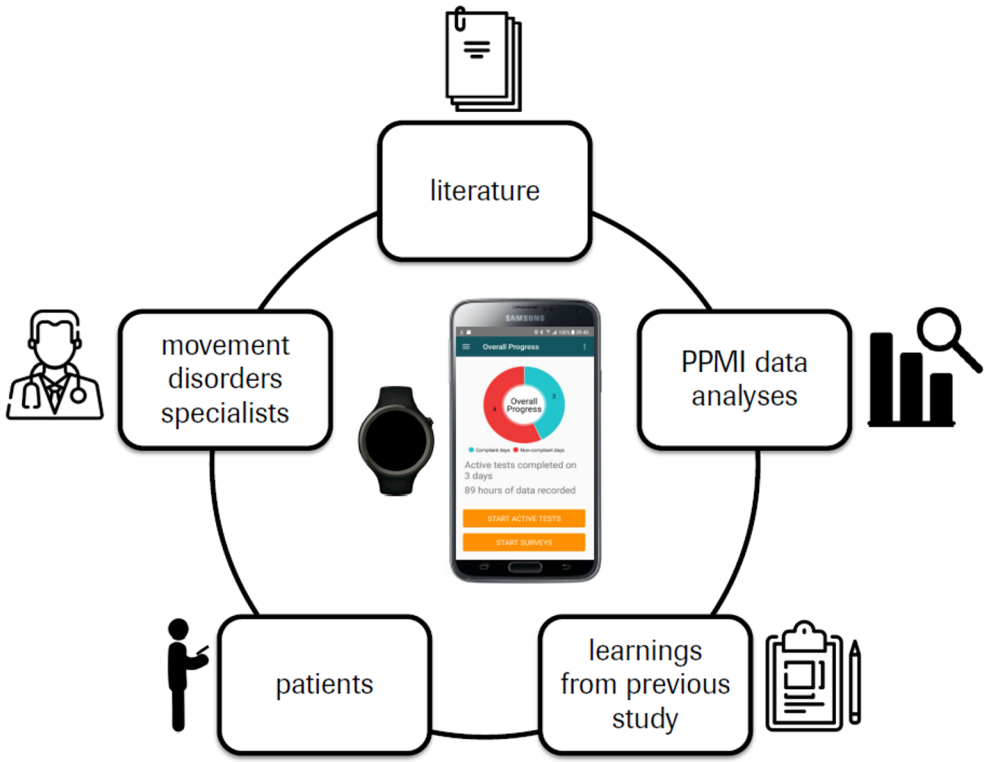
- Digital Health Technology tools (DHTTs) enable remote and therefore frequent assessments
  - Ecological validity: in environments where individuals live and work
  - Sensors highly sensitive to motor manifestations

- **DHTTs may provide highly sensitive markers of disease progression and treatment response**

Roche PD Mobile Application v2 is designed to measure core motor signs of PD





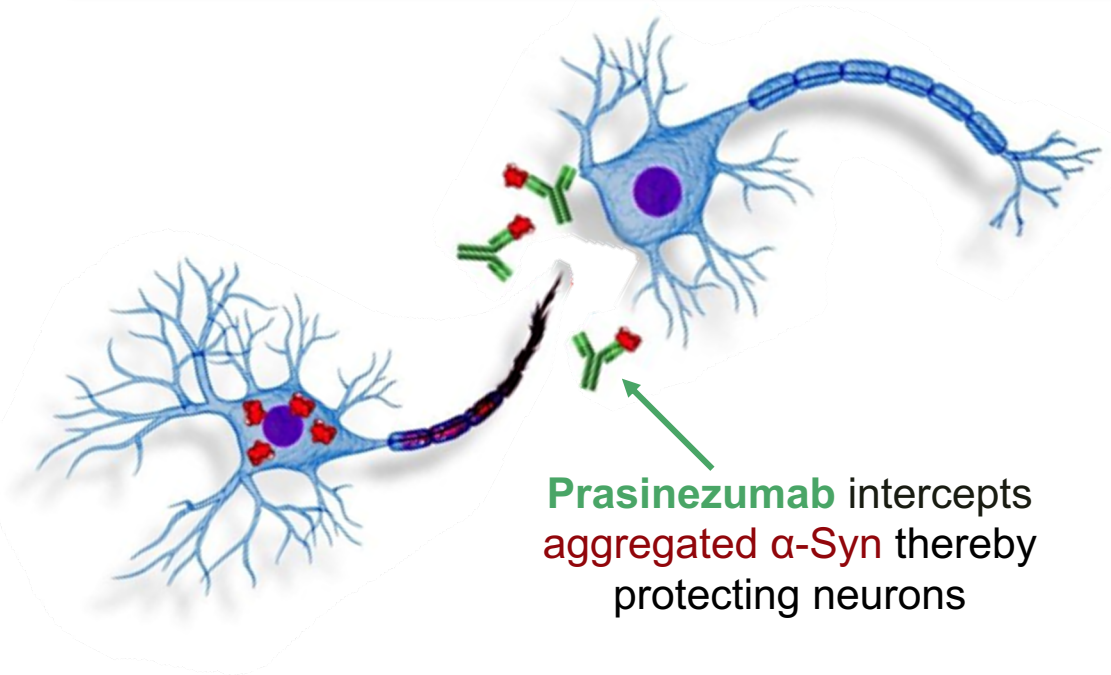
PASSIVE MONITORING		
Bradykinesia and Activities of Daily Living		
Gait	Armswing & Gesture	Mobility
Daily	Daily	Daily

