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

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

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

BACKGROUND

- Intraneuronal accumulation of abnormal alpha-synuclein (α-Syn) in form of Lewy bodies is the hallmark of Parkinson's disease (PD) and aggregated neurotoxic α-Syn is proposed to play a key role in the pathogenesis of PD.[1–10]
- No available PD treatments can slow the progression of the disease.[11,12]
- Prasinezumab is a humanised monoclonal antibody designed to bind aggregated α-Syn with the potential to stop α-Syn-related neurodegeneration, thereby slowing the progression of PD.[13–17]
- In Phase I single-ascending and multiple-ascending-dose studies, all tested dose levels had an acceptable safety and tolerability profile.[14,18]

Objective: Evaluate efficacy and safety of prasinezumab following 52 weeks of treatment in early PD.

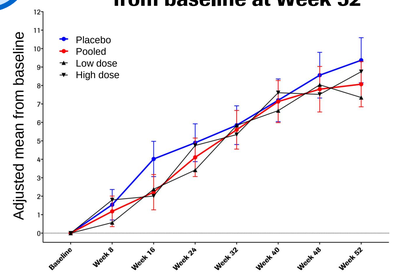
METHODS

- PASADENA Part I (NCT03100149)[18] was a 52-week multicentre, randomised, double-blind, placebo-controlled study evaluating IV prasinezumab (low [1500 mg] or high dose [4500 mg/3500 mg based on body weight]) every month in early PD.
- Participants had been diagnosed with PD for ≤2 years at screening, were in Hoehn & Yahr Stages I or II, and were either treatment naïve or treated with monoamine oxidase B inhibitors (MAO-Bi) and were not expected to require dopaminergic therapy for at least 52 weeks.
- The study was designed with 80% power and one-sided alpha of 0.10 to detect a 37.5% relative between group reduction from baseline to Week 52, based on simulations from the mixed-effect model for repeated measures (MMRM) analysis planned for the primary endpoint.
- The primary endpoint was changed from baseline at Week 52 in the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS) total score (Sum of Parts I, II and III which assess non-motor [I and II] and motor [III] experiences in daily living respectively), assessed using an MMRM and including participants until the last visit before symptomatic treatment initiation (hypothetical estimate).
- Secondary endpoints included change from baseline at Week 52 in MDS-UPDRS Part III and dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), among others. Exploratory analyses included digital biomarker data derived from patients using wearables and smartphones to remotely and frequently assess changes in motor function.

RESULTS

- Overall, 316 participants were enrolled in this study.
- The study did not meet the primary endpoint of change in MDS-UPDRS total score (Figure 1a; –21.5% Low dose: –2.02 80% CI –4.21,–0.18; –6.6% High dose: –0.62 80% CI –2.82,–1.58).
- Signals of efficacy were observed in change from baseline in MDS-UPDRS Part III (Figure 1b).
- Exploratory analyses, including MDS-UPDRS Part III central rating, digital endpoints and time to worsening of motor symptoms (Figure 2), supported this signal.
- DaT-SPECT signal changes showed no differences between groups, but there was limited progression (<11%) in placebo and treated participants.
- Prasinezumab was generally well tolerated with a favourable safety profile, no life-threatening adverse events (AEs) or immunogenicity concerns.

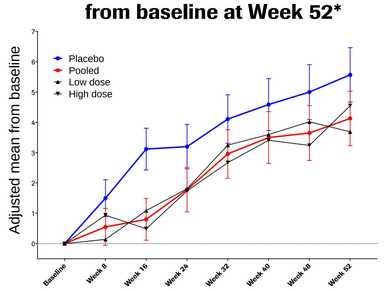
A. Change in MDS-UPDRS total score from baseline at Week 52



MDS-UDPRS total score relative difference versus placebo

Arm	N	Difference adjusted mean	Difference adjusted 80% CI	p-value	Relative change
Pooled‡	147	–1.3	–3.18, 0.58	0.38	–14%
Low	74	–2.02	–4.21, 0.18	0.24	–21.5%
High	73	–0.62	–2.82, 1.58	0.72	–6.6%

B. Change in MDS-UPDRS Part III from baseline at Week 52*



MDS-UDPRS Part III score relative difference versus placebo

Arm	N	Difference adjusted mean	Difference adjusted 80% CI	p-value†	Relative change
Pooled§	147	–1.44	–2.83, –0.06	0.18	–25%
Low	74	–1.88	–3.49, –0.27	0.14	–34%
High	73	–1.02	–2.64, 0.61	0.42	–18%

***The positive motor signal was confirmed by both site and central rating and was consistent between high and low doses**

Figure 1.

†Patients who started dopaminergic treatment or changed MAO-Bi dose are included until the last visit before starting or changing treatment, respectively. Bars represent 80% CI. Estimates are based on a MMRM with the following covariates: MAO-Bi at baseline (y/n), treatment, week, age <60 versus ≥60, sex, DaT-SPECT putamen binding ratio (contralateral to most clinically affected side), baseline MDS-UPDRS total score. ‡*Study was powered for two-sided alpha of 0.2 – no correction for multiple comparisons.* §*Pooled dose was a post-hoc analysis.*

