PASADENA long-term open-label extension continue to show reduced motor and functional progression in prasinezumab-treated individuals with early-stage Parkinson's disease compared to a real-world data arm

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Disclosures

- **Gennaro Pagano, Annabelle Monnet, Nima Shariati, Paulo Fontoura, Geoffrey A. Kerchner, Patrik Brundin, Azad Bonni and Tania Nikolcheva** are full-time employees and own shares of F. Hoffmann-La Roche Ltd.
- **Adriana Reyes and Krzysztof Smigorski** are full-time employees of F. Hoffmann-La Roche Ltd.
- **Tanya Simuni** has served as a consultant for AcureX, Adamas, AskBio, Amneal, Blue Rock Therapeutics, Critical Path for Parkinson's Consortium (CPP), Denali, Michael J Fox Foundation, Neuroderm, Sanofi, Sinopia, Roche, Takeda and Vanqua Bio. She has also served on advisory boards for AcureX, Adamas, AskBio, Denali, and Roche, and as a member of the scientific advisory board of Neuroderm, Sanofi and UCB. In addition, she has received research funding from Amneal, Biogen, Neuroderm, Prevail, Roche, and UCB and is an investigator for NINDS, MJFF, Parkinson's Foundation.
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- **Fabrizio Stocchi** is a consultant for AbbVie, Bial Pharma, Biogen, F. Hoffmann-La Roche Ltd., H. Lundbeck A S, Mitsubishi Tanabe Pharma America, Inc., Sunovion Pharmaceuticals, Inc., Teva Pharmaceutical Industries, Zambon, and Britannia.
- **Valentina Gerbaldo** is a full-time employee of Excelya Germany GmbH and was an external business partner of F. Hoffmann-La Roche Ltd.
- **Riorge Thomas** is a full-time employee of Roche Products Ltd.
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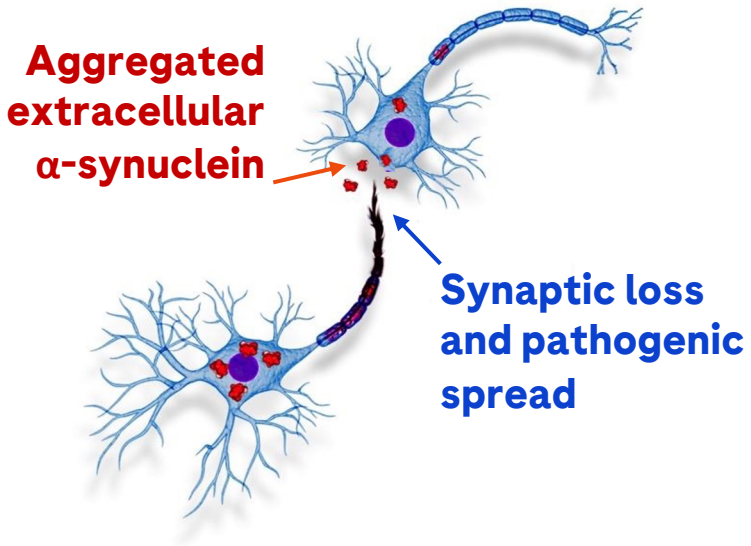
- **Rachelle Doody** is a full-time employee of Genentech and F. Hoffmann-La Roche Ltd.
- **Kenneth Marek** is a consultant for Michael J. Fox Foundation for Parkinson's Research, F. Hoffmann-La Roche Ltd., UCB, Denali, Takeda, Biohaven, Neuron23, Aprinoia, Prothena, Calico, Inhibikase, Invicro, Koneksa, and Lilly.

Prasinezumab is a humanised IgG1 monoclonal antibody that selectively binds aggregated α-synuclein

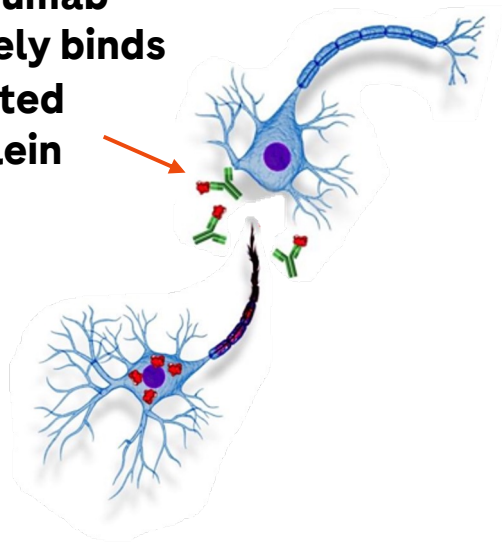
Proposed mode of action of prasinezumab for the treatment of Parkinson's disease[1–13]