ACTIVE TESTS									
Bradykinesia			*Tremor/Bradykinesia*	*Tremor*			*Rigidity/Postural Instability*		*Cognition*
Draw A Shape	Dexterity	Hand Turning	Speech	Phonation	Postural Tremor	Rest Tremor	Balance	U-Turn	Cognitive Test (SDMT)
Bradykinesia Days (Every 2nd Day)			Alternating		Tremor and Stability Days (Every 2nd Day)				Fortnightly

PPMI = Parkinson's Progression Markers Initiative

Prasinezumab is a humanized monoclonal antibody, designed to target aggregated α-Syn in PD

No treatments exist that can affect the underlying cause of PD[1–3]
Currently available treatments have powerful effects on symptoms but do not prevent or slow disease progression[2,3]



- **α-Syn** is genetically and neuropathologically validated as a **key target in PD[4]**
- **Prasinezumab binds aggregated α-Syn at the C-terminus[5–7]**
  - The targeted epitope results in higher selectivity for aggregated α-Syn, as well as consistently high levels of efficacy across several preclinical models
- **Prasinezumab demonstrated efficacy in multiple *in vivo* and cellular α-synucleinopathy models:[5–9]**
  - Reducing build-up of intracellular α-Syn pathology and protecting neurons
  - Blocking cell-to-cell transmission of α-Syn
  - Protecting synapses and reduceing gliosis
  - Ameliorating motor and cognitive behavioral deficits

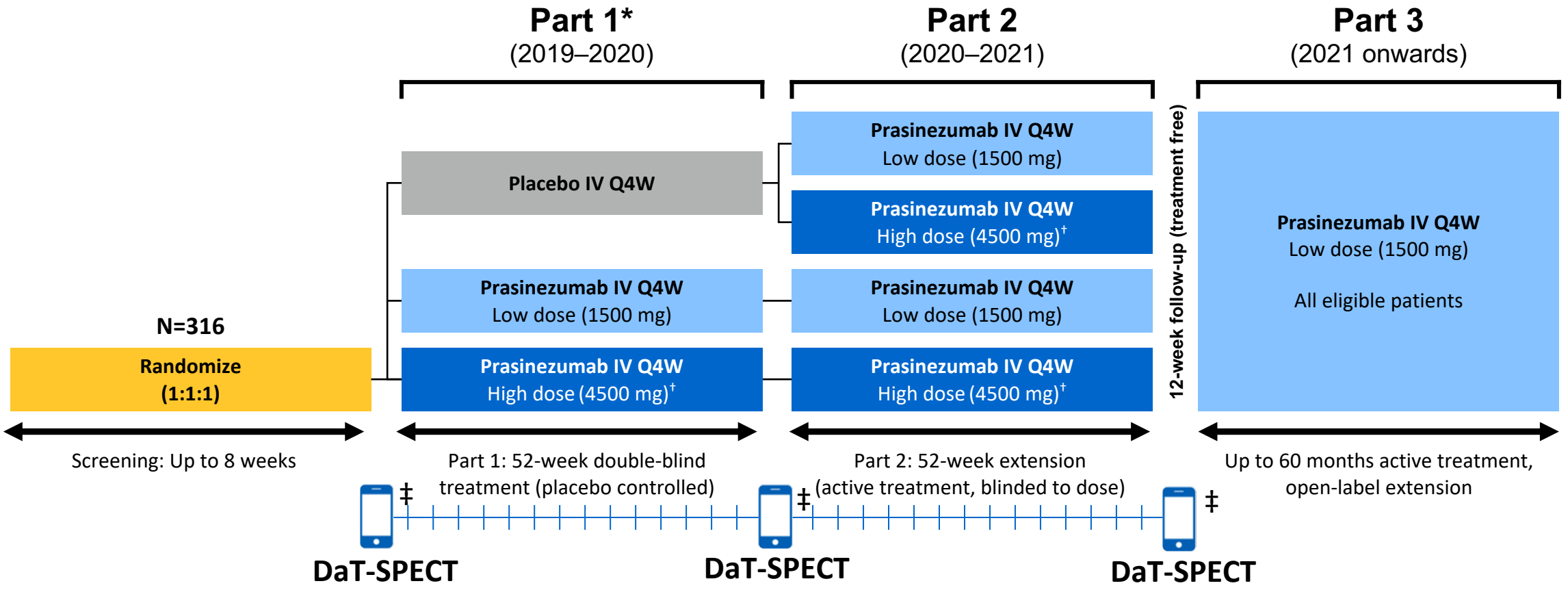
Prasinezumab has the potential to slow disease progression by protecting neurons from toxic α-Syn species

