A study to evaluate the efficacy and safety of intravenous prasinezumab in participants with early Parkinson's disease (PADOVA): Rationale, design, and baseline data

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Disclosures

- **Tania Nikolcheva, Gennaro Pagano, Nathalie Pross, Gesine Respondek, Annabelle Monnet, Nima Shariati, Loes Rutten-Jacobs, Thomas Kustermann, Kirsten Taylor, Dylan Trundell, Azad Bonni, Paulo Fontoura and Rachelle Doody** are full-time employees and own shares of F. Hoffmann-La Roche Ltd.
- **Hanno Svoboda** is a full-time employee of Roche Diagnostics GmbH and owns shares in 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.
- **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.
- **Ron Postuma** is a consultant for Biogen, Clinilabs, Curasen, Eisai, Inc., F. Hoffmann-La Roche Ltd., Merck, Takeda California, Inc., and Vaxxinity**.**
- **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.
- **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.
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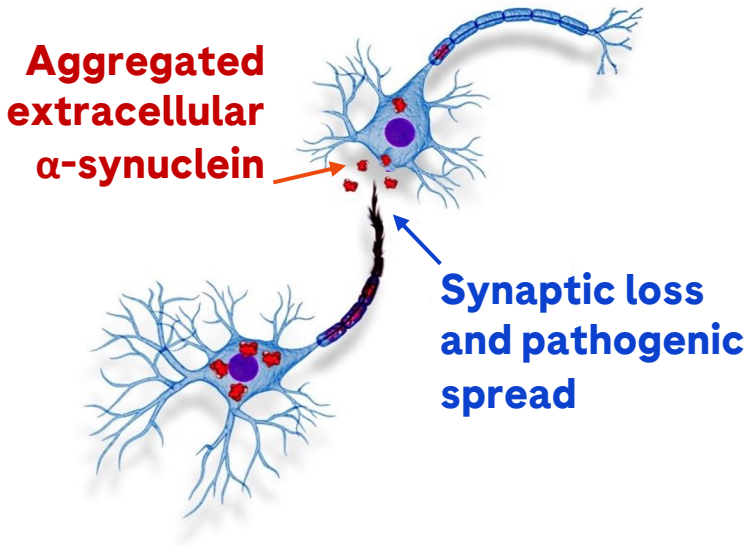
Prasinezumab is a humanised IgG1 monoclonal antibody that selectively binds aggregated α-synuclein

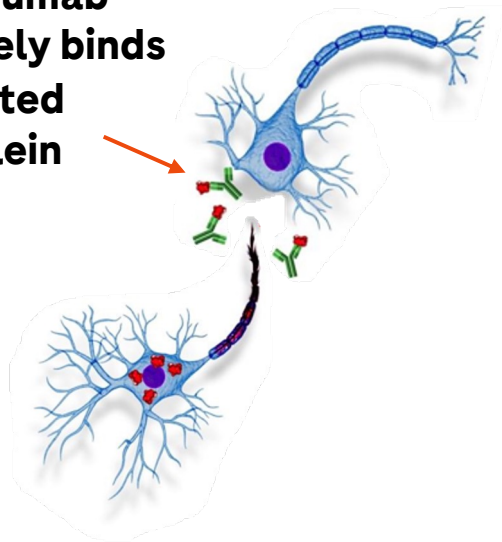
Proposed mode of action of prasinezumab for the treatment of Parkinson's disease[1–13]