Parkinson's disease



Prasinezumab's mode of action

Prasinezumab selectively binds aggregated α-synuclein



Proposed effects:

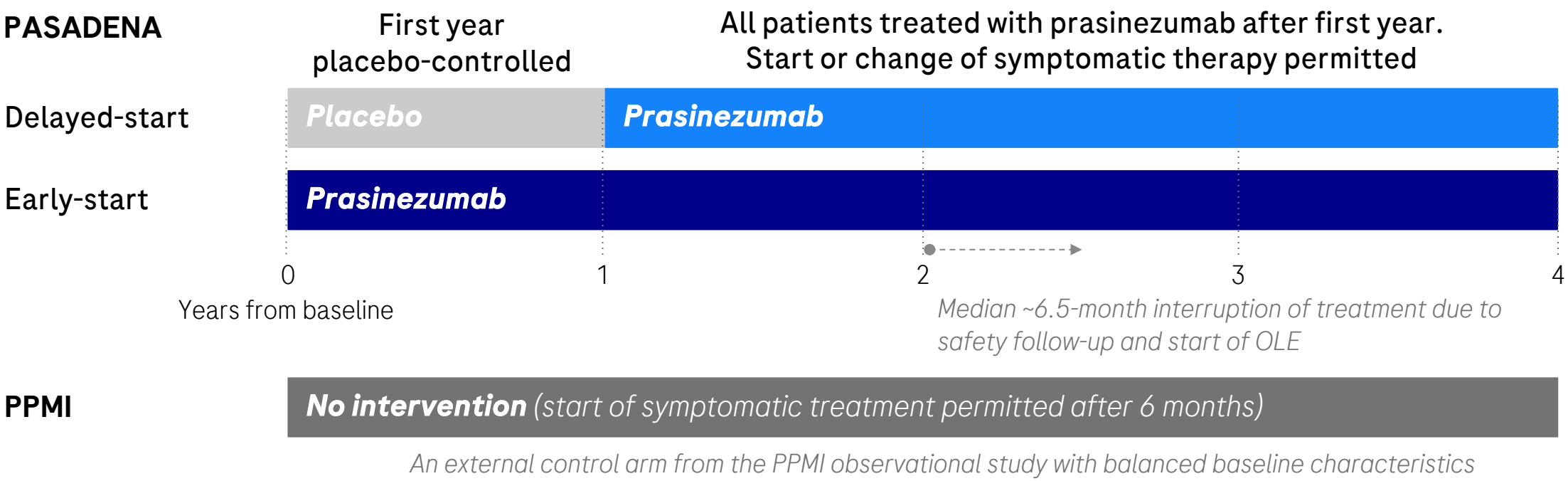
- Reducing neuronal toxicity
- Preventing cell-to-cell transfer of pathogenic α-synuclein aggregates
- Slowing disease progression

IgG, immunoglobulin.

1. Kalia LV & Lang AE. *Lancet.* 2015;386:896–9125; 2. Nakamori M, *et al. Neurotherapeutics.* 2019;16(2):287–98; 3. Benskey MJ, *et al. J Neurochem.* 2016;137:331–59; 4. Braak H, *et al. Neurobiol Aging.* 2003;24:197–211; 4. Mollenhauer B, *et al.* Presented at MDS 2018. Abstract:255; 5. Spillantini MG, *et al. Nature.* 1997;388:839–40. Reviewed by Goedert M, *Science.* 2015; 349:1255555; 6. Braak H, *et al. Neurobiol.* 2003;24:197–211; 7. Ulusoy A, *et al. EMBO Mol Med.* 2013;5:1051–9; 8. Kordower JH, *et al. Neurobiol Dis.* 2011;43:552–7; 9. Games D, *et al. J Neurosci.* 2014; 34:9441–54; 10. Masliah E, *et al. PLoS One.* 2011;6:e19338; 11. Masliah E, *et al. Neuron.* 2005;46:857–68; 12. ClinicalTrials.gov. NCT03100149. PASADENA Phase II clinical trial. Available at: https://clinicaltrials.gov/ct2/show/NCT03100149 (last accessed February 2024); 13. ClinicalTrials.gov. NCT04777331. PADOVA Phase II clinical trial. Available at: https://clinicaltrials.gov/ct2/show/NCT04777331 (last accessed February 2024).