α-Syn, alpha-synuclein; PD, Parkinson's disease.

1. Verschuur CVM, et al. *N Engl J Med*. 2019; 380:315–324; 2. Lang AE & Espay AJ. *Mov Disord*. 2018; 33:660–677; 3. Cheng H, et al. *Ann Neurol*. 2010; 67: 715–725; 4. Dehay B, et al. *Lancet* Neurol. 2015; 14:855–866; 5. Masliah E, et al. *Neuron*. 2005; 46:857–868; 6. Masliah E, et al. *PLoS ONE*. 2011; 6:e19338; 7. Games D, et al. *J Neurosci*. 2014; 34:9441–9454; 8. Spencer B, et al. *Acta Neuropathol Commun*. 2017; 5:7; 9. Jankovic J et al. *JAMA Neurol*. 2018; 75:1206–1214.

PASADENA Phase II study in individuals with early PD

A 52-week multicenter, randomized, double-blind, placebo-controlled study



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

*COVID-19 did not affect assessments during PASADENA Part 1 as these were completed before the pandemic. †High dose = 4500 mg for ≥65 kg; 3500 mg for <65 kg. ‡Digital biomarkers (smartphone and wrist-worn wearable assessments). COVID-19, coronavirus disease 2019; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; IV, intravenous; MDS-UPDRS, Movement Disorder Society-Unified PD Rating Scale; PD, Parkinson's disease; Q4W, every month. ClinicalTrials.gov. NCT03100149. (Accessed February 2021).

The mentioned compounds and their use are investigational and have not yet received regulatory approval in any country.

Baseline characteristics are generally well balanced among treatment arms

For further details, see Pagano et al., ADPD 2021

	Placebo (n=105)*	Prasinezumab 1500 mg (n=105)*	Prasinezumab 4500 mg† (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)
Time from diagnosis Mean (SD)	9.9 (6.8)	10.2 (6.3)	10.1 (6.5)	10.1 (6.5)
MAO-B inhibitor				
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)
Sub-phenotypes				
Diffuse malignant	15 (14.3)	21 (20.0)	23 (21.7)	59 (18.7)
Mild motor predominant	39 (37.1)	28 (26.7)	39 (36.8)	106 (33.5)
Intermediate	51 (48.6)	56 (53.3)	44 (41.5)	151 (47.8)
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)

*n represents number of participants contributing to summary statistics. Percentages are based on n. †3500 mg for <65 kg. ‡Visits are time windowed. Non-evaluable data are considered as patient starting symptomatic PD treatment, an increase on MAO-B inhibitor (if the patient was on MAO-B inhibitor at baseline), or withdrawal from the study.

