PADOVA: Topline results from a Phase IIb study of prasinezumab in early-stage Parkinson's disease participants on stable symptomatic treatment

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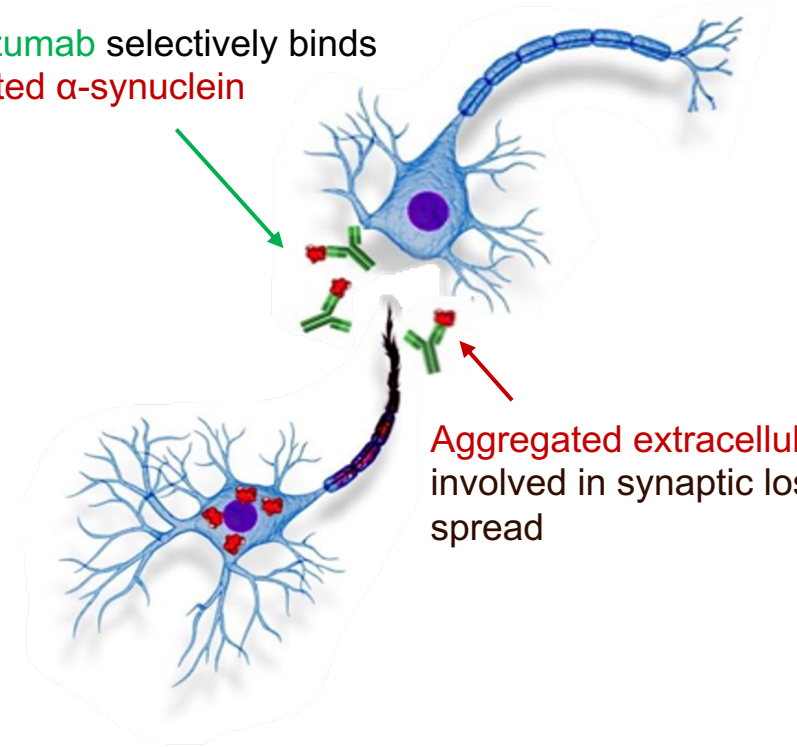
Disclosures

- **Tania Nikolcheva, Gennaro Pagano, Nathalie Pross, Annabelle Monnet, Gesine Respondek, Loes Rutten-Jacobs, Valerie Schlegel, Lauren Boak, Geoffrey A. Kerchner, Patrik Brundin, Hanno Svoboda, and Azad Bonni** are full-time employees and own shares of F. Hoffmann-La Roche Ltd.
- **Judith Anzures-Cabrera** is a full-time employee of Roche Products 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.
- **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.
- **Nicola Pavese** reports participating in advisory boards for Britannia, Boston Scientific, Benevolent AI, Hoffmann-La Roche, inc., and Abbvie. He also reports receiving honoraria from Britannia, Abbvie, GE Healthcare, and Boston Scientific, and grants from the Independent Research Fund Denmark, Danish Parkinson's disease Association, Parkinson's UK, Center of Excellence in Neurodegeneration (CoEN) network award, GE Healthcare Grant, Multiple System Atrophy Trust, Weston Brain Institute, EU Joint Program Neurodegenerative Disease Research (JPND), EU Horizon 2020 research, the Michael J. Fox Foundation for Parkinson's Research, and F. Hoffmann-La Roche, inc.
- **Klaus Seppi** is a recipient of grants from the FWF Austrian Science Fund, The Michael J. Fox Foundation, International Parkinson and Movement Disorder Society, AOP Orphan Pharmaceuticals AG, and EU (all to the institution). He has received payment for consultations from Ono Pharma UK, Lundbeck, and Ever Pharma and payment for lectures from Teva, UCB, AOP Orphan Pharmaceuticals AG, Roche, Grünenthal, Stada, Licher Pharma, Biogen, Bial, and AbbVie. He has also received payment for participation in advisory boards from Bial, Stada, and AbbVie, and honoraria from the International Parkinson and Movement Disorders Society.
- **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.
- **Ron Postuma** is a consultant for Biogen, Clinilabs, Curasen, Eisai, Inc., F. Hoffmann-La Roche Ltd., Merck, Takeda California, Inc., and Vaxxinity.

Prasinezumab is a humanised IgG1 monoclonal antibody that selectively binds aggregated α-synuclein[1,2]

Prasinezumab's proposed mode of action for the treatment of Parkinson's disease[1]

Prasinezumab selectively binds aggregated α-synuclein



Aggregated extracellular α-synuclein involved in synaptic loss and pathogenic spread

Proposed effects:

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

IgG, immunoglobulin.

1. Angot E, *et al. Lancet Neurol*. 2010; 9(11):1128–38; 2. Vekrellis K & Stefanis L. *Expert Opin Ther Targets*. 2012;16(4):421–32.

Global Phase IIb PADOVA study design

Novel time-to-event approach allows measuring treatment effect on top of standard-of-care symptomatic therapies

110 sites in Austria, Canada, France, Italy, Luxembourg, Poland, Spain, UK and US

Stratification
L-DOPA or MAO-Bi

Randomise (1:1)

N=586

Screening
Up to 12 weeks

Placebo
IV Q4W

Prasinezumab 1500 mg IV Q4W

Double-blind treatment period:
≥ 248 confirmed motor progression events AND ≥76-weeks treatment

(Longest treatment duration ~3.5 years)

Open-label extension
Prasinezumab 1500 mg IV Q4W

OLE (2 years) OR
Safety follow-up (up to 70 days)

Key inclusion criteria

Idiopathic PD

- Diagnosis by MDS criteria
- DaT-SPECT consistent with dopamine transporter deficit

Early-stage PD

- Time from diagnosis: 3 months–3 years
- H&Y stage I or II
  MDS-UPDRS Part IV score = 0

Stable L-DOPA or MAO-Bi dose

- ≥3 months prior to baseline

The mentioned compounds and their use are investigational and have not yet received regulatory approval in any country.
DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn & Yahr; IV, intravenous; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS, Movement Disorder Society; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; OLE, open-label extension; PD, Parkinson's disease; Q4W, every 4 weeks.
ClinicalTrials.gov. NCT04777331. PADOVA Phase II clinical trial. Available at: https://clinicaltrials.gov/ct2/show/NCT04777331 (last accessed 06 March 2025).
1. Pagano G, *et al. N Engl J Med.* 2022;387(5):421–32; 2. Pagano G, *et al. Nat Med.* 2024;30(12):3669–75.