Contextualising the PD progression rate in the PASADENA open-label extension (OLE) vs PPMI cohort after a 4-year follow-up

Objective: To compare progression on MDS-UPDRS in the PASADENA[1,2] prasinezumab population with a propensity score-balanced cohort from the PPMI dataset



Note: PASADENA is a multicentre, randomised, double-blind, placebo-controlled Phase II study of prasinezumab in individuals with early PD with an OLE phase. Participants received monthly intravenous doses of prasinezumab (1,500 or 4,500 mg) or placebo for a 52-week period (Part 1), followed by a 52-week extension (Part 2) in which all participants received active treatment. Different dose strengths arms of prasinezumab not depicted during year 1 and 2. OLE of PASADENA started after 2 years and a planned 3-month (min 2.80, max 17.70) safety wash-out.
PASADENA: data cut-off 2nd Oct 2023; PPMI: the current study only included the sporadic PD cohort, data cut-off Aug 2021.
MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PPMI, Parkinson Progression Marker Initiative.
1. Pagano G, *et al. Front Neurol*. 2021:12:705407; 2. ClinicalTrials.gov. NCT03100149. PASADENA Phase 2 clinical trial. Available at: https://clinicaltrials.gov/ct2/show/NCT03100149 (accessed February 2024).

Primary endpoints evaluating PD progression in PASADENA OLE vs PPMI cohort

Primary endpoints

Change in MDS-UPDRS Parts II and III total score from baseline over 4 years*

- Motor sub-scores (bradykinesia, rigidity, resting tremor, and axial signs) were also assessed
- MDS-UPDRS Part III total score and sub-scores were assessed in ON and OFF state

*Additionally, a logistic model was fitted to the number of patients with H&Y stage ≥3 vs <3 at year 4 including the following covariates: age, sex, education, H&Y stage at baseline and arm.
H&Y, modified Hoehn and Yahr stage; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; OLE, open-label extension; PD, Parkinson's disease; PPMI, Parkinson Progression Marker Initiative.

Steps taken to validate reliability of the PASADENA OLE 4-year follow-up and external PPMI cohort comparison

STEP1: PASADENA inclusion/ exclusion criteria applied to the PPMI cohort

PPMI PD participants
n=397

Bradykinesia and either resting tremor or rigidity
n=320

PD duration ≤24 months
n=315

H&Y Stage I or II
n=315

No PD meds. within 6 months prior to baseline
n=315

Age 40–80 years
n=303

Includes the sporadic PD cohort from the PPMI dataset

Note: PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
H&Y, modified Hoehn and Yahr stage; OLE, open-label extension; PD, Parkinson's disease; PPMI, Parkinson Progression Marker Initiative.

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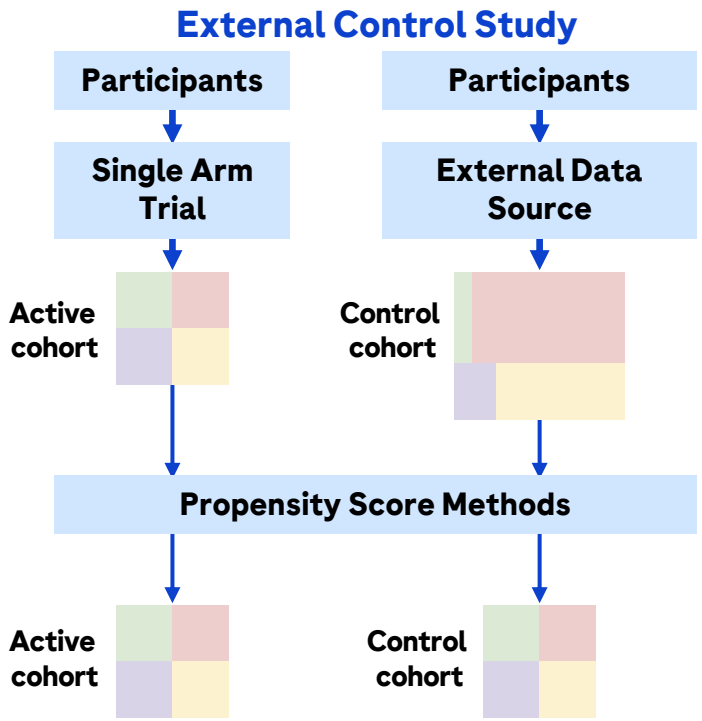
STEP 2: Propensity score weighting performed to mimic characteristics of RCT*



Validity confirmed by comparability of baseline characteristics and progression over 1 year between PASADENA Part 1 placebo group and weighted PPMI cohort