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

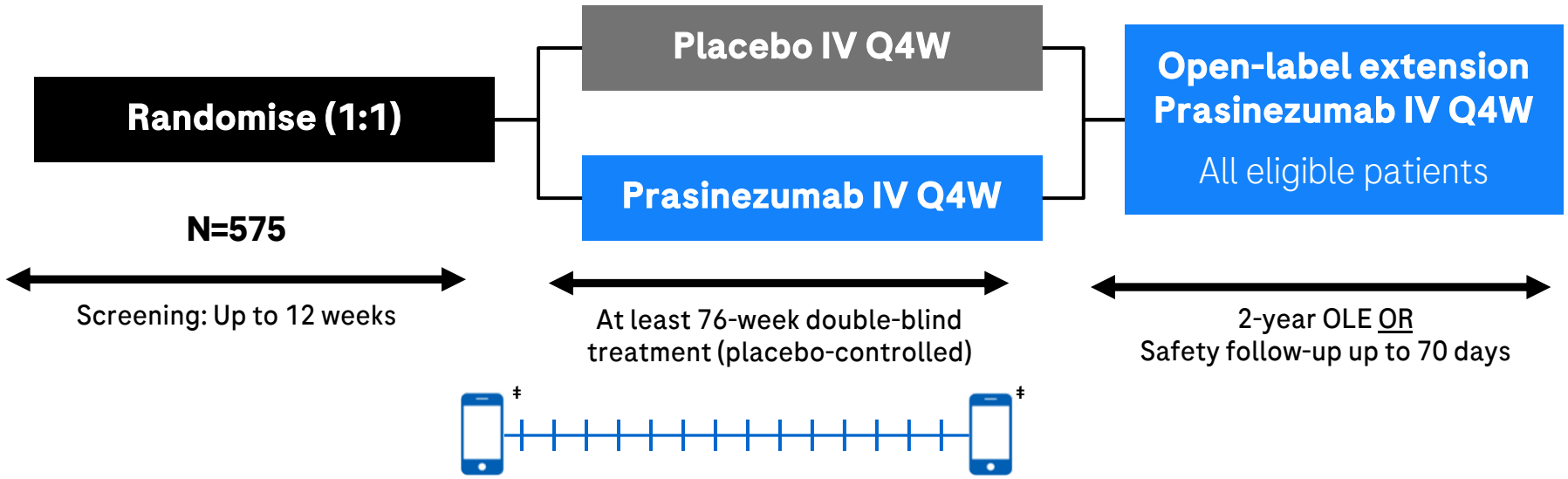
IgG, immunoglobulin.

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).

The PADOVA study explores the safety and efficacy of prasinezumab in individuals with early PD on stable symptomatic therapy*

Phase IIb multicentre, randomised, double-blind, placebo-controlled study

A **total of 112 sites** in Austria, Canada, France, Italy, Luxembourg, Poland, Spain, UK and US
RECRUITMENT COMPLETE IN MARCH 2023 (N=586)



The study follows up on signals of slowing motor progression observed in PASADENA

Details on the ***Results of the PASADENA long-term open-label extension in individuals with early-stage Parkinson's disease compared to a matched PPMI real-world data arm (Pagano, et al.)*** are available at **ADPD 2024**

*Stable doses (> 3mo) of L-DOPA or MAO-Bi as monotherapy; ‡Digital biomarkers (smartphone and wrist-worn wearable assessments). DaT-SPECT measured at baseline. ^{123}I-Ioflupane SPECT. 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; IV, intravenous; 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; OFF, practically defined OFF state, i.e. 12 hours after last dose; PD, Parkinson's disease; SPECT, single-photon emission computed tomography; Q4W, every 4 weeks.
ClinicalTrials.gov. NCT04777331. PADOVA Phase II clinical trial. Available at: https://clinicaltrials.gov/ct2/show/NCT04777331 (last accessed 15 February 2024).

PADOVA key inclusion & exclusion criteria

Key inclusion criteria

- 50–85 years
  Idiopathic PD (diagnosis by MDS criteria)
  Time from diagnosis 3 months–3 years
- DaT-SPECT consistent with dopamine transporter deficit
- H&Y Stage I or II AND
  MDS-UPDRS Part IV score = 0
- Stable dose of MAO-Bi OR L-DOPA
  ≥3 months prior to baseline
- No anticipated changes in PD medication throughout the study duration

Key exclusion criteria

- Medical history of Parkinsonian syndrome other than idiopathic PD
- Diagnosis of PD dementia
- Diagnosis of significant neurological disease other than PD
- Treatment with dopamine agonists

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, Movement Disorder Society; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease.