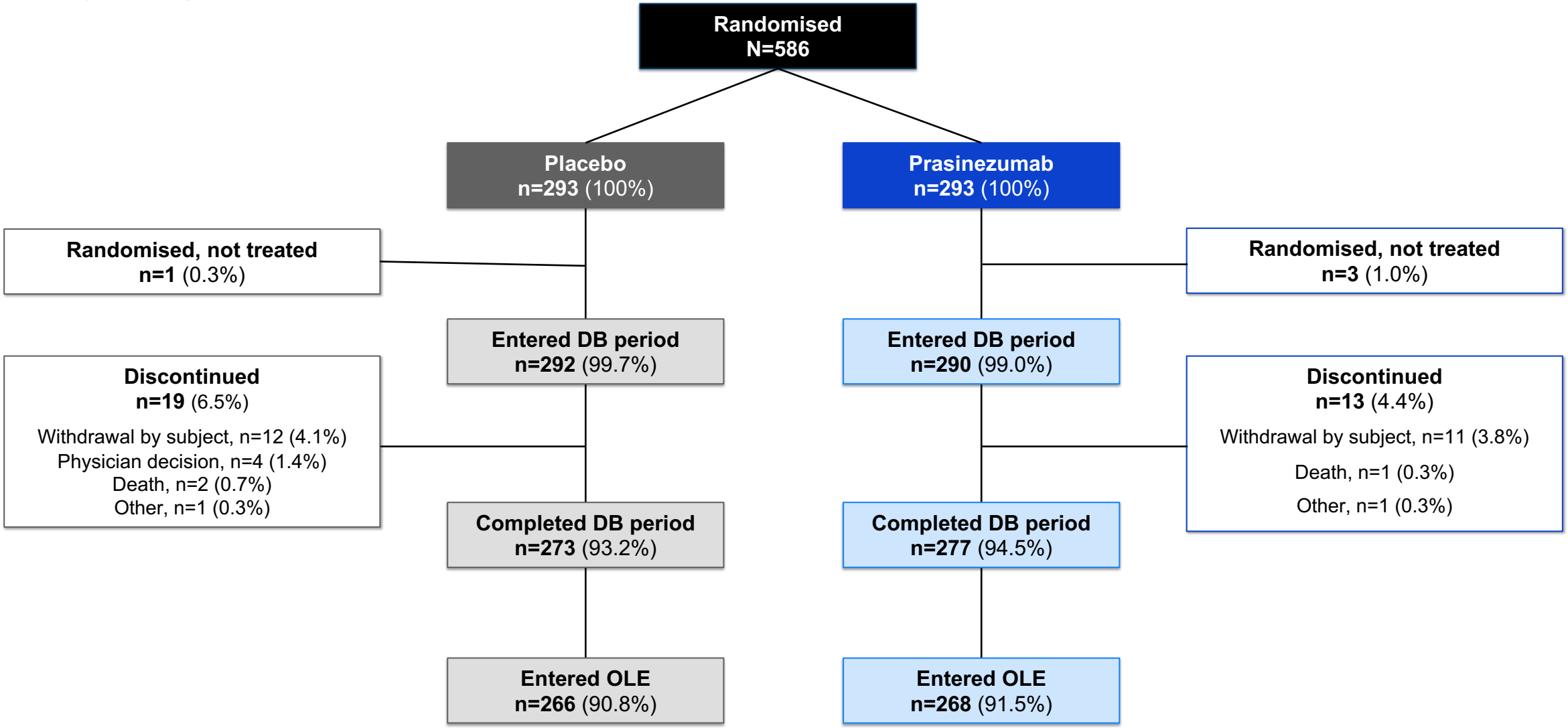
PADOVA endpoints

	Time-to-event (TTE)	**Continuous** (Change from baseline)
Primary	■ ≥5 points in MDS-UPDRS Part III OFF* (confirmed motor progression)	
Secondary	■ ≥3 points in MDS-UPDRS Part II in the presence of confirmed motor event (motor function) ■ Meaningful worsening of CGI-C# ■ Meaningful worsening of PGI-C# ■ ≥1 point in MDS UPDRS Part IV	■ MDS-UPDRS Part III OFF (76 weeks) ■ MDS-UPDRS Part III OFF bradykinesia/rigidity (76 weeks)
Exploratory	■ ≥ 3 points in MDS-UPDRS Part II (confirmed) ■ Increase in LEDD ■ 10% decline in SE-ADL ■ Advanced stage assessed with 5-2-1 criteria	■ MDS-UPDRS Part III OFF (104 weeks) ■ MDS-UPDRS Part II, MDS-UPDRS Part IV, MDS-NMS, MoCA, SE-ADL (76 weeks)
Biomarker		■ Imaging: MRI neuromelanin and iron ■ Fluid: CSF (subset) SAA, aSyn; plasma ■ Digital
Safety	■ AEs, IRRs, vital signs, ECG, C-SSRS, ADA	
PK	■ Serum PK parameters, PK/PD relationships	

*Practically defined OFF-medication state (≥12 hours since the last dose of L-DOPA); #Defined as a rating of 'very much worse', 'much worse' or 'minimally worse'.
ADA, antidrug antibody; AE, adverse event; CGI-C, Clinical Global Impression of Change; CSF, cerebrospinal fluid; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; IRR, infusion-related reaction; LEDD, levodopa equivalent daily dose; L-DOPA, levodopa; MDS-NMS, Movement Disorder Society–sponsored Nonmotor Symptoms Rating Scale; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; PGI-C, Patient Global Impression of Change; PK, pharmacokinetic; PK/PD, pharmacokinetics/pharmacodynamics; SAA, synuclein amplification assay; SE-ADL, Schwab and England Activities of Daily Living Scale, TTE, time-to-event.

Well-conducted study with high rate of retention

Participant disposition



DB, double-blind; OLE, open-label extension.

Baseline characteristics well balanced across arms

Population consistent with early-stage PD; 74% of participants on L-DOPA

Key baseline demographic and disease characteristics		Placebo n=293	Prasinezumab n=293	All N=586
Age (yr)	mean (SD)	64.4 (7.5)	`	64.2 (7.3)
Sex, male	n (%)	189 (64.5%)	183 (62.5%)	372 (63.5%)
Time from diagnosis (months)	mean (SD)	18.4 (9.0)	18.8 (9.5)	18.6 (9.2)
Hoehn & Yahr stage	n (%)			
1		40 (13.7%)	38 (13.0%)	78 (13.3%)
2		250 (85.3%)	251 (85.7%)	501 (85.5%)[#]
MDS-UPDRS Part II	mean (SD)	5.1 (4.1)	4.9 (3.5)	5.0 (3.8)
MDS-UPDRS Part III OFF*	mean (SD)	24.6 (10.8)	24.3 (9.9)	24.5 (10.4)
MDS-UPDRS Part III ON**	mean (SD)	19.5 (9.8)	19.0 (8.9)	19.2 (9.4)
MDS-UPDRS Part IV = 0	n (%)	283 (96.6%)	282 (96.2%)	565 (96.4%)
MoCA	mean (SD)	26.4 (2.7)	26.6 (2.9)	26.5 (2.8)
SE-ADL completely independent	n (%)	288 (98.3%)	285 (97.3%)	573 (97.8%)
Striatal binding ratio: putamen ipsilateral	mean (SD)	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)
Stratification factor	n (%)			
L-DOPA		217 (74.1%)	218 (74.4%)	435 (74.2%)
MAO-Bi		76 (25.9%)	75 (25.6%)	151 (25.8%)

*Practically defined OFF-medication state (≥12 hours since the last dose of L-DOPA); ** Refers to the L-DOPA population; #7 patients were randomised with Hoen & Yahr stage 3 in PADOVA (3 in the placebo group and 4 in the prasinezumab group).
L-DOPA, levodopa; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MAO-Bi, monoamine oxidase type B inhibitor; MoCA, Montreal Cognitive Assessment; SD, standard deviation;
SE-ADL, Schwab and England Activities of Daily Living Scale; yr, year.

Prasinezumab continues to have a favourable safety & tolerability profile

Safety summary

- IRRs comparable between groups (11% prasinezumab vs 12.8% placebo); no serious IRRs
- Three deaths: two in placebo, one in prasinezumab arm; the latter due to sinus adenocarcinoma and deemed unrelated to study drug
- SAEs incidence: 11.6% in prasinezumab and 11.7% in placebo arm
- AEs Grade 3–5 incidence: 12.7% in prasinezumab and 14.1% in placebo arm
- Two AEs leading to study drug discontinuation in prasinezumab and three in placebo arm
- Most frequently reported AE by system organ class: infection and infestation (57.9% in prasinezumab and 54.1% in placebo arm)

AE, adverse event; IRR, infusion-related reaction; SAE, serious adverse event.