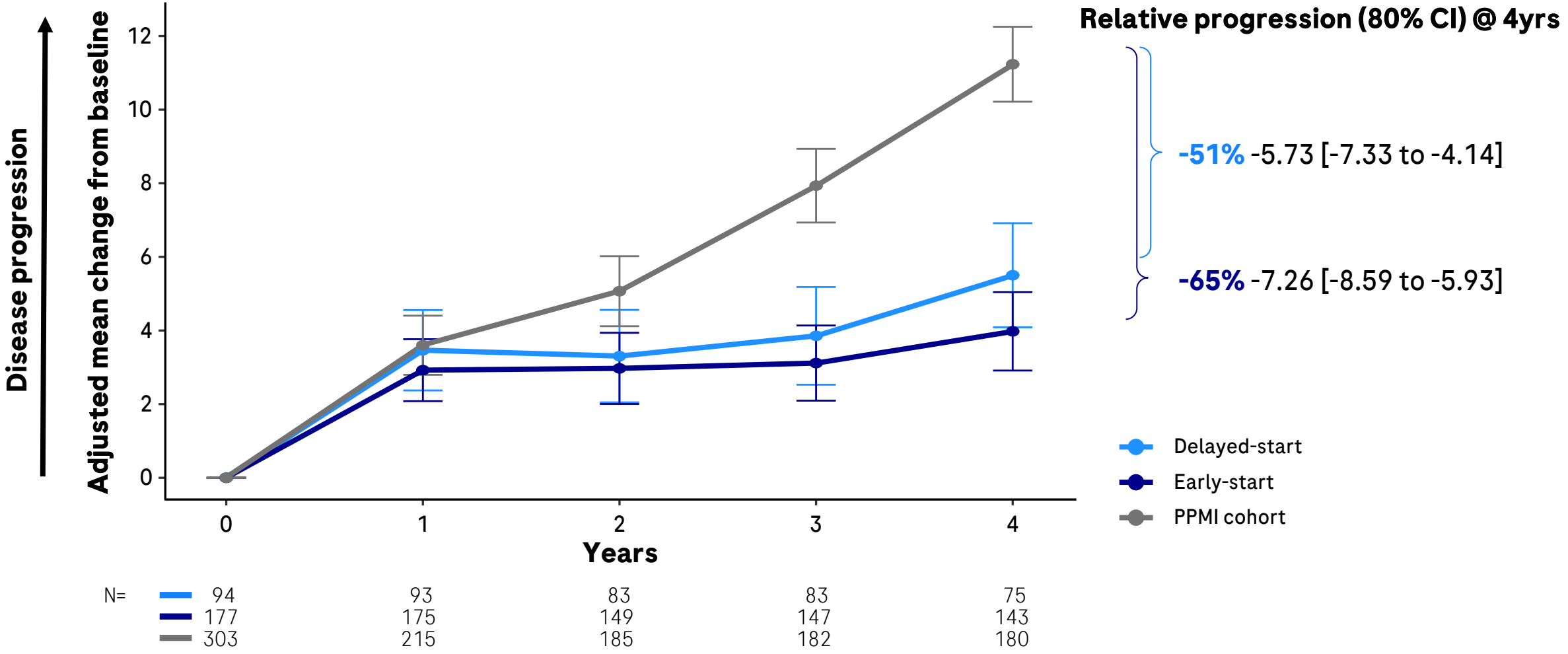
*Methodology provides a technique to control for confounding bias and ensure comparability in observational studies.
Note: PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
H&Y, modified Hoehn and Yahr stage; OLE, open-label extension; PD, Parkinson's disease; PPMI, Parkinson Progression Marker Initiative; RCT, randomised controlled trial.

Baseline characteristics are balanced after weighting with propensity scores

Baseline demographic and disease characteristics	PASADENA N=271	Before propensity score weighting		After propensity score weighting	
		PPMI N=303	SMD	PPMI N=269.88	SMD
Age (years) (mean (SD))	59.98 (9.0)	62.11 (8.53)	0.243	61.20 (9.28)	0.133
Sex = male, n (%)	188 (69.4)	202 (66.7)	0.058	189.3 (70.1)	0.017
MDS-UPDRS Part III (mean (SD))	21.15 (8.96)	21.17 (8.85)	0.003	21.13 (9.71)	0.001
H&Y stage II, n (%)	201 (74.2)	183 (60.4)	0.297	205.7 (76.2)	0.047
PD diagnosis (months) (mean (SD))	9.89 (6.34)	4.87 (5.36)	0.855	9.20 (5.61)	0.115
Years of education ≥12, n (%)	244 (90.0)	279 (92.1)	0.072	236.2 (87.5)	0.080
Montreal Cognitive Assessment (MoCA) (mean (SD))	28.17 (1.79)	27.23 (2.26)	0.462	28.02 (1.89)	0.082
DaT-SPECT putamen bilateral (mean (SD))	0.92 (0.26)	0.81 (0.28)	0.436	0.92 (0.31)	0.018