Schedule of assessment

Clinical, imaging and biomarker data collected over the course of the study

Assessment	Screening	Baseline	Double-blind period	End of study visit
RBDSQ	x			
MDS-UPDRS part II, III & IV	x	x	Monthly	x
SE-ADL, CGI, PGI		x	Monthly	x
MDS-NMS		x	Every 3 months	x
MoCA		x	@ 18 months	x
DaT-SPECT	x			
MRI	x		@ 18 months	x
Digital biomarkers (active and passive measures)	x	x	Daily at home and monthly in clinic	x

DaT-SPECT measured at screening: ^{123}I-Ioflupane SPECT.
CGI, Clinical Global Impression; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; MoCA, Montreal Cognitive Assessment; 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; MRI, magnetic resonance imaging; PGI, Patient Global Impression; RBDSQ, rapid eye movement sleep behaviour disorder screening questionnaire; SE-ADL, Schwab and England Activities of Daily Living Scale; SPECT, single-photon emission computed tomography.

Primary endpoint of PADOVA 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[3]
- Anchor-based analysis conducted by Horváth *et al*[4]

Time to Event (TTE) approach was used to mitigate impact of change of symptomatics on scale[5]

- 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

*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.
1. Sánchez-Ferro Á, *et al. Mov Disord Clin Pract*. 2018;5(4):448–50; 2. Zanigni S, *et al.* Presented at AD/PD 2022, Barcelona, Spain; 3. Trundell D, *et al.* Presented at MDS 2022, Madrid, Spain; 4. Horváth K, *et al. Parkinsonism Relat Disord*. 2015;21(12):1421–6; 5. Zanigni S, *et al.* Presented at MDS 2022, Madrid, Spain.

Other endpoints focus on motor and non-motor function and global scales

Clinical and digital measures used to better understand the safety and efficacy profile of prasinezumab

Secondary endpoints

- Time to worsening of motor function (≥3 points in MDS-UPDRS Part II) in the presence of a confirmed motor progression event (≥5 points in MDS-UPDRS Part III in OFF)
- Time to meaningful worsening of Patient Global Impression of Change (PGI-C) and Clinical Global Impression of Change (CGI-C)
- Change from Baseline to week 76 in MDS-UPDRS Part III (total and subscores)

Exploratory endpoints

- Change from Baseline to week 76 in MDS-UPDRS Part II, Part IV, MDS-NMS, MoCA, SE-ADL
- Digital biomarkers

Safety and tolerability

- AEs, AEs of special interest, treatment discontinuation due to AEs
- Infusion-related reactions (IRRs)
- Vital signs, ECG, labs, physical & neurological examination, C-SSRS

AE, adverse event; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; MoCA, Montreal Cognitive Assessment; 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; SE-ADL, Schwab and England Activities of Daily Living Scale.

How does the PADOVA study population compare with other datasets?

Comparison with the PASADENA and PPMI studies

	PADOVA	PASADENA	PPMI*
Population	Early PD, H&Y I-II	Early PD, H&Y I-II	Early PD, H&Y I-II
Age	50–85 yrs	40–80 yrs	40–80 yrs
Time from diagnosis	3 months to 3 years	Up to 2 years	Up to 2 years
Concomitant medication	Stable L-DOPA or MAO-Bi	Treatment naive or stable MAO-Bi	Treatment naive

*PPMI sporadic PD cohort with bradykinesia and either resting tremor or rigidity. PPMI is an observational study sponsored by The Michael J. Fox Foundation, launched in 2010 to identify biomarkers of PD onset and progression, which enrols individuals with early-stage PD in 12 countries.
From the August 2021 version of the Analytic Dataset.
H&Y, Hoehn and Yahr; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative.