PADOVA primary endpoint focuses on meaningful motor progression

Time to confirmed motor progression event defined as ≥5 points on MDS-UPDRS Part III in OFF medication state#

A threshold of meaningful motor progression in early-stage PD was defined[1]

Threshold of 5 points on MDS-UPDRS Part III is supported by:

- Anchor-based meaningful within-patient worsening analysis using PASADENA data (with CGI-I as the anchor)[2]
- Modified Delphi study in which clinician consensus was reached after two rounds[2]
- Anchor-based analysis conducted by Horváth *et al*[3]

Time to Event (TTE) approach was used to mitigate impact of change of symptomatics on scale[4]

- Results from PASADENA TTE analysis using treatment policy* or hypothetical strategy† estimands were consistent, suggesting minimal/no impact
- Change in medication occurred after reaching milestone in majority of subjects and likely contributes to this

#Practically defined OFF-medication state (≥12 hours since the last dose of L-DOPA);
*Treatment effect is estimated irrespective of symptomatic treatment start or changes in MAO-Bi treatment; †Assumes scenario in which events of start of symptomatic therapy or change in MAO-Bi dose did not occur.
CGI, Clinical Global Impression; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; TTE, time-to-event.
1. Sánchez-Ferro Á, *et al. Mov Disord Clin Pract*. 2018;5(4):448–50; 2. Trundell D, *et al. J Parkinsons Dis*. 2025;0(0). 10.1177/1877718X241302337; 3. Horváth K, *et al. Parkinsonism Relat Disord*. 2015;21(12):1421–6; 4. Zanigni S, *et al.* Presented at MDS 2022, Madrid, Spain.

Primary endpoint

Time to confirmed motor progression event

Motor progression event definition

- **≥5 points in MDS-UPDRS Part III OFF**
- **Confirmation:**
  - Sustained over two consecutive visits OR
  - Levodopa equivalent daily dose (LEDD) increase prior to visit following the event

#Estimand strategy for other intercurrent events: Treatment discontinuation prior to confirmed motor progression (treatment policy). Death prior to confirmed motor progression (composite).
DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn & Yahr; LEDD, levodopa equivalent daily dose; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale.

Primary endpoint

Time to confirmed motor progression event

Motor progression event definition

- **≥5 points in MDS-UPDRS Part III OFF**
- **Confirmation:**
  - Sustained over two consecutive visits OR
  - Levodopa equivalent daily dose (LEDD) increase prior to visit following the event

Statistical analysis

- **Primary:** Stratified log-rank test and stratified Cox proportional hazards model (*non-adjusted*)
- **Supplementary:** Cox proportional hazards model with baseline covariate adjustment (*adjusted*)
  - MAO-Bi vs L-DOPA, H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral binding, <60 vs ≥60 years of age, male vs female, baseline MDS-UPDRS Part III

#Estimand strategy for other intercurrent events: Treatment discontinuation prior to confirmed motor progression (treatment policy). Death prior to confirmed motor progression (composite).
DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn & Yahr; LEDD, levodopa equivalent daily dose; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale.

Primary endpoint

Time to confirmed motor progression event

Motor progression event definition

- **≥5 points in MDS-UPDRS Part III OFF**
- **Confirmation:**
  - Sustained over two consecutive visits OR
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Statistical analysis

- **Primary:** Stratified log-rank test and stratified Cox proportional hazards model (*non-adjusted*)
- **Supplementary:** Cox proportional hazards model with baseline covariate adjustment (*adjusted*)
  - MAO-Bi vs L-DOPA, H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral binding, <60 vs ≥60 years of age, male vs female, baseline MDS-UPDRS Part III

Estimand strategy LEDD increase[#]

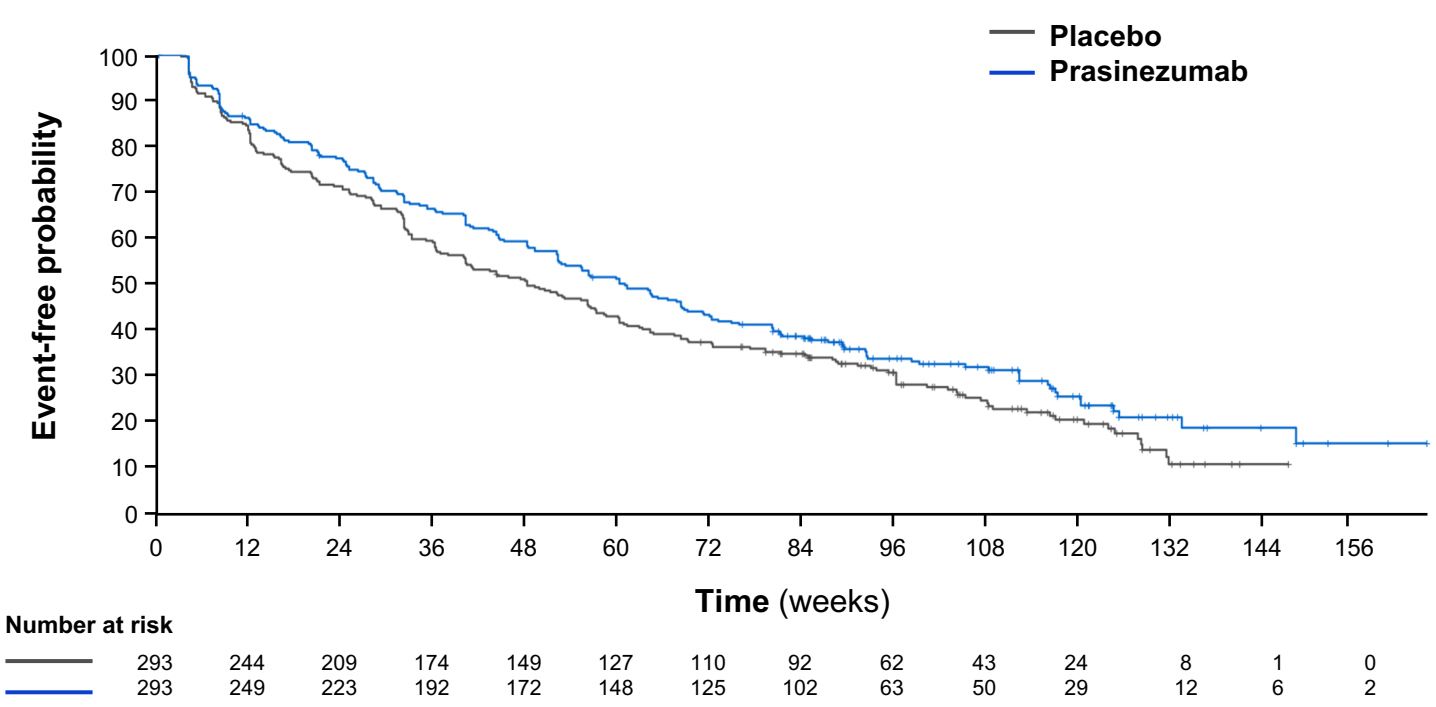
- **Treatment policy:** all data irrespective of change in symptomatic medication

[#]Estimand strategy for other intercurrent events: Treatment discontinuation prior to confirmed motor progression (treatment policy). Death prior to confirmed motor progression (composite).
DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn & Yahr; LEDD, levodopa equivalent daily dose; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale.