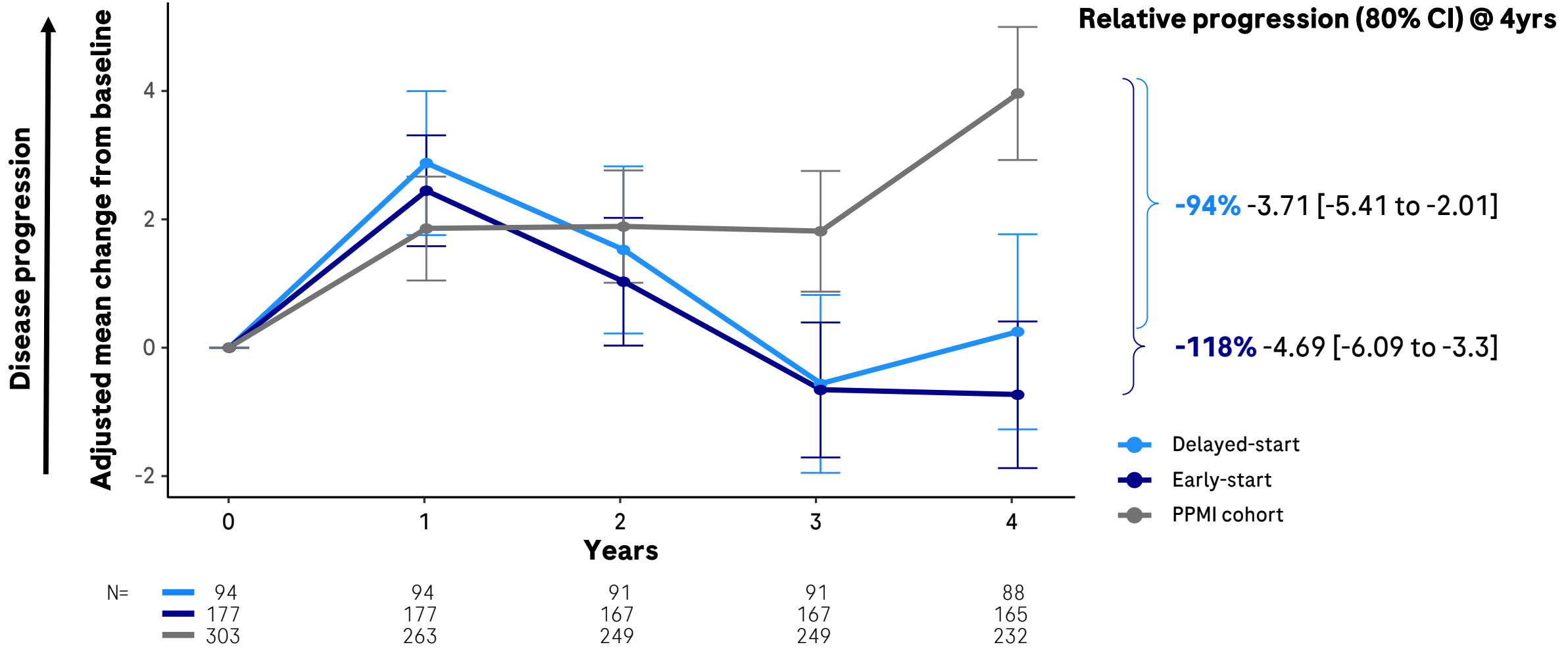
Note: SMD ≤0.2 indicates balance between groups. PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
DaT-SPECT, dopamine transporter imaging with single photon emission computed tomography; H&Y, modified Hoehn and Yahr stage; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative; SD, standard deviation; SMD, standardised mean difference.

Prasinezumab-treated individuals progress less than PPMI on MDS-UPDRS Part III OFF (motor examination)



Note: Data and analysis is not intended as a delayed-start analysis (compare between PASADENA arms). PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
CI, confidence interval; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative.