PADOVA Demographic and clinical baseline characteristics

Subjects in the L-DOPA group have longer disease duration and are clinically more advanced compared to the MAO-Bi group

	All patients (n=586)	L-DOPA (n=436)	MAO-Bi (n=150)
Age (years) (mean (SD))	64.2 (7.3)	64.8 (7.5)	62.5 (6.7)
Gender			
Male	373 (63.7%)	273 (62.6%)	100 (66.7%)
Female	213 (36.3%)	163 (37.4%)	50 (33.3%)
Time since diagnosis at randomisation (months) (mean (SD))	18.61 (9.22)	19.53 (9.26)	15.92 (8.59)
Education, years (mean (SD))	15.31 (4.17)	15.25 (4.18)	15.48 (4.16)
Hoehn–Yahr Stage			
I	93 (15.9%)	61 (14.0%)	32 (21.5%)
II	491 (83.9%)*	374 (85.8%)	117 (78.5%)
MDS-UPDRS Part II (mean (SD))	5.0 (3.7)	5.16 (3.80)	4.50 (3.38)
MDS-UPDRS Part III (mean (SD))	24.46 (10.32)	25.11 (10.31)	22.60 (10.17)
SBR putamen average (mean (SD))	0.79 (0.25)	0.77 (0.24)	0.84 (0.27)
MoCA total score (mean (SD))	26.54 (2.79)	26.48 (2.82)	26.71 (2.70)

*7 patients were randomised in PADOVA with H&Y Stage III.
H&Y, Hoehn and Yahr; L-DOPA, levodopa; MAO-Bi, monoamine oxidase type B inhibitor; MoCA, Montreal Cognitive Assessment; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; SBR, striatal binding ratio; SD, standard deviation.

Comparison with other early PD cohorts

PADOVA enrolled subjects have longer disease duration and are clinically more advanced compared to the PASADENA and the PPMI cohorts

	PADOVA All patients (n=586)	PASADENA All patients (n=316)	PPMI (n=303)
Age (years) (mean (SD))	64.2 (7.3)	59.9 (9.1)	62.1 (8.5)
Gender			
Male	373 (63.7%)	213 (67.4%)	202 (66.7%)
Female	213 (36.3%)	103 (32.6%)	101 (33.3%)
Time since diagnosis at randomisation (months) (mean (SD))	18.6 (9.22)	10.1 (6.50)	4.9 (5.36)
Education, years (mean (SD))	15.3 (4.17)	16.4 (3.9)	15.6 (2.99)
Hoehn–Yahr Stage			
I	80 (13.8%)	78 (24.7%)	120 (39.6%)
II	494 (85.0%)*	238 (75.3%)	183 (60.4%)
MDS-UPDRS Part II (mean (SD))	5 (3.70)	5.3 (4.04)	6.1 (4.22)
MDS-UPDRS Part III (mean (SD))	24.5 (10.32)	21.5 (9.0)	21.2 (8.85)
SBR putamen average (mean (SD))	0.79 (0.25)	0.93 (0.27)	0.80 (0.28)
MoCA total score (mean (SD))	26.5 (2.79)	27.9 (2.05)	27.2 (2.26)

*7 patients were randomised in PADOVA with H&Y Stage III.
H&Y, Hoehn and Yahr; MoCA, Montreal Cognitive Assessment; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PPMI, Parkinson's Progression Markers Initiative; SBR, striatal binding ratio; SD, standard deviation.

Summary

- PADOVA was designed to follow up on a signal of slowing of motor progression observed in PASADENA in a population on stable background symptomatic therapy
- A TTE design was used to measure the impact of prasinezumab on meaningful motor progression and to mitigate the impact of symptomatic medication
- PADOVA enrolled 586 individuals with early-stage PD, of whom 74.4% were on stable L-DOPA and 25.6% on MAO-Bi therapy at baseline
- As expected, the PADOVA study population is slightly more advanced than the PASADENA and PPMI cohorts, based on disease duration, MDS-UPDRS Part III score and H&Y stage
- The PADOVA study population is suitable for investigating the potential of prasinezumab to slow disease progression in individuals with early PD on stable symptomatic therapy

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; PD, Parkinson's disease; PPMI, Parkinson's Progression Markers Initiative; SBR, striatal binding ratio; TTE, time-to-event.

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PASADENA and PPMI

PPMI, Parkinson's Progression Markers Initiative.