Prasinezumab showed a trend towards delaying motor progression

Primary endpoint: Study missed statistical significance

Time to ≥5 points on MDS-UPDRS Part III OFF



	n	n events	Median (weeks)	95% CI
Prasinezumab	293	200	**61.1**	52.3, 71.9
Placebo	293	220	**49.7**	40.1, 58.1

Primary analysis (unadjusted)

Hazard ratio (95% CI) = 0.84 (0.69, 1.01)

p=0.0657

Supplementary analysis (adjusted)*

Hazard ratio (95% CI) = 0.81 (0.67, 0.98)

p=0.0334#

Difference in medians: 11.4 weeks (23%)

*Covariates used for adjustment: Medication at baseline (MAO-Bi vs L-DOPA), H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral, age (<60 vs ≥60), sex (male vs female), baseline dependent parameter (MDS-UPDRS Part III).

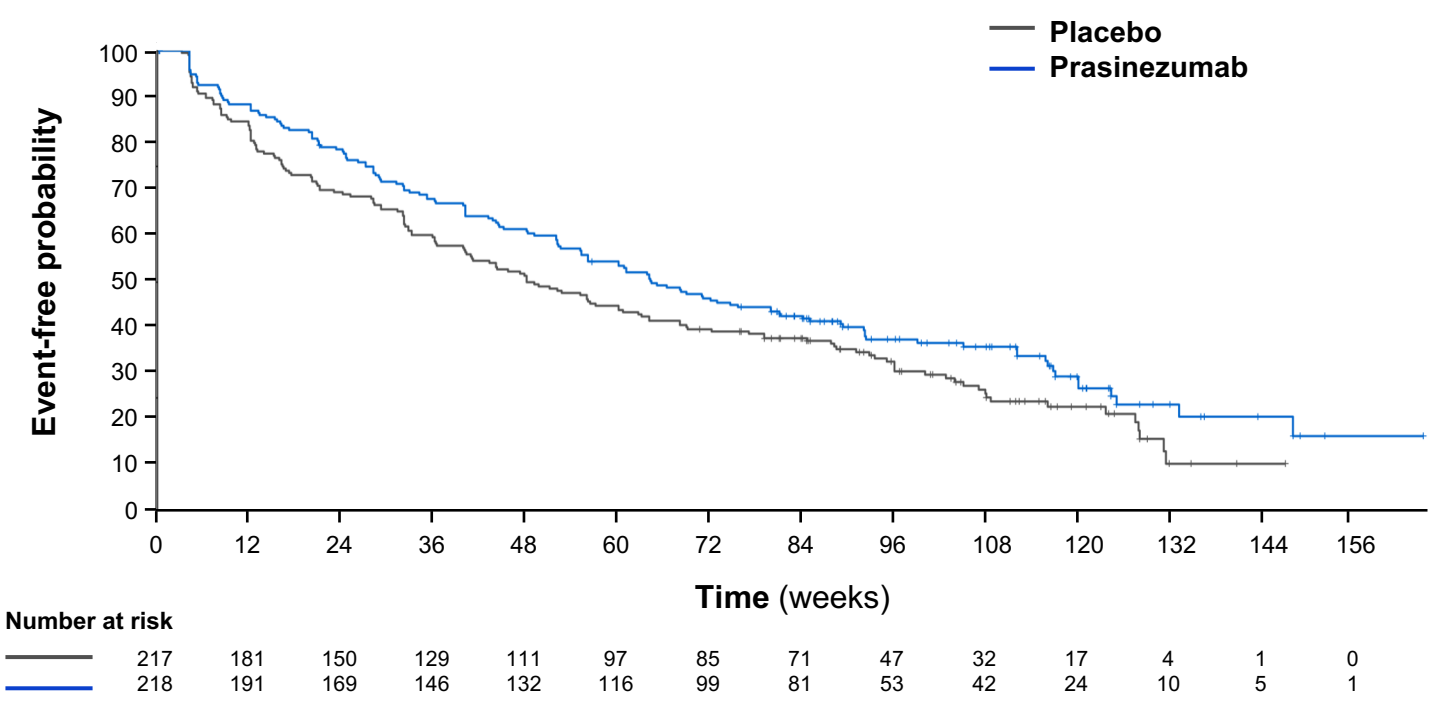
#For descriptive purposes, nominal p-values are displayed.

Participants received prasinezumab 1500 mg or placebo Q4W.
CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn and Yahr; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; Q4W, every four weeks.

Prasinezumab showed a trend towards delaying motor progression

Primary endpoint: Trend more pronounced in prespecified L-DOPA subgroup

Time to ≥5 points on MDS-UPDRS Part III OFF



	n	n events	Median (weeks)	95% CI
Prasinezumab	218	145	**64.4**	55.3, 81.1
Placebo	217	160	**48.6**	40.1, 62.7

Primary analysis (unadjusted)

Hazard ratio (95% CI) = 0.79 (0.63, 0.99)

p=0.0431#

Supplementary analysis (adjusted)*

Hazard ratio (95% CI) = 0.76 (0.61, 0.95)

p=0.0175#

Difference in medians: 15.8 weeks (32%)

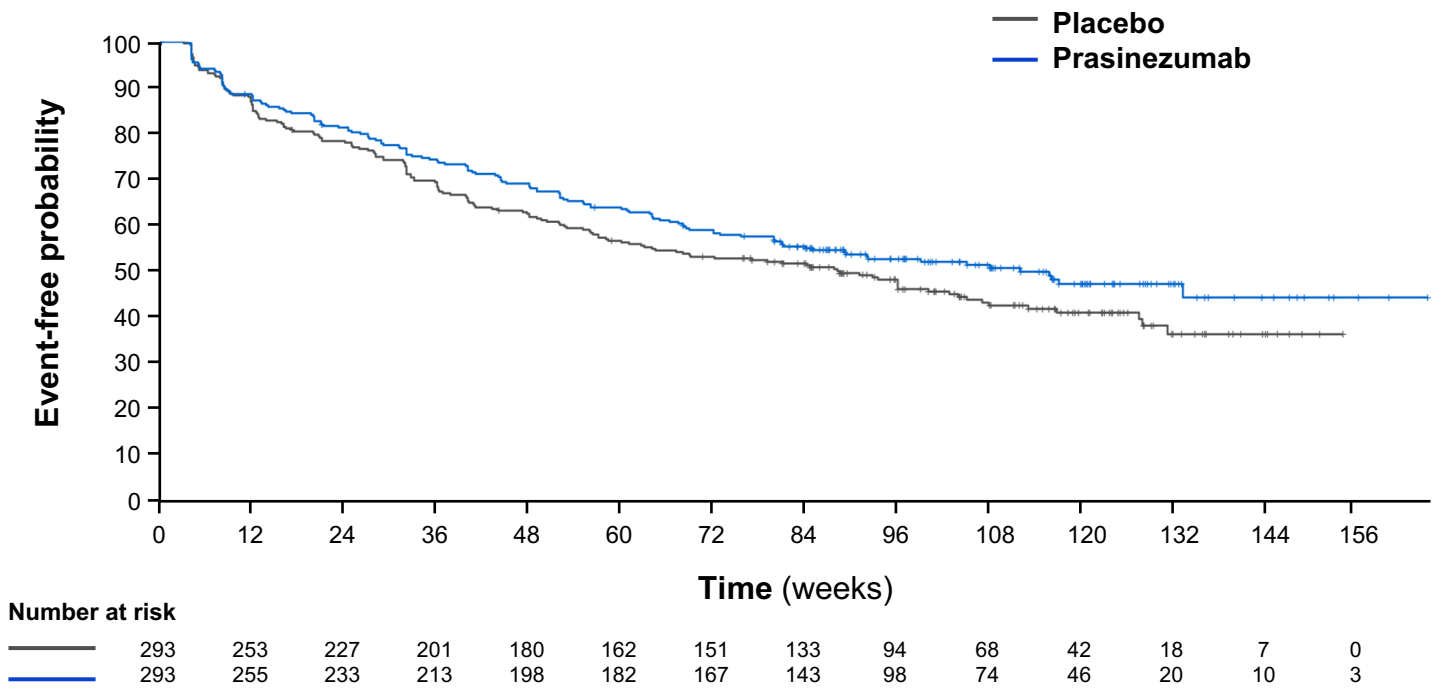
*Covariates used for adjustment: Medication at baseline (MAO-Bi vs L-DOPA), H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral, age (<60 vs ≥60), sex (male vs female), baseline dependent parameter (MDS-UPDRS Part III).