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

Continuous data over 52 weeks enabled testing of divergence of *slopes* of motor sign progression



- A total of 17 pre-specified sensor features*, one per task/side and from passive monitoring
- Sensor features aggregated (median) over all data points within each two-week (fortnight) window** over entire 52 weeks of study
- Data censored at the start of symptomatic PD treatment
- Prasinezumab treatment groups combined (“pooled”)
- **Linear mixed effect (LME) model with random slope** (fortnights) of change from baseline
  - Covariates: baseline MAO-Bi therapy Yes/No; Age; Sex; baseline DaT-SPECT Specific Binding Ratio in ipsilateral putamen
  - Alpha = 0.2, beta = 0.8; multiple comparison correct = 15% False Discovery Rate (FDR)
  - Non-normally distributed residuals, report **Mixed Models with Repeated Measures (MMRM)**
  - **Effect of interest: interaction of fortnight by treatment group**

*median gesture power of passively monitored gestures, median turn speed in U-turn test and passively monitored gait, jerk in balance test, mel frequency cepstrum 2 in speech test, voice jitter in sustained phonation, number correct in Symbol Digit Modalities Test; for least and most affected sides separately: speeded tapping variability, maximum speed of hand-turning, spiral celerity in draw-a-shape task, median squared energy in rest and postural tremor tasks.
** If <3 data points per fortnight, then missing

Prasinezumab treatment associated with decreased progression of upper limb bradykinesia

category	Source	Feature	Result
Bradykinesia	Speeded tapping test	Variability, L	
		Variability, M	
	Hand turning test	Maximum speed, L	
		Maximum speed, M	
	Passive gestures	Power	
	Draw-a-shape	Spiral celerity, L	
		Spiral celerity, M	
Gait, balance	U-turn test	Median turn speed	
	Passive turning	Median turn speed	
	Balance test	Jerk	
Tremor	Postural tremor test	Median squared energy, L	
		Median squared energy, M	
	Rest tremor test	Median squared energy, L	
		Median squared energy, M	
Speech	Free speech test	Mel frequency cepstrum 2	
	Sustained phonation test	Voice jitter	
Cognition	SDMT	Number correct	

	Effect favors prasinezumab
	No effect
	Effect favors placebo

L = less affected side; M = most affected side
Celerity = accuracy / speed

Prasinezumab treatment associated with decreased progression of upper limb bradykinesia

category	Source	Feature	Result
Bradykinesia	**Speeded tapping test**	***Variability, L**	
		Variability, M	
	Hand turning test	Maximum speed, L	
		Maximum speed, M	
	Passive gestures	***Power**	
	Draw-a-shape	Spiral celerity, L	
		Spiral celerity, M	
Gait, balance	U-turn test	Median turn speed	
	Passive turning	Median turn speed	
	Balance test	Jerk	
Tremor	Postural tremor test	Median squared energy, L	
		Median squared energy, M	
	Rest tremor test	Median squared energy, L	
		Median squared energy, M	
Speech	Free speech test	Mel frequency cepstrum 2	
	Sustained phonation test	Voice jitter	
Cognition	SDMT	Number correct	

	Effect favors prasinezumab
	No effect
	Effect favors placebo

***FDR <= 0.2**

L = less affected side; M = most affected side

Celerity = accuracy / speed

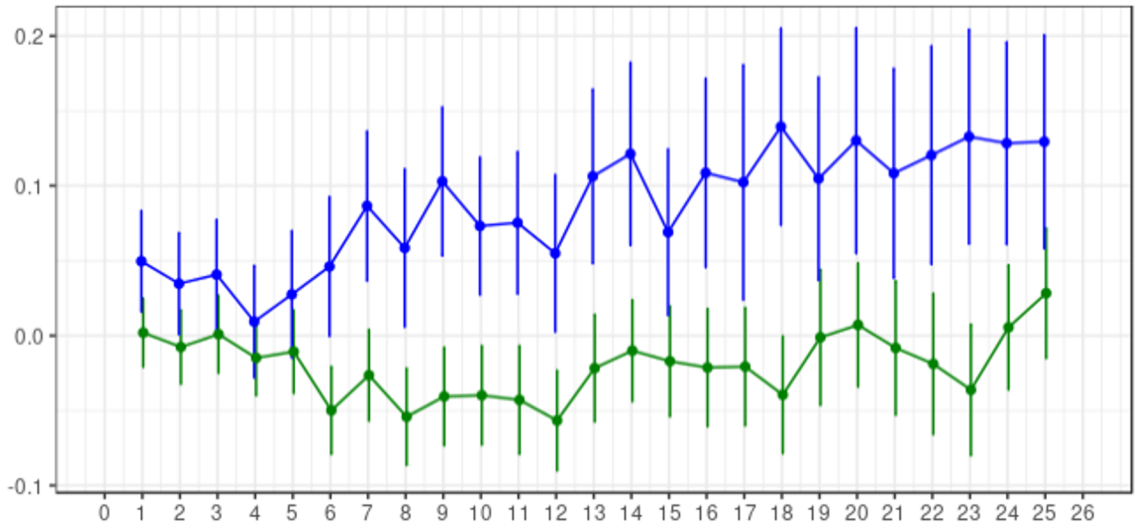
Less bradykinesia progression in treatment group