Prasinezumab-treated individuals progress less than PPMI on MDS-UPDRS Part III ON (motor examination)



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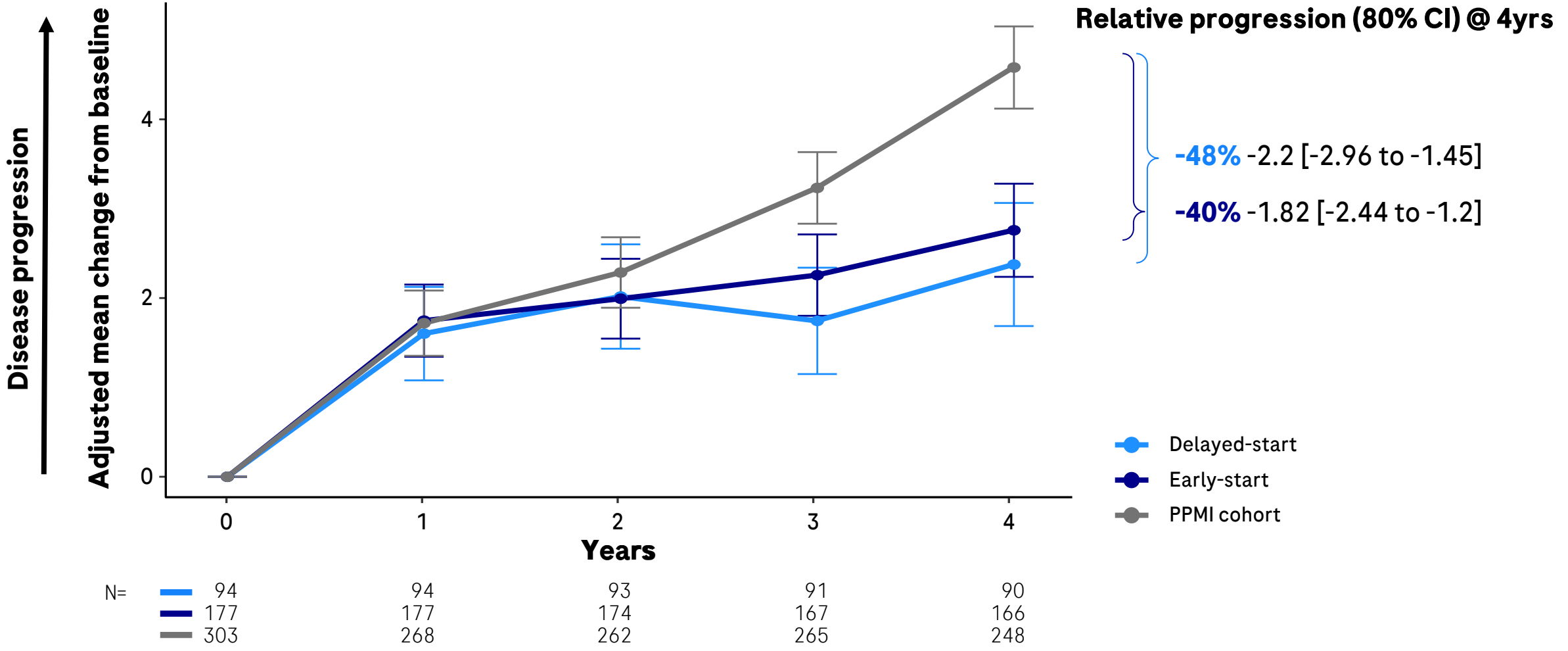
Prasinezumab-treated individuals progress less than PPMI on MDS-UPDRS Part II (motor experiences of daily living)



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Includes the sporadic PD cohort from the PPMI dataset

STEP 2: Propensity score weighting performed to mimic characteristics of RCT*

External Control Study

Participants

Single Arm Trial

Active cohort

Participants

External Data Source

Control cohort

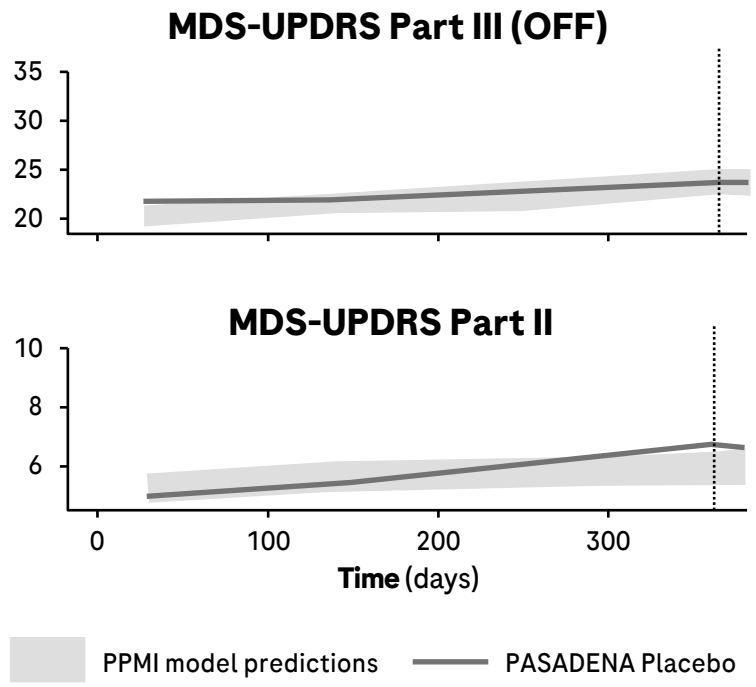
Propensity Score Methods

Active cohort

Control cohort

Validity confirmed by comparability of baseline characteristics and progression over 1 year between PASADENA Part 1 placebo group and weighted PPMI cohort