PASADENA baseline data

	Placebo (n=105)	Low dose (n=105)	High dose (n=106)
Age, years			
Mean (SD)	59.9 (8.7)	60.3 (8.8)	59.4 (9.8)
Gender			
Male	71 (67.6%)	71 (67.6%)	71 (67.0%)
Female	34 (32.4%)	34 (32.4%)	35 (33.0%)
Weight (kg)			
Mean (SD)	75.74 (14.48)	78.02 (13.66)	76.17 (13.03)
MAO-Bi			
Yes	38 (36.2)	38 (36.2)	39 (36.8)
No	67 (63.8)	67 (63.8)	67 (63.2)
MDS-UPDRS total			
Mean (SD)	32.01 (12.98)	31.49 (13.32)	30.75 (12.10)
MDS-UPDRS Part III			
Mean (SD)	21.54 (9.11)	21.90 (9.14)	20.97 (8.81)
MDS-UPDRS Part II			
Mean (SD)	5.55 (4.09)	4.94 (3.99)	5.50 (4.07)
H&Y Stage category			
I	20 (19.0%)	29 (27.6%)	29 (27.4%)
II	65 (81.0%)	76 (72.4%)	77 (72.6%)
MDS-UPDRS Part I			
Mean (SD)	4.91 (3.71)	4.64 (4.16)	4.27 (3.57)
MoCA total score			
Mean (SD)	27.83 (2.01)	27.97 (1.94)	27.81 (2.15)
SCOPA-AUT			
Mean (SD)	7.68 (5.36)	7.95 (5.83)	8.52 (5.93)
PDSS-2			
Mean (SD)	9.41 (6.41)	8.57 (6.21)	8.49 (5.94)
REM sleep behaviour disorder score category			
Positive (≥5)	24 (22.9%)	34 (32.4%)	27 (25.7%)
Negative (<5)	81 (77.1%)	71 (67.6%)	78 (74.3%)
SE-ADL current level of disability category			
Independent	104 (99.0%)	104 (100%)	106 (100%)
Not independent	1 (1.0%)	0	0
CGI-S			
Mean (SD)	3.05 (0.63)	3.05 (0.63)	3.06 (0.64)
PDQ-39			
Mean (SD)	10.08 (7.06)	9.59 (7.54)	9.36 (6.82)
DaT-SPECT imaging – Putamen ipsilateral			
Mean (SD)	1.06 (0.30)	1.04 (0.33)	1.08 (0.34)

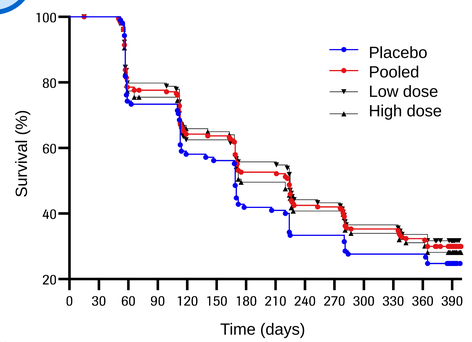
At Week 52, 72.4% of placebo, 73.5% of low-dose and 70.9% of high-dose patients were evaluable. Non-evaluable data is considered as patient starting symptomatic PD treatment, an increase of MAO-Bi (if the patient was on MAO-Bi at baseline), or withdrawal from the study.

Prasinezumab was generally safe and well tolerated

Group	Placebo (n=105)	Low dose 1500 mg (n=105)	High dose 4500 mg (n=106)	All patients (n=316)
Total number of AEs*	411	428	549	1388
Total number of AE with fatal outcome*	0	0	0	0
Total number of patients with at least one (%):†				
AE	87 (82.9)	98 (93.3)	97 (91.5)	282 (89.2)
Related AE	28 (26.7)	26 (24.8)	41 (38.7)	95 (30.1)
SAE	5 (4.8)	7 (6.7)	8 (7.5)	20 (6.3)
Related SAE	0	2 (1.9)	2 (1.6)	4 (1.3)
Grade 3–5 AE	8 (7.6)	4 (3.8)	8 (7.5)	20 (6.3)
AE or SAE leading to withdrawal from treatment or dose interruption	1 (0.9)	2 (1.9)	5 (4.7)	8 (2.5)

Percentages are relative to group size (n). Only treatment-emergent AEs are displayed where the study medication adjustment Case Report Form question is answered as "drug withdrawn".
*Multiple occurrences of the same AE in an individual are counted separately. †Multiple occurrences of the same AE in an individual are counted only once.

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



Relative change compared to placebo

Arm	Hazard ratio	Difference adjusted 80% CI*	p-value*
Low	0.77	0.63, 0.96	0.12
High	0.87	0.70, 1.07	0.37
Pooled†	0.82	0.64, 0.99	0.17

*No correction for multiple comparisons.
†Pooled dose was a post-hoc analysis.

Figure 2.

Conclusions

- PASADENA Part 1 did not reach the primary endpoint (change in MDS-UPDRS total score).
- However, prasinezumab showed positive signals of efficacy on multiple pre-specified secondary assessments of motor function, which support the further investigation into its potential as a disease-modifying treatment for PD.
- Prasinezumab was generally safe and well tolerated.
- PASADENA Part II, a 52-week blinded extension is ongoing.

- **Additional data further supporting signals of efficacy will be presented in the oral presentation on September 15th.**

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Abbreviations

α-Syn, alpha-synuclein; AE, adverse event; CGI-S, Clinical Global Impression-Severity; CI, confidence interval; DaT-SPECT, dopamine transporter imaging with single-photon emission computed tomography; IV, intravenous; MAO-Bi, monoamine oxidase B inhibitor; MDS-UPDRS, Movement Disorder Society–Unified PD Rating Scale; MMRM, mixed-effect model for repeated measures; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; PDQ-39, 39-item Parkinson's Disease Questionnaire; PDSS-2, Parkinson's Disease Sleep Scale 2; REM, rapid eye movement; SAE, serious AE; SCOPA-AUT, Scales for Outcomes in PD; SD, standard deviation; SD-ADL, Schwabb and England Activities of Daily Living scale.

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