Features with FDR≤0.2

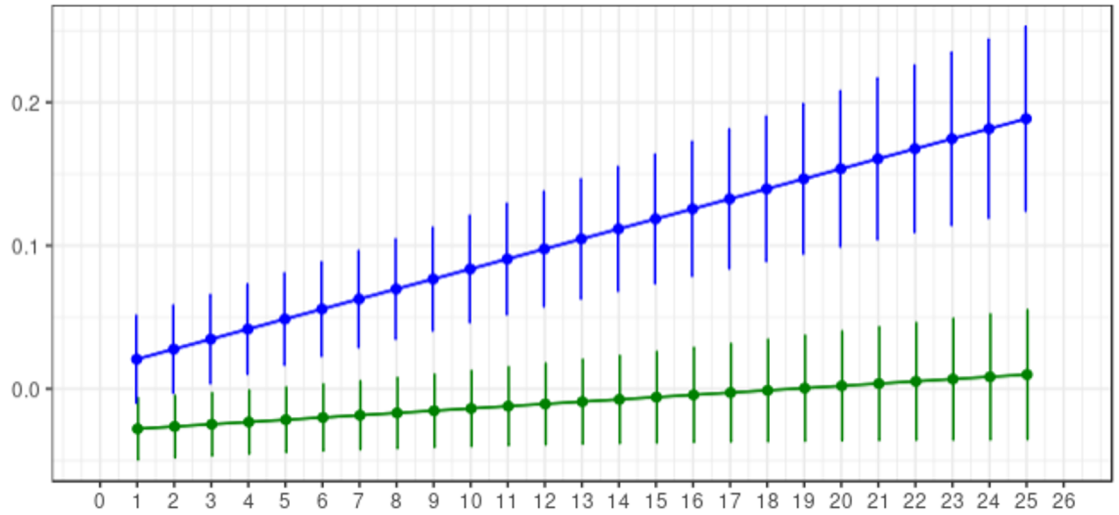
Placebo Pooled prasinezumab

Speeded tapping variability, less affected side

Raw change from baseline (80% CI)

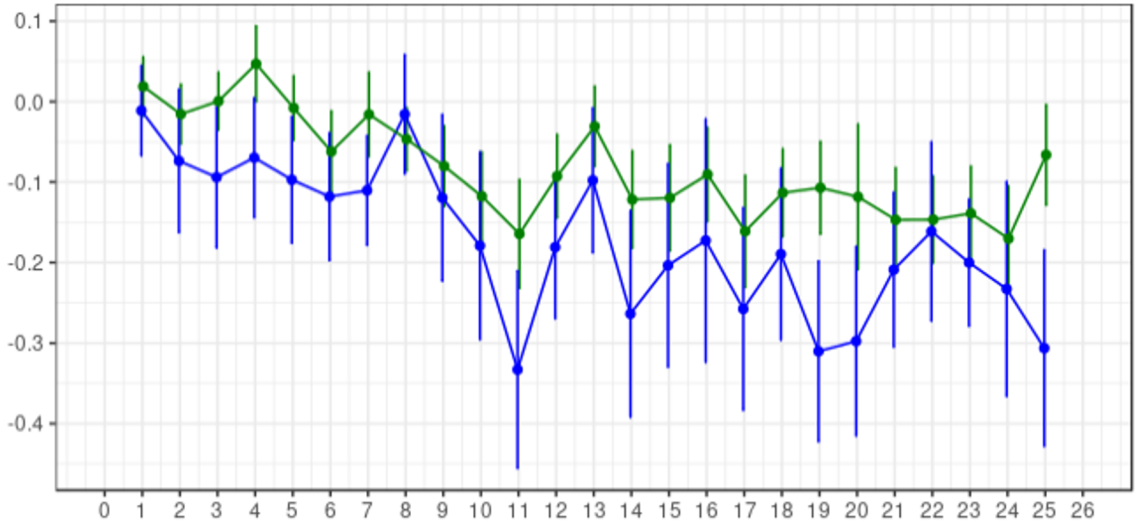


Results of Linear Mixed Effect model (80% CI)