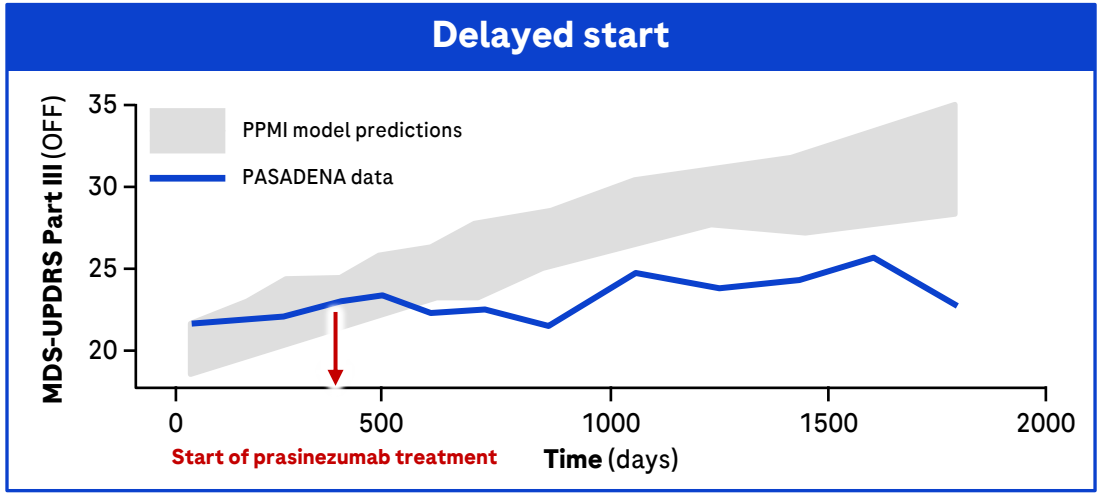
STEP 3: Disease modelling used to predict progression related to symptomatic use