#For descriptive purposes, nominal p-values are displayed.

Participants received prasinezumab 1500 mg or placebo Q4W.
CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn and Yahr; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; Q4W, every four weeks.

Prasinezumab showed a trend towards delaying the decline of function

Time to ≥3 points on MDS-UPDRS Part II in the presence of a confirmed motor event



	n	n events	Median (weeks)	95% CI
Prasinezumab	293	142	**112.1**	81.1, NE
Placebo	293	163	**88.3**	62.7, 105.1

Adjusted Cox model*

Hazard ratio (95% CI) = 0.82 (0.66, 1.03)

p=0.0914#

Difference in medians: 23.8 weeks (27%)

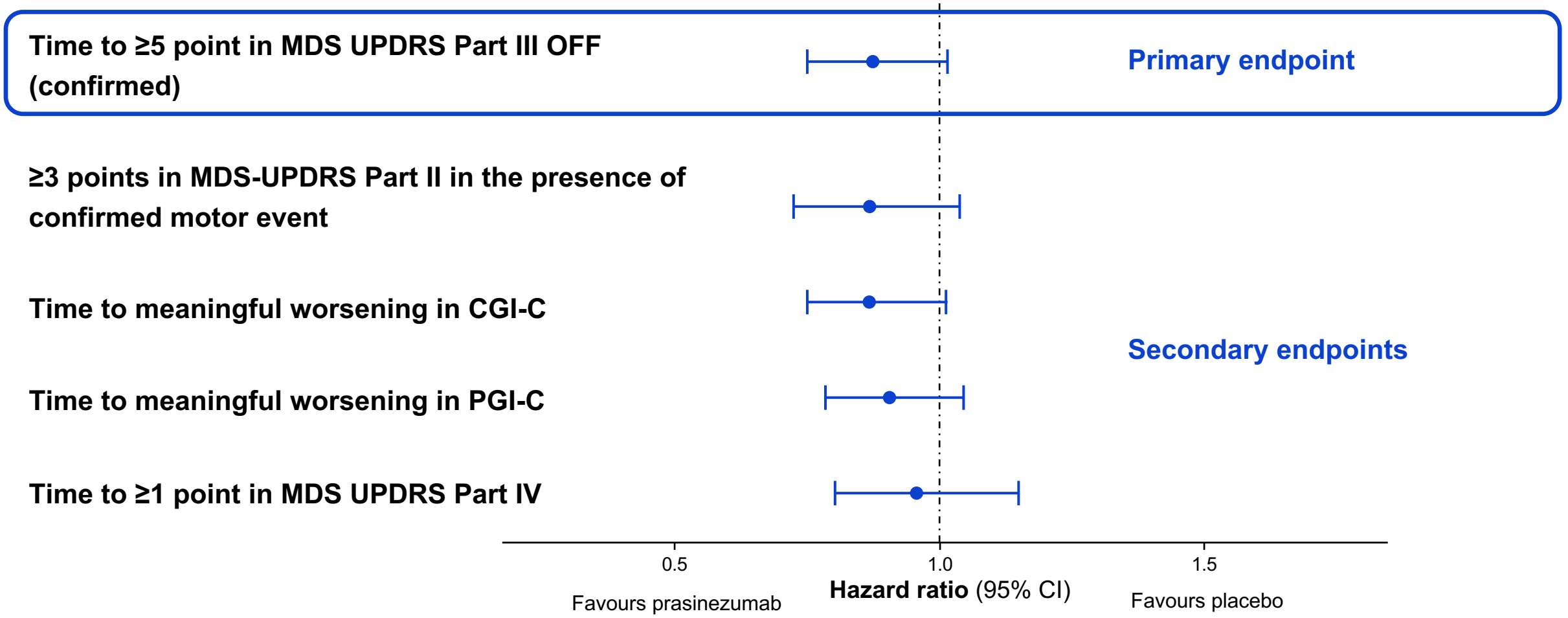
*Covariates used for adjustment: Medication at baseline (MAO-Bi vs L-DOPA), H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral, age (<60 vs ≥60), sex (male vs female), baseline dependent parameter (MDS-UPDRS Parts II and III).

#For descriptive purposes, nominal p-values are displayed.

Participants received prasinezumab 1500 mg or placebo Q4W.
CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn and Yahr; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; NE, not evaluable; Q4W, every four weeks.

Consistent trends in favour of prasinezumab across TTE endpoints

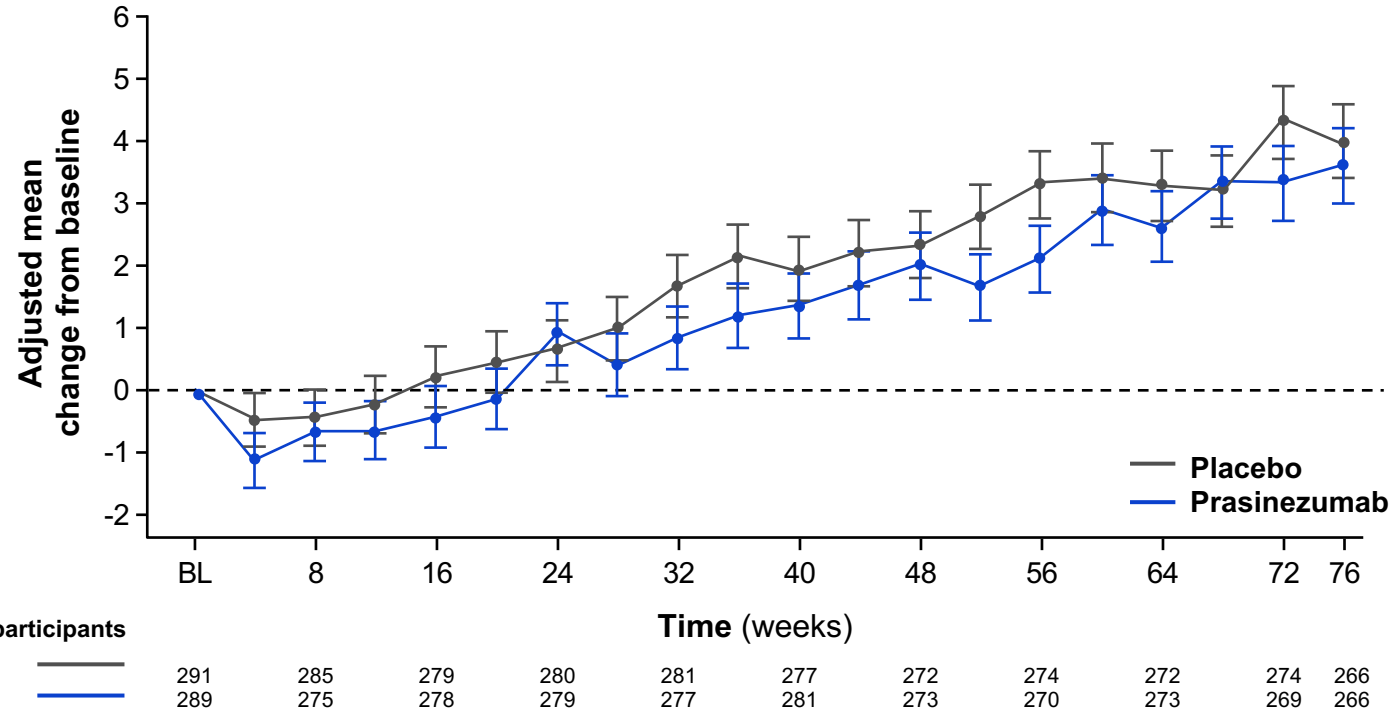
Forest plot of primary and secondary TTE endpoints



Participants received prasinezumab 1500 mg or placebo Q4W.
CGI-C, Clinical Global Impression of Change; CI, confidence interval; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PGI-C, Patient Global Impression of Change; Q4W, every four weeks; TTE, time-to-event.