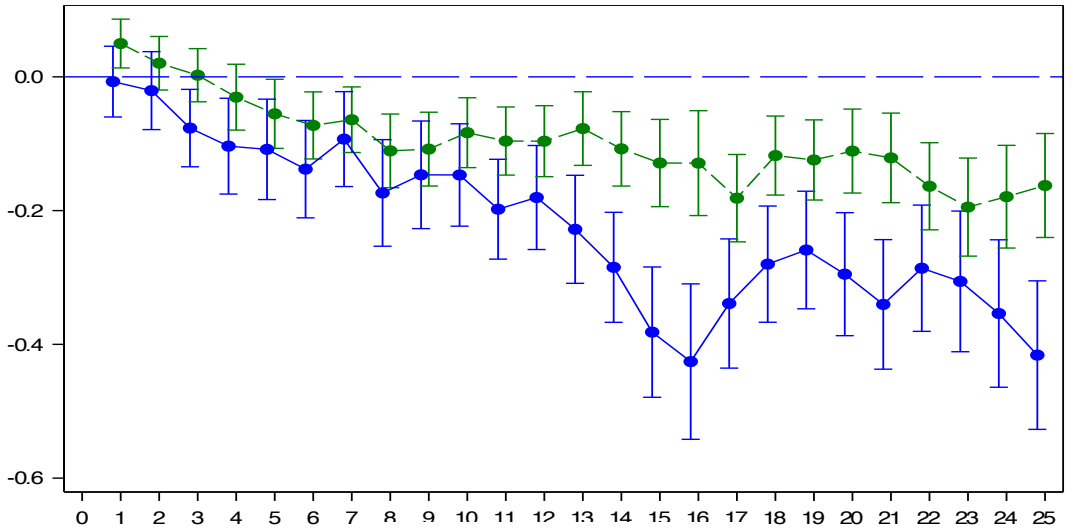
Passively monitored hand gesture power

Raw change from baseline (80% CI)



Fortnight (2-week period)

Result of Mixed Model with Repeated Measures (80% CI)



Fortnight (2-week period)

Summary and outlook

- DHTT measurements of the core signs of PD **remotely, continuously and objectively** enable the modelling of **slopes of motor sign progression**
- Daily quantification via the Roche PD Mobile Application in early-stage PD demonstrated a **divergence of slopes in bradykinesia progression**
- These results are consistent with a potential effect of prasinezumab in slowing PD progression
    - In line with PASADENA part 1 results (see ADPD presentation from Pagano et al, 2021)

Outlook:

- **Digital endpoints** for use in drug development decision-making (e.g. Taylor et al., 2020)
- **Data sharing** initiatives important to facilitate progress (e.g. Critical Path for Parkinson's Disease, Michael J. Fox Foundation)

Taylor KI, Staunton H, Lipsmeier F, Nobbs D, Lindemann M. Outcome measures based on digital health technology sensor data: data- and patient-centric approaches. npj Digit Med. 2020 Dec;3(1):97. https://doi.org/10.1038/s41746-020-0305-8; Pagano et al. ADPD 2021. A Phase II study to evaluate the safety and efficacy of prasinezumab in early Parkinson's disease (PASADENA): Results from Part 1 Week 52.

Acknowledgments

We thank all participants and their families, without whom completion of this and future studies would not be possible, the PASADENA investigators and the Prasinezumab Study Group for their cooperation and support with this study

PASADENA investigators: Jean-Philippe Azulay, Ernest Balaguer Martinez, James Boyd, Kathrin Brockmann, 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, Wassilios Meissner, Brit Mollenhauer, Peter Morrison, Anthony Nicholas, Rajesh Pahwa, Elizabeth Peckham, Werner Poewe, Olivier Rascol, Philippe Remy, Irene Richard, David Russell, Julie Schwartzbard, Klaus Seppi, Tanya Simuni, Alfons Schnitzler, Caroline Tanner, Lydia Vela, Ryan Walsh

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