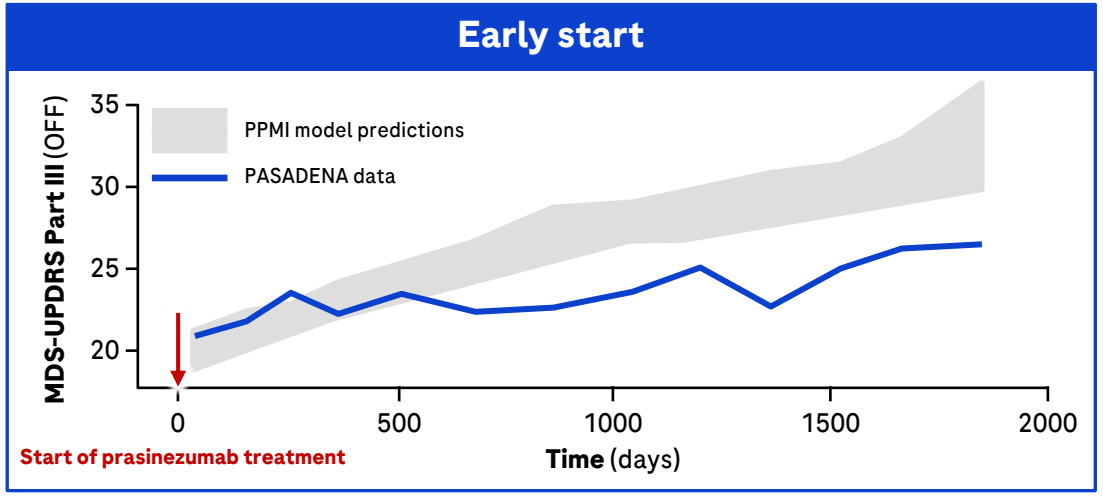


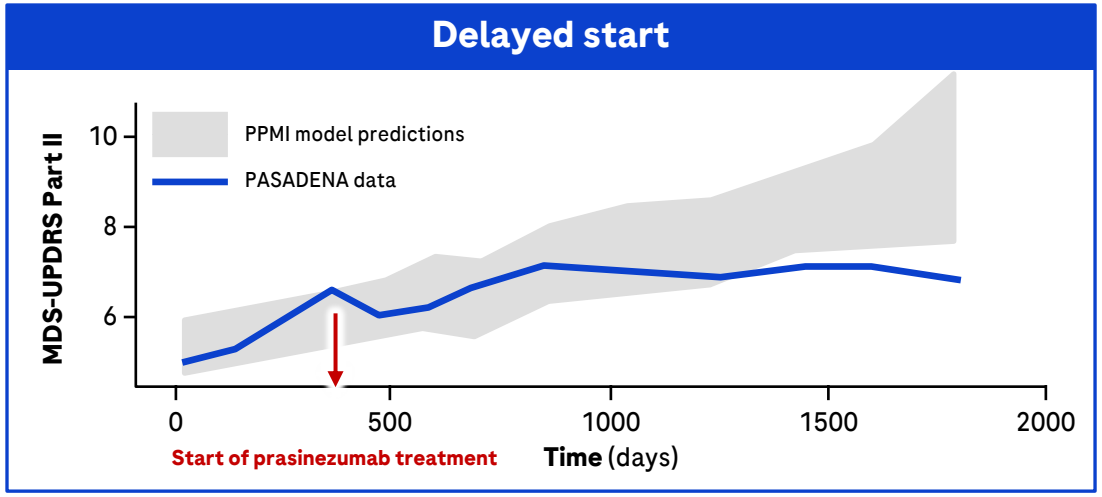
Model based on a hypothetical population using the baseline characteristics of PASADENA and a model of progression previously generated from PPMI

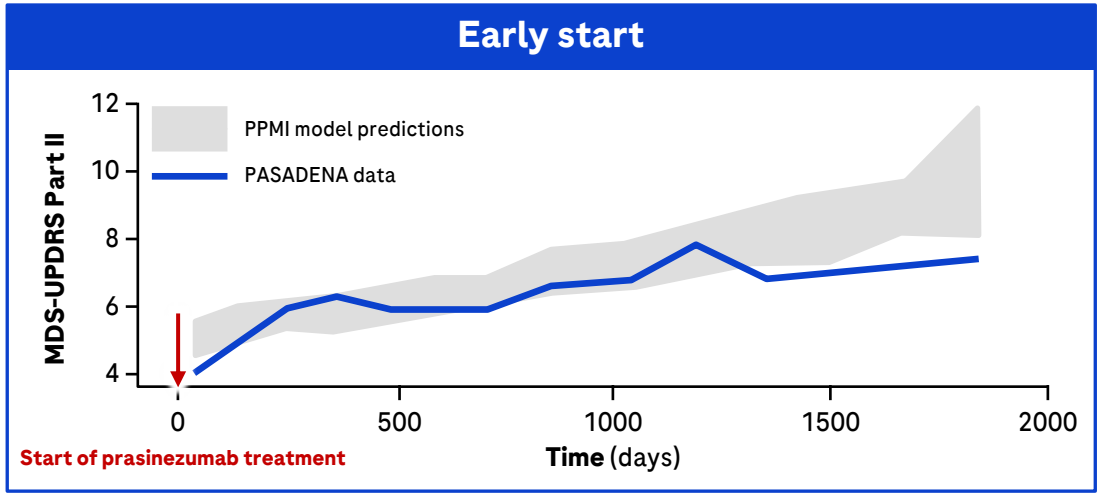
*Methodology provides a technique to control for confounding bias and ensure comparability in observational studies.
Note: PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
H&Y, modified Hoehn and Yahr stage; OLE, open-label extension; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PPMI, Parkinson Progression Marker Initiative; RCT, randomised controlled trial.

Results were confirmed based on disease progression modelling









Note: PPMI-based median prediction confidence intervals (grey areas) overlayed with PASADENA median data (blue lines). PASADENA: data cut-off 2nd Oct 2023; PPMI cohort: data cut-off Aug 2021.
MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative.

Summary

The comparison of PASADENA and PPMI data suggests potential benefit in slowing motor progression in favour of prasinezumab on multiple endpoints

- ❑ Slowing of progression on MDS-UPDRS Part III (clinician-rated motor examination) OFF and ON symptomatic medication state, **consistent** with previous data analyses
- ❑ Slowing of progression on MDS-UPDRS Part II (patient-reported motor experiences of daily living) emerges **after** the effect on Part III

The 2 approaches (propensity score and disease progression modelling) demonstrated consistent results

These findings are exploratory and need to be confirmed in an independent trial such as the Phase IIb PADOVA study and its OLE

Details on the ***Rationale, Design, and Baseline data of the PADOVA study (2024 (Nikolcheva, et al.)*** are available at **ADPD 2024**

MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative.

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PPMI, Parkinson's Progression Markers Initiative.