Prasinezumab showed no effect on motor progression at 76 weeks

Change from baseline to Week 76 on MDS-UPDRS Part III OFF



Bars represent least square means ± SE.

*For descriptive purposes, nominal p-values are displayed.

Difference in adjusted means (SE)
–0.39 (0.74); 95% CI (–1.84 to 1.05)

No difference vs placebo
p=0.5994*

Disease modelling[1]: >2 years may be needed to show treatment effect for a therapy with 30% effect size

Mixed Model for Repeated Measures (MMRM). Covariates used for adjustment: MAO-Bi vs L-DOPA, H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral binding, <60 vs ≥60 years of age, male vs female, baseline MDS-UPDRS Part III
Participants received prasinezumab 1500 mg or placebo Q4W.

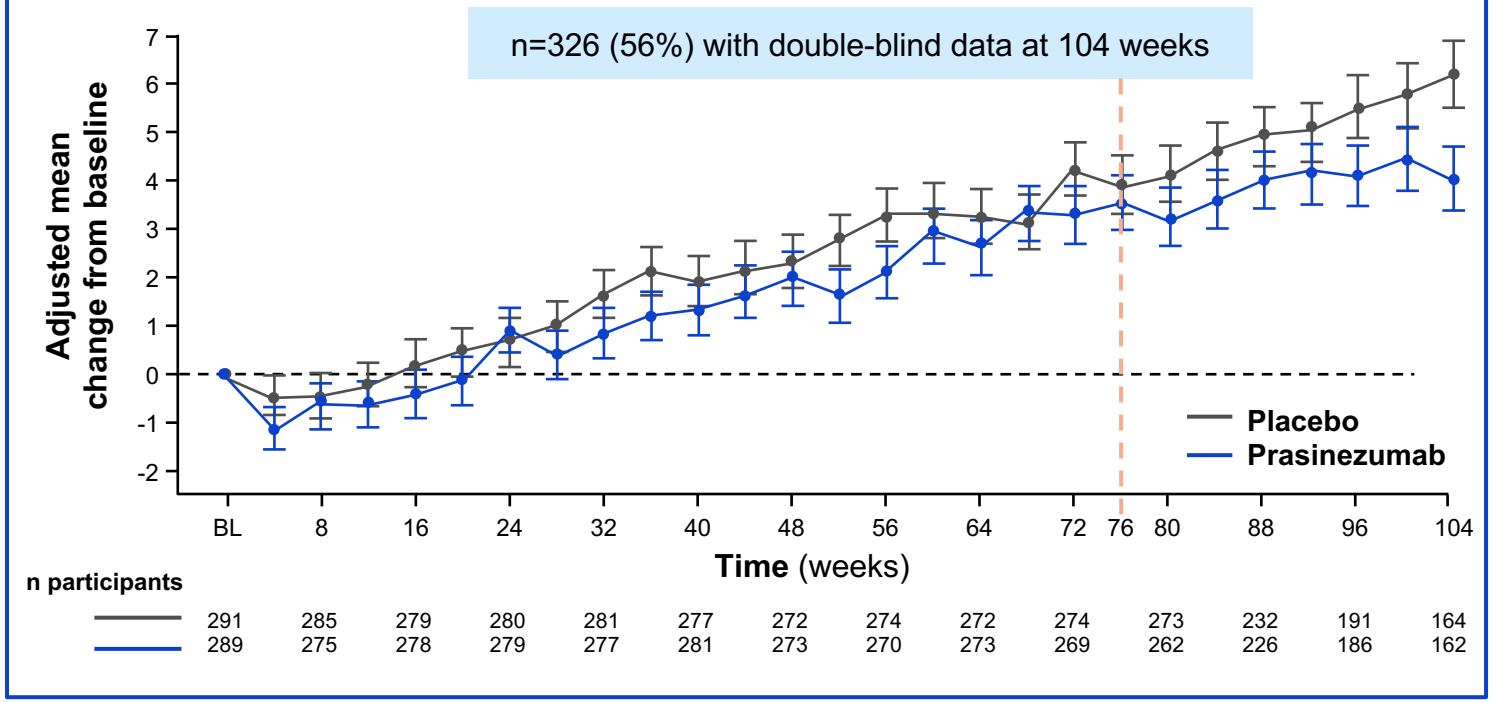
[1]Ribba B, *et al. J Parkinsons Dis.* 2024;14(6):1225–35.

BL, baseline; CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn and Yahr; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; SE, standard error; Q4W, every four weeks; TTE, time-to-event.

Prasinezumab showed a trend towards reduction of motor progression at 104 weeks

Treatment duration longer than 18 months may be needed to measure treatment effect

Change from baseline to Week 104 on MDS-UPDRS Part III OFF



Difference in adjusted means (SE)
–2.18 (0.862); 95% CI (–3.87 to -0.49)

~35% relative reduction vs placebo
p=0.0117#

Baseline characteristics in subset well balanced between treatment arms

Bars represent least square means ± SE.

*Covariates used for adjustment in MMRM model: Medication at baseline (MAO-Bi vs L-DOPA), H&Y stage (1 vs ≥2), DaT-SPECT putamen ipsilateral, age (<60 vs ≥60), sex (male vs female), MDS-UPDRS Part III.

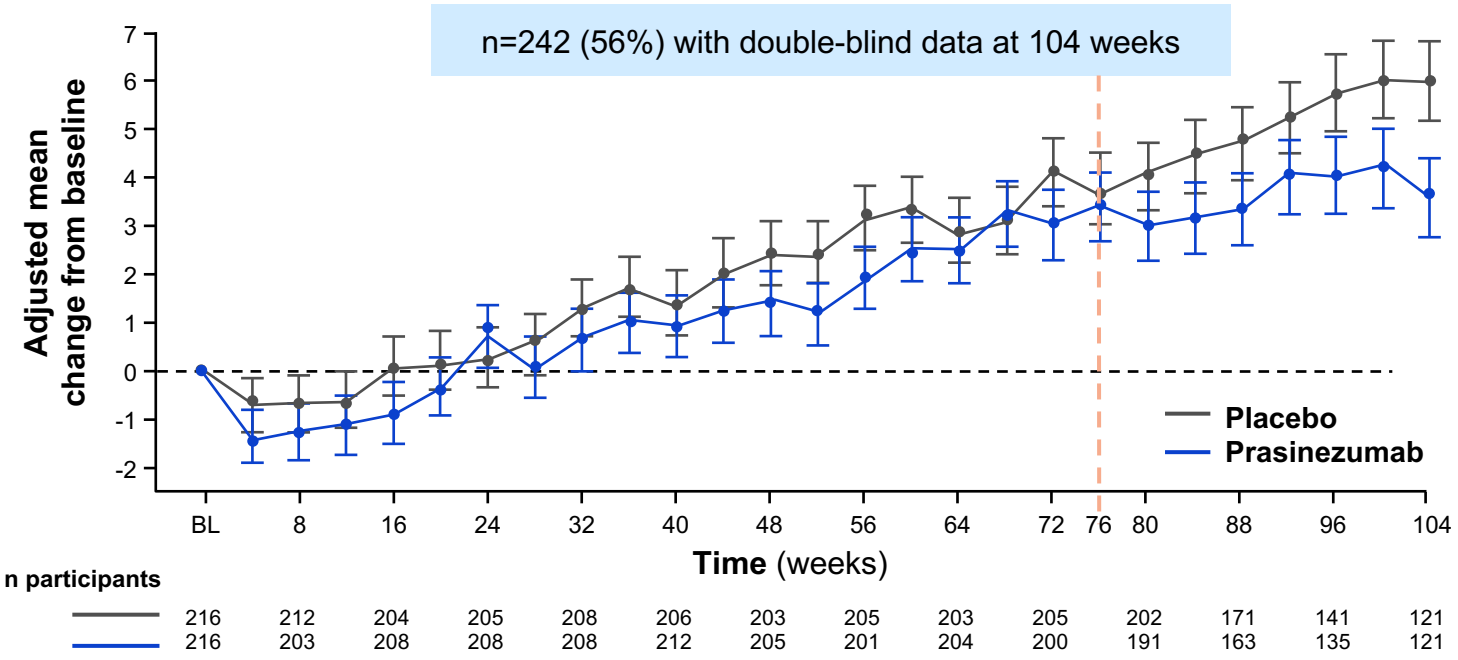
#For descriptive purposes, nominal p-values are displayed.

Participants received prasinezumab 1500 mg or placebo Q4W.
BL, baseline; CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn and Yahr; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MRMM, Mixed Model for Repeated Measures; Q4W, every four weeks; SE, standard error.

Prasinezumab showed a trend towards reduction of motor progression at 104 weeks in the L-DOPA-treated population

Treatment duration longer than 18 months may be needed to measure treatment effect

Change from baseline to Week 104 on MDS-UPDRS Part III OFF



Difference in adjusted means (SE)
–2.43 (1.02); 95% CI (–4.44 to -0.43)

~40% relative reduction vs placebo
p=0.0177#

Baseline characteristics in subset well balanced between treatment arms

Bars represent least square means ± SE.

*Covariates used for adjustment: Medication at baseline (MAO-Bi vs L-DOPA), H&Y stage (1 vs >2), DaT-SPECT putamen ipsilateral, age (<60 vs >60), sex (male vs female), baseline dependent parameter (MDS-UPDRS Part III).

#For descriptive purposes, nominal p-values are displayed.

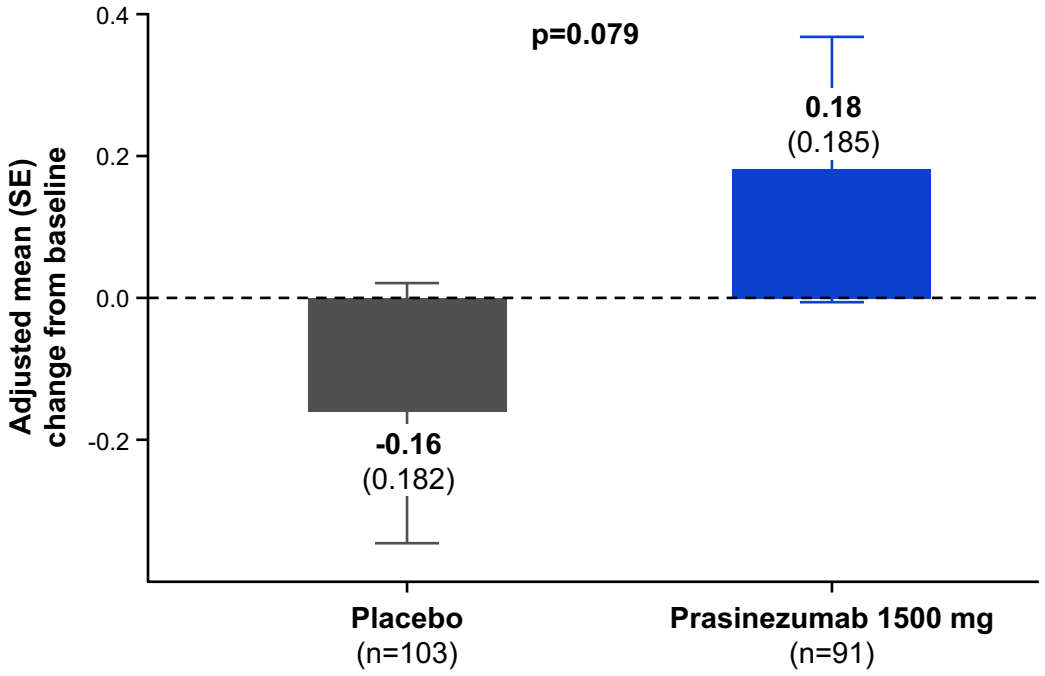
Participants received prasinezumab 1500 mg or placebo Q4W.
BL, baseline; CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; H&Y, Hoehn and Yahr; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; Q4W, every four weeks; SE, standard error.

Exploratory endpoint

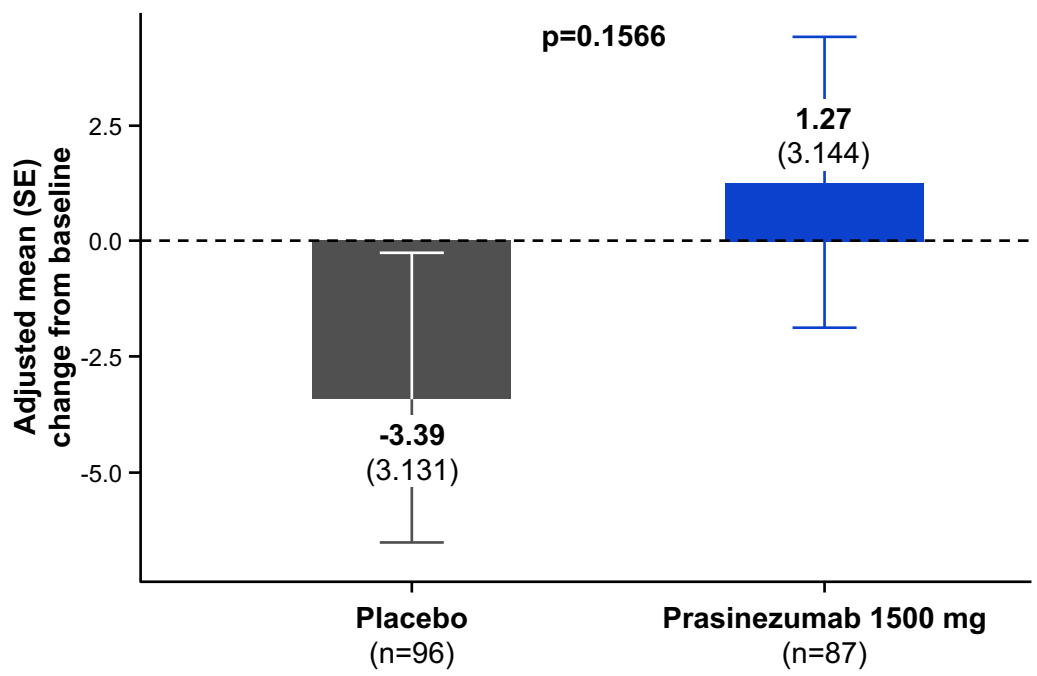
Prasinezumab showed a trend towards reduction in neuromelanin loss in substantia nigra

Change from baseline to Week 76 in Neuromelanin MRI*

Substantia nigra pars compacta intensity



Substantia nigra pars compacta volume



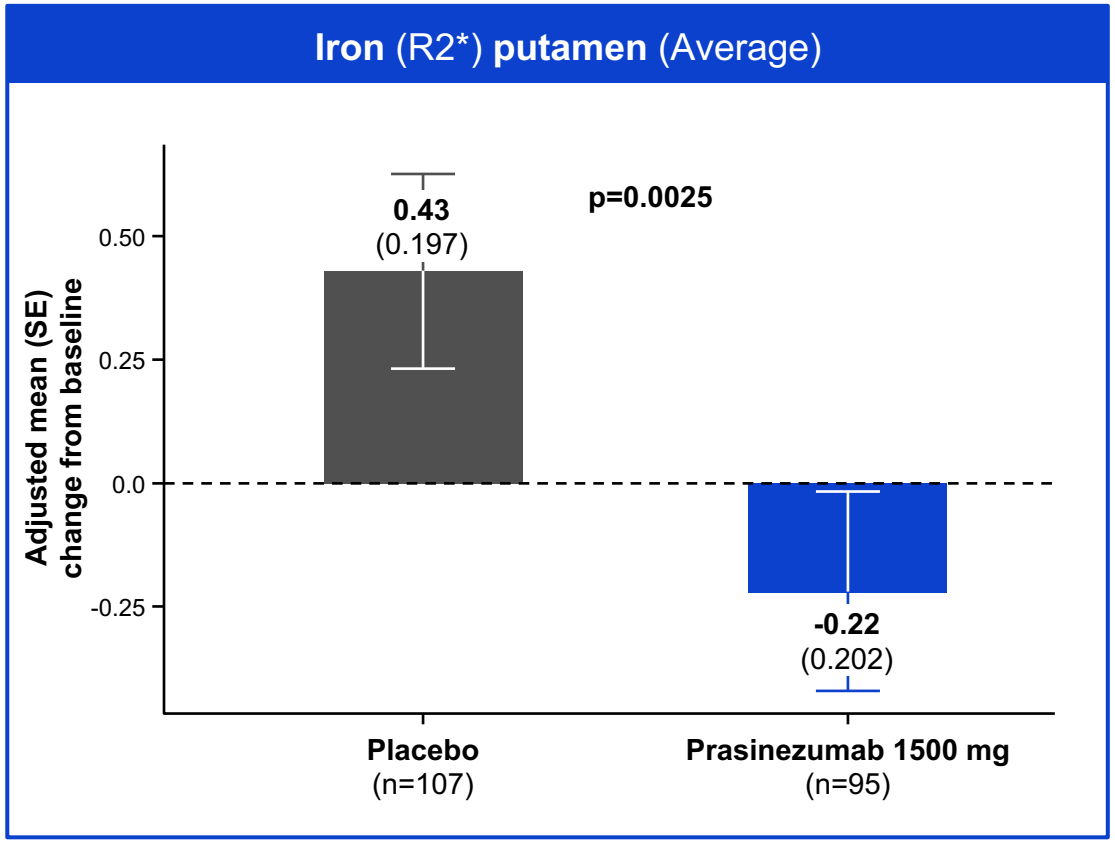
Error bars represent SE; p-values are nominal.

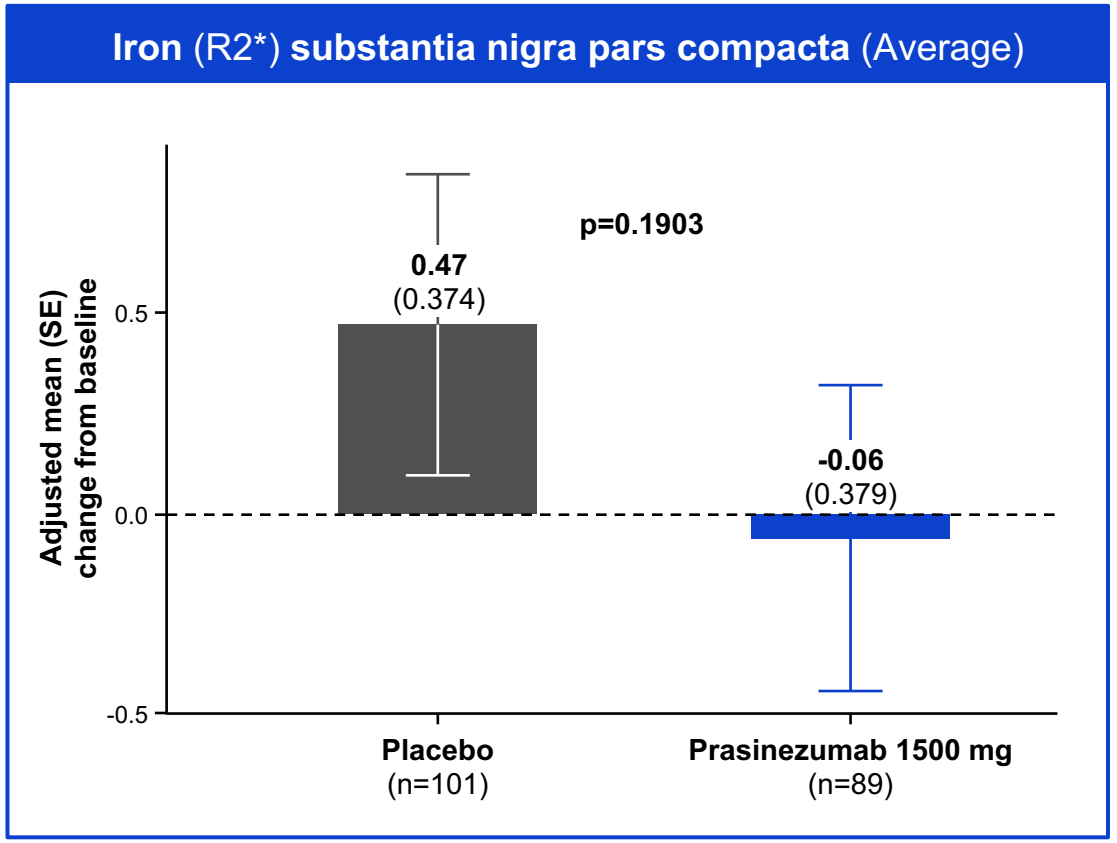
*Data generated in sites that had access to MRI sequence.
MRI, magnetic resonance imaging; SE, standard error.

Exploratory endpoint

Prasinezumab showed a trend towards reduction in iron accumulation in putamen and substantia nigra

Change from baseline to Week 76 in Iron R2* MRI#





Error bars represent SE; p-values are nominal.

*R2 MRI sequence used for imaging; #Data generated in sites that had access to MRI sequence.
MRI, magnetic resonance imaging; SE, standard error.

PADOVA: potential clinical benefit of prasinezumab in early-stage Parkinson's disease on top of symptomatic treatment

While primary endpoint missed, TTE analyses showed trends towards delaying motor progression

- More pronounced in L-DOPA treated population
- Consistent trends across secondary endpoints, including patient-reported function

Change from baseline analyses showed trends towards reduced motor progression at 104 weeks

- No treatment difference at 76 weeks
- Longer time may be needed to measure treatment effects on top of symptomatics

Prasinezumab has a favourable safety and tolerability profile

- High retention rate and rollover in OLE will contribute to long-term data generation

First biomarker evidence of a potential impact on underlying pathology

Next steps for prasinezumab programme remain under consideration

Novel TTE approach enables trials in populations treated with standard-of-care will inform future studies

Details on ***PADOVA study endpoint rationale and methodology (Pross, et al.)*** are available at **ADPD 2